Appendix A: Detailed Electronic Database Search Strategies

PubMed Strategy

Search	String
#1	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (“metformin”[mh] or “thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] or “Dipeptidyl-Peptidase IV Inhibitors”[mh] or “Glucagon-Like Peptide 1”[mh] or biguanide*[tiab] or metformin[tiab] or thiazolidinedione*[tiab] or pioglitazone[tiab] or rosiglitazone[tiab] or sulfonylurea*[tiab] or sulphonylurea*[tiab] or glipizide[tiab] or glyburide[tiab] or glimepiride[tiab] or glibenclamide[tiab] or “insulin secretagogues”[tiab] or sitagliptin*[tiab] or saxagliptin*[tiab] or dpp-4[tiab] or dpp-iv[tiab] or liraglutide[tiab] or exenatide[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt]) AND (("2009/04/01"[edat] : "2014/07/11"[edat]))
#2	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (linagliptin*[tiab] or alogliptin*[tiab] or albiglutide*[tiab] or dulaglutide*[tiab] or "sodium-glucose co-transporter 2 inhibitors”[tiab] or “sodium-glucose co-transporter 2 inhibitor” [tiab] or “SGLT-2” [tiab] or “canagliflozin”[tiab] or “dapagliflozin”[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])
#3	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (empagliflozin*[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])

EMBASE Strategy

Search	String	Hits
#1	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND ('thiazolidinedione'/exp or 'rosiglitazone'/exp or 'pioglitazone'/exp or 'glipizide'/exp or 'glyburide'/exp or ‘glimepiride’/exp or 'metformin'/exp or ‘sitagliptin’/exp or thiazolidinedione*:ti,ab or pioglitazone:ti,ab or rosiglitazone:ti,ab or sulfonylurea*:ti,ab or sulphonylurea*:ti,ab or glipizide:ti,ab or glyburide:ti,ab or glimepiride:ti,ab or glibenclamide:ti,ab or biguanide*:ti,ab or metformin:ti,ab or ‘insulin secretagogues’:ti,ab or ‘Dipeptidyl-Peptidase IV Inhibitor’/de or saxagliptin/exp or saxagliptin*:ti,ab or sitagliptin/exp or sitagliptin*:ti,ab or dpp-4:ti,ab or dpp-iv:ti,ab or exenatide/exp or exenatide:ti,ab or liraglutide/exp or liraglutide:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it) AND [2009-2014]/py	15183
#2	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND (linagliptin/exp or linagliptin*:ti,ab or alogliptin/exp or alogliptin*:ti,ab or albiglutide/exp or albiglutide*:ti,ab or dulaglutide/exp or dulaglutide*:ti,ab or ‘sodium glucose cotransporter 2 inhibitor’/de or ‘sodium-glucose co-transporter 2 inhibitors’:ti,ab or ‘sodium-glucose co-transporter 2 inhibitor’:ti,ab or ‘sodium glucose cotransporter 2 inhibitors’:ti,ab or ‘sodium glucose cotransporter 2 inhibitor’:ti,ab or ‘SGLT-2”:ti,ab or canagliflozin/exp or canagliflozin:ti,ab or dapagliflozin/exp or dapagliflozin:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)	1966
#3	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND (empagliflozin/exp or empagliflozin*:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)	166

Cochrane Strategy

Search	String	Hits
#1	((diabetes near type-2):ti,ab,kw or (diabet*:ti,ab,kw and (“non-insulin dependent”:ti,ab,kw or type-2:ti,ab,kw or “type II”:ti,ab,kw or “type 2”:ti,ab,kw))) AND (thiazolidinedione*:ti,ab,kw or pioglitazone:ti,ab,kw or rosiglitazone:ti,ab,kw or sulfonylurea*:ti,ab,kw or sulphonylurea*:ti,ab,kw or glipizide:ti,ab,kw or glyburide:ti,ab,kw or glimepiride:ti,ab,kw or glibenclamide:ti,ab,kw or biguanide*:ti,ab,kw or metformin:ti,ab,kw or “insulin secretagogues”:ti,ab,kw or “Dipeptidyl-Peptidase IV Inhibitors”:ti,ab,kw or saxagliptin*:ti,ab,kw or sitagliptin*:ti,ab,kw or liraglutide:ti,ab,kw or exenatide:ti,ab,kw) Publication Year from 2009 to 2014	1536
#2	((diabetes near type-2):ti,ab,kw or (diabet*:ti,ab,kw and (“non-insulin dependent”:ti,ab,kw or type-2:ti,ab,kw or “type II”:ti,ab,kw or “type 2”:ti,ab,kw))) AND (linagliptin*:ti,ab,kw or alogliptin*:ti,ab,kw or albiglutide*:ti,ab,kw or dulaglutide*:ti,ab,kw or ‘sodium-glucose co-transporter 2 inhibitors’:ti,ab,kw or ‘sodium-glucose co-transporter 2 inhibitor’:ti,ab,kw or ‘sodium glucose cotransporter 2 inhibitors’:ti,ab,kw or ‘sodium glucose cotransporter 2 inhibitor’:ti,ab,kw or ‘SGLT-2’:ti,ab,kw or canagliflozin:ti,ab,kw or dapagliflozin:ti,ab,kw)	214
#3	((diabetes near type-2):ti,ab,kw or (diabet*:ti,ab,kw and (“non-insulin dependent”:ti,ab,kw or type-2:ti,ab,kw or “type II”:ti,ab,kw or “type 2”:ti,ab,kw))) AND (empagliflozin*:ti,ab,kw)	21

Appendix B: Forms

Title Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Does this article POTENTIALLY apply to any of our key questions? Yes No

- Metformin
- TZDs (rosiglitazone, pioglitazone)
- Sulfonylureas (glyburide, glibenclamide, glipizide, glimepiride)
- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- SGLT2 inhibitors (dapagliflozin, canagliflozin)
- GLP1 agonists (exenatide, liraglutide, albiglutide, dulaglutide)

Submit Form and go to or Skip to Next

Abstract Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

Diabetes Medications Update-3
Abstract Review Form

1. **Exclude** article because (check any that apply):

- ☐ Exclude, but pull for **handsearching** (e.g., systematic review article that applies to key question)
- ☐ No **original data** (e.g., review article, commentary, or editorial)
- ☐ No **human** data reported (e.g., evaluated outcomes in animals only)
- ☐ No subjects **≥18 years of age**
- ☐ No subjects with **type 2 diabetes mellitus**, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes (e.g. exclude if only type 1 diabetes, MODY, gestational diabetes)
- ☐ No **concurrent control or comparison group** (e.g., case series or case report or pre-post design; note: that case-control studies should be included)
- ☐ Does not have a **drug comparison of interest** (see below)
- ☐ Does not evaluate an **FDA-approved formulation** (e.g., transdermal or sublingual)
- ☐ Followup less than **90 days or 3 months**
- ☐ **Does not apply** to any of the key questions
- ☐ Other reason for exclusion (specify:)
- ☐ **Placebo-controlled trial** where patients are not on background oral diabetes medications

2. **Include or unclear** so include to pull full article

- ☐ Include/unclear
- ☐ Pooled analysis

Priority Medication Comparisons Included for Each Key Question*

	Main Intervention	Comparisons
Monotherapy as main intervention	Metformin	• Placebo • Thiazolidinediones • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT2 inhibitor • Combination of metformin plus GLP-1 agonist
	Thiazolidinedione (rosiglitazone, pioglitazone)	• Placebo • Another thiazolidinedione • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	Sulfonylurea (glyburide, glibenclamide, glipizide, glimepiride)	• Placebo • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	DPP-4 inhibitor (sitagliptin, saxagliptin, linagliptin, alogliptin)	• Placebo • Another DPP-4 inhibitor • SGLT2 inhibitors • GLP-1 agonists
	SGLT2 inhibitor (dapagliflozin, canagliflozin, empagliflozin)	• Placebo • Another SGLT2 inhibitors • GLP-1 agonists
	GLP-1 agonists (exenatide, liraglutide, albiglutide, dulaglutide)	• Placebo • Another GLP-1 agonists
Combination therapy as main intervention	Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin [insulin glargine, insulin detemir, neutral protamine Hagedorn (NPH) insulin] or premixed insulin [NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, insulin aspart 70/30])	• Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin or premixed insulin)

* Do not include if only comparison is with insulin only or with triple combination therapy.

List of fixed-dose combinations to include:
- Metformin/rosiglitazone (Avandamet)
- Metformin/pioglitazone (Actoplus Met)
- Metformin/glipizide (Metaglip)
- Metformin/glyburide (Glucovance)
- Metformin/saxagliptin (Kombiglyze XR)
- Metformin/linagliptin (Jentadueto)
- Metformin/sitagliptin (Janumet)
- Metformin/alogliptin (Kazano)

3. Comments

Submit Form and go to or Skip to Next

Article Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications Update-3
Article Review Form

MAJOR EXCLUSION CRITERIA

1) Exclude article because (check any that apply):

- ☐ Exclude, but pull for **handsearching** (e.g., systematic review article that applies to key question)
- ☐ No **original** data (e.g., review article, commentary, or editorial)
- ☐ Meeting abstract
- ☐ No **human** data reported (e.g., evaluated outcomes in animals only)
- ☐ No subjects **≥18 years of age**
- ☐ No subjects with **type 2 diabetes mellitus**, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes (e.g. exclude if only type 1 diabetes, MODY, gestational diabetes) or no stratification of results by type of diabetes
- ☐ Does not meet any of the **study design criteria** listed in table 1
- ☐ Does not have a **drug comparison of interest** in table 2
- ☐ Only a **placebo-controlled comparison** (please make sure that they are not on background metformin which could make it a comparison of interest in table 2)
- ☐ Does not evaluate an **FDA-approved formulation** (e.g., transdermal or sublingual)
- ☐ Does not specify **background medications** or no stratification of results by treatment (and for RCTS: no stratified randomization by background medications)
- ☐ No **outcome** of interest
- ☐ Followup less than **3 months or 90 days or 12 weeks**
- ☐ Conducted in a population where everyone is required to have at least one of the following **comorbid conditions** [i.e., end-stage liver disease (e.g., cirrhosis); end-stage renal disease (e.g., stage 5 or dialysis); cancer; or new onset diabetes after transplant; recent cardiovascular event within 3 months (e.g., acute coronary syndrome, acute myocardial infarction, post-CABG, or with drug-eluting stents)]. **(specify comorbid condition):**
- ☐ **Does not apply** to any of the key questions
- ☐ Other (specify):
- ☐ Not written in English
- ☐ Head-to-head intraclass comparison that is NOT rosiglitazone vs. pioglitazone

NON-RANDOMIZED STUDIES (no need to answer if excluded in Q1)

2) Does the article describe a NON-RANDOMIZED STUDY?

Select an Answer

INCLUSION

7) Include article for data abstraction

- ☐ Include
- ☐ do not use
- ☐ Include but comparison of interest is dulaglutide or glargine u300 only
- ☐ Pooled analysis that meets all the inclusion criteria
- ☐ Meets inclusion criteria and is related to another article (enter reference number)

Comments (limit 250 characters)

Table 1. Study design criteria

Key Question	Study design criteria	Comparison limitations
KQ1 - Intermediate outcomes: • HbA1c • Weight • Systolic blood pressure	Include only if: • RCT	HbA1c • Not metformin vs. sulfonylurea Weight • Not metformin vs. thiazolidinedione • Not metformin vs. sulfonylurea Systolic blood pressure • Only for comparisons with SGLT-2 inhibitors or GLP-1 agonists
KQ2 - Long-term clinical outcomes • All-cause mortality • Cardiovascular and cerebrovascular morbidity and mortality • Retinopathy • Nephropathy • Neuropathy	Include only if • RCT • non-randomized clinical trial • cohort with a comparison group, or • case-control study	Include for all comparisons
KQ3 - Adverse events • Liver injury • Severe lactic acidosis • Pancreatitis • Hypoglycemia • Congestive heart failure	Include only if • RCT • non-randomized clinical trial • cohort with a comparison group, or • case-control study	Urinary tract infections, impaired renal function, genital mycotic infections, fracture, volume depletion • Only for comparisons with SGLT-2 inhibitors Heart rate increase • Only for comparisons with SGLT-2 inhibitors or GLP-1 agonists

• Cancer • Severe allergic reactions • Macular edema or decreased vision • Gastrointestinal side effects • Urinary tract infections • Impaired renal function • Genital mycotic infections • Fracture • Volume depletion • Heart rate increase		
KQ4 – Subgroups • Age • Sex • Race/ethnicity • BMI	Follow study design criteria for outcomes as stated above	Follow comparison limitations as stated above

Table 2. Priority Medication Comparisons Included for Each Key Question*

	Main Intervention	Comparisons
Monotherapy as main intervention	Metformin	• Thiazolidinediones • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT2 inhibitor • Combination of metformin plus GLP-1 agonist
	Thiazolidinedione (rosiglitazone, pioglitazone)	• Another thiazolidinedione • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	Sulfonylurea (glyburide, glibenclamide, glipizide, glimepiride)	• DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	DPP-4 inhibitor (sitagliptin, saxagliptin, linagliptin, alogliptin)	• Another DPP-4 inhibitor • SGLT2 inhibitors • GLP-1 agonists
	SGLT2 inhibitor (dapagliflozin, canagliflozin, empagliflozin)	• Another SGLT2 inhibitor • GLP-1 agonists
	GLP-1 agonists (exenatide, liraglutide, albiglutide, dulaglutide)	• Another GLP-1 agonist
Combination therapy as main intervention	Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin [insulin glargine, insulin detemir, neutral protamine Hagedorn (NPH) insulin] or premixed insulin [NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, insulin aspart 70/30])	• Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin or premixed insulin)

* Do not include if only comparison is with insulin only or with triple combination therapy.
List of fixed-dose combinations to include:
• Metformin/rosiglitazone (Avandamet)
• Metformin/pioglitazone (Actoplus Met)
• Metformin/glipizide (Metaglip)
• Metformin/glyburide (Glucovance)
• Metformin/saxagliptin (Kombiglyze XR)
• Metformin/linagliptin (Jentadueto)
• Metformin/sitagliptin (Janumet)
• Metformin/alogliptin (Kazano)

Submit Form and go to or Skip to Next

Study Design

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to [ ] or Skip to Next

Diabetes Medications
Study Design Form

Fill out this form for all included studies.

1. In what country does the study occur? **(check all that apply)**

- [ ] United States
- [ ] Canada
- [ ] United Kingdom
- [ ] Japan
- [ ] Multinational Europe
- [ ] Multi-continent
- [ ] Other (specify): [ ]
- [ ] Not reported

2. What study design is used? **(check only one response)**

Select an Answer

3. Select trial type **(check all that apply)**

- [ ] Parallel arms
- [ ] Factorial design
- [ ] Crossover design
- [ ] Other (specify): [ ]
- [ ] None of the above apply to the trial/Not applicable (not a trial)

4. Was there a run-in period (i.e., a period of observation prior to randomization, including wash-out periods)? **(check only one response)**

Select an Answer

6. Was there pharmaceutical support or involvement (funding of study, co-authorship, or drug given for free) of the study? **(check only one response)**

Select an Answer

7. Study enrollment period (preferred) or dates of study. **Enter 4-digit year for start, end or both years.**

- [ ] Start year: [ ]
- [ ] End year: [ ]
- [ ] Neither year reported

8. For RCTs and non-randomized trials, what was the total intended followup duration? ○ Duration: [ ] ○ Not reported ○ Not applicable Clear Response	9. Specify units: **(check only one response)** Select an Answer
10. For cohort studies, what was the mean/median followup duration? Select an Answer	11. Specify units: **(check only one response)** Select an Answer

12. Was a subgroup of interest (age, gender, race, obesity/BMI) mentioned in the methods or reported in the results?

Select an Answer

Study Population Questions

14. What was the source(s) of the population from which subjects were enrolled in the study? **(check all that apply)**

- [ ] Inpatient/hospital
- [ ] Outpatient: primary care
- [ ] Outpatient: subspecialty care setting
- [ ] Community
- [ ] Other (specify): [ ]
- [ ] Not reported
- [ ] Administrative database

15. **If an administrative database was used, please answer. Otherwise skip.**
Name of database (e.g., MarketScan, VA, Denmark):
[ ]

16. **In an administrative database was used, please answer. Otherwise skip.**
Databases used **(check all that apply)**:

- ☐ Inpatient diagnosis/procedures
- ☐ Outpatient diagnosis/procedures
- ☐ Inpatient pharmacy records
- ☐ Outpatient pharmacy records
- ☐ Cancer registry
- ☐ Death registry
- ☐ Other (specify):

17. What was the total number at randomization or cohort inception?

- ○ N:
- ○ Not reported

18. Please select and specify the exclusion criteria. Any inclusion criteria should be entered as exclusion criteria e.g. if the inclusion criteria is type 2 diabetes, the exclusion criteria would be no type 2 diabetes.

- ☐ Age (specify):
- ☐ HbA1c > (specify):
- ☐ HbA1c < (specify):
- ☐ BMI or weight (specify):
- ☐ Duration of diabetes (e.g., number of years or newly diagnosed diabetes) (specify):

- ☐ Prior use of any diabetes treatment
- ☐ Prior or current use of insulin
- ☐ Prior or current use of study drug
- ☐ Male
- ☐ Female
- ☐ Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT))
- ☐ Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance)
- ☐ History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina); DO NOT MARK IF RECENT ACUTE EVENT IN PAST 6 MONTHS
- ☐ Contraindication or history of intolerance to metformin
- ☐ Neuropathy
- ☐ Retinopathy
- ☐ Pregnant
- ☐ Nursing
- ☐ Not using adequate contraception
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Not reported

19. Does the study have a registered protocol?

- ○ Yes (enter registration number)
- ○ No

Clear Response

20. Does the study reference a protocol?

- ○ Yes (specify reference number)
- ○ No

Clear Response

21. Comments **(limit 250 characters)**

22. Comments **(limit 250 characters)**

23. Comments **(limit 250 characters)**

Submit Form and go to or Skip to Next

Intervention Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to ⇕ or Skip to Next

Oral Diabetes Medications Update
Intervention Form

Instructions:
1) Complete this form for all RCT's, cohort studies, and cross-over studies. Do not use this form for case-control studies.
2) For cross-over studies, please record each portion of the crossover as a separate comparison
3) Please use "Case Control Intervention and Outcomes Form" for case-control studies

1. Specify the intervention/exposure for this form: **(Mandatory question; please check one)**

Select an Answer ⇕

For monotherapy comparisons where the main intervention is using a single drug, complete the first row only.
For combination comparisons, complete the first row for metformin, and complete the second row for the additional drug.
Only abstract clinically relevant doses.

Intervention (Select one; interventions listed in order of priority)	**Dosing**	**Total daily dose after run-in** (include units; OK to calculate if not explicitly stated) Fill in all dosing information.
◯ Metformin **TZDs** ◯ Rosiglitazone ◯ Pioglitazone ◯ Any in the TZD class **Sulfonylureas** ◯ Glyburide ◯ Glibenclamide ◯ Glipizide ◯ Glimepiride ◯ SU not specified **DPP-4 Inhibitors** ◯ Sitagliptin ◯ Saxagliptin ◯ Linagliptin ◯ Alogliptin ◯ Any in the DPP-4 inhibitor class **SGLT-2 inhibitors** ◯ Dapagliflozin ◯ Canagliflozin ◯ Empagliflozin ◯ Any in the SGLT-2 inhibitor class **GLP-1 agonist** ◯ Exenatide ◯ Liraglutide ◯ Albiglutide ◯ Dulaglutide ◯ Any in the GLP-1 agonist class Clear Response	◯ Fixed ◯ Titrated ◯ Not specified Clear Response	4. Dosing information ☐ Fixed dose (specify): ____ ☐ Mean daily dose recorded during study (specify): ____ ☐ Median daily dose recorded during study (specify): ____ ☐ Maximum titration dose (specify): ____ ☐ Other (specify): ____ ☐ Not specified/unclear
5. Complete this row ONLY if another drug is added on to metformin. Additional drug (specify): **TZDs** ◯ Rosiglitazone ◯ Pioglitazone ◯ Any in the TZD class **Sulfonylureas** ◯ Glyburide ◯ Glibenclamide ◯ Glipizide ◯ Glimepiride ◯ SU not specified **DPP-4 Inhibitors** ◯ Sitagliptin ◯ Saxagliptin ◯ Linagliptin ◯ Alogliptin ◯ Any in the DPP-4 inhibitor class **SGLT-2 inhibitors** ◯ Dapagliflozin ◯ Canagliflozin ◯ Empagliflozin ◯ Any in the SGLT-2 inhibitor class **GLP-1 agonist**	◯ Fixed ◯ Titrated ◯ Not specified Clear Response	7. Dosing information ☐ Fixed dose (specify): ____ ☐ Mean daily dose recorded during study (specify): ____ ☐ Median daily dose recorded during study (specify): ____ ☐ Maximum titration dose (specify): ____ ☐ Other (specify): ____ ☐ Not specified/unclear

◯ Exenatide ◯ Liraglutide ◯ Albiglutide ◯ Dulaglutide ◯ Any in the GLP-1 agonist class **Basal insulin** ◯ Insulin glargine ◯ NPH ◯ Insulin detemir ◯ Any basal insulin **Premixed insulin** ◯ NPH/regular 70/30 ◯ Insulin aspart 70/30 ◯ Insulin lispro 75/25 ◯ Insulin lispro 50/50 ◯ Any premixed insulin Clear Response		
8. Indicate if placebo was provided ◯ Placebo Clear Response		

Rescue therapy

9. Was rescue therapy used in this arm? Rescue therapy includes additional pharmacologic therapies that are added to the study intervention.

Select an Answer

12. Comments **(limit 250 characaters)**

13. Comments **(limit 250 characaters)**

14. Comments **(limit 250 characaters)**

Submit Form and go to or Skip to Next

Population characteristics

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Oral Diabetes Medications Update
Population Form – Baseline Characteristics

Instructions:
1) Use this form for all RCTs, cohort studies, and cross-over studies. Do NOT use this form for case-control studies.
2) For cross-over studies, please record each portion of the crossover as a separate comparison
3) Please use "Case Control Intervention and Outcomes Form" for case-control studies.
4) Only enter data for the first measure that you are able to for each row.

	Main intervention	Comparison A	Comparison B
Total N at enrollment (i.e., at randomization or at beginning of exposure period) Total N not reported Clear Response			
N for baseline characteristics N for baseline characteristics not reported Clear Response			
Age Age not reported Clear Response	Mean Median Range Other, only age categories reported	Mean Median Range Other, only age categories reported	Mean Median Range Other, only age categories rep
Male Male not reported Clear Response	%: N:	%: N:	%: N:
Race/Ethnicity Race/ethnicity not reported Clear Response	Caucasian, %: Caucasian, N: African American, %: African American, N: Asian or Asian American, %: Asian or Asian American, N: Hispanic or Latino, % Hispanic or Latino, N Other race/ethnicity, %: Other race/ethnicity, N:	Caucasian, %: Caucasian, N: African American, %: African American, N: Asian or Asian American, %: Asian or Asian American, N: Hispanic or Latino, % Hispanic or Latino, N Other race/ethnicity, %: Other race/ethnicity, N:	Caucasian, %: Caucasian, N: African American, %: African American, N: Asian or Asian American, %: Asian or Asian American, N: Hispanic or Latino, % Hispanic or Latino, N Other race/ethnicity, %: Other race/ethnicity, N:
Weight/BMI (weight units are preferred) Weight/BMI not reported Clear Response	Mean weight (include units): Median weight (include units): Mean BMI (kg/m2): Median BMI (kg/m2): Other, only weight/BMI categories reported	Mean weight (include units): Median weight (include units): Mean BMI (kg/m2): Median BMI (kg/m2): Other, only weight/BMI categories reported	Mean weight (include units): Median weight (include units): Mean BMI (kg/m2): Median BMI (kg/m2): Other, only weight/BMI categc
Baseline HbA1c % mmol/mol mmol/L HbA1c not reported Clear Response	Mean HbA1c: Median HbA1c:	Mean HbA1c: Median HbA1c:	Mean HbA1c: Median HbA1c:
Duration of diabetes Days Weeks Months Years Duration of diabetes not reported Clear Response	Mean: Median:	Mean: Median:	Mean: Median:
Number of withdrawals and/or losses to followup Withdrawals/loss to followup not reported Not applicable (i.e., time to event analysis) Clear Response	%: N:	%: N:	%: N:

Comments (limit 250 characters)

Comments (limit 250 characters)

Comments (limit 250 characters)

76. Results only reported by subgroup

Subgroup (specify):
Clear Response

Submit Form and go to or Skip to Next

Outcomes Form KQ1 – KQ3

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications Outcomes Form

Fill out this form for all included studies*
Outcome of interest being reported on this form (check only one outcome under KQ1, KQ2, or KQ3 on this form):

Key Question 1 (Intermediate outcomes)

Outcome	Units
Key Question 1 (Intermediate outcomes) HbA1c (Do NOT abstract for Met vs. SU comparison) Weight (Do NOT abstract for Met vs. SU or MET vs. TZD) BMI (ONLY if weight is not reported) Systolic blood pressure (ONLY FOR SGLT-2 or GLP-1 comparisons) Heart rate (ONLY FOR SGLT-2 or GLP-1 comparisons) Clear Response	Indicate units % mmol/mol mmol/L kg lb kg/m2 mmHg BPM Clear Response

Key Question 2 (Long-term outcomes)

Outcome	Definition
Key Question 2 (Long-term outcomes) All-cause mortality Cardiovascular mortality Cardiovascular morbidity (e.g., myocardial infarction, acute coronary syndrome, arrhythmia, cardiac procedures, like percutaneous coronary intervention) Cerebrovascular mortality/disease (e.g., stroke, TIA) Incident diabetic retinopathy (macular edema will be captured under Key Question 3) Incident diabetic nephropathy (e.g., mean eGFR, urinary albumin:creatinine ratio, changes in proteinuria or microalbuminuria, ESRD, dialysis outcomes, etc) Incident diabetic neuropathy Clear Response	

Key Question 3 (Adverse event or side effect – Do NOT abstract for Met vs SU comparisons except cancer outcomes)

Outcome	Definition
Key Question 3 (Adverse event or side effect) Hypoglycemia - mild/moderate Hypoglycemia - severe/major Hypoglycemia - total (only if not separated by mild/moderate/severe) Liver failure Congestive heart failure Lactic acidosis Cancer Severe allergic reaction (including hypersensitivity reaction) Hip fracture (for SGLT-2 inhibitor comparisons only) Non-hip fracture (for SGLT-2 inhibitor comparisons only) Pancreatitis Volume depletion (for SGLT-2 inhibitor comparisons only) Macular edema Decreased vision Gastrointestinal side effects (nausea, vomiting, diarrhea, dyspepsia, abdominal pain, total) Impaired renal function (for SGLT-2 inhibitor comparisons only; same outcomes as nephropathy) Genital or mycotic infection ((e.g., sexually transmitted disease or yeast or Bacterial vaginosis) Urinary tract infections (for SGLT-2 inhibitors only) Other serious adverse event (e.g., nocturnal hypoglycemia, osmotic diuresis) Clear Response	Defined as... Specify: Unspecified Clear Response

If applies to Key Question 3 (adverse events and/or safety outcomes), please answer questions 12.

12. Was the mode of adverse event collection active or passive?
If administrative database study, select passive.

Active (Active ascertainment of harms indicates (a) that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests, usually performed at pre-specified time intervals and/or (b) that the potential occurrence of harmful events are collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery. These events are potentially expected harms as a result of the intervention.)
Passive (Passive ascertainment of harms occurs when study participants spontaneously report (on their own initiative) or are allowed to report harmful events not probed with active ascertainment. In some studies, laboratory or diagnostic tests are only ordered if a particular event is suspected. For example, a study participant is suspected of having a stroke based on clinical presentation; the authors would indicate that brain imaging tests would then be ordered to confirm the presence or absence of the stroke.)
Not reported/unclear
Clear Response

ANSWER FOR ALL OUTCOMES:

13. Were results available for an "intention-to-treat" analysis (i.e., not per-protocol or "on treatment" analysis) for this outcome?

- ◯ Yes
- ◯ No
- ◯ Not reported
- ◯ Not applicable (e.g., cohort)

Clear Response

14. What is the followup time for this outcome? **(Only report the longest followup time.)**	Specify units:
◯ (specify): ____ ◯ Not reported Clear Response	Select an Answer

Continuous outcomes (Most of outcomes for Key Question 1)

Table I. Mean difference from other intervention group measures of outcome (between-group difference). When filling out this table, please note that the point estimate should reflect this formula: (Final - Baseline for the intervention group) - (Final - Baseline for the reference group). You do not need to calculate this.

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ◯ Mean ◯ Median ◯ Other (specify): ____ ◯ Not reported Clear Response	Measure of variability ◯ SE ◯ SD ◯ Other (specify): ____ ◯ Not reported Clear Response	95% CI or IQR ◯ 95% CI ◯ IQR ◯ Not reported Clear Response	p-value (Record exact p-value) ◯ Not reported Clear Response	Indicate reference group
Main Intervention	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____		Select an Answer
Comparison A	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____		Select an Answer
Comparison B	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____		Select an Answer
Comparison C	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____		Select an Answer
Comparison D	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____		Select an Answer
Comparison E	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____		Select an Answer

Table II. Mean difference from baseline to final measures of outcome (within-group difference)
(This should be Final - Baseline. If values decrease, be sure to indicate with a negative sign (-)).

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ◯ Mean ◯ Median ◯ Other (specify): ____ ◯ Not reported Clear Response	Measure of variability ◯ SE ◯ SD ◯ Other (specify): ____ ◯ Not reported Clear Response	95% CI or IQR ◯ 95% CI ◯ IQR ◯ Not reported Clear Response	p-value (Record exact p-value) ◯ Not reported Clear Response
Main Intervention	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____	
Comparison A	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____	
Comparison B	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____	
Comparison C	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____	
Comparison D	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____	
Comparison E	◯ N for analysis ____ ◯ Baseline N ____ Clear Response			☐ Lower limit ____ ☐ Upper limit ____	

Table III. Baseline measures of cohort

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) Mean Median Other (specify): Not reported Clear Response	Measure of variability SE SD Other (specify): Not reported Clear Response	95% CI or IQR 95% CI IQR Not reported Clear Response	p-value (Record exact p-value) Not reported Clear Response	Indicate reference group
Main Intervention	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison A	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison B	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison C	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison D	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison E	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer

Table IV. Final measures of outcome

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) Mean Median Other (specify): Not reported Clear Response	Measure of variability SE SD Other (specify): Not reported Clear Response	95% CI or IQR 95% CI IQR Not reported Clear Response	p-value (Record exact p-value) Not reported Clear Response	Indicate reference group
Main Intervention	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison A	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison B	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison C	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison D	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison E	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer

Dichotomous Outcomes (Most of outcomes for Key Questions 2 and 3)

Table V. Incidence of the outcome by intervention group

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Outcome measure/numerator Not reported Clear Response	Denominator Select an Answer	p-value (Record exact p-value) Not reported Clear Response	Indicate reference group
Main intervention	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison A	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison B	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison C	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison D	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison E	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer

Table VI. Measures of association for comparison of outcome between intervention groups

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate Relative risk Relative hazard Odds ratio Risk difference Other: Not reported Clear Response	Measure of variability SE SD Not reported Clear Response	95% Confidence interval Not reported Clear Response	p-value (Record exact p-value) Not reported Clear Response	Indicate reference group
Main intervention	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison A	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison B	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison C	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison D	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison E	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer

What were the results adjusted for in the final model?

- [ ] Results are not adjusted
- [ ] Age
- [ ] Sex
- [ ] Race/SES
- [ ] BMI or weight
- [ ] Glycemic control
- [ ] Comorbidities
- [ ] Duration of diabetes
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):

244. Comments **(limit 250 characters)**

245. Comments **(limit 250 characters)**

246. Comments **(limit 250 characters)**

247. Results reported for subgroup

- ( ) Subgroup (specify)

Clear Response

Submit Form and go to or Skip to Next

Study Quality Form for Randomized Controlled Trials

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications
Quality Form for Trials

Complete this form only for randomized controlled trials.

1. Was the study described as **randomized** (this includes the use of words such as randomly, random and randomization)?

   Yes No Not reported Clear Response

3. Was the study described as **double blind**?

   Yes No Not reported/Can't tell Clear Response

5. Was there a description of **withdrawals and dropouts**?

   Yes: the number and the reasons for withdrawals in each group was stated or it was stated that there were no withdrawals
   (if subjects were not included in the analysis, they must state the number and reasons for not including them in the analysis)

   No Clear Response

6. Comments **(limit 250 characters)**

7. Comments **(limit 250 characters)**

8. Comments **(limit 250 characters)**

Submit Form and go to or Skip to Next

Study Quality Form for Non-randomized study

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to ⇕ or Skip to Next

Diabetes Medications
Downs and Black Checklist for Measuring Study Quality

Complete this form only for non-randomized studies.

REPORTING

1. Is the **hypothesis/aim/objective** of the study clearly described?

   ◯ Yes ◯ No Clear Response

2. Are the **main outcomes** to be measured clearly described in the **Introduction or Methods section**?
   If the main outcomes are first mentioned in the Results section, the question should be answered 'no.'

   ◯ Yes ◯ No Clear Response

3. Are the **characteristics of the subjects** included in the study clearly described?
   In trials, inclusion and/or exclusion criteria should be given.

   ◯ Yes ◯ No Clear Response

4. Are the **interventions of interest** clearly described?
   Treatment and placebo (where relevant) that are to be compared should be clearly described

   ◯ Yes ◯ No Clear Response

5. Are the **distributions of principal confounders** in each group of subjects to be compared clearly described?
   A list of principal confounders is provided.

   ◯ Yes ◯ No Clear Response

6. Are the **main findings** of the study clearly described?
   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does NOT cover statistical tests which are considered below).

   ◯ Yes ◯ No Clear Response

7. Does the study provide estimates of the **random variability** in the data for the main outcomes?
   In non-normally distributed data the inter-quartile range of results should be reported.
   In normally distributed data the standard error, standard deviation or confidence intervals should be reported.
   If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

   ◯ Yes ◯ No Clear Response

8. Have all important **adverse events** tht may be a consequence of the intervention been reported?
   This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events.
   If administrative database, select "Not applicable."

   ◯ Yes ◯ No ◯ Not applicable Clear Response

9. Have the characteristics of **subjects lost to follow-up** been described?
   This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion.
   This should be answered 'no' where a study does not report the number of patients lost to follow-up.

   ◯ Yes ◯ No Clear Response

10. Have **actual probability values** been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

    ◯ Yes ◯ No Clear Response

EXTERNAL VALIDITY

11. Were the **subjects asked to participate in the study representative** of the entire population from which they were recruited?
    The study must identify the source population for patients and describe how the patients were selected.
    Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered 'unable to determine.'
    If administrative database study, select "Not applicable."

    ◯ Yes ◯ No ◯ Unable to determine ◯ Not applicable Clear Response

12. Were those **subjects who were prepared to participate representative** of the entire population from which they were recruited?
    The proportion of those asked who agreed should be stated.
    Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.
    If administrative database study, select "Not applicable."

    ◯ Yes ◯ No ◯ Unable to determine ◯ Not applicable Clear Response

13. Were the **staff, places, and facilities** where the subjects were treated/tested **representative** of the testing the majority of subjects receive?
    For the question to be answered 'yes' the study should demonstrate that the testing was representative of that in use in the source population. The question should be answered 'no' if, for example, the testing was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.

    ◯ Yes ◯ No ◯ Unable to determine Clear Response

INTERNAL VALIDITY - BIAS

14. Was an attempt made to **blind study subjects** to the intervention they have received?
    For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

    ◯ Yes ◯ No Clear Response

15. Was an attempt made to **blind those measuring the main outcomes** of the intervention?

    ◯ Yes ◯ No ◯ Unable to determine ◯ Not feasible Clear Response

16. If any of the results of the study were based on **"data dredging"**, was this made clear?
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes.'

◯ Yes ◯ No ◯ Unable to determine Clear Response

17. In **trials and cohort studies**, do the analyses **adjust for different lengths** of follow-up of patients?
Where follow-up was the same for all study participants the answer should be 'yes.' If different lengths of follow-up were adjusted, for example, by survival analysis, the answer should be 'yes.'
Studies where differences in follow-up are ignored should be answered 'no.'

◯ Yes ◯ No ◯ Unable to determine ◯ Not applicable (i.e. no followup for this type of study) Clear Response

18. Were the **statistical tests** used to assess the main outcomes appropriate?
The statistical techniques used must be appropriate to the data. For example nonparametric
methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes.' If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

◯ Yes ◯ No ◯ Unable to determine Clear Response

19. Was **compliance** with the interventions reliable?
Where there was non compliance with the allocated treatment or where htere was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.
For administrative database studies:
• If they assessed adherence/compliance (such as using the medication possession ratio or days supply in-hand) and adherence/compliance
was 80% or greater, enter Yes
was less than 80%, enter No
was not reported, enter Unable to Determine
• If patients were censored/changed to different medication group when switched medications, enter Yes
• If the exposure period (i.e., examined medication use in 180 days prior to event) was shorter than 6 months, enter Yes
• If they required a minimum duration of medication use (such as 180 days) and the duration of follow up was short (such as 1 year), enter Yes (However, if they required a minimum duration of medication use (such as 180 days) and the duration of follow up was long (such as 5 years), enter Unable to Determine)
• If pts were assigned to a treatment group based on initial/baseline prescription only without mention of follow up assessment, enter Unable to Determine
• If the participants were allowed to change medications but were analyzed according to baseline medication, enter Unable to Determine (However, if baseline and censored medication analyses were done and yielded similar magnitude of effect/statistical significance results, enter Yes)

◯ Yes ◯ No ◯ Unable to determine Clear Response

20. Were the **main outcome measures** used accurate (valid and reliable)?
For studies where the outcome measures are clearly described, the question should be answered 'yes.' For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'yes.'
For administrative database studies:
• If all outcomes came from state/national cancer registry or death master file, enter Yes
• If all outcomes confirmed by chart review, enter Yes
• If a subset of outcomes were chart reviewed and performance statistics (i.e., sensitivity/specificity) provided for their validity, enter Yes
• If outcomes were identified by ICD-9-CM or ICD-10-CM and a citation is provided based on this exact cohort that the codes used have been confirmed with a chart review, enter Yes
• If outcomes were identified by ICD-9-CM or ICD-10-CM and a different cohort is cited OR no citation of validity is provided, enter Unable to Determine
• If some outcomes meet the definition of Yes and others meet the definition for Unable to Determine, enter Unable to Determine

◯ Yes ◯ No ◯ Unable to determine Clear Response

INTERNAL VALIDITY - CONFOUNDING AND SELECTION BIAS

21. Were the subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) **recruited from the same population**?
For example, subjects for all comparison groups should be selected from the same school. The question should be answered unable to determine for cohort where there is no information concerning the source of subjects included in the study.

◯ Yes ◯ No ◯ Unable to determine Clear Response

22. Were study subjects in different testing groups (trials and cohort studies) or were the cases and controls (case-control studies) **recruited over the same period of time**?
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

◯ Yes ◯ No ◯ Unable to determine Clear Response

23. Were study subjects **randomized** to intervention groups?
Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example, alternate allocation would score no because it is predictable.

◯ Yes ◯ No ◯ Unable to determine Clear Response

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

◯ Yes ◯ No ◯ Unable to determine Clear Response

25. Was there **adequate adjustment for confounding** in the analyses from which the main findings were drawn?
This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses.
In non-randomized studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'no.'
"Yes" for adjusted for all major confounders (demographic and common comorbidities) and "Yes, some" if some, not all major confounders were adjusted for.

◯ Yes (adjusted for all confounders) ◯ Yes, some (adjusted for some confounders) ◯ No (did not adjust for confounders) ◯ Unable to determine
◯ Not applicable (i.e. diagnostic test paper) Clear Response

26. Were **losses of subjects to follow-up** taken into account?
If the numbers of subjects lost to follow-up are not reported, the question should be answered 'unable to determine.' If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes.'

◯ Yes ◯ No ◯ Unable to determine ◯ Not applicable (i.e. no followup period such as KQ1) Clear Response

POWER

27. Did they report a power calculation?

◯ Yes ◯ No Clear Response

28. Comments (limit 250 characters)

29. Comments (limit 250 characters)

30. Comments (limit 250 characters)

Submit Form and go to ⇕ or Skip to Next

Appendix C: Exclusion Report

. A therapeutic option for the management of type 2 diabetes. 2013;79. *No original data;*

. Once-weekly exenatide more effective in glycaemic control than twice-daily. Australian Journal of Pharmacy. 2009;90(1067):79. *Meeting abstract;*

. Risk of acute pancreatitis with 'gliptins'. Drug Ther Bull. 2012;50(12):134. *No original data;*

. The LEAD study program - Liraglutide: Glycemic control with weight reduction. MMW-Fortschritte der Medizin. 2009;151(26-29):7-8. *Meeting abstract;*

Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor sitagliptin improves glycaemic control, but does not improve GLP-1 secretion, in patients with type 2 diabetes - A randomised trial. Diabetologia. 2009;52(S1):S294. *Meeting abstract;*

Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, Sitagliptin, Reduces total PYY and PYY3-36 and increases PYY1-36 but has no effect on intact GLP-2 in subjects with type 2 diabetes Mellitus-A randomized trial. Diabetes. 2009;58((Aaboe K.; Knop F.K.; Vilsboll T.; Deacon C.F.; Holst J.J.; Madsbad S.; Krarup T.)). *Meeting abstract;*

Aaboe K, Vilsboll T, Knop FK, et al. Twelve weeks treatment with the DPP-4 Inhibitor, Sitagliptin, Improves the Insulin-Secreting capacity of the P-Cells in subjects with type 2 diabetes Mellitus-A randomized trial. Diabetes. 2009;58((Aaboe K.; Vilsboll T.; Knop F.K.; Deacon C.F.; Holst J.J.; Madsbad S.; Krarup T.)). *Meeting abstract;*

Abbatecola AM, Lattanzio F, Molinari AM, et al. Rosiglitazone and cognitive stability in older individuals with type 2 diabetes and mild cognitive impairment. Diabetes Care. 2010 Aug;33(8):1706-11. PMID: 20435794. *Does not meet study design criteria;No outcome of interest;*

Abbatecola AM, Paolisso G. Rosiglitazone and cognitive stability in older persons with type 2 diabetes and mild cognitive impairment. Diabetologia. 2009;52(S1):S67. *Meeting abstract;*

Abdulkadir AA, Thanoon IA. Comparative Effects of Glibenclamide and Metformin on C-Reactive Protein and Oxidant/Antioxidant Status in Patients with Type II Diabetes Mellitus. Sultan Qaboos Univ Med J. 2012 Feb;12(1):55-61. PMID: 22375259. *Followup less than 3 months;NRS does not account for confounding*

Abe M, Okada K, Maruyama T, et al. Clinical effectiveness and safety evaluation of long-term pioglitazone treatment for erythropoietin responsiveness and insulin resistance in type 2 diabetic patients on hemodialysis. Expert Opin Pharmacother. 2010 Jul;11(10):1611-20. PMID: 20540652. *Background medications;Comorbidity;HD;*

Agarwala A, Givens E, McGuire DK, et al. Rosiglitazone increases cholesterol efflux capacity in patients with type 2 diabetes. Journal of Investigative Medicine. 2014;62(2):510-1. *Meeting abstract;*

Agrawal A, Pradeep. To study the pattern of use and efficacy of anti-diabetic drugs in controlling adequate glycemic levels in diabetic patients in Navi Mumbai. Australasian Medical Journal. 2012;5(1):88-9. *Meeting abstract;*

Ajdi F, Khabbal Y, Safi S. ADR of oral antidiabetic. Drug Safety. 2009;32(10):949-50. *Meeting abstract;*

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Appendix D: Evidence Tables

Table 1. Characteristics of studies evaluating diabetes medications in terms of intermediate outcomes

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Aaboe, 2010[1] Denmark NCT00838903	2007 2008 12 Wks	No	Not Extracted	Yes	NR/ 24 Outpatient clinic not specified and in response to local advertisement	HbA1c >10% or <7%, on metformin monotherapy for less than 3 months, taking additional medication that affect glucose control, history of GI surgery, positive measurements of islet cell auto-antibodies (ICA) and/ or glutamate decarboxylase-65 (GAD-65) auto-antibodies, elevated liver enzymes (ALAT or ASAT) twice the respective upper normal value, elevated serum creatinine concentration (>130µmol/L), severe CVD (NYHA group III or IV), Albuminuria
Ahren, 2014[2] Country NR NCT01126580	2009 2013 104 Wks	Yes	Not Extracted	Yes	NR/ 1049 NR	Age <18 yrs, HbA1c > 10.00% or <7.00%, BMI <20 or >45 kg/m2, any liver disease, any kidney disease, adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening, abnormal thyroid-stimulating hormone concentration and not clinically euthyroid, ongoing symptomatic biliary disease, history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function, history of most cancers not in remission for at least 3 yrs, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, resting SBP >160mmHg and/or DBP>100mmHg,
Alba, 2013[3] Multi-continent NCT00734474	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 211 NR	Age <30 or >65 yrs, HbA1c >10% or < 7% if drug naive, HbA1c >9% or <6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, duration of type 2 DM >5 yrs, any liver disease, any kidney disease, history of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week 12

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Apovian, 2010[4] US No	2006 -2008 24 Wks	No	Not Extracted	No	NR/ 194 NR	Age <18 and >75 yrs, HbA1c >10% or < 6.6%, BMI <25 and >39.9kg/m2 lacking history of stable body weight(varying by >5% in last 6 months), not treated for at least 6 wks with a stable dose of metformin or a sulfonylurea, use of exogenous insulin, alpha-glucosidase inhibitors, a thiazolidinedione, use of weight loss agents within 6 months before study entry, evidence of poorly controlled hypertension within the previous 3 months, history or presence of cardiac disease within 3 yrs of screening
Arechavaleta, 2011[5] Multi-national NCT01023581	Neither year reported 30 Wks	Yes	Not Extracted	Yes	NR/ 1035 NR	Age <18 yrs, HbA1c >9% or <6.50%, not on a stable dose of metformin (>1500 mg/day) as well as diet and exercise for past 12 wks, history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable medications for hypertension, thyroid disease, Hormone replacement therapy, oral contraceptive pills
Arjona Ferreira, 2013[6] Multinational NCT00915772	Neither year reported 58 Wks	Yes	Not Extracted	Yes	NR/ 426 NR	Age <30yrs, HbA1c > 9.00% or <7.00%, prior or current use of insulin, any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duration of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, at visit 2 FPG>260mg/dl and unlikely to improve with diet/exercise, at visit 3, FPG>250mg/dl consistently (i.e., measurement repeated and confirmed within 7 days), at visit 4 FPG>240mg/dl consistently, at visit5, finger-stick glucose > 240 or <120mg/dl
Aschner, 2010[7] Multi-continent Not extracted	Neither year reported 24 wks	Run-in period but number excluded was NR	NR	Yes	2068/1050 NR	Age <18 or >78 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, creatine kinase (CK) > 2x upper limit normal

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Aschner, 2012[8] Multi-continent NCT01106677	2008 -2011 24 Wks	No	Not Extracted	Yes	NR/ 515 NR	Age <35 or >70 yrs, HbA1c >=11% or <7, BMI <25 or >45 kg/m^2, duration of type 2 DM <6 months, any liver disease, any kidney disease, FPG >14.4 mmol/L, treated with oral anti-diabetic drugs other than metformin in past 3 months, received SU+MET In past year, prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudld compromise the patient's safety, unwilling to self-monitor blood glucose (BG) or keep diary
Bailey, 2005[9] UK, 14 European countries Not extracted	Not extracted 24 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >70 yrs, history of CVD, no Type 2 DM, other
Bailey, 2013[10] Multi-continent NCT00968812	2007- 2008 102 Wks	Yes	Not Extracted	Yes	NR/ 546 NR	Age <18 or >77 yrs, HbA1c > 10% or < 7%, BMI >45 kg/m^2, any liver disease, any kidney disease, history of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, SBP >=180 mmHg, DBP >=110 mmHg, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, NYHA class III or IV congestive heart failure
Bakris, 2003[11] US and UK Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	NR
Bakris, 2006[12] US, Multi-continent, South America, Europe Not extracted	Neither year reported 32 Wks	Yes	< 6 months	Yes	560/514 NR	Age <40 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI <22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Barnett, 2012[13] Multi-continent NCT00707993	2008- 2010 52 Wks	Yes	Not Extracted	Yes	227 NR	Age <18 or >80 yrs, HbA1c >10.0% (9.0% for Canada) or <7.0% for treatment naïve patients, HbA1c > 9.0% or <6.5% for patients receiving an oral anti-diabetes drug, BMI >40kg/m^2, Prior or current use of insulin, any liver disease, any kidney disease, contraindication or history of intolerance to metformin, pregnant, nursing, not using adequate contraception, MI, stoke, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an anti-obesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs
Bergenstal, 2010[14] Multi-continent NCT00528879	2008- 2008 26 Wks	No	Not Extracted	Yes	NR/ 514 Outpatient: primary care	Age <18yrs, HbA1c > 11% or < 7.10%, BMI <25 or >45kg/m^2, prior or current use of insulin, prior or current use of study drug, pregnant, nursing, not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 DM, FPG >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use
Bergenstal, 2012[15] Multi-continent NCT00740051	2008 - 2011 156 Wks	No	Not Extracted	Yes	NR/ 666 clinical sites unspecified	Age <18 or >75yrs, HbA1c > 10% or <7%, BMI <25kg/m^2 (<23 kg/m^2 for Asians) or >45kg/m^2, prior or current use of insulin, history of CVD, neuropathy, retinopathy, NOT receiving metformin (stable dose >/=1,500 mg/day or maximally tolerated dose for >/=12 wks before screening), diabetic nephropathy, GI disease, previous bariatric surgery, pancreatitis, previous exposure to other oral anti-hyperglycemic or weight-lowering drugs within 12 wks, >1 week of insulin within 6 months, or another GLP-1 mimetic or analog at any time.

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Blonde, 2002[16] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other
Bolinder, 2012[17] Europe NCT00622284	2009 2011 102 Wks	Yes	Not Extracted	Yes	NR/ 182 NR	Age <55 or >75 yrs (women), <30 or >75 yrs (men), HbA1c > 8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, prior or current use of insulin, any liver disease, any kidney disease, pregnant, nursing, FPG >240 mg/dl (>13.2 mmol/l), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment perimenopausal women, body weight change >5% within 3 months serum total bilirubin >34 μ mol/L; hemoglobin <105 g/L (10.5 g/dL) for men and <95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than 2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, SBP >/=180 mmHg and/or DBP >/=110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure; significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications); alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrollment
Borges, 2011[18] Multi-continent NCT01318109	2006 2008 80 Wks	No	Not Extracted	Yes	NR/ 688 NR	Age <18 or >75 yrs, HbA1c > 10.5% or <7.5%. BMI <= 25 kg/m^2, prior use of any diabetes treatment, fasting glucose <7 mmol/l

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Bunck, 2009[19] Sweden, Finland, and Netherlands Not extracted	Start year 2004 End year 2007 56 wks	No run-in period	< 6 months	Yes	150/69 NR	Age <30 or >75 yrs, HbA1c <6.5% or >9.5%, BMI <25 kg/m^2 or >40 kg/m^2, metformin treatment not at a stable dose for at least 2 months, no other blood glucose lowering medications allowed in 3 months prior to study, no changes in other medications known to affect beta cell function (ACEI, beta blockers)
Bunck, 2011[20] Europe NCT00642278	2004 2009 3 Years	No	Not Extracted	Yes	NR/ 69 NR	Age <30 or >75 yrs, HbA1c >9.50% or <6.50%, BMI <25 or >40 kg/m2; not on a stable dose of metformin treatment for at least 2 months
Bunck, 2011[21] Europe NCT00328627	2004 2009 3.5 Years	No	Not Extracted	Yes	NR/ 69 NR	Age <30 or >75 yrs, HbA1c <6.50% or >9.50%, BMI <25 or >40 kg/m^2, Not undergoing stable metformin treatment for at least 2 months prior enrollment Using any other blood glucose lowering agents 3 months prior to screening, besides metformin
Campbell, 1994[22] UK Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >69 yrs, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Cefalu, 2013[23] Multi-continent NCT00643851	2009 2011 52 Wks	Yes	Not Extracted	Yes	NR/ 1452 NR	Age <18, >80 yrs, HbA1c < 7% or >9.5%, Any kidney disease, Not on stable metformin therapy (for at least 10 wks prior TZD use in 16 wks before screening, history of more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15.0 mmol/L or more during the pretreatment phase;

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Charbonnel, 2006[24] Multi-continent Not extracted	Neither year reported 24 Wks	Run-in period but number excluded was NR	NR	Yes	1464/701 NR	Age <18 or >78 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 wks of screening, FPG >14.4mmol/l
Charpentier, 2001 France Not extracted	Not extracted 20 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age ≤34 or ≥71 yrs, any kidney disease, history of CVD, no Type 2 DM, other
Chawla, 2013[26] India NCT00798161	2008 2009 16 Wks	No	Not Extracted	No	NR/ 52 NR	Age <18 yrs, HbA1c < 7.5% or >11%, Any liver disease ,Any kidney disease, History of CVD, not on metformin monotherapy of >=1500mg/day for at least 1 month, FPG<140mg/dl or >270 mg/dl
Chien, 2007[27] Taiwan Not extracted	Neither year reported 16 Wks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age <30 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c > 12% and FPG>250 mg/dL at screening visit, HbA1c < 7% and FPG<140 mg/dL at screening visit, BMI <18.5 kg/m^2 or >35 kg/m2, current significant GI disorder, hyperglycemic hyperosmolar non-ketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 wks, history of cancer in 5 yrs, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or gliclazide<10 mg/day, glimepiride<4mg/d, gliclazide<160mg/d)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Comaschi, 2007[28] Italy Not extracted	Neither year reported 6 Months	Run-in period but number excluded was NR	< 6 months	Yes	398/250 NR	Age <35 yrs, HbA1c < 7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3months, fasting C-peptide <0.33 nmol/L
Davies, 2007[29] United Kingdom Not extracted	Neither year reported 4 months	Run-in period but number excluded was NR	< 6 months	NR	NR/82 NR	Age <30 or >80 yrs, history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c >7.0%, BMI >43 kg/m^2, not using adequate contraception, history of previous insulin use for >2 wks, duration of Type 2 DM <12 months, c-peptide levels <0.33, severe concurrent disease, serum Cr >150umol/l
DeFronzo, 1995[30] US Not extracted	Not extracted 29 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >70 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
DeFronzo, 2009[31] NR	Neither year reported 24 wks	Yes	< 6 months	Yes	1462/743 NR	Age <18 or >77 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BMI >40 kg/m^2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40%
DeFronzo, 2010[32] US Not extracted	Start Year 2006 End Year 2008 20 wks	No run-in period	< 6 months	Yes	NR/137 NR	Age <18 or >75 yrs, HbA1c <6.8% or >10%, BMI <25 kg/m^2 or >40 kg/m^2, not on stable dose of metformin for at least 6 wks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other ODM (other than metformin)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
DeFronzo, 2012[33] Multi-continent NCT00855166	Neither year reported 26 Wks	Yes	Not Extracted	Yes	NR/ 1554 NR	Age <18 or >80 yrs, HbA1c > 10% before and after run-in/stabilization period or <7.5% before and after run-in/stabilization period, BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopathy, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization
Derosa, 2004[34] Italy Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <46 or >67 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Derosa, 2005[35] Italy Not extracted	Neither year reported 12 Months	No run-in period	< 6 months	NR	NR/99 case-report forms or computerized clinic registers	Age ≤18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c <7.5%, BMI ≤25.3 kg/m^2, pregnant, nursing, not using adequate contraception, if no Type 2 DM for minimum 6 months based on ADA criteria, if no metabolic syndrome based on NCEP ATP III, if no hypertension, triglycerides ≤150mg/dl, C-peptide ≤1.0ng/ml, history of ketoacidosis, anemia, receiving lipid-lowering meds, anticoagulation, glimepiride, or a TZD

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2005[36] Italy Not extracted	Neither year reported 12 Months	No run-in period	< 6 months	NR	NR/99 case notes and/or clinic registers	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications
Derosa, 2005[37] Italy Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <18 yrs, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other
Derosa, 2009[38] Italy Not extracted	Neither year reported 15 Months	Fewer than 10% of participants were excluded during run-in	< 6 months	NR	271/252 Outpatient primary care, computerized clinic registry	Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5%, BMI <25 kg/m^2 or >30 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia
Derosa, 2010[39] Italy Not extracted	Neither year reported 12 months	No run-in period	< 6 months	No	128/128 patients identified from case notes and clinical registers	Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m^2 or ≥30 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2011[40] Italy NCT00660907	Neither year reported 12 Months	No	Not Extracted	No	NR/ 111 Inpatient/hospital Outpatient: primary care	Age < 18 yrs, HbA1c <=8%, BMI <25 or >=30 kg/m2, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, not taking 1000-2000 mg/d of metformin, history of ketoacidosis, history of cerebrovascular condition, severe anemia, serious CVD (eg, NYHA classes II-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment also were excluded, not intolerant of metformin 2500-3000 mg/d
Derosa, 2012[41] Italy NCT00601250	Neither year reported 12 Months	Yes	Not Extracted	No	NR/ 178 outpatient clinic within a hospital but not further specified	Age <=18yrs ,HbA1c <=8%, BMI <25 and >= 33kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, severe anemia, Patients with serious cardiovascular disease (CVD) (e.g., NYHA class I-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months
Derosa, 2013[42] Italy NCT00309608	2008 2010 12 Months	Yes	Not Extracted	NR	NR/ 178 NR	Age <=18 yrs, HbA1c <=7.5%, BMI <25 or >=31 kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, ketoacidosis, severe anemia, NYHA 1-4 congestive heart failure
Derosa, 2013[43] Italy NCT00395512	2008 2010 12 Months	Yes	Not Extracted	No	NR/ 171 NR	Age <=18 yrs, HbA1c <=7.5%, BMI<25 or >=34.9kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, acute or chronic pancreatitis, severe anemia, serous CVD (e.g. NYHA class 1-4 CHF, MI, stroke) or cerebrovascular conditions within 6 months before study enrollment, taking gygtemic glucocorticoids, taking weight reducing drugs such as sibutramine or orlistat, or any medications that miht preclude safe participation in the study

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Diamant, 2010[44] Multi-continent NCT00286442	2008 2009 26 Wks	Yes	Not Extracted	Yes	NR/ 321 NR	Age 18 yrs or older, HbA1c >11% or <7.1%, BMI <25kg/m2 and >45kg/m2, Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoids, treatment for longer than 2 wks with insulin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening
Einhorn, 2000[45] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other
Erdem, 2008[46] Turkey Not extracted	Neither year reported 12 Wks	No run-in period	< 6 months	No	53/44 outpatient department of internal medicine clinic	Age <30 or >70 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >35 kg/m^2, other chronic disease as detected by history and physical
Erem, 2014[47] Turkey NCT00263276	Neither year reported 52 Wks	Yes	Not Extracted	No	NR/ 60 NR	Age <30 or >70 yrs, HbA1c < 8% when FPG<126mg/dl, <7% if FBG is 126 - 139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria, NYHAC Class 3/4 CHF, history of lactic acidosis, malignancy, thyroid disease, or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Esposito, 2011[48] Italy NCT00749190	Neither year reported 24 Wks	No	Not Extracted	Yes	NR/ 110 investigators' practices	Age <30 and >75 yrs, HbA1c >10% or <7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l)
Esteghamati, 2014[49] Iran NCT01177813	2011 2011 12 Wks	No	Not Extracted	No	NR/ 98 Outpatient: subspecialty care setting	not newly diagnosed with diabetes, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, current use of oral antihyperglycemic medication sofr treatment of diabetes or other hyperglycemia-associated conditions(e.g. polycystic ovary syndrome), taking corticosteroids, regularly consuming alcoholic beverages
Farcasiu, 2011[50] Multi-continent NCT01012037	2006 2009 16 Wks	Yes	Not Extracted	Yes	NR/ 302 NR	Age <30 - >75 yrs, HbA1c > 1.8 X ULN or <1.2 X ULN, BMI >40 kg/m2, Any liver disease, metformin <1500mg, on other oral dm med besides metofrmin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle
Feinglos, 2005[51] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >81 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Ferrannini, 2013[52] Multi-continent NCT01167881	Neither year reported 90 Wks	Yes	Not Extracted	Yes	NR/ 659 NR	Age <18 or>79 yrs, HbA1c >=10% or <7%, BMI>40, successfully completed one of the two 12-wk dose-finding studies (refid 584 or 1334)
Fidan, 2011[53] Turkey (assumed based on affilations) NCT01340664	Neither year reported 12 Wks	Yes	Not Extracted	NR	NR/ 40 NR	Age <40 yrs, HbA1c >10% or <7%, Prior use of any diabetes treatment, Any kidney disease, Pregnant, Not using adequate contraception, malignancy, chronic inflammatory diseases, active infection, COPD, lacking combination of the following (HbA1c 8-<10 or FPG <=140) or (HbA1c 7-8 AND (FPG 120-140 or HOMA-IR >3)), class 3-4 coronary insufficiency, not completing uptitration run-in
Fonseca, 2000[54] US Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other
Fonseca, 2012[55] US and Latin America NCT01159600	2009 2010 18 Wks	Yes	Not Extracted	Yes	NR/ 282 NR	Adults, HbA1c >11% or <7.5%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradindicated to or history of treatment with saxagliptin

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Forst, 2010[56] Europe NCT00881530	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 333 NR	Age <21 or >75 yrs, HbA1c >9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase or <7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, <3 months, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening, one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months
Forst, 2012[57] NR NCT01593371	Neither year reported 12 Wks	No	Not Extracted	Yes	NR/ 44 NR	Age <30- > 65 yrs, HbA1c < =7%, Retinopathy, not on metformin, receiving any other anti-diabetic drugs, SBP >160 mmHg, DBP >90 mmHg, GFR <60, Smoking in last 6 months
Forst, 2014[58] Germany No	Neither year reported 12 Wks	No	Not Extracted	Yes	NR/ 40 outpatient but unclear if primary or specialty care	Age <45 or >75yrs, HbA1c >8.5% or <6.5%, Any liver disease, Any kidney disease, more than one unexplained episode of severe hypoglycaemia within 6 months, pre-treatment with anti-diabetic drugs other than metformin within the last 3 months, uncontrolled hypertension (SBP>160mmHg, and/or DBP>90mmHg), MI or stroke in last 6 month
Gallwitz, 2011[59] Germany NCT00885378	Neither year reported 26 Wks	No	Not Extracted	Yes	NR/ 363 NR	Adults, HbA1c >10% or <6.5%, not on metformin

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Gallwitz, 2012[60] Multi-continent NCT00562172	2008 2010 104 Wks	Yes	Not Extracted	Yes	NR/ 1552 Outpatient: primary care Outpatient: subspecialty care setting	Age <18, >80 yrs, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening
Gallwitz, 2012[61] Multi-continent No	2006 2011 48 Months	No	Not Extracted	Yes	NR/ 1029 NR	Age <18 or >85 yrs, HbA1c >9% or <6.5%, BMI <25 or >=40 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides
Garber, 2002[62] US Not extracted	Not extracted 20 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other
Garber, 2003[63] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >79 yrs, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Garber, 2006[64] US Not extracted	Not extracted 24 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >78 yrs, any liver disease, any kidney disease, history of CVD, HbA1c ≤7% or ≥12% no Type 2 DM, other
Garber, 2009[65] US, Mexico Not extracted	Start year 2006 End year 2007 52 wks	Fewer than 10 % participants excluded during run-in period	< 6 months	Yes	NR/746 NR	Age <18 or >80 yrs, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m^2, either not treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range)
Garber, 2011[66] US Mexico No	2006 2008 104 Wks	No	Not Extracted	Yes	NR/ 746 NR	Age <18 or >80 yrs, HbA1c >11% if on diet/exercise or >10% if on monotherapy or <7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia
Genovese, 2013[67] Italy NCT00511108	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 213 NR	Age <35 or >75 yrs, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin, acute or chronic pancreatitis or familial polyposis, history of chronic alcohol or drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Genovese, 2013[68] Country NR No	Neither year reported 16 Wks	Yes	Not Extracted	Yes	NR/ 58 Outpatient: subspecialt y care setting	Age <35 or >75 yrs, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures, participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, CHF (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,, known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients (pioglitazone, met marked above)
Goke, 2010[69] Multi-continent No	2007 2010 104 Wks	Yes	Not Extracted	Yes	NR/ 858 NR	Age <18 yrs, HbA1c >10% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Γüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment, congestive heart failure, significant cardiovascular history within the past 6 months
Goldstein, 2003[70] US Not extracted	Not extracted 18 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% and >12.0%, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Goldstein, 2007[71] Multi-continent Not extracted	Neither year reported 24 Wks	Run-in period but number excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with less than 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose >280 mg/dl after run-in period, no Type 2 DM, Type 1 DM
Gomez-Perez, 2002[72] Mexico Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Gupta, 2009[73] NR Not extracted	Neither year reported 16 Wks	No run-in period	< 6 months	Yes	247/51 NR	Age <35 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), pregnant, not using adequate contraception, FPG >200 mg/dL, individuals using orlistat, sibutramine, ephedrine, steroids, significant lung diseases, significant neurologic diseases, baseline BP>140/90 mmHg, prior use of TZD, beta blockers, smokers, alcohol abuse and using drugs, patients using metal objects precluding required scans
Gupta, 2010[74] India NCT00772174	Neither year reported 12 Wks	No	Not Extracted	NR	NR/ 94 Outpatient: subspecialt y care setting	Age <30 yrs , Any kidney disease, History of CVD, Pregnant, Nursing, history of serious or hypersensitivity reactions to any of study drugs, uncontrolled hyper tension, HF NYHA class IV, recent unstable angina, MI, coronary artery bypass surgery, angioplasty within previous 2 months, TIA, cerebrovascular accident, oral contraceptive use, chronic alcohilism

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gupta, 2013[75] India NCT00363948	2012 2013 24 Wks	No	Not Extracted	NR	NR/ 167 Outpatient: primary care	Any liver disease, Any kidney disease, Pregnant, Nursing, history of hypersensitivity to sulphonylurea and DPP-IV inhibitors, psychiatric, GI, hematological, metabolic, neurological, hepatic, or renal disorders, clinically significant heart disease (NYHA III or IV), acute infection
Haak, 2012[76] Multi-continent ACTRN126080 00534381	2008 2010 24 Wks	Yes	Not Extracted	Yes	NR/ 791 NR	Age <18 or >80 yrs, HbA1c >10.5% if on OAD or >=11% if treatment naïve or <7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months
Haak, 2013[77] Multi-continent IRCT20110227 5917N1	2009 2011 52 Wks	Yes	Not Extracted	Yes	NR/ 567 NR	Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication, alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation
Hallsten, 2002[78] Finland Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[79] Multinational Europe, Mexico Not extracted	Neither year reported 52 Wks	Yes	< 6 months	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any oral antidiabetic drug other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin <11.0 g/dl for men and <10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg
Hanefeld, 2004[80] Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands Not extracted	Not extracted NR	Not extracted	Not extracted	Yes	Not extracted	Age <35 or >75 yrs, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hanefeld, 2007[81] Multinational Europe Not extracted	Neither year reported 52 Wks	Run-in period but number excluded was NR	< 6 months	Yes	NR/598 NR	Age <40 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG < 7mmol/l or >15 mmol/l, C peptide <0.27 nmol/l
Haring, 2014[82] Multi-continent NCT00509262	2010 2012 24 Wks	Yes	Not Extracted	Yes	NR/ 638 NR	Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d, eGFR<30
Henry, 2012[83] Multi-continent NCT00754988	2008 2009 24 Wks	Yes	Not Extracted	Yes	NR/ 603 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), NYHA Class III or IV congestive heart failure, SBP ΓÇí 180 or DBP ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Henry, 2012[83] Multi-continent No	2009 2010 24 Wks	Yes	Not Extracted	Yes	NR/ 641 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), NYHA Class III or IV congestive heart failure, SBP ΓÇí 180 or DBP ΓÇí 110 mmHg., a cardiovascular event within 6 months
Hermann, 1991[84] Sweden Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	No Type 2 DM, other
Hermann, 1991[84] Sweden Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Hermann, 1994[85] Sweden Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	No Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hermans, 2012[86] Europe NCT01006590)	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 286 NR	Age <18 yrs, HbA1c >10% or <7%, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu- cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d
Home, 2007[87] Multinational Europe, Australia and New Zealand Not extracted	Start year 2000 End year 2002 18 Months	Run-in period but number excluded was NR	>= 6 months	NR	7428/4458 NR	Age <40 or >75 yrs, HbA1c <7% or >9%, BMI <25 kg/m^2
Home, 2009[88] Multinational Europe Not extracted	Start year 2001 End year 2003 7.5 Years	Run-in period but number excluded was NR	>= 6 months	Yes	7428/4458 Outpatient primary care	Age <40 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, BMI <25 kg/m^2, pregnant, nursing, not using adequate contraception
Iliadis, 2007[89] Greece Not extracted	Neither year reported 18 Wks	Run-in period but number excluded was NR	NR	NR	NR/48 Outpatient subspecialt y care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), diagnosis of Type 2 DM >3 yrs, use of any diabetes medication, no Type 2 DM, any heart failure

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jadzinsky, 2009[90] Multi-continent Not extracted	Start year 2006 End year 2008 24 wks	Fewer than 10% participants excluded during run-in period	< 6 months	Yes	2936/1394 Outpatient Primary care setting	Age <18 or >77 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c <8% or >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CV events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
Jain, 2006[91] US, Puerto Rico Not extracted	Neither year reported 56 Wks	Run-in period but number excluded was NR	< 6 months	NR	NR/502 NR	Age <18 or >80 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <7.5% or >11.5%, pregnant, nursing, duration of diabetes > than 2 yrs, intolerance to rosiglitazone, pioglitazone, or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg /day, oral anti-diabetic drugs, concurrent participation in another investigational study, serum creatinine level >1.5 mg/dl for men, 1.4 mg/dl for women, 1+ proteinuria, anemia (<10 g/dl women, <12 g/dl men), BMI ≤20 kg/m^2 or >45 kg/m^2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 yrs
Jonker, 2009[92] Netherlands Not extracted	Neither year reported 24 wks	Run-in period but number excluded was NR	< 6 months	Yes	173/78 Outpatient Primary care setting	Age <45 or >65 yrs, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, no Type 2 DM, prior use of TZD/insulin, BP >150/85 mm Hg

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kadoglou, 2011[93] Greece No	2006 2008 6 Months	No	Not Extracted	No	NR/ 140 NR	Age <50 and >75 yrs, HbA1c <=7%, BMI <=25kg/m2, Any liver disease, Any kidney disease, usage of antidiabetic medications, autoimmune or life threatening illnesses, on diet therapy for diabets for at least 3 mo, CHF (NYHA class IIIV), clinical evidence of cardiovascular (coronary, peripheral arteries), autoimmune or life-threatening diseases, alcohol / drug abuse, uncontrolled hypertension (blood pressure > 170 / 100 mmHg), recently diagnosed / or untreated hormonic disorders, free from microvascular compl, maintained body weight for 3 mo before study
Kadowaki, 2013[94] Japan No	2006 2008 12 Wks	Yes	Not Extracted	Yes	NR/ 149 NR	Age <20 or >=75yrs, HbA1c >9.4% for patients receiving an OHA other than metformin at screening, >10.5% for patients with metformin only at screening, >10.5% for all patients completing the run-in period, or <6.4% for patients receiving an OHA other than metformin at screening, 6.9% for patients with metformin only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks
Kahn, 2006[95] Multi-continent Not extracted	Start year 2000 End year 2006 6 Years	No run-in period	NR	Yes	6676/4360 NR	Age <30 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or >180 mg/dL, history of lactic acidosis
Kaku, 2009[96] Japan Not extracted	Start year 2005 40 Wks	Yes	< 6 months	Yes	NR/236 NR	Age ≤ 20 and ≥65 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, GI, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre-coma within the preceding 26 wks, if on any medications that might affect glycemic control, drug or alcohol dependency

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kaku, 2011[97] Japan No	2006 52 Wks	Yes	Not Extracted	Yes	NR/ 411 NR	Age <20 yrs, HbA1c >10.4% or <7.4%, not able to self monitor blood glucoses
Kato, 2009[98] Multinational Europe Not extracted	Neither year reported 12 wks	No run-in period	NR	NR	NR/50 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, no Type 2 DM, no metabolic syndrome, not on continuous diet/exercise therapy, no anemia, no history of heart failure
Kikuchi, 2012[99] Japan NCT00359762, EudraCT 2005-005448-21	2005 2007 28 Wks	No	Not Extracted	Yes	NR/ 373 NR	Age <20 - >75 yrs, HbA1c <7.4%, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy, edema, unstable or serious angina, MI in past year, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy, serious neuropathy requiring tx
Kim, 2007[100] South Korea Not extracted	Neither year reported 12 Wks	Fewer than 10% of participants were excluded during run-in	< 6 months	No	NR/120 Outpatient primary care, Outpatient subspecialty care setting	Age <30 or >70 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), duration of diabetes >5 yrs, not on a stable medication with a SU and/or alpha glucosidase inhibitor for at least 3 months, episodes of ketonuria or ketoacidosis, current malignancy, tuberculosis, rheumatic disease, thyroid disease, corticosteroid treatment, previous TZD or metformin treatment
Kim, 2014[101] South Korea NCT00751114	2007 2009 26 Wks	Yes	Not Extracted	Yes	NR/ 209 NR	HbA1c >10% or <7%, , Pregnant, treated with metformin 500-1000mg alone for at least 4 wks prior to study, unable to complete diary to monitor SMBG, acute complications such as diabetic ketoacidosis, hyperglycemic hypoerosmolar state within 3 months, clinically significatn renal or hepatic disorders

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kiyici, 2009[102] Turkey Not extracted	Neither year reported 52 wks	No run-in period	< 6 months	No	NR/50 Outpatient subspecialty care setting	Age <30 or >65 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >8%, BMI >40 kg/m^2, GI disease, rheumatological, or neoplastic, infectious diseases, history of using anti-diabetic medications, any endocrine disease except diabetes or hyperlipidemia, smoking, microvascular complications of diabetes, history of substance abuse
Kvapil, 2006[103] Multinational Europe Not extracted	Neither year reported 16 Wks	No run-in period	< 6 months	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria is not adequately controlled on metformin
Lavalle-Gonzalez, 2013[104] Multi-continent NCT00813995	Neither year reported 56 Wks	Yes	Not Extracted	Yes	NR/ 1284 NR	Age <18 or >80 yrs, HbA1c >10.5% or <7%, Prior or current use of insulin, Any kidney disease, not on MFM (ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG) ΓëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening;, CVD(including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening, uncontrolled HTN
Lawrence, 2004[105] UK Not extracted	Not extracted 12 titration and 12 maintenance wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <45 or >80 yrs, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes <7% or >10% and for low-dose ODM >7.5%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Leiter, 2005[106] Canada Not extracted	Neither year reported 32 Wks	No run-in period	< 6 months	Yes	720/613 Outpatient primary care	Age <20 or >80 yrs, HbA1c <9.5%, no Type 2 DM, FBG <7 and >14 mmol/l
List, 2009[107] US Canada, Mexico, Puerto Rico NCT00297063	2005 2006 12 Wks	Yes	Not Extracted	Yes	NR/ 389 "98 clinical centers"	Age <18 or >79 yrs, HbA1c >10% or <7%, BMI >40 kg/m2, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml
Madsbad, 2004[108] Multinational Europe Not extracted	Start year 2000 End year 2001 12 wks	No run-in period	< 6 months	Yes	311/193 Outpatient Primary Care setting	Age <30 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs
Maffioli, 2013[109] Italy NCT 01208012	Neither year reported 6 Months	Yes	Not Extracted	No	NR/ 170 outpatient care - unclear if specialty or primary care	Age <18 yrs, HbA1c <8.0%, BMI < 25.0 or >34.9 kg/m2, Prior use of any diabetes treatment, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, does not have hepatic steatosis by ultrasound diagnosis, history of ketoacidosis, muscle toxicity, serum creatine phosphokinase values higher than 2 times the ULN, severe anemia, known contraindications to pioglitazone, glibenclamide, or HMG-CoA inhibitors

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Malone, 2003[110] 14 countries not specified Not extracted	Neither year reported 16 Wks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test	Age <30 or >75 yrs, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days
Marre, 2002[111] Netherlands, Denmark, Portugal, France, Belgium Not extracted	Not extracted 4 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 yrs, any liver disease, any kidney disease, history of CVD, other
Moon, 2014[112] Korea NCT00676338	2007 2009 48 Wks	Yes	Not Extracted	Yes	NR/ 75 NR	Age <18 or >75 yrs, HbA1c >12.00% or <7.50%, BMI>=35kg/m2, Any liver disease, Any kidney disease, not on metformin monotherapy (at a dose of >1000mg/day for 3 months prior to enrollment), Taking medications (other than antidiabetic medications) known to affect glycemic control such as glucocorticoids
Nakamura, 2000[113] Japan Not extracted	Not extracted 3 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other
Nakamura, 2004[114] Japan Not extracted	Neither year reported 12 Months	No run-in period	>= 6 months	NR	NR/45 Inpatient/hospital	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >6.5%, BP <140/90 mm Hg, controlled on diet alone, C-peptide <0.33 mmol/l, creatinine <1.5 mg/dL, no antihypertensive medications, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Natali, 2004[115] London and Italy Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c >10% after washout, other
Nauck, 2007[116] US, Multinational Europe, Multi-continent Not extracted	Neither year reported 52 Wks	Yes	< 6 months	Yes	2141/1172 NR	Age <18 or >78 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia
Nauck, 2009[117] Multi-continent NCT00960076	Neither year reported 26 Wks	Yes	Not Extracted	Yes	NR/ 527 NR	Age <18 or >80 yrs, HbA1c >10.00% or <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months, after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen, h/o cardiac surgery or CVDin last 6 months, history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 yrs), laser treatment for proliferative diabetic retinopathy within 6 months, history of treated diabetic gastroparesis, NYHA Class 3 or 4 heart failure

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2011[118] Multi-continent NCT00393718	2008 52 Wks	Yes	Not Extracted	Yes	NR/ 814 NR	Age < 18 yrs, HbA1c >10% or <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment
Nauck, 2014[119] Country NR No	Neither year reported 52 Wks	Yes	Not Extracted	Yes	NR/ 1098 NR	Age <18 or >75 yrs, HbA1c >= 9.5% or <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry
Oz Gul, 2010[120] Turkey UMIN000004582	Neither year reported 12 Wks	No	Not Extracted	NR	NR/ 60 NR	Prior use of any diabetes treatment, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, Pregnant, Nursing, cerebrovascular conditions, impaired kidney function, statins, ACE inhibitor use, need of insulin for acute complications, any medications known to affect sRAGE metabolism
Pavo, 2003[121] Russia and Hungary Not extracted	Not extracted 32 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Perez-Monteverde, 2011[122] Country NR NCT00661362	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 492 NR	Age <18 - >78 yrs, HbA1c >12% or <7.5%, Contraindication or history of intolerance to metformin, type 1 Diabetes, history of ketoacidosis, symptomatic hyperglycemia, hypersens or contraind to study drug, not taking an antihyperglycaemic agent (AHA) within the previous 3 months and not more than 4 wks cumulatively in the previous 3 year, likely to need a drug that is a CYP2C8 inhib or inducer, symptomatic hyperglycaemia or a site fingerstick glucose < 130 mgГüä dl or > 320 mgГüä dl at the randomisation visi
Perez, 2009[123] US, multinational Europe Not extracted	Neither year reported 24 wks	Run-in period but number excluded was NR	< 6 months	Yes	1436/600 NR	Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m^2, pregnant, nursing, triglycerides >500 mg/dL, discontinued metformin and TZD therapy due to lack of efficacy
Petrica, 2009[124] Romania NCT00097500	Neither year reported 12 Months	No	Not Extracted	No	NR/ 44 Outpatient: subspecialt y care setting	HbA1c <7%, no poor glycemic control with previous medication, no stable therapy with metformin for at least 6 months, CKD of non-diabetic origin, symptoms or history of cerebrovascular disease (TIA, stroke), micro/macroalbuminuria, thyroid dysfunction, abnormal albuminuria, microangiogrpahic complications
Pfutzner, 2005 Germany Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <6.6% or >9.9%, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Pfutzner, 2011[126] Germany (assumed based on author affiliations) NCT00541450	Neither year reported 24 Wks	No	Not Extracted	Yes	NR/ 305 NR	Age <18 - >75, HbA1c <6.5%, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV)
Pfutzner, 2011[127] Multi-continent NCT00386100	Neither year reported 76 Wks	Yes	Not Extracted	Yes	NR/ 1306 Community outpatient settings (unspecified)	Age <18 or >77 yrs, HbA1c >12.00% or <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV CHF and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests
Pratley, 2010[128] Multi-continent Europe, US, and Canada Not extracted	Start year 2008 End year 2009 26 months	No run-in period	>= 6months	Yes	1302/665 “Office-based”-possibly out patient	Age <18 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m^2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemic or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Pratley, 2014[129] Multi-continent No	Neither year reported 26 Wks	Yes	Not Extracted	Yes	784 NR	Age <18 yrs or >80 yrs, HbA1c >10% or <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Γëñ 12 and Γëñ 10 g/dL for men and women, respectively), elevated blood pressure (ΓëÑ 150 and ΓëÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy
Qiu, 2014[130] Multi-continent No	Neither year reported 22 Wks	Yes	Not Extracted	Yes	NR/ 279 NR	Age <18 or >80 yrs, HbA1c >10.5% or <7%, Any kidney disease, FPG and/or fasting self-monitored blood glucose 15.0 mmol/L during the pretreatment phase, diabetic ketoacidosis, history of CVD(including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks, not completing the placebo run-in period
Ramachandran, 2004[131] India Not extracted	Not extracted 14 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <30 or >60 yrs, treatment experienced, HbA1c >11%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Raskin, 2007[132] US Not extracted	Neither year reported 28 Wks	Run-in period but number excluded was NR	< 6 months	NR	N/NR NR	Age <18 or >75 yrs, HbA1c ≤8.0%, BMI >40 kg/m^2 or weight >125 kg (275lbs), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use
Reasner, 2011[133] US NCT00770653	2007 2009 44 Wks	Yes	Not Extracted	Yes	NR/ 1250 NR	Age <18 or >78 yrs, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes
Ridderstrale, 2014[134] Multi-continent NCT00770653	2010 2011 104 Wks	Yes	Not Extracted	Yes	NR/ 1549 NR	Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization, blood glucose concentration greater than 13┬╥3 mmol/L after an overnight fast during the placebo run-in, confi rmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2009[135] US, Multicontinent Not extracted	Start year 2007 End year 2008 16 months	No run-in period	< 6 months	Yes	356/169 NR	Age <18 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% (6.5% if on metformin combination therapy) or >10% (9.5% if on metformin combination therapy), BMI > 40 kg/m^2, LDL <50 mg/dL or triglycerides ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 yrs, any serious disorder including pulmonary, hepatic, GI, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 yrs), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening
Robbins, 2007[136] US, Multinational Europe, Multi-continent, India, Australia Not extracted	Neither year reported 24 Wks	Run-in period but number excluded was NR	< 6 months	NR	433/317 NR	Age <35 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Roden, 2013[137] Multi-continent No	2010 2012 24 Wks	Yes	Not Extracted	Yes	NR/ 899 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting academic medical ctrs, hospitals, and private practices	Age <18, <20 in Japan, <18 or >65 in India, HbA1c >10% or 9% in Germany, <7%, BMI >45 kg/m2, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13┬╖3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label,, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent,, any uncontrolled endocrine disorder apart from type 2 diabetes., did not meet inclusion criteria after placebo run-in
Rosenstock, 2006[138] Multi-continent Not extracted	Start year 2003 to 2004 32 Wks	Yes	< 6 months	Yes	1252/468 multicenter	Age <18 or >70 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2010[139] Country NR NCT00482729	Neither year reported 26 Wks	Yes	Not Extracted	Yes	NR/ 655 NR	Age <18 or >80 yrs, HbA1c >11% or <7.50%, BMI <23 or >45 kg/m2, not drug-naive (current antihyperglycemmic medication or >6 days of any such agent within 3 months of screening), successful glycemic control with diet and exercise for >=2 months prior to screening
Rosenstock, 2012[140] Multi-continent NCT00327015	Neither year reported 12 Wks	No	Not Extracted	Yes	NR/ 451 NR	Age <18, >65 yrs, HbA1c >10.50% or <7%, unstable weight or BMI <25 or >45 kg/m^2 (<24 or >45 kg/m^2 for Asians), Diagnosed with type 2 diabetes for less than 3 months, On metformin monotherapy dose <1500mg/day, On metformin monotherapy for less than 3 months, Serum creatinine >1.5mg/dl for men and >1.4 mg/dl for women
Rosenstock, 2013[141] Multi-continent NCT00434954	Neither year reported 52 Wks	Yes	Not Extracted	Yes	NR/ 441 NR	Age <65 or >90 yrs, HbA1c >9.0% for patients on diet and exercise therapy alone,>8.0% for patients on oral antidiabetic monotherapy & >9.0% after washout period without medications within 2 wks or < 6.50%, not able or unwilling to self-monitor blood glucose with a home glucose monitor
Rosenstock, 2013[142] Multi-continent No	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 495 NR	Age <18 or >80 yrs, HbA1c >9% if on metformin and one other OAD or >10 if on metformin monotherapy or <6.5% if on metformin and one other OAD, <7 if on MFM monotherapy, BMI >40 kg/m2, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ГёÑ1500 mg/day or maximum tolerated dose);, diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity;, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months., h/o of MI, CVA, or TIA in past 6 mo, HbA1c <7 or >10 at start of placebo run-in, history of clinically relevant allergy/hypersensitivity, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Ross, 2012[143] Multi-continent NCTC00294723	2009 2010 12 Wks	Yes	Not Extracted	Yes	NR/ 491 NR	Age <18 or > 80 yrs, HbA1c >10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in for or HbA1c < 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study), treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months
Russell-Jones, 2012[144] Multi-continent NCT00701090	2008 2010 36 Wks	No	Not Extracted	Yes	NR/ 820 NR	Adults, HbA1c >11% or <7.1%, BMI <23 - >45 kg/m2, Prior use of any diabetes treatment, unstable weight
Schernthaner, 2004[145] Europe Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <35 or >75 yrs, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Schondorf, 2011[146] Germany No	Neither year reported 24 Wks	No	Not Extracted	Yes	NR/ 46 NR	HbA1c >9.00% or <6.50%, Prior or current use of insulin, Any liver disease, Any kidney disease, not treated with metformin monotherapy in a maximal individually tolerated dose of 850 to 2000 mg, no dyslipidemia, significant cardiovascular disorder (NYHA I-IV), previous treatment with other oral antidiabetes drugs in addition to metformin

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Scott, 2007[147] US Not extracted	Neither year reported 12 Wks	Run-in period but number excluded was NR	< 6 months	Yes	2186/743 NR	Age <21 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK
Scott, 2008[148] Multi-continent Not extracted	Neither year reported 18 Wks	Run-in period but number excluded was NR	< 6 months	Yes	486/273 NR	Age <18 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose >270 mg/dL
Seck, 2010[149] NR Not extracted	Neither year reported 2 years	Run-in period but number excluded was NR	< 6 months	Yes	2141/1172 NR	Age <17 or >78 yrs
Seino, 2010[150] Japan Not extracted	Neither year reported 24 wks	Yes	< 6 months	Yes	NR/464 NR	Age <20 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Seino, 2012[151] Japan No	2008 2009 12 Wks	Yes	Not Extracted	Yes	NR/ 288 outpatient, but not specified	Age <20 or >=65 yrs, HbA1c >=10.4% after 8 wks of observation or <6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis, h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, GI disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg
Shihara, 2011[152] Japan NCT00575588	2007 2010 6 Months	No	Not Extracted	No	NR/ 191 NR	Age <30 - >75 yrs, HbA1c >=10.4% or <6.9%, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, CHF, Any hematological condition, Any pancreas condition, not committed to stable diet & exercise regimen, use of any dim med in past month, capable of reading consent form
Srivastava, 2012[153] India NCT00641056	2008 2009 18 Wks	No	Not Extracted	NR	NR/ 50 Outpatient (not specified if PC or subsp)	Age <=18 yrs, HbA1c >=10% or <=7%, Any liver disease, Any kidney disease, History of CVD, not on metformin monotherapy for at least 3 mo, type 1 diabetes, other terminal illness
St John Sutton, 2002[154] US Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Stewart, 2006[155] Multinational Europe Not extracted	Start year 2003 to 2004 32 Wks	Yes	< 6 months	Yes	1397/526 NR	Age < 18 or > 70 yrs, history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG <6.0 mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Tan, 2004[156] Denmark, Finland, Norway, and Sweden Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5 or >9.5 for patients receiving ODM, no Type 2 DM, other
Tan, 2004[157] Mexico Not extracted	Not extracted NR	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >11% in patients who were not receiving ODMs, and <7.5 or >9.5 in patients who were receiving ODM monotherapy, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Taskinen, 2011[158] Multi-continent NCT00637273	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 701 NR	Age <18 or >80 yrs, HbA1c < 10.0% for metformin monotherapy patients, 9.0% for patients treated with an additional medication; by the start of the placebo run-in, 10.0% for all patients or HbA1c < 7.0% for met mono patients, 6.5% for patients treated with an additional medication; by the start of the placebo run-in, 7.0% for all patients, BMI >40 kg/m2, Any liver disease, Any kidney disease, not receiving met at a dose of >=1500mg/day (or max tolerated dose), more than one other oral antidiabetes medication, antidiabetes medications have changed within 10 wks prior to the date of informed consent or the dose of met was not stable for >=12 wks before randomization, treated with rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, changed dosage of thyroid hormone treatment within 6 wks or were being treated with systemic steroids at the date of informed consent, acute or chronic metabolic acidosis, hereditary galactose intolerance, dehydration, have participated in another trial of an investigational drug within the previous 2 months, acute MI, stroke, or TIA within last 6 months or acute or unstable CHF
Taslimi, 2013[159] Iran NCT00103857	2011 2011 3 Months	No	Not Extracted	No	NR/ 60 NR	HbA1c <7%, Prior use of any diabetes treatment, Prior or current use of study drug, Any liver disease, Any kidney disease, Pregnant, Diabetes diagnosed before the age of 30, congestive heart failure
Teramoto, 2007[160] Japan Not extracted	Neither year reported 24 Wks	Yes	NR	No	126/92 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), any medication affecting glucose metabolism, history of diabetic ketoacidosis, history of diabetic coma or pre-coma, Cushing's syndrome, history of allergy to thiazolizinediones, tumor therapy, receiving insulin for severe infection

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Tosi, 2003[161]* Italy Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other
Turkmen Kemal, 2007[162] Turkey Not extracted	Start year 2005 6 Months	No run-in period	< 6 months	NR	46/46 Outpatient subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient on diuretics, uncontrolled hypertension
Turner, 1999[163] United Kingdom Not extracted	Start year 1977 End year 1991 9 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/4075 23 UKPDS centers	Age <25 or >65 yrs, FPG<6 mmol/l x 2, individuals on diet only therapy who maintained their blood sugars <6 mmol/l on followup visits
Umpierrez, 2006[164] US Not extracted	Neither year reported 28 Wks	Run-in period but number excluded was NR	< 6 months	Yes	538/210 Outpatient primary care, Outpatient subspecialty care setting	Age <18 or >79 yrs, HbA1c <7.5% and >10%, BMI <24 kg/m^2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Umpierrez, 2014[165] Multi-continent No	2010 2012 52 Wks	Yes	Not Extracted	Yes	NR/ NR	Age <18 yrs, HbA1c >9.50% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months
van der Meer, 2009[166] Netherlands Not extracted	Neither year reported 24 Wks	Fewer than 10% of participa nts were excluded during run-in	< 6 months	Yes	173/80 NR	Age <45 or >65 yrs, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, SBP <150 mmHg, DBP <85 mmHg, prior TZD or insulin use
Weissman, 2005[167] US Not extracted	Not extracted 24 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <6.5% or >8.5% for patients having received prior combination treatment, HbA1c <7% or >10% prior monotherapy or drug naive patients, no Type 2 DM, other
White, 2014[168] Multi-continent NCT00885378	2009 2010 12 Wks	Yes	Not Extracted	Yes	NR/ 160 outpatient	Age <18 and >78 yrs, HbA1c >10% or <7%, BMI >45, Pregnant, Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies
Williams-Herman, 2009[169] NR Not extracted	Neither year reported 54 Wks	Run-in period but number excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 yrs, HbA1c <7.5% or >11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (>=75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Williams-Herman, 2010[170] Multi-continent No	Neither year reported 104 Wks	Yes	Not Extracted	Yes	NR/ 1091 NR	Age <18 or >78 yrs, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication
Yamanouchi, 2005[171] Japan Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other
Yang, 2011[172] Multinational Asia (China - India – SouthKorea No	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 570 NR	Age <18 yrs, HbA1c >10% or <7%, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducersHemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past year, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhibitor
Yang, 2011[173] Asia - Korea, China, India No	Neither year reported 16 Wks	Yes	Not Extracted	Yes	NR/ 929 NR	Age <18 and >80 yrs, HbA1c >11% for subjects on OAD monotherapy and 10% for subjects on OAD combination therapy or <7%, BMI >45kg/m2, not treated with one or more oral antidiabetic drugs (OADs) for at least 3 months, treated with insulin within the last 3 months, after run-in with up-titration of metformin to 2000 mg/day and 3-wk maint at that dose, subj with FG 7-12.8 mmol/l could be randomized
Yang, 2012[174] China No	2009 2010 24 Wks	Yes	Not Extracted	Yes	NR/ 395 NR	Age <18 - >78 yrs, HbA1c >11% or 7.5%, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Yoon, 2011[175] Korea NCT00097500	2007 2008 48 Wks	Yes	Not Extracted	Yes	NR/ 349 NR	Age <30 - >65 yrs, HbA1c >9.5% or <6.5%, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant
Yuan, 2012[176] China No	Neither year reported 26 Wks	No	Not Extracted	NR	NR/ 59 NR	Age <=18 yrs, HbA1c >10% or <7%, BMI <=28or >=40kg/m2, >=1months, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table 2. Population characteristics of studies evaluating diabetes medications for intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seino, 2010[150]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Derosa, 2010[39]	Metformin + glibenclamide, 65	NR	51	NR	28.5 NR	8.9	NR	8
	Metformin + exenatide, 45	NR	67	NR	28.7 NR	8.8	NR	4
DeFronzo, 2010[32]	Metformin + rosiglitazone, 45	NR	NR	NR	NR NR	7.9	NR	11
	Metformin + exenatide, 45	NR	NR	NR	NR NR	7.8	NR	12
Aschner, 2010[7]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[149]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, Other: 4	30.9 NR	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, Other: 3.1	31.3 NR	7.3	5.7	328
Pratley, 2010[128]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, Other: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, Other: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, Other: 4	33.1 94.6 kg	8.4	6.4	52
Home, 2009[88]	Metformin + rosiglitazone, 1117	57	53.8	C: 98.9	NR 93.5kg	7.8	6.1	NR
	Metformin + sulfonylurea, 1105	57.2	52.9	C: 98.4	NR 93.3 kg	7.8	6.3	NR
	Metformin + sulfonylurea, 1122	59.7	50.6	C: 99.1	NR 84.3kg	8	7.9	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + sulfonylurea, 2227	58.5	51.7	C: 98.7	31.5 NR	7.9	7.1	233
	Rosiglitazone, 2220	58.4	51.4	C: 99.1	31.6 NR	7.9	7	218
	Rosiglitazone + sulfonylurea, 1103	59.8	49	NR	30.3 85.0kg	8	7.9	NR
Derosa, 2009[38]	Metformin, 67	55 (50 to 60)	51	C: 100	27.2 77.7 kg	9.1	NR	7
	Metformin + glimepiride, 66	57.7 (51.7-64.7)	48	C: 100	27.1 77.4 kg	9	NR	6
	Metformin + pioglitazone, 69	57 (50 to 64)	49	C: 100	27.4 76.4 kg	9.3	NR	9
	Pioglitazone, 69	54 (48 to 60)	46	C: 100	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[166]	Metformin + glimepiride, 39	56.4	100	NR	29.3 NR	7	3	2
	Pioglitazone + glimepiride, 39	56.8	100	NR	28.2 NR	7.1	4	5
Kaku, 2009[96]	Metformin, 86	53	57	NR	25.4 NR	7.55	5.6	7
	Metformin + pioglitazone, 83	52	66	NR	25.6 NR	7.58	4.5	9
Gupta, 2009[73]	Metformin, 17	56.9	37.5	C: 62.5	36.4 97.8 kg	6.0	NR	1
	Pioglitazone, 16	59.2	25	C: 78.5	35.7 98.5 kg	6.2	NR	2
	Pioglitazone, 18	55.7	33	C: 50	34.3 95.3 kg	6.4	NR	0
Williams-Herman, 2009[169]	Metformin, 182	54.2	45	NR	32 NR	8.5	4.1	46
	Metformin, 182	53.7	48	NR	32 NR	8.7	4.1	56
	Metformin + sitagliptin, 182	53.6	41	NR	32 NR	8.7	4.6	41

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + sitagliptin, 190	53.7	53	NR	32 NR	8.8	4.1	42
	Sitagliptin, 179	53.5	52	NR	31 NR	8.7	3.9	57
Kiyici, 2009[102]	Metformin, 16	52.4	NR	NR	31.6 NR	6.7	NR	NR
	Rosiglitazone, 19	50.7	NR	NR	31.2 NR	7.1	NR	NR
Jonker, 2009[92]	Metformin + glimepiride, 39	56.4	100	NR	29.1 NR	7	NR	NR
	Pioglitazone + glimepiride, 39	56.8	100	NR	28 NR	7.1	NR	NR
Perez, 2009[123]	Metformin, 210	53.7	46.7	AA: 6.7, Asian: 2.4, C: 88.1, H: 26.2	30.8 NR	8.65	NR	68
	Metformin + pioglitazone, 201	54.7	44.8	AA: 6, Asian: 1.5, C: 91.5, H: 24.4	30.8 NR	8.89	NR	44
	Pioglitazone, 189	54	34.9	AA: 6.9, Asian: 2.6, C: 87.3, H: 25.9	31.2 NR	8.69	NR	64
Rigby, 2009[135]	Metformin + rosiglitazone, 56	54.7	41	AA: 3.6, Asian: 0, C: 28.6, H: 67.9	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2	NR 79.6 kg	8.17	8.35	11
Jadzinsky, 2009[90]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, Other: 5	29.9 NR	9.4	2	58
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, Other: 5.9	30.3 NR	9.5	1.4	62
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, Other: 6.4	30.2 NR	9.4	1.7	85
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, Other: 5.4	30.2 NR	9.6	1.7	110
DeFronzo, 2009[31]	Metformin + saxagliptin, 192	54.7	43.2	AA: 3.9, Asian: 4.2, C: 79.7, Other: 12	31.7 NR	8.1	6.7	44
	Metformin + saxagliptin, 191	54.7	53.9	AA: 5.8, Asian: 1.6, C: 83.2, Other: 9.4	31.2 NR	8.1	6.4	48

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + saxagliptin, 181	54.2	52.5	AA: 7.7, Asian: 2.8, C: 79.6, Other: 9.9	31.1 NR	8.0	6.3	41
	Metformin, 179	54.8	53.6	AA: 3.9, Asian: 2.2, C: 83.8, Other: 10.1	31.6 NR	8.1	6.7	40
Bunck, 2009[19]	Metformin + exenatide, 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	6
	Metformin + glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	3
Garber, 2009[65]	Glimepiride, 248	53.4	54	AA: 12, Asian: 4, C: 77, H: 38, Other: 7	33.2 93.4 kg	8.4	5.6	96
	Liraglutide, 247	52	49	AA: 12, Asian: 6, C: 75, H: 35, Other: 7	32.8 92.8 kg	8.3	5.3	74
	Liraglutide, 251	53.7	47	AA: 14, Asian: 2, C: 80, H: 32, Other: 5	32.3 92.5 kg	8.3	5.2	89
Kato, 2009[98]	Metformin, 25	58.6	56	NR	27.5 NR	7.1	NR	NR
	Pioglitazone, 25	51.4	48	NR	28.4 NR	7.4	NR	NR
Erdem, 2008[46]	Metformin, 27	55.09	33	NR	31.41 NR	6.74	NR	4
	Pioglitazone, 26	54.9	31	NR	30.41 NR	6.34	NR	5
Iliadis, 2007[89]	Metformin, 16	57.8	NR	NR	30.8 80.8 kg	7.8	20.9 months	1
	Rosiglitazone, 16	56.3	NR	NR	31 83.2 kg	7.2	30.7 months	2
Scott, 2008[148]	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, Others: 3	30.4 84.9 kg	7.7	4.6	2
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Others: 1	30.3 83.1 kg	7.8	4.9	9
Robbins, 2007[136]	Metformin + glargine, 159	58.1	49.4	AA: 5.7, Asian: 14.6, C: 63.3, H: 16.4	32 88.1kg	7.8	12.5	22

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + insulin lispro 50/50, 158	57.4	50.3	AA: 5.7, Asian: 14, C: 65, H: 15.3	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[79]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9kg	8	6.4	71
Chien, 2007[27]	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
Turkmen Kemal, 2007[162]	Metformin, 16	56.8 (40 to 70)	25	NR	34.5 NR	6.3	1.5	0
	Rosiglitazone, 13	55.92 (42 to 68)	30	NR	30.8 75 kg	6.2	2.75	1
Comaschi, 2007[28]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14
Home, 2007[87]	Metformin + rosiglitazone, 259	57	54	NR	32.7 93kg	7.9	6.1	52
	Metformin + sulfonylurea, 265	57	52	NR	NR 91kg	7.8	7	22
	Metformin + sulfonylurea, 284	60	52	NR	NR 83kg	8	8.1	54
	Rosiglitazone + sulfonylurea, 311	61	49	NR	NR 84kg	8	7.9	74
Teramoto, 2007[160]	Glibenclamide, 46	56.4	76	NR	25.2 NR	8.36	NR	5

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 46	57	72	NR	24.7 NR	8.01	NR	7
Goldstein, 2007[71]	Metformin, 182	53.4	48.9	AA: 6.6, Asian: 7.7, C: 47.8, H: 30.2, not specified: 7.7	32.1 NR	8.9	4.5	29
	Metformin, 182	53.2	45.1	AA: 4.9, Asian: 5.5, C: 58.2, H: 21.4, not specified: 9.9	32.2 NR	8.7	4.4	182
	Metformin + sitagliptin, 182	53.3	42.3	AA: 7.7, Asian: 6, C: 52.2, H: 26.9, not specified: 7.1	32.4 NR	8.7	4.4	18
	Metformin + sitagliptin, 190	54.1	55.3	AA: 6.8, Asian: 4.7, C: 53.7, H: 28.9, not specified: 5.8	32.1 NR	8.8	4.5	26
	Sitagliptin, 179	53.3	52	AA: 6.1, Asian: 3.4, C: 52, H: 29.1, not specified: 9.5	31.2 NR	8.9	4.4	37
Nauck, 2007[116]	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, Other: 3.4	31.3 89.7 kg	7.6	6.2	172
	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, Other: 3.7	31.2 89.5 kg	7.7	6.5	202
Kim, 2007[100]	Metformin + glimepiride, 60	57.6	50	NR	25.8 66.7 kg	7.7	3.4	4
	Rosiglitazone + glimepiride, 60	56.5	52.63	NR	25.7 68.1 kg	8.1	3.5	3
Raskin, 2007[132]	Metformin + aspart 70/30, 79	52	52	AA: 13, Asian: 3, C: 52, H: 32, Other: 1	31.2 88.7kg	9.9	NR	12
	Metformin + glargine, 78	51.7	54	AA: 15, Asian: 4, C: 47, H: 32, Other: 1	30.8 86.2kg	9.9	NR	6
Hanefeld, 2007[81]	Glibenclamide, 203	60.1	70	AA: 0, C: 99, Other: 1	28.7 NR	8.2	6.4	13
	Rosiglitazone, 189	60.6	58	AA: 0, C: 97, Other: 3	28.8 NR	8.2	6	9
	Rosiglitazone, 195	60.4	68	AA: 0, C: 8, Other: 2	28.7 NR	8.1	5.9	12
Scott, 2007[147]	Glipizide, 123	54.7 (21-76)	56.9	AA: 3.3, Asian: 4.9, C: 61, Other: 24.4, Multiracial: 6.5	30.6 NR	7.9	4.7	23
	Sitagliptin, 123	56.2 (34-75)	48	AA: 4.9, Asian: 4.9, C: 63.4, multiracial: 5.7, Other: 21.1	30.5 NR	7.9	4.9	7

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Sitagliptin, 123	55.6 (34-76)	57.7	AA: 8.9, Asian: 4.9, C: 61, Multiracial: 6.5, Other: 18.7	31.4 NR	7.9	5	15
	Sitagliptin, 124	55.1 (28 - 75)	52.4	AA: 4.8, Asian: 2.4, C: 69.4, Multiracial: 7.3, Other: 16.1	30.4 NR	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 - 76)	49.6	AA: 6.4, Asian: 7 5.6, C: 68.8, multiracial: 6.4, Other: 12.8	30.8 NR	7.9	4.3	18
Davies, 2007[29]	Metformin + NPH, 29	57.9	48.28	AA: 0, Asian: 21, C: 66	32.6 90.4 kg	10	7.3	5
	Metformin + BHI 70/30, 27	57.4	80	AA: 4, Asian: 22, C: 70	30.2 82.2 kg	9	9.1	0
Kahn, 2006[95]	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, Other: 0.3	32.2 92 kg	7.35	(<1: 44, 1-2: 52, >2: 4)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, Other: 1	32.1 91.6 kg	7.36	(<1: 46, 1-2: 50, >2: 4)	551
	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 76 5.2, Other: 0.7	32.2 91.5 kg	7.36	(<1: 45, 1-2: 52, >2: 3)	539
Charbonnel, 2006[24]	Metformin, 237	54.7	59.5	AA: 5.9, Asian: 11, C: 67.1, H: 11.8, Other: 4.2	31.5 NR	(<8: 54, 8 -8.9: 30, ≥9: 15)	6.6	45
	Metformin + sitagliptin, 464	54.4	55.8	AA: 6.7, Asian: 10.6, C: 63.1, H: 15.5	30.9 NR	(<8: 55, 8 -8.9: 31, ≥9: 14)	6	48
Rosenstock, 2006[138]	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, Other: <1	32.5 NR	8.8	2.9	31
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, Other: 3	32.8 NR	8.8	2.7	22

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Jain, 2006[91]	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, Other: 0.4	32.8 94.3 kg	9.2	0.78	123
	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, 0ther: 0.4, Native American: 1 0.4	32.5 93.9 kg	9.2	0.8	117
Stewart, 2006[155]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/Other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian /Other pacific islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[12]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Umpierrez, 2006[164]	Metformin + glimepiride, 96	51.6	55.2	AA: 13.5, Asian: 1.0, C: 79.2, H: 5.2, Other: 1.0	34.54 NR	8.4	4.9	11
	Metformin + pioglitazone, 109	55.7	52.3	AA: 15.9, Asian: 3.7, C: 78.5, H: 1.9, Other: 0	33.81 NR	8.31	5.9	17
Kvapil, 2006[103]	Metformin + aspart 70/30, 116	56.4	46	NR 11	30.4 85.1 kg	9.	6.7	11
	Metformin + glibenclamide, 114	58.1	46	NR	30.5 84.0 kg	9.4	8.1	5
Derosa, 2005[35]	Metformin + glimepiride, 49	52	47	NR	26.8 75.6 kg	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 74.2 kg	8.0	5	2
Derosa, 2005[36]	Metformin + glimepiride, 49	52	47	NR	26.8 NR	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 NR	8.0	5	2

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Nakamura, 2004[114]	Glibenclamide, 15	55	53	NR	NR NR	7.8	19.2	0
	Pioglitazone, 15	57	60	NR	NR NR	7.9	17.5	NR
Malone, 2003[110]	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, Other: 4	29.6 81.7 kg	9.27	7.4	29
	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, Other: 3	29.8 83.0 kg	9.17	8.0	25
Turner, 1999[163]	Any in the Sulfonylurea class, 1305	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 340	NR	NR	NR	NR NR	NR	NR	NR
	Total, 4075	53	NR	AA: 9, Asian: 10, C: 81	29 NR	(median : 9.1)	NR	4 loss to followup
Leiter, 2005[106]	Metformin, 78	60	56	C: 78, Other: 22	32.2 NR	7.5	5.7	13
	Metformin + rosiglitazone, 158	58	65	C: 76, Other: 24	33 NR	7.5	5.3	18
Garber, 2006[64]	Metformin + rosiglitazone, 158	56 (24 - 78)	65	AA: 6, C: 79, Asian: 3, H: 10, O: 3	32 94 kg	8.4	6	Not extracted
	Metformin + glibenclamide, 160	56 (31 - 78)	56	AA: 5, C: 80, Asian: 3, H: 11, O: 2	32 93 kg	8.5	5	Not extracted
Nakamura, 2006[177]	Pioglitazone, 17	56	53	NR	NR NR	8	16	NR
	Glibenclamide, 18	53.5	56	NR	NR NR	7.8	16.5	NR
Weissman, 2005[167]	Metformin + rosiglitazone, 358	55.5	NR	NR	34.4 98.2 kg	8.05	NR	Not extracted
	Metformin, 351	55.7	NR	NR	33.8 96.7 kg	7.97	NR	Not extracted
Bailey, 2005[9]	Metformin + rosiglitazone, 288	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9 kg	7.4	6	Not extracted
	Metformin, 280	57.6	57	AA: <1, C: 98, Asian: 1, H: 0, O: 1	32.1 89.5 kg	7.5	6.1	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Yamanouchi, 2005[171]	Pioglitazone, 38	55.2	47	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.8 NR	10.2	3.2 months	Not extracted
	Glimepiride, 37	55.6	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.6 NR	9.8	3.3 months	Not extracted
	Metformin, 39	54.7	20	AA: 0, C: 0, Asian: 0, H: 0, O: 100	26.2 NR	9.9	3 months	Not extracted
Pfutzner, 2005[125]	Glimepiride, 84	63	61.9	AA: 0, C: 96.4, Asian: 0, H: 0, O: 3.7	31.8 NR	7.44	6.9	Not extracted
	Pioglitazone, 89	62.2	61.8	AA: 0, C: 98.8, Asian: 0, H: 0, O: 1.1	31.7 NR	7.52	7.4	Not extracted
Derosa, 2005[37]	Metformin + glimepiride, 47	52	49	NR	26.8 NR	7.9	4	Not extracted
	Metformin + rosiglitazone, 48	54	52	NR	26.6 NR	8	5	Not extracted
Feinglos, 2005[51]	Metformin + glipizide, 61	57.7 (30-80)	46	AA: 8.2, C: 78.7, Asian: 3.3, H: 8.2, O: 1.6	31.7 90 kg	7.45	6.5	Not extracted
	Metformin, 61	58.8 (40-81)	41	AA: 16.4, C: 68.9, Asian: 3.3, H: 8.2, O: 3.3	32.1 90.8 kg	7.64	4.6	Not extracted
Ramachandran, 2004[131]	Glimepiride, 18	45.3	50	AA: 0, C: 0, Asian: 0, H: 0, O: 100	24.6 65.7 kg	10.2	0	Not extracted
	Metformin, 21	44.4	71	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.7 67.7 kg	9.6	0	Not extracted
	Pioglitazone, 23	45.1	74	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.5 68.9 kg	9.3	0	Not extracted
Schernthaner, 2004[145]	Metformin, 597	56	57.8	NR	31.4 89.7 kg	8.7	3.1	Not extracted
	Pioglitazone, 597	57	52.6	NR	31.2 88.2 kg	8.7	3.4	Not extracted
Derosa, 2004[34]	Glimepiride, 81	56	47	NR	27.6 NR	8.5	NR	Not extracted
	Metformin, 83	58	51	NR	28.1 NR	8.4	NR	Not extracted
Tan, 2004[156]	Glibenclamide, 109	57.9	73	AA: 0, C: 100, Asian: 0, H: 0, O: 0	29.6 89 kg	8.5	62.6 months	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 91	60	62	AA: 0, C: 99, Asian: 0, H: 0, O: 1	30.2 88.4 kg	8.4	57.1 months	Not extracted
Tan, 2004[157]	Glimepiride, 123	55.7	53	AA: 0, C: 1, Asian: 0, H: 99, O: 0	28.8 74.5 kg	8.45	81.2 months	Not extracted
	Pioglitazone, 121	55.1	45	AA: 0, C: 0, Asian: 0, H: 100, O: 0	29.3 74.2 kg	8.54	77.8 months	Not extracted
Natali, 2004[115]	Metformin, 28	58	79	NR	28 NR	7.8	6.3	Not extracted
	Rosiglitazone, 24	59	92	NR	27.6 NR	7.7	6.5	Not extracted
Hanefeld, 2004[80]	Metformin + unspecified Sulfonylurea, 320	60	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0, O: 0.6	30 84.9 kg	8.8	7.1	Not extracted
	Unspecified sulfonylurea + pioglitazone, 31	60	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	Not extracted
Lawrence, 2004[105]	Metformin, 20	59.5	60	NR	(Median 29.2) NR	8.04	NR	Not extracted
	Pioglitazone, 20	60.4	70	NR	(Median 30.6) NR	7.43	NR	Not extracted
Madsbad, 2004[108]	Glimepiride, 27	57	59	NR	30.2 NR	7.8	3.8	0
	Liraglutide, 26	53	85	NR	30.2 NR	7.4	4.1	3
	Liraglutide, 25	58	60	NR	32 NR	7.9	4.4	3
	Liraglutide, 27	57	67	NR	30.1 NR	7.7	4.5	7
	Liraglutide, 30	57	67	NR	30.4 NR	7.4	4.6	2
	Liraglutide, 29	58	55	NR	31.9 NR	7.4	6.1	2
Garber, 2003[63]	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	Not extracted
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	Not extracted
Tosi, 2003[161]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	Not extracted
	Glibenclamide, 21	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 39	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin, 20	NR	NR	NR	NR NR	NR	NR	Not extracted
Goldstein, 2003[70]	Glipizide, 84	57.4	64.3	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	Not extracted
	Metformin + glipizide, 87	54.6	58.6	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	Not extracted
	Metformin, 76	56.6	61.8	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	Not extracted
Pavo, 2003[121]	Metformin, 100	55.8	56	NR	31.1 88.9 kg	8.6	0.53	Not extracted
	Pioglitazone, 105	54.2	43.8	NR	31.3 86.6 kg	8.6	0.47	Not extracted
Bakris, 2003[11]	Rosiglitazone, 57	5.1	75	NR	NR NR	9.1	NR	Not extracted
	Glyburide, 64	56.1	71	NR	NR NR	9.5	NR	Not extracted
Hallsten, 2002[78]	Metformin, 13	57.8	62	NR	29.9 NR	6.9	NR	Not extracted
	Rosiglitazone, 14	58.6	71	NR	29.3 NR	6.8	NR	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Blonde, 2002[16]	Glyburide, 164	55.8	57.3	AA: 12.2, C: 66.5, Asian: 0, H: 17.1, O: 4.3	30.3 88 kg	9.64	7.01	Not extracted
	Metformin + glyburide, 160	55.4	55.6	AA: 12.5, C: 70, Asian: 0, H: 15.6, O: 1.9	30.7 89.4 kg	9.41	7.36	Not extracted
	Metformin + glyburide, 162	55.6	63.6	AA: 9.3, C: 67.9, Asian: 0, H: 19.1, O: 3.7	30.6 89.6 kg	9.42	6.97	Not extracted
	Metformin, 153	57.6	62.1	AA: 10.5, C: 69.3, Asian: 0, H: 17, O: 3.3	30.6 89.5 kg	9.51	8.18	Not extracted
St John Sutton, 2002[154]	Glyburide, 99	56.1 (40 - 76)	71	AA: 3, C: 76, Asian: 0, H: 0, O: 21	(BMI ≥27: 65.7) NR	9.5	6.2	Not extracted
	Rosiglitazone, 104	55.1 (40 - 77)	75	AA: 5, C: 73, Asian: 0, H: 0, O: 22	(BMI ≥27: 67.3) NR	9.1	5.3	Not extracted
Marre, 2002[111]	Glibenclamide, 103	58.7	55	NR	29.3 82.5 kg	7.88	6.6	Not extracted
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7 kg	7.89	5.9	Not extracted
	Metformin + glibenclamide, 103	60.7	54	NR	29.7 83.1 kg	7.62	6.7	Not extracted
	Metformin, 104	57.5	60	NR	29.9 84.9 kg	8.09	5.4	Not extracted
Garber, 2002[62]	Glyburide, 161	56.5	50.9	AA: 9.3, C: 78.3, Asian: 0, H: 8.7, O: 3.7	30.3 87.2 kg	8.21	2.81	Not extracted
	Metformin + glyburide, 158	56.9	57.6	AA: 12.7, C: 74.1, Asian: 0, H: 11.4, O: 1.9	30.1 88.8 kg	8.25	3.52	Not extracted
	Metformin + glyburide, 165	58.1	58.2	AA: 6.1, C: 79.4, Asian: 0, H: 9.7, O: 4.9	29.6 86.7 kg	8.18	3.3	Not extracted
	Metformin, 161	56	57.8	AA: 4.3, C: 80.7, Asian: 0, H: 12.4, O: 2.5	30.4 88.6 kg	8.26	2.98	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Gomez-Perez, 2002[72]	Metformin + rosiglitazone, 35	51.7 (40 - 73)	29	AA: 0, C: 0, Asian: 0, H: 80, O: 20	28 NR	NR	11.1	Not extracted
	Metformin + rosiglitazone, 36	54.2 (42 - 76)	19	AA: 0, C: 11, Asian: 0, H: 72, O: 17	27.6 NR	NR	10.7	Not extracted
	Metformin, 34	53.4 (40 - 68)	29	AA: 0, C: 3, Asian: 0, H: 76, O: 21	28.5 NR	NR	9.1	Not extracted
Charpentier, 2001[25]	Metformin + glimepiride, 147	56.8 (36 - 70)	59	NR	29.5 81.2 kg	6.4	5.6	Not extracted
	Glimepiride, 150	55.4 (35 - 70)	58	NR	29.3 81 kg	6.5	5.3	Not extracted
	Metformin, 75	56.7 (36 - 69)	60	NR	29.2 82.2 kg	6.8	7	Not extracted
Amador-Licona, 2000[178]	Glibenclamide, 23	48.2	30	NR	30.4 73.2 kg	8.4	4	Not extracted
	Metformin, 28	49.3	39	NR	26.8 70.7 kg	8.5	4.5	Not extracted
Einhorn, 2000[45]	Metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, Asian: 0, H: 10.1, O: 0.6	32.11 NR	9.86	NR	Not extracted
	Metformin, 160	55.7	60	AA: 6.3, C: 86.9, Asian: 0, H: 3.8, O: 3.1	32.12 NR	9.75	NR	Not extracted
Fonseca, 2000[54]	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, Asian: 0, H: 0, O: 12.7	29.8 NR	8.9	8.3	Not extracted
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, Asian: 0, H: 0, O: 12.9	30.2 NR	8.9	7.5	Not extracted
	Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, Asian: 0, H: 0, O: 15	30.3 NR	8.6	7.3	Not extracted
Nakamura, 2000[113]	Glibenclamide, 15	61	53	NR	NR NR	7.8	14	Not extracted
	Pioglitazone, 15	60	47	NR	NR NR	7.7	16	Not extracted
DeFronzo, 1995[30]	Metformin + glyburide, 213	55	46	NR	29 92.1 kg	8.8	7.8	Not extracted
	Metformin, 143	53	43	NR	29.9 94.4 kg	8.4	6	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Glyburide, 209	56	49	NR	29.1 92.6 kg	8.5	8.7	Not extracted
	Metformin, 210	55	46	NR	29.4 92.6 kg	8.9	8.4	Not extracted
Hermann, 1994[85]	Glibenclamide, 21	NR	NR	NR	NR 82.6 kg	6.7	NR	Not extracted
	Metformin + glibenclamide, 13	NR	NR	NR	NR 84.6 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 13	NR	NR	NR	NR 76 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 18	NR	NR	NR	NR 83.2 kg	8.4	NR	Not extracted
	Metformin + glibenclamide, 54	NR	NR	NR	NR 80.2 kg	6.8	NR	Not extracted
	Metformin, 25	60 (34 - 74)	NR	NR	NR 78.6 kg	6.9	4	Not extracted
Campbell, 1994[22]	Glipizide, 24	57	33	NR	31.2 82.2 kg	11.8	2.8	Not extracted
	Metformin, 24	57	33	NR	29.6 78.2 kg	11.5	2.3	Not extracted
Hermann, 1991[84]	Metformin, 16	60 overall (38 - 73)	64 overall	NR	27 76.5 kg	6.7	NR	Not extracted
	Glibenclamide, 17	60 overall (38 - 73)	64 overall	NR	29.2 84.1 kg	6.6	NR	Not extracted
	Metformin + glibenclamide, 11	60 overall (38 - 73)	64 overall	NR	26.1 74.4 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 12	60 overall (38 - 73)	64 overall	NR	30 87.3 kg	7.7	NR	Not extracted
Hermann, 1991[84]	Glibenclamide, 34	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 72	60 (34 - 74)	79	NR	28.4 82.3 kg	NR	NR	Not extracted
	Metformin, 38	NR	NR	NR	NR NR	NR	NR	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Aaboe, 2010[1]	Metformin + sitagliptin 12	39-64	67	NR	33.2 102 kg median	8 median	3.6 median	NR
	Metformin + placebo 12	31-72	75	NR	30.7 100 kg median	7.7 median	5.8 median	NR
Ahren, 2014[2]	Metformin + placebo 104	56.1	49.5	C: 63.4, AA: 22.8, Asian: 5, H: 31.7	32.8 91.6 kg	8.2	6.7	42
	Metformin + glimepiride + placebo, 317	54.4	51.5	C: 71.7, AA: 12.7, Asian: 5.2, H: 34.9	32.5 91.8 kg	8.1	6	99
	Metformin + sitagliptin + placebo, 313	54.3	46	C: 74.5, AA: 11.6, Asian: 6.6, H: 36.8	32.5 90.3 kg	8.1	5.8	101
	Metformin + albiglutide + placebo, 315	54.3	44.7	C: 70.9, AA: 17.5, Asian: 6, H: 32.8	32.7 89.6 kg	8.1	6	100
Alba, 2013[3]	Pioglitazone, 54	53.4	42.6	C: 79.6, AA: 16.7, Asian: 1.9, H: 38.9, O: 1.9	NR 86.6kg	7.9	2.4	2
	Sitagliptin, 52	54.6	53.8	C: 86.5, AA: 11.5, Asian: 1.9, H: 36.4	NR 85.7kg	7.7	2.4	6
Apovian, 2010[4]	Metformin, 51	55	39	NR	NR 94.9kg	7.2	3.9	26
	Metformin + exenatide, 52	53.4	29	NR	NR 91.4 kg	7.5	4.3	26
Arechavaleta, 2011[5]	Metformin + glimepiride + placebo, 519	56.2	53.8	C: 57.4, AA: 1.2, Asian: 21.4, O: 20	NR 82 kg	NR	6.7	51
	Metformin + sitagliptin + placebo, 516	56.3	55	C: 57.6, AA: 1.2, Asian: 21.1, O: 20.1	NR 80.6 kg	NR	6.8	48
Arjona Ferreira, 2013[6]	Glipizide + placebo, 212	64.3	54.9	C: 28.2, AA: 1.4, Asian: 58.5, H: 28.9, O: 12	NR 70.2kg	7.8	10.1	NR
	Sitagliptin + placebo, 211	64.8	59.3	C: 29.6, AA: 1.5, Asian: 53.3, H: 33.3, O: 15.5	NR 68.0kg	7.8	10.7	NR
Aschner, 2012[8]	Metformin + sitagliptin, 265	53.3	52	NR	NR 84.2 kg	8.5	4.8	12
	Metformin + insulin glargine, 250	53.9	50	NR	NR 83.4 kg	8.5	3.9	23

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bailey, 2013[10]	Metformin + placebo, 137	53.7	55	NR	31.8 NR	8.11	5.8	64
	Metformin + dapagliflozin + placebo, 137	55	51	NR	31.6 NR	7.99	6	55
	Metformin + dapagliflozin, 137	54.3	50	NR	31.4 NR	8.17	6.4	48
	Metformin + dapagliflozin + placebo, 135	52.7	57	NR	31.2 NR	7.92	6.1	40
Barnett, 2012[13]	Glimepiride, 76	56.7	43.4	C: 67.1, Asian: 27.6, O: 5.3	NR 80.9 kg	8.1	NR	18
	Linagliptin, 151	56.4	36.4	C: 70.2, Asian: 27.8, O: 2	NR 77.0 kg	8.1	NR	32
Bergenstal, 2010[14]	Metformin + pioglitazone + placebo, 165	53	48	C: 39, AA: 8, Asian: 24, H: 27, O: 2	NR 88 kg	8.5	6	NR
	Metformin + sitagliptin + placebo, 166	52	52	C: 30, AA: 12, Asian: 25, H: 30, O: 3	NR 87 kg	8.5	5	NR
	Metformin + exenatide + placebo, 160	52	56	C: 33, AA: 12, Asian: 23, H: 31, O: 1	32 89 kg	8.6	6	NR
Bergenstal, 2012[15]	Metformin + placebo, 93	56.1	52	C: 77, AA: 6, Asian: 10, H: 11, O: 8	NR 91.1 kg	8.03	5.5	10
	Metformin + sitagliptin + placebo, 185	55.5	59	C: 76, AA: 6, Asian: 11, H: 16, O: 7	NR 92.5 kg	7.94	6	13
Bolinder, 2012[17]	Metformin + placebo, 91	60.8	56	C: 100	31.7 90.9 kg	7.16	5.5	20
	Metformin + dapagliflozin, 91	60.6	55.1	C: 100	32.1 92.1 kg	7.19	6	20
Borges, 2011[18]	Metformin, 340	50.7	53	C: 55, AA: 4, Asian: 34, O: 6	NR 90.6 kg	8.6	2.6	154
	Metformin + rosiglitazone, 348	51.5	53	C: 53, AA: 5, Asian: 35, O: 6	NR 87.1 kg	8.6	2.3	131
Bunck, 2011[20]	Metformin + exenatide, 36	58.4	63.9	NR	NR 90.6 kg	7.6	5.7	20
	Metformin + insulin glargine, 33	58.3	66.7	NR	NR 92. kg	7.4	4	13

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bunck, 2011[21]	Metformin + exenatide, 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	20
	Metformin + insulin glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	17
Cefalu, 2013[23]	Metformin + glimepiride, 484	56.3	55	C: 67, AA: 5, Asian: 19, O: 9	NR 86.5 kg	7.8	6.6	98
	Metformin + canagliflozin, 483	56.4	52	C: 67, AA: 4, Asian: 21, O: 9	NR 86.9 kg	7.8	6.5	88
	Metformin + canagliflozin, 485	55.8	50	C: 69, AA: 4, Asian: 19, O: 9	NR 86.6 kg	7.8	6.7	105
Chawla, 2013[26]	Metformin + pioglitazone, 25	52.2	56	NR	NR 72.6 kg	NR	4.458	0
	Metformin + sitagliptin, 27	49.48	56	NR	NR 72.1 kg	NR	4.107	2
DeFronzo, 2012[33]	Metformin + placebo, 129	55.2	47.3	C: 72.1, AA: 6.2, Asian: 3.9, H: 48.8, O: 17.8	30.6 NR	8.5	6	NR
	Metformin + pioglitazone + placebo, 130	54.1	46.9	C: 65.4, AA: 6.2, Asian: 8.5, H: 48.5, O: 20	31.3 NR	8.5	5.7	NR
	Metformin + pioglitazone + placebo, 129	56.1	48.8	C: 74.4, AA: 4.7, Asian: 7.8, H: 51.9, O: 13.2	31.4 NR	8.5	7.6	NR
	Metformin + pioglitazone + placebo, 129	54.5	41.1	C: 65.9, AA: 7, Asian: 9.3, H: 47.3, O: 17.8	30.7 NR	8.5	5.7	NR
	Metformin + alogliptin + placebo, 128	53.1	52.3	C: 69.5, AA: 4.7, Asian: 10.9, H: 46.9, O: 14.8	31 NR	8.6	6.2	NR
	Metformin + alogliptin + placebo, 129	53.7	38.8	C: 62, AA: 3.9, Asian: 11.6, H: 48.8, O: 22.5	31.5 NR	8.6	5.6	NR
Derosa, 2011[40]	Metformin + glimepiride, 54	55	48	C: 100	NR 81.4kg	8.8	NR	NR
	Metformin + exenatide, 57	56	49	C: 100	NR 80.2kg	8.7	NR	NR
Derosa, 2012[41]	Metformin + placebo, 87	54.8	51	C: 100	NR 78.6kg	8	5.4	5

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + sitagliptin, 91	55.9	46	C: 100	NR 78.4kg	8.1	5.8	7
Derosa, 2013[42]	Metformin + placebo, 87	54.8	51	NR	NR 78.6kg	8	5.4	5
	Metformin + sitagliptin, 91	55.9	46	NR	NR 78.4kg	8.1	5.8	7
Derosa, 2013[43]	Metformin + placebo, 85	56.7	48	C: 100	NR 90.5kg	7.9	7.8	5
	Metformin + exenatide, 86	57.3	50	C: 100	NR 89.0kg	8.1	7.6	5
Diamant, 2010[44]	Metformin + exenatide, 164	NR	NR	NR	NR NR	NR NR	NR NR	NR NR
	Metformin + insulin glargine, 157	NR	NR	NR	NR NR	NR NR	NR NR	NR NR
Erem, 2014[47]	Metformin, 20	52.2	30	NR	NR 87.5 kg	7.62	NR	1
	Pioglitazone, 20	52.5	25	NR	NR 81.9 kg	8.03	NR	1
Esposito, 2011[48]	Metformin, 55	54.9	50.9	NR	NR 83.5kg	8.1	NR	4
	Pioglitazone + pioglitazone, 55	54.2	54.5	NR	NR 84.5kg	8	NR	4
Esteghamati, 2014[49]	Metformin, 43	50.03	47	NR	NR 74.3 kg	8.2	NR	2
	Pioglitazone, 55	51.25	25	NR	NR 77.01	8.1	NR	5
Farcasiu, 2011[50]	Metformin + insulin lispro 75/25, 151	58.4	45.7	C: 98.7, AA: 1.3, O: 1.3	85.1 kg	8.5	11.5	23
	Metformin + insulin lispro 50/50, 151	57	39.1	C: 99.3, AA: 0.7	32.3, 88.6 kg	8.6	10.9	23
Ferrannini, 2013[52]	Metformin, 56	58	50	C: 69.6, AA: 1.8, Asian: 25	NR 85.8kg	8.15	NR	NR
	Empagliflozin, 106	59	46.2	C: 79.2, AA: 0, Asian: 19.8	NR 82.9kg	7.89	NR	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Empagliflozin, 109	59	52.3	C: 77.1, AA:0, Asian: 21.1	NR 84.6kg	8	NR	NR
	Empagliflozin, 109	59	52.3	C: 77.1, AA: 0, Asian: 21.1	NR 84.6kg	8	NR	NR
	Metformin + sitagliptin, 56	60	51.8	C: 100, AA: 0, Asian: 0	NR 88.6	8.03	NR	NR
	Metformin + empagliflozin, 166	60	50	C: 98.2, AA: 1.8, Asian: 0	NR 89.6 kg	7.88	NR	NR
	Metformin + empagliflozin, 166	60	53	C: 98.8, AA: 1.2, Asian: 0	NR 89.5 kg	7.91	NR	NR
Fidan, 2011[53]	Metformin, 20	52.6	70	NR	30.1 NR	NR	NR	NR
	Rosiglitazone, 20	54.1	55	NR	30.9 NR	NR	NR	NR
Fonseca, 2012[55]	Metformin, 144	55.5	51	C: 13, AA: 4, H: 61, O: 23	31 NR	8.4	5.9	25
	Metformin + saxagliptin, 138	55.2	41	C: 9, AA: 7, H: 61, O: 23	30.8 NR	8.3	6.5	8
Forst, 2010[56]	Metformin + placebo, 71	60.1	62	C: 97, AA: 1, Asian: 1	NR 93.1kg	8.4	6.2	14
	Metformin + glimepiride, 65	59.4	63.1	C: 99, AA: 0, Asian: 2	NR 90.5kg	8.2	6.7	4
	Metformin + linagliptin, 66	59.6	56.1	C: 100, AA: 0, Asian: 0	NR 90.7kg	8.5	7.3	10
Forst, 2012[57]	Metformin, 22	57.9	45	NR	NR 96.9 kg	6.36	4.8	3
	Metformin + liraglutide, 22	55.1	45	NR	NR 93.2 kg	6.32	3.8	1
Forst, 2014[58]	Metformin + glimepiride, 20	63	70	NR	NR 95.1 kg	7.4	8	0
	Metformin + linagliptin, 20	65	65	NR	NR 89.6 kg	7.3	7.7	1
Gallwitz, 2011[59]	Metformin + exenatide, 182	57	NR	NR	33.4 NR	NR	5	47

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + insulin aspart 70/30, 181	57	NR	NR	32.9 NR	NR	5	44
Gallwitz, 2012[60]	Metformin + glimepiride + placebo, 775	59.8	61	C: 85, AA: 2, Asian: 12, O: <1	30.3 86.8 kg	7.7	NR	NR
	Metformin + linagliptin + placebo, 777	59.8	60	C: 85, AA: 3, Asian: 12, O: <1	30.2 86.1 kg	7.7	NR	NR
Gallwitz, 2012[61]	Metformin + glimepiride, 514	56	52	C: 91, H: 7, O: 2	32.3 91.1 kg	7.4	5.5	128
	Metformin + exenatide, 515	56	56	C: 92, H: 7, O: <1	32.6 92.8 kg	7.5	5.8	174
Garber, 2011[66]	Glimepiride + placebo, 248	53.4	54	C: 77, AA: 12, Asian: 4, H: 38, O: 7	NR 93.3 kg	8.2	5.6	151
	Liraglutide + placebo, 251	53.7	47	C: 80, AA: 14, Asian: 2, H: 32, O: 5	NR 92.1 kg	8.2	5.2	141
	Liraglutide + placebo, 247	52	49	C: 75, AA: 12, Asian: 5, H: 35, O: 8	NR 92.6 kg	8.2	5.3	132
Genovese, 2013[67]	Metformin + placebo, 103	57.8	60.2	C: 100	NR 89kg	7.02	5.7	6
	Metformin + pioglitazone, 110	57	59.1	C: 100	NR 88.8kg	6.92	5.8	13
Genovese, 2013[68]	Metformin 29	56.4	65.5	NR	NR 87.8kg	6.8	3.9	3
	Pioglitazone + placebo 29	59.1	48.3	NR	NR 84.1kg	6.9	4.4	5
Goke, 2010[69]	Metformin + glipizide 430	57.6	54	C: 84.2, AA: 0, Asian: 15.1, O: 0.7	31.3, 88.6 kg	7.7	5.4	283
	Metformin + saxagliptin 428	57.5	49.5	C: 82.2, AA: 0.2, Asian: 17.1, O: 0.5	31.5 88.7 kg	7.7	5.5	263
Gupta, 2010[74]	Metformin	50.9	NR	NR	25.7 60.5 kg	8.71	NR	NR
	Glipizide	49.5	NR	NR	25.7 57.9 kg	8.59	NR	NR
	Rosiglitazone	50.5	NR	NR	24.3 56.4 kg	8.3	NR	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Gupta, 2013[75]	Sitagliptin 84	39.12	NR	NR	25.4 60.2 kg	8.03	NR	7
	Glimepiride 83	40.07	NR	NR	26.18 61.1 kg	8.02	NR	12
Haak, 2012[76]	Metformin 144	52.9	56.9	C: 64.6, AA: 0, Asian: 35.4, O: 0	NR 79.9 kg	8.7	NR	17
	Metformin 147	55.2	53.1	C: 64.6, AA: 1.4, Asian: 34, O: 0	NR 80 kg	8.5	NR	21
	Linagliptin 142	56.2	56.3	C: 68.3, AA: 0, Asian: 31.7, O: 0	NR 79.1 kg	8.7	NR	21
Haak, 2012[76]	Metformin + linagliptin 143	55.6	51	C: 72, AA: 1.4, Asian: 25.9, O: 0.7	NR 80.8 kg	8.7	NR	16
	Metformin + linagliptin 143	56.4	53.8	C: 65.7, AA: 0.7, Asian: 33.6, O: 0	NR 76.7 kg	8.7	NR	11
Haak, 2013[77]	Metformin, 170	55.6	54.1	C: 62.4, AA: 0.9, Asian: 36.7	29.2 NR	7.31	NR	NR
	Metformin, 170	55.7	55.7	C: 63.9, AA: 0, Asian: 36.1	29.5 NR	7.76	NR	NR
	Metformin + linagliptin, 225	56.8	51.3	C: 71.7, AA: 1.8, Asian: 26.5	29.8 NR	7.34	NR	NR
	Metformin + linagliptin, 225	55.1	55.4	C: 65.2, AA: 0, Asian: 34.8	28.3 NR	7.95	NR	NR
	Metformin + linagliptin, 171	56.1	61.7	C: 68.3, AA: 0, Asian: 31.7	28.8 NR	8.15	NR	NR
	Metformin + linagliptin, 171	55.6	54.1	C: 60.4, AA: 0.9, Asian: 38.7	28.5 NR	6.93	NR	NR
Haring, 2014[82]	Metformin + placebo, 207	56	56	C: 55, AA: 1, Asian: 44, O: 0	NR 79.7kg	7.9	NR	21
	Metformin + empagliflozin, 217	55.5	58	C: 52, AA: 2, Asian: 46, O: 1	NR 81.6kg	7.94	NR	8
	Metformin + empagliflozin, 214	55.6	56	C: 53, AA: 0, Asian: 46, O: 1	NR 82.2kg	7.86	NR	18
Henry, 2012[83]	Metformin + placebo, 201	51.8	24	NR	NR 85.6kg	9.2	0.6	30

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Dapagliflozin + placebo, 203	52.3	22	NR	NR 86.2kg	9.1	0.4	33
	Metformin + dapagliflozin, 194	51.7	21	NR	NR 84.1kg	9.2	0.3	17
Henry, 2012[83]	Metformin + placebo, 208	52.7	46.6	NR	NR 87.2 kg	9.1	0.5	27
	Dapagliflozin + placebo, 219	51.1	47.9	NR	NR 88.5 kg	9.1	0.6	31
	Metformin + dapagliflozin, 211	51	50.2	NR	NR 88.4 kg	9.1	0.6	28
Hermans, 2012[86]	Metformin, 139	58.6	54.7	C: 97.1, AA: 0.7, Asian: 1.4, O: 0.7	31.2 NR	NR	6.9	32
	Metformin + saxagliptin, 147	58.7	59.9	C: 98.6, AA: 0.7, Asian: 0.7, O: 0	32.1 NR	NR	6	28
Kadoglou, 2011[93]	Metformin, 70	62.7	27	NR	30.04 NR	7.56	2.7	NR
	Metformin + rosiglitazone, 70	62	26	NR	29.68 NR	7.58	1.8	NR
Kadowaki, 2013[94]	Metformin + placebo, 72	57.2	68.1	NR	25 NR	8.4	7.3	NR
	Metformin + sitagliptin, 77	59.6	71.4	NR	25.2 NR	8.2	7.7	NR
Kaku, 2011[97]	Glibenclamide	58.5	65.2	Asian: 100	NR 65.4 kg	9.18	8.5	NR
	Liraglutide	58.2	68.3	Asian: 100	NR 66.2 kg	9.32	8.1	NR
Kikuchi, 2012[99]	Rosiglitazone 160	55	62.9	Asian: 100	24.5 NR	8.9	5	11
	Pioglitazone 159	56	62.3	Asian: 100	24.9 NR	8.8	4.2	22
Kim, 2014[101]	Metformin 108	56.1	47.2	NR	25.7 66.9 kg	7.8		14
	Metformin + glimepiride 101	55.2	51.5	NR	25.5 66.5 kg	7.9		6

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Lavalle-Gonzalez, 2013{Lavalle-Gonzalez, 2013	Metformin + placebo, 183	55.3	51.4	C: 70.5, AA: 1.6, Asian: 16.4, O: 11.5	NR 86.6kg	8	6.8	28
	Metformin + sitagliptin, 366	55.5	47	C: 72.1, AA: 3.6, Asian: 11.2, O: 13.1	NR 87.7kg	7.9	6.8	47
	Metformin + canagliflozin, 368	55.5	47.3	C: 68.5, AA: 4.3, Asian: 13.9, O: 13.3	NR 88.8kg	7.9	6.7	46
	Metformin + canagliflozin, 367	55.3	45	C: 69.8, AA: 3.5, Asian: 16.3, O: 10.4	NR 85.4kg	7.9	7.1	44
List, 2009[107]	Metformin 56	54	48	NR	NR 88 kg	7.6	NR	5
	Dapagliflozin 58	55	48	NR	NR 89 kg	8	NR	3
	Dapagliflozin 47	54	53	NR	NR 86 kg	8	NR	7
Maffioli, 2013[109]	Metformin + pioglitazone, 86	62.8	48	NR	NR 83.5 kg	8.4	NR	3
	Metformin + glibenclamide, 84	61.4	50	NR	NR 83.1 kg	8.2	NR	2
Moon, 2014[112]	Metformin + glimepiride 36	54.9	47.1	NR	NR 66.0 kg	8.9	95.6	2
	Metformin + insulin glargine, 39	51.3	31.6	NR	NR 62.7 kg	8.8	79	0
Nauck, 2009[117]	Metformin + placebo 104	56	48	C: 76, AA: 7, Asian: 6, H: 24, O: 11	32 NR	8	6	NR
	Metformin + alogliptin 210	54	54.3	C: 76, AA: 6, Asian: 9, H: 32, O: 9	32 NR	7.9	6	NR
	Metformin + alogliptin 213	55	47.4	C: 80, AA: 2, Asian: 8, H: 31, O: 10	32 NR	7.9	6	NR
Nauck, 2011[118]	Metformin + glipizide 408	59	54.9	C: 80.5, AA: 6, Asian: 8.5, O: 5	31.2 NR	7.7	7	94
	Metformin + dapagliflozin 406	58	55.3	C: 81.8, AA: 6.5, Asian: 6.8, O: 5	31.7 NR	7.7	6	84
Nauck, 2014[119]	Metformin + placebo 177	55	51	C: 51, AA: 5, Asian: 22, H: 22, O: 0	NR 87 kg	8.1	7	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + sitagliptin 315	54	48	C: 50, AA: 2, Asian: 26, H: 21, O: 1	NR 86 kg	8.1	7	NR
	Metformin + dulaglutide 302	54	44	C: 54, AA: 4, Asian: 26, H: 17, O: 0	NR 86 kg	8.2	7	NR
	Metformin + dulaglutide 304	54	48	C: 52, AA: 5, Asian: 25, H: 18, O: 0	NR 87 kg	8.1	7	NR
Oz Gul, 2010[120]	Rosiglitazone 20	NR	NR	NR	NR 29.6	7.3	NR	NR
	Pioglitazone 19	NR	NR	NR	29.3 NR	7.6	NR	NR
	+ placebo 21	NR	NR	NR	29.6 NR	7.3	NR	NR
Perez-Monteverde, 2011[122]	Sitagliptin 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	NR 82.2kg	9.1	3.5	17
	Pioglitazone 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	NR 82.2kg	9.1	3.5	17
Petrica, 2009[124]	Metformin + rosiglitazone 22	63	32	NR	33.55 NR	7.72	10.53	5
	Metformin + glimepiride 22	63.2	32	NR	33.58 NR	7.58	10.4	5
Pfutzner, 2011[126]	Metformin + pioglitazone	59	66	NR	32.6 NR		6.2	32
	Metformin + glimepiride	59	64	NR	32.5 NR		5.9	29
Pfutzner, 2011[127]	Metformin + placebo 328	51.8	49.7	C: 76.5, AA: 1.2, Asian: 15.9, O: 6.4	30.2 NR	9.4	1.7	109
	Saxagliptin + placebo 335	52.1	50.4	C: 76.1, AA: 1.8, Asian: 16.7, O: 5.4	30.2 NR	9.6	1.7	126
	Metformin + saxagliptin 320	52	51.6	C: 76.9, AA: 2.2, Asian: 15.9, O: 5	29.9 NR	9.4	2	91
	Metformin + saxagliptin 323	52.1	45.2	C: 75.2, AA: 2.2, Asian: 16.7, O: 5.9	30.4 NR	9.5	1.4	92
Pratley, 2014[129]	Metformin 114	54.6	41.2	C: 74.6, AA: 5.3, Asian: 16.7, O: 3.5	30.2 NR	8.5	3.8	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin 111	52.6	45.9	C: 71.2, AA: 5.4, Asian: 18, O: 5.4	30.5 NR	8.39	4.1	NR
	Metformin + alogliptin 111	53.7	43.2	C: 68.5, AA: 5.4, Asian: 18, O: 8.1	30.9 NR	8.5	4.1	NR
	Metformin + alogliptin 114	54.6	54.4	C: 68.4, AA: 4.4, Asian: 22.8, O: 4.4	31 NR	8.43	4.2	NR
	+ alogliptin 112	52.6	42.9	C: 75, AA: 2.7, Asian: 15.2, O: 7.1	30.8 NR	8.3	3.6	NR
Qiu, 2014[130]	Metformin + placebo 93	57	49.5	C: 78.5, AA: 4.3, Asian: 9.7, O: 7.5	NR 90.5kg	7.7	7	7
	Metformin + canagliflozin 93	58.6	43	C: 80.6, AA: 5.4, Asian: 3.2, O: 10.8	NR 91.2kg	7.6	6.7	8
	Metformin + canagliflozin 93	56.7	47.3	C: 89.2, AA: 1.1, Asian: 6.5, O: 3.2	NR 90.2kg	7.6	7.3	13
Reasner, 2011[133]	Metformin	50	57	C: 79, AA: 14, Asian: 4, H: 30, O: 3	33.7 97.2 kg	9.8	3.2	215
	Metformin + sitagliptin	49.4	56	C: 81, AA: 13, Asian: 3, H: 36, O: 3	32.9 94.7 kg	9.9	3.5	216
Ridderstrale, 2014[134]	Metformin + glimepiride 780	55.7	54	C: 67, AA: 1, Asian: 32, H: 20, O: 0	NR 83.0kg	7.92	NR	132
	Metformin + empagliflozin, 769	56.2	56	C: 65, AA: 2, Asian: 33, H: 20, O: <1	NR 82.5kg	7.92	NR	121
Roden, 2013[137]	Sitagliptin 223	55.1	63	C: 34, AA: 1, Asian: 64, O: <1	NR 79.3kg	7.85	NR	17
	Sitagliptin 223	55.1	63	C: 34, AA: 1, Asian: 64, O: <1	NR 79.3kg	7.85	NR	17
	Empagliflozin 224	56.2	63	C: 34, AA: 1, Asian: 64, O: 0	NR 78.4kg	7.87	NR	18
	Empagliflozin 224	53.8	65	C: 33, AA: 3, Asian: 64, O: 0	NR 77.8kg	7.86	NR	20
Rosenstock, 2010[139]	Pioglitazone + placebo 163	NR	NR	NR	NR NR	8.76	NR	37
	Alogliptin + placebo 164	NR	NR	NR	NR NR	8.8	NR	38

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Rosenstock, 2012[140]	Metformin + placebo 65	53.3	48	NR	NR 85.9 kg	7.75	6.4	10
	Metformin + sitagliptin 65	51.7	58	NR	NR 87.2 kg	7.64	5.6	5
	Metformin + canagliflozin 64	51.7	56	NR	NR 87.7 kg	7.83	6.1	5
	Metformin + canagliflozin 65	52.9	51	NR	NR 87.7 kg	7.61	6.4	9
	Metformin + canagliflozin 64	52.3	56	NR	NR 87.3 kg	7.69	5.9	8
Rosenstock, 2013[141]	Alogliptin 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	NR
	Glipizide 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	NR
Rosenstock, 2013[142]	Metformin + placebo 71	60	47	C: 90, AA: 1, H: 9, O: 0	NR 87.7kg	8	NR	5
	Metformin + sitagliptin 71	58	54	C: 87, AA: 0, H: 13, O: 0	NR 88.0kg	8.1	NR	1
	Metformin + empagliflozin, 71	59	47	C: 78, AA: 3, H: 20, O: 0	NR 87.9kg	7.9	NR	5
	Metformin + empagliflozin, 70	59	53	C: 83, AA: 1, H: 16, O: 0	NR 90.5kg	8.1	NR	0
Ross, 2012[143]	Metformin + placebo 44	59.9	47.7	C: 72.7, Asian: 27.3, O: 0	NR 77.7kg	7.92	NR	1
	Metformin + linagliptin + placebo, 224	58.4	54	C: 62.1, Asian: 36.6, O: 1.3	NR 80.6kg	7.98		10
Russell-Jones, 2012[144]	Metformin + placebo 246	54	62.6	C: 65, AA: 4.5, Asian: 20.7, H: 8.5, O: 1.2	NR 85.9 kg	8.6	2.6	NR
	Pioglitazone + placebo 163	55	59.5	C: 67.5, AA: 2.5, Asian: 20.9, H: 9.2, O: 0	86.1 kg NR	8.5	2.7	NR
	Sitagliptin + placebo 163	52	57.7	C: 69.3, AA: 1.8, Asian: 20.2, H: 8, O: 0.6	NR 88.7 kg	8.5	2.7	NR
	Exenatide + placebo 248	54	56	C: 68.1, AA: 2.8, Asian: 22.2, H: 6.5, O: 0.4	NR 87.5 kg	8.5	2.7	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Schondorf, 2011[146]	Metformin + pioglitazone + placebo, 25	59.4	76	NR	32 NR	7.4	6.7	NR
	Metformin + glimepiride 21	57.5	67	NR	32 NR	6.7	5.9	NR
Seino, 2012[151]	Metformin + placebo 100	52.1	72	NR	NR 69.9 kg	8	6.04	0
	Metformin + alogliptin 92	53.4	65.2	NR	NR 69.5 kg	7.89	6.34	1
	Metformin + alogliptin 96	52.3	68.8	NR	NR 69.7kg	8.02	6.62	3
Shihara, 2011[152]	Pioglitazone 96	56.8	68	Asian: 100	NR 65.5 kg	7.8	4.1	5
	SU 95	57.7	65	Asian: 100	NR 65.6 kg	7.8	6	9
Srivastava, 2012[153]	Metformin + glimepiride 25	NR	NR	Asian: 100	26.5 NR	NR	NR	0
	Metformin + sitagliptin 25	NR	NR	Asian: 100	25.3 NR	NR	NR	0
Taskinen, 2011[158]	Metformin + placebo 177	56.6	57	C: 79, Asian: 18, O: 3	NR 83.3 kg	8.02	NR	14
	Metformin + linagliptin 523	56.5	53	C: 75, Asian: 22, O: 3	NR 82.2 kg	8.09	NR	39
Taslimi, 2013[159]	Metformin 30	51	50	NR	NR 76.8kg	8.4	24	NR
	Pioglitazone 30	56	43	NR	NR 73.8kg	8.2	36	NR
Umpierrez, 2014[165]	Metformin + placebo 268	55	45	C: 75, AA: 5, Asian: 8, H: 35, O: 13	33, 92 kg	7.6	3	55
	Dulaglutide + placebo 270	56	44	C: 73, AA: 8, Asian: 7, H: 32, O: 11	33, 92 kg	7.6	3	52
	Dulaglutide + placebo 269	56	42	C: 75, AA: 6, Asian: 8, H: 33, O: 12	34, 93 kg	7.6	3	49
White, 2014[168]	Metformin + placebo 86	56.6	52.3	C: 93, AA: 3.5, Asian: 2.3, H: 40.7, O: 1.2	32.5 NR	7.97	6.2	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + saxagliptin 74	53.9	54.1	C: 86.5, AA: 10.8, Asian: 2.7, H: 39.2, O: 0	33.7 NR	7.92	5.8	NR
Williams-Herman, 2010[170]	Metformin + placebo, 42	54.1	50	NR	31.9 NR	8.1	4	20
	Metformin + placebo, 65	55.9	46	NR	32.2 NR	8.6	4	27
	Metformin + placebo, 88	54.3	44	NR	31.9 NR	8.5	3.9	26
	Sitagliptin + placebo, 52	54.1	58	NR	30.3 NR	8.5	3.7	38
	Metformin + sitagliptin, 100	54.5	50	NR	31.6 NR	8.7	3.7	36
	Metformin + sitagliptin, 107	53.9	37	NR	31.4 NR	8.6	4.4	21
Yang, 2011[172] Yang, 2011[172]	Metformin + placebo 287	54.4	48.4	Asian: 100	NR 69.0 kg	7.9	5.1	40
	Metformin + saxagliptin 283	53.8	48.1	Asian: 100	NR 68.9 kg	7.9	5.1	29
	Metformin + glimepiride + placebo, 231	53.6	58.4	Asian: 100	NR 68.2 kg	8.5	7.8	NR
	Metformin + liraglutide + placebo, 231	53.5	54.1	Asian: 100	NR 68.6 kg	8.5	7.4	NR
	Metformin + liraglutide + placebo, 233	53.5	54.9	Asian: 100	NR 67.4 kg	8.6	7.5	NR
	Metformin + liraglutide + placebo, 234	52.7	53.8	Asian: 100	NR 68.2 kg	8.6	7.2	NR
Yang, 2012[174]	Metformin + placebo, 198	55.1	55	Asian: 100	NR 68.9 kg	NR	7.3	16
	Metformin + sitagliptin, 197	54.1	47	Asian: 100	NR 67.9 kg	NR	6.4	23
Yoon, 2011[175]	Metformin 114	51.8	57.89	Asian: 100	NR 68.9 kg	7.9	NR	43
	Rosiglitazone 117	50.1	52.14	Asian: 100	NR 69.1 kg	7.8	NR	43

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Glimepiride 118	50.8	55.93	Asian: 100	NR 67.9 kg	7.8	NR	36
Yuan, 2012[176]	Metformin 26	56.8	46	NR	NR 83.7kg	8.11	NR	0
	Exenatide 33	58.5	52	NR	NR 82.2kg	8.27	NR	1
Zhang, 2012[179]	Metformin + glimepiride 23	52	57	NR	24.8 NR	9	4.1	5
	Metformin + exenatide 19	50.2	53	NR	24.9 NR	8.7	4.2	6

Abbreviations: AA = African American; BHI = biphasic human insulin; BMI = body mass index; C = Caucasian; H = Hispanic; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptidase-1; HbA1c = glycated hemoglobin; kg = kilogram; NPH = neutral protamine Hagedorn; NR = Not Reported; O = Other; SU = sulfonylurea; sd = standard deviation;

Some data may not have been extracted because the question was not asked.

Table 3. Results of studies evaluating diabetes medications on intermediate outcomes

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Aaboe, 2010[1]	Grp1: Metformin + sitagliptin Fixed (100mg daily) Grp2: Metformin + placebo ITT: NR Followup (wks): 12	Grp1: F: 7.25 (6.6-8.2) F-B: -1 (-2.2-0.5) p 0.005 Grp2: F: 7.25 (6.6-8.2) F-B: -0.1 (-3.9-0.9) p NS Between-group difference: p 0.1	Grp1: F: 101.7 (83-125) Grp2: F: 100.5 (83-125)		
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Grp2: Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (0.9) F: 8.4 (0.12) F-B: 0.27 Grp2: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.36 Between-group difference: Grp1: 0.9 (0.7-1.2) p <0.0001 Grp2: 0.3 (0.1-0.5) p 0.0033	Grp1: B: 91.7 (1.2) F: 90.7 (1.6) F-B: -1 Grp2: B: 89.6 (0.6) F: 88.4 (1) F-B: -1.21	Grp1: B: 128.1 (13.2) F-B: 2.2 (14) Grp2: B: 127.4 (13.6) F-B: 0.2 (14.7)	Grp1: B: 72 (11.2) F-B: 2.3 (9.5) Grp2: B: 73.1 (10.2) F-B: 1.3 (10.3)
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Grp2: Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (0.9) F: 8.4 (0.12) F-B: 0.27 Grp2: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.28 Between-group difference: Grp1: 0.9 (0.7-1.2) p <0.0001 Grp2: 0.4 (0.2-0.5) p 0.0001	Grp1: B: 91.7 (1.2) F: 90.7 (1.6) F-B: -1 Grp2: B: 91.9 (1.6) F: 93 (0.9) F-B: 1.17 Between-group difference: p <0.0001	Grp1: B: 128.1 (13.2) F-B: 2.2 (14) Grp2: B: 127.9 (14.3) F-B: 1.5 (14.1)	Grp1: B: 72 (11.2) F-B: 2.3 (9.5) Grp2: B: 73.1 (10.2) F-B: 0.8 (10.7)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Grp2: Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (0.9) F: 8.4 (0.12) F-B: 0.27 Grp2: B: 8.1 (0.8) F: 7.5 (0.06) F-B: -0.63 Between-group difference: Grp1: 0.9 (0.7-1.2) p <0.0001	Grp1: B: 91.7 (1.2) F: 90.7 (1.6) F-B: -1 Grp2: B: 90.4 (1.6) F: 89.5 (0.9) F-B: -0.86	Grp1: B: 128.1 (13.2) F-B: 2.2 (14) Grp2: B: 128.4 (13.9) F-B: -1 (14.2)	Grp1: B: 72 (11.2) F-B: 2.3 (9.5) Grp2: B: 72 (9.5) F-B: -0.5 (9.6)
Ahren, 2014[2]	Grp1: Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2: Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.36 Grp2: B: 8.1 (0.8) F: 7.5 (0.06) F-B: -0.63 Between-group difference: Grp1: 0.3 (0.1-0.5) p 0.0033	Grp1: B: 91.9 (1.6) F: 93 (0.9) F-B: 1.17 Grp2: B: 89.6 (0.6) F: 88.4 (1) F-B: -1.21 Between-group difference: p <0.0001	Grp1: B: 127.9 (14.3) F-B: 1.5 (14.1) Grp2: B: 127.4 (13.6) F-B: 0.2 (14.7)	Grp1: B: 72 (9.5) F-B: -0.5 (9.6) Grp2: B: 73.1 (10.2) F-B: 0.8 (10.7)
Ahren, 2014[2]	Grp1: Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2: Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd)	Grp1: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.36 Grp2: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.28 Between-group difference: Grp1: 0.3 (0.1-0.5) p 0.0033	Grp1: B: 91.9 (1.6) F: 93 (0.9) F-B: 1.17 Grp2: B: 90.4 (1.6) F: 89.5 (0.9) F-B: -0.86 Between-group difference: p <0.0001	Grp1: B: 127.9 (14.3) F-B: 1.5 (14.1) Grp2: B: 128.4 (13.9) F-B: -1 (14.2)	Grp1: B: 72 (9.5) F-B: -0.5 (9.6) Grp2: B: 73.1 (10.2) F-B: 1.3 (10.3)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: Yes Followup (wks): 104	Grp2: 0.4 (0.2-0.5) p 0.0001			
Ahren, 2014[2]	Grp1: Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2: Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qw up-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.28 Grp2: B: 8.1 (0.8) F: 7.5 (0.06) F-B: -0.63 Between-group difference: Grp1: 0.4 (0.2-0.5) p 0.0001	Grp1: B: 90.4 (1.6) F: 89.5 (0.9) F-B: -0.86 Grp2: B: 89.6 (0.6) F: 88.4 (1) F-B: -1.21	Grp1: B: 127.4 (13.6) F-B: 0.2 (14.7) Grp2: B: 128.4 (13.9) F-B: -1 (14.2) p	Grp1: B: 73.1 (10.2) F-B: 0.8 (10.7) Grp2: B: 73.1 (10.2) F-B: 1.3 (10.3)
Alba, 2013[3]	Grp1: Pioglitazone Fixed (30mg) Grp2: Sitagliptin Fixed (100mg) ITT: NR Followup (wks): 12	Grp1: B: 7.9 (0.9) F-B: -0.56 (-0.85-0.27) p <0.001 Grp2: B: 7.7 (0.8) F-B: -0.79 (-1.08-0.49) p <0.001			
Amador-Licona, 2000[178]	Grp1: Metformin Varied Start: 850 mg, Max: NR Grp2: Glibenclamide Varied Start: 5 mg, Max: NR	Grp1 B: 8.5 (1.5) F: 7.6 (0.8) F-B: -0.9 p: 0.003 Grp2 B: 8.4 (1.4) F: 7.6 (0.8) F-B: -0.8 p: 0.009 Grp1-Grp2: -0.1	Grp1 B: 70.7 (14.8) F: 69.6 (14.3) F-B: -0.9 p: 0.07 Grp2 B: 73.2 (11.8) F: 74.1 (12.6) F-B: 0.9 p: 0.1 Grp1-Grp2: -1.7		
Apovian, 2010[4]	Grp1: Metformin Fixed Grp2: Metformin + exenatide Fixed Titrated (Max: 10ug twice daily) ITT: No Followup (wks): 24	Grp1: F-B: -0.4 (0.1) p </=0.0009 Grp2: F-B: -0.9 (0.1) p </=0.0009 Between-group difference:	Grp1: F-B: -4.3 (0.7) p <0.05 Grp2: F-B: -7.3 (0.7) p <0.05 Between-group difference: p <0.01		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		p 0.0002			
Arechavaleta, 2011[5]	Grp1: Metformin + glimepiride + placebo Not specified Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2: Metformin + sitagliptin + placebo Not specified Fixed (100mg daily) ITT: No Followup (wks): 30	Grp1: B: 7.51 (0.76) F: 7.02 (0.92) F-B: -0.52 (-0.6-0.45) Grp2: B: 7.5 (0.7) F: 7.09 (0.86) F-B: -0.46 (-0.54-0.38) Between-group difference: Grp2: 0.07 (-0.02-0.16)	Grp1: B: 82 (16.7) F-B: 1.2 (0.9-1.5) Grp2: B: 80.6 (15.2) F-B: -0.8 (-1.1--0.5) Between-group difference: Grp2: -2 p <0.001		
Arjona Ferreira, 2013[6]	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 54	Grp1: B: 7.8 (0.7) F-B: -0.6 (-0.8-0.5) Grp2: B: 7.8 (0.7) F-B: -0.8 (-0.9-0.6) Between-group difference: Grp2: -0.11 (-0.29-0.06)	Grp1: B: 70.2 (15.9) F-B: 1.2 (0.2) Grp2: B: 68 (14.8) F-B: -0.6 (0.2) Between-group difference: Grp2: -1.8 p <0.001		
Aschner, 2010[7]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1903 D: 5 Wks Grp2: Sitagliptin Fixed	Grp1 F-B: -0.55 (CI: -0.61, -0.5) Grp2 F-B: -0.38 (CI: -0.43, -0.32) Grp1-Grp2: -0.18 (CI: -	Grp1 F-B: -1.9 (CI: -2.2, -1.7) Grp2 F-B: -0.6 (CI: -0.9, -0.4) Grp1-Grp2: -1.3 p:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Mean: 100 mg	0.25, -0.1)	<0.001		
Aschner, 2012[8]	Grp1: Metformin + sitagliptin Not specified Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 24	Grp1: F-B: -1.13 (0.06) Grp2: F-B: -1.72 (0.06) Between-group difference: Grp2: -0.59 (-0.77-0.42) p <0.0001	Grp1: F-B: -1.08 (0.2) Grp2: F-B: 0.44 (0.22) Between-group difference: Grp2: 1.51 (0.93-2.09) p <0.0001		
Bailey, 2005[9]	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2000 mg; Start: 4 mg, Max: 8 mg	Grp1 B: 7.5 (1.0) F: 7.4 (1.1) F-B: -0.13 Grp2 B: 7.4 (1.0) F: 7.1 (1.1) F-B: -0.33 Grp1-Grp2: 0.22 p: 0.001	Grp1 B: 89.5 (14.4) F: 88.6 F-B: -0.9 (SE: 0.2) Grp2 B: 90.9 (15.6) F: 92.2 F-B: 1.3 (SE: 0.22) Grp1-Grp2: -2.2		
Bailey, 2013[10]	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: No Followup (wks): 102	Grp1: B: 8.12 (0.96) F-B: 0.02 (-0.2-0.23) Grp2: B: 7.92 (0.82) F-B: -0.78 (-0.97-0.68) Between-group difference: Grp2: -0.8 (-1.08-0.52) p <0.0001	Grp1: B: 87.74 (19.24) F-B: 1.36 (0.53-2.2) Grp2: B: 84.73 (16.26) F-B: -1.7 (-2.48--0.91) Between-group difference: Grp2: -3.06 (-4.21--1.92) p <0.0001	Grp1: B: 128 (15) F-B: 1.5 (13.7) Grp2: B: 127 (14) F-B: 0.7 (16.1) Between-group difference: p 0.1111	
Bailey, 2013[10]	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mg Median: 2000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 102	Grp1: B: 8.12 (0.96) F-B: 0.02 (-0.2-0.23) Grp2: B: 8.17 (0.96) F-B: -0.58 (-0.77-0.39) Between-group difference:	Grp1: B: 87.74 (19.24) F-B: 1.36 (0.53-2.2) Grp2: B: 86.28 (17.53) F-B: -1.74 (-2.51--0.96) Between-group difference: Grp2: -3.1 (-4.24--1.96)	Grp1: B: 128 (15) F-B: 1.5 (13.7) Grp2: B: 126 (16) F-B: -0.3 (15) Between-group difference: p 0.0067	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp2: -0.6 (-0.89-0.31) p <0.0001	p <0.0001		
Bailey, 2013[10]	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mg Median: 1500 mg) Fixed (2.5 mg) ITT: No Followup (wks): 102	Grp1: B: 8.12 (0.96) F-B: 0.02 (-0.2-0.23) Grp2: B: 7.99 (0.9) F-B: -0.48 (-0.68-0.29) p Between-group difference: Grp2: -0.5 (-0.79-0.21) p 0.0008	Grp1: B: 87.74 (19.24) F-B: 1.36 (0.53-2.2) Grp2: B: 84.9 (17.77) F-B: -1.1 (-1.91--0.29) Between-group difference: Grp2: -2.46 (-3.63--1.3) p <0.0001	Grp1: B: 128 (15) F-B: 1.5 (13.7) Grp2: B: 127 (14) F-B: -1.1 (13.2) Between-group difference: p 0.0136	
Bakris, 2003[11]	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Start: NR, Max: 20 mg	Grp1 B: 9.1 (1.68) F: 8.2 F-B: -0.9 (1.38) Grp2 B: 9.5 (1.59) F: 8.6 F-B: -0.9 (1.39) Grp1-Grp2: 0 p: NS			
Bakris, 2006[12]	Grp1: Metformin + rosiglitazone Varied; Varied, glucose: <=6.6 mmol/L Unclear; Start: 4 mg D: 3 wks Grp2: Metformin + glyburide Varied; Glucose: <=6.6 mmol/L Unclear; Start: 5 mg D: 3 wks; NR	Grp1 F-B: 0.72 (SE: 0.1) Grp2 F-B: 0.92 (SE: 0.08) Grp1-Grp2: -0.2 (SE: 0.12)	Grp1 F-B: 1.94 (4.63) Grp2 F-B: 1.5 (3.53) Grp1-Grp2: 0.44		
Barnett, 2012[13]	Grp1: Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if 84asting blood glucose was >110mg/dl (6.1mmol/l)) Grp2: Linagliptin Fixed (5mg qdstarted this at	Grp1: B: 8.1 (0.9) F-B: -0.72 (0.15) Grp2: B: 8.1 (1) F-B: -0.44 (0.1)	Grp1: B: 80.9 (19.1) F-B: 1.3 (0.57) Grp2: B: 77 (18.8) F-B: -0.2 (0.42)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	randomization and on for all 52 wks) ITT: No Followup (wks): 52				
Bergenstal, 2010[14]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.1) F: 7.4 (0.1) F-B: -1.2 (-1.4-1) Grp2: B: 8.5 (1.2) F: 7.7 (0.1) p F-B: -0.9 (-1.1-0.7) Between-group difference: Grp1: 0.3 (0.1-0.6) p 0.0165 Grp2: 0.6 (0.4-0.9) p <0.0001	Grp1: B: 88 (20) F-B: 2.8 (2.2-3.4) Grp2: B: 87 (20) F-B: -0.8 (-1.4--0.1) Between-group difference: Grp1: 5.1 (4.3-5.9) p <0.0001 Grp2: 1.5 (0.7-2.4) p 0.0002	Grp1: B: 127 (14) F-B: -1.6 (1) Grp2: B: 126 (14) F-B: -3.6 (1) Between-group difference: p NS	
Bergenstal, 2010[14]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.1) F: 7.4 (0.1) p F-B: -1.2 (-1.4-1) Grp2: B: 8.6 (1.2) F: 7.2 (0.1) F-B: -1.5 (-1.7-1.4) Between-group difference: Grp1: 0.3 (0.1-0.6) p 0.0165	Grp1: B: 88 (20) F-B: 2.8 (2.2-3.4) Grp2: B: 89 (20) F-B: -2.3 (-2.9--1.7) Between-group difference: Grp1: 5.1 (4.3-5.9) p <0.0001	Grp1: B: 127 (14) F-B: -1.6 (1) Grp2: B: 126 (14) F-B: 0.19 (0.6) Between-group difference: p NS Grp2: 4 (1-6) p 0.0055	
Bergenstal, 2010[14]	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.2) F: 7.7 (0.1) F-B: -0.9 (-1.1-0.7) Grp2: B: 8.6 (1.2) F: 7.2 (0.1) F-B: -1.5 (-1.7-1.4) Between-group difference:	Grp1: B: 87 (20) F-B: -0.8 (-1.4--0.1) Grp2: B: 89 (20) F-B: -2.3 (-2.9--1.7) Between-group difference: Grp1: 1.5 (0.7-2.4) p 0.0002	Grp1: B: 126 (14) F-B: 0.19 (0.6) Grp2: B: 126 (14) F-B: -3.6 (1) Between-group difference: Grp1: 4 (1-6) p 0.0055	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1: 0.6 (0.4-0.9) p <0.0001			
Bergenstal, 2012[15]	Grp1: Metformin + placebo Fixed (Stable dose of >/=1,500mg/day) Grp2: Metformin + sitagliptin + placebo Fixed (Stable dose of >/=1,500mg/day) Fixed (100mg QD) ITT: NR Followup (wks): 24	Grp1: B: 8.03 (0.83) F: 7.9 (0.2) F-B: -0.1 (0.08) Grp2: B: 7.94 (0.85) F: 7.2 (0.1) F-B: -0.89 (0.06)	Grp1: B: 91.1 (19) F-B: -0.5 (0.4) Grp2: B: 92.5 (19.7) F-B: -0.9 (0.3)		
Blonde, 2002[16]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Fixed Start: 10 mg bid	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.64 (1.44) F: 9.5 F-B: -0.11 Grp1-Grp2: 0.5	Grp1 B: 89.5 (16.9) F: 87.5 F-B: -2 Grp2 B: 88 (15.9) F: 88.5 F-B: 0.5 Grp1-Grp2: -2.5		
Blonde, 2002[16]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.42 (1.24) F: 7.9 F-B: -1.38 Grp1-Grp2: 1.77 p: <0.001			
Blonde, 2002[16]	Grp1: Metformin Varied Start: 500 mg , Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.41 (1.47) F: 7.9 F-B: -1.64 Grp1-Grp2: 2.03 p: <0.001			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Bolinder, 2012[17]	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin Fixed (10 mg) ITT: NR Followup (wks): 102	Grp1: B: 7.16 (0.53) F-B: 0.12 (-0.02-0.27) Grp2: B: 7.19 (0.44) F-B: -0.3 (-0.43-0.16) Between-group difference: Grp2: -0.42 (-0.62-0.22) p	Grp1: B: 90.9 (13.7) F-B: -2.12 (-2.97--1.27) Grp2: B: 92.1 (14.1) F-B: -4.54 (-5.43--3.66) Between-group difference: Grp2: -2.42 (-3.64--1.21) p	Grp1: B: 133.3 (13.7) F-B: 1.1 (-1.4-3.7) Grp2: B: 136.1 (13.8) F-B: -1.3 (-4.3-1.7)	Grp1: B: 71.9 (7.8) F-B: 1.5 (-0.6-3.6) p Grp2: B: 70.9 (10) F-B: 1.6 (-0.4-3.6) p
Borges, 2011[18]	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: No Followup (wks): 80	Grp1: B: 8.6 (0.9) F-B: -1.7 (0.1) Grp2: B: 8.6 (0.9) F-B: -1.9 (0.1)	Grp1: F-B: -3.37 Grp2: F-B: 1.42		
Bunck, 2009[19]	Grp1: Metformin + exenatide Fixed Mean: 2058 mg; Start: 5 ug b.i.d., Max: 20 micro g t.i.d. Grp2: Metformin + glargine Fixed Mean: 1798 mg; Start: 10 Units, Mean: 33.6	Grp1 B: 7.6 (0.1) F: 6.8 F-B: -0.8 (SD: 0.1) Grp2 B: 7.4 (0.1) F: 6.8 F-B: -0.7 (SD: 0.2) p: 0.55 Grp1-Grp2: -0.1	Grp1-Grp2: -4.6 (1.1) p: 0.0001		
Bunck, 2011[20]	Grp1: Metformin + exenatide Fixed (Mean: 2058 mg) Titrated (Max: 60 mcg) Grp2: Metformin + insulin glargine Fixed (Mean: 1798 mg) Titrated (Mean: 33.7 Iuinitial dose of 10 IU) AE collection method: Passive ITT: NR Followup (wks): 156	Grp1: B: 7.6 (0.1) F: 6.6 (0.2) Grp2: B: 7.4 (0.1) F: 6.9 (0.2) p0.186	Grp1: F-B: -5.7 (1.3) Grp2: F-B: 2.1 (1.3) Between-group difference: Grp1: -7.9 1.8 p <0.001		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Bunck, 2011[21]	Grp1: Metformin + exenatide Fixed (pre-enrollment dose) Titrated (Max: 60 ug) Grp2: Metformin + insulin glargine Fixed (pre-enrollment dose) Titrated (Mean: 33.7 IU) ITT: NR Followup (wks): 168	Grp1: B: 7.6 (0.1) F: 6.6 (0.2) p0.186 Grp2: B: 7.4 (0.1) F: 6.9 (0.2)	Grp1: B: 90.6 (2.1) F-B: -5.7 (1.3) Grp2: B: 92.4 (2.4) F-B: 2.1 (1.3) Between-group difference: Grp1: -7.9 1.8 p <0.001		
Campbell, 1994[22]	Grp1: Metformin Varied Start: 500 mg bid, Max: 3000 mg Grp2: Glipizide Varied Start: 5 mg, Max: 30 mg	Grp1 B: 11.46 (1.92) F: 8.64 (1.21) F-B: -2.57 Grp2 B: 11.75 (2.11) F: 9.72 (1.91) F-B: -1.93 Grp1-Grp2: -0.64 p: <0.05	Grp1 B: 78.2 (15.7) F: 76.23 F-B: -1.97 Grp2 B: 82.2 (16.8) F: 84.8 F-B: 2.67 Grp1-Grp2: -4.57 p: <0.001		
Cefalu, 2013[23]	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg)	Grp1: B: 7.8 (0.8) F-B: -0.81 (0.04) Grp2: B: 7.8 (0.8) F-B: -0.93 (0.04) Between-group difference: Grp2: -0.12 (-0.22-0.02)	Grp1: B: 86.6 (19.8) F-B: 0.7 (0.2) Grp2: B: 86.6 (19.3) F-B: -4 (0.2) Between-group difference: Grp2: -4.7 (-5.2--4.3)	Grp1: B: 129.5 (13.5) F-B: 0.2 (0.6) Grp2: B: 130 (12.4) F-B: -3.3 (0.6) Between-group difference: Grp2: -3.5 (-4.9-2.1)	Grp1: B: 73.5 F-B: 0.5 (8.3) Grp2: B: 74.2 F-B: -1.1 (8.5)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: No Followup (wks): 52				
Cefalu, 2013[23]	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT: No Followup (wks): 52	Grp1: B: 7.8 (0.8) F-B: -0.81 (0.04) Grp2: B: 7.8 (0.8) F-B: -0.82 (0.04) Between-group difference: Grp2: -0.01 (-0.11-0.09)	Grp1: B: 86.6 (19.8) F-B: 0.7 (0.2) Grp2: B: 86.8 (20) F-B: -3.7 (0.2) Between-group difference: Grp2: -4.4 (-4.8--3.9)	Grp1: B: 129.5 (13.5) F-B: 0.2 (0.6) Grp2: B: 130 (13.8) F-B: -4.6 (0.6) Between-group difference: Grp2: -4.8 (-6.2-3.4) p	Grp1: B: 73.5 F-B: 0.5 (8.3) Grp2: B: 74.6 F-B: -1.2 (8.7)
Charbonnel, 2006[24]	Grp1: Metformin Varied, glucose: , HbA1c: 7% - 10% Start: >=1500 mg D: 19 wks Grp2: Metformin + sitagliptin Varied; Fixed Start: >=1500 mg; Mean: 100 mg D: 19 wks	Grp1 B: 8.03 (0.82) F: 7.95 (1.1) F-B: -0.02 (CI: -0.15, 0.1) Grp2 B: 7.96 (0.81) F: 7.26 (0.97) F-B: -0.67 (CI: -0.77, -0.57) Grp1-Grp2: 0.65 (SE 0.08)	Grp1 F-B: 0.6-0.7 p: <0.05 Grp2 F-B: 0.6-0.7 p: <0.05 Grp1-Grp2: p=0.835		
Charpentier, 2001[25]	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Glimepiride Varied	Grp1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE: 0.14) Grp2	Grp1 B: 82.2 F: 81.46 F-B: -0.74 (2.58) Grp2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 1 mg, Max: 6 mg	B: 6.52 (1.13) F: 6.79 (1.43) F-B: 0.27 (SE: 0.09) Grp1-Grp2: -0.12 p: 0.369	B: 81 F: 81.78 F-B: 0.78 (2.98) Grp1-Grp2: -1.52		
Charpentier, 2001[25]	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Metformin + glimepiride Fixed; Varied Start: 850 mg tid; Start: 1 mg, Max: 6 mg	Grp1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE: 0.14) Grp2 B: 6.42 (1.08) F: 5.68 (0.99) F-B: -0.74 (SE: 0.8) Grp1-Grp2: 0.92 p: <0.001	Grp1 B: 82.2 F: 81.46 F-B: -0.74 (2.58) Grp2 B: 81.2 F: 81.8 F-B: 0.6 (2.86) Grp1-Grp2: -1.34		
Chawla, 2013[26]	Grp1: Metformin + pioglitazone Fixed (usual doses as that prior to the studyMean: 1830mg) Fixed (30mg) Grp2: Metformin + sitagliptin Fixed (usual doses as that prior to the studyMean: 1865.38) Fixed (100mg) ITT: No Followup (wks): 16	Grp1: B: 8.228 (0.822) F: 7.48 (0.662) F-B: -0.748 (0.35) p <0.0001 Grp2: B: 8.076 (0.722) F: 7.42 (0.661) F-B: -0.656 (0.21) p <0.0001 Between-group difference: p 0.268	Grp1: B: 72.68 (10.76) F-B: 0.9 Grp2: B: 72.1 (13.8) F-B: -0.58		
Chien, 2007[27]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean dose: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg, Max: 20 mg, Final mean dose: 19 mg D: 4 wks	Grp1 B: 8.88 (1.08) F: 8.98 F-B: 0.09 (SE: 0.37) p: NS Grp2 B: 8.69 (0.94) F: 9.21 F-B: 0.52 (SE: 0.24) p: 0.018			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1-Grp2: -0.43 (SE: 0.44)			
Chien, 2007[27]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1723 mg; Start: 10 mg, Max: 20 mg, Final mean: 17.2 mg D: 4 wks	Grp1-Grp2: -1.3 p: 0.005			
Chien, 2007[27]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5mg, Max: 10 mg, Final mean: 8.4 mg D: 4 wks	Grp1-Grp2: -1.34 p: 0.002			
Comaschi 2007[28]	Grp1: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3g; Start: 2.5 mg D: 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50%; Varied Start: 15 mg, Max: 30 mg; Unclear D: 22 wks; NR	Grp1 F-B: -1.29 p: 0.192 Grp2 F-B: -1.29 p: <0.001 Grp1-Grp2: 0.01 (SE: 0.27) p: 0.975			
Comaschi, 2007[28]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3 g; Start: 2.5 mg	Grp1 F-B: -0.99 p: <0.001 Grp2 F-B: -1.29 p: 0.192 Grp1-Grp2: 0.31 p: 0.054			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	D: 22 wks				
Comaschi, 2007[28]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50%; Varied, NR Start: 15 mg, Max: 30 mg; Unclear D: 22 wks;	Grp1 F-B: -0.99 p: <0.001 Grp2 F-B: -1.29 p: <0.001 Grp1-Grp2: 0.3 p: 0.043			
Davies, 2007[29]	Grp1: Metformin + NPH Varied NR; Start: 10, Mean: 0.58 IU/kg D: NR Grp2: Metformin + BHI 70/30 Varied NR; Start: 10 IU, Mean: 0.63 IU/kg D: NR	Grp1 B: 10 (2.2) F: 9.2 (1.4) F-B: -0.8 Grp2 B: 9 (1.1) F: 7.9 (1.1) F-B: -1.1 Grp1-Grp2: 0.3	Grp1-Grp2: 0.7		
DeFronzo, 1995[30]	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	Grp1 B: 8.9 F: 8.5 F-B: -0.4 (SE: 0.1) Grp2 B: 8.5 F: 8.7 F-B: 0.2 (SE: 0.1) Grp1-Grp2: -0.6 p: <0.001	Grp1 B: 92.6 (14.5) F: 87.8 F-B: -3.8 (SE: 0.2) p: <0.001 Grp2 F-B: -0.3 (SE: 0.2) p: NS Grp1-Grp2: -3.5		
DeFronzo, 1995[30]	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	Grp1 B: 8.9 F: 8.5 F-B: -0.4 (SE: 0.1) Grp2 B: 8.8 F: 7.1 F-B: -1.7 (SE: 0.1) Grp1-Grp2: 1.3 p: <0.001	Grp1 F-B: -3.8 (SE: 0.2) p: <0.001 Grp2 F-B: 0.4 (SE: 0.2) p: NS Grp1-Grp2: -4.2		
DeFronzo,	Grp1: Metformin	Grp1			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2009[31]	Fixed Grp2: Metformin + Saxagliptin Fixed NR; Mean: 2.5 mg	F-B: Grp2 F-B: -0.59 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.73 (SE: 0.1) (CI: 0.53, 0.92) p: <0.0001			
DeFronzo, 2009[31]	Grp1: Metformin Fixed Grp2: Metformin + Saxagliptin Fixed NR; Mean: 5 mg	Grp1 F-B: 0 Grp2 F-B: -0.69 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.83 (SE: 0.1) (CI: 0.63, 1.02) p: <0.0001			
DeFronzo, 2009[31]	Grp1: Metformin Fixed Grp2: Metformin+ Saxagliptin Fixed NR; Mean: 10 mg	Grp1 F-B: 0 Grp2 F-B: -0.58 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.72 (SE: 0.1) (CI: 0.52, 0.91) p: <0.0001			
Defronzo, 2010[32]	Grp1: Metformin + rosiglitazone Varied NR; Start: 4 mg, Max: 8 mg D: NR Grp2: Metformin + exenatide Varied Start: 0.010 mg, Max: 0.02 mg D: NR	Grp1 F-B: -1 (SD: 0.1) p: <0.05 Grp2 F-B: -0.9 (SD: 0.1) p: <0.05 Grp1-Grp2: -0.1 p: 0.72	Grp1 F-B: 1.5 (0.5) p: <0.05 Grp2 F-B: -2.8 (0.5) p: <0.05 Grp1-Grp2: 4.3 p: <0.001		
DeFronzo, 2012[33]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) ITT: No	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.5 (0.7) F-B: -1 (0.08)	Grp1: F-B: -0.7 Grp2: F-B: -0.7		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 26				
DeFronzo, 2012[33]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)	Grp1: F-B: -0.7 Grp2: F-B: -0.02		
DeFronzo, 2012[33]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.5 (0.7) F-B: -0.9 (0.1)	Grp1: F-B: -0.7		
DeFronzo, 2012[33]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.5 (0.7) F-B: -0.7 (0.07)	Grp1: F-B: -0.7		
DeFronzo, 2012[33]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp1: F-B: -0.7		
DeFronzo, 2012[33]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after	Grp1: B: 8.5 (0.7) F-B: -0.7 (0.07)	Grp2: F-B: -0.02		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)			
DeFronzo, 2012[33]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -0.7 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)	Grp2: F-B: -0.7		
DeFronzo, 2012[33]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -0.9 (0.1) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)	Grp2: F-B: -0.7		
DeFronzo, 2012[33]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -0.9 (0.1) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp2: F-B: -0.02		
DeFronzo, 2012[33]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg)	Grp1: B: 8.5 (0.7) F-B: -1 (0.08) Grp2:	Grp2: F-B: -0.02		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	B: 8.6 (0.7) F-B: -0.9 (0.06)			
DeFronzo, 2012[33]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -1 (0.08) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp2: F-B: -0.7		
Derosa, 2004[34]	Grp1: Metformin Varied Start: 1000 mg, Max: 1000 mg tid Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg bid	Grp1 B: 8.4 (1.0) F: 7 (0.9) F-B: -1.4 (CI: -5.7, -0.51) p: 0.01 Grp2 B: 8.5 (1.2) F: 6.9 (0.7) F-B: -1.6 (CI: -6.4, -0.47) p: 0.01 Grp1-Grp2: 0.2			
Derosa, 2005[35]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid; Start: 2 mg Grp2: Metformin + glimepiride Fixed Start: 500mg tid; Start: 4mg qday		Grp1 B: 74.2 (3.6) F: 68.3 (3) p: <0.01 F-B: -5.9 Grp2 B: 75.6 (4.2) F: 71.1 (3.2) p: <0.05 F-B: -4.5 Grp1-Grp2: -1.4		
Derosa, 2005[36]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid, Max: 500 mg tid;	Grp1 B: 8 (0.7) F: 6.8 (0.6) p: <0.01			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 4 mg, Max: 4 mg Grp2: Metformin + glimepiride Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 2 mg, Max: 2 mg	F-B: -1.2 Grp2 B: 7.9 (0.6) F: 7 (0.7) p: <0.05 F-B: -0.9 Grp1-Grp2: -0.3 (SE: 0.23)			
Derosa, 2009[38]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Pioglitazone Varied Start: 15 mg, Max: 45 mg D: 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9.2 (1.3) F: 8.2 (0.7) p: <0.01 F-B: -1 (0.7) p: <0.01 Grp1-Grp2: -0.1 (SE: 0.33)			
Derosa, 2009[38]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Metformin + pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 Grp1-Grp2: 1.0 (SE: 0.27)	BMI Grp1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% Grp2 B: 27.4 (1.6) F: 26.9 (1.3) F-B: -1.8% Grp1-Grp2: 0		
Derosa, 2009[38]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Metformin + glimepiride Fixed Start: 850 mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NR; 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9 (1.1) F: 7.8 (0.4) F-B: -1.2 (0.4) p: <0.01 Grp1-Grp2: 0.1 (SE: 0.29)	BMI Grp1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% Grp2 B: 27.1 (1.4) F: 28.4 (2.2) F-B: 4.8% p: <0.05 Grp1-Grp2: -1.8		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Derosa, 2009[38]	Grp1: Metformin + Pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos Grp2: Metformin + glimepiride Fixed; Varied, prespecified target dose Start: 850 mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NA; 3 mos	Grp1 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 Grp2 B: 9 (1.1) F: 7.8 (0.4) p: <0.01 F-B: -1.2 (0.4) p: <0.01 Grp1-Grp2: -0.9 (SE: 0.25)			
Derosa, 2010[39]	Grp1: Metformin + glibenclamide Mean: 1500 mg; Start: 7.5 mg, Max: 15 mg D: NR Grp2: Metformin + exenatide NR NR; Start: 10 mcg, Max: 20 mcg D: NR	Grp1 B: 8.9 (0.8) F: 7.1 (0.2) p:NS F-B: -1.8 p: <0.001 Grp2 B: 8.8 (0.7) F: 7.3 (0.3) F-B: -1.5 p: <0.001 Grp1-Grp2: -0.3 p: NS	Grp1 B: 82.4 (9.1) F: 86.7 (11.2) p: <0.05 F-B: 4.3 p: <0.05 Grp2 B: 82 (8.3) F: 74 (4.1) F-B: -8 p: <0.001 Grp1-Grp2: 12.3		
Derosa, 2011[40]	Grp1: Metformin + glimepiride Not specified Titrated (Max: 2mg tidstart 1mg tid) Grp2: Metformin + exenatide Not specified Titrated (Max: 10 ug bidstart 5 ug bid) ITT: No Followup (wks): 48	Grp1: B: 8.8 (0.8) F: 7.4 (0.2) F-B:p <0.01 Grp2: B: 8.7 (0.7) F: 7.5 (0.3) F-B:p <0.01 Between-group difference: p NS	Grp1: B: 81.4 (8.1) F: 80.5 (7.7) F-B:p >0.05 Grp2: B: 80.2 (7.5) F: 75.1 (6.5) F-B:p <0.001		
Derosa, 2012[41]	Grp1: Metformin + placebo Titrated (Mean: 2500 mg) Grp2: Metformin + sitagliptin Titrated (Mean: 2500 mg) Fixed (100mg daily) ITT: No Followup (wks): 48	Grp1: B: 8 (0.7) F: 7.3 (0.2) F-B:p <0.01 Grp2: B: 8.1 (0.8) F: 6.7 (0.1) F-B:p <0.001 Between-group	Grp1: B: 78.6 (6.7) F: 76.3 (5.2) F-B:p <0.05 Grp2: B: 78.4 (6.6) F: 75.9 (5) F-B:p <0.05		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		difference: p <0.05			
Derosa, 2013[42]	Grp1: Metformin + placebo Fixed (2500+/-500mg/day as previously determined during run-in period) Grp2: Metformin + sitagliptin Fixed (2500+/-500mg/day as previously determined during run-in period) Fixed (100mg) ITT: No Followup (wks): 48	Grp1: B: 8 (0.7) F: 7.3 (0.2) p<0.05 F-B:p <0.01 Grp2: B: 8.1 (0.8) F: 6.7 (0.1) F-B:p <0.001	Grp1: B: 78.6 (6.7) F: 76.3 (5.2) F-B:p <0.05 Grp2: B: 78.4 (6.6) F: 75.9 (5) F-B:p <0.05		
Derosa, 2013[43]	Grp1: Metformin + placebo Fixed (Mean: 2500 +/- 500mg titrated up during run-in for 8+/- 2 months) Grp2: Metformin + exenatide Fixed (Mean: 2500 +/- 500mg titrated up during run-in over 8+/- 2 months) Titrated (Max: 20 ug daily5ug b.i.d. for the first 4 wks and then 10 ug b.i.d. thereafter) ITT: No Followup (wks): 48	Grp1: B: 7.9 (0.6) F: 7.5 (0.3) F-B:p <0.01 Grp2: B: 8.1 (0.8) F: 6.9 (0.2) F-B:p <0.001 Between-group difference: p <0.05	Grp1: B: 90.5 (10.3) F: 88.2 (8.9) F-B:p <0.05 Grp2: B: 89 (9.7) F: 82.6 (5.2) F-B:p <0.001 Between-group difference: p <0.01	Grp1: B: 131.6 (6.1) F: 128.6 (5) F-B:p >0.05 Grp2: B: 132.5 (7.4) F: 125.7 (4.1) F-B:p <0.05 Between-group difference: p not statistically significant	
Diamant, 2010[44]	Grp1: Metformin + exenatide Not specified Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: No Followup (wks): 26	Grp1: F-B: -1.5 (0.06) Grp2: F-B: -1.4 (0.07) Between-group difference: Grp1: -0.18 0.08 (-0.34-0.02) p 0.031	Grp1: F-B: -3.2 Grp2: F-B: 1.1 Between-group difference: Grp1: -4.4 (-5--3.6)		
Diamant, 2010[44]	Grp1: Metformin + exenatide Not specified Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified Titrated (started at 10 IU per day but	Grp1: F-B: -1.5 Grp2: F-B: -1.4 Between-group difference:	Grp1: F-B: -2.5 (0.3) Grp2: F-B: 2.2 (0.3) Between-group difference:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: No Followup (wks): 26	Grp1: -0.18 0.08 (-0.34-0.02) p 0.031	Grp1: -4.7 0.4 (-5.4--4) p <0.001 p		
Einhorn, 2000[45]	Grp1: Metformin NR Grp2: Metformin + pioglitazone NR; Fixed NR; Start: 30 mg	Grp1 B: 9.75 (SE: 1.3) F-B: p: <0.05 Grp2 B: 9.86 (SE: 1.4) F-B: p: <0.05 Grp1-Grp2: -0.83 p: <0.05	Grp1 F-B: -1.36 Grp2 F-B: 0.95 Grp1-Grp2: -2.31		
Erdem, 2008[46]	Grp1: Metformin Varied, glucose: 110 mg/dL Start: 1000 mg, Max: 2000 mg D: every 2 wks until goal Grp2: Pioglitazone Varied, glucose: 110 mg/dL Start: 15 mg, Max: 45 mg D: every 2 wks until goal	Grp1 B: 6.74 (1.3) F: 6.15 (0.53) p: 0.02 F-B: -0.59 Grp2 B: 6.34 (1.2) p: 0.31 F: 5.6 (0.7) p: 0.01 F-B: -0.74 Grp1-Grp2: 0.15 (SE: 0.50)			
Erem, 2014[47]	Grp1: Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg) Grp2: Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT: No Followup (wks): 48	Grp1: B: 7.62 (1.06) F: 6.4 (0.7) F-B:p 0.001 Grp2: B: 8.03 (1.7) F: 6.46 (0.56) F-B:p 0.033			
Esposito, 2011[48]	Grp1: Metformin Titrated (Max: 1000mg twice dailyend of titration: 36% on 1500 mg/d and 64% on 2000 mg/d)	Grp1: B: 8.1 (1) F-B: -0.9 (0.5) Grp2:			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Pioglitazone + pioglitazone Titrated (Max: 45 mgend of titration period: 27% on 30 mg/d and 72% on 45 mg/d) Titrated (Max: 30-45mg daily) ITT: Yes Followup (wks): 24	B: 8 (1) F-B: -0.9 (0.5) Between-group difference: Grp1: 0 (-0.3-0.3)			
Esteghamati, 2014[49]	Grp1: Metformin Fixed (1000mg) Grp2: Pioglitazone Fixed (30mg) ITT: No Followup (wks): 12	Grp1: B: 66 (12.8) F: 57 (15.5) F-B: -9.1 (-12.6-5.6) p <0.001 Grp2: B: 65 (16.5) F: 57 (17.7) F-B: -7.9 (-12.2-3.5) p 0.001	Grp1: B: 74.34 (12.81) F: 74.49 (12.31) F-B: 0.15 (-0.86-0.56) p 0.672 Grp2: B: 77.01 (13.61) F: 77.74 (14.73) F-B: 0.18 (-0.84-1.21) p 0.258		
Feinglos, 2005[51]	Grp1: Metformin Fixed Start: at least 1000 mg Grp2: Metformin + glipizide Fixed Start: at least 1000 mg; Start: 2.5 mg	Grp1 B: 7.64 F: 7.46 (SE: 0.1) F-B: -0.19 Grp2 B: 7.45 F: 6.8 (SE: 0.1) F-B: -0.66 Grp1-Grp2: 0.47 p: <0.0002	Grp1 B: 90.8 (18.4) F: 89.1 F-B: -1.7 Grp2 B: 90 (18.7) F: 90.4 F-B: 0.4 Grp1-Grp2: -2.1 p: < 0.0001		
Ferrannini, 2013[52]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Empagliflozin Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) p Grp2: B: 7.88 F-B: -0.34 (-0.54-0.14)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) p Grp2: B: 83.5 F-B: -2.6 (-3.5--1.8)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) p Grp2: B: 131.9 F-B: -1.7 (-4.9-1.6)	
Ferrannini, 2013[52]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg	Grp1: B: 8.15	Grp1: B: 85.8	Grp1: B: 131.7	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	twice daily or the maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	F-B: -0.56 (-0.79-0.33) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	F-B: -1.3 (-2.3--0.3) Grp2: B: 83.5 F-B: -2.6 (-3.5--1.8)	F-B: 2 (-1.8-5.7) Grp2: B: 131.9 F-B: -1.7 (-4.9-1.6)	
Ferrannini, 2013[52]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[52]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Empagliflozin Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.99 F-B: -0.47 (-0.66-0.27)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[52]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.99 F-B: -0.47 (-0.66-0.27)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 131.6 F-B: 0.1 (-3.2-3.4)	
Ferrannini, 2013[52]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg)	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 83.4 F-B: -2.2 (-3.1--1.4)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: No Followup (wks): 90				
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (10 mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 7.88 F-B: -0.34 (-0.54-0.14) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 83.4 F-B: -2.2 (-3.1--1.4) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.6 F-B: 0.1 (-3.2-3.4) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (10 mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 7.88 F-B: -0.34 (-0.54-0.14) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 83.4 F-B: -2.2 (-3.1--1.4) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.6 F-B: 0.1 (-3.2-3.4) Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (10 mg) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg) ITT: No Followup (wks): 90	Grp1: B: 7.88 F-B: -0.34 (-0.54-0.14) Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp1: B: 83.4 F-B: -2.2 (-3.1--1.4) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.6 F-B: 0.1 (-3.2-3.4) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (25mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (25mg) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini,	Grp1: Empagliflozin	Grp1:	Grp1:	Grp1:	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2013[52]	Fixed (25 mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (25mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (25 mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) p Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[52]	Grp1: Empagliflozin Fixed (25 mg) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) p Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) p Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) p Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[52]	Grp1: Metformin + sitagliptin Not specified Fixed (100 mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 8.03 F-B: -0.4 (-0.6-0.2) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 88.6 F-B: -0.4 (-1.5-0.7) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 137.4 F-B: 1.8 (-1.5-5.2) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[52]	Grp1: Metformin + sitagliptin Not specified	Grp1: B: 8.03	Grp1: B: 88.6	Grp1: B: 137.4	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (100 mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	F-B: -0.4 (-0.6-0.2) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	F-B: -0.4 (-1.5-0.7) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	F-B: 1.8 (-1.5-5.2) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Fidan, 2011[53]	Grp1: Metformin Fixed (Max: 1700 mgtitrated after rz but before observational period - from 850 mg/d up to 850mg tid up at 10 days intervals) Grp2: Rosiglitazone Fixed (Max: 8 mgtitrated after rz but before 12-wk observational period - from 4 to 8 mg/d) ITT: NR Followup (wks): 12	Grp1: B: 7.8 (0.9) F: 6.6 (1) F-B:p <0.05 Grp2: B: 7.9 (0.8) F: 6.9 (1) p>0.05 F-B:p <0.05			
Fonseca, 2000[54]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 8 mg	Grp1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 Grp2 B: 8.9 (1.5) F: 8.12 F-B: -0.78 Grp1-Grp2: 1.2 p: <0.001	Grp1 F-B: -1.2 Grp2 F-B: 0.7 Grp1-Grp2: -1.9 p: 0.0001		
Fonseca, 2000[54]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg	Grp1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 Grp2 B: 8.9 (1.3) F: 8.34 F-B: -0.56 Grp1-Grp2: -1 p: <0.001	Grp1 F-B: -1.2 Grp2 F-B: 1.9 Grp1-Grp2: -3.1 p: 0.0001		
Fonseca, 2012[55]	Grp1: Metformin Titrated (Max: 2000 mg/duptitration	Grp1: B: 8.28 (0.077)	Between-group difference:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	from 1500 to 2000 mg/d) Grp2: Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT: No Followup (wks): 18	F: 7.9 (0.1) F-B: -0.35 (0.081) Grp2: B: 8.41 (0.076) F: 7.5 (0.1) F-B: -0.88 (0.076) Between-group difference: Grp2: -0.52 (-0.73-0.31) p <0.001	Grp1: -0.5 (-0.88--0.12) Grp2: 0.4 (-0.07-0.82)		
Forst, 2010[56]	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) ITT: No Followup (wks): 12	Grp1: B: 8.4 (0.7) F-B: 0.25 (0.1) Grp2: B: 8.2 (0.7) F-B: -0.68 Between-group difference: Grp2: -0.9 p <0.0001	Grp1: B: 93.1 (16.8) F-B: -0.84 Grp2: B: 90.5 (15) F-B: 0.73		
Forst, 2010[56]	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: No Followup (wks): 12	Grp1: B: 8.4 (0.7) F-B: 0.25 (0.1) Grp2: B: 8.5 (0.8) F-B: -0.48 (0.14) Between-group difference: Grp2: -0.75 (-1.02-0.48) p <0.001	Grp1: B: 93.1 (16.8) F-B: -0.84 Grp2: B: 90.7 (14.2) F-B: -0.57		
Forst, 2010[56]	Grp1: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met;	Grp1: B: 8.2 (0.7) F-B: -0.68 Grp2: B: 8.5 (0.8) F-B: -0.48 (0.14) Between-group difference:	Grp1: B: 90.5 (15) F-B: 0.73 Grp2: B: 90.7 (14.2) F-B: -0.57		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: No Followup (wks): 12	Grp1: -0.9 p <0.0001 Grp2: -0.75 (-1.02-0.48) p <0.001			
Forst, 2012[57]	Grp1: Metformin Not specified Grp2: Metformin + liraglutide Not specified Titrated (Max: 1.8 mg/dstarted at 0.6 mg/day and increased to max by 6 wks) ITT: No Followup (wks): 12	Grp1: B: 6.36 (0.37) F: 6.32 (0.29) Grp2: B: 6.32 (0.37) F: 5.77 (0.3) p<0.05 F-B:p <0.05	Grp1: B: 96.9 (17.5) F: 96.7 (18) F-B:p Grp2: B: 93.2 (17.1) F: 89.7 (16.6) p<0.05 F-B:p <0.05	Grp1: B: 129 (12) F: 128 (13) F-B:p Grp2: B: 131 (12) F: 128 (12) F-B:p	
Forst, 2014[58]	Grp1: Metformin + glimepiride Not specified Titrated (individually titrated in the range of 1-4mg to achieve best possible glycemic control as judged by the investigator) Grp2: Metformin + linagliptin Not specified Fixed (5mg) ITT: Yes Followup (wks): 12	Grp1: B: 57.7 (7.1) F-B: -8.2 (5.1) p <0.0001 Grp2: B: 56.8 (6.9) F-B: -6 (6) p <0.0001 Between-group difference: p NS	Grp1: B: 95.1 (21.7) F-B: 0.7 (2.5) Grp2: B: 89.6 (13.6) F-B: -1.2 (1.7)		
Gallwitz, 2011[59]	Grp1: Metformin + exenatide Fixed (Median: 2000mgcontinued at prestudy dose) Titrated (Max: 20 micrograms/daystart 5ugBID 4 w then 10ug) Grp2: Metformin + insulin aspart 70/30 Not specified Titrated (Mean: 28.4 IU/dayto reach glucose target of 5.0 -7.2 mmol/L; titrated “without a structured insulin dosing algorithm”) ITT: No Followup (wks):	Grp1: F-B: -1 Grp2: F-B: -1.14 Between-group difference: Grp1: 0.14 (-0.003-0.291)	Grp1: F-B: -4.1 (0.22) Grp2: F-B: 1 (0.22) Between-group difference: p <0.001		
Gallwitz,	Grp1: Metformin + glimepiride +	Grp1:	Grp1:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2012[60]	placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: No Followup (wks): 104	B: 7.69 (0.03) F-B: -0.36 (0.03) Grp2: B: 7.69 (0.03) F-B: -0.16 (0.03) Between-group difference: Grp2: 0.2 0.05 (0.09-0.3) p 0.0004	B: 87 (0.6) F-B: 1.3 (0.2) Grp2: B: 86 (0.7) F-B: -1.4 (0.2) Between-group difference: Grp2: -2.7 (-3.2--2.2) p <0.0001		
Garber, 2002[62]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.21 (1.09) F: 6.97 F-B: -1.24 Grp1-Grp2: 0.21	Grp1 F-B: -0.6 p: <0.05 Grp2 F-B: 1.7 Grp1-Grp2: 2.3		
Garber, 2002[62]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.18 (1.14) F: 6.65 F-B: -1.53 Grp1-Grp2: 0.5 p: <0.001	Grp1 F-B: -0.6 Grp2 F-B: 1.4 p: <0.05 Grp1-Grp2: -2		
Garber, 2002[62]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.25 (1.11) F: 6.77	Grp1 F-B: -0.6 Grp2 F-B: 1.9 p: <0.05 Grp1-Grp2: -2.5		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -1.48 Grp1-Grp2: 0.45 p: <0.001			
Garber, 2003[63]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 Grp2 B: 8.67 (1.4) F: 6.75 F-B: -1.9 Grp1-Grp2: 0.37	Grp1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 Grp2 B: 91 (16.0) F: 93 F-B: 2 p: NS Grp1-Grp2: -3.1		
Garber, 2003[63]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Grp1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 Grp2 B: 8.78 (1.5) F: 6.43 F-B: -2.27 Grp1-Grp2: -0.74 p: 0.0003	Grp1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 Grp2 B: 91.9 (17.4) F: 93.5 F-B: 1.6 p: NS Grp1-Grp2: -2.7		
Garber, 2006[64]	Grp1: Metformin + rosiglitazone Varied Start: 1500-2000 mg, Max: 2000 mg; Start: 4 mg, Max: 8 mg Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 2000 mg; Start: 5 mg, Max: 10 mg		Grp1 B: 94 F: 95.4 F-B: 1.4 Grp2 B: 92 F: 95 F-B: 3 Grp1-Grp2: -1.5 p: <0.001		
Garber, 2009[65]	Grp1: Glimepiride Varied, prespecified target dose Start: 2 mg, Max: 8 mg D: 2 Wks Grp2: Liraglutide Varied, prespecified target dose Start: 0.6 mg, Max: 1.2 mg	Grp1 F-B: 0.51 (SD: 1.2) Grp2 F-B: 0.84 (SD: 1.23) Grp1-Grp2: 0.62 (CI: 0.42, 0.83) p<0.0001	Grp1 F-B: 1 (0.5) Grp2 F-B: -2 (0.5) Grp1-Grp2: 3		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	D: 2 Wks				
Garber, 2009[65]	Grp1: Glimepiride Varied, prespecified target dose Start: 2 mg, Max: 8 mg D: 2 Wks Grp2: Liraglutide Varied, prespecified target dose Start: 0.6 mg, Max: 1.8 mg D: 2 Wks	Grp1 F-B: 0.51 (SD: 1.2) Grp2 F-B: 1.14 (SD: 1.24) Grp1-Grp2: 0.33 (CI: 0.13, 0.53) p: 0.0014	Grp1 F-B: 1 (0.5) Grp2 F-B: -2.5 (0.5) Grp1-Grp2: 3.5		
Garber, 2011[66]	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (1.1) F: 7.5 (0.15) F-B: -0.3 Grp2: B: 8.2 (1.1) F: 7.1 (0.1) F-B: -0.6 Between-group difference: Grp2: -0.31 (-0.54-0.08) p 0.0076	Grp1: B: 93.3 (19) F-B: 0.95 Grp2: B: 92.6 (20.85) F-B: -2.7 Between-group difference: Grp2: -3.65 (-4.44--2.86) p <0.0001	Grp1: B: 130 (16.1) F-B: -0.49 Grp2: B: 127.6 (14.3) F-B: -1.35 Between-group difference: Grp2: -0.86 (-3.18-1.46) p 0.46574	Grp1: F-B: 0.67 Grp2: F-B: 2.04 Grp2: 1.36 (-0.17-2.9) p 0.0821
Garber, 2011[66]	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (1.1) F: 7.5 (0.15) F-B: -0.3 Grp2: B: 8.2 (1.1) F: 6.9 (0.1) F-B: -0.9 Between-group difference: Grp2: -0.6 (-0.83-0.38) p <0.0001	Grp1: B: 93.3 (19) F-B: 0.95 Grp2: B: 92.1 (19) F-B: -1.89 Between-group difference: Grp2: -2.84 (-3.63--2.06) p <0.0001	Grp1: B: 130 (16.1) F-B: -0.49 Grp2: B: 128 (13.9) F-B: -2.37 Between-group difference: Grp2: -1.88 (-4.21-0.45) p 0.1135	Grp1: F-B: 0.67 Grp2: F-B: 0.92 Between-group difference: Grp2: 0.24 (-1.3-1.78) p 0.7589
Genovese, 2013[67]	Grp1: Metformin + placebo Fixed (2550 mg) Grp2: Metformin + pioglitazone Fixed (2550 mg) Fixed (45titrated from 30 mg to 45 mg in first four wks then fixed at 45 for 20	Grp1: B: 7.02 (0.46) F: 6.96 (0.74) F-B:p Grp2: B: 6.92 (0.42)	Grp1: B: 89 (17.2) F: 87.2 (17.2) F-B:p Grp2: B: 88.8 (14)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	wks) ITT: Yes Followup (wks): 24	F: 6.41 (0.65) F-B:p Between-group difference: p <0.001	F: 89.4 (14.7) F-B:p Between-group difference: p 0.32		
Genovese, 2013[68]	Grp1: Metformin Titrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response) Grp2: Pioglitazone + placebo Titrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response) ITT: No Followup (wks): 16	Grp1: B: 6.7 (0.7) F: 6.5 (0.7) F-B:p <0.01 Grp2: B: 6.9 (0.9) F: 6.5 (0.8) F-B:p <0.05 Between-group difference: p 0.36			
Goke, 2010[69]	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin Fixed (5 mg) ITT: No Followup (wks): 104	Grp1: B: 7.65 (0.04) F: 7.27 F-B: -0.41 (0.04) Grp2: B: 7.65 (0.04) F: 7.27 F-B: -0.35 (0.04) Between-group difference: Grp2: -0.05 0.06 (-0.17-0.06) p	Grp1: B: 88.6 (1) F-B: 1.3 (0.2) Grp2: B: 88.7 (0.9) F-B: -1.5 (0.2) Between-group difference: Grp2: -2.8 0.3 (-3.3--2.2) p		
Goldstein, 2003[70]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Fixed Start: 15 mg bid	Grp1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 Grp2 B: 8.9 (1.1) F: 8.5 (0.1) F-B: -0.4 Grp1-Grp2: 0.2	Grp1 B: 94.2 (16.7 F: 91.5 F-B: -2.7 (SE: 0.3) Grp2 B: 90 (17.4) F: 89.6 F-B: -0.4 (SE: 0.3) Grp1-Grp2: -2.3		
Goldstein,	Grp1: Metformin	Grp1	Grp1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2003[70]	Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 Grp2 B: 8.7 (1.2) F: 7.4 (0.1) F-B: -1.3 Grp1-Grp2: 1.06 p: <0.001	B: 94.2 (16.7) F: 91.5 F-B: -2.7 (SE: 0.3) Grp2 B: 95.1 (17.8) F: 94.8 F-B: -0.3 (SE: 0.3) Grp1-Grp2: -2.4 p: <0.001		
Goldstein, 2007[71]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Sitagliptin Varied, prespecified target dose Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -0.66 (CI: -0.83, -0.5) Grp1-Grp2: -0.47	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: 0		
Goldstein, 2007[71]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Sitagliptin Varied, prespecified target dose Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -0.66 (CI: -0.83, -0.5) Grp1-Grp2: -0.16	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: 0		
Goldstein, 2007[71]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -1.4 (CI: -1.56, -1.24) Grp1-Grp2: 0.58	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		
Goldstein, 2007[71]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Metformin + sitagliptin	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -1.9 (CI: -2.06, -	Grp1 F-B: significant reduction relative to baseline Grp2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Varied, prespecified target dose Start: 500 mg, Max: 2000 mg; Start: 50 mg, Max: 100 mg D: 3 wks; 1wk	1.74) Grp1-Grp2: 1.08	F-B: significant reduction relative to baseline		
Goldstein, 2007[71]	Grp1: Metformin Fixed Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -1.4 (CI: -1.56, -1.24) Grp1-Grp2: 0.27	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		
Goldstein, 2007[71]	Grp1: Metformin Fixed Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg; Start: 50 mg, Max: 100 mg D: 3 wks; 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -1.9 (CI: -2.06, -1.74) Grp1-Grp2: 0.77 (SE: 0.12)	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		
Gomez-Perez, 2002[72]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid	Grp1 B: 9.8 (SE: 0.3) F: 10.2 (SE: 0.3) F-B: 0.3 p: 0.2651 Grp2 B: 10.2 (SE: 0.2) F: 9.5 (SE: 0.3) F-B: -0.7 p: 0.052 Grp1-Grp2: 1 p: 0.0132			
Gomez-Perez, 2002[72]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg bid	Grp1 B: 9.8 (SE: 0.3) F: 10.2 (SE: 0.3) F-B: 0.3 p: 0.2651 Grp2 B: 9.75 (SE: 0.2) F: 8.6 (SE: 0.4)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -1.2 p: 0.008 Grp1-Grp2: 1.5 p: 0.0002			
Gupta, 2009[73]	Grp1: Metformin + ADA diet Varied, prespecified target dose Start: 500 mg, Max: 2000 mg D: every 1 wk increment by 500 mg Grp2: Pioglitazone + ADA diet Varied, glucose: FPG > 100 mg, HbA1c: 7.0% Start: 30 mg, Max: 45 mg D: 8 wks	Grp1 F-B: -0.24 (0.14) Grp2 F-B: -0.09 (0.13) Grp1-Grp2: -0.15 (SE: 0.22)	Grp1 F-B: -3.21 (0.7) Grp2 F-B: 2.15 (1.09) Grp1-Grp2: -5.36		
Gupta, 2009[73]	Grp1: Metformin + ADA diet Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day D: every 1 wk increment by 500 mg Grp2: Pioglitazone + PC diet Varied, glucose: FPG > 100 mg, HbA1c: 7% Start: 30 mg, Max: 45 mg D: 8 wks	Grp1 F-B: -0.24 (0.14) Grp2 F-B: -0.42 (0.17) Grp1-Grp2: 0.18 (SE: 0.23)	Grp1 F-B: -3.21 (0.7) Grp2 F-B: -2.59 (1.25) Grp1-Grp2: -0.62		
Gupta, 2013[75]	Grp1: Sitagliptin Titrated (Max: 200mg/day) Grp2: Glimepiride Titrated (Max: 4mg/day) ITT: NR Followup (wks): 24	Grp1: B: 8.03 (0.11) F: 7.26 (0.23) p<0.001 Grp2: B: 8.02 (0.11) F: 7.13 (0.24) p<0.001			
Haak, 2012[76]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8 (0.1) F-B: -0.6 (0.1) Grp2: B: 7.4 (0.1) F-B: -1.2 (0.1) Between-group difference: Grp2: -0.6 0.1 (-0.8-0.4) p <0.0001	Grp1: B: 79.9 (18.4) F-B: -0.7 (0.3) Grp2: B: 76.7 (16) F-B: -0.8 (0.3) Between-group difference: Grp2: -0.2 (-0.9-0.5) p 0.52		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Haak, 2012[76]	Grp1: Metformin Fixed (1000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8 (0.1) F-B: -0.6 (0.1) Grp2: B: 8.2 (0.1) F-B: -0.5 (0.1)	Grp1: B: 79.9 (18.4) F-B: -0.7 (0.3) Grp2: B: 79.1 (17.3) F-B: 0.2 (0.3)		
Haak, 2012[76]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8 (0.1) F-B: -0.6 (0.1) Grp2: B: 7.1 (0.1) F-B: -1.6 (0.1) Between-group difference: Grp2: -0.5 0.1 (-0.7-0.3) p <0.0001	Grp1: B: 79.9 (18.4) F-B: -0.7 (0.3) Grp2: B: 80.8 (19) F-B: -0.1 (0.3) Between-group difference: Grp2: 0.6 (-0.1-1.3) p 0.1		
Haak, 2012[76]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 7.6 (0.1) F-B: -1.1 (0.1) Grp2: B: 7.1 (0.1) F-B: -1.6 (0.1) Between-group difference: Grp2: -0.5 0.1 (-0.7-0.3) p <0.0001	Grp1: B: 80 (18.5) F-B: -0.5 (0.3) Grp2: B: 76.7 (16) F-B: -0.8 (0.3) Between-group difference: Grp2: -0.2 (-0.9-0.5) p 0.52		
Haak, 2012[76]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 7.6 (0.1) F-B: -1.1 (0.1) Grp2: B: 8.2 (0.1) F-B: -0.5 (0.1)	Grp1: B: 80 (18.5) F-B: -0.5 (0.3) Grp2: B: 80.8 (19) F-B: -0.1 (0.3) Grp2: 0.6 (-0.1-1.3) p 0.1		
Haak, 2012[76]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg)	Grp1: B: 7.6 (0.1) F-B: -1.1 (0.1) Grp2: B: 7.4 (0.1)	Grp1: B: 80 (18.5) F-B: -0.5 (0.3) Grp2: B: 79.1 (17.3)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: No Followup (wks): 24	F-B: -1.2 (0.1) Between-group difference: Grp2: -0.6 0.1 (-0.8-0.4) p <0.0001	F-B: 0.2 (0.3)		
Haak, 2012[76]	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8.2 (0.1) F-B: -0.5 (0.1) Grp2: B: 7.1 (0.1) F-B: -1.6 (0.1) Between-group difference: Grp2: -0.5 0.1 (-0.7-0.3) p <0.0001	Grp1: B: 79.1 (17.3) F-B: 0.2 (0.3) Grp2: B: 76.7 (16) F-B: -0.8 (0.3) Between-group difference: Grp2: -0.2 (-0.9-0.5) p 0.52		
Haak, 2012[76]	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8.2 (0.1) F-B: -0.5 (0.1) Grp2: B: 7.4 (0.1) F-B: -1.2 (0.1) Between-group difference: Grp2: -0.6 0.1 (-0.8-0.4) p <0.0001	Grp1: B: 79.1 (17.3) F-B: 0.2 (0.3) Grp2: B: 80.8 (19) F-B: -0.1 (0.3) Between-group difference: Grp2: 0.6 (-0.1-1.3) p 0.1		
Haak, 2013[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 78	Grp1: B: 8.47 (0.85) F-B: -1.25 (0.1) Grp2: B: 8.61 (0.87) F-B: -1.32 (0.1)			
Haak, 2013[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 78	Grp1: B: 8.47 (0.85) F-B: -1.25 (0.1) Grp2: B: 8.61 (0.96) F-B: -1.63 (0.1)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Haak, 2013[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 52	Grp1: B: 7.76 (1.1) F-B: -0.42 (0.76) Grp2: B: 7.95 (1.04) F-B: -0.63 (0.83)	Grp1: F-B: -0.4 (2.7) Grp2: F-B: -0.7 (3.2)		
Haak, 2013[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 52	Grp1: B: 7.76 (1.1) F-B: -0.42 (0.76) Grp2: B: 8.15 (1.15) F-B: -0.96 (1.05)	Grp1: F-B: -0.4 (2.7) Grp2: F-B: 0.2 (3)		
Hallsten, 2002[78]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid	Grp1 B: 6.9 (0.2) F: 6.2 (0.2) F-B: -0.7 p: <0.0001 Grp2 B: 6.8 (0.2) F: 6.5 (0.2) F-B: -0.3 p: <0.05 Grp1-Grp2: -0.4 p: NS	Grp1 B: 83.7 (7.9) F: 84.3 (3.5) F-B: 0.6 p: NS Grp2 B: 88.8 (10.8) F: 86.8 F-B: -2 p: <0.05 Grp1-Grp2: -2.6		
Hamann, 2008[79]	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Max: 2 g; Unclear D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Max: 2 g; Unclear D: 12 wks	Grp1 F-B: -0.78 (SE: 0.06) Grp2 F-B: -0.86 (SE: 0.06) Grp1-Grp2: 0.09 (CI: -0.08, 0.25)	Grp1 F-B: 2.7 (SE: 0.3) Grp2 F-B: 1.6 (SE: 0.3) Grp1-Grp2: 1.1 p: 0.0016		
Hanefeld, 2004[80]	Grp1: Metformin + sulfonylurea Varied; NR Start: 850 mg, Max: 850 mg tid; NR Grp2: Pioglitazone + sulfonylurea Varied; NR Start: 15 mg, Max: 45 mg; NR	Grp1 B: 8.8 (0.97) F: 7.45 (0.06) F-B: -1.36 Grp2 B: 8.82 (0.98) F: 7.61 (0.06) F-B: -1.2	Grp1 B: 85.3 (15.1) F: 88.1 F-B: 2.8 Grp2 B: 84.9 (14.5) F: 83.9 F-B: -1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1-Grp2: -0.16 p: 0.065	Grp1-Grp2: 3.8		
Hanefeld, 2007[81]	Grp1: Rosiglitazone Fixed Mean: 4 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1 F-B: -0.3 p: 0.0003 Grp2 F-B: -0.7 p: <0.0001 Grp1-Grp2: 0.4	Grp1 F-B: 1.75 Grp2 F-B: 1.9 Grp1-Grp2: -0.15		
Hanefeld, 2007[81]	Grp1: Rosiglitazone Fixed Mean: 8 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1 F-B: -0.5 p: <0.0001 Grp2 F-B: -0.7 p: <0.0001 Grp1-Grp2: 0.2 (SE: 0.24)	Grp1 F-B: 2.95 Grp2 F-B: 1.9 Grp1-Grp2: 1.05 p: 0.01		
Haring, 2014[82]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (25mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.9 (0.88) F: 7.77 (0.07) F-B: -0.13 (0.05) Grp2: B: 7.86 (0.87) F: 7.11 (0.06) F-B: -0.77 (0.05) Between-group difference: Grp2: -0.64 0.07 (-0.77-0.5) p <0.001	Grp1: B: 79.7 (18.6) F: 79.33 (1.28) F-B: -0.45 (0.17) Grp2: B: 81.6 (18.5) F: 79.51 (1.22) F-B: -2.08 (0.17) Between-group difference: Grp2: -1.63 0.24 (-2.11--1.15) p <0.001	Grp1: B: 128.6 (14.7) F: 128.5 (1) F-B: -0.4 (0.7) Grp2: B: 129.6 (14.1) F: 125 (0.9) F-B: -4.5 (0.7) Between-group difference: Grp2: -4.1 1 (-6.2-2.1) p <0.001	
Haring, 2014[82]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (10mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.9 (0.88) F: 7.77 (0.07) F-B: -0.13 (0.05) Grp2: B: 7.94 (0.79) F: 7.22 (0.05) F-B: -0.7 (0.05) Between-group difference: Grp2: -0.57 0.07 (-0.7-	Grp1: B: 79.7 (18.6) F: 79.33 (1.28) F-B: -0.45 (0.17) Grp2: B: 82.2 (19.3) F: 79.71 (1.27) F-B: -2.46 (0.17) Between-group difference: Grp2: -2.01 0.24 (-2.49--	Grp1: B: 128.6 (14.7) F: 128.5 (1) F-B: -0.4 (0.7) Grp2: B: 130 (15.1) F: 124.6 (1) F-B: -5.2 (0.7) Between-group difference: Grp2: -4.8 1 (-6.9-2.7) p	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		0.43) p <0.001	1.53) p <0.001	<0.001	
Henry, 2012[83]	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 9.14 (1.32) F: 7.79 (1.53) F-B: -1.35 (-1.53-1.18) Grp2: B: 9.21 (1.31) F: 7.13 (1.2) F-B: -2.05 (-2.23-1.88) Between-group difference: Grp1: 0.7 (0.45-0.94) p <0.0001	Grp1: B: 85.75 (19.93) F: 84.45 (19.67) F-B: -1.29 (-1.76--0.82) Grp2: B: 84.24 (19.51) F: 81.62 (18.88) F-B: -2.66 (-3.14--2.19) Between-group difference: Grp1: 1.37 (0.71-2.04) p <0.0001	Grp1: B: 127.9 (14.1) F-B: -1.8 (0.9) Grp2: B: 126.2 (13.9) F-B: -2.9 (0.9)	
Henry, 2012[83]	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mg Median: 2000 mgMax: 2000mg) Grp2: Dapagliflozin + placebo Fixed (5mg) ITT: No Followup (wks): 24	Grp1: B: 9.14 (1.32) F: 7.79 (1.53) p F-B: -1.35 (-1.53-1.18) Grp2: B: 9.14 (1.37) F: 7.96 (1.44) p F-B: -1.19 (-1.36-1.02) Between-group difference: Grp1: 0.7 (0.45-0.94) p <0.0001 Grp2: 0.86 (0.62-1.11) p <0.0001	Grp1: B: 85.75 (19.93) F: 84.45 (19.67) p F-B: -1.29 (-1.76--0.82) Grp2: B: 86.2 (21.13) F: 83.57 (20.85) F-B: -2.61 (-3.07--2.15) Between-group difference: Grp1: 1.37 (0.71-2.04) p <0.0001 Grp2: 0.05 (-0.61-0.72) p 0.8769	Grp1: B: 127.9 (14.1) F-B: -1.8 (0.9) Grp2: B: 128 (14.4) F-B: -4.2 (0.9)	
Henry, 2012[83]	Grp1: Dapagliflozin + placebo Fixed (5mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 9.14 (1.37) F: 7.96 (1.44) F-B: -1.19 (-1.36-1.02) Grp2: B: 9.21 (1.31) F: 7.13 (1.2)	Grp1: B: 86.2 (21.13) F: 83.57 (20.85) F-B: -2.61 (-3.07--2.15) Grp2: B: 84.24 (19.51) F: 81.62 (18.88) F-B: -2.66 (-3.14--2.19)	Grp1: B: 128 (14.4) F-B: -4.2 (0.9) Grp2: B: 126.2 (13.9) F-B: -2.9 (0.9)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -2.05 (-2.23-1.88) Between-group difference: Grp1: 0.86 (0.62-1.11) p <0.0001	Between-group difference: Grp1: 0.05 (-0.61-0.72) p 0.8769		
Henry, 2012[83]	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Dapagliflozin + placebo Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 9.03 (1.3) F: 7.6 (1.42) F-B: -1.44 (-1.59-1.29) Grp2: B: 9.03 (1.27) F: 7.59 (1.23) F-B: -1.45 (-1.59-1.31) p Between-group difference: Grp1: 0.01 (-0.2-0.22) p 0.9144 Grp2: 0.53 (0.32-0.74) p <0.0001	Grp1: B: 87.24 (19.42) F: 85.92 (19.1) F-B: -1.36 (-1.83--0.89) Grp2: B: 88.56 (19.72) F: 85.21 (18.86) F-B: -3.33 (-3.8--2.86) Between-group difference: Grp2: -1.97 (-2.64--1.3) p <0.0001	Grp1: B: 130.6 (15.2) F-B: -1.2 (1) Grp2: B: 127.6 (15.6) F-B: -3.3 (0.9)	
Henry, 2012[83]	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 9.03 (1.3) F: 7.6 (1.42) F-B: -1.44 (-1.59-1.29) Grp2: B: 9.1 (1.28) F: 7.1 (1) F-B: -1.98 (-2.13-1.83) Between-group difference: Grp1: 0.01 (-0.2-0.22) p 0.9144 Grp2: -0.54 (-0.75-0.33) p <0.0001	Grp1: B: 87.24 (19.42) F: 85.92 (19.1) F-B: -1.36 (-1.83--0.89) Grp2: B: 88.53 (19.33) F: 85.78 (18.67) F-B: -2.73 (-3.19--2.27) Between-group difference: Grp2: -1.37 (-2.03--0.71) p <0.0001	Grp1: B: 130.6 (15.2) F-B: -1.2 (1) Grp2: B: 127.8 (13.7) F-B: -4 (0.9	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Henry, 2012[83]	Grp1: Dapagliflozin + placebo Fixed (10 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 9.03 (1.27) F: 7.59 (1.23) p F-B: -1.45 (-1.59-1.31) p Grp2: B: 9.1 (1.28) F: 7.1 (1) p F-B: -1.98 (-2.13-1.83) p Between-group difference: Grp1: 0.53 (0.32-0.74) p <0.0001 Grp2: -0.54 (-0.75-0.33) p <0.0001	Grp1: B: 88.53 (19.33) F: 85.78 (18.67) F-B: -2.73 (-3.19--2.27) Grp2: B: 88.56 (19.72) F: 85.21 (18.86) F-B: -3.33 (-3.8--2.86) Between-group difference: Grp1: -1.37 (-2.03--0.71) p <0.0001 Grp2: -1.97 (-2.64--1.3) p <0.0001	Grp1: B: 127.8 (13.7) F-B: -4 (0.9) Grp2: B: 127.6 (15.6) F-B: -3.3 (0.9)	
Hermann, 1991[84]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Fixed; Varied Start: 3000 mg; Start: 3.5 mg, Max: 14 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 7.7 (1.1) F: 5.4 (0.9) F-B: -2.3 p: <0.001 Grp1-Grp2: 1.4	Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NS Grp2 B: 87.3 (15.6) F: 87.3 (15.9) F-B: 0 p: NS Grp1-Grp2: -0.4		
Hermann, 1991[84]	Grp1: Metformin + diet Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 3000 mg; Start: 10.5 mg, Max: 14 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 7.8 (1.4) F: 5.7 (0.8) F-B: -2.2 p: <0.001 Grp1-Grp2: 1.3	Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NS Grp2 B: 74.4 (11.4) F: 76 (11.8) F-B: 1.6 p: <0.001 Grp1-Grp2: -2		
Hermann, 1991[84]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glibenclamide Varied	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2	Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NS Grp2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 3.5 mg, Max: 10.5 mg	B: 6.6 (1.3) F: 5.3 (0.5) F-B: -1.3 p: <0.001 Grp1-Grp2: 0.4	B: 84.1 (13.2) F: 87.4 (14.8) F-B: 3.3 p: <0.01 Grp1-Grp2: 3.7		
Hermann, 1994[85]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 6.7 (SE: 0.3) F: 5.3 (SE: 0.1) F-B: -1.3 (SE: 0.2) p: 0.001 Grp1-Grp2: 0.4	Grp1 B: 78.6 (SE: 2.9) F: 78.8 (SE: 2.9) F-B: -0.8 (SE: 0.5) p: >0.1 Grp2 B: 82.6 (SE: 2.7) F: 86.2 (SE: 3.3) F-B: 2.8 (SE: 0.7) p: 0.001 Grp1-Grp2: -3.6		
Hermann, 1994[85]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 1000 mg, Max: 3000 mg; Start: 10.5 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 7.8 (SE: 0.3) F: 5.7 (SE: 0.3) F-B: -2.0 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.1 p: >0.1 across all treatment groups	Grp1 B: 78.6 (SE: 2.9) F: 78.8 (SE: 2.9) F-B: -0.2 (SE: 0.5) p: >0.1 Grp2 B: 80.2 (SE: 2.4) F: 81 (SE: 2.5) F-B: 0.7 (SE: 0.4) p: >0.1 Grp1-Grp2: -0.9		
Hermann, 1994[85]	Grp1: Metformin Varied Start: 1000 mg , Max: 3000 mg Grp2: Metformin + glyburide Fixed; Varied Start: 3000 mg; Start: 3.5 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 7.8 (SE: 0.3) F: 5.4 (SE: 0.3) F-B: -2.3 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.4 p: >0.1			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		across all treatment groups			
Hermann, 1994[85]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 2000 mg, Max: 3000 mg; Start: 7.0 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 8.4 (SE: 0.4) F: 6.2 (SE: 0.3) F-B: -2.2 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.3 p: >0.1 across all treatment groups			
Hermann, 1994[85]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 1500 mg; Start: 1.75 mg, Max: 5.25 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 6.8 (SE: 0.1) F: 5.6 (SE: 0.1) F-B: -1.2 (SE: 0.1) p: 0.001 Grp1-Grp2: 0.3 p: >0.1 across all treatment groups			
Hermans, 2012[86]	Grp1: Metformin Titrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination) Grp2: Metformin + saxagliptin Fixed (1500 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 7.8 (0.8) F-B: -0.38 (0.06) Grp2: B: 7.7 (0.9) F-B: -0.47 (0.06) Between-group difference: Grp2: -0.1 (-0.26-0.07) p 0.26			
Home,	Grp1: Metformin + rosiglitazone	Grp1	Grp1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2007[87]	Varied, HbA1c: <=7% Max: 2550 mg; Start: 4 mg, Max: 8 mg Grp2: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks; NR	F-B: -0.48 (CI: -0.59, -0.36) Grp2 F-B: -0.55 (CI: -0.66, -0.44) Grp1-Grp2: 0.07 (CI: -0.09, 0.23)	F-B: 2.3 (CI: 1.7, 2.9) Grp2 F-B: 1.1 (CI: 0.6, 1.6) (cohort1), -0.9 (CI: -1.4, -0.4) (cohort2) Grp1-Grp2 (cohort 1): 1.2 (CI: 0.4, 2) p: 0.003; Grp1-Grp2 (cohort 2): 4.3 (CI: 3.6, 5.1) p: <0.001		
Home, 2007[87]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7% Max: 2550 mg; Start: 4 mg, Max: 8 mg Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; Unclear D: 8 wks	Grp1 F-B: -0.48 (CI: -0.59, -0.36) Grp2 F-B: -0.55 (CI: -0.67, -0.44) Grp1-Grp2: 0.06 (CI: -0.09, 0.2)	Grp1 F-B: 2.3 (CI: 1.7, 2.9) Grp2 F-B: 3.4 (CI: 2.9, 4) Grp1-Grp2: -1.1		
Home, 2007[87]	Grp1:Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; Unclear	Grp1 F-B: -0.61 (CI: -0.7, -0.51) Grp2 F-B: -0.55 (CI: -0.67, -0.44) Grp1-Grp2: 0.06 (CI: -0.09, 0.2)	Grp1 F-B: -0.9 (CI: -1.4, -0.4) Grp2 F-B: 3.4 (CI: 2.9, 4) Grp1-Grp2: 4.3 (CI: 3.6, 5.1) p: <0.001		
Home, 2009[88]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7.0% Max: 2550 mg; Start: 4 mg, Max: 8 mg D: 8 wks; NR Grp2: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks	Grp1 F-B: -0.28 (SE: 0.03) Grp2 F-B: 0.01 (SE: 0.04) Grp1-Grp2: -0.29 (SE: 0.05) p: <0.0001	Grp1 F-B: 3.8 (SE: 0.24) Grp2 F-B: 0 (SE: 0.2) and -1.5 (SE: 0.2) Grp1-Grp2: 3.8		
Home, 2009[88]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7.0% Max: 2550 mg; Start: 4 mg, Max: 8 mg D: 8 wks; NR	Grp1 F-B: -0.28 (SE: 0.03) Grp2 F-B: -0.44 (SE: 0.03)	Grp1 F-B: 3.8 (SE: 0.24) Grp2 F-B: 4.1 (SE: 0.2)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; NR D: Unclear; NR	Grp1-Grp2: 0.16 (SE: 0.04) p: <0.0001	Grp1-Grp2: -0.3		
Home, 2009[88]	Grp1: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; NR D: Unclear; NR	Grp1 F-B: -0.18 (SE: 0.04) Grp2 F-B: -0.44 (SE: 0.03) Grp1-Grp2: 0.26 (SE: 0.05) p: <0.0001	Grp1 F-B: -1.5 (SE: 0.2) Grp2 F-B: 4.1 (SE: 0.2) Grp1-Grp2: -5.6 p: <0.001		
Iliadis, 2007[89]	Grp1: Metformin Varied, glucose: euglycemia Max: 1700 mg Grp2: Rosiglitazone Varied, glucose: euglycemia Max: 8 mg	Grp1 F-B: -1.7 (1.1) p: <0.001 Grp2 F-B: -1 (0.7) p: <0.01 Grp1-Grp2: -0.7 (SE: 0.59)	Grp1 F-B: -2.5 (3.5) p: <0.05 Grp2 F-B: -0.3 (3.3) p: NS Grp1-Grp2: -2.2		
Jadzinsky, 2009[90]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Wks Grp2: Saxagliptin Fixed	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -1.7 Grp1-Grp2: -0.3	Grp1 F-B: -1.6 Grp2 F-B: -1.1 Grp1-Grp2: -0.5		
Jadzinsky, 2009[90]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Wks Grp2: Metformin + saxagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 5mg D: 1 Wks	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -2.5 p: <0.0001 Grp1-Grp2: 0.5 p: <0.0001	Grp1 F-B: -1.6 Grp2 F-B: -1.8 Grp1-Grp2: 0.2		
Jadzinsky, 2009[90]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Wks Grp2: Metformin + saxagliptin Varied, prespecified target dose	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -2.5 p: <0.0001 Grp1-Grp2: 0.8 p: <0.0001	Grp1 F-B: -1.6 Grp2 F-B: -1.4 Grp1-Grp2: -0.2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 500 mg, Max: 1000 mg; Mean: 10 mg D: 1 Wks				
Jain, 2006[91]	Grp1: Pioglitazone Varied, glucose: FPG: 69-141 mg/dL Start: 15 mg, Max: 45 mg, Median: 45 mg D: 16 wks Grp2: Glyburide Varied, glucose: FPG: 69-141 mg/dL Start: 5 mg, Max: 15 mg, Median: 10 mg D: 16 wks	Grp1 B: 9.2 (1.26) F: 7.13 (1.26) F-B: -2.07 Grp2 B: 9.2 (1.20) F: 7.18 (1.20) F-B: -2.02 Grp1-Grp2: -0.05 p: 0.669	Grp1 F-B: 3.66 (6.14) p: <0.001 Grp2 F-B: 1.95 (5.35) Grp1-Grp2: 1.71		
Jonker, 2009[92]	Grp1: Metformin + glimepiride Fixed Start: 500 mg BD, Max: 1000 mg BD; NR D: 2 Wks Grp2: Pioglitazone + glimepiride Fixed Start: 15 mg OD, Max: 30 mg OD; NR D: 2 Wks	Grp1 B: 7 (0.1) F: 6.3 (SE: 0.1) p:0.146 F-B: -0.7 Grp2 B: 7.1 (0.2) F: 6.5 (SE: 0.1) F-B: -0.6 Grp1-Grp2: -0.1			
Kadoglou, 2011[93]	Grp1: Metformin Fixed (1700mg daily) Grp2: Metformin + rosiglitazone Fixed (500mg daily) Fixed (4mg daily) ITT: No Followup (wks): 24	Grp1: B: 7.56 (0.64) F: 6.87 (1.13) F-B:p <0.001 Grp2: B: 7.58 (0.6) F: 6.6 (1.1) F-B:p <0.001 Between-group difference: p discrepancy (see below)			
Kadowaki, 2013[94]	Grp1: Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500	Grp1: B: 8.3 (1) F: 8.5 (1.2) F-B: 0.3 (0.1-0.5)	Grp1: F-B: -0.29 p 0.048 Grp2: F-B: 0.42 p 0.006		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	mg/day) Grp2: Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT: No Followup (wks): 12	Grp2: B: 8.1 (0.9) F: 7.5 (0.9) F-B: -0.4 (-0.6-0.2) Between-group difference: Grp1: -0.7 (-0.9-0.5) p <0.001			
Kahn, 2006[95]	Grp1: Metformin Varied, glucose: <140 mg Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: <140 mg Start: 4 mg, Max: 8 mg	Grp1: Annualized slope: 0.14 (CI: 0.13, 0.16) Grp2: Annualized slope: 0.07 (CI: 0.06, 0.09) Grp2-Grp1: -0.13 (CI: -0.22, -0.05) p: 0.002	Grp1: Annualized slope: -0.3 (CI: -0.4, - 0.2) Grp2: Annualized slope: 0.7 (CI: 0.6, 0.8) Grp1-Grp2: 6.9 (CI: 6.3, 7.4) p: <0.001		
Kahn, 2006[95]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: Annualized slope: 0.14 (CI: 0.13, 0.16) Grp2: Annualized slope: 0.24 (CI: 0.23, 0.26)	Grp1: Annualized slope: -0.3 (CI: -0.4, - 0.2) Grp2: Annualized slope: -0.2 (CI: -0.3, 0.0)		
Kahn, 2006[95]	Grp1: Rosiglitazone Varied, glucose: <140 mg/dL Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1-Grp2: -0.42 (CI: -0.5, -0.33) p: <0.001	Grp1-Grp2: -2.5 (CI: -3.1, -2) p: <0.001		
Kaku, 2009[96]	Grp1: Metformin Varied Start: 500 mg, Max: 750 mg D: Unclear Grp2: Metformin + pioglitazone Varied Start: 500 mg, Max: 750 mg; Start: 15 mg, Max: 30 mg D: Unclear; 16 wks	Grp1 F-B: 0.25 (0.92) (CI: 0.06, 0.45) p: 0.012 Grp2 F-B: -0.67 (0.8) (CI: -0.84, -0.49) p: <0.0001 Grp1-Grp2: 0.92 (SE: 0.13)	Grp1 F-B: -0.47 Grp2 F-B: 1.68 Grp1-Grp2: -2.15		
Kaku,	Grp1: Glibenclamide	Grp1:			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2011[97]	Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 52	B: 9.18 (0.97) F: 8.2 (0.1) F-B:p Grp2: B: 9.32 (1.08) F: 7.7 (0.1) F-B:p Between-group difference: Grp2: -0.49 (-0.71-0.27) p			
Kaku, 2011[97]	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 52		Grp1: B: 65.4 (12.9) F-B: 1 Grp2: B: 66.2 (12.6) F-B: -0.8 Between-group difference: Grp2: -1.7 (-2.3--1.2) p		
Kato, 2009[98]	Grp1: Metformin Fixed Max: 500 mg Grp2: Pioglitazone Fixed Max: 15 mg	Grp1 B: 7.14 (1.4) F: 6.31 (0.9) p:<0.01 F-B: -0.83 Grp2 B: 7.37 (1.8) F: 6.32 (1.2) p:<0.01 F-B: -1.05 Grp1-Grp2: 0.22			
Kim, 2007[100]	Grp1: Metformin + glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 1000 mg; Start: 2 mg, Max: 7 mg Grp2: Rosiglitazone + glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 4 mg; Start: 2 mg, Max: 7 mg	Grp1 F-B: -1.1 (CI: -1.4, -0.8) p: <0.001 Grp2 F-B: -1.1 (CI: -1.5, -0.8) p: <0.001 Grp1-Grp2: 0 (SE: 0.24) p: 0.615	Grp1 F-B: -0.5 (CI: -1.2, -0.2) p: 0.187 Grp2 F-B: 1.3 (CI: 0.8, 1.9) p: <0.00 Grp1-Grp2: -1.8 p: <0.001		
Kim, 2014[101]	Grp1: Metformin Titrated (Max: 2500 mg/day)	Grp1: B: 7.8 (0.7)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + glimepiride Titrated (Max: 2000 mg/day) Fixed (1-8 mg/day) ITT: NR Followup (wks): 26	F: 7 (0.7) p F-B: -0.8 (-0.9-0.6) Grp2: B: 7.9 (0.8) F: 6.6 (0.7) p F-B: -1.2 (-1.3-1.1) p <0.0001 Between-group difference: Grp2: -0.4 (-0.6-0.3) p <0.001			
Kiyici, 2009[102]	Grp1: Metformin Fixed Mean: 850 mg Grp2: Rosiglitazone Fixed Mean: 4 mg	Grp1 B: 6.7 (0.9) F: 6.4 (0.6) p:> 0.05 F-B: -0.3 Grp2 B: 7.1 (0.9) F: 6.4 (0.6) p:0.008 F-B: -0.7 Grp1-Grp2: 0.4			
Kvapil, 2006[103]	Grp1: Metformin + aspart 70/30 Fixed; Varied, glucose: 5 - 8 mmol/L Mean: 1660 mg; Start: 0.2 U/kg, Mean: 0.30 U/kg Start freq: BID, Final freq: BID D: NA; Unclear Grp2: Metformin + glibenclamide Fixed; Varied Mean: 1660 mg; Start: 1.75 mg, Max: 10.5 mg, Mean: 6.58 mg D: NA; Unclear	Grp1 F-B: -1.7 Grp2 F-B: -1.7 Grp1-Grp2: 0.2 (SE: 0.15) p: >0.05	Grp1 F-B: 0.8 Grp2 F-B: 0.1 Grp1-Grp2: -0.66 (0.41) p: 0.1		
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + placebo Fixed (>=(2,000 mg/day [or >=1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose]))	Grp2: B: 7.9 (0.9) F-B: -0.73 (0.05)	Grp2: B: 85.4 (20.7) F-B: -3.7 (0.2) Between-group difference: Grp2: -2.9 (-3.4--2.3) p <0.001	Grp1: B: 128 (13.5) F-B: -1.8 (0.6) Grp2: B: 128.7 (13) F-B: -5.1 (0.6) Between-group difference:	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (100mg) ITT: No Followup (wks): 52			Grp1: -3.3 (-5.3-1.4) p no statistical comparison, not prespecified Grp2: -6.6 (-8.5-4.7) p <0.001	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 52	Grp2: B: 7.9 (0.9) F-B: -0.73 (0.05) Between-group difference: Grp2: 0 (-0.12-0.12) p	Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp2: -2.4 (-3--1.8) p <0.001	Grp2: B: 128 (13.5) F-B: -0.7 (0.6)	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 52	Grp1: F-B:p Grp2: B: 8 (0.9) F-B: -0.88 (0.05) p Between-group difference: Grp2: -0.15 (-0.27-0.03) p	Grp1: F-B:p Grp2: B: 87.6 (20.9) F-B: -1.2 (0.2)	Grp1: F-B:p Grp2: B: 128 (12.7) F-B: -3.5 (0.6) Between-group difference: Grp2: 2.9 (-4.5-1.3) p <0.001	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No	Grp1: B: 7.9 (0.9) F-B: -0.73 (0.05) Grp2: B: 8 (0.9) F-B: -0.88 (0.05) Between-group difference: Grp2: -0.15 (-0.27-0.03) p	Grp1: B: 87.6 (20.9) F-B: -1.2 (0.2) Grp2: B: 85.4 (20.7) F-B: -3.7 (0.2) Between-group difference: Grp2: -2.9 (-3.4--2.3) p <0.001	Grp1: F-B: Grp2: B: 128.7 (13) F-B: -4.7 (0.6) Between-group difference: Grp2: -4 (-5.6-2.4) p <0.001	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 52				
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 52	Grp1: B: 7.9 (0.9) F-B: -0.73 (0.05) Grp2: B: 7.9 (0.9) F-B: -0.73 (0.05) Between-group difference: Grp2: 0 (-0.12-0.12)	Grp1: B: 87.6 (20.9) F-B: -1.2 (0.2) Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp2: -2.4 (-3--1.8) p <0.001	Grp1: B: 128 (13.5) F-B: -0.7 (0.6) Grp2: B: 128 (12.7) F-B: -3.5 (0.6) Between-group difference: Grp2: 2.9 (-4.5-1.3) p <0.001	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.17 (0.06) Grp2: B: 7.9 (0.9) F-B: -0.82 (0.04) Between-group difference: Grp2: -0.66 (-0.8-0.52) p Statistical comparison vs PBO not performed (not pre-specified).	Grp1: B: 86.7 (22.5) F-B: -1.1 (0.2) Grp2: B: 87.6 (20.9) F-B: -1.1 (0.2) Between-group difference: Grp2: 0 (-0.6-0.6) p No statistical comparison made, not pre-specified	Grp1: B: 128 (12.7) F-B: 1.5 (0.8) Grp2: B: 128.7 (13) F-B: -5.1 (0.6) Between-group difference: Grp2: -6.6 (-8.5-4.7) p <0.001	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.17 (0.06) Grp2: B: 7.9 (0.9) F-B: -0.79 (0.04) Between-group difference: Grp2: -0.62 (-0.76-0.48) p <0.001	Grp1: B: 86.7 (22.5) F-B: -1.1 (0.2) Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp2: -2.5 (-3.1--1.9) p <0.001	Grp1: B: 128 (12.7) F-B: 1.5 (0.8) Grp2: B: 128 (12.7) F-B: -3.8 (0.6) Between-group difference: Grp2: -5.4 (-7.3-3.4) p <0.001	
Lavalle-Gonzalez,	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500	Grp1: B: 8 (0.9)	Grp1: B: 86.7 (22.5)	Grp1: B: 128 (12.7)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2013[104]	mg/day if unable to tolerate higher dose]) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 26	F-B: -0.17 (0.06) Grp2: B: 8 (0.9) F-B: -0.94 (0.04) Between-group difference: Grp2: -0.77 (-0.91-0.64) p <0.001	F-B: -1.1 (0.2) Grp2: B: 85.4 (20.7) F-B: -3.6 (0.2) Between-group difference: Grp2: -2.9 (-3.5--2.3) p <0.001	F-B: 1.5 (0.8) Grp2: B: 128 (13.5) F-B: -1.8 (0.6) Between-group difference: Grp2: -3.3 (-5.3-1.4) p no statistical comparison, not prespecified	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 26	Grp1: B: 7.9 (0.9) F-B: -0.82 (0.04) Grp2: B: 7.9 (0.9) F-B: -0.79 (0.04) Between-group difference: Grp1: -0.66 (-0.8-0.52) p Statistical comparison vs PBO not performed (not pre-specified). Grp2: -0.62 (-0.76-0.48) p <0.001	Grp1: B: 87.6 (20.9) F-B: -1.1 (0.2) Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp1: 0 (-0.6-0.6) p No statistical comparison made, not pre-specified Grp2: -2.5 (-3.1--1.9) p <0.001	Grp1: B: 128 (13.5) F-B: -1.8 (0.6) Grp2: B: 128 (12.7) F-B: -3.8 (0.6) Between-group difference: Grp1: -3.3 (-5.3-1.4) p no statistical comparison, not prespecified Grp2: -5.4 (-7.3-3.4) p <0.001	
Lavalle-Gonzalez, 2013[104]	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 26	Grp1: B: 7.9 (0.9) F-B: -0.82 (0.04) p Grp2: B: 8 (0.9) F-B: -0.94 (0.04) Between-group difference: Grp1: -0.66 (-0.8-0.52) p Statistical comparison vs PBO not performed (not pre-specified). Grp2: -0.77 (-0.91-	Grp1: B: 87.6 (20.9) F-B: -1.1 (0.2) p Grp2: B: 85.4 (20.7) F-B: -3.6 (0.2) Between-group difference: Grp1: 0 (-0.6-0.6) p No statistical comparison made, not pre-specified Grp2: -2.9 (-3.5--2.3) p <0.001	Grp1: B: 128 (13.5) F-B: -0.7 (0.6) p Grp2: B: 128.7 (13) F-B: -4.7 (0.6) Between-group difference: Grp2: -4 (-5.6-2.4) p <0.001	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		0.64) p <0.001			
Lawrence, 2004[105]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.04 (0.9) F: 6.9 (0.5) F-B: -1.12 (0.84) p: <0.01 Grp2 B: 7.43 (0.9) F: 6.62 (0.5) F-B: -0.81 (0.63) p: <0.01 Grp1-Grp2: -0.31 p: NS			
Leiter, 2005[106]	Grp1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks Grp2: Metformin + rosiglitazone Fixed; Varied, glucose: < 7 mmol/L Start: 1500 mg, Max: 1500 mg; Start: 4 mg, Max: 8 mg D: 8 wks	Grp1 F-B: -0.14 p: 0.93 Grp2 F-B: p: <0.001 Grp1-Grp2: -0.36 CI: 0.15 - 0.56	Grp1 F-B: no significant weight change Grp2 F-B: 1.6 (CI: 0.9, 2.3)		
List, 2009[107]	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (5mg) ITT: Yes Followup (wks): 12	Grp1: B: 7.6 (0.8) F-B: -0.73 (0.1) Grp2: B: 8 (0.9) F-B: -0.72 (0.09)		Grp1: B: 126 (13) F-B: -0.4 (12.4) Grp2: B: 127 (16) F-B: -6.4 (11.4)	Grp1: B: 68 (10) F-B: 1.1 (9.6) Grp2: B: 70 (10) F-B: -1 (8.9)
List, 2009[107]	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 12	Grp1: B: 7.6 (0.8) F-B: -0.73 (0.1) Grp2: B: 8 (0.8) F-B: -0.85 (0.11)		Grp1: B: 126 (13) F-B: -0.4 (12.4) Grp2: B: 126 (13) F-B: -2.9 (12.7)	Grp1: B: 68 (10) F-B: 1.1 (9.6) Grp2: B: 69 (8) F-B: -0.03 (8.9)
Madsbad, 2004[108]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.75 p: <0.0001 Grp1-Grp2: 0.01	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.74 p: 0.1544 Grp1-Grp2: 1.68		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed Mean: 0.75 mg				
Madsbad, 2004[108]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.045 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: 0.25 p: 0.1905 Grp1-Grp2: -0.49	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.03 p: 0.9602 Grp1-Grp2: 0.97		
Madsbad, 2004[108]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.225 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.34 p: 0.0877 Grp1-Grp2: -0.4	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -1.2 p: 0.0184 Grp1-Grp2: 2.14		
Madsbad, 2004[108]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.45 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.3 p: 0.1131 Grp1-Grp2: -0.44	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: 0.27 p: 0.5838 Grp1-Grp2: 0.67		
Madsbad, 2004[108]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.60 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.7 p: 0.0002 Grp1-Grp2: -0.04	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.39 p: 0.4391 Grp1-Grp2: 1.33		
Maffioli, 2013[109]	Grp1: Metformin + pioglitazone Fixed (2550 mg) Fixed (30 mg) Grp2: Metformin + glibenclamide Fixed (2550 mg) Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 68.3 (13.6) F: 61.7 (15.8) p F-B:p NS Grp2: B: 66.1 (15.8) F: 57.4 (19.1) p<0.05 F-B:p <0.05 Between-group	Grp1: B: 83.5 (9) F: 84.4 (9.2) p F-B:p NS Grp2: B: 83.1 (8.8) F: 83.6 (8.9) pNS F-B:p NS		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		difference: p <0.05			
Malone, 2003[110]	Grp1: Metformin + lispro 75/25 Varied; Varied, glucose: fasting and premeal glucose<7 mmol/L and 2-h post-prandial glucose <10 mmol/L Max: 2550 mg; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks; titrated throughout study period Grp2: Metformin + glibenclamide Varied; Varied, glucose: fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10 mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks; titrated throughout study period	Grp2 B: 9.17 (1.5) F: 7.29 (1) F-B: -1.87 (1.35) p: <0.001 Grp1 B: 9.27 (1.55) p: 0.181 F: 7.33 (1.14) p: 0.661 F-B: -1.98 (1.28) p: <0.001 Grp1-Grp2: 011 (SE: 0.33) p: 0.288	Grp1 B: 83 (15.2) F: 84 (15.1) F-B: 1 Grp2 B: 81.7 (15.7) F: 82.2 (15.4) p: 0.33 F-B: 0.5 Grp1-Grp2: 0.5		
Marre, 2002[111]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 20 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.88 (1.65) F: 7.58 F-B: -0.3 Grp1-Grp2: 0.1 p: NS	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 82.5 (15.4) F: 83.4 F-B: 0.9 Grp1-Grp2: -1.7		
Marre, 2002[111]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.89 (1.62) F: 6.69 F-B: -1.2 Grp1-Grp2: 1 p: <0.05	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 84.7 (15.1) F: 85.3 F-B: 0.6 Grp1-Grp2: -1.4		
Marre, 2002[111]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg	Grp1 B: 8.09 (1.84) F: 7.89	Grp1 B: 84.9 (17.6) F: 84.1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 10 mg	F-B: -0.2 Grp2 B: 7.62 (1.61) F: 6.72 F-B: -0.9 Grp1-Grp2: 0.7 p: <0.05	F-B: -0.8 Grp2 B: 83.1 (13.3) F: 84.1 F-B: 1 Grp1-Grp2: -1.8		
Moon, 2014[112]	Grp1: Metformin + glimepiride Fixed (Mean: 1426.5mgdose the same as met dose prior to study, discontinued if FBG was controlled at target level with glimepiride<=0.25mg/day) Titrated (Mean: 4.3Max: 8mgstarting 1mg/day, increased to 2mg/day at second week, up to 8mg/day at week 3,5,7 with target FBG of 90-130mg/dl as per the investigator's discretion) Grp2: Metformin + insulin glargine Fixed (Mean: 1365.1mgdose the same as met dose prior to study) Titrated (Mean: 22.8 unitsstarting at 0.2U/kg of body weight, titrated every 3 days by 2IU with target FBG of 90-130mg/dl as per the investigator's discretion; discontinued if FBG was controlled at target level with glargine<=8IU) ITT: No Followup (wks): 48	Grp1: B: 8.9 (1.3) F: 7.2 (1) F-B: -1.8 (1.2) Grp2: B: 8.8 (1.2) F: 7 (0.7) F-B: -1.8 (1.3) Between-group difference: p 0.43	Grp1: B: 66 (11.1) F-B: 0 (3.1) Grp2: B: 62.7 (9.1) F-B: 1.7 (2.7) Between-group difference: p 0.02		
Nakamura, 2000[113]	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Glibenclamide Fixed Start: 5 mg	Grp1 B: 7.7 (1.2) F: 6.8 (1.0) F-B: -0.9 p: <0.05 Grp2 B: 7.8 (1.1) F: 6.9 (1.2) F-B: -0.9 p: <0.05 Grp1-Grp2: 0			
Nakamura,	Grp1: Pioglitazone	Grp1			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2004[114]	Fixed Start: 30 mg Grp2: Glibenclamide Fixed Start: 5 mg	F-B: 1.7 (1) p: <0.05 Grp2 F-B: 1.5 (1.1) p: <0.05 Grp1-Grp2: 0.2 (SE: 0.62)			
Natali, 2004[115]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Rosiglitazone Fixed Start: 4 mg bid		Grp1 B: 80.4 (SEM 10.1) F: 80.9 F-B: 0.5 (0.5) p: NS Grp2 B: 77.3 (SEM 12.5) F: 76.7 F-B: -0.6 (0.4) p: NS Grp1-Grp2: 1.1 p: NS		
Nauck, 2007[116]	Grp1: Metformin + glipizide Varied; Varied, glucose: <6.1 mmol/l NR; Start: 5 mg, Max: 20 mg D: Unclear; 18 wks Grp2: Metformin + sitagliptin Varied; Fixed NR	Grp1-Grp2: -0.01 (CI: -0.09, 0.08)	Grp1-Grp2: -2.5 (CI: -3.1, -2) p: <.001		
Nauck, 2009[117]	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.1 (0.1) Grp2: B: 7.9 (0.8) F-B: -0.6 (0.1) Between-group difference: p <0.001	Between-group difference: Grp2: -0.3 (-0.9-0.4)		
Nauck, 2009[117]	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.1 (0.1) Grp2: B: 7.9 (0.7) F-B: -0.6 (0.1) Between-group difference: p <0.001	Between-group difference: Grp2: 0 (-0.7-0.7)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Nauck, 2011[118]	Grp1: Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2: Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT: No Followup (wks): 104	Grp1: B: 7.74 (0.9) F-B: -0.14 (-0.25-0.03) Grp2: B: 7.69 (0.9) F-B: -0.32 (-0.42-0.21) p Between-group difference: Grp2: -0.18 (-0.33-0.3) p 0.0211	Grp1: B: 87.6 F-B: 1.4 (0.9-1.8) Grp2: B: 88.4 F-B: -3.7 (-4.2--3.2) Between-group difference: Grp2: -5.1 (-5.7--4.4)	Grp1: B: 133.8 F-B: 1.2 (-0.4-2.8) Grp2: B: 132.8 F-B: -2.7 (-4.2-1.2) Between-group difference: Grp2: -3.9 (-6.1-1.7)	
Nauck, 2014[119]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.99 F-B: 0.03 (0.07) Grp2: B: 8.1 (1.1) F: 7.37 F-B: -0.61 (0.05) Between-group difference: Grp2: -0.64 p <0.001	Grp1: B: 87 (17) F-B: -1.67 (0.15) Grp2: B: 86 (17) F-B: -1.46 (0.15)	Grp1: B: 127 (13) F-B: -0.5 (0.7) Grp2: B: 129 (14) F-B: -0.8 (0.7) Between-group difference: p >0.05	Grp1: B: 73.7 (10.3) F-B: 0.3 (0.5) p >0.05 Grp2: B: 74.1 (10.9) F-B: -0.1 (0.5) p >0.05
Nauck, 2014[119]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.99 F-B: 0.03 (0.07) Grp2: B: 8.2 (1.1) F: 6.95 F-B: -1.01 (0.06) Grp2: -1.05 p <0.001	Grp1: B: 87 (17) F-B: -1.67 (0.15) Grp2: B: 87 (17) F-B: -3.23 (0.15) Between-group difference: p <0.001	Grp1: B: 128 (13) F-B: 1.1 (0.9) Grp2: B: 127 (13) F-B: -1.9 (0.7) Between-group difference: p <0.05	Grp1: F-B: -0.2 (0.7) Grp2: F-B: -0.1 (0.5) Between-group difference: p >0.05
Nauck, 2014[119]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.99 p F-B: 0.03 (0.07) p Grp2: B: 8.1 (1.1) F: 6.72 p	Grp1: B: 87 (17) F-B: -1.67 (0.15) Grp2: B: 86 (18) F-B: -2.63 (0.15) Between-group	Grp1: B: 128 (13) F-B: 1.1 (0.9) Grp2: B: 128 (14) F-B: -1.4 (0.7) Between-group	Grp1: F-B: -0.2 (0.7) p Grp2: F-B: 1.9 (0.5) Between-group difference: p <0.05

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -1.22 (0.05) p Between-group difference: Grp2: -1.26 p <0.001	difference: p <0.001	difference: p <0.05	
Nauck, 2014[119]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.37 p F-B: -0.61 (0.05) p Grp2: B: 8.2 (1.1) F: 6.95 p F-B: -1.01 (0.06) p Between-group difference: Grp1: -0.64 p <0.001 Grp2: -1.05 p <0.001	Grp1: B: 86 (17) F-B: -1.46 (0.15) Grp2: B: 86 (18) F-B: -2.63 (0.15) Between-group difference: p <0.001	Grp1: B: 128 (13) F-B: 1.1 (0.9) Grp2: B: 129 (14) F-B: -1.7 (0.7) Between-group difference: p <0.05	Grp1: F-B: -0.2 (0.7) Grp2: F-B: 2.6 (0.5) Between-group difference: p <0.001
Nauck, 2014[119]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.37 p F-B: -0.61 (0.05) p Grp2: B: 8.1 (1.1) F: 6.72 p F-B: -1.22 (0.05) p Between-group difference: Grp1: -0.64 p <0.001 Grp2: -1.26 p <0.001	Grp1: B: 86 (17) F-B: -1.46 (0.15) Grp2: B: 87 (17) F-B: -3.23 (0.15) Between-group difference: p <0.001	Grp1: B: 127 (13) F-B: -1.9 (0.7) p Grp2: B: 129 (14) F-B: -1.7 (0.7) p Between-group difference: p <0.05 p <0.05	Grp1: F-B: -0.1 (0.5) p Grp2: F-B: 1.9 (0.5) p Between-group difference: p >0.05 p <0.05
Nauck, 2014[119]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: Yes Followup (wks): 52	Grp1: F-B:p Grp2: B: 8.1 (1.1) F: 7.57 F-B: -0.39 (0.06)	Grp1: F-B:p Grp2: B: 86 (17) F-B: -1.53 (0.22)	Grp1: B: 127 (13) F-B: -1.9 (0.7) Grp2: B: 128 (14) F-B: -1.4 (0.7) p Between-group difference: p <0.05 p <0.05	Grp1: F-B: -0.1 (0.5) Grp2: F-B: 2.6 (0.5) Between-group difference: p >0.05 p <0.001

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Nauck, 2014[119]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 52	Grp1: F-B:p Grp2: B: 8.2 (1.1) F: 7.08 F-B: -0.87 (0.06) Between-group difference: Grp2: -0.47 (-0.63-0.31) p <0.001	Grp1: F-B:p Grp2: B: 87 (17) F-B: -3.03 (0.22) Between-group difference: Grp2: -1.5 p <0.001	Grp1: F-B:p Grp2: B: 129 (14) F-B: -0.8 (0.7) Between-group difference: p >0.05	Grp1: F-B:p Grp2: F-B: -0.3 (0.5)
Nauck, 2014[119]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 52	Grp1: F-B:p Grp2: B: 8.1 (1.1) F: 6.83 F-B: -1.1 (0.06) Between-group difference: Grp2: -0.71 (-0.87-0.55) p <0.001	Grp1: F-B:p Grp2: B: 86 (18) F-B: -2.6 (0.23) Between-group difference: Grp2: -1.07 p <0.05	Grp1: F-B:p Grp2: B: 127 (13) F-B: -0.5 (0.7)	Grp1: F-B:p Grp2: F-B: 2.1 (0.5) Between-group difference: p <0.001
Nauck, 2014[119]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 52	Grp1: B: 8.1 (1.1) F: 7.57 F-B: -0.39 (0.06) Grp2: B: 8.2 (1.1) F: 7.08 F-B: -0.87 (0.06) Between-group difference: Grp2: -0.47 (-0.63-0.31) p <0.001	Grp1: B: 86 (17) F-B: -1.53 (0.22) Grp2: B: 86 (18) F-B: -2.6 (0.23) Between-group difference: Grp2: -1.07 p <0.05	Grp1: F-B:p Grp2: B: 128 (14) F-B: -0.5 (0.7) p Between-group difference: p >0.05	Grp1: F-B:p Grp2: F-B: 2.4 (0.5) Between-group difference: p <0.001
Nauck, 2014[119]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes	Grp1: B: 8.1 (1.1) F: 7.57 F-B: -0.39 (0.06) Grp2: B: 8.1 (1.1) F: 6.83	Grp1: B: 86 (17) F-B: -1.53 (0.22) Grp2: B: 87 (17) F-B: -3.03 (0.22) Between-group	Grp1: B: 127 (13) F-B: -0.5 (0.7) Grp2: B: 128 (14) F-B: -0.5 (0.7) Between-group	Grp1: F-B: -0.3 (0.5) Grp2: F-B: 2.4 (0.5) Between-group difference: p <0.001

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 52	F-B: -1.1 (0.06) Between-group difference: Grp2: -0.71 (-0.87-0.55) p <0.001	difference: Grp2: -1.5 p <0.001	difference: p >0.05	
Oz Gul, 2010[120]	Grp1: Rosiglitazone Fixed (4 mg/day) Grp2: + placebo ITT: Yes Followup (wks): 12	Grp1: B: 7.3 (1.3) F: 6.2 (0.5) p0.003 F-B:p Grp2: B: 7.3 (0.9) F: 7.2 (0.7)			Grp1: F-B: -0.3 (0.5) Grp2: F-B: 2.1 (0.5) Between-group difference: p <0.001
Oz Gul, 2010[120]	Grp1: Pioglitazone Fixed (30 mg/day) Grp2: + placebo ITT: Yes Followup (wks): 12	Grp1: B: 7.6 (1.5) F: 6.5 (0.6) p<0.001 F-B:p Grp2: B: 7.3 (0.9) F: 7.2 (0.7) F-B:p			
Pavo, 2003[121]	Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.6 F: 7.1 F-B: -1.5 p: <0.0001 Grp2 B: 8.6 F: 7.3 F-B: -1.3 p: <0.0001 Grp1-Grp2: -0.2 p: 0.28	Grp1 B: 86.1 (15.6) F: 86.8 F-B: -0.7 (0.4) Grp2 B: 88.9 (15.9) F: 90.2 F-B: 2.4 Grp1-Grp2: -3.1 p: <0.0001		
Perez, 2009[123]	Grp1: Metformin Fixed Start: 850 mg Grp2: Pioglitazone Fixed	Grp1 F-B: -0.99 Grp2 F-B: -0.96 Grp1-Grp2: -0.03 (0.17)	Grp1 F-B: -1.28 Grp2 F-B: 1.64 Grp1-Grp2: -2.92		
Perez, 2009[123]	Grp1: Metformin Fixed Start: 850 mg	Grp1 F-B: -0.99 Grp2	Grp1 F-B: -1.28 Grp2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + pioglitazone Fixed	F-B: -1.83 p: <0.0001 Grp1-Grp2: 0.84 (SE: 0.17)	F-B: 0.69 Grp1-Grp2: -1.97		
Petrica, 2009[124]	Grp1: Metformin + rosiglitazone Fixed (1700 mg/day) Fixed (4 mg/day) Grp2: Metformin + glimepiride Fixed (1700 mg/day) Fixed (4 mg/day) ITT: No Followup (wks): 48	Grp1: B: 7.72 (1.2) F: 6.74 (0.81) p0.39 F-B:p Grp2: B: 7.58 (1.01) F: 7.06 (0.86) F-B:p			
Pfutzner, 2005[125]	Grp1: Pioglitazone Fixed Start: 45 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 6 mg	Grp1 B: 7.52 (0.85) F: 6.71 (0.89) F-B: -0.81 p: <0.05 Grp2 B: 7.44 (0.89) F: 6.83 (0.85) F-B: -0.61 p: <0.05 Grp1-Grp2: -0.2			
Pfutzner, 2011[126]	Grp1: Metformin + pioglitazone Fixed (1700 mg/d) Fixed (30 mg/d) Grp2: Metformin + glimepiride Fixed (1700 mg/d) Fixed (2mg/d) ITT: No Followup (wks): 24	Grp1: B: 7.3 (0.9) F: 6.5 (0.9) F-B: -0.8 (0.9) p <0.05 Grp2: B: 7.3 (0.8) F: 6.3 (0.8) F-B: -1 (0.9) p <00.05 Between-group difference: p NS	Grp1: B: 96.2 (17.5) F: 96.9 (17.8) F-B:p <0.05 Grp2: B: 94.1 (18) F: 94.8 (18.2) F-B:p <0.05		
Pfutzner, 2011[127]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: No Followup (wks): 76	Grp1: B: 9.43 (0.07) F-B: -1.79 (0.07) (-1.93-1.65) p Grp2: B: 9.61 (0.08)	Grp1: B: 82.8 (17.5) F-B: -1 Grp2: B: 83.1 (16.9) F-B: -0.3		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -1.55 (0.08) (-1.7-1.4)			
Pfutzner, 2011[127]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 76	Grp1: B: 9.43 (0.07) F-B: -1.79 (0.07) (-1.93-1.65) Grp2: B: 9.41 (0.07) F-B: -2.31 (0.07) (-2.44-2.18) p Between-group difference: Grp2: -0.52 0.1 (-0.71-0.33) p <0.0001	Grp1: B: 82.8 (17.5) F-B: -1 Grp2: B: 82.1 (16.3) F-B: -1.2		
Pfutzner, 2011[127]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 76	Grp1: B: 9.43 (0.07) F-B: -1.79 (0.07) (-1.93-1.65) p Grp2: B: 9.53 (0.07) F-B: -2.33 (0.07) (-2.46-2.2) p Between-group difference: Grp2: -0.54 0.1 (-0.73-0.35) p <0.0001	Grp1: B: 82.8 (17.5) F-B: -1 Grp2: B: 82.5 (16.9) F-B: -0.7		
Pfutzner, 2011[127]	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 76	Grp1: B: 9.61 (0.08) F-B: -1.55 (0.08) (-1.7-1.4) p Grp2: B: 9.41 (0.07) F-B: -2.31 (0.07) (-2.44-2.18) p Between-group difference: Grp2: -0.52 0.1 (-0.71-0.33) p <0.0001	Grp1: B: 83.1 (16.9) F-B: -0.3 Grp2: B: 82.5 (16.9) F-B: -0.7		
Pfutzner,	Grp1: Saxagliptin + placebo	Grp1:	Grp1:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2011[127]	Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 76	B: 9.61 (0.08) F-B: -1.55 (0.08) (-1.7-1.4) p Grp2: B: 9.53 (0.07) F-B: -2.33 (0.07) (-2.46-2.2) p Between-group difference: Grp2: -0.54 0.1 (-0.73-0.35) p <0.0001	B: 83.1 (16.9) F-B: -0.3 Grp2: B: 82.1 (16.3) F-B: -1.2		
Pratley, 2010[128]	Grp1: Metformin + sitagliptin Varied NR; Max: 100 mg D: NR Grp2: Metformin + liraglutide Varied, HbA1c: 7.5-10% NR; Start: 0.6 mg, Max: 1.2 mg D: NR	Grp1 F-B: -0.9 (CI: -1.03, -0.77) Grp2 F-B: -1.24 (CI: -1.37, -1.11) Grp1-Grp2: 0.34 (CI: 0.16, 0.51) p<0.0001	Grp1 F-B: -0.96 (CI: -1.5, -0.42) Grp2 F-B: -3.38 (CI: -3.91, -2.84) Grp1-Grp2: 2.42 (CI: 1.7, 3.14)		
Pratley, 2010[128]	Grp1: Metformin + sitagliptin Varied NR; Max: 100 mg D: NR Grp2: Metformin + liraglutide Varied, HbA1c: 7.5-10% Unclear; Start: 0.6 mg, Max: 1.8 mg D: NR	Grp1 F-B: -0.9 (CI: -1.03, -0.77) Grp2 F-B: -1.5 (CI: -1.63, -1.37) Grp1-Grp2: 0.6 (CI: 0.43, 0.77) p<0.0001	Grp1 F-B: -0.96 (CI: -1.5, -0.42) Grp2 F-B: -2.86 (CI: -3.39, -2.32) Grp1-Grp2: 1.9 (CI: 1.18, 2.61)		
Pratley, 2014[129]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -0.65 (0.094) Grp2: B: 8.5 F-B: -1.22 (0.094)	Grp1: B: 81.69 F-B: -0.8 (0.283) Grp2: B: 82.69 F-B: -0.57 (0.28)		
Pratley, 2014[129]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg)	Grp1: B: 8.5 F-B: -0.65 (0.094) Grp2: B: 8.43	Grp1: B: 81.69 F-B: -0.8 (0.283) Grp2: B: 81.82		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: Yes Followup (wks): 26	F-B: -1.55 (0.09)	F-B: 0.13 (0.29)		
Pratley, 2014[129]	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -0.65 (0.094) Grp2: B: 8.3 F-B: -0.52 (0.1)	Grp1: B: 81.69 F-B: -0.8 (0.283) Grp2: B: 86.57 F-B: -1.17 (0.268)		
Pratley, 2014[129]	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.39 F-B: -1.11 (0.092) Grp2: B: 8.43 F-B: -1.55 (0.09)	Grp1: B: 81.79 F-B: -1.25 (0.27) Grp2: B: 86.57 F-B: -1.17 (0.268)		
Pratley, 2014[129]	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.39 F-B: -1.11 (0.092) Grp2: B: 8.3 F-B: -0.52 (0.1)	Grp1: B: 81.79 F-B: -1.25 (0.27) Grp2: B: 81.82 F-B: 0.13 (0.29)		
Pratley, 2014[129]	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.39 F-B: -1.11 (0.092) Grp2: B: 8.5 F-B: -1.22 (0.094)	Grp1: B: 81.79 F-B: -1.25 (0.27) Grp2: B: 82.69 F-B: -0.57 (0.28)		
Pratley, 2014[129]	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -1.22 (0.094) Grp2: B: 8.3 F-B: -0.52 (0.1)	Grp1: B: 82.69 F-B: -0.57 (0.28) Grp2: B: 81.82 F-B: 0.13 (0.29)		
Pratley, 2014[129]	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin	Grp1: B: 8.43 F-B: -1.55 (0.09) Grp2:	Grp1: B: 86.57 F-B: -1.17 (0.268) Grp2:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (25mg qd) ITT: Yes Followup (wks): 26	B: 8.3 F-B: -0.52 (0.1	B: 81.82 F-B: 0.13 (0.29)		
Qiu, 2014[130]	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT: Yes Followup (wks): 18	Grp1: B: 7.7 (0.9) F: 7.6 (0.1) F-B: -0.01 (0.07) Grp2: B: 7.6 (0.9) F: 6.9 (0.1) F-B: -0.61 (0.07) Between-group difference: Grp2: -0.6 p <0.001	Grp1: B: 90.5 (18.1) F-B: -0.5 Grp2: B: 90.2 (19.1) F-B: -3.1 Between-group difference: Grp2: -2.6 p <0.001	Grp1: B: 128.6 (11) F-B: 3.3 (1.1) Grp2: B: 128.2 (12) F-B: -2.4 (1.1) Between-group difference: Grp2: -5.7 (-8.7-2.6) p	Grp1: F-B: 0 Grp2: F-B: 1.4
Qiu, 2014[130]	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT: Yes Followup (wks): 18	Grp1: B: 7.7 (0.9) F: 7.6 (0.1) F-B: -0.01 (0.07) Grp2: B: 7.6 (0.9) F: 7.2 (0.1) F-B: -0.45 (0.07) Between-group difference: Grp2: -0.44 p <0.001	Grp1: B: 90.5 (18.1) F-B: -0.5 Grp2: B: 91.2 (23.9) F-B: -2.6 Between-group difference: Grp2: -2.1 p <0.001	Grp1: B: 128.6 (11) F-B: 3.3 (1.1) Grp2: B: 131.1 (12.4) F-B: -2.1 (1.1) Between-group difference: Grp2: -5.4 (-8.4-2.3)	Grp1: F-B: 0 Grp2: F-B: 0.9
Ramachandran, 2004[131]	Grp1: Metformin Varied Start: 250 mg, Max: 850 mg Grp2: Pioglitazone Varied Start: 15 mg, Max: 30 mg	Grp1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: 0.05 Grp2 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: 0.01 Grp1-Grp2: 1.2	Grp1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 Grp2 B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 Grp1-Grp2: -0.4		
Ramachand	Grp1: Metformin	Grp1	Grp1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
ran, 2004[131]	Varied Start: 250 mg, Max: 850 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: <0.05 Grp2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 Grp1-Grp2: 1.1	B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 Grp2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 Grp1-Grp2: -2.5		
Ramachandran, 2004[131]	Grp1: Pioglitazone Varied Start: 15 mg, Max: 30 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: <0.01 Grp2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 Grp1-Grp2: -0.1	Grp1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 Grp2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 Grp1-Grp2: -2.9		
Raskin, 2007[132]	Grp1: Metformin + glargine Fixed; Varied, glucose: 4.4 - 6.1 mmol/L before breakfast and dinner NR; Start: 12 U/day, Mean: 0.57 IU/kg Start freq: QD, Final freq: QD Grp2: Metformin + aspart 70/30 Fixed; Varied, glucose: 4.4 - 6.1 mmol/L NR; Start: 12 IU/day, Mean: 0.91 IU/kg Start freq: BID, Final freq: BID	Grp1 F-B: -2.46 (SE: 1.6) Grp2 F-B: -2.89 (SE: 1.6) Grp1-Grp2: 0.43 (SE: 2.26) p: 0.035	Grp1 F-B: 3 (4.3) Grp2 F-B: 5.6 (4.6) Grp1-Grp2: -2.6 p: 0.0004		
Raz, 2008[180]	Grp1: Metformin Fixed NR Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg	Grp1 F-B: 0 (CI: -0.2, 0.3) Grp2 F-B: -1 (CI: -1.3, -0.7) p: <0.001 Grp1-Grp2: -1 (CI: -1.4, -0.6) p: <0.001	Grp1 F-B: -0.5 Grp2 F-B: -0.5 Grp1-Grp2: 0		
Reasner, 2011[133]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No	Grp1: B: 9.8 (1.8) F-B: -1.8 (-1.9-1.6) Grp2: B: 9.9 (1.8) F-B: -2.3 (-2.4-2.1)	Grp1: B: 97.6 (25.3) F-B: -1.2 (-1.7--0.6) Grp2: B: 95.4 (22.9) F-B: -1.1 (-1.7--0.6)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 44	Between-group difference: Grp2: -0.5 (-0.7-0.3) p <0.001			
Ridderstrale, 2014[134]	Grp1: Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(>=1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2: Metformin + empagliflozin Fixed ((ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT: No Followup (wks): 104	Grp1: B: 7.92 (0.86) F: 7.37 (7.31-7.43) F-B: -0.55 (-0.61-0.49) Grp2: B: 7.92 (0.81) F: 7.26 (7.31-7.43) p F-B: -0.66 (-0.72-0.6) Between-group difference: Grp2: -0.11 (-0.19-0.02) p <0.0001 (non-inferiority), 0.0153 (superiority)	Grp1: B: 83 (19.2) F: 84.1 (83.9-84.4) F-B: 1.3 (1.1-1.6) Grp2: B: 82.5 (19.2) F: 79.7 (83.9-84.4) F-B: -3.1 (-3.4--2.9) Between-group difference: Grp2: -4.5 (-4.8--4.1) p <0.0001	Grp1: B: 133.5 (16) F: 136 (135.2-136.8) F-B: 2.5 (1.7-3.4) Grp2: B: 133.4 (15.9) F: 130.4 (135.2-136.8) F-B: -3.1 (-3.9-2.2) Between-group difference: Grp2: -5.6 (-6.8-4.4) p <0.0001	
Rigby, 2009[135]	Grp1: Metformin + rosiglitazone Fixed Mean: 4 mg Grp2: Metformin + sitagliptin Fixed Mean: 100 mg	Grp1 B: 8.09 F: 7.53 F-B: -0.6 (CI: -0.83, -0.32) p: <0.0001 Grp2 B: 8.19 F: 7.79 F-B: -0.4 (CI: -0.64, -0.13) p: 0.0087 Grp1-Grp2: -0.2	Grp1 F-B: 0.26 p: 0.5935 Grp2 F-B: -1.15 p: 0.0008 Grp1-Grp2: 1.41		Grp1: F-B: 0.59 (9.8) Grp2: F-B: -1.36 (9.2)
Robbins, 2007[136]	Grp1: Metformin + glargine Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg tid, Max: 1000 mg tid, Mean: 1636 mg; Mean: 0.6 U/kg Start: QD, Final: QD Grp2: Metformin + insulin lispro 50/50 Fixed; Varied, glucose: <6.7 mmol/L Start: 500 mg tid, Max: 1000 mg tid, Mean: 1641 mg; Mean: 0.7 U/kg Start	Grp1 F-B: -0.4 (0.9) Grp2 F-B: -0.7 (0.9) p: <0.001 Grp1-Grp2: 0.3 (SE: 0.32) p: <0.001	Grp1 B: 88.1 (19) F: 87.6 (19.3) p: 0.04 F-B: -0.5 Grp2 B: 89.1 (20.4) F: 90 (20.5) p: <0.001 F-B: 0.9 Grp1-Grp2:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	freq: NR, Final freq: tid		-1.4 p: <0.001		
Roden, 2013[137]	Grp1: Sitagliptin Fixed (100mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.87 (0.85) F: 7.21 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Between-group difference: Grp2: 0 (-0.15-0.14) p 0.9697	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 77.8 (18) F: 75.32 (76.78-82.18) F-B: -2.48 (-2.82--2.14) Between-group difference: Grp2: -2.67 (-3.15--2.18) p <0.0001	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 133 (16.6) F: 129.5 (130.4-135) F-B: -2.9 (-4.5-1.3) Between-group difference: Grp2: -3.4 (-5.7-1.2) p 0.0031	Grp1: F-B: 0.22 (9.53) Grp2: F-B: 0.02 (8.77)
Roden, 2013[137]	Grp1: Sitagliptin Fixed (100mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.86 (0.88) F: 7.2 (7.08-7.33) F-B: -0.78 (-0.88-0.67) Between-group difference: Grp2: -0.12 (-0.26-0.03) p 0.106	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 78.4 (18.7) F: 76.08 (76.78-82.18) F-B: -2.26 (-2.6--1.92) Between-group difference: Grp2: -2.45 (-2.93--1.96) p <0.0001	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 129.9 (17.5) F: 126.7 (130.4-135) F-B: -3.7 (-5.3-2.1) Between-group difference: Grp2: -4.2 (-6.5-2) p 0.0003	Grp1: F-B: 0.22 (9.53) Grp2: F-B: -0.25 (8.63)
Roden, 2013[137]	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.86 (0.88) F: 7.2 (7.08-7.33) F-B: -0.78 (-0.88-0.67)	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 78.4 (18.7) F: 76.08 (76.78-82.18) F-B: -2.26 (-2.6--1.92) Between-group difference:	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 129.9 (17.5) F: 126.7 (130.4-135) F-B: -3.7 (-5.3-2.1) Between-group difference:	Grp1: F-B: 0.22 (9.53) Grp2: F-B: 0.02 (8.77)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Between-group difference: Grp2: -0.12 (-0.26-0.03) p 0.106	Grp2: -2.45 (-2.93--1.96) p <0.0001	Grp2: -4.2 (-6.5-2) p 0.0003	
Roden, 2013[137]	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.87 (0.85) F: 7.21 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Between-group difference: Grp2: 0 (-0.15-0.14) p 0.9697	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 77.8 (18) F: 75.32 (76.78-82.18) F-B: -2.48 (-2.82--2.14) Between-group difference: Grp2: -2.67 (-3.15--2.18) p <0.0001	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 133 (16.6) F: 129.5 (130.4-135) F-B: -2.9 (-4.5-1.3) Between-group difference: Grp2: -3.4 (-5.7-1.2) p 0.0031	Grp1: F-B: 0.22 (9.53) Grp2: F-B: -0.25 (8.63)
Rosenstock, 2006[138]	Grp1: Metformin Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Rosiglitazone Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 4 mg, Max: 8 mg, Mean: 7.7 mg D: 32 wks	Grp1 B: 8.8 (1.0) F: 7.0 (1.0) F-B: -1.8 Grp2 B: 8.8 (1.0) F: 7.2 (1.0) F-B: -1.6 Grp1-Grp2: -0.2 (SE 0.20)	Grp1 F-B: Median: -2.2 (IQR: -5.5, -0.5) Grp2 F-B: Median: 1.7 (IQR: -1.2, - 4.5)		
Rosenstock, 2006[138]	Grp1: Metformin Varied, mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 D: 32 wks Grp2: Metformin + rosiglitazone Varied, mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean:	Grp1 B: 8.8 (1.0) F: (1.0) F-B: -1.8 Grp2 B: 8.9 (1.1) F: 6.6 (1.0) F-B: -2.3 Grp1-Grp2: 0.5 (SE: 0.20) p: 0.008	Grp1 F-B: Median: -2.2 (IQR: -5.5, -0.5) Grp2 F-B: Median: 0.05 (IQR: -3.45, 3)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	1799 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2 mg D: 32 wks				
Rosenstock, 2010[139]	Grp1: Pioglitazone + placebo Fixed (30mg qd) Grp2: Alogliptin + placebo Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.76 (1.005) F-B: -1.15 (0.083) Grp2: B: 8.8 (0.988) F-B: -0.96 (0.081	Grp1: F-B: 2.19 (0.302) Grp2: F-B: -0.29 (0.291)		
Rosenstock, 2012[140]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.83 (0.96) F: 7.1 (0.85) F-B: -0.76 (0.992) Between-group difference: p <0.001	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87.7 (15.49) F-B: -2.6 (2.3) Between-group difference: p <0.001	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 128.7 (13.4) F-B: -0.8 (1.4)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 71 (12.4) F-B: -0.2 (1.1)
Rosenstock, 2012[140]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.61 (0.8) F: 6.9 (0.68) F-B: -0.7 (0.72) Between-group difference: p <0.001	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87.7 (17.22) F-B: -2.7 (3) Between-group difference: p <0.001	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 126.5 (13.3) F-B: 1 (1.3)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 70.8 (9.9) F-B: 0.6 (1)
Rosenstock, 2012[140]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615)	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87 (18) F-B: -0.6 (3) Between-group difference:	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 124.3 (11.1) F-B: -2.1 (1.8)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 72.9 (10.8) F-B: -1.7 (0.9)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Between-group difference: p <0.001	p NS		
Rosenstock, 2012[140]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.69 (1.02) F: 6.8 (0.82) F-B: -0.92 (0.695) Between-group difference: p <0.001	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87.8 (15.79) F-B: -3.4 (2.8) Between-group difference: p <0.001	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 126.1 (11.6) F-B: -4.9 (1.5)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 72.6 (10.5) F-B: -1.7 (1.2)
Rosenstock, 2012[140]	Grp1: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2: Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Grp2: B: 7.69 (1.02) F: 6.8 (0.82) F-B: -0.92 (0.695) Between-group difference: p <0.001 p <0.001	Grp1: B: 87 (18) F-B: -0.6 (3) Grp2: B: 87.8 (15.79) F-B: -3.4 (2.8) Between-group difference: p NS p <0.001	Grp1: B: 128.7 (13.4) F-B: -0.8 (1.4) Grp2: B: 126.1 (11.6) F-B: -4.9 (1.5)	Grp1: B: 72.9 (10.8) F-B: -1.7 (0.9) Grp2: B: 72.6 (10.5) F-B: -1.7 (1.2)
Rosenstock, 2012[140]	Grp1: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2: Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Grp2: B: 7.61 (0.8) F: 6.9 (0.68) F-B: -0.7 (0.72) Between-group difference: p <0.001 p <0.001	Grp1: B: 87 (18) F-B: -0.6 (3) Grp2: B: 87.7 (15.49) F-B: -2.6 (2.3) Between-group difference: p NS p <0.001	Grp1: B: 128.7 (13.4) F-B: -0.8 (1.4) Grp2: B: 124.3 (11.1) F-B: -2.1 (1.8)	Grp1: B: 72.9 (10.8) F-B: -1.7 (0.9) Grp2: B: 70.8 (9.9) F-B: 0.6 (1
Rosenstock	Grp1: Metformin + sitagliptin	Grp1:	Grp1:	Grp1:	Grp1:

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
, 2012[140]	Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2: Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT: Yes Followup (wks): 12	B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Grp2: B: 7.83 (0.96) F: 7.1 (0.85) F-B: -0.76 (0.992) Between-group difference: p <0.001 p <0.001	B: 87 (18) F-B: -0.6 (3) Grp2: B: 87.7 (17.22) F-B: -2.7 (3) Between-group difference: p NS p <0.001	B: 128.7 (13.4) F-B: -0.8 (1.4) Grp2: B: 126.5 (13.3) F-B: 1 (1.3)	B: 72.9 (10.8) F-B: -1.7 (0.9) Grp2: B: 71 (12.4) F-B: -0.2 (1.1)
Rosenstock, 2013[142]	Grp1: Metformin + placebo Not specified Grp2: Metformin + sitagliptin Not specified Fixed (100mg) ITT: Yes Followup (wks): 12	Grp1: F-B: 0.15 (0-0.3) Grp2: F-B: -0.45 (-0.65-0.25) p Between-group difference: p <0.0001	Grp1: F-B: -1.2 (-1.8--0.5) Grp2: F-B: -2.7 (-3.4--2.1) Between-group difference:p p â‰¤0.001	Grp1: F-B: -2.23 (14.84) Grp2: F-B: -8.52 (23.83)	
Rosenstock, 2013[142]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (10mg) ITT: Yes Followup (wks): 12	Grp1: F-B: 0.15 (0-0.3) p Grp2: F-B: -0.56 (-0.71-0.41) p Between-group difference: p <0.0001	Grp1: F-B: -1.2 (-1.8--0.5) Grp2: F-B: -2.6 (-3.2--2) Between-group difference: p â‰¤0.001	Grp1: F-B: -2.23 (14.84) Grp2: F-B: -4.39 (13.09	
Rosenstock, 2013[142]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (25mg) ITT: Yes Followup (wks): 12	Grp1: F-B: 0.15 (0-0.3) Grp2: F-B: -0.55 (-0.7-0.4) Between-group difference: p <0.0001	Grp1: F-B: -1.2 (-1.8--0.5) Grp2: F-B: -0.8 (-1.5--0.2) Between-group difference:	Grp1: F-B: -2.23 (14.84) Grp2: F-B: -1.79 (11.65)	
Rosenstock, 2013[142]	Grp1: Metformin + sitagliptin Not specified Fixed (100mg) Grp2: Metformin + empagliflozin Not specified	Grp1: F-B: -0.45 (-0.65-0.25) Grp2: F-B: -0.55 (-0.7-0.4)	Grp1: F-B: -0.8 (-1.5--0.2) Grp2: F-B: -2.6 (-3.2--2) Between-group	Grp1: F-B: -1.79 (11.65) Grp2: F-B: -4.39 (13.09)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (25mg) ITT: Yes Followup (wks): 12	Between-group difference: p <0.0001 p <0.0001	difference: p pâ‰¤0.001		
Rosenstock, 2013[142]	Grp1: Metformin + sitagliptin Not specified Fixed (100mg) Grp2: Metformin + empagliflozin Not specified Fixed (10mg) ITT: Yes Followup (wks): 12	Grp1: F-B: -0.45 (-0.65-0.25) Grp2: F-B: -0.56 (-0.71-0.41) Between-group difference: p <0.0001 p <0.0001	Grp1: F-B: -0.8 (-1.5--0.2) Grp2: F-B: -2.7 (-3.4--2.1) Between-group difference: p pâ‰¤0.001		
Ross, 2012[143]	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: No Followup (wks): 12	Grp1: B: 7.92 (0.74) F-B: 0.28 (0.11) Grp2: B: 7.98 (0.72) F-B: -0.52 (0.05) Between-group difference: Grp2: -0.8 (-1.02-0.58) p <0.0001	Grp1: B: 77.7 (19.4) F-B: -1.1 (1.9) Grp2: B: 80.6 (17.5) F-B: -1 (2.2)	Grp1: F-B: -1.79 (11.65) Grp2: F-B: -8.52 (23.83)	
Russell-Jones, 2012[144]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.6 (1.2) F: 6.99 (0.07) F-B: -1.48 (0.07) Grp2: B: 8.5 (1.2) F: 6.94 (0.07) F-B: -1.43 (0.07) Between-group difference: Grp1: (-0.26-0.17) p 0.62	Grp1: B: 85.9 (19.6) F-B: -2 (0.2) Grp2: B: 87.5 (18.9) F-B: -2 (0.2) Between-group difference: p 0.892	Grp1: F-B:p Grp2: F-B: -1.3 (0.8)	Grp1: F-B: 0.3 (9.5) Grp2: F-B: 1.5 (10)
Russell-Jones, 2012[144]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg)	Grp1: B: 8.6 (1.2) F: 6.99 (0.07)	Grp1: B: 85.9 (19.6) F-B: -2 (0.2)	Grp1: F-B:p Grp2:	Grp1: F-B: 0.3 (9.5) Grp2:

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Sitagliptin + placebo Not specified ITT: No Followup (wks): 26	F-B: -1.48 (0.07) Grp2: B: 8.5 (1.3) F: 7.32 (0.08) F-B: -1.15 (0.08) Between-group difference: Grp1: (-0.26-0.17) p 0.62 Grp2: (-0.62-0.13) p <0.001	Grp2: B: 86.1 (17.8) F-B: 1.5 (0.3) Between-group difference: p 0.892 p <0.001	F-B: -1.8 (1)	F-B: 0.5 (9.7)
Russell-Jones, 2012[144]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT: No Followup (wks): 26	Grp1: B: 8.6 (1.2) F: 6.99 (0.07) F-B: -1.48 (0.07) Grp2: B: 8.5 (1.2) F: 6.84 (0.08) F-B: -1.63 (0.08) Between-group difference: Grp1: (-0.26-0.17) p 0.62 Grp2: (-0.15-0.35) p 0.328	Grp1: B: 85.9 (19.6) F-B: -2 (0.2) Grp2: B: 88.7 (18.7) F-B: -0.8 (0.3) Between-group difference: p 0.892 p <0.001	Grp1: F-B:p Grp2: F-B: -1.7 (1)	Grp1: F-B: 0.3 (9.5) Grp2: F-B: -1.7 (8.7)
Russell-Jones, 2012[144]	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Sitagliptin + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.2) F: 6.84 (0.08) F-B: -1.63 (0.08) Grp2: B: 8.5 (1.3) F: 7.32 (0.08) F-B: -1.15 (0.08) Between-group difference: Grp1: (-0.15-0.35) p 0.328 Grp2: (-0.62-0.13) p <0.001	Grp1: B: 86.1 (17.8) F-B: 1.5 (0.3) Grp2: B: 87.5 (18.9) F-B: -2 (0.2) Between-group difference: p <0.001	Grp1: F-B: -1.7 (1) Grp2: F-B: -1.3 (0.8)	Grp1: F-B: -1.7 (8.7) Grp2: F-B: 1.5 (10)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Russell-Jones, 2012[144]	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.2) F: 6.84 (0.08) p F-B: -1.63 (0.08) p Grp2: B: 8.5 (1.2) F: 6.94 (0.07) p F-B: -1.43 (0.07) p Between-group difference: Grp1: (-0.15-0.35) p 0.328	Grp1: B: 86.1 (17.8) F-B: 1.5 (0.3) Grp2: B: 88.7 (18.7) F-B: -0.8 (0.3) Between-group difference: p <0.001 p <0.001	Grp1: F-B: -1.7 (1) Grp2: F-B: -1.8 (1)	Grp1: F-B: -1.7 (8.7) Grp2: F-B: 0.5 (9.7)
Russell-Jones, 2012[144]	Grp1: Sitagliptin + placebo Not specified Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.3) F: 7.32 (0.08) F-B: -1.15 (0.08) Grp2: B: 8.5 (1.2) F: 6.94 (0.07) F-B: -1.43 (0.07) Between-group difference: Grp1: (-0.62-0.13) p <0.001	Grp1: B: 88.7 (18.7) F-B: -0.8 (0.3) Grp2: B: 87.5 (18.9) F-B: -2 (0.2) Between-group difference: p <0.001		
Russell-Jones, 2012[144]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26			Grp1: F-B: -1.8 (1) Grp2: F-B: -1.3 (0.8)	
Schernthaner, 2004[145]	Grp1: Metformin Varied Start: 850 mg up to 3 times/day, Max: 2550 mg Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.68 (0.98) F: 7.18 F-B: -1.5 Grp2 B: 8.69 (1.02) F: 7.28 F-B: -1.41	Grp1 F-B: 1.9 Grp2 F-B: -2.5 Grp1-Grp2: 4.4		Grp1: F-B: 0.5 (9.7) Grp2: F-B: 1.5 (10

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1-Grp2: -0.09			
Schondorf, 2011[146]	Grp1: Metformin + pioglitazone + placebo Fixed (1700 mg) Fixed (30 mg) Grp2: Metformin + glimepiride Fixed (1700 mg) Fixed (2 mg) ITT: NR Followup (wks): 24	Grp1: B: 7.4 (0.8) F: 6.6 (0.9) F-B:p <0.05 Grp2: B: 6.7 (0.5) F: 6 (0.5) p F-B:p <0.05 Between-group difference: p NS	Grp1: F-B: -0.24 (4.99) p NS Grp2: F-B: 0.1 (3.21) p NS		
Scott, 2007[147]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 100 mg, Max: 100 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.83 (0.95) F: 7.34 (1.01) F-B: -0.54 (CI: -0.68, -0.4) Grp1-Grp2: -0.22	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		
Scott, 2007[147]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 50 mg, Max: 50 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.89 (0.94) F: 7.5 (1.14) F-B: -0.43 (CI: -0.56, -0.29) Grp1-Grp2: -0.33	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		
Scott, 2007[147]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62)	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed Start: 25 mg, Max: 25 mg	Grp2 B: 7.85 (0.88) F: 7.48 (0.98) F-B: -0.41 (CI: -0.55, -0.27) Grp1-Grp2: -0.35			
Scott, 2007[147]	Grp1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks Grp2: Sitagliptin Fixed Start: 10, Max: 10	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.89 (0.94) F: 7.77 (1.22) F-B: -0.15 (CI: -0.29, -0.01) Grp1-Grp2: -0.61	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		
Scott, 2008[148]	Grp1: Metformin Fixed Start: >1500 mg Grp2: Metformin + rosiglitazone Fixed Start: >1500 mg; Start: 8 mg, Mean: 8 mg	Grp1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 (CI: -0.36, -0.08) Grp2 B: 7.73 (0.88) F: 6.94 (0.75) F-B: -0.79 (CI: -0.92, -0.65) Grp1-Grp2: 0.57 (CI: 0.37, 0.76)	Grp1 F-B: -0.8 (CI: -1.2, -0.4) Grp2 F-B: 1.5 (CI: 1.0, 1.9) Grp2-Grp1: 2.3 (CI: 1.7, -2.9)		
Scott, 2008[148]	Grp1: Metformin Fixed Total starting dose: > 1500 mg Grp2: Metformin + sitagliptin Fixed Total starting dose: > 1500 mg; Start: 100 mg, Mean: 100 mg	Grp1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 (CI: -0.36, -0.08) Grp2 B: 7.75 (0.99) F: 7.01 (0.86) F-B: -0.73 (CI: -0.87, -0.6)	Grp1 F-B: -0.8 (CI: -1.2, -0.4) Grp2 F-B: -0.4 (CI: -0.8, 0) Grp1-Grp2: -0.4		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1-Grp2: -0.51 (CI: -0.7, -0.32) p: <0.001			
Scott, 2008 [148]	Grp1: Metformin + rosiglitazone NR; Fixed Start: >=1500 mg; Mean: 8 mg D: 10 wks; NA Grp2: Metformin + sitagliptin Fixed Start: > 1500 mg; Start: 100 mg, Mean: 100 mg	Grp1-Grp2: -0.06 (CI: -0.25, 0.14)	Grp1 F-B: 1.5 (CI: 1, 1.9) Grp2 F-B: -0.4 (CI: -0.8, 0) Grp1-Grp2: 1.9 (CI: 1.3, 2.5)		
Seck, 2010[149]	Grp1: Metformin + glipizide Fixed NR; Start: 5, Max: 20, Mean: 9.2 mg D: 2 Years Grp2: Metformin + sitagliptin Fixed NR D: 2 Years	Grp1 F-B: -0.35 (CI: -0.44, -0.26) Grp2 F-B: -0.33 (CI: -42, -0.25) Grp1-Grp2: -0.01 (CI: -0.1, 0.08)	Grp1 F-B: 0.7 (CI: 0, 1.3) p: NS Grp2 F-B: -1.6 (CI: -2.3, -1) p: NS Grp1-Grp2: 2.3 (1.6, 3) p: NS		
Seino, 2010[150]	Grp1: Glibenclamide Varied, prespecified target dose Start: 1.25 mg, Max: 2.5 mg D: 4 Wks Grp2: Liraglutide Varied, prespecified target dose Start: 0.3 mg, Max: 0.9 mg D: 2 Wks	Grp1 F-B: -1.88 (SE: 0.07) p: <0.0001 Grp2 F-B: -1.38 (SE: 0.09) p:<0.0001 Grp1-Grp2: 0.5 (CI: 0.3, 0.7) p<0.0001	Grp1 F-B: -0.92 (2.15) p: p<0.0001 Grp2 F-B: 0.99 (1.84) p: p<0.0001 Grp1-Grp2: 1.91 (CI: 1.48, 2.34) p: <0.0001		
Seino, 2012[151]	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (25mg) ITT: Yes Followup (wks): 12	Grp1: B: 8 (0.86) F-B: 0.21 (0.64) (0.11-0.33) p Grp2: B: 8.02 (0.73) F-B: -0.64 (0.49) (-0.75-0.53) p	Grp1: B: 69.89 (14.23) F-B: -0.23 (1.37) Grp2: B: 69.47 (12.46) F-B: 0.17 (1.38)		
Seino, 2012[151]	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (12.5mg)	Grp1: B: 8 (0.86) F-B: 0.21 (0.64) (0.11-0.33) p Grp2:	Grp1: B: 69.89 (14.23) F-B: -0.23 (1.37) Grp2: B: 69.65 (12.67)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: Yes Followup (wks): 12	B: 7.89 (0.82) F-B: -0.54 (0.56) (-0.67-0.44) p	F-B: -0.09 (1.29)		
Shihara, 2011[152]	Grp1: Pioglitazone Titrated (Mean: 23.24 mgMax: 30mg for women-45mg for menstarting 15mg/d) Grp2: SU Titrated (Mean: 23.24Max: 6mg/dstarting 0.5mg/d) ITT: No Followup (wks): 24	Grp1: B: 7.8 (0.9) F: 7.2 (0.8) F-B: -0.85 (1) p <0.001 Grp2: B: 7.8 (0.9) F: 6.8 (0.7) pNS F-B: -0.98 (0.75) p <0.001 Between-group difference: p 0.31	Grp1: B: 65.5 (15.1) F: 66.2 (14.4) p F-B:p ns Grp2: B: 66 (12) F: 66.4 (11.7) p F-B:p 0.036 Between-group difference: p NS		
Srivastava, 2012[153]	Grp1: Metformin + glimepiride Fixed (kept at starting dose (dose on prior to study)) Titrated (Max: 4 mg/daystarted at 1-2 mg/day) Grp2: Metformin + sitagliptin Fixed (metformin dose prior to the study kept constant) Titrated (Max: 200 mg/daystarted at 50/100 mg/day) ITT: Yes Followup (wks):	Grp1: B: 8.25 (0.57) F: 7.08 (0.36) F-B: -1.17 (0.25) p <0.001 Grp2: B: 8.28 (0.42) F: 7.64 (0.42) F-B: -0.64 (0.99) p <0.001 Between-group difference: p <0.001			
Tan, 2004[156]	Grp1: Pioglitazone Varied Start: 30 mg, Max: 45 mg Grp2: Glibenclamide Varied Start: 1.75 mg, Max: 10.5 mg	Grp1 B: 8.4 (0.7) F: 7.9 F-B: -0.5 p: <0.005 Grp2 B: 8.5 (0.8) F: 8.1 F-B: -0.4 p: <0.005 Grp1-Grp2: -0.1	Grp1 B: 86.2 (15.6) F: 91.2 F-B: 5 (CI: 3.7, 6.2) p: <0.05 Grp2 B: 85.1 (13.6) F: 88.5 F-B: 3.4 (CI: 2.7, 4.1) p: <0.05		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
			Grp1-Grp2: 1.6		
Tan, 2004[156]	Grp1: Pioglitazone Varied Start: 15 mg, Max: 45 mg Grp2: Glimepiride Varied Start: 2 mg, Max: 8 mg	Grp1 B: 8.54 (0.903) F: 7.76 F-B: -0.78 (0.162) p: <0.001 Grp2 B: 8.45 (1.02) F: 7.77 F-B: -0.68 (0.169) p: <0.001 Grp1-Grp2: -0.1 p: 0.638	Grp1 B: 88.7 (17.4) F: 91.7 F-B: 3 p: <0.001 Grp2 B: 89.1 (16) F: 90.2 F-B: 1.1 p: 0.008 Grp1-Grp2: 1.9 p: 0.002		
Taskinen, 2011[158]	Grp1: Metformin + placebo Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Grp2: Metformin + linagliptin Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Fixed (5mg) ITT: No Followup (wks): 24	Grp1: B: 8.02 (0.07) F-B: 0.15 (0.06) Grp2: B: 8.09 (0.04) F-B: -0.49 (0.04) Between-group difference: Grp2: -0.64 0.07 (-0.78-0.5) p <0.0001	Grp1: B: 83.3 (16.6) F-B: -0.5 Grp2: B: 82.2 (17.2) F-B: -0.4		
Taslimi, 2013[159]	Grp1: Metformin Fixed (1000mg) Grp2: Pioglitazone Fixed (30mg) ITT: Yes Followup (wks): 12	Grp1: B: 8.4 (1.5) F: 7 (1.4) F-B:p <0.01 Grp2: B: 8.2 (1.8) F: 7.3 (1.6) F-B:p <0.05			
Teramoto, 2007[160]	Grp1: Pioglitazone Varied, glucose: <= 126 mg/dL Start: 15 mg, Max: 30 mg D: 15 wks Grp2: Glibenclamide Varied, glucose: <= 126 mg/dL	Grp1 F-B: -0.8 (1.14) p: <0.05 Grp2 F-B: -1.43 (1.09) p: <0.05			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 1.25 mg, Max: 2.5 mg D: 15 wks	Grp1-Grp2: 0.63 (SE: 0.48)			
Tosi, 2003[161]	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 15 mg	Grp1 B: 7.7 (1.4) F: 7.3 F-B: -0.4 Grp2 B: 7.85 (1.4) F: 7.4 F-B: -0.45 Grp1-Grp2: 0.05			
Tosi, 2003[161]	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 400 mg, Max: 2400 mg; Start: 2.5 mg, Max: 15 mg	Grp1 B: 7.8 (1.4) F: 7.3 F-B: -0.5 Grp2 B: 7.8 (1.0) F: 5.9 F-B: -1.9 Grp1-Grp2: 1.4			
Turkmen Kemal, 2007[162]	Grp1: Metformin Fixed Start: 1700 mg D: 6 mos Grp2: Rosiglitazone Fixed Start: 8 mg	Grp1 B: 5.95 Range: 5.6 F: 5.85 Range: 1.9 Grp2 B: 6 Range: 2.4 F: 5.95 Range: 1.9			
Turner, 1999[163]	Grp1: Metformin Varied, glucose: FPG <6 mmol/L Max: 2550 mg/day D: 9 yrs Grp2: Any in the Sulfonylurea class Varied, glucose: 6 mmol/L Max: Chlorpropramide-500 mg; Glyburide 20 mg D: 9 yrs	Grp1 Proportion achieving HbA1c<7% at 3 yrs: 44 (CI: 42, 46) 6 yrs: 34 (CI: 32, 37) 9 yrs: (CI: 11, 15) Grp2 Proportion achieving HbA1c<7% at 3 yrs: 45 (CI: 43, 48) 6 yrs: 28 (CI: 26, 30) 9 yrs: (CI: 19, 23)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Umpierrez, 2006[164]	Grp1: Metformin + pioglitazone NR; Varied, glucose: <120 mg/dL, HbA1c: <8.0% Start: 1.54 g, Max: 1.57g; Start: 30 mg, Max: 45 mg D: NR; Unclear Grp2: Metformin + glimepiride NR; Glucose: <120 mg/dL Start: 1.47 g, Max: 1.49 g; Start: 2 mg, Max: 8 mg D: NR; 6 wks	Grp1 F-B: -1.23 (SE: 0.073) p: 0.4825 Grp2 F-B: -1.3 (SE: 0.077) Grp1-Grp2: 0.07 (SE: 0.11)	Grp1 F-B: 1.85 (SE: 0.38) Grp2 F-B: 1.74 (SE: 0.41) Grp1-Grp2: 0.11		
Umpierrez, 2014[165]	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT: Yes Followup (wks):	Grp1: B: 7.6 (0.8) F-B: -0.51 (0.07) Grp2: B: 7.6 (0.9) F-B: -0.55 (0.07)	Grp1: B: 92 (19) F-B: -2.3 (0.24) Grp2: B: 92 (19) F-B: -0.8 (0.24)	Grp1: B: 129 (16) F-B: -1 (0.88) Grp2: B: 130 (16) F-B: -0.1 (0.88)	Grp1: F-B: 1.1 (0.57) Grp2: F-B: 1.6 (0.57
Umpierrez, 2014[165]	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT: Yes Followup (wks):	Grp1: B: 7.6 (0.8) F-B: -0.51 (0.07) Grp2: B: 7.6 (0.9) F-B: -0.7 (0.07)	Grp1: B: 92 (19) F-B: -2.3 (0.24) Grp2: B: 93 (19) F-B: -1.6 (0.24	Grp1: B: 129 (16) F-B: -1 (0.88) Grp2: B: 130 (16) F-B: -2.7 (0.88	Grp1: F-B: 1.1 (0.57) Grp2: F-B: 1.8 (0.57)
van der Meer, 2009[166]	Grp1: Metformin + glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks Grp2: Pioglitazone + glimepiride Fixed; Varied	Grp1 B: 7 (SE: 0.1) F: 6.3 (SE: 0.1) p: <0.001 F-B: -0.7 Grp2	Grp1 B: 92 (2) F: 92 (3) F-B: 0 Grp2 B: 91 (2)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR	B: 7.1 (SE: 0.2) F: 6.5 (SE: 0.1) p: <0.001 F-B: -0.6 Grp1-Grp2: -0.1 (SE: 0.32) p: 0.146	F: 94 (4) F-B: 3 Grp1-Grp2: -3 p: <0.001		
Weissman, 2005[167]	Grp1: Metformin Varied Start: 1000 mg, Max: 2000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg	Grp1 B: 7.97 (1.2) F: 7.26 F-B: -0.71 Grp2 B: 8.05 (1.2) F: 7.12 F-B: -0.93 Grp1-Grp2: 0.2			
White, 2014[168]	Grp1: Metformin + placebo Fixed (fixed dose metformin at >=1500 mg) Grp2: Metformin + saxagliptin Fixed (fixed dose but could be >=1500 mg) Fixed (5 mg) ITT: No Followup (wks):	Grp1: B: 7.97 (0.09) F: 7.75 (0.12) F-B: -0.22 (0.08) (-0.39-0.06) Grp2: B: 7.92 (0.11) F: 7.36 (0.13) F-B: -0.56 (0.09) (-0.74-0.38) Between-group difference: Grp2: -0.34 0.12 p 0.006	Grp1: F-B: -0.4 (-0.83-0.02) Grp2: F-B: -0.32 (-0.97-0.34)		
Williams-Herman, 2009[169]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -0.8 (CI: -1, -0.6) Grp1-Grp2: -0.5	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: 0.6 (CI: -0.2, 1.4)		
Williams-Herman, 2009[169]	Grp1: Metformin Fixed Mean: 1000 mg	Grp1 F-B: -1 (CI: -1.2, -0.8)	Grp1 F-B: -1 (CI: -1.7, -0.3)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Sitagliptin Fixed Mean: 100 mg	Grp2 F-B: -0.8 (CI: -1, -0.6) Grp1-Grp2: -0.2	Grp2 F-B: 0.6 (CI: -0.2, 1.4)		
Williams-Herman, 2009[169]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Metformin + sitagliptin Fixed Mean: 2000 mg; Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -1.8 (CI: -2, -1.7) Grp1-Grp2: 0.5	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: -1.7 (CI: -2.4, -1.1)		
Williams-Herman, 2009[169]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg; Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -1.4 (CI: -1.6, -1.3) Grp1-Grp2: 0.1	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: -0.7 (CI: -1, 0) Grp1-Grp2: -0.8		
Williams-Herman, 2009[169]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Metformin + sitagliptin Fixed Mean: 2000 mg; Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -1.8 (CI: -2, -1.7) Grp1-Grp2: 0.8	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: -1.7 (CI: -2.4, -1.1) Grp1-Grp2: 0.7		
Williams-Herman, 2009[169]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg; Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -1.4 (CI: -1.6, -1.3) Grp1-Grp2: 0.4	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: -0.7 (CI: -1, 0) Grp1-Grp2: -0.3		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: F-B:p Grp2: B: 8.6 (1) F: 8.6 (1) F-B: -1.7 (-1.8-1.5)	Grp1: F-B:p Grp2: F-B: -1.2 (-2--0.3)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: F-B:p Grp2: B: 8.7 (0.9) F: 8.7 (0.9) p F-B: -1.4 (-1.6-1.2) p	Grp1: F-B:p Grp2: F-B: 0.5 (-0.7-1.7) p		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: F-B:p Grp2: B: 8.5 (0.9) F: 7.4 (0.7) F-B: -1.2 (-1.4-0.9)	Grp1: F-B:p Grp2: F-B: 0 (-0.8-0.9)		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.6 (0.9) F: 7.5 (0.7) F-B: -1.1 (-1.3-0.9) Grp2: B: 8.6 (1) F: 8.6 (1) F-B: -1.7 (-1.8-1.5)	Grp1: F-B: -0.8 (-1.9-0.3) Grp2: F-B: 0.5 (-0.7-1.7)		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.6 (0.9) F: 7.5 (0.7) F-B: -1.1 (-1.3-0.9) Grp2: B: 8.5 (0.9) F: 7.4 (0.7) F-B: -1.2 (-1.4-0.9)	Grp1: F-B: -0.8 (-1.9-0.3) Grp2: F-B: 0 (-0.8-0.9) p		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.6 (0.9) F: 7.5 (0.7) F-B: -1.1 (-1.3-0.9) Grp2: B: 8.7 (0.9) F: 8.7 (0.9) F-B: -1.4 (-1.6-1.2)	Grp1: F-B: -0.8 (-1.9-0.3) Grp2: F-B: -1.2 (-2--0.3)		
Williams-Herman,	Grp1: Metformin + placebo Titrated (Max: 2000 mg)	Grp1: B: 8.5 (0.8)	Grp1: F-B: -2.4 (-3.3--1.5)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2010[170]	Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	F: 7.2 (0.9) F-B: -1.3 (-1.5-1.2) Grp2: B: 8.6 (1) F: 8.6 (1) F-B: -1.7 (-1.8-1.5)	Grp2: F-B: -1.2 (-2--0.3)		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.8) F: 7.2 (0.9) p F-B: -1.3 (-1.5-1.2) p Grp2: B: 8.5 (0.9) F: 7.4 (0.7) p F-B: -1.2 (-1.4-0.9) p	Grp1: F-B: -2.4 (-3.3--1.5) p Grp2: F-B: 0.5 (-0.7-1.7) p		
Williams-Herman, 2010[170]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.8) F: 7.2 (0.9) p F-B: -1.3 (-1.5-1.2) p Grp2: B: 8.7 (0.9) F: 8.7 (0.9) p F-B: -1.4 (-1.6-1.2) p	Grp1: F-B: -2.4 (-3.3--1.5) p Grp2: F-B: 0 (-0.8-0.9) p		
Williams-Herman, 2010[170]	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.9) F: 7.4 (0.7) p F-B: -1.2 (-1.4-0.9) p Grp2: B: 8.7 (0.9) F: 8.7 (0.9) p F-B: -1.4 (-1.6-1.2) p	Grp1: F-B: 0.5 (-0.7-1.7) p Grp2: F-B: -1.2 (-2--0.3) p		
Williams-Herman, 2010[170]	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.9) F: 7.4 (0.7) p F-B: -1.2 (-1.4-0.9) p Grp2: B: 8.6 (1) F: 8.6 (1) p F-B: -1.7 (-1.8-1.5) p	Grp1: F-B: 0.5 (-0.7-1.7) p Grp2: F-B: 0 (-0.8-0.9) p		
Yamanouch	Grp1: Metformin	Grp1			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
i, 2005[171]	Fixed Start: 750 mg Grp2: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men	B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 Grp2 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 Grp1-Grp2: 0.2			
Yamanouchi, 2005[171]	Grp1: Metformin Fixed Start: 750 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 Grp2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 Grp1-Grp2: 0			
Yamanouchi, 2005[171]	Grp1: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 mg	Grp1 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 Grp2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 Grp1-Grp2: -0.2			
Yang, 2011[172]	Grp1: Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2: Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT: No Followup (wks): 18	Grp1: B: 7.9 (0.8) F: 7.55 (0.8) F-B: -0.37 (0.107) Grp2: B: 7.9 (0.8) F: 7.1 (0.8) F-B: -0.78 (0.183)	Grp1: B: 68.9 (0.7) F: 67.8 (0.7) F-B: -0.97 (0.1) Grp2: B: 68.9 (0.8) F: 67.7 (0.7) F-B: -1.05 (0.1)		
Yang, 2011[173]	Grp1: Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects;	Grp1: B: 8.5 (1.1) F-B: -1.39 (0.11) (-1.5-)	Grp1: B: 68.2 (11.9) F-B: 0.08 (0.26) Grp2:	Grp1: B: 126 (14.9) F-B: -0.91 Grp2:	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2: Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT: No Followup (wks): 16	Grp2: B: 8.6 (1.1) F-B: -1.36 (0.14) (-1.5-) Between-group difference: Grp2: 0.03 (-0.14-0.2) p non-inferior	B: 68.6 (11.6) F-B: -1.8 (0.18) Between-group difference: p <0.0001	B: 126 (14.3) F-B:	
Yang, 2011[173]	Grp1: Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2: Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT: No Followup (wks): 16	Grp1: B: 8.5 (1.1) F-B: -1.39 (0.11) (-1.5-) Grp2: B: 8.6 (1.1) F-B: -1.45 (0.15) (-1.6-) Between-group difference: Grp2: -0.06 (-0.23-0.11) p non-inferior	Grp1: B: 68.2 (11.9) F-B: 0.08 (0.26) Grp2: B: 67.4 (11.3) F-B: -2.35 (0.14) Between-group difference: p <0.0001	Grp1: B: 126 (14.9) F-B: -0.91 Grp2: B: 126 (14.1) F-B:p Between-group difference: p <0.05	
Yang, 2011[173]	Grp1: Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2: Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT: No	Grp1: B: 8.5 (1.1) F-B: -1.39 (0.11) (-1.5-) Grp2: B: 8.5 (1.1) F-B: -1.14 (0.16) (-1.3-)	Grp1: B: 68.2 (11.9) F-B: 0.08 (0.26) Grp2: B: 68.2 (11.9) F-B: -2.44 (0.14) Between-group difference: p <0.0001		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 16				
Yang, 2012[174]	Grp1: Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2: Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT: No Followup (wks): 24	Grp1: B: 8.6 (0.9) F-B: -0.1 (-0.3-0) Grp2: B: 8.5 (0.9) F-B: -1 (-1.2-0.9) Between-group difference: Grp2: 0.9 (-1.1-0.7) p<0.001	Grp1: B: 68.9 (13.3) F-B: -0.5 (-0.9--0.1) p Grp2: B: 67.9 (10.7) F-B: 0 (-0.3-0.4) p Between-group difference: Grp2: 0.5 (0.1-0.9) p 0.018	Grp1: B: 126 (14.9) F-B: -0.91 Grp2: B: 127 (14) F-B:p Between-group difference: p <0.05	
Yoon, 2011[175]	Grp1: Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2: Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) ITT: Yes Followup (wks): 48	Grp1: B: 7.9 (0.8) F: 7 p F-B: -0.92 (0.96) p <0.001 Grp2: B: 7.8 (0.8) F: 7 p0.62 F-B: -0.82 (0.79) p <0.001	Grp1: B: 68.9 (11.1) F: 69.9 (0.95) F-B: -1.1 Grp2: B: 67.9 (10.9) F: 71.2 (0.99) F-B: 1.4		
Yoon, 2011[175]	Grp1: Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2: Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT: Yes Followup (wks): 48	Grp1: B: 7.9 (0.8) F: 7 p F-B: -0.92 (0.96) p <0.001 Grp2: B: 7.8 (0.8) F: 6.9 F-B: -0.89 (0.76) p 0.001	Grp1: B: 68.9 (11.1) F: 69.9 (0.95) p F-B: -1.1 p Grp2: B: 69.1 (12.1) F: 73.1 (1.36) F-B: 1.5		
Yoon, 2011[175]	Grp1: Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) Grp2: Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am)	Grp1: B: 7.8 (0.8) F: 7 p0.62 F-B: -0.82 (0.79) p <0.001 Grp2:	Grp1: B: 69.1 (12.1) F: 73.1 (1.36) F-B: 1.5 Grp2: B: 67.9 (10.9)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: Yes Followup (wks): 48	B: 7.8 (0.8) F: 6.9 p F-B: -0.89 (0.76) p 0.001	F: 71.2 (0.99) F-B: 1.4		
Yuan, 2012[176]	Grp1: Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2: Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT: Yes Followup (wks): 26	Grp1: B: 8.11 (1.92) F-B: -1.66 (1.38) p<0.001 Grp2: B: 8.27 (1.58) F-B: -2.1 (1.79) p<0.001 Between-group difference: p 0.045	Grp1: B: 83.7 (10.7) F-B: -3.81 (1.38) p<0.05 Grp2: B: 82.2 (12.8) F-B: -5.8 (1.66) p<0.05 Between-group difference: p <0.01		
Zhang, 2012[179]	Grp1: Metformin + glimepiride Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (1-4mg, adjusted in accordance with the levels of blood glucose) Grp2: Metformin + exenatide Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (initiated at 10ug for the first 4 wks, 20ug in the subsequent 12 wks then went into 16 week treatment period) ITT: No Followup (wks): 16	Grp1: B: 9 (0.9) F: 7.4 (0.6) F-B:p <0.01 Grp2: B: 8.7 (1) F: 7.4 (0.6) F-B:p <0.01 Between-group difference: p 0.08		Grp1: B: 139 (15) F: 137 (10) F-B:p >0.05 Grp2: B: 136 (13) F: 132 (9) F-B:p <0.01 Between-group difference: p >0.1	

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m^2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table 4. Quality of studies evaluating diabetes medications on intermediate outcomes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Aaboe, 2010[1]	Yes	No	Yes	Not described	No
Ahren, 2014[2]	Yes	Not described	Yes	Yes	Yes
Alba, 2013[3]	Yes	Yes	Yes	Not described	Yes
Apovian, 2010[4]	Yes	Yes	Yes	Not described	Yes
Arechavaleta, 2011[5]	Yes	Yes	Yes	Not described	Yes
Arjona Ferreira, 2013[6]	Yes	Yes	Yes	Yes	Yes
Aschner, 2012[8]	Yes	Yes	No	Not described	Yes
Bailey, 2013[10]	Yes	Yes	Yes	Yes	Yes
Barnett, 2012[13]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2010[14]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2012[15]	Yes	Yes	Yes	Yes	Yes
Bolinder, 2012[17]	Yes	Yes	Yes	Yes	Yes
Borges, 2011[18]	Yes	Not described	Yes	Not described	No
Bunck, 2011[21]	Yes	Yes	NR/Can't tell	Not described	Yes
Cefalu, 2013[23]	Yes	Yes	Yes	Yes	Yes
Chawla, 2013[26]	Yes	Yes	NR/Can't tell	Not described	Yes
DeFronzo, 2012[33]	Yes	Not described	Yes	Yes	No
Derosa, 2011[40]	Yes	Yes	No	Not described	Yes
Derosa, 2013[42]	Yes	Yes	Yes	Yes	Yes
Derosa, 2013[43]	Yes	Yes	Yes	Yes	Yes
Diamant, 2010[44]	Yes	Yes	No	Not described	Yes
Erem, 2014[47]	Yes	Not described	No	Not described	No
Esposito, 2011[48]	Yes	Yes	Yes	Yes	Yes
Esteghamati, 2014[49]	Yes	Yes	No	Not described	No
Ferrannini, 2013[52]	Yes	No	No	Not described	No
Fidan, 2011[53]	Yes	Not described	No	Not described	No
Fonseca, 2012[55]	Yes	Yes	Yes	Not described	Yes
Forst, 2010[56]	Yes	Yes	Yes	Yes	Yes
Forst, 2012[57]	Yes	Not described	No	Not described	Yes
Forst, 2014[58]	Yes	Not described	No	Not described	Yes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Gallwitz, 2011[59]	Yes	Not described	No	Not described	No
Gallwitz, 2012[60]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[61]	Yes	Yes	NR/Can't tell	Not described	Yes
Garber, 2011[66]	Yes	Yes	No	Not described	Yes
Genovese, 2013[67]	Yes	Not described	Yes	Yes	Yes
Genovese, 2013[68]	Yes	Yes	Yes	Yes	Yes
Goke, 2010[69]	Yes	Yes	Yes	Yes	Yes
Gupta, 2010[74]	Yes	Not described	No	Not described	No
Gupta, 2013[75]	Yes	Yes	No	Not described	Yes
Haak, 2012[76]	Yes	Not described	Yes	Not described	Yes
Haak, 2013[77]	Yes	Yes	Yes	Yes	Yes
Haring, 2014[82]	Yes	Yes	Yes	Yes	Yes
Henry, 2012[83]	Yes	Yes	Yes	Not described	No
Henry, 2012[83]	Yes	Yes	Yes	Not described	Yes
Hermans, 2012[86]	Yes	Not described	Yes	Not described	Yes
Kadoglou, 2011[93]	Yes	Not described	No	Not described	Yes
Kadowaki, 2013[94]	Yes	Yes	Yes	Yes	Yes
Kaku, 2011[97]	Yes	Not described	No	Not described	
Kim, 2014[101]	Yes	Not described	No	Not described	Yes
Lavalle-Gonzalez, 2013[104]	Yes	Yes	Yes	Yes	Yes
List, 2009[107]	Yes	Yes	Yes	Yes	Yes
Maffioli, 2013[109]	Yes	Yes	Yes	Yes	Yes
Moon, 2014[112]	Yes	Not described	No	Not described	Yes
Nauck, 2009[117]	Yes	Yes	Yes	Not described	Yes
Nauck, 2011[118]	Yes	Yes	Yes	Yes	Yes
Nauck, 2014[119]	Yes	Not described	Yes	Not described	Yes
Petrica, 2009[124]	Yes	Not described	No	Not described	Yes
Pfutzner, 2011[126]	Yes	Not described	Yes	Not described	No
Pfutzner, 2011[127]	Yes	Yes	Yes	Not described	Yes
Pratley, 2014[129]	Yes	Not described	Yes	Not described	Yes
Qiu, 2014[130]	Yes	Yes	Yes	Not described	Yes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Reasner, 2011[133]	Yes	Not described	Yes	Not described	Yes
Ridderstrale, 2014[134]	Yes	Yes	Yes	Yes	Yes
Roden, 2013[137]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2010[139]	Yes	Not described	Yes	Yes	Yes
Rosenstock, 2012[140]	Yes	Not described	Yes	Not described	Yes
Rosenstock, 2013[142]	Yes	Yes	Yes	Yes	Yes
Ross, 2012[143]	Yes	Yes	Yes	Yes	Yes
Russell-Jones, 2012[144]	Yes	Yes	Yes	Yes	Yes
Schondorf, 2011[146]	Yes	Not described	Yes	Not described	Yes
Seino, 2012[151]	Yes	Yes	Yes	Yes	Yes
Shihara, 2011[152]	Yes	Yes	No	Not described	Yes
Taskinen, 2011[158]	Yes	Not described	Yes	Not described	Yes
Taslimi, 2013[159]	Yes	Not described	NR/Can't tell	Not described	Yes
Umpierrez, 2014[165]	Yes	Yes	Yes	Yes	Yes
White, 2014[168]	Yes	Yes	Yes	Yes	Yes
Williams-Herman, 2010[170]	Yes	Yes	Yes	Yes	Yes
Yang, 2011[172]	Yes	Yes	Yes	Not described	Yes
Yang, 2011[173]	Yes	Not described	Yes	Yes	Yes
Yang, 2012[174]	Yes	Yes	Yes	Yes	Yes
Yoon, 2011[175]	Yes	Not described	Yes	Not described	Yes
Yuan, 2012[176]	Yes	Yes	No	Not described	Yes
Zhang, 2012[179]	Yes	Not described	No	Not described	Yes

Table 5. Characteristics of studies evaluating diabetes medications on long-term outcomes

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Agarwal, 2005{Agarwal, 2005 #35339} US Not extracted	RCT	Start year: 2001 End year: 2003 16 Wks	No run-in period	Yes	102/54 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m^2, class III or IV heart failure, NSAID use
Alba, 2013[3] Multi-continent NCT00511108	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 211 NR	Age <30 or >65 yrs, HbA1c >10% if drug naive, 9% if on antihyperglycaemic agent monotherapy or low-dose combination therapy or <7% if drug naive, 6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, Any liver disease, Any kidney disease, History of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week -2
Amador-Licona, 2000[178] Mexico Not extracted	RCT	12 wks (planned duration)	Not extracted	No	Not extracted	Age >65 years, any liver disease, history of CVD, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Andersson, 2010[181] Denmark No	Retrospective cohort	1997 2006 844 days	Not applicable	Yes	10,920 / 5,852 Administrative database, The Danish National Patient Register - The Danish Register of Medicinal Product Statistics and The National Causes of Death Register Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <= 30 yrs, No diagnosis/hospitalization for CHF, not using MET, SU and/or Insulin, Use of other glucose lowering meds, patients with previous hospitalisations for HF during the period from 1978 until 1996 (diagnosis codes [ICD-10] I50, I42, J81, I11.0 and [ICD-8] 425, 4270, 4271) were excluded from the study, not alive 30 days after discharge for CHF, not receiving drug of interest 30 days after discharge for CHF, use of study drug within 90 days of hospitalization fro CHF
Arechavaleta, 2011[5] multi-national NCT00701090	RCT	Neither year reported 30	Yes	Yes	Not Extracted/ 1035 NR	Age <18 years, HbA1c >9% or <6.50%, Not on a stable dose of metformin (ГёÑ1500 mg/day) as well as diet and exercise for past 12 wks, history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable meds for HTN, thyroid dz, HRT, OCPs
Arjona Ferreira, 2013[6] Multinational NCT00509262	RCT	Neither year reported 58	Yes	Yes	Not Extracted/ 426 NR	Age <30 yrs, HbA1c >9.00% or <7.00%, Prior or current use of insulin, Any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duratoin of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, visit2, FPG>260mg/dl, unlikely to improve with diet/exercise, visite 3, FPG>250mg/dl consistently (i.e., measure=ment repeated and confirmed within 7 days); visite 4, FPG>240mg/dl consistently visit5, finger-stick glucose > 240 or <120mg/dl

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Aschner, 2010[7] Multi-continent Not extracted	RCT	Neither year reported 24 wks	Run-in period but number of participants excluded NR	Yes	2068/1050 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, CK > 2x upper limit normal
Aschner, 2012[8] Multi-continent NCT00751114	RCT	2008 2011 24	No	Yes	Not Extracted/ 515 NR	Age <35 - >70 yrs, HbA1c >=11% or <7%, BMI <25 - >45, Any liver disease, Any kidney disease, FPG >14.4 mmol/L, tx'd w/ oral other than metformin in past 3 mo, received SU+MET In past year prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudl compromise the patient's safety, unwilling to self-monitor BG or keep diary
Bailey, 2005[9] UK, 14 European countries Not extracted	RCT	24 wks (planned duration)	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other
Bailey, 2013[10] Multi-continent NCT00528879	RCT	2007 2008 102	Yes	Yes	Not Extracted/ 546 NR	Age <18 and >77 yrs, HbA1c >10% or 7%, BMI >45 kg/m^2, Any liver disease, Any kidney disease, History of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, systolic blood pressure >=180 mmHG, diastolic blood pressure >=110 mmHG, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, New York Heart Association class III or IV congestive heart failure
Bakris, 2003[11] likely US and UK Not extracted	RCT	52 wks (planned duration)	Not extracted	Yes	Not extracted	NR

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Bakris, 2006[12] US, Multi-continent, South America, Europe Not extracted	RCT	Neither year reported 32 Wks	Yes	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg
Barnett, 2012[13] Multi-continent NCT00740051	RCT	2008 2010 52	Yes	Yes	Not Extracted/ 227 NR	Age <18 or >80 yr, HbA1c: If treatment naive: L10.0%(9.0% for Canada); If receiving an oral antidiabetes drug: 9.0%, HbA1c: If treatment naive: <7.0%; If receiving an oral antidiabetes drug: 6.5%, BMI >40kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, MI, stokre, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an antiobesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Bergenstal, 2010[14] Multi-continent NCT00637273	RCT	2008 2008 26	No	Yes	Not Extracted/ 514 Outpatient: primary care	Age <18years, HbA1c >11% or <7.10%, BMI <25 and greater than 45kg/m2, Prior or current use of insulin, Prior or current use of study drug, Pregnant, Nursing, Not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 diabetes, fasting plasma glucose >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Bolinder, 2012[17] Europe NCT00855166	RCT	2009 2011 102	Yes	Yes	Not Extracted/ 182 NR	Women age <55 or >75 years. Men <30 or >75 years, HbA1c >8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, Fasting plasma glucose >240 mg/dl (>13.2 mmol/liter), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment, perimenopausal women, body weight change >5% within 3 months, serum total bilirubin >34 ╝╚ mol/L; hemoglobin (Hb) Γëñ105 g/L (10.5 g/dL) for men and Γëñ95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than ΓêÆ2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, systolic blood pressure ΓëÑ180 mmHg and/or diastolic blood pressure ΓëÑ110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications) alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment
Borges, 2011[18] Multi-continent NCT00386100	RCT	2006 2008 80	No	Yes	Not Extracted/ 688 NR	Age <18 - >75 yrs, HbA1c >10.5% or <7.5%, BMI < =25 Prior use of any diabetes treatment fasting glucose <7 mmol/l

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Brownstein, 2010 [182] United States Not extracted	Cohort	Start year: 2000 End year: 2006 7 years	NA	No	NA/34252 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age ≤18 years, HbA1c ≤ 6.0%, no diagnosis of DM with ICD-9 code of 250.XX
Bunck, 2011[21] Europe NCT00097500	RCT	2004 2009 3.5	No	Yes	Not Extracted/ 69 NR	Age <30 or >75 years, HbA1c >9.50% or <6.50%, BMI <25 or >40 kg/m^2, Not undergoing stable metformin treatment for at least 2 months prior enrollment, Using any other blood glucose lowering agents 3 months prior to screening, besides metformin
Cefalu, 2013[23] Multi-continent NCT00968812	RCT	2009 2011 52	Yes	Yes	Not Extracted/ 1452 NR	Age <18, >80 yrs, HbA1c >9.5 or <7%, Any kidney disease, Not on stable metformin therapy (ГëÑ2000 mg per day or ГëÑ1500 mg per day if unable to tolerate a higher dose) for at least 10 wks, prior TZD use in 16 wks before screening, h/o more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15┬╗0 mmol/L or more during the pretreatment phase;
Comaschi, 2007[28] Italy Not extracted	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33 nmol/L

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Corrao, 2011[183] Italy	Retrospective cohort	2001 2003 4.8-5.1	Not applicable	No	Not Extracted/ 70,437 Administrative database, health service databases of Lombardy, Inpatient diagnosis/procedure, Outpatient pharmacy records, database for regional National Health demographic and administrative data	Age <40, >90 yrs, Prior use of any diabetes treatment, Prior or current use of insulin, History of CVD, macrovascular disease hospitalization, resident of Lombardy region, < 1 year FU, started treatment on combination therapy of MET + SU, received fewer than 2 prescriptions for diabetes drugs during follow up
DeFronzo, 1995[30] US Not extracted	RCT	29 wks (planned duration)	Not extracted	No	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
DeFronzo, 2012[33] Multi-continent NCT00328627	RCT	Neither year reported 26	Yes	Yes	Not Extracted/ 1554 NR	Age <18 or >80 yr, HbA1c >10% before and after run-in/stabilization period or <7.5% before and after run-in/stabilization period, BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopathy, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Diamant, 2010[44] Multi-continent NCT00641056	RCT	2008 2009 26	Yes	Yes	Not Extracted/ 321 NR	Age <18 years or older, HbA1c >11% or <7.1%, BMI <25kg/m2 and >45kg/m2. Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoids, treatment for longer than 2 wks with insulin, thiazolidinediones, ╬-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening
Ekstrom, 2012[184] Sweden	Retrospective cohort	2004 2010 3.9	Not applicable	No	Not Extracted/ 51675 Outpatient: primary care and subspecialty care setting, National Diabetes Register, prescribed drug register, the patient register and the cause of death register, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age >=85 or <45 yrs, not registered in Nat'l diabetes Register 1 yr prior to and 1 yr following first prescription of glucose-lowering tx, less then 3 prescriptions or less than 18 fills of mulidose dispensed drugs during 12 months of continuous use of glucose-lowering med

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Erem, 2014[47] Turkey Not Extracted	RCT	Neither year reported 52	Yes	No	Not Extracted/ 60 NR	Age <30 or >70 yr, HbA1c <8% when FPG<126mg/dl, <7% if FBG is 126 -139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria NYHAC Class 3/4 CHF, history of lactic acidosis, malignancy, thyroid disease or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection
Esposito, 2011[48] Italy Not Extracted	RCT	Neither year reported 24	No	Yes	Not Extracted/ 110 investigators' practices	Age <30 and >75 years, HbA1c >10% or 7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l)
Farcasiu, 2011[50] Multi-continent Not Extracted	RCT	2006 2009 16	Yes	Yes	Not Extracted/ 302 NR	Age <30 - >75 yrs, HbA1c >1.8 X ULN or <1.2 X ULN, BMI >40 kg/m2, Any liver disease, metformin <1500mg, on other oral dm med besides metformin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Ferrannini, 2013[185] Multi-continent NCT00789035	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 408 NR	Age, <18 or >79 years, HbA1c> 9% if on antidiabetic drug, >10 if tx naïve or <6.5 if on antidiabetic drug, <7 if treatment naïve, BMI >40 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, not treatment naive or on stable dose of more than one antidiabetic drug (except GLP1, insulin, TZDs) in past 10 wks, myocardial infarction, stroke or transient ischaemic attack Γëñ6 months prior, unstable or acute congestive heart failure, acute or chronic acidosis; disease of CNS, psychiatric d/o or clinically relevant neuro d/o, chronic or clinically relevant acute infection, current or chornic urogenital tract inf, dehydration, hereditary galactose intolerance, tx with antiobesity drugs, systemic steroids, alchol abuse, tx with investigational drug <=2 m prior, neurologic/psychiatric issues that might interfere with participation
Fonseca, 2000[54] US Not extracted	RCT	26 wks (planned duration)	Not extracted	No	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other
Fonseca, 2012[55] US and Latin America NCT00960076	RCT	2009 2010 18	Yes	Yes	Not Extracted/ 282 NR	Adults, HbA1c >11% or <7.5%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradind to / h/o tx w/ saxa

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Forst, 2010[56] Europe NCT00309608	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 333 NR	Age <21 or >75 yr, HbA1c>9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase or HbA1c >7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening, one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months
Gallwitz, 2012[60] Multi-continent NCT00622284	RCT	2008 2010 104	Yes	Yes	Not Extracted/ 1552 Outpatient: primary care, Outpatient: subspecialty care setting	Age <18, >80 years, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening
Gallwitz, 2012[61] Multi-continent NCT00359762, EudraCT 2005-005448-21	RCT	2006 2011 48	No	Yes	Not Extracted/ 1029 NR	Age <18 or >85 yrs, HbA1c >9% or <6.5%, BMI <25 or >=40 prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Garber, 2003[63] US Not extracted	RCT	16 wks (planned duration)	Not extracted	Yes	Not extracted	Age < 20 or >79 years, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other
Garber, 2011[66] US Mexico NCTC00294723	RCT	2006 2008 104	No	Yes	Not Extracted/ 746 NR	Age <18 or >80, HbA1c >11% if on diet/exercise or >10% if on monotherapy or <7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia
Genovese, 2013[67] Italy NCT00772174	RCT	Neither year reported 24	Yes	Yes	Not Extracted/ 213 NR	Age <35 or >75 yr, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin, acute or chronic pancreatitis or familial polyposis, history of chronic alcohol or drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Genovese, 2013[68] NR ACTRN12608000534381	RCT	Neither year reported 16	Yes	Yes	Not Extracted/ 58 Outpatient: subspecialty care setting	Age <35 or >75 yr, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures, participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, congestive heart failure (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,, known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients (pioglitazone, met marked above)
Goke, 2010[69] Multi-continent NCT00575588	RCT	2007 2010 104	Yes	Yes	Not Extracted/ 858 NR	Age <18 years, HbA1c >10% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Гüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment, congestive heart failure, significant cardiovascular history within the past 6 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Goldstein, 2003[70] US Not extracted	RCT	18 wks (planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >12.0%, other
Gomez-Perez, 2002[72] Mexico Not extracted	RCT	26 wks (planned duration)	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Haak, 2012[76] Multi-continent NCT00798161	RCT	2008 2010 24	Yes	Yes	Not Extracted/ 791 NR	Age <18 or >80 years, HbA1c >10.5% if on OAD or >=11% if treatment naïve or <7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months
Haak, 2013[77] Multi-continent NCT00915772	RCT	2009 2011 52	Yes	Yes	Not Extracted/ 567 NR	Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication, alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation
Hallsten, 2002[78] Finland Not extracted	RCT	26 wks (planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[79] Multinational Europe, Mexico Not extracted	RCT	Neither year reported 52 Wks	Yes	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any ODM other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/dl for men and < 10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170 mmHg, DBP >100 mmHg
Hanefeld, 2004[80] Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and Netherlands Not extracted	RCT	NR	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other
Hanefeld, 2007[81] Multinational Europe Not extracted	RCT	Neither year reported 52 Wks	Run-in period but number of participants excluded was NR	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG: <7 mmol/l or >15 mmol/l, C-peptide <0.27 nmol/l

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Haring, 2014[82] Multi-continent NCT01159600	RCT	2010 2012 24	Yes	Yes	Not Extracted/ 638 NR	Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d, eGFR<30
Henry, 2012[83] Multi-continent NCT00643851	RCT	2008 2009 24	Yes	Yes	Not Extracted/ 603 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease
Henry, 2012[83] Multi-continent NCT00859898	RCT	2009 2010 24	Yes	Yes	Not Extracted/ 641 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months
Hermann, 1994[85] Sweden Not extracted	RCT	6 months (planned duration)	Not extracted	Yes	Not extracted	No Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hermans, 2012[86] Europe NCT01006590	RCT	Neither year reported 24	Yes	Yes	Not Extracted/ 286 NR	Age <18 yrs, HbA1c >10, HbA1c <7, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu- cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d
Home, 2009[88] Multinational Europe Not extracted	RCT	Start year: 2001 End year: 2003 7.5 Years	Run-in period but number of participants excluded was NR	Yes	7428/4458 Outpatient: primary care	Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, HbA1c < 7% or >9%, BMI <25 kg/m^2, pregnant, nursing, not using adequate contraception, recent CAD event, heart failure
Hong, 2013[186] China NCT00513630	RCT	2004 2007 36	Yes	Yes	Not Extracted/ 304 clinical centers	Age >80yr, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, not diagnosed as CAD (either having a history of acute myocardial infarction diagnosed by a representative set of electrocardiograms, cardiac enzyme values, and typical symptoms or by angiographically identified stenosis of >50% of lumen diameter in at le, severe dysfunction of the heart (NYHA class > phase 3), other severe organic heart diseases, including but not limited to congenital heart disease, rheumatic heart disease, hypertrophic or dilated cardiomyopathy; psychiatric disease, severe infection, severe anemia, Neutropenia, allergic to study drugs, fasting plasma glucose>=15 mmol/l, recent drug or alcohol abuse

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Horsdal, 2011[187] Denmark Not Extracted	Case-control	1996 2004 6	No	Yes	Not Extracted/ 101313 Administrative database, Danish National Patient Registry, Registry of Medicinal Product Statistics, National Health Insurance Service Registry, Inpatient diagnosis/ procedures, Outpatient diagnosis/ procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <30, controls matched up to 10:1 to the cases based on age and gender
Hsiao, 2009 {Hsiao, 2009 #35295} Taiwan Not extracted	Cohort	Start year: 2000 End year: 2005 6 years	NA	NR	NA/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hung, 2012[188] US Not extracted	Retrospective cohort	2001 2008 0.7-0.9	Not applicable	No	Not Extracted/ 93577 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting, VA health system, VA health system, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Any liver disease, Any kidney disease, less than 365 days of active use of VHA pharmacy services with diabetes drug filled, unknown birthdate, gender, race, less than 365 days of baseline data, missing eGFR, missing creatinine, CHF, HIV/AIDS, cancer except non-melanoma skin ca, transplant, cocaine use, baseline Cr>1.5, eGFR<60, combo therapy
Hung, 2013[189] Taiwan Not extracted	Retrospective cohort	1998 2007 3.1-3.8	Not applicable	No	Not Extracted/ 1159 Administrative database, Taiwan National Health Insurance Research Database, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures	Age <30 yrs, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, cancer, followup <0.5 yr, Use of concomitant DM2 medications

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hung, 2013[190] US Not extracted	Retrospective cohort	1999 2008 About 1 year	Not applicable	No	Not Extracted/ 13238 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting, VA Mid-South VISN 9 Data Warehouse, VA Mid-South VISN 9 Data Warehouse, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, receive regular care in Veterans Health, Administration healthcare system, HIV/AIDS, cancer, end stage respiratory disease, organ transplant during baseline yr, CHF, ESRD, end stage liver disease
Jadzinsky, 2009 {Jadzinsky, 2009 #35267} Multi-continent Not extracted	RCT	Start year: 2006 End year: 2007 24 wks	Fewer than 10% participants excluded	Yes	2936/1394 Outpatient: primary care, Outpatint: subspecialty care	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c < 8% or >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[91] US, Puerto Rico Not extracted	RCT	Neither year reported 56 Wks	Run-in period but number of participants excluded was NR	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c< 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to Rosi, Pio or Troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg/day, oral antidiabetic drugs, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria , anemia (< 10g/dl women, < 12g/dl men), BMI ≤20kg/m^2 or >45kg/m^2, hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Johnson, 2005[191] Canada Not extracted	Cohort	Median follow-up periods for each group ranged from 4.6 to 5.6 yeas	Not extracted	No	Not extracted	Age < 30 years, no Type 2 DM, other
Jones, 2003[192] US Not extracted	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	NR	NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history chronic insulin, FPG <140 or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Kadowaki, 2013[94] Japan NCT00363948	RCT	2006 2008 12	Yes	Yes	Not Extracted/ 149 NR	Age <20 or >=75yr, HbA1c >9.4% for patients receiving an OHA other than met at screening, 10.5% for patients with met only at screening, 10.5% for all patients completing the run-in period, HbA1c <6.4% for patients receiving an OHA other than met at screening, 6.9% for patients with met only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks
Kahler, 2007[193] US Not extracted	Cohort	Start year: 1998 End year: 2001 3 Years	NA	No	> 1500000/39721 VHA Medical facilities	Age <18 years, non-respondents to 1999 LHSVE survey, medical facilities that do not have assays certified by the National Glycohemoglobin Standardization Program, less than 15 month window period after 1 year exposure to drug, alive as of 31 December 2000, fixed one year window of drug exposure
Kahn, 2006[95] Multi-continent Not extracted	RCT	Start year: 2000 End year: 2006 6 Years	No run-in period	Yes	6676/4360 NR	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or > 180 mg/dL, history of lactic acidosis
Kaku, 2011[97] Japan NCT00393718	RCT	2006 52	Yes	Yes	Not Extracted/ 411 NR	Age <20 yrs, HbA1c >10.4%, HbA1c <7.4%, not able to self monitor blood glucoses

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Kikuchi, 2012[99] Japan NCT00297063	RCT	2005 2007 28	No	Yes	Not Extracted/ 373 NR	Age <20 - >75, HbA1c <7.4, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy, edema, unstable or serious angina, MI in past yr, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy, serious neuropathy requiring tx
Kvapil, 2006[103] Multinational Europe Not extracted	RCT	Neither year reported 16 Wks	No run-in period	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria includes not adequately controlled on metformin
Lavalle-Gonzalez, 2013[104] Multi-continent NCT01106677	RCT	Neither year reported 56	Yes	Yes	Not Extracted/ 1284 NR	Age <18 or >80, HbA1c >10.5, HbA1c <7, Prior or current use of insulin, Any kidney disease, not on MFM (ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG), ГëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening; cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening uncontrolled HTN
Lawrence, 2004[105] UK Not extracted	RCT	12 titration, 12 week maintenance (planned duration)	Not extracted	Yes	Not extracted	Age <45 or >80 years, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes: <7% or >10% for low-dose ODM: >7.5%, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
List, 2009[107] US Canada Mexico, Puerto Rico NCT00263276	RCT	2005 2006 12	Yes	Yes	Not Extracted/ 389 "98 clinical centers"	Age <18, >79, HbA1c >10, HbA1c >7, BMI >40, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml
Malone, 2003[110] 14 countries not specified Not extracted	randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 Wks	Fewer than 10% of participants were excluded during run-in	Yes	NR/597 subgroup completing test meals	Age <30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days
Malone, 2004[194] US Not extracted	RCT	Neither year reported 32 Wks	Yes	Yes	145/111 NR	Not extracted Age <30 or >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m^2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start
Malone, 2005 {Malone, 2005 #35308} Multinational Europe Not extracted	RCT	Neither year reported 32 wks	Yes	Yes	119/97 NR	Age <30 or >75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Masica, 2013[195] US Not extracted	Retrospective cohort	1998 2009 2.8 - 3.2	Not applicable	No	Not Extracted/ 1921 electronic health record encounters, Baylor Health Care System (BHCS; Dallas, TX) and Christiana Care Health System (CCHS; Newark, DE), Outpatient diagnosis/procedures	Age <21, Prior use of any diabetes treatment, Prior or current use of insulin, ΓÇóPatients with a T2D-related bill with a date of serviceΓëÑ90 days before EHR problem onset date were designated as pre-existing and excluded from the cohort, <90 days of exposure to metformin, sulfonylureas, or thiazolidinediones (or any combination of those three agents) over the study period
Mogensen, 2014[196] Denmark Not extracted	Retrospective cohort	2007 2011 2.1	Not applicable	No	Not Extracted/ 40028 National databases of inpatient, outpatient, medication and mortality information Administrative database, Danish National Patient Registry, Danish Registry of Medicinal Product Statistics, Danish National Population Registry, National Causes of Death Register, Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Users of glucose lowering treatment before 1 January 1997 with unknown treatment duration, Prior myocardial infarction (ICD-10: I21-I22, ICD-8: 410), Prior stroke (ICD-10: I61-I64, ICD-8: 431ΓÇô434)

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Nakamura, 2000[113] Japan Not extracted	RCT	3 months (planned duration)	Not extracted	No	Not extracted	Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other
Nakamura, 2004[114] Japan Not extracted	RCT	Neither year reported 12 Months	No run-in period	NR	NR/45 Inpatient/hospital	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c > 6.5%, BP <140/90 mm Hg, controlled on diet alone, no history ketoacidosis, c peptide <0.33mmol/L, creatinine <1.5, no BP meds, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease
Nakamura, 2006 {Nakamura, 2006 #35221} Japan Not extracted	RCT	Neither year reported 12 months	No run-in period	NR	NR/68 NR	HbA1c >6.5%, history of ketoacidosis, treatment other than by diet alone, fasting C-peptide level < 0.33 mmol/L, hematuria, non-diabetic renal disease, microalbuminura defined as a median urinary albumin excretion of 20 to 200 ug/min
Nauck, 2007[116] US, Multinational Europe, Multi-continent Not extracted	RCT	Neither year reported 52 Wks	Yes	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2009[117] Multi-continent NCT00286442	RCT	Neither year reported 26	Yes	Yes	Not Extracted/ 527 NR	Age<18 or >80 yr, HbA1c >10.00%, HbA1c <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen, h/o cardiac surgery or cardiovascular disease in last 6 months, history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years), laser treatment for proliferative diabetic retinopathy within 6 months, history of treated diabetic gastroparesis, New York Heart Association Class 3 or 4 heart failure
Nauck, 2011[118] Multi-continent NCT00660907	RCT	2008 52	Yes	Yes	Not Extracted/ 814 NR	Age < 18 years, HbA1c >10%, HbA1c <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2014[119] NR NCT00734474	RCT	Neither year reported 52	Yes	Yes	Not Extracted/ 1098 NR	Age<18 or >75 years, HbA1c >= 9.5%, HbA1c <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, Duration of diabetes <6 months, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry
Pantalone, 2009 {Pantalone, 2009 #35281} United States Not extracted	Cohort	Start year: 1998 End year: 2006 8 years	NA	Yes	NA/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF
Pantalone, 2012[197] US Not extracted	Retrospective cohort	1998 2006 2.2	Not applicable	Yes	Not Extracted/ 23915 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting, Cleveland Clinic EMR including main campus or family health centres, Cleveland Clinic EMR including main campus or family health centres, Inpatient diagnosis/procedure, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Prior or current use of insulin, Prior or current use of study drug, Any kidney disease, does not have at least two encounters for diabetes after visiting the Cleveland Clinic main campus or family health centres, Patients prescribed insulin or other injectable diabetes medications (as monotherapy or in conjunction with oral agents), and those on multiple oral agents at baseline, were excluded.

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Petrica, 2009[124] Romania Not extracted	RCT	Neither year reported 12	No	No	Not Extracted/ 44 Outpatient: subspecialty care setting	HbA1c <7%, < 5 years, no poor glycemic control with previous medication, no stable therapy with metformin for at least 6 months CKD of non-diabetic origin, symptoms or history of, cerebrovascular disease (TIA, stroke), micro/macroalbuminuria, thyroid dysfunction, abnormal albuminuria, microangiogrpahic complications
Pfutzner, 2011[126] Germany (assumed based on author affiliations) NCT00770653	RCT	Neither year reported 24	No	Yes	Not Extracted/ 305 NR	Age <18 - >75, HbA1c <6.5, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV)
Pfutzner, 2011[127] Multi-continent NCT00327015	RCT	Neither year reported 76	Yes	Yes	Not Extracted/ 1306 Community outpatient settings (unspecified)	Age <18 or >77 years, HbA1c >12.00%, HbA1c <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV congestive heart failure and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests
Pratley, 2010 {Pratley, 2010 #7211} Multi-continent, Europe, USA and Canada Not extracted	RCT	Neither year reported 2 years	No run-in period	Yes	1302/665 “office based”- possibly outpatient	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin ODM in past 3 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Pratley, 2014[129] Multi-continent NCT01023581	RCT	Neither year reported 26	Yes	Yes	Not Extracted/ 784 NR	Age <18yr or >80 yr, HbA1c >10%, HbA1c <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Гёñ 12 and Гёñ 10 g/dL for men and women, respectively), elevated blood pressure (ГёÑ 150 and ГёÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy;
Qiu, 2014[130] Multi-continent NCT01340664	RCT	Neither year reported 22	Yes	Yes	Not Extracted/ 279 NR	Age <18 or >80, HbA1c >10.5 or <7, Any kidney disease, FPG and/or fasting self-monitored blood glucose 15.0 mmol/L during the pretreatment phas, diabetic ketoacidosis, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks, not completing the placebo run-in period

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Raz, 2008[180] Multi-continent Not extracted	RCT	Neither year reported 30 Wks	Run-in period but number of participants excluded was NR	Yes	544/190 NR	Age <18 or >78 years, HbA1c <8% after run-in or HbA1c >11% after run-in, BMI <20 kg/m^2 or >43 kg/m^2, pregnant, nursing, insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, Type 1 DM, FPG <7.2 mmol/l or >15.6 mmol/L consistently during run-in, no Type 2 DM
Reasner, 2011[133] US NCT00482729	RCT	2007 2009 44	Yes	Yes	Not Extracted/ 1250 NR	Age <18 or >78 years, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes
Ridderstrale, 2014[134] Multi-continent NCT01167881	RCT	2010 2011 104	Yes	Yes	Not Extracted/ 1549 NR	Age <18, HbA1c >10 or <7, BMI>45, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization, blood glucose concentration greater than 13 mmol/L after an overnight fast during the placebo run-in, confirmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2009 {Rigby, 2009 #7711} United States, Multi-continent Not extracted	RCT	Start year: 2007 End year: 2008 16 wks	No run-in period	Yes	356/169 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c < 7% (6.5% if on metformin combination therapy), BMI > 40 kg/m2, LDL<50mg/dl or TG > = 500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for >=3 months (1500-2550 mg/day, Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening
Roden, 2013[137] Multi-continent NCT01177813.	RCT	2010 2012 24	Yes	Yes	Not Extracted/ 899 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting, academic medical ctrs, hospitals, and private practices	Age <18, <20 in Japan, <18 or >65 in India HbA1c >10 or 9 in Germany or <7, BMI >45, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13 3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label,, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent, any uncontrolled endocrine disorder apart from type 2 diabetes., did not meet inclusion criteria after placebo run-in

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2006[138] Multi-continent Not extracted	RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1252/468 multicenter	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half live of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis
Rosenstock, 2013[141] Multi-continent NCT00707993	RCT	Neither year reported 52	Yes	Yes	Not Extracted/ 441 NR	Age <65 or >90 yr, HbA1c> 9.0% for patients on diet and exercise therapy alone, 8.0% for patients on oral antidiabetic monotherapy & 9.0% after washout period without medications within 2 wks 6.50%, not able or unwilling to self-monitor blood glucose with a home glucose monitor
Rosenstock, 2013[142] Multi-continent NCT00749190	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 495 NR	Age <18 or >80, HbA1c >9 if on MFM and one other OAD or >10 if on MFM monotherapy or < 6.5 if on MFM and one other OAD, <7 if on MFM monotherapy, BMI >40, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ГёÑ1500 mg/day or maximum tolerated dose); diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity; treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months. h/o of MI, CVA, or TIA in past 6 mo HbA1c <7 or >10 at start of placebo run-in history of clinically relevant allergy/hypersensitivity treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Ross, 2012[143] Multi-continent NCT01012037	RCT	2009 2010 12	Yes	Yes	Not Extracted/ 491 NR	Age <18 or > 80yr, HbA1c> 10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in or < 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study) treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months
Roumie, 2012[198] US	Retrospective cohort	2001 2008 0.78 (metformin), 0.61 (sulfonylurea)	Not applicable	No	Not Extracted/ 253690 VA databases linked to Medicare files, VA databases linked to Medicare files, Inpatient diagnosis/ procedures, Outpatient diagnosis/ procedures, Inpatient pharmacy records, Outpatient pharmacy records	Age <18, Prior use of any diabetes treatment, Prior or current use of insulin, Any kidney disease, initiating oral monotherapy before 10/1/2001 or after 9/30/2008, not receiving regular VHA care (a VHA encounter or prescription fill at least once every 180 days) for at least the past 365 days, not a new user (<365 days since filled prescription for oral or injectable diabetic drug), serious mental illness, serious medical conditions identi∩¼ued at baseline (heart failure, HIV, cancer except for nonmelanoma skin cancer, organ transplantation, end-stage kidney or liver disease, or respiratory failure), baseline serum creatinine level of 133 mol/L (1.5 mg/dL) or greater, cocaine use, combination therapy
Russell-Jones, 2012[144] Multi-continent NCT00676338	RCT	2008 2010 36	No	Yes	Not Extracted/ 820 NR	Adults, HbA1c >11 or <7.1, BMI <23 - >45, Prior use of any diabetes treatment, unstable weight

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Scheller, 2014[199] Denmark	Retrospective cohort	2007 2011 0.9-1.8	Not applicable	No	Not Extracted/ 84756 Administrative database, The Danish National Patient Register - The Danish Register of Medicinal Product Statistics and the National Causes of Death Register, Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <20, The metformin group was restricted to patients who had not received glucose-lowering drugs prior to the therapy with metformin, DPP-IV inhibitor users were only included if they had not received a glucose-lowering drug, except for metformin, prior to the treatment with sitagliptin, excluded if the duration of treatment with sitagliptin or metformin monotherapy was less than 30 days
Schernthaner, 2004[145] Europe Not extracted	RCT	12 months (planned duration)	Not extracted	No	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Schramm, 2011[200] Denmark	Retrospective cohort	1997 2006 3.3	Not applicable	No	Not Extracted/ 107806 Administrative database, The National Patient Registry (Denmark) and The Danish Registry of Medicinal Product Statistics Inpatient diagnosis/ Procedures, Outpatient pharmacy records, Death registry	Age >20, initiated single-agent treatment with an IS or metformin
Scott, 2008[148] Multi-continent Not extracted	RCT	Neither year reported 18 Wks	Run-in period but number of participants excluded was NR	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c < 7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL
Seck, 2010 {Seck, 2010 #7175} NR Not extracted	RCT	Neither year reported 2 years	Run-in period but number of participants excluded NR	Yes	2141/1172 NR	Age <17 or >78 years

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Seino, 2010[150] Japan Not extracted	RCT	Neither year reported 24 wks	Yes	Yes	NR/464 NR	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c < 7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Seino, 2012[151] Japan NCT01318109	RCT	2008 2009 12	Yes	Yes	Not Extracted/ 288 outpatient, but not specified	Age <20 or >=65years, HbA1c >=10.4% after 8 wks of observation or <6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, HbA1c >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis, h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, gastrointestinal disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg
St John Sutton, 2002[154] US Not extracted	RCT	52 wks (planned duration)	Not extracted	Yes	Not extracted	Age <40 or age >80 years, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Stenlof, 2014[201] NR NCT01081834	RCT	Neither year reported 52	Yes	Yes	Not Extracted/ 587 NR	Age <18 or >80, HbA1c >10 or <7, Prior or current use of study drug, Any kidney disease, if on AHA other than PPAR agonist or combination MFM+SU, FPG >15 mmol/l, h/o type 1 dm, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening
Stewart, 2006[155] Multinational Europe Not extracted	RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1397/526 NR	Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG < 6.0 mmol/l or > 8 mmol/l, prior history of exposure to thiazolidinediones within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Umpierrez, 2014[165] Multi-continent NCT01126580	RCT	2010 2012 52	Yes	Yes	NR	Age <18 years, HbA1c >9.50% or <6.50%, <3 months or >5 years, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months
Weissman, 2005[167] US Not extracted	RCT	Neither year reported 24 wks (planned duration)	Run-in period but number of participants excluded was NR	Yes	1270/766 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% for subjects having received prior combination treatment (metformin + SU), HbA1c >8.5% for subjects having received prior combination treatment (Metformin + SU), BMI <27 kg/m^2, HbA1c < 7% for drug naive or prior monotherapy subjects, HbA1c > 10% for drug naive or prior monotherapy subjects, FPG < 126 mg/dL or >270 mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non -compliant patient with metformin up-titration

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Wheeler, 2013[202] US	Retrospective cohort	2004 2009 1.4-1.7	Not applicable	No	Not Extracted/ 193,172 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting, VA, Inpatient diagnosis/procedures, Outpatient diagnosis/ procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Prior use of any diabetes treatment, less than 2 consecutive prescription of SU, MFM or rosi within 200 days between 1/1/2004 and 12/31/2009, veterans who did not have prescriptions for non-diabetes medications during the year before this first prescription for an oral diabetes medication, because for these individuals we could not distinguish whether they were new users of oral diabetes therap, persons without an outpatient visit to a VHA facility in the year before the first prescription for an oral diabetes medication., renal allograft, type 1 diabetes, history of CHF, serum creatinine level ГёÑ132.6 ╝╜ mol/l (or were missing values), initial dm2 prescription not a study drug or started on dual therapy, other medical exclusions including ketoacidosis, diabetic coma, kidney transplant
White, 2014[168] Multi-continent NCT00885378	RCT	2009 2010 12	Yes	Yes	Not Extracted/ 160 outpatient	Age <18 and >78 years, HbA1c >10% or <7%, BMI >45, Pregnant Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies
Williams-Herman, 2010[170] Multi-continent NCT00103857	RCT	Neither year reported 104	Yes	Yes	Not Extracted/ 1091 NR	Age <18 or >78 years, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Yang, 2011[172] Multinational Asia (China - India – SouthKorea NCT00661362	RCT	Neither year reported 24	Yes	Yes	Not Extracted/ 570 NR	Age <18, HbA1c >10 or <7, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducersHemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past yr, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhib
Yang, 2012[174] China NCT00813995	RCT	2009 2010 24	Yes	Yes	Not Extracted/ 395 NR	Age <18 - >78, HbA1c >11 or <7.5, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Diabetes type 1, history of ketoacidosis, CHF, unstable CHD, not Chinese, able to get off other diabetes meds during run-in prior use of TZDs
Zhang, 2012[179] China Not extracted	RCT	Neither year reported 16	Yes	Yes	Not Extracted/ 42 check up center at hospital	HbA1c >10.00% or <7.00%, Prior or current use of insulin, Any liver disease, History of CVD, did NOT have a 24h urinary albumin level <30 or >300 mg/24h after determination from 2 samples, statins, angiotensin II receptor blocker, angiotensin-converting enzyme inhibitors in the previous 2 wks, had primary nephropathy or secondary kidney disease besides diabetic nephropathy, had rheumatic disease, had acute diabetic complications, patients failed to keep FPG between 4.4-8.0mmol/l and maintain 2h-PG<11.1mmol/l

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table 6. Population characteristics of studies evaluating diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Brownstein, 2010[182]	Pioglitazone, 806	63.7	52	NR	NR NR	8.1	NR	NR
	Rosiglitazone, 1879	64	51.7	NR	NR NR	8	NR	NR
	Metformin, 12490	61.7	49.9	NR	NR NR	7.8	NR	NR
	Any in the Sulfonylurea class, 11200	65.8	57.5	NR	NR NR	7.7	NR	NR
Seino, 2010[150]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Aschner, 2010[7]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[149]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, O: 4	30.9 88.5 kg	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, O: 3.1	31.3 90.3 kg	7.3	5.7	328
Pratley, 2010[128]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, O: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, O: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, O: 4	33.1 94.6 kg	8.4	6.4	52
Pantalone, 2009[203]	Rosiglitazone, 1079	61.4	45.5	C: 86.8	32.7 NR	7.3	NR	NR
	Any in the Sulfonylurea Class, 7427	66.1	49.5	C: 78	31.1 NR	7.6	NR	NR

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 1508	61.6	48.3	C: 83.5	33 NR	7.4	NR	NR
	Metformin, 10436	56.8	41.18	C: 76.9	33.8 NR	7.7	NR	NR
Hsiao, 2009[204]	Metformin, 46444	59	48.22	NR	NR NR	NR	NR	NR
	Rosiglitazone, 2093	61.24	53.46	NR	NR NR	NR	NR	NR
	Pioglitazone, 495	60.75	52.02	NR	NR NR	NR	NR	NR
	Any in the Sulfonylurea class, 97651	60.71	54.1	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 267754	57.17	54.45	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 2408	57.3	49.8	NR	NR NR	NR	NR	NR
Rigby, 2009[135]	Metformin + rosiglitazone, 56	54.7	41.1	AA: 3.6, Asian: 0, C: 28.6, H: 67.9, O: 0	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2, Unspecified: 1.8	NR 79.6 kg	8.17	8.35	11
Jadzinsky, 2009[90]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, O: 5	29.9 NR	9.4	2	NR
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, O: 5.9	30.3 NR	9.5	1.4	NR
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, O: 6.4	30.2 NR	9.4	1.7	NR
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, O: 5.4	30.2 NR	9.6	1.7	NR
Home, 2009[88]	Rosiglitazone, 2220	58.4	51.4	C: 99.1	31.6 NR	7.9	7	218
	Rosiglitazone + sulfonylurea, 1103	59.8	49	NR	30.3 85.0 kg	8	7.9	NR

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + sulfonylurea, 1122	59.7	50.6	C: 99.1	NR 84.3 kg	8	7.9	NR
	Metformin + sulfonylurea, 1105	57.2	52.9	C: 98.4	NR 93.3 kg	7.8	6.3	NR
	Metformin + rosiglitazone, 1117	57	53.8	C: 98.9	NR 93.5 kg	7.8	6.1	NR
	Metformin + sulfonylurea, 2227	58.5	51.7	C: 98.7	31.5 NR	7.9	7.1	233
Scott, 2008 [148]	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, Others: 3	30.4 84.9 kg	7.7	4.6	2
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Others: 1	30.3 83.1 kg	7.8	4.9	9
	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
Raz, 2008[180]	Metformin + sitagliptin, 96	53.6	51	AA: 3, C: 42, H: 32, Multiracial: 22, Not Specified: 1	30.1 81.5 kg	9.3	8.4	18
	Metformin, 94	56.1	41.5	AA: 1, C: 47, H: 25, Multiracial: 25, Not Specified: 2	30.4 81.2 kg	9.1	7.3	16
Hamann, 2008[79]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4 kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9 kg	8	6.4	71
Chien, 2007[27]	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
Comaschi, 2007[28]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14
Kahler, 2007[193]	Any in the Sulfonylurea class, 19053	68.2	NR	AA: 12.6, C: 78.6, O: 8.8	29.6 NR	7.2	(<1: 12.8, 1-3: 32.2, 4-10: 33.4, > 11: 20)	NR
	Metformin, 2988	64.9	96.9	AA: 12.7, C: 78.7, O: 8.7	30.4 NR	7	(<1: 20.5, 1-3: 41.5, 4-10: 25.1, >11: 11.6)	NR
	Metformin + sulfonylurea, 13820	65.6	98.1	AA: 13.2, C: 77.5, O: 9.3	30.3 NR	8	(<1: 4.5, 1-3: 21.2, 4-10: 43.3, >11: 29.1)	NR
	TZD, 675	67.1	97.5	AA: 8.7, C: 80.9, O: 10.4	30.7 NR	7.9	(<1: 3.3, 1-3: 18.2, 4-10: 39.9, >11: 37.5)	NR
Nauck, 2007[116]	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, O: 3.7	NR NR	7.7	6.5	202
	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, O: 3.4	31.3 89.7 kg	7.6	6.2	172
Hanefeld, 2007[81]	Rosiglitazone, 189	60.6	57.7	AA: 0, C: 97, O: 3	28.8 NR	8.2	6	9
	Glibenclamide, 203	60.1	70.4	AA: 0, C: 99, O: 0.5	28.7 NR	8.2	6.4	13
	Rosiglitazone, 195	60.4	68.2	AA: 0, C: 98.5, O: 1.5	28.7 NR	8.1	5.9	12
	Glibenclamide, 18	53.5	55.6	NR	NR NR	7.8	16.5	NR
Kahn, 2006[95]	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 5.2, O: 0.7	32.2 91.5 kg	7.36	(<1: 651, 1-2: 758, >2: 47)	539
	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, O: 0.3	32.2 92 kg	7.35	(<1 year: 637, 1-2: 751, >2: 53)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, O: 1	32.1 91.6 kg	7.36	(< 1 year: 673, 1-2: 724, >2: 57)	551

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Rosenstock, 2006[138]	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, O: 3	32.8 NR	8.8	2.7	22
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, O: <1	32.5 NR	8.8	2.9	31
Jain, 2006[91]	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, O: 0.4, Native American: 0.4	32.5 93.9 kg	9.2	0.8	117
	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, O: 0.4	32.8 94.3 kg	9.2	0.78	123
Stewart, 2006[155]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/Other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian/Other Pacific Islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[12]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Kvapil, 2006[103]	Metformin + glibenclamide, 114	58.1	45.6	NR	30.5 84.0 kg	9.4	8.1	5
	Metformin + aspart 70/30, 116	56.4	45.7	NR	30.4 85.1 kg	9.3	6.7	11
Malone, 2005[205]	Metformin + lispro 75/25, 50	59.18	50	NR	29.41 77.82 kg	8.5	13.52	3
	Metformin + glargine, 47	59.63	38	NR	29.64 77.21 kg	8.48	11.9	10
Agarwal, 2005[206]	Pioglitazone, 22	67	100	AA: 14, C: 86	32 97 kg	7.7	16	1

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Glipizide, 22	64	100	AA: 27, C: 73	34 102 kg	7.7	14	3
Malone, 2004[194]	Pooled arms		63	NR	30.9 91.5 kg	8.7	9	NR
	Metformin + lispro 75/25	NR	NR	NR	NR NR	NR	NR	3 during this arm
	Metformin + glargine	NR	NR	NR	NR NR	NR	NR	7
Nakamura, 2004[114]	Pioglitazone, 15	57	60	NR	NR NR	7.9	17.5	NR
	Glibenclamide, 15	55	53.3	NR	NR NR	7.8	19.2	0
Malone, 2003[110]	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, O: 3	29.8 83.0 kg	9.17	8.0	25
	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, O: 4	29.6 81.7 kg	9.27	7.4	29
Jones, 2003[192]	Metformin, 82	60	74	NR	28 NR	8.8	6	NR
	Metformin, 22	64	9	NR	23 NR	8.6	6.5	NR
	Metformin + rosiglitazone, 35	62	71	NR	23 NR	9.3	8	NR
	Metformin + rosiglitazone, 141	58	69	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 142	57	57	NR	34 NR	8.8	5	NR
	Metformin, 121	58	70	NR	34 NR	8.7	5	0
Weissman, 2005[167]	Metformin, 384	55.7	NR	NR	33.8 96.7 kg	7.97	NR	95
	Metformin + rosiglitazone, 382	55.5	NR	NR	34.4 98.2 kg	8.05	NR	76

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Bailey, 2005[9]	Metformin, 280	57.6	57	AA: <1, Asian: 1, C: 98, O: 1	32.1 89.5 kg	7.5	6.1	44
	Metformin + rosiglitazone, 288	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9 kg	7.4	6	30
Johnson, 2005[191]	Unspecified Sulfonylurea, 2138	67.8	59	NR	NR NR	NR	NR	NR
	Metformin, 923	64.3	52	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 1081	62	54	NR	NR NR	NR	NR	NR
Schernthaner, 2004[145]	Placebo + diet + Metformin, 597	56	57.8	NR	31.4 89.7 kg	8.7	3.1	96
	Placebo + diet + pioglitazone, 597	57	52.6	NR	31.2 88.2 kg	8.7	3.4	98
Hanefeld, 2004[80]	Placebo + unspecified Sulfonylurea + pioglitazone, 319	60	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	259
	Placebo + Metformin + unspecified Sulfonylurea, 320	60	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0 Other: 0.6	30 84.9 kg	8.8	7.1	279
Lawrence, 2004[105]	Metformin, 20	59.5	60	NR	29.2 NR	NR	NR	NR
	Pioglitazone, 20	60.4	70	NR	30.6 NR	NR	NR	NR
Garber, 2003[63]	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	NR
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	NR
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	NR
Goldstein, 2003[70]	Metformin + glipizide, 87	54.6	58.60	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	NR

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Glipizide, 84	57.4	64.30	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	NR
	Metformin, 76	56.6	61.80	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	NR
Bakris, 2003[11]	Rosiglitazone, 104	55.1	72.1	NR	NR NR	9.1	NR	NR
	Glyburide, 99	56.1	71.7	NR	NR NR	9.5	NR	NR
Hallsten, 2002[78]	Diet + rosiglitazone, 14	58.6	71.4	NR	29.3 NR	6.8	NR	NR
	Placebo + diet, 14	57.7	71.4	NR	30.3 NR	6.3	NR	NR
	Diet + Metformin, 13	57.8	61.5	NR	29.9 NR	6.9	NR	NR
St John Sutton, 2002[154]	Rosiglitazone, 104	55.1	75	AA: 5, C: 73, Asian: 0, H: 0, O: 22	67.3% >=27kg/m^2 86.2 kg	9.1	5.3	NR
	Glyburide, 99	56.1	71	AA: 3, C: 76, Asian: 0, H: 0, O: 21	65.7% >=27 kg/m^2 85.1 kg	9.5	6.2	NR
Gomez-Perez, 2002[72]	Placebo + Metformin, 34	53.4	29.4	C: 2.9, H: 76.5, Mestizo: 20.6	28.5 NR	NR	9.1	NR
	Metformin + rosiglitazone, 35	51.7	28.6	C: 0, H: 80, Mestizo: 20	28 NR	NR	11.1	NR
	Metformin + rosiglitazone, 36	54.2	19.4	C: 11.1, H: 72.2, Mestizo: 16.7	27.6 NR	NR	10.7	NR
Amador-Licona, 2000[178]	Glibenclamide, 23	48.2	30.4	NR	30.4 73.2 kg	8.4	4	NR
	Metformin, 28	49.3	39.3	NR	26.8 70.7 kg	8.5	4.5	NR

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Fonseca, 2000[54]	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, Asian: 0, H: 0, O: 12.7	29.8 NR	8.9	8.3	18
	Placebo + Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, Asian: 0, H: 0, O: 15	30.3 NR	8.6	7.3	22
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, Asian: 0, H: 0, O: 12.9	30.2 NR	8.9	7.5	18
Nakamura, 2000[113]	Pioglitazone, 15	60	46.7	NR	NR NR	7.7	16	NR
	Glibenclamide, 15	61	53.3	NR	NR NR	7.8	14	NR
DeFronzo, 1995[30]	Metformin, 143	53	43.4	NR	29.9 94.4 kg	8.4	6	NR
	Metformin + glyburide, 213	55	46.0	NR	29 92.1 kg	8.8	7.8	NR
	Placebo + glyburide, 209	56	49.3	NR	29.1 92.6 kg	8.5	8.7	NR
	Placebo + Metformin, 210	55	45.7	NR	29.4 92.6 kg	8.9	8.4	NR
Hermann, 1994[85]	Diet + Metformin, 25	60	63	NR	NR 78.6 kg	6.9	4	NR
	Diet + glibenclamide, 21	NR	NR	NR	NR NR	NR	NR	NR
	Diet + Metformin + glibenclamide + Other, 54	NR	80.2	NR	NR NR	NR	NR	NR
Alba, 2013[3]	Pioglitazone 54	53.4	42.6	C: 79.6, AA: 16.7, Asian: 1.9, H: 38.9, O: 1.9	NR 86.6kg	7.9	2.4	2
	Sitagliptin 52	54.6	53.8	C: 86.5, AA: 11.5, Asian: 1.9, H: 36.4, O: 0	NR 85.7kg	7.7	2.4	6
Andersson, 2010[181]	Metformin 688	69	62	NR	NR NR	NR	NR	Not applicable
	Sulfonylurea	76	57	NR	NR NR	NR	NR	Not applicable

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + Sulfonylurea	71	56	NR	NR NR	NR	NR	Not applicable
Arechavaleta, 2011[5]	Metformin + glimepiride + placebo, 519	56.2	53.8	C: 57.4, AA: 1.2, Asian: 21.4, O: 20	NR 82kg	NR	6.7	51
	Metformin + sitagliptin + placebo, 516	56.3	55	C: 57.6, AA: 1.2, Asian: 21.1, O: 20.1	NR 80.6kg	NR	6.8	48
Arjona Ferreira, 2013[6]	Glipizide + placebo 212	64.3	54.9	C: 28.2, AA: 1.4, Asian: 58.5, H: 28.9, O: 12	NR 70.2kg	7.8	10.1	19.8 %
	Sitagliptin + placebo 211	64.8	59.3	C: 29.6, AA: 1.5, Asian: 53.3, H: 33.3, O: 15.5	NR 68.0kg	7.8	10.7	22.3 %
Aschner, 2012[8]	Metformin + sitagliptin 265	53.3	52	NR	NR 84.2kg	8.5	4.8	12
	Metformin + insulin glargine, 250	53.9	50	NR	NR 83.4kg	8.5	3.9	23
Bailey, 2013[10]	Metformin + placebo 137	53.7	55	NR	31.8 NR	8.11	5.8	64
	Metformin + dapagliflozin + placebo, 137	55	51	NR	31.6 NR	7.99	6	55
	Metformin + dapagliflozin, 137	54.3	50	NR	31.4 NR	8.17	6.4	48
	Metformin + dapagliflozin + placebo, 135	52.7	57	NR	31.2 NR	7.92	6.1	40
Barnett, 2012[13]	Glimepiride 76	56.7	43.4	C: 67.1, Asian: 27.6, O: 5.3	NR 80.9 kg	8.1	NR	18
	Linagliptin 151	56.4	36.4	C: 70.2, Asian: 27.8, O: 2	NR 77.0 kg	8.1	NR	32
Bergenstal, 2010[14]	Metformin + pioglitazone + placebo 165	53	48	C: 39, AA: 8, Asian: 24, H: 27, O: 2	NR 88 kg	8.5	6	21 %
	Metformin + sitagliptin + placebo, 166	52	52	C: 30, AA: 12, Asian: 25, H: 30, O: 3	NR 87 kg	8.5	5	13 %

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + exenatide + placebo, 160	52	56	C: 33, AA: 12, Asian: 23, H: 31, O: 1	32 89 kg	8.6	6	21%
Bolinder, 2012[17]	Metformin + placebo 91	60.8	56	C: 100, AA: 0, A: 0, H: 0, O: 0	31.7 90.9 kg	7.16	5.5	20
	Metformin + dapagliflozin, 91	60.6	55.1	C: 100, AA: 0, A: 0, H: 0, O: 0	32.1 92.1 kg	7.19	6	20
Borges, 2011[18]	Metformin 340	50.7	53	C: 55, AA: 4, Asian: 34, O: 6	NR 90.6 kg	8.6	2.6	154
	Metformin + rosiglitazone, 348	51.5	53	C: 53, AA: 5, Asian: 35, O: 6	NR 87.1 kg	8.6	2.3	131
Bunck, 2011[21]	Metformin + exenatide 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	20
	Metformin + insulin glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	17
Cefalu, 2013[23]	Metformin + glimepiride, 484	56.3	55	C: 67, AA: 5, Asian: 19, O: 9	NR 86.5 kg	7.8	6.6	98
	Metformin + canagliflozin, 483	56.4	52	C: 67, AA: 4, Asian: 21, O: 9	NR 86.9 kg	7.8	6.5	88
	Metformin + canagliflozin, 485	55.8	50	C: 69, AA: 4, Asian: 19, O: 9	NR 86.6 kg	7.8	6.7	105
Corrao, 2011[183]	Metformin 21,810	60	53	NR	NR NR	NR	NR	NA
	Sulfonylurea 48,267	64.8	54.4	NR	NR NR	NR	NR	NA
DeFronzo, 2012[33]	Metformin + placebo 129	55.2	47.3	C: 72.1, AA: 6.2, Asian: 3.9, H: 48.8, Other 17.8	30.6 NR	8.5	6	14%
	Metformin + pioglitazone + placebo 130	54.1	46.9	C: 65.4, AA: 6.2, Asian: 8.5, H: 48.5, Other 20	31.3 NR	8.5	5.7	18.5%
	Metformin + pioglitazone + placebo 129	56.1	48.8	C: 74.4, AA: 4.7, Asian: 7.8, H: 51.9, iOther 13.2	31.4 NR	8.5	7.6	12.4%
	Metformin +	54.5	41.1	C: 65.9, AA: 7, Asian: 9.3, H:	30.7	8.5	5.7	16.3%

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	pioglitazone + placebo 129			47.3, O: 17.8	NR			
	Metformin + alogliptin + placebo, 128	53.1	52.3	C: 69.5, AA: 4.7, Asian: 10.9, H: 46.9, O: 14.8	31 NR	8.6	6.2	10.2%
	Metformin + alogliptin + placebo, 129	53.7	38.8	C: 62, AA: 3.9, Asian: 11.6, H: 48.8, O: 22.5	31.5 NR	8.6	5.6	9.3%
Diamant, 2010[44]	Metformin + exenatide 164			NR	NR NR	NR	NR	NR
	Metformin + insulin glargine, 157			NR	NR NR	NR	NR	NR
Ekstrom, 2012[184]	Metformin 14697	63.8	55.3	NR	30.7 NR	NR	4.6	NR
	Metformin + basal insulin, 7109	64.6	56.5	NR	31.6 NR	NR	11.6	NR
Erem, 2014[47]	Metformin 20	52.2	30	NR	NR 87.47kg	7.62	NR	1
	Pioglitazone 20	52.5	25	NR	NR 81.93kg	8.03	NR	1
Esposito, 2011[48]	Metformin 55	54.9	50.9	NR	NR 83.5kg	8.1	NR	4
	Pioglitazone 55	54.2	54.5	NR	NR 84.5kg	8	NR	4
Farcasiu, 2011[50]	Metformin + insulin lispro 75/25, 151	58.4	45.7	C: 98.7, AA: 1.3, O: 1.3	NR 85.1kg	8.5	11.5	23
	Metformin + insulin lispro 50/50, 151	57	39.1	C: 99.3, AA: 0.7	32.3 88.6kg	8.6	10.9	23
Ferrannini, 2013[185]	Metformin	58 median	48.8	C: 60, Asian: 35, O: 5	81.1kg median	NR	NR	NR
	Empagliflozin	58 median	49.4	C: 64.2, Asian: 34.6, O: 1.2	76.8kg median	NR	NR	NR
	Empagliflozin	57	50	C: 65.9, Asian: 32.9, O: 1.2	81.2kg	NR	NR	

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
		median			median			NR
Fonseca, 2012[55]	Metformin 144	55.5	51	C: 13, AA: 4, H: 61, O: 23	31 NR	8.4	5.9	25
	Metformin + saxagliptin 138	55.2	41	C: 9, AA: 7, H: 61, O: 23	30.8 NR	8.3	6.5	8
Forst, 2010[56]	Metformin + placebo 71	60.1	62	C: 97, AA: 1, Asian: 1	NR 93.1kg	8.4	6.2	14
	Metformin + glimepiride 65	59.4	63.1	C: 99, AA: 0, Asian: 2	NR 90.5kg	8.2	6.7	4
	Metformin + linagliptin 66	59.6	56.1	C: 100, AA: 0, Asian: 0	NR 90.7kg	8.5	7.3	10
Gallwitz, 2012[60]	Metformin + glimepiride + placebo, 775	59.8	61	C: 85, AA: 2, Asian: 12, O: <1	30.3 86.8 kg	7.7	NR	NR
	Metformin + linagliptin + placebo, 777	59.8	60	C: 85, AA: 3, Asian: 12, O: <1	30.2 86.1 kg	7.7	NR	NR
	Metformin + glimepiride, 514	56	52	C: 91, H: 7, O: 2	32.3 91.1 kg	7.4	5.5	128
	Metformin + exenatide 515	56	56	C: 92, H: 7, O: <1	32.6 92.8 kg	7.5	5.8	174
Garber, 2011[66]	Glimepiride + placebo 248	53.4	54	C: 77, AA: 12, Asian: 4, H: 38, O: 7	NR 93.3 kg	8.2	5.6	151
	Liraglutide + placebo 251	53.7	47	C: 80, AA: 14, Asian: 2, H: 32, O: 5	NR 92.1 kg	8.2	5.2	141
	Liraglutide + placebo 247	52	49	C: 75, AA: 12, Asian: 5, H: 35, O: 8	NR 92.6 kg	8.2	5.3	132
Genovese, 2013[67]	Metformin + placebo 103	57.8	60.2	C: 100	NR 89kg	7.02	5.7	6
	Metformin + pioglitazone, 110	57	59.1	C: 100	NR 88.8kg	6.92	5.8	13
Genovese, 2013[68]	Metformin 29	56.4	65.5	NR	NR 87.8kg	6.8	3.9	3
Genovese, 2013[68]	Pioglitazone + placebo	59.1	48.3	NR	NR	6.9	4.4	5

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	29				84.1kg			
Goke, 2010[69]	Metformin + glipizide 430	57.6	54	C: 84.2, AA: 0, Asian: 15.1, O: 0.7	31.3 88.6 kg	7.7	5.4	283
	Metformin + saxagliptin 428	57.5	49.5	C: 82.2, AA: 0.2, Asian: 17.1, O: 0.5	31.5 88.7 kg	7.7	5.5	263
Haak, 2012[76]	Metformin 144	52.9	56.9	C: 64.6, AA: 0, Asian: 35.4, O: 0	NR 79.9kg	8.7	NR	17
	Metformin 147	55.2	53.1	C: 64.6, AA: 1.4, Asian: 34, O: 0	NR 80kg	8.5	NR	21
	Linagliptin 142	56.2	56.3	C: 68.3, AA: 0, Asian: 31.7, O: 0	NR 79.1kg	8.7	NR	21
	Metformin + linagliptin 143	55.6	51	C: 72, AA: 1.4, Asian: 25.9, O: 0.7	NR 80.8kg	8.7	NR	16
	Metformin + linagliptin 143	56.4	53.8	C: 65.7, AA: 0.7, Asian: 33.6, O: 0	NR 76.7kg	8.7	NR	11
Haak, 2013[77]	Metformin, 170	55.6	54.1	C: 62.4, AA: 0.9, Asian: 36.7	29.2 NR	7.31	NR	NR
	Metformin, 170	55.7	55.7	C: 63.9, AA: 0, Asian: 36.1	29.5 NR	7.76	NR	NR
	Metformin + linagliptin, 225	55.1	55.4	C: 65.2, AA: 0, Asian: 34.8	28.3 NR	7.95	NR	NR
	Metformin + linagliptin, 225	56.8	51.3	C: 71.7, AA: 1.8, Asian: 26.5	29.8 NR	7.34	NR	
	Metformin + linagliptin 171	55.6	54.1	C: 60.4, AA: 0.9, Asian: 38.7	28.5 NR	6.93	NR	NR
	Metformin + linagliptin 171	56.1	61.7	C: 68.3, AA: 0, Asian: 31.7	28.8 NR	8.15	NR	NR
Haring, 2014[82]	Metformin + placebo 207	56	56	C: 55, AA: 1, Asian: 44, O: 0	NR 79.7kg	7.9	NR	21
	Metformin + empagliflozin, 217	55.5	58	C: 52, AA: 2, Asian: 46, O: 1	NR 81.6kg	7.94	NR	8
	Metformin + empagliflozin, 214	55.6	56	C: 53, AA: 0, Asian: 46, O: 1	NR 82.2kg	7.86	NR	18

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Henry, 2012[83]	Metformin + placebo, 201	51.8	24	NR	NR 85.6kg	9.2	0.6	30
	Dapagliflozin + placebo, 203	52.3	22	NR	NR 86.2kg	9.1	0.4	33
	Metformin + dapagliflozin, 194	51.7	21	NR	NR 84.1kg	9.2	0.3	17
Henry, 2012[83]	Metformin + placebo, 208	52.7	46.6	NR	NR 87.2kg	9.1	0.5	27
	Dapagliflozin + placebo, 219	51.1	47.9	NR	NR 88.5kg	9.1	0.6	31
	Metformin + dapagliflozin, 211	51	50.2	NR	NR 88.4kg	9.1	0.6	28
Hermans, 2012[86]	Metformin 139	58.6	54.7	C: 97.1, AA: 0.7, Asian: 1.4, O: 0.7	31.2 NR	NR	6.9	32
	Metformin + saxagliptin, 147	58.7	59.9	C: 98.6, AA: 0.7, Asian: 0.7, O: 0	32.1 NR	NR	6	28
Hong, 2013[186]	Metformin + placebo 156	62.8	78.2	NR	NR 69.6kg	7.6	5.6	32
	Glipizide + placebo 148	63.8	77	NR	NR 68.7kg	7.6	5.6	31
Hung, 2012[188]	Metformin 61104	60 median	95	C: 79, AA: 16, H: 4, O: 1	32.3 median	NR	NR	NA
	Sulfonylurea 30550	62 median	97	C: 76, AA: 18, H: 5, O: 1	30.7 median	NR	NR	NA
	Rosiglitazone 1923	64 median	97	C: 72, AA: 16, Asian: 11, O: 1	30.9 median	NR	NR	NA
Hung, 2013[189]	Metformin 595	58.7	46.2	NR	NR NR	NR	NR	NA
	Glyburide 330	60.5	56.4	NR	NR NR	NR	NR	NA

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Glimepiride 234	59.2	55.6	NR	NR NR	NR	NR	NA
Hung, 2013[190]	Metformin 7728	59 median	95	C: 77, AA: 12, O: 11	32 median	NR	NR	NA
	Sulfonylurea 4425	60 median	97	C: 77, AA: 17, O: 8	30 median	NR	NR	NA
	Metformin + Sulfonylurea 1000	58 median	96	C: 69, AA: 19, O: 13	31 median	NR	NR	NA
Kadowaki, 2013[94]	Metformin + placebo 72	57.2	68.1	NR	25 NR	8.4	7.3	5.6%
	Metformin + sitagliptin 77	59.6	71.4	NR	25.2 NR	8.2	7.7	1.3%
Kaku, 2011[97]	Glibenclamide	58.5	65.2	Asian: 100	NR 65.4 kg	9.18	8.5	16.7%
	Liraglutide	58.2	68.3	Asian: 100	NR 66.2 kg	9.32	8.1	16%
Kikuchi, 2012[99]	Rosiglitazone 160	55	62.9	Asian: 100	24.5 NR	8.9	5	11
	Pioglitazone 159	56	62.3	Asian: 100	24.9 NR	8.8	4.2	22
Lavalle-Gonzalez, 2013[104]	Metformin + placebo 183	55.3	51.4	C: 70.5, AA: 1.6, Asian: 16.4, O: 11.5	NR 86.6kg	8	6.8	28
	Metformin + sitagliptin 366	55.5	47	C: 72.1, AA: 3.6, Asian: 11.2, O: 13.1	NR 87.7kg	7.9	6.8	47
	Metformin + canagliflozin, 368	55.5	47.3	C: 68.5, AA: 4.3, Asian: 13.9, O: 13.3	NR 88.8kg	7.9	6.7	46
	Metformin + canagliflozin, 367	55.3	45	C: 69.8, AA: 3.5, Asian: 16.3, O: 10.4	NR 85.4kg	7.9	7.1	44
List, 2009[107]	Metformin 56	54	48	NR	NR 88 kg	7.6	NR	5

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Dapagliflozin 58	55	48	NR	NR 89 kg	8	NR	3
	Dapagliflozin 47	54	53	NR	NR 86 kg	8	NR	7
Masica, 2013[195]	Metformin 1314	53.9	47.8	C: 60.7, AA: 18.9, H: 6, O: 14.5	35.4 NR	7.97	NR	NA
	Sulfonylurea 209	53.7	50.6	C: 60.6, AA: 19.9, H: 5.3, O: 14.1	36.2 NR	8.06	NR	NA
	TZD 103	53.9	42.8	C: 61.5, AA: 15.1, H: 6.9, O: 16.5	34.7 NR	7.57	NR	NA
Mogensen, 2014[196]	Metformin + Sulfonylurea, 25092	62.3	59.4	NR	NR NR	NR	NR	NA
	Metformin + dpp-4 inhibitor, 11138	59.7	59.8	NR	NR NR	NR	NR	NA
	Metformin + glp-1 agonist, 4345	54.3	56.1	NR	NR NR	NR	NR	NA
	Metformin + basal insulin, 6858	57.1	60.8	NR	NR NR	NR	NR	NA
Nauck, 2009[117]	Metformin + placebo 104	56	48	C: 76, AA: 7, Asian: 6, H: 24, O: 11	32 NR	8	6	6.7 %
	Metformin + alogliptin 210	54	54.3	C: 76, AA: 6, Asian: 9, H: 32, O: 9	32 NR	7.9	6	13.3 %
	Metformin + alogliptin 213	55	47.4	C: 80, AA: 2, Asian: 8, H: 31, O: 10	32 NR	7.9	6	8 %
Nauck, 2011[118]	Metformin + glipizide 408	59	54.9	C: 80.5, AA: 6, Asian: 8.5, O: 5	31.2 NR	7.7	7	94
	Metformin + dapagliflozin, 406	58	55.3	C: 81.8, AA: 6.5, Asian: 6.8, O: 5	31.7 NR	7.7	6	84
Nauck, 2014[119]	Metformin + placebo 177	55	51	C: 51, AA: 5, Asian: 22, H: 22, O: 0	NR 87 kg	8.1	7	65 %
	Metformin + sitagliptin 315	54	48	C: 50, AA: 2, Asian: 26, H: 21, O: 1	NR 86 kg	8.1	7	77 %
	Metformin +	54	44	C: 54, AA: 4, Asian: 26, H: 17,	NR	8.2	7	59 %

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	dulaglutide, 302			O: 0	86 kg			
	Metformin + dulaglutide, 304	54	48	C: 52, AA: 5, Asian: 25, H: 18, O: 0	NR 87 kg	8.1	7	66 %
Pantalone, 2012[197]	Metformin 12774	57.7	45.8	C: 74.3	33.6 NR	NR	NR	NA
	Glipizide 4325	66.1	56	C: 74.8	30.8 NR	NR	NR	NA
	Glyburide 4279	67.8	56.3	C: 74.9	30.8 NR	NR	NR	NA
	Glimepiride 2537	65.6	54	C: 80.6	31.1 NR	NR	NR	NA
Petrica, 2009[124]	Metformin + rosiglitazone, 22	63	32	NR	33.55 NR	7.72	10.53	5
	Metformin + glimepiride, 22	63.2	32	NR	33.58 NR	7.58	10.4	5
Pfutzner, 2011[126]	Metformin + pioglitazone	59	66	NR	32.6 NR	NR	6.2	32
	Metformin + glimepiride	59	64	NR	32.5 NR	NR	5.9	29
Pfutzner, 2011[127]	Metformin + placebo, 328	51.8	49.7	C: 76.5, AA: 1.2, Asian: 15.9, O: 6.4	30.2 NR	9.4	1.7	109
	Saxagliptin + placebo, 335	52.1	50.4	C: 76.1, AA: 1.8, Asian: 16.7, O: 5.4	30.2 NR	9.6	1.7	126
	Metformin + saxagliptin, 320	52	51.6	C: 76.9, AA: 2.2, Asian: 15.9, O: 5	29.9 NR	9.4	2	91
	Metformin + saxagliptin, 323	52.1	45.2	C: 75.2, AA: 2.2, Asian: 16.7, O: 5.9	30.4 NR	9.5	1.4	92
Pratley, 2014[129]	Metformin 114	54.6	41.2	C: 74.6, AA: 5.3, Asian: 16.7, O: 3.5	30.2 NR	8.5	3.8	17.5%
	Metformin 111	52.6	45.9	C: 71.2, AA: 5.4, Asian: 18, O: 5.4	30.5 NR	8.39	4.1	14.4%
	Metformin + alogliptin 111	53.7	43.2	C: 68.5, AA: 5.4, Asian: 18, O: 8.1	30.9 NR	8.5	4.1	17.1%

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + alogliptin 114	54.6	54.4	C: 68.4, AA: 4.4, Asian: 22.8, O: 4.4	31 NR	8.43	4.2	17.5%
	+ alogliptin 112	52.6	42.9	C: 75, AA: 2.7, Asian: 15.2, O: 7.1	30.8 NR	8.3	3.6	20.5%
Qiu, 2014[130]	Metformin + placebo 93	57	49.5	C: 78.5, AA: 4.3, Asian: 9.7, O: 7.5	NR 90.5kg	7.7	7	7
	Metformin + canagliflozin, 93	58.6	43	C: 80.6, AA: 5.4, Asian: 3.2, O: 10.8	NR 91.2kg	7.6	6.7	8
	Metformin + canagliflozin, 93	56.7	47.3	C: 89.2, AA: 1.1, Asian: 6.5, O: 3.2	NR 90.2kg	7.6	7.3	13
Reasner, 2011[133]	Metformin	50	57	C: 79, AA: 14, Asian: 4, H: 30, O: 3	33.7 97.2 kg	9.8	3.2	215
	Metformin + sitagliptin	49.4	56	C: 81, AA: 13, Asian: 3, H: 36, O: 3	32.9 94.7 kg	9.9	3.5	216
Ridderstrale, 2014[134]	Metformin + glimepiride, 780	55.7	54	C: 67, AA: 1, Asian: 32, H: 20, O: 0	NR 83.0kg	7.92	NR	132
	Metformin + empagliflozin, 769	56.2	56	C: 65, AA: 2, Asian: 33, H: 20, O: <1	NR 82.5kg	7.92	NR	121
Roden, 2013[137]	Sitagliptin, 223	55.1	63	C: 34, AA: 1, Asian: 64, O: O<1	NR 79.3kg	7.85	NR	17
	Empagliflozin, 224	56.2	63	C: 34, AA: 1, Asian: 64, O: 0	NR 78.4kg	7.87	NR	18
	Empagliflozin, 224	53.8	65	C: 33, AA: 3, Asian: 64, O: 0	NR 77.8kg	7.86	NR	20
Rosenstock, 2013[141]	Alogliptin 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	42.9
	Glipizide 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	42.9
Rosenstock, 2013[142]	Metformin + placebo 71	60	47	C: 90, AA: 1, H: 9, O: 0	NR 87.7kg	8	NR	5
	Metformin + sitagliptin 71	58	54	C: 87, AA: 0, A: 0, H: 13, O: 0	NR 88.0kg	8.1	NR	1
	Metformin +	59	47	C: 78, AA: 3, H: 20, O: 0	NR	7.9	NR	5

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	empagliflozin, 71				87.9kg			
	Metformin + empagliflozin, 70	59	53	C: 83, AA: 1, H: 16, O: 0	NR 90.5kg	8.1	NR	0
Ross, 2012[143]	Metformin + placebo, 44	59.9	47.7	C: 72.7, Asian: 27.3, O: 0	NR 77.7kg	7.92	NR	1
	Metformin + linagliptin + placebo, 224	58.4	54	C: 62.1, Asian: 36.6, O: 1.3	NR 80.6kg	7.98	NR	10
Roumie, 2012[198]	Metformin 155025	62 median	95	C: 74, AA: 12, H/O: 6	31.9 median NR	NR	NR	NA
	Sulfonylurea 98665	67 median	97	C: 75, AA: 13, H/O: 6	30.2 median NR	NR	NR	NA
Russell-Jones, 2012[144]	Metformin + placebo 246	54	62.6	C: 65, AA: 4.5, Asian: 20.7, H: 8.5, O: 1.2	NR 85.9 kg	8.6	2.6	13.4%
	Pioglitazone + placebo 163	55	59.5	C: 67.5, AA: 2.5, Asian: 20.9, H: 9.2 0	NR 86.1 kg	8.5	2.7	18.4%
	Sitagliptin + placebo 163	52	57.7	C: 69.3, AA: 1.8, Asian: 20.2, H: 8, O: 0.6	NR 88.7 kg	8.5	2.7	14.1%
	Exenatide + placebo 248	54	56	C: 68.1, AA: 2.8, Asian: 22.2, H: 6.5, O: 0.4	NR 87.5 kg	8.5	2.7	15.3 %
Scheller, 2014[199]	Metformin	59	51.6	NR	NR NR	NR	NR	NA
	Sitagliptin	62.5	54.2	NR	NR NR	NR	NR	NA
Schramm, 2011[200]	Metformin, 43340	52.5	51	NR	NR NR	NR	NR	NR
	Metformin 2906	65.8	73	NR	NR NR	NR	NR	NR
	Glibenclamide	70.9	70	NR	NR NR	NR	NR	NR
	Glibenclamide	63.2	54	NR	NR	NR	NR	NR

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	12495				NR			
	Glipizide	70.5	70	NR	NR NR	NR	NR	NR
	Glipizide 6965	63	54	NR	NR NR	NR	NR	NR
	Glimepiride 36313	60.9	55	NR	NR NR	NR	NR	NR
	Glimepiride	70.9	70	NR	NR NR	NR	NR	NR
Seino, 2012[151]	Metformin + placebo 100	52.1	72	NR	69.89 kg NR	8	6.04	0
	Metformin + alogliptin 92	53.4	65.2	NR	69.47 kg NR	7.89	6.34	1
	Metformin + alogliptin 96	52.3	68.8	NR	69.65 kg NR	8.02	6.62	3
Stenlof, 2014[201]	Sitagliptin 170	55.1	41.5	C: 63.6, AA: 9.2, Asian: 13.8, O: 13.3	NR 85.8kg	8.1	4.5	18
	Canagliflozin 170	55.3	45.2	C: 69.5, AA: 7.1, Asian: 14.7, O: 8.6	NR 86.9kg	8	4.3	5
	Canagliflozin 155	55.7	45.8	C: 69.8, AA: 4.7, Asian: 15.1, O: 10.4	NR 87.6kg	8	4.2	20
Umpierrez, 2014[165]	Metformin + placebo 268	55	45	C: 75, AA: 5, Asian: 8, H: 35, O: 13	33 92 kg	7.6	3	55
	Dulaglutide + placebo 270	56	44	C: 73, AA: 8, Asian: 7, H: 32, O: 11	33 92 kg	7.6	3	52
	Dulaglutide + placebo 269	56	42	C: 75, AA: 6, Asian: 8, H: 33, O: 12	34 93 kg	7.6	3	49
Wheeler, 2013[202]	Metformin 132,306	62.3	95.3	C: 66.6, AA: 10.5, O: 3.1, Missing:19.8	NR NR	7.3 (12.1% missing)	NR	NA
Wheeler, 2013[202]	Glipizide 28,957	66.4	97.4	C: 71.7, AA: 13.1, 15.2 (O: 2.3, Missing: 12.9)	NR NR	7.5 (13.2% missing)	NR	NA

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Wheeler, 2013[202]	Glibenclamide 28,156	64.9	97.2	C: 71.3, AA: 11.9, 16.8 (O: 4.2, Missing: 12.6)	NR NR	7.6 (12.9% missing)	NR	NA
Wheeler, 2013[202]	Rosiglitazone 3,753	66.9	97.3	C: 74.6, AA: 9.5, 15.8 (O: 6.0, Missing: 9.8)	NR NR	6.8 (18.0% missing)	NR	NA
White, 2014[168]	Metformin + placebo 86	56.6	52.3	C: 93, AA: 3.5, Asian: 2.3, H: 40.7, O: 1.2	32.5 NR	7.97	6.2	9.3%
	Metformin + saxagliptin 74	53.9	54.1	C: 86.5, AA: 10.8, Asian: 2.7, H: 39.2, O: 0	33.7 NR	7.92	5.8	10.8%
Williams-Herman, 2010[170]	Metformin + placebo	54.1	50	NR	31.9 NR	8.1	4	20
	Metformin + placebo	55.9	46	NR	32.2 NR	8.6	4	27
	Metformin + placebo	54.3	44	NR	31.9 NR	8.5	3.9	26
	Sitagliptin + placebo	54.1	58	NR	30.3 NR	8.5	3.7	38
	Metformin + sitagliptin	54.5	50	NR	31.6 NR	8.7	3.7	36
	Metformin + sitagliptin	53.9	37	NR	31.4 NR	8.6	4.4	21
Yang, 2011[172]	Metformin + placebo 287	54.4	48.4	Asian: 100	NR 69.0 kg	7.9	5.1	40
	Metformin + saxagliptin 283	53.8	48.1	Asian: 100	NR 68.9 kg	7.9	5.1	29
Yang, 2012[174]	Metformin + placebo 198	55.1	55	Asian: 100	NR 68.9 kg	NR	7.3	16
	Metformin + sitagliptin 197	54.1	47	Asian: 100	NR 67.9 kg	NR	6.4	23
Zhang, 2012[179]	Metformin + glimepiride 23	52	57	NR	24.8 NR	9	4.1	5
	Metformin + exenatide	50.2	53	NR	24.9	8.7	4.2	6

Author, year	Group, N	Mean age (age range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	19				NR			

Abbreviations: AA = African American; BHI = biphasic human insulin; BMI = body mass index; C = Caucasian; H = Hispanic; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptidase-1; HbA1c = glycated hemoglobin; kg = kilogram; NA – Not applicaple; NR = Not reported; O = Other; SU = sulfonylurea;

Some data may not have been extracted because the question was not asked.

Table 7. Results of studies evaluating diabetes medications on long-term clinical outcomes

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Alba, 2013[3] RCT	Grp1: Pioglitazone Fixed (30mg) Grp2: Sitagliptin Fixed (100mg) ITT: Yes Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Persons p NR Incidence Grp2: 0 Persons p NR			
Andersson, 2010[181] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Persons p NR Incidence Grp2: 0 Persons p NR			
Andersson, 2010[181] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 315 Persons p NR			
Andersson, 2010[181] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 2 315 Persons p NR			
Andersson, 2010[181] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 302 Persons p NR			
Andersson, 2010[181]	Grp1: SU	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Retrospective cohort	Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52	Incidence Grp1: Persons p NR Incidence Grp2: 0 302 Persons p NR			
Andersson, 2010[181] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 1 304 Persons p NR			
Arechavaleta, 2011[5] RCT	Grp1: Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2: Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 1 304 Persons p NR			
Arechavaleta, 2011[5] RCT	Grp1: Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at	Def:All-cause mortality Incidence Grp1: 0 315 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2: Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT: Yes Followup (wks): 26	Incidence Grp2: 0 302 Persons p NR			
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: 2 315 Persons p NR Incidence Grp2: 0 302 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: 2 315 Persons p NR Incidence Grp2: 1 304 Persons p NR			
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal	Def:All-cause mortality Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 1 304 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: Yes Followup (wks): 26				
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 26 Active				
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Aschner, 2010[7] RCT	Grp1: Metformin Varied, prespecified target	Grp1: 0 (0) Grp2: 1 (<1)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	dose Start: 500 mg, Max: 2000 mg, Mean: 1903 D: 5 wks Grp2: Sitagliptin Fixed Mean: 100 mg				
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg)	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active				
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Bailey, 2005[9] RCT	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2500mg; Start: 4 mg, Max: 8 mg	Grp1: 0 (0) Grp2: 1 (<1)	Def: CVD mortality/sudden cardiac death Grp1: 0 (0) Grp2: 1 (<1)	Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI Grp1: 0 (0) Grp2: 1 (<1)	
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg)	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 2			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 52 Passive				
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 1			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 1 (0.6) NR p NR Incidence Grp2: 0 (0) NR p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT: No	Def:All-cause mortality Incidence Grp1: 1 (0.6) NR p NR Incidence Grp2: 0 (0) NR p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 26 Active				
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 1 (0.3) Persons p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 0 (0) Persons p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 1 (0.3) Persons p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin +	Def:All-cause mortality Incidence Grp1: 1 (0.3) Persons p NR Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: Yes Followup (wks): 52 Passive	Persons p NR			
Bakris, 2006[12] RCT	Grp1: Metformin + rosiglitazone Varied, NS; Varied, glucose: ≤ 6.6 mmol/L Unclear; Start: 4mg D: 3 wks Grp2: Metformin + glyburide Varied, NS; Varied, glucose: ≤ 6.6mmol/L Unclear; Start: 5 mg D: 3 wks	Grp1: 1 (1) Grp2: 0 (0)			
Barnett, 2012[13] RCT	Grp1: Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2: Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: 1 (0.3) Persons p NR Incidence Grp2: 1 (0.3) Persons p NR			
Barnett, 2012[13] RCT	Grp1: Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and	Def:All-cause mortality Incidence Grp1: 2 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2: Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT: No Followup (wks): 52 NR/unclear				
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: No Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence Grp1: 2 Incidence Grp2: 2			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 102 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.7) Incidence Grp2: 2 (1.5)			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo	Def:All-cause mortality Incidence Grp1: 1 (0.7) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 102 NR/unclear				
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 102 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.7) Incidence Grp2: 0 (0)			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 4 (1) Incidence Grp2: 4 (1)			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 1 (0.5)			
Bergenstal, 2010[14]	Grp1: Metformin +	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 24 NR/unclear	Incidence Grp1: 0 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg)	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (2mg weekly) ITT: Yes Followup (wks): 24				
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo	Def:All-cause mortality Incidence Grp1: 1			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bolinder, 2012[17] RCT	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bolinder, 2012[17] RCT	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment)	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 1 (1.1)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: Yes Followup (wks): 102				
Bolinder, 2012[17] RCT	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: Yes Followup (wks): 104 Active	Def:All-cause mortality Incidence Grp1: 4 (1) 408 Persons p Incidence Grp2: 0 (0) 406 Persons p			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000	Def:All-cause mortality Incidence Grp1: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 26 Active	Incidence Grp2: 1			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Brownstein, 2010[182] Cohort	Grp1: Metformin NS Grp2: Rosiglitazone NS			Def: Hospitalization for acute MI Grp1: ref Grp2: HR: 3.0 (CI: 2.4-3.7)	
Brownstein, 2010[182] Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea			Def: Hospitalization for acute MI Grp1: HR: 1.3 (CI: 1.0-1.7) Grp2: ref	
Bunck, 2011[21] RCT	Grp1: Metformin + exenatide Fixed (pre-enrollment dose) Titrated (Max: 60 ug) Grp2: Metformin + insulin glargine Fixed (pre-enrollment dose) Titrated (Mean: 33.7 IU) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Cefalu, 2013[23] RCT	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT: Yes Followup (wks): 12				
Cefalu, 2013[23] RCT	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Chien, 2007[27] RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 1000mg, Mean: 1910 mg, Max: 2000 mg D: 4 wks Grp2: Glyburide Varied, glucose: 140 Start: 10 mg, Mean: 19 mg, Max: 20 mg D: 4 wks	Grp1: 0 (0) Grp2: 0 (0)			
Chien, 2007[27] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5 mg, Max: 10 mg, Final mean: 8.4 mg D: 4 wks	Grp1: 0 (0) Grp2: 0 (0)			
Corrao, 2011[183] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Corrao, 2011[183] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
DeFronzo, 1995[30] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	Grp1: 1 (0.5) Grp2: 0 (0)	Def: CVD mortality/Fatal MI Grp1: 1 (0.5) Grp2: 0 (0)		
DeFronzo, 1995[30] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	Grp1: 1 (1)) Grp2: 0 (0)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) ITT: No Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) ITT: No	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 24				
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) ITT: No Followup (wks): 104 NR/unclear	Def:All-cause mortality Incidence Grp1: 5 Persons p NR Incidence Grp2: 5 Persons p NR			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) ITT: Yes Followup (wks): 18	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: (0)			
DeFronzo, 2012[33]	Grp1: Metformin + placebo	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) ITT: Yes Followup (wks): 18	Incidence Grp1: (0) Incidence Grp2: 1 (1.1)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 24	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: (0)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 24	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: (0)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in)	Def:All-cause mortality Incidence Grp1: 0 p Incidence Grp2: 0 p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): NR/unclear				
DeFronzo, 2012[33] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 0 p Incidence Grp2: 0 p			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 23 3246 Person-years p Rate ratio (poisson) 0.77 Incidence Grp2: 304 6916 Person-years p Rate ratio (poisson) 1.95			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg)	Def:All-cause mortality Incidence Grp1: 644 31497 Person-years p Rate ratio (poisson) 1 (ref)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Incidence Grp2: 23 3246 Person-years p Rate ratio (poisson) 0.77			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 644 31497 Person-years p Rate ratio (poisson) 1 (ref) Incidence Grp2: 118 11619 Person-years p Rate ratio (poisson) 0.65			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 644 31497 Person-years p Rate ratio (poisson) 1 (ref) Incidence Grp2: 304 6916 Person-years p Rate ratio (poisson) 1.95			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo	Def:All-cause mortality Incidence Grp1:			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	118 11619 Person-years p Rate ratio (poisson) 0.65 Incidence Grp2: 23 3246 Person-years p Rate ratio (poisson) 0.77			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 118 11619 Person-years p Rate ratio (poisson) 0.65 Incidence Grp2: 304 6916 Person-years p Rate ratio (poisson) 1.95			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Yes Followup (wks):	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 222258 Person-years p NR RH 1 Incidence Grp2: 5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 222258 Person-years p NR RH 1 Incidence Grp2: 47604 Person-years p NR RH 1.55			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g.,	Def:All-cause mortality Incidence Grp1: 222258 Person-years p NR RH 1 Incidence Grp2: 48238 Person-years p NR RH 1.38			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	cohort) Followup (wks):				
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 47604 Person-years p NR RH 1.55 Incidence Grp2: 5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females)			
DeFronzo, 2012[33] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 48238 Person-years p NR RH 1.38 Incidence Grp2: 5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females)			
Diamant, 2010[44] RCT	Grp1: Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified (continued stable dose)	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: Yes Followup (wks): 12 Active				
Diamant, 2010[44] RCT	Grp1: Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: Yes Followup (wks): 24 Passive	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Ekstrom, 2012[184] Retrospective cohort	Grp1: Metformin Not specified (Median: 1100mg) Grp2: Metformin + basal insulin Not specified (Median: 1700mg) Not specified ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Ekstrom, 2012[184] Retrospective cohort	Grp1: Metformin Not specified (Median: 1100mg) Grp2: Metformin + basal insulin Not specified (Median:	Def:All-cause mortality Incidence Grp1: 7 Incidence Grp2: 3			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	1700mg) Not specified ITT: No Followup (wks): 58				
Ekstrom, 2012[184] Retrospective cohort	Grp1: Metformin Not specified (Median: 1100mg) Grp2: Metformin + basal insulin Not specified (Median: 1700mg) Not specified ITT: Yes Followup (wks): 144	Def:All-cause mortality Incidence Grp1: 7 NA p 0.55 Incidence Grp2: 14 NA p			
Erem, 2014[47] RCT	Grp1: Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg) Grp2: Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT: Yes Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.7) Persons p Incidence Grp2: 1 (0.7) Persons p			
Erem, 2014[47] RCT	Grp1: Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg)	Def:All-cause mortality Incidence Grp1: 971 NA p NR RH 1.00 REF Incidence Grp2: 818 NA p NR RH 1.25			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear				
Esposito, 2011[48] RCT	Grp1: Metformin Titrated (Max: 1000mg twice dailyend of titration: 36% on 1500 mg/d and 64% on 2000 mg/d) Grp2: Pioglitazone Titrated (Max: 45 mgend of titration period: 27% on 30 mg/d and 72% on 45 mg/d) ITT: No Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 5 Persons p NR Incidence Grp2: 5 Persons p NR			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 (0) p Incidence Grp2: 0 (0) p			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of	Def:All-cause mortality Incidence p RH Incidence p RH 1.64			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 114.4				
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: Not applicable (e.g., cohort) Followup (wks): 114.4	Def:All-cause mortality Incidence p RH Incidence p RH 1.59			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 114.4	Def:All-cause mortality Incidence p RH Incidence p RH 1.68			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of	Def:All-cause mortality Incidence Grp1: 1 p Incidence p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 36 NR/unclear				
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 p Incidence p			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 p Incidence p			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final	Def:All-cause mortality Incidence p Incidence p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 36 NR/unclear				
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence p Incidence p			
Ferrannini, 2013[185] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence p Incidence p			
Fonseca, 2000[54] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 8 mg	Grp1: 0 (0) Grp2: 1 (1)	Def: CVD mortality/unclear mortality + Fatal MI Grp1: 0 (0) Grp2: 0 (0)		
Fonseca, 2012[55] RCT	Grp1: Metformin Titrated (Max: 2000	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	mg/duptitration from 1500 to 2000 mg/d) Grp2: Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT: No Followup (wks): 52 NR/unclear	Incidence p Incidence Grp2: 1 p			
Forst, 2010[56] RCT	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) ITT: Yes Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence p Incidence p			
Forst, 2010[56] RCT	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: No Followup (wks): 80	Def:All-cause mortality Incidence Grp1: 1 p Incidence Grp2: 2 p			
Forst, 2010[56] RCT	Grp1: Metformin + glimepiride	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: Not applicable (e.g., cohort) Followup (wks): 91.52 NR/unclear	Incidence Grp1: 1548 p RH 1 Incidence Grp2: 1546 p RH 1.19			
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 213 p RH 1 Incidence Grp2: 265 p RH 1.47			
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or	Def:All-cause mortality Incidence Grp1: 1548 p RH 1			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): 91.52 NR/unclear	Incidence Grp2: 947 p RH 1.27			
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 213 p RH 1 Incidence Grp2: 141 p RH 1.53			
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose	Def:All-cause mortality Incidence Grp1: 213 p RH 1 Incidence Grp2: 737 p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	RH 1.3			
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): 91.52 NR/unclear	Def:All-cause mortality Incidence Grp1: 1548 p RH 1 Incidence Grp2: 4081 p RH 1.32			
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))	Def:All-cause mortality Incidence Grp1: 2 (0.3) Incidence Grp2: 1 (0.2)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Yes Followup (wks): 44 Active				
Gallwitz, 2012[60] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 5 (1.5) Incidence Grp2: 2 (0.6)			
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum	Def:All-cause mortality Incidence Grp1: 5 (1.5) Incidence Grp2: 1 (0.3)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	tolerated dose and country guidelines) Grp2: Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT: Yes Followup (wks): 76				
Garber, 2003[63] RCT	Grp1: Metformin Varied Start: 500 mg, max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, max: 10 mg	Grp1: 0 (0) Grp2: 0 (0)			
Garber, 2003[63] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 1.25 mg, Max: 20 mg	Grp1: 0 (0) Grp2: 2 (1)			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 5 (1.5) Incidence Grp2: 2 (0.6)			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo	Def:All-cause mortality Incidence Grp1: 2 (0.6)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 76	Incidence Grp2: 1 (0.3)			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 2 (0.6) Incidence Grp2: 2 (0.6)			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Persons p NR Incidence Grp2: 0 Persons p NR			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 104 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 0			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 104 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 1			
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: No Followup (wks): 30	Def:All-cause mortality Incidence Grp1: 1 Persons p NR Incidence Grp2: 0 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Garber, 2011[66] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence p RH Incidence p RH 1.37			
Genovese, 2013[67] RCT	Grp1: Metformin + placebo Fixed (2550 mg) Grp2: Metformin + pioglitazone Fixed (2550 mg) Fixed (45titrated from 30 mg to 45 mg in first four wks then fixed at 45 for 20 wks) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (0.5) Incidence Grp2: 4 (0.9)			
Genovese, 2013[68] RCT	Grp1: Metformin Titrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response) Grp2: Pioglitazone + placebo Titrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 239 (35) 1533 Person-years p NR 0.85 Incidence Grp2: 2344 (65) 9570 Person-years p NR 1.00 REF			
Goke, 2010[69] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7	Def:All-cause mortality Incidence Grp1: 239 (35) 1533 Person-years p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	0.85 Incidence Grp2: 759 (49) 4280 Person-years p NR 0.89			
Goke, 2010[69] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 2344 (65) 9570 Person-years p NR 1.00 REF Incidence Grp2: 759 (49) 4280 Person-years p NR 0.89			
Goke, 2010[69] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Goke, 2010[69] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean:	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: No Followup (wks): 26	Incidence Grp1: 0 Persons p Incidence Grp2: 0 Persons p			
Goke, 2010[69] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: Yes Followup (wks): 26 NR/unclear	Def:All-cause mortality Incidence Grp1: Incidence Grp2: 1			
Goldstein, 2003[70] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Fixed Start: 15mg bid	Grp1: 0 (0) Grp2: 0 (0)			
Goldstein, 2003[70] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1: 0 (0) Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Gomez-Perez, 2002[72] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid			Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia Grp1: 1 (3) Grp2: 1 (3)	
Gomez-Perez, 2002[72] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg bid			Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia Grp1: 1 (3) Grp2: 2 (5)	
Haak, 2012[76] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 26 NR/unclear	Def:All-cause mortality Incidence Grp1: Incidence Grp2:			
Haak, 2012[76] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 26 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2:			
Haak, 2012[76] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Haak, 2012[76] RCT	Grp1: Metformin Titrated (Max: 2000 mg)	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 104	Incidence Grp1: 1 (0.5) Incidence Grp2: 0 (0)			
Haak, 2012[76] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (1.1) Incidence Grp2: 0 (0)			
Haak, 2012[76] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (1.1) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Metformin Titrated (Max: 2000 mg)	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Incidence Grp1: 2 (1.1) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			
Haak, 2012[76] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			
Haak, 2012[76]	Grp1: Linagliptin	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (5 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Incidence Grp1: 3024 (3.6) p NR RR 1.0 REF Incidence Grp2: 49 (4) p NR RR 1.25			
Haak, 2012[76] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0			
Haak, 2012[76] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0			
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 315 Persons p NR

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 302 Persons p NR
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 1 304 Persons p NR
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 0 302 Persons p NR
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 1 304 Persons p NR
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg)				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: No Followup (wks): 26 Active				Incidence Grp1: 1 315 Incidence Grp2:
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2:
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2: 1 304
Haak, 2013[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2:
Hamann, 2008[79] RCT	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Start: 2 g; Start: 4 mg D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Start: 2 g; Start: 5 mg D: 12 wks	Grp1: 2 (1) Grp2: 2 (1)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hanefeld, 2004[80] RCT	Grp1: Metformin + sulfonylurea Varied; NR Start: 850 mg, Max: 850 mg tid; NR Grp2: Pioglitazone + sulfonylurea Varied; NR Start: 15 mg, Max: 45 mg; NR	Grp1: 2 (1) Grp2: 1 (<1)		Def: Coronary heart diseases/cardiac disorders Grp1: (3.1) Grp2: (4.1)	
Hanefeld, 2007[81] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg D: 12 wks Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 0 (0)			
Hanefeld, 2007[81] RCT	Grp1: Rosiglitazone Fixed Start: 8 mg D: 12 wks Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 0 (0)			
Haring, 2014[82] RCT	Grp1: Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2: Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label))				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (10mg) ITT: No Followup (wks): 26 Active				
Haring, 2014[82] RCT	Grp1: Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2: Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (25mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: Incidence Grp2:
Henry, 2012[83] RCT	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2: Dapagliflozin + placebo Fixed (5mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: Incidence Grp2:
Henry, 2012[83] RCT	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg)				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (5 mg) ITT: No Followup (wks): 26 Active				
Henry, 2012[83] RCT	Grp1: Dapagliflozin + placebo Fixed (5mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: Yes Followup (wks): 52 Passive				Def:Cerebrovascular Not-fatal stroke (non-fatal stroke) Incidence Grp1: 1 Incidence Grp2: 1
Henry, 2012[83] RCT	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Dapagliflozin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 52 Passive				Def:Cerebrovascular Not-fatal stroke (non-fatal stroke) Incidence Grp1: 1 Incidence Grp2:
Henry, 2012[83] RCT	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104				Def:Cerebrovascular Other cerebrovascular (cerebral infarction) Incidence Grp1: 4 (0.5) Incidence Grp2: 0 (0)
Henry, 2012[83]	Grp1: Dapagliflozin +				Def:Cerebrovascular

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	placebo Fixed (10 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104				Not-fatal stroke (not defined) Incidence Grp1: 11 NA p NR RR Incidence Grp2: 3 NA p NR RR 0.27
Hermann, 1994[85] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg			Def: CVD morbidity/unclear CHD Grp1: 2 (5) Grp2: 3 (9)	
Hermann, 1994[85] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 1500 mg; Start: 1.75mg, Max: 5.25 mg			Def: CVD morbidity/unclear CHD Grp1: 2(5) Grp2: 10 (14)	
Hermans, 2012[86] RCT	Grp1: Metformin Titrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination) Grp2: Metformin + saxagliptin Fixed (1500 mg) Fixed (5 mg) ITT: No				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 26 NR/unclear				
Home, 2009[88] RCT	Grp1: Metformin + sulfonylurea Varied, HgbA1c: ≤7.0% Max: 2550 mg; Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mg D: 8 wks Grp2: Rosiglitazone + metformin or sulfonylurea Varied, HgbA1c: ≤7.0% Start: 4 mg, Max: 8 mg; Metformin, Max: 2550 mg, Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mg D: 8 wks	Grp1: 157 Grp2: 136 HR: 0.86 (CI: 0.68 to 1.08), p: 0.19	Grp1: 71 Grp2: 60 HR: 0.84 (CI: 0.59 to 1·18), p: 0.32	Def: Fatal and non-fatal MI Grp1: 56 Grp2: 64 HR: 1.14 (CI: 0.80 to 1·63), p: 0.47	Def: Fatal and non-fatal stroke Grp1: 63 Grp2: 46 HR: 0.72 (CI: 0.49 to 1·06), p: 0.10
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: No Followup (wks): 26 NR/unclear				
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax:				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:
Hong, 2013[186] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l,				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				
Horsdal, 2011[187] Case-control	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:
Hsiao, 2009[204] Cohort	Grp1: Metformin NS Grp2: Pioglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 22 (4.51) HR: 1.15 (CI: 0.6 to 2.21) p: 0.6753 Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 44 (8.89) HR: 1.0 (CI: 0.26 to 3.89) p: 0.9954	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 2 (0.41) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 5 (1.03)
Hsiao, 2009[204] Cohort	Grp1: Metformin NS			Def: Angina pectoris defined by ICD-9-CM	Def: ICD-9-CM diagnostic codes of

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Rosiglitazone NS			diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 154 (7.52) HR: 1.79 (CI: 1.39 to 2.3) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 266 (12.71) HR: 2.09 (CI: 1.36 to 3.24) p: 0.0007	hospitalization Grp1: 116 (0.25) Grp2: 16 (0.8) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 23 (1.14)
Hsiao, 2009[204] Cohort	Grp1: Metformin NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 940 (0.99)
Hsiao, 2009[204] Cohort	Grp1: Metformin NS Grp2: Metformin + rosiglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 103 (4.26) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 25 (1.03)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 12 (0.49) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 11 (0.45)
Hsiao, 2009[204] Cohort	Grp1: Metformin NS			Def: Angina pectoris defined by ICD-9-CM	Def: ICD-9-CM diagnostic codes of

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + sulfonylurea NS			diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 5910 (2.2) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 11435 (4.27)	hospitalization Grp1: 116 (0.25) Grp2: 588 (0.22) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 1637 (0.61)
Hsiao, 2009[204] Cohort	Grp1: Rosiglitazone NS Grp2: Pioglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 154 (7.52) Grp2: 22 (4.51) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 266 (12.71) Grp2: 44 (8.89)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 16 (0.8) Grp2: 2 (0.41) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 23 (1.14) Grp2: 5 (1.03)
Hsiao, 2009[204] Cohort	Grp1: Pioglitazone NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 22 (4.51) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 44 (8.89) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 2 (0.41) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 5 (1.03) Grp2: 940 (0.99)
Hsiao, 2009[204] Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 154 (7.52)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 16 (0.8) Grp2: 318 (0.34)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 266 (12.71) Grp2: 1678 (1.76)	Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 23 (1.14) Grp2: 940 (0.99)
Hsiao, 2009[204] Cohort	Grp1: Metformin + rosiglitazone NS Grp2: Metformin + sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 103 (4.26) Grp2: 5910 (2.2) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 25 (1.03) Grp2: 11435 (4.27)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 12 (0.49) Grp2: 588 (0.22) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 11 (0.45) Grp2: 1637 (0.61)
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 24				Def:Cerebrovascular Other cerebrovascular (transient ischemic attack NOS) Incidence Grp1: Incidence Grp2: 1 NA p NR
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: NR Followup (wks): 24 NR/unclear				Def:Cerebrovascular Other cerebrovascular (CVA) Incidence Grp1: Incidence Grp2: 1
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: NR				Def:Cerebrovascular Other cerebrovascular (CVA) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 24 NR/unclear				
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 144				Def:Cerebrovascular Not-fatal stroke (no specific definition but confirmed by medical record) Incidence Grp1: 10 Incidence Grp2: 15
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 168				Def:Cerebrovascular Other cerebrovascular (cerebrovascular incident) Incidence Grp1: Incidence Grp2: 1 (4)
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 80				Def:Cerebrovascular Other cerebrovascular (not clearly predefined (just said 'cerebrovascular events'stem infarction) Incidence Grp1: 3 Persons p Incidence Grp2: 5 (1) Persons p
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence Grp2: 1 p
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 76				accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[188] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[188] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[188] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: No Followup (wks): 30				Def:Cerebrovascular Fatal stroke Incidence Grp1: 1 p Incidence p
Hung, 2012[188] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: Yes				Def:Cerebrovascular Other cerebrovascular (transient ischemic attack) Incidence Grp1: 1

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 104				Incidence Grp2:
Hung, 2012[188] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 104				Def:Cerebrovascular Fatal stroke Incidence Grp1: 1 Incidence Grp2:
Hung, 2012[188] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: No Followup (wks): 26				Def:Cerebrovascular Other cerebrovascular (Cerebrovascular accident) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 1 (1) Persons p
Hung, 2013[189] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glyburide Not specified ITT: No Followup (wks): 26				Def:Cerebrovascular Other cerebrovascular (Cerebrovascular accident) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p
Hung, 2013[189] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glimepiride Not specified ITT: No Followup (wks): 26				Def:Cerebrovascular Other cerebrovascular (Cerebrovascular accident) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p
Hung, 2013[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Active				
Hung, 2013[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	
Hung, 2013[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	
Hung, 2013[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	
Hung, 2013[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hung, 2013[190] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[190] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[190] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Nonfatal MI (non-fatal MI) Incidence Grp1: 1 Incidence Grp2: 3	
Jadzinsky, 2009[90] RCT	Grp1: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week Gpr2: Saxagliptin Fixed	Grp1: 3 (1) Grp2: 0 (0)			
Jadzinsky, 2009[90] RCT	Grp1: Metformin + saxagliptin Varied, prespecified target dose; Fixed Start: 500 mg, Max: 1000 mg; Mean: 10 mg D: 1 week Grp2: Metformin	Grp1: 0 (0) Grp2: 3 (1)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week				
Jadzinsky, 2009[90] RCT	Grp1: Metformin + saxagliptin Varied, prespecified target dose; Fixed Start: 500 mg, Max: 1000 mg; Mean: 5 mg Grp2: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week	Grp1: 0 (0) Grp2: 3 (1)			
Jain, 2006[91] RCT	Grp1: Pioglitazone Varied, glucose: 69-141 mg/dL Start: 15 mg, Median: 45 mg, Max: 45 mg D: 12 wks Grp2: Glyburide Varied, glucose: 69-141 mg/dL Start: 5 mg, Median: 10 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 2 (0.8)		Def: Non-fatal MI Grp1: 2 (0.8) Grp2: 2 (0.8)	
Johnson, 2005[191] Cohort	Grp1: Metformin Varied Min: 250 mg Grp2: Sulfonylurea Varied		Def: CVD mortality/CVD mortality registry + CVD mortality + ICD-9 codes 410, 411-414, 420-427, 429, 428, 430-432, 433-434, 436-438, 440 Grp1: 14.4/1000 patient-years Grp2: 25.5/1000 patient-years	Def: Non-fatal cardiovascular hospitalization/used ICD-9 codes 410-414, 420-427, 429, 428, 440, 430-432, 433-434, 436-438 Grp1: 53.7/1000 patient-years Grp2: 75.3/1000 patient-years	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Jones, 2003[192] RCT	Grp1: Metformin Fixed Start: 2.5 g Grp2: Metformin + rosiglitazone Fixed; Varied, NS Start: 2.5 g; Max: 8 mg	Grp1: 0 (0) Grp2: 1 (1)			
Kadowaki, 2013[94] RCT	Grp1: Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day) Grp2: Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Other CVD morbidity (unstable angina) Incidence Grp1: Incidence Grp2: 2	
Kadowaki, 2013[94] RCT	Grp1: Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day) Grp2: Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Nonfatal MI (non-fatal MI) Incidence Grp1: 1 Incidence Grp2:	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Kahler, 2007[193] Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 82 (2.7) Grp2: 1005 (5.3)			
Kahler, 2007[193] Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 82 (2.7) Grp2: 468 (3.4)			
Kahn, 2006[95] RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: 140 mg/dL Start: 4 mg, Max: 8 mg	Grp1: 31 (2) Grp2: 34 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 2 (0.1)	Grp1: 21 (1.4) Grp2: 25 (1.7)	Def: Stroke not defined Grp1: 19 (1.3) Grp2: 16 (1.1)
Kahn, 2006[95] RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: 140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: 31 (2) Grp2: 31 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 3 (0.2)	Def: Not defined Grp1: 21 (1.4) Grp2: 15 (1)	Def: Stroke not defined Grp1: 19 (1.3) Grp2: 17 (1.2)
Kahn, 2006[95] RCT	Grp1: Rosiglitazone Varied, glucose: 140 mg/dL Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: 140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: 34 (2) Grp2: 31 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 3 (0.2)	Def: Non-fatal MI Grp1: 25 (1.7) Grp2: 15 (1)	Def: Stroke not defined Grp1: 16 (1.1) Grp2: 17 (1.2)
Kaku, 2011[97] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Other CVD morbidity (unstable angina) Incidence Grp1: Incidence Grp2: 2	
Kaku, 2011[97] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide			Def:CVD morbidity CVD morbidity composite outcome	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 26			(see comments) Incidence p Incidence p	
Kaku, 2011[97] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 26			Def:CVD morbidity CVD morbidity composite outcome (see comments) Incidence p Incidence p	
Kaku, 2011[97] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 26			Def:CVD morbidity CVD morbidity composite outcome (see comments) Incidence p Incidence p	
Kvapil, 2006[103] RCT	Grp1: Metformin + sulfonylurea Fixed; Varied Start: 1660 mg; Start: 1.75 mg, Max: 10.5, Mean: 6.58 Grp2: Metformin + aspart 70/30 Fixed; Varied Start: 1660 mg; Start: 0.2 U/kg BID, Mean: 0.3 BID	Grp1: 0 (0) Grp2: 1	Def: Fatal MI Grp1: 0 (0) Grp2: 1		
Lavalle-Gonzalez, 2013[104] RCT	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg)			Def:CVD morbidity Nonfatal MI (not specified) Incidence Grp1: 1 Incidence Grp2: 0	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 52 Active				
Lavalle-Gonzalez, 2013[104] RCT	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity Nonfatal MI (not defined) Incidence Grp1: 10 NA p NR RR Incidence Grp2: 6 NA p NR RR 0.6	
Lavalle-Gonzalez, 2013[104] RCT	Grp1: Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity CVD morbidity composite outcome (Must have one of following: cardiovascular death, myocardial infarction, stroke, admission to hospital due to unstable angina) Incidence Grp1: 26 NA p NR RR Incidence Grp2: 12 NA p NR RR 0.46	
Lavalle-Gonzalez, 2013[104] RCT	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose]))			Def:CVD morbidity Other CVD morbidity (Admission to hospital due to unstable angina) Incidence Grp1: 3 NA	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: Yes Followup (wks): 104			p NR RR Incidence Grp2: 3 NA p NR RR 1	
Lavalle-Gonzalez, 2013[104] RCT	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 50			Def:CVD morbidity Other CVD morbidity (acute MI) Incidence Grp1: Incidence Grp2:	
Lawrence, 2004[105] RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1: 1 (5) Grp2: 0 (0)	Def: CVD mortality/Fatal MI Grp1: 1 (5) Grp2: 0 (0)	Def: CVD morbidity/MI (non-fatal) Grp1: 0 (0) Grp2: 0 (0)	
List, 2009[107] RCT	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (5mg) ITT: Yes			Def:CVD morbidity Unspecified CVD morbidity outcomeincreased blood glucose	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 12 Active			Incidence Grp1: 0 Incidence Grp2: 0	
List, 2009[107] RCT	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 12 Active			Def:CVD morbidity Unspecified CVD morbidity outcomeincreased blood glucose Incidence Grp1: 0 Incidence Grp2: 0	
Malone, 2003[110] RCT	Grp1: Metformin + glibenclamide Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks; 16 wks Grp2: Metformin + lispro 75/25 Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/L Max: 2550 mg; Mean: 0.19 U/kg in am and 0.14 U/kg in evening D: 4 wks; 16 wks	Grp1: 0 (0) Grp2: 1 (<1)			
Malone, 2005[205] RCT	Grp1: Metformin + lispro 75/25 Varied, pre-meal glucose 90-126 mg/dL; 2-hr postprandial 144-180 mg/dL Start: 1500 mg, Max: 2550 mg, Mean: 2146 mg; Mean: 0.42 U/kg BID D: 4 wks, 16 wks Grp2: Metformin + glargine Varied, pre-meal glucose	Grp1: 1 (2) Grp2: 1 (2)	Grp1: 1 (2) Grp2: 0 (0)		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	90-126 mg/dL Start: 1500 mg, Max: 2500 mg, Mean: 2146 mg; Mean: 0.36 U/Kg QD D: 4 wks, 16 wks				
Masica, 2013[195] Retrospective cohort	Grp1: Metformin Not specified Grp2: TZD Not specified ITT: Yes Followup (wks): 12 Active			Def:CVD morbidity Unspecified CVD morbidity outcomeincreased blood glucose Incidence Grp1: 0 Incidence Grp2: 0	
Masica, 2013[195] Retrospective cohort	Grp1: Metformin Not specified Grp2: TZD Not specified ITT: Yes Followup (wks): 26 Passive			Def:CVD morbidity Other CVD morbidity (discontinuation due to hypertensive heart disease. Discontinuation because of serious adverse event.) Incidence Grp1: Incidence Grp2:	
Masica, 2013[195] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 26 Passive			Def:CVD morbidity Other CVD morbidity (discontinuation due to hypertensive heart disease. Discontinuation because of serious adverse event.) Incidence Grp1: Incidence Grp2: 1	
Masica, 2013[195] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 12			Def:CVD morbidity Other CVD morbidity (CEC-confirmed cardiovascular event - ST elevation myocardial infarction) Incidence Grp1:	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				Incidence Grp2: 1	
Masica, 2013[195] Retrospective cohort	Grp1: SU Not specified Grp2: TZD Not specified ITT: Yes Followup (wks): 12			Def:CVD morbidity Other CVD morbidity (acute MI) Incidence Grp1: 0 Incidence Grp2: 2	
Masica, 2013[195] Retrospective cohort	Grp1: SU Not specified Grp2: TZD Not specified ITT: No Followup (wks): 12 NR/unclear			Def:CVD morbidity Other CVD morbidity (Prinzmetal angina) Incidence Grp1: 1 Incidence Grp2:	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + glp-1 agonist Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 12 NR/unclear			Def:CVD morbidity Other CVD morbidity (Prinzmetal angina) Incidence Grp1: 1 Incidence Grp2:	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + glp-1 agonist Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 48			Def:CVD morbidity Nonfatal MI (no definition) Incidence Grp1: 0 Incidence Grp2: 0	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + su Not specified			Def:CVD morbidity Nonfatal MI (non ST	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Yes Followup (wks): Active			segment myocardial infarction with pulmonary edema and stent placed) Incidence Grp1: Incidence Grp2: 1	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (ICD9 410-413, 414-414.05, 414.8, 414.9, 428.9, 430-438, 440-448 (Except 440 and 440.1)) Incidence Grp1: 2241 Person-years p NR RH 0.31 Incidence Grp2: 1017 Person-years p NR RH ref	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + dpp-4 inhibitor Not specified Not specified ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (ICD9 410-413, 414-414.05, 414.8, 414.9, 428.9, 430-438, 440-448 (Except 440 and 440.1)) Incidence Grp1: 2241 Person-years p NR RH 0.31 Incidence Grp2: 745 Person-years p NR RH 0.52	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + su Not specified Not specified			Def:CVD morbidity Nonfatal MI (Discontinuation due to	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + dpp-4 inhibitor Not specified Not specified ITT: Yes Followup (wks): 16 NR/unclear			myocardial ischemia - did not specify as fatal or nonfatal) Incidence Grp1: 1 Incidence Grp2:	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 58			Def:CVD morbidity CVD morbidity composite outcome (vascular events) Incidence Grp1: 11 Incidence Grp2: 8	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 58			Def:CVD morbidity CVD morbidity composite outcome (vascular event) Incidence Grp1: 100 Person-years p NR Incidence Grp2: 100 Person-years p NR	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Yes Followup (wks): 144			Def:CVD morbidity CVD morbidity composite outcome (including nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization by PTCA or by coronary artery bypass graft, death from a cardiovascular cause,	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				and death from any cause, obtained and confirmed by th Incidence Grp1: 39 NA p NR RH 0.54 Incidence Grp2: 52 NA p NR RH	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Yes Followup (wks): 144 Active			Def:CVD morbidity Other CVD morbidity (new peripheral vascular disease events not further specified but confirmed by medical record) Incidence Grp1: 1 NA p NR RH 0.13 Incidence Grp2: 6 NA p NR RH	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: Yes Followup (wks): 144			Def:CVD morbidity Other CVD morbidity (new or worsening angina confirmed by medical record) Incidence Grp1: 77 NA p NR RH 1.07 Incidence Grp2: 71 NA p NR RH	
Mogensen, 2014[196] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: Yes Followup (wks): 144			Def:CVD morbidity Other CVD morbidity (new critical cardiac arrhythmia confirmed by medical record) Incidence Grp1: 30 NA p NR RH 1.01 Incidence Grp2: 27 NA p NR RH	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Nauck, 2007[116] RCT	Grp1: Metformin + glipizide NR Grp2: Metformin + sitagliptin NR	Grp1: 2 (0.3) Grp2: 1 (0.2)	Def: Fatal MI Grp1: 1 (0.2) Grp2: 0 (0)		
Nauck, 2009[117] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT: Yes Followup (wks): 144			Def:CVD morbidity Nonfatal MI (no specific definition - confirmed by medical records at each institution) Incidence Grp1: 5 Incidence Grp2: 6	
Nauck, 2009[117] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT: Yes Followup (wks): 144			Def:CVD morbidity Other CVD morbidity (arterial revascularization by PTCA or by coronary artery bypass graft confirmed by medical records) Incidence Grp1: 21 Incidence Grp2: 25	
Nauck, 2009[117] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg)			Def:CVD morbidity CVD morbidity composite outcome (AMI and stroke events only) Incidence Grp1: 179351 Person-years p NR RH 1.00 (ref) Incidence	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): 260			Grp2: 101125 Person-years p NR RH 1.15	
Nauck, 2009[117] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks): 260			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence Grp1: 179351 Person-years p NR RH 1.00 (Ref) Incidence Grp2: 101125 Person-years p NR RH 1.21	
Nauck, 2009[117] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence p RH 1 Incidence p RH 1.18	
Nauck, 2009[117] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose)			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence p RH 1	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Incidence p RH 1.28	
Nauck, 2011[118] RCT	Grp1: Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2: Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity Other CVD morbidity Incidence p RH 1 Incidence p RH 1.24	
Nauck, 2011[118] RCT	Grp1: Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2: Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence p RH 1 Incidence p RH 1.18	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (diagnosis of myocardial infarction, angina pectoris, intracerebral haemorrhage, cerebral	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	NR/unclear			infarction, unspecified stroke, peripheral vascular disease, or intervention with percutaneous coronary intervention or coronary arte Incidence Grp1: 1734 p RH 1.00 REF Incidence Grp2: 1338 p RH 1.28	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: No Followup (wks): 25 NR/unclear			Def:CVD morbidity Other CVD morbidity (UNstable angina) Incidence Grp1: 0 p NR Incidence Grp2: 2 p NR	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: No Followup (wks): 25 NR/unclear			Def:CVD morbidity Other CVD morbidity (carotid artery occlusion) Incidence Grp1: 0 p Incidence Grp2: 1 p	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: No Followup (wks): 25 NR/unclear			Def:CVD morbidity Nonfatal MI (Acute myocardial infarction) Incidence Grp1: 1 Incidence Grp2: 0	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin +			Def:CVD morbidity Other CVD morbidity (Angina pectoris)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Followup (wks): 25 NR/unclear			Incidence Grp1: 1 Persons p NR Incidence Grp2: 1 Persons p NR	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: No Followup (wks): 18 NR/unclear			Def:CVD morbidity Nonfatal MI (Acute cardiovascular event-Myocardial ischemia or MI) Incidence Grp1: 1 Persons p Incidence Grp2: 1 Persons p	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: No Followup (wks): 52 NR/unclear			Def:CVD morbidity Other CVD morbidity (Vascular Disorders') Incidence Grp1: 10 (7.6) p Incidence Grp2: 17 (6.3) p	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: No Followup (wks): 52 NR/unclear			Def:CVD morbidity Other CVD morbidity (Cardiac disorders') Incidence Grp1: 14 (10.6) NA p Incidence Grp2: 17 (6.3) NA p	
Nauck, 2014[119] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week)			Def:CVD morbidity Other CVD morbidity (defined as 'acute cardiovascuar event') Incidence Grp1: 1 p Incidence Grp2: 1 p	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 24				
Nauck, 2014[119] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: No Followup (wks): 80 NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (ischemic events') Incidence Grp1: 4 (1) p Incidence Grp2: 6 (2) p	
Nauck, 2014[119] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 1646 p RH 1 Incidence Grp2: 1376 p RH 1.12	
Nauck, 2014[119] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 245 p RH 1	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				Incidence Grp2: 267 p RH 1.29	
Nauck, 2014[119] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 1646 p RH 1 Incidence Grp2: 820 p RH 1.17	
Nauck, 2014[119] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 245 p RH 1 Incidence Grp2: 154 p RH 1.46	
Nauck, 2014[119] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Not applicable (e.g., cohort)			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): NR/unclear			(I00 â€“I99)) Incidence Grp1: 245 p RH 1 Incidence Grp2: 751 p RH 1.29	
Pantalone, 2009[203] Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR	Grp1: ref Grp2: HR: 1.33 (CI: 0.93 to 1.91) p: 0.11		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 0.96 (CI: 0.76 to 1.21) p: 0.74	
Pantalone, 2009[203] Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR	Grp1: ref Grp2: HR: 1.08 (CI: 0.78 to 1.51) p: 0.64		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 1.11 (CI: 0.91 to 1.34) p: 0.32	
Pantalone, 2009[203] Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: HR: 0.54 (CI: 0.46 to 0.64) p: <0.001 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 0.94 (CI: 0.85 to 1.05) p: 0.23 Grp2: ref	
Pantalone, 2009[203] Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR	Grp1: ref Grp2: HR: 0.81 (CI: 0.52 to 1.27) p: 0.36		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 1.15 (CI: 0.87 to 1.53) p: 0.32	
Pantalone, 2009[203] Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR	Grp1: HR: 0.73 (CI: 0.51 to 1.02) p: 0.08 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 0.90 (CI: 0.71 to 1.14) p: 0.41 Grp2: ref	
Pantalone, 2009[203] Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR	Grp1: HR: 0.59 (CI: 0.43 to 0.81) p: <0.001 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 1.04 (CI:	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				0.86 to 1.26) p: 0.69 Grp2: ref	
Pantalone, 2012[197] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glipizide Not specified ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 1646 p RH 1 Incidence Grp2: 3517 p RH 1.21	
Pantalone, 2012[197] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glyburide Not specified ITT: No Followup (wks): 24			Def:CVD morbidity CVD morbidity composite outcome (not prespecified as a composite outcome but this is what is reported on - CAD, carotid artery stenosis, peripheral artery disease) Incidence p Incidence p	
Pantalone, 2012[197] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glimepiride Not specified ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity Nonfatal MI (ï¬□rst-time discharge diagnosis of MI) Incidence Grp1: 599 5927 Persons p OR 0.86 Incidence Grp2: 3080 26778 Persons p OR 1 REF	
Petrica, 2009[124]	Grp1: Metformin +			Def:CVD morbidity	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	rosiglitazone Fixed (1700 mg/day) Fixed (4 mg/day) Grp2: Metformin + glimepiride Fixed (1700 mg/day) Fixed (4 mg/day) ITT: Yes Followup (wks): 76 NR/unclear			Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: (2.1) Incidence Grp2:	
Petrica, 2009[124] RCT	Grp1: Metformin + rosiglitazone Fixed (1700 mg/day) Fixed (4 mg/day) Grp2: Metformin + glimepiride Fixed (1700 mg/day) Fixed (4 mg/day) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: (2.1) Incidence Grp2: (0.3)	
Pfutzner, 2011[126] RCT	Grp1: Metformin + pioglitazone Fixed (1700 mg/d) Fixed (30 mg/d) Grp2: Metformin + glimepiride Fixed (1700 mg/d) Fixed (2mg/d) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: (2.1) Incidence Grp2:	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: Incidence Grp2: (0.3)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: Incidence Grp2:	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity Nonfatal MI (myocardial infarction, judged to have a possible relationship to trial drug by investigator) Incidence Grp1: 1 Incidence Grp2: 1	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Followup (wks): 104			Def:CVD morbidity Other CVD morbidity (cardiac disorders) Incidence Grp1: 14 (6) Incidence Grp2: 8 (3)	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Followup (wks): 104			Def:CVD morbidity Other CVD morbidity (cardiac disorders) Incidence Grp1: 14 (6) Incidence Grp2: 11 (5)	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity Nonfatal MI (myocardial infarction, judged to have a possible relationship to trial drug by investigator) Incidence Grp1: 1 Incidence Grp2: 1	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (death from any cause or first hospitalization for myocardial infarction (ICD-9 code 410-412.99 and 414. xx), cerebrovascular disease (430â€“437.1 and procedure code 38.12), coronary artery bypass graft (36.10â€“36.16 and 3 Incidence p RH Incidence p RH 1.15	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: NR Followup (wks): 104			Def:CVD morbidity CVD morbidity composite outcome (CV AEs (qualitatively reported)) Incidence p Incidence p	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Unstable Angina) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin			Def:CVD morbidity Other CVD morbidity (Coronary artery occlusion)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 26			Incidence Grp1: 2 (1) Persons p NR Incidence Grp2: 0 (0) Persons p NR	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Unstable Angina) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p	
Pfutzner, 2011[127] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Coronary artery occlusion) Incidence Grp1: 2 (1) Persons p NR Incidence Grp2: 0 (0) Persons p NR	
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Unstable Angina) Incidence Grp1: 0 (0) Persons p Incidence Grp2: 0 (0) Persons p	
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No			Def:CVD morbidity Other CVD morbidity (Coronary artery occlusion) Incidence Grp1: 0 (0) Persons p NR Incidence Grp2: 0 (0)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 26			Persons p NR	
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (all-cause mortality, AMI and stroke) Incidence Grp1: 4286 (5.1) p RR REF Incidence Grp2: 62 (5) p RR 1.22	
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 102		Def:CVD mortality Other CVD mortality (cardiopulmonary arrest and myocardial infarction) Incidence Grp1: Incidence Grp2: 2		
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 102		Def:CVD mortality Other CVD mortality (cardiopulmonary arrest and myocardial infarction) Incidence Grp1: Incidence Grp2:		
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 102		Def:CVD mortality Other CVD mortality (cardiopulmonary arrest and myocardial infarction) Incidence Grp1: Incidence Grp2:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 52 Active		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 1		
Pfutzner, 2011[127] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104		Def:CVD mortality Composite CVD mortality outcome (sudden cardiac death, fatal myocardial infarction, and fatal stroke) Incidence Grp1: 2 NA p NR RR Incidence Grp2: 2 NA p NR RR 1		
Pratley, 2010[128] RCT	Grp1: Metformin + sitagliptin NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HgbA1c: 7.5-10% NS; Start: 0.6 mg, Max: 1.8 mg		Def: Fatal cardiac arrest Grp1: 1 (<1) Grp2: 0 (0)		
Pratley, 2010[128] RCT	Grp1: Metformin + sitagliptin NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HgbA1c: 7.5-10% NS; Start: 0.6 mg, Max: 1.2 mg		Def: Fatal cardiac arrest Grp1: 1 (<1) Grp2: 0 (0)		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2: 1		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg)		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: 1		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: 1 Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin		Def:CVD mortality Fatal MI Incidence Grp1: 0		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 1 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 1 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (2000 mg)		Def:CVD mortality Fatal MI		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Incidence Grp1: 1 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[129] RCT	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 104		Def:CVD mortality Fatal MI Incidence Grp1: 1 408 Persons p NR Incidence Grp2: 0 406 Persons p NR		
Pratley, 2014[129] RCT	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 12		Def:CVD mortality Other CVD mortality (no fatal adverse events were reported) Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[129]	Grp1: Metformin + alogliptin		Def:CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Not applicable (e.g., cohort) Followup (wks):		Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 10 3246 Person-years p Rate ratio (poisson) 0.89 Incidence Grp2: 91 6916 Person-years p Rate ratio (poisson) 1.57		
Pratley, 2014[129] RCT	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 256 31497 Person-years p Rate ratio (poisson) 1 (Ref) Incidence Grp2: 10 3246 Person-years p Rate ratio (poisson) 0.89		
Pratley, 2014[129] RCT	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 256 31497 Person-years p Rate ratio (poisson) 1 (Ref) Incidence Grp2: 38 11619 Person-years p Rate ratio (poisson) 0.57		
Qiu, 2014[130] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin +		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 256 31497 Person-years p Rate ratio (poisson) 1 (Ref)		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT: Not applicable (e.g., cohort) Followup (wks):		Incidence Grp2: 91 6916 Person-years p Rate ratio (poisson) 1.57		
Qiu, 2014[130] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 38 11619 Person-years p Rate ratio (poisson) 0.57 Incidence Grp2: 10 3246 Person-years p Rate ratio (poisson) 0.89		
Qiu, 2014[130] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >=		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 38 11619 Person-years p Rate ratio (poisson) 0.57 Incidence Grp2: 91 6916 Person-years p Rate ratio (poisson)		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT: Not applicable (e.g., cohort) Followup (wks):		1.57		
Qiu, 2014[130] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT: No Followup (wks): 48		Def:CVD mortality Unspecified CVD mortality Incidence Grp1: 0 Incidence Grp2: 0		
Raz, 2008[180] RCT	Grp1: Metformin Fixed Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg	Grp1: 1 (1) Grp2: 0 (0)	Def: Fatal MI Grp1: 1 (1) Grp2: 0 (0)		
Reasner, 2011[133] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 58		Def:CVD mortality Fatal MI Incidence Grp1: 2 Incidence Grp2:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Reasner, 2011[133] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 144		Def:CVD mortality Other CVD mortality (not specified but confirmed by medical record and death certificates at each institution) Incidence Grp1: 7 Incidence Grp2: 11		
Ridderstrale, 2014[134] RCT	Grp1: Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2: Metformin + empagliflozin Fixed ((ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Composite CVD mortality outcome (death within 28 days of CVD was defined as diagnosis of myocardial infarction (ICD â€☐ 10 code I21), angina pectoris (ICD â€☐ 10 code I20.0), intracerebral haemorrhage, cerebral infarction, unspecified stroke (ICD â€☐ 10 c Incidence Grp1: 264 NA p NR RH 1.00 REF Incidence Grp2: 276 NA p NR RH Non-Proportional hazard, excluded from analysis		
Ridderstrale, 2014[134] RCT	Grp1: Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ГёÑ1500 mg/day, maximum tolerated dose, or		Def:CVD mortality Other CVD mortality (fata MI) Incidence p Incidence p		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	maximum dose according to the local label) Titrated (Max: 4mg) Grp2: Metformin + empagliflozin Fixed ((ГëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT: No Followup (wks): 80 NR/unclear				
Rigby, 2009[135] RCT	Grp1: Metformin + rosiglitazone Fixed NS; Mean: 4 mg Grp2: Metformin + sitagliptin NS: Mean: 100 mg			Def: Transient ischemic cerebrovascular accident Grp1: 1 (2) Grp2: 0 (0)	
Roden, 2013[137] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 169 p RH 1 Incidence Grp2: 207 p RH 1.5		
Roden, 2013[137] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 827 p RH 1 Incidence Grp2: 876 p RH 1.14		
Roden, 2013[137] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (10 mg)		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Incidence Grp1: 827 p RH 1 Incidence Grp2: 559 p RH 1.25		
Roden, 2013[137] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 169 p RH 1 Incidence Grp2: 115 p RH 1.63		
Rosenstock, 2006[138] RCT	Grp1: Metformin Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1847 mg, Max: 2000 mg D: 32 wks Grp2: Rosiglitazone Varied, glucose: 6.1 mmol/l Start: 4 mg, Mean: 7.7 mg, Max: 8 mg D: 32 wks	Grp1: 0 (0) Grp2: 0 (0)		Def: Not defined ischemic heart disease Grp1: 2 (1) Grp2: 2 (1)	
Rosenstock, 2006[138] RCT	Grp1: Metformin Varied, glucose: 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1799 mg, Max: 2000 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2mg D: 32 wks	Grp1: 0 (0) Grp2: 0 (0)		Def: Not defined ischemic heart disease Grp1: 2 (1) Grp2: 1 (1)	
Rosenstock, 2013[142] RCT	Grp1: Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose)		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + sitagliptin Not specified (prestud dose: ΓëÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Incidence Grp1: 827 p RH 1 Incidence Grp2: 2251 p RH 1.28		
Rosenstock, 2013[142] RCT	Grp1: Metformin + placebo Not specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 169 p RH 1 Incidence Grp2: 591 p RH 1.32		
Rosenstock, 2013[142] RCT	Grp1: Metformin + placebo Not specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT: Yes Followup (wks): 44		Def:CVD mortality Composite CVD mortality outcome (fatal acute myocardial infarction and cario-respiratory arrest) Incidence Grp1: 1 Incidence Grp2: 1		
Rosenstock, 2013[142] RCT	Grp1: Metformin + sitagliptin Not specified (prestud dose: ΓëÑ1500 mg/day or		Def:CVD mortality Other CVD mortality (sudden death, cardiac		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	maximum tolerated dose) Fixed (100mg) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT: Yes Followup (wks): 76		arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 3 Incidence Grp2: 1		
Rosenstock, 2013[142] RCT	Grp1: Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 3 Incidence Grp2: 0		
Ross, 2012[143] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 3 Incidence Grp2: 2		
Ross, 2012[143]	Grp1: Metformin + placebo		Def:CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 76		Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 1 Incidence Grp2: 0		
Ross, 2012[143] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 1 Incidence Grp2: 2		
Ross, 2012[143] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 104		Def:CVD mortality Composite CVD mortality outcome (cardiac failure, myocardial infarction) Incidence Grp1: 1 Incidence Grp2: 1		
Roumie, 2012[198]	Grp1: Metformin		Def:CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Retrospective cohort	Not specified Grp2: SU Not specified ITT: Not applicable (e.g., cohort) Followup (wks):		Other CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99)) Incidence Grp1: 109 1533 Person-years p 0.79 Incidence Grp2: 1378 9570 Person-years p 1 REF		
Roumie, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99)) Incidence Grp1: 109 1533 Person-years p 0.79 Incidence Grp2: 447 4280 Person-years p 0.94		
Roumie, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99)) Incidence Grp1: 1378 9570 Person-years p 1 REF Incidence Grp2: 447 4280 Person-years p 0.94		
Roumie, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD)		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 104		Incidence Grp1: Incidence Grp2:		
Roumie, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Roumie, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: 1 Incidence Grp2:		
Russell-Jones, 2012[144] RCT	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2: 1		
Russell-Jones, 2012[144] RCT	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: 1 Incidence Grp2: 1		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Russell-Jones, 2012[144] RCT	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2: 1		
Russell-Jones, 2012[144] RCT	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Russell-Jones, 2012[144] RCT	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Russell-Jones, 2012[144] RCT	Grp1: Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) Grp2: Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT: Yes		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: 1 Incidence Grp2:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 104				
Scheller, 2014[199] Retrospective cohort	Grp1: Metformin Not specified Grp2: Sitagliptin Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2: 1		
Scheller, 2014[199] Retrospective cohort	Grp1: Metformin Not specified Grp2: Sitagliptin Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Schernthaner, 2004[145] RCT	Grp1: Metformin Varied Max: 850 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1: 2 (0.3) Grp2: 3 (0.5)			
Seck, 2010[149] RCT	Grp1: Metformin + sitagliptin Fixed Grp2: Metformin + glipizide Fixed; Varied, glucose > 110 mg/dl NR; Start: 5 mg, Max: 20 mg, Mean: 9.2 mg	Grp1: 8 (1.4) Grp2: 1 (0.2)	Def: Sudden cardiac death Grp1: 2 (<1) Grp2: 0 (0)		
St John Sutton, 2002[154] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Max: 20 mg			Def: CVD morbidity/heart disease Grp1: 9 (9) Grp2: 5 (5)	
Stewart, 2006[155] RCT	Grp1: Metformin Varied Start: 500 mg, Mean: 2627.9 mg, Max: 3000 mg			Def: MI, angina pectoris, myocardial ischemic, coronary artery insufficiency	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	D: 20wks Grp2: Metformin + rosiglitazone Varied Start: 500 mg, Mean: 1812.9 mg, Max: 2000 mg D: 18 wks			Grp1: 0 (0) Grp2: 4 (2)	
van der Meer, 2009[166] RCT	Grp1: Metformin + glimepiride Fixed Start: 1000 mg, Max: 2000 mg; Start: 15 mg, Max: 30 mg D: 8 wks Grp2: Pioglitazone + glimepiride Varied Not specified D: 8 wks		Def: CVD event Grp1: 0 (0) Grp2: 0 (0)		
Weissman, 2005[167] RCT	Grp1: Metformin Varied Start: 1000mg, Max: 2000mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg	Grp1: 0 (0) Grp2: 1 (<1)		Def: CVD morbidity/MI (non-fatal) Grp1: 0 (0) Grp2: 2 (1)	
Weissman, 2005[167] RCT	Grp1: Metformin Varied Start: 1000mg, Max: 2000mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg			Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI Grp1: 3 + 1 withdrew (1) Grp2: 5 (1)	

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular

diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table 8. Results of studies evaluating diabetes medications on nephropathy and neuropathy

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: Yes Followup (wks): 52, Active	Def:Nephropathy Nephropathy defined as (Renal adverse event) Incidence Grp1: (0.6) Incidence Grp2: (0)	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: Yes Followup (wks): 52, Active	Def:Nephropathy Nephropathy defined as (Renal adverse event) Incidence Grp1: (0.6) Incidence Grp2: (0.6)	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: No Followup (wks): 12, NR/unclear	Def:Nephropathy Nephropathy defined as (diabetic nephropathy) Incidence Grp1: (1.3) Incidence Grp2: (2.5)	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: No Followup (wks): 12, Active	Def:Nephropathy Nephropathy defined as (microalbuminuria) Incidence Grp1: (1.3) Incidence Grp2: (3.7)	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: No Followup (wks): 12, Active	Def:Nephropathy Nephropathy defined as (microalbuminuria) Incidence Grp1: (1.3) Incidence Grp2: (0)	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: No Followup (wks): 12, NR/unclear	Def:Nephropathy Nephropathy defined as (diabetic nephropathy) Incidence Grp1: (1.3) Incidence Grp2: (1.2)	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.86 Incidence p RH Ref	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (GFR event or ESRD) Incidence p RH 0.78 Incidence p RH ref	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.85 Incidence p RH Ref	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.85 Incidence p RH 1.01	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.86 Incidence p RH 1.04	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (GFR event or ESRD) Incidence p RH 0.78 Incidence p RH 1.11	
Schramm, 2011[200] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH Ref Incidence p RH 1.04	
Seino, 2012[151] RCT	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (12.5mg)	Def:Nephropathy Nephropathy defined as (GFR event or ESRD) Incidence p RH ref Incidence p RH 1.11	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive		
Seino, 2012[151] RCT	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH Ref Incidence p RH 1.01	
Stenlof, 2014[201] RCT	Grp1: Sitagliptin Fixed (100mg) Grp2: Canagliflozin Fixed (100mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (renal function decline endpoint was reached if a patient with an eGFR â‰¥60 ml/min/1.73m2 at first measurement had an ensuing eGFR that was <60 ml/min/1.73m2 during follow-up) Incidence p RH 1.00 (ref) Incidence p RH 1.04	
Stenlof, 2014[201] RCT	Grp1: Sitagliptin Fixed (100mg) Grp2: Canagliflozin Fixed (300mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (proteinuria: defined as microalbuminuria or worse), we required that patients have a negative urine protein test at first urine measurement following T2D diagnosis that subsequently became positive during follow-up. Positive test d Incidence p RH 1.00 (ref) Incidence p RH 1	
Umpierrez, 2014[165] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (proteinuria: defined as microalbuminuria or worse), we required that patients have a negative urine protein test at first urine measurement following T2D diagnosis that subsequently became positive during follow-up. Positive test d Incidence p RH 1.00 (ref) Incidence p RH 1.27	
Umpierrez, 2014[165] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg)	Def:Nephropathy Nephropathy defined as (renal function decline endpoint was reached if a patient with an eGFR â‰¥60 ml/min/1.73m2 at first measurement had an ensuing eGFR that was <60 ml/min/1.73m2 during follow-up) Incidence p RH 1.00 (ref)	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Incidence p RH 1.41	
Wheeler, 2013[202] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Rosiglitazone, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (renal function decline endpoint was reached if a patient with an eGFR â‰¥60 ml/min/1.73m2 at first measurement had an ensuing eGFR that was <60 ml/min/1.73m2 during follow-up) Incidence p RH 1.41 Incidence p RH 1.04	
Wheeler, 2013[202] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (proteinuria: defined as microalbuminuria or worse), we required that patients have a negative urine protein test at first urine measurement following T2D diagnosis that subsequently became positive during follow-up. Positive test d Incidence p RH 1.27 Incidence p RH 1	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence Grp1: 77420 Person-years p NR RH ref Incidence Grp2: 2014 Person-years p NR RH 0.92	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH ref Incidence p RH 1.21	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence Grp1: 77420 Person-years p NR RH ref Incidence Grp2: 36592 Person-years p NR RH 1.2	
Williams-Herman, 2010[170]	Grp1: Metformin + placebo	Def:Nephropathy	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
RCT	Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p ref Incidence p 1.19	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH ref Incidence p RH 1.21	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH ref Incidence p RH 1.18	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH 1.21 Incidence p RH	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH 1.18 Incidence p RH	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg)	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant))	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks):	Incidence p 1.19 Incidence p	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence Grp1: 36592 Person-years p NR RH 1.2 Incidence Grp2: 2014 Person-years p NR RH 0.92	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH 1.21 Incidence p RH	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 104	Def:Nephropathy Nephropathy defined as (renal and urinary disorders) Incidence Grp1: 15 (6) Incidence Grp2: 13 (5)	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 104	Def:Nephropathy Nephropathy defined as (renal and urinary disorders) Incidence Grp1: 15 (6) Incidence Grp2: 11 (5)	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 26	Def:Nephropathy Nephropathy defined as (Change in albumin to creatinine ratio (%)) Incidence p Incidence p	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 26	Def:Nephropathy Nephropathy defined as (Change in albumin to creatinine ratio (%)) Incidence p Incidence p	
Williams-Herman, 2010[170] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 26	Def:Nephropathy Nephropathy defined as (Change in albumin to creatinine ratio (%)) Incidence p Incidence p	
Williams-Herman, 2010[170] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 48	Def:Nephropathy Nephropathy defined as (GFR (ml/min per 1.73 m2)) Incidence p Incidence p	
Williams-Herman, 2010[170] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 48	Def:Nephropathy Nephropathy defined as (urine albumin/creatine (mg/g)) Incidence p Incidence p	
Williams-Herman, 2010[170] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 26, Passive	Def:Neuropathy Unspecified neuropathy Incidence p Incidence Grp2: 1 p	
Williams-Herman, 2010[170] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg)	Def:Neuropathy Unspecified neuropathy Incidence p Incidence Grp2: 1 p	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	Titrated (Max: 100 mg) ITT: Yes Followup (wks): 26, Passive		
Yang, 2011[172] RCT	Grp1: Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2: Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT: Yes Followup (wks): 12, NR/unclear	Def:Retinopathy Unspecified retinopathy Incidence Grp1: 1 Incidence Grp2: 1	
Yang, 2011[172] RCT	Grp1: Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2: Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT: Yes Followup (wks): 12, NR/unclear	Def:Retinopathy Unspecified retinopathy Incidence Grp1: 1 Incidence Grp2: 0	
Yang, 2012[174] RCT	Grp1: Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2: Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT: Yes Followup (wks): 12	Def:Retinopathy Unspecified retinopathy Incidence Grp1: 1 Incidence Grp2: 0	
Zhang, 2012[179] RCT	Grp1: Metformin + glimepiride Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (1-4mg, adjusted in accordance with the levels of blood glucose) Grp2: Metformin + exenatide Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (initiated at 10ug for the first 4 wks, 20ug in the subsequent 12 wks then went into 16 week treatment period)	Def:Retinopathy Retinopathy defined as (Diabetic retinopathy) Incidence Grp1: 9 (6.8) Incidence Grp2: 16 (6)	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: No Followup (wks): 52, Active		

g/day = grams per day; g/dl = grams per deciliter; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; pmol/l = picomoles per liter; SU = sulfonylurea; TZD = thiazolidinedione; U/kg = units per kilogram; yrs = years

Some data may have not been extracted because the question was not asked.

Table 9. Quality of studies evaluating long-term clinical outcomes

Author, year	Randomized	Randomization Scheme	Double-Blind	Blinding Method	Dropouts Description
Alba, 2013[3]	Yes	Yes	Yes	Not described	Yes
Arechavaleta, 2011[5]	Yes	Yes	Yes	Not described	Yes
Arjona Ferreira, 2013[6]	Yes	Yes	Yes	Yes	Yes
Aschner, 2012[8]	Yes	Yes	No	Not described	Yes
Bailey, 2013[10]	Yes	Yes	Yes	Yes	Yes
Barnett, 2012[13]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2010[14]	Yes	Yes	Yes	Yes	Yes
Bolinder, 2012[17]	Yes	Yes	Yes	Yes	Yes
Borges, 2011[18]	Yes	Not described	Yes	Not described	No
Bunck, 2011[21]	Yes	Yes	NR/Can't tell	Not described	Yes
Cefalu, 2013[23]	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2012[33]	Yes	Not described	Yes	Yes	No
Diamant, 2010[44]	Yes	Yes	No	Not described	Yes
Erem, 2014[47]	Yes	Not described	No	Not described	No
Esposito, 2011[48]	Yes	Yes	Yes	Yes	Yes
Ferrannini, 2013[185]	Yes	Yes	No	Yes	No
Fonseca, 2012[55]	Yes	Yes	Yes	Not described	Yes
Forst, 2010[56]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[60]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[61]	Yes	Yes	NR/Can't tell	Not described	Yes
Garber, 2011[66]	Yes	Yes	No	Not described	Yes
Genovese, 2013[67]	Yes	Not described	Yes	Yes	Yes
Genovese, 2013[68]	Yes	Yes	Yes	Yes	Yes
Goke, 2010[69]	Yes	Yes	Yes	Yes	Yes
Haak, 2012[76]	Yes	Not described	Yes	Not described	Yes
Haak, 2013[77]	Yes	Yes	Yes	Yes	Yes
Haring, 2014[82]	Yes	Yes	Yes	Yes	Yes
Henry, 2012[83]	Yes	Yes	Yes	Not described	No
Henry, 2012[83]	Yes	Yes	Yes	Not described	Yes
Hermans, 2012[86]	Yes	Not described	Yes	Not described	Yes

Author, year	Randomized	Randomization Scheme	Double-Blind	Blinding Method	Dropouts Description
Hong, 2013[186]	Yes	Yes	Yes	Yes	Yes
Kadowaki, 2013[94]	Yes	Yes	Yes	Yes	Yes
Kaku, 2011[97]	Yes	Not described	No	Not described	
Lavalle-Gonzalez, 2013[104]	Yes	Yes	Yes	Yes	Yes
List, 2009[107]	Yes	Yes	Yes	Yes	Yes
Nauck, 2009[117]	Yes	Yes	Yes	Not described	Yes
Nauck, 2011[118]	Yes	Yes	Yes	Yes	Yes
Nauck, 2014[119]	Yes	Not described	Yes	Not described	Yes
Petrica, 2009[124]	Yes	Not described	No	Not described	Yes
Pfutzner, 2011[126]	Yes	Not described	Yes	Not described	No
Pfutzner, 2011[127]	Yes	Yes	Yes	Not described	Yes
Pratley, 2014[129]	Yes	Not described	Yes	Not described	Yes
Qiu, 2014[130]	Yes	Yes	Yes	Not described	Yes
Reasner, 2011[133]	Yes	Not described	Yes	Not described	Yes
Ridderstrale, 2014[134]	Yes	Yes	Yes	Yes	Yes
Roden, 2013[137]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2013[142]	Yes	Yes	Yes	Yes	Yes
Ross, 2012[143]	Yes	Yes	Yes	Yes	Yes
Russell-Jones, 2012[144]	Yes	Yes	Yes	Yes	Yes
Seino, 2012[151]	Yes	Yes	Yes	Yes	Yes
Stenlof, 2014[201]	Yes	Yes	Yes	Yes	Yes
Umpierrez, 2014[165]	Yes	Yes	Yes	Yes	Yes
White, 2014[168]	Yes	Yes	Yes	Yes	Yes
Williams-Herman, 2010[170]	Yes	Yes	Yes	Yes	Yes
Yang, 2011[172]	Yes	Yes	Yes	Not described	Yes
Yang, 2012[174]	Yes	Yes	Yes	Yes	Yes
Zhang, 2012[179]	Yes	Not described	No	Not described	Yes

Table 10. Characteristics of studies evaluating diabetes medications on safety

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Agarwal, 2005{Agarwal, 2005 #35339} US RCT	Start year: 2001 End year: 2003 16 Wks	No run-in period	Yes	102/54 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m^2 <7.5 kg/m^2, class III or IV heart failure, NSAID use
Ahren, 2014[2] Country NR RCT	2009 2013 104 Wks	Yes	Yes	Not Extracted/ 1049 NR	Age <18yr, HbA1c >10.00% or <7.00%, weight <20 or >45 kg/m2, Any liver disease, Any kidney disease, adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening, abnormal thyroid-stimulating hormone concentration and not clinically euthyroid, ongoing symptomatic biliary disease, history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function, history of most cancers not in remission for at least 3 years, personal or family history of medullary thyroid, carcinoma or multiple endocrine neoplasia, type 2, resting systolic blood pressure (SBP)>160mmHg and/or diastolic blood pressure(DBP)>100mmHg,
Alba, 2013[3] Multi-continent RCT Factorial design	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 211 NR	Age <30 or >65 yr, HbA1c >10% if drug naive, 9% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, 7% if drug naive, 6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, diagnosis >5 years, Any liver disease, Any kidney disease, History of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks, fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week -2
Amador-Licona, 2000{Amador-Licona, 2000 #35254} Mexico RCT	12 wks (Planned duration)	Not extracted	No	Not extracted	Age >65 years, any liver disease, history of CVD, other
Andersson, 2010[181]	1997	Not	Yes	Not Extracted/	Age <= 30, No diagnosis/hospitalization for CHF, not using MET, SU

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Denmark Retrospective cohort	2006 Not applicable	applicable		10,920 / 5,852 Administrative database	and/or Insulin, Use of other glucose lowering meds, patients with previous hospitalisations for HF during the period from 1978 until 1996 (diagnosis codes [ICD-10] I50, I42, J81, I11.0 and [ICD-8] 425, 4270, 4271) were excluded from the study, not alive 30 days after discharge for CHF, not receiving drug of interest 30 days after discharge for CHF, use of study drug within 90 days of hospitalization fro CHF
Arechavaleta, 2011[5] "multi-national" RCT	Neither year reported 30 Wks	Yes	Yes	Not Extracted/ 1035 NR	Age <18 years, HbA1c >9% or <6.50%, Not on a stable dose of metformin (ГёÑ1500 mg/day) as well as diet and exercise for past 12 wks history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable meds for HTN, thyroid dz, HRT, OCPs
Arjona Ferreira, 2013[6] multinational RCT	Neither year reported 58 Wks	Yes	Yes	Not Extracted/ 426 NR	Age <30yr, HbA1c >9.00% or <7.00%, Prior or current use of insulin, Any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duratoin of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, visit2, FPG>260mg/dl, unlikely to improve with diet/exercise, visite 3, FPG>250mg/dl consistently (i.e., measure=ment repeated and confirmed within 7 days); visite 4, FPG>240mg/dl consistentlyvisit5, finger-stick glucose > 240 or <120mg/dl
Aschner, 2010{Aschner, 2010 #7461} Multi-continent RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	2068/1050 NR	Age <18 and > 78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 mg/dL or >250 mg/dL, triglycerides >600 mg/dL, CK > 2 times normal upper limit
Aschner, 2012[8] Multi-continent	2008 2011	No	Yes	Not Extracted/ 515	Age <35 - >70, HbA1c >=11 or <7, BMI <25 - >45, diagnosis <6 months, Any liver disease, Any kidney disease, FPG >14.4 mmol/L, tx'd w/ oral other than metformin in past 3 mo, received SU+MET In past year, prior

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	24 Wks			NR	use of GLP-1 or DPP-4, any disorder that the investigator felt woudl compromise the patient's safety, unwilling to self-monitor BG or keep diary
Bailey, 2005{Bailey, 2005 #35231} UK, 14 European Countries RCT	24 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other
Bailey, 2013[10] Multi-continent RCT	2007 2008 102 Wks	Yes	Yes	Not Extracted/ 546 NR	Age <18 and >77, HbA1c >10% or 7%, BMI >45 kg/m^2, Any liver disease, Any kidney disease, History of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, systolic blood pressure >=180 mmHG, diastolic blood pressure >=110 mmHG, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, New York Heart Association class III or IV congestive heart failure
Bakris, 2006{Bakris, 2006 #35219} US, Multi-continent, South America, Europe RCT	Neither year reported 32 Wks	Yes	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg
Barnett, 2012[13] Multi-continent RCT	2008 2010 52 Wks	Yes	Yes	Not Extracted/ 227 NR	Age <18 or >80 yr, If treatment naive: 10.0%(9.0% for Canada); If receiving an oral antidiabetes drug: 9.0%, If treatment naive: 7.0%; If receiving an oral, antidiabetes drug: 6.5%, BMI >40kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, MI, stokre, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an antiobesity drug within the previous 3 months, or

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs
Bergenstal, 2010[14] Multi-continent RCT	2008 2008 26 Wks	No	Yes	Not Extracted/ 514 Outpatient: primary care	Age <18years, HbA1c >11% or <7.10%, BMI <25 and greater than 45kg/m2, Prior or current use of insulin, Prior or current use of study drug, Pregnant, Nursing, Not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 diabetes fasting plasma glucose >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use
Bergenstal, 2012[15] Multi-continent RCT	2008 2011 156 Wks	No	Yes	Not Extracted/ 666 clinical sites unspecified	Age <18 years and >75years, HbA1c >10% or <7%, BMI <25kg/m2 and >45kg/m2 (<23 kg/m2 for asians), Prior or current use of insulin, History of CVD, Neuropathy, Retinopathy, were NOT receiving metformin (stable dose >/=1,500 mg/day or maximally tolerated dose for >/=12 wks before screening). diabetic nephropathy, gastrointestinal disease, previous bariatric, surgery, pancreatitis, previous exposure to other oral antihyperglycemic or weightlowering drugs within 12 wks, >1 week of insulin within 6 months, or another GLP-1 mimetic or analog at any time.
Blonde, 2002 US RCT	16 wks (Planned duration)	Not extracted	Yes		Age <30 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other
Bolinder, 2012[17] Europe	2009 2011 102	Yes	Yes	Not Extracted/ 182 NR	Women age <55 or >75 years. Men <30 or >75 years, HbA1c >8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, Fasting plasma glucose >240 mg/dl (>13.2 mmol/liter), diabetes

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	Wks				treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment, perimenopausal women, body weight change >5% within 3 months serum total bilirubin >34 ╝╙ mol/L; hemoglobin (Hb) Γëñ105 g/L (10.5 g/dL) for men and Γëñ95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than ΓêÆ2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, systolic blood pressure ΓëÑ180 mmHg and/or diastolic blood pressure ΓëÑ110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure, significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications) alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment
Borges, 2011[18] Multi-continent RCT	2006 2008 80 Wks	No	Yes	Not Extracted/ 688 NR	Age <18 - >75, HbA1c >10.5 or <7.5, BMI < =25, Prior use of any diabetes treatment, fasting glucose <7 mmol/l
Bunck, 2009 {Bunck, 2009 #35268} Sweden, Finland, Netherlands RCT	Start year: 2004 End year: 2007 56 Wks	None	Yes	150/69 NR	Age <30 and >75 years, HbA1c<6.5% or >9.5%, BMI <25 kg/m^2 or BMI >40 kg/m^2, metformin treatment not at a stable dose for at least 2 months, no other blood glucose lowering medications allowed in 3 months prior to study, no changes in other medications known to affect B cell function (ACEI, B Blockers)
Bunck, 2011[21] Europe	2004 2009 3.5	No	Yes	Not Extracted/ 69 NR	Age <30 or >75 years, HbA1c >9.50% or <6.50%, BMI <25 or >40 kg/m^2, Not undergoing stable metformin treatment for at least 2 months prior enrollment, Using any other blood glucose lowering agents 3 months prior to screening, besides metformin

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	Years				
Cefalu, 2013[23] Multi-continent RCT	2009 2011 52 Wks	Yes	Yes	Not Extracted/ 1452 NR	Age <18, >80, HbA1c >9.5 or <7, Any kidney disease, Not on stable metformin therapy (ГёÑ2000 mg per day or ГёÑ1500 mg per day if unable to tolerate a higher dose) for at least 10 wks, prior TZD use in 16 wks before screening, h/o more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15┬╖0 mmol/L or more during the pretreatment phase;
Charbonnel, 2006[24] Multi-continent RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	1464/701 NR	Age < 18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 wks of screening, FPG > 14.4mmol/l
Charpentier, 2001[25] France RCT	20 wks (Planned duration)	Not extracted	Yes	Not extracted	Age ≤34 or ≥71 years, any kidney disease, history of CVD, no Type 2 DM, other
Chawla, 2013[26] India RCT	2008 2009 16 Wks	No	No	Not Extracted/ 52 NR	Age <18yr, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, not on met monotherapy of >=1500mg/day for at least 1 month, FPG<140mg/dl or >270 mg/dl
Chien, 2007[27] Taiwan, Multi-center RCT	Neither year reported 16 Wks	No run-in period	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c >12% and FPG>250 mg/dL at screening visit, HbA1c <7% and FPG<140 mg/dL at screening visit, BMI <18.5 or >35 kg/m^2, current significant GI disorder, hyperosmolar nonketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 wks, history of cancer in 5 years, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or glicazide<10 mg/day, glimepiride<4mg/d, glicazide<160mg/d)
Comaschi, 2007[28] Italy RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33nmol/L
Curkendall, 2014[207] US Retrospective cohort	2009 2010 Not applicable	Not applicable	Yes	Not Extracted/ 22,592 Administrative database	Age <18, less than 180 days continuous insurance eligibility prior to index date, used insulin or other dm2 drug (other than met, su or saxa) within 180 days prior to index date, did not have a metformin prescription within 180 days prior to the index date, did not receive metformin on or after the index date, did not have 120 days of continuous insurance coverage immediately after the index date, did not have a subsequent saxa or SU prescription after the index date, gestational diabetes or dm1 during study perioddid not have a code for dm2 during study period
Currie, 2009{Currie, 2009 #35295} Taiwan Prospective or retrospective cohort	Start year: 2000 End year: 2005 6 Years	NA	NR	1432850/473483 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period
Davies, 2007[29] United Kingdom RCT	Neither year reported 4 Months	Run-in period but number of participants excluded was NR	NR	82/NR NR	Age <30 or >80 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c <7.0%, BMI >43 kg/m^2, not using adequate contraception, history of previous insulin use for >2wks, duration of Type 2 DM <12 months, C-peptide levels <0.33, severe concurrent disease, serum creatine

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					>150umol/l
Davies, 2013[208] Country NR RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 222 NR	Age <18yr, HbA1c >10.00% or <7.10%, BMI <25 or >45kg/m2, or unstable, weight(>5% variability) for 3 months, Not using adequate contraception, not on following therapy: stable dose of met(>1000mg/day) alone or in combination with with a stable dose of SU as a separate formulation for at least 3 months before randomization, have a clinically significant medical condition that could preclude safe participation in this study, had more than 3 major hypoglycemic episodes in the past 6 months, had been treated with a drug that promotes weight loss within 3 months of screening
DeFronzo, 1995[30] +US RCT	29 wks (Planned duration)	Not extracted	No	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
DeFronzo, 2009[31] NR RCT	Neither year reported 24 Wks	Yes	Yes	1462/743 NR	Age >18 and <77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BM >40 kg/m^2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40
Defronzo, 2010[32] United States RCT	Start year: 2006 End year: 2008 20 Wks	None	Yes	NR/137 NR	Age <18 or >75 years, HbA1c <6.8% or >10%, BMI <25 kg/m^2 or >40 kg/m^2, not on stable dose of metformin for at least 6 wks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other antidiabetic medication (other than metformin)
DeFronzo, 2012[33] Multi-continent RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 1554 NR	Age <18 or >80 yr, HbA1c >10% before and after run-in/stabilization period, 7.5% before and after run-in/stabilization period BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopath, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					<10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization
Derosa, 2004{Derosa, 2004 #35237} Italy RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Age <46 or >67 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Derosa, 2009{Derosa, 2009 #35191} Italy RCT	Neither year reported 15 Months	Fewer than 10% of participants were excluded during run-in	NR	271/252 Outpatient: primary care, computerized clinic registry	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 6.5%, BMI <25 kg/m2 or >30 kg/m2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia
Derosa, 2010{Derosa, 2010 #7394} Italy RCT	Neither year reported 12 Months	No run-in period	No	128/128	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m^2 or ≥30 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy
Derosa, 2005[36] Italy RCT	Neither year reported 12 Months	No run-in period	NR	NR/99 case notes and/or clinic registers	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications
Derosa, 2005[37] Italy RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Age <18 years, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other
Derosa, 2013[42] Italy RCT	2008 2010 12 Months	Yes	Not reported	Not Extracted/ 178 NR	Age <=18yr, HbA1c <=7.5%, BMI <25 or >=31 kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, ketoacidosis, severe anemia, New York Heart Association 1-4 congestive heart failure
Derosa, 2013[43] Italy RCT	2008 2010 12 Months	Yes	No	Not Extracted/ 171 NR	Age <=18yr, HbA1c <=7.5%, BMI<25 or >=34.9kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, acute or chronic pancreatitis, severe anemia, serous CVD (e.g. New York Heart Association class 1-4 CHF, MI, stroke) or cerebrovascular conditions within 6 months before study enrollment, taking gygtemic glucocorticoids, taking weight reducing drugs such as sibutramine or orlistat, or any medications that miht preclude safe participation in the study
Diamant, 2010[44] Multi-continent RCT	2008 2009 26 Wks	Yes	Yes	Not Extracted/ 321 NR	Age 18 years or older, HbA1c >11 or <7.1, BMI <25kg/m2 and >45kg/m2. Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoidstreatment for longer than 2 wks with insulin, thiazolidinediones, ╬▒-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening
Dormuth, 2009{Dormuth, 2009 #35304}	Start year: 1998 End year:	NA	No	127581/ 84339	Had received insulin or other ODMs besides metformin, SU or TZD, gestational DM, fractures, admitted to long term facility

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Canada Prospective or retrospective cohort	2007 11 Years			Community	
Einhorn, 2000[45] US RCT	16 wks (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other
Erem, 2014[47] Turkey RCT	Neither year reported 52 Wks	Yes	No	Not Extracted/ 60 NR	Age <30 or >70 yr, HbA1c >8% when FPG<126mg/dl, <7% if FBG is 126 -139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria, NYHAC Class 3/4 CHF history of lactic acidosis, malignancy, thyroid disease or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection
Esposito, 2011[48] Italy RCT	Neither year reported 24 Wks	No	Yes	Not Extracted/ 110 investigators' practices	Age <30 and >75 years, HbA1c >10% or <7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l)
Farcasiu, 2011[50] Multi-continent RCT	2006 2009 16 Wks	Yes	Yes	Not Extracted/ 302 NR	Age <30 - >75, 1.8 X ULN, 1.2 X ULN, BMI >40, Any liver disease, metformin <1500mg, on other oral dm med besides metformin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle
Feinglos, 2005[51]	16 wks	Not	Yes	Not extracted	Age <30 or >81 years, any liver disease, any kidney disease, history of

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
US RCT	(Planned duration)	extracted			CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other
Ferrannini, 2013[52] Multi-continent RCT	Neither year reported 90 Wks	Yes	Yes	Not Extracted/ 659 NR	Age <18 or>79, HbA1c >=10 or 7, BMI>40, successfully completed one of the two 12-wk dose-finding studies (refid 584 or 1334)
Ferrannini, 2013[185] Multi-continent RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 408 NR	Age <18 or >79, HbA1c >9 if on antidiabetic drug, >10 if tx naïve, 6.5 if on antidiabetic drug, <7 if treatment naïve, BMI >40, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, not treatment naive or on stable dose of more than one antidiabetic drug (except GLP1, insulin, TZDs) in past 10 wks, myocardial infarction, stroke or transient ischaemic attack Γëñ6 months prior, unstable or acute congestive heart failure, acute or chronic acidosis; disease of CNS, psychiatric d/o or clinically relevant neuro d/o, chronic or clinically relevant acute infection, current or chornic urogenital tract inf, dehydration, hereditary galactose intolerance, tx with antiobesity drugs, systemic steroids, alchol abuse, tx with investigational drug <=2 m prior neurologic/psychiatric issues that might interfere with participation
Fonseca, 2000 [54] US RCT	26 wks (Planned duration)	Not extracted	No	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no type 2 DM, other
Fonseca, 2012[55] US and Latin America RCT	2009 2010 18 Wks	Yes	Yes	Not Extracted/ 282 NR	Adults, HbA1c >11 or <7.5, BMI >45, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradind to / h/o

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					tx w/ saxa
Forst, 2010[56] Europe RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 333 NR	Age <21 or >75 yr, HbA1c >9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase, 7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, diagnosis <3 months, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months
Forst, 2014[58] Germany RCT	Neither year reported 12 Wks	No	Yes	Not Extracted/ 40 Outpatient but unclear if primary or specialty care	Age <45 or >75yr, HbA1c >8.5 or <6.5, Any liver disease, Any kidney disease, more than one unexplained episode of severe hypoglycaemia within 6 months, pre-treatment with anti-diabetic drugs other than metformin within the last 3 months, uncontrolled hypertension (SBP>160mmHg, and/or DBP>90mmHg), MI or stroke in last 6 month
Gallwitz, 2011[59] Germany RCT	Neither year reported 26 Wks	No	Yes	Not Extracted/ 363 NR	Adults, HbA1c >10 or <6.5, not on metformin
Gallwitz, 2012[60] Multi-continent RCT	2008 2010 104 Wks	Yes	Yes	Not Extracted/ 1552 Outpatient: primary care Outpatient: subspecialty care setting	Age <18, >80 years, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Gallwitz, 2012[61] Multi-continent RCT	2006 2011 48 Months	No	Yes	Not Extracted/ 1029 NR	Age <18 or >85, HbA1c >9 or <6.5, BMI <25 or >=40, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides
Garber, 2009 United States, Mexico RCT	Start year: 2006 End year: 2007 52 Wks	Fewer than 10% of participants were excluded during run-in	Yes	NR/746 NR	Age <18 or >80 years, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m^2, either not treated with diet and exercise or up to half the highest dose of ODM monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range)
Garber, 2002{Garber, 2002 #35251} US RCT	20 wks (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other
Garber, 2003{Garber, 2003 #35242} US RCT	16 wks (Planned duration)	Not extracted	Yes	Not extracted	NR
Garber, 2006[64] US	24 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <20 or >78 years, any liver disease, any kidney disease, history of CVD, HbA1c ≤7.0% or ≥12.0%, no Type 2 DM, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT					
Garber, 2011[66] US Mexico RCT	2006 2008 104 Wks	No	Yes	Not Extracted/ 746 NR	Age <18 or >80, HbA1c >11% if on diet/exercise or >10% if on monotherapy, 7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia
Genovese, 2013[67] Italy RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 213 NR	Age <35 or >75 yr, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin acute or chronic pancreatitis or familial polyposis history of chronic alcohol or, drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria
Genovese, 2013[68] Country NR RCT	Neither year reported 16 Wks	Yes	Yes	Not Extracted/ 58 Outpatient: subspecialty care setting	Age <35 or >75 yr, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, congestive heart failure (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					corticosteroids,known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients (pioglitazone, met marked above)
Goke, 2010[69] Multi-continent RCT	2007 2010 104 Wks	Yes	Yes	Not Extracted/ 858 NR	Age <18 years, HbA1c >10% and <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Γüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment congestive heart failure, significant cardiovascular history within the past 6 months
Goldstein, 2003[70] US RCT	18 wks (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5 and >12.0, other
Goldstein, 2007[71] Multi-continent RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	3544/1091 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with < 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose > 280 mg/dl after run-in period, no Type 1 DM or Type 2 DM
Gomez-Perez, 2002[72] Mexico RCT	26 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Gupta, 2013[75] India	2012 2013	No	NR	Not Extracted/ 167	Any liver disease, Any kidney disease, Pregnant, Nursing, hx of hypersensitivity to sulphonylurea and DPP-IV inhibitors psychiatric, GI, hematological, metabolic, neurological, hepatic, or renal

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	24 Wks			Outpatient: primary care	disorders, clinically significant heart disease (NYHA III or IV), acute infection
Haak, 2012[76] Multi-continent RCT	2008 2010 24 Wks	Yes	Yes	Not Extracted/ 791 NR	Age <18 or >80 years, HbA1c >10.5% if on OAD or >=11% if treatment naïve 7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months
Haak, 2013[77] Multi-continent RCT	2009 2011 52 Wks	Yes	Yes	Not Extracted/ 567 NR	Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation
Hamann, 2008[79] Multinational Europe, Mexico RCT	Neither year reported 52 Wks	Yes	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any ODM other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/ dl for men and < 10.0 g/ dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg
Hanefeld, 2004[80]	NR	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Canada, UK, Hungary, Finland, U.K., Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands RCT					
Hanefeld, 2007[81] Multinational Europe RCT	Neither year reported 52 Wks	Run-in period but number of participants excluded was NR	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG <7mmol/l or > 15mmol/l, C-peptide <0.27 nmol/l
Haring, 2014[82] Multi-continent RCT	2010 2012 24 Wks	Yes	Yes	Not Extracted/ 638 NR	Age <18, HbA1c >10 or <7, BMI >45, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d eGFR<30
Henry, 2012[83] Multi-continent	2008 2009 24 Wks	Yes	Yes	Not Extracted/ 603 Inpatient/hospital Outpatient: primary	Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT				care Outpatient: subspecialty care setting	systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease
Henry, 2012[83] Multi-continent RCT	2009 2010 24 Wks	Yes	Yes	Not Extracted/ 641 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months
Hermann, 1994[85] Sweden RCT	6 months (Planned duration),	Not extracted	Yes	Not extracted	No Type 2 DM, other
Hermans, 2012[86] Europe RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 286 NR	Age <18, HbA1c >10 or <7, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu-cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d
Hong, 2013[186] China RCT	2004 2007 36 Months	Yes	Yes	Not Extracted/ 304 clinical centers	Age >80yr, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, not diagnosed as CAD (either having a history of acute myocardial infarction diagnosed by a representative set of, electrocardiograms, cardiac enzyme values, and typical symptoms or by angiographically identified stenosis of >50% of lumen diameter in at le, severe dysfunction of the heart (NYHA class > phase 3), other severe

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					organic heart diseases, including but not limited to congenital heart disease, rheumatic heart disease, hypertrophic or dilated, cardiomyopathy;, psychiatric disease, severe infection, severe anemia, neutropenia, allergic to study drugs, fasting plasma glucose>=15 mmol/l, recent drug or alcohol abuse
Jadzinsky, 2009[90] Multi-continent RCT	Start year: 2006 End year: 2007 24 Wks	Fewer than 10% of participants were excluded during run-in	Yes	2936/1394 Outpatient: primary care, Outpatient: subspecialty care setting, Community	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c< 8% >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
Jain, 2006{Jain, 2006 #35218} US, Puerto Rico RCT	Neither year reported 56 Wks	Run-in period but number of participants excluded was NR	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c < 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to rosiglitazone, pioglitazone or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin , SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin > 250 mg/day, ODM, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria, anemia(< 10g/dl women, < 12g/dl men, BMI <20 kg/m^2 or >45 kg/m^2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Jones, 2003 US RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	NR	NR/N: NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history of chronic insulin, FPG <140

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days
Kadoglou, 2011[93] ?Greece RCT	2006 2008 6 Months	No	No	Not Extracted/ 140 NR	Age <50 and >75, HbA1c <=7%, BMI <=25kg/m2, Any liver disease, Any kidney disease, usage of antidiabetic medications, autoimmune or life threatening illnesses, on diet therapy for diabets for at least 3 mo, congestive heart failure (NYHA class IIIV), clinical evidence of cardiovascular (coronary, peripheral arteries), autoimmune or life-threatening diseases, alcohol / drug abuse, uncontrolled hypertension (blood pressure > 170 / 100 mmHg), recently diagnosed / or untreated hormonic disorders, free from microvascular compl, maintained body weight for 3 mo before study
Kadowaki, 2013[94] Japan RCT	2006 2008 12 Wks	Yes	Yes	Not Extracted/ 149 NR	Age <20 or >=75yr, 9.4% for patients receiving an OHA other than met at screening, 10.5% for patients with met only at screening, 10.5% for all patients completing the run-in period, 6.4% for patients receiving an OHA other than met at screening, 6.9% for patients with met only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks
Kahn, 2006{Kahn, 2006 #35215} Multi-continent RCT	Start year: 2000 End year: 2006 6 Years	No run-in period	Yes	6676/4360 NR	Age < 30 or > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, fasting plasma glucose <126 or > 180 mg/dL, history of lactic acidosis
Kahn, 2008{Kahn, 2008 #35320} US, Multinational Europe RCT	Neither year reported 4 Years	No run-in period	Yes	4360/4351 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), history of lactic acidosis, uncontrolled hypertension, corticosteroid use
Kaku, 2009 {Kaku,	Start year: 2005	Yes	Yes	NR/236	Age ≤20 or ≥65 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2009 #35192} Japan RCT	40 Wks			NR	as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, gastrointestinal, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre coma within the preceding 26 wks, if on any medications that might affect glycemic control, drug or alcohol dependency
Kaku, 2011[97] Japan RCT	2006 52 Wks	Yes	Yes	Not Extracted/ 411 NR	Age <20, HbA1c >10.4 or <7.4, not able to self monitor blood glucoses
Karter, 2005{Karter, 2005 #35290} US Cohort	Start year: 1999 End year: 2001 10 Months	NA	No	NA (for cohort studies, claims data, etc)/23440 managed care organization	CHF, no pharmacy benefit, Type 1 DM, >80% pill adherence, filled a refill of index medication, member of health plan >1 year, any utilization of the index therapy in the 12 months prior to initiation of the study
Kikuchi, 2012[99] Japan RCT fixed titration of both drugs during tx period	2005 2007 28 Wks	No	Yes	Not Extracted/ 373 NR	Age <20 - >75, HbA1c <7.4, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy Edema, unstable or serious angina, MI in past yr, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy serious neuropathy requiring tx
Kim, 2014[101] South Korea RCT	2007 2009 26 Wks	Yes	Yes	Not Extracted/ 209 NR	HbA1c >10 or <7, 3 months, Pregnant, treated with metformin 500-1000mg alone for at least 4 wks prior to study unable to complete diary to monitor SMBG acute complications such as diabetic ketoacidosis, hyperglycemic hypoerosmolar state within 3 months

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					clinically significatn renal or hepatic disorders
Komajda, 2010{Komajda, 2010 #55136} Multi-continent RCT	Start year: 2001 End year: 2003 5.5 Years	None	Yes	NR/4447	Age <40 or > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c ≤7% or > 9%, BMI ≤25 kg/m^2, planned cardiovascular intervention, uncontrolled hypertension, no Type 2 DM, current use of other anti-DM medications, hospitalization within last 3 months for CVD event, heart failure
Kvapil, 2006[103] Multinational Europe RCT	Neither year reported 16 Wks	No run-in period	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, adequately controlled on metformin
Lavalle-Gonzalez, 2013[104] Multi-continent RCT	Neither year reported 56 Wks	Yes	Yes	Not Extracted/ 1284 NR	Age <18 or >80, HbA1c >10.5 or <7, Prior or current use of insulin, Any kidney disease, not on MFM (ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG) ΓëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening;, cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening, uncontrolled HTN
Lee, 2013[209] S. Korea Prospetive cohort	2011 2013 24 Wks	Not applicable	No	Not Extracted/ 116 Outpatient: subspecialty care setting	HbA1c >7.5, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, hematologic disease, GI disease systemic steroids in past 12 wks, recent (Γëñ6 months) history of major cardiovascular event, including myocardial infarction, unstable angina, moderate to severe congestive heart failure, and/or stroke. first time visitors to diabetes center

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Lehman, 2012[210] US Retrospective cohort	1999 2006 Not applicable	Not applicable	No	Not Extracted/ 5042 Veteran's Large Health Survey + VA databases with medicaiton and encounter information	Age <19 or >90, Female, Any liver disease, Any kidney disease, did not have prescription of SU or MFM solely for 180 days or more, PCa event occuring within 180 days of MFM or SU baseline exposure, prescription for Ins or TZD during study period, CA dx before baseline, missing data on baseline covariates (age, ethnicity, HbA1c, BMI, diabetes dur, Charlson comorbidity score, smoking status), did not have at least 1 primary care and 1 dm2 encounter per year 1999 to 2000
Leiter, 2005{Leiter, 2005 #35229} Canada RCT	Neither year reported 32 Wks	No run-in period	Yes	720/613 Outpatient: primary care	Age <20 or >80 years, HbA1c < 9.5%, no Type 2 DM, FBG <7 but >14mmol/L
List, 2009[107] US Canada Mexico, Puerto Rico RCT	2005 2006 12 Wks	Yes	Yes	Not Extracted/ 389 "98 clinical centers"	Age <18, >79, HbA1c >10 or <7, BMI >40, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml
Madsbad, 2004[108] Multinational Europe RCT	Start year: 2000 End year: 2001 12 Wks	No run-in period	Yes	311/193 Outpatient: primary care, Outpatient: subspecialty care setting, Community	Age <30 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Maffioli, 2013[109] Italy RCT	Neither year reported 6 Months	Yes	No	Not Extracted/ 170 outpatient care - unclear if specialty or primary care	Age <18 years, HbA1c <8.0%, BMI < 25.0 or >34.9 kg/m2, Prior use of any diabetes treatment, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, does not have hepatic steatosis by ultrasound diagnosis, history of ketoacidosis, muscle toxicity, serum creatine phosphokinase values higher than, 2 times the ULN, severe anemia, known contraindications to pioglitazone, glibenclamide, or HMG-CoA inhibitors
Malone, 2005{Malone, 2005 #35308} Multinational Europe RCT	Neither year reported 32 Wks	Yes	Yes	97/119 NR	Age <30 or>75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control
Malone, 2003[110] 14 countries not specified randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 Wks	Fewer than 10% of participants were excluded during run-in	Yes	NR/597 subgroup completing test meals	Age < 30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at max clinically effective dose for previous 30 days
Malone, 2004[194] US RCT	Neither year reported 32 Wks	Yes	Yes	145/111 NR	Age <30 OR >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m^2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start
Marre, 2002{Marre, 2002 #35250} Netherlands, Denmark, Portugal, France, Belgium RCT	4 months (Planned duration)	Not extracted	Yes		Age <18 years, any liver disease, any kidney disease, history of CVD, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Moon, 2014[112] Korea RCT	2007 2009 48 Wks	Yes	Yes	Not Extracted/ 75 NR	Age <18 or >75 yr, HbA1c >12.00% or <7.50%, BMI>=35kg/m2, Any liver disease, Any kidney disease, not on metformin monotherapy (at a dose of >1000mg/day for 3 months prior to enrollment), Taking medications (other than antidiabetic medications) known to affect glycemic control such as glucocorticoids
Nauck, 2007{Nauck, 2007 #35210} US, Multinational Europe, Multi-continent RCT	Neither year reported 52 Wks	Yes	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia
Nauck, 2009[117] Multi-continent RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 527 NR	Age <18 or >80 yr, NbA1c >10.00% or <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months, after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen h/o cardiac surgery or cardiovascular disease in last 6 months history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years) laser treatment for proliferative diabetic retinopathy within 6 months history of treated diabetic gastroparesis New York Heart Association Class 3 or 4 heart failure
Nauck, 2011[118] Multi-continent RCT	2008 52 Wks	Yes	Yes	Not Extracted/ 814 NR	Age < 18 years, HbA1c >10% or <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment
Nauck, 2014[119] Country NR RCT adaptive, seamless	Neither year reported 52 Wks	Yes	Yes	Not Extracted/ 1098 NR	Age <18 or >75 years, HbA1c >= 9.5%, <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, diagnosed <6 months, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry
Pantalone, 2009[203] United States Prospective or retrospective cohort	Start year: 1998 End year: 2006 8 Years	NA	Yes	NR/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF
Pavo, 2003 Russia and Hungary RCT	32 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <40 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other
Perez-Monteverde, 2011[122] Country NR RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 492 NR	Age <18 - >78, HbA1c >12 or <7.5, Contraindication or history of intolerance to metformin, type 1 Diabetes, history of ketoacidosis, symptomatic hyperglycemia, hypersens or contraind to study drug, not taking an antihyperglycaemic agent (AHA) within the previous 3 months and not more than 4 wks cumulatively in the previous 3 year, likely to need a drug that is a CYP2C8 inhib or inducer, symptomatic hyperglycaemia or a site fingerstick glucose < 130 mgΓüä dl or > 320 mgΓüä dl at the randomisation visit
Perez, 2009{Perez, 2009 #7676}	Neither year reported	Run-in period but number of	Yes	1436/600 NR	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
United States, Multinational Europe RCT	24 Wks	participants excluded was NR			creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m^2, pregnant, nursing, triglyceride level 500, if they were NOT discontinued metformin and TZD therapy due to lack of efficacy
Pfutzner, 2011[126] Germany (assumed based on author affiliations RCT	Neither year reported 24 Wks	No	Yes	Not Extracted/ 305 NR	Age <18 - >75, HbA1c <6.5, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV)
Pfutzner, 2011[127] Multi-continent RCT	Neither year reported 76 Wks	Yes	Yes	Not Extracted/ 1306 Community outpatient settings (unspecified)	Age <18 or >77 years, HbA1c >12.00% or <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV congestive heart failure and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests
Pratley, 2010{Pratley, 2010 #7211} Multi-continent, Europe, USA and Canada RCT	Start year: 2008 End year: 2009 26 months	None	Yes	1302/665	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7.5% or >10%, BMI >45 kg/m^2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months
Pratley, 2014[129] Multi-continent	Neither year reported	Yes	Yes	Not Extracted/ 784	Age <18yr or >80 yr, HbA1c >10% or <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	26 Wks			NR	history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Гёñ 12 and Гёñ 10 g/dL for men and women, respectively), elevated blood pressure (ГёÑ 150 and ГёÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy;
Qiu, 2014[130] Multi-continent RCT	Neither year reported 22 Wks	Yes	Yes	Not Extracted/ 279 NR	Age <18 or >80, HbA1c >10.5 or <7, Any kidney disease, FPG and/or fasting self-monitored blood glucose, 15.0 mmol/L during the pretreatment phas, diabetic ketoacidosis, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks not completing the placebo run-in period
Rajagopalan, 2005[211] US Cohort		Not extracted	Yes	Not extracted	Age <18 years, any liver disease, no Type 2 DM, other
Raskin, 2007[132] US RCT	Neither year reported 28 Wks	Run-in period but number of participants excluded was NR	NR	N:/NR NR	Age <18 or >75 years, HbA1c ≤8.0%, BMI >40 kg/m^2 or weight >125 kg (275 lbs.), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use
Raz,	Neither year	Run-in	Yes	544/190	Age <18 or >78 years, HbA1c <8% after run-in, HbA1c >11% after run-

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2008{Raz, 2008 #35199} Multi-continent RCT	reported 30 Wks	period but number of participants excluded was NR		NR	in, BMI <20 or >43 kg/m^2, pregnant, nursing, insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, Type 1 DM, FPG <7.2 or >15.6 mmol/L consistently during run-in, no Type 2 DM
Reasner, 2011[133] US RCT	2007 2009 44 Wks	Yes	Yes	Not Extracted/ 1250 NR	Age <18 or >78 years, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes
Ridderstrale, 2014[134] Multi-continent RCT	2010 2011 104 Wks	Yes	Yes	Not Extracted/ 1549 NR	Age <18, HbA1c >10 or <7, BMI >45, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization blood glucose concentration greater than 13 3 mmol/L after an overnight fast during the placebo run-in, confi rmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation
Rigby, 2009{Rigby, 2009 #7711} United States, Multi-continent RCT	Start year: 2007 End year: 2008	NA	Yes	169/356 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c <7% (6.5% if on metformin combination therapy), BMI> 40 kg/m^2, LDL<50mg/dl or TG ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Robbins, 2007[136] US, Multinational Europe, Multi-continent, India, Australia RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	NR	433/317 NR	Age <35 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)
Roden, 2013[137] Multi-continent RCT	2010 2012 24 Wks	Yes	Yes	Not Extracted/ 899 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting academic medical ctrs, hospitals, and private practices	Age <18, <20 in Japan, <18 or >65 in India, 10 or 9 in Germany, HbA1c <7, BMI >45, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13┬╖3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent,, any uncontrolled endocrine disorder apart from type 2 diabetes. did not meet inclusion criteria after placebo run-in
Rosenstock, 2006[138] Multi-continent RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1252/468 multicenter	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis
Rosenstock,	Neither year	Yes	Yes	Not Extracted/	Age <18 or >80yr, HbA1c >11% or <7.50%, BMI <23 or >45 kg/m2, not

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2010[139] Country NR RCT	reported 26 Wks			655 NR	drug-naive (current antihyperglycemmic medication or >6 days of any such agent within 3 months of screening), successful glycemic control with diet and exercise for >=2 months prior to screening
Rosenstock, 2012[140] Multi-continent RCT	Neither year reported 12 Wks	No	Yes	Not Extracted/ 451 NR	Age <18, >65, HbA1c >10.50% or <7, unstable weight or BMI <25 or >45 kg/m^2 (<24 or >45 kg/m^2 for Asians), Diagnosed with type 2 diabetes for less than 3 months, On metformin monotherapy dose <1500mg/day, On metformin monotherapy for less than 3 months, Serum creatinine >1.5mg/dl for men and >1.4 mg/dl for women
Rosenstock, 2013[141] Multi-continent RCT	Neither year reported 52 Wks	Yes	Yes	Not Extracted/ 441 NR	Age <65 or >90 yr, HbA1c >9.0% for patients on diet and exercise therapy alone, 8.0% for patients on oral antidiabetic monotherapy & 9.0% after washout period without medications within 2 wks 6.50% not able or unwilling to self-monitor blood glucose with a home glucose monitor
Rosenstock, 2013[142] Multi-continent RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 495 NR	Age <18 or >80, HbA1c >9 if on MFM and one other OAD or >10 if on MFM monotherapy, 6.5 if on MFM and one other OAD, <7 if on MFM monotherapy, BMI >40, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ГёÑ1500 mg/day or maximum tolerated dose);, diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity;, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months., h/o of MI, CVA, or TIA in past 6 mo, HbA1c <7 or >10 at start of placebo run-in, history of clinically relevant allergy/hypersensitivity, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months
Ross, 2012[143] Multi-continent RCT	2009 2010 12 Wks	Yes	Yes	Not Extracted/ 491 NR	Age <18 or > 80yr, HbA1c >10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in for 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, total

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study), treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months
Russell-Jones, 2012[144] Multi-continent RCT	2008 2010 36 Wks	No	Yes	Not Extracted/ 820 NR	Adults, HbA1c >11 or <7.1, BMI <23 - >45, Prior use of any diabetes treatment, unstable weight
Schernthaner, 2004[145] Europe RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Scott, 2008[148] Multi-continent RCT	Neither year reported 18 Wks	Run-in period but number of participants excluded was NR	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL
Scott, 2007[147] US RCT	Neither year reported 12 Wks	Run-in period but number of participants excluded was NR	Yes	2186/743 NR	Age <21 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK
Seck, 2010{Seck, 2010 #7175} NR RCT	Neither year reported 2 Years	Run-in period but number of participants excluded was NR	Yes	2141/1172 NR	Age <17 years or >78 years
Seino, 2010	Neither year reported	Yes	Yes	NR/464	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Japan RCT	24 Wks			NR	microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or reccurent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Seino, 2012[151] Japan RCT	2008 2009 12 Wks	Yes	Yes	Not Extracted/ 288 outpatient, but not specified	Age <20 or >=65years, HbA1c >=10.4% after 8 wks of observation, 6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, gastrointestinal disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg
Shihara, 2011[152] Japan RCT	2007 2010 6 Months	No	No	Not Extracted/ 191 NR	Age <30 - >75, HbA1c >=10.4 <6.9, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, CHF, Any hematological condition, Any pancreas condition, not committed to stable diet & exercise regimen, use of any dim med in past month, capable of reading consent form
Skrivanek, 2014[212] Country NR RCT	Neither year reported Not applicable	Yes	Yes	Not Extracted/ 230 NR	Age <18 or >75 years, HbA1c >9.50, <8.0% if on diet and exercise alone and <7.0% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, diagnosed <6 months
Srivastava, 2012[153] India	2008 2009 18	No	NR	Not Extracted/ 50 Outpatient (not	Age <=18, HbA1c >=10 of <=7, Any liver disease, Any kidney disease, History of CVD, not on metformin monotherapy for at least 3 mo, type 1 diabetes, other terminal illness

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	Wks			specified if PC or subsp)	
St John Sutton, 2002[154] US RCT	52 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, no type 2 DM, other
Stenlof, 2014[201] Country NR RCT	Neither year reported 52 Wks	Yes	Yes	Not Extracted/ 587 NR	Age <18 or >80, HbA1c >10 or <7, Prior or current use of study drug, Any kidney disease, if on AHA other than PPAR agonist or combination MFM+SU, FPG >15 mmol/l, h/o type 1 dm history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening
Stewart, 2006[155] Multinational Europe RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1397/526 NR	Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >9%, drug naive patients with FPG <7 mmol/l or >9mmol/l, patient on monotherapy with FPG < 6.0mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Tan, 2004{Tan, 2004 #35238} Denmark, Finland, Norway, and Sweden. RCT	52 wks (Planned duration)	Not extracted	Yes	Not extracted	Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5% or > 9.5% for patients receiving ODM, no Type 2 DM, other
Taskinen, 2011[158] Multi-continent RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 701 NR	Age <18 or >80 years at screening, HbA1c >10.0% for met mono patients, 9.0% for patients treated with an additional medication; by the start of the placebo run-in, 10.0% for all patients at screening, 7.0% for met mono patients, 6.5% for patients treated with an additional medication; by the start of the placebo run-in, 7.0% for all patients, BMI >40 kg/m2, Any liver disease, Any kidney disease, not receiving met at a dose of >=1500mg/day (or max tolerated dose), more than one other oral antidiabetes medication, antidiabetes medications have changed within 10 wks prior to the date of informed consent or the dose of met was not

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					stable for >=12 wks before randomization, treated with rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, changed dosage of thyroid hormone treatment within 6 wks or were being treated with systemic steroids at the date of informed consent, acute or chronic metabolic acidosis, hereditary galactose intolerance, dehydration, have participated in another trial of an investigational drug within the previous 2 months, acute MI, stroke, or TIA within last 6 months or acute or unstable CHF
Tosi, 2003{Tosi, 2003 #35243} Italy RCT, cross-over	6 months (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other
Umpierrez, 2006[164] US RCT	Neither year reported 28 Wks	Run-in period but number of participants excluded was NR	Yes	538/210 Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >79 years, HbA1c <7.5% or >10%, BMI <24 kg/m^2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2 months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3 months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis
Umpierrez, 2014[165] Multi-continent RCT	2010 2012 52 Wks	Yes	Yes	Not Extracted/ NR NR	Age <18 years, HbA1c >9.50% or <6.50, <3 months or >5 years, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months
van der Meer, 2009[166] Netherlands RCT	Neither year reported 24 Wks	Fewer than 10% of participants were excluded during run-	Yes	173/80 NR	Age <45 or >65 years, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, SBP <150 mm Hg, DBP <85 mm Hg, prior TZD or insulin use

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
		in			
Weir, 2011[213] Canada Retrospective cohort	1997 2008 Not applicable	Not applicable	No	Not Extracted/ 2650 Administrative database	Age <66, no treatment for diabetes for at least 1 year, no SCr measurement available between 2002-2008, no use of a dm2 medication in the 120 days prior to the case's index date Ontario resident
Weissman, 2005[167] US RCT	Neither year reported 24 wks (Planned duration)	Run-in period but number of participants excluded was NR	Yes	1270/766 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5% for subjects having received prior combination treatment (metformin + SU), HbA1c < 7% or > 10% for drug naive or prior monotherapy subjects, BMI <27 kg/m2, FPG < 126mg/dL or >270mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non-compliant patient with metformin up-titration
White, 2014[168] Multi-continent RCT	2009 2010 12 Wks	Yes	Yes	Not Extracted/ 160 outpatient	Age <18 and >78 years, HbA1c >10% or <7%, BMI >45, Pregnant, Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies
Williams-Herman, 2009[169] NR RCT	Neither year reported 54 Wks	Run-in period but number of participants excluded was NR	Yes	3544/1091 NR	Age <18 or >78 years, HbA1c ≤7.5% or ≥11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (≥75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM
Williams-Herman, 2010[170] Multi-continent RCT	Neither year reported 104 Wks	Yes	Yes	Not Extracted/ 1091 NR	Age <18 or >78 years, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication
Wright,	Start year:	Fewer than	Yes	7616/4191	Age <25 or >65 years, any kidney disease (such as microalbuminuria,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2006{Wright, 2006 #35314} UK RCT	1977 End year: 1991 6 Years	10% of participants were excluded during run-in		23 clinical Center	macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG ≤6 mmol/l x2 after being diagnosed with diabetes, ketonuria> 3 mmol/l, mixed ethnicity, severe previous illness that would limit life expectancy or require systemic treatment, serum creatinine>175 umol/l, if on same treatment for <6 years
Yamanouchi, 2005[171] Japan RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other
Yang, 2003{Yang, 2003 #3073} China RCT	Neither year reported 12 Wks	Run-in period but number of participants excluded was NR	Yes	NR/211 NR	Age <35 or >70 years, poorly controlled on prior treatments (e.g. failed initial treatment), no Type 2 DM as defined by WHO, not treated with diet and sulfonylurea for 6-months
Yang, 2011[172] Multinational Asia (China - India - SouthKorea RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 570 NR	Age <18, HbA1c >10 or >7, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducers Hemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past yr, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhib
Yang, 2011[173] Asia - Korea, China, India RCT	Neither year reported 16 Wks	Yes	Yes	Not Extracted/ 929 NR	Age <18 and >80 years, HbA1c >11% for subjects onOAD monotherapy and 10% for subjects onOAD combination therapy 7%, BMI >45kg/m2, not treated with one or more oral antidiabetic drugs (OADs) for at least 3 months, treated with insulin within the last 3 months, after run-in with up-titration of metformin to 2000 mg/day and 3-wk maint at that dose, subj with FG 7-12.8 mmol/l could be ranodomized
Yang, 2012[174]	2009 2010	Yes	Yes	Not Extracted/ 395	Age <18 - >78, HbA1c >11 or <7.5, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Diabetes type 1,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
China RCT	24 Wks			NR	history of ketoacidosis, CHF, unstable CHD, not Chinese, able to get off other diabetes meds during run-in, prior use of TZDs
Yoon, 2011[175] Korea RCT	2007 2008 48 Wks	Yes	Yes	Not Extracted/ 349 NR	Age <30 - >65, HbA1c >9.5 or <6.5, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, history of lactic acidosis glucocorticoid users, contraind to SU
Yuan, 2012[176] China RCT	Neither year reported 26 Wks	No	NR	Not Extracted/ 59 NR	Age <=18yr. HbA1c >10% or <7%, BMI <=28 or >=40kg/m2, diagnosis>=1months, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, waist circumstance <=90cm for male or <85cm for female (could be excluded if did not meet this OR the BMI criteria), have ever been treated with lipd lowering agents, blood pressure > 150/100mmHg, clinically suspected hyper- or hypothyroid disease and Cushing syndrome

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = NR; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table 11. Population characteristics of studies evaluating diabetes medications on safety

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seino, 2010[150]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Derosa, 2010[39]	Metformin + glibenclamide, 65	56	51	NR	28.5 NR	8.9	NR	8
	Metformin + exenatide, 63	57	48	NR	28.7 NR	8.8	NR	4
Defronzo, 2010[32]	Metformin + rosiglitazone, 45	NR	NR	NR	NR NR	7.9	NR	11
	Metformin + exenatide, 45	NR	NR	NR	NR NR	7.8	NR	12
Aschner, 2010[7]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[149]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, O: 4	30.9 88.5 kg	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, O: 3.1	31.3 90.3 kg	7.3	5.7	328
Komajda, 2010[214]	Metformin + rosiglitazone, 2220	NR	NR	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 2227	NR	NR	NR	NR NR	NR	NR	NR
Pratley, 2010[128]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, O: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, O: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, O: 4	33.1 94.6 kg	8.4	6.4	52
Derosa, 2009[38]	Metformin, 67	55	51	C: 100	27.2 77.7 kg	9.1	NR	7

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + glimepiride, 66	57.7	48	C: 100	27.1 77.4 kg	9	NR	6
	Metformin + pioglitazone, 69	57	49	C: 100	27.4 76.4	9.3	NR	9
	Pioglitazone, 69	54	46	C: 100	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[166]	Metformin + glimepiride, 39	56.4	100	NR	29.3 NR	7	3	2
	Pioglitazone + glimepiride, 39	56.8	100	NR	28.2 NR	7.1	4	5
Kaku, 2009[96]	Metformin, 86	53	57	NR	25.4 NR	7.55	5.6	7
	Metformin + pioglitazone, 83	52	66	NR	25.6 NR	7.58	4.5	9
Williams-Herman, 2009[169]	Metformin, 182	54.2	45	NR	32 NR	8.5	4.1	46
	Metformin, 182	53.7	48	NR	32 NR	8.7	4.1	56
	Metformin + sitagliptin, 182	53.6	41	NR	32 NR	8.7	4.6	41
	Metformin + sitagliptin, 190	53.7	53	NR	32 NR	8.8	4.1	42
	Sitagliptin, 179	53.5	52	NR	31 NR	8.7	3.9	57
Pantalone, 2009[203]	Rosiglitazone, 1079	61.4	45.5	C: 86.8, Non-Caucasian: 13.2	32.7 NR	7.3	NR	NR
	Any in the SU class, 7427	66.1	49.5	C: 78, Non-Caucasian: 22	31.1 NR	7.6	NR	NR
	Pioglitazone, 1508	61.6	48.3	C: 83.5, Non-Caucasian: 16.5	33 NR	7.3	NR	NR
	Metformin, 10436	56.8	41.8	C: 76.9, Non-Caucasian: 23.1	33.8 NR	7.7	NR	NR
Hsiao, 2009[204]	Metformin, 46444	59	48.22	NR	NR NR	NR	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Rosiglitazone, 2093	61.24	53.46	NR	NR NR	NR	NR	NR
	Pioglitazone, 495	60.75	52.02	NR	NR NR	NR	NR	NR
	Any in the SU class, 97651	60.71	54.1	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 267754	57.17	54.45	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 2408	57.3	49.8	NR	NR NR	NR	NR	NR
Perez, 2009[123]	Metformin, 210	53.7	46.7	AA: 6.7, Asian: 2.4, C: 88.1, H: 26.2	30.8 NR	8.65	NR	68
	Metformin + pioglitazone, 201	54.7	44.8	AA: 6, Asian: 1.5, C: 91.5, H: 24.4	30.8 NR	8.89	NR	44
	Pioglitazone, 189	54	34.9	AA: 6.9, Asian: 2.6, C: 87.3, H: 25.9	31.2 NR	8.69	NR	64
Rigby, 2009[135]	Metformin + rosiglitazone, 56	54.7	41	AA: 3.6, Asian: 0, C: 28.6, H: 67.9, O: 0	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2, unspecified: 1.8	NR 79.6 kg	8.17	8.35	11
Dormuth, 2009[215]	THIAZOLIDINEDIONE, 10476	56	48	NR NR	NR NR	NR	4.6	NR
	Rosiglitazone, 6880	56	48	NR NR	NR NR	NR	4.6	NR
	Pioglitazone, 3596	57	48	NR NR	NR NR	NR	4.7	NR
	Any in the SU class, 73863	60	47	NR NR	NR NR	NR	4	NR
Jadzinsky, 2009[90]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, O: 5	29.9 NR	9.4	2	58
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, O: 5.9	30.3 NR	9.5	1.4	62

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, O: 6.4	30.2 NR	9.4	1.7	85
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, O: 5.4	30.2 NR	9.6	1.7	110
DeFronzo, 2009[31]	Metformin + saxagliptin, 192	54.7	43.2	AA: 3.9, Asian: 4.2, C: 79.7, O: 12	31.7 86 kg	8.1	6.7	44
	Metformin + saxagliptin, 191	54.7	53.9	AA: 5.8, Asian: 1.6, C: 83.2, O: 9.4	31.2 87.3 kg	8.1	6.4	48
	Metformin + saxagliptin, 181	54.2	52.5	AA: 7.7, Asian: 2.8, C: 79.6, O: 9.9	31.1 87.8 kg	8.0	6.3	41
	Metformin, 179	54.8	53.6	AA: 3.9, Asian: 2.2, C: 83.8, O: 10.1	31.6 87.1 kg	8.1	6.7	40
Bunck, 2009[19]	Metformin + exenatide, 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	6
	Metformin + glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	3
Garber, 2009[65]	Glimepiride, 248	53.4	54	AA: 12, Asian: 4, C: 77, H: 38, O: 7	33.2 93.4 kg	8.4	5.6	96
	Liraglutide, 247	52	49	AA: 12, Asian: 6, C: 75, H: 35, O: 7	32.8 92.8 kg	8.3	5.3	74
	Liraglutide, 251	53.7	47	AA: 14, Asian: 2, C: 80, H: 32, O: 5	33.2 92.5 kg	8.3	5.2	NR
Kahn, 2008[216]	Glyburide, 1441	NR	58	NR	NR NR	NR	NR	0
	Metformin, 1454	NR	59.4	NR	NR NR	NR	NR	0
	Rosiglitazone, 1456	NR	56	NR	NR NR	NR	NR	0
Scott, 2008[148]	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, O: 3	30.4 84.9 kg	7.7	4.6	2
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, O: 1	30.3 83.1	7.8	4.9	9

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Raz, 2008[180]	Metformin, 94	56.1 (36 to 77)	41	AA: 1, C: 47, H: 25, multiracial: 25, not specified: 2	30.4 81.2 kg	9.1	7.3	16
	Metformin + sitagliptin, 96	53.6 (29 to 73)	51	AA: 3, C: 42, H: 32, multiracial: 22, not specified: 1	30.1 81.5 kg	9.3	8.4	18
Robbins, 2007[136]	Metformin + glargine, 159	58.1	49.4	AA: 5.7, Asian: 14.6, C: 63.3, H: 16.4	32 88.1kg	7.8	12.5	22
	Metformin + insulin lispro 50/50, 158	57.4	50.3	AA: 5.7, Asian: 14, C: 65, H: 15.3	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[79]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9kg	8	6.4	71
Chien, 2007[27]	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
Comaschi, 2007[28]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2007[71]	Metformin, 182	53.4	48.9	AA: 6.6, Asian: 7.7, C: 47.8, H: 30.2, not specified: 7.7	32.1 NR	8.9	4.5	29
	Metformin, 182	53.2	45.1	AA: 4.9, Asian: 5.5, C: 58.2, H: 21.4, not specified: 9.9	32.2 NR	8.7	4.4NR	182
	Metformin + sitagliptin, 182	53.3	42.3	AA: 7.7, Asian: 6, C: 52.2, H: 26.9, not specified: 7.1	32.4 NR	8.7	4.4	18
	Metformin + sitagliptin, 190	54.1	55.3	AA: 6.8, Asian: 4.7, C: 53.7, H: 28.9, not specified: 5.8	32.1 NR	8.8	4.5	26
	Sitagliptin, 179	53.3	52	AA: 6.1, Asian: 3.4, C: 52, H: 29.1, not specified: 9.5	31.2 NR	8.9	4.4	37
Davies, 2007[29]	Metformin + NPH, 29	57.9	48.28	AA: 0, Asian: 21, C: 66	32.6 90.4kg	10	7.3	5
	Metformin + BHI 70/30, 27	57.4	80	AA: 4, Asian: 22, C: 70	30.2 82.2 kg	9	9.1	0
Nauck, 2007[116]	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, O: 3.4	31.3 89.7 kg	7.6	6.2	172
	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, O: 3.7	NR NR	7.7	6.5	202
Raskin, 2007[132]	Metformin + aspart 70/30, 79	52	52	AA: 13, Asian: 3, C: 52, H: 32, O: 1	31.2 88.7 kg	9.9	NR	12
	Metformin + glargine, 78	51.7	54	AA: 15, Asian: 4, C: 47, H: 32, O: 1	30.8 86.2 kg	9.9	NR	6
Hanefeld, 2007[81]	Glibenclamide, 203	60.1	70	AA: 0, C: 99, O: <1	28.7 NR	8.2	6.4	13
	Rosiglitazone, 189	60.6	58	AA: 0, C: 97, O: 3	28.8 NR	8.2	6	9
	Rosiglitazone, 195	60.4	68	AA: 0, C: 98, O: 2	28.7 NR	8.1	5.9	12

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Scott, 2007[147]	Glipizide, 123	54.7 (21 to 76)	56.9	AA: 3.3, Asian: 4.9, C: 61, O: 24.4, Multiracial: 6.5	30.6 NR	7.9	4.7	23
	Sitagliptin, 123	56.2 (34 to 75)	48	AA: 4.9, Asian: 4.9, C: 63.4, multiracial: 5.7, O: 21.1	30.5 NR	7.9	4.9	7
	Sitagliptin, 123	55.6 (34 to 76)	57.7	AA: 8.9, Asian: 4.9, C: 61, Multiracial: 6.5, O: 18.7	31.4 NR	7.9	5	15
	Sitagliptin, 124	55.1 (28 to 75)	52.4	AA: 4.8, Asian: 2.4, C: 69.4, Multiracial: 7.3, O: 16.1	30.4 NR	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 to 76)	62 49.6	AA: 6.4, Asian: 5.6, C: 68.8, multiracial: 6.4, O: 12.8	30.8 NR	7.9	4.3	18
Kahn, 2006[95]	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, O: 0.3	32.2 92 kg	7.35	(<1: 44, 1-2: 52, >2: 4)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, O: 1	32.1 91.6 kg	7.36	(<1: 46, 1-2: 50, >2: 4)	551
	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 5.2, O: 0.7	32.2 91.5 kg	7.36	(<1: 45, 1-2: 52, >2: 3)	539
Charbonnel, 2006[24]	Metformin, 237	54.7	59.5	AA: 5.9, Asian: 11, C: 67.1, H: 11.8, O: 4.2	31.5 NR	(<8: 54, 8 -8.9: 30, ≥9: 15)	6.6	45
	Metformin + sitagliptin, 464	54.4	55.8	AA: 6.7, Asian: 10.6, C: 63.1, H: 15.5	30.9 NR	(<8: 55, 8 -8.9: 31, ≥9: 14)	6	48
Wright, 2006[217]	Any in the sulfonylurea class, 1687	NR	NR	NR	NR NR	NR	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 336	NR	NR	NR	NR NR	NR	NR	NR
	Total, 5063	52.4	59	AA: 8, Asian: 9, C: 83	27.5 NR	6.9	NR	NR
Rosenstock, 2006[138]	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, O: <1	32.5 NR	8.8	2.9	31
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, O: 3	32.8 NR	8.8	2.7	22
Jain, 2006[91]	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, O: 0.4	32.8 94.3kg	9.2	0.78	123
	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, O: 0.4, Native American: 0.4	32.5 93.9kg	9.2	0.8	117
Stewart, 2006[155]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian /other pacific islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[12]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Umpierrez, 2006[164]	Metformin + glimepiride, 96	51.6	55.2	AA: 13.5, Asian: 1.0, C: 79.2, H: 5.2, O: 1.0	34.54 NR	8.4	4.9	11
	Metformin + pioglitazone, 109	55.7	52.3	AA: 15.9, Asian: 3.7, C: 78.5, H: 1.9, O: 0	33.81 NR	8.31	5.9	17
Kvapil, 2006[103]	Metformin + aspart 70/30, 116	56.4	46	NR	30.4 85.1 kg	9.3	6.7	11
	Metformin + glibenclamide, 114	58.1	46	NR	30. 84.0 kg	9.4	8.1	5

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Karter, 2005[218]	Any in the sulfonylurea class, 5921	59.9	54.8	NR	NR NR	8.9	NR	0
	Metformin, 11937	59.9	52.5	NR	NR NR	9.6	NR	0
	Pioglitazone, 3556	60.2	51.1	NR	NR NR	9.6	NR	0
Agarwal, 2005[206]	Glipizide, 22	64	100	AA: 27, C: 73	34 102 kg	7.7	14	3
	Pioglitazone, 22	67	100	AA: 14, C: 86	32 97 kg	7.7	16	1
Derosa, 2005[36]	Metformin + glimepiride, 49	52	47	NR	26.8 NR	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 NR	8.0	5	2
Malone, 2004[194]	Metformin + glargine,	NR	NR	NR	NR NR	NR	NR	7
	Metformin + lispro 75/25,	NR	NR	NR	NR NR	NR	NR	3
	Pooled arms	NR	63	NR	30.9 91.5kg	8.7	9	NR
Malone, 2005[205]	Metformin + lispro 75/25, 50	59.18	50	NR	29.41 77.82 kg	8.5	13.52	3
	Metformin + glargine, 47	59.63	38	NR	29.64 77.21 kg	8.48	11.9	10
Madsbad, 2004[108]	Glimepiride, 27	57	59	NR	30.2 NR	7.8	3.8	0
	Liraglutide, 26	53	85	NR	30.2 NR	7.4	4.1	3
	Liraglutide, 25	58	60	NR	32 NR	7.9	4.4	3
	Liraglutide, 27	57	67	NR	30.1 NR	7.7	4.5	7
	Liraglutide, 30	57	67	NR	30.4 NR	7.4	4.6	2

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Liraglutide, 29	58	55	NR	31.9 NR	7.4	6.1	2
Malone, 2003[110]	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, O: 4	29.6 81.7 kg	9.27	7.4	29
	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, O: 3	29.8 83.0 kg	9.17	8.0	25
Jones, 2003[192]	Metformin, 121	58 (38 to 78)	70	NR	34 NR	8.7	5	0
	Metformin, 22	64 (46 to 81)	9	NR	23 NR	8.6	6.5	NR
	Metformin, 82	60 (40 to 81)	74	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 141	58 (36 to 82)	69	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 142	57 (39 to 80)	57	NR	34 NR	8.8	5	NR
	Metformin + rosiglitazone, 35	62 (42 to 78)	71	NR	23 NR	9.3	8	NR
Leiter, 2005[106]	Metformin, 78	60	56	C: 86, Others: 22	32.2 NR	7.5	5.7	13
	Metformin + rosiglitazone, 158	58	65	C: 76, Others: 24	33 NR	7.5	5.3	18
Garber, 2006[64]	Diet + metformin + glibenclamide, 160	56 (31-78)	56	AA: 5, C: 80, Asian: 3, H: 11, O: 2	32 93 kg	8.5	5	NR
	Diet + metformin + rosiglitazone, 158	56 (24-78)	65	AA: 6, C: 79, Asian: 3, H: 10, O: 3	32 94 kg	8.4	6	NR
Weissman, 2005[167]	Metformin, 384	55.7	NR	NR	33.8 96.7kg	7.97	NR	95
	Metformin + rosiglitazone, 382	55.5	NR	NR	34.4 98.2kg	8.05	NR	76
	Metformin + rosiglitazone, 358	55.5	NR	NR	34.4 98.2kg	8.05	NR	95

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 351	55.7	NR	NR	33.8 96.7kg	7.97	NR	76
Bailey, 2005{Bailey, 2005 #35231	Metformin, 280	57.6	57	AA: <1, Asian: 1, C: 98, O: 1	32.1 89.5kg	7.5	6.1	44
	Metformin + rosiglitazone, 289	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9kg	7.4	6	30
	Metformin + rosiglitazone, 288	58.1	58	AA: 1, Asian: 1, C: 97, O: 1	32.2 90.9kg	7.4	6	30
Yamanouchi, 2005[171]	Diet + exercise + glimepiride, 37	55.6 (46.3 - 64.9)	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.6 NR	9.8	3.3 months	3
	Diet + exercise + metformin, 39	54.7 (44.9 - 64.5)	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	26.2 NR	9.9	3 months	2
	Diet + exercise + pioglitazone, 38	55.2 (46 - 64.4)	47	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.8 NR	10.2	3.2 months	2
	Glimepiride, 37	55.6	51	NR	25.6 NR	9.8	3.3	3
	Metformin, 39	54.7	51	NR	26.2 NR	9.9	3	2
	Pioglitazone, 38	55.2	47	NR	25.8 NR	10.2	3.2	3
Derosa, 2005[37]	Diet + exercise + behavioral therapy + metformin + glimepiride, 47	52 (47 -57)	49	NR	26.8 NR	7.9	4	NR
	Diet + exercise + behavioral therapy + metformin + rosiglitazone, 48	54 (50 -58)	52	NR	26.6 NR	8	5	NR
Rajagopalan, 2005[211]	metformin, 1137	52.5 (19-88)	49.6	NR	NR NR	NR	NR	NR
	Pioglitazone, 1847	54.3 (18-91)	52.4	NR	NR NR	NR	NR	NR
	Unspecified sulfonylurea, 1474	54.5 (19-94)	52.9	NR	NR NR	NR	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 1137	52.7 (18-90)	50	NR	NR NR	NR	NR	NR
	Pioglitazone, 1474	54.6 (18-91)	54.3	NR	NR NR	NR	NR	NR
	Rosiglitazone, 1847	54.3 (18-92)	51.8	NR	NR NR	NR	NR	NR
Feinglos, 2005[51]	Metformin + glipizide, 61	57.7 (30-80)	46	AA: 8.2, C: 78.7, Asian: 3.3, H: 8.2, O: 1.6	31.7 90 kg	7.45	6.5	NR
	Placebo + metformin, 61	58.8 (40-81)	41	AA: 16.4, C: 68.9, Asian: 3.3, H: 8.2, O: 3.3	32.1 90.8 kg	7.64	4.6	NR
Schernthaner, 2004[145]	Metformin, 597	56 (35 to 75)	58	NR	31.4 89.7kg	8.7	3.1	96
	Pioglitazone, 597	57 (35 to 75)	53	NR	31.2 88.2kg	8.7	3.4	98
	Placebo + diet + metformin, 597	56	57.8	NR	31.4 89.7kg	8.7	3.1	NR
	Placebo + diet + pioglitazone, 597	57	52.6	NR	31.2 88.2kg	8.7	3.4	NR
Derosa, 2004[34]	Placebo + diet + exercise + glimepiride, 81	56	47	NR	27.6 NR	8.5	NR	NR
	Placebo + diet + exercise + metformin, 83	58	51	NR	28.1 NR	8.4	NR	NR
Tan, 2004[156]	Glibenclamide, 109	57.9	73	AA: 0, C: 100, Asian: 0, H: 0, O: 0	29.6 89 kg	8.5	5.22	41
	Pioglitazone, 91	60	62	C: 99, Unspecified: 1	30.2 88.4 kg	8.4	4.76	36
Hanefeld, 2004[80]	Metformin + sulfonylurea, 320	60 (36 to 75)	54.7	AA: 0.9, C: 98.4, O: 0.6	30 84.9 kg	8.8	7.1	279
	Pioglitazone + sulfonylurea, 319	60 (36 to 75)	53,6	AA: 0.6, C: 99.4, O: 0	30.2 85.3 kg	8.82	60	259
	Placebo + metformin + unspecified sulfonylurea, 320	60 (36 to 75)	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0, O: 0.6	30 84.9 kg	8.8	7.1	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Placebo + unspecified sulfonylurea + pioglitazone, 31	60 (36 to 75)	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	NR
Garber, 2003[63]	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	NR
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	NR
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	NR
Tosi, 2003[161]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	NR
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	NR
Goldstein, 2003[70]	Metformin + glipizide, 87	54.6	58.6	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	NR
	Glipizide, 84	57.4	64.3	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	NR
	Metformin, 76	56.6	61.8	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	NR
Pavo, 2003[121]	Metformin, 100	55.8	56	NR	31.1 88.9 kg	8.6	6.3	9
	Pioglitazone, 105	54.2	56.2	NR	31.3 86.6 kg	8.6	5.6	5
Blonde, 2002[16]	Metformin + glyburide, 162	55.6	63.6	AA: 9.3, C: 67.9, Asian: 0, H: 19.1, O: 3.7	30.6 89.6 kg	9.42	6.97	NR
	Glyburide, 164	55.8	57.3	AA: 12.2, C: 66.5, Asian: 0, H: 17.1, O: 4.3	30.3 88 kg	9.64	7.01	NR
	Metformin + glyburide, 160	55.4	55.6	AA: 12.5, C: 70, Asian: 0, H: 15.6, O: 1.9	30.7 89.4 kg	9.41	7.36	NR
	Metformin, 153	57.6	62.1	AA: 10.5, C: 69.3, Asian: 0, H: 17, O: 3.3	30.6 89.5 kg	9.51	8.18	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
St John Sutton, 2002[154]	Glyburide, 99	56.1	72	AA: 3, C: 76, others: 21	NR 85.1 kg	9.5	6.2	NR
	Rosiglitazone, 104	55.1	72	AA: 5, C: 73, others: 22	NR 82.6 kg	9.1	5.3	NR
Marre, 2002[111]	Glibenclamide, 103	58.7	55	NR	29.3 82.5 kg	7.88	6.6	NR
	Metformin, 104	57.5	60	NR	29.9 84.9 kg	8.09	5.4	NR
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7 kg	7.89	5.9	NR
	Metformin + glibenclamide, 103	60.7	54	NR	29.7 83.1 kg	7.62	6.7	NR
Garber, 2002[62]	Metformin + glyburide, 165	58.1	58	AA: 6, C: 79, Asian: 0, H: 10, O: 5	29.6 86.7 kg	8.18	3.3	NR
	Glyburide, 161	56.5	51	AA: 9, C: 78, Asian: 0, H: 9, O: 4	30.3 87.2 kg	8.21	2.81	NR
	Metformin + glyburide, 158	56.9	58	AA: 13, C: 74, Asian: 0, H: 11, O: 2	30.1 88.8 kg	8.25	3.52	NR
	Metformin, 161	56	58	AA: 4, C: 81, Asian: 0, H: 12, O: 2	30.4 88.6 kg	8.26	2.98	NR
Gomez-Perez, 2002[72]	Metformin, 34	53.4 (40 - 68)	29.4	C: 2.9, H: 76.5, Mestizo: 20.6	28.5 NR	NR	9.1	NR
	Metformin + rosiglitazone, 35	51.7 (40 - 73)	28.6	C: 0, H: 80, Mestizo: 20	28.0 NR	NR	11.1	NR
	Metformin + rosiglitazone, 36	54.2 (42-76)	40	C: 11.1, H: 72.2, Mestizo: 16.7	27.6 NR	NR	10.7	NR
Charpentier, 2001[25]	Metformin + glimepiride, 147	56.8 (36-70)	59	NR	29.5 81.2 kg	6.4	5.6	NR
	Placebo + glimepiride, 150	55.4 (35-70)	58	NR	29.3 81 kg	6.5	5.3	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Placebo + metformin, 75	56.7 (36-69)	60	NR	29.2 82.2 kg	6.8	7	NR
Amador-Licona, 2000[178]	Metformin, 28	49.3	39	NR	26.8 70.7 kg	8.5	4.5	NR
	Glibenclamide, 23	48.2	30	NR	30.4 73.2 kg	8.4	4	NR
Einhorn, 2000[45]	Diet + metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, Asian: 0, H: 10.1, O: 0.6	32.11 NR	9.86	NR	NR
	Metformin, 160	55.7	60	AA: 6.3, C: 86.9, H: 3.8, Others: 3.1	32.12 NR	9.75	NR	37
	Metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, H: 10.1, Others: 0.6	32.11 NR	9.86	NR	21
	Placebo + diet + metformin, 160	55.7	60	AA: 6.3, C: 86.9, Asian: 0, H: 3.8, O: 3.1	32.12 NR	9.75	NR	NR
Fonseca, 2000[54]	Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, O: 15	30.3 NR	8.6	7.3	22
	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, others: 12.7	29.8 NR	8.9	8.3	18
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, others: 12.9	30.2 NR	8.9	7.5	18
DeFronzo, 1995[30]	Metformin, 143	53	43	NR	29.9 94.4 kg	8.4	6	NR
	Metformin + glyburide, 213	55	46	NR	29 92.1 kg	8.8	7.8	NR
	Placebo + glyburide, 209	56	49	NR	29.1 92.6 kg	8.5	8.7	NR
	Placebo + metformin, 210	55	46	NR	29.4 92.6 kg	8.9	8.4	NR
Hermann, 1994[85]	Diet + metformin + glibenclamide, 54	NR	NR	NR	NR 80.2 kg	6.8	NR	NR
	Diet + metformin, 25	NR	NR	NR	NR 78.6 kg	6.9	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Diet + metformin + glibenclamide, 13	NR	NR	NR	NR 84.6 kg	7.8	NR	NR
	Diet + metformin + glibenclamide, 13	NR	NR	NR	NR 76 kg	7.8	NR	NR
	Diet + metformin + glibenclamide, 18	NR	NR	NR	NR 83.2 kg	8.4	NR	NR
	Diet + glibenclamide, 21	NR	NR	NR	NR 82.6 kg	6.7	NR	NR
Ahren, 2014[2]	Metformin + placebo 104	56.1	49.5	C: 63.4, AA: 22.8, Asian: 5, H: 31.7	32.8 91.6 kg	8.2	6.7	42
	Metformin + glimepiride + placebo 317	54.4	51.5	C: 71.7, AA: 12.7, Asian: 5.2, H: 34.9	32.5 91.8 kg	8.1	6	99
	Metformin + sitagliptin + placebo 313	54.3	46	C: 74.5, AA: 11.6, Asian: 6.6, H: 36.8	32.5 90.3 kg	8.1	5.8	101
	Metformin + albiglutide + placebo 315	54.3	44.7	C: 70.9, AA: 17.5, Asian: 6, H: 32.8	32.7 89.6 kg	8.1	6	100
Alba, 2013[3]	Pioglitazone 54	53.4	42.6	C: 79.6, AA: 16.7, Asian: 1.9, H: 38.9, O: 1.9	86.6kg	7.9	2.4	2
	Sitagliptin 52	54.6	53.8	C: 86.5, AA: 11.5, Asian: 1.9, H: 36.4, O: 0	85.7kg	7.7	2.4	6
Andersson, 2010[181]	Metformin 688	69	62		NR			
	Sulfonylurea	76	57		NR			
	Metformin + Sulfonylurea	71	56		NR			
Arechavaleta, 2011[5]	Metformin + glimepiride + placebo, 519	56.2	53.8	C: 57.4, AA: 1.2, Asian: 21.4, O: 20	82		6.7	51
	Metformin + sitagliptin + placebo, 516	56.3	55	C: 57.6, AA: 1.2, Asian: 21.1, O: 20.1	80.6		6.8	48

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Arjona Ferreira, 2013[6]	Glipizide + placebo 212	64.3	54.9	C: 28.2, AA: 1.4, Asian: 58.5, H: 28.9, O: 12	70.2kg	7.8	10.1	
	Sitagliptin + placebo 211	64.8	59.3	C: 29.6, AA: 1.5, Asian: 53.3, H: 33.3, O: 15.5	68.0kg	7.8	10.7	
Aschner, 2012[8]	Metformin + sitagliptin 265	53.3	52		84.2	8.5	4.8	12
	Metformin + insulin glargine 250	53.9	50		83.4	8.5	3.9	23
Bailey, 2013[10]	Metformin + placebo 137	53.7	55		31.8	8.11	5.8	64
	Metformin + dapagliflozin + placebo, 137	55	51		31.6	7.99	6	55
	Metformin + dapagliflozin 137	54.3	50		31.4	8.17	6.4	48
	Metformin + dapagliflozin + placebo, 135	52.7	57		31.2	7.92	6.1	40
Barnett, 2012[13]	Glimepiride 76	56.7	43.4	C: 67.1, Asian: 27.6, O: 5.3	80.9 kg	8.1		18
	Linagliptin 151	56.4	36.4	C: 70.2, Asian: 27.8, O: 2	77.0 kg	8.1		32
Bergenstal, 2010[14]	Metformin + pioglitazone + placebo 165	53	48	C: 39, AA: 8, Asian: 24, H: 27, O: 2	88 kg	8.5	6	
	Metformin + sitagliptin + placebo 166	52	52	C: 30, AA: 12, Asian: 25, H: 30, O: 3	87 kg	8.5	5	
	Metformin + exenatide + placebo 160	52	56	C: 33, AA: 12, Asian: 23, H: 31, O: 1	32 89 kg	8.6	6	
Bergenstal, 2012[15]	Metformin + placebo 93	56.1	52	C: 77, AA: 6, Asian: 10, H: 11, O: 8	91.1 kg	8.03	5.5	10
	Metformin + sitagliptin + placebo, 185	55.5	59	C: 76, AA: 6, Asian: 11, H: 16, O: 7	92.5 kg	7.94	6	13

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bolinder, 2012[17]	Metformin + placebo 91	60.8	56	C: 100, AA: 0, Asian: 0, H: 0, O: 0	31.7 90.9 kg	7.16	5.5	20
	Metformin + dapagliflozin 91	60.6	55.1	C: 100, AA: 0, Asian: 0, H: 0, O: 0	32.1 92.1 kg	7.19	6	20
Borges, 2011[18]	Metformin 340	50.7	53	C: 55, AA: 4, Asian: 34, O: 6	90.6 kg	8.6	2.6	154
	Metformin + rosiglitazone 348	51.5	53	C: 53, AA: 5, Asian: 35, O: 6	87.1 kg	8.6	2.3	131
Bunck, 2011[21]	Metformin + exenatide 36	58.4	63.9		30.9 90.6kg	7.6	5.7	20
	Metformin + insulin glargine 33	58.3	66.7		30.1 92.4kg	7.4	4	17
Cefalu, 2013[23]	Metformin + glimepiride 484	56.3	55	C: 67, AA: 5, Asian: 19, O: 9	86.5 kg	7.8	6.6	98
	Metformin + canagliflozin 483	56.4	52	C: 67, AA: 4, Asian: 21, O: 9	86.9 kg	7.8	6.5	88
	Metformin + canagliflozin 485	55.8	50	C: 69, AA: 4, Asian: 19, O: 9	86.6 kg	7.8	6.7	105
Chawla, 2013[26]	Metformin + pioglitazone 25	52.2	56		72.68kg		4.458	0
	Metformin + sitagliptin 27	49.48	56		72.1		4.107	2
Curkendall, 2014[207]	Metformin + Sulfonylurea	56.5	55.9		NR			
	Metformin + saxagliptin	55.4	53.2		NR			
Davies, 2013[208]	Metformin + exenatide 111	59	64	C: 94, AA: 1, Asian: 5	96.7kg	8.37	8	
	Metformin + insulin detemir 105	58	69	C: 97, AA: 0, Asian: 3	97.9kg	8.35	7	
DeFronzo, 2012[33]	Metformin + placebo 129	55.2	47.3	C: 72.1, AA: 6.2, Asian: 3.9, H: 48.8, O: 17.8	30.6	8.5	6	

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + pioglitazone + placebo, 130	54.1	46.9	C: 65.4, AA: 6.2, Asian: 8.5, H: 48.5, O: 20	31.3	8.5	5.7	
	Metformin + pioglitazone + placebo, 129	56.1	48.8	C: 74.4, AA: 4.7, Asian: 7.8, H: 51.9, O: 13.2	31.4	8.5	7.6	
	Metformin + pioglitazone + placebo, 129	54.5	41.1	C: 65.9, AA: 7, Asian: 9.3, H: 47.3, O: 17.8	30.7	8.5	5.7	
	Metformin + alogliptin + placebo, 128	53.1	52.3	C: 69.5, AA: 4.7, Asian: 10.9, H: 46.9, O: 14.8	31	8.6	6.2	
	Metformin + alogliptin + placebo, 129	53.7	38.8	C: 62, AA: 3.9, Asian: 11.6, H: 48.8, O: 22.5	31.5	8.6	5.6	
Derosa, 2013[42]	Metformin + placebo 87	54.8	51		78.6kg	8	5.4	5
	Metformin + sitagliptin 91	55.9	46		78.4kg	8.1	5.8	7
Derosa, 2013[43]	Metformin + placebo 85	56.7	48	C: 100	90.5kg	7.9	7.8	5
	Metformin + exenatide 86	57.3	50	C: 100	89.0kg	8.1	7.6	5
Diamant, 2010[44]	Metformin + exenatide 164				NR			
	Metformin + insulin glargine 157				NR			
Erem, 2014[47]	Metformin 20	52.2	30		87.47kg	7.62		1
	Pioglitazone 20	52.5	25		81.93kg	8.03		1
Esposito, 2011[48] }	Metformin 55	54.9	50.9		83.5kg	8.1		4
	Pioglitazone 55	54.2	54.5		84.5kg	8		4
Farcasiu, 2011[50]	Metformin + insulin lispro 75/25 151	58.4	45.7	C: 98.7, AA: 1.3, O: 1.3	85.1 kg	8.5	11.5	23

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + insulin lispro 50/50 151	57	39.1	C: 99.3, AA: 0.7	32.3 88.6 kg	8.6	10.9	23
Ferrannini, 2013[52]	Metformin 56	58	50	C: 69.6, AA: 1.8, Asian: 25	85.8kg	8.15		
	Empagliflozin 106	59	46.2	C: 79.2, AA: 0, Asian: 19.8	82.9kg	7.89		
	Empagliflozin 109	59	52.3	C: 77.1		8		
	Metformin + sitagliptin 56	60	51.8	C: 100		8.03		
	Metformin + empagliflozin 166	60	50	C: 98.2		7.88		
	Metformin + empagliflozin 166	60	53	C: 98.8		7.91		
Ferrannini, 2013[185]	Metformin		48.8	C: 60				
	Empagliflozin		49.4	C: 64.2				
	Empagliflozin		50	C: 65.9				
Fonseca, 2012[55]	Metformin 144	55.5	51	C: 13		8.4	5.9	25
	Metformin + saxagliptin 138	55.2	41	C: 9		8.3	6.5	8
Forst, 2010[56]	Metformin + placebo 71	60.1	62	C: 97		8.4	6.2	14
	Metformin + glimepiride 65	59.4	63.1	C: 99		8.2	6.7	4
	Metformin + linagliptin 66	59.6	56.1	C: 100		8.5	7.3	10
Forst, 2014[58]	Metformin + glimepiride 20	63	70			7.4	8	0
	Metformin + linagliptin	65	65			7.3	7.7	1

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	20							
Gallwitz, 2011[59]	Metformin + exenatide 182	57					5	47
	Metformin + insulin aspart 70/30, 181	57					5	44
Gallwitz, 2012[60]	Metformin + glimepiride + placebo, 775	59.8	61	C: 85		7.7		
	Metformin + linagliptin + placebo, 777	59.8	60	C: 85		7.7		
Gallwitz, 2012[61]	Metformin + glimepiride 514	56	52	C: 91		7.4	5.5	128
	Metformin + exenatide 515	56	56	C: 92		7.5	5.8	174
Garber, 2011[66]	Glimepiride + placebo 248	53.4	54	C: 77		8.2	5.6	151
	Liraglutide + placebo 251	53.7	47	C: 80		8.2	5.2	141
	Liraglutide + placebo 247	52	49	C: 75		8.2	5.3	132
Genovese, 2013[67]	Metformin + placebo 103	57.8	60.2	C: 100		7.02	5.7	6
	Metformin + pioglitazone 110	57	59.1	C: 100		6.92	5.8	13
Genovese, 2013[68]	Metformin 29	56.4	65.5			6.8	3.9	3
	Pioglitazone + placebo 29	59.1	48.3			6.9	4.4	5
Goke, 2010[69]	Metformin + glipizide 430	57.6	54	C: 84.2		7.7	5.4	283
	Metformin + saxagliptin 428	57.5	49.5	C: 82.2		7.7	5.5	263
Gupta, 2013[75]	Glimepiride 83	40.07				8.02		12
	Sitagliptin 84	39.12				8.03		7

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Haak, 2012[76]	Metformin 144	52.9	56.9	C: 64.6, AA: 0, Asian: 35.4, O: 0	79.9	8.7		17
	Metformin 147	55.2	53.1	C: 64.6, AA: 1.4, Asian: 34, O: 0	80	8.5		21
	Linagliptin 142	56.2	56.3	C: 68.3, AA: 0, Asian: 31.7, O: 0	79.1	8.7		21
	Metformin + linagliptin 143	55.6	51	C: 72, AA: 1.4, Asian: 25.9, O: 0.7	80.8	8.7		16
	Metformin + linagliptin 143	56.4	53.8	C: 65.7, AA: 0.7, Asian: 33.6, O: 0	76.7	8.7		11
Haak, 2013[77]	Metformin 170	55.7	55.7	C: 63.9, AA: 0, Asian: 36.1	Median92.6 kg 29.5	7.76		
	Metformin + linagliptin 170	55.6	54.1	C: 62.4, AA: 0.9, Asian: 36.7	Median89 kg 29.2	7.31		
	Metformin + linagliptin 225	55.1	55.4	C: 65.2, AA: 0, Asian: 34.8	Median88.8kg 28.3	7.95		
Haring, 2014[82]	Metformin + placebo 225	56.8	51.3	C: 71.7, AA: 1.8, Asian: 26.5	Median87.8kg 29.8	7.34		
	Metformin + empagliflozin 171	56.1	61.7	C: 68.3, AA: 0, Asian: 31.7	Median84.1kg 28.8	8.15		
	Metformin + empagliflozin 171	55.6	54.1	C: 60.4, AA: 0.9, Asian: 38.7	Median88.6 kg 28.5	6.93		
Henry, 2012[83]	Metformin + placebo 207	56	56	C: 55, AA: 1, Asian: 44, O: 0	79.7kg	7.9		21
	Dapagliflozin + placebo 217	55.5	58	C: 52, AA: 2, Asian: 46, O: 1	81.6kg	7.94		8
	Metformin + dapagliflozin 214	55.6	56	C: 53, AA: 0, Asian: 46, O: 1	82.2kg	7.86		18
Henry, 2012[83]	Metformin + placebo	51.8	24		85.6kg	9.2	0.6	30

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Dapagliflozin + placebo	52.3	22		86.2kg	9.1	0.4	33
	Metformin + dapagliflozin	51.7	21		84.1kg	9.2	0.3	17
Hermans, 2012[86]	Metformin	52.7	46.6		87.2	9.1	0.5	27
	Metformin + saxagliptin	51.1	47.9		88.5	9.1	0.6	31
Hong, 2013[186]	Metformin + placebo	51	50.2		88.4	9.1	0.6	28
	Glipizide + placebo 139	58.6	54.7	C: 97.1, AA: 0.7, Asian: 1.4, O: 0.7	31.2		6.9	32
Kadoglou, 2011[93]	Metformin 147	58.7	59.9	C: 98.6, AA: 0.7, Asian: 0.7, O: 0	32.1		6	28
	Metformin + rosiglitazone 156	62.8	78.2		69.6kg	7.6	5.6	32
Kadowaki, 2013[94]	Metformin + placebo 148	63.8	77		68.7kg	7.6	5.6	31
	Metformin + sitagliptin 70	62.7	27		30.04	7.56	2.7	
Kaku, 2011[97]	Glibenclamide 70	62	26		29.68	7.58	1.8	
	Liraglutide 72	57.2	68.1		25	8.4	7.3	
Kikuchi, 2012[99]	Rosiglitazone 77	59.6	71.4		25.2	8.2	7.7	
	Pioglitazone	58.5	65.2	Asian: 100	65.4 kg	9.18	8.5	
Kim, 2014[101]	Metformin	58.2	68.3	Asian: 100	66.2 kg	9.32	8.1	
	Metformin + glimepiride 160	55	62.9	Asian: 100	24.5	8.9	5	11
Lavalle-	Metformin + placebo	56	62.3	Asian: 100	24.9	8.8	4.2	22

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Gonzalez, 2013[104]	159							
	Metformin + sitagliptin 108	56.1	47.2		25.7 66.9 kg	7.8		14
	Metformin + canagliflozin 101	55.2	51.5		25.5 66.5 kg	7.9		6
Lavalle-Gonzalez, 2013[104]	Metformin + canagliflozin 183	55.3	51.4	C: 70.5, AA: 1.6, Asian: 16.4, O: 11.5	86.6kg	8	6.8	28
Lee, 2013[209]	Metformin + pioglitazone 366	55.5	47	C: 72.1, AA: 3.6, Asian: 11.2, O: 13.1	87.7kg	7.9	6.8	47
Lee, 2013[209]	Metformin + sitagliptin 368	55.5	47.3	C: 68.5, AA: 4.3, Asian: 13.9, O: 13.3	88.8kg	7.9	6.7	46
Lee, 2013[209]	Albiglutide + Sulfonylurea 367	55.3	45	C: 69.8, AA: 3.5, Asian: 16.3, O: 10.4	85.4kg	7.9	7.1	44
Lehman, 2012[210]	Metformin	55.2	60	Asian: 100	26.3 71.4 kg	8.8	5	3
	Sulfonylurea	50.2	63.2	Asian: 100	74.5 27.3	9.4	1	5
List, 2009[107]	Metformin	54.8	51.6	Asian: 100	26.5 69.9kg	8.9	1	3
	Dapagliflozin 175	67.81	100	C: 84, AA: 7.43, H: 8.57, O: 0	29.67	6.52		
	Dapagliflozin 533	64.7	100	C: 82.36, AA: 9.94, H: 7.32, O: 0.38	30.97	6.48		
Maffioli, 2013[109]	Metformin + pioglitazone 1930	72.33	100	C: 79.74, AA: 13.32, H: 6.42, O: 0.52	28.91	6.77		
	Metformin + glibenclamide 2404	69.87	100	C: 82.12, AA: 10.94, H: 6.61, O: 0.33	29.86	6.79		
Moon, 2014[112]	Metformin + glimepiride 56	54	48		88 kg	7.6		5
	Metformin + insulin glargine 58	55	48		89 kg	8		3
Nauck, 2009[117]	Metformin + placebo 47	54	53		86 kg	8		7
Nauck,	Metformin + alogliptin	62.8	48		83.5	8.4		3

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2009[117]	86							
	Metformin + alogliptin 84	61.4	50		83.1	8.2		2
Nauck, 2011[118]	Metformin + glipizide 36	54.9	47.1		66.0 kg	8.9	95.6	2
	Metformin + dapagliflozin 39	51.3	31.6		62.7 kg	8.8	79	0
Nauck, 2014[119]	Metformin + placebo 104	56	48	C: 76, AA: 7, Asian: 6, H: 24, O: 11	32	8	6	
	Metformin + sitagliptin 210	54	54.3	C: 76, AA: 6, Asian: 9, H: 32, O: 9	32	7.9	6	
	Metformin + dulaglutide 213	55	47.4	C: 80, AA: 2, Asian: 8, H: 31, O: 10	32	7.9	6	
	Metformin + dulaglutide 408	59	54.9	C: 80.5, AA: 6, Asian: 8.5, O: 5	31.2	7.7	7	94
Perez-Monteverde, 2011[122]	Pioglitazone 406	58	55.3	C: 81.8, AA: 6.5, Asian: 6.8, O: 5	31.7	7.7	6	84
	Sitagliptin 177	55	51	C: 51, AA: 5, Asian: 22, H: 22, O: 0	87 kg	8.1	7	
Pfutzner, 2011[126] }	Metformin + pioglitazone 315	54	48	C: 50, AA: 2, Asian: 26, H: 21, O: 1	86 kg	8.1	7	
	Metformin + glimepiride 302	54	44	C: 54, AA: 4, Asian: 26, H: 17, O: 0	86 kg	8.2	7	
Pfutzner, 2011[127]	Metformin + placebo 304	54	48	C: 52, AA: 5, Asian: 25, H: 18, O: 0	87 kg	8.1	7	
	Saxagliptin + placebo 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	82.2 kg	9.1	3.5	17
	Metformin + saxagliptin 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	82.2 kg	9.1	3.5	17
	Metformin + saxagliptin	59	66		32.6		6.2	32
Pratley, 2014[129]	Metformin	59	64		32.5		5.9	29
	Metformin 328	51.8	49.7	C: 76.5, AA: 1.2, Asian: 15.9, O: 6.4	30.2	9.4	1.7	109

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + alogliptin 335	52.1	50.4	C: 76.1, AA: 1.8, Asian: 16.7, O: 5.4	30.2	9.6	1.7	126
	Metformin + alogliptin 320	52	51.6	C: 76.9, AA: 2.2, Asian: 15.9, O: 5	29.9	9.4	2	91
	+ alogliptin 323	52.1	45.2	C: 75.2, AA: 2.2, Asian: 16.7, O: 5.9	30.4	9.5	1.4	92
Qiu, 2014[130]	Metformin + placebo 114	54.6	41.2	C: 74.6, AA: 5.3, Asian: 16.7, O: 3.5	30.2	8.5	3.8	
	Metformin + canagliflozin 111	52.6	45.9	C: 71.2, AA: 5.4, Asian: 18, O: 5.4	30.5	8.39	4.1	
	Metformin + canagliflozin 111	53.7	43.2	C: 68.5, AA: 5.4, Asian: 18, O: 8.1	30.9	8.5	4.1	
Reasner, 2011[133]	Metformin 114	54.6	54.4	C: 68.4, AA: 4.4, Asian: 22.8, O: 4.4	31	8.43	4.2	
	Metformin + sitagliptin 112	52.6	42.9	C: 75, AA: 2.7, Asian: 15.2, O: 7.1	30.8	8.3	3.6	
Ridderstrale, 2014[134]	Metformin + glimepiride 93	57	49.5	C: 78.5, AA: 4.3, Asian: 9.7, O: 7.5	90.5kg	7.7	7	7
	Metformin + empagliflozin 93	58.6	43	C: 80.6, AA: 5.4, Asian: 3.2, O: 10.8	91.2kg	7.6	6.7	8
Roden, 2013[137]	Sitagliptin 93	56.7	47.3	C: 89.2, AA: 1.1, Asian: 6.5, O: 3.2	90.2kg	7.6	7.3	13
	Empagliflozin	50	57	C: 79, AA: 14, Asian: 4, H: 30, O: 3	33.7 97.2 kg	9.8	3.2	215
	Empagliflozin	49.4	56	C: 81, AA: 13, Asian: 3, H: 36, O: 3	32.9 94.7 kg	9.9	3.5	216
Rosenstock, 2010[139]	Pioglitazone + placebo 780	55.7	54	C: 67, AA: 1, Asian: 32, H: 20, O: 0	83.0kg	7.92		132
	Alogliptin + placebo 769	56.2	56	C: 65, AA: 2, Asian: 33, H: 20, O: <1	82.5kg	7.92		121
Rosenstock, 2012[140]	Metformin + placebo 223	55.1	63	C: 34, AA: 1, Asian: 64, O: <1	79.3kg	7.85		17
	Metformin + sitagliptin 224	56.2	63	C: 34, AA: 1, Asian: 64, O: 0	78.4kg	7.87		18
	Metformin + canagliflozin	53.8	65	C: 33, AA: 3, Asian: 64,	77.8kg	7.86		20

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	224			O: 0				
	Metformin + canagliflozin 163					8.76		37
	Metformin + canagliflozin 164					8.8		38
Rosenstock, 2013[141]	Glipizide 65	53.3	48		85.9 kg	7.75	6.4	10
	Alogliptin 65	51.7	58		87.2 kg	7.64	5.6	5
Rosenstock, 2013[142]	Metformin + placebo 64	51.7	56		87.7 kg	7.83	6.1	5
	Metformin + sitagliptin 65	52.9	51		87.7 kg	7.61	6.4	9
	Metformin + empagliflozin 64	52.3	56		87.3 kg	7.69	5.9	8
	Metformin + empagliflozin 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02	7.45	5.94	
Ross, 2012[143]	Metformin + placebo 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02	7.45	5.94	
	Metformin + linagliptin + placebo 71	60	47	C: 90, AA: 1, H: 9, O: 0	87.7kg	8		5
Russell-Jones, 2012[144]	Metformin + placebo 71	58	54	C: 87, AA: 0, H: 13, O: 0	88.0kg	8.1		1
	Pioglitazone + placebo 71	59	47	C: 78, AA: 3, H: 20, O: 0	87.9kg	7.9		5
	Sitagliptin + placebo 70	59	53	C: 83, AA: 1, H: 16, O: 0	90.5kg	8.1		0
	Exenatide + placebo 44	59.9	47.7	C: 72.7, Asian: 27.3, O: 0	77.7kg	7.92		1
Seino, 2012[151]	Metformin + placebo 224	58.4	54	C: 62.1, Asian: 36.6, O: 1.3	80.6kg	7.98		10
	Metformin + alogliptin 246	54	62.6	C: 65, AA: 4.5, Asian: 20.7, H: 8.5, O: 1.2	85.9 kg	8.6	2.6	
	Metformin + alogliptin	55	59.5	C: 67.5, AA: 2.5, Asian:	86.1 kg	8.5	2.7	

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	163			20.9, H: 9.2, O: 0				
Shihara, 2011[152]	Pioglitazone 163	52	57.7	C: 69.3, AA: 1.8, Asian: 20.2, H: 8, O: 0.6	88.7 kg	8.5	2.7	
	Sulfonylurea 248	54	56	C: 68.1, AA: 2.8, Asian: 22.2, H: 6.5, O: 0.4	87.5 kg	8.5	2.7	
Skrivanek, 2014[212]	Metformin + placebo 100	52.1	72		69.89 kg	8	6.04	0
	Metformin + sitagliptin 92	53.4	65.2		69.47 kg	7.89	6.34	1
	Metformin + dulaglutide 96	52.3	68.8		69.65 kg	8.02	6.62	3
	Metformin + dulaglutide 96	56.8	68	Asian: 100	65.5 kg	7.8	4.1	5
	Metformin + dulaglutide 95	57.7	65	Asian: 100	65.6 kg	7.8	6	9
Srivastava, 2012{Srivastava, 2012	Metformin + glimepiride 38	53	32	C: 40, AA: 5, Asian: 11, H: 45, O: 0	32	8.1	7	4
	Metformin + sitagliptin 42	53	50	C: 48, AA: 5, Asian: 10, H: 38, O: 0	32	8.4	9	0
Stenlof, 2014[201]	Sitagliptin 21	52	48	C: 62, AA: 0, Asian: 5, H: 33, O: 0	33	8.2	7	0
	Canagliflozin 10	55	30	C: 40, AA: 0, Asian: 0, H: 60, O: 0	34	7.9	7	2
	Canagliflozin 25	53	40	C: 40, AA: 8, Asian: 8, H: 44, O: 0	32	8.7	9	1
Taskinen, 2011[158]	Metformin + placebo 25			Asian: 100	26.5			0
	Metformin + linagliptin 25			Asian: 100	25.3			0
Umpierrez, 2014[165]	Metformin + placebo 170	55.1	41.5	C: 63.6, AA: 9.2, Asian: 13.8, O: 13.3	85.8kg	8.1	4.5	18
	Dulaglutide + placebo 170	55.3	45.2	C: 69.5, AA: 7.1, Asian: 14.7, O: 8.6	86.9kg	8	4.3	5
	Dulaglutide + placebo 155	55.7	45.8	C: 69.8, AA: 4.7, Asian: 15.1, O: 10.4	87.6kg	8	4.2	20

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
van Staa, 2012[219]	Metformin 177	56.6	57	C: 79, Asian: 18, O: 3	83.3 kg	8.02		14
	Thiazolidinedione 523	56.5	53	C: 75, Asian: 22, O: 3	82.2 kg	8.09		39
	Sulfonylurea 268	55	45	C: 75, AA: 5, Asian: 8, H: 35, O: 13	33 92 kg	7.6	3	55
Weir, 2011[213]	Metformin 270	56	44	C: 73, AA: 8, Asian: 7, H: 32, O: 11	92 kg 33	7.6	3	52
	Glyburide 269	56	42	C: 75, AA: 6, Asian: 8, H: 33, O: 12	34 93 kg	7.6	3	49
	+ basal insulin 109,708	63	56.3		31	8.8		
White, 2014[168]	Metformin + placebo 31,372	63	57.3		31	8.9		
	Metformin + saxagliptin 68,029	65	56.1		30	9		
Williams-Herman, 2010[170]	Metformin + placebo 572		51.4		NR			
	Metformin + placebo 580		46.7		NR			0
	Metformin + placebo 193		50.8		NR			
	Sitagliptin + placebo 444		51.4		NR			0
	Metformin + sitagliptin				NR			
	Metformin + sitagliptin				NR			
Yang, 2011[172]	Metformin + placebo 86	56.6	52.3	C: 93, AA: 3.5, Asian: 2.3, H: 40.7, O: 1.2	32.5	7.97	6.2	
	Metformin + saxagliptin 74	53.9	54.1	C: 86.5, AA: 10.8, Asian: 2.7, H: 39.2, O: 0	33.7	7.92	5.8	
Yang, 2011[173]	Metformin + glimepiride + placebo	54.1	50	NR	31.9	8.1	4	20
	Metformin + liraglutide +	55.9	46	NR	32.2	8.6	4	27

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	placebo							
	Metformin + liraglutide + placebo	54.3	44	NR	31.9	8.5	3.9	26
	Metformin + liraglutide + placebo	54.1	58	NR	30.3	8.5	3.7	38
Yang, 2012[174]	Metformin + placebo	54.5	50	NR	31.6	8.7	3.7	36
	Metformin + sitagliptin	53.9	37	NR	31.4	8.6	4.4	21
Yoon, 2011[175]	Metformin 287	54.4	48.4	Asian: 100	69.0 kg	7.9	5.1	40
	Rosiglitazone 283	53.8	48.1	Asian: 100	68.9 kg	7.9	5.1	29
	Glimepiride 231	53.6	58.4	Asian: 100	68.2 kg	8.5	7.8	
Yuan, 2012[176]	Metformin 231	53.5	54.1	Asian: 100	68.6 kg	8.5	7.4	
	Exenatide 233	53.5	54.9	Asian: 100	67.4 kg	8.6	7.5	

Abbreviations: AA = African American; BHI = biphasic human insulin; BMI = body mass index; C = Caucasian; H = Hispanic; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptidase-1; HbA1c = glycated hemoglobin; kg = kilogram; NR = NR; SU = sulfonylurea;

Some data may have not been extracted because the question was not asked.

Table 12. Results of studies evaluating diabetes medications on safety

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Agarwal, 2005[206] RCT	Grp1: Pioglitazone Varied, glucose: 140 mg/dL, HbA1c: 8% Start: 15 mg D: 16 wks Grp2: Glipizide Varied, glucose: 140 mg/dL, HbA1c: 8% Start: 5 mg D: 16 wks	Grp1: 2 events Grp2: 3 events		Grp1: 2 (2) Grp2: 2 (2)			
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: based on all reports of hypoglycemia; a concurrent glucose measurement was NOT required Grp1: 2 NA p NR Grp2: 0 NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c	Def: symptomatic + fingerstick glucose <=70 mg/dl Grp1: 283.4Person-years p NR Grp2: 37 283.4 Person-years p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	thresholds) ITT:No Mode of AE collection:Active Followup (wks):104						
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptomatic + fingerstick glucose <=50 mg/dl Grp1: 283.4Person-years p Grp2: 4 283.4 Person-years p					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: any symptomatic hypoglycemia w/ or w/o glucose measurement Grp1: 114 (22) NA p NR Grp2: 36 (7) 73 NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + sitagliptin + placebo	Def: symptomatic hypoglycemia and did not require documentation of a glucose measurement					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Grp1: 36 NA p 0.001 Grp2: 13 NA p					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptomatic hypogly w PG <=3.9 mmol/l Grp1: 28 (11) Person-years p NR Grp2: 86 (36) 0.47 Person-years p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: all symptomatic hypoglycemia Grp1: 35 (13) 1Person-years p Grp2: 108 (46) 4.21 1 Person-years p					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified	Def: symptomatic hypogl BG< 3.1 mmol Grp1: 12 (5) Person-					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	years p NR Grp2: 56 (24) 0.9 Person-years p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: total patients with hypoglycemia Grp1: 8 (5.8) NA p NR Grp2: 5 (3.6) NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum	Def: total patients with hypoglycemia Grp1: 8 (5.8) NA p NR Grp2: 7 (5.1) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104						
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: total patients with hypoglycemia Grp1: 8 (5.8) NA p NR Grp2: 7 (5.2) NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: All hypoglycaemia cases (see comments) Grp1: 5 (5.5) NA p NR Grp2: 4 (4.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptomatic hypoglycemia Grp1: 10 (3) p Grp2: 20 (6) p					
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active	Def: documented - biochemically (glucose <=3.9 mmol/l) +/- sxs Grp1: 165 (34) p Grp2: 27 (6) p <0.0001					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):104						
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: documented - biochemically (glucose <=3.9 mmol/l) +/- sxs Grp1: 165 (34) p Grp2: 24 (5) p <0.0001					
Ahren, 2014[2] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: diagnosis of hypoglycemia (ICD-9-CM 250.8x, diabetes with other specified manifestations; 251.0x, hypoglycemic coma; 251.1x, other specified hypoglycemia 251.2x, hypoglycemia, unspecified) on an outpatient or ER insurance claim, a principal di					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp1: p Grp2: 9 p					
Ahren, 2014[2] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: FPG<60mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
Alba, 2013[3] RCT	Grp1:Pioglitazone Fixed (30mg) Grp2:Sitagliptin	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (100mg) ITT:Yes Mode of AE collection:Active Followup (wks):12						
Amador-Licona, 2000[178] RCT	Grp1: Metformin Varied Start: 850 mg Grp2: Glibenclamide Varied Start: 5 mg					Def: Diarrhea + Diffuse abdominal pain Grp1: 4 (14.3) Grp2: NR	
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 1 (0.9) NA p NR					
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day)	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 2 (1.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30						
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 2 (3.6) NA p NR					
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 3 (1.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30						
Arjona Ferreira, 2013[6] RCT	Grp1:Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2:Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT:No Mode of AE collection:Active Followup (wks):58	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 4 (2.4) NA p NR					
Arjona Ferreira, 2013[6] RCT	Grp1:Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2:Sitagliptin + placebo	Def: plasma glucose <=70mg/dL Grp1: 1 (0.9) NA p NR Grp2: 2 (3.6) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT:No Mode of AE collection:Active Followup (wks):58						
Aschner, 2010[7] RCT	Grp1: Metformin Varied, prespecified dose Start: 500 mg, Max: 2000 mg; Mean: 1903 mg D: 5 wks Grp2: Sitagliptin Fixed Mean: 100 mg	Coll: Passive Timing: Unspecified ITT: No Grp1: Severe: 0 (0) Mild/moderate: 17 (3.3); 23 events Grp2: Severe: 2 (<1) Mild/moderate: 9 (1.7); 17 events				Def: Combined GI events; Nausea; Diarrhea; Vomiting; Abdominal pain Coll: NR Timing: Unspecified ITT: No Grp1: (20.7, 3.1, 10.9, 1.3, 3.8) Grp2: (11.6, 1.1, 3.6, 0.4, 2.1)	
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin	Def: plasma glucose <=70mg/dL Grp1: 2 (1.8) NA p NR Grp2: 2 (3.6) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):	NR					
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):	Def: plasma glucose <=70mg/dL Grp1: 1 (0.9) NA p NR Grp2: 3 (1.8) NA p NR					
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):24	Def: plasma glucose <=70mg/dL Grp1: 1 (0.9) NA p NR Grp2: 4 (2.4) NA p NR					
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin glargine	Def: plasma glucose <=70mg/dL Grp1: 2 (1.8) NA p NR Grp2: 3 (1.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):25						
Bailey, 2005[9] RCT	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg D: 24 wks Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2000 mg; Start: 4 mg, Max: 8 mg D: 24 wks	Grp1: Serious: 0, Mild or moderate: 1 (<1) Grp2: Serious: 0, Mild or moderate: 3 (1)				Def: diarrhea and abdominal pain Grp1: (5.4) Grp2: (3.2)	Def: acute cholecystitis, serious cholelithiasis and cholestatic jaundice Coll: Active Timing: Specified ITT: Yes Grp1: 1 (<1) Grp2: 0 (0)
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: plasma glucose <=70mg/dL Grp1: 2 (1.8) NA p NR Grp2: 4 (2.4) NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg)	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	NR Grp2: 3 (1.8) NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 4 (2.4) NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: hypoglycaemia, either symptomatic or laboratory-documented Grp1: 1 NA p NR Grp2: 0 NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT:Yes	Def: hypoglycaemia, either symptomatic or laboratory-documented Grp1: 1 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):102						
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: Unspecified AE Grp1: 2 (1.4) Persons p NR Grp2: 5 (3.6) Persons p NR					
Bakris, 2006[12] RCT	Grp1: Metformin + rosiglitazone Varied, glucose: ≤6.6 mmol/L Unclear; Start: 4 mg D: 3 wks Grp2: Metformin + glyburide Varied, glucose: ≤ 6.6 mmol/L Unclear; Start: 5 mg D: 3 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 2 (1) Grp2: 22 (12)					
Barnett, 2012[13] RCT	Grp1:Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2:Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT:Yes Mode of AE collection:Active Followup (wks):34	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 3 NA p NR					
Barnett, 2012[13]	Grp1:Glimepiride	Def: Unspecified AE					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2:Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT:Yes Mode of AE collection:Active Followup (wks):34	Grp1: 0 NA p NR Grp2: 0 NA p NR					
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 3 NA p NR Grp2: 0 NA p NR					
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT:No Mode of AE collection: NR/unclear	Def: typical symptoms of hypoglycemia that recovered after the ingestion of glucose and/or a confirmed blood glucose level < 3.3mmol/l Grp1: NA p NR Grp2: 2 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):26						
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: BG < =3.0 mmol/L Grp1: (1.8) p Grp2: (6.3) p NS					
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 280 (36) NA p Grp2: 58 (7) NA p <0.0001					
Bergenstal, 2010[14] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: at least one episode of hypoglycemia reported Grp1: 338 (67) Persons p <0.0001 Grp2: 186 (36) Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Bergenstal, 2010[14] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: <3.9 mmol + symptomatic Grp1: 240 (47) Persons p <0.0001 Grp2: 102 (20) Persons p					
Bergenstal, 2012[15] RCT	Grp1:Metformin + placebo Fixed (Stable dose of >/=1,500mg/day) Grp2:Metformin + sitagliptin + placebo Fixed (Stable dose of >/=1,500mg/day) Fixed (100mg QD) ITT:No Mode of AE collection:Active Followup (wks):24	Def: <2.8mmol + symptomatic Grp1: 63 (12) Persons p 0.002 Grp2: 34 (7) Persons p					
Blonde, 2002[16] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Fixed Start: 10 mg	Def: Mild or moderate, Fsg≤60mg/dl + symptomatic Grp1: 1 (<1) Grp2: 3 (1.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6); (12.4); (2) Grp2: (3); (5.5); (0)	
Blonde, 2002[16] RCT	Grp1: Metformin Varied	Def: FSG≤60mg/dl + symptomatic				Def: Dyspepsi	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1: Mild or moderate: 1 (<1) Grp2: Mild or moderate: 22 (6.8)				a and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6; 12.4; 2) Grp2: (3.7; 6.8; 2.5)	
Blonde, 2002[16] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: FSG≤60mg/dl + symptomatic Grp1: Mild or moderate: 1 (<1) Grp2: Mild or moderate: 22 (6.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6; 12.4; 2) Grp2: (5; 10; 6.3)	
Bolinder, 2012[17] RCT	Grp1:Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2:Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: NR Mode of AE collection:Active Followup (wks):102	Def: hypoglycemic episodes Grp1: NA p NR Grp2: 4 NA p NR					
Bolinder, 2012[17]	Grp1:Metformin + placebo Fixed (Patients continued open-	Def: combination of reports of signs or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	label metformin dosage from prior to enrollment) Grp2:Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	symptoms consistent with hypoglycemia, with or without documented glucose levels, or reported low glucose levels without symptoms Grp1: (38.4) NA p NR Grp2: (3.5) NA p NR					
Bolinder, 2012[17] RCT	Grp1:Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2:Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: Confirmed <50 mg/dl plasma glucose levels with associated symptoms Grp1: (9.1) NA p NR Grp2: (0) NA p NR					
Borges, 2011[18] RCT	Grp1:Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2:Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT:No Mode of AE collection:Active Followup (wks):80	Def: Unspecified AE Grp1: p Grp2: 3 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Bunck, 2009[19] RCT	Grp1: Metformin + exenatide Fixed; Varied, HbA1c: 7.1%-7.5% Mean: 2058 mg; Start: 5 ug bid, 20 ug tid Grp2: Metformin + glargine Fixed; Varied, SMBG: 4.5-5.5 mmol/L Mean: 1798 mg; Start: 10 U, Mean: 33.6 U qd	Def: <3.3mmol/L Coll: Active Timing: Unspecified ITT: NR Grp1: (8.3) Grp2: (24.2)				Def: Mild to moderate nausea, vomiting, diarrhea Grp1: NR Grp2: (50)	Def: Pancreatitis Grp1: 1 (3) Grp2: 0 (0)
Bunck, 2011[21] RCT	Grp1:Metformin + exenatide Fixed (pre-enrollment dose) Titrated (Max: 60 ug) Grp2:Metformin + insulin glargine Fixed (pre-enrollment dose) Titrated (Mean: 33.7 IU) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):168	Def: Unspecified AE Grp1: (2.9) NA p NR Grp2: (4.9) NA p NR					
Bunck, 2011[21] RCT	Grp1:Metformin + exenatide Fixed (pre-enrollment dose) Titrated (Max: 60 ug) Grp2:Metformin + insulin glargine Fixed (pre-enrollment dose) Titrated (Mean: 33.7 IU) ITT:Yes Mode of AE collection:Active Followup (wks):168	Def: Unspecified AE Grp1: (2.9) NA p NR Grp2: (6.4) NA p NR					
Cefalu, 2013[23] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of	Def: â€ Events consistent with hypoglycemia and with plasma glucose levels of <=3.9 mmol/L and/or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	>=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	requiring assistance Grp1: 1 (0.5) NA p NR Grp2: 4 (1.8) NA p NR					
Cefalu, 2013[23] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during	Def: Events consistent with hypoglycemia and with plasma glucose levels of <=3.9 mmol/L and/or requiring assistance Grp1: 1 (0.5) NA p NR Grp2: 3 (1.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT:Yes Mode of AE collection:Active Followup (wks):52						
Cefalu, 2013[23] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT:No Mode of AE collection:Active Followup (wks):52	Def: None led to discontinuation from study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol, Grp1: 0 (0) NA p NR Grp2: 0 NA p NR					
Cefalu, 2013[23] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-	Def: None led to discontinuation from					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT:No Mode of AE collection:Active Followup (wks):52	study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, Grp1: 0 (0) NA p NR Grp2: 5 (2.6) NA p NR					
Charbonnel, 2006[24] RCT	Grp1: Metformin Varied, HbA1c: 7 -10% Start: ≥1500 mg D: 19 wks Grp2: Metformin + sitagliptin Varied; Fixed Start: ≥1500 mg; Mean: 100 mg D: 19 wks	Def: Mild or moderate Grp1: 5 (2.1) Grp2: 6 (1.3)				Def: Abdominal pain, nausea, vomiting, or diarrhea Coll: NR Timing: Unspecified ITT: No Grp1:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						(10.5) Grp2: (11.9)	
Charpentier, 2001[25] RCT	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Glimepiride Fixed or Varied 1 mg (either fixed or increased stepwise to 2, 4, 6 mg od depending on clinical symptoms of hypoglycemia)	Def: Clinical symptoms Grp1: Serious: 0 (0), Mild or moderate: 8 (11) Grp2: Serious: 3 (2), Mild or moderate: 17 (11)				Def: Diarrhea Grp1: (7) Grp2: (1)	
Charpentier,2001[25] RCT	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Metformin + glimepiride Fixed Start: 850 mg tid; Start: 1 mg	Def: Clinical symptoms Grp1: Serious: 0 (0), Mild or moderate: 8 (11) Grp2: Serious: 2 (1.4), Mild or moderate: 30 (21)				Def: diarrhea Grp1: (7) Grp2: (3)	
Chien, 2007[27] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg, Max: 20 mg, Mean: 19 mg D: 4 wks	Def: Mild or moderate Coll: Passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)			Def: Right metacarpal bone fracture Coll: passive Timing: Unspecified ITT: Yes Grp1: 0 Grp2: 1 (6)	Def: Diarrhea, dry mouth, increased appetite, GI disease Coll: Passive Timing: Unspecified ITT: Yes Grp1: (32) Grp2: (13)	
Chien, 2007[27]	Grp1: Metformin	Def: Mild or			Def:	Def:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1680 mg; Start: 5 mg, Max: 10 mg, Mean: 8.4 mg D: 4 wks	moderate Coll: Passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)			Right metacarpal bone fracture Coll: passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)	Diarrhea, dry mouth, increased appetite, GI disease Coll: Passive Timing: Unspecified ITT: NR Grp1: (32) Grp2: (13)	
Comaschi, 2007[28] RCT	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR, 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3 g; Start: 2.5 mg D: 22 wks	Def: Mild or moderate Grp1: 0 (0) Grp2: 1 (1)					
Comaschi, 2007[28] RCT	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50% Start: 15 mg, Max: 30 mg; Unclear D: 22 wks; NR	Def: Mild or moderate Grp1: 0 (0) Grp2: 0 (0)					
Curkendall,	Grp1:Metformin + su	Def: None led to					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2014[207] Retrospective cohort	Not specified Not specified Grp2:Metformin + saxagliptin Not specified Not specified ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):16	discontinuation from study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, Grp1: 0 NA p NR Grp2: 5 (2.6) NA p NR					
Davies, 2007[29] RCT	Grp1: Metformin + NPH Varied, glucose < 6.0 mmol/L NR; Start: 10 IU/kg; Mean: 0.58 IU/kg D: 6 wks Grp2: Metformin + BHI 70/30 Varied, glucose < 6.0 mmol/L NR; Start: 10 IU bid, Mean: 0.63 IU bid	Def: Clinical hypoglycemia Coll: Active Timing: Specified ITT: NR Grp1: (25) Grp2: (29.6)					
Davies, 2013[208] RCT	Grp1:Metformin + exenatide Fixed (met dosage prior to study (>=1000mg/day)) Fixed (2mg qweek) Grp2:Metformin + insulin detemir Fixed (met dosage prior to study (>=1000 mg/day)) Titrated (mean initial dose 0.21+/-0.10IU/Kg per day	Def: Unspecified AE Grp1: 6 (2.9) NA p NR Grp2: 2 (0.9) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	(20.8+/-10.8IU/day), end dose 0.51+/-0.3IU/Kg per day(50.8=5+/-28.1 IU/day).Initiated and titrated according to manufacturer labeling and a published treat-to-target titration algorithm described by Hol ITT:Yes Mode of AE collection:Active Followup (wks):26						
Davies, 2013[208] RCT	Grp1:Metformin + exenatide Fixed (met dosage prior to study (>=1000mg/day)) Fixed (2mg qweek) Grp2:Metformin + insulin detemir Fixed (met dosage prior to study (>=1000 mg/day)) Titrated (mean initial dose 0.21+/-0.10IU/Kg per day (20.8+/-10.8IU/day), end dose 0.51+/-0.3IU/Kg per day(50.8=5+/-28.1 IU/day).Initiated and titrated according to manufacturer labeling and a published treat-to-target titration algorithm described by Hol ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 6 (2.9) NA p NR Grp2: 7 (3.3) NA p NR					
DeFronzo, 1995[30] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied	Def: Mild or moderate Grp1: 4 (2) Grp2: 6 (3)				Def: Nausea + diarrhea Grp1: (1.4)	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 10 mg, Max: 20 mg					Grp2: (1)	
DeFronzo, 1995[30] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20mg	Def: Mild or moderate Grp1: 4 (2) Grp2: 38 (18)				Def: Nausea + diarrhea Grp1: (1.4) Grp2: (0.9)	
DeFronzo, 2009[31] RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 10 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 7 (4)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 10 (6)	
DeFronzo, 2009[31] RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 5 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 10 (5)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 11 (6)	
DeFronzo, 2009[31] RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 2.5 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 15 (8)				Def: Diarrhea Coll: Active Timing:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Unspecified ITT: Yes Grp1: 20 (11) Grp2: 19 (10)	
Defronzo, 2010[32] RCT	Grp1: Metformin + rosiglitazone Varied, prespecified dose NR: Start: 4 mg; Max: 8 mg Grp2: Metformin + exenatide Varied, prespecified dose NR: Start: 0.010 mg; Max: 0.02 mg BID D: 2 months	Coll: NR Timing: Unspecified ITT: No Grp1: Severe: 0 (0); Mild/moderate: 0 (0) Grp2: Severe: 0 (0); Mild/moderate: 2 (4)				Def: Vomiting; Diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (0; 9) Grp2: (49; 16)	
Derosa, 2004[34] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 4 mg	Grp1: 0 (0) Grp2: 0 (0)				Def: Nausea + diarrhea Grp1: 2 (2.4) Grp2: NR	
Derosa, 2005[36] RCT	Grp1: Metformin + rosiglitazone Fixed Start dose: 500 mg tid, Max: 500 mg tid; Start dose: 4mg, Max: 4 mg Grp2: Metformin + glimepiride Fixed Start dose: 500 mg tid, Max: 500 mg tid; Start dose: 2 mg, Max: 2 mg		Def: Transiently elevated LFT to 1.5 times upper limit of normal Coll: NR				

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
			Timing: Unspecified ITT: NR Grp1: 3 events out of 48 participants Grp2: NR				
Derosa, 2005[37] RCT	Grp1: Metformin + rosiglitazone Fixed Start: 1500 mg; Start: 4 mg Grp2: Metformin + glimepiride Fixed Start: 1500 mg; Start: 2 mg					Def: Transient flatulence Grp1: (4.2) Grp2: (2.1)	
Derosa, 2010[39] RCT	Grp1: Metformin + glibenclamide NR Mean: 1500 mg; Start: 7.5 mg; Max: 15 mg Grp2: Metformin + exenatide NR NR; Start: 10 mcg; Max: 20 mcg	Def: FPG < 60 mg/dL Coll: Active Timing: Specified ITT: No Grp1: 3 (5) Grp2: 0 (0)				Def: Vomiting; Diarrhea Coll: Active Timing: Specified ITT: No Grp1: (2; 2) Grp2: (2; 3)	
Derosa, 2013[42] RCT	Grp1:Metformin + placebo Fixed (2500+/-500mg/day as previously determined during run-in period) Grp2:Metformin + sitagliptin Fixed (2500+/-500mg/day as	Def: Unspecified AE Grp1: 2 (0.9) NA p NR Grp2: 7 (3.3) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	previously determined during run-in period) Fixed (100mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):48						
Derosa, 2013[43] RCT	Grp1:Metformin + placebo Fixed (Mean: 2500 +/- 500mg titrated up during run-in for 8+/- 2 months) Grp2:Metformin + exenatide Fixed (Mean: 2500 +/- 500mg titrated up during run-in over 8+/- 2 months) Titrated (Max: 20 ug daily5ug b.i.d. for the first 4 wks and then 10 ug b.i.d. thereafter) ITT:No Mode of AE collection:Active Followup (wks):48	Def: Hypoglycaemic events were defined as: an episode with symptoms and confirmed low glucose; an episode with low glucose; or an episode with symptoms when glucose was not measured Grp1: 10 (6.8) 147Persons p Grp2: 3 (2.2) 139 Persons p					
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 0 Persons p NR Grp2: 0 Persons p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:No Mode of AE collection: NR/unclear Followup (wks):84	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: Persons p Grp2: (4.1) Persons p					
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: Persons p Grp2: (6.8)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:No Mode of AE collection: NR/unclear Followup (wks):84	Persons p					
Dormuth, 2009[215] Cohort	Grp1: Thiazolidinedione NR Grp2: Sulfonylurea NR				Def: Hip fractures Coll: Passive Timing: Unspecified ITT: NA Grp1: HR: 1.28 (CI: 1.12 to 1.45) Grp2: ref		
Einhorn, 2000[45] RCT	Grp1: Metformin NR Grp2: Metformin + pioglitazone NR; Fixed NR; 30 mg	Grp1: 1 (0.6) Grp2: 1 (0.6)					
Erem, 2014[47] RCT	Grp1:Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg) Grp2:Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: Persons p Grp2: (6.8) Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	pts on 30 mg and 1 pt on 45 mg)) ITT:No Mode of AE collection: NR/unclear Followup (wks):48						
Feinglos, 2005[51] RCT	Grp1: Metformin Fixed Start: ≥1000 mg Grp2: Metformin + glipizide Fixed Start: ≥1000 mg; 2.5 mg	Def: FSG <60 mg/dl w/ symptoms or FSG <50 mg/dl w/o symptoms or FPG<55 mg/dl w/o symptoms Grp1: Serious: 0, Mild or moderate: 2 (3.3) Grp2: Serious: 0, Mild or moderate: 9 (14.8)					
Ferrannini, 2013[52] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Empagliflozin Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: (4.1) Persons p Grp2: (6.8) Persons p					
Ferrannini, 2013[52] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Empagliflozin Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: (4.1) Persons p Grp2: (6.8) Persons p					
Ferrannini,	Grp1:Metformin	Def: Unspecified AE					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2013[52] RCT	Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Metformin + sitagliptin Not specified Fixed (100 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Grp1: (9) NA p NR Grp2: (10) 6 NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: Unspecified AE Grp1: (9) NA p NR Grp2: (6) 3 NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: withdrawal due to hypoglycemia Grp1: 0 NA p NR Grp2: 1 NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Empagliflozin Fixed (10 mg) Grp2:Metformin + sitagliptin Not specified Fixed (100 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 20 (6.1) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		NR Grp2: 7 (2.1) NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Empagliflozin Fixed (25 mg) Grp2:Metformin + sitagliptin Not specified Fixed (100 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 20 (6.1) NA p NR Grp2: 15 (4.7) NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Empagliflozin Fixed (10 mg) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 20 (6.1) NA p NR Grp2: 22 (6.8) NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Empagliflozin Fixed (10 mg) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 7 (2.1) NA p NR Grp2: 15 (4.7) NA p NR					
Ferrannini,	Grp1:Empagliflozin	Def: events					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2013[52] RCT	Fixed (25 mg) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 7 (2.1) NA p NR Grp2: 22 (6.8) NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Empagliflozin Fixed (25 mg) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented hypoglycemia (oncurrent fi ngerstick or plasma glucose <= 3.9 mmol/L with or without symptoms) Grp1: (3.2) NA p NR Grp2: (4.3) NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Metformin + sitagliptin Not specified Fixed (100 mg) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented hypoglycemia (oncurrent fi ngerstick or plasma glucose <= 3.9 mmol/L with or without symptoms) Grp1: (3.2) NA p NR Grp2: (3.2) NA p NR					
Ferrannini, 2013[52] RCT	Grp1:Metformin + sitagliptin Not specified Fixed (100 mg) Grp2:Metformin + empagliflozin Not specified	Def: Unspecified AE Grp1: 23 (3.7) NA p NR Grp2: 19 (3) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78						
Ferrannini, 2013[185] RCT	Grp1:Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2:Empagliflozin Fixed (10mg) ITT:No Mode of AE collection: NR/unclear Followup (wks):12	Def: confi rmed hypoglycaemic adverse events (plasma glucose â‰¤3Â·9 mmol/L or requiring assistance) Grp1: 189 (24) Persons p NR Grp2: 19 (2) Persons p NR					
Ferrannini, 2013[185] RCT	Grp1:Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2:Empagliflozin Fixed (25mg) ITT:No Mode of AE collection: NR/unclear Followup (wks):12	Def: â€ Confi rmed events, plasma glucose <3Â·9 mmol/L or requiring assistance, or both Grp1: NA p NR Grp2: 1 NA p NR					
Fonseca, 2000[54] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4-8 mg	Def: mild or moderate Grp1: 2 (2) Grp2: 5 (4)					
Fonseca, 2012[55] RCT	Grp1:Metformin Titrated (Max: 2000 mg/duptitration from 1500 to	Def: â€ Confi rmed events, plasma glucose <3Â·9					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	2000 mg/d) Grp2:Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT:No Mode of AE collection:Active Followup (wks):18	mmol/L or requiring assistance, or both Grp1: NA p NR Grp2: 1 NA p NR					
Fonseca, 2012[55] RCT	Grp1:Metformin Titrated (Max: 2000 mg/duptitration from 1500 to 2000 mg/d) Grp2:Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT:No Mode of AE collection:Active Followup (wks):18	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 3 (5) NA p NR					
Forst, 2010[56] RCT	Grp1:Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2:Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) ITT:Yes Mode of AE collection:Passive Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 1 (2) NA p NR					
Forst, 2010[56] RCT	Grp1:Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2:Metformin + linagliptin Fixed (11 of 62 were on <1500	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 4 (6) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):12						
Forst, 2010[56] RCT	Grp1:Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) Grp2:Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 0 (0) NA p NR					
Forst, 2014[58] RCT	Grp1:Metformin + glimepiride Not specified Titrated (individually titrated in the range of 1-4mg to achieve best possible glycemic control as judged by the investigator) Grp2:Metformin + linagliptin Not specified Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 3 (5) NA p NR Grp2: 1 (2) NA p NR					
Forst, 2014[58] RCT	Grp1:Metformin + glimepiride Not specified Titrated (individually titrated in the range of 1-4mg to achieve	Def: Symptomatic of hypoglycemic events Grp1: 3 (5) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	best possible glycemic control as judged by the investigator) Grp2:Metformin + linagliptin Not specified Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):12	Grp2: 4 (6) NA p NR					
Gallwitz, 2011[59] RCT	Grp1:Metformin + exenatide Fixed (Median: 2000mgcontinued at prestudy dose) Titrated (Max: 20 micrograms/daystart 5ugBID 4 w then 10ug) Grp2:Metformin + insulin aspart 70/30 Not specified (Median: 2000mgcontinued at prestudy dose) Titrated (Mean: 28.4 IU/dayto reach glucose target of 5.0 -7.2 mmol/L; titrated "without a structured insulin dosing algorithm") ITT:No Mode of AE collection:Active Followup (wks):26	Def: Symptomatic of hypoglycemic events Grp1: 3 (5) NA p NR Grp2: 0 (0) NA p NR					
Gallwitz, 2011[59] RCT	Grp1:Metformin + exenatide Fixed (Median: 2000mgcontinued at prestudy dose) Titrated (Max: 20 micrograms/daystart 5ugBID 4 w then 10ug) Grp2:Metformin + insulin aspart 70/30	Def: Defined by preferred MedDRA terms Grp1: (0) NA p NR Grp2: (2.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Not specified (Median: 2000mgcontinued at prestudy dose) Titrated (Mean: 28.4 IU/dayto reach glucose target of 5.0 -7.2 mmol/L; titrated "without a structured insulin dosing algorithm") ITT:No Mode of AE collection:Active Followup (wks):26						
Gallwitz, 2012[60] RCT	Grp1:Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2:Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):104	Def: Defined by preferred MedDRA terms Grp1: (0) NA p NR Grp2: (0) NA p NR					
Gallwitz, 2012[60] RCT	Grp1:Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4	Def: Defined by preferred MedDRA terms Grp1: (0) NA p NR Grp2: (0) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg once daily) Grp2:Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):104						
Gallwitz, 2012[61] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):	Def: Defined by preferred MedDRA terms Grp1: (2.8) NA p NR Grp2: (0) NA p NR					
Gallwitz, 2012[61] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines)	Def: Defined by preferred MedDRA terms Grp1: (2.8) NA p NR Grp2: (0) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:No Mode of AE collection: NR/unclear Followup (wks):						
Gallwitz, 2012[61] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:No Mode of AE collection: NR/unclear Followup (wks):	Def: symptomatic but not confirmed by measurement Grp1: 10 (4.1) p Grp2: 6 (3.7) p					
Gallwitz, 2012[61] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide	Def: symptomatic but not confirmed by measurement Grp1: 10 (4.1) p Grp2: 5 (3.1) p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:No Mode of AE collection: NR/unclear Followup (wks):						
Garber, 2002[62] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10mg	Def: Mild or moderate Grp1: 0 (0) Grp2: 10 (6)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: (43) Grp2: (24)	
Garber, 2002[62] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg; Start: 1.25 mg	Def: Mild or moderate Grp1: NR Grp2: 18 (11.4)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: IR - 43 Grp2: IR - 32	
Garber, 2002[62] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg; Start: 2.5 mg	Def: Mild or moderate Grp1: NR Grp2: 61 (37.7)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: IR - 43 Grp2: IR - 38	
Garber, 2003[63] RCT	Grp1: Metformin Varied	Def: Mild or moderate				Def: Abdomina	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 500 mg (adjusted to patient response), Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 (adjusted to patient response), Max: 10 mg	Grp1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) Grp2: Symptomatic: 98 (57.6), Fingerstick: 16 (10.6)				l pain; Nausea & Vomiting; Diarrhea Grp1: (6.1; 10.4; 18.3) Grp2: (4; 6.6; 5.3)	
Garber, 2003[63] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Def: Mild or moderate Grp1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) Grp2: Symptomatic: 59 (39.1), Fingerstick: 19 (11.2)				Def: Abdominal pain; nausea + vomiting; Diarrhea Grp1: (6.1; 10.4; 18.3) Grp2: (4.1; 4.7; 7.6)	
Garber, 2006[64] RCT	Grp1: Metformin + rosiglitazone Varied Start: 1500 or 2000 mg, Max: 2000 mg; Start: 4 mg, Max: 8 Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 2000; Start: 5 mg , Max: 10 mg	Grp1: Severe: 0 (0), Mild or moderate: 2 (1) Grp2: Severe: 7 (4), Mild or moderate: 53 (33)				Def: Diarrhea + abdominal pain + other GI symptoms ; Diarrhea; Abdominal pain Grp1: (10; 3; 4) Grp2: (11; 6; 6)	
Garber, 2009[65]	Grp1: Glimepiride	Def: Not requiring				Def: Total	Def:

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Varied, prespecified dose Start: 2 mg, Max: 8 mg D: 2 wks Grp2: Liraglutide Varied, prespecified dose Start: 0.6 mg, Max 1.8 mg D: 2 wks	assistance, PG < 3.1 mmol/L Coll: NR Timing: Unspecified ITT: No Grp1: 24 events Grp2: 8 events				GI events; Nausea and vomiting Coll: Passive Timing: Unspecified ITT: No Grp1: (26, 51) Grp2: (12, 38)	Pancreatitis Coll: Passive Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (<1)
Garber, 2009[65] RCT	Grp1: Glimepiride Varied, prespecified dose Start: 2 mg, Max: 8 mg D: 2 wks Grp2: Liraglutide Varied, prespecified dose Start: 0.6 mg, Max 1.2 mg D: 2 wks	Def: Not requiring assistance, PG < 3.1 mmol/L Coll: NR Timing: Unspecified ITT: No Grp1: 24 events Grp2: 12 events				Def: Total GI events; Nausea and vomiting Coll: Passive Timing: Unspecified ITT: No Grp1: (26, 49) Grp2: (12, 39)	Def: Pancreatitis Coll: Passive Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (<1)
Garber, 2011[66] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.2 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic but not confirmed by measurement Grp1: 10 (4.1) p Grp2: 13 (5.2) p					
Garber, 2011[66]	Grp1:Glimepiride + placebo	Def: symptomatic					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.8 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	but not confirmed by measurement Grp1: 6 (3.7) p Grp2: 5 (3.1) p					
Garber, 2011[66] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.2 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic but not confirmed by measurement Grp1: 6 (3.7) p Grp2: 13 (5.2) p					
Garber, 2011[66] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.8 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic but not confirmed by measurement Grp1: 5 (3.1) p Grp2: 13 (5.2) p					
Genovese, 2013[68] RCT	Grp1:Metformin Titrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response) Grp2:Pioglitazone + placebo Titrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response) ITT:No Mode of AE collection: NR/unclear Followup (wks):16	Def: BG < 60mg/dl Grp1: 5 Persons p Grp2: 6 Persons p NS					
Goke, 2010[69] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883	Def: Unspecified AE Grp1: (8) NA p no					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	statistically significant difference between groups' Grp2: (4) 1 NA p					
Goke, 2010[69] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: (12.7) Persons p NR Grp2: (11.1) Persons p NR					
Goke, 2010[69] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):104	included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: (12.7) Persons p NR Grp2: (12.3) Persons p NR					
Goke, 2010[69] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: 1Person-years p NR Grp2: 0.47 1 Person-years p NR					
Goke, 2010[69] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day)	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):104	hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: 1Person-years p NR Grp2: 0.89 1 Person-years p NR					
Goke, 2010[69] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 27 p Grp2: 53 p					
Goldstein, 2003[70] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Varied Start: 30 mg, Max: 30 mg					Def: Diarrhea Grp1: (17.3) Grp2: (13.1)	
Goldstein, 2003[70] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg;					Def: Diarrhea Grp1: (17.3) Grp2: (13.1)	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 5 mg, Max: 20 mg						
Goldstein, 2007[71] RCT	Grp1: Metformin Varied, prespecified target Start: 500 mg, Max: 2000 mg Grp2: Sitagliptin Varied, prespecified target Start: 50 mg, Max: 100 mg	Grp1: 3 (2) Grp2: 1 (1)					
Goldstein, 2007[71] RCT	Grp1: Metformin Fixed Start: 500 mg or 1000 mg bid Grp2: Metformin + sitagliptin Fixed Start: 500 mg or 1000 mg bid; Start: 50 mg bid	Def: Mild or moderate Grp1: 3 (2) Grp2: 6 (3)					
Gomez-Perez, 2002[72] RCT	Grp1: Metformin Fixed Start: 2.5 g Grp2: Metformin + rosiglitazone Fixed Start: 2.5 g; Start: 2-4 mg bid					Def: Nausea + vomiting + diarrhea + flatulence and abdominal pain Grp1: (15.4) Grp2: (16.8)	
Gupta, 2013[75] RCT	Grp1:Glimepiride Titrated (Max: 4mg/day) Grp2:Sitagliptin Titrated (Max: 200mg/day) ITT: NR Mode of AE collection: NR/unclear Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0,					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		E16.1 or E16.2) Grp1: 29 p Grp2: 109 p					
Haak, 2012[76] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 27 p p					
Haak, 2012[76] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 29 p p					
Haak, 2012[76] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8,					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):24	251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 53 p p					
Haak, 2012[76] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 109 p p					
Haak, 2012[76] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 5 (2.8) NA p NR Grp2: 2 (1.1) NA p NR					
Haak, 2012[76] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes	Def: Unspecified AE Grp1: 3 (1.6) NA p NR Grp2: 2 (1.1) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):24						
Haak, 2012[76] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 4 (2.2) NA p NR Grp2: 2 (1.1) NA p NR					
Haak, 2012[76] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 5 (2.8) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[76] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 5 (2.8) NA p NR Grp2: 9 (4.9) NA p NR					
Haak, 2012[76] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 3 (1.6) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[76] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin	Def: Unspecified AE Grp1: 3 (1.6) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Grp2: 9 (4.9) NA p NR					
Haak, 2012[76] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 4 (2.2) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[76] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 4 (2.2) NA p NR Grp2: 9 (4.9) NA p NR					
Haak, 2012[76] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 2 (1.1) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[76] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 2 (1.1) NA p NR Grp2: 9 (4.9) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Haak, 2012[76] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: symptoms only Grp1: Person-years p NR Grp2: 0.18 Person-years p NR					
Haak, 2013[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: symptoms only Grp1: Person-years p NR Grp2: 0.18 Person-years p NR					
Haak, 2013[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: symptoms only Grp1: Person-years p NR Grp2: 0.16 Person-years p NR					
Haak, 2013[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: symptomatic or biochemica Grp1: 3 (1.5) p Grp2: 1 (0.5) p					
Haak, 2013[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg)	Def: symptomatic hypoglycemia - presence of typical adrenergic or neuroglycopenic					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):52	symptoms and signs, regardless of the data for self-monitoring of blood glucose Grp1: (3.51) p 0 Grp2: (6.84) 8 p NS					
Hamann, 2008[79] RCT	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Max: 2 g; Start: 4 mg, Max: 8 mg D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Max: 2 g; Start: 5 mg, Max: 15 mg D: 12 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 18 (6) Grp2: 90 (30)				Coll: Active Timing: Specified ITT: Yes Grp1: (13) Grp2: (18)	
Hanefeld, 2004[80] RCT	Grp1: Metformin + sulfonylurea Varied; Fixed Start: 850 mg, Max: 2550 mg; NR D: 12 wks Grp2: Pioglitazone + sulfonylurea Varied; Fixed Start: 15 mg (, Max: 45 mg; NR D: 12 wks	Def: Serious Grp1: 0 (0) Grp2: 0 (0)				Def: Diarrhea Grp1: (12.2) Grp2: (23.4)	
Hanefeld, 2007[81] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg	Coll: NR Timing: Unspecified ITT: Yes Grp1: 1 (0.5) Grp2: Serious: 2 (<1), Mild or moderate: 23 (11)				Def: Unspecified Coll: NR Timing: Unspecified ITT: Yes Grp1: 11	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						(5.5) Grp2: 7 (3.4)	
Hanefeld, 2007[81] RCT	Grp1: Rosiglitazone Fixed Start: 8 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Coll: NR Timing: Unspecified ITT: Yes Grp1: 3 (1.6) Grp2: Serious: 2 (<1), Mild or moderate: 23 (11)				Def: Unspecified Coll: NR Timing: Unspecified ITT: Yes Grp1: 5 (2.6) Grp2: 7 (3.4)	
Haring, 2014[82] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (10mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic hypoglycemia - presence of typical adrenergic or neuroglycopenic symptoms and signs, regardless of the data for self-monitoring of blood glucose Grp1: (3.51) p 0 Grp2: (19.49) 23 p 0					
Haring, 2014[82] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max	Def: symptomatic hypoglycemia - presence of typical adrenergic or neuroglycopenic symptoms and signs, regardless of the data for self-					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	tolerated dose or max dose according to local label)) Fixed (25mg) ITT:No Mode of AE collection:Active Followup (wks):24	monitoring of blood glucose Grp1: (6.84) p NS Grp2: (19.49) 23 p 0					
Haring, 2014[82] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (10mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Haring, 2014[82] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (25mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax:	Def: Severe hypoglycemia, required assistance					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	2000mg) Grp2:Dapagliflozin + placebo Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):24	of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Dapagliflozin + placebo Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):24	Grp2: 0 NA p NR					
Henry, 2012[83] RCT	Grp1:Dapagliflozin + placebo Fixed (5mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: requiring medical or non-medical assistance Grp1: 283.4Person-years p NR Grp2: 2 283.4 Person-years p NR					
Henry, 2012[83] RCT	Grp1:Dapagliflozin + placebo Fixed (5mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: requiring (nonmedical) assistance of others, requiring medical intervention, or exhibiting markedly depressed level of consciousness, loss of consciousness, or seizure were considered severe Grp1: (2.8) NA p NR Grp2: (1.4) NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Dapagliflozin + placebo Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: severe symptomatic hypogly Grp1: 1 Person-years p NR Grp2: 3 (1) 0.76 Person-years p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Dapagliflozin + placebo Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/l and prompt recovery after glucose or glucagon administration Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/l and prompt recovery after glucose or glucagon administration Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Henry, 2012[83] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000	Def: symptomatic episode requiring external assistance					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/l and prompt recovery after glucose or glucagon administration Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Henry, 2012[83] RCT	Grp1:Dapagliflozin + placebo Fixed (10 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: requiring third-party assistance to administer resuscitative action Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[83] RCT	Grp1:Dapagliflozin + placebo Fixed (10 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		lower than 3 mmol/L. Grp1: 0 p NR Grp2: 0 p NR					
Hermann, 1994[85] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg	Def: Serious Grp1: 8 (21) Grp2: 12 (35)				Def: Nausea + diarrhea + dyspepsia and digestive Grp1: (63) Grp2: (32)	
Hermann, 1994[85] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 3000 mg; Start: 1.75 mg, Max: 14 mg	Def: Mild or moderate Grp1: 8 (21) Grp2: 24 (33)					
Hermans, 2012[86] RCT	Grp1:Metformin Titrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination) Grp2:Metformin + saxagliptin Fixed (1500 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L. Grp1: 0 p NR Grp2: 0 p NR					
Hong, 2013[186] RCT	Grp1:Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g,	Def: loss of consciousness, seizure, or coma					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2:Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT:Yes Mode of AE collection:Active Followup (wks):144	that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L. Grp1: 0 p NR Grp2: 0 p NR					
Hong, 2013[186] RCT	Grp1:Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2:Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT:No Mode of AE collection:Active Followup (wks):144	Def: an event requiring assistance of another Grp1: 0 NA p NR Grp2: 0 NA p NR					
Hsiao, 2009[204] Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: ICD-9-CM diagnostic codes of			

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 578 (1.26); ref Grp2: 67 (3.33); HR: 1.30 (CI: 0.89 to 1.89)			
Hsiao, 2009[204] Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 578 (1.26); ref Grp2: 13 (2.66); HR: 1.54 (CI: 0.65 to 3.64)			
Hsiao, 2009[204] Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR			

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				Timing: Unspecified ITT: NA Grp1: 67 (3.33) Grp2: 13 (2.66)			
Hsiao, 2009[204] Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 67 (3.33); Grp2: 1872 (1.97)			
Hsiao, 2009[204] Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 13 (2.66) Grp2: 1872 (1.97)			
Jadzinsky, 2009[90]	Grp1: Metformin Varied	Coll: Active Timing: Unspecified				Def: Diarrhea	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Saxagliptin Fixed Mean: 10 mg	ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 0 (0) Mild/moderate: 5 (1)				Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 10 (3)	
Jadzinsky, 2009[90] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Metformin + saxagliptin Varied, prespecified dose Start: 500 mg, Max: 1000 mg; Start: 5 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 0 (0) Mild/moderate: 11 (3)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 22 (7)	
Jadzinsky, 2009[90] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Metformin + saxagliptin Varied, prespecified dose Start: 500 mg, Max: 1000 mg; Start: 10 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 2 (1) Mild/moderate: 16 (5)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 31 (10)	
Jain, 2006[91] RCT	Grp1: Pioglitazone Varied, glucose: FPG (69-141 mg/dl)	Def: Mild or moderate Coll: Active			Def: Ankle Coll:	Def: diarrhea Coll:	Def: stage IV colon ca

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 15 mg, Max: 45 mg, Median: 45 mg Grp2: Glyburide Varied, glucose: FPG: 69-141 mg/dl Start: 5 mg, Max: 15 mg, Median: 10 mg	Timing: Unspecified ITT: Yes Grp1: 11 (4.4) Grp2: 61 (24.3)			Active Timing: No ITT: Yes Grp1: (0) Grp2: (0.8)	active Timing: Unspecified ITT: Yes Grp1: (6) Grp2: (6.4)	Coll: active Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 2 (0.8)
Jones, 2003[192] RCT	Grp1: Metformin Fixed Max: 2.5 g Grp2: Metformin + rosiglitazone Fixed; Varied, prespecified target Max: 2.5 g; Max: 8 mg	Def: Symptomatic hypoglycemia Grp1: All: (0.4), Obese: (1.7) Grp2: All: (2.1), Obese: (1.9)					
Kadoglou, 2011[93] RCT	Grp1:Metformin Fixed (1700mg daily) Grp2:Metformin + rosiglitazone Fixed (500mg daily) Fixed (4mg daily) ITT:No Mode of AE collection: NR/unclear Followup (wks):24	Def: requiring external assistance due to severely impaired consciousness or behaviour, with capillary or plasma glucose levels <3.0 mmol/l and recovery after glucose or glucagon administration Grp1: 0 NA p NR Grp2: 0 NA p NR					
Kadowaki, 2013[94] RCT	Grp1:Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day)	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT:Yes Mode of AE collection:Active Followup (wks):12						
Kahn, 2006[95] RCT	Grp1: Metformin Varied, glucose: <140 mg Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: <140 mg Start: 4 mg, Max: 8 mg	Def: Self reported Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 168 (11.6), Severe: 1 (0.1) Grp2: All: 142 (9.8), Severe: 1 (0.1)		Def: Investigator reported Grp1: 19 (1.3) Grp2: 22 (1.5)		Def: Nausea, vomiting, diarrhea, abdominal discomfort Coll: NR Timing: Unspecified ITT: Yes Grp1: (38.3) Grp2: (23)	
Kahn, 2006[95] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Def: Self reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 168 (11.6), Severe: 1 (0.1) Grp2: All: 557 (38.7), Severe: 8 (0.6)		Def: Investigator reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 19 (1.3), Serious: 12 (0.8) Grp2: All: 9		Def: Nausea, vomiting, diarrhea, abdominal discomfort Coll: NR Timing: Unspecified ITT: Yes Grp1: (38.3)	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				(0.6), Serious: 3 (0.2)		Grp2: (21.9)	
Kahn, 2006[95] RCT	Grp1: Rosiglitazone Varied, glucose: <140 mg/dl Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dl Start: 2.5 mg, Max: 15 mg	Def: Self reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: Serious events: 1 (0.1), Mild or moderate events: 142 (9.8) Grp2: Serious events: 8 (0.6), Mild or moderate events: 557 (38.7)		Def: Investigator reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 22 (1.5), Serious: 12 (0.8) Grp2: All: 9 (0.6), Serious: 3 (0.2), p: ≤ 0.05		Def: Nausea, vomiting, diarrhea, abdominal discomfort Grp1: (23) Grp2: (21.9)	
Kahn, 2008[216] RCT	Grp1: Metformin Varied, glucose: < 140 Start dose: 500g, Max: 2g Grp2: Rosiglitazone Varied, glucose: < 140 Start dose: 4mg, Max: 8mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.2/ 100 patient-years Grp2: 1.86/ 100 patient-years HR: 1.57		

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
					(CI: 1.13 - 2.17), p: 0.0073		
Kahn, 2008[216] RCT	Grp1: Metformin Varied, glucose: < 140 mg/dL Start dose: 500 mg, Max: 2 g Grp2: Glyburide Varied, glucose: < 140 mg/dL Start dose: 2.5 mg, Max: 15 mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.2/100 patient-years Grp2: 1.15/100 patient-years		
Kaku, 2009[96] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 750 mg Grp2: Metformin + pioglitazone Varied Start: 500 mg, Max: 750 mg; Start: 15 mg, Max: 30 mg D: NR; 16 wks	Def: Mild or moderate Grp1: 0 (0) Grp2: 1 (1)				Def: abdominal pain and constipation Grp1: (2.3) Grp2: (2.4)	
Kaku, 2011[97] RCT	Grp1:Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2:Liraglutide Titrated (Max: 0.9 mg/d) ITT:No Mode of AE collection:Active Followup (wks):52	Def: those needing assistance of another individual or resulting in sei zure or loss of consciousness Grp1: 15 (3) p NR Grp2: 2 p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kaku, 2011[97] RCT	Grp1:Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2:Liraglutide Titrated (Max: 0.9 mg/d) ITT:No Mode of AE collection:Active Followup (wks):52	Def: those needing assistance of another individual or resulting in sei zure or loss of consciousness Grp1: 15 (3) p NR Grp2: 3 p NR					
Kaku, 2011[97] RCT	Grp1:Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2:Liraglutide Titrated (Max: 0.9 mg/d) ITT:No Mode of AE collection:Active Followup (wks):52	Def: either any hypoglycemic episode with symptoms consistent with hypoglycemia that led to loss of consciousness or seizure, with prompt recovery in response to glucagon or glucose administration, or documented hypoglycemia [plasma glucose <3.0mmol Grp1: 0 NA p NR Grp2: 0 NA p NR					
Kawai, 2008[220] Non-randomized	Grp1: Metformin NR Start: 500-750mg, Max: 750mg Grp2: Pioglitazone Fixed NR	Def: Mild, moderate and severe Coll: NR Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)					
Kawai, 2008[220] Non-randomized	Grp1: Metformin NR Start: 500-750 mg, Max: 750	Def: Mild, moderate and severe Coll: NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg Grp2: Metformin + pioglitazone NR; Fixed Start: 500-750 mg, Max: 750 mg; NR	Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 0 (0)					
Kim, 2014[101] RCT	Grp1:Metformin Titrated (Max: 2500 mg/day) Grp2:Metformin + glimepiride Titrated (Max: 2000 mg/day) Fixed (1-8 mg/day) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: Any episode with symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose lower than 3.0 mmol/L necessitating the assistance of another person because of sev Grp1: 1 NA p NR Grp2: 1 NA p NR					
Kvapil, 2006[103] RCT	Grp1: Metformin + glibenclamide Fixed; Varied Mean: 1660 mg; Start: 1.75 mg, Max: 10.5 mg, Mean: 6.58 mg Grp2: Metformin + aspart 70/30 Fixed; Varied, glucose: 5 - 8 mmol/L Mean: 1660 mg; Start: 0.2 U/kg bid, Mean: 0.30 U/kg bid	Coll: NR Timing: Unspecified ITT: Yes Grp1: Severe: 0, Mild or moderate: 9 (8) Grp2: Severe: 0, Mild or moderate: 13 (12)					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + sitagliptin	Def: de fi ned as a hypoglycemic episode in which the patient had a documented blood					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	glucose <3.0 mmol/L and lost con- sciousness or required the assistance of another person because of severe impair- ment in consciousness or behavior) Grp1: 0 Persons p Grp2: 0 Persons p					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: symptoms of blurry vision, confusion, coma, seizure requiring assistance of another person Grp1: NA p NR Grp2: 0 NA p NR					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 12 NA p NR Grp2: 1 NA p NR					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 0 (0) Persons p 0.319 Grp2: 1 Persons p					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: required third-party assistance Grp1: NA p NR NA p NR					
Lavalle-	Grp1:Metformin + sitagliptin	Def: required third-					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Gonzalez, 2013[104] RCT	Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	party assistance Grp1: NA p NR Grp2: 1 NA p NR					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: severe events (>/= 1 major event or recurring minor events) Grp1: 7 NA p NR Grp2: 0 NA p NR					
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active	Def: requiring medical assistance Grp1: 4 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):52						
Lavalle-Gonzalez, 2013[104] RCT	Grp1:Metformin + sitagliptin Fixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: symptomatic episodes requiring external assistance, with blood glucose level <63 mg/dL [<3.5 mmol/L] and prompt recovery [start and stop of event on same date] Grp1: NA p NR Grp2: 0 NA p NR					
Lee, 2013[209] Prospetive cohort	Grp1:Metformin + pioglitazone Not specified (Mean: 1000mg) Fixed (15mg) Grp2:Metformin + sitagliptin Not specified (Mean: 1000mg) Fixed (150mg) ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Lee, 2013[209] Prospetive cohort	Grp1:Metformin + pioglitazone Not specified (Mean: 1000mg) Fixed (15mg) Grp2:Albiglutide + su Not specified (Mean: 1000mg) Not specified (Max: 30-60mg for gliclazide, 2.5-4mg for glimeperide) ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 1 NA p NR Grp2: 0 NA p NR					
Lee, 2013[209] Prospetive	Grp1:Metformin + sitagliptin Not specified (Mean: 1000mg)	Def: number of events requiring the					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
cohort	Fixed (150mg) Grp2:Albiglutide + su Not specified (Mean: 1000mg) Not specified (Max: 30-60mg for gliclazide, 2.5-4mg for glimeperide) ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):	assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Leiter 2005[106] RCT	Grp1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks Grp2: Rosiglitazone Varied, glucose: <7.0 mmol/L Start: 4 mg, Max: 8 mg D: 8 wks			Grp1: 0 (0) Grp2: 3 (1)			
List, 2009[107] RCT	Grp1:Metformin Titrated (Max: 1500 mg/d) Grp2:Dapagliflozin Fixed (5mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
List, 2009[107] RCT	Grp1:Metformin Titrated (Max: 1500 mg/d) Grp2:Dapagliflozin Fixed (10 mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 1 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Madsbad, 2004[108] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.75 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[108] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.60 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 1 (3)					
Madsbad, 2004[108] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.45 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[108] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.225 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[108] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.045 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Maffioli, 2013[109]	Grp1:Metformin + pioglitazone Fixed (2550 mg)	Def: number of events requiring the					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed (30 mg) Grp2:Metformin + glibenclamide Fixed (2550 mg) Fixed (10 mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):24	assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 1 NA p NR Grp2: 0 NA p NR					
Malone, 2003[110] RCT	Grp1: Metformin + glibenclamide Varied, glucose: fasting and pre-meal <7mmol.L, 2-hour post-prandial <10mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks Grp2: Metformin + lispro 75/25 fasting and pre-meal <7mmol.L, 2-hour post-prandial <10mmol/L Max: 2550 mg; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks	Def: Symptomatic or BG <3.5mmol/l Timing: Unspecified ITT: NR Grp1: (1) Grp2: (1.3)					
Malone, 2004[194] RCT	Grp1: Metformin + glargine Fixed; Varied, glucose: 90 – 126 mg/dL Start: 1500 mg, Max: 2550 mg; Mean: 0.57 U/kg qd Grp2: Metformin + lispro 75/25 Varied, glucose: 90 – 126 mg/dL Start: 1500 mg, Max: 2550 mg; Mean: 0.62 U/kg bid	Def: Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 0 (0), Mild or moderate: 40 (40) Grp2: Severe: 0 (0), Mild or moderate: 57 (57)		Coll: Active Timing: Specified ITT: Yes Grp1: 0 (0) Grp2: 1 (1)			
Malone, 2005[205] RCT	Grp1: Metformin + lispro 75/25 Varied, pre-meal glucose 90-126 mg/dL 2-hr PPG 144-180 mg/dL Start: 1500 mg; Max: 2550 mg;	Def: Overall Coll: Active Timing: Specified ITT: NR Grp1: 0.61 episodes/					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mean: 2146 mg; Mean: 0.42 U/kg bid D: 4 wks; 16 wks Grp2: Metformin + glargine Varied, glucose 90-126 mg/dL Start: 1500 mg; Max: 2550 mg; Mean: 2146 mg; Mean: 0.36 U/kg qd D: 4 wks; 16 wks	patient/30 days Grp2: 0.44 episodes/ patient/30 days					
Marre, 2002[111] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 20 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 (0) Grp2: Serious: 1 (1.0), Mild or moderate: 7 (7)					
Marre, 2002[111] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 Grp2: Serious: 0, Mild or moderate: 11 (10.9)				Def: Not specified Grp1: (14.4) Grp2: (6.9)	
Marre, 2002[111] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 Grp2: Serious: 2 (1.9), Mild or moderate: 12 (11.4)					
Moon, 2014[112] RCT	Grp1:Metformin + glimepiride Fixed (Mean: 1426.5mgdose the same as met dose prior to study, discontinued if FBG was	Def: number of events requiring the assistance of another person to					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	controlled at target level with glimepiride<=0.25mg/day) Titrated (Mean: 4.3Max: 8mgstarting 1mg/day, increased to 2mg/day at second week, up to 8mg/day at week 3,5,7 with target FBG of 90-130mg/dl as per the investigator's discretion) Grp2:Metformin + insulin glargine Fixed (Mean: 1365.1mgdose the same as met dose prior to study) Titrated (Mean: 22.8 unitsstarting at 0.2U/kg of body weight, titrated every 3 days by 2IU with target FBG of 90-130mg/dl as per the investigator's discretion; discontinued if FBG was controlled at target level with glargine<=8IU) ITT:No Mode of AE collection:Active Followup (wks):48	actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Moon, 2014[112] RCT	Grp1:Metformin + glimepiride Fixed (Mean: 1426.5mgdose the same as met dose prior to study, discontinued if FBG was controlled at target level with glimepiride<=0.25mg/day) Titrated (Mean: 4.3Max: 8mgstarting 1mg/day, increased to 2mg/day at second week, up to 8mg/day at week 3,5,7 with target FBG of 90-130mg/dl as per the investigator's discretion)	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + insulin glargine Fixed (Mean: 1365.1mgdose the same as met dose prior to study) Titrated (Mean: 22.8 unitsstarting at 0.2U/kg of body weight, titrated every 3 days by 2IU with target FBG of 90-130mg/dl as per the investigator's discretion; discontinued if FBG was controlled at target level with glargine<=8IU) ITT:No Mode of AE collection:Active Followup (wks):48						
Nauck, 2007[116] RCT	Grp1: Metformin + glipizide Varied; Varied, glucose: <6.1 mmol/l NR; Start: 5 mg, Max: 20 mg D: NR, 18 wks Grp2: Metformin + sitagliptin Varied; Fixed NR	Def: Severe Coll: Active Timing: Specified ITT: Yes Grp1: 7 (1) Grp2: 1 (<1)				Def: Diarrhea, abdominal pains, nausea, vomiting Coll: Active Timing: Specified ITT: Yes Grp1: 69 (12) Grp2: 70 (12)	
Nauck, 2009[117] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin	Def: required assistance of another person to actively administer carbohydrate,					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Nauck, 2009[117] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Nauck, 2009[117] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: requring assistance Grp1: 0 p Grp2: 0 p					
Nauck, 2009[117] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean:	Def: requring assistance Grp1: 0 p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):26						
Nauck, 2009[117] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol, and prompt recovery after glucose or glucagon administration). Grp1: 0 p Grp2: 0 p					
Nauck, 2009[117] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol â□„ l, and prompt recovery after					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		glucose or glucagon administration). Grp1: 0 p Grp2: 0 p					
Nauck, 2011[118] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol â□„ l, and prompt recovery after glucose or glucagon administration). Grp1: 0 p Grp2: 0 p					
Nauck, 2011[118] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, and prompt recovery after glucose or glucagon administration					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp1: 0 p Grp2: 0 p					
Nauck, 2011[118] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, and prompt recovery after glucose or glucagon administration Grp1: 0 p Grp2: 0 p					
Nauck, 2011[118] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, and prompt recovery after glucose or glucagon administration Grp1: 0 p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: hypoglycemic attack: severe hypoglycemia in which the subject required assistance and/or a plasma glucose level <56 mg/dl [3.1mmol/l] Grp1: 3 NA p 0.651 Grp2: 4 NA p					
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic attack: severe hypoglycemia in which the subject required assistance and/or a plasma glucose level <56 mg/dl [3.1mmol/l] - this is in group excluding those needing hyperglycemic rescue with insulin Grp1: 0 NA p 0.08 Grp2: 3 NA p					
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: hypoglicemia requiring 3rd part assistance Grp1: 0 p Grp2: 0 0 p					
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day)	Def: Unspecified AE Grp1: 0 (0) p Grp2: 0 (0) 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52						
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: requring assistance Grp1: Persons p Grp2: 1 Persons p					
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: requring assistance Grp1: Persons p Grp2: 1 Persons p					
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: requring assistance Grp1: Persons p Persons p					
Nauck, 2014[119] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: requring assistance Grp1: 1 Persons p Grp2: 1 Persons p					
Nauck, 2014[119]	Grp1:Metformin + placebo	Def: requring					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	assistance Grp1: 1 Persons p Persons p					
Nauck, 2014[119] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: A major hypoglycemic event was defined as blood glucose â‰¤60 mg/dL accompanied by neurological symptoms consistent with hypoglycemia or an episode requiring intervention with intravenous glucose. Grp1: NA p NR Grp2: 0 NA p NR					
Nauck, 2014[119] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: A major hypoglycemic event was defined as blood glucose â‰¤60 mg/dL accompanied by neurological symptoms consistent with hypoglycemia or an episode requiring intervention with intravenous glucose. Grp1: NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Nauck, 2014[119] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: A major hypoglycemic event was defined as blood glucose â‰¤60 mg/dL accompanied by neurological symptoms consistent with hypoglycemia or an episode requiring intervention with intravenous glucose. Grp1: NA p NR Grp2: 0 NA p NR					
Nauck, 2014[119] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: severe hypoglycemia: any episode requiring the assistance of another party accompanied by plasma glucose value < 2.0mmol/l or symptom resolved after oral or intravenous glucose or intravenous glucagon ingestion Grp1: 0 NA p Grp2: 0 NA p N/A					
Nauck, 2014[119] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes	Def: any episode that requires assistance associated with a documented blood glucose < 60mg/dl Grp1: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):52	Grp2: 0 NA p NR					
Nauck, 2014[119] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: any episode that requires assistance associated with a documented blood glucose < 60mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pantalone, 2009[203] Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.16 (CI: 0.78 to 1.73)			
Pantalone, 2009[203] Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.38 (CI: 1.00 to 1.90)			
Pantalone, 2009[203] Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR:			

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				0.76 (CI: 0.64 to 0.91) Grp2: ref			
Pantalone, 2009[203] Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.19 (CI: 0.74to 1.91)			
Pantalone, 2009[203] Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 0.88 (CI: 0.60 to 1.31) Grp2: ref			
Pantalone, 2009[203] Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 1.05 (95% CI 0.77 to 1.43) Grp2: ref			
Pavo, 2003[121] RCT	Grp1: Metformin Varied, glucose: < 126 mg/dl Start: 850 mg, Max: 2550 mg,					Def: Diarrhea Grp1: (16)	Def: Cholecystitis

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mean: 2292 mg D: 8 wks Grp2: Pioglitazone Varied, glucose: < 126 mg/dl Start: 35 mg, Max: 45 mg, Mean: 41.5 mg D: 8 wks					Grp2: (3)	Coll: Active Timing: Unspecified ITT: NR Grp1: 0 (0) Grp2: 1 (1)
Perez, 2009[123] RCT	Grp1: Metformin Fixed Mean: 850 mg Grp2: Pioglitazone Fixed				Def: Wrist fractures Coll: Active Timing: Specified ITT: NR Grp1: 1 (<1) Grp2: 0 (0)	Def: Diarrhea Coll: Active Timing: Specified ITT: NR Grp1: (15.3) Grp2: (2.6)	
Perez, 2009[123] RCT	Grp1: Metformin Fixed Mean: 850 mg Grp2: Metformin + pioglitazone Fixed				Def: Wrist fractures Coll: Active Timing: Specified ITT: NR Grp1: 1 (<1) Grp2: 1 (<1)	Def: Diarrhea Coll: Active Timing: Specified ITT: NR Grp1: (15.3) Grp2: (9)	
Pfutzner, 2011[126] RCT	Grp1:Metformin + pioglitazone Fixed (1700 mg/d) Fixed (30 mg/d)	Def: discontinued study due to hypoglycemia					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + glimepiride Fixed (1700 mg/d) Fixed (2mg/d) ITT:No Mode of AE collection: NR/unclear Followup (wks):24	Grp1: 7 (1.7) 408Persons p NR Grp2: 0 (0) 406 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Saxagliptin + placebo Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required external assistance because of severely impaired consciousness or behavior, with capillary or plasma glucose levels <3.0 mmol/L and recovery after glucose or glucagon administration Grp1: 3 (0.7) 408Persons p NR Grp2: 0 (0) 406 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Saxagliptin + placebo Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: Persons p NR Grp2: 0 315 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg)	Def: required the assistance of another person to actively administer therapy					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):76	Grp1: 0 177Persons p NR Grp2: 0 315 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: Persons p NR Grp2: 0 302 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: Persons p NR Grp2: 0 304 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 177Persons p NR Grp2: 0 302 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes	Def: required the assistance of another person to actively administer therapy Grp1: 0 177Persons					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):76	p NR Grp2: 0 304 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons p NR Grp2: 0 302 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons p NR Grp2: 0 304 Persons p NR					
Pfutzner, 2011[127] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons p NR Grp2: 0 302 Persons p NR					
Pratley, 2010[128] RCT	Grp1: Metformin + sitagliptin Varied, HbA1c : 7.5% - 10% NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HbA1c: 7.5% - 10% NS; Start: 0.6 mg Max: 1.2 mg					Def: GI events Coll: NR Timing: Unspecified ITT: No	Def: Neoplasm Coll: NR Timing: Unspecified ITT: No

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Grp1: 4 (2) Grp2: 3 (1)	Grp1: 1 (<1) Grp2: 0 (0) Def: Pancreatitis Grp1: 0 (0) Grp2: 0 (0)
Pratley, 2010[128] RCT	Grp1: Metformin + sitagliptin Varied, HbA1c : 7.5% - 10% NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HbA1c: 7.5% - 10% NS; Start: 0.6 mg Max: 1.8 mg					Def: GI events Coll: NR Timing: Unspecified ITT: No Grp1: 4 (2) Grp2: 3 (1)	Def: Neoplasm Coll: NR Timing: Unspecified ITT: No Grp1: 1 (<1) Grp2: 1 (<1) Def: Pancreatitis Grp1: 0 (0) Grp2: 0 (0)
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):26	p NR Grp2: 0 304 Persons p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):26						
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg)	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: requiring assistance or seizure or LOC Grp1: 0 p Grp2: 0 p					
Pratley,	Grp1:Metformin	Def: requiring					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2014[129] RCT	Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	assistance or seizure or LOC Grp1: 0 p Grp2: 0 p					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: required medical or non-medical assistance or exhibited marked severity (markedly depressed level of consciousness, loss of consciousness, or seizure) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: event requiring assistance Grp1: NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: event requiring assistance Grp1: NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg)	Def: any episode requiring assistance from another person					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[129] RCT	Grp1:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Qiu, 2014[130] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Qiu, 2014[130] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Qiu, 2014[130] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18						
Qiu, 2014[130] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18	Def: assistance of another person was required to actively administer carbohydrate, glucagon or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Raskin, 2007[132] RCT	Grp1: Metformin + glargine Fixed; Varied, premeal glucose: 4.4 - 6.1mmol/L NR; Start: 12 U/kg QD, Mean: 0.57 IU/kg QD Grp2: Metformin + aspart 70/30 Fixed; Varied, premeal glucose: 4.4 - 6.1mmol/L NR; Start: 12 IU/kg BID, Mean: 0.91 IU/kg	Def: mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 11 (14) Grp2: 33 (42)					
Raz, 2008[180] RCT	Grp1: Metformin Fixed	Def: Mild or moderate			Def: Limb fracture	Def: abdominal	Def: Neoplasm

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: ≥1500 mg Grp2: Metformin + sitagliptin Fixed Start: ≥ 1500 mg; Start: 100 mg	Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (1)			Coll: NR Timing: Unspecified ITT: No Grp1: 1 (1) Grp2: 0 (0)	pain, nausea, vomiting, or diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (7.4) Grp2: (10.4)	s Coll: NR Timing: Unspecified ITT: No Grp1: 3 (3) Grp2: 0 (0)
Reasner, 2011[133] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):44	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Reasner, 2011[133] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:Yes	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):44	of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Ridderstrale, 2014[134] RCT	Grp1:Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2:Metformin + empagliflozin Fixed ((ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Robbins, 2007[136] RCT	Grp1: Metformin + glargine Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg bid, Max: 1000 mg bid, Mean: 1636 mg; Mean: 0.6 U/kg QD Grp2: Metformin + insulin lispro 50/50 Fixed; Varied, glucose: <6.7 mmol/l	Def: Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 2 (1), Mild or moderate: 75 (47) Grp2: Severe: 3 (2), Mild or moderate: 79				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (5.7)	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 500 mg bid, Max: 1000 mg bid, Mean: 1641 mg; Mean: 0.7 U/kg tid	(50)				Grp2: (6.4)	
Roden, 2013[137] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Roden, 2013[137] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Roden, 2013[137] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Roden, 2013[137] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: plasma glucose concentration<=3.9 mmol/l, requiring assistance Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2006[138] RCT	Grp1: Metformin Varied, mean daily glucose ≤ 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Rosiglitazone Varied, mean daily glucose ≤ 6.1 mmol/l Start: 4 mg, Max: 8 mg, Mean: 7.7 mg D: 32 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 14 (9) Grp2: 13 (8)				Def: Diarrhea, nausea, vomiting, dyspepsia Coll: Active Timing: Specified ITT: Yes Grp1: (51) Grp2: (35)	
Rosenstock,	Grp1: Metformin	Def: Self reported				Def:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2006[138] RCT	Varied, mean daily glucose ≤6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Metformin + rosiglitazone Varied, mean daily glucose ≤6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1799 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2 mg D: 32 wks	mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 14 (9) Grp2: 19 (12)				Diarrhea, nausea, vomiting Dyspepsia Coll: Active Timing: Specified ITT: Yes Grp1: (51) Grp2: (47)	
Rosenstock, 2010[139] RCT	Grp1:Pioglitazone + placebo Fixed (30mg qd) Grp2:Alogliptin + placebo Fixed (25mg qd) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: hypoglycemia requiring help from a third party to actively administer therapy Grp1: 0 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: hypoglycemia requiring help from a third party to actively administer therapy Grp1: 0 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock,	Grp1:Metformin + placebo	Def: required					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2012[140] RCT	Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 2 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 1 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp1: NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 2 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 2 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day)	Def: required assistance or exhibited marked severity (i.e., depressed level of					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	consciousness, loss of consciousness or seizure) Grp1: 1 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 1 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[140]	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day)	Def: required third-party assistance					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Grp1: 2 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2013[142] RCT	Grp1:Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Grp2:Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: required third-party assistance Grp1: 2 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2013[142] RCT	Grp1:Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: required third-party assistance Grp1: 2 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2013[142] RCT	Grp1:Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose)	Def: requiring assistance Grp1: 0 Persons p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Grp2: 0 Persons p NR					
Rosenstock, 2013[142] RCT	Grp1:Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: patients with hypoglycemia and need someone to help or to the hospital for treatment Grp1: 0 NA p Grp2: 0 NA p					
Rosenstock, 2013[142] RCT	Grp1:Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Ross, 2012[143] RCT	Grp1:Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2:Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (4) NA p NR Grp2: (17.9) NA p NR					
Ross, 2012[143] RCT	Grp1:Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2:Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p NR					
Ross, 2012[143] RCT	Grp1:Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2:Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose)	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (5mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	American Diabetes Association guidelines Grp1: (4) NA p NR Grp2: (1.7) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (4) NA p NR Grp2: (3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000	Def: Asymptomatic hypoglycemia, no symptoms but					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg) Grp2:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):26	plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (17.9) NA p NR Grp2: (1.7) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: (1.3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (17.9) NA p NR Grp2: (3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1.3) NA p NR Grp2: (1.3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Exenatide + placebo	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1.7) NA p NR Grp2: (3) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: plasma glucose <=3.9mmol/l(70mg/dl) and/or symptoms of hypoglycemia Grp1: (7.8) NA p NR Grp2: (2.2) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: report of symptoms consistent with hypoglycaemia and glucose of lower than 3 mmol/L before treatment of the episode Grp1: 1 (1) NA p NR Grp2: 5 (3) 9 NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Sitagliptin + placebo	Def: report of symptoms consistent with hypoglycaemia and					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	glucose of lower than 3 mmol/L before treatment of the episode Grp1: 1 (1) NA p NR Grp2: 2 (1) 2 NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: report of symptoms consistent with hypoglycaemia and glucose of lower than 3 mmol/L before treatment of the episode Grp1: 5 (3) NA p NR Grp2: 2 (1) 2 NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: symptomatic episode with capillary or plasma glucose levels <3.5 mmol/l, irrespective of the need for external assistance; or an asymptomatic episode with capillary or plasma glucose levels <3.5 mmol/l that does not qualify as a major episode Grp1: 4 (4.4) NA p NR Grp2: 4 (4.4) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		NR					
Russell-Jones, 2012[144] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: blood glucose <3.0 mmol/l Grp1: (19) NA p NR Grp2: (28) NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: symptoms of hypoglycemia that were treated by the patient or resolved on their own, with documented plasma glucose <3.0mmol/l Grp1: 0 NA p NR Grp2: 1 NA p NR					
Russell-Jones, 2012[144] RCT	Grp1:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: any time a patient felt that they had a sign or symptom, associated with concurrent blood glucose lower than 3Â·0 mmol/L, that was either selftreated by the patient or resolved independently Grp1: (2.5) Persons p <0.0001 Grp2: (18.8) Persons p					
Russell-Jones, 2012[144]	Grp1:Sitagliptin + placebo Fixed (100 mgimplies fixed daily	Def: Defined as any time a patient felt					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	dose and makes sense clinically for sita) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	that he or she had a sign or symptom of hypoglycemia that was associated with concurrent blood glucose <3.0 mmol/L and that was either self-treated by the patient or resolved independently Grp1: 13 (8) Persons p <0.001 Grp2: 51 (32) Persons p					
Russell-Jones, 2012[144] RCT	Grp1:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: symptomatic + Plasma glucose <= 50mg/dl Grp1: 0 p Grp2: 2 p					
Schernthaner, 2004[145] RCT	Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg Grp2: Pioglitazone Varied Start: 35 mg, Max: 45 mg					Def: Diarrhea; Nausea Grp1: (11.1); (4.2) Grp2: (3.2); (2.3)	
Scott, 2007[147] RCT	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks	Def: Mild or moderate Grp1: 21 (17.1) Grp2: 0 (0)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2: Sitagliptin Fixed Start: 5 mg bid to 50 mg bid						
Scott, 2008[148] RCT	Grp1: Metformin Fixed Start: >1500 mg D: 10 wks Grp2: Metformin + rosiglitazone Fixed Start: >1500 mg; Start: 8 mg, Mean: 8 mg D: 10 wks	Def: Mild or moderate Coll: NR Timing: Unspecified Grp1: 2 (2) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (9) Grp2: (7)	
Scott, 2008{Scott, 2008 {Scott, 2008 #35198} RCT	Grp1: Metformin Fixed Start: ≥1500 mg Grp2: Metformin + sitagliptin Fixed Start: ≥1500 mg; Start: 100 mg	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 2 (2) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (9) Grp2: (1)	
Scott, 2008[148] RCT	Grp1: Metformin + rosiglitazone Fixed Start: > 1500 mg; Mean: 8 mg D: 10 wks Grp2: Metformin + sitagliptin Fixed Start: > 1500 mg; Mean: 100 mg	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 1 (1) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	D: 10 wks					Unspecified ITT: No Grp1: (7) Grp2: (1)	
Seck, 2010[149] RCT	Grp1: Metformin + sitagliptin Fixed NR Grp2: Metformin + glipizide Fixed; Varied NR; Start: 5 mg, Max: 20 mg; Mean: 9.2 mg	Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 18 (3) Mild/moderate: 31 (5.3) Grp2: Severe: 2 (<1) Mild/moderate: 199 (34.1)					
Seino, 2010[150] RCT	Grp1: Glibenclamide Varied, prespecified dose Start: 1.25 mg; Max: 2.5 mg D: 4 wks Grp2: Liraglutide Varied, prespecified dose Start: 0.3 mg; Max: 0.9 mg D: 2 wks	Coll: Passive Timing: Unspecified ITT: No Grp1: Symptoms: 45 (34.1); 228 events; IR: 3.927/year Severe: 0 (0) Grp2: Symptoms: 36 (13.4) 61 events; IR: 0.525/year Severe: 0 (0)				Def: Diarrhea; Constipation Coll: NR Timing: Unspecified ITT: No Grp1: (3.8; 3.8) Grp2: (6.3; 5.6)	Def: Pancreatitis Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 0 (0)
Shihara, 2011[152] RCT	Grp1:Pioglitazone Titrated (Mean: 23.24 mgMax: 30mg for women-45mg for menstarting 15mg/d) Grp2:SU Titrated (Mean: 23.24Max: 6mg/dstarting 0.5mg/d) ITT:No Mode of AE collection:Active Followup (wks):24	Def: self-treated plasma glucose < 3.1 mmol/l (56 mg/dl) Grp1: (26) 1Person-years p Grp2: (12) 0.21 1 Person-years p <0.0001					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Srivastava, 2012[153] RCT	Grp1:Metformin + glimepiride Fixed (kept at starting dose (dose on prior to study)) Titrated (Max: 4 mg/daystarted at 1-2 mg/day) Grp2:Metformin + sitagliptin Fixed (metformin dose prior to the study kept constant) Titrated (Max: 200 mg/daystarted at 50/100 mg/day) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):	Def: self-treated plasma glucose < 3.1 mmol/l (56 mg/dl) Grp1: (26) 1Person-years p Grp2: (10) 0.22 1 Person-years p <0.0001					
St John Sutton, 2002[154] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg Grp2: Glyburide Varied Start: NR, Max: 20 mg D: 8 wks	Def: Signs and symptoms Grp1: (1.9) Grp2: (7.1)		Def: NR Grp1: 1 (1.0) Grp2: 0 (0)			
Stewart, 2006[155] RCT	Grp1: Metformin Varied, prespecified Start: 500 mg, Max: 3000 mg, Mean: 2627.9 mg D: 20 wks Grp2: Metformin + rosiglitazone Varied, prespecified Start: 500 mg, Max: 2000 mg, Mean: 1812.2 mg; Start: 4 mg, Max: 8 mg, Mean: 6.8 mg D: 18 wks; 16 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 10 (4) Grp2: 17 (7)				Def: Diarrhea Grp1: (18) Grp2: (8)	
Tan, 2004[156] RCT	Grp1: Pioglitazone Varied Start: 30 mg, Max: 45 mg Grp2: Glibenclamide	Def: Symptoms or SMBG < 50 mg/dl Grp1: 4 (4) Grp2: 32 (29)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Varied Start: 1.75 mg, Max: 10.5 mg						
Taskinen, 2011[158] RCT	Grp1:Metformin + placebo Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Grp2:Metformin + linagliptin Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):24	Def: moderate: discomfort enough to cause some interference with usual activity Grp1: (12.5) NA p NR Grp2: (23.4) NA p NR					
Taskinen, 2011[158] RCT	Grp1:Metformin + placebo Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Grp2:Metformin + linagliptin Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):24	Def: Unspecified AE Grp1: 2 (1.4) NA p NR Grp2: 0 (0) NA p NR					
Tosi, 2003[161] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000; Start:	Grp1: Severe: 2 (10.5), Mild or moderate: 1 (5) Grp2: NR				Def: Diarrhea + constipation + discomfort and	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	2.5 mg, Max: 10mg					abdominal pain and anorexia Grp1: (10.5) Grp2: (2.6)	
Umpierrez, 2006[164] RCT	Grp1: Metformin + pioglitazone Varied, glucose: <120 mg/dl, HbA1c: <8.0% Start: 1.54 g, Max: 1.57 g; Start: 30 mg, Max: 45 mg Grp2: Metformin + glimepiride Varied, glucose: <120 mg/dL Start: 1.47 g, Max: 1.49 g; Start: 2 mg, Max: 8 mg D: NR, 6 wks	Def: mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 10 (9) Grp2: 32 (33)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (4.7) Grp2: (6)	
Umpierrez, 2014[165] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 5 (3.4) NA p NR Grp2: 0 (0) NA p NR					
Umpierrez, 2014[165] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon	Def: Unspecified AE Grp1: 2 (1.4) NA p NR Grp2: 5 (3.5) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):52						
Umpierrez, 2014[165] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 2 (1.4) NA p NR Grp2: 0 (0) NA p NR					
Umpierrez, 2014[165] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 5 (3.4) NA p NR Grp2: 5 (3.5) NA p NR					
Umpierrez, 2014[165] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up	Def: Unspecified AE Grp1: 5 (3.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Grp2: 0 (0) NA p NR					
Umpierrez, 2014[165] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 5 (3.5) NA p NR					
van der Meer, 2009[166] RCT	Grp1: Metformin + glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks Grp2: Pioglitazone + glimepiride Fixed, Varied Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR			Grp1: 0 (0) Grp2: 0 (0)			
Weir, 2011[213] Retrospective cohort	Grp1:Metformin Not specified Grp2:Glyburide Not specified	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	NR					
Weir, 2011[213] Retrospective cohort	Grp1:Metformin Not specified Grp2:Glyburide Not specified ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: minor - self treated hypoglycemia Grp1: Person-years p Grp2: 0.19 Person-years p					
Weir, 2011[213] Retrospective cohort	Grp1:Metformin Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: symptoms-only hypoglycemia Grp1: Person-years p NR Grp2: 0.51 Person-years p NR					
Weir, 2011[213] Retrospective cohort	Grp1:Metformin Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: symptomatic hypoglycemia: symptoms consistent with hypoglycemia and resolved shortly after oral glucose ingestion Grp1: 19 NA p Grp2: 10 NA p 0.01					
Weir, 2011[213] Retrospective cohort	Grp1:Glyburide Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: symptomatic and blood glucose < 60mg/dl Grp1: 1 NA p NR Grp2: 0 NA p NR					
Weir, 2011[213] Retrospective cohort	Grp1:Glyburide Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort)	Def: symptomatic and blood glucose < 60mg/dl Grp1: 1 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):	Grp2: 1 NA p NR					
Weissman, 2005[167] RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 12 mg	Def: Mild or moderate Grp1: 4 (1) Grp2: 4 (1)				Def: Withdrawn due to GI Grp1: (6.8) Grp2: (3.1)	
White, 2014[168] RCT	Grp1:Metformin + placebo Fixed (fixed dose metformin at >=1500 mg) Grp2:Metformin + saxagliptin Fixed (fixed dose but could be >=1500 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):	Def: symptomatic or asymptomatic and blood glucose < 50mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
White, 2014[168] RCT	Grp1:Metformin + placebo Fixed (fixed dose metformin at >=1500 mg) Grp2:Metformin + saxagliptin Fixed (fixed dose but could be >=1500 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):	Def: symptomatic or asymptomatic and blood glucose < 50mg/dl Grp1: 0 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2009[169] RCT	Grp1: Metformin Fixed Mean: 1000 mg or 2000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Def: Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 2 (1)				Def: Nausea; Diarrhea; Abdominal pain; Vomiting; Nausea/	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 7; 4; 0; 20 for 1000 mg and 10; 12; 6; 3; 31 for 2000 mg) Grp2: (1; 4; 5; 1; 20)	
Williams-Herman, 2009[169] RCT	Grp1: Metformin Fixed Mean: 1000 mg bid Grp2: Metformin + sitagliptin Fixed Mean: 500 mg bid; Mean: 50 mg bid	Def: Mild or moderate Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 4 (2)				Def: Nausea; vomiting; diarrhea; abdominal pain; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 0; 7; 4; 31) Grp2: (5; 2; 9; 3; 26)	
Williams-Herman,	Grp1: Metformin Fixed	Def: Mild or moderate				Def: Nausea;	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2009[169] RCT	Mean: 1000 mg bid Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg bid; Mean: 50 mg bid	Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 5 (3)				vomiting; diarrhea; abdominal pain; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 0; 7; 4; 31) Grp2: (NR; 4; 13; 4; 29)	
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: either symptomatic episode with capillary or plasma glucose levels < 3.5 mmol/L, irrespective of the need for external assistance or an asymptomatic episode with capillary or plasma glucose levels < 3.5 mmol/L that does not qualify as a major e Grp1: 173 (42.4) 408Persons p Grp2: 10 (2.5) 406 Persons p					
Williams-	Grp1:Metformin + placebo	Def: other -					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Herman, 2010[170] RCT	Titrated (Max: 1000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	symptoms suggestive of hypoglycemia but without confirmative measurement Grp1: 45 (11) 408Persons p NR Grp2: 8 (2) 406 Persons p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: Person-years p NR Grp2: (4.8) 0.1 1 Person-years p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: Person-years p NR Grp2: (5.3) 0.3 1 Person-years p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: Person-years p NR Grp2: (10.2) 0.4 1 Person-years p NR					
Williams-	Grp1:Metformin + placebo	Def: plasma glucose					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Herman, 2010[170] RCT	Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	<= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: (4.8) 1Person-years p NR Grp2: (5.3) 0.3 1 Person-years p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: (4.8) 1Person-years p NR Grp2: (10.2) 0.4 1 Person-years p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: mild or moderate nature' Grp1: p Grp2: 5 p					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
Williams-Herman,	Grp1:Metformin + placebo Titrated (Max: 1000 mg)	Def: hypoglycemic episodes -					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2010[170] RCT	Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Symptomatic, blood glucose<70mg/dl Grp1: 5 NA p NR Grp2: 0 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 0 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 0 NA p NR Grp2: 1 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):104						
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 5 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 5 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg)	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Grp1: 2 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 1 NA p NR Grp2: 0 NA p NR					
Williams-Herman, 2010[170] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 1 NA p NR Grp2: 0 NA p NR					
Wright, 2006[217] RCT	Grp1: Metformin Varied, glucose: <6 mmol/L Max: 2550 mg Grp2: Sulfonylurea Varied, glucose: <6 mmol/L Max: glipizide 40 mg, chlorpropramide 500 mg, glibenclamide 20 mg	Def: Mean annual % Coll: Active Timing: Specified ITT: NR Grp1: Substantive hypo: 0.3, (CI: 0.1-1.1); Any: 1.7, (CI: 1-3) Grp2: Substantive					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		hypo: 1.2, (CI: 0.4-3.4); Any: 7.9, (CI: 5.1-11.9)					
Yamanouchi, 2005[171] RCT	Grp1: Metformin Fixed Start: 750 mg Grp2: Pioglitazone Fixed Start: 30 mg women, 45 mg men	Def: NR Grp1: 0 (0) Grp2: 0 (0)					
Yamanouchi, 2005[171] RCT	Grp1: Metformin Fixed 750 mg Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 after 1 month in 8 cases. Rest on 1 mg	Grp1: Severe: 0 (0); Mild/moderate: 0 (0) Grp2: Severe: 0 (0); Mild/moderate: 1 (2.7)					
Yamanouchi, 2005[171] RCT	Grp1: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0	Grp1: Serious: 0 (0), Mild or moderate: 0 (0) Grp2: Serious: 0 (0), Mild or moderate: 1 (2.7)					
Yang, 2011[172] RCT	Grp1:Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2:Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 1 NA p NR Grp2: 2 NA p NR					
Yang, 2011[172]	Grp1:Metformin + placebo	Def: hypoglycemic					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2:Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):24	episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT:No Mode of AE collection:Active Followup (wks):16	Def: total incidence of pateints with either of the MedDRA terms'hypoglycaemia' Grp1: (2.3) NA p NR Grp2: (0.9) NA p NR					
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted	Def: plasma glucose concentration < 54mg/dl (3.0mmol/l) Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT:No Mode of AE collection:Active Followup (wks):16						
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT:No Mode of AE collection:Active Followup (wks):16	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 0 Persons p					
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould	Def: signs or symptoms associated with					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT: NR Mode of AE collection:Active Followup (wks):16	blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 0 Persons p					
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT: NR Mode of AE collection:Active Followup (wks):16	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 5 (2) Persons p					
Yang, 2011[173]	Grp1:Metformin + glimepiride +	Def: signs or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT: NR Mode of AE collection:Active Followup (wks):16	symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 0 Persons p					
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT: NR	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 5 (2) Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):16						
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT: NR Mode of AE collection:Active Followup (wks):16	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 5 (2) Persons p					
Yang, 2011[173] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d)	Def: plasma glucose concentration<=3.9 mmol/l, of mild intensity and not requiring assistance Grp1: 5 NA p NR Grp2: 3 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT: NR Mode of AE collection:Active Followup (wks):16						
Yang, 2012[174] RCT	Grp1:Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2:Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT:No Mode of AE collection:Active Followup (wks):	Def: NR but sppears to be self report Grp1: 1 (1.2) Persons p NR Grp2: 4 (5.4) Persons p NR					
Yang, 2012[174] RCT	Grp1:Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2:Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT: NR Mode of AE collection:Active Followup (wks):24	Def: symptoms not confirmed with BG Grp1: 4 p Grp2: 4 p					
Yoon, 2011[175] RCT	Grp1:Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2:Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) ITT:No Mode of AE collection:Active Followup (wks):48	Def: symptoms with confirmed with BG <= 2.8 Grp1: 0 p Grp2: 0 p					
Yoon, 2011[175] RCT	Grp1:Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2:Glimepiride	Def: symptoms and PG<3.1 mmol/l and self-treated Grp1: Person-years p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT:No Mode of AE collection:Active Followup (wks):48	Grp2: 0.09 Person-years p <0.0001					
Yoon, 2011[175] RCT	Grp1:Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) Grp2:Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT:No Mode of AE collection:Active Followup (wks):48	Def: symptoms and PG<3.1 mmol/l and self-treated Grp1: Person-years p Grp2: 0 Person-years p <0.0001					
Yuan, 2012[176] RCT	Grp1:Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2:Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT:Yes Mode of AE collection:Passive Followup (wks):26	Def: symptoms and PG<3.1 mmol/l and self-treated Grp1: Person-years p Grp2: 0.09 Person-years p <0.0001					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Yuan, 2012[176] RCT	Grp1:Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2:Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT:Yes Mode of AE collection:Passive Followup (wks):26	Def: Unspecified AE Grp1: Person-years p NR Grp2: 0.46 Person-years p NR					
Yuan, 2012[176] RCT	Grp1:Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2:Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed	Def: Unspecified AE Grp1: 1 p <0.05 Grp2: 4 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT:Yes Mode of AE collection:Passive Followup (wks):26						

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table 13. Quality of studies evaluating diabetes medications on safety

Author, year	Randomized study	Randomization scheme	Double-blind	Blinding method	Dropouts description
Ahren, 2014[2]	Yes	Not described	Yes	Yes	Yes
Alba, 2013[3]	Yes	Yes	Yes	Not described	Yes
Arechavaleta, 2011[5]	Yes	Yes	Yes	Not described	Yes
Arjona Ferreira, 2013[6]	Yes	Yes	Yes	Yes	Yes
Aschner, 2012[8]	Yes	Yes	No	Not described	Yes
Bailey, 2013[10]	Yes	Yes	Yes	Yes	Yes
Barnett, 2012[13]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2010[14]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2012[15]	Yes	Yes	Yes	Yes	Yes
Bolinder, 2012[17]	Yes	Yes	Yes	Yes	Yes
Borges, 2011[18]	Yes	Not described	Yes	Not described	No
Bunck, 2011[21]	Yes	Yes	NR	Not described	Yes
Cefalu, 2013[23]	Yes	Yes	Yes	Yes	Yes
Chawla, 2013[26]	Yes	Yes	NR	Not described	Yes
Davies, 2013[208]	Yes	Yes	No	Not described	Yes
DeFronzo, 2012[33]	Yes	Not described	Yes	Yes	No
Derosa, 2013[42]	Yes	Yes	Yes	Yes	Yes
Derosa, 2013[43]	Yes	Yes	Yes	Yes	Yes
Diamant, 2010[44]	Yes	Yes	No	Not described	Yes
Erem, 2014[47]	Yes	Not described	No	Not described	No
Esposito, 2011[48]	Yes	Yes	Yes	Yes	Yes
Ferrannini, 2013[52]	Yes	No	No	Not described	No
Ferrannini, 2013[185]	Yes	Yes	No	Yes	No
Fonseca, 2012[55]	Yes	Yes	Yes	Not described	Yes
Forst, 2010[56]	Yes	Yes	Yes	Yes	Yes
Forst, 2014[58]	Yes	Not described	No	Not described	Yes
Gallwitz, 2011[59]	Yes	Not described	No	Not described	No
Gallwitz, 2012[60]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[61]	Yes	Yes	NR	Not described	Yes
Garber, 2011[66]	Yes	Yes	No	Not described	Yes

Author, year	Randomized study	Randomization scheme	Double-blind	Blinding method	Dropouts description
Genovese, 2013[67]	Yes	Not described	Yes	Yes	Yes
Genovese, 2013[68]	Yes	Yes	Yes	Yes	Yes
Goke, 2010[69]	Yes	Yes	Yes	Yes	Yes
Gupta, 2013[75]	Yes	Yes	No	Not described	YES
Haak, 2012[76]	Yes	Not described	Yes	Not described	Yes
Haak, 2013[77]	Yes	Yes	Yes	Yes	Yes
Haring, 2014[82]	Yes	Yes	Yes	Yes	Yes
Henry, 2012[83]	Yes	Yes	Yes	Not described	No
Henry, 2012[83]	Yes	Yes	Yes	Not described	Yes
Hermans, 2012[86]	Yes	Not described	Yes	Not described	Yes
Hong, 2013[186]	Yes	Yes	Yes	Yes	Yes
Kadoglou, 2011[93]	Yes	Not described	No	Not described	Yes
Kadowaki, 2013[94]	Yes	Yes	Yes	Yes	Yes
Kaku, 2011[97]	Yes	Not described	No	Not described	
Kim, 2014[101]	Yes	Not described	No	Not described	Yes
Lavalle-Gonzalez, 2013[104]	Yes	Yes	Yes	Yes	Yes
List, 2009[107]	Yes	Yes	Yes	Yes	Yes
Maffioli, 2013[109]	Yes	Yes	Yes	Yes	Yes
Moon, 2014[112]	Yes	Not described	No	Not described	Yes
Nauck, 2009[117]	Yes	Yes	Yes	Not described	Yes
Nauck, 2011[118]	Yes	Yes	Yes	Yes	Yes
Nauck, 2014[119]	Yes	Not described	Yes	Not described	Yes
Pfutzner, 2011[126]	Yes	Not described	Yes	Not described	No
Pfutzner, 2011[127]	Yes	Yes	Yes	Not described	Yes
Pratley, 2014[129]	Yes	Not described	Yes	Not described	Yes
Qiu, 2014[130]	Yes	Yes	Yes	Not described	Yes
Reasner, 2011[133]	Yes	Not described	Yes	Not described	Yes
Ridderstrale, 2014[134]	Yes	Yes	Yes	Yes	Yes
Roden, 2013[137]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2010[139]	Yes	Not described	Yes	Yes	Yes
Rosenstock, 2012[140]	Yes	Not described	Yes	Not described	Yes

Author, year	Randomized study	Randomization scheme	Double-blind	Blinding method	Dropouts description
Rosenstock, 2013[142]	Yes	Yes	Yes	Yes	Yes
Ross, 2012[143]	Yes	Yes	Yes	Yes	Yes
Russell-Jones, 2012[144]	Yes	Yes	Yes	Yes	Yes
Seino, 2012[151]	Yes	Yes	Yes	Yes	Yes
Shihara, 2011[152]	Yes	Yes	No	Not described	Yes
Skrivanek, 2014[212]	Yes	Not described	Yes	Not described	Yes
Taskinen, 2011[158]	Yes	Not described	Yes	Not described	Yes
Umpierrez, 2014[165]	Yes	Yes	Yes	Yes	Yes
White, 2014[168]	Yes	Yes	Yes	Yes	Yes
Williams-Herman, 2010[170]	Yes	Yes	Yes	Yes	Yes
Yang, 2011[172]	Yes	Yes	Yes	Not described	Yes
Yang, 2011[173]	Yes	Not described	Yes	Yes	Yes
Yang, 2012[174]	Yes	Yes	Yes	Yes	Yes
Yoon, 2011[175]	Yes	Not described	Yes	Not described	Yes
Yuan, 2012[176]	Yes	Yes	No	Not described	Yes

Table 14. Results from randomized controlled trials reporting outcomes in a sub-population

Subgroup	Outcome				
	HbA1c	**Weight**	**Long-term clinical outcomes**	**Nephropathy**	**Other AEs**
Age	**Metformin vs. sitagliptin**[7] **Metformin vs. alogliptin**[129] **Pioglitazone vs. alogliptin**[139] **Pioglitazone vs sitagliptin**[122] **Glipizide vs sitagliptin**[6] No difference by age subgroups **Metformin vs. metformin + DPP-4**[2, 56, 60, 71, 94, 117, 129, 133, 168, 180] No difference by age subgroups **Metformin vs. metformin + SU**[2, 56, 60] No difference by age subgroups **Metformin + thiazolidinedione vs. metformin + DPP4 :**[33, 148] No difference by age subgroups	No evidence	**Metformin vs. glyburide vs. glimepiride**[189] Favors metformin and glimepiride over glyburide in patients below age 51, but only metformin vs. glyburide for older participants. **Metformin vs SU**[198] No difference by age subgroups	**Metformin vs SU vs rosiglitazone**[188] No difference by age subgroups	**Hypoglycemia:** **Metformin+SU vs metformin+DPP-4**[5, 69] No difference by age subgroups
Sex	**Metformin vs sitagliptin**[7] **Metformin vs alogliptin**[129] **Pioglitazone vs alogliptin**[139] **Pioglitazone vs sitagliptin**[122] **Glipizide vs sitagliptin**[6] No difference by sex **Metformin vs metformin +**	**Metformin vs metformin + dapaglifozin**[17] Increased weight loss for men with combined therapy	**Cardiovascular events:** **Metformin vs. glyburide vs. glimepiride**:[189] No differences by sex **Metformin vs SU**[198] No differences by sex **All-cause mortality:**		**Hypoglycemia:** **Metformin + SU vs metformin + DPP-4**[5] No differences by sex **Fractures:** **Metformin vs. glyburide vs.**

	DPP-4[2, 56, 71, 94, 117, 129, 133, 168, 180] Favors combined therapy in men and women **Metformin vs metformin + SU**[2, 56, 60] Favors combined therapy in men and women **Metformin + thiazolidinedione vs metformin + DPP-4**[33, 148] No difference by sex		**Metformin vs glipizide vs glibenclamide vs rosiglitazone**[202] Women on rosiglitazone were at higher risk of death		**rosiglitazone**[216] Higher risk of fractures for women on rosiglitazone; no excess risk for men
Race	**Metformin vs sitagliptin**[7] **Metformin vs alogliptin**[129] **Pioglitazone vs alogliptin**[139] **Glipizide vs sitagliptin**[6] No differences by race **Metformin vs metformin + DPP-4**[2, 56, 60, 71, 117, 129, 133, 168, 180] Favors combined therapy across race groups **Metformin vs metformin + SU**[2, 56, 60] Favors combined therapy across race groups **Metformin + thiazolidinedione vs metformin + DPP-4**[33, 148] No differences by race	No evidence	No evidence	**Metformin vs SU vs rosiglitazone**[188] No differences by race	No evidence
Body mass index	**Metformin vs SU**[163] Favors sulfonylurea among obese patients in long-term treatment (over 9 years)		No evidence	No evidence	No evidence

	Metformin vs sitagliptin[7] **Metformin vs alogliptin**[129]: **Pioglitazone vs alogliptin**[139] **Glipizide vs sitagliptin**[6] No differences by baseline BMI **Metformin vs metformin + DPP-4**[2, 56, 71, 117, 129, 133] Favors combined therapy across BMI groups **Metformin vs metformin + SU**[2, 56, 60] Favors combined therapy across BMI groups **Metformin + thiazolidinedione vs metformin + DPP-4**[33, 148] No differences by baseline BMI **Metformin + rosiglitazone vs metformin + sitagliptin**[148] No differences by baseline BMI-				

BMI = body mass index; CHF = congestive heart failure; HbA1c = hemoglobin A1c
The summary of results above is based on qualitative synthesis of the studies. Statistical significance for interactions is provided in the text if reported in the publication

Table 15. Number of comparisons for select outcomes where the strength of evidence has changed

Outcome	Change in strength of evidence	Total comparisons (N=29)	Metformin monotherapy comparisons	Other monotherapy comparisons	Metformin monotherapy versus metformin-based combination therapy	Metformin-based combination comparisons
HbA1c	Newly moderate	3	0	0	1	2
	Newly high	4	2	1	1	0
Weight	Newly moderate	9	0	3	1	5
	Newly high	3	1	0	1	1
All-cause mortality	Newly moderate	2	2	0	0	0
	Newly high	1	0	0	1	0
CVD mortality	Newly moderate	1	1	0	0	0
	Newly high	1	1	0	0	0
Hypoglycemia	Newly moderate	2	0	0	0	2
	Newly high	4	0	0	3	1
GI side effects	Newly moderate	4	0	1	0	3
	Newly high	2	1	0	0	1

CVD = cardiovascular; GI = gastrointestinal; HbA1c = hemoglobin A1c

Appendix E: Grey Literature

We searched the Food and Drug Administration (FDA) Web site for unpublished trials of the following drugs: albiglutide, alogliptin, canagliflozin, dapagliflozin, dulaglutide, empagliflozin, linagliptin, liraglutide, saxagliptin, pioglitazone and rosiglitazone. After reviewing the data from the FDA medical reviews and statistical reviews, we found 40 studies with drug comparisons of interest. Thirty-seven of these 40 trials were published in the peer-reviewed literature and were included in this report. The published data were consistent with the data described in the FDA reviews on select outcomes (HbA1c, hypoglycemia, and all-cause mortality). One trial was not published in the peer-reviewed literature until October 2014 and was therefore not included in this report.[221] Two trials were published only as meeting abstracts in 2014; therefore, they were not included in this report.[222]

Additionally, we found 38 unpublished studies from our search of the ClinicalTrials.gov registry. Fourteen of these studies were either ongoing or not yet open therefore no data was available. Twenty-four of these studies were completed and 10 of them had study results available on the website.

KQ1 Intermediate Outcomes

We found 10 unpublished reports from ClinicalTrials.gov that reported on HbA1c outcomes for our comparison of interest. These results were not entirely consistent with the results from the published studies included in the review.

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

Two short RCTs compared metformin with DPP-4 inhibitors. One RCT (NCT01289119) was an international multicenter phase-3 trial. The study had 98 participants in the metformin monotherapy arm (mean daily dose of 1484.2 mg) group, and 92 participants in the alogliptin monotherapy (25 mg daily) arm. The mean change from baseline in HbA1c at week 16 was -0.22 ± 0.065% (mean ± standard error) for metformin monotherapy group and was -0.99 ± 0.074% for alogliptin monotherapy group.

Another RCT (NCT01076088) was a multicenter phase 3 trial conducted in China. The study had 124 participants in the metformin monotherapy (1700 mg daily) group, and 120 participants in the sitagliptin monotherapy (100 mg daily) group. The mean change in HbA1c from baseline to week 24 was -1.6% (95% CI, -1.8% to -1.3%) for the metformin group and -0.99 (95% CI, -1.2% to -0.75%) for the sitagliptin monotherapy group.

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three RCTs lasting 4 to 6 months compared metformin with the combination of metformin plus a DPP-4 inhibitor. The results were consistent with the results from the published study, as all favored the combination arm. One unpublished 16-week trial (NCT01289119) reported statistically significant between-group difference in mean HbA1c change of -0.69% (95% CI, -0.87% to -0.51%; $P < 0.001$), favoring metformin plus 25mg of daily alogliptin (-0.91 ± 0.065%, n=99) over metformin monotherapy (-0.22 ± 0.065%, n=98). Another trial in China (NCT01076088) reported a greater decrease in mean HbA1c at week 24 in patients treated with 100 mg of sitagliptin daily as add-on therapy to metformin (-1.8%; 95% CI, -2.1% to -1.6%)

compared with those treated with metformin monotherapy (-1.6%, 95% CI, -1.8% to -1.3%), after adjustment for differences between groups. Another trial (NCT00960076) randomized 144 participants to the metformin (2000 mg daily) group and 138 to the metformin (1500 mg daily) plus saxagliptin (5 mg daily) group, and favored the combination arm with a mean between-group difference in HbA1c from baseline to week 18 of -0.52% (95% CI, -0.73% to -0.31%).

Thiazolidinediones Versus DPP-4 Inhibitors

One unpublished 30-week RCT (NCT01183013) had 134 participants receiving 45mg of pioglitazone daily and 130 participants receiving 5mg of linagliptin. The mean change from baseline in HbA1c was -0.87 ± 0.09% (mean ± standard error) in the pioglitazone group, which exceeded than that in the linagliptin group (-0.39 ± 0.09%).

Thiazolidinediones Versus GLP-1 Agonists

One unpublished trial (NCT01147627) had 136 subjects in the pioglitazone 30 mg arm and 142 in the exenatide arm (10 μg twice daily titrated up to 20 μg twice daily). The mean change from baseline in HbA1c at week 48 was greater in the exenatide group (mean ± standard deviation, -1.8 ± 1.3%) than in the pioglitazone group (-1.5 ± 1.3%). This was inconsistent with the one published study included in this report.[144]

Sulfonylureas Versus DPP-4 Inhibitors

Two unpublished RCTs compared glimepiride (1 to 6 mg) with DPP-4 inhibitors in older patients, and both studies favored glimepiride over DPP-4 inhibitors. One trial (NCT01006603) evaluated glimepiride against 5 mg of saxagliptin daily. The study had 360 subjects in both arms and the mean change from baseline in HbA1c at week 52 was greater in the glimepiride arm than in the saxagliptin arm (-0.64% versus -0.44%). Another 30-week trial (NCT01189890) had 239 subjects in the glimepiride arm and 241 in the sitagliptin group. The between-group difference in change in HbA1c of 0.19% (95% CI, 0.03% to 0.34%) favored glimepiride over sitagliptin.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One large, unpublished trial (NCT00856284) compared metformin plus 5 mg of glipizide to metformin plus 25 mg of alogliptin. The metformin plus alogliptin combination was not inferior to the metformin plus glipizide combination, with a mean between-group difference of -0.13%.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

One unpublished trial in Japan (NCT01368081) had 63 subjects treated with 500 mg of metformin as add-on therapy to background sulfonylurea, and 65 treated with empagliflozin at 25mg daily as add-on therapy to background metformin. Unlike the published study favoring the metformin plus SGLT-2 inhibitor combination group, the mean change from baseline in HbA1c was very similar for both the metformin plus sulfonylurea combination group (-0.97 ± 0.08%) and the metformin plus empagliflozin combination group (-0.98 ± 0.06%) after 52 weeks of treatment.

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

The combination of metformin and insulin detemir was evaluated against the combination of metformin and biphasic insulin aspart 30 in a 50-week RCT (NCT01068652). The study had 200 subjects in the metformin plus insulin detemir group and 203 in the metformin plus biphasic insulin aspart 30 group, and similar to previously published studies, reported no statistically-significant between-group difference in HbA1c at week 50 (0.11%; 95% CI, -0.12% to 0.34). The change in HbA1c from baseline was -1.2% in the metformin plus glipizide group, and -1.3% in the metformin plus alogliptin group.

KQ2 Long-term outcomes

We found nine unpublished reports from the ClinicalTrials.gov site that reported on long-term clinical outcomes for our comparisons of interest. These results were generally consistent with the results from the published studies included in the review.

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

One 24-week RCT (NCT01076088) evaluated sitagliptin against metformin, both as monotherapy. The study reported one case of cerebral infarction out of 120 participants in sitagliptin arm and no cases in the metformin group. One subarachnoid hemorrhage was reported among 124 patients treated with metformin while none was reported in sitagliptin arm.

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Two short-term RCTs compared the combination of metformin plus saxagliptin with metformin monotherapy. One (NCT00960076) reported the occurrence of cardiac disorders in two subjects in the metformin monotherapy group (one atherosclerotic disease and one myocardial infarction) (n=144), while none was reported for the metformin plus saxagliptin combination group (n=138). The other trial (NCT01076088) reported one subarachnoid hemorrhage in the metformin monotherapy arm (n=124) and none in the combination therapy arm (n=125). No cerebral infarction was reported for either the metformin monotherapy arm or the metformin plus saxagliptin combination therapy arm.

Thiazolidinediones Versus DPP-4 Inhibitors

One 54-week study (NCT01183013) reported the occurrence of a cardiac outcome in one subject treated with pioglitazone (atrial fibrillation) and three subjects treated with linagliptin (one coronary artery disease, one myocardial infarction, and one tachycardia). One nervous system disorder was reported in the pioglitazone arm (peripheral nerve palsy) and one in the linagliptin arm (radiculopathy). No other cardiac disorders (acute myocardial infarction, cardiopulmonary failure, supraventricular tachycardia, congestive cardiomyopathy) were reported.

Thiazolidinediones Versus GLP-1 Agonists

One study (NCT01147627) reported one case of a nervous system disorder (facial neuritis) in the pioglitazone group (1/136). Both arms had one case of cerebral infarction. Blurred vision was

reported in three participants treated with pioglitazone monotherapy and in participants treated with exenatide monotherapy.

Sulfonylureas Versus DPP-4 Inhibitors

Two unpublished trials tested glimepiride against DPP-4 inhibitors. One (NCT01006603) was a 52-week trial comparing glimepiride with saxagliptin, and the other (NCT01189890) was a 30-week trial comparing glimepiride to sitagliptin. Both trials had one death in the glimepiride arm while no patient died in the DPP-4 inhibitors arms. The incidences of cardiac disorders were low in both arms for both studies. The 52-week study reported three patients in glimepiride arm versus one in saxagliptin arm having heart failure, and three patients in each arm with myocardial infarction. The 30-week trial reported that 2 of 236 participants in the glimepiride arm had cardiac events (one angina unstable and one chronic cardiac failure) and 1 of 241 in the sitagliptin arm (atrial fibrillation). The 30-week study also reported on the occurrence of nervous system disorders in two patients treated with glimepiride (one nerve compression and one syncope), and none in those treated with sitagliptin.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One study (NCT00856284) had 869 subjects treated with the combination of metformin plus 5 mg of glipizide, and 378 treated with the combination of metformin plus 25 mg of alogliptin. One sudden death was reported in the glipizide combination arm, but none was reported in alogliptin combination arm. Cardiac disorders were rare. The study reported coronary artery disease in three subjects in the metformin with alogliptin arm versus two subjects in the metformin with glipizide arm; one versus five for acute myocardial infarction (a statistically significant difference), three versus two with atrial fibrillation, three versus one with heart failure, none versus one with myocardial ischemia, and one in each arm with a cardiomyopathy. Cerebrovascular accident was reported in one patient in the alogliptin combination arm, and in three patients in the glipizide combination arm. Ischemic stroke (including transient ischemic attack) was reported in three patients in the alogliptin combination arm, and none in the glipizde combination arm.

Combination of Metformin Plus a Basal-bolus Insulin Versus a Combination of Metformin Plus a Premixed Insulin

One study (NCT01068652) compared the effect of the combination of metformin plus basal-bolus insulin analogs (insulin detemir and aspart) with the combination of metformin plus 70/30 insulin aspart. Incidence of cardiac disorders were 2 among 200 in the metformin plus insulin detemir arm and 4 among 203 in the metformin plus biphasic insulin aspart 30 arm.

KQ3 Safety outcomes

We found 10 unpublished reports from the ClinicalTrials.gov site that reported on safety outcomes for our comparisons of interest.

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

One 24-week trial (NCT01076088) compared metformin monotherapy with 100 mg of sitagliptin monotherapy. The study reported a greater incidence of GI adverse events in the metformin arm (9/124 subjects reported diarrhea and 4/124 reported nausea) than in the sitagliptin arm (2/120 for diarrhea and 0/120 for nausea). Hypoglycemia was reported in four subjects in the sitagliptin arm, and two subjects in the metformin arm.

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Two short-term RCTs compared the combination of metformin plus saxagliptin with metformin monotherapy. One trial (NCT00960076) reported diarrhea in five out of 144 patients in the metformin monotherapy group (3.5%), which was comparable to the incidence among patients treated with saxagliptin as add-on therapy to metformin (8/138, 5.8%). The other trial (NCT01076088) reported a similar incidence of GI adverse events in both the metformin monotherapy group (nine people reported diarrhea and four reported nausea) and the metformin plus sitagliptin combination group (four for diarrhea and eight for nausea). Hypoglycemia events did not differ significantly among patients treated with combination therapy (7/125) and patients treated with metformin monotherapy (2/124).

Thiazolidinediones Versus DPP-4 Inhibitors

One trial (NCT01183013) reported no cases of diarrhea, vomiting, hypoglycemia, or acute pancreatitis in any of the 134 patients receiving pioglitazone at 45 mg daily or the 130 patients receiving linagliptin at 5 mg daily. Cancer was reported in two patients in the pioglitazone arm and no patients in the linagliptin arm.

Thiazolidinediones Versus GLP-1 Agonists

One RCT (NCT01147627) described one patient on exenatide who developed acute pancreatitis (n=142) compared with none in the pioglitazone group (0/136). The incidence of GI disorders in the exenatide group was much higher than in the pioglitazone group (37/142 versus 1/136 for nausea, 15/142 versus 1/136 for vomiting, 6/142 versus 4/136 for diarrhea).

Sulfonylureas Versus DPP-4 Inhibitors

Two unpublished trials evaluated glimepiride against DPP-4 inhibitors. A 52-week RCT (NCT01006603) reported a much higher proportion of patients having experienced at least one hypoglycemic event (confirmed or severe) in the glimepiride group (15.3%) compared with the saxagliptin group (1.1%). Incidence of cancer was higher in the saxagliptin group (10/359) than in the glimepiride group (3/359). The incidence of GI disorders did not differ significantly among patients receiving glimepiride monotherapy and those receiving saxagliptin monotherapy (19/359 verses 15/359 for diarrhea, and 8/359 versus 4/359 for nausea).

The other trial (NCT01189890) reported symptomatic hypoglycemia up to week 30 in 11 subjects in the glimepiride monotherapy group and two subjects in the sitagliptin monotherapy group. The between-group difference in hypoglycemia incidence was -3.9% (95% CI, -7.5% to -1.2%), favoring glimepiride over sitagliptin. Three cases of cancer were reported in patients treated with sitagliptin (colon cancer, malignant melanoma, and prostate cancer), and none in those treated with glimepiride.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One study (NCT00856284) had 869 subjects treated with the combination of metformin plus glipizide 5 mg, and 378 treated with the combination of metformin plus alogliptin at 25 mg daily. Hypoglycemia was rare and did not differ between arms. The metformin plus glipizide combination therapy arm reported had the only participant developing pancreatitis. The occurrence of GI adverse events was more frequently among patients receiving metformin plus alogliptin combination therapy (32 nausea, 1 severe vomiting, 60 diarrhea) than metformin plus glipizide combination therapy (20 nausea and 63 diarrhea), but this was not statistically significant. No severe diarrhea was reported in either group. Two cases of cancer were reported in the glipizide combination group (breast cancer and endometrial cancer), while three were reported in the alogliptin combination group (colon cancer and ovarian cancer).

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

One 52-week trial in Japan (NCT01368081) evaluated several safety outcomes for the combination of metformin plus sulfonylurea relative to the combination of metformin plus empagliflozin. Five out of 63 participants in the metformin plus sulfonylurea combination group experienced confirmed hypoglycemic events, which did not differ from the incidence in the metformin plus empagliflozin combination group (1 out of 65 participants). Five diarrhea cases were reported in metformin plus sulfonylurea arm, compared with four in the metformin plus empagliflozin arm. No drug-induced liver injury, no urinary tract infection, and no fractures were seen in either arm.

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

One study (NCT01068652) had 200 subjects in the metformin plus insulin detemir combination therapy group and 203 in the metformin plus biphasic insulin aspart 30 combination therapy group. One cancer case was reported in subjects treated with combination of metformin plus insulin detemir (breast cancer) but none in the comparison group. Diarrhea was reported in 13 subjects in the metformin plus insulin detemir combination group, and 15 in the metformin plus biphasic insulin aspart 30 combination group.

Articles Reporting More Than One Study

Fifteen studies reported on more than one study (see Table 1).[223-237] Since many of these studies pooled data from studies already included in our review, we did not abstract that data. For articles that pooled data from studies not included in our review, we abstracted and reported the results. The results from these studies are consistent with the findings from our review.

Table 1. Summary of studies reporting on more than one study

Author, year	Results of pooled studies if not duplicated or already in our report
Del Prato[230]	Individual studies were included in the report
Sjostrand, 2014[231]	Individual studies were included in the report
Davidson, 2014[232]	Individual studies were included in the report
Grimm, 2013[233]	Individual studies were included in the report
Rosenstock, 2013[234]	Individual studies were included in the report
Karyekar, 2011[235]	Individual studies were included in the report
Home, 2010[236]	Individual studies were included in the report
Jendle, 2009[237]	Individual studies were included in the report
Belcher, 2004[223]	Mean blood pressure was slightly reduced by all treatments, with pioglitazone treatment resulting in the largest falls (approximately 1.5 mmHg). Hospitalizations for cardiac or cerebrovascular events were similar with the different treatments. Overall mortality was 7 of 1857 for pioglitazone and 10 of 1856 for non-pioglitazone treatments, of which 3 and 6 were cardiac deaths, respectively. The incidence of congestive cardiac failure was similar with pioglitazone (12/1857) and non-pioglitazone (10/1856) treatments.
Lester, 2005[224]	Individual studies were included in the report
Belcher, 2005[225]	Individual studies were included in the report
Belcher, 2005[226]	Individual studies were included in the report
Charbonnel, 2005[227]	Individual studies were included in the report
Ceriello, 2005[228]	Individual studies were included in the report
Rendell, 2003[229]	Individual studies were included in the report

mmHg = millimeters of mercury; HR =hazard ratio; CI =confidence interval; mmol/L = millimoles per liter

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