Comparative Effectiveness and Safety of Diabetes Medications for Adults with Type 2 Diabetes

Appendixes

Appendix A: Technical Experts

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Appendix B: Detailed Electronic Database Search Strategies

MEDLINE Strategy

Terms	Returns
(“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 (“thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] or “metformin”[mh] or “acarbose”[mh] 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 biguanide*[tiab] or metformin[tiab] or “insulin secretagogues”[tiab] or meglitinide*[tiab] or repaglinide[tiab] or nateglinide[tiab] or “alpha-glucosidase inhibitors”[tiab] or “alpha-glucosidase inhibitor”[tiab] or acarbose[tiab] or “Dipeptidyl-Peptidase IV Inhibitors”[mh] or sitagliptin*[tiab] or dpp-4[tiab] or dpp-iv[tiab] or bromocriptine[mh] or bromocriptine[tiab] or colesevelam[tiab]) AND English[lang] NOT (animal[mh] NOT human [mh]) NOT (letter[pt] or comment[pt] or editorial[pt])	5814

EMBASE Strategy

('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 'alpha glucosidase inhibitor'/exp or 'acarbose'/exp or ‘sitagliptin’/exp or ‘colesevelam”/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 meglitinide*:ti,ab or repaglinide:ti,ab or nateglinide:ti,ab or ‘alpha-glucosidase inhibitors’:ti,ab or ‘alpha-glucosidase inhibitor’:ti,ab or acarbose:ti,ab or ‘Dipeptidyl-Peptidase IV Inhibitor’/exp or sitagliptin*:ti,ab or dpp-4:ti,ab or dpp-iv:ti,ab or 'bromocriptine mesilate'/exp or bromocriptine:ti,ab or colesevelam:ti,ab) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)	11772

The Cochrane Central Register of Controlled Trials (CENTRAL)

(diabetes near type-2) 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 meglitinide*:ti,ab,kw or repaglinide:ti,ab,kw or nateglinide:ti,ab,kw or “alpha-glucosidase inhibitors”:ti,ab,kw or “alpha-glucosidase inhibitor”:ti,ab,kw or acarbose:ti,ab,kw or “Dipeptidyl-Peptidase IV Inhibitors”:ti,ab,kw or sitagliptin*:ti,ab,kw or bromocriptine:ti,ab,kw or colesevelam:ti,ab,kw)	6057

Appendix C: Hand Searched Journals

All Journals Hand Searched
February 2009 – September 2009

American Journal of Medicine
Clinical Therapeutics
Diabetic Medicine
Diabetes and Metabolism
Diabetes
Diabetes Care
Diabetes, Obesity & Metabolism
Diabetes Research and Clinical Practice
Diabetologia
Hormone and Metabolic Research
Journal of Clinical Endocrinology and Metabolism
Lancet
Metabolism: Clinical and Experimental
Practical Diabetes International

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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? Click here to see drug matrix. Yes No

Submit Form and go to or Skip to Next

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

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Diabetes Medications
Abstract Review Form

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

- [ ] Exclude, but pull for handsearching (e.g. systematic review article that applies to key question)
- [ ] Does not apply to any of the key questions
- [ ] No original data (e.g. Review article, commentary or editorial)
- [ ] 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 list below)
- [ ] No subjects with type 2 diabetes mellitus, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes
- [ ] Only applies to KQ1 and is not a RCT - DO NOT USE
- [ ] Number of subjects in study < 40
- [ ] Study participants on drug < 30 days or 1 month
- [ ] No human data reported (e.g. evaluates outcomes in animals only)
- [ ] Not written in English
- [ ] No subjects > or = 18 years old
- [ ] Other reason for exclusion:

2. Unclear

- [ ] Unclear — pull for full article review

To see the drug matrix, click here.
To see the list of drug names, click here. To see the key questions, click here.

3. Article includes the following comparisons of medications **(check all that apply; drugs/combinations are listed in order of priority):**

Monotherapy - Green	Main intervention **(select one)**	Comparison **(select all that apply)**
	○ Metformin alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) Clear Response	☐ TZD alone ☐ Sulfonylurea alone ☐ Sitagliptin alone (DPP-4 inhibitor) ☐ Meglitinides alone ☐ Metformin + TZD (only vs. metformin alone) ☐ Metformin + SU (only vs. metformin alone) ☐ Metformin + sitagliptin (only vs. metformin alone) ☐ Metformin + meglitinides (only vs. metformin alone)

Combination - Green	Main intervention **(select one)**	Comparison **(select all that apply)**
	○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + any HG ○ Metformin + basal insulin ○ Metformin + premixed insulin Clear Response	☐ Metformin + TZD ☐ Metformin + SU ☐ Metformin + meglitinides ☐ Metformin + sitagliptin ☐ Metformin + exenatide ☐ Metformin + any HG ☐ Metformin + basal insulin ☐ Metformin + premixed insulin ☐ TZD + SU ☐ TZD + meglitinides

4. TALLY - Article includes the following comparisons of medications **(check all that apply; drugs/combinations are listed in order of priority):**

Monotherapy - Yellow	Main intervention **(select one)**	Comparison **(select all that apply)**
	○ Metformin alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Combination - Yellow	**Main intervention (select one)**	**Comparison (select all that apply)**
	○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + any HG ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides ○ SU + sitagliptin ○ SU + exenatide ○ Meglitinides + sitagliptin ○ Meglitinides + exenatide ○ Sitagliptin + exenatide Clear Response	☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide ☐ Meglitinides + basal insulin ☐ Meglitinides + premixed insulin ☐ Sitagliptin + exenatide ☐ Sitagliptin + basal insulin ☐ Sitagliptin + premixed insulin

11. Comments (limit: 250 characters)

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

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Diabetes Medication

Article Review Form

Key Question	**Study Design Criteria**
In adults ≥ age 18 with type 2 diabetes mellitus what is the comparative effectiveness of the treatment options in terms of HgBA1c, weight or lipids?	Exclude if not a randomized controlled trial
In adults ≥ age 18 with type 2 diabetes mellitus what is the comparative effectiveness of the treatment options in terms of the following clinical outcomes? • All cause mortality (study must report # deaths or how many were alive at end of study) • Cardiovascular morbidity (e.g. myocardial infarction and peripheral arterial disease) • Cerebrovascular disease (e.g. stroke) • Retinopathy • Nephropathy • Neuropathy	Exclude if this is not a randomized controlled trial, non-randomized controlled trial, cohort wi comparison group or a case-control study
In adults ≥ age 18 with type 2 diabetes mellitus what is the comparative safety of the treatment options in terms of the following adverse events and side effects? • Hypoglycemia • Liver failure • Congestive heart failure • Severe lactic acidosis • Cancer • Severe allergic reactions • Hip and non-hip fractures • Pancreatitis • Cholecystitis • Macular edema and decreased vision • GI side effects • All Other Serious Adverse events	Exclude if this is not a randomized controlled trial, non-randomized controlled trial, cohort wi comparison group or a case-control study

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

- ☐ Does not apply to any of the key questions
- ☐ Does not meet the study design criteria for any of the corresponding questions (see above)
- ☐ Study duration < 3-months or 90-days
- ☐ No original data (e.g. Review article, commentary or editorial)
- ☐ No comparison group (e.g. case series or case report or pre/post design; note: case-control studies should be included)
- ☐ Does not have a drug comparison of interest (see list of comparisons). (Exclude if additional medications are not specified, such as "any oral hypoglycemic" or "any of the following...", or if study lists possible medications withc

- ☐ No subjects with type 2 diabetes mellitus, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes (e.g. Exclude if it only evaluates people with impaired glucose tolerance, impaired fasting glucose, metabol
- ☐ Only includes pregnant women with diabetes
- ☐ Number of type 2 diabetes patients in study < 40
- ☐ No human data reported (e.g. evaluates outcomes in animals only)
- ☐ Not written in English
- ☐ No subjects > or = 18 years old
- ☐ Exclude, but pull for handsearching (e.g. systematic review article that applies to key question)
- ☐ Other reason for exclusion:

2. Exclude, but tally, studies that evaluate adverse outcomes and are 1-3-months long

- ☐ Evaluates adverse outcomes and is 1-3 months long

If not excluded in Q1, then please answer Q3.

3. Comparisons of Interest

A. Green Comparisons

Monotherapy - Green ☐ Check here if green monotherapy comparison and skip to end	Main intervention • Metformin alone • TZD alone • Sulfonylurea alone • Sitagliptin alone (DPP-4 inhibitor)	Comparison • TZD alone • Sulfonylurea alone • Sitagliptin alone (DPP-4 inhibitor) • Meglitinides alone • Metformin + TZD (only vs. metformin alone) • Metformin + SU (only vs. metformin alone) • Metformin + sitagliptin (only vs. metformin alone) • Metformin + meglitinides (only vs. metformin alone)
Combination - Green ☐ Check here if green combination comparison and skip to end	Main intervention • Metformin + TZD • Metformin + SU • Metformin + meglitinides • Metformin + sitagliptin • Metformin + exenatide • Metformin + basal insulin • Metformin + premixed insulin	Comparison • Metformin + TZD • Metformin + SU • Metformin + meglitinides • Metformin + sitagliptin • Metformin + exenatide • Metformin + basal insulin • Metformin + premixed insulin • TZD + SU • TZD + meglitinides

B. Yellow Comparisons

If article does NOT include one of the green comparisons, please check off which of the following other comparisons it addresses **(check all that apply)**

If article includes both a green and a yellow comparison, mark the green comparison in Q3A and skip to the end. The yellow comparison will be captured during data abstraction. Do NOT mark the yellow comparison here.

Monotherapy - Yellow	Main intervention **(select one)** ○ Metformin alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) Any insulin (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides ○ SU + sitagliptin ○ SU + exenatide ○ Meglitinides + sitagliptin ○ Meglitinides + exenatide ○ Sitagliptin + exenatide Clear Response	Comparison **(select all that apply)** ☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide ☐ Meglitinides + basal insulin ☐ Meglitinides + premixed insulin ☐ Sitagliptin + exenatide ☐ Sitagliptin + basal insulin ☐ Sitagliptin + premixed insulin

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

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

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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)**

- ○ Randomized controlled trial
- ○ Non-randomized trial
- ○ Prospective or retrospective cohort
- ○ Cross-sectional study
- ○ Case-control
- ○ Other (specify):

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 in which >10% of participants were excluded? **(check only one response)**

- ○ Yes
- ○ Fewer than 10% of participants were excluded during run-in
- ○ Run-in period but number of participants excluded was not reported
- ○ No run-in period
- ○ Not applicable

5. Was there a washout period? **(check only one response)**

- ○ Yes (specify how long in days):
- ○ No
- ○ Not reported
- ○ Not applicable/Not a crossover trial

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

- ○ Yes
- ○ No
- ○ Not reported

7. Study enrollment period (years of medical record collection for cohort inception) **Enter 4-digit year for start, end or both years**

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

8. What was the total intended followup duration or maximum possible followup?	9. Specify units: **(check only one response)**
○ Duration: ○ Not reported	○ Weeks ○ Months ○ Years ○ Not applicable

10. What was the planned interval for any contact with the study participants after study drug was titrated (e.g. monitoring)? **(check only one response)**

- ○ < 6 months
- ○ >= 6 months
- ○ Not reported
- ○ Not applicable

11. Which subgroup analyses were conducted? **(check all that apply)**

- ☐ Age
- ☐ Baseline HbA1c
- ☐ Comorbid conditions
- ☐ Gender
- ☐ Obesity
- ☐ Prior treatment
- ☐ Other (specify):
- ☐ No subgroup analyses were conducted

Study Population Questions

12. 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

13. What was the total number of patients screened?

- ○ N:
- ○ Not reported
- ○ Not applicable (for cohort studies, claims data, etc)

14. What was the total number at enrollment or cohort inception?

- ○ N:
- ○ Not reported

15. 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):
- ☐ 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)
- ☐ Poorly controlled on prior treatments (e.g. "failed initial treatment")
- ☐ Contraindication or history of intolerance to metformin
- ☐ Neuropathy
- ☐ Retinopathy
- ☐ HbA1c > (specify):
- ☐ HbA1c < (specify):
- ☐ BMI or weight (specify):
- ☐ 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

TALLY - Article includes the following comparisons of medications **(check all that apply; drugs/combinations are listed in order of priority)**:

Monotherapy - Yellow	Main intervention **(select one)** ○ Metformine alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Monotherapy - Yellow	Main intervention **(select one)** ○ Metformine alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)

Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + any HG ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides ○ SU + sitagliptin ○ SU + exenatide ○ Meglitinides + sitagliptin ○ Meglitinides + exenatide ○ Sitagliptin + exenatide Clear Response	Comparison **(select all that apply)** ☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide ☐ Meglitinides + basal insulin ☐ Meglitinides + premixed insulin ☐ Sitagliptin + exenatide ☐ Sitagliptin + basal insulin ☐ Sitagliptin + premixed insulin
Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + any HG ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides ○ SU + sitagliptin ○ SU + exenatide ○ Meglitinides + sitagliptin ○ Meglitinides + exenatide ○ Sitagliptin + exenatide Clear Response	Comparison **(select all that apply)** ☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide ☐ Meglitinides + basal insulin ☐ Meglitinides + premixed insulin ☐ Sitagliptin + exenatide ☐ Sitagliptin + basal insulin ☐ Sitagliptin + premixed insulin

24.
Comments **(limit 250 characters)**

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

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

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

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Oral Diabetes Medications Update
Intervention Form

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

1. Indicate the following: **(Mandatory question; please check one)**

○ Main intervention ○ Comparison A ○ Comparison B ○ Comparison C ○ Comparison D ○ Comparison E ○ Total ○ Other (specify): _____

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 or a TZD, and complete the second row for the additional drug. For metformin and TZD combinations, use the first row for metformin and the second row for TZD.

Intervention **(Please select one; interventions listed in order of priority)**	Dosing	Total daily dose after run-in **(include units; OK to calculate if not explicitly stated)**	Duration of dose titration
○ Metformin **Thiazolidinediones** ○ Rosiglitazone ○ Pioglitazone ○ Any in the TZD class **Sulfonylureas** ○ Glyburide ○ Glibenclamide ○ Glipizide ○ Glimepiride ○ Any in the SU class **DPP-IV Inhibitors** ○ Sitagliptin **Meglitinides** ○ Nateglinide ○ Repaglinide Clear Response	○ Fixed ○ Varied (specify target below) ○ Not specified Clear Response If varied, please indicate the target: ☐ Glucose _____ ☐ HgbA1c _____ ☐ Prespecified target dose ☐ Not specified	**Titration of drug** ☐ Total starting dose: _____ ☐ Maximum total dose _____ ☐ Unclear ☐ Not specified ☐ Fixed dose **(i.e. No titration)** **Other** ☐ **Mean total dose** _____ ☐ Median total dose _____	☐ Duration of dose titration (specify #:) _____ ☐ Unclear ☐ Not specified ☐ Not applicable Units ○ Days ○ Weeks ○ Months ○ Years ○ Other (specify): _____ Clear Response
Complete this row ONLY if another		Titration of d	Units

Complete this row ONLY if another drug is added on to metformin or a TZD. Additional drug (specify): ○ Rosiglitazone ○ Pioglitazone ○ Any in the TZD class **Sulfonylureas** ○ Glyburide ○ Glibenclamide ○ Glipizide ○ Glimepiride ○ Any in the SU class **DPP-IV Inhibitors** ○ Sitagliptin **Meglitinides** ○ Nateglinide ○ Repaglinide **GLP-1** ○ Exenatide **Basal insulin** ○ Insulin glargine ○ NPH ○ Insulin detemir **Premixed insulin** ○ NPH/regular 70/30 ○ Insulin aspart 70/30 ○ Insulin lispro 75/25 ○ No additional drug/monotherapy ○ Insulin lispro 50/50 Clear Response	○ Fixed ○ Varied (specify target below) ○ Not specified Clear Response If varied, please indicate the target: ☐ Glucose ☐ ☐ HgbA1c ☐ ☐ Prespecified target dose ☐ Not specified	**Titration of drug** ☐ Total starting dose: ☐ ☐ Maximum total dose ☐ ☐ Unclear ☐ Not specified Starting frequency of administration **(insulin only)** ○ QD ○ BID ○ TID ○ Other ☐ ○ Not specified Clear Response Frequency of administration for final dose **(insulin only)** ○ QD ○ BID ○ TID ○ Other ☐ ○ Not specified Clear Response ☐ Fixed dose **(i.e. No titration)** **Other** ☐ **Mean total dose** ☐ ☐ Median total dose ☐	☐ Duration of dose titration (specify #:) ☐ ☐ Unclear ☐ Not specified ☐ Not applicable Units ○ Days ○ Weeks ○ Months ○ Years ○ Other (specify): ☐ Clear Response

Please complete the baseline characteristics for this study group:

Total N at enrollment for this intervention group ☐

Age

☐ Mean ☐ ☐ Range ☐

Report age categories in addition to mean or range if provided

Age category ☐ specify ☐ ☐ n ☐ ☐ % ☐
Age category ☐ specify ☐ ☐ n ☐ ☐ % ☐
Age category ☐ specify ☐ ☐ n ☐ ☐ % ☐

Age category ☐ specify ☐ ☐ n ☐ ☐ % ☐
Age category ☐ specify ☐ ☐ n ☐ ☐ % ☐
Age category ☐ specify ☐ ☐ n ☐ ☐ % ☐

☐ Age not reported

Male

☐ n ☐ ☐ % ☐ ☐ Gender not reported

Race/Ethnicity

African American ☐ n ☐ ☐ % ☐
Asian or Asian American ☐ n ☐ ☐ % ☐
Caucasian ☐ n ☐ ☐ % ☐
Hispanic or Latino ☐ n ☐ ☐ % ☐
Other race/ethnicity ☐ specify: ☐ ☐ n ☐ ☐ % ☐
Other race/ethnicity ☐ specify: ☐ ☐ n ☐ ☐ % ☐
Other race/ethnicity ☐ specify: ☐ ☐ n ☐ ☐ % ☐
Other race/ethnicity ☐ specify: ☐ ☐ n ☐ ☐ % ☐
Other race/ethnicity ☐ specify: ☐ ☐ n ☐ ☐ % ☐
Other race/ethnicity ☐ specify: ☐ ☐ n ☐ ☐ % ☐

☐ Race/ethnicity not reported

BMI/Weight

☐ Mean weight (include units) ☐ ☐ Mean BMI ☐

Only report other measures if mean weight or BMI is not reported

Other measures ☐ specify measure: ☐ ☐ value: ☐
Other measures ☐ specify measure: ☐ ☐ value: ☐

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

☐ BMI/weight not reported

HgbA1c

☐ Mean HgbA1c

Only report other measures if mean HgbA1c is not reported

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

☐ HgbA1c not reported

Duration of diabetes

☐ Mean (years)

Only report other measures if mean duration of diabetes is not reported

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

Other measures ☐ specify measure: ☐ value:

☐ Duration of diabetes not reported

Number of withdrawals

Comments **(limit 250 characters)**

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

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

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Rethnam U, Yesupalan RS, Sinha A.

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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

Outcome	Units
☐ HgbA1c	☐ % ☐ Cut-point (only if mean or median not reported; specify):
☐ LDL	☐ mmol/L ☐ umol/L ☐ mg/dL
☐ HDL	☐ mmol/L ☐ umol/L ☐ mg/dL
☐ Triglycerides	☐ mmol/L ☐ umol/L ☐ mg/dL
☐ Weight	☐ kg ☐ lbs
☐ BMI (only if weight is not reported)	☐ kg/m2

Key Question 2

☐ All cause mortality

Cardiovascular Mortality

☐ Fatal myocardial infarction
☐ Other (e.g., sudden cardiac death) (specify):
☐ Composite outcome (list if specified):
☐ Unspecified

Cardiovascular Morbidity

☐ Non-fatal myocardial infarction (specify how defined):
☐ Other (e.g., acute coronary syndrome, arrhythmia, cardiac procedures, like percutaneous coronary intervention (PCI)) (congestive heart failure will be captured under Key Question 3) (specify):
☐ Composite outcome (list if specified):
☐ Unspecified

Cerebrovascular Mortality/Disease

☐ Fatal stroke
☐ Non-fatal stroke (specify how defined):
☐ Other (e.g., transient ischemic attack) (specify):

Incident diabetic retinopathy (macular edema will be captured under Key Question 3)

☐ Incident diabetic retinopathy (specify):
☐ Not specified

Incident diabetic nephropathy (e.g., changes in proteinuria or microalbuminuria, ESRD, dialysis outcomes, etc.)

☐ Incident diabetic nephropathy (specify):
☐ Not specified

Incident diabetic neuropathy

☐ Incident diabetic neuropathy (specify):
☐ Not specified

Key Question 3

Adverse event or side effect	
☐ Hypoglycemia - mild/minor (specify):	
☐ Hypoglycemia - moderate (specify):	
☐ Hypoglycemia - severe/major (specify):	
☐ Liver failure (specify):	
☐ Congestive heart failure (specify):	
☐ Severe lactic acidosis (specify):	
☐ Cancer (specify):	
☐ Severe allergic reaction (specify):	
☐ Hip fracture (specify):	
☐ Non-hip fracture (specify):	
☐ Pancreatitis (specify):	
☐ Cholecystitis (specify):	

- ☐ Macular edema (specify):
- ☐ Decreased vision (specify):
- ☐ Gastrointestinal side effects (specify):
- ☐ Other severe adverse event (specify):

If applies to Key Question 3 (adverse events and/or safety outcomes), please answer questions 21-23.

21. Was the mode of Adverse Event collection Active or 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

22. Did the study specify frequency and timing of adverse event collection?

☐ Yes
☐ No
☐ Not applicable

23. Was the analysis for this outcome "Intention-to-treat" (i.e., not per-protocol or "on treatment analysis")?

☐ Yes
☐ No
☐ Not reported

Please report results for outcome specified above

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

Table I. Incidence of the outcome by intervention group

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis (use number enrolled in each group)	Outcome measure	Denominator (specify):	p-value (Record exact p-value)	Indicate reference group
			☐ Days ☐ Weeks ☐ Months ☐ Years ☐ Persons ☐ Person-years ☐ Other (specify): ☐ Not applicable		
Main intervention		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison B		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Comparison D		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Table II. Measure 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**	**Measure of variability**	**95% Confidence Interval**	**p-value (Record exact p-value)**	**Indicate reference group**
Main intervention		☐ Relative risk (RR) ☐ Relative hazrad (HR) ☐ Odds ratio (OR) ☐ Risk difference ☐ Other (specify):	☐ SE ☐ SD ☐ Other (specify):	☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison B				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison D				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

What were the results adjusted for in the final model?

- ☐ Age
- ☐ Sex
- ☐ Race
- ☐ 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): ____
- ☐ Other (specify): ____
- ☐ Results are not adjusted
- ☐ RCT that did not adjust for any baseline difference

Continuous outcomes (Most of outcomes for Key Question 1)

Table III. Mean difference from other intervention group 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): ____	Measure of variability ☐ SE ☐ SD ☐ Other (specify): ____	☐ 95% Confidence interval ☐ IQR	p-value (Record exact p-value)	Indicate reference group
Main intervention	____	____	____	☐ Lower limit ____ ☐ Upper limit ____	____	☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify): ____
Comparison A	____	____	____	☐ Lower limit ____ ☐ Upper limit ____	____	☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify): ____
Comparison B	____	____	____	☐ Lower limit ____ ☐ Upper limit ____	____	☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify): ____
Comparison C	____	____	____	☐ Lower limit ____ ☐ Upper limit ____	____	☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify): ____
Comparison D	____	____	____	☐ Lower limit ____ ☐ Upper limit ____	____	☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify): ____
Comparison E	____	____	____	☐ Lower limit ____ ☐ Upper limit ____	____	☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify): ____

Table IV. Mean difference from baseline to final measures of outcome
(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):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence interval ☐ IQR	p-value (Record ex value)
Main intervention				☐ Lower limit ☐ Upper limit	
Comparison A				☐ Lower limit ☐ Upper limit	
Comparison B				☐ Lower limit ☐ Upper limit	
Comparison C				☐ Lower limit ☐ Upper limit	
Comparison D				☐ Lower limit ☐ Upper limit	
Comparison E				☐ Lower limit ☐ Upper limit	

Complete tables V and VI only if the point estimate AND measure of variability in tables III and IV are not reported.

Table V. Baseline measure 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):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence interval ☐ IQR	p-value (Record ex value)
Main intervention				☐ Lower limit ☐ Upper limit	
Comparison A				☐ Lower limit ☐ Upper limit	
Comparison B				☐ Lower limit ☐ Upper limit	
Comparison C				☐ Lower limit ☐ Upper limit	
Comparison D				☐ Lower limit ☐ Upper limit	
Comparison E				☐ Lower limit ☐ Upper limit	

Table VI. 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):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence interval ☐ IQR	p-value (Record exact p-value)	Indicate reference group
Main intervention				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):

Comparison A				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison B				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison C				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison D				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison E				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):

Table VII. Other measures

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Other measure	Other measure	p-value (Record exact p-value)	Indicate reference group
Main intervention					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison B					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Comparison D					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Comments **(limit 250 characters)**

Comments **(limit 250 characters)**

Comments **(limit 250 characters)**

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Rethnam U, Yesupalan RS, Sinha A.

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Diabetes Medications

Quality Form for Trials

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

- Yes
- No
- Not reported

2. If yes to Q1, was the randomization scheme described AND appropriate?

- Yes: Appropriate randomization is if each study participant is allowed to have the same chance of receiving study drug
- No: Randomization described and inappropriate (e.g. allocation using date of birth)
- No:not described

3. Was the study described as double blind?

- Yes
- No
- Not reported/Can't tell

4. If yes to Q3, was the method of double blinding described AND appropriate?

- Yes: appropriate double blinding is if neither the person doing the assessments nor the study participant could identify the intervention being assessed OR if the use of active placebos, identical palcebos or dummies is mentioned
- No: the study was described as double blind AND inappropriate (e.g. comparison of tablet vs. lifestyle)
- No: no description of double blinding available and unable to tell if appropriate or not

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

6. Please rate the overall quality of the study

- Good (low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
- Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
- Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Clear Response

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

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

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

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Rethnam U, Yesupalan RS, Sinha A.

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Diabetes Medications
Quality Form for Observational Trials

1. Did the study describe the setting or population from which the study sample was drawn?

- Yes, complete description including an appropriate sampling scheme (consecutive, random)
- Yes, but without description of sampling scheme or used a scheme that could bias results (convenience)
- No or insufficient to replicate

2. Were the inclusion and exclusion criteria for subjects described?

- Yes
- No

3. Is there description of key characteristics of the enrolled subjects that could affect outcomes?

- Yes with detailed description of covariates expected to affect outcomes (e.g. age, duration of diabetes, other therapies)
- Some description of covariates (e.g., age, sex)
- No

4. Is there sufficient detail about the treatment?

- Yes, describes the treatment type, dose, timing and duration of medications AND the results for all subjects who took medication
- No, Either omits relevant information on treatment and intensity (dose or duration) OR does not report the results for all subjects exposed to the medication
- No, does neither

5. Is there sufficient detail about one or more outcomes and are they objectively measured?

- Yes
- Some description of outcomes but poorly detailed
- No

6. Is the statistical analysis described and appropriate for the primary comparison?

- Yes
- No

7. Are the results presented adjusted or stratified for differences in groups or stated that the groups were comparable at baseline?

- Yes
- No
- Not applicable

8. Does the study describe the number of participants who were lost to follow-up after the start of the period of observation?

- Yes
- No
- Not applicable (e.g. cross-sectional study)
- Unclear

9. What percentage of patients was lost to follow-up?

- <10% in any group
- 10-20% in any group
- >20%
- Not reported

10. Please rate the overall quality of the study.

- Good (low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
- Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
- Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

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

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

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

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Appendix E: Tallies for Comparisons Not Included in Review

Main intervention	Comparator	Number of studies
Metformin	Acarbose	3
Metformin	Any insulin	2
Metformin	Placebo or any non-drug intervention	21
Metformin	Metformin + exenatide	2
Metformin	Metformin + insulin	3
Thiazolidinedione	Acarbose	1
Thiazolidinedione	Placebo or any non-drug intervention	36
Sulfonylurea	Acarbose	6
Sulfonylurea	Placebo or any non-drug intervention	18
Sitagliptin	Placebo or any non-drug intervention	6
Meglitinides	Placebo or any non-drug intervention	10
Metformin + thiazolidinedione	Sulfonylurea + meglitinides	1
Metformin + sulfonylurea	Thiazolidinedione + basal insulin	1
Metformin + sulfonylurea	Sulfonylurea + basal insulin	2
Metformin + basal insulin	Sulfonylurea + basal insulin	2

Additionally, our team attempted to tally, but found no studies evaluating the following comparisons:

- metformin versus bromocriptine
- metformin versus colesevalam
- sitagliptin versus acarbose
- meglitinides versus acarbose
- combination of metformin and either thiazolidinediones, meglitinides, sitagliptin, or premixed insulin versus combinations of thiazolidinedione and either sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of metformin and thiazolidinedione versus a combination that contains either a sulfonylurea, meglitinides, or sitagliptin and either a meglitinides, sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of metformin and sulfonylurea versus combinations of thiazolidinedione and either sitagliptin, exenatide, or premixed insulin
- combination of metformin and sulfonylurea versus a combination of sulfonylurea and either meglitinides, sitagliptin, exenatide, or premixed insulin
- combination of metformin and sulfonylurea versus a combination that contains either a meglitinides or sitagliptin and either a sitagliptin, exenatide, or premixed insulin
- combination of metformin and a basal insulin versus a combination of thiazolidinedione and either sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of metformin and basal insulin versus a combination that contains either a meglitinides or sitagliptin and either a sitagliptin, exenatide, or premixed insulin
- combination of thiazolidinedione and either sulfonylurea, meglitinides, sitagliptin, or exenatide versus a combination of thiazolidinediones and either meglitinides, sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of sulfonylurea and either meglitinides, sitagliptin, or exenatide versus a combination of sulfonylureas and either sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of meglitinides and either sitagliptin or exenatide versus a combination of meglitinides and either exenatide, basal insulin, or premixed insulin
- combination of sitagliptin and exenatide versus a combination of sitagliptin and either basal insulin or premixed insulin

Appendix F: List of Excluded Articles

Abbasi, A. A., Kasmikha, R., and Sotingeanu, D. G. Metformin-induced lacticacidemia in patients with type 2 diabetes mellitus. Endocr Pract 2000; 6(6):442-6. **Does not have a drug comparison of interest**

Abbatecola, A. M., Rizzo, M. R., Barbieri, M., Grella, R., Arciello, A., Laieta, M. T., Acampora, R., Passariello, N., Cacciapuoti, F., and Paolisso, G. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. Neurology 2006; 67(2):235-40. **Does not apply**

Abe, M., Okada, K., Kikuchi, F., and Matsumoto, K. Clinical investigation of the effects of pioglitazone on the improvement of insulin resistance and blood pressure in type 2-diabetic patients undergoing hemodialysis. Clin Nephrol 2008; 70(3):220-8. **Does not have a drug comparison of interest**

Abraira, C., Duckworth, W. C., and Moritz, T. Glycaemic separation and risk factor control in the Veterans Affairs Diabetes Trial: an interim report. Diabetes Obes Metab 2009; 11(2):150-6. **No original data**

Agarwal, R. Anti-inflammatory effects of short-term pioglitazone therapy in men with advanced diabetic nephropathy. Am J Physiol Renal Physiol 2006; 290(3):F600-5. **Does not apply**

Agrawal, A., Sautter, M. C., and Jones, N. P. Effects of rosiglitazone maleate when added to a sulfonylurea regimen in patients with type 2 diabetes mellitus and mild to moderate renal impairment: a post hoc analysis. Clin Ther 2003; 25(11):2754-64. **Does not have a drug comparison of interest**

Aguilar, C., Reza, A., Garcia, J. E., and Rull, J. A. Biguanide related lactic acidosis: incidence and risk factors. Arch Med Res 92; 23(1):19-24. **Does not have a drug comparison of interest**

Ahren, B., Lundquist, I., and Schersten, B. Effects of glipizide on various consecutive insulin secretory stimulations in patients with type 2 diabetes. Diabetes Res 86; 3(6):293-300. **Number of type 2 diabetes patients in study < 40**

Ahren, B., Simonsson, E., Larsson, H., Landin-Olsson, M., Torgeirsson, H., Jansson, P. A., Sandqvist, M., Bavenholm, P., Efendic, S., Eriksson, J. W., Dickinson, S., and Holmes, D. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. Diabetes Care 2002; 25(5):869-75. **Study duration < 3 months**

Akanuma, Y., Kosaka, K., Kanazawa, Y., Kasuga, M., Fukuda, M., and Aoki, S. Long-term comparison of oral hypoglycemic agents in diabetic retinopathy. Gliclazide vs. other sulfonylureas. Diabetes Res Clin Pract 88; 5(2):81-90. **Does not have a drug comparison of interest**

Albertini, J. P., McMorn, S. O., Chen, H., Mather, R. A., and Valensi, P. Effect of rosiglitazone on factors related to endothelial dysfunction in patients with type 2 diabetes mellitus. Atherosclerosis 2007; 195(1):e159-66. **Does not have a drug comparison of interest**

Alfonso, A., Koops, M. K., Mong, D. P., and Vigersky, R. A. Glycemic control with regular versus lispro insulin sliding scales in hospitalized Type 2 diabetics. J. Diabetes Complications 2006; 20(3):153-157. **Does not have a drug comparison of interest**

Aljabri, K., Kozak, S. E., and Thompson, D. M. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004; 116(4):230-5. **Does not have a drug comparison of interest**

Allen, K. V., McAulay, V., Sommerfield, A. J., and Frier, B. M. Hypoglycaemia is uncommon with a combination of antidiabetic drugs and bedtime NPH insulin for type 2 diabetes. Pract. Diabetes Int. 2004; 21(5):179-182. **Does not meet study design criteria**

Alvarez Guisasola, F., Mavros, P., Nocea, G., Alemao, E., Alexander, C. M., and Yin, D. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab 2008; 10 Suppl 1:15-Aug. **Does not apply**

Anon. "PROactive" study shows Takeda's ACTOS(registered trademark) (pioglitazone HCl) reduces heart attacks, strokes and deaths in patients with type 2 diabetes. Publ. Takeda Res. Lab. 2005; 2005. **Other reason**

Anon. A randomised, multi-centre, phase IV, double-blind, parallel group study comparing the effects of 52 weeks' administration of AVANDAMET and metformin plus sulphonylurea on change in HbA1c from baseline in overweight type 2 diabetics poorly controlled on m. **. Other reason**

Anon. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (Diabetes Care (1999) 22 (960-964)). Diabetes Care 99; 22(11):1922. **No original data**

Anon. Cardiovascular risk reduction with pioglitazone. Cardiovasc J S Afr 2002; 13(4):218. **No original data**

Anon. Clinical news updates from the 2005 AHA Scientific Sessions. Formulary 2006; 41(1):18-26. **No original data**

Anon. Diabetes drugs may cause heart-failure hazard. Health News 2004; 10(1):15. **No original data**

Anon. DPP-IV inhibitor better tolerated than metformin. Pharm. J. 2005; 275(7370):436. **No original data**

Anon. Drugs for type 2 diabetes. Treat Guidel Med Lett 2008; 6(71):47-54. **No original data**

Anon. Dual PPAR agonist improves glycemic control, lipids in type 2 diabetes. Geriatrics 2005; 60(8):12. **No original data**

Anon. Effect of AC2993 (synthetic exendin-4) compared with insulin glargine in patients with type 2 diabetes also using combination therapy with sulfonylurea and metformin. Eli Lilly Clinical Trial Registry Summary 2007. **. Does not have a drug comparison of interest**

Anon. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 98; 352(9131):854-65. **Does not have a drug comparison of interest**

Anon. Effects of metformin or repaglinide therapy for diabetes on serum markers for CVD. Nat. Clin. Pract. Endocrinol. Metab. 2008; 4(8):427. **No original data**

Anon. Efficacy and safety of pioglitazone. Aust. J. Pharm. 2008; 89(1064):62-63. **No original data**

Anon. Efficacy of exenatide [AC2993, synthetic exendin-4, LY2148568] compared with twice-daily biphasic insulin aspart in patients with type 2 diabetes using sulfonylurea and metformin. Eli Lilly Clinical Trial Registry Summary 2007. **. Does not have a drug comparison of interest**

Anon. Exenatide (Byetta) for type 2 diabetes. Med. Lett. Drugs Ther. 2005; 47(1210):45-46. **No original data**

Anon. First reports of serious adverse drug reactions in recent weeks. Drugs Ther. Perspect. 2006; 22(3):20-21. **No original data**

Anon. GlaxoSmithKline: Study no 049653/211: a 52-week double blind study of the effect of rosiglitazone on cardiovascular structure. **. Does not have a drug comparison of interest**

Anon. Glimepiride--well tolerated in daily practice. Cardiovasc J S Afr 2002; 13(4):214-5. **No original data**

Anon. Glitazones linked to heart failure. Pharm. J. 2003; 271(7266):312. **No original data**

Anon. Glyburide/metformin (Glucovance) for type 2 diabetes. Med Lett Drugs Ther 2000; 42(1092):105-6. **No original data**

Anon. Improved risk profile with pioglitazone. Br. J. Diabetes Vasc. Dis. 2003; 3(6):446. **No original data**

Anon. Inhaled insulin superior to rosiglitazone in patients with uncontrolled type 2 diabetes. Formulary 2003; 38(7):408. **No original data**

Anon. Insulin sensitizer affects lipids. Health News 2005; 11(1):2. **No original data**

Anon. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 98; 352(9131):837-53. **Does not have a drug comparison of interest**

Anon. Janumet. JAAPA 2007; 20(6):14. **No original data**

Anon. Landmark PROactive trial investigates effect of ACTOS (pioglitazone HCl) on cardiovascular disease progression: More than 5,000 patients with type 2 diabetes studied. Publ. Takeda Res. Lab. 2004; 2004. **Other reason**

Anon. Lipid effects of pioglitazone studied. Br. J. Diabetes Vasc. Dis. 2004; 4(3):209. **No original data**

Anon. Metformin less effective than sensible diet. J. Endocrinol. Metab. Diabetes S. Afr. 2001; 6(3):82. **No original data**

Anon. Nateglinide improves postprandial glucose as monotherapy or in combination with metformin. Geriatrics 2002; 57(8):35. **No original data**

Anon. New data shows Takeda's ACTOS(registered trademark) (pioglitazone HCl) reduced heart attacks by 28 percent in people with type 2 diabetes. Publ. Takeda Res. Lab. 2005; 2005. **Other reason**

Anon. PERISCOPE: pioglitazone offers the right cluster of effects to confer benefit in type 2 diabetes. Cardiovasc J Afr 2008; 19(3):159-62. **No original data**

Anon. Pioglitazone ineffective in secondary prevention of macrovascular complications (PROactive). J. Natl. Med. Assoc. 2006; 98(1):102-103. **No original data**

Anon. Pioglitazone of benefit in high-risk diabetes patients. Pharm. J. 2005; 275(7367):330. **No original data**

Anon. Pioglitazone reduces stroke, MI, and death but increases HF. Geriatr. Aging 2006; 9(1):48. **No original data**

Anon. Pioglitazone shows anti-atherosclerotic effect in type 2 diabetes. Geriatrics 2007; 62(2):14. **No original data**

Anon. Pioglitazone/glimepiride (Duetact) for diabetes. Med Lett Drugs Ther 2007; 49(1253):11-Sep. **No original data**

Anon. Pioglitazone: Fractures in women. WHO Drug Inf. 2007; 21(3):207. **No original data**

Anon. Pre-meal inhaled insulin lowers HbA1c levels more effectively than rosiglitazone. Formulary 2005; 40(11):396. **No original data**

Anon. Repaglinide improves blood glucose control in patients with type 2 diabetes. Formulary 2004; 39(11):528. **No original data**

Anon. Rosiglitazone decreases coronary restenosis. Cardiol. Rev. 2003; 20(8):11. **No original data**

Anon. Rosiglitazone increased heart failure but did not differ from metformin plus sulphonylurea for other CV outcomes at interim analysis. Evid.-Based Med. 2007; 12(6):170. **No original data**

Anon. Rosiglitazone plus metformin combination improves glycaemic control in diabetes. Pharm. J. 2004; 273(7317):375. **No comparison group**

Anon. Sitagliptin combined with sulphonylureas: new indication. Other treatments are preferable. Prescrire Int 2009; 18(99):14-5. **No original data**

Anon. Summaries for patients. A comparison of three insulin regimens (morning glargine, bedtime glargine, or bedtime neutral protamine Hagedorn) in addition to a pill for treating type 2 diabetes. Ann Intern Med 2003; 138(12):I33. **No original data**

Anon. Summaries for patients. Comparison of two types of insulin added to diabetes pills in poorly controlled type 2 diabetes. Ann Intern Med 2008; 149(8):I-46. **No original data**

Anon. Takeda Pharmaceuticals North America, Inc. Observation of an increased risk of fractures in female patients who received long-term treatment with ACTOS1 (pioglitazone HCl) tablets for type II diabetes mellitus. Deerfield, Illinois: Takeda Pharmaceuticals. **No original data**

Anon. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: A randomized trial (Annals of Internal Medicine (2007) 146 (477-485)). Ann. Intern. Med. 2007; 146(12):896. **No original data**

Anon. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. Diabetes Care 2005; 28(2):421-2. **No comparison group**

Anon. Thiazolidinediones could exacerbate BMD loss in elderly women. Nat. Clin. Pract. Endocrinol. Metab. 2006; 2(12):654-655. **No original data**

Anon. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes 95; 44(11):1249-58. **Does not have a drug comparison of interest**

Anon. U.K. prospective diabetes study. II. Reduction in HbA1c with basal insulin supplement, sulfonylurea, or biguanide therapy in maturity-onset diabetes. A multicenter study. Diabetes 85; 34(8):793-8. **Does not have a drug comparison of interest**

Anon. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 95; 310(6972):83-8. **Does not have a drug comparison of interest**

Anon. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Pro. Ann Intern Med 98; 128(3):165-75. **Does not have a drug comparison of interest**

Anon. Variation in diabetes response. Pharm. J. 2003; 271(7272):572. **No original data**

Anonymous. RAS - Rosiglitazone and Atherosclerosis Study: a 1 year randomised, double-blind. parallel group, placebo controlled study to evaluate the efficacy of rosiglitazone on the progression of intima-media thickness in the carotid artery in subjects with insuli. http://ctr.gsk.co.uk/summary/rosiglitazone/IV_049653_334.pdf 2004. **No original data**

Anwar, A., Azmi, K. N., Hamidon, B. B., and Khalid, B. A. An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan. Med J Malaysia 2006; 61(1):28-35. **Study duration < 3 months**

Arauz-Pacheco, C., Ramirez, L. C., Rios, J. M., and Raskin, P. Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. Am J Med 90; 89(6):811-3. **No comparison group**

Aronoff, S., Rosenblatt, S., Braithwaite, S., Egan, J. W., Mathisen, A. L., and Schneider, R. L. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 2000; 23(11):1605-11. **Does not have a drug comparison of interest**

Asche, C. V., McAdam-Marx, C., Shane-McWhorter, L., Sheng, X., and Plauschinat, C. A. Association between oral antidiabetic use, adverse events and outcomes in patients with type 2 diabetes. Diabetes Obes Metab 2008; 10(8):638-45. **Does not have a drug comparison of interest**

Ascic-Buturovic, B. The effects of combined insulin and metformin therapy in obese patients with diabetes mellitus type 2 in the early stage of the disease. Bosn J Basic Med Sci 2006; 6(2):54-8. **Does not meet study design criteria**

Avery, M. A., Chittiboyina, A., and Patny, A. Novel Tricyclic (alpha)-Alkoxyphenyl Propanoic Acid Derivatives: Dual PPAR(alpha)/(gamma) Agonists with Hypolipidemic and Antidiabetic Activity. Chemtracts 2003; 16(11):653-659. **No original data**

Baba, S., Nakagawa, S., Takebe, K., Goto, Y., Maezawa, H., Takeda, R., Sakamoto, N., and Fukui, I. Comparison of gliclazide and glibenclamide treatment in non-insulin-dependent diabetes. Tohoku J Exp Med 83; 141 Suppl:693-706. **Does not have a drug comparison of interest**

Babich, M. M., Pike, I., and Shiffman, M. L. Metformin-induced acute hepatitis. Am J Med 98; 104(5):490-2. **No comparison group**

Bachmann, W., Sieger, C., Haslbeck, M., and Lotz, N. Combination of insulin and glibenclamide (gl) in the treatment of adult-onset diabetes (type 2). DIABETOLOGIA 81; 21(3):21. **Number of type 2 diabetes patients in study < 40**

Bahadori, B., Trinker, M., Wallner, S. J., Yazdani-Biuki, B., and Wascher, T. C. Diabetes mellitus and weight control: Differences of respiratory quotient in type 2 diabetic obese subjects receiving sulfonylureas and non-diabetic obese controls. Nutrition 2003; 19(2):159-160. **Number of type 2 diabetes patients in study < 40**

Baksi, A., James, R. E., Zhou, B., and Nolan, J. J. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. Acta Diabetol 2004; 41(2):63-9. **Does not have a drug comparison of interest**

Balkrishnan, R., Rajagopalan, R., Shenolikar, R. A., Camacho, F. T., and Anderson, R. T. Outcomes associated with introduction of thiazolidinedione therapy in Medicaid enrolled patients with type 2 diabetes: an updated and expanded retrospective analysis. Curr Med Res Opin 2006; 22(3):551-9. **Does not have a drug comparison of interest**

Ballani, P., Tran, M. T., Navar, M. D., and Davidson, M. B. Clinical experience with U-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. Diabetes Care 2006; 29(11):2504-2505. **Does not have a drug comparison of interest**

Ballary, C. and Desai, A. Efficacy and safety of a combination of metformin and rosiglitaone in patients with type 2 diabetes mellitus--a postmarketing study. J Indian Med Assoc 2003; 101(2):113-4, 123. **No comparison group**

Barnes DJ, Mattock MB. Microalbuminuria in type 2 diabetic patients: a cross sectional study. Annals of clinical biochemistry 94; 31 (Pt 6):588-9. **No original data**

Barnett AH, Bowen JD Burden AC Janes JM Sinclair A Small M Tindall H. Multicentre study to assess quality of life and glycaemic control of Type 2 diabetic patients treated with insulin compared with oval hypoglycaemic agents. Practical Diabetes International. 96; 13(6):179-183. **Does not have a drug comparison of interest**

Barnett, A. H., Burger, J., Johns, D., Brodows, R., Kendall, D. M., Roberts, A., and Trautmann, M. E. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther 2007; 29(11):2333-48. **Does not have a drug comparison of interest**

Barnett, A. H., Dreyer, M., Lange, P., and Serdarevic-Pehar, M. An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with glibenclamide as adjunctive therapy in patients with type 2 diabetes poorly controlled on metformin. Diabetes Care 2006; 29(8):1818-25. **Does not have a drug comparison of interest**

Barnett, A. H., Grant, P. J., Hitman, G. A., Mather, H., Pawa, M., Robertson, L., and Trelfa, A. Rosiglitazone in Type 2 diabetes mellitus: an evaluation in British Indo-Asian patients. Diabet Med 2003; 20(5):387-93. **Does not have a drug comparison of interest**

Barranco, C. Pioglitazone improves cardiovascular risk markers for patients with diabetes. Nat. Clin. Pract. Cardiovasc. Med. 2005; 2(9):438. **No original data**

Barzilay JI, Kronmal RA Bittner V Eaker E Evans C Foster ED. Coronary artery disease and coronary artery bypass grafting in diabetic patients aged > or = 65 years (report from the Coronary Artery Surgery Study [CASS] Registry). The American journal of cardiology 94; 74(4):334-9. **Does not apply**

Baynes, C., Feher, M. D., and Elkeles, R. S. The effect of treatment of non-insulin-dependent diabetes mellitus (NIDDM) on serum lipids and lipoproteins. Q. J. MED. 89; 72(267):579-587. **No original data**

Bays, H. E., Goldberg, R. B., Truitt, K. E., and Jones, M. R. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. Arch Intern Med 2008; 168(18):1975-83. **Does not have a drug comparison of interest**

Bech, P., Moses, R., and Gomis, R. The effect of prandial glucose regulation with repaglinide on treatment satisfaction, wellbeing and health status in patients with pharmacotherapy naive Type 2 diabetes: a placebo-controlled, multicentre study. Qual Life Res 2003; 12(4):413-25. **Does not have a drug comparison of interest**

Beck-Nielsen, H., Lindskov, H. O., and Richelsen, B. Mechanism of action of glibenclamide in type 2 (non-insulin dependent) diabetes during long-term treatment. DIABETOLOGIA 82; 23(2):No. 16. **Does not apply**

Belcher, G. and Matthews, D. R. Safety and tolerability of pioglitazone. Exp Clin Endocrinol Diabetes 2000; 108(Suppl 2):267-273. **No original data**

Belden, H. First in DPP-4 inhibitor class cleared for diabetes. Drug Topics 2006; 150(22)**. No original data**

Belden, H. New diabetes treatment combines two drugs into one. Drug Topics 2006; 150(17)**. No original data**

Bell, D. S. and Mayo, M. S. Improved glycemic control with use of oral hypoglycemic therapy with or without insulin. Endocr Pract 98; 4(2):82-5. **Does not apply**

Bell, D. S. and Mayo, M. S. Outcome of metformin-facilitated reinitiation of oral diabetic therapy in insulin-treated patients with non-insulin-dependent diabetes mellitus. Endocr Pract 97; 3(2):73-6. **Does not apply**

Bell, D. S. and Mayo, M. S. Weight loss in patients with diabetes treated with a metformin-sulfonylurea combination in comparison with twice-daily mixed insulin. Endocr Pract 98; 4(6):360-4. **Does not meet study design criteria**

Bell, D. S. and Yumuk, V. Frequency of severe hypoglycemia in patients with non-insulin-dependent diabetes mellitus treated with sulfonylureas or insulin. Endocr Pract 97; 3(5):281-3. **Does not apply**

Bell, D. S. H. and Wyne, K. L. Use of fixed-dose oral combinations. Postgrad. Med. 2006; 119(2)**. No original data**

Ben-Ami, H., Nagachandran, P., Mendelson, A., and Edoute, Y. Drug-induced hypoglycemic coma in 102 diabetic patients. Arch Intern Med 99; 159(3):281-4. **Does not have a drug comparison of interest**

Bengel, F. M., Abletshauser, C., Neverve, J., Schnell, O., Nekolla, S. G., Standl, E., and Schwaiger, M. Effects of nateglinide on myocardial microvascular reactivity in Type 2 diabetes mellitus--a randomized study using positron emission tomography. Diabet Med 2005; 22(2):158-63. **Does not have a drug comparison of interest**

Berberoglu, Z., Gursoy, A., Bayraktar, N., Yazici, A. C., Bascil Tutuncu, N., and Guvener Demirag, N. Rosiglitazone decreases serum bone-specific alkaline phosphatase activity in postmenopausal diabetic women. J Clin Endocrinol Metab 2007; 92(9):3523-30. **Does not have a drug comparison of interest**

Berger, W. Incidence of severe sideeffects during therapy with sulfonylureas and biguanides. Horm Metab Res Suppl 85; 15:111-5. **No original data**

Berghout, L. M., Gorter, K. J., and Rutten, G. E. H. M. Course of glycaemia in poorly controlled type 2 diabetes patients 2.5 years after optimizing oral treatment in general practice. Eur. J. Gen. Pract. 2006; 12(2):80-82. **Does not apply**

Bergman, A. J., Cote, J., Yi, B., Marbury, T., Swan, S. K., Smith, W., Gottesdiener, K., Wagner, J., and Herman, G. A. Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-4 inhibitor. Diabetes Care 2007; 30(7):1862-4. **No subjects with type 2 diabetes**

Bermudez-Pirela, V. J., Cano, C., Medina, M. T., Souki, A., Lemus, M. A., Leal, E. M., Seyfi, H. A., Cano, R., Ciscek, A., Bermudez-Arias, F., Contreras, F., Israili, Z. H., Hernandez-Hernandez, R., and Valasco, M. Metformin plus low-dose glimeperide significantly improves Homeostasis Model Assessment for insulin resistance (HOMA(IR)) and beta-cell function (HOMA(beta-cell)) without hyperinsulinemia in patients with type 2 diabetes mellitus. Am J Ther 2007; 14(2):194-202. **Does not have a drug comparison of interest**

Bhansali, A. and Masoodi, S. R. Efficacy of once- or twice-daily extended release metformin compared with thrice-daily immediate release metformin in type 2 diabetes mellitus. J Assoc Physicians India 2005; 53:441-5. **Does not have a drug comparison of interest**

Biesenbach, G., Bodlaj, G., and Pieringer, H. Weight gain and metabolic control in newly insulin-treated patients with type 2 diabetes with different insulin regimens. Can. J. Diabetes 2006; 30(4):384-389. **Does not have a drug comparison of interest**

Blonde, L., Klein, E. J., Han, J., Zhang, B., Mac, S. M., Poon, T. H., Taylor, K. L., Trautmann, M. E., Kim, D. D., and Kendall, D. M. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab 2006; 8(4):436-47. **Does not have a drug comparison of interest**

Bloomgarden, Z. T. Pharmacologic treatment of type 2 diabetes. Diabetes Care 2003; 26(2):526-533. **No original data**

Bodmer, M., Meier, C., Krahenbuhl, S., Jick, S. S., and Meier, C. R. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care 2008; 31(11):2086-91. **Does not have a drug comparison of interest**

Bokhari, S. U., Gopal, U. M., and Duckworth, W. C. Beneficial effects of a glyburide/metformin combination preparation in type 2 diabetes mellitus. Am J Med Sci 2003; 325(2):66-9. **Does not meet study design criteria**

Boord, J. B., Graber, A. L., Christman, J. W., and Powers, A. C. Practical management of diabetes in critically III patients. Am. J. Respir. Crit. Care Med. 2001; 164(10 I):1763-1767. **No original data**

Boucher, M., McAuley, L., Brown, A., Keely, E., and Skidmore, B. Comparative clinical and budget evaluations of rosiglitazone and pioglitazone with other anti-diabetic agents. Ottawa Canadian Coordinating Office for Health Technology Assessment 2002; Technology overview no. 9**. No original data**

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comparison of interest

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Tholakanahalli, V. N., Potti, A., and Heyworth, M. F. Glibenclamide-induced cholestasis. West J Med 98; 168(4):274-7. **No comparison group**

Thrainsdottir I, Erdmann E Ryden L Spanheimer R. Adjudication of serious heart failure in patients with type 2 diabetes and cardiovascular disease: results from PROactive. American Heart Association Annual Scientific Meeting 2006 2006. **No original data**

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Tong, P. C., Chow, C. C., Jorgensen, L. N., and Cockram, C. S. The contribution of metformin to glycaemic control in patients with Type 2 diabetes mellitus receiving combination therapy with insulin. Diabetes Res Clin Pract 2002; 57(2):93-8. **Does not have a drug comparison of interest**

Tovi, J., Theobald, H., and Engfeldt, P. Effect of metabolic control on 24-h ambulatory blood pressure in elderly non-insulin-dependent diabetic patients. J Hum Hypertens 96; 10(9):589-94. **Number of type 2 diabetes patients in study < 40**

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comparison of interest

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Appendix G: Evidence Tables

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Hemoglobin A1c

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Thiazolidinedione						
13	Medium	Consistent for short duration studies. One long term study inconsistent.	Indirect	Precise	No effect; Neither drug favored	Moderate
Met vs. SU						
19	Low	Consistent	Indirect	Precise	No effect; Neither drug favored	High
Met vs. Sitagliptin						
1	High	NA	Indirect	Precise	Small; Favored metformin	Low
Met vs. Nateglinide						
1	Medium	NA	Indirect	Imprecise	Small; Metformin favored	Low
Met vs. Repaglinide						
2	Medium	Consistent	Indirect	Imprecise	No effect; Neither drug favored	Low
Met vs. Met + TZD						
10	Low	Consistent	Indirect	Precise	Small; Favored combination Met + TZD	High
Met vs. Met + SU						
14	Low	Consistent	Indirect	Precise	Small; Favored combination Met + SU	High
Met vs. Met + Sitagliptin						
4	Medium	Consistent	Indirect	Precise	Small; Favored the combination of Met + Sita	Moderate
Met vs. Met + Nateglinide						
2	Low	Consistent	Indirect	Imprecise	Small; Favored the combination of Met+Nateg	Low
Met vs Met+Repaglinide						
1	Low	NA	Indirect	Precise	Small; Favored the combination of Met+Repag	Low
TZD vs. TZD						
2	Medium	Consistent	Indirect	Precise	No effect; Neither drug favored	Moderate
TZD vs. SU						

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Hemoglobin A1c

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
13	Medium	Consistent	Indirect	Precise	No effect: Neither drug favored	Moderate
TZD vs. Meglitinide						
2	High	Inconsistent	Indirect	Precise	Small; Unable to determine which drug favored	Low
SU vs. Sitagliptin						
1	Low	NA	Indirect	Imprecise	No effect: Neither drug favored	Low
SU vs. Repaglinide						
7	Low	Consistent	Indirect	Precise	No effect; Neither drug favored	High
SU vs Nateglinide						
1	Medium	NA	Indirect	Imprecise	No effect: Neither drug favored	Low
Met and TZD vs. Met and SU						
8	Low	Consistent for short term trials. One long term study inconsistent.	Indirect	Precise	No effect: Neither drug combination is favored in the short term	Moderate
Met and TZD vs. Met and Sita						
1	Medium	NA	Indirect	Precise	No effect: Neither drug combination is favored	Low
Met and TZD vs. Met and Repaglinide						
1	Medium	NA	Indirect	Precise	No effect" Neither drug is favored	Low
Met and SU vs. Met and Nateglinide						
2	Low	Inconsistent	Indirect	Imprecise	Unable to determine	Low
Met and SU vs. Met and Sitagliptin						
1	Low	NA	Indirect	Precise	No effect: Neither drug is favored	Low
Met and TZD vs. TZD and SU						
1	Medium	NA	Indirect	Imprecise	Small; Favored combination of TZD and SU	Low
Met and SU vs. TZD and SU						
6	Medium	Consistent for short term trials. One longer study inconsistent.	Indirect	Precise	No effect: Neither drug is favored	Moderate

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Hemoglobin A1c

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met and Basal Insulin vs. Met and Premixed Insulin						
2	Low	Consistent	Indirect	Precise	Small; Favored the Met and Premixed Insulin arms	Low
Met and SU vs. Met and Premixed Insulin						
2	Medium	Inconsistent	Indirect	Imprecise	Unable to determine	Low

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence Outcome: Weight

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Thiazolidinedione						
9	Low	Consistent.	Indirect	Precise	Small; Favored metformin	High
Met vs. SU						
13	Medium	Consistent	Indirect	Precise	Small; Favored metformin	High
Met vs. Sitagliptin						
1(in 2 articles)	High	NA	Indirect	Imprecise	Unable to determine	Low
Met vs. Meglitinides (both repaglinide)						
2	High	Possibly inconsistent	Indirect	Imprecise	Unable to determine	Low
Met vs. Met + TZD						
6	Medium	Consistent	Indirect	Precise	Small; Favored Metformin monotherapy	High
Met vs. Met + SU						
10	Low	Consistent	Indirect	Precise	Small; Favored Metformin monotherapy	High
Met vs. Met + Sitagliptin						
4	Medium	Consistent	Indirect	Imprecise	No effect; Neither drug favored	Low
Met vs. Met + Meglitinides						
2	Low	Consistent	Indirect	Imprecise	Small; Favored metformin monotherapy	Low
TZD vs. TZD						
2	Medium	Consistent	Indirect	Imprecise	No effect: neither drug favored	Low
TZD vs. SU						
6	High	Consistent	Indirect	Precise	Small; Favored sulfonylurea	Low
TZD vs. Meglitinide						
2	High	Consistent	Indirect	Imprecise	Unable to determine	Low
SU vs. Sitagliptin						
1	Low	NA	Indirect	Imprecise	Unable to determine	Low
SU vs. Meg (all repaglinide)						
6	Low	Consistent	Indirect	Precise	No effect; Neither drug favored	High
Met and TZD vs. Met and SU						

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Weight

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
6	Low	Consistent	Indirect	Precise	Small; Favored metformin plus sulfonylurea	Moderate
Met and TZD vs. Met and Sita						
1	Medium	NA	Indirect	Imprecise	Unable to determine	Low
Met and TZD vs. Met and Meg						
1	Medium	NA	Indirect	Imprecise	Unable to determine	Low
Met and SU vs. Met and Meg						
2	Low	Inconsistent	Indirect	Imprecise	Unable to determine	Low
Met and SU vs. Met and Sitagliptin						
1	Low	NA	Indirect	Precise	Small; Favored metformin plus sitagliptin	Low
Met and SU vs. TZD and SU						
4	Low	Consistent	Indirect	Imprecise	Small; Favored Met and SU	Moderate
Met and Basal Insulin vs. Met and Premixed Insulin						
2	Low	Consistent	Indirect	Precise	Small; Favored Met plus Basal Insulin	Low
Met and SU vs. Met and Premixed Insulin						
2	Low	Consistent	Indirect	Precise	No effect; Neither drug favored	Low

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Low density lipoprotein

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Rosiglitazone						
6	low	consistent	indirect	imprecise	Large effect, favors metformin	moderate
Met vs Pioglitazone						
5	low	consistent	Indirect	Precise	Large effect, favors metformin	high
Met vs. SU						
5	medium	Consistent	Indirect	Precise	Large effect, favors metformin	high
Met vs. Sitagliptin						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + rosiglitazone						
7	Low	Consistent	Indirect	Precise	Large effect, favors metformin	High
Met vs Met + pioglitazone						
2	Medium	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + SU						
7	Medium	Inconsistent	Indirect	Imprecise	No effect, favors neither	Low
Met vs. Met + Sitagliptin						
3	Medium	Inconsistent	Indirect	Imprecise	No effect, unable to determine	Low
Met vs. Met + Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
TZD vs. TZD						
2	High	Consistent	Indirect	Imprecise	Small effect, favors pioglitazone	Low
Pioglitazone vs. SU						
3	High	Consistent	Indirect	Precise	Small effect, favors sulfonylurea	Low
Rosiglitazone vs SU						
2	Medium	Consistent	Indirect	Imprecise	Large effect, favors sulfonylurea	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Low density lipoprotein

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
TZD vs. Sitagliptin						
0	n/a	n/a	n/a	n/a	n/a	insufficient
Pioglitazone vs. Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Rosiglitazone vs meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
SU vs. Sitagliptin						
1	Low	n/a	Indirect	Imprecise	No effect, favors neither	Low
SU vs. Meglitinide						
2	Medium	Consistent	Indirect	Imprecise	No effect, favors neither	Low
Sitagliptin vs. Meglitinide						
0	n/a	n/a	n/a	n/a	n/a	insufficient
Met and rosiglitazone vs. Met and sulfonylurea						
4	Low	Consistent	Indirect	Imprecise	Large effect, favors metformin and sulfonylurea	Moderate
Met and pioglitazone vs met and sulfonylurea						
1	Low	n/a	Indirect	Imprecise	Small effect, favors metformin and sulfonylurea	Low
Met and rosiglitazone vs. metformin and SITA						
1	Medium	n/a	Indirect	Imprecise	Unable to determine, favors metformin and sitagliptin	Low
Met and rosi vs. met and meglitinide						
1		N/a	Indirect	Precise	Large effect, favors metformin and meglitinide	Low
Met and pio vs pio and SU						
1	Medium	n/a	Indirect	Imprecise	No effect, favors neither	Low
Met and SU vs. Met and meglitinide						
2	Low	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met and SU vs rosi and SU						

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Low density lipoprotein

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
2	Medium	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met and SU vs pio and SU						
2	Medium	Consistent	Indirect	Imprecise	Small effect, favors metformin and SU	Low
Met and Meglitinide vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Sitagliptin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Exenatide vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Basal Insulin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Premixed Insulin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Meglitinide vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Sitagliptin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Exenatide vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Basal Insulin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Premixed Insulin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: High density lipoprotein

Number Of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Rosiglitazone						
5	Medium	Consistent	indirect	Precise	No effect, favors neither	Moderate
Met vs Pioglitazone						
7	Medium	consistent	Indirect	Precise	Small effect, favors pioglitazone	High
Met vs. SU						
12	medium	Consistent	Indirect	Precise	No effect, favors neither	High
Met vs. Sitagliptin						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + rosiglitazone						
7	Low	Consistent	Indirect	Precise	Small effect, favors rosiglitazone	High
Met vs Met pioglitazone						
2	Medium	Consistent	Indirect	Imprecise	Large effect, favors metformin and pioglitazone	Low
Met vs. Met + SU						
7	Medium	Inconsistent	Indirect	Imprecise	No effect, favors neither	Low
Met vs. Met + Sitagliptin						
3	Medium	Inconsistent	Indirect	Imprecise	No effect, favors neither	Low
Met vs. Met + Meglitinide						
1	Low	n/a	Indirect	Imprecise	No effect, favors neither	Low
TZD vs. TZD						
2	High	Consistent	Indirect	Imprecise	Small effect, favors pioglitazone	Low
Pioglitazone vs. SU						
5	High	Inconsistent	Indirect	Imprecise	Small effect, favors pioglitazone	Low
Rosiglitazone vs SU						
2	Medium	Consistent	Indirect	Imprecise	Large effect, favors rosiglitazone	Low
TZD vs. Sitagliptin						
0	n/a	n/a	n/a	n/a	n/a	Insufficient

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: High density lipoprotein

Number Of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Pioglitazone vs. Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Rosiglitazone vs meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
SU vs. Sitagliptin						
1	Low	n/a	Indirect	Imprecise	No effect, favors neither	Low
SU vs. Meglitinide						
5	Low	Consistent	Indirect	Precise	No effect, favors neither	High
Sitagliptin vs. Meglitinide						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and rosiglitazone vs. Met and sulfonylurea						
4	Low	Consistent	Indirect	Imprecise	Small effect, favors metformin and rosiglitazone	Moderate
Met and pioglitazone vs met and sulfonylurea						
2	Medium	Consistent	Indirect	Precise	Large effect, favors metformin plus pioglitazone	Moderate
Met and rosiglitazone vs met and SITA						
1	Medium	n/a	Indirect	Imprecise	Unable to determine, favors metformin and rosiglitazone	Low
Met and rosi vs. met and meglitinide						
1	?	N/a	Indirect	Precise	Small effect, favors metformin and rosiglitazone	Low
Met and pio vs pio and SU						
1	Medium	n/a	Indirect	Imprecise	Small effect, favors metformin and pioglitazone	Low
Met and SU vs. Met and meglitinide						
2	Low	Consistent	Indirect	imprecise	No effect, favors neither	Low
Met and SU vs rosi and SU						
2	Medium	Inconsistent	Indirect	imprecise	Unable to determine, unable to determine	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: High density lipoprotein

Number Of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met and SU vs pio and SU						
3	Medium	Consistent	Indirect	imprecise	Small effect, favors pioglitazone and SU	Low
Met and Meglitinide vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Sitagliptin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Exenatide vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Basal Insulin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Premixed Insulin vs. Met and SU						
1	Low	n/a	Indirect	imprecise	No effect, favors neither	Low
Met and TZD vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and SU vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Meglitinide vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Sitagliptin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Exenatide vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Basal Insulin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Premixed Insulin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Triglycerides

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Rosiglitazone						
6	Medium	Consistent	indirect	imprecise	Large effect, favors metformin	moderate
Met vs Pioglitazone						
7	Medium	consistent	Indirect	Precise	Large effect, favors pioglitazone	High
Met vs. SU						
12	medium	Consistent	Indirect	Imprecise	Small effect, favors metformin	Moderate
Met vs. Sitagliptin						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + rosiglitazone						
7	Low	Consistent	Indirect	Precise	Large effect, favors metformin	High
Met vs Met + pioglitazone						
2	Medium	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + SU						
8	Medium	Inconsistent	Indirect	Imprecise	No effect, favors neither	Low
Met vs. Met + Sitagliptin						
3	Medium	Consistent	Indirect	Imprecise	Large effect, favors combination of metformin and sitagliptin	Low
Met vs. Met + Meglitinide						
1	Low	n/a	Indirect	Imprecise	Small effect, favors combination of metformin and meglitinide	Low
TZD vs. TZD						
2	High	Consistent	Indirect	Imprecise	Large effect, favors pioglitazone	Low
Pioglitazone vs. SU						
5	High	Consistent	Indirect	Imprecise	No effect, neither favored	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Triglycerides

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Rosiglitazone vs SU						
2	Medium	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Low
TZD vs. Sitagliptin						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Pioglitazone vs. Meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
Rosiglitazone vs meglitinide						
1	High	n/a	Indirect	Imprecise	Unable to determine, unable to determine	Low
SU vs. Sitagliptin						
1	Low	n/a	Indirect	Imprecise	No effect, favors neither	Low
SU vs. Meglitinide						
5	Medium	Consistent	Indirect	Imprecise	No effect, favors neither	Low
Sitagliptin vs. Meglitinide						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and rosiglitazone vs. Met and sulfonylurea						
4	Low	Consistent	Indirect	Imprecise	No effect, favors neither	Moderate
Met and pioglitazone vs met and sulfonylurea						
2	Medium	Consistent	Indirect	Precise	Large effect, favors metformin plus pioglitazone	Moderate
Met and rosiglitazone vs met and SITA						
1	Medium	n/a	Indirect	Imprecise	Unable to determine, favors metformin and SITA	Low
Met and rosi vs. met and meglitinide						
1		N/a	Indirect	Imprecise	No effect, favors neither	Low
Met and pio vs pio and SU						
1	Medium	n/a	Indirect	Imprecise	Small effect, favors pioglitazone and SU	Low
Met and SU vs. Met and meglitinide						
2	Low	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Insufficient

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Triglycerides

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met and SU vs rosi and SU						
2	Medium	Inconsistent	Indirect	Imprecise	Unable to determine, unable to determine	Insufficient
Met and SU vs pio and SU						
3	Medium	Consistent	Indirect	Imprecise	Unable to determine, favors pioglitazone and SU	Low
Met and Meglitinide vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Sitagliptin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Exenatide vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Basal Insulin vs. Met and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Premixed Insulin vs. Met and SU						
1	Low	n/a	Indirect	Unable to determine	No effect, favors neither	Low
Met and TZD vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and SU vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Meglitinide vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Sitagliptin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Exenatide vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Basal Insulin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient
Met and Premixed Insulin vs. TZD and another agent						
0	n/a	n/a	n/a	n/a	n/a	Insufficient

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Home, 2009[14] Multinational Europe	Start year: 2001 - End year: 2003 7.5 Years	Run-in period but number of participants excluded was NR	>= 6 months	Yes	7428/4458 Outpatient: primary care	Age: <40, >75, 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 >: 9, HbA1c <: 7, BMI or weight: <25, Pregnant, Nursing, Not using adequate contraception, Recent CAD event, heart failure
Raskin, 2009[110] NR	Neither year reported 26 Weeks	No run-in period	< 6 months	Yes	1093/383 Outpatient: primary care	Age: <18y, Pregnant, Nursing, currently not under monotherapy at least 2 months or dual therapy, FBG >260, Any disease or abnormality as judged by the investigator, treatment with the investigational drug for 4 weeks, Allergy to study drugs or related compounds, H/O hypoglycemia unawareness or recurrent severe hyperglycemia
Derosa, 2009[36] Italy	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, 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 or weight: <2.5 or >30, Pregnant, Nursing, Not using adequate contraception, No type 2 DM, h/o ketoacidosis, severe anemia
van der Meer, 2009[116] Netherlands	Neither year reported 24 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	173/80 NR	Age: <45 or >65, 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 >: >8.5, HbA1c <: <6.5, BMI or weight: <25 or >32, <45 or >65, Systolic BP <150, Diastolic BP <85, Prior TZD or insulin use

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kaku, 2009[70] Japan	Start year: 2005 40 Weeks	Yes	< 6 months	Yes	NR/236 NR	Age: <= 20 and >=65, 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 >: <6.5, HbA1c <: >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 26weeks, if on any medications that might affect glycemic control, drug or alcohol dependency
Gupta, 2009[37] NR	Neither year reported 16 Weeks	No run-in period	< 6 months	Yes	247/51 NR	Age: 35 to 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), Pregnant, Not using adequate contraception, FPG >200 mg%, Individuals using orlistat, sibutramine, ephedrine, steroids, Significant lung diseases, Significant Neurologic diseases, Baseline BP>140/90, prior use of TZD, B Blockers, smokers; alcohol abuse and using drugs, Patients using metal objects precluding required scans
Williams-Herman, 2009[63] NR	Neither year reported 54 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age: >78; <18 yrs, lack of A1c >=7.5% but <=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

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2009[111] Italy	Neither year reported 12 Months	Fewer than 10% of participants were excluded during run-in	>= 6 months	NR	NR/248 Inpatient/hospital	Age: >18, 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 <: 7, BMI or weight: BMI <25 >28, Pregnant, Nursing, Not using adequate contraception, No type 2 DM, h/o ketoacidosis, severe anemia, No HTN
Nauck, 2009[78] Multi-continent	Neither year reported 26 Weeks	Run-in period but number of participants excluded was NR	>= 6 months	Yes	1662/1087 NR	Age: <18, >80y, HbA1c >: 11 if on monotherapy; 10 if on combination therapy (both greater than 3 m), HbA1c <: 7, BMI or weight: >40, used insulin in last 3 m
Erdem, 2008[31] Turkey	Neither year reported 12 Weeks	No run-in period	< 6 months	No	53/44 outpatient dept of internal medicine clinic	Age: >70; <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), BMI or weight: >35, other chronic disease as detected by history and physical
Iliadis, 2007[38] Greece	Neither year reported 18 Weeks	Run-in period but number of participants excluded was NR	NR	NR	NR/48 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), diagnosis of type 2 DM >3years, use of any diabetes medication, no type 2 DM, any heart failure

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Scott, 2008[71] Multi-continent	Neither year reported 18 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	486/273 NR	Age: <18, >75, 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 >: 11, HbA1c <: 7, not on 10 wks on stable dose of MET, insulin use, type 1 dm, glucose > 270
Seufert, 2008[117] Multi-continent	Neither year reported 104 Weeks	No run-in period	NR	Yes	NR/1269 NR	Age: < 35, >75, 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%, HbA1c <: > 11%, Pregnant, Nursing, fasting c-peptide >1.5, ketoacidosis, symptomatic heart failure, acute malabsorption, chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years
Robbins, 2007[120] United States, Multinational Europe, Multi-continent, India, Australia	Neither year reported 24 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	433/317 NR	Age: <35 or >75, 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 >: >11, HbA1c <: <6.5, Pregnant, Nursing, Not using adequate contraception, Patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0U/kg or who had a change in type or dose of lipid-altering medications or thiazolidinedione use up to 3 months before the study, fasting triglyceride level >4.5mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[103] Multinational Europe, Mexico	Neither year reported 52 Weeks	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: >10, HbA1c <: <7, BMI or weight: BMI <25, used any oral antidiabetic drug other than metformin in the prior 12 weeks, 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
Chien, 2007[47] Taiwan, Multi-center	Neither year reported 16 Weeks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age: <30, >75, 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 or weight: <18.5, >35 kg/sq-meter, current significant GI disorder, HONK, hypersensitivity to Glyburide or Metformin, current infection, treatment with insulin in last 6 m, surgery in past 4 weeks, history of cancer in 5 yr, 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 glicazide<10 mg/day, glimepiride<4mg/d, gliclizide<160mg/d)

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2007[226] Italy	Neither year reported 12 Months	Fewer than 10% of participants were excluded during run-in	< 6 months	No	NR/248 NR	Age: <18, 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 <: <7.0, BMI or weight: BMI <25 or >28, Pregnant, Nursing, Not using adequate contraception, History of ketoacidosis, Severe anemia, Non-Caucasians, SBP<=130/<=85
Schwarz, 2008[125] United States	Neither year reported 104 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	75/69 NR	Age: <18 or >77, 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, HbA1c >: <7.0, HbA1c <: >11.0, BMI or weight: <22 or >45, FBG >270, History of lactic acidosis, Congestive cardiac failure requiring pharmacologic treatment, Type 1 DM or secondary forms of DM,
Comaschi, 2008[131] Italy	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age: <35, HbA1c >: <7.5, HbA1c <: >11, Fasting C-peptide <0.33nmol/L, Had not received treatment with a stable dose of either metformin or an SU as a monotherapy for at least 3months before study entry, On other Oral Hypoglycemic agents, insulin , benzoic acid, long treatments with Beta-blockers, or corticosteroids.

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Turkmen Kemal, 2007[46] Turkey	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Patient on Diuretics, Uncontrolled Hypertension
Comaschi, 2007[109] Italy	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age: <35, HbA1c >: 11, HbA1c <: 7.5, Had not received SU or Metformin as a monotherapy at a stable dose for at least 3months, Fasting C-peptide <0.33nmol/L
Home, 2007[104] Multinational Europe, Australia and New Zealand	Start year: 2000 - End year: 2002 18 Months	Run-in period but number of participants excluded was NR	>= 6 months	NR	7428/4458 NR	Age: <40 or >75 years, HbA1c >: <7, HbA1c <: >9, BMI or weight: <25
Teramoto, 2007[33] Japan	Neither year reported 24 Weeks	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Any medication affecting glucose metabolism, History of DKA, History of Diabetic coma or pre-coma, Cushings Syndrome, History of allergy to thiazolizinediones, Tumor therapy, Receiving insulin for severe infection

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Goldstein, 2007[64] Multi-continent	Neither year reported 24 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age: <18 , >78, 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 less than 75% compliance during placebo run in period, Patient with A1c <7.5 or >11 % after diet/exercise run in/wash-out period, patients with Fasting glucose >280mg/dl after run-in period, no type 2 diabetes, type 1 diabetes
Lund, 2007[160] Denmark	Start year: 2001 - End year: 2002 8 Months	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	127/96 Outpatient: subspecialty care setting	Age: <40 for onset of diabetes diagnosis, 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 >: 9.5 with ongoing OHAs prior to study start; 10.5 on 2 visits with >1m interval, HbA1c <: 6.5 after run in period, BMI or weight: >27 kg/m^2, Pregnant, insulin treated T2DM, secondary DM, Factor II, VII, X <0.7, ongoing co-existing illness with life shortening prognosis, mental retardation or reduced intellectual behavior, h/o drug abuse, weight loss of >5kg in past 6 months prior to study start, fasting C-peptide <300 of non fasting glucagon stimulated C peptide <600, Ketonuria; Ketoacidosis
Nauck, 2007[113] United States, Multinational Europe, Multi-continent	Neither year reported 52 Weeks	Yes	< 6 months	Yes	2141/1172 NR	Age: <18 or >78, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15, Insulin use within 8weeks of screening, History of Type 1 DM, Other treatments for Hypoglycemia

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kim, 2007[34] South Korea	Neither year reported 12 Weeks	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, 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), Duration of diabetes > 5years, Not on a stable medication with a sulfonylurea and / or alpha glucosidase inhibitor for at least 3months, Episodes of ketonuria or ketoacidosis, Current malignancy, Tuberculosis, Rheumatic disease, Thyroid disease, corticosteroid treatment, Previous Thiazolidinedione or metformin treatment.
Raskin, 2007[121] United States	Neither year reported 28 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	N:/NR NR	Age: <18 or >75, HbA1c <: <=8.0, BMI or weight: BMI>40 or weight >125kg (275lbs), Pregnant, Nursing, Not using adequate contraception, If not on metformin >=1,000mg /day as a single agent or in OAD combination therapy for at least 3months before the trial., History of insulin use
Hanefeld, 2007[84] Multinational Europe	Neither year reported 52 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/598 NR	Age: <40/>80, 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 or weight: <22. >38, 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
Scott, 2007[94] United States	Neither year reported 12 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	2186/743 NR	Age: <21/ >75, 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

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kahn, 2006[30] Multi-continent	Start year: 2000 - End year: 2006 6 Years	No run-in period	NR	Yes	6676/4360 NR	Age: < 30 / > 75, 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, History of Lactic acidosis
Charbonnel, 2006[80] Multi-continent	Neither year reported 24 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	1464/701 NR	Age: < 18/ >78, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c >: 10, HbA1c <: 7, Type 1 DM, Insulin use within 8 weeks of screening, FPG > 14.4mmol/l
Rosenstock, 2006[39] Multi-continent	Start year: 2003 to 2004 32 Weeks	Yes	< 6 months	Yes	1252/468 multicenter	Age: <18 / >70, 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 >: 11, HbA1c <: 7, 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 30days 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 DKA

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[85] United States, Puerto Rico	Neither year reported 56 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/502 NR	Age: <18 , >80, 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 >: 11.5, HbA1c <: 7.5, Pregnant, Nursing, Duration of DM > than 2years, Intolerance to Rosi, Pio or Troglitazone, Drug or alcohol abuse, Previous treatment with meglitinide analog, alpha glycosidase inhibitor, metformin, insulin , SU for 3months or more, Use of Hydrochlorothiazide, joint injections, niacin greater than 250mg /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=<20, >45 ; Hypertension, Chronic pulmonary disease, history of cancer not in remission for at least 5years
Stewart, 2006[129] Multinational Europe	Start year: 2003 to 2004 32 Weeks	Yes	< 6 months	Yes	1397/526 NR	Age: < 18 , > 70, History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: 9, HbA1c <: 7, Drug naive patients with FPG <7mmol/l or >9mmol/l, patient on monotherapy with FPG < 6.0mmol/l or >8mmol/l, Prior history of exposure to thiazolidinediones within previous 6months, Use of insulin anytime in the past, Uncontrolled hypertension
Bakris, 2006[105] United States, Multi-continent, South America, Europe	Neither year reported 32 Weeks	Yes	< 6 months	Yes	560/514 NR	Age: <40 or >80 years, Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI or weight: BMI < 22, Use of any TZD in the 3months prior to screening, Use of insulin for >= 6months at any time prior to screening, Anemia, severe Angina, SBP >159 (can't adjust the BP meds during the trial), DBP >99

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Umpierrez, 2006[106] United States	Neither year reported 28 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	538/210 Outpatient: primary care, Outpatient: subspecialty care setting	Age: <18 or >79years, HbA1c >: >10, HbA1c <: <7.5, BMI or weight: BMI <24, Diagnosis of Type 2 DM <6months, No taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 - 2.0g/day) as their only OAD for at least 2months prior to the study, C-peptide <0.27nmol/L, Subjects treated with insulin, TZDs or sulpphonyurea 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
Kvapil, 2006[119] Multinational Europe	Neither year reported 16 Weeks	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 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=not adequately controlled on metformin
Derosa, 2005[124] Italy	Neither year reported 12 Months	No run-in period	< 6 months	NR	NR/99 case-report forms or computerized clinic registers	Age: < =18, 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 or weight: <= 25.3, Pregnant, Nursing, Not using adequate contraception, if no type 2 dm for min 6 months based on ADA criteria, if no metabolic syndrome based on NCEP ATP III, if no HTN, TG<=150mg/dl, c-peptide <= 1.0ng/ml, h/o ketoacidosis, anemia, receiving lipid-lowering meds, anticoagulation, Glimepiride, or a TZD

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gerich, 2005[112] United States	Neither year reported 2 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	908/428 NR	Age: <18 and >77, 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), Neuropathy, Retinopathy, HbA1c >: 11, HbA1c <: 7, BMI or weight: < 22 and >45 kg/m2, Not using adequate contraception, FPG >=15mmol/L, if type 1 dm, symptomatic hypoglycemia with >10% weight loss in previous 8 weeks, h/o lactic acidosis or CHF requiring meds, other medical conditions that could interfere with interpretation of results or pose sig risk to the subject, had to be drug naive
Derosa, 2005[107] Italy	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 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, BMI or weight: , 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 6mo, consumption of Glimepiride or TZDs or prior intolerance to these meds
Smith, 2004[227] United States, Multinational Europe	Neither year reported 52 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/598 NR	Age: 36 to 81, BMI or weight: 22 to 38, FPG 126-270, fasting C peptide >0.79ng/ml, ERROR!O3

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hallsten, 2004[126] Finland	Neither year reported 26 Weeks	Run-in period but number of participants excluded was NR	>= 6 months	Yes	NR/44 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), Neuropathy, Retinopathy, diabetes meds, oral corticosteroid treatment, BP>160/100, ERROR!O4
Nakamura, 2004[86] Japan	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: 6.5, BP < 140/90, controlled on diet alone, c peptide <0.33mmol/L, creatinine <1.5, no BP meds, malignancy, no microalbuminuria, collagen vascular disease, nondiabetic renal disease
Horton, 2004[66] NR	Neither year reported 24 Weeks	Yes	< 6 months	Yes	701/401 NR	Age: >30 y, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), Neuropathy, Retinopathy, HbA1c >: 6.8, HbA1c <: 11, type 1 or 2ry diabetes, diabetes>3m duration, FPG <15mmol/L, diabetic complication, on corticosteroids, non treatment naive
Malone, 2003[118] 14 countries not specified	Neither year reported 16 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test	Age: Not 30-75, HbA1c >: <125% of upper limit of normal by local lab within 4 weeks prior to entry, BMI or weight: >40, not type 2 dm, not use of single oral agent (metformin or SU) for 3 mo prior to study at max clinically effective dose for previous 30 days
Yang, 2003[114] China	Neither year reported 12 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/211 NR	Age: <35, >70, 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-mos

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Marre, 2002[81] Multi-continent	Neither year reported 24 Weeks	Yes	< 6 months	Yes	680/467 NR	Age: at least 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), HbA1c >: 6.8, HbA1c <: 11, BMI or weight: 20 to 35, DM at least 6m, FPG>15mmol/l, gastroparesis, change in body weight during run-in, treated with diabetes meds other than metformin 3m before study
Turner, 1999[29] United Kingdom	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; >65 yrs, FPG<6mmol/L x 2, Please note that individuals on diet only therapy who maintained their BS <6mmol/L of Fu visits were excluded
Moses, 1999[68] Australia	Neither year reported 4 to 5 Months	No run-in period	NR	NR	108/83 NR	Age: <40 or >75, 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, HbA1c <: 7.1, BMI or weight: , No Type 2 DM, Not on Metformin for more than 6 months, Alcohol Abuse, Drug Use, Intention to become pregnant, h/o Lactic Acidosis, Vitamin B12<150 pmol/l with anemia
Jibran, 2006[95] Pakistan	Start year: 2000 - End year: 2001 12 Months	NA	< 6 months	NR	NR/100 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), Poorly controlled on prior treatments (e.g. failed initial treatment), No type 2 DM, On insulin

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Leiter, 2005[69] Canada	Neither year reported 32 Weeks	No run-in period	< 6 months	Yes	720/613 Outpatient: primary care	Age: <20 or >80, HbA1c <: 9.5, no type 2 DM, FBG >=7 but <=14mmol/L
Derosa, 2006[130] Italy	Neither year reported 12 months	No run-in period	< 6 months	NR	NR/99 Outpatient: primary care, Outpatient: subspecialty care setting	history of ketoacidosis, background retinopathy, nephropathy, neuropathy, impaired liver or kidney function, anemia, CVD or cerebrovascular conditions, pregnant, lactating, of child bearing potential while not taking adequate contraceptive
Garber, 2006[108] US	24 weeks (planned duration)			Yes		Age<20 or >78, any liver disease, any kidney disease, history of CVD, HbA1c <=7.0 or >=12.0, no type 2 diabetes, other
Weissman, 2005[72] US	24 weeks (planned duration)			Yes		Age <18 or >75, any liver disease, any kidney disease, history of CVD, HbA1c <6.5 or >8.5 for patients having received prior combination treatment, <7 or >10 prior monotherapy or drug naive patients, no type 2 diabetes, other
Bailey, 2005[73] UK, 14 European countries	24 weeks (planned duration)			Yes		Age <18 or >70, history of CVD, no type 2 diabetes, other
Betteridge, 2005[228] UK	104 weeks (planned duration)			Yes		Age<35 or >75, HbA1c <7.5 or >11, no type 2 diabetes
Yamanouchi, 2005[40] Japan	12 months (planned duration)			NR		Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0, no type 2 diabetes, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Goldberg, 2005[83] US, Puerto Rico, Mexico, and Columbia	24 weeks (planned duration)			Yes		Age <35, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7 or >11.5, if naive to antihyperglycemic therapy, <7 or >9.5 if previously treated with oral antihyperglycemic therapy, no type 2 diabetes, other
Pfutzner, 2005[89] Germany	26 weeks (planned duration)			Yes		Age <40 or >75, any liver disease, any kidney disease, history of CVD, HbA1c <6.6% or >9.9%, other
Derosa, 2005[133] Italy	12 months (planned duration)			NR		Age <18, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5, no type 2 diabetes, other
Feinglos, 2005[77] US	16 weeks (planned duration)			Yes		Age <30 or >81, any liver disease, any kidney disease, history of CVD, HbA1c <7.0 or >8.5, no type 2 diabetes, other
Ramachandran, 2004[41] India	14 weeks (planned duration)			NR		Age <30 or >60, treatment experienced, HbA1c >11%, no type 2 diabetes, other
Schernthaner, 2004[42] Europe	12 months (planned duration)			NR		Age <35 or >75, treatment experienced, HbA1c <7.5 or >11, no type 2 diabetes
Derosa, 2004[48] Italy	12 months (planned duration)			NR		Age <46 or >67, any liver disease, any kidney disease, history of CVD, treatment experienced, no type 2 diabetes, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Tan, 2004[90] Denmark, Finland, Norway, and Sweden	52 weeks (planned duration)			Yes		Treatment experienced, HbA1c <7.5 or >11 for patients not receiving ODM, <7.5 or >9.5 for patients receiving ODM, no type 2 diabetes, other
Tan, 2004[91] Mexico	NR			Yes		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 diabetes, other
Natali, 2004[122] London and Italy	16 weeks (planned duration)			Yes		Age <40 or >80, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c >10 after washout, other
Raskin, 2004[92] US	12 titration and 12 maintenance weeks (planned duration)			Yes		Age <18, HbA1c <7 or >12 during previous monotherapy with sulfonylurea or metformin at 50% or more of maximal recommended dose for at least 3 months, no type 2 diabetes, other
Jovanovic, 2004[93] US	12 titration and 12 maintenance weeks (planned duration)			Yes		Age <18, HbA1c <7 or >12, no type 2 diabetes, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hanefeld, 2004[115] Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands	NR			Yes		Age <35 or >75, history of CVD, HbA1c <7.5 or >11, no type 2 diabetes, other
Lawrence, 2004[43] UK	12 titration and 12 maintenance weeks (planned duration)			Yes		Age <45 or >80, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes: <7% or >10% and for low-dose oral hypoglycemic therapy: >7.5, no type 2 diabetes, other
Garber, 2003[49] US	16 weeks (planned duration)			Yes		Age<20 or >79, any liver disease, any kidney disease, treatment experienced, HbA1c >7 or <12, no type 2 diabetes, other
Tosi, 2003[28]* Italy	6 months (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3, no type 2 diabetes, other
Goldstein, 2003[50] US	18 weeks (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, HbA1c <7.5 and >12.0, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2003[67] Italy	12 months (planned duration)			NR		Any kidney disease, history of CVD, treatment experienced, HbA1c <7, no type 2 diabetes, other
Derosa, 2003[96] Italy	12 months (planned duration)			NR		Any kidney disease, history of CVD, HbA1c <7.0%, no type 2 diabetes, other
Pavo, 2003[44] Russia and Hungary	32 weeks (planned duration)			Yes		Age<40, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5 or >11.0, no type 2 diabetes, other
Bakris, 2003[88] US and UK	52 weeks (planned duration)			Yes		NR
Virtanen, 2003[127] Finland	26 weeks (planned duration)			Yes		Age <45 or >75, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, no type 2 diabetes, other
Vakkilainen, 2002[102] Finland	Neither year reported 12 weeks (planned duration)	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/48 NR	Age: <18 or >75years, 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%, HbA1c <: >10%, BMI or weight: BMI >33, FPG >15mmol/L, Total Cholesterol >6.5mmol/L, Triglycerides >4.5mmol/L, Thyroid disease, Smoking, Nicotine therapy, Use of lipid lowering agents, insulin , hormone replacement therapy

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hallsten, 2002[45] Finland	26 weeks (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, no type 2 diabetes, other
Blonde, 2002[51] US	16 weeks (planned duration)			Yes		Age<30 or >75, any liver disease, any kidney disease, history of CVD, HbA1c <7.4, no type 2 diabetes, other
St John Sutton, 2002[123] US	52 weeks (planned duration)			Yes		Age<40 or >80, any liver disease, any kidney disease, history of CVD, no type 2 diabetes, other
Marre, 2002[52] Netherlands, Denmark, Portugal, France, Belgium	4 months (planned duration)			Yes		Age<18, any liver disease, any kidney disease, history of CVD, other
Garber, 2002[53] US	20 weeks (planned duration)			Yes		Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no type 2 diabetes, other
Gomez-Perez, 2002[74] Mexico	26 weeks (planned duration)			Yes		Age <40 or >80, any liver disease, any kidney disease, history of CVD, treatment experienced, no type 2 diabetes, other
Khan, 2002[82] US	16 weeks (planned duration)			NR		Any liver disease, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Charpentier, 2001[59] France	20 weeks (planned duration)			Yes		Age <= 34 or >= 71, any kidney disease, history of CVD, no type 2 diabetes, other
Madsbad, 2001[97] Denmark and Scandinavia	12 months (planned duration)			Yes		Age <=39 or >=76, any liver disease, any kidney disease, HbA1c <6.5 or >10, no type 2 diabetes, other
Amador-Licona, 2000[54] Mexico	12 weeks (planned duration)			NR		Age >65, any liver disease, history of CVD, other
Einhorn, 2000[75] US	16 weeks (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0, no type 2 diabetes, other
Fonseca, 2000[76] US	26 weeks (planned duration)			NR		Age <40 or >80, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no type 2 diabetes, other
Nakamura, 2000[87] Japan	3 months (planned duration)			NR		Any liver disease, history of CVD, treatment experienced, HbA1c <6.5, no type 2 diabetes, other
Horton, 2000[65] US	24 weeks (planned duration)			Yes		Age <30, any kidney disease, HbA1c <6.8 or >11, no type 2 diabetes, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Landgraf, 1999[98] Germany, Austria, and Netherlands	14 weeks (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, treatment experienced, no type 2 diabetes, other
Marbury, 1999[100] US and Canada	12 months (planned duration)			Yes		Age >37 or <75, any liver disease, any kidney disease, history of CVD, treatment experienced, retinopathy, HbA1c <6.5% or 14.6%, no type 2 diabetes, other
Wolffenbuttel, 1999[99] Germany, Austria, and Netherlands	12 months (planned duration)			NR		Age <40 or >75, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.5 if treated with diet only, >12 if treated with diet plus ODM, other
DeFronzo, 1995[58] US	29 weeks (planned duration)			NR		Age <40 or >70, any liver disease, any kidney disease, history of CVD, treatment experienced, no type 2 diabetes, other
Hermann, 1994[56] Sweden	6 months (planned duration)			Yes		No type 2 diabetes, other
Campbell, 1994[55] UK	52 weeks (planned duration)			NR		Age <40 or >69, any liver disease, any kidney disease, history of CVD, no type 2 diabetes, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Wolffenbuttel, 1993[101] Netherlands	12 (4 week titration, 8 week treatment) (planned duration)			Yes		Any liver disease, any kidney disease, HbA1c <7.0 or >12.0, no type 2 diabetes, other
Hermann, 1991[57] Sweden	6 months (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, no type 2 diabetes, other
Hermann, 1991[128] Sweden	6 months (planned duration)			NR		No type 2 diabetes, other

*Cross over study, no washout period

ALT=Alanine aminotransferase; AST=Asparate aminotransferase; DM= Diabetes mellitus; BMI=body mass index; BP=blood pressure; CAD= Coronary artery disease; CVD= Cardio Vascular Diseases; FPG= fasting plasma glucose; g/day= grams per day; g/dl= grams per deciliter; GI disorder= Gastrointestinal Disorders; HbA1c = Hemoglobin A1c; HTN=hypertension; kg= kilogram; GFR= glomerular filtration rate; met=metformin; mg/d= milligrams per day; mg= milligram; mmhg= millimeters of mercury; mmol/l= millimoles per liter; ng/ml= nanograms per milliliter; nmol/l= nanomoles per liter; NR=not reported; pmol/l=picomoles per liter; SBP= systolic blood pressure; SGOT=Serum glutamyl oxaloacetic transaminase; SGPT=Serum glutamyl pyruvic transaminase; TG= Triglyceride; TZD= thiazolidinedione; UKPDS= The UK Prospective Diabetes Study; WHO=world health organization; yrs=years

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Home, 2009[14]	Metformin+Rosiglitazone, 1117	57	601 (53.8)	C: 1105 (98.9)	93.5kg	7.8	6.1	NR
	Metformin+Sulfonylurea, 1105	57.2	584 (52.9)	C: 1087 (98.4)	93.3 kg	7.8	6.3	NR
	Metformin+Sulfonylurea, 1122	59.7	568 (50.6)	C: 1112 (99.1)	84.3kg	8	7.9	NR
	Metformin+Sulfonylurea, 2227	58.5	1152 (51.7)	C: 2199 (98.7)	31.5	7.9	7.1	233
	Rosiglitazone, 2220	58.4	1142 (51.4)	C: 2200 (99.1)	31.6	7.9	7	218
	Rosiglitazone+Sulfonylurea, 1103	59.8	541 (49)	NR	30.3 85.0kg	8	7.9	NR
Raskin, 2009[110]	Metformin+Repaglinide, 187	54.8 (20 to 87)	108	AA: 30 , Asian: 8 , C: 140 , American Indian: 1 , Other: 8	32.9	8.45	7.4	62
	Metformin+Repaglinide, 187	54.5	110	AA: 25 , Asian: 9 , C: 149 , American Indian: 1 , other: 3	32.5	8.29	7.3	58
	Metformin+Rosiglitazone, 187	55.5 (28 to 83)	95	AA: 25 , Asian: 4 , C: 148 , American Indians: 2 , Others: 8	32.2	8.46	7.1	58
Derosa, 2009[36]	Metformin, 67	55 (50 to 60)	34	C: (100)	27.2 77.7 kg	9.1	NR	7
	Metformin+Glimepiride, 66	57.7 (51.7-64.7)	32	C: (100)	27.1 77.4 kg+_5.8	9	NR	6
	Metformin+Pioglitazone, 69	57 (50 to 64)	34	C: (100)	27.4 76.4+_5.1	9.3	NR	9
	Pioglitazone, 69	54 (48 to 60)	32	C: (100)	27.5 76.7 kg	9.2	NR	9

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
van der Meer, 2009[116]	Metformin+Glimepiride, 39	56.4	39 (100)	NR	29.3	7	3	2
	Pioglitazone+Glimepiride, 39	56.8	39 (100)	NR	28.2	7.1	4	5
Kaku, 2009[70]	Metformin, 86	53	49	NR	25.4	7.55	5.6	7
	Metformin+Pioglitazone, 83	52	55	NR	25.6	7.58	4.5	9
Gupta, 2009[37]	Metformin, 17	56.9 sd 2.0	6 (37.5)	C: (62.5)	36.4 sd 1.7 97.8 sd 3.8	6.0 sd 0.2	NR	1
	Pioglitazone, 16	59.2 sd 2.5	4	C: (78.5)	35.7 sd 1.7 98.5 sd 3.4	6.2 sd 0.2	NR	2
	Pioglitazone, 18	55.7 sd 2.4	6	C: (50)	34.3 sd 1.4 95.3 sd 4.5	6.4 sd 0.2	NR	0
Williams-Herman, 2009[63]	Metformin, 182	54.2	62 (45)	NR	32 sd 7	8.5	4.1	46
	Metformin, 182	53.7	58 (48)	NR	32	8.7	4.1	56
	Metformin+Sitagliptin, 182	53.6	65 (41)	NR	32	8.7	4.6	41
	Metformin+Sitagliptin, 190	53.7	78 (53)	NR	32	8.8	4.1	42
	Sitagliptin, 179	53.5	55 (52)	NR	31	8.7	3.9	57
Derosa, 2009[111]	Metformin+Glibenclamide, 114	56 (52 to 60)	58	NR	26.5	8.2	4	5
	Metformin+Nateglinide, 119	55 (50 to 60)	58	NR	26.4	8.1	4	5
Nauck, 2009[78]	Metformin, 122	56 years	(60)	AA: (3), Asian: (7), C: (88), other: (3)	31.6	8.4	8 years	48
	Metformin+Glimepiride, 244	57	(57)	AA: (2), Asian: (9), C: (89), other: (1)	31.2	8.4	8	34
Erdem, 2008[31]	Metformin, 27	55.09 sd 9.9	9	NR	31.41 sd 3.8	6.74 sd 1.3	NR	4
	Pioglitazone, 26	54.9 sd 7.8	8	NR	30.41 sd 4.2	6.34 sd 1.2	NR	5

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Iliadis, 2007[38]	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[71]	Metformin, 92	55.3	54 (59)	Asian: 36 (39), C: 56 (61)	30 84.6 kg	7.7	5.4	9
	Metformin+Rosiglitazone, 87	54.8	55 (63)	Asian: 33 (38), C: 51 (59), others: 3 (3)	30.4 84.9 kg	7.7	4.6	2
	Metformin+Sitagliptin, 94	55.2	52 (55)	Asian: 36 (38), C: 57 (61), others: 1 (1)	30.3 83.1	7.8	4.9	9
Seufert, 2008[117]	Metformin+Sulfonylurea, 320	60	175 (54.7)	NR	30	8.8	7.1	58
	Pioglitazone+Sulfonylurea, 319	60	171 (53.6)	NR	30.2	8.81	7	38
Robbins, 2007[120]	Metformin+Glargine, 159	58.1	78 (49.4)	AA: 9 (5.7), Asian: 23 (14.6), C: 100 (63.3), H: 26 (16.4)	32 88.1kg	7.8	12.5	22
	Metformin+Insulin lispro 50/50, 158	57.4	79 (50.3)	AA: 9 (5.7), Asian: 22 (14), C: 102 (65), H: 24 (15.3)	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[103]	Metformin+Rosiglitazone, 294	58.5	155 (53)	C: 277 (94)	33 91.4kg	8	6.3	61
	Metformin+Sulfonylurea, 302	59.3	158 (52)	C: 286 (95)	32.2 88.9kg	8	6.4	71

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Chien, 2007[47]	Glyburide, 25	63	9 (53)	NR	25.3 63.7 kg	8.69	8.6 years	6
	Metformin, 25	59	7 (41)	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin+Glyburide, 26	60	15 (71)	NR	24.2 63.8 kg	8.71	9	5
	Metformin+Glyburide, 26	57	13 (62)	NR	24.2 61.3 kg	8.85	6.6 years	5
Derosa, 2007[226]	Metformin+Glibenclamide, 114	56	58		26.5	8.2	4	10
	Metformin+Nateglinide, 119	55	58	NR	26.4	8.1	5	5
Schwarz, 2008[125]	Metformin+Glyburide, 40	70.4	18 (50)	AA: 4 (11.1), C: 28 (77.8), Other: 4 (11)	33.5	7.7	2.5	18
	Metformin+Nateglinide, 35	70.1	17 (51.5)	AA: 3 (9.1), C: 26 (78.8), Other: 4 (12.1)	30.4	7.8	1.7	14
Comaschi, 2008[131]	Metformin+Glibenclamide, 80	59.9	44 (55)	NR	29.85 81.9	8.57	NR	13
	Metformin+Pioglitazone, 103	57	47 (45.63)	NR	32.2 85.8	8.4	NR	27
	Pioglitazone+Sulfonylurea, 67	62.2	38 (56.72)	NR	28.9 78.8	8.7	NR	15
Turkmen Kemal, 2007[46]	Metformin, 16	56.8 (40 to 70)	4 (25)	NR	34.5	6.3	1.5	0
	Rosiglitazone, 13	55.92 (42 to 68)	3 (30)	NR	30.8 75	6.2	2.75	1

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Comaschi, 2007[109]	Metformin+Pioglitazone, 103	57	47 (45.63)	NR	32.2 85.8	8.4	NR	27
	Metformin+Sulfonylurea, 80	59.9	44 (55)	NR	29.9 81.9	8.6	NR	13
	Pioglitazone+Sulfonylurea, 67	62.2	38 (56.72)	NR	28.9 78.8	8.7	NR	14
Home, 2007[104]	Metformin+Rosiglitazone, 259	57	141 (54)	NR	32.7 93kg	7.9	6.1	52
	Metformin+Sulfonylurea, 265	57	139 (52)	NR	91kg	7.8	7	22
	Metformin+Sulfonylurea, 284	60	149 (52)	Asian: NR	83kg	8	8.1	54
	Rosiglitazone+Sulfonylurea, 311	61	152 (49)	NR	84kg	8	7.9	74
Teramoto, 2007[33]	Glibenclamide, 46	56.4 (66.9)	35 (76)	NR	25.2	8.36	NR	5
	Pioglitazone, 46	57 (46.3-67.7)	33 (72)	NR	24.7	8.01	NR	7

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2007[64]	Metformin, 182	53.4	89 (48.9)	AA: 12 (6.6), Asian: 14 (7.7), C: 87 (47.8), H: 55 (30.2), not specified: 14 (7.7)	32.1	8.9	4.5	29
	Metformin, 182	53.2	82 (45.1)	AA: 9 (4.9), Asian: 10 (5.5), C: 106 (58.2), H: 39 (21.4), not specified: 18 (9.9)	32.2	8.7	4.4NR	182
	Metformin+Sitagliptin, 182	53.3	77 (42.3)	AA: 14 (7.7), Asian: 11 (6), C: 95 (52.2), H: 49 (26.9), not specified: 13 (7.1)	32.4	8.7	4.4	18
	Metformin+Sitagliptin, 190	54.1	105 (55.3)	AA: 13 (6.8), Asian: 9 (4.7), C: 102 (53.7), H: 55 (28.9), not specified: 11 (5.8)	32.1	8.8NR	4.5	26
	Sitagliptin, 179	53.3	93 (52)	AA: 11 (6.1), Asian: 6 (3.4), C: 93 (52), H: 52 (29.1), not specified: 17 (9.5)	31.2	8.9	4.4	37
Lund, 2007[160]	Metformin, 48	59.45	37 (77)	C: (100)	24.71 74.81 kg	7.34	(median: 3 years)	5 while on metformin prior to second crossover; 2 during washout period; and 5 while on repaglinide after crossover

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Repaglinide, 48	63.31	36 (75)	C: (100)	24.82 75.57 kg	7.57	(median: 5 years)	2 excluded on repaglinide prior to first crossover; 1 during washout, and 5 after first crossover while on metformin
Nauck, 2007[113]	Metformin+Glipizide, 584	56.6	358 (61.3)	AA: 35 (6), Asian: 49 (8.4), C: 434 (74.3), H: 46 (7.9), other: 20 (3.4)	31.3 89.7	7.6	6.2	172
	Metformin+Sitagliptin, 588	56.8 (47.5 - 66.1)	336 (57.1)	AA: 41 (7), Asian: 50 (8.5), C: 432 (73.5), H: 43 (7.3), other: 22 (3.7)		7.7	6.5	202
Kim, 2007[34]	Metformin+Glimepiride, 60	57.6	28 (50)	NR	25.8 66.7	7.7	3.4	4
	Rosiglitazone+Glimepiride, 60	56.5	30 (52.63)	NR	25.7 68.1	8.1	3.5	3
Raskin, 2007[121]	Metformin+Aspart 70/30, 79	52	41	AA: (13), Asian: (3), C: (52), H: (32), Other: (1)	31.2 88.7kg	9.9	NR	12
	Metformin+Glargine, 78	51.7	42	AA: (15), Asian: (4), C: (47), H: (32), other: (1)	30.8 86.2kg	9.9	NR	6
Hanefeld, 2007[84]	Glibenclamide, 203	60.1 (+/- 8.3)	143	AA: 0 (0), C: 201 , other: 1	28.7	8.2	6.4	13
	Rosiglitazone, 189	60.6 (+/- 9.2)	109	AA: 0 , C: 183 , other: 6	28.8	8.2	6	9
	Rosiglitazone, 195	60.4 (+/- 8.2)	133	AA: 0 (0), C: 192 , other: 3	28.7	8.1	5.9	12

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Scott, 2007[94]	Glipizide, 123	54.7 (21 to 76)	70 (56.9)	AA: 4 (3.3), Asian: 6 (4.9), C: 75 (61), other: 30 (24.4), Multiracial: 8 (6.5)	30.6	7.9	4.7	23
	Sitagliptin, 123	56.2 (34 to 75)	59 (48)	AA: 6 (4.9), Asian: 6 (4.9), C: 78 (63.4), multiracial: 7 (5.7), other: 26 (21.1)	30.5	7.9	4.9	7
	Sitagliptin, 123	55.6 (34 to 76)	71 (57.7)	AA: 11 (8.9), Asian: 6 (4.9), C: 75 (61), Multiracial: 8 (6.5), Other: 23 (18.7)	31.4	7.9	5	15
	Sitagliptin, 124	55.1 (28 to 75)	65 (52.4)	AA: 6 (4.8), Asian: 3 (2.4), C: 86 (69.4), Multiracial: 9 (7.3), Other: 20 (16.1)	30.4	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 to 76)	62 (49.6)	AA: 8 (6.4), Asian: 7 (5.6), C: 86 (68.8), multiracial: 8 (6.4), other: 16 (12.8)	30.8	7.9	4.3	18
Kahn, 2006[30]	Glyburide, 1441	56.4 (+/- 10.2)	836 (58)	AA: 61 (4.2), Asian: 32 (2.2), C: 1282 (89), H: 61 (4.2), Other: 5 (0.3)	32.2 92	7.35	(<1 year: 637, 02-Jan: 751, >2: 53)	634
	Metformin, 1454	57.9 (+/- 9.9)	864 (59.4)	AA: 54 (3.7), Asian: 35 (2.4), C: 1295 (89.1), H: 55 (3.8), Other: 15 (1)	32.1 91.6	7.36	(< 1 year: 673, 02-Jan: 724, >2: 57)	551
	Rosiglitazone, 1456	56.3 (+/- 10.0)	811 (55.7)	AA: 61 (4.2), Asian: 39 (2.7), C: 1270 (87.2), H: 76 (5.2), other: 10 (0.7)	32.2 91.5	7.36	(<1: 651, 02-Jan: 758, >2: 47)	539
Charbonnel, 2006[80]	Metformin, 237	54.7 (+/- 9.7)	141 (59.5)	AA: 14 (5.9), Asian: 26 (11), C: 159 (67.1), H: 28 (11.8), other: 10 (4.2)	31.5	(<8: 128, >= 8 -8.9: 71, >=9: 36)	6.6	45

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin+Sitagliptin, 464	54.4 (+/- 10.4)	259 (55.8)	AA: 31 (6.7), Asian: 49 (10.6), C: 293 (63.1), H: 72 (15.5)	30.9	(<8: 253, >=8 -8.9: 146, >=9: 64)	6	48
Rosenstock, 2006[39]	Metformin, 154	51.5 (+/- 10.4)	87 (56)	AA: 8 (5), Asian: 22 (14), C: 90 (58), H: 33 (21), other: 1 (<1)	32.5	8.8	2.9	31
	Metformin+Rosiglitazone, 155	50.1 (+/- 10.7)	89 (57)	AA: 10 (6), Asian: 19 (12), C: 83 (54), H: 41 (26)	33.2	8.9	2.3	19
	Rosiglitazone, 159	50.6 (+/- 10.26)	93 (58)	AA: 8 (5), Asian: 22 (14), C: 94 (59), H: 31 (19), Other: 4 (3)	32.8	8.8	2.7	22
Jain, 2006[85]	Glyburide, 251	52.1 (+/- 12.39)	141 (56.2)	AA: 34 (13.5), Asian: 0 (0), C: 165 (65.7), H: 50 (19.9), Native American: 1 (0.4), Other: 1 (0.4)	32.8 94.3kg	9.2	0.78 (9.4 mo)	123
	Pioglitazone, 251	52.1 (+/- 11.28)	133 (53)	AA: 40 (15.9), Asian: 4 (1.6), C: 153 (61), H: 52 (20.7), 0ther: 1 (0.4), Native American: 1 (0.4)	32.5 93.9kg	9.2	0.8 (9.6 months)	117
Stewart, 2006[129]	Metformin, 272	59 (+/- 7.9)	151 (56)	AA: 1 (<1), Asian: 1 (<1), C: 268 (99), H: 1 (<1), Native Hawaiian/other Pacific Islander: 1 (<1)	30.6 87.2	7.2 (Range: 5.4-10.7)	3.7	54
	Metformin+Rosiglitazone, 254	58.8 (+/- 8.4)	139 (55)	AA: 0 (0), Asian: 3 (1), C: 250 (98), H: 1 (<1), Native Hawaiian /other pacific islander: 0 (0)	30.9 88.1	7.2 (Range: 5.8-9.4)	3.7	50
Bakris, 2006[105]	Metformin+Glyburide, 185	58.8	124 (69)	C: 137 (76)	31.8 90.3	8.3	7.6	5
	Metformin+Rosiglitazone, 204	60	122 (63)	C: 151 (78)	31.6 89.2	8.5	8	10

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Umpierrez, 2006[106]	Metformin+Glimepiride, 96	51.6	53 (55.2)	NR	34.54	8.4	4.9	11
	Metformin+Pioglitazone, 109	55.7	56 (52.3)	AA: 17 (15.9), Asian: 4 (3.7), C: 84 (78.5), H: 2 (1.9), OTHER: 0 (0)	33.81	8.31	5.9	17
Kvapil, 2006[119]	Metformin+Aspart 70/30, 116	56.4 (+/- 9.0)	53	NR	30.4 +/- 4.0 85.1kg +/- 15.1	9.3 +/- 1.3	6.7 +/- 5.7	11
	Metformin+Glibenclamide, 114	58.1 (+/- 8.8)	52	NR	30.5 +/-4.4 84.0 +/- 13.4	9.4 +/-1.4	8.1 +/- 6.2	5
Derosa, 2005[124]	Metformin+Glimepiride, 49	52 (+/-5)	23	NR	26.8 +/-1.5 75.6 +/-4.2	7.9 +/- 0.6	4 +/-3	2
	Metformin+Rosiglitazone, 50	54 (+/-4)	25	NR	26.6+/-1.3 74.2+/-3.6	8.0 +/-0.7	5 +/-3	2
Gerich, 2005[112]	Metformin+Glyburide, 209	53.5 (+/- 11.6)	95 (48)	AA: 33 (16.7), Asian: 1 (0.5), C: 129 (65.2), other: 35 (17.7)	33.5 +/- 5.6	8.3 +/- 1.1	2.0+/- 4.3	87
	Metformin+Nateglinide, 219	52.6 (+/- 11.6)	106 (51)	AA: 27 (13), Asian: 5 (2.4), C: 134 (64.4), other: 42 (20.2)	33.3 +/- 6.0	8.4 +/- 1.2	1.5 +/- 2.9	78
Derosa, 2005[107]	Metformin+Glimepiride, 49	52 (+/-5)	23	NR	26.8+/-1.5	7.9+/-0.6	4+/-3	2
	Metformin+Rosiglitazone, 50	54 (+/-4)	25	NR	26.6 +/- 1.3	8.0 +/- 0.7	5 +/-3	2
Smith, 2004[227]	Glyburide, 203	60	142 (70)	NR	28.7	8.2	6.4	0
	Rosiglitazone, 384	61	125	NR	28.7	8.1	6	NR
Hallsten, 2004[126]	Metformin, 9	54	5	NR	29.9	6.8	NR	2
	Rosiglitazone, 14	59.4	11		29	6.6	NR	NR
Nakamura, 2004[86]	Glibenclamide, 15	55	8	NR	NR NR	7.8	19.2	0
	Pioglitazone, 15	57	9	NR	NR NR	7.9	17.5	NR

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Horton, 2004[66]	Metformin, 104	55.4	70 (67.3)	NR	29.9	8.3	3.7	NR
	Metformin+Nateglinide, 89	57.7	58 (65.2)		30.6	8.2	3.4	NR
	Nateglinide, 104	(57.9)	59 (56.7)	NR	29.9	8.1	4.7	NR
Malone, 2003[118]	Metformin+Glibenclamide, 301	59 (+/-9.3)	146 (49)	AA: 3 (1), C: 268 (89), H: 18 (6), other: 12 (4)	29.6 +/- 4.5 81.7 +/- 15.7 kg	9.27 +/- 1.55	7.4 +/- 5.4	29
	Metformin+Lispro 75/25, 296	58 (+/-8.8)	169 (57)	AA: 2 (0.7), C: 263 (88.9), H: 22 (7.4), other: 9 (3)	29.8 +/- 4.4 83.0+/- 15.2	9.17 +/- 1.50	8.0 +/-5.8	25
Yang, 2003[114]	Metformin+Sulfonylurea,	NR	NR	NR	NR NR	8.59	NR	NR
	Rosiglitazone+Sulfonylurea,	NR	NR	NR	NR NR	8.61	NR	NR
Marre, 2002[81]	Metformin, 152	56.4	84 (55.3)	AA: 5 (3.3), Asian: 4 (2.6), C: 138 (30/8)	29.6	8.25	6.5	16
	Metformin+Nateglinide, 155	57.9	95 (61.3)	AA: 7 (4.5), Asian: 5 (3.2), C: 140 (90.3)	29.4	7.99	7.2	18
	Metformin+Nateglinide, 160	57.3	98 (61.3)	AA: 6 (3.8), Asian: 5 (3.1), C: 146 (91.3)	29.3	8.18	6.8	15
Turner, 1999[29]	Any in the Sulfonylurea class, 1305	NR	NR	NR	NR	NR	NR	NR
	Metformin, 340	NR	NR	NR	NR	NR	NR	NR by group
	Total, 4075	53	NR	AA: (9), Asian: (10), C: (81)	29	(median: 9.1)	NR	4 loss to followup
Moses, 1999[68]	Metformin, 27	57.8	17	Asian: 2 , C: 23 , not specified: 2	31.8	8.6	8	0
	Metformin+Repaglinide, 27	57.2	18	C: 26 , 1: not specified	33.2	8.3	5.9	0
	Repaglinide, 28	60.3	15	Asian: 2 , C: 26	31.3	8.6	7	0

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Jibran, 2006[95]	Glibenclamide, 50	45.8	10	NR	30.4 72.7 kg	10.2	0	0
	Repaglinide, 50	46.6	16	NR	27.1 65.8 kg	9.9	0	0
Leiter, 2005[69]	Metformin, 78	60	44	C: 61 , Others: 17	32.2	7.5	5.7	13
	Metformin+Rosiglitazone, 158	58	103	C: 120 , Others: 38	33	7.5	5.3	18
Derosa, 2006[130]	Metformin+Rosiglitazone, 48	54	25 (52)	NR	26.6	8	5	4 from both groups
	Metformin+Glimepiride, 47	52	23(49)	NR	26.8	7.9	4	4 from both groups
Garber, 2006[108]	Diet + Metformin + Rosiglitazone, 158	56 (24 - 78)	102	AA: 9 (6), C: 125 (79), Asian: 4 (3), H: 16 (10), O: 4 (3)	32 94	8.4	6	
	Diet + Metformin + glibenclamide, 160	56 (31 - 78)	90	AA: 8 (5), C: 128 (80), Asian: 4 (3), H: 17 (11), O: 3 (2)	32 93	8.5	5	
Weissman, 2005[72]	Metformin + Rosiglitazone, 358	55.5	NR	NR	34.4 98.2	8.05	NR	
	Metformin, 351	55.7	NR	NR	33.8 96.7	7.97	NR	
Bailey, 2005[73]	Metformin + Rosiglitazone, 288	58.1	168 (58)	AA: 2 (1), C: 280 (97), Asian: 3 (1), H: 0, O: 3 (1)	32.2 90.9	7.4	6	
	Metformin, 280	57.6	159 (57)	AA: 1 (<1), C: 273 (98), Asian: 3 (1), H: 0, O: 3 (1)	32.1 89.5	7.5	6.1	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Betteridge, 2005[228]	Metformin + Pioglitazone, 317	NR	NR	NR	NR NR	NR	NR	
	Metformin + unspecified Sulfonylurea, 320	NR	NR	NR	NR NR	NR	NR	
	Unspecified Sulfonylurea + Pioglitazone, 319	NR	NR	NR	NR NR	NR	NR	
Yamanouchi, 2005[40]	Diet + exercise + Pioglitazone, 38	55.2 (46 - 64.4)	18	AA: 0, C: 0, Asian: 0, H: 0, O: (100)	25.8 NR	10.2	3.2 months	
	Diet + exercise + glimepiride, 37	55.6 (46.3 - 64.9)	19	AA: 0, C: 0, Asian: 0, H: 0, O: (100)	25.6 NR	9.8	3.3 months	
	Diet + exercise + Metformin, 39	54.7 (44.9 - 64.5)	20	AA: 0, C: 0, Asian: 0, H: 0, O: (100)	26.2 NR	9.9	3 months	
Goldberg, 2005[83]	Diet + Pioglitazone, 369	55.9	199 (53.9)	AA: 9 (2.4), C: 239 (64.8), Asian: 10 (2.7), H: 105 (28.5), O: 6 (1.6)	33.7 93.7	7.6	3.9	
	Diet + Rosiglitazone, 366	56.3	201 (54.9)	AA: 10 (2.7), C: 219 (59.8), Asian: 12 (3.3), H: 118 (32.2), O: 7 (1.9)	32.6 92.5	7.5	4	
Pfutzner, 2005[89]	Glimepiride, 84	63	52 (61.9)	AA: 0, C: 81 (96.4), Asian: 0, H: 0, O: 3 (3.7)	31.8 NR	7.44	6.9	
	Pioglitazone, 89	62.2	58 (61.8)	AA: 0, C: 88 (98.8), Asian: 0, H: 0, O: 1 (1.1)	31.7 NR	7.52	7.4	
Derosa, 2005[133]	Diet + exercise + behavioral therapy + Metformin + glimepiride, 47	52 (47 - 57)	23	NR	26.8 NR	7.9	4	
	Diet + exercise + behavioral therapy Metformin + Rosiglitazone, 48	54 (50 - 58)	25	NR	26.6 NR	8	5	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Feinglos, 2005[77]	Metformin + glipizide, 61	57.7 (30-80)	28	AA: 5 (8.2), C: 48 (78.7), Asian: 2 (3.3), H: 5 (8.2), O: 1 (1.6)	31.7 90	7.45	6.5	
	Placebo + Metformin, 61	58.8 (40-81)	25	AA: 10 (16.4), C: 42 (68.9), Asian: 2 (3.3), H: 5 (8.2), O: 2 (3.3)	32.1 90.8	7.64	4.6	
Ramachandran, 2004[41]	Diet + glimepiride, 18	45.3	14	AA: 0, C: 0, Asian: 0, H: 0, O: 100	24.6 65.7	10.2	0	
	Diet + Metformin, 21	44.4	15	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.7 67.7	9.6	0	
	Diet + Pioglitazone, 23	45.1	17	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.5 68.9	9.3	0	
Schernthaner, 2004[42]	Placebo + diet + Metformin, 597	56	345 (57.8)	NR	31.4 89.7	8.7	3.1	
	Placebo + diet + Pioglitazone, 597	57	314 (52.6)	NR	31.2 88.2	8.7	3.4	
Derosa, 2004[48]	Placebo + diet + exercise + glimepiride, 81	56	38	NR	27.6 NR	8.5	NR	
	Placebo + diet + exercise + Metformin, 83	58	42	NR	28.1 NR	8.4	NR	
Tan, 2004[90]	Glibenclamide, 109	57.9	80 (73)	AA: 0, C: 109 (100), Asian: 0, H: 0, O: 0	29.6 89	8.5	62.6 months	
	Pioglitazone, 91	60	56 (62)	AA: 0, C: 90 (99), Asian: 0, H: 0, O: 1 (1)	30.2 88.4	8.4	57.1 months	

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Tan, 2004[91]	Diet + exercise + glimepiride, 123	55.7	65 (53)	AA: 0, C: 1 (1), Asian: 0, H: 122 (99), O: 0	28.8 74.5	8.45	81.2 months	
	Diet + exercise + Pioglitazone, 121	55.1	54 (45)	AA: 0, C: 0 (0), Asian: 0, H: 121 (100), O: 0	29.3 74.2	8.54	77.8 months	
Natali, 2004[122]	Metformin, 28	58	22	NR	28 NR	7.8	6.3	
	Rosiglitazone, 24	59	22	NR	27.6 NR	7.7	6.5	
Raskin, 2004[92]	Repaglinide + Rosiglitazone, 127	57.5	65	AA: 21, C: (83), Asian: 0, H: 4, O: 19	NR NR	NR	7.3	
	Repaglinide, 63	58.5	39	AA: 10, C: (40), Asian: 0, H: 1, O: 12	NR NR	NR	7.2	
	Rosiglitazone, 62	56.6	33	AA: 8, C: (42), Asian: 0, H: 0, O: 12	NR NR	NR	7.4	
Jovanovic, 2004[93]	Pioglitazone, 62	56.2	31	AA: 7, C: 51, Asian: 0, H: 2, O: 2	32.1 NR	9.1	6.1	
	Repaglinide, 61	57.8	36	AA: 7, C: 46, Asian: 0, H: 3, O: 5	31.2 NR	9	6.9	
Hanefeld, 2004[115]	Placebo + Metformin + unspecified Sulfonylurea, 320	60	175 (54.7)	AA: 3 (0.9), C: 315 (98.4), Asian: 0, H: 0, O: 2 (0.6)	30 84.9	8.8	7.1	
	Placebo + unspecified Sulfonylurea + Pioglitazone, 31	60	171 (53.6)	AA: 2 (0.6), C: 317 (99.4), Asian: 0, H: 0, O: 0 (0)	30.2 85.3	8.82	7	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Lawrence, 2004[43]	Metformin, 20	59.5	12	NR	(Median 29.2) NR	8.04	NR	
	Pioglitazone, 20	60.4	14	NR	(Median 30.6) NR	7.43	NR	
Garber, 2003[49]	Glyburide, 151	55.3	66 (43.7)	AA: 11 (7.3), C: 123 (81.5), Asian: 0, H: 12 (7.9), O: 5 (3.3)	31.1 91	8.7	3	
	Metformin + glyburide, 171	55.6	76 (44)	AA: 18 (10.5), C: 132 (77.2), Asian: 0, H: 15 (8.8), O: 6 (3.5)	31.4 91.9	8.8	3	
	Metformin, 164	54.7	71 (43.3)	AA: 11 (6.7), C: 132 (80.5), Asian: 0, H: 15 (9.1), O: 6 (3.7)	31.4 92.8	8.5	2.6	
Tosi, 2003[28]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	
	Glibenclamide, 21	NR	NR	NR	NR NR	NR	NR	
	Metformin + glibenclamide, 39	NR	NR	NR	NR NR	NR	NR	
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	
	Metformin, 20	NR	NR	NR	NR NR	NR	NR	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2003[50]	Glipizide, 84	57.4	(64.3)	AA: (11.9), C: (71.4), Asian: (2.4), H: (14.3), O: 0	30.6 89.9	8.9	6.5	
	Metformin + glipizide, 87	54.6	(58.6)	AA: (11.5), C: (72.4), Asian: (0), H: (16.1), O: 0	31.7 94	8.7	5.9	
	Metformin, 76	56.6	(61.8)	AA: (15.8), C: (65.8), Asian: (1.3), H: (17.1), O: 0	31.6 93.8	8.7	7.3	
Derosa, 2003[67]	Diet + exercise + Metformin, 56	52	27	NR	24.7 72.3	7.4	5	
	Diet + exercise + Repaglinide, 56	55	29	NR	25.2 70.2	7.6	4	
Derosa, 2003[96]	Placebo + glimepiride, 62	54	30	NR	26.4 77.1	7.8	NR	
	Placebo + Repaglinide, 62	56	31	NR	26.1 76.4	8	NR	
Pavo, 2003[44]	Placebo + Metformin, 100	55.8	(56)	NR	31.1 88.9	8.6	0.53	
	Placebo + Pioglitazone, 105	54.2	(43.8)	NR	31.3 86.6	8.6	0.47	
Bakris, 2003[88]	Rosiglitazone, 57	5.1	(75)	NR	NR NR	9.1	NR	
	Glyburide, 64	56.1	(71)	NR	NR NR	9.5	NR	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Virtanen, 2003[127]	Diet + Metformin, 13	58	8	NR	29.9 88.8	6.9	NR	
	Diet + Rosiglitazone, 14	58	10	NR	29.1 83.7	6.8	NR	
Vakkilainen, 2002[102]	Placebo + glibenclamide, 20	63 NR	AA: 0, C: (100), Asian: 0, H: 0, O: 0	28.8	NR 7.6	NR		
	Placebo + Nateglinide, 23	63 NR	AA: 0, C: (100), Asian: 0, H: 0, O: 0	27.8	NR 7.6	NR		
Hallsten, 2002[45]	Diet + Metformin, 13	57.8	8	NR	29.9 NR	6.9	NR	
	Diet + Rosiglitazone, 14	58.6	10	NR	29.3 NR	6.8	NR	
Blonde, 2002[51]	Glyburide, 164	55.8	94 (57.3)	AA: 20 (12.2), C: 109 (66.5), Asian: 0, H: 28 (17.1), O: 7 (4.3)	30.3 88	9.64	7.01	
	Metformin + glyburide, 160	55.4	89 (55.6)	AA: 20 (12.5), C: 112 (70), Asian: 0, H: 25 (15.6), O: 3 (1.9)	30.7 89.4	9.41	7.36	
	Metformin + glyburide, 162	55.6	103 (63.6)	AA: 15 (9.3), C: 110 (67.9), Asian: 0, H: 31 (19.1), O: 6 (3.7)	30.6 89.6	9.42	6.97	
	Metformin, 153	57.6	95 (62.1)	AA: 16 (10.5), C: 105 (69.3), Asian: 0, H: 26 (17), O: 5 (3.3)	30.6 89.5	9.51	8.18	
St John Sutton, 2002[123]	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	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	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	
Marre, 2002[52]	Glibenclamide, 103	58.7	57	NR	29.3 82.5	7.88	6.6	
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7	7.89	5.9	
	Metformin + glibenclamide, 103	60.7	56	NR	29.7 83.1	7.62	6.7	
	Metformin, 104	57.5	62	NR	29.9 84.9	8.09	5.4	
Garber, 2002[53]	Glyburide, 161	56.5	82	AA: 126, C: 126, Asian: 0, H: 14, O: 6	30.3 87.2	8.21	2.81	
	Metformin + glyburide, 158	56.9	91	AA: 117, C: 117, Asian: 0, H: 18, O: 3	30.1 88.8	8.25	3.52	
	Metformin + glyburide, 165	58.1	96	AA: 131, C: 131, Asian: 0, H: 16, O: 8	29.6 86.7	8.18	3.3	
	Metformin, 161	56	93	AA: 130, C: 130, Asian: 0, H: 20, O: 4	30.4 88.6	8.26	2.98	
Gomez-Perez, 2002[74]	Metformin + Rosiglitazone, 35	51.7 (40 - 73)	10	AA: 0, C: 0, Asian: 0, H: 28, O: 7	28 NR	NR	11.1	
	Metformin + Rosiglitazone, 36	54.2 (42 - 76)	7	AA: 0, C: 4, Asian: 0, H: 26, O: 6	27.6 NR	NR	10.7	
	Placebo + Metformin, 34	53.4 (40 - 68)	10	AA: 0, C: 1, Asian: 0, H: 26, O: 7	28.5 NR	NR	9.1	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Khan, 2002[82]	Pioglitazone, 67	57.8	35	NR	35.2 NR	8	NR	
	Rosiglitazone, 60	57.1	27	NR	35.6 NR	7.9	NR	
Charpentier, 2001[59]	Metformin + glimepiride, 147	56.8 (36 - 70)	87 (59)	NR	29.5 81.2	6.4	5.6	
	Placebo + glimepiride, 150	55.4 (35 - 70)	87 (58)	NR	29.3 81	6.5	5.3	
	Placebo + Metformin, 75	56.7 (36 - 69)	45 (60)	NR	29.2 82.2	6.8	7	
Madsbad, 2001[97]	Placebo + glipizide, 81	62	52	NR	28 83.6	7.2	7	
	Repaglinide, 175	60.2	107	NR	28 82.9	7.3	8.1	
Amador-Licona, 2000[54]	Glibenclamide, 23	48.2	7	NR	30.4 73.2	8.4	4	
	Metformin, 28	49.3	11	NR	26.8 70.7	8.5	4.5	
Einhorn, 2000[75]	Diet + Metformin + Pioglitazone, 168	55.5	92 (54.8)	AA: 14 (8.3), C: 136 (81), Asian: 0, H: 17 (10.1), O: 1 (0.6)	32.11 NR	9.86	NR	
	Placebo + diet + Metformin, 160	55.7	96 (60)	AA: 10 (6.3), C: 139 (86.9), Asian: 0, H: 6 (3.8), O: 5 (3.1)	32.12 NR	9.75	NR	
Fonseca, 2000[76]	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	

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Author, year	Group, N	Mean age (age range)	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	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	
	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	
Nakamura, 2000[87]	Glibenclamide, 15	61	8	NR	NR NR	7.8	14	
	Pioglitazone, 15	60	7	NR	NR NR	7.7	16	
Horton, 2000[65]	Metformin + Nateglinide, 172	58.4	101	AA: (11.6), C: (82.6), Asian: (0.6), H: 0, O: 5.2	30 NR	8.4	4.5	
	Metformin, 178	56.8	121	AA: (9.6), C: (79.2), Asian: (2.2), H: 0, O: 9	29.6 NR	8.4	7.5	
	Nateglinide, 179	58.6	110	AA: (9.5), C: (82.1), Asian: (2.8), H: 0, O: 5.6	29.6 NR	8.3	4.7	
Landgraf, 1999[98]	Placebo + glibenclamide, 100	63	57	AA: 6, C: 93, Asian: 0, H: 0, O: 1	27.5 79	8	10	
	Repaglinide, 94	61	56	AA: 0, C: 90, Asian: 0, H: 0, O: 4	27.6 80	7.8	10	
Marbury, 1999[100]	Placebo + glyburide, 182	58.7	120 (66)	AA: 16 (9), C: 144 (79), Asian: 0, H: 0, O: 22 (12)	29.1 NR	8.9	8.3	
	Repaglinide, 362	58.3	242 (67)	AA: 33 (9), C: 279 (77), Asian: 0, H: 0, O: 50 (14)	29.4 NR	8.7	7.2	

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Wolffenbuttel, 1999[99]	Placebo + glyburide, 139	61	(68)	NR	28 81.3	7	(Median 6)	
	Repaglinide, 286	61	(62)	NR	28.4 81.5	7.1	(Median 6)	
DeFronzo, 1995[58]	Metformin + glyburide, 213	55	98	NR	29 92.1	8.8	7.8	
	Metformin, 143	53	62	NR	29.9 94.4	8.4	6	
	Placebo + glyburide, 209	56	103	NR	29.1 92.6	8.5	8.7	
	Placebo + Metformin, 210	55	96	NR	29.4 92.6	8.9	8.4	
Hermann, 1994[56]	Diet + glibenclamide, 21	NR	NR	NR	NR 82.6	6.7	NR	
	Diet + Metformin + glibenclamide, 13	NR	NR	NR	NR 84.6	7.8	NR	
	Diet + Metformin + glibenclamide, 13	NR	NR	NR	NR 76	7.8	NR	
	Diet + Metformin + glibenclamide, 18	NR	NR	NR	NR 83.2	8.4	NR	
	Diet + Metformin + glibenclamide, 54	NR	NR	NR	NR 80.2	6.8	NR	
	Diet + Metformin, 25	60 (34 - 74)	(0.63)	NR	NR 78.6	6.9	4	

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Campbell, 1994[55]	Glipizide, 24	57	8	NR	31.2 82.2	11.8	2.8	
	Metformin, 24	57	8	NR	29.6 78.2	11.5	2.3	
Wolffenbuttel, 1993[101]	Glibenclamide, 15	62 (45 - 75)	25	NR	26.1 70.9	(Range7.0 - 12.0)	9	
	Repaglinide, 29	62 (45 - 75)	25	NR	26.1 74	(Range7.0 - 12.0)	9	
Hermann, 1991[57]	Diet + Metformin, 16	60 overall (38 - 73 overall)	(64 overall)	NR	27 76.5	6.7	NR	
	Diet + glibenclamide, 17	60 overall (38 - 73 overall)	(64 overall)	NR	29.2 84.1	6.6	NR	
	Diet + Metformin + glibenclamide, 11	60 overall (38 - 73 overall)	(64 overall)	NR	26.1 74.4	7.8	NR	
	Diet + Metformin + glibenclamide, 12	60 overall (38 - 73 overall)	(64 overall)	NR	30 87.3	7.7	NR	
Hermann, 1991[128]	Diet + glibenclamide, 34	NR	NR	NR	NR NR	NR	NR	
	Diet + Metformin + glibenclamide, 72	60 (34 - 74)	79	NR	28.4 82.3	NR	NR	
	Diet + Metformin, 38	NR	NR	NR	NR NR	NR	NR	

AA=African American; C=Caucasian; H=Hispanic; kg=kilogram; NR=Not reported; sd=Standard deviation

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Metformin vs Thiazolidinedione						
Derosa 2009[36]	GP1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos GP2: Pioglitazone Varied Start: 15 mg, Max: 45 mg D: 3 mos	GP1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 GP2 B: 9.2 (1.3) F: 8.2 (0.7) p: <0.01 F-B: -1 (0.7) p: <0.01				
Gupta 2009[37]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day D: every 1 wk increment by 500 mg GP2: Pioglitazone Varied, glucose: FPG > 100mg%, HgbA1c: 7.0% Start: 30, Max: 45 D: 8 wks	GP1 F-B: -0.24 (0.14) GP2 F-B: -0.09 (0.13)	GP1 F-B: -2.54 (5.36) GP2 F-B: 14.3 (4.43)	GP1 F-B: 1.67 (0.91) GP2 F-B: 6.2 (1.94)		GP1 F-B: -3.21 (0.7) GP2 F-B: 2.15 (1.09)
Gupta 2009[37]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day D: every 1 wk increment by 500 mg GP2: Pioglitazone Varied, glucose: FPG 100, HgbA1c: 7% Start: 30, Max: 45 D: 8 wks	GP1 F-B: -0.24 (0.14) GP2 F-B: -0.42 (0.17)	GP1 F-B: -2.54 (5.36) GP2 F-B: 8.85 (6.45)	GP1 F-B: 1.67 (0.91) GP2 F-B: 8.11 (1.7)	GP1 F-B: -23.7 (14.7) GP2 F-B: -155.6 (95.6)	GP1 F-B: -3.21 (0.7) GP2 F-B: -2.59 (1.25)
Erdem 2008[31]	GP1: Metformin Varied, glucose: 110 mg/dL Start: 1000 mg/day, Max: 2000 mg/day D: every 2 wks until goal GP2: Pioglitazone Varied, glucose: 110 mg/dL Start: 15 mg/day, Max: 45 mg/day D: at biwkly visits until goal	GP1 B: 6.74 (1.3) F: 6.15 (0.53) p: 0.02 GP2 B: 6.34 (1.2) p: 0.31 (between group) F: 5.6 (0.7) p: 0.01	GP1 B: 132.42 (30.9) F: 112.57 (27.8) p: <0.001 GP2 B: 132.66 (35.6) p: 0.98 F: 128.62 (30.51) p: 0.76	GP1 B: 48.31 (13.1) F: 49.37 (11.8) p: 0.39 GP2 B: 48.04 (9.4) p: 0.94 F: 53.25 (10.7) p: 0.01	GP1 B: 166.05 (81.8) F: 150.05 (67.3) p:0.32 GP2 B: 183.95 (105.04) p: 0.54 F: 162.23 (84.6) p: 0.29	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Iliadis 2007[38]	GP1: Metformin Varied, glucose: euglycemia Max: 1700 mg/day GP2: Rosiglitazone Varied, glucose: euglycemia Max: 8 mg/day	GP1 F-B: -1.7 (1.1) p: <0.001 GP2 F-B: -1 (0.7) p: <0.01	GP1 F-B: 1 (17) p: NSG GP2 F-B: 3 (24) p: NSG	GP1 F-B: 1 (3) p: NSG GP2 F-B: 0.8 (5) p: NSG	GP1 F-B: -29 (101) p: NSG GP2 F-B: 22 (73) p: NSG	GP1 F-B: -2.5 (3.5) p: <0.05 (for within-group change) GP2 F-B: -0.3 (3.3) p: NSG (for within-group change)
Turkmen Kemal, 2007[46]	GP1: Metformin Fixed Start: 1700mg D: 6 mos GP2: Rosiglitazone Fixed Start: 8mg	GP1 B: Median: 5.95 Range: 5.6 F: Median: 5.85 Range: 1.9 GP2 B: Median: 6 Range: 2.4 F: Median: 5.95 Range: 1.9	GP1 B: Median: 3.4 range: 2.69 mmol/l F: Median: 2.62 range: 1.78 mmol/l GP2 B: Median: 2.88 range: 2.48 mmol/l F: Median: 2.48 range: 1.81 mmol/l		GP1 B: Median: 4.27 range: 5.93 F: Median: 3.36 range: 5.36 GP2 B: Median: 3.17 range: 3.96 F: Median: 3.28 range: 3.31	
Kahn, 2006[30]	GP1: Metformin Varied, glucose: <140mg Start: 500mg, Max: 2000mg GP2: Rosiglitazone Varied, glucose: <140 Start: 4mg, Max: 8mg	GP1: Annualized slope: 0.14 CI: 0.13-0.16 GP2: Annualized slope: 0.07 CI: 0.06-0.09 GP2-GP1: -0.13 CI: -0.22 - -0.05 p: 0.002				GP1: Annualized slope: -0.3 CI: -0.4 to -0.2 GP2: Annualized slope: 0.7 CI: 0.6-0.8 GP1-GP2: 6.9 CI: 6.3-7.4 p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Rosenstock 2006[39]	GP1: Metformin Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 500mg, Max: 2000mg, Mean: 1847 D: 32 wks GP2: Rosiglitazone Varied, glucose: Mean daily glucose <= 6.1 Start: 4mg, Max: 8mg, Mean: 7.7 D: 32 wks	GP1 B: 8.8 (1.0) F: (1.0) F-B: -1.8 GP2 B: 8.8 (1.0) F: (1.0) F-B: -1.6	GP1 B: 116 (coefficient of variation: 33.9) F: 103.6 (coefficient of variation: 35.5) GP2 B: 114.6 (coefficient of variation: 40.5) F: 119.7 (coefficient of variation: 58)	GP1 B: 42.9 Coefficient of variation: 23.8 F: 43 Coefficient of variation: 23 GP2 B: 42.8 Coefficient of variation: 24.5 F: 44.1 Coefficient of variation: 27	GP1 B: 175.7 Coefficient of variation: 62.3 F: 148.7 Coefficient of variation: 58.3 GP2 B: 166.6 Coefficient of variation: 67.6 F: 158.5 Coefficient of variation: 74.8	GP1 F-B: Median: -2.2 IQR: -5.5 - -0.5 GP2 F-B: Median: 1.7 IQR: -1.2 - 4.5
Hallsten, 2004[126]	GP1 : Metformin Varied Start: 500mg bid, Max: 1g bid D: 2wks GP2: Rosiglitazone Varied Start: 2mg bid, Max: 4mg bid D: 2wks	GP1 F-B: -0.2 (SE: 0.2) p:>0.05 GP2 F-B: 0.7 (SE: 0.2) p:>0.05		GP1 F-B: 0.1 (SE: 0.1) p: >0.05 GP2 F-B: 0.1 (SE: 0.1) p: >0.05	GP1 F-B: 0.2 (0.2) p: >0.05 GP2 F-B: -0.2 (0.2) p: >0.05	
Yamanouchi, 2005[40]	GP1: Metformin Fixed Start: 750mg GP2: Pioglitazone Fixed Start: 30mg for women and 45mg for men	GP1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 vs. baseline GP2 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 vs. baseline GP1-GP2: 0.2		GP1 B: 53.82 (4.68) F: 58.11 (3.51) F-B: 4.29 p: NSG vs. baseline GP2 B: 51.87 (3.51) F: 51.48 (4.68) F-B: -0.39 p: NSG vs. baseline GP1-GP2: 4.68	GP1 B: 219.83 (112.14) F: 185.12 (96.12) F-B: -39.16 p:NSG vs. baseline GP2 B: 205.59 (101.46) F: 197.58 (94.34) F-B: -8.01 p:NSG vs. baseline GP1-GP2: -31.15	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Ramachandran, 2004[41]	GP1: Metformin Varied Start: 250mg, Max: 850mg GP2: Pioglitazone Varied Start: 15mg, Max: 30mg	GP1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: p<0.05 vs. baseline GP2 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: p<0.01 vs. baseline GP1-GP2: 1.2		GP1 B: 38.22 (5.85) F: 42.9 (7.8) F-B: 4.68 p: <0.01 vs. baseline GP2 B: 39 (7.8) F: 42.9 (11.7) F-B: 3.9 GP1-GP2: 0.78	GP1 B: 258.1 (213.6) F: 195.8 (124.6) F-B: -62.3 p: <0.05 vs. baseline GP2 B: 249.2 (222.5) F: 222.5 (160.2) F-B: -26.7 GP1-GP2: -35.6	GP1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 GP2 B: 67.7 (11.5) F: 67 (11.4) F-B: 0.7 GP1-GP2: -0.4
Schernthaner, 2004[42]	GP1: Metformin Varied Start: 850mg up to 3 times/day, Max: 2550mg GP2: Pioglitazone Varied Start: 30mg, Max: 45mg	GP1 B: 8.68 (0.98) F: 7.18 F-B: -1.5 GP2 B: 8.69 (1.02) F: 7.28 F-B: -1.41 GP1-GP2: -0.09	GP1 B: 138.84 F: 134.16 F-B: -4.68 GP2 B: 138.84 F: 149.37 F-B: 10.53 GP1-GP2: -15.21	GP1 B: 44.07 F: 50.31 F-B: 6.24 GP2 B: 44.07 F: 47.19 F-B: 3.12 GP1-GP2: 3.12 p: 0.001 vs. GP2	GP1 B: 234.96 F: 180.67 F-B: -54.29 GP2 B: 232.29 F: 205.59 F-B: -26.7 GP1-GP2: -27.59 p: 0.001 vs. GP2	GP1 F-B: 1.9 GP2 F-B: -2.5 GP1-GP2: 4.4
Lawrence, 2004[43]	GP1: Metformin Varied Start: 500mg bid, Max: 1000mg tid GP2: Pioglitazone Varied Start: 30mg, Max: 45mg	GP1 B: 8.04 (0.9) F: 6.9 (0.5) F-B: -1.12 (0.84) p: <0.01 vs. baseline GP2 B: 7.43 (0.9) F: 6.62 (0.5) F-B: -0.81 (0.63) p: <0.01 vs. baseline and GP1-GP2: -0.31 p: NSG vs. GP1	GP1 B: 200.5 (42.6) F: 200.9 (50.5) F-B: 0.4 GP2 B: 194.2 (43.2) F: 202.4 (46.9) F-B: 8.2 GP1-GP2: -7.8	GP1 B: 49.6 (11.8) F: 52.7 (11.1) F-B: 3.1 p: <0.05 vs. baseline GP2 B: 48.7 (9.4) F: 46.8 (8.5) F-B: -1.9 p: NSG vs. baseline GP1-GP2: 5	GP1 B: 203 (149) F: 176 (115) F-B: -27 p:NSG vs. baseline GP2 B: 202 (110) F: 175.6 (114.4) F-B: -6.4 GP1-GP2: -0.6	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Pavo, 2003[44]	GP1: Metformin Varied Start: 850mg, Max: 2550mg GP2: Pioglitazone Varied Start: 30mg, Max: 45mg	GP1 B: 8.6 F: 7.1 F-B: -1.5 p: <0.0001 vs. baseline GP2 B: 8.6 F: 7.3 F-B: -1.3 p: <0.0001 vs. baseline GP1-GP2: -0.2 p: 0.28 vs. GP1	GP1 F-B: -7.02 p: 0.04 vs. baseline GP2 F-B: 6.24 p: 0.055 vs. baseline GP1-GP2: -13.26 p: 0.003 vs. GP2	GP1 F-B: 8.58 GP2 F-B: 5.07 GP1-GP2: 3.51 p: 0.02 vs. GP2	GP1 F-B: -80.99 p: 0.001 vs. baseline GP2 F-B: -56.07 p: 0.03 vs. baseline GP1-GP2: -24.92	GP1 B: 86.1 (15.6) F: 86.8 F-B: 0.7 (0.4) GP2 B: 88.9 (15.9) F: 90.2 F-B: -2.4 GP1-GP2: 3.1 p: <0.0001 vs. GP2
Hallsten, 2002[45]	GP1: Metformin Varied Start: 500mg bid, Max: 1000mg bid GP2: Rosiglitazone Varied Start: 2mg bid, Max: 4mg bid	GP1 B: 6.9 (0.2) F: 6.2 (0.2) F-B: -0.7 p: <0.0001 vs. baseline GP2 B: 6.8 (0.2) F: 6.5 (0.2) F-B: -0.3 p: <0.05 vs. baseline GP1-GP2: -0.4 p: NSG vs. GP1	GP1 F-B: -0.2 (SE: 0.2) mmol/l p: >0.05 GP2 F-B: 0.7 (SE: 0.2) mmol/l p: >0.05			GP1 B: 83.7 (7.9) F: 84.3 (3.5) F-B: 0.6 p: NSG vs. baseline GP2 B: 88.8 (10.8) F: 86.8 F-B: -2 p: <0.05 vs. baseline GP1-GP2: 2.6

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Natali, 2004[122]	GP1: Metformin Fixed Start: 500mg tid GP2: Rosiglitazone Fixed Start: 4mg bid		GP1 B: 118 (SE 25) F: 120 F-B: 2 GP2 B: 120 (SE 29) F: 131 F-B: 11 GP1-GP2: 10 (-4 to 23)	GP1 B: 46 (SEM: 9) F: 50 F-B: 4 GP2 B: 46 (SEM: 15) F: 49 F-B: 3 GP1-GP2: 0.4 (-5 to 6) p:NSG vs GP2	GP1 B: 142 (SEM 7.3) F: 178 F-B: 36 (32) GP2 B: 196 (SEM 251) F: 152 F-B: -44 (41) GP1-GP2: 47 p: NSG vs. GP2	GP1 B: 80.4 (SEM 10.1) F: 80.9 F-B: 0.5 (0.5) p: NSG vs. baseline GP2 B: 77.3 (SEM 12.5) F: 76.7 F-B: -0.6 (0.4) p: NSG vs. baseline GP1-GP2: 1.2 p: NSG vs. GP2
Virtanen, 2003[127]	GP1: Metformin Varied Start: 500mg bid, Max: 1000 bid GP2: Rosiglitazone Varied Start: 2mg bid, Max: 4mg bid		GP1 B: 109.2 (SE 7.8) F: 101.4 (SE 7.8) F-B: -7.8 GP2 B: 113.1 (SE 7.8) F: 136.5 (SE 7.8) F-B: 23.4 GP1-GP2: -31.2	GP1 B: 42.9 (SE: 3.9) F: 46.8 (SE: 3.9) F-B: 3.9 p: NSG vs. baseline GP2 B: 42.9 (SE: 3.9) F: 46.8 (SE: 3.9) F-B: 3.9 p: NSG vs. baseline GP1-GP2: 0	GP1 B: 151.3 (SE 17.8) F: 133.5 (SE 17.8) F-B: -17.8 GP2 B: 106.8 (SE 8.9) F: 115.7 (SE 17.8) F-B: 8.9 GP1-GP2: -26.7 p: NSG vs. GP2	
Metformin vs Sulfonylurea						

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Chien 2007[47]	GP1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean dose: 1910 mg/day D: 4 wks GP2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg/day, Max: 20 mg/day, Final mean dose: 19 mg/day D: 4 wks	GP1 B: 8.88 (1.08) F: 8.98 F-B: 0.09 (SE: 0.37) p: NS GP2 B: 8.69 (0.94) F: 9.21 F-B: 0.52 (SE: 0.24) p: 0.018				
Kahn, 2006[30]	GP1: Metformin Varied, glucose: <140mg Start: 500mg, Max: 2000mg GP2: Glyburide Varied, glucose: <140 Start: 2.5, Max: 15	GP1: Annualized slope: 0.14 CI: 0.13-0.16 GP2: Annualized slope: 0.24 CI: 0.23-0.26				GP1: Annualized slope: -0.3 CI: -0.4 to -0.2 GP2: Annualized slope: -0.2 CI: -0.3 to 0.0
Turner, 1999[29]	GP1: Metformin Varied, glucose: fpg < 6 mmol/L Max: 2550 mg/day D: 9 yrs GP2: Any in the Sulfonylurea class Varied, glucose: 6 mmol/L Max: Chlorpropramide-500 mg/day; Glyburide 20mg/day D: 9 yrs	GP1 Proportion achieving HbA1c<7% at 3 yrs: 44, CI(42-46) 6 yrs: 34, CI(32-37) 9 yrs: CI 11-15% GP2 Proportion achieving HbA1c<7% at 3 yrs: 45, CI(43-48) 6 yrs: 28, CI(26-30) 9 yrs: CI 19-23%				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Yamanouchi, 2005[40]	GP1: Metformin Fixed Start: 750mg GP2: Glimepiride Varied Start: 1mg, Max: 2mg	GP1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 vs. baseline GP2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 vs. baseline GP1-GP2: 0		GP1 B: 51.87 (3.51) F: 51.48 (4.68) F-B: -0.39 p: NSG vs. baseline GP2 B: 52.65 (4.29) F: 52.26 (4.29) F-B: -0.39 p: NSG vs. baseline GP1-GP2: 0	GP1 B: 205.59 (101.46) F: 197.58 (94.34) F-B: -8.01 p: NSG vs. baseline GP2 B: 234.07 (121.93) F: 229.62 (112.14) F-B: -4.45 p: NSG vs. baseline GP1-GP2: -3.56	
Ramachandran, 2004[41]	GP1: Metformin Varied Start: 250mg, Max: 850mg GP2: Glimepiride Varied Start: 1mg, Max: 2mg	GP1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: <0.05 vs. baseline GP2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 vs. baseline GP1-GP2: 1.1		GP1 B: 39 (7.8) F: 42.9 (11.7) F-B: 3.9 p: NSG vs. baseline GP2 B: 37.05 (11.7) F: 42.9 (7.8) F-B: 5.85 p: NSG vs. baseline GP1-GP2: -1.95	GP1 B: 249.2 (222.5) F: 222.5 (160.2) F-B: -26.7 GP2 B: 195.8 (124.6) F: 151.3 (80.1) F-B: -44.5 p: <0.05 vs. baseline GP1-GP2: 17.8	GP1 B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 GP2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 vs. baseline GP1-GP2: -2.5
Derosa, 2004[48]	GP1: Metformin Varied Start: 1000mg, Max: 1000mg tid GP2: Glimepiride Varied Start: 1mg, Max: 2mg bid	GP1 B: 8.4 (1.0) F: 7 (0.9) F-B: -1.4 (-5.7 to -0.51) p: 0.01 vs. baseline GP2 B: 8.5 (1.2) F: 6.9 (0.7) F-B: -1.6 (-6.4 to -0.47) p: 0.01 vs. baseline GP1-GP2: 0.2	GP1 B: 144 (20) F: 130 (25) F-B: -14 (-42 to -8) GP2 B: 135 (20) F: 130 (15) F-B: -5 (2.8 to 9.6) GP1-GP2: -9 p:<0.05 vs. baseline	GP1 B: 43 (5) F: 45 (4) F-B: 2 p: NSG vs. baseline GP2 B: 42 (4) F: 44 (6) F-B: 2 p: NSG vs. baseline GP1-GP2: 0	GP1 B: 180 (25) F: 165 (25) F-B: -15 p: NSG vs. baseline GP2 B: 160 (20) F: 145 (25) F-B: -15 p: NSG vs. baseline GP1-GP2: 0	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Garber, 2003[49]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Glyburide (no trade drug specified) Varied Start: 2.5mg, Max: 10mg	GP1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 GP2 B: 8.67 (1.4) F: 6.75 F-B: -1.9 GP1-GP2: 0.37	GP1 B: 122.7 (3.2) F: 117 F-B: -5.7 p:<0.05 vs. baseline GP2 B: 122.2 (3.2) F: 124.5 F-B: 2.3 p: NSG vs. baseline GP1-GP2: -8	GP1 B: 42.3 (0.9) F: 41.9 F-B: -0.4 p: NSG vs. baseline GP2 B: 41.6 (1) F: 42.1 F-B: 0.5 p: NSG vs. baseline GP1-GP2: -0.9	GP1 B: 256.8 (26.7) F: 217.2 F-B: -39.6 p: NSG vs. baseline GP2 B: 236.3 (19.1) F: 221.2 F-B: -15.1 p: NSG vs. baseline GP1-GP2: -24.5	GP1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 vs. baseline GP2 B: 91 (16.0) F: 93 F-B: 2 p: NSG vs. baseline GP1-GP2: -3.1
Tosi, 2003[28]	GP1: Metformin Varied Start: 500mg, Max: 3000mg GP2: Glibenclamide Varied Start: 5mg, Max: 15mg	GP1 B: 7.7 (1.4) F: 7.3 F-B:-0.4 GP2 B: 7.85 (1.4) F: 7.4 F-B: -0.45 GP1-GP2: 0.05				
Goldstein, 2003[50]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Glipizide Fixed Start: 15mg bid	GP1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 GP2 B: 8.9 (1.1) F: 8.5 (0.1) F-B: -0.4 GP1-GP2: 0.2	GP1 B: 109.7 (35.2) F: 102.5 F-B: -7.2 (-15 to 0.6) GP2 B: 111.2 (34.6) F: 110.8 F-B: -0.4 (-6.7 to 5.8) GP1-GP2: -6.8	GP1 B: 42.3 (9.7) F: 42.7 F-B: 0.4 p: NSG vs. baseline GP2 B: 43.5 (9.8) F: 43.9 F-B: 0.4 p: NSG vs. baseline GP1-GP2: 0	GP1 B: 218.7 (120.2) F: 217.1 F-B: -1.6 (-25.3 to 22) p: <0.05 vs. baseline GP2 B: 213.8 (127.2) F: 273.6 F-B: 59.8 (22.5 to 97.1) p: <0.05 vs. baseline GP1-GP2: -70.4	GP1 B: 94.2 (16.7 F: 91.5 F-B: -2.7 (SE 0.3) GP2 B: 90 (17.4) F: 89.6 F-B: -0.4 (SE 0.3) GP1-GP2: -2.3

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Blonde, 2002[51]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Glyburide Fixed Start: 10mg bid	GP1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 GP2 B: 9.64 (1.44) F: 9.5 F-B: -0.11 GP1-GP2: 0.5		GP1-GP2: p: NSG vs. GP2	GP1 F-B: p: NSG vs. baseline GP2 F-B: p: NSG vs. baseline	GP1 B: 89.5 (16.9) F: 87.5 F-B: -2 GP2 B: 88 (15.9) F: 88.5 F-B: 0.5 GP1-GP2: -2.5
Marre, 2002[52]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Glibenclamide Varied Start: 5mg, Max: 20mg	GP1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 GP2 B: 7.88 (1.65) F: 7.58 F-B: -0.3 GP1-GP2: 0.1 p: NSG vs. GP2	GP1 B: 148.2 (SE 39) F: 136.5 F-B: -11.7 (SE 31.2) GP2 B: 152.1 (SE 42.9) F: 148.2 F-B: -3.9 (SE 39) GP1-GP2: -7.8 p: NSG vs. GP2	GP1 B: 46.8 (11.7) F: 47.97 F-B: 1.17 p: NSG vs. baseline GP2 B: 46.8 (11.7) F: 47.19 F-B: 0.39 p: NSG vs. baseline GP1-GP2: 0.78	GP1 B: 204.7 (169.1) F: 186.9 F-B: -17.8 (89) GP2 B: 204.7 (151.3) F: 204.7 (133.5) F-B: GP1-GP2: -17.8 p: NSG vs. GP2	GP1 B: 84.9 (17.6) F: 84.1 F-B: 0.8 GP2 B: 82.5 (15.4) F: 83.4 F-B: 0.9 GP1-GP2: -1.7
Garber, 2002[53]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Glyburide Varied Start: 2.5mg, Max: 10mg	GP1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 GP2 B: 8.21 (1.09) F: 6.97 F-B: -1.24 GP1-GP2: 0.21				GP1 F-B: -0.6 p: <0.05 vs. baseline GP2 F-B: 1.7 GP1-GP2: 2.3

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Amador-Licona, 2000[54]	GP1: Metformin Varied Start: 850, Max: NR GP2: Glibenclamide Varied Start: 5, Max: NR	GP1 B: 8.5 (1.5) F: 7.6 (0.8) F-B: -0.9 p: 0.003 GP2 B: 8.4 (1.4) F: 7.6 (0.8) F-B: -0.8 p: 0.009 GP1-GP2: 0.1		GP1 B: 31.98 (8.97) F: 35.49 (8.97) F-B: 3.51 p: 0.0001 vs. baseline GP2 B: 36.66 (7.02) F: 39 (10.92) F-B: 2.34 p: 0.01 vs. baseline GP1-GP2: 1.17	GP1 B: 195.8 (81.88) F: 178 (65.86) F-B: -17.8 p: 0.04 vs. baseline GP2 B: 174.44 (81.88) F: 166.43 (97.9) F-B: -8.01 p: 0.67 vs. baseline GP1-GP2: -10.68	GP1 B: 70.7 (14.8) F: 69.6 (14.3) F-B: -0.9 p: 0.07 vs. baseline GP2 B: 73.2 (11.8) F: 74.1 (12.6) F-B: 0.9 p: 0.1 vs. baseline GP1-GP2: -1.7
Campbell, 1994[55]	GP1: Metformin Varied Start: 500mg bid, Max: 3000mg GP2: Glipizide Varied Start: 5mg, Max: 30mg	GP1 B: 11.46 (1.92) F: 8.64 (1.21) F-B: -2.57 GP2 B: 11.75 (2.11) F: 9.72 (1.91) F-B: -1.93 GP1-GP2: -0.64 p: <0.05 vs. GP2	GP1 B: 4.65 (1.07) F: 4.58 (1.19) F-B: -0.07 GP2 B: 4.51 (1.26) F: 4.99 (1.16) F-B: 0.48 GP1-GP2: -0.55 p: NSG vs. GP2	GP1 B: 35.88 (11.31) F: 37.05 (11.31) F-B: 1.17 GP2 B: 36.27 (8.58) F: 36.27 (8.58) F-B: 0 GP1-GP2: 1.17 p: NSG vs. GP2	GP1 B: 191.35 (130.83) F: 202.92 (163.76) F-B: 11.57 p: NSG vs. baseline GP2 B: 183.34 (61.41) F: 205.59 (108.58) F-B: 22.25 GP1-GP2: -10.68	GP1 B: 78.2 (15.7) F: 76.23 F-B: -1.97 GP2 B: 82.2 (16.8) F: 84.8 F-B: 2.67 GP1-GP2: -4.57 p: <0.001 vs. GP2

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1994[56]	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Glyburide Varied Start: 3.5mg, Max: 10.5mg	GP1 B: 6.9 (SE 0.3) F: 5.8 (SE 0.2) F-B: -0.9 (SE 0.2) p: 0.001 vs. baseline GP2 B: 6.7 (SE 0.3) F: 5.3 (SE 0.1) F-B: -1.3 (SE 0.2) p: 0.001 vs. baseline GP1-GP2: 0.4	GP1 B: 142.74 (SE 9.75) F: 131.82 (SE 8.97) F-B: -5.85 (SE 2.73) p: 0.052 vs. baseline GP2 B: 153.27 (SE 5.46) F: 157.56 (SE 5.07) F-B: 4.68 (SE 3.51) p: >0.1 vs. baseline GP1-GP2: -10.53	GP1 B: 31.59 (SE: 2.34) F: 30.03 (SE: 1.56) F-B: 0.78 (SE: 0.78) p: >0.1 vs. baseline GP2 B: 34.71 (SE: 1.95) F: 35.88 (SE: 1.95) F-B: 1.17 (SE: 0.78) p: >0.1 vs. baseline GP1-GP2: -0.39	GP1 B: 179.78 (SE 18.69) F: 173.55 (SE 14.24) F-B: -6.23 (SE 12.46) GP2 B: 178.89 (SE 32.93) F: 186.9 (SE 31.15) F-B: 8.01 (SE 11.57) GP1-GP2: -14.24 p: >0.1 vs. GP2	GP1 B: 78.6 (SE 2.9) F: 78.8 (SE 2.9) F-B: -0.8 (SE 0.5) p: >0.1 vs. baseline GP2 B: 82.6 (SE 2.7) F: 86.2 (SE 3.3) F-B: 2.8 (SE 0.7) p: 0.001 vs. baseline GP1-GP2: -3.6
Hermann, 1991[57]	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Glibenclamide Varied Start: 3.5mg, Max: 10.5mg	GP1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 vs. baseline GP2 B: 6.6 (1.3) F: 5.3 (0.5) F-B: -1.3 p: <0.001 vs. baseline GP1-GP2: 0.4	GP1 F-B: 0.78 (SE 3.9) GP2 F-B: 5.07 (SE 7.41) GP1-GP2: -5.85			GP1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NSG vs. baseline GP2 B: 84.1 (13.2) F: 87.4 (14.8) F-B: 3.3 p: <0.01 vs. baseline GP1-GP2: 3.7

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
DeFronzo, 1995[58]	GP1: Metformin Varied Start: 500mg, Max: 2500mg GP2: Glyburide Varied Start: 5mg bid, Max: 10mg bid	GP1 B: 8.9 F: 8.5 F-B: -0.4 (SE 0.1) GP2 B: 8.5 F: 8.7 F-B: 0.2 (SE 0.1) GP1-GP2: -0.6 p: <0.001 vs. GP2	GP1 B: 134 (SE 3) F: 129 (SE 3) F-B: -6 (SE 2) GP2 B: 136 (SE 3) F: 141 (SE 3) F-B: 5 (SE 2) GP1-GP2: -11 p: 0.009 vs GP2	GP1 B: 37 (SE 1) F: 38 (SE 1) F-B: 1 GP2 B: 39 (SE 1) F: 40 (SE 1) F-B: 0 GP1-GP2:	GP1 B: 231 (SE 12) F: 221 (SE 13) F-B: -16 (SE 7) GP2 B: 210 (SE 8) F: 227 (SE 11) F-B: 21 (SE 9) GP1-GP2: -37 p: 0.001 vs. GP2	GP1 B: 92.6 (14.5) F: 87.8 F-B: -3.8 (SE 0.2) p: <0.001 vs. baseline GP2 F-B: -0.3 (SE 0.2) p: NSG vs. baseline GP1-GP2: -3.5
Charpentier, 2001[59]	GP1: Metformin Fixed Start: 850mg tid GP2: Glimepiride Varied Start: 1mg, Max: 6mg	GP1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE 0.14) GP2 B: 6.52 (1.13) F: 6.79 (1.43) F-B: 0.27 (SE 0.09) GP1-GP2: -0.12 p: 0.369 vs. GP1		GP1 B: 46.41 (13.65) F: 48.36 F-B: 1.95 GP2 B: 45.24 (12.87) F: 45.63 F-B: 0.39 GP1-GP2: 1.56 p: 0.14 all group comparison	GP1 B: 171.77 (119.26) F: 185.12 F-B: 13.35 (104.13) GP2 B: 189.57 (143.29) F: 200.25 F-B: 10.68 (108.58) GP1-GP2: 2.67 p: 0.029 for all treatment groups	GP1 B: 82.2 (range 53-115) F: 81.46 F-B: -0.74 (2.58) GP2 B: 81 (range 48-135) F: 81.78 F-B: 0.78 (2.98) GP1-GP2: -1.52
Metformin vs DPP-IV inhibitors						
Williams-Herman, 2009[63]	GP1: Metformin Fixed Mean: 2000 mg/day GP2: Sitagliptin Fixed Mean: 100 mg/day	GP1 F-B: -1.3 CI: -1.5 - -1.2 GP2 F-B: -0.8 CI: -1 - -0.6	GP1 B: 105.3 (32.3) F: 102.3 (33.6) GP2 B: 115.1 (35.1) F: 113.5 (34.5)	GP1 B: 43.2 (9.4) F: 44.6 (10.4) GP2 B: 42.7 (9.5) F: 43.2 (10.1)	GP1 B: 172 (113.5) F: 179 (107) GP2 B: 149 (97.7) F: 155 (113.5)	GP1 F-B: -1.5 CI: -2.2 - -0.8 GP2 F-B: 0.6 CI: -0.2 - 1.4

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Williams-Herman, 2009[63]	GP1: Metformin Fixed Mean: 1000 mg/day GP2: Sitagliptin Fixed Mean: 100 mg/day	GP1 F-B: -1 CI: -1.2 - -0.8 GP2 F-B: -0.8 CI: -1 - -0.6	GP1 B: 106.8 (34.2) F: 103.6 (31.5) GP2 B: 111.4 (35.1) F: 113 (35.3)	GP1 B: 42.7 (10.5) F: 45 (12.4) GP2 B: 42.7 (9.5) F: 43.2 (10.1)	GP1 B: Median: 167 (104.2) F: Median: 173 (120) GP2 B: Median 147.5 (87.4 F: Median: 162.5 (94)	GP1 F-B: -1 CI: -1.7 - -0.3 GP2 F-B: 0.6 CI: -0.2 - 1.4
Goldstein, 2007[64]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day D: 3 wks GP2: Sitagliptin Varied, prespecified target dose Start: 50 mg/day, Max: 100 mg/day D: 1 wk	GP1 F-B: -1.13 CI: -1.29 - -0.97 GP2 F-B: -0.66 CI: -0.83 - -0.5				GP1 F-B: significant reduction relative to baseline GP2 F-B: 0
Goldstein, 2007[64]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 100 mg/day D: 1 wk GP2: Sitagliptin Varied, prespecified target dose Start: 50 mg/day, Max: 100 mg/day D: 1 wk	GP1 F-B: -0.82 CI: -0.98 - -0.66 GP2 F-B: -0.66 CI: -0.83 - -0.5				GP1 F-B: significant reduction relative to baseline GP2 F-B: 0
Metformin vs Meglitinides						

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Lund, 2007[160]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day, Mean: 1629 mg D: 12 dys GP2: Repaglinide Varied, prespecified target dose Start: 1 mg/day, Max: 6 mg/day, Mean: 4.72 mg D: 12 dys					GP1 B: 74.81 (10.1) F: 73.94 (9.88) F-B: -0.88 CI: -1.45 - -0.3 GP2 B: 75.57 (9.85) F: 75.47 (10.08) F-B: 0.7 CI: 0.12 - 1.28 GP1-GP2: -1.58 CI: -2.17 - -0.99 p: <0.001
Horton, 2004[66]	GP1: Metformin Fixed Start: 500 mg tid GP2: Nateglinide Fixed Start: 120 mg qac	GP1 F-B: -0.8 (SE: 0.1) p: <0.001 GP2 F-B: -0.8 (SE: 0.1) p: <0.001 GP1-GP2: -0.8 (SE: 0.1) p: <0.005				
Moses 1999[68]	GP1: Metformin NR GP2: Repaglinide Fixed Start: 0.5 mg, Max: 4.0 mg D: 12 to 28 days	GP1 F-B: -0.33 (SE: 0.24) CI: -0.8 - -0.5 GP2 F-B: -0.38 (SE: 0.23) CI: -0.84 - -0.08				GP1 F-B: -0.86 (SE: 0.5) GP2 F-B: 2.98 (SE: 0.49) p: <0.05

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Derosa, 2003[67]	GP1: Metformin Varied Start: 500mg bid, Max: 2500mg GP2: Repaglinide Varied Start: 0.5mg bid, Max: 4mg	GP1 B: 7.4 (0.9) F: 6.5 F-B: -0.9 p: <0.01 vs. baseline GP2 B: 7.6 (0.9) F: 6.8 F-B: -0.8 p: <0.01 vs. baseline GP1-GP2: -0.1 p: NSG vs. GP2	GP1 B: 132.21 (26.13) F: 117 F-B: -15.21 (-34.32 to -8.19) p: <0.05 vs. baseline GP2 B:127.14 (25.35) F: 115.05 F-B: -12.09 (-29.05 to 20.28) p: <0.065 vs. baseline GP1-GP2: -3.12	GP1 B: 46.41 (8.19) F: 45.224 F-B: -1.17 GP2 B: 42.51 (7.02) F: 45.63 F-B: 3.12 GP1-GP2: -4.29 p: NSG vs. GP2	GP1 B: 176.22 (4.806) F: 152.19 F-B: -24.03 (-55.18 to -15.13) p: <0.05 vs. baseline GP2 B: 156.64 (52.51) F: 140.62 F-B: -16.02 (-38.27 to 17.8) p: 0.065 vs. baseline GP1-GP2: -8.01	GP1 B: 72.3 (7.1) F: 70.3 F-B: -2 (-6 to 4) p: 0.14 vs. baseline GP2 B: 70.0 (6.5) F: 69.6 F-B: -0.4 (-0.8 to 0.28) p: >0.2 vs. baseline GP1-GP2: -1.6 p: NSG vs. GP2
Horton, 2000[65]	GP1: Metformin Fixed Start: 500mg tid GP2: Nateglinide Fixed Start: 120mg tid	GP1 B: 8.4 (1.2) F: 7.6 F-B: -0.8 (SE 0.1) p: 0.0001 vs. baseline GP2 B: 8.3 (1.0) F: 7.8 F-B: -0.5 (SE 0.1) p: 0.0001 vs. baseline GP1-GP2: -0.3 p: NSG vs. GP1				
Metformin vs Metformin+Thiazolidinedione						
Derosa, 2009[36]	GP1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos GP2: Metformin+Pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos	GP1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 GP2 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01				BMI GP1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% GP2 B: 27.4 (1.6) F: 26.9 (1.3) F-B: -1.8%

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Rosenstock, 2006[39]	GP1: Metformin Varied, mean daily glucose <= 6.1 mmol/l Start: 500mg, Max: 2000mg, Mean: 1847 D: 32 wks GP2: Metformin+Rosiglitazone Varied, mean daily glucose <= 6.1 mmol/l Start: 500mg, Max: 2000mg, Mean: 1799; Start: 2mg, Max: 8mg, Mean: 7.2mg D: 32 wks	GP1 B: 8.8 (1.0) F: (1.0) F-B: -1.8 GP2 B: 8.9 (1.1) F: 6.6 (1.0) F-B: -2.3 GP1-GP2: p: 0.008	GP1 B: 116 (coefficient of variation: 33.9) F: 103.6 (coefficient of variation: 35.5) GP2 B: 113.8 (coefficient of variation: 32.5) F: 113.5 (coefficient of variation: 30.4)	GP1 B: 42.9 Coefficient of variation: 23.8 F: 43 Coefficient of variation: 23 GP2 B: 42.6 Coefficient of variation: 21.8 F: 45 Coefficient of variation: 25.5	GP1 B: 175.7 Coefficient of variation: 62.3 F: 148.7 Coefficient of variation: 58.3 GP2 B: 180.3 Coefficient of variation: 67.7 F: 146.6 Coefficient of variation: 68.6	GP1 F-B: Median: -2.2 IQR: -5.5 - -0.5 GP2 F-B: Median: 0.05 IQR: -3.45 - 3
Leiter, 2005[69]	GP1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks GP2: Metformin+Rosiglitazone Fixed; Varied, glucose: < 7 mmol/L Start: 1500 mg, Max: 1500 mg; Start: 4 mg, Max: 8 mg D: 8 wks	GP1 F-B: -0.14 p: 0.93 GP2 F-B: p: <0.001 GP1-GP2: -0.36 CI: 0.15 - 0.56				GP1 F-B: no significant weight change GP2 F-B: 1.6 CI: 0.9-2.3
Kaku, 2009[70]	GP1: Metformin Varied Start: 500mg, Max: 750mg D: Unclear GP2: Metformin+Pioglitazone Varied Start: 500, Max: 750; Start: 15mg, Max: 30mg D: Unclear; 16 wks	GP1 F-B: 0.25 (0.92) CI: 0.057 - 0.452 p: 0.0122 GP2 F-B: -0.67 (0.8) CI: -0.84 - -0.49 p: <0.0001	GP1 F-B: 0.9 (20) CI: -3.34 - 5.23 p: 0.6632 GP2 F-B: 3.5 (23.2) CI: -1.59 - 8.62 p: 0.1746	GP1 F-B: -1.1 (8.5) CI: -2.96 - 0.68 p: 0.2175 GP2 F-B: 5.3 (8.1) CI: 3.52 - 7.09 p: <0.0001	GP1 F-B: -15.4 (93.8) CI: -35.5 - 4.7 p: 0.1316 GP2 F-B: -9.3 (76.3) CI: -26.1 - 7.4 p: 0.2714	GP1 F-B: -0.47 GP2 F-B: 1.68

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Scott, 2008[71]	GP1: Metformin Fixed Start: > 1500 mg GP2: Metformin+Rosiglitazone Fixed Start: > 1500 mg; Start: 8 mg, Mean: 8 mg	GP1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 CI: -0.36 - -0.08 GP2 B: 7.73 (0.88) F: 6.94 (0.75) F-B: -0.79 CI: -0.92 - -0.65 GP1-GP2: -0.57 CI: -0.76 - -0.37	GP1 B: 95.6 (30.8) F: 108.4 (33.6) F-B: mean % change: 16.7 CI: 10.2 to 23.3 GP2 B: 99.2 (29.4) F: 119.6 (37.6) F-B: mean % change: 26.2 CI: 19.7 to 32.7	GP1 B: 43.5 (10.5) F: 44.1 (12.1) F-B: mean % change from baseline: 1.8 CI: -1.3 - 4.9 GP2 B: 42.2 (10) F: 45.7 (10.5) F-B: mean % change from baseline: 9.2 CI: 6.1 - 12.2	GP1 B: 171.1 (73.3) F: 191.5 (111.1) F-B: mean % change from baseline: 11.9 CI: 3.9 - 19.9 GP2 B: 201.6 (126.2) F: 199.8 (108.4) F-B: mean % change from baseline: 13.1 CI: 5.2 - 21.1	GP1 F-B: -0.8 CI: -1.2 to -0.4 GP2 F-B: 1.5 CI 1.0-1.9 GP2-GP1: 2.3 CI: 1.7-2.9
Stewart, 2006[129]	GP1: Metformin Varied, prespecified target dose Start: 500, Max: 3000, Mean: 2627.9 D: 20 wks GP2: Metformin+Rosiglitazone Varied, prespecified target dose Start: 500, Max: 2000, Mean: 1812.2; Start:4mg , Max:8mg, Mean: 6.8mg D: 18wks		GP1 B: Geometric mean: 3.14 (cv%: 34.53) F: Geometric mean: 2.92 (cv%: 35.66) GP2 B: Geometric mean: 3.15 (cv%: 37.08) F: Geometric mean: 3.29 (cv%: 34.06)	GP1 B: Geometric mean: 1.17 (cv%: 24.3) F: Geometric mean: 1.19 (cv%: 25.01) GP2 B: Geometric mean: 1.17 (cv%: 23.03) F: Geometric mean: 1.25 (cv%: 27.97)	GP1 B: Geometric mean: 1.99 (cv%: 55.39 F: Geometric mean: 1.82 (cv%: 55.08 GP2 B: Geometric mean: 1.92 (cv%: 53.65 F: Geometric mean: 1.92 (cv%: 57.35	
Weissman, 2005[72]	GP1: Metformin Varied Start: 1000mg, Max: 2000mg GP2: Metformin + Rosiglitazone Fixed; Varied Start: 1000mg; Start: 4mg, Max: 8mg	GP1 B: 7.97 (1.2) F: 7.26 F-B: -0.71 GP2 B: 8.05 (1.2) F: 7.12 F-B: -0.93 GP1-GP2: 0.2	GP1 B: 105.1 (103.4 to 106.8) F: 101.6 (99.7 to 103.6) F-B: -3.5 GP2 B: 106.3 (104.5 to 108.2) F: 118.5 (116.3 to 120.7) F-B: 12.2 GP1-GP2: -15.7	GP1 B: 43.7 F: 45.3 F-B: 1.6 GP2 B: 45 F: 49.1 F-B: 4.1 GP1-GP2: -2.5	GP1 B: 179.2 F: 176.8 (170.9 to 182.9) F-B: -2.4 p: NSG vs. baseline GP2 B: 184.8 F: 196.6 (189.2 to 204.2) p: NSG vs. baseline F-B: 11.8 GP1-GP2: -14.2	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Bailey, 2005[73]	GP1: Metformin Varied Start: 2500mg, Max: 3000mg GP2: Metformin + Rosiglitazone Fixed; Varied Start: 2000mg; Start: 4mg, Max: 8mg	GP1 B: 7.5 (1.0) F: 7.4 (1.1) F-B: -0.13 GP2 B: 7.4 (1.0) F: 7.1 (1.1) F-B: -0.33 GP1-GP2: 0.22 p: 0.001 vs. GP1	GP1 B: 111.9 (109.7 to 114.1) F: 114.9 (112.6 to 117.2) F-B: 3 GP2 B: 109.5 (107.1 to 111.8) F: 125.9 (122.9 to 128.9) F-B: 16.4 GP1-GP2: -13.4	GP1 B: 47.2 F: 46.4 F-B: -0.8 p: <0.05 vs. baseline GP2 B: 45.3 F: 47.1 F-B: 1.8 p: <0.05 vs. baseline GP1-GP2: -2.6	GP1 B: 180.8 (175.5 to 186.3) F: 167.5 (161.8 to 173.4) p: <0.05 vs. baseline F-B: -13.3 GP2 B: 189.3 (183.5 to 195.2) F: 189.4 (183.1 to 195.9) p: NSG vs. baseline F-B: 0.1 GP1-GP2: -13.4	GP1 B: 89.5 (14.4) F: 88.6 F-B: -0.9 (SE 0.2) GP2 B: 90.9 (15.6) F: 92.2 F-B: 1.3(SE 0.22) GP1-GP2: -2.2
Gomez-Perez, 2002[74]	GP1: Metformin Fixed Start: 2500mg GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 2mg bid	GP1 B: 9.8 (SE 0.3) F: 10.2 (SE 0.3) F-B: 0.3 p: 0.2651 vs. baseline GP2 B: 10.2 (SE 0.2) F: 9.5 (SE 0.3) F-B: -0.7 p: 0.052 vs. baseline GP1-GP2: 1 p: 0.0132 vs. GP1	GP1 B: 116 (27.7) F: 115 F-B: -1 (20.9) GP2 B: 106.9 (25.7) F: 123.5 F-B: 16.6 (24.7) GP1-GP2: -15.9 (-4.73 to -27)	GP1 B: 49.4 (11.9) F: 48.9 F-B: -0.5 (7.2) GP2 B: 51.5 (10) F: 56.7 F-B: 5.2 (7) GP1-GP2: -5.7 p: <0.05 vs. GP1	GP1 B: 227.2 (126.8) F: 233.4 F-B: 6.2 GP2 B: 204.4 (113.3) F: 199.9 F-B: -4.5 GP1-GP2: 10.7	
Gomez-Perez, 2002[74]	GP1: Metformin Fixed Start: 2500mg GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 4mg bid	GP1 B: 9.8 (SE 0.3) F: 10.2 (SE 0.3) F-B: 0.3 p: 0.2651 vs. baseline GP2 B: 9.75 (SE 0.2) F: 8.6 (SE 0.4) F-B: -1.2 p: 0.008 vs. baseline GP1-GP2: 1.5 p: 0.0002 vs. GP1	GP1 B: 116 (27.7) F: 115 F-B: -1 (20.9) GP2 B: 108.2 (30) F: 114.3 F-B: 6.1 (22.5) GP1-GP2: -7.1 p: NSG vs. GP2	GP1 B: 49.4 (11.9) F: 48.9 F-B:-0.5 (7.2) GP2 B: 51.5 (10.9) F: 57.9 F-B: 6.4 (7) GP1-GP2: -6.9 p: <0.05 vs. GP1	GP1 B: 227.2 (126.8) F: 233.4 F-B: 6.2 GP2 B: 199.6 (133.2) F: 193.8 F-B: -5.8 GP1-GP2: 12	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Einhorn, 2000[75]	GP1: Metformin NR GP2: Metformin + Pioglitazone NR; Fixed NR; Start: 30mg	GP1 B: 9.75 (SE 1.3) F-B: p: <0.05 vs. baseline GP2 B: 9.86 (SE 1.4) F-B: p: <0.05 vs. baseline GP1-GP2: -0.83 p: <0.05 vs. GP1	GP1 B: 119.3 (3.07) F: 128.5 F-B: 7.7% p: <0.05 vs. baseline GP2 B: 118 (6.9) F: 132 F-B: 11.9% GP1-GP2: 4.20%	GP1 B: 42.9 (0.95) F: 53.1 F-B: 10.2 GP2 B: 42.1 (1) F: 43.6 F-B: 1.5 GP1-GP2: 8.7 p: <=0.05 vs. GP2	GP1 B: 298.9 (24.9) F: 289.2 F-B: -9.7 GP2 B: 300.4 (25.86) F: 308.9 F-B: 8.5 GP1-GP2: -18.2 p: 0.05 vs. GP2	GP1 F-B: -1.36 GP2 F-B: 0.95 GP1-GP2: -2.31
Fonseca, 2000[76]	GP1: Metformin Fixed Start: 2500mg GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 8mg	GP1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 GP2 B: 8.9 (1.5) F: 8.12 F-B: -0.78 GP1-GP2: 1.2 p: <0.001 vs. GP1	GP1 B: 118.17 (34.32) F: 122.07 (37.83) F-B: 3.9 GP2 B: 116.61 (30.42) F: 134.94 (33.54) F-B: 18.33 GP1-GP2: -14.04	GP1 B: 44.46 (10.92) F: 46.8 (11.31) F-B: 2.34 GP2 B: 46.8 (14.43) F: 53.04 (16.38) F-B: 6.24 GP1-GP2: -3.9 p: 0.0002 vs. GP1	GP1 B: 246.53 (194.91) F: 247.42 (159.31) F-B: 0.89 GP2 B: 228.73 (184.23) F: 228.73 (166.43) F-B: 0 GP1-GP2: 0.89 p: 0.56 vs. GP1	GP1 F-B: -1.2 GP2 F-B: 0.7 GP1-GP2: -1.9 p: 0.0001 vs GP1
Fonseca, 2000[76]	GP1: Metformin Fixed Start: 2500mg GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 4mg	GP1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 GP2 B: 8.9 (1.3) F: 8.34 F-B: -0.56 GP1-GP2: -1 p: <0.001 vs. GP1	GP1 B: 118.17 (34.32) F: 122.07 (37.83) F-B: 3.9 GP2 B: 113.49 (32.76) F: 134.55 (40.56) F-B: 21.06 GP1-GP2: -17.16 p:<0.0001 vs. GP1	GP1 B: 44.4 (10.92) F: 46.8 (11.31) F-B: 2.4 GP2 B: 46.02 (11.31) F: 51.48 (13.26) F-B: 5.46 GP1-GP2: -3.06 p: 0.0002 vs. GP1	GP1 B: 246.53 (194.91) F: 247.42 (159.31) F-B: 0.89 GP2 B: 226.06 (138.84) F: 233.18 (139.73) F-B: 7.12 GP1-GP2: -6.23 p: 0.73 vs. GP1	GP1 F-B: -1.2 GP2 F-B: 1.9 GP1-GP2: -3.1 p: 0.0001 vs GP1
Metformin vs Metformin+Sulfonylurea						

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Derosa, 2009[36]	GP1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos GP2: Metformin+Glimepiride Fixed Start: 850mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NR; 3 mos	GP1 B: 9.1 (1.2) F: 7.9 (0.5) F-B: -1.1 (0.5) p: <0.01 GP2 B: 9 (1.1) F: 7.8 (0.4) F-B: -1.2 (0.4) p: <0.01				GP1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% GP2 B: 27.1 (1.4) F: 28.4 (2.2) F-B: 4.8% p: <0.05
Nauck, 2009[78]	GP1: Metformin Varied Start: 2000 mg/day, Max: 2000 mg/day GP2: Metformin+Glimepiride Varied; Fixed Start: 2000 mg/day, Max: 2000 mg/day; Start: 1 mg/day, Max: 4 mg/day D: NR; 3 wks	GP1 F-B: 0.1 (SE: 0.1) GP2 F-B: -1 (SE: 0.1)				GP1 F-B: -1.5 (SE: 0.3) GP2 F-B: 1 (SE: 0.2)
Chien, 2007[47]	GP1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean: 1910 mg/day D: 4 wks GP2: Metformin+Glyburide Varied, glucose: <140 mg/dL Start: 1000mg/day, Max: 2000 mg/day, Final mean: 1723 mg/day; Start: 10 mg/day, Max: 20 mg/day, Final mean: 17.2 mg/day D: 4 wks	GP1-GP2: -1.3 p: 0.005				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Chien, 2007[47]	GP1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean: 1910 mg/day D: 4 wks GP2: Metformin+Glyburide Varied, glucose: <140 mg/dL Start: 1000mg/day, Max: 2000 mg/day, Final mean: 1680 mg/day; Start: 5mg/day, Max: 10 mg/day, Final mean: 8.4 mg/day D: 4 wks	GP1-GP2: -1.34 p: 0.002				
Feinglos, 2005[77]	GP1: Metformin Fixed Start: at least 1000mg GP2: Metformin + glipizide Fixed Start: at least 1000mg; Start: 2.5mg	GP1 B: 7.64 F: 7.46 (SE 0.1) F-B: -0.19 GP2 B: 7.45 F: 6.8 (SE 0.1) F-B: -0.66 GP1-GP2: 0.47 p: <0.0002 vs. GP2		GP1 F-B: p: NSG vs. baseline GP2 F-B: p: NSG vs. baseline	GP1 F-B: p: NSG vs. baseline GP2 F-B: p: NSG vs. baseline	GP1 B: 90.8 (18.4) F: 89.1 F-B: -1.7 GP2 B: 90 (18.7) F: 90.4 F-B: 0.4 GP1-GP2: -2.1 p: < 0.0001 vs. GP2
Garber, 2003[49]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glyburide Varied Start: 250mg, Max: 1000mg; Start: 1.25mg, Max: 5mg	GP1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 GP2 B: 8.78 (1.5) F: 6.43 F-B: -2.27 GP1-GP2: -0.74 p: 0.0003 vs. GP1	GP1 B: 122.7 (3.2) F: 115 F-B: -5.7 p:<0.05 vs. baseline GP2 B: 118.3 (3.5) F: 122.8 F-B: 4.5 p:<0.05 vs. baseline GP1-GP2: -10.2	GP1 B: 42.3 (0.9) F: 41.9 F-B: -0.4 p: NSG vs. baseline GP2 B: 41.3 (0.9) F: 42.1 F-B: 0.8 p: NSG vs. baseline GP1-GP2: -1.2	GP1 B: 256.8 (26.7) F: 217.2 F-B: -39.6 p: NSG vs. baseline GP2 B: 248.4 (26.2) F: 196.4 F-B: -52 p: <0.05 vs. baseline GP1-GP2: 12.4	GP1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 vs. baseline GP2 B: 91.9 (17.4) F: 93.5 F-B: 1.6 p: NSG vs. baseline GP1-GP2: -2.7

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Tosi, 2003[28]	GP1: Metformin Varied Start: 500mg, Max: 3000mg GP2: Metformin + glibenclamide Varied Start: 400mg, Max: 2400mg; Start: 2.5mg, Max: 15mg	GP1 B: 7.8 (1.4) F: 7.3 F-B: -0.5 GP2 B: 7.8 (1.0) F: 5.9 F-B: -1.9 GP1-GP2: 1.4				
Goldstein, 2003[50]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glipizide Varied Start: 500mg, Max: 2000mg; Start: 5mg, Max: 20mg	GP1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 GP2 B: 8.7 (1.2) F: 7.4 (0.1) F-B: -1.3 GP1-GP2: 1.06 p: <0.001 vs. GP1	GP1 B: 109.7 (35.2) F: 102.5 F-B: -7.2 (-15 to 0.6) GP2 B: 119.7 (29.5) F: 119.5 F-B: -0.2 (-6.7 to 6.3) GP1-GP2: -7	GP1 B: 42.3 (9.7) F: 42.7 F-B: 0.4 p: NSG vs. baseline GP2 B: 43.2 (10.0) F: 44.1 F-B: 0.9 p: NSG vs. baseline GP1-GP2: -0.5	GP1 B: 218.7 (120.2) F: 217.1 F-B: -1.6 (-25.3 to 22) p: NSG vs. baseline GP2 B: 237.5 (192.2) F: 256 F-B: 18.5 (-16.8 to 53.7) p: NSG vs. baseline GP1-GP2: -20.1	GP1 B: 94.2 (16.7) F: 91.5 F-B: -2.7 (SE 0.3) GP2 B: 95.1 (17.8) F: 94.8 F-B: -0.3 (SE 0.3) GP1-GP2: -2.4 p: <0.001 vs. GP2
Blonde, 2002[51]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glyburide Varied Start: 500mg, Max: 2000mg; Start: 5mg, Max: 20mg	GP1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 GP2 B: 9.42 (1.24) F: 7.9 F-B: -1.38 GP1-GP2: 1.77 p: <0.001 vs. GP1	GP1-GP2: NSG vs. GP2	GP1-GP2: p: NSG vs. GP2	GP1-GP2: p: NSG vs. GP2	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Blonde, 2002[51]	GP1: Metformin Varied Start: 500mg , Max: 2000mg GP2: Metformin + glyburide Varied Start: 500mg, Max: 2000mg; Start: 2.5mg, Max: 10mg	GP1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 GP2 B: 9.41 (1.47) F: 7.9 F-B: -1.64 GP1-GP2: 2.03 p: <0.001 vs. GP1	GP1-GP2: NSG vs. GP2	GP1-GP2: p: NSG vs. GP2	GP1-GP2: p: NSG vs. GP2	
Marre, 2002[52]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glibenclamide Varied Start: 500mg, Max: 2000mg; Start: 2.5mg, Max: 10mg	GP1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 GP2 B: 7.89 (1.62) F: 6.69 F-B: -1.2 GP1-GP2: 1 p: <0.05 vs. GP1	GP1 B: 148.2 (39) F: 136.5 F-B: -11.7 (31.2) p: NSG vs. baseline GP2 B: 152.1 (42.9) F: 144.3 F-B: -7.8 (27.3) p: NSG vs. baseline GP1-GP2: -3.9		GP1 B: 204.7 (169.1) F: 186.9 F-B: -17.8 (89) GP2 B: 213.6 (160.2) F: 195.8 F-B: -17.8 (151.3) GP1-GP2: 0 p: NSG vs. GP2	GP1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 GP2 B: 84.7 (15.1) F: 85.3 F-B: 0.6 GP1-GP2: -1.4
Marre, 2002[52]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glibenclamide Varied Start: 500mg, Max: 2000mg; Start: 5mg, Max: 10mg	GP1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 GP2 B: 7.62 (1.61) F: 6.72 F-B: -0.9 GP1-GP2: 0.7 p: <0.05 vs. GP1	GP1 B: 148.2 (39) F: 136.5 F-B: -11.7 (31.2) p:NSG vs. baseline GP2 B: 152.1 (35.1) F: 144.3 F-B: -7.8 (27.3) p:NSG vs. baseline GP1-GP2: -3.9		GP1 B: 204.7 (169.1) F: 186.9 F-B: -17.8 (89) GP2 B: 222.5 (284.8) F: 178 F-B: -44.5 (186.9) GP1-GP2: 26.7 p: NSG vs. GP2	GP1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 GP2 B: 83.1 (13.3) F: 84.1 F-B: 1 GP1-GP2: -1.8

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Garber, 2002[53]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glyburide Varied Start: 500mg, Max: 2000mg; Start: 2.5mg, Max: 10mg	GP1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 GP2 B: 8.18 (1.14) F: 6.65 F-B: -1.53 GP1-GP2: 0.5 p: <0.001 vs. GP1		GP1 B: 46.8 (11.7) F: 58.5 F-B: 1.17 p: NSG vs. baseline GP2 B: 50.7 (11.7) F: 50.7 F-B: 0 p: NSG vs. baseline GP1-GP2: 1.17		GP1 F-B: -0.6 GP2 F-B: 1.4 p: <0.05 vs. baseline GP1-GP2: -2
Garber, 2002[53]	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + glyburide Varied Start: 250mg, Max: 1000mg; Start: 1.25mg, Max: 5mg	GP1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 GP2 B: 8.25 (1.11) F: 6.77 F-B: -1.48 GP1-GP2: 0.45 p: <0.001 vs. GP1		GP1 B: 46.8 (11.7) F: 47.97 F-B: 1.17 p: NSG vs. baseline GP2 B: 46.8 (15.6) F: 47.19) F-B: 0.39 p: NSG vs. baseline GP1-GP2: 0.78		GP1 F-B: -0.6 GP2 F-B: 1.9 p: <0.05 vs. baseline GP1-GP2: 2.5

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1994[56]	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Metformin + glyburide Varied Start: 1000mg, Max: 3000mg; Start: 10.5mg, Max: 14.0mg	GP1 B: 6.9 (SE 0.3) F: 5.8 (SE 0.2) F-B: -0.9 (SE 0.2) p: 0.001 vs. baseline GP2 B: 7.8 (SE 0.3) F: 5.7 (SE 0.3) F-B: -2.0 (SE 0.4) p: 0.001 vs. baseline GP1-GP2: 1.1 p: >0.1 all group comparison	GP1 B: 142.74 (SE 9.75) F: 131.82 (SE 8.97) F-B: -5.85 (SE 2.73) GP2 B: 143.13 (SE 5.46) F: 139.62 (SE 4.68) F-B: -2.73 (SE 2.34) GP1-GP2: -3.12	GP1 B: 31.59 (SE 2.34) F: 30.03 (SE 1.56) F-B: 0.78 (SE 0.78) p: >0.1 vs. baseline GP2 B: 35.49 (SE 1.56) F: 37.05 (SE 1.95) F-B: 1.56 (SE 1.17) p: >0.1 vs. baseline GP1-GP2: -0.78	GP1 B: 179.78 (SE 18.69) F: 173.55 (SE 14.24) F-B: 8.01 (SE 12.46) p: >0.1 vs. baseline GP2 B: 175.33 (SE 20.47) F: 168.21 (SE 17.8) F-B: 5.34 (SE 11.57) p: >0.1 vs. baseline GP1-GP2: 2.67	GP1 B: 78.6 (SE 2.9) F: 78.8 (SE 2.9) F-B: -0.2 (SE 0.5) p: >0.1 vs. baseline GP2 B: 80.2 (SE 2.4) F: 81 (SE 2.5) F-B: 0.7 (SE 0.4) p: >0.1 vs. baseline GP1-GP2: -0.9
Hermann, 1994[56]	GP1: Metformin Varied Start: 1000mg , Max: 3000mg GP2: Metformin + glyburide Fixed; Varied Start: 3000mg; Start: 3.5mg, Max: 14.0mg	GP1 B: 6.9 (SE 0.3) F: 5.8 (SE 0.2) F-B: -0.9 (SE 0.2) p: 0.001 vs. baseline GP2 B: 7.8 (SE 0.3) F: 5.4 (SE 0.3) F-B: -2.3 (SE 0.4) p: 0.001 vs. baseline GP1-GP2: 1.4 p: >0.1 all group comparison				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1994[56]	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Metformin + glyburide Varied Start: 2000mg, Max: 3000mg; Start: 7.0mg, Max: 14.0mg	GP1 B: 6.9 (SE 0.3) F: 5.8 (SE 0.2) F-B: -0.9 (SE 0.2) p: 0.001 vs. baseline GP2 B: 8.4 (SE 0.4) F: 6.2 (SE 0.3) F-B: -2.2 (SE 0.4) p: 0.001 vs. baseline GP1-GP2: 1.3 p: >0.1 all group comparison				
Hermann, 1994[56]	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Metformin + glyburide Varied Start: 500mg, Max: 1500mg; Start: 1.75mg, Max: 5.25mg	GP1 B: 6.9 (SE 0.3) F: 5.8 (SE 0.2) F-B: -0.9 (SE 0.2) p: 0.001 vs. baseline GP2 B: 6.8 (SE 0.1) F: 5.6 (SE 0.1) F-B: -1.2 (SE 0.1) p: 0.001 vs. baseline GP1-GP2: 0.3 p: >0.1 all group comparison				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Hermann, 1991[128]	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Metformin + glibenclamide Fixed; Varied Start: 3000mg; Start: 3.5mg, Max: 14mg	GP1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 vs. baseline GP2 B: 7.7 (1.1) F: 5.4 (0.9) F-B: -2.3 p: <0.001 vs. baseline GP1-GP2: 1.4	GP1 F-B: 0.78 (SE 3.9) GP2 F-B: -6.24 (SE 2.34) GP1-GP2: 7.02 p:<0.05 vs. GP2			GP1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NSG vs. baseline GP2 B: 87.3 (15.6) F: 87.3 (15.9) F-B: 0 p: NSG vs. baseline GP1-GP2: -0.4
Hermann, 1991[128]	GP1: Metformin + diet Varied Start: 1000mg, Max: 3000mg GP2: Metformin + glibenclamide Varied Start: 1000mg, Max: 3000mg; Start: 10.5mg, Max: 14mg	GP1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 vs. baseline GP2 B: 7.8 (1.4) F: 5.7 (0.8) F-B: -2.2 p: <0.001 vs. baseline GP1-GP2: 1.3				GP1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NSG vs. baseline GP2 B: 74.4 (11.4) F: 76 (11.8) F-B: 1.6 p: <0.001 vs. baseline GP1-GP2: -2

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Charpentier, 2001[59]	GP1: Metformin Fixed Start: 850mg tid GP2: Metformin + glimepiride Fixed; Varied Start: 850mg tid; Start: 1mg, Max: 6mg	GP1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE 0.14) GP2 B: 6.42 (1.08) F: 5.68 (0.99) F-B: -0.74 (SE 0.8 GP1-GP2: 0.92 p: <0.001 vs. GP1		GP1 B: 46.41 (13.65) F: 60.06 F-B: 0.24 (9.36) GP2 B: 46.41 (12.09) F: 45.24 F-B: -1.17 (9.87) GP1-GP2: 3.12 p:0.14 all group comparison	GP1 B: 171.77 (119.26) F: 185.12 F-B: 13.35 (104.13) GP2 B: 169.99 (110.36) F: 167.32 F-B: -2.67 (93.45) GP1-GP2: 16.02 p: 0.029 in all groups	GP1 B: 82.2 (range 53-115) F: 81.46 F-B: -0.74 (2.58) GP2 B: 81.2 (range 52.6-116) F: 81.8 F-B: 0.6 (2.86) GP1-GP2: -1.34
DeFronzo, 1995[58]	GP1: Metformin Varied Start: 500mg, Max: 2500mg GP2: Metformin + glyburide (no trade drug specified) Varied Start: 500mg, Max: 2500mg; Start: 10mg, Max: 20mg	GP1 B: 8.9 F: 8.5 F-B: -0.4 (SE 0.1) GP2 B: 8.8 F: 7.1 F-B: -1.7 (SE 0.1) GP1-GP2: 1.3 p: <0.001 vs. GP2	GP1 B: 134 (SE 3) F: 129 (SE 3) F-B: -6 (SE 2) GP2 B: 137 (SE 3) F: 128 (SE 3) F-B: -8 (SE 2) GP1-GP2: 2 p: NSG vs. GP2		GP1 B: 231 (SE 12) F: 221 (SE 13) F-B: -16 (SE 7) GP2 B: 216 (SE 10) F: 194 (SE 9) F-B: -20 (SE 7) GP1-GP2: 4	GP1 F-B: -3.8 (SE 0.2) p: <0.001 vs. baseline GP2 F-B: 0.4 (SE 0.2) p: NSG vs. baseline GP1-GP2: -4.2
Metformin vs Metformin+DPP-IV						
Williams-Herman, 2009[63]	GP1: Metformin Fixed Mean: 2000 mg/day GP2: Metformin+Sitagliptin Fixed Mean: 2000 mg/day; Mean: 100 mg/day	GP1 F-B: -1.3 CI: -1.5 - -1.2 GP2 F-B: -1.8 CI: -2 - -1.7	GP1 B: 105.3 (32.3) F: 102.3 (33.6) GP2 B: 115.1 (39.1) F: 110.1 (37.1)	GP1 B: 42.8 (9) F: 45.2 (11) GP2 B: 43.9 (11.1) F: 46.6 (13.5)		GP1 F-B: -1.5 CI: -2.2 - -0.8 GP2 F-B: -1.7 CI: -2.4 - -1.1
Williams-Herman, 2009[63]	GP1: Metformin Fixed Mean: 2000 mg/day GP2: Metformin+Sitagliptin Fixed Mean: 1000 mg/day; Mean: 100 mg/day	GP1 F-B: -1.3 CI: -1.5 - -1.2 GP2 F-B: -1.4 CI: -1.6 - -1.3	GP1 B: 107.3 (33.4) F: 102.5 (36.7) GP2 B: 115.1 (39.1) F: 110.1 (37.1)	GP1 B: 43.3 (10.8) F: 46.4 (12) GP2 B: 43.7 (9.3) F: 45.4 (11.3)		GP1 F-B: -1.5 CI: -2.2 - -0.8 GP2 F-B: -0.7 CI: -1 - 0

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Williams-Herman, 2009[63]	GP1: Metformin Fixed Mean: 1000 mg/day GP2: Metformin+Sitagliptin Fixed Mean: 2000 mg/day; Mean: 100 mg/day	GP1 F-B: -1 CI: -1.2 - -0.8 GP2 F-B: -1.8 CI: -2 - -1.7	GP1 B: 106.8 (34.2) F: 103.6 (31.5) GP2 B: 114.7 (37.1) F: 111 (32.4)	GP1 B: 43.2 (9.4) F: 44.6 (10.4) GP2 B: 43.1 (9.2) F: 44.3 (10.4)		GP1 F-B: -1 CI: -1.7 - -0.3 GP2 F-B: -1.7 CI: -2.4 - -1.1
Williams-Herman, 2009[63]	GP1: Metformin Fixed Mean: 1000 mg/day GP2: Metformin+Sitagliptin Fixed Mean: 1000 mg/day; Mean: 100 mg/day	GP1 F-B: -1 CI: -1.2 - -0.8 GP2 F-B: -1.4 CI: -1.6 - -1.3	GP1 B: 108.2 (34.4) F: 104.6 (33.8) GP2 B: 114.7 (37.1) F: 111 (32.4)	GP1 B: 43.2 (9.4) F: 44.6 (10.4) GP2 B: 44.2 (10.9) F: 46 (12.2)		GP1 F-B: -1 CI: -1.7 - -0.3 GP2 F-B: -0.7 CI: -1 - 0
Raz, 2008[79]	GP1: Metformin Fixed NR GP2: Metformin+Sitagliptin Fixed Max: 2550 mg/day; Mean: 100 mg/day	GP1 F-B: 0 CI: -0.2 - 0.3 GP2 F-B: -1 CI: -1.3 - -0.7 p: <0.001 GP1-GP2: -1 CI:-1.4 - -0.6 p: <0.001				GP1 F-B: -0.5 GP2 F-B: -0.5
Goldstein, 2007[64]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 100 mg/day D: 1 wk GP2: Metformin+Sitagliptin Varied, prespecified target dose Start: 500 mg/day, Max: 1000 mg/day; Start: 50 mg/day, Max: 100 mg /day D: 1 wk	GP1 F-B: -0.82 CI: -0.98 - -0.66 GP2 F-B: -1.4 CI: -1.56 - -1.24				GP1 F-B: significant reduction relative to baseline GP2 F-B: significant reduction relative to baseline

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Goldstein, 2007[64]	GP1: Metformin Varied, prespecified target dose Start: 500 mg/day, Max: 100 mg/day D: 1 wk GP2: Metformin+Sitagliptin Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day; Start: 50 mg/day, Max: 100 mg /day D: 3 wks; 1wk	GP1 F-B: -0.82 CI: -0.98 - -0.66 GP2 F-B: -1.9 CI: -2.06 - -1.74				GP1 F-B: significant reduction relative to baseline GP2 F-B: significant reduction relative to baseline
Goldstein, 2007[64]	GP1: Metformin Fixed Start: 500 mg/day, Max: 2000 mg/day D: 3 wks GP2: Metformin+Sitagliptin Varied, prespecified target dose Start: 500 mg/day, Max: 1000 mg/day; Start: 50 mg/day, Max: 100 mg /day D: 1 wk	GP1 F-B: -1.13 CI: -1.29 - -0.97 GP2 F-B: -1.4 CI: -1.56 - -1.24				GP1 F-B: significant reduction relative to baseline GP2 F-B: significant reduction relative to baseline
Goldstein, 2007[64]	GP1: Metformin Fixed Start: 500 mg/day, Max: 2000 mg/day D: 3 wks GP2: Metformin+Sitagliptin Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day; Start: 50 mg/day, Max: 100 mg /day D: 3 wks; 1 wk	GP1 F-B: -1.13 CI: -1.29 - -0.97 GP2 F-B: -1.9 CI: -2.06 - -1.74				GP1 F-B: significant reduction relative to baseline GP2 F-B: significant reduction relative to baseline

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Charbonnel, 2006[80]	GP1: Metformin Varied, glucose: , HgbA1c: btw 7 and 10 Start: >=1500 D: 19 wks GP2: Metformin+Sitagliptin Varied; Fixed Start: >=1500 mg; Mean: 100 D: 19 wks	GP1 B: 8.03 (0.82) F: 7.95 (1.1) F-B: -0.02 CI: -0.15 - 0.1 GP2 B: 7.96 (0.81) F: 7.26 (0.97) F-B: -0.67 CI: -0.77 - -0.57	GP1 F-B: 4.1 CI: -0.7 - 8.9 GP2 F-B: 3.3 CI: -0.6 - 7.1	GP1 F-B: -0.7 CI: -2.8 - 1.4 GP2 F-B: 1.3 CI: -0.4 - 3	GP1 F-B: 24.6 CI: 16.8 - 32.3 GP2 F-B: 7.7 CI: 1.5 - 14	GP1 F-B: 0.6-0.7 p: <0.05 GP2 F-B: 0.6-0.7 p: <0.05 GP1-GP2: p=0.835
Scott, 2008[71]	GP1: Metformin Fixed Total starting dose: > 1500 mg GP2: Metformin+Sitagliptin Fixed Total starting dose: > 1500 mg; Start: 100 mg, Mean: 100 mg	GP1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 CI: -0.36 - -0.08 GP2 B: 7.75 (0.99) F: 7.01 (0.86) F-B: -0.73 CI: -0.87 - -0.6 GP1-GP2: -0.51 CI: -0.7 - -0.32 p: <0.001	GP1 B: 95.6 (30.8) F: 108.4 (33.6) F-B: Mean % change from baseline: 16.7 CI: 10.2 - 23.3 GP2 B: 95.4 (30.8) F: 104.6 (35.1) F-B: Mean % change from baseline: 11.4 CI: 5 - 17.8 GP1-GP2: -5.3 CI: -14.5 - 3.9	GP1 B: 43.5 (10.5) F: 44.1 (12.1) F-B: Mean % change from baseline: 1.8 CI: -1.3 - 4.9 GP2 B: 43.9 (11.6) F: 45.7 (13.4) F-B: Mean % change from baseline: 4.3 CI: 1.2 - 7.3	GP1 B: 171.1 (73.3) F: 191.5 (111.1) F-B: Mean % change from baseline: 11.9 CI: 3.9 - 19.9 GP2 B: 177.8 (80.7) F: 163.3 (74) F-B: Mean % change from baseline: -4.8 CI: -12.7 - 3.1	GP1 F-B: -0.8 CI: -1.2 - -0.4 GP2 F-B: -0.4 CI: -0.8 - 0 GP2-GP1: 1.9 CI: 1.3 - 2.5
Metformin vs Metformin+Meglitinides						
Horton, 2004[66]	GP1: Metformin Fixed Start: 500 mg tid GP2: Metformin+Nateglinide Fixed Start: 500 mg qac; Start: 120 mg qac	GP1 F-B: -0.8 (SE: 0.1) p: <0.001 GP2 F-B: -1.6 (SE: 0.1) p: <0.001				
Marre, 2002[81]	GP1: Metformin Fixed Start: 1000mg bid GP2: Metformin+Nateglinide Fixed Start: 1000mg bid; Start: 60 mg ac	GP2-GP1: -0.36 CI: -0.59 - -0.13 p: 0.003	GP1 F-B: 0 p:1 GP2 F-B: 0 CI: -0.1 - 0.2 p: > 0.05	GP1 F-B: 0 GP2 F-B: 0	GP1 F-B: 0 GP2 F-B: -0.1 GP2-GP1: -0.1 CI: -0.3 - 0.2 p: > 0.05	GP1 F-B: 0.1 GP2 F-B: 0.4 GP2-GP1: 0.3 CI: -0.2 - 0.8 p: >0.05

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Marre, 2002[81]	GP1: Metformin Fixed Start: 1000mg bid GP2: Metformin+Nateglinide Fixed Start: 1000mg bid; Start: 120 mg qac	GP2-GP1: -0.51 CI: -0.82 - -0.36 p: <0.001	GP1 F-B: 0 p: 1 GP2 F-B: 0.1 CI: 0 - 0.3 p: > 0.05	GP1 F-B: 0 GP2 F-B: 0	GP1 F-B: 0 GP2 F-B: -0.2 GP2-GP1: -0.2 CI: -0.4 - 0 p: < 0.05	GP1 F-B: 0.1 GP2 F-B: 1 GP2-GP1: 0.9 CI: 0 - 1.4 p: <0.001
Moses, 1999[68]	GP1: Metformin NR GP2: Metformin+Repaglinide NR NR; Start: 0.5 mg tid, Max: 4.0 mg tid D: NR; 12 to 28 days	GP1 F-B: -0.33 (SE: 0.24) CI: -0.8 - -0.5 GP2 F-B: -1.41 (SE: 0.23) CI: -1.87 - -0.95 GP1-GP2: -1.08 (SE: 0.33) CI: -1.84 - -0.33 p: 0.05				GP1 F-B: -0.86 (SE: 0.51) GP2 F-B: 2.41 (SE: 0.5) p: <0.05
Thiazolidinedione vs Thiazolidinedione						
Goldberg, 2005[83]	GP1: Rosiglitazone Varied Start: 4mg, Max: 8mg GP2: Pioglitazone Varied Start: 30mg, Max: 45mg		GP1 B: 109.1 (SE 1.4) F: 130.4 F-B: 21.3 (SE 1.6) p: < 0.05 vs. baseline GP2 B: 107.1 (SE 1.3) F: 119.4 F-B: 12.3 (SE 1.6) p: < 0.05 vs. baseline GP1-GP2: 9	GP1 B: 39.8 (SE 0.6) F: 42.2 F-B: 2.4 (SE 0.5) GP2 B: 38.8 (SE 0.5) F: 44 F-B: 5.2 (SE 0.5) GP1-GP2: -2.8 p: <0.001 vs. GP2	GP1 B: 235.3 (SE 6.6) F: 248.4 F-B: 13.1 (SE 7.8) p: NSG vs. baseline GP2 B: 257.8 (SE 8.2) F: 205.9 F-B: -51.9 (SE 7.8) p: <0.05 vs. baseline GP1-GP2: 65 p: <0.05 vs. baseline	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Khan, 2002[82]	GP1: Rosiglitazone Fixed Start: 2-8mg GP2: Pioglitazone Fixed Start: 15-45mg		GP1 B: 105.9 (29.7) F: 103.9 F-B: -2 p: NSG vs. baseline GP2 B: 116.2 (38) F: 98.2 F-B: -18 p: <0.01 vs baseline GP1-GP2: 16	GP1 B: 45.3 (15.2) F: 48.6 F-B: 1.5 p: NSG vs. baseline GP2 B: 44.7 (15.6) F: 46.7 F-B: 2.0 p: NSG vs. baseline GP1-GP2: -0.5	GP1 B: 236 (222) F: 242 F-B: 6 p: NSG vs. baseline GP2 B: 181 (110.1) F: 166 F-B: -15 p: NSG vs. baseline GP1-GP2: 21	
Thiazolidinedione vs Sulfonylurea						
Teramoto, 2007[33]	GP1: Pioglitazone Varied, glucose: < =126 Start: 15mg, Max: 30mg D: 15 wks GP2: Glibenclamide Varied, glucose: <=126 Start: 1.25, Max: 2.5 D: 15 wks	GP1 F-B: -0.8 (1.14) p: <0.05 GP2 F-B: -1.43 (1.09) p: <0.05	GP1 F-B: 8.65 (23.47) GP2 F-B: -1.31 (24.94)	GP1 F-B: 3.8 (8.2) p: <0.05 GP2 F-B: -1.2 (6.3)	GP1 F-B: -57.7 (111.5) p: <0.05 GP2 F-B: 7.3 (112.7)	
Hanefeld, 2007[84]	GP1: Rosiglitazone Fixed Mean: 4mg GP2: Glibenclamide Varied Start: 2.5, Max: 15 D: 12 wks	GP1 F-B: -0.3 p: 0.0003 GP2 F-B: -0.7 p: <0.0001	GP1 F-B: 0.2 (0.7) GP2 F-B: 0.1 (0.7)	GP1 F-B: Median: 0.12 CI: 0.09 - 0.15 p: <0.0001 GP2 F-B: Median: 0.08 CI: 0.05 - 0.12 p: <0.0001	GP1 F-B: -10 (351) p: NSG vs baseline GP2 F-B: -3 (86) p: NSG vs. baseline	GP1 F-B: 1.75 GP2 F-B: 1.9
Hanefeld, 2007[84]	GP1: Rosiglitazone Fixed Mean: 8mg GP2: Glibenclamide Varied Start: 2.5, Max: 15 D: 12 wks	GP1 B: (1.4) F: (1.4) F-B: -0.5 p: <0.0001 GP2 B: (1.3) F: (1.3) F-B: -0.7 p: <0.0001	GP1 F-B: 0.4 (0.9) GP2 F-B: -0.1 (0.7)	GP1 F-B: Median: 0.17 CI: 0.12 - 0.22 p: <0.0001 GP2 F-B: Median: 0.08 CI: 0.05 - 0.12 p: <0.0001	GP1 F-B: 12 (92) p:NSG GP2 F-B: -3 (86) p:NSG	GP1 F-B: 2.95 GP2 F-B: 1.9 GP1-GP2: p: 0.01 (relative to GP2)

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Kahn, 2006[30]	GP1: Rosiglitazone Varied, glucose: <140 Start: 4mg, Max: 8mg GP2: Glyburide Varied, glucose: <140 Start: 2.5, Max: 15	GP1-GP2: -0.42 95% CI: -0.5 - -0.33 p: <0.001				GP2-GP1: 2.5 CI: 2 - 3.1 p: <0.001
Jain, 2006[85]	GP1: Pioglitazone Varied, glucose: FPG (69-141mg/dl) Start: 15mg, Max: 45mg, Median: 45mg D: 16 wks GP2: Glyburide Varied, glucose: FPG:69-141mg/dl Start: 5mg, Max: 15, Median: 10 D: 16 wks	GP1 B: (1.26) F: (1.26) GP2 B: (1.20) F: (1.20) GP1-GP2: -0.05 p: 0.669				GP1 F-B: 3.66 (6.14) p: <0.001 GP2 F-B: 1.95 (5.35)
Smith, 2004[227]	GP1: Rosiglitazone Varied Start: 8mg/day GP2: Glyburide Varied Median: 7.5mg/d D: 12 wks	GP1 F-B: -0.4 GP2 F-B: 0.72 GP1-GP2: -1.1 p: >0.05				
Nakamura, 2004[86]	GP1: Pioglitazone Fixed Start: 30mg/day GP2: Glibenclamide Fixed Start: 5mg/day	GP1 F-B: 1.7 (1) p: <0.05 GP2 F-B: 1.5 (1.1) p: <0.05				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Yamanouchi, 2005[40]	GP1: Pioglitazone Fixed Start: 30mg for women and 45mg for men GP2: Glimepiride Varied Start: 1.0mg, Max: 2.0mg	GP1 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 vs. baseline GP2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 vs. baseline GP1-GP2: -0.2		GP1 B: 53.82 (4.68) F: 58.11 (3.51) F-B: 4.29 p: NSG vs baseline GP2 B: 52.65 (4.29) F: 52.26 (4.29) F-B: -0.39 p: NSG vs baseline GP1-GP2: 4.68	GP1 B: 219.83 (112.14) F: 185.12 (96.12) F-B: -34.71 p: NSG vs. baseline GP2 B: 234.07 (121.93) F: 229.62 (112.14) F-B: -4.45 p: NSG vs. baseline GP1-GP2: -30.26	
Pfutzner, 2005[89]	GP1: Pioglitazone Fixed Start: 45mg GP2: Glimepiride Varied Start: 1mg, Max: 6mg	GP1 B: 7.52 (0.85) F: 6.71 (0.89) F-B: -0.81 p: <0.05 vs. baseline GP2 B: 7.44 (0.89) F: 6.83 (0.85) F-B: -0.61 p: <0.05 vs. baseline GP1-GP2: -0.2	GP1 B: 136 (29) F: 133 (31) F-B: -3 GP2 B: 137 (25) F: 129 (27) F-B: -8 GP1-GP2: 5 p: NSG vs GP2	GP1 B: 46 (11) F: 54 (13) F-B: 8 GP2 B: 46 (14) F: 47 (12) F-B: 1 GP1-GP2: 7 p: 0.001 vs GP2	GP1 B: 190 (109) F: 168 (102) F-B: -22 p: <0.005 vs. baseline GP2 B: 202 (111) F: 185 (106) F-B: -17 p: <0.001 vs. baseline GP1-GP2: -5	
Ramachandran, 2004[41]	GP1: Pioglitazone Varied Start: 15mg, Max: 30mg GP2: Glimepiride Varied Start: 1mg, Max: 2mg	GP1 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: <0.01 vs. baseline GP2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 vs. baseline GP1-GP2: -0.1		GP1 B: 38.22 (5.85) F: 42.9 (7.8) F-B: 4.68 p: <0.01 vs baseline GP2 B: 37.05 (11.7) F: 42.9 (7.8) F-B: 5.85 p: NSG vs baseline GP1-GP2: -1.17	GP1 B: 258.1 (213.6) F: 195.8 (124.6) F-B: -62.3 p: <0.05 vs. baseline GP2 B: 195.8 (124.6) F: 151.3 (80.1) F-B: -44.5 p: <0.05 vs. baseline GP1-GP2: -17.8	GP1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 GP2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 vs. baseline GP1-GP2: -2.9

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Tan, 2004[90]	GP1: Pioglitazone Varied Start: 30mg, Max: 45mg GP2: Glibenclamide Varied Start: 1.75mg, Max: 10.5mg	GP1 B: 8.4 (0.7) F: 7.9 F-B: -0.5 p: <0.005 vs. baseline GP2 B: 8.5 (0.8) F: 8.1 F-B: -0.4 p: <0.005 vs. baseline GP1-GP2: -0.1	GP1 B: 141.18 F: 146.64 F-B: 5.46 p: NSG vs baseline GP2 B: 135.72 F: 134.55 F-B: -1.17 p: NSG vs baseline GP1-GP2: 6.63			GP1 B: 88.7 (17.4) F: 91.7 F-B: 3 p: <0.001 vs. baseline GP2 B: 89.1 (16) F: 90.2 F-B: 1.1 p: 0.008 vs. baseline GP1-GP2: 1.9 p: 0.002 vs. GP2
Tan, 2004[90]	GP1: Pioglitazone Varied Start: 15mg, Max: 45mg GP2: Glimepiride Varied Start: 2mg, Max: 8mg	GP1 B: 8.54 (0.903) F: 7.76 F-B: -0.78 (0.162) p: <0.001 vs. baseline GP2 B: 8.45 (1.02) F: 7.77 F-B: -0.68 (0.169) p: <0.001 vs. baseline GP1-GP2: -0.1 p: 0.638 vs. GP2		GP1 B: 46.02 F: 54.21 F-B: 8.19 p: <0.001 vs baseline GP2 B: 43.68 F: 44.85 F-B: 1.17 p: NSG vs baseline GP1-GP2: 7.02	GP1 B: 182.45 F: 150.45 F-B: -32.04 p: <0.05 vs. baseline GP2 B: 202.03 F: 199.36 F-B: -2.67 p: NSG vs. baseline GP1-GP2: -29.37	
Bakris, 2003[88]	GP1: Rosiglitazone Fixed Start: 4mg bid GP2: Glyburide Varied Start: NR, Max: 20mg	GP1 B: 9.1 (1.68) F: 8.2 F-B: -0.9 (1.38) GP2 B: 9.5 (1.59) F: 8.6 F-B: -0.9 (1.39) GP1-GP2: 0 p: NSG vs. GP2				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Nakamura, 2000[87]	GP1: Pioglitazone Fixed Start: 30mg GP2: Glibenclamide Fixed Start: 5mg	GP1 B: 7.7 (1.2) F: 6.8 (1.0) F-B: -0.9 p: <0.05 vs. baseline GP2 B: 7.8 (1.1) F: 6.9 (1.2) F-B: -0.9 p: <0.05 vs. baseline GP1-GP2: 0				
St John Sutton, 2002[123]	GP1: Rosiglitazone Fixed Start: 4mg bid GP2: Glyburide Varied Start: NR, Max: 20		GP1 B: 140.2 F: 146.5 F-B: 6.3 to 7.7 GP2 B: 135.4 F: 126.5 F-B: -8.9 GP1-GP2: 15.2		GP1 B: 226.6 F: 223.8 F-B: -2.8 p: NSG vs. baseline GP2 B: 189.6 F: 175.8 F-B: -13.8 p: NSG vs. baseline GP1-GP2: 11	GP1 B: 86.2 (15.6) F: 91.2 F-B: 5(3.7-6.2) p: <0.05 vs. baseline GP2 B: 85.1 (13.6) F: 88.5 F-B: 3.4 (2.7-4.1) p: <0.05 vs. baseline GP1-GP2: 1.6
Thiazolidinedione vs Meglitinides						
Raskin, 2004[92]	GP1: Rosiglitazone Varied Start: 2mg bid, Max: 4mg bid GP2: Repaglinide Varied Start: 0.5mg tid if HbA1c <8% and 1mg tid if HbA1c>8% , Max: 4mg tid	GP1 B: 9 F: 8.5 F-B: -0.56 (SE 0.14) GP2 B: 9.3 F: 9.1 F-B: -0.17 (SE 0.14) GP1-GP2: -0.39	GP1 B: 125 (23.5) F: 139 (34.3) F-B: 14 GP2 B: 124 (33.8) F: 123 (32.3) F-B: -1 GP1-GP2: 15	GP1 B: 39.9 (10.6) F: 42.5 (11.3) F-B: 2.6 GP2 B: 39.2 (10.5) F: 40.5 (11.5) F-B: 1.3 GP1-GP2: 1.3	GP1 B: 245 (211) F: 246 (174) F-B: 1 GP2 B: 306 (246) F: 284 (211) F-B: -22 GP1-GP2: 23	GP1 F-B: 2.3 GP2 F-B: 1.6 GP1-GP2: 0.7

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Jovanovic, 2004[93]	GP1: Pioglitazone Fixed Start: 30mg GP2: Repaglinide Varied Start: 0.5mg tid if HbA1c<8% and 1mg tid if HbA1c>8%, Max: 4mg tid	GP1 B: 9.1 F: 9.5 F-B: 0.32 (SE 0.16) GP2 B: 9 F: 8.9 F-B: (-0.18 (SE 0.17) GP1-GP2: 0.5 p: NSG vs. GP2	GP1 B: 106 (37) F: 116 (42) F-B: 10 GP2 B: 124 (36) F: 118 (38) F-B: -6 GP1-GP2: 16	GP1 B: 41 (8.8) F: 47.2 (9.4) F-B: 6.2 GP2 B: 45.4 (12.5) F: 44.6 (11.8) F-B: -0.8 GP1-GP2: 7	GP1 B: 291 (232) F: 200 (99) F-B: -91 GP2 B: 174 (80) F: 179 (78) F-B: 5 GP1-GP2: 96	GP1 F-B: 2 p: <0.05 vs. baseline GP2 F-B: 0.3 GP1-GP2: 1.7
Sulfonylurea vs Sitagliptin						
Scott, 2007[94]	GP1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks GP2: Sitagliptin Fixed Start: 100, Max: 100	GP1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 CI: -0.9 - -0.62 GP2 B: 7.83 (0.95) F: 7.34 (1.01) F-B: -0.54 CI: -0.68 - -0.4	GP1 B: 2.95 (1.01) F: 2.93 (0.9) F-B: 2 CI: -1.8 - 5.8 GP2 B: 2.96 (0.78) F: 2.96 (0.8) F-B: 1.7 CI: -1.9 - 5.4	GP1 B: 1.14 (0.25) F: 1.16 (0.28) F-B: 2.8 CI: 0.4 - 5.1 GP2 B: 1.16 (0.27) F: 1.17 (0.29) F-B: 1.1 CI: -1.1 - 3.4	GP1 B: 1.93 (0.96) F: 1.96 (0.94) F-B: 7 CI: -0.1 - 14.1 GP2 B: 2.02 (1.11) F: 2.16 (1.46) F-B: 9.8 CI: 2.9 - 16.7	GP1 F-B: 0.9 CI: 0.5-1.3 GP2 F-B: no significant weight change
Scott, 2007[94]	GP1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks GP2: Sitagliptin Fixed Start: 50, Max: 50	GP1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 CI: -0.9 - -0.62 GP2 B: 7.89 (0.94) F: 7.5 (1.14) F-B: -0.43 CI: -0.56 - -0.29	GP1 B: 2.95 (1.01) F: 2.93 (0.9) F-B: 2 CI: -1.8 - 5.8 GP2 B: 3.05 (0.82) F: 3.07 (0.84) F-B: 3 CI: -0.7 - 6.7	GP1 B: 1.14 (0.25) F: 1.16 (0.28) F-B: 2.8 CI: 0.4 - 5.1 GP2 B: 1.16 (0.27) F: 1.18 (0.26) F-B: 3 CI: 0.8 - 5.3	GP1 B: 1.93 (0.96) F: 1.96 (0.94) F-B: 7 CI: -0.1 - 14.1 GP2 B: 1.99 (1.19) F: 1.85 (0.99) F-B: -0.5 CI: -7.3 - 6.4	GP1 F-B: 0.9 CI: 0.5-1.3 GP2 F-B: no significant weight change
Scott, 2007[94]	GP1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks GP2: Sitagliptin Fixed Start: 25, Max: 25	GP1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 CI: -0.9 - -0.62 GP2 B: 7.85 (0.88) F: 7.48 (0.98) F-B: -0.41 CI: -0.55 - -0.27	GP1 B: 2.95 (1.01) F: 2.93 (0.9) F-B: 2 CI: -1.8 - 5.8 GP2 B: 2.96 (0.8) F: 2.96 (0.85) F-B: 1.9 CI: -1.8 - 5.6	GP1 B: 1.14 (0.25) F: 1.16 (0.28) F-B: 2.8 CI: 0.4 - 5.1 GP2 B: 1.12 (0.25) F: 1.16 (0.26) F-B: 4.1 CI: 1.8 - 6.4	GP1 B: 1.93 (0.96) F: 1.96 (0.94) F-B: 7 CI: -0.1 - 14.1 GP2 B: 1.99 (0.98) F: 1.96 (0.94) F-B: 4.9 CI: -2.1 - 11.9	GP1 F-B: 0.9 CI: 0.5-1.3 GP2 F-B: no significant weight change

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Scott, 2007[94]	GP1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks GP2: Sitagliptin Fixed Start: 10, Max: 10	GP1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 CI: -0.9 - -0.62 GP2 B: 7.89 (0.94) F: 7.77 (1.22) F-B: -0.15 CI: -0.29 - -0.01	GP1 B: 2.96 (1.01) F: 2.93 (0.9) F-B: 2 CI: -1.8 - 5.8 GP2 B: 3 (0.98) F: 3.07 (0.97) F-B: 5.5 CI: -1.8 - 9.2	GP1 B: 1.14 (0.25) F: 1.16 (0.28) F-B:2.8 CI: 0.4 - 5.1 GP2 B: 1.16 (0.23) F: 1.2 (0.24) F-B: 4.6 CI: 2.3 - 6.8	GP1 B: 1.93 (0.96) F: 1.96 (0.94) F-B: 7 GP2 B: 1.81 (0.99) F: 1.81 (0.99) F-B: 3.6	GP1 F-B: 0.9 CI: 0.5-1.3 GP2 F-B: no significant weight change
Sulfonylurea vs Meglitinides						
Jibran, 2006[95]	GP1: Glibenclamide Varied, glucose: fasting < 130 mg/dl, PP < 175 mg/dl Start: 5mg, Max: 15mg, Mean: 8.8mg/day GP2: Repaglinide Varied, glucose: fasting < 130 mg/dl, PP < 175 mg/dl Start: 0.5 mg tid, Max: 1.5 mg tid, Mean: 4.27mg/day	GP1 B: 10.2 (1.6) F: 9.4 (1.5) F-B: 0.7 (0.5) GP2 B: 9.9 (1.6) F: 8.8 (1.7) F-B: 1.1 (0.3) GP1-GP2: p: 0.001				GP1 B: 72.7 (17.4) F: 71.7 (15.2) GP2 B: 65.8 (9.4) F: 66 (8.8)
Derosa, 2003[96]	GP1: Glimepiride Varied Start: 1mg, Mean: 3mg GP2: Repaglinide Varied Start: 1mg, Mean: 2.5mg	GP1 B: 7.8 (1.2) F: 6.7 (0.9) F-B: -1.1 (-5.6 to -0.54) p: <0.01 vs. baseline GP2 B: 8 (1.1) F: 6.8 (0.8) F-B: (-1.2 (-6.2 to -0.48) p: <0.01 vs. baseline GP1-GP2: 0.1 p: NSG vs. GP2	GP1 B: 142 (24) F: 136 (25) F-B: -6 GP2 B: 139 (22) F: 132 (18) F-B: -7 GP1-GP2: 1 p: NSG vs. GP2	GP1 B: 44 (5) F: 43 (6) F-B: -1 GP2 B: 43 (7) F: 45 (7) F-B: 2 GP1-GP2: -3 p: NSG vs GP2	GP1 B: 170 (36) F: 155 (39) F-B: -15 GP2 B: 153 (32) F: 135 (36) F-B: -18 GP1-GP2: 3 p: NSG vs. GP2	GP1 B: 77.1 (5.9) F: 76.6 (5.3) F-B: -0.5 GP2 B: 76.4 (5.2) F: 76.5 (5.3) F-B: 0.1 GP1-GP2: -0.6 p: NSG vs. GP2

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Madsbad, 2001[97]	GP1: Glipizide Varied Start: 5mg, Max: 15mg GP2: Repaglinide Varied Start: 0.5mg, Max: 4mg	GP1 B: 7.2 (1.4) F: 7.7 (SE 0.2) F-B: 0.78 (0.46 to 1.1) GP2 B: 7.3 (1.2) F: 7.4 (SE 0.15) F-B: 0.19 (-0.02 to 0.4) GP1-GP2: 0.59 p: <0.05 vs. GP1		GP1 F-B: 0.78 p: NSG vs baseline GP2 F-B: 0 p: NSG vs baseline GP1-GP2: 1.17 (1.56 to 3.5)	GP1 F-B: 3.56 (-23.14 to 29.37) GP2 F-B: 3.56 (-14.24 to 20.47) GP1-GP2: 0 (-31.15 to 31.15) p: NSG vs. GP2	
Landgraf, 1999[98]	GP1: Glibenclamide Varied Start: 1.75mg, 3.5mg, 7.0mg, 10.5mg, Max: 10.5mg GP2: Repaglinide Varied Start: 0.5mg, 1.0mg, 2.0mg, 4.0mg tid, Max: 4mg tid	GP1 B: 8 F: 7.6 (SE 0.1) F-B: -0.4 GP2 B: 7.8 F: 7.5 (SE 0.1) F-B: -0.3 GP1-GP2: -0.1		GP1 F-B: 1.11 (SE 0.03) GP2 F-B: 1.15 (SE 0.03) GP1-GP2: -0.04 p: 0.005 vs GP1		GP1 B: 78.9 (12.8) F: 77.5 F-B: -1.4 p: NSG vs. baseline GP2 B: 79.6 (10.3) F: 78.9 F-B: -0.7 p: NSG vs. baseline GP1-GP2: -0.7 p: NSG vs. GP2

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Wolffenbuttel, 1999[99]	GP1: Glyburide Varied Start: 1.75mg, Max: 10.5mg GP2: Repaglinide Varied Start: 1.5mg, Max: 12mg	GP1 B: 7 (1.2) F: 7.45 F-B: 0.45 (0.22 to 0.69) GP2 B: 7.1 (1.4) F: 7.68 F-B: 0.58 (0.41 to 0.7) GP1-GP2: -0.13 p: NSG vs. GP2		GP1 B: 45.63 (12.48) F: 45.63 (12.48) F-B: 0 p: NSG vs baseline GP2 B: 44.85 (14.82) F: 46.02 (14.43) F-B: 1.17 p: NSG vs baseline GP1-GP2: -1.17	GP1 B: 163.76 F: 174.44 F-B: 10.68 p: NSG vs. baseline GP2 B: 170.88 F: 178 F-B: 7.12 p: NSG vs. baseline GP1-GP2: 3.56	GP1 B: 81.3 (12.2) F: 82 (11.9) F-B: 0.7 p: NSG vs. baseline GP2 B: 81.5 (13.4) F: 81.5 (13.5) F-B: 0 p: NSG vs. baseline GP1-GP2: 0.7
Wolffenbuttel, 1993[101]	GP1: Glyburide Varied Start: 5mg, Max: 15mg GP2: Repaglinide Varied Start: 0.5mg, Max: 4mg					GP1 B: 70.9 (10.8) F: 70.5 (10.2) F-B: -0.4 p: NSG vs. baseline GP2 B: 74 (9.6) F: 72.3 (9.4) F-B: -1.7 p: <0.05 vs. baseline GP1-GP2: 1.3

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Marbury, 1999[100]	GP1: Glyburide Varied Start: 2.5mg, Max: 15mg GP2: Repaglinide Varied Start: 0.5mg, Max: 12mg	GP1 B: 8.9 (1.6) F: 9.0 F-B: 0.1 (0.11) GP2 B: 8.7 (1.7) F: 8.78 F-B: 0.08 (0.07) GP1-GP2: 0.02	GP1 F-B: -6.51 GP2 F-B: -5.03 GP1-GP2: -1.48 (-6.499 to 3.532) p: NSG vs. GP2	GP1 F-B: -0.13 p: NSG vs baseline GP2 F-B: -0.81 p: NSG vs baseline GP1-GP2: 0.68 (-0.8 to 2.15)	GP1 F-B: -6.45 GP2 F-B: 6.57 GP1-GP2: -13.02 (-31.24 to 57.28) p: NSG vs. GP2	GP1 F-B: 0.05 (SE 0.5) GP2 F-B: -0.22 (SE 0.5) GP1-GP2: 0.27 p: NSG vs. GP2
Vakkilainen, 2002[102]	GP1: Glibenclamide Varied Start: 5, Max: 10 GP2: Nateglinide Fixed Start: 120 tid	GP1 B: 7.6 (7.2 to 8.1) F: 6.9 (6.5 to 7.3) F-B: -0.7 p: <0.001 vs. baseline GP2 B: 7.6 (7.2 to 8.0) F: 7.4 (7.0 to 7.9) F-B: -0.2 GP1-GP2: -0.5 p: NSG vs. baseline	GP1 F-B: NSG vs. baseline GP2 F-B: NSG vs. baseline	GP1 F-B: p: NSG vs baseline GP2 F-B: p: NSG vs baseline		
Metformin + Thiazolidinedione vs Metformin+Sulfonylurea						
Home, 2009[14]	GP1: Metformin+Rosiglitazone Varied, HgbA1c: <=7.0 Max: 2550mg; Start: 4mg, Max: 8mg D: 8 wks; NR GP2: Metformin+Sulfonylurea Varied, HgbA1c: <=7.0 Max: 2550mg; Unclear D: 8 wks	GP1 F-B: -0.28 (SE: 0.03) GP2 F-B: 0.01 (SE: 0.04) GP1-GP2: p: <0.0001	GP1 F-B: -0.33 (SE 0.04) GP2 F-B: -0.53 (SE 0.03)	GP1 F-B: 0.12 (SE: 0.01) GP2 F-B: 0.07 (SE: 0.01)	GP1 F-B: -0.14 (SE 0.04) GP2 F-B: -0.14 (SE 0.04)	GP1 F-B: 3.8 (SE: 0.24) GP2 F-B: 0 (SE: 0.2) and -1.5 (SE: 0.2)
Derosa 2009[36]	GP1: Metformin+Pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos GP2: Metformin+Glimepiride Fixed; Varied, prespecified target dose Start: 850mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NA; 3 mos	GP1 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 GP2 B: 9 (1.1) F: 7.8 (0.4) p: <0.01 F-B: -1.2 (0.4) p: <0.01				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hamann 2008[103]	GP1: Metformin+Rosiglitazone Varied, glucose: 6.1mmol/l Max: 2g/day; Unclear D: 12 wks GP2: Metformin+Sulfonylurea Varied, glucose: 6.1mmol/l Max: 2g/day; Unclear D: 12 wks	GP1 F-B: -0.78 (SE: 0.06) GP2 F-B: -0.86 (SE: 0.06) GP1-GP2: 0.09 CI: -0.08 - 0.25	GP1 B: Geometric mean: 2.85 Coefficient of variation%: 33.29 F: Geometric mean: 2.98 Coefficient of variation%: 35.93 GP2 B: Geometric mean: 2.93 Coefficient of variation%: 37.68 F: Geometric mean: 2.77 Coefficient of variation%: 37.3	GP1 B: Geometric mean: 1.2 Coefficient of variation%: 23.99 F: Geometric mean: 1.32 Coefficient of variation%: 30.1 GP2 B: Geometric mean: 1.19 Coefficient of variation%: 21.6 F: Geometric mean: 1.22 Coefficient of variation%: 21.76	GP1 B: Geometric mean: 2.13 Coefficient of variation%: 56.4 F: Geometric mean: 1.93 Coefficient of variation%: 65.97 GP2 B: Geometric mean: 2.03 Coefficient of variation%: 47.72 F: Geometric mean: 1.77 Coefficient of variation%: 42.82	GP1 F-B: 2.7 (SE: 0.3) GP2 F-B: 1.6 (SE: 0.3) GP1-GP2: p: 0.0016
Comaschi 2007[109]	GP1: Metformin+Pioglitazone Varied Max: 3g/day; Start: 15mg/day, Max: 30mg/day D: NR; 22 wks GP2: Metformin+Sulfonylurea Varied, HgbA1c: 7.50% Start: 400, Max: 3g/day; Start: 2.5 D: 22 wks	GP1 B: (0.81) F: (0.87) F-B: -0.99 p: <0.001 GP2 B: (0.94) F: (1.02) F-B: -1.29 p: 0.192 GP1-GP2: 0.31 p: 0.054		GP1 B: 1.09 (SE: 0.31) F: 1.15 (SE: 0.28) F-B: 0.06 p: 0.009 GP2 B: 1.17 (SE: 0.34) F: 1.08 (SE:0.33) p: <0.001 F-B: -0.09 p: <0.001 GP1-GP2: -0.09 CI: -0.13 - -0.05 p: <0.001		

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Comaschi, 2008[131]	GP1: Metformin+Pioglitazone Varied Max: 3g/day; Start: 15mg/day, Max: 30mg/day D: NR; 22wks GP2: Metformin+Sulfonylurea Varied, HgbA1c: 7.50%; Fixed Start: 400mg; Start: 2.5mg D: 22wks				GP1 B: 2.13 (SE 1.1) F: 1.93 (1.14) F-B: -0.2 p: 0.067 GP2 B: 2.01 (SE 1.29) F: 2.04 (SE 1.35) F-B: 0.03 CI: -0.16 - 0.23 p: 0.733	
Home 2007[104]	GP1: Metformin+Rosiglitazone Varied, HgbA1c: <=7 Max: 2550mg; Start: 4mg/day, Max: 8mg/day GP2: Metformin+Sulfonylurea Varied, HgbA1c: <=7.0 Max: 2550 mg; Unclear D: 8 wks; NR	GP1 F-B: -0.48 CI: -0.59 - -0.36 GP2 F-B: -0.55 CI: -0.66 - -0.44 GP1-GP2: 0.07 CI: -0.09 - 0.23	GP1 F-B: 0.04 CI: -0.07 - 0.15 GP2 F-B: -0.26 CI: -0.36 - -0.16 GP1-GP2: 0.06 CI: 0.02 - 0.1 p: 0.01	GP1 F-B: 0.08 CI: 0.05 - 0.11 GP2 F-B: 0.02 CI: -0.06 GP1-GP2: 0.26 CI: 0.05 - 0.47 p: 0.016	GP1 F-B: 0.4 CI: 0.25 - 0.55 GP2 F-B: 0.15 CI: 0.01 - 0.29	GP1 F-B: 2.3 CI: 1.7 - 2.9 GP2 F-B: 1.1 CI: 0.6-1.6 (cohort1), -0.9 CI: -1.4 to -0.4 (cohort2) GP1-GP2 (cohort 1): 1.2 CI: 0.4-2 p: 0.003; GP1-GP2 (cohort 2): 4.3 CI: 3.6-5.1 p: <0.001
Bakris 2006[105]	GP1: Metformin+Rosiglitazone Varied; Varied, glucose: <= 6.6mmol/L Unclear; Start: 4mg/day D: 3 wks GP2: Metformin+Glyburide Varied; Glucose: <=6.6 Unclear; Start: 5mg/day D: 3 wks; NR	GP1 F-B: 0.72 (SE: 0.1) GP2 F-B: 0.92 (SE: 0.08)				GP1 F-B: 1.94 (4.63) GP2 F-B: 1.5 (3.53)

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Umpierrez 2006[106]	GP1: Metformin+Pioglitazone NR; Varied, glucose: <120, HgbA1c: <8.0 Start: 1.54gday, Max: 1.57gday; Start: 30mg/day, Max: 45mg/day D: NR; Unclear GP2: Metformin+Glimepiride NR; Glucose: <120mg/dL Start: 1.47gday, Max: 1.49gday; Start: 2mg/day, Max: 8mg/day D: NR; 6 wks	GP1 F-B: -1.23 (SE: 0.073) p: 0.4825 GP2 F-B: -1.3 (SE: 0.077)	GP1 F-B: 8.5 (SE: 2.81) GP2 F-B: -0.1 (SE: 2.87) GP1-GP2: -5.4 (SE: 0.94) p: 0.0001	GP1 F-B: 4.8 (SE: 0.66) GP2 F-B: -0.6 (SE: 0.7) p: 0.0001 GP1-GP2: 10 (SE 9.53) p: 0.2953	GP1 F-B: -14.2 (SE 6.57) GP2 F-B: -4.2 (SE 7.06) p: 0.2953	GP1 F-B: 1.85 (SE: 0.38) GP2 F-B: 1.74 (SE: 0.41)
Derosa 2005[107]	GP1: Metformin+Rosiglitazone Fixed Start: 500mg tid, Max: 500mg tid; Start: 4mg po qday, Max: 4mg po qday GP2: Metformin+Glimepiride Fixed Start: 500mg po tid, Max: 500mg po tid; Start: 2mg po qday, Max: 2mg po qday	GP1 B: 8 (0.7) F: 6.8 (0.6) p: <0.01 GP2 B: 7.9 (0.6) F: 7 (0.7) p: <0.05				
Derosa, 2005[124]	GP1: Metformin+Rosiglitazone Fixed Start: 500mg po tid; Start: 2mg po qday GP2: Metformin+Glimepride Fixed Start: 500mg po tid; Start: 4mg po qday					GP1 B: 74.2 (3.6) F: 68.3 (3) p: <0.01 GP2 B: 75.6 (4.2) F: 71.1 (3.2) p: <0.05
Derosa, 2006[130]	GP1: Metformin+Rosiglitazone Fixed Start: 500mg tid, Max: 500mg tid; Start: 4mg po qday, Max: 4mg po qday GP2: Metformin+Glimepride Fixed Start: 500mg po tid, Max: 500mg po tid; Start: 2mg po qday, Max: 2mg po qday		GP1 B: 116 (15) F: 120 (17) F-B: 4 GP2 B: 118 (13) F: 102 (11) F-B: -16 p: <0.05 vs. baseline GP1-GP2: 20 p: <0.05 vs GP1	GP1 B: 42 (4) F: 44 (3) F-B: 2 GP2 B: 43 (5) F: 43 (4) F-B: 0 GP1-GP2: 2 p: NSG vs GP2	GP1 B: 186 (28) F: 129 (18) F-B: -57 GP2 B: 178 (23) F: 137 (20) F-B: -41 GP1-GP2: -16 p: NSG vs. GP2	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Garber, 2006[108]	GP1: Metformin+Rosiglitazone Varied Start: 1500-2000, Max: 2000; Start: 4, Max: 8mg GP2: Metformin+Glibenclamide Varied Start: 1000, Max: 2000; Start: 5, Max: 10		GP1 B: 116 F: 125 F-B: 9 (35) GP2 B: 119 F: 115 F-B: -4 (26) GP1-GP2: -14 (-6 to 22) p: NSG vs. GP2	GP1 B: 45 F: 48 F-B: 3 (10) GP2 B: 47 F: 45 F-B: -2 (10) GP1-GP2: 4 (1 to 7) p: <0.05 vs GP2	GP1 B: 218 F: 238 F-B: 21 (113) GP2 B: 226 F: 238 F-B: 12 (133) GP1-GP2: 9 (-22 t0 40) p: NSG vs. GP2	GP1 B: 94 F: 95.4 F-B: 1.4 GP2 B: 92 F: 95 F-B: 3 GP1-GP2: -1.5 p: <0.001 vs. GP1
Derosa, 2005[133]	GP1: Metformin+Rosiglitazone Fixed Start: 1500; Start: 4mg GP2: Metformin+Glimepride Fixed Start: 1500, Start: 2 mg				GP1 B: 186 (28) F: 129 (18) F-B: -57 GP2 B: 178 (23) F: 137 (20) F-B: -41 GP1-GP2: -16 p: NSG and vs. GP2	
Metformin+Thiazolidinedione vs Metformin+Meglitinides						
Raskin, 2009[110]	GP1: Metformin+Rosiglitazone Varied, prespecified target dose; Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 8 mg D: 4 wks GP2: Metformin+Repaglinide Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 10 mg D: 4 wks	GP1-GP2: -0.21 CI 0.031 - -0.452	GP1 B: 108.2 (SE: 2.88) F: 121.2 (SE: 3.51) F-B: 9.576 p:0.0008 GP2 B: 111.9 (SE: 2.87) F: 104.6 (SE: 2.89) F-B: -2.604 p: 0.4637	GP1 B: 44.8 (SE:0.85) F: 49.4 (SE: 1.05) F-B: 4.479 p: <0.0001 GP2 B: 44.3 (SE: 0.91) F: 44.2 (SE: 1.05) F-B: -0.151 p: 0.7546	GP1 B: 208.8 (SE 21.88) F: 208.2 (SE 16.20) F-B: 6.529 p: 0.9493 GP2 B: 190.3 (SE 10.77) F: 194.9 (SE 10.66) F-B: -0.908 p: 0.8607 GP1-GP2: 6.529 GP1-GP2: -0.908 p: 0.6007	GP1-GP2: not clinically relevant
Metformin+Thiazolidinedione vs Metformin+Sitagliptin						

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Scott, 2008[71]	GP1: Metformin+Rosiglitazone NR; Fixed Start: >= 1500mg; Mean: 8mg D: 10 wks; NA GP2: Metformin+Sitagliptin Fixed Start: > 1500 mg; Start: 100 mg, Mean: 100 mg	GP1-GP2: -0.06 CI: -0.25 - 0.14	GP1 B: 99.2 (29.4) F: 119.6 (37.6) F-B: Mean % change from baseline: 26.2 CI: 19.7 - 32.7 GP2 B: 95.4 (30.8) F: 104.6 (35.1) F-B: Mean % change from baseline: 11.4 CI: 5 - 17.8	GP1 B: 42.2 (10) F: 45.7 (10.5) F-B: Mean % change from baseline: 9.2 CI: 6.1 - 12.2 GP2 B: 43.9 (11.6) F: 45.7 (13.4) F-B: Mean % change from baseline: 4.3 CI: 1.2 - 7.3	GP1 B: 201.6 (126.2) F: 199.8 (108.4) F-B: Mean % change from baseline: 13.1 CI: 5.2 - 21.1 GP2 B: 177.8 (80.7) F: 163.3 (74) F-B: Mean % change from baseline: -4.8 CI: -12.7 - 3.1	GP1 F-B: 1.5 CI: 1-1.9 GP2 F-B: -0.4 CI: -0.8 to 0 GP1-GP2: 1.9 CI: 1.3-2.5
Metformin+Thiazolidinedione vs Thiazolidinedione + Sulfonylurea						
Home, 2009[14]	GP1: Metformin+Rosiglitazone Varied, HgbA1c: <=7.0 Max: 2550mg; Start: 4mg, Max: 8mg D: 8 wks; NR GP2: Rosiglitazone+Sulfonylurea Varied, HgbA1c: <=7.0 Start: 4mg/day, Max: 8mg/day; NR D: Unclear; NR	GP1 F-B: -0.28 (SE: 0.03) GP2 F-B: -0.44 (SE: 0.03) GP1-GP2: p: <0.0001	GP1 F-B: -0.33 (SE: 0.04) GP2 F-B: -0.22 (SE: 0.04)	GP1 F-B: 0.12 (SE: 0.01) GP2 F-B: 0.11 (SE: 0.01)	GP1 F-B: -0.14 (SE 0.04) GP2 F-B: -0.13 (SE 0.04) GP1-GP2: p:0.82	GP1 F-B: 3.8 (SE: 0.24) GP2 F-B: 4.1 (SE: 0.2)
Comaschi, 2008[131]	GP1: Metformin+Pioglitazone Varied, HgbA1c: NR Max: 3g/day; Start: 15mg, Max: 30mg GP2: Pioglitazone+Sulfonylurea Varied, HgbA1c: <=7.5 Start: 15mg/day, Max: 30mg/day; NR D: 22wks		GP1-GP2: no significant difference (p: 0.28)		GP1 B: 2.13 (SE 1.1) F: 1.93 (SE 1.14) F-B: -0.2 p: 0.067 GP2 B: 2.09 (SE 1.35) F: 1.77 (SE 0.94) F-B: -0.32 p: 0.017 GP1-GP2: p: <0.05	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Comaschi, 2007[109]	GP1: Metformin+Pioglitazone Varied Max: 3g/day; Start: 15mg/day, Max: 30mg/day D: NR; 22 wks GP2: Pioglitazone+Sulfonylurea Varied, HgbA1c: 7.50%; Varied, NR Start: 15mg/dl, Max: 30mg/dl; Unclear D: 22 wks; NR	GP1 F-B: -0.99 p: <0.001 GP2 F-B: -1.29 p: <0.001 GP1-GP2: 0.3 p: 0.043		GP1 B: 1.09 (SE: 0.31) F: 1.15 (SE: 0.28) F-B: 0.06 p: 0.009 GP2 B: 1.07 (SE: 0.33) F: 1.09 (SE: 0.34) F-B: 0.01 p: 0.617 GP1-GP2: 0.05		
Home, 2007[104]	GP1: Metformin+Rosiglitazone Varied, HgbA1c: <=7 Max: 2550mg; Start: 4mg/day, Max: 8mg/day GP2: Rosiglitazone+Sulfonylurea Varied, HgbA1c: <=7.0 Start: 4mg, Max: 8mg; Unclear D: 8 wks	GP1 F-B: -0.48 CI: -0.59 - -0.36 GP2 F-B: -0.55 CI: -0.67 - -0.44 GP1-GP2: 0.06 CI: -0.09 - 0.2	GP1 F-B: 0.04 CI: -0.07 - 0.15 GP2 F-B: 0.19 CI: 0.08 - 0.3	GP1 F-B: 0.08 CI: 0.05 - 0.11 GP2 F-B: 0.1 CI: 0.07 - 0.13 GP1-GP2: 0.01 CI: -0.02 - 0.05	GP1 F-B: 0.4 CI: 0.25 - 0.55 GP2 F-B: 0.24 CI: 0.06 - 0.42 GP1-GP2: 0.06 CI: -0.2 - 0.32	GP1 F-B: 2.3 CI: 1.7-2.9 GP2 F-B: 3.4 CI: 2.9-4
Metformin+Sulfonylurea vs Metformin+Meglitinides						
Derosa 2009[111]	GP1: Metformin+Glibenclamide Fixed Start: 1500 mg, Max: 3000 mg, Mean: 2500 mg; Start: 7.5 mg, Max: 15 mg, Mean: 12.5 mg D: 6 mos GP2: Metformin+Nateglinide Fixed Start: 1500 mg, Max: 3000 mg, Mean: 2500 mg; Start: 180 mg, Max: 360 mg, Mean: 300 mg D: 6 mos	GP1 B: 8.2 (1.1) F: 7.3 (0.6) F-B: p: <0.05 GP2 B: 8.1 (1.0) F: 6.4 (0.4) F-B: p: <0.01 GP1-GP2: p: 0.05	GP1 B: Median: 119 (12) F: Median: 104 (10) GP2 B: Median: 121 (13) F: Median: 113 (11)	GP1 B: Median: 42 (5) F: Median: 41 (4) GP2 B: Median: 42 (5) F: Median: 43 (6)		BMI GP1 B: 26.5 (1.5) F: 26.9 (1.7) GP2 B: 26.4 (1.4) F: 26.8 (1.6)

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Derosa, 2007[226]	GP1: Metformin+Glibenclamide Fixed Start: 1500 mg, Max: 3000 mg, Mean: 2500 mg; Start: 7.5 mg, Max: 15 mg, Mean: 12.5 mg GP2: Metformin+Nateglinide Fixed Start: 1500 mg, Max: 3000 mg, Mean: 2500 mg; Start: 7.5 mg, Max: 15 mg, Mean: 12.5 mg				GP1 B: 161 (42) F: 140 (31) p:NSG GP2 B: 156 (40) F: 141 (33)p:NSG	
Schwarz 2008[125]	GP1: Metformin+Glyburide Varied, glucose: <120mg/dL Start: 500mg, Max: 2000mg; Start: 1.25mg, Max: 10mg D: 12 wks GP2: Metformin+Nateglinide Varied, glucose: <120mg/dL Start: 500mg, Max: 2000mg; Start: 360mg, Max: 360mg D: 12 wks	GP1 F-B: -1.2 (SE: 0.1) p: <0.001 GP2 F-B: -1.2 (SE: 0.2) p: <0.001				GP1-GP2: no clinically relevant difference in weight
Gerich 2005[112]	GP1: Metformin+Glyburide Varied, glucose: FPG >=6.7; Fixed Start: 500mg po qday, Max: 2000mg daily, Mean: 1459mg daily; Start: 120mg po qac, Mean: 357mg daily D: 12 wks; NA GP2: Metformin+Nateglinide Varied, glucose: FPG>=6.7 Start: 500mg po qday, Max: 2000mg po daily, Mean: 1105mg daily; Start: 1.25 mg po qday, Max: 10mg daily, Mean: 5.1mg daily D: 12 wks	GP1 B: 8.4 (1.2) F: 6.4 p: <0.0001 F-B: -1.5 (SE: 0.1) p: <0.0001 GP2 B: 8.3 (1.1) F: 6.7 p: <0.0001 F-B: -1.2 (SE: 0.1) p: <0.0001 GP1-GP2: p: 0.173				GP1 F-B: -0.4 (0.4) p: 0.8143 GP2 F-B: 0.8 (0.5) p: 0.0011 GP1-GP2: -1.2 p: 0.0115
Metformin +Sulfonylurea vs Metformin+Sitagliptin						

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Nauck, 2007[113]	GP1: Metformin+Glipizide Varied; Varied, glucose: <6.1mmol/l NR; Start: 5mg/day, Max: 20mg/day D: Unclear; 18 wks GP2: Metformin+Sitagliptin Varied; Fixed NR	GP1-GP2: -0.01 CI: -0.09 - 0.08				GP1-GP2: -2.5 CI: -3.1 - -2 p: <.001
Metformin +Sulfonylurea vs Thiazolidinedione+Sulfonylurea						
Seufert, 2008[117]	GP1: Metformin+Sulfonylurea Fixed Max: 2550mg/day, Mean: 2081mg/day; NR D: 12 wks GP2: Pioglitazone+Sulfonylurea Fixed Max: 45, Mean: 37 mg; NR D: 12 wks	GP1 B: 8.8 F-B: -1.16 GP2 B: 8.82 F-B: -1.03 GP1-GP2: adjusted difference: 0.13 CI: -0.06 - 0.31 p: 0.173		GP1 B: 42.51 (9.36) F: 48.75 (0.39) F-B: 6.24 GP2 B: 43.29 (10.53) F: 46.41 (0.39) F-B: 3.12 GP1-GP2: 3.12 p: <0.0001 vs GP2		GP1 F-B: -1.7 (4.5) GP2 F-B: 3.2 (4.7)
Home, 2009[14]	GP1: Metformin+Sulfonylurea Varied, HgbA1c: <=7.0 Max: 2550mg GP2: Rosiglitazone+Sulfonylurea Varied, HgbA1c: <=7.0 Start: 4mg/day, Max: 8mg/day; NR D: Unclear; NR	GP1 F-B: -0.18 (SE: 0.04) GP2 F-B: -0.44 (SE: 0.03) GP1-GP2: p: <0.0001	GP1 F-B: -0.53 (SE: 0.03) GP2 F-B: -0.22 (SE: 0.04)	GP1 F-B: 0.07 (SE: 0.01) GP2 F-B: 0.11 (SE: 0.01)	GP1 F-B: -0.14 (SE 0.04) GP2 F-B: -0.13 (SE 0.04) GP1-GP2: p: 0.82	GP1 F-B: -1.5 (SE: 0.2) GP2 F-B: 4.1 (SE: 0.2) GP1-GP2: p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
van der Meer 2009[116]	GP1: Metformin+Glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks GP2: Pioglitazone+Glimepiride Fixed; Varied Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR	GP1 B: 7 (SE: 0.1) F: 6.3 (SE: 0.1) p: <0.001 GP2 B: 7.1 (SE: 0.2) F: 6.5 (SE: 0.1) p: <0.001 GP1-GP2: p: 0.146	GP1 B: 2.9 (SE: 0.1) F: 2.6 (SE: 0.2) p: 0.001 GP2 B: 2.5 (SE: 0.1) F: 2.5 (Se: 0.1) p: 0.38	GP1 B: Median: 1.13 (IQR: 0.9 - 1.42) p: 0.133 F: Median: 1.02 (IQR: 0.86 - 1.26) p: 0.133 GP2 B: Median: 1.07 (IQR: 0.94 - 1.28) p: 0.003 F: Median: 1.23 (IQR: 0.99 - 1.46) p: 0.133	GP1 B: Median: 1.5 (IQR: 0.9 - 2.1) F: Median: 1.7 (IQR: 0.9 - 2.3) p: 0.519 GP2 B: Median: 1.4 (IQR: 1 - 2.2) F: Median: 1.4 (IQR: 0.9 - 2.3) p: 0.926 GP1-GP2: p:0.596	GP1 B: 92 (2) F: 92 (3) GP2 B: 91 (2) F: 94 (4) GP1-GP2: p: <0.001
Comaschi 2007[109]	GP1: Metformin+Sulfonylurea Varied, HgbA1c: 7.50% Start: 400, Max: 3g/day; Start: 2.5 D: 22 wks GP2: Pioglitazone+Sulfonylurea Varied, HgbA1c: 7.50%; Varied Start: 15mg/dl, Max: 30mg/dl; Unclear D: 22 wks; NR	GP1 B: (0.94) F: (1.02) F-B: -1.29 p: 0.192 GP2 B: (0.9) F: (0.94) F-B: -1.29 p: <0.001 GP1-GP2: 0.01 p: 0.975				
Comaschi, 2008[131]	GP1: Metformin+Glibenclamide Varied, HgbA1c: 7.50% Start: 400mg; Start: 2.5mg D: 22 wks GP2: Pioglitazone+Sulfonylurea Varied, HgbA1c: 7.50% Start: 15mg/day, Max: 30mg/day; Unclear D: 22 wks			GP1 B: Median: 1.17 (SE: 0.34) F: Median: 1.08 (SE: 0.33) p: <0.001 F-B: -0.09 p: <0.001 GP2 B: Median: 1.07 (SE: 0.33) F: Median: 1.09 (SE: 0.34) F-B: 0.01 p: 0.617	GP1 B: 2.01 (SE: 1.29) F: 2.04 (SE: 1.35) F-B: 0.03 CI: -0.16 - 0.23 p: 0.733 GP2 B: 2.09 (SE 1.35) F: 1.77 (SE 0.94) F-B: -0.32 p: 0.017 GP1-GP2: p: <0.05	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglyercerides, mean (SD)	Weight, mean (SD)
Home 2007[104]	GP1:Metformin+Sulfonylurea Varied, HgbA1c: <=7.0 Max: 2550mg; Unclear D: 8 wks GP2: Rosiglitazone+Sulfonylurea Varied, HgbA1c: <=7.0 Start: 4mg, Max: 8mg; Unclear	GP1 F-B: -0.61 CI: -0.7 - -0.51 GP2 F-B: -0.55 CI: -0.67 - -0.44 GP1-GP2: 0.06 CI: -0.09 - 0.2	GP1 F-B: -0.29 CI: -0.4 - -0.19 GP2 F-B: 0.19 CI: 0.08 - 0.3	GP1 F-B: 0.08 CI: 0.05 - 0.11 GP2 F-B: 0.1 CI: 0.07 - 0.13 GP1-GP2: 0.01 CI: -0.02 - 0.05	GP1 F-B: 0.17 CI: -0.02 - 0.36 GP2 F-B: 0.24 CI: 0.06 - 0.42 GP1-GP2: 0.06 CI: -0.2 - 0.32	GP1 F-B: -0.9 CI: -1.4 - -0.4 GP2 F-B: 3.4 CI: 2.9 - 4 GP1-GP2: 4.3 CI: 3.6 - 5.1 p: <0.001
Kim 2007[34]	GP1: Metformin+Glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 1000mg/day; Start: 2mg /day, Max: 7mg/day GP2: Rosiglitazone+Glimepiride Fixed; Varied, glucose: 7.2 - 9.4mmol/L Max: 4mg/day; Start: 2mg/day, Max: 7mg/day	GP1 F-B: -1.1 CI: -1.4 - -0.8 p: <0.001 GP2 F-B: -1.1 CI: -1.5 - -0.8 p: <0.001 GP1-GP2: 0 p: 0.615	GP1 F-B: -0.16 CI: -0.33 - -0.02 p: 0.082 GP2 F-B: -0.23 CI: -0.04 - 0.49 p:0.158	GP1 F-B: -0.04 CI: -0.1 - -0.03 p: 0.246 GP2 F-B: -0.11 CI: -0.27 - -0.04 p: 0.158 GP1-GP2: p: 0.868	GP1 F-B: -0.1 CI: -0.33 - -0.13 p: 0.389 GP2 F-B: -0.33 CI: -0.53 - -0.13 p: 0.002 GP1-GP2: 0.631	GP1 F-B: -0.5 CI: -1.2 to -0.2 p: 0.187 GP2 F-B: 1.3 CI: 0.8-1.9 p: <0.00 GP1-GP2: p: <0.001
Yang 2003[114]	GP1: Metformin+Sulfonylurea Fixed; NR Start: 1000 mg; NR GP2: Rosiglitazone+Sulfonylurea Fixed Start: 4mg; NR	GP1 B: 8.59 (1.78) F: 7.61 (1.47) p: <0.01 F-B: -0.95 (1.5) p: <0.01 GP2 B: 8.61 (1.77) F: 7.46 (1.44) p: <0.01 F-B: -1.09 (1.65) p: <0.01				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hanefeld, 2004[115]	GP1: Metformin + unspecified sulfonylurea Varied; NR Start: 850mg, Max: 850mg tid; NR GP2: Pioglitazone + unspecified sulfonylurea Varied; NR Start: 15mg, Max: 45mg; NR	GP1 B: 8.8 (0.97) F: 7.45 (0.06) F-B: -1.36 GP2 B: 8.82 (0.98) F: 7.61 (0.06) F-B: -1.2 GP1-GP2: -0.16 p: 0.065 vs. GP2	GP1 B: 139.23 (33.54) F: 142.74 (1.56) F-B: 3.12 GP2 B: 139.62 (35.58) F: 132.99 (1.56) F-B: -6.24 GP1-GP2: 9.36 p: 0.0002 vs. GP2		GP1 B: 219.83 (150.41) F: 178.89 (5.34) F-B: -40.94) GP2 B: 211.82 (153.08) F: 191.35 (5.34) F-B: -20.47 GP1-GP2: -20.47 p: 0.008 vs. GP2	GP1 B: 85.3 (15.1) F: 88.1 F-B: 2.8 GP2 B: 84.9 (14.5) F: 83.9 F-B: -1 GP1-GP2: 3.8
Metformin+long-acting insulin vs Metformin+Premixed insulin						
Robbins, 2007[120]	GP1: Metformin+Glargine Fixed; Varied, glucose: <6.7mmol/l Start: 500mg twice daily, Max: 1000mg twice daily, Mean: 1636 mg; Mean: 0.6 U/kg Start: QD, Final: QD GP2: Metformin+Insulin lispro 50/50 Fixed; Varied, glucose: <6.7mmol/L Start: 500mg twice a day, Max: 1000mg twice daily, Mean: 1641 mg; Mean: 0.7 U/kg Start freq: NR, Final freq: tid	GP1 F-B: -0.4 (0.9) GP2 F-B: -0.7 (0.9) p: <0.001 GP1-GP2: p: <0.001				GP1 B: 88.1 (19) F: 87.6 (19.3) p: 0.04 GP2 B: 89.1 (20.4) F: 90 (20.5) p: <0.001 GP1-GP2: p: <0.001
Raskin, 2007[121]	GP1: Metformin+Glargine Fixed; Varied, glucose: 4.4 - 6.1mmol/L before before breakfast and dinner NR; Start: 12 U /day, Mean: 0.57 IU/kg Start freq: QD, Final freq: QD GP2: 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	GP1 F-B: -2.46 (SE: 1.6) GP2 F-B: -2.89 (SE: 1.6) GP1-GP2: p: 0.035				GP1 F-B: 3 (4.3) GP2 F-B: 5.6 (4.6) GP1-GP2: p: 0.0004
Metformin+Premixed insulin vs Metformin + Sulfonylurea						

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes: hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Kvapil, 2006[119]	GP1: Metformin+Aspart 70/30 Fixed; Varied, glucose: 5 to 8mmol/L Mean: 1660; Start: 0.2U/kg, Mean: 0.30 +/-0.12 Start freq: BID, Final freq: BID D: NA; Unclear GP2: Metformin+Glibenclamide Fixed; Varied Mean: 1660; Start: 1.75, Max: 10.5, Mean: 6.58 +/-4.18 D: NA; Unclear	GP1 F-B: -1.7 GP2 F-B: -1.7 GP1-GP2: 0.2 (SE: 0.15) p: >0.05		GP1-GP2: -0.05 (SE:0.03)	GP1 F: 2.3 (SE 1.5) GP2 F: 2 (SE 1.1) F-B: 0.2 GP1-GP2: -0.15 (SE 0.14)	GP1 F-B: 0.8 GP2 F-B: 0.1 GP1-GP2: -0.66 (0.41) p: 0.1
Malone, 2003[118]	GP1: Metformin+Lispro 75/25 Varied; Varied, glucose: fasting and premeal glucose<7mmol/L and 2-h post-prandial glucose <10mmol/L Max: 2550mg/day; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks; titrated throughout study period GP2: Metformin+Glibenclamide Varied; Varied, glucose: fasting and pre-meal goal <7mmol.L, 2-hour post-prandial goal <10mmol/L Max: 2550mg/day, Mean: 1968mg/day; Mean: 14.2mg/day D: 4 wks; titrated throughout study period	GP2 B: 9.17 (1.5) F: 7.29 (1) F-B: -1.87 (1.35) p: <0.001 GP1 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 GP1-GP2: p: 0.288				GP1 B: 83 (15.2) F: 84 (15.1) GP2 B: 81.7 (15.7) F: 82.2 (15.4) p: 0.33

ac or qac=before each meal ; B=baseline; bid= twice a day; BMI=body mass index; CI=confidence interval; cv=coefficient of variation; D=duration of dose titration; dl=deciliter; F=final; F-B=mean difference from baseline to final; FPG=fasting plasma glucose; GP1-GP2=mean difference between the two groups; HDL=high density lipoprotein; IQR=inter quartile range; LDL=low density lipoprotein; Max=maximum; mg=milligram; mmol/l=millimoles per liter; mos=months; NA=not applicable; NR=not reported; NSG=not significant; po=per oral; qday or qd=daily; SD=standard deviation; SE or SEM =standard error of the mean; tid= thrice a day; wks= weeks

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: All-cause mortality

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Thiazolidinedione						
4 RCTs	Low	Consistent	Direct	Imprecise	Unclear	Low
Met vs. SU						
5 RCTs, 9 obs	Medium	Inconsistent	Direct	Precise	Small, favors metformin	Low
Met vs. Sitagliptin						
0						Insufficient
Met vs. Meglitinide						
1 RCT	Low	N/A	Direct	Imprecise	Unclear	Low
Met vs. Met + TZD						
5 RCTs	Low	Consistent	Direct	Imprecise	Unclear	Low
Met vs. Met + SU						
4 RCTs, 7 obs	Medium	Consistent	Direct	Precise	Small, neither favored	Low
Met vs. Met + Sitagliptin						
1 RCT	Medium	N/A	Direct	Imprecise	Unclear	Low
Met vs. Met + Meglitinide						
1 RCT	Low	N/A	Direct	Imprecise	Unclear	Low
TZD vs. TZD						
0						Insufficient
TZD vs. SU						
3 RCTs	Low	Consistent	Direct	Imprecise	Unclear	Low
TZD vs. Sitagliptin						
0						Insufficient
TZD vs. Meglitinide						
0						Insufficient
SU vs. Sitagliptin						
0						Insufficient
SU vs. Meglitinide						
1 RCT	Medium	N/A	Direct	Imprecise	Unclear	Low
Sitagliptin vs. Meglitinide						
0						Insufficient
Met and TZD vs. Met and SU						
2 RCTs	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and SU vs. Met and Meg						
2 RCTs, 1 obs	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and SU vs Met and Sitagliptin						
1 RCT	Low	N/A	Direct	Imprecise	Unclear	Low
Met and Meglitinide vs. Met and another agent						
0						Insufficient
Met and Sitagliptin vs. Met and another agent						
0						Insufficient
Met and Exenatide vs. Met and another agent						
0						Insufficient
Met and Basal Insulin vs. Met and another agent						
0						Insufficient
Met and Premixed Insulin vs. Met and SU						
2 RCTs	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and TZD vs. TZD and SU						

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: All-cause mortality

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
0						Insufficient
Met and SU vs. TZD and SU						
1 RCT	Medium	N/A	Direct	Imprecise	Unclear	Low
Met and Meglitinide vs. TZD and Met						
1 RCT	Medium	N/A	Direct	Imprecise	Unclear	Low
Met and Sitagliptin vs. TZD and another agent						
0						Insufficient
Met and Exenatide vs. TZD and another agent						
0						Insufficient
Met and Basal Insulin vs. TZD and another agent						
0						Insufficient
Met and Premixed Insulin vs. TZD and another agent						
0						Insufficient

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Cardiovascular disease mortality

# Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Thiazolidinedione						
2 RCTs	Medium	Consistent	Direct	Imprecise	Small. Neither favored.	Low
Met vs. SU						
1 RCT 4 obs	Medium	Consistent	Direct	Imprecise	Small. Met favored.	Low
Met vs. Sitagliptin						
No studies						Insufficient.
Met vs. Meglitinide						
1 RCT {20140}	Low	n/a	Direct	Imprecise	Unclear	Low.
Met vs. Met + TZD						
3 RCTs	Low	Consistent	Direct	Imprecise	Small. Unclear.	Low.
Met vs. Met + SU						
2 obs	Medium	Consistent	Direct	Imprecise	Unclear	Low.
Met vs. Met + Sitagliptin						
1	Low	n/a	Direct	Imprecise	Unclear.	Low.
Met vs. Met + Meglitinide						
1	Low	N/a	Direct	Imprecise	Unclear	Low.
TZD vs. TZD						
None						Insufficient
TZD vs. SU						
1	Low	n/a	Direct	Imprecise	Unclear	Low
TZD vs. Sitagliptin						
None						Insufficient
TZD vs. Meglitinide						
None						Insufficient
SU vs. Sitagliptin						
None						Insufficient
SU vs. Meglitinide						
1	Low	n/a	Direct	Imprecise	Unclear	Low
Sitagliptin vs. Meglitinide						
None						Insufficient
Met and TZD vs. Met and another agent						
1 RCT	Low	n/a	Direct	Imprecise	Unclear	Low
Met and SU vs. Met and another agent						
2 RCTs	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met and Meglitinide vs. Met and another agent						
None						Insufficient
Met and Sitagliptin vs. Met and another agent						
None						Insufficient
Met and Exenatide vs. Met and another agent						
None						Insufficient
Met and Basal Insulin vs. Met and another agent						
None						Insufficient
Met and Premixed Insulin vs. Met and another agent						
1	Low	n/a	Direct	Imprecise	Unclear.	Low.
Met and TZD vs. TZD and another agent						
none						Insufficient
Met and SU vs. TZD and another agent						

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Cardiovascular disease mortality

# Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
None						Insufficient
Met and Meglitinide vs. TZD and another agent						
None						Insufficient
Met and Sitagliptin vs. TZD and another agent						
None						Insufficient
Met and Exenatide vs. TZD and another agent						
None						Insufficient
Met and Basal Insulin vs. TZD and another agent						
None						Insufficient
Met and Premixed Insulin vs. TZD and another agent						
None						Insufficient

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Cardiovascular and cerebrovascular disease morbidity

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Thiazolidinedione						
3 RCTs 1 obs	Low	Consistent	Direct	Imprecise	Small. Neither favored.	Low
Met vs. SU						
2 RCTs, 2 obs	Low	Consistent	Direct	Imprecise	Small. MET favored.	Low
Met vs. Sitagliptin						
None						Insufficient
Met vs. Meglitinide						
1 RCT	Low	n/a	Indirect	Imprecise	Unclear	Low
Met vs. Met + TZD						
6 RCTs	Low	Consistent	Direct	Imprecise	Unclear	Low
Met vs. Met + SU						
1 RCT, 1 obs	Medium	Inconsistent	Direct	Imprecise	Small. Met favored.	Low
Met vs. Met + Sitagliptin						
2 RCTs	Low	Consistent	Direct	Imprecise	Unclear.	Low
Met vs. Met + Meglitinide						
1	Low	n/a	Indirect	Imprecise	Unclear	Low
TZD vs. TZD						
None						Insufficient
TZD vs. SU						
3 RCTs 1 obs	Low	Inconsistent	Direct	Imprecise	Unclear.	Low
TZD vs. Sitagliptin						
None						Insufficient
TZD vs. Meglitinide						
None						Insufficient
SU vs. Sitagliptin						
None						Insufficient
SU vs. Meglitinide						
2 RCTs	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Sitagliptin vs. Meglitinide						
None						Insufficient
Met and TZD vs. Met and another agent						
3 RCTs	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met and SU vs. Met and another agent						
2 RCTs	Low	n/a	Direct	Precise	Unclear	Low.
Met and Meglitinide vs. Met and another agent						
None						Insufficient
Met and Sitagliptin vs. Met and another agent						
None						Insufficient
Met and Exenatide vs. Met and another agent						
None						Insufficient
Met and Basal Insulin vs. Met and another agent						
1 cross-over	Medium	n/a/	Direct	Imprecise	Unclear	low.
Met and Premixed Insulin vs. Met and another agent						
None						Insufficient
Met and TZD vs. TZD and another agent						

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Cardiovascular and cerebrovascular disease morbidity

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
2 RCTs	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met and SU vs. TZD and another agent						
1 RCT	Low	n/a	Indirect	imprecise	Unclear	Low
Met and Meglitinide vs. TZD and another agent						
None						Insufficient
Met and Sitagliptin vs. TZD and another agent						
None						Insufficient.
Met and Exenatide vs. TZD and another agent						
None						Insufficient.
Met and Basal Insulin vs. TZD and another agent						
none						Insufficient
Met and Premixed Insulin vs. TZD and another agent						
None						Insufficient.

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence Outcome: Nephropathy

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias:	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Thiazolidinedione						
2 RCT's	low	consistent	indirect	precise	Small. Favors pioglitazone	moderate
Met vs. SU						
1 RCT's	high	n.a.	indirect	imprecise	unclear	low
TZD vs. SU						
4 RCT's	high	inconsistent	indirect	imprecise	unclear	low
Met and TZD vs. Met and another agent						
1 RCT's	low	n.a.	indirect	imprecise	unclear	low

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence Outcome: Neuropathy

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias:	Consistency	Directness	Precision	Magnitude and direction of effect	
Met vs. Met and TZD						
1 RCT's	moderate	n.a.	indirect	imprecise	Unclear	low
Met vs. Met and sitagliptin						
1 RCT's	high	n.a.	indirect	Imprecise	Unclear	low
Met and TZD vs. Met and another agent						
1 RCT's	high	n.a.	indirect	Imprecise	Unclear	low

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = replaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione
All other comparisons were graded as insufficient since there were no studies of those comparisons.
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
McAfee, 2007[149] US	Cohort	Start year: 2000 to 2004 - End year: 2005 NR	NA	NA	Yes	NA (for cohort studies, claims data, etc)/31075 Ingenix research claims database	Age: >18 years old, less than 6 months in insurance plan, insulin or study drug given within 6 months prior to study, insulin or other drug given within 30 days after monotherapy initiation, no medical or pharmacy benefits
Monami, 2008[148] Italy	Cohort	Start year: 1993 - End year: 2001 28 Months	NA	NR	NR	NA (for cohort studies, claims data, etc)/1108 Outpatient: primary care, Geriatric clinic	insulin treatment was an exclusion, not type 2 diabetes by WHO 1985 criteria
Kahler, 2007[142] US	Cohort	Start year: 1998 - End year: 2001 3 Years	NA	NA	No	> 1500000/39721 VHA Medical facilities	Age: < 18, 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
Rosak, 2006[150] Germany	Cohort	Neither year reported 6 Months	NA	< 6 months	Yes	NR/22808 Outpatient: primary care, Outpatient: subspecialty care setting	not all treated with Rosi
Simpson, 2006[138] Canada	Cohort	Start year: 1991 - End year: 1999 8 Years	NA	NA	No	12272/5795 Saskatchewan health databases	Age: <30, Patients on Insulin, Patients on two or more OAD
Fisman, 1999[146]	Cohort	Neither year reported	NA	NA	NR	NR/14440	Age: < 45, and > 75, Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT,

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
NR		6 Years				Community	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), pacemaker, hepatitis, renal disease, malignancy, Insulin, Estrogen replacement
Evans, 2005[143] Scotland	Cohort	Neither year reported 8 Years		NA	NR	6089/5730 NR	Diagnosed under the age of 35years, requirement for insulin within 90days of diagnosis or their first OHA prescription, OHA users before Jan. 1994
Eurich, 2005[141] Canada	Cohort	2.1 years (mean followup)			No		History of CVD, treatment experienced, other
Johnson, 2005[139] Canada	Cohort	Median followup periods for each group ranged from 4.6 to 5.6 yeas			No		Age <30, no type 2 diabetes, other
Gulliford, 2004[144] UK, Wales, Scotland, and Ireland	Cohort	Median followup for each group ranged from 1.67 to 3.49 years			No		Treatment experienced, no type 2 diabetes, other,
Johnson, 2002[140] Canada	Cohort	5.1 years (mean			No		Age <30, other

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
		followup)					
Fisman, 2001[145] Israel	Cohort	7.7 years (mean followup)			No		Age < 45 or >74, any liver disease, any kidney disease, other
Malone, 2003[118] 14 countries not specified	randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test meals	Age: Not 30-75, HbA1c >: <125% of upper limit of normal by local lab within 4 weeks prior to entry, BMI or weight: >40, not type 2 dm, not use of single oral agent (metformin or SU) for 3 mo prior to study at max clinically effective dose for previous 30 days
Home, 2009[14] Multinational Europe	RCT	Start year: 2001 - End year: 2003 7.5 Years	Run-in period but number of participants excluded was NR	>= 6 months	Yes	7428/4458 Outpatient: primary care	Age: <40, >75, 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 >: 9, HbA1c <: 7, BMI or weight: <25, Pregnant, Nursing, Not using adequate contraception, Recent CAD event, heart failure
Raskin, 2009[110] NR	RCT	Neither year reported 26 Weeks	No run-in period	< 6 months	Yes	1093/383 Outpatient: primary care	Age: <18y, Pregnant, Nursing, currently not under monotherapy at least 2 months or dual therapy, FBG >260, Any disease of abnormality as judged by the investigator, treatment with the investigational drug for 4 weeks, Allergy to study drugs or related compounds, H/O hypoglycemia unawareness or recurrent severe hyperglycemia
Scott, 2008[71] Multi-continent	RCT	Neither year reported 18 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	486/273 NR	Age: <18, >75, 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 >: 11, HbA1c <: 7, not on 10 wks on stable dose of MET, insulin use, type 1 dm,

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
							glucose > 270
Raz, 2008[79] Multi-continent	RCT	Neither year reported 30 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	544/190 NR	Age: <18,>78 yrs, HbA1c >: <8% after run-in, HbA1c <: >11% after run-in, BMI or weight: <20, >43 kg/m^2, Pregnant, Nursing, Rx Insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, type 1 DM, fpg <7.2, >15.6 mmol/L consistently during run-ind, no type 2 DM
Hamann, 2008[103] Multinational Europe, Mexico	RCT	Neither year reported 52 Weeks	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: >10, HbA1c <: <7, BMI or weight: BMI <25, used any oral antidiabetic drug other than metformin in the prior 12 weeks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, oedema 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
Chien, 2007[47] Taiwan, Multi-center	RCT	Neither year reported 16 Weeks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age: <30, >75, 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

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
							and FPG<140 mg/dL at screening visit, BMI or weight: <18.5, >35 kg/sq-meter, current significant GI disorder, HONK, hypersensitivity to Glyburide or Metformin, current infection, treatment with insulin in last 6 m, surgery in past 4 weeks, history of cancer in 5 yr, 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 glicazide<10 mg/day, glimepiride<4mg/d, gliclizide<160mg/d)
Schwarz, 2008[125] US	RCT	Neither year reported 104 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	75/69 NR	Age: <18 or >77, 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, HbA1c >: <7.0, HbA1c <: >11.0, BMI or weight: <22 or >45, FBG >270, History of lactic acidosis, Congestive cardiac failure requiring pharmacologic treatment, Type 1 DM or secondary forms of DM
Comaschi, 2007[109] Italy	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age: <35, HbA1c >: 11, HbA1c <: 7.5, Had not received SU or Metformin as a monotherapy at a stable dose for at least 3months, Fasting C-peptide <0.33nmol/L
Nauck, 2007[113] US, Multinational Europe, Multi-continent	RCT	Neither year reported 52 Weeks	Yes	< 6 months	Yes	2141/1172 NR	Age: <18 or >78, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15, Insulin use within 8weeks of screening, History of Type 1 DM, Other treatments for Hypoglycemia

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hanefeld, 2007[84] Multinational Europe	RCT	Neither year reported 52 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/598 NR	Age: <40/>80, 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 or weight: <22. >38, 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
Kahn, 2006[30] Multi-continent	RCT	Start year: 2000 - End year: 2006 6 Years	No run-in period	NR	Yes	6676/4360 NR	Age: < 30 / > 75, 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, History of Lactic acidosis
Rosenstock, 2006[39] Multi-continent	RCT	Start year: 2003 to 2004 32 Weeks	Yes	< 6 months	Yes	1252/468 multicenter	Age: <18 / >70, 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 >: 11, HbA1c <: 7, 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

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
							30days 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 DKA
Jain, 2006[85] US, Puerto Rico	RCT	Neither year reported 56 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/502 NR	Age: <18 , >80, 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 >: 11.5, HbA1c <: 7.5, Pregnant, Nursing, Duration of DM > than 2years, Intolerance to Rosi, Pio or Troglitazone, Drug or alcohol abuse, Previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin , SU for 3months or more, Use of Hydrochlorothiazide, joint injections, niacin greater than 250mg/lday, 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=<20, >45 ; Hypertension, Chronic pulmonary disease, history of cancer not in remission for at least 5years
Stewart, 2006[129] Multinational Europe	RCT	Start year: 2003 to 2004 32 Weeks	Yes	< 6 months	Yes	1397/526 NR	Age: < 18 , > 70, History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: 9, HbA1c <: 7, Drug naive patients with FPG <7mmol/l or >9mmol/l, patient on monotherapy with FPG < 6.0mmol/l or >8mmol/l, Prior history of exposure to thiazolidinediones within previous 6months, Use of insulin anytime in the past, Uncontrolled hypertension

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Bakris, 2006[105] US, Multi-continent, South America, Europe	RCT	Neither year reported 32 Weeks	Yes	< 6 months	Yes	560/514 NR	Age: <40 or >80 years, Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI or weight: BMI < 22, Use of any TZD in the 3months prior to screening, Use of insulin for >= 6months at any time prior to screening, Anemia, severe Angina, SBP >159 (can't adjust the BP meds during the trial), DBP >99
Kvapil, 2006[119] Multinational Europe	RCT	Neither year reported 16 Weeks	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 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=not adequately controlled on metformin
Gerich, 2005[112] US	RCT	Neither year reported 2 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	908/428 NR	Age: <18 and >77, 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), Neuropathy, Retinopathy, HbA1c >: 11, HbA1c <: 7, BMI or weight: < 22 and >45 kg/m2, Not using adequate contraception, FPG >=15mmol/L, if type 1 dm, symptomatic hypoglycemia with >10% weight loss in previous 8 weeks, h/o lactic acidosis or CHF requiring meds, other medical conditions that could interfere with interpretation of results or pose sig risk to the subject, had to be drug naive
Agarwal, 2005[151] US	RCT	Start year: 2001 - End year: 2003	No run-in period	< 6 months	Yes	102/54 Outpatient: subspecialty	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
		16 Weeks				care setting	attack, coronary artery disease, angina), BMI or weight: >40, class III or IV heart failure, NSAID use
Malone, 2004[137] US	RCT	Neither year reported 32 Weeks	Yes	< 6 months	Yes	145/111 NR	Age: <30 OR >80, HbA1c >: <1.3 or >2.0 X normal, BMI or weight: >40, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30days before the study, while using 1 or more OAM without insulin for 30 or more days before study start
Nakamura, 2004[86] Japan	RCT	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: 6.5, BP < 140/90, 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
Jones, 2003[147] US	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	NR	NR	Age: <40 or >80, 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, prior rosi study, use on any investigational drug within 30d
Weissman, 2005[72] US	RCT	Neither year reported 24 weeks (planned duration)	Run-in period but number of participants excluded was NR	< 6 months	Yes	1270/766 NR	Age: <18 or >75years, 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

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
							>: <6.5% for subjects having received prior combination treatment (Metformin + Sulphonylurea), HbA1c <: >8.5% for subjects having received prior combination treatment (Metformin + Sulphonylurea), BMI or weight: BMI <27, HbA1c < 7% for drug naive or prior monotherapy subjects., HbA1c > 10% for drug naive or prior monotherapy subjects., FPG < 126mg/dL (7mmol/L), FPG >270mg/dL (15mmol/L), Anemia, severe edema, prior insulin use within 3months of study start, Non - compliant patient with metformin up-titration
Bailey, 2005[73] UK, 14 European countries	RCT	24 weeks (planned duration)			Yes		Age <18 or >70, history of CVD, no type 2 diabetes, other
Schernthaner, 2004[42] Europe	RCT	12 months (planned duration)			No		Age <35 or >75, treatment experienced, HbA1c <7.5% or >11%, no type 2 diabetes
Hanefeld, 2004[115] Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and Netherlands	RCT	NR			Yes		Age <35 or >75, history of CVD, HbA1c <7.5 or >11, no type 2 diabetes, other

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Lawrence, 2004[43] UK	RCT	12 titration, 12 week maintenance (planned duration)			Yes		Age <45 or >80, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes: <7% or >10% for low-dose oral hypoglycemic therapy: >7.5%, no type 2 diabetes, other
Garber, 2003[49] US	RCT	16 weeks (planned duration)			Yes		Age < 20 and age>79, any liver disease, any kidney disease, treatment experienced, HbA1c > 7 and <12%, no type 2 diabetes, other
Goldstein, 2003[50] US	RCT	18 weeks (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, HbA1c <7.5 and >12.0, other
Bakris, 2003[88] likely US and UK	RCT	52 weeks (planned duration)			Yes		NR
Hallsten, 2002[45] Finland	RCT	26 weeks (planned duration)			Yes		Any liver disease, any kidney disease, history of CVD, no type 2 diabetes, other
St John Sutton, 2002[123] US	RCT	52 weeks (planned duration)			Yes		Age <40 or age >80, any liver disease, any kidney disease, history of CVD, no type 2 diabetes, other
Gomez-Perez, 2002[74] Mexico	RCT	26 weeks (planned duration)			Yes		Age <40 or >80, any liver disease, any kidney disease, history of CVD, treatment experienced, no type 2 diabetes, other

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Amador-Licona, 2000[54] Mexico	RCT	12 weeks (planned duration)			No		Age >65, any liver disease, history of CVD, other
Fonseca, 2000[76] US	RCT	26 weeks (planned duration)			No		Age <40 or >80, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no type 2 diabetes, other
Nakamura, 2000[87] Japan	RCT	3 months (planned duration)			No		Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no type 2 diabetes, other
Horton, 2000[65] US	RCT	24 weeks (planned duration)			Yes		Age <30, any kidney disease, HbA1c <6.8% or >11%, no type 2 diabetes, other
Marbury, 1999[100] US and Canada	RCT	12 months (planned duration)			Yes		Age >37 or <75, any liver disease, any kidney disease, history of CVD, treatment experienced, retinopathy, HbA1c <6.5% or 14.6%, no type 2 diabetes, other
Wolffenbuttel, 1999[99] Germany, Austria, and Netherlands	RCT	12 months (planned duration)			No		Age <40 or >75, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.5 if treated with diet only, >12% if treated with diet plus oral, other
DeFronzo, 1995[58] US	RCT	29 weeks (planned duration)			No		Age <40 or >70, any liver disease, any kidney disease, history of CVD, treatment experienced, no type 2 diabetes, other
Hermann, 1994[56]	RCT				Yes		No type 2 diabetes, other

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Sweden		6 months (planned duration)					

ALT= Alanine aminotransferase; AST= Asparate aminotransferase; BMI=Body mass index; BP=Blood Pressure; CAD= Coronary artery disease; CHF=Congestive heart failure; CK= Creatine kinase; CVD= Cardio Vascular Diseases; DBP= Diastolic blood pressure; DKA= Diabetic Ketoacidosis; DM= Diabetes mellitus; FPG= Fasting plasma glucose; g/dl= grams per deciliter; GFR= Glomerular filtration rate; HbA1c= Hemoglobin A1c; HONK= Hyper Osmolar Non Ketotic; kg/m2= kilogram per meter squared; kg=kilogram; LHSVE= Large Health Survey of Veteran Enrollees; mg/d= milligrams per day; mg/dl= milligrams/deciliter; mmHg= millimeters of mercury; mmol/L= millimoles per liter; NA=Not applicable; nmol/L= nanomoles per liter; NR=Not reported; NSAID= Non-steroidal anti-inflammatory drugs; OAD=Oral antidiabetic; OHA= Oral Hypoglycemic Agent; RCT=Randomized controlled trial; SBP= Systolic blood pressure; SGOT= glutamyl oxaloacetic transaminase; SGPT= Serum glutamyl pyruvic transaminase; SU=Sulfonylurea; TZD= thiazolidinedione; VHA=Veterans Health Administration; WHO=World Health Organization

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Home, 2009[14]	Rosi, 2220	58.4	1142 (51.4)	C: 2200 (99.1)	31.6	7.9	7	218
	Rosi+SU, 1103	59.8	541 (49)		30.3 85.0kg	8	7.9	NR
	Met+SU, 1122	59.7	568 (50.6)	C: 1112 (99.1)	84.3kg	8	7.9	NR
	Met+SU, 1105	57.2	584 (52.9)	C: 1087 (98.4)	93.3 kg	7.8	6.3	NR
	Met+Rosi, 1117	57	601 (53.8)	C: 1105 (98.9)	93.5kg	7.8	6.1	NR
	Met+SU, 2227	58.5	1152 (51.7)	C: 2199 (98.7)	31.5	7.9	7.1	233
Raskin, 2009[110]	Met+Repa, 187	54.5	110	AA: 25 , Asian: 9 , C: 149 , American Indian: 1 , other: 3	32.5	8.29	7.3	58
	Met+Rosi, 187	55.5 (28 to 83)	95	AA: 25 , Asian: 4 , C: 148 , American indians: 2 , Others: 8	32.2	8.46	7.1	58
	Met+Repa, 187	54.8	108	AA: 30 , Asian: 8 , C: 140 , americal indian and alaska native: 1 , : 8	32.9	8.45	7.4	62
Scott, 2008[71]	Met+Rosi, 87	54.8	55 (63)	Asian: 33 (38), C: 51 (59), others: 3 (3)	30.4 84.9 kg	7.7	4.6	2
	Met+Sita, 94	55.2	52 (55)	Asian: 36 (38), C: 57 (61), others: 1 (1)	30.3 83.1	7.8	4.9	9
	Met, 92	55.3	54 (59)	Asian: 36 (39), C: 56 (61)	30 84.6 kg	7.7	5.4	9
Raz, 2008[79]	Met+Sita, 96	53.6 (29 to 73)	49	AA: 3 (3), C: 40 (42), H: 31 (32), multiracial: 21 (22), not specified: 1 (1)	30.1 81.5 kg	9.3	8.4	18

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	Met, 94	56.1 (36 to 77)	39	AA: 1 (1), C: 44 (47), H: 24 (25), multiracial: 23 (25), not specified: 2 (2)	30.4 81.2 kgs	9.1	7.3	16
Hamann, 2008[103]	Met+Rosi, 294	58.5	155 (53)	C: 277 (94)	33 91.4kg	8	6.3	61
	Met+SU, 302	59.3	158 (52)	C: 286 (95)	32.2 88.9kg	8	6.4	71
Chien, 2007[47]	Met+Glyburide, 26	60	15 (71)	NR	24.2 63.8 kg	8.71	9	5
	Met+Glyburide, 26	57	13 (62)	NR	24.2 61.3 kg	8.85	6.6 years	5
	Met, 25	59	7 (41)	NR	25.7 65.6 kg	8.88	6.4	8
	Glyburide, 25	63	9 (53)	NR	25.3 63.7 kg	8.69	8.6 years	6
Schwarz, 2008[125]	Met+Glyburide, 40	70.4	18 (50)	AA: 4 (11.1), C: 28 (77.8), Other: 4 (11)	33.5	7.7	2.5	18
	Met+Nate, 35	70.1	17 (51.5)	AA: 3 (9.1), C: 26 (78.8), Other: 4 (12.1)	30.4	7.8	1.7	14
Comaschi, 2007[109]	Met+Pio, 103	57	47 (45.63)	NR	32.2 85.8	8.4	NR	27
	Met+SU, 80	59.9	44 (55)	NR	29.9 81.9	8.6	NR	13
	Pio+SU, 67	62.2	38 (56.72)	NR	28.9 78.8	8.7	NR	14

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McAfee, 2007[149]	Any in the SU class, 8977	52 (+/- 11.8) 18 to 29 (272; 3), 30 to 39 (1006; 11), 40 to 49 (2225; 25), 50 to 64 (4406; 49), 65+ (1068; 12)	4984 (56)	NR	NR	NR	NR	NR
	Rosi+SU, 1362	52 18 to 29 (24; 2), 30 to 39 (146; 11), 40 to 49 (379; 28), 50 to 64 (688; 51), >=65 (125; 9)	806 (59)	NR	NR	NR	NR	NR
	Met+Rosi, 1362	52 (+/- 10.4) 18 to 29 (21; 2), 30 to 39 (152; 11), 40 to 49 (370; 27), 50 to 64 (704; 52), 65+ (115; 8)	810 (59)	NR	NR	NR	NR	NR
	Rosi, 8977	52 18 to 29 (260; 3), 30 to 39 (1005; 11), 40 to 49 (2231; 25), 50 to 64 (4420; 49), 65+ (1061; 12)	4960 (55)	NR	NR	NR	NR	NR

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Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Met, 8977	52 18 to 29 (260; 3), 30 to 39 (990; 11), 40 to 49 (2257; 25), 50 to 64 (4401; 49), 65+ (1069; 12)	4976 (55)	NR	NR	NR	NR	NR
	Met+SU, 1362	51 (+/- 10.7) 18 to 29 (26; 2), 30 to 39 (156; 11), 40 to 49 (373; 27), 50 to 64 (694; 51), 65+ (113; 8)	829 (61)	NR	NR	NR	NR	NR
Monami, 2008[148]	Met+Repa	NR	NR	NR	NR	NR	NR	0
	Met+SU	NR	NR	NR	NR	NR	NR	0
Kahler, 2007[142]	Any in the SU class, 19053	68.2 (+/- 10)		AA: (12.6), C: (78.6), other: (8.8)	29.6	7.2	(<1: 12.8, 03-Jan: 32.2, 10-Apr: 33.4, > 11: 20)	NR
	Met, 2988	64.9 (+/- 10.2)	2895 (96.9)	AA: (12.7), C: (78.7), H: , other: (8.7)	30.4	7	(<1: 20.5, 03-Jan: 41.5, 10-Apr: 25.1, >11: 11.6)	NR
	Met+SU, 13820	65.6 (+/- 9.8)	(98.1)	AA: (13.2), C: (77.5), other: (9.3)	30.3	8	(<1: 4.5, 03-Jan: 21.2, 10-Apr: 43.3, >11: 29.1)	NR
	TZD, 675	67.1 (+/- 9.4)	(97.5)	AA: (8.7), C: (80.9), : (10.4)	30.7	7.9	(<1: 3.3, 03-Jan: 18.2, 10-Apr: 39.9, >11: 37.5)	NR

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Nauck, 2007[113]	Met+Sita, 588	56.8 (47.5 - 66.1)	336 (57.1)	AA: 41 (7), Asian: 50 (8.5), C: 432 (73.5), H: 43 (7.3), other: 22 (3.7)		7.7	6.5	202
	Met+Glipizide, 584	56.6	358 (61.3)	AA: 35 (6), Asian: 49 (8.4), C: 434 (74.3), H: 46 (7.9), other: 20 (3.4)	31.3 89.7	7.6	6.2	172
Hanefeld, 2007[84]	Rosi, 189	60.6 (+/- 9.2)	109	AA: 0 , C: 183 , other: 6	28.8	8.2	6	9
	Glibenclamide, 203	60.1 (+/- 8.3)	143	AA: 0 (0), C: 201 , other: 1	28.7	8.2	6.4	13
	Rosi, 195	60.4 (+/-8.2)	133	AA: 0 (0), C: 192 , other: 3	28.7	8.1	5.9	12
Kahn, 2006[30]	Rosi, 1456	56.3 (+/- 10.0)	811 (55.7)	AA: 61 (4.2), Asian: 39 (2.7), C: 1270 (87.2), H: 76 (5.2), other: 10 (0.7)	32.2 91.5	7.36	(<1: 651, 02-Jan: 758, >2: 47)	539
	Glyburide, 1441	56.4 (+/- 10.2)	836 (58)	AA: 61 (4.2), Asian: 32 (2.2), C: 1282 (89), H: 61 (4.2), Other: 5 (0.3)	32.2 92	7.35	(<1 year: 637, 02-Jan: 751, >2: 53)	634
	Met, 1454	57.9 (+/- 9.9)	864 (59.4)	AA: 54 (3.7), Asian: 35 (2.4), C: 1295 (89.1), H: 55 (3.8), Other: 15 (1)	32.1 91.6	7.36	(< 1 year: 673, 02-Jan: 724, >2: 57)	551
Rosenstock, 2006[39]	Rosi, 159	50.6 (+/-10.26)	93 (58)	AA: 8 (5), Asian: 22 (14), C: 94 (59), H: 31 (19), Other: 4 (3)	32.8	8.8	2.7	22
	Met+Rosi, 155	50.1 (+/-10.7)	89 (57)	AA: 10 (6), Asian: 19 (12), C: 83 (54), H: 41 (26)	33.2	8.9	2.3	19
	Met, 154	51.5 (+/- 10.4)	87 (56)	AA: 8 (5), Asian: 22 (14), C: 90 (58), H: 33 (21), other: 1 (<1)	32.5	8.8	2.9	31

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Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Jain, 2006[85]	Pio, 251	52.1 (+/- 11.28)	133 (53)	AA: 40 (15.9), Asian: 4 (1.6), C: 153 (61), H: 52 (20.7), 0ther: 1 (0.4), Native American: 1 (0.4)	32.5 93.9kg	9.2	0.8 (9.6 months)	117
	Glyburide, 251	52.1 (+/- 12.39)	141 (56.2)	AA: 34 (13.5), Asian: 0 (0), C: 165 (65.7), H: 50 (19.9), Native American: 1 (0.4), Other: 1 (0.4)	32.8 94.3kg	9.2	0.78 (9.4 mo)	123
Stewart, 2006[129]	Met, 272	59 (+/- 7.9)	151 (56)	AA: 1 (<1), Asian: 1 (<1), C: 268 (99), H: 1 (<1), Native Hawaiian/other Pacific Islander: 1 (<1)	30.6 87.2	7.2 (Range: 5.4-10.7)	3.7	54
	Met+Rosi, 254	58.8 (+/- 8.4)	139 (55)	AA: 0 (0), Asian: 3 (1), C: 250 (98), H: 1 (<1), Native Hawaiian /other pacific islander: 0 (0)	30.9 88.1	7.2 (Range: 5.8-9.4)	3.7	50
Bakris, 2006[105]	Met+Glyburide, 185	58.8	124 (69)	C: 137 (76)	31.8 90.3	8.3	7.6	5
	Met+Rosi, 204	60	122 (63)	C: 151 (78)	31.6 89.2	8.5	8	10
Rosak, 2006[150]	Met+Rosi, 7705	60	3594 (50.2)	NR	29.3 87.2	8.1	3.9	545
	Rosi+SU, 5511	65	2423 (48.2)	NR	81.3kg	8.3	5.3	478
	Rosi, 1559	62,0	(47.7)	NR	28.7 83.8	8.1 (median)	4.5	542

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Simpson, 2006[138]	Met, 768	64.6 (+/- 12.4)	409 (53)	NR	NR NR	NR	NR	NR
	Glyburide, 2067	67.8 (+/- 12.6)	1240 (60)	NR	NR NR	NR	NR	NR
Kvapil, 2006[119]	Met+Glibenclamide, 114	58.1 (+/- 8.8)	52	NR	30.5 +/-4.4 84.0 +/- 13.4	9.4 +/-1.4	8.1 +/- 6.2	5
	Met+Aspart 70/30, 116	56.4 (+/- 9.0)	53	NR	30.4 +/- 4.0 85.1kg +/- 15.1	9.3 +/- 1.3	6.7 +/- 5.7	11
Gerich, 2005[112]	Met+Glyburide, 209	53.5 (+/-11.6)	95 (48)	AA: 33 (16.7), Asian: 1 (0.5), C: 129 (65.2), other: 35 (17.7)	33.5 +/- 5.6	8.3 +/- 1.1	2.0+/- 4.3	87
	Met+Nate, 219	52.6 (+/-11.6)	106 (51)	AA: 27 (13), Asian: 5 (2.4), C: 134 (64.4), other: 42 (20.2)	33.3 +/- 6.0	8.4 +/- 1.2	1.5 +/- 2.9	78
Agarwal, 2005[151]	Pio, 22	67 (17)	22 (100)	AA: 3 (14), C: 19 (86)	32 97	7.7	16	1
	Glipizide, 22	64 (17)	22 (100)	AA: 6 (27), C: 16 (73)	34 102	7.7	14	3
Malone, 2004[137]	pooled arms		66 (63)	NR	30.9 91.5kg	8.7	9	NR
	Met+Lispro 75/25	NR	NR	NR	NR	NR	NR	3 during this arm
	Met+Glargine	NR	NR	NR	NR	NR	NR	7
Nakamura, 2004[86]	Pio, 15	57	9	NR	NR NR	7.9	17.5	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Glibenclamide, 15	55	8	NR	NR NR	7.8	19.2	0
Malone, 2003[118]	Met+Lispro 75/25, 296	58 (+/-8.8)	169 (57)	AA: 2 (0.7), C: 263 (88.9), H: 22 (7.4), other: 9 (3)	29.8 +/- 4.4 83.0+/- 15.2	9.17 +/- 1.50	8.0 +/-5.8	25
	Met+Glibenclamide, 301	59 (+/-9.3)	146 (49)	AA: 3 (1), C: 268 (89), H: 18 (6), other: 12 (4)	29.6 +/- 4.5 81.7 +/- 15.7 kg	9.27 +/- 1.55	7.4 +/- 5.4	29
Jones, 2003[147]	Met, 82	60 (40 to 81)	61 (74)	NR	28	8.8	6	NR
	Met, 22	64 (46 to 81)	13 (9)	NR	23	8.6	6.5	NR
	Met+Rosi, 35	62 (42 to 78)	25 (71)	NR	23	9.3	8	NR
	Met+Rosi, 141	58 (36 to 82)	97 (69)		28	8.8	6	NR
	Met+Rosi, 142	57 (39 to 80)	93 (57)	NR	34	8.8	5	NR
	Met, 121	58 (38 to 78)	85 (70)	NR	34	8.7	5	0
Fisman, 1999[146]	Any in the SU class, 1041	60.5	(76)	NR	27 76	NR	NR	NR
	Met + SU, 266	60.9	(66)	NR	27 75	NR	NR	0
	Met, 78	59.5	(65)	NR	29 80	NR	NR	NR
Evans, 2005[143]	Met, 2286	60.2	51.20	NR	32.9	7.7	2.7	NR
	SU, 3331	65.9	56.30	NR	28.6	7.8	4.6	NR
	Met + SU, 985	61.2	47.00	NR	33.2	8.1	4.4	NR
	Met + SU, 1252	63.6	55.10	NR	30.2	8.2	4.8	NR
	Met + SU,113	64	49.60	NR	30	8	8.8	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Weissman, 2005[72]	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	8.058.05	NR	76
Bailey, 2005[73]	Metformin, 280	57.6	159 (57)	AA: 1 (<1), Asian: 3 (1), C: 273 (98), Other: 3 (1)	32.1 89.5kg	7.5	6.1	44
	Metformin + rosiglitazone, 288	58.1	168 (58)	AA: 2 (1), C: 280 (97), Asian: 3 (1), H: 0, O: 3 (1)	32.2 90.9kg	7.4	6	30
Eurich, 2005[141]	Unspecified sulfonylurea, 773	74.8	451 (58)	NR	NR	NR	NR	NR
	Metformin, 208	72.5	123 (59)	NR	NR	NR	NR	NR
	Metformin + unspecified sulfonylurea, 852	70	472 (55)	NR	NR	NR	NR	NR
Johnson, 2005[139]	Unspecified sulfonylurea, 2138	67.8 (55.4 - 80.2)	59	NR	NR NR	NR	NR	NR
	Metformin, 923	64.3 (51.9 - 76.7)	52	NR	NR NR	NR	NR	NR
	Metformin + unspecified sulfonylurea, 1081	62 (49.7 - 74.3)	54	NR	NR NR	NR	NR	NR
Schernthaner, 2004[42]	Placebo + diet + metformin, 597	56 (35 to 75)	345 (57.8)	NR	31.4 89.7kg	8.7	3.1	96
	Placebo + diet + pioglitazone, 597	57 (35 to 75)	314 (52.6)	NR	31.2 88.2kg	8.7	3.4	98

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Gulliford, 2004[144]	Unspecified sulfonylurea, 6620	67	3644 (55)	NR	NR NR	NR	NR	NR
	Metformin + unspecified sulfonylurea, 1868	61	945 (51)	NR	NR NR	NR	NR	NR
	Metformin, 2232	61	1120 (50)	NR	NR NR	NR	NR	NR
	Metformin + unspecified sulfonylurea, 867	58	389 (45)	NR	NR NR	NR	NR	NR
Hanefeld, 2004[115]	Placebo + unspecified sulfonylurea + pioglitazone, 319	60 (36 to 75)	171 (53.6)	AA: 2 (0.6), C: 317 (99.4), Asian: 0, H: 0, O: 0 (0)	30.2 85.3	8.82	7	259
	Placebo + metformin + unspecified sulfonylurea, 320	60 (36 to 75)	175 (54.7)	AA: 3 (0.9), C: 315 (98.4), Asian: 0, H: 0, O: 2 (0.6)	30 84.9	8.8	7.1	279
Lawrence, 2004[43]	Metformin, 20	59.5	12	NR	median 29.2 8.04	NR	NR	NR
	Glyclazide, 20	63.5	13	NR	median 28.7 7.85	NR	NR	NR
	Pioglitazone, 20	60.4	14	NR	median 30.6 7.43	NR	NR	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Garber, 2003[49]	Metformin + glyburide, 171	55.6	76 (44)	AA: 18 (10.5), C: 132 (77.2), Asian: 0, H: 15 (8.8), O: 6 (3.5)	31.4 91.9	8.8	3	NR
	Glyburide, 151	55.3	66 (43.7)	AA: 11 (7.3), C: 123 (81.5), Asian: 0, H: 12 (7.9), O: 5 (3.3)	31.1 91	8.7	3	NR
	Metformin, 164	54.7	71 (43.3)	AA: 11 (6.7), C: 132 (80.5), Asian: 0, H: 15 (9.1), O: 6 (3.7)	31.4 92.8	8.5	2.6	NR
Goldstein, 2003[50]	Metformin + glipizide, 87	54.6	58.60	AA: (11.5), C: (72.4), Asian: (0), H: (16.1), O: 0	31.7 94	8.7	5.9	NR
	Glipizide, 84	57.4	64.30	AA: (11.9), C: (71.4), Asian: (2.4), H: (14.3), O: 0	30.6 89.9	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	8.7	7.3	NR
Bakris, 2003[88]	Rosiglitazone, 104	55.1	75	NR	NR	9.1	NR	NR
	Glyburide, 99	56.1	71	NR	NR	9.5	NR	NR
Johnson, 2002[140]	Unspecified sulfonylurea, 3033	67.2	1789 (59)	NR	NR	NR	NR	NR
	Metformin, 1150	63.8	621 (54)	NR	NR NR	NR	NR	NR
	Metformin + unspecified sulfonylurea, 4683	62.1	2543 (54.3)	NR	NR NR	NR	NR	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Hallsten, 2002[45]	Diet + rosiglitazone, 14	58.6	10	NR	29.3 NR	6.8	NR	NR
	Placebo + diet, 14	57.7	10	NR	30.3 NR	6.3	NR	NR
	Diet + metformin, 13	57.8	8	NR	29.9 NR	6.9	NR	NR
St John Sutton, 2002[123]	Rosiglitazone, 104	55.1 (40-77)	(75)	AA: (5), C: (73), Asian: 0, H: 0, O: (22)	67.3 >=27 86.2	9.1	5.3	NR
	Glyburide, 99	56.1 (40-76)	(71)	AA: (3), C: (76), Asian: 0, H: 0, O: (21)	65.7 >=27 85.1	9.5	6.2	NR
Gomez-Perez, 2002[74]	Placebo + metformin, 34	53.4 (40-68)	10 (29.4)	C: 1 (2.9), H: 26 (76.5), Mestizo: 7 (20.6)	28.5 (3.9) NR	NR	9.1 (5.6) yrs	NR
	Metformin + rosiglitazone, 35	51.7 (40-73)	10 (28.6)	C: 0 (0), H: 28 (80), Mestizo: 7 (20)	28 (4.0) NR	NR	11.1 (7.1) yrs	NR
	Metformin + rosiglitazone, 36	54.2 (42-76)	7 (19.4)	C: 4 (11.1), H: 26 (72.2), Mestizo: 6 (16.7)	27.6 (3.2) NR	NR	10.7 (7.0) years	NR
Fisman, 2001[145]	Glyburide, 953	59.8	(76)	NR	27 77	NR	NR	NR
	Metformin, 79	59.5	(66)	NR	29 81	NR	NR	NR
	Metformin + glyburide, 253	60.7	(66)	NR	27 75	NR	NR	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Amador-Licona, 2000[54]	Glibenclamide, 23	48.2	7	NR	30.4 73.2	8.4	4	NR
	Metformin, 28	49.3	11	NR	26.8 70.7	8.5	4.5	NR
Fonseca, 2000[76]	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
	Met+Rosi, 119Metformin + 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[87]	Pioglitazone, 15	60	7	NR	NR NR	7.7	16	NR
	Glibenclamide, 15	61	8	NR	NR NR	7.8	14	NR
Horton, 2000[65]	Nateglinide, 179	58.6	110	AA: (9.5), C: (82.1), Asian: (2.8), H: 0, O: 5.6	29.6 NR	8.3	4.7	NR
	Metformin, 178	56.8	121	AA: (9.6), C: (79.2), Asian: (2.2), H: 0, O: 9	29.6 NR	8.4	7.5	NR
	Metformin + nateglinide, 172	58.4	101	AA: (11.6), C: (82.6), Asian: (0.6), H: 0, O: 5.2	30 NR	8.4	4.5	NR
Wolffenbuttel, 1999[99]	Repaglinide, 286	61 years	(62)	NR	28.4 81.5	7.1	Median 6	NR
	Placebo + glyburide, 139	61 years	(68)	NR	28 81.3	7	Median 6	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
DeFronzo, 1995[58]	Metformin, 143	53	62	NR	29.9 94.4	8.4	6	NR
	Metformin + glyburide, 213	55	98	NR	29 92.1	8.8	7.8	NR
	Placebo + glyburide, 209	56	103	NR	29.1 92.6	8.5	8.7	NR
	Placebo + metformin, 210	55	96	NR	29.4 92.6	8.9	8.4	NR
Hermann, 1994[56]	Diet + metformin, 25	60 (34-74)	63	NR	NR 78.6	6.9	4	NR
	Diet + glibenclamide, 21	NR	NR	82.6	6.7 NR	NR	NR	NR
	Diet + metformin + glibenclamide + other A, 54	NR	80.2	6.8	NR NR	NR	NR	NR
Marbury, 1999[100]	Repaglinide, 362	58.3	242 (67)	AA: 33 (9), C: 279 (77), Asian: 0, H: 0, O: 50 (14)	29.4 NR	8.7	7.2	NR
	Placebo + glyburide, 182	58.7	120 (66)	AA: 16 (9), C: 144 (79), Asian: 0, H: 0, O: 22 (12)	29.1 NR	8.9	8.3	NR

AA= African American; C= Caucasian; H=Hispanic; Kg=kilogram; Met=Metformin; NR=Not reported; Repa=Repaglinide; Rosi=Rosiglitazone; Sita=Sitagliptin; SU=Sulfonylurea; sd=standard deviation

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin vs Thiazolidinedione						
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes	
		GP1:Metformin NR			GP1:149	
		GP2:Rosiglitazone NR			GP2:152	
McAfee, 2007[149]	Cohort				Def: MI based on ICD-9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Metformin NR			GP1: 62	
		GP2:Rosiglitazone NR			GP2: 70	
Lawrence, 2004[43]	RCT			Def: CVD mortality/Fatal MI	Def: CVD morbidity/MI (non-fatal)	
		GP1:Metformin Varied Start:500 mg bid, Max: 1000 mg tid	GP1: 1	GP1: 1	GP1: 0	
		GP2:Pioglitazone Varied Start:30 mg, Max: 45 mg	GP2: 0	GP2: 0	GP2: 0	
Rosenstock, 2006[39]	RCT				Def: Not Defined Ischemic heart disease	
		GP1:Metformin Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1847 mg, Max: 2000 mg D: 32 wks	GP1: 0		GP1: 2	
		GP2:Rosiglitazone Varied, glucose: 6.1 mmol/l Start: 4mg, Mean: 7.7 mg, Max: 8 mg D:32 wks	GP2: 0		GP2: 2	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Kahn, 2006[30]	RCT			Def: Fatal MI		Def: Stroke not defined
		GP1:Metformin Varied, glucose: 140 Start: 500 mg, Max: 2000 mg	GP1: 31	GP1: 2 (0.1)	GP1: 21 (1.4)	GP1: 19 (1.3)
		GP2:Rosiglitazone Varied, glucose: 140 Start: 4 mg, Max: 8 mg	GP2: 34	GP2: 2 (0.1)	GP2: 25 (1.7)	GP2: 16 (1.1)
Schernthaner, 2004[42]	RCT					
		GP1:Metformin Varied Max: 850 mg tid	GP1:2			
		GP2:Pioglitazone Varied Start: 30 mg, Max: 45 mg	GP2:3			
Metformin vs Sulfonylurea						
Simpson, 2006[138]	Cohort			Def: Fatal MI		
		GP1:Metformin NR	GP1:39.6/1000 person-years	GP1:11.5		
		GP2:Glyburide NR	GP2:61.4/1000 person-years	GP2:17.6		
Eurich, 2005[141]	Cohort					
		GP1:Metformin NR	GP1: 69 Adjusted HR 0.70			
		GP2:Sulfonylurea NR	GP2: 404			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Fisman, 2001[145]	Cohort			Def: CVD mortality/CVD mortality + ICD-9 codes 410-414 + matched the patients ID number with their life status in the population registry + ischemic heart disease		
		GP1:Metformin	GP1: 25	GP1: Age-adjusted IR 30 per 1000 person-years		
		NR				
		GP2:Glyburide	GP2: 324	GP2: Age-adjusted IR 24.5 per 1000 person-years		
		NR				
Johnson, 2005[139]	Cohort			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	Def: Non-fatal cardiovascular hospitalization/used ICD-9 codes 410-414 , 420-427 , 429 , 428 , 440 , 430-432 , 433-434 , 436-438	
		GP1:Metformin Varied Min: 250 mg		GP1: 14.4	GP1: 53.7	
		GP2:Sulfonylurea Varied		GP2: 25.5	GP2: 75.3	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Johnson, 2002[140]	Cohort			Def: CVD mortality/Fatal MI + fatal stroke + CVD mortality + ICD-9 codes 390-398 , 401-417 , 420-438 , 440-444 , 446-448 , 451-459		
		GP1:Metformin NR	GP1: 159	GP1: 80(7)		
		GP2:Sulfonylurea NR	GP2: 750	GP2: 351(11.6)		
McAfee, 2007[149]	Cohort				Def:Inpatient MI and coronary revascularization using ICD-9 and CPT codes	
		GP1:Metformin NR			GP1:149	
		GP2:Sulfonylurea NR			GP2:152	
McAfee, 2007[149]	Cohort				Def: MI based on ICD-9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Metformin NR			GP1: 62	
		GP2:Sulfonylurea NR			GP2: 94	
Evans, 2006[143]	Cohort					
		GP1:Metformin NR	GP1: 4.7% Adjusted RR: 1.43 for SU vs Met	GP1: Adjusted HR: 1.7 for SU vs Met		
		GP2:Sulfonylurea NR	GP2: 17.9%	GP2:		
Kahler, 2007[142]	Cohort					
		GP1:Metformin NR	GP1:82(2.7)			
		GP2:Sulfonylurea NR	GP2:1005(5.3)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hermann, 1994[56]	RCT				Def: CVD morbidity/unclear CHD	
		GP1:Metformin Varied Start: 1000 mg, Max: 3000 mg			GP1:2(5)	
		GP2:Glyburide Varied Start: 3.5 mg, Max: 10.5 mg			GP2:3(9)	
Goldstein, 2003[50]	RCT					
		GP1:Metformin Varied Start: 500 mg, Max: 2000 mg	GP1:0			
		GP2:Glipizide Fixed Start: 15mg bid	GP2:0			
Garber, 2003[49]	RCT					
		GP1:Metformin Varied Start:500 mg, max: 2000 mg	GP1:0			
		GP2:Glyburide Varied Start: 2.5 mg, max: 10 mg	GP2:0			
DeFronzo, 1995[58]	RCT			Def: CVD mortality/Fatal MI		
		GP1:Metformin Varied Start: 500 mg, Max: 2500 mg	GP1: 1	GP1: 1		
		GP2:Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	GP2: 0	GP2:0		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Chien, 2007[47]	RCT					
		GP1:Metformin Varied, glucose: 140 Start:1000mg, Mean: 1910 mg, Max: 2000 mg D: 4 wks	GP1:0			
		GP2: Glyburide Varied, glucose: 140 Start:10 mg, Mean: 19 mg, Max: 20 mg D: 4 wks	GP2:0			
Kahn, 2006[30]	RCT			Def: Fatal MI	Def: Not defined	Def: Stroke not defined
		GP1:Metformin Varied, glucose: 140 Start: 500 mg, Max: 2000 mg	GP1:31	GP1:2(0.1)	GP1:21(1.4)	GP1:19(1.3)
		GP2:Glyburide Varied, glucose: 140 Start: 2.5 mg, Max: 15 mg	GP2:31	GP2:3(0.2)	GP2:15(1)	GP2:17(1.2)
Gulliford, 2004[144]	Cohort					
		GP1:Metformin NR	GP1: 144			
		GP2:Sulfonylurea NR	GP2: 1030			
Fisman, 1999[146]	Cohort					
		GP1: Metformin NR	GP1: 78			
		GP2: Sulfonylurea NR	GP2: 234			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin vs Meglitinide						
Horton, 2000[65]	RCT			Def: CVD mortality/due to arteriolosclerotic and hypertensive heart disease + unclear CHD	Def: CVD morbidity/electrocardio-gram abnormalities	
		GP1: Metformin Fixed Start: 500 mg tid	GP1: 1	GP1:1	GP1:0	
		GP2: Nateglinide Fixed Start: 120 mg tid	GP2: 0	GP2:0	GP2:0	
Metformin vs Metformin+Thiazolidinedione						
McAfee, 2007[149]	Cohort				Def: Composite outcome	
		GP1: Metformin NR			GP1:149	
		GP2: Metformin+Rosiglitazone NR			GP2:24	
McAfee, 2007[149]	Cohort				Def: Non-fatal MI	
		GP1:Metformin NR			GP1:62	
		GP2:Metformin+Rosiglitazon e NR			GP2:6	
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes	
		GP1:Metformin NR			GP1: OR:6.1	
		GP2:Metformin+Rosiglitazon e NR			GP2:	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Weissman, 2005[72]	RCT				Def: CVD morbidity/MI (non-fatal)	
		GP1: Metformin Varied Start:1000mg,Max:2000mg	GP1:0		GP1:0	
		GP2: Metformin+Rosiglitazone Fixed; Varied Start: 1000mg; Start:4mg, Max:8mg	GP2:1		GP2:2	
Weissman, 2005[72]	RCT				Def:CVD morbidity/MI (non-fatal) + pulmonary edema with MI	
		GP1:Metformin Varied Start:1000mg,Max:2000mg			GP1:3+1 withdrew	
		GP2:Metformin+Rosiglitazon e Fixed; Varied Start: 1000mg; Start:4mg, Max:8mg			GP2:5	
Gomez-Perez, 2002[74]	RCT				Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia	
		GP1: Metformin Fixed Start:2500mg			GP1:1	
		GP2: Metformin+Rosiglitazone Fixed Start: 2500mg; Start: 2mg bid			GP2:1	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Gomez-Perez, 2002[74]	RCT				Def:CVD morbidity/ischemic heart disease + bundle branch block + tachycardia	
		GP1:Metformin Fixed Start:2500mg			GP1:1	
		GP2:Metformin+Rosiglitazone Fixed Start: 2500mg; Start: 4mg bid			GP2:2	
Fonseca, 2000[76]	RCT			Def:CVD mortality/unclear mortality + Fatal MI		
		GP1:Metformin Fixed Start: 2500 mg	GP1: 0	GP1:0		
		GP2:Metformin+Rosiglitazone Fixed Start:2500mg; Start:8mg	GP2: 1	GP2:0		
Bailey, 2005[73]	RCT			Def: CVD mortality/sudden cardiac death	Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI	
		GP1:Metformin Varied Start:2500 mg, Max:3000 mg	GP1: 0	GP1:0	GP1:0	
		GP2:Metformin+Rosiglitazone Fixed; Varied Start: 2500mg; Start:4mg,Max:8mg	GP2: 1	GP2:1	GP2:1	
Stewart, 2006[129]	RCT				Def: Myocardiac infarction, Angina pectoris, myocardial ischaemic, coronary artery insufficiency	
		GP1:Metformin Varied Start:500mg, Mean:2627.9, Max:3000mg D:20wks			GP1:0(0)	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
		GP2:Metformin+Rosiglitazone Varied Start:500mg, Mean:1812.9, Max:2000mg D:18 wks			GP2:4(2)	
Rosenstock, 2006[39]	RCT				Def: Not defined Ischemic heart disease	
		GP1:Metformin Varied, glucose: 6.1mmol/l Start: 500mg, Max: 2000mg, Mean: 1847 D:32 wks	GP1:0		GP1:2	
		GP2:Metformin+Rosiglitazone Varied, glucose: 6.1mmol/l Start:500mg, Mean: 1799mg, Max: 2000mg; Start: 2mg, Max: 8mg, Mean: 7.2mg D:32 wks	GP2:0		GP2:1	
Jones, 2003[147]	RCT					
		GP1:Metformin Fixed Start: 2.5g/day	GP1: 0			
		GP2:Metformin+Rosiglitazone Fixed; Varied, NS Start: 2.5g/day; Max: 8mg/day	GP2: 1			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin vs Metformin+Sulfonylurea						
Fisman, 1999[146]	Cohort			Def: Fatal MI	Def: CVD mortality/CVD mortality +ICD-9 codes 410-414 + matched the patients ID number with their life status in the population registry + ischemic heart disease	
		GP1:Metformin NR	GP1:20	GP1:39.3	GP1: IR: 30 per 1000 person-years	
		GP2:Metformin+Suflonylurea NR	GP2:84	GP2:35.3	GP2: IR: 31.2 per 1000 person-years	
Gulliford, 2004[144]	Cohort					
		GP1:Metformin NR	GP1:144			
		GP2:Metformin+Suflonylurea NR	GP2:159			
Kahler, 2007[142]	Cohort					
		GP1:Metformin NR	GP1:82(2.7)			
		GP2:Metformin+Suflonylurea NR	GP2:468(3.4)			
Evans, 2006[143]	Cohort			Def:Cardiovascular mortality		
		GP1:Metformin NR		GP1: Adjusted RR 2.29 (1.45-3.61)		
		GP2:Metformin+later addition of sulfonylurea NR		GP2:		
Evans, 2006[143]	Cohort			Def:Cardiovascular mortality		
		GP1:Metformin NR		GP1: Adjusted RR 2.43 (1.61-3.66)		
		GP2: Sulfonylurea+later addition of metformin NR		GP2:		
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
					using ICD-9 and CPT codes	
		GP1:Metformin NR GP2:Metformin+Sulfonylurea NR			GP1:149 GP2:36	
McAfee, 2007[149]	Cohort				Def: MI based on ICD-9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Metformin NR GP2:Metformin+Sulfonylurea NR			GP1:62 GP2:17	
Garber, 2003[49]	RCT					
		GP1: Metformin Varied Start: 500 mg, Max:2000 mg GP2: Metformin+Glyburide Varied Start: 500 mg, Max:2000 mg; Start: 1.25mg, Max: 20mg	GP1: 0 GP2: 2			
Goldstein, 2003[50]	RCT					
		GP1:Metformin Varied Start:500 mg, Max:2000 mg GP2:Metformin+Glipizide Varied Start:500 mg, Max:2000 mg; Start: 5mg, Max:20mg	GP1:0 GP2:0			
DeFronzo, 1995[58]	RCT			Def: CVD mortality/Fatal MI		
		GP1:Metformin Varied Start:500 mg, Max: 2500 mg GP2:Metformin+Glyburide Varied Start:500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	GP1:1 GP2:0	GP1: GP2:		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hermann, 1994[56]	RCT				Def: CVD morbidity/unclear CHD	
		GP1: Metformin Varied Start:1000 mg, Max: 3000 mg			GP1:2(5)	
		GP2: Metformin+Glyburide Varied Start:500mg,Max:1500mg; Start:1.75mg,Max:5.25 mg			GP2:10(14)	
Chien, 2007[47]	RCT					
		GP1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean: 1910 mg/day D: 4 wks	GP1: 0			
		GP2: Metformin+Glyburide Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean:1680 mg/day; Start:5 mg/day, Max: 10 mg/day, Final mean:8.4 mg/day D: 4 wks	GP2: 0			
Johnson, 2002[140]	Cohort					
		GP1: Metformin NR	GP1: 159			
		GP2:Metformin+Sulfonylurea NR	GP2: 635			
Eurich, 2005[141]	Cohort					
		GP1: Metformin NR	GP1: 69			
		GP2:Metformin+Sulfonylurea NR	GP2: 263			
Fisman, 2001[145]	Cohort					
		GP1: Metformin NR	GP1: 25			
		GP2: Metformin+Glyburide NR	GP2: 111			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin vs Metformin+DPP-IV Inhibitor						
Raz, 2008[79]	RCT			Def:Fatal MI		
		GP1:Metformin Fixed	GP1: 1	GP1:1		
		GP2:Metformin+Sitagliptin Fixed Max:2550 mg; Mean: 100 mg/day	GP2: 0	GP2:0		
Thiazolidinedione vs Sulfonylurea						
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD-9 and cpt codes	
		GP1:Rosiglitazone NR			GP1:152	
		GP2: Sulfonylurea NR			GP2:191	
McAfee, 2007[149]	Cohort				Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Rosiglitazone NR			GP1:70	
		GP2: Sulfonylurea NR			GP2:94	
Hanefeld, 2007[84]	RCT					
		GP1:Rosiglitazone Fixed Start: 4 mg D:12 wks	GP1:0			
		GP2:Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D:12 wks	GP2:0			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hanefeld, 2007[84]	RCT					
		GP1:Rosiglitazone Fixed Start: 8 mg D:12 wks	GP1:0			
		GP2:Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D:12 wks	GP2:0			
Kahn, 2006[30]	RCT			Def: Fatal MI	Def: Non-fatal MI	Def: Stroke not defined
		GP1:Rosiglitazone Varied, glucose: 140 Start: 4mg, Max: 8 mg	GP1:34	GP1:2(0.1)	GP1:25(1.7)	GP1:16(1.1)
		GP2:Glyburide Varied, glucose: 140 Start: 2.5 mg, Max: 15 mg	GP2:31	GP2:3(0.2)	GP2:15(1)	GP2:17(1.2)
Jain, 2006[85]	RCT				Def: Non-fatal MI	
		GP1:Pioglitazone Varied, glucose: 69-141 Start:15mg, Median: 45 mg, Max: 45 mg D: 12 wks	GP1: 0		GP1:2(0.8)	
		GP2:Glyburide Varied, glucose: 69-141 Start:5mg, Median: 10 mg, Max: 15 mg D: 12 wks	GP2: 2		GP2:2(0.8)	
St John Sutton, 2002[123]	RCT				Def: CVD morbidity/heart disease	
		GP1:Rosiglitazone Fixed Start: 4mg bid			GP1:9	
		GP2:Glyburide Varied Max: 20 mg			GP2:5	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Sulfonylurea vs Meglitinide						
Marbury, 1999[100]	RCT				Def: CVD morbidity/unclear CHD	
		GP1:Glyburide Varied Start:2.5mg, Max: 4 mg bid	GP1:1		GP1:4	
		GP2:Repaglinide Varied Start: 0.5 mg, Max: 12 mg	GP2:3		GP2:19	
Wolffenbuttel, 1999[99]	RCT				Def: Cardiac events NOS	
		GP1:Glyburide Varied Start:1.75mg, Max: 10.5 mg bid			GP1: Authors stated similar frequencies in each group but no data given	
		GP2:Repaglinide Varied Start: 1.5 mg, Max: 12 mg				
Metformin+Thiazolidinedione vs Metformin+Sulfonylurea						
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes	
		GP1:Metformin+Rosiglitazone NR			GP1:24	
		GP2:Metformin+Sulfonylurea NR			GP2:36	
McAfee, 2007[149]	Cohort				Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Metformin+Rosiglitazone NR			GP1:6	
		GP2:Metformin+Sulfonylurea NR			GP2:17	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hamann, 2008[103]	RCT					
		GP1:Metformin+Rosiglitazone Varied, glucose: 6.1mmol/l Start: 2g/day; Start: 4mg/day D: 12 wks	GP1: 2			
		GP2:Metformin+Sulfonylurea Varied, glucose: 6.1mmol/l Start: 2g/day; Start: 5mg/day D: 12 wks	GP2: 2			
Bakris 2006[105]	RCT					
		GP1:Metformin+Rosiglitazone Varied, NS; Varied, glucose: <= 6.6mmol/L Unclear; Start: 4mg/day D: 3 wks	GP1: 1			
		GP2:Metformin+Glyburide Varied, NS; Varied, glucose: <= 6.6mmol/L Unclear; Start: 5mg/day D: 3 wks	GP2: 0			
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD -9 and CPT codes	
		GP1:Metformin+Rosiglitazone NR			GP1: HR: 0.61 (0.37 to 1.03)	
		GP2:Metformin+Sulfonylurea NR			GP2:	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin + Thiazolidinediones vs Metformin + Meglitinides						
Raskin, 2009[110]	RCT			Defn: Sudden cardiac death		
		GP1:Metformin+Rosiglitazone Varied, prespecified target dose Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 8 mg D: 4 wks	GP1: 0	GP1: 0		
		GP2:Metformin+Repaglinide Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 10 mg D: 4 wks	GP2: 1	GP2: 1		
Metformin+Thiadolidinedione vs Thiazolidinedione+Sulfonylurea						
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD -9 and CPT codes	
		GP1:Metformin+Rosiglitazone NR			GP1:24	
		GP2:Rosiglitazone+Sulfonylurea NR			GP2:6	
McAfee, 2007[149]	Cohort				Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Metformin+Rosiglitazone NR			GP1:6	
		GP2:Rosiglitazone+Sulfonylurea NR			GP2:21	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes	
		GP1: Metformin+Rosiglitazone NR			GP1: HR: 0.61 (0.37 to 1.03)	
		GP2: Rosiglitazone+Sulfonylurea NR			GP2:	
Rosak, 2006[150]	RCT				Def: Not defined	Def: Not defined
		GP1: Metformin+Rosiglitazone Varied			GP1: 0.08(0.04)	GP1: 0.03(0.36)
		GP2: Rosiglitazone+Sulfonylurea Varied NS; Start:4mg,Max:8 mg			GP2: 0.22(0.11)	GP2: 0.01(0.18)
Metformin+Sulfonylurea vs Metformin+Meglitinide						
Monami, 2008[148]	Cohort					
		GP1:Metformin+Sulfonylurea NR	GP1:35			
		GP2:Metformin+Repaglinide NR	GP2:5			
Schwarz, 2008[125]	RCT					
		GP1:Metformin+Glyburide Varied, Glucose: 6.7mmol/l Start:500mg, Max:2000mg D:12 wks	GP1:1			
		GP2:Metformin+Nateglinide Varied, Glucose: 6.7mmol/l Start:500mg; Max:2000mg D:12 wks	GP2:0			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Gerich, 2005[112]	RCT					
		GP1:Metformin+Glyburide Varied, Glucose:6.7 mmol/l Start:500mg,Max:2000mg, Mean:1105mg D: 12 wks	GP1:1			
		GP2:Metformin+Nateglinide Varied, Glucose:6.7 mmol/l Start:500mg,Max:2000mg, Mean:1459mg D: 12 wks	GP2:1			
Metformin+Sulfonylurea vs Metformin+DPP-IV Inhibitors						
Nauck, 2007[113]	RCT			Def: Fatal MI		
		GP1:Metformin+Glipizide NR	GP1:2(0.3)	GP1:1		
		GP2:Metformin+Sitagliptin NR	GP2:1(0.2)	GP2:0		
Metformin+Sulfonylurea vs Thiazolidinedione+Sulfonylurea						
McAfee, 2007[149]	Cohort				Def: Inpatient MI and coronary revascularization using ICD -9 and CPT codes	
		GP1:Metformin+Sulfonylurea NR			GP1:36	
		GP2: Rosiglitazone+Sulfonylurea NR			GP2:39	
McAfee, 2007[149]	Cohort				Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly)	
		GP1:Metformin+Sulfonylurea NR			GP1:17	
		GP2: Rosiglitazone+Sulfonylurea NR			GP2:21	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hanefeld, 2004[115]	RCT				Def: Coronary heart diseases/cardiac disorders	
		GP1:Metformin+Sulfonylurea Varied; NR Start:850mg,Max:850mg tid; NR	GP1:2		GP1:(3.1)	
		GP2: Pioglitazone+Sulfonylurea Varied; NR Start:15mg,Max:45mg; NR	GP2:1		GP2:(4.1)	
van der Meer, 2009[116]	RCT			Def: CVD event		
		GP1:Metformin+Glimepiride Fixed Start:1000mg,Max:2000mg; Start:15mg,Max:30 mg D:8 wks		GP1:0		
		GP2: Pioglitazone+Glimepiride Varied Not specified D: 8 weeks		GP2:0		
Metformin+Sulfonylurea vs Metformin+Premixed Insulin						
Kvapil, 2006[119]	RCT			Def: Fatal MI		
		GP1:Metformin+Sulfonylurea Fixed;Varied Start: 1660 mg; Start:1.75 mg, Max:10.5, Mean: 6.58 +/-4.18	GP1: 0	GP1: 0		
		GP2:Metformin+Aspart 70/30 Fixed;Varied Start:1660mg; Start:0.2U/kg, Mean:0.3+/-0.12, Start: BID, Final: BID	GP2: 1	GP2: 1		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Malone, 2003[118]	RCT					
		GP1: Metformin+Glibenclamide Varied; Varied, fasting and pre-meal goal <7mmol.L, 2-hour post-prandial goal <10mmol/L Max: 2550mg/day, Mean: 1968mg/day; Mean: 14.2mg/day D: 4 wks; 16 wks	GP1: 0			
		GP2: Metformin+Lispro 75/25 Varied; Varied, fasting and premeal glc <7mmol/L and 2-h post-prandial glc <10mmol/L Max: 2550mg/day; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks; 16 wks	GP2: 1			
Metformin + Sulfonylureas vs Metformin or Sulfonylureas + Thiazolidinediones						
Home, 2009[14]	RCT				Def: Fatal and non-fatal MI	Def: Fatal and non-fatal stroke
		GP1:Metformin+Sulfonylurea Varied, HgbA1c: <=7.0 Max: 2550 mg; Glibenclamide, Max: 15mg, Glimepiride, Max: 4mg D: 8 wks	GP1: 157	GP1: 71	GP1: 56	GP1: 63
		GP2: Rosiglitazone+ Metformin or Sulfonylurea Varied, HgbA1c: <=7.0 Start: 4mg/day, Max: 8mg/day; Metformin, Max: 2550 mg, Glibenclamide, Max: 15mg, Glimepiride, Max: 4mg D: 8 wks	GP2: 136	GP2: 60	GP2: 64	GP2: 46
			HR: 0·86 (0·68 to 1·08), p: 0·19	HR: 0·84 (0·59 to 1·18), p: 0·32	HR: 1·14 (0·80 to 1·63), p: 0·47	HR: 0·72 (0·49 to 1·06), p: 0·10

bid= twice; CHD= Coronary heart dissease; CPT=Current procedural terminology; CVD=Cardiovascular disease; Def=Definition; D=Duration of titration; g/day = grams per day;

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

GP= Group; HgbA1c = hemoglobin A1c; HR= Hazard ratio; ICD=International classification of diseases; ID= Identification; IR= Incidence ratio; Met= Metformin; Mg = milligram; MI= Myocardial infarction; mmol/l = millimoles/liter; NOS= Not otherwise specified; NR= Not reported; OR= Odds ratio; RCT= Randomized controlled trial; RR=Risk ratio; SU= Sulfonylurea; tid = thrice; U/kg = unit per kilogram; wks = weeks

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Metformin vs Thiazolidinedione				
Schernthaner, 2004[42]	RCT		Def: urinary albumin/creatinine ratio	
		GP1: Metformin Varied Start: 850mg, Max: 2550mg	GP1: 1%	
		GP2: Pioglitazone Varied Start: 30mg, Max: 45mg	GP2: 19%, p: 0.002 vs. GP2	
Metformin vs Sulfonylurea				
Amador-Licona, 2000[54]	RCT		Def: change in glomerular filtration rate	
		GP1: Metformin Varied Start: 850mg, Max: NR	GP1: B: 138 mL/min F: 134 mL/min, p=0.46 vs. baseline	
		GP2: Glibenclamide Varied Start: 5mg, Max: NR	GP2: B: 136 mL/min F: 151 mL/min, p=0.04 vs. baseline	
Amador-Licona, 2000[54]	RCT		Def: change in microalbumin (mg/d)	
		GP1: Metformin Varied Start: 850mg, Max: NR	GP1: B: 74 mg/d F: 49 mg/d, p=0.008 vs. baseline	
		GP2: Glibenclamide Varied Start: 5mg, Max: NR	GP2: B: 83 mg/d F: 102 mg/d, p=0.09 vs. baseline	
Metformin vs Metformin + Thiazolidinedione				
Gomez-Perez, 2002[74]	RCT			Def: Unclear neuropathy
		GP1: Metformin Fixed Start: 2500mg		GP1: 1
		GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 2mg bid		GP2: 0
Gomez-Perez, 2002[74]	RCT			Def: Unclear neuropathy
		GP1: Metformin Fixed Start: 2500mg		GP1: 1
		GP2: Metformin + Rosiglitazone Fixed		GP2: 0

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
		Start: 2500mg; Start: 4mg bid		
Metformin vs Metformin + DPP-IV inhibitors				
Raz, 2008[79]	RCT			Def: NR
		GP1: Metformin Fixed NR		GP1: 2 (2.1)
		GP2: Metformin + Sitagliptin Fixed Max: 2550mg; Mean: 100mg/day		GP2: 4 (4.2)
Thiazolidinedione vs Sulfonylurea				
Nakamura, 2004[86]	RCT		Def: Urine albumin excretion (microgram/min), mean (SD)	
		GP1:Pioglitazone Fixed Start: 30mg/day	GP1: 6 mos: 86.5 (24.5); 12 mos: 44.5 (16.4)	
		GP2:Glibenclamide Fixed Start: 5mg/day	GP2: 6 mos: 142.5 (42.5); 12 mos: 146.8 (38.5)	
			GP1-GP2: 6 mos, p: <0.05; 12 mos: <0.01	
Agarwal, 2005[151]	RCT		Def: Proteinuria	
		GP1:Pioglitazone Varied, glucose: 140, HgbA1c: 8 Start: 15mg, Mean 33mg, Max: 41mg D: 3.8 mos	GP1: % mean reduction: 7.2, CI: -24.9 - 10.6	
		GP2:Glipizide Varied, glucose: 140, HgbA1c: 8 Start: 5mg, Mean: 16mg, Max: 19 mg D: 3.7 mos	GP2: % mean increase: 6.1, CI: -11.7-23.8	
			GP1-GP2: % reduction: 13.2, CI: -38.4 -11.9, p: 0.294	
Bakris, 2003[88]	RCT		Def: n (%) with normal albuminuria at baseline who progressed to microalbuminuria by study end	
		GP1: Rosiglitazone Fixed Start: 4mg bid	GP1: 3 (7)	
		GP2: Glyburide Varied Start: NR, Max: 20mg	GP2: 5 (10.6)	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Bakris, 2003[88]	RCT		Def: albumin/creatinine ratio	
		GP1: Rosiglitazone Fixed Start: 4mg bid	GP1: (-45 to -4) p: NSG vs. GP2	
		GP2: Glyburide Varied Start: NR, Max: 20mg	GP2: (-22 to 4)	
Nakamura, 2000[87]	RCT		Def: urinary albumin excretion	
		GP1: Pioglitazone Fixed Start: 30mg bid	GP1: B: 142.8 ug/min F: 48.4 ug/min, p: < 0.05	
		GP2: Glibenclamide Fixed Start: 5mg	GP2: B: NR F: NR, p: > 0.05	
Metformin+Thiazolidinedione vs Metformin+Sulfonylurea				
Bakris, 2006[105]	RCT		Def: % change in UACR (urine albumin:creatinine ratio >=30), Mean (SD)	
		GP1: Metformin+Rosiglitazone Varied; Varied, glucose: <= 6.6mmol/L NS; Start: 4mg D: 3 wks	GP1: -22.7 (15), p: <0.01	
		GP2: Met+Glyburide Varied; Varied, glucose: <=6.6 NR; Start: 5mg D: 3 wks	GP2: -5.5 (14.5), p: NSG	
			GP1-GP2: -15.5%, p: 0.07	
Comaschi, 2007[109]	RCT	GP1: Metformin + Pioglitazone Varied, NR Max: 3g/day; Start: 15mg, Max: 30mg/day D: NR; 22 wks		GP1: 1
		GP2: Metformin + Glibenclamide Varied, HgbA1c: 7.50% Start: 400mg, Max: 3g; Start: 2.5mg D: 22 wks		GP2: 0

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Metformin + Sulfonylurea vs Thiazolidinedione + Sulfonylurea				
Hanefeld, 2004[115]	RCT		Def: albumin/ creatinine ratio	
		GP1: Metformin + Unspecified sulfonylurea + Placebo Varied Start: 850mg, Max: 2550mg; NR	GP1:	
		GP2: Pioglitazone + Unspecified sulfonylurea + Placebo Varied Start: 15mg, Max: 45mg; NR	GP2: CI: 0.73-0.97, p: 0.017 vs. GP1	
Hanefeld, 2004[115]	RCT		Def: microalbuminuria resolved	
		GP1: Metformin + Unspecified sulfonylurea + Placebo Varied Start: 850mg, Max: 2550mg; NR	GP1: 7.7%	
		GP2: Pioglitazone + Unspecified sulfonylurea + Placebo Varied Start: 15mg, Max: 45mg; NR	GP2: 10.2%	

B=Baseline; bid=twice; CI= Confidence interval; Def=Definition; D= Duration of titration; F=Final; GP=Group; HgbA1c = hemoglobin A1c; mos=Months; mg = milligram; mL/min = milliliter per minute; mmol/l = millimoles/liter; NR=Not reported; NSG=Not significant; RCT = Randomized controlled trial; ug/min= micrograms per minute; UACR= Urine albumin:creatinineratio; wks=weeks

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Hypoglycemia

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	**Consistency**	**Directness**	**Precision**	**Magnitude and direction of effect**	
metformin versus Thiazolidinedione						
1 trial	Medium	Unknown	Direct	Precise	Small, No favorite	Moderate
metformin versus SU						
12 RCTs, 1 obs.	Medium	Consistent	Direct	Precise	Large, Favors Met	High
Met versus Sitagliptin						
1 RCT	High	Unknown	Direct	Imprecise	Small, Unclear	Low
Met versus Meglitinide						
5 RCTs	Medium	Consistent	Direct	Imprecise	Small, Favors Met	Moderate
Met versus Met + TZD						
9 RCTs	Medium	Consistent	Direct	Precise	Small, Favors Met alone	Moderate
Met versus Met + SU						
9 RCTs	Medium	Consistent	Direct	Imprecise	Large, Favors Met alone	Moderate
Met versus Met + Sitagliptin						
4 RCTs	High	Consistent	Direct	Precise	Small, No favorite	Moderate
Met versus Met + Meglitinide						
3 RCTs	Medium	Inconsistent	Direct	Imprecise	Large, Favors Met alone	Low
Pio versus Rosi						
1 obs.	High	Unknown	Direct	Imprecise	Small, Favors Rosi	Low
TZD versus SU						
7 RCTs, 1 obs	Medium	Consistent	Direct	Precise	Large, Favors TZD	High
TZD versus Meglitinide						
2 RCTs	High	Consistent	Direct	Precise	Small, Favors TZD	Low
SU versus Sitagliptin						
1 RCT	Low	Unknown	Direct	Precise	Large, Favors Sitagliptin	Moderate
SU versus Meglitinide						
8 RCTs	Medium	Consistent	Direct	Precise	Small Favors MEG	Low
Met and TZD versus Met and another agent (mostly SU)						
8 RCTs, 1 obs	Medium	Consistent	Direct	Precise	Large, Favors Met +TZD	High
Met and SU versus Met and another agent						
5 RCTs	Low	Inconsistent	Direct	Imprecise	Small, Unclear	Low – depends on “other agent”
Met and Exenatide versus Met and another agent						
None						Insufficient

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Hypoglycemia

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias: Design/ Quality	**Consistency**	**Directness**	**Precision**	**Magnitude and direction of effect**	
Met and Basal Insulin versus Met and Another Insulin						
3 RCTs	High	Consistent	Direct	Precise	Small, Favors Met plus basal insulin	Low
Met and TZD versus TZD and SU						
1 obs	High	Unknown	Direct	Precise	Large, Favors Met plus TZD	Low
Met and SU versus TZD and SU						
1 RCT	High	Unknown	Direct	Precise	Small, Favors TZD and SU	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Liver injury

Number of Studies	**Domains Pertaining to Strength of Evidence**					**Strength of Evidence**
	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
metformin versus SU						
1 RCT	Low	Unknown	Direct	imprecise	Unclear.	Low.
metformin and thiazolidinedione versus metformin and another agent SU						
1 RCT	Low	Unknown	Direct	imprecise	No difference	low
metformin and SU versus thiazolidinedione and SU						
1 RCT	High	Unknown	Direct	Precise	No difference	Low
Pio versus Rosi						
1 Obs	Low	Unknown	Direct	Precise	Unclear.	Low.
thiazolidinedione versus SU						
1Obs, 1 RCT	moderate	Consistent	Direct	Precise	Small, no favorite	Moderate
metformin versus thiazolidinedione						
1 Obs	Low	Unknown	Direct	precise	Small, no favorite	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Congestive heart failure

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met versus TZD						
	Low	Inconsistent	Direct	Imprecise	Small. increase risk with TZD	Low
TZD versus SU						
	Low	consistent	Direct	Imprecise	Small. Increase risk with TZD	Moderate
Metformin versus Sulfonylurea						
	High	Consistent	Direct	Precise	Moderate. increase risk with SU	Low
Pioglitazone versus Rosiglitazone						
	High	Unknown	Direct	Imprecise	Unclear.	Low
Metformin + SU vs Thiazolidinedione and other						
	Low	Unknown	Direct	Imprecise	Favors SU + Met	Low
Thiazolidinedione and Metformin versus Thiazolidinedione and Sulfonylurea						
	High	Unknown	Direct	Imprecise	Small. increase risk with TZD and SU combination	Low
Met and Basal Insulin versus Met and Another Insulin						
	Low	Inconsistent	Direct	Imprecise	Unclear	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Severe lactic acidosis

Table X. Strength of the Evidence Regarding Lactic Acidosis

Number of Studies	**Domains Pertaining to Strength of Evidence**				**Strength of Evidence**	
	Risk of Bias: Design/ Quality	**Consistency**	**Directness**	**Precision**	**Magnitude and direction of effect**	
metformin versus sulfonylurea						
2 RCTs	Low	Consistent	Direct	Imprecise	Weak; no increased risk with Metformin	Moderate
metformin + sulfonylurea versus metformin						
2 RCTs	Low	Consistent	Direct	Imprecise	Weak; no favorite	Moderate

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Severe lactic acidosis

Table X. Strength of the Evidence Regarding Cancer

Number of Studies	**Domains Pertaining to Strength of Evidence**				**Strength of Evidence**	
	Risk of Bias: Design/ Quality	**Consistency**	**Directness**	**Precision**	**Magnitude and direction of effect**	
TZD versus SU						
1 RCT	Low	Unknown	Direct	Imprecise	Weak; favors the use of TZD	Low
metformin versus metformin+Sitagliptin						
1 RCT	High	Unknown	Direct	Imprecise	Weak; favors the use of metformin+Sitagliptin	Low
metformin versus MEG						
1 RCT	High	Unknown	Direct	Imprecise	Weak; favors the use of Meglitinides	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Fractures

Number of Studies	**Domains Pertaining to Strength of Evidence**					**Strength of Evidence**
	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
metformin versus thiazolidinedione						
1 RCT {#835)	Low	unknown	Direct	precise	Small. Favors metformin.	High
metformin metformin versus SU						
2 RCTs {#835}{#929}	Medium	Consistent	Direct	Imprecise	Unclear.	low
metformin versus metformin + any SU						
1 RCT	Medium	Unknown	Direct	imprecise	Unclear.	Low
metformin versus metformin+DPP4						
1 RCT	medium	Unknown	Direct	imprecise	Unclear	Low
thiazolidinedione versus SU						
1 RCT		Unknown	Direct	Precise	No difference	Low
metformin + SU versus thiazolidinedione + other oral medication						
1 RCT {22}	Low	unknown	Direct	Precise	Small. Favors metformin + SU	High

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Pancreatitis

Number of Studies	Domains Pertaining to Strength of Evidence				Strength of Evidence	
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
metformin vs metformin +SU						
1 RCT	Low	Unknown	Direct	Imprecise	Unclear	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Cholecystitis

Number of Studies	Domains Pertaining to Strength of Evidence				Strength of Evidence	
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
metformin versus TZD						
1 RCT	Low	Unknown	Direct	Imprecise	Small, Unclear	Low
metformin +TZD versus metformin						
1 RCT	Low	Unknown	Direct	Imprecise	Small, Unclear	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Macular edema

Number of Studies	Domains Pertaining to Strength of Evidence				Strength of Evidence	
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
metformin+thiazolidinedione versus metformin+Other agent						
1 RCT	Low	Unknown	Direct	Imprecise	Small, increased risk with metformin + TZD	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Gastrointestinal effects

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
Met versus Thiazolidinedione						
4 RCTs	Low	Consistent	Direct	Precise	Large; Favors TZD	High
Met versus SU						
11 RCTs, 1 Obs.	Medium	Consistent	Direct	Precise	Large; Favors SU	Moderate
Met versus Sitagliptin						
1 RCT	High	Unknown	Direct	Imprecise	Large; Favors Sitagliptin	Low
Met versus Meglitinide						
4 RCTs	Medium	Inconsistent	Direct	Imprecise	Small; Unclear for “any GI effect”; favors MEG for diarrhea	Low
Met versus Met + TZD						
7 RCTs	Medium	Consistent	Direct	Imprecise	Small; Unclear for “any GI effect”; favors Met+TZD for diarrhea	Moderate
Met versus Met + SU						
9 RCTs	Medium	Consistent	Direct	Imprecise	Small; Unclear favorite; favors combination arm when combination dose of metformin lower	Moderate
Met versus Met + Sitagliptin						
4 RCTs	Medium	Consistent	Direct	Precise	Small; Unclear favorite	Low
Met versus Met + Meglitinide						
1 RCT	Low	Unknown	Direct	Imprecise	Small; Unclear favorite	Low
TZD versus SU						
3 RCTs	Low	Consistent	Direct	Precise	Small; Unclear favorite	High
TZD versus Meglitinide						
1 RCT	Medium	Unknown	Direct	Imprecise	Small; Unclear favorite	Low
Met and TZD versus Met and SU						
4 RCTs	Low	Inconsistent	Direct	Imprecise	Small; Favors neither	Low
Met and TZD versus Met and Sitagliptin						

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence
Outcome: Gastrointestinal effects

Number of Studies	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Magnitude and direction of effect	
1 RCT	Low	Unknown	Direct	Imprecise	Small; Favors neither	Low
Met and SU versus Met and Sitagliptin						
1 RCT	Low	Unknown	Direct	Imprecise	Small; Favors neither	Low
Met and SU versus Met and MEG						
1 RCT	Low	Unknown	Direct	Imprecise	Small; Unclear favorite for "any GI side effects"; Favors metformin+MEG for abdominal dyspepsia	Low
Met and basal insulin versus Met and another insulin						
1 RCT	Low	Unknown	Direct	Imprecise	Small; Unclear favorite	Low
Met and SU versus TZD and SU						
2 RCTs	Medium	Consistent	Direct	Precise	Small; Favors TZD combination arm	Moderate

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Asche, 2008[162] US	Cohort	Start year: 1996 - End year: 2005 395 days NA	NA	NA	Yes	1129573/5438 General Electric Research Database	Age: <65 years, took any oral antidiabetic medication within 395 days prior to first prescription for monotherapy with metformin, SU, or TZD, less than two HbA1c levels (first recorded within 90 days prior to index date or 30 days post-index date and the second level drawn either (longer of the two) 90 days after index date or baseline A1c), no type 2 diabetes (defined by ICD-9 , FBG >= 125 mg/dL, on oral antidiabetic medication, or prescription for injectable incretic mimetic)
McAlister, 2008[168] Canada	Cohort	Start year: 1991 - End year: 1996 9 Years	NA	NA	No	NR/5631 Saskatchewan Health database	Age: <30years, treatment with insulin, did not receive at least one new prescription for an oral antidiabetic medication (metformin or sulfonylurea) between 01/01/1991 and 12/31/96, not eligible for prescription drug benefits, less than one year of coverage in the provincial health plan, history of heart failure (by ICD-9 for hospitalization for heart failure) in last 3 years prior to starting first oral antidiabetic agent, receipt of more than one oral antidiabetic agent at any time (concurrently or not)
Rosak, 2006[150] Germany	Cohort	Neither year reported 6 Months	NA	< 6 months	Yes	NR/22808 Outpatient: primary care, Outpatient: subspecialty care setting	not all treated with Rosi

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hanefeld, 2006[163] Germany	Cohort	Neither year reported 42 Months	NA	>= 6 months	Yes	NR/500 Outpatient: primary care	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), Pregnant, Known hypersensitivity to pioglitazone, glibenclamide, or their metabolites, ketoacidosis, diabetic coma,pre-coma, type 1 DM, Serious impairment of adrenocortical function
Karter, 2005[167] US	Cohort	Start year: 1999 - End year: 2001 10 Months	NA	NA	No	NA (for cohort studies, claims data, etc)/23440 managed care organization	CHF, no pharmacy benefit, type 1 diabetes, >80% pill adherence, filled a refill of index medication, member of health plan >1y, any utilization of the index therapy in the 12 months prior to initiation of the study
Rajagopalan, 2005[166] US	Cohort	Start year: 1999 - End year: 2001 Duration: NA	NA	NA	Yes	NA (for cohort studies, claims data, etc)/1123645 pharmacy database	Age: <18, Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), use of troglitazone, in cohort <12m prior to study, follow up <3m after study started, prior treated with rosi, metformin, pio, or SU, not continuously having insurance or medication coverage
Hussein, 2004[164] Australia	Cohort	Start year: 2000 - End year: 2002 30 Months	NA	NA	No	2500/203 Outpatient: subspecialty care setting	HbA1c <: 8, treated at Melbourne Hospital, treated with rosi or pio>2m

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rajagopalan, 2005[157] US	Cohort	294.2, 296.1, 300.1, 321.9, 295.9, 319.9 Groups 1 and 2: Pioglitazone vs. rosiglitazone, Groups 3 and 4: Pioglitazone vs. sulfonylurea, Groups 5 and 6: Pioglitazone vs. metformin (Mean follow-up)			Yes		Age <18, Any liver disease, No type 2 diabetes, Other
Maru, 2005[158] UK	Cohort	130 (Mean follow-up)			Yes		Age <35, Treatment experienced, No type 2 diabetes, Other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Nichols, 2005[159] US	Cohort	144.4 total sulfonylurea monotherapy group- mean MONTHS of followup is 26.4, metformin monotherapy- mean MONTHS of followup is 23.1, sulfonylurea + metformin- mean months of followup is 28.3 (Mean follow-up)			Yes		Other
Seufert, 2008[117] Multi-continent	randomized but does not no control; comparative study	Neither year reported 104 Weeks	No run-in period	NR	Yes	NR/1269 NR	Age: < 35, >75, 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%, HbA1c <: > 11%, Pregnant, Nursing, fasting c-peptide >1.5, ketoacidosis, symptomatic heart failure, acute malabsorption, chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Malone, 2003[118] 14 countries not specified	randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test meals	Age: Not 30-75, HbA1c >: <125% of upper limit of normal by local lab within 4 weeks prior to entry, BMI or weight: >40, not type 2 dm, not use of single oral agent (metformin or SU) for 3 mo prior to study at max clinically effective dose for previous 30 days
Jibran, 2006[95] Pakistan	randomized, open-label, 2 arm parallel prospective study	Start year: 2000 - End year: 2001 12 Months	NA	< 6 months	NR	NR/100 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), Poorly controlled on prior treatments (e.g. failed initial treatment), No type 2 DM, On insulin
Raskin, 2009[110] NR	RCT	Neither year reported 26 Weeks	No run-in period	< 6 months	Yes	1093/383 Outpatient: primary care	Age: <18y, Pregnant, Nursing, currently not under monotherapy at least 2 months or dual therapy, FBG >260, Any disease of abnormality as judged by the investigator, treatment with the investigational drug for 4 weeks, Allergy to study drugs or related compounds, H/O hypoglycemia unawareness or recurrent severe hyperglycemia
van der Meer, 2009[116] Netherlands	RCT	Neither year reported 24 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	173/80 NR	Age: <45 or >65, 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 >: >8.5, HbA1c <: <6.5, BMI or weight: <25 or >32, <45 or >65, Systolic BP <150, Diastolic BP <85, Prior TZD or insulin use

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kaku, 2009[70] Japan	RCT	Start year: 2005 40 Weeks	Yes	< 6 months	Yes	NR/236 NR	Age: <= 20 and >=65, 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 >: <6.5, HbA1c <: >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 26weeks, if on any medications that might affect glycemic control, drug or alcohol dependency
Williams-Herman, 2009[63] NR	RCT	Neither year reported 54 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age: >78; <18 yrs, lack of A1c >=7.5% but <=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
Nauck, 2009[78] Multi-continent	RCT	Neither year reported 26 Weeks	Run-in period but number of participants excluded was NR	>= 6 months	Yes	1662/1087 NR	Age: <18, >80y, HbA1c >: 11 if on monotherapy; 10 if on combination therapy (both greater than 3 m), HbA1c <: 7, BMI or weight: >40, used insulin in last 3 m

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kahn, 2008[170] US, Multinational Europe	RCT	Neither year reported 4 Years	No run-in period	NR	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
Scott, 2008[71] Multi-continent	RCT	Neither year reported 18 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	486/273 NR	Age: <18, >75, 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 >: 11, HbA1c <: 7, not on 10 wks on stable dose of MET, insulin use, type 1 dm, glucose > 270
Raz, 2008[79] Multi-continent	RCT	Neither year reported 30 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	544/190 NR	Age: <18,>78 yrs, HbA1c >: <8% after run-in, HbA1c <: >11% after run-in, BMI or weight: <20, >43 kg/m^2, Pregnant, Nursing, Rx Insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, type 1 DM, fpg <7.2, >15.6 mmol/L consistently during run-ind, no type 2 DM

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Robbins, 2007[120] US, Multinational Europe, Multi-continent, India, Australia	RCT	Neither year reported 24 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	433/317 NR	Age: <35 or >75, 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 >: >11, HbA1c <: <6.5, Pregnant, Nursing, Not using adequate contraception, Patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0U/kg or who had a change in type or dose of lipid-altering medications or thiazolidinedione use up to 3 months before the study, fasting triglyceride level >4.5mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women),
Hamann, 2008[103] Multinational Europe, Mexico	RCT	Neither year reported 52 Weeks	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 cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: >10, HbA1c <: <7, BMI or weight: BMI <25, used any oral antidiabetic drug other than metformin in the prior 12 weeks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, oedema 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

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Chien, 2007[47] Taiwan, Multi-center	RCT	Neither year reported 16 Weeks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age: <30, >75, 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 or weight: <18.5, >35 kg/sq-meter, current significant GI disorder, HONK, hypersensitivity to Glyburide or Metformin, current infection, treatment with insulin in last 6 m, surgery in past 4 weeks, history of cancer in 5 yr, 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 glicazide<10 mg/day, glimepiride<4mg/d, gliclizide<160mg/d)

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Schwarz, 2008[125] US	RCT	Neither year reported 104 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	75/69 NR	Age: <18 or >77, 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, HbA1c >: <7.0, HbA1c <: >11.0, BMI or weight: <22 or >45, FBG >270, History of lactic acidosis, Congestive cardiac failure requiring pharmacologic treatment, Type 1 DM or secondary forms of DM
Lund, 2007[160] Denmark	RCT	Start year: 2001 - End year: 2002 8 Months	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	127/96 Outpatient: subspecialty care setting	Age: <40 for onset of diabetes diagnosis, 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 >: 9.5 with ongoing OHAs prior to study start; 10.5 on 2 visits with >1m interval, HbA1c <: 6.5 after run in period, BMI or weight: >27 kg/m^2, Pregnant, insulin treated T2DM, secondary DM, Factor II, VII, X <0.7, ongoing co-existing illness with life shortening prognosis, mental retardation or reduced intellectual behavior, h/o drug abuse, weight loss of >5kg in past 6 months prior to study start, fasting C peptide <300 of non fasting glucagon stimulated C peptide <600, Ketonuria; Ketoacidosis

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2007[113] US, Multinational Europe, Multi-continent	RCT	Neither year reported 52 Weeks	Yes	< 6 months	Yes	2141/1172 NR	Age: <18 or >78, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15, Insulin use within 8weeks of screening, History of Type 1 DM, Other treatments for Hypoglycemia
Raskin, 2007[121] US	RCT	Neither year reported 28 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	N:/NR NR	Age: <18 or >75, HbA1c <: <=8.0, BMI or weight: BMI>40 or weight >125kg (275lbs), Pregnant, Nursing, Not using adequate contraception, If not on metformin >=1,000mg /day as a single agent or in OAD combination therapy for at least 3months before the trial., History of insulin use
Hanefeld, 2007[84] Multinational Europe	RCT	Neither year reported 52 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/598 NR	Age: <40/>80, 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 or weight: <22. >38, 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
Scott, 2007[94] US	RCT	Neither year reported 12 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	2186/743 NR	Age: <21/ >75, 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

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kahn, 2006[30] Multi-continent	RCT	Start year: 2000 - End year: 2006 6 Years	No run-in period	NR	Yes	6676/4360 NR	Age: < 30 / > 75, 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, History of Lactic acidosis
Charbonnel, 2006[80] Multi-continent	RCT	Neither year reported 24 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	1464/701 NR	Age: < 18/ >78, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c >: 10, HbA1c <: 7, Type 1 DM, Insulin use within 8 weeks of screening, FPG > 14.4mmol/l
Wright, 2006[161] UK	RCT	Start year: 1977 - End year: 1991 6 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	7616/4191 23 clinical Center	Age: <25, >65 yrs, Any kidney disease (such as microalbuminuria, 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

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2006[39] Multi-continent	RCT	Start year: 2003 to 2004 32 Weeks	Yes	< 6 months	Yes	1252/468 multicenter	Age: <18 / >70, 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 >: 11, HbA1c <: 7, 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 30days 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 DKA

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[85] US, Puerto Rico	RCT	Neither year reported 56 Weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/502 NR	Age: <18 , >80, 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 >: 11.5, HbA1c <: 7.5, Pregnant, Nursing, Duration of DM > than 2years, Intolerance to Rosi, Pio or Troglitazone, Drug or alcohol abuse, Previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin , SU for 3months or more, Use of Hydrochlorothiazide, joint injections, niacin greater than 250mg/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=<20, >45 ; Hypertension, Chronic pulmonary disease, history of cancer not in remission for at least 5years
Stewart, 2006[129] Multinational Europe	RCT	Start year: 2003 to 2004 32 Weeks	Yes	< 6 months	Yes	1397/526 NR	Age: < 18 , > 70, History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >: 9, HbA1c <: 7, Drug naive patients with FPG <7mmol/l or >9mmol/l, patient on monotherapy with FPG < 6.0mmol/l or >8mmol/l, Prior history of exposure to thiazolidinediones within previous 6months, Use of insulin anytime in the past, Uncontrolled hypertension

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Bakris, 2006[105] US, Multi-continent, South America, Europe	RCT	Neither year reported 32 Weeks	Yes	< 6 months	Yes	560/514 NR	Age: <40 or >80 years, Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI or weight: BMI < 22, Use of any TZD in the 3months prior to screening, Use of insulin for >= 6months at any time prior to screening, Anemia, severe Angina, SBP >159 (can't adjust the BP meds during the trial), DBP >99
Umpierrez, 2006[106] US	RCT	Neither year reported 28 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	538/210 Outpatient: primary care, Outpatient: subspecialty care setting	Age: <18 or >79years, HbA1c >: >10, HbA1c <: <7.5, BMI or weight: BMI <24, Diagnosis of Type 2 DM <6months, No taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only OAD for at least 2months prior to the study, C-peptide <0.27nmol/L, Subjects treated with insulin, TZDs or sulpphonyurea 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
Kvapil, 2006[119] Multinational Europe	RCT	Neither year reported 16 Weeks	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 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=not adequately controlled on metformin

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gerich, 2005[112] US	RCT	Neither year reported 2 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	908/428 NR	Age: <18 and >77, 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), Neuropathy, Retinopathy, HbA1c >: 11, HbA1c <: 7, BMI or weight: < 22 and >45 kg/m2, Not using adequate contraception, FPG >=15mmol/L, if type 1 dm, symptomatic hypoglycemia with >10% weight loss in previous 8 weeks, h/o lactic acidosis or CHF requiring meds, other medical conditions that could interfere with interpretation of results or pose sign risk to the subject, had to be drug naive
Derosa, 2005[107] Italy	RCT	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 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, BMI or weight: , 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 6mo, consumption of glimeperide or TZDs or prior intolerance to these meds

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Malone, 2004[137] US	RCT	Neither year reported 32 Weeks	Yes	< 6 months	Yes	145/111 NR	Age: <30 OR >80, HbA1c >: <1.3 or >2.0 X normal, BMI or weight: >40, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30days before the study, while using 1 or more OAM without insulin for 30 or more days before study start
Horton, 2004[66] NR	RCT	Neither year reported 24 Weeks	Yes	< 6 months	Yes	701/401 NR	Age: >30 y, Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), Neuropathy, Retinopathy, HbA1c >: 6.8, HbA1c <: 11, type 1 or 2ry diabetes, diabetes>3m duration, FPG <15mmol/L, diabetic complication, on corticosteroids, non treatment naive
Yang, 2003[114] China	RCT	Neither year reported 12 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/211 NR	Age: <35, >70, 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-mos
Marre, 2002[81] Multi-continent	RCT	Neither year reported 24 Weeks	Yes	< 6 months	Yes	680/467 NR	Age: at least 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), HbA1c >: 6.8, HbA1c <: 11, BMI or weight: 20 to 35, DM at least 6m, FPG>15mmol/l, gastroparesis, change in body weight during run-in, treated with diabetes meds other than metformin 3m before study

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Moses, 1999[68] Australia	RCT	Neither year reported 4 to 5 Months	No run-in period	NR	NR	108/83 NR	Age: <40 or >75, 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, HbA1c <: 7.1, BMI or weight: , No Type 2 DM, Not on Metformin for more than 6 months, Alcohol Abuse, Drug Use, Intention to become pregnant, h/o Lactic Acidosis, Vitamin B12<150 pmol/l with anemia
Leiter, 2005[69] Canada	RCT	Neither year reported 32 Weeks	No run-in period	< 6 months	Yes	720/613 Outpatient: primary care	Age: <20 or >80, HbA1c <: 9.5, no type 2 DM, FBG >=7 but <=14mmol/L
Garber, 2006[108] US	RCT	24 weeks (Planned duration)			Yes		Age <20 or age>78, Any liver disease, Any kidney disease, History of CVD, HbA1c <=7.0% or >=12.0%, No type 2 diabetes, Other

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Weissman, 2005[72] US	RCT	Neither year reported 24 weeks (Planned duration)	Run-in period but number of participants excluded was NR	< 6 months	Yes	1270/766 NR	Age: <18 or >75years, 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 + Sulphonylurea), HbA1c <: >8.5% for subjects having received prior combination treatment (Metformin + Sulphonylurea), BMI or weight: BMI <27, HbA1c < 7% for drug naive or prior monotherapy subjects., HbA1c > 10% for drug naive or prior monotherapy subjects., FPG < 126mg/dL (7mmol/L), FPG >270mg/dL (15mmol/L), Anemia, severe edema, prior insulin use within 3months of study start, Non - compliant patient with metformin up-titration
Bailey, 2005[73] UK, 14 European Countries	RCT	24 weeks (Planned duration)			Yes		Age <18 or >70, History of CVD, No type 2 diabetes, Other
Yamanouchi, 2005[40] Japan	RCT	12 months (Planned duration)			No		Any liver disease, Any kidney disease, History of CVD, Treatment experienced, Neuropathy, Retinopathy, HbA1c <7.0%, No type 2 diabetes, Other
Derosa, 2005[133] Italy	RCT	12 months (Planned duration)			No		Age <18 , Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, HbA1c <7.5, No type 2 diabetes, Other

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Feinglos, 2005[77] US	RCT	16 weeks (Planned duration)			Yes		Age <30 or age >81, Any liver disease, Any kidney disease, History of CVD, HbA1c <7.0% or >8.5%, No type 2 diabetes, Other
Schernthaner, 2004[42] Europe	RCT	12 months (Planned duration)			No		Age <35 or >75, Treatment experienced, HbA1c <7.5% or >11%, No type 2 diabetes,
Derosa, 2004[48] Italy	RCT	12 months (Planned duration)			No		Age <46 or >67, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, No type 2 diabetes, Other
Tan, 2004[90] 22 centers in Denmark, Finland, Norway, and Sweden.	RCT	52 weeks (Planned duration)			Yes		Treatment experienced, HbA1c <7.5 or > 11 for pts not receiving OAM, <7.5, > 9.5 for patients receiving OAM, No type 2 diabetes, Other
Raskin, 2004[92] US	RCT	12 titration and 12 maintenance weeks (Planned duration)			Yes		Age <18 , HbA1c <7 or >12% during previous monotherapy with sulfonylurea or metformin at 50% or more of maximal recommended dose for at least 3 months, No type 2 diabetes, Other
Jovanovic, 2004[93] US	RCT	12 week titration then 12 week maintenance (Planned duration)			Yes		Age <18, HbA1c <7 or >12, No type 2 diabetes, Other

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Hanefeld, 2004[115] Canada, UK, Hungary, Finland, U.K., Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands	RCT	NR			Yes		Age <35 or >75, History of CVD, HbA1c <7.5 or >11, No type 2 diabetes, Other
Garber, 2003[49] US	RCT	16 weeks (Planned duration)			Yes		NR
Goldstein, 2003[50] US	RCT	18 weeks (Planned duration)			Yes		Any liver disease, Any kidney disease, History of CVD, HbA1c <7.5 and >12.0, Other
Derosa, 2003[67] Italy	RCT	12 months (Planned duration)			No		Any kidney disease, History of CVD, Treatment experienced, HbA1c < 7 %, No type 2 diabetes, Other
Pavo, 2003[44] Russia and Hungary	RCT	32 weeks (Planned duration)			Yes		Age <40, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, HbA1c <7.5% or >11.0%, No type 2 diabetes, Other

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Vakkilainen, 2002[102] Finland	RCT	12 weeks (Planned duration)			Yes		Age <18 or >75, Any liver disease, Any kidney disease, HbA1c <6.5 or >10, No type 2 diabetes, Other
Blonde, 2002[51] US	RCT	16 weeks (Planned duration)			Yes		Age <30 or >75, Any liver disease, Any kidney disease, History of CVD, HbA1c <7.4%, No type 2 diabetes, Other
St John Sutton, 2002[123] US	RCT	52 weeks (Planned duration)			Yes		Age <40 or age>80, Any liver disease, Any kidney disease, History of CVD, No type 2 diabetes, Other
Marre, 2002[52] Netherlands, Denmark, Portugal, France, Belgium	RCT	4 months (Planned duration)			Yes		Age <18, Any liver disease, Any kidney disease, History of CVD, Other
Garber, 2002[53] US	RCT	20 weeks (Planned duration)			Yes		Any liver disease, Any kidney disease, Treatment experienced, HbA1c <7% or >11%, No type 2 diabetes, Other
Gomez-Perez, 2002[74] Mexico	RCT	26 weeks (Planned duration)			Yes		Age <40 or >80, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, No type 2 diabetes, Other
Charpentier, 2001[59] France	RCT	20 weeks (Planned duration)			Yes		Age <= 34 or >= 71, Any kidney disease, History of CVD, No type 2 diabetes, Other

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Madsbad, 2001[97] Denmark, Scandinavia	RCT	12 months (Planned duration)			Yes		Age <=39 or >=76, Any liver disease, Any kidney disease, HbA1c <6.5 or >10%, No type 2 diabetes, Other
Amador-Licona, 2000[54] Mexico	RCT	12 weeks (Planned duration)			No		Age >65, Any liver disease, History of CVD, Other
Einhorn, 2000[75] US	RCT	16 weeks (Planned duration)			Yes		Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, HbA1c <8.0, No type 2 diabetes, Other
Fonseca, 2000[76] US	RCT	26 weeks (Planned duration)			No		Age <40 or >80, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, Neuropathy, No type 2 diabetes, Other
Horton, 2000[65] US	RCT	24 weeks (Planned duration)			Yes		Age <30, Any kidney disease, HbA1c <6.8% or >11%, No type 2 diabetes, Other
Landgraf, 1999[98] Germany, Austria, and Netherlands	RCT	14 weeks (Planned duration)			Yes		Any liver disease, Any kidney disease, History of CVD, Treatment experienced, No type 2 diabetes, Other
Marbury, 1999[100] US, Canada	RCT	12 months (Planned duration)			Yes		Age >37 or <75, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, Retinopathy, HbA1c <6.5% or 14.6%, No type 2 diabetes, Other

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Wolffenbuttel, 1999[99] Germany, Austria, Netherlands	RCT	12 months (Planned duration)			No		Age <40 or >75, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, HbA1c <6.5 if treated w/diet only, >12% if treated with diet plus oral, Other
DeFronzo, 1995[58] US	RCT	29 weeks (Planned duration)			No		Age <40 or >70, Any liver disease, Any kidney disease, History of CVD, Treatment experienced, No type 2 diabetes, Other
Hermann, 1994[56] Sweden	RCT	6 months (Planned duration),			Yes		No type 2 diabetes, Other,
Wolffenbuttel, 1993[101] Netherlands	RCT	12 (4 week titration, 8 week treatment) (Planned duration)			Yes		Any liver disease, Any kidney disease, HbA1c <7.0 or >12.0%, No type 2 diabetes, Other,
Derosa, 2009[36] Italy	RCT	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, 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 or weight: <2.5 or >30, Pregnant, Nursing, Not using adequate contraception, No type 2 DM, h/o ketoacidosis, severe anemia

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Comaschi, 2007[109] Italy	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age: <35, HbA1c >: 11, HbA1c <: 7.5, Had not received SU or Metformin as a monotherapy at a stable dose for at least 3months, Fasting C-peptide <0.33nmol/L
Goldstein, 2007[64] Multi-continent	RCT	Neither year reported 24 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age: <18 , >78, 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 less than 75% compliance during placebo run in period, Patient with A1c <7.5 or >11 % after diet/exercise run in/wash-out period, patients with Fasting glucose > 280mg/dl after run-in period, no type 2 diabetes, type 1 diabetes
Agarwal, 2005[151] US	RCT	Start year: 2001 - End year: 2003 16 Weeks	No run-in period	< 6 months	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 or weight: >40, class III or IV heart failure, NSAID use

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Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jones, 2003[147] US	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/N: NR	Age: <40 or >80, 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 or >300, prior rosi study, use on any investigational drug within 30d
Tosi, 2003[28] Italy	RCT, cross-over	6 months (Planned duration)			Yes		Any liver disease, Any kidney disease, History of CVD, Treatment experienced, HbA1c <6.3, No type 2 diabetes, Other

ALT= Alanine aminotransferase; AST= Asparate aminotransferase; BMI=Body mass index; BP=Blood pressure; CAD= Coronary artery disease; CHF=Congestive heart failure; CVD= CVD= Cardio Vascular Diseases; DBP= Diastolic blood pressure; DKA= Diabetic Ketoacidosis; DM= Diabetes mellitus; FPG= Fasting plasma glucose; FBG=Fasting blood glucose; GFR= Glomerular filtration rate; HbA1c= Hemoglobin A1c; HONK= Hyper Osmolar Non Ketotic; HTN=Hypertension; ICD=International classification disease; MHS=Military health system; mg/d= milligrams per day; mg/dl= milligrams/deciliter; mmHg= millimeters of mercury; mmol/L= millimoles per liter; mmol=millimoles; NA=Not applicable; NR=Not reported; OAD=Oral antidiabetic; OAM= Oral antihyperglycemic medications; PPAR-G= Peroxisome proliferator-activated receptors-gamma; PPG= Postprandial glucose; RCT=Randomized controlled trial; SGOT= glutamyl oxaloacetic transaminase; SGPT= Serum glutamyl pyruvic transaminase; SU=Sulfonylurea; TZD= thiazolidinedione; U/kg=Unit per kilogram; y=years

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Raskin, 2009[110]	Metformin+Repaglinide, 187	54.8	108	AA: 30 , Asian: 8 , C: 140 , American Indian and Alaska native: 1 , : 8	32.9	8.45	7.4	62
	Metformin+Repaglinide, 187	54.5	110	AA: 25 , Asian: 9 , C: 149 , American Indian: 1 , other: 3	32.5	8.29	7.3	58
	Metformin+Rosiglitazone, 187	55.5 (28 to 83)	95	AA: 25 , Asian: 4 , C: 148 , American Indians: 2 , Others: 8	32.2	8.46	7.1	58
Derosa, 2009[36]	Metformin, 67	55 (50 to 60)	34	C: (100)	27.2 77.7 kg	9.1	NR	7
	Metformin+Glimepiride, 66	57.7 (51.7-64.7)	32	C: (100)	27.1 77.4 kg+_5.8	9	NR	6
	Metformin+Pioglitazone, 69	57 (50 to 64)	34	C: (100)	27.4 76.4+_5.1	9.3	NR	9
	Pioglitazone, 69	54 (48 to 60)	32	C: (100)	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[116]	Metformin+Glimepiride, 39	56.4	39 (100)	NR	29.3	7	3	2
	Pioglitazone+Glimepiride, 39	56.8	39 (100)	NR	28.2	7.1	4	5
Kaku, 2009[70]	Metformin, 86	53	49	NR	25.4	7.55	5.6	7
	Metformin+Pioglitazone, 83	52	55	NR	25.6	7.58	4.5	9
Williams-Herman, 2009[63]	Metformin, 182	54.2	62 (45)	NR	32 sd 7	8.5	4.1	46
	Metformin, 182	53.7	58 (48)	NR	32	8.7	4.1	56
	Metformin+Sitagliptin, 182	53.6	65 (41)	NR	32	8.7	4.6	41
	Metformin+Sitagliptin, 190	53.7	78 (53)	NR	32	8.8	4.1	42
	Sitagliptin, 179	53.5	55 (52)	NR	31	8.7	3.9	57

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Nauck, 2009[78]	Metformin, 122	56 years	(60)	AA: (3), Asian: (7), C: (88), other: (3)	31.6	8.4	8 years	48
	Metformin+Glimepiride, 244	57	(57)	AA: (2), Asian: (9), C: (89), other: (1)	31.2	8.4	8	34
Asche, 2008[162]	Any in the Sulfonylurea class, 2117	NR	NR	NR	NR NR	NR	NR	not applicable--retrospective cohort
	Metformin, 2138	NR	NR	NR	NR NR	NR	NR	not applicable--retrospective cohort
	Thiazolidinedione, 702	NR	NR	NR	NR NR	NR	NR	not applicable--retrospective cohort
McAlister, 2008[168]	Any in the Sulfonylurea class, 4162	66.59	2420 (58.1)	NR	NR NR	NR	NR	0
	Metformin, 1469	63.37	790 (53.8)	NR	NR NR	NR	NR	0
Kahn, 2008[170]	Glyburide, 1441		836 (58)	NR	NR NR	NR	NR	0
	Metformin, 1454		864 (59.4)	NR	NR NR		NR	0
	Rosiglitazone, 1456	NR	811 (56)	NR	NR NR	NR	NR	0

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Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Scott, 2008[71]	Metformin, 92	55.3	54 (59)	Asian: 36 (39), C: 56 (61)	30 84.6 kg	7.7	5.4	9
	Metformin+Rosiglitazone, 87	54.8	55 (63)	Asian: 33 (38), C: 51 (59), others: 3 (3)	30.4 84.9 kg	7.7	4.6	2
	Metformin+Sitagliptin, 94	55.2	52 (55)	Asian: 36 (38), C: 57 (61), others: 1 (1)	30.3 83.1	7.8	4.9	9
Raz, 2008[79]	Metformin, 94	56.1 (36 to 77)	39	AA: 1 (1), C: 44 (47), H: 24 (25), multiracial: 23 (25), not specified: 2 (2)	30.4 81.2 kgs	9.1	7.3	16
	Metformin+Sitagliptin, 96	53.6 (29 to 73)	49	AA: 3 (3), C: 40 (42), H: 31 (32), multiracial: 21 (22), not specified: 1 (1)	30.1 81.5 kg	9.3	8.4	18
Seufert, 2008[117]	Metformin+Sulfonylurea, 320	60	175 (54.7)	NR	30	8.8	7.1	58
	Pioglitazone+Sulfonylurea, 319	60	171 (53.6)	NR	30.2	8.81	7	38
Robbins, 2007[120]	Metformin+Glargine, 159	58.1	78 (49.4)	AA: 9 (5.7), Asian: 23 (14.6), C: 100 (63.3), H: 26 (16.4)	32 88.1kg	7.8	12.5	22
	Metformin+Insulin lispro 50/50, 158	57.4	79 (50.3)	AA: 9 (5.7), Asian: 22 (14), C: 102 (65), H: 24 (15.3)	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[103]	Metformin+Rosiglitazone, 294	58.5	155 (53)	C: 277 (94)	33 91.4kg	8	6.3	61
	Metformin+Sulfonylurea, 302	59.3	158 (52)	C: 286 (95)	32.2 88.9kg	8	6.4	71

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Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Chien, 2007[47]	Glyburide, 25	63	9 (53)	NR	25.3 63.7 kg	8.69	8.6 years	6
	Metformin, 25	59	7 (41)	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin+Glyburide, 26	60	15 (71)	NR	24.2 63.8 kg	8.71	9	5
	Metformin+Glyburide, 26	57	13 (62)	NR	24.2 61.3 kg	8.85	6.6 years	5
Schwarz, 2008[125]	Metformin+Glyburide, 40	70.4	18 (50)	AA: 4 (11.1), C: 28 (77.8), Other: 4 (11)	33.5	7.7	2.5	18
	Metformin+Nateglinide, 35	70.1	17 (51.5)	AA: 3 (9.1), C: 26 (78.8), Other: 4 (12.1)	30.4	7.8	1.7	14
Comaschi, 2007[109]	Metformin+Pioglitazone, 103	57	47 (45.63)	NR	32.2 85.8	8.4	NR	27
	Metformin+Sulfonylurea, 80	59.9	44 (55)	NR	29.9 81.9	8.6	NR	13
	Pioglitazone+Sulfonylurea, 67	62.2	38 (56.72)	NR	28.9 78.8	8.7	NR	14

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Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2007[64]	Metformin, 182	53.4	89 (48.9)	AA: 12 (6.6), Asian: 14 (7.7), C: 87 (47.8), H: 55 (30.2), not specified: 14 (7.7)	32.1	8.9	4.5	29
	Metformin, 182	53.2	82 (45.1)	AA: 9 (4.9), Asian: 10 (5.5), C: 106 (58.2), H: 39 (21.4), not specified: 18 (9.9)	32.2	8.7	4.4NR	182
	Metformin+Sitagliptin, 182	53.3	77 (42.3)	AA: 14 (7.7), Asian: 11 (6), C: 95 (52.2), H: 49 (26.9), not specified: 13 (7.1)	32.4	8.7	4.4	18
	Metformin+Sitagliptin, 190	54.1	105 (55.3)	AA: 13 (6.8), Asian: 9 (4.7), C: 102 (53.7), H: 55 (28.9), not specified: 11 (5.8)	32.1	8.8NR	4.5	26
	Sitagliptin, 179	53.3	93 (52)	AA: 11 (6.1), Asian: 6 (3.4), C: 93 (52), H: 52 (29.1), not specified: 17 (9.5)	31.2	8.9	4.4	37

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Lund, 2007[160]	Metformin, 48	59.45	37 (77)	C: (100)	24.71 74.81 kg	7.34	(median: 3 years)	5 while on metformin prior to second crossover; 2 during washout period; and 5 while on repaglinide after crossover
	Repaglinide, 48	63.31	36 (75)	C: (100)	24.82 75.57 kg	7.57	(median: 5 years)	2 excluded on repaglinide prior to first crossover; 1 during washout, and 5 after first crossover while on metformin
Nauck, 2007[113]	Metformin+Glipizide, 584	56.6	358 (61.3)	AA: 35 (6), Asian: 49 (8.4), C: 434 (74.3), H: 46 (7.9), other: 20 (3.4)	31.3 89.7	7.6	6.2	172
	Metformin+Sitagliptin, 588	56.8 (47.5 - 66.1)	336 (57.1)	AA: 41 (7), Asian: 50 (8.5), C: 432 (73.5), H: 43 (7.3), other: 22 (3.7)		7.7	6.5	202
Raskin, 2007[121]	Metformin+Aspart 70/30, 79	52	41	AA: (13), Asian: (3), C: (52), H: (32), Other: (1)	31.2 88.7kg	9.9	NR	12
	Metformin+Glargine, 78	51.7	42	AA: (15), Asian: (4), C: (47), H: (32), other: (1)	30.8 86.2kg	9.9	NR	6

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Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Hanefeld, 2007[84]	Glibenclamide, 203	60.1 (+/- 8.3)	143	AA: 0 (0), C: 201 , other: 1	28.7	8.2	6.4	13
	Rosiglitazone, 189	60.6 (+/- 9.2)	109	AA: 0 , C: 183 , other: 6	28.8	8.2	6	9
	Rosiglitazone, 195	60.4 (+/- 8.2)	133	AA: 0 (0), C: 192 , other: 3	28.7	8.1	5.9	12
Scott, 2007[94]	Glipizide, 123	54.7 (21 to 76)	70 (56.9)	AA: 4 (3.3), Asian: 6 (4.9), C: 75 (61), other: 30 (24.4), Multiracial: 8 (6.5)	30.6	7.9	4.7	23
	Sitagliptin, 123	56.2 (34 to 75)	59 (48)	AA: 6 (4.9), Asian: 6 (4.9), C: 78 (63.4), multiracial: 7 (5.7), other: 26 (21.1)	30.5	7.9	4.9	7
	Sitagliptin, 123	55.6 (34 to 76)	71 (57.7)	AA: 11 (8.9), Asian: 6 (4.9), C: 75 (61), Multiracial: 8 (6.5), Other: 23 (18.7)	31.4	7.9	5	15
	Sitagliptin, 124	55.1 (28 to 75)	65 (52.4)	AA: 6 (4.8), Asian: 3 (2.4), C: 86 (69.4), Multiracial: 9 (7.3), Other: 20 (16.1)	30.4	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 to 76)	62 (49.6)	AA: 8 (6.4), Asian: 7 (5.6), C: 86 (68.8), multiracial: 8 (6.4), other: 16 (12.8)	30.8	7.9	4.3	18
Kahn, 2006[30]	Glyburide, 1441	56.4 (+/- 10.2)	836 (58)	AA: 61 (4.2), Asian: 32 (2.2), C: 1282 (89), H: 61 (4.2), Other: 5 (0.3)	32.2 92	7.35	(<1 year: 637, 02-Jan: 751, >2: 53)	634
	Metformin, 1454	57.9 (+/- 9.9)	864 (59.4)	AA: 54 (3.7), Asian: 35 (2.4), C: 1295 (89.1), H: 55 (3.8), Other: 15 (1)	32.1 91.6	7.36	(< 1 year: 673, 02-Jan: 724, >2: 57)	551
	Rosiglitazone, 1456	56.3 (+/- 10.0)	811 (55.7)	AA: 61 (4.2), Asian: 39 (2.7), C: 1270 (87.2), H: 76 (5.2), other: 10 (0.7)	32.2 91.5	7.36	(<1: 651, 02-Jan: 758, >2: 47)	539

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Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Charbonnel, 2006[80]	Metformin, 237	54.7 (+/- 9.7)	141 (59.5)	AA: 14 (5.9), Asian: 26 (11), C: 159 (67.1), H: 28 (11.8), other: 10 (4.2)	31.5	(<8: 128, >= 8 -8.9: 71, >=9: 36)	6.6	45
	Metformin+Sitagliptin, 464	54.4 (+/- 10.4)	259 (55.8)	AA: 31 (6.7), Asian: 49 (10.6), C: 293 (63.1), H: 72 (15.5)	30.9	(<8: 253, >=8 -8.9: 146, >=9: 64)	6	48
Wright, 2006[161]	Any in the Sulfonylurea class, 1687	NR	NR	NR	NR	NR	NR	NR
	Metformin, 336	NR	NR	NR	NR	NR	NR	NR
	Total, 5063	52.4	2985 (59)	AA: 387 (8), Asian: 496 (9), C: 4180 (83)	27.5	6.9	NR	NR
Rosenstock, 2006[39]	Metformin, 154	51.5 (+/- 10.4)	87 (56)	AA: 8 (5), Asian: 22 (14), C: 90 (58), H: 33 (21), other: 1 (<1)	32.5	8.8	2.9	31
	Metformin+Rosiglitazone, 155	50.1 (+/- 10.7)	89 (57)	AA: 10 (6), Asian: 19 (12), C: 83 (54), H: 41 (26)	33.2	8.9	2.3	19
	Rosiglitazone, 159	50.6 (+/- 10.26)	93 (58)	AA: 8 (5), Asian: 22 (14), C: 94 (59), H: 31 (19), Other: 4 (3)	32.8	8.8	2.7	22
Jain, 2006[85]	Glyburide, 251	52.1 (+/- 12.39)	141 (56.2)	AA: 34 (13.5), Asian: 0 (0), C: 165 (65.7), H: 50 (19.9), Native American: 1 (0.4), Other: 1 (0.4)	32.8 94.3kg	9.2	0.78 (9.4 months)	123
	Pioglitazone, 251	52.1 (+/- 11.28)	133 (53)	AA: 40 (15.9), Asian: 4 (1.6), C: 153 (61), H: 52 (20.7), 0ther: 1 (0.4), Native American: 1 (0.4)	32.5 93.9kg	9.2	0.8 (9.6 months)	117

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Stewart, 2006[129]	Metformin, 272	59 (+/- 7.9)	151 (56)	AA: 1 (<1), Asian: 1 (<1), C: 268 (99), H: 1 (<1), Native Hawaiian/other Pacific Islander: 1 (<1)	30.6 87.2	7.2 (Range: 5.4-10.7)	3.7	54
	Metformin+Rosiglitazone, 254	58.8 (+/- 8.4)	139 (55)	AA: 0 (0), Asian: 3 (1), C: 250 (98), H: 1 (<1), Native Hawaiian /other pacific islander: 0 (0)	30.9 88.1	7.2 (Range: 5.8-9.4)	3.7	50
Bakris, 2006[105]	Metformin+Glyburide, 185	58.8	124 (69)	C: 137 (76)	31.8 90.3	8.3	7.6	5
	Metformin+Rosiglitazone, 204	60	122 (63)	C: 151 (78)	31.6 89.2	8.5	8	10
Rosak, 2006[150]	Metformin+Rosiglitazone, 7705	60	3594 (50.2)		29.3 87.2	8.1	3.9	545
	Rosiglitazone, 1559	62,0	(47.7)		28.7 83.8	8.1 (median)	4.5	542
	Rosiglitazone+Sulfonylurea, 5511	65	2423 (48.2)	NR	81.3kg	8.3	5.3	478
Hanefeld, 2006[163]	Metformin+Glibenclamide, 250	61	138 (55)	NR	32 91.8kg	8.6	4.6	138
	Metformin+Pioglitazone, 250	61	135 (54)	NR	32 90.2kg	8.5	4.8	55
Umpierrez, 2006[106]	Metformin+Glimepiride, 96	51.6	53 (55.2)	NR	34.54	8.4	4.9	11
	Metformin+Pioglitazone, 109	55.7	56 (52.3)	AA: 17 (15.9), Asian: 4 (3.7), C: 84 (78.5), H: 2 (1.9), OTHER: 0 (0)	33.81	8.31	5.9	17

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Kvapil, 2006[119]	Metformin+Aspart 70/30, 116	56.4 (+/- 9.0)	53	NR	30.4 +/- 4.0 85.1kg +/- 15.1	9.3 +/- 1.3	6.7 +/- 5.7	11
	Metformin+Glibenclamide, 114	58.1 (+/- 8.8)	52	NR	30.5 +/- 4.4 84.0 +/- 13.4	9.4 +/-1.4	8.1 +/- 6.2	5
Gerich, 2005[112]	Metformin+Glyburide, 209	53.5 (+/- 11.6)	95 (48)	AA: 33 (16.7), Asian: 1 (0.5), C: 129 (65.2), other: 35 (17.7)	33.5 +/- 5.6	8.3 +/- 1.1	2.0+/- 4.3	87
	Metformin+Nateglinide, 219	52.6 (+/- 11.6)	106 (51)	AA: 27 (13), Asian: 5 (2.4), C: 134 (64.4), other: 42 (20.2)	33.3 +/- 6.0	8.4 +/- 1.2	1.5 +/- 2.9	78
Karter, 2005[167]	Any in the Sulfonylurea class, 5921	59.9	3244 (54.8)	NR	NR NR	8.9	NR	0
	Metformin, 11937	59.9	6266 (52.5)	NR	NR NR	9.6	NR	0
	Pioglitazone, 3556	60.2	1821 (51.1)	NR	NR NR	9.6	NR	0
Agarwal, 2005[151]	Glipizide, 22	64 (17)	22 (100)	AA: 6 (27), C: 16 (73)	34 102	7.7	14	3
	Pioglitazone, 22	67 (17)	22 (100)	AA: 3 (14), C: 19 (86)	32 97	7.7	16	1
Derosa, 2005[107]	Metformin+Glimepiride, 49	52 (+/-5)	23	NR	26.8+/-1.5	7.9+/-0.6	4+/-3	2
	Metformin+Rosiglitazone, 50	54 (+/-4)	25	NR	26.6 +/- 1.3	8.0 +/- 0.7	5 +/-3	2

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Malone, 2004[137]	Metformin+Glargine,	NR	NR	NR	NR	NR	NR	7
	Metformin+Lispro 75/25,	NR	NR	NR	NR	NR	NR	3 during this arm
	pooled arms,	NR	66 (63)	NR	30.9 91.5kg	8.7	9	NR
Rajagopalan, 2005[166]	Any in the Sulfonylurea class, 1474	54.5	(52.9)	NR	NR NR	NR	NR	NR
	Metformin, 1137	52.5	(49.6)	NR	NR NR	NR	NR	NR
	Pioglitazone, 1137	52.7	(50)	NR	NR NR	NR	NR	NR
	Pioglitazone, 1474	54.6	(54.3)	NR	NR NR	NR	NR	0
	Pioglitazone, 1847	54.3	(52.4)	NR	NR	NR	NR	0
	Rosiglitazone, 1847	54.3	(51.8)	NR	NR	NR	NR	0
Hussein, 2004[164]	Pioglitazone, 107	64.4 (36 to 86)	51	NR	84.3	9.5	17	0
	Rosiglitazone, 96	64.6 (41 to 82)	53	NR	82.3	9.6	14.5	0
Horton, 2004[66]	Metformin, 104	55.4	70 (67.3)	NR	29.9	8.3	3.7	NR
	Metformin+Nateglinide, 89	57.7	58 (65.2)		30.6	8.2	3.4	NR
	Nateglinideglinide, 104	(57.9)	59 (56.7)	NR	29.9	8.1	4.7	NR

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Malone, 2003[118]	Metformin+Glibenclamide, 301	59 (+/-9.3)	146 (49)	AA: 3 (1), C: 268 (89), H: 18 (6), other: 12 (4)	29.6 +/- 4.5 81.7 +/- 15.7 kg	9.27 +/- 1.55	7.4 +/- 5.4	29
	Metformin+Lispro 75/25, 296	58 (+/-8.8)	169 (57)	AA: 2 (0.7), C: 263 (88.9), H: 22 (7.4), other: 9 (3)	29.8 +/- 4.4 83.0+/- 15.2	9.17 +/- 1.50	8.0 +/-5.8	25
Yang, 2003[114]	Metformin+Sulfonylurea,	NR	NR	NR	NR NR	8.59	NR	NR
	Rosiglitazone+Sulfonylurea,	NR	NR	NR	NR NR	8.61	NR	NR
Jones, 2003[147]	Metformin, 121	58 (38 to 78)	85 (70)	NR	34	8.7	5	0
	Metformin, 22	64 (46 to 81)	13 (9)	NR	23	8.6	6.5	NR
	Metformin, 82	60 (40 to 81)	61 (74)	NR	28	8.8	6	NR
	Metformin+Rosiglitazone, 141	58 (36 to 82)	97 (69)	NR	28	8.8	6	NR
	Metformin+Rosiglitazone, 142	57 (39 to 80)	93 (57)	NR	34	8.8	5	NR
	Metformin+Rosiglitazone, 35	62 (42 to 78)	25 (71)	NR	23	9.3	8	NR
Marre, 2002[81]	Metformin, 152	56.4	84 (55.3)	AA: 5 (3.3), Asian: 4 (2.6), C: 138 (30/8)	29.6	8.25	6.5	16
	Metformin+Nateglinide, 155	57.9	95 (61.3)	AA: 7 (4.5), Asian: 5 (3.2), C: 140 (90.3)	29.4	7.99	7.2	18
	Metformin+Nateglinide, 160	57.3	98 (61.3)	AA: 6 (3.8), Asian: 5 (3.1), C: 146 (91.3)	29.3	8.18	6.8	15

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Moses, 1999[68]	Metformin, 27	57.8	17	Asian: 2 , C: 23 , not specified: 2	31.8	8.6	8	0
	Metformin+Repaglinide, 27	57.2	18	C: 26 , 1: not specified	33.2	8.3	5.9	0
	Repaglinide, 28	60.3	15	Asian: 2 , C: 26	31.3	8.6	7	0
Jibran, 2006[95]	Glibenclamide, 50	45.8	10	NR	30.4 72.7 kg	10.2	0	0
	Repaglinide, 50	46.6	16	NR	27.1 65.8 kg	9.9	0	0
Leiter, 2005[69]	Metformin, 78	60	44	C: 61 , Others: 17	32.2	7.5	5.7	13
	Metformin+Rosiglitazone, 158	58	103	C: 120 , Others: 38	33	7.5	5.3	18
Garber, 2006[108]	Diet + Metformin + glibenclamide, 160	56 (31-78)	90	AA: 8 (5), C: 128 (80), Asian: 4 (3), H: 17 (11), O: 3 (2)	32 93	8.5	5	
	Diet + Metformin + Rosiglitazone, 158	56 (24-78)	102	AA: 9 (6), C: 125 (79), Asian: 4 (3), H: 16 (10), O: 4 (3)	32 94	8.4	6	
Weissman, 2005[72]	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
	Metformin, 351	55.7	NR	NR	33.8 96.7kg	7.97	NR	76

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bailey, 2005[73]	Metformin, 280	57.6	159 (57)	AA: 1 (<1), Asian: 3 (1), C: 273 (98), Other: 3 (1)	32.1 89.5kg	7.5	6.1	44
	Metformin+Rosiglitazone, 289	58.1	168 (58)	AA: 2 (1), C: 280 (97), Asian: 3 (1), H: 0, O: 3 (1)	32.2 90.9kg	7.4	6	30
	Metformin + Rosiglitazone, 288	58.1	168 (58)	AA: 2 (1), Asian: 3 (1), C: 280 (97), other: 3 (1)	32.2 90.9kg	7.4	6	30
Yamanouchi, 2005[40]	Diet + exercise + glimepiride, 37	55.6 (46.3 - 64.9)	19	AA: 0, C: 0, Asian: 0, H: 0, O: (100)NR	25.6 NR	9.8	3.3 months	3
	Diet + exercise + Metformin, 39	54.7 (44.9 - 64.5)	20	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)	18	AA: 0, C: 0, Asian: 0, H: 0, O: (100)	25.8 NR	10.2	3.2 months	2
	Glimepiride, 37	55.6	19	NR	25.6 NR	9.8	3.3	3
	Metformin, 39	54.7	20	NR	26.2 NR	9.9	3	2
	Pioglitazone, 38	55.2	18	NR	25.8 NR	10.2	3.2	3
Derosa, 2005[133]	Diet + exercise + behavioral therapy + Metformin + glimepiride, 47	52 (47 -57)	23	NR	26.8 NR	7.9	4	
	Diet + exercise + behavioral therapy + Metformin + Rosiglitazone, 48	54 (50 -58)	25	NR	26.6 NR	8	5	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Rajagopalan, 2005[157]	Metformin, 1137	52.5 (19-88)	(0.496)	NR	NR NR	NR	NR	
	Pioglitazone, 1847	54.3 (18-91)	(0.524)	NR	NR NR	NR	NR	
	Unspecified Sulfonylurea, 1474	54.5 (19-94)	(0.529)	NR	NR NR	NR	NR	
	Pioglitazone, 1137	52.7 (18-90)	(0.5)	NR	NR NR	NR	NR	
	Pioglitazone, 1474	54.6 (18-91)	(0.543)	NR	NR NR	NR	NR	
	Rosiglitazone, 1847	54.3 (18-92)	(0.518)	NR	NR NR	NR	NR	
Feinglos, 2005[77]	Metformin + glipizide, 61	57.7 (30-80)	28	AA: 5 (8.2), C: 48 (78.7), Asian: 2 (3.3), H: 5 (8.2), O: 1 (1.6)	31.7 90	7.45	6.5	
	Placebo + Metformin, 61	58.8 (40-81)	25	AA: 10 (16.4), C: 42 (68.9), Asian: 2 (3.3), H: 5 (8.2), O: 2 (3.3)	32.1 90.8	7.64	4.6	
Maru, 2005[158]	Unspecified Sulfonylurea, 11350	64	5953 (52.5)	NR	(BMI>=30, n=2422) NR	NR	NR	
	Metformin, 4579	59	2206 (48.2)	NR	(BMI>=30, n=2197) NR	NR	NR	
	No diabetes medications, 21245	63	11516 (54.2)	NR	(BMI>=30, n=5702) NR	NR	NR	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Schernthaner, 2004[42]	Metformin, 597	56 (35 to 75)	345	NR	31.4 89.7kg	8.7	3.1	96
	Pioglitazone, 597	57 (35 to 75)	314	NR	31.2 88.2kg	8.7	3.4	98
	Placebo + diet + Metformin, 597	56	345 (57.8)	NR	31.4 89.7kg	8.7	3.1	
	Placebo + diet + Pioglitazone, 597	57	314 (52.6)	NR	31.2 88.2kg	8.7	3.4	
Nichols, 2005[159]	Unspecified Sulfonylurea, 1085	62	(0.559)	NR	NR NR	8	4	
	Metformin + unspecified Sulfonylurea, 1834	61.1	(0.524)	NR	NR NR	8.3	5.8	
	Metformin, 272	60	(0.511)	NR	NR NR	7.8	4.3	
Derosa, 2004[48]	Placebo + diet + exercise + glimepiride, 81	56	38	NR	27.6 NR	8.5	NR	
	Placebo + diet + exercise + Metformin, 83	58	42	NR	28.1 NR	8.4	NR	
Tan, 2004[90]	Glibenclamide, 109	57.9	80 (73)	AA: 0, C: 109 (100), Asian: 0, H: 0, O: 0	29.6 89kg	8.5	5.22	41
	Pioglitazone, 91	60	56 (62)	C: 90 (99), Unspecified: 1 (1)	30.2 88.4kg	8.4	4.76	36
Raskin, 2004[92]	Repaglinide, 63	58.5	39	AA: 10 , C: 40 , H: 1 , Unspecified: 12	30.4	9.3	7.2	25
	Rosiglitazone, 62	56.6	33	AA: 8 , C: 42 , H: 0 , Unspecified: 12	31.4	9	7.4	25

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Jovanovic, 2004[93]	Pioglitazone, 62	56.2	31 (50)	AA: 7 (11), C: 51 (82), H: 2 (3), other: 2 (3)	32.1	9.1	6.1	36
	Pioglitazone+Repaglinide, 123	58.9 (+/- 10.7)	84 (68.3)	AA: 18 (15), C: 101 (82), H: 1 (1), others: 3 (2.4)	32.3	9.3	7.1	18
	Repaglinide, 61	57.8 (+/- 13.1)	36 (58)	AA: 7 (11), C: 46 (75), H: 3 (4.9), other: 5 (8.1)	31.2	9	6.9	25
Hanefeld, 2004[115]	Metformin+Sulfonylurea, 320	60 (36 to 75)	175 (54.7)	AA: 3 (0.9), C: 315 (98.4), other: 2 (0.6)	30 84.9	8.8	7.1	279
	Pioglitazone+Sulfonylurea, 319	60 (36 to 75)	171 (53,6)	AA: 2 (0.6), C: 317 (99.4), other: 0 (0)	30.2 85.3	8.82	60	259
	Placebo + Metformin + unspecified Sulfonylurea, 320	60 (36 to 75)	175 (54.7)	AA: 3 (0.9), C: 315 (98.4), Asian: 0, H: 0, O: 2 (0.6)	30 84.9	8.8	7.1	
	Placebo + unspecified Sulfonylurea + Pioglitazone, 31	60 (36 to 75)	171 (53.6)	AA: 2 (0.6), C: 317 (99.4), Asian: 0, H: 0, O: 0 (0)	30.2 85.3	8.82	7	
Garber, 2003[49]	Metformin + glyburide, 171	55.6	76 (44)	AA: 18 (10.5), C: 132 (77.2), Asian: 0, H: 15 (8.8), O: 6 (3.5)	31.4 91.9	8.8	3	
	Metformin, 164	54.7	71 (43.3)	AA: 11 (6.7), C: 132 (80.5), Asian: 0, H: 15 (9.1), O: 6 (3.7)	31.4 92.8	8.5	2.6	
	Glyburide, 151	55.3	66 (43.7)	AA: 11 (7.3), C: 123 (81.5), Asian: 0, H: 12 (7.9), O: 5 (3.3)	31.1 91	8.7	3	
Tosi, 2003[28]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2003[50]	Metformin + glipizide, 87	54.6	(0.586)	AA: (11.5), C: (72.4), Asian: (0), H: (16.1), O: 0	31.7 94	8.7	5.9	
	Glipizide, 84	57.4	(0.643)	AA: (11.9), C: (71.4), Asian: (2.4), H: (14.3), O: 0	30.6 89.9	8.9	6.5	
	Metformin, 76	56.6	(0.618)	AA: (15.8), C: (65.8), Asian: (1.3), H: (17.1), O: 0	31.6 93.8	8.7	7.3	
Derosa, 2003[67]	Diet + exercise + Metformin, 56	52	27	NR	24.7 72.3	7.4	5	
	Diet + exercise + Repaglinide, 56	55	29	NR	25.2 70.2	7.6	4	
Pavo, 2003[44]	Metformin, 100	55.8 (+/- 8.4)	56 (56)	NR	31.1 88.9	8.6	6.3	9
	Pioglitazone, 105	54.2 (+/- 9.1)	59 (56.2)		31.3 86.6	8.6	5.6	5
	Placebo + Pioglitazone, 105	54.2	(0.438)	NR	31.3 86.6	8.6	0.47	
	Placebo + Metformin, 100	55.8	(0.56)	NR	31.1 88.9	8.6	0.53	
Vakkilainen, 2002[102]	Placebo + glibenclamide, 20	63	NR	AA: 0, C: (100), Asian: 0, H: 0, O: 0	28.8 NR	7.6	NR	
	Placebo + Nateglinideglinide, 23	63	NR	AA: 0, C: (100), Asian: 0, H: 0, O: 0	27.8 NR	7.6	NR	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Blonde, 2002[51]	Metformin + glyburide, 162	55.6	103 (63.6)	AA: 15 (9.3), C: 110 (67.9), Asian: 0, H: 31 (19.1), O: 6 (3.7)	30.6 89.6	9.42	6.97	
	Glyburide, 164	55.8	94 (57.3)	AA: 20 (12.2), C: 109 (66.5), Asian: 0, H: 28 (17.1), O: 7 (4.3)	30.3 88	9.64	7.01	
	Metformin + glyburide, 160	55.4	89 (55.6)	AA: 20 (12.5), C: 112 (70), Asian: 0, H: 25 (15.6), O: 3 (1.9)	30.7 89.4	9.41	7.36	
	Metformin, 153	57.6	95 (62.1)	AA: 16 (10.5), C: 105 (69.3), Asian: 0, H: 26 (17), O: 5 (3.3)	30.6 89.5	9.51	8.18	
St John Sutton, 2002[123]	Glyburide, 99	56.1	71	AA: (3), C: (76), others: (21)	85.1	9.5	6.2	
	Rosiglitazone, 104	55.1	75	AA: (5), C: (73), others: (22)	82.6	9.1	5.3	
Marre, 2002[52]	Glibenclamide, 103	58.7	57	NR	29.3 82.5	7.88	6.6	
	Metformin, 104	57.5	62	NR	29.9 84.9	8.09	5.4	
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7	7.89	5.9	
	Metformin + glibenclamide, 103	60.7	56	NR	29.7 83.1	7.62	6.7	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Garber, 2002[53]	Metformin + glyburide, 165	58.1	96	AA: 10, C: 131, Asian: 0, H: 16, O: 8	29.6 86.7	8.18	3.3	
	Glyburide, 161	56.5	82	AA: 15, C: 126, Asian: 0, H: 14, O: 6	30.3 87.2	8.21	2.81	
	Metformin + glyburide, 158	56.9	91	AA: 20, C: 117, Asian: 0, H: 18, O: 3	30.1 88.8	8.25	3.52	
	Metformin, 161	56	93	AA: 7, C: 130, Asian: 0, H: 20, O: 4	30.4 88.6	8.26	2.98	
Gomez-Perez, 2002[74]	Metformin, 34	53.4 (7.5) (40 - 68)	10 (29.4)	C: 1 (2.9), H: 26 (76.5), Mestizo: 7 (20.6)	28.5 (3.9)		9.1 (5.6) yrs	
	Metformin+Rosiglitazone, 35	51.7 (8.6) (40 - 73)	10 (28.6)	C: 0 (0), H: 28 (80), Mestizo: 7 (20)	28.0 (4.0)		11.1 (7.1) yrs	
	Metformin+Rosiglitazone, 36	54.2 (9.3) (42-76)	19.40	C: 4 (11.1), H: 26 (72.2), Mestizo: 6 (16.7)	27.6 (3.2)		10.7 (7.0) years	
Charpentier, 2001[59]	Glimepiride, 980	57.9	576 (59)	NR	30 NR	8.9	3.7	
	Metformin + glimepiride, 147	56.8 (36-70)	87 (59)	NR	29.5 81.2	6.4	5.6	
	Placebo + glimepiride, 150	55.4 (35-70)	87 (58)	NR	29.3 81	6.5	5.3	
	Placebo + Metformin, 75	56.7 (36-69)	45 (60)	NR	29.2 82.2	6.8	7	
Madsbad, 2001[97]	Repaglinide, 175	60.2	107	NR	28 82.9	7.3	8.1	
	Placebo + glipizide, 81	62	52	NR	28 83.6	7.2	7	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Amador-Licona, 2000[54]	Metformin, 28	49.3	11	NR	26.8 70.7	8.5	4.5	
	Glibenclamide, 23	48.2	7	NR	30.4 73.2	8.4	4	
Einhorn, 2000[75]	Diet + Metformin + Pioglitazone, 168	55.5	92 (54.8)	AA: 14 (8.3), C: 136 (81), Asian: 0, H: 17 (10.1), O: 1 (0.6)	32.11 NR	9.86	NR	
	Metformin, 160	55.7 sd 10.34 years	96 (60)	AA: 10 (6.3), C: 139 (86.9), H: 6 (3.8), Others: 5 (3.1)	32.12 sd 5.5	9.75 sd 1.3		37
	Metformin+Pioglitazone, 168	55.5 sd 10.34 years	92 (54.8)	AA: 14 (8.3), C: 136 (81), H: 17 (10.1), Others: 1 (0.6)	32.11 sd 5.3	9.86 sd 1.4		21
	Placebo + diet + Metformin, 160	55.7	96 (60)	AA: 10 (6.3), C: 139 (86.9), Asian: 0, H: 6 (3.8), O: 5 (3.1)	32.12 NR	9.75	NR	
Fonseca, 2000[76]	Metformin, 116	58.8 y sd 9.2	74.30	AA: (3.5), C: (81.4), other: (15)	30.3 sd 4.4	8.6 sd 1.3	7.3 sd 5.7 years	22
	Metformin+Rosiglitazone, 113	58.3 sd 8.8 years	68.20	AA: (10), C: (77.3), others: (12.7)	29.8 sd 3.9	8.9 sd 1.5	8.3 sd 6.3	18
	Metformin+Rosiglitazone, 119	57.5 sd 10.5 years	62.10	AA: (6.9), C: (80.2), others: (12.9)	30.2 sd 4.2	8.9 sd 1.3	7.5 sd 6.3 years	18
	Metformin + Rosiglitazone , 110	58.3	68.2	AA: (10), C: (77.3), Asian: 0, H: 0, O: (12.7)	29.8 NR	8.9	8.3	
	Metformin + Rosiglitazone , 116	57.5	62.1	AA: (6.9), C: (80.2), Asian: 0, H: 0, O: (12.9)	30.2 NR	8.9	7.5	
	Placebo + Metformin, 113	58.8	74.3	AA: (3.5), C: (81.4), Asian: 0, H: 0, O: (15)	30.3 NR	8.6	7.3	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Horton, 2000[65]	Metformin, 178	56.8	121	AA: (9.6), C: (79.2), Asian: (2.2), H: 0, O: (9)	29.6 NR	8.4	7.5	
	Nateglinideglinide, 179	58.6	110	AA: (9.5), C: (82.1), Asian: (2.8), H: 0, O: (5.6)	29.6 NR	8.3	4.7	
Landgraf, 1999[98]	Repaglinide, 94	61	56	AA: 0, C: 90, Asian: 0, H: 0, O: 4	27.6 80	7.8	10	
	Placebo + glibenclamide, 100	63	57	AA: 6, C: 93, Asian: 0, H: 0, O: 1	27.5 79	8	10	
Marbury, 1999[100]	Placebo + glyburide, 182	58.7	120 (66)	AA: 16 (9), C: 144 (79), Asian: 0, H: 0, O: 22 (12)	29.1 NR	8.9	8.3	
	Repaglinide, 362	58.3	242 (67)	AA: 33 (9), C: 279 (77), Asian: 0, H: 0, O: 50 (14)	29.4 NR	8.7	7.2	
Wolffenbuttel, 1999[99]	Placebo + glyburide, 139	61	(0.68)	NR	28 81.3	7	median 6	
	Repaglinide, 286	61	(0.62)	NR	28.4 81.5	7.1	median 6	
DeFronzo, 1995[58]	Metformin, 143	53	62	NR	29.9 94.4	8.4	6	
	Metformin + glyburide, 213	55	98	NR	29 92.1	8.8	7.8	
	Placebo + glyburide, 209	56	103	NR	29.1 92.6	8.5	8.7	
	Placebo + Metformin, 210	55	96	NR	29.4 92.6	8.9	8.4	

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events

Author, year	Group, N	Mean age (age range),	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Hermann, 1994[56]	Diet + Metformin + glibenclamide, 54	NR	NR	NR	NR 80.2	6.8	NR	
	Diet + Metformin, 25	NR	NR	NR	NR 78.6	6.9	NR	
	Diet + Metformin + glibenclamide, 13	NR	NR	NR	NR 84.6	7.8	NR	
	Diet + Metformin + glibenclamide, 13	NR	NR	NR	NR 76	7.8	NR	
	Diet + Metformin + glibenclamide, 18	NR	NR	NR	NR 83.2	8.4	NR	
	Diet + glibenclamide, 21	NR	NR	NR	NR 82.6	6.7	NR	
Wolffenbuttel, 1993[101]	Glibenclamide, 15	62 (45-75)	25	NR	26.1 70.9	Range 7.0-12.0	9	
	Repaglinide, 29	62 (45-75)	25	NR	26.1 74	Range 7.0-12.0	9	

AA=African American; C=Caucasian; H=Hispanic; kg=kilogram; NR=Not reported; sd=Standard deviation

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin vs Thiazolidinediones								
Karter, 2005[167]	Cohort	GP1: Metformin NR GP2: Pioglitazone NR			Def: ICD-9-CM codes for primary discharge diagnosis (HR relative to sulfonylurea use) Collection: Passive Timing/Frequency: Unspecified ITT: NR GP1: HR: 0.7, CI: 0.49 - 0.99, p: 0.05 GP2: HR: 1.28, CI: 0.85 - 1.92, p: 0.2			
Asche, 2008[162]	Cohort	GP1: Metformin NR GP2: Thiazolidinediones NR			Def: NR Collection: NR Timing/Frequency: Unspecified ITT: NR GP1: NR GP2: 18 (2.6%)		Def: Nausea & Vomiting; Diarrhea; Dyspepsia Collection: NR Timing/frequency: NR ITT: NR GP1: 1.3%; 1.6%; 2.8% GP2: NR	Def: Lactic acidosis Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 6 (0.3) GP2: NR
Kawai, 2008[175]	Non-randomized	GP1: Metformin NR Start: 500-750mg, Max: 750mg GP2: Pioglitazone Fixed NR	Def: mild, moderate and severe Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 0 GP2: 0					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rosenstock, 2006[39]	RCT	GP1: Metformin Varied, mean daily glucose <= 6.1 mmol/l Start: 500mg, Max: 2000mg, Mean: 1847 D: 32 wks GP2: Rosiglitazone Varied, mean daily glucose <= 6.1 mmol/l Start: 4mg, Max: 8mg, Mean: 7.7 D: 32 wks	Def: mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 14 GP2: 13				Def: Diarrhoea, nausea, vomiting, dyspepsia Collection: Active Timing/frequency: Specified ITT: Yes GP1: 51% GP2: 35%	
Kahn, 2006[30]	RCT	GP1: Metformin Varied, glucose: <140mg Start: 500mg, Max: 2000mg GP2: Rosiglitazone Varied, glucose: <140mg Start: 4mg, Max: 8mg	Def: Self reported Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: All: 168 (11.6), Severe: 1 (0.1) GP2: All: 142 (9.8), Severe: 1 (0.1)		Def: investigator reported GP1: 19 (1.3) GP2: 22 (1.5)		Def: nausea, vomiting, diarrhea, abdominal discomfort Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 38.3% GP2: 23%	
Yamanouchi, 2005[40]	RCT	GP1: Metformin Fixed Start: 750mg GP2: Pioglitazone Fixed Start: 30mg women, 45mg men	Def: NR GP1: 0 GP2: 0					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Pavo, 2003[44]	RCT	GP1: Metformin Varied, glucose: < 126mg/dl Start: 850, Max: 2550, Mean: 2292mg D: 8 wks GP2: Pioglitazone Varied, glucose: < 126mg/dl Start: 35mg, Max: 45mg, Mean: 41.5 D: 8 wks					Def: Diarrhea GP1: 16% GP2: 3%	Def: Cholecystitis Collection: Active Timing/frequency: Unspecified ITT: NR GP1: 0 GP2: 1
Schernthaner, 2004[42]	RCT	GP1: Metformin Varied Start: 850, Max: 2550 GP2: Pioglitazone Varied Start: 35mg, Max: 45mg					Def: Diarrhea; Nausea GP1: 11.1%; 4.2% GP2: 3.2%; 2.3%	
Leiter 2005[69]	RCT	GP1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks GP2: Rosiglitazone Varied, glucose: <7.0 mmol/L Start: 4 mg, Max: 8 mg D: 8 wks			GP1: 0 GP2: 3			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rajagopalan, 2005[166]	Cohort	GP1: Metformin NR GP2: Pioglitazone NR		Def: Visit with ICD9 code liver failure or hepatitis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 0.8% incidence GP2: 0.5% incidence HR: 1.139 (95% CI: 0.439 - 2.96)				
Rajagopalan, 2005[166]	Cohort	GP1: Metformin NR GP2: Rosiglitazone NR		Def: visit with ICD9 code 'liver failure' or 'hepatitis' Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 0.8% incidence GP2: 0.4% incidence				

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2008[170]	RCT	GP1: Metformin Varied, glucose: < 140 Start dose: 500g, Max: 2g GP2: Rosiglitazone Varied, glucose: < 140 Start dose: 4mg, Max: 8mg				Def: Fractures (NS) Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 1.2 per 100 patient-years GP2: 1.86 per 100 patient-years HR GP2 vs GP1: 1.57 (95% CI: 1.13 - 2.17), p: 0.0073		
Metformin vs Sulfonylurea								
Asche, 2008[162]	Cohort	GP1: Metformin NR GP2: Any drug in the sulfonylurea class NR					Def: Nausea/vomiting; Diarrhea; Dyspepsia Collection: NR Timing/frequency: No ITT: NR GP1: 1.3%; 1.6%; 2.8% GP2: NR	Def: Lactic acidosis Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 6 (0.3) GP2: NR

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
McAlister, 2008[168]	Cohort	GP1: Metformin NR Median: 726 mg daily GP2: Any sulfonylurea Varied Median: 4 mg for glyburide, 198 mg for chlorpropamide, 425 mg for tolbutamide			Def: Primary, secondary or most responsible diagnosis of HF using ICD-9 codes Collection: Passive ITT: NR GP1: 3.3 cases/100yrs GP2: 4.4 cases/100 yrs, adjusted HR relative to GP1: 1.16 (0.96-1.41)			
Karter, 2005[167]	Cohort	GP1: Metformin NR GP2: Any sulfonylurea NR			Def: ICD-9-CM codes for primary discharge diagnosis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: HR relative to GP2: 0.7 (0.49-0.99), p: 0.05 GP2: NA			
Chien, 2007[47]	RCT	GP1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean: 1910 mg/day D: 4 wks GP2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg/day, Max: 20 mg/day, Final mean: 19 mg/day D: 4 wks	Def: mild or moderate Collection: Passive Timing/frequency: Unspecified ITT: Yes GP1: 0 GP2: 0				Def: diarrhea, dry mouth, increased appetite, GI disease Collection: Passive Timing/frequency: Unspecified ITT: Yes GP1: 32% GP2: 13%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2006[30]	RCT	GP1: Metformin Varied, glucose: <140mg Start: 500mg, Max: 2000mg GP2: Glyburide Varied, glucose: <140mg Start: 2.5mg, Max: 15mg	Def: self reported events Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: All: 168 (11.6), Severe: 1 (0.1) GP2: All: 557 (38.7), Severe: 8 (0.6)		Def: Investigator reported events Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: All: 19 (1.3), Serious: 12 (0.8) GP2: All: 9 (0.6), Serious: 3 (0.2)		Def: nausea, vomiting, diarrhea, abdominal discomfort Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 38.3% GP2: 21.9%	
Wright, 2006[161]	RCT	GP1: Metformin Varied, glucose: <6 mmol/L Max: 2550mg/day GP2: Sulfonylurea Varied, glucose: <6 mmol/L Max: glipizide 40 mg/day, chlorpropramide 500 mg/day, glibenclamide 20 mg/day	Def: mean annual % Collection: Active Timing/frequency: Specified ITT: NR GP1: Substantive hypo: 0.3, CI: 0.1-1.1; Any: 1.7, CI: 1-3 GP2: Substantive hypo: 1.2, CI: 0.4-3.4; Any: 7.9, CI: 5.1-11.9					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Yamanouchi, 2005[40]	RCT	GP1: Metformin Fixed 750mg GP2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 after 1 month in 8 cases. Rest on 1 mg	GP1: Severe: 0; Mild/moderate: 0 GP2: Severe: 0; Mild/moderate: 1 (2.7)					
Derosa, 2004[48]	RCT	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Glimepiride Varied Start: 1mg, Max: 4mg	GP1: 0 GP2: 0				Def: Nausea + diarrhea GP1: 2 (2.4) GP2: NR	
Garber, 2003[49]	RCT	GP1: Metformin Varied Start: 500 mg (adjusted to patient response), Max: 2000 mg GP2: Glyburide Varied Start: 2.5 (adjusted to patient response), Max: 10 mg	Def: Mild or moderate GP1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) GP2: Symptomatic: 98 (57.6), Fingerstick: 16 (10.6)				Def: Abdominal pain; Nausea & Vomiting; Diarrhea GP1: 6.1%; 10.4%; 18.3% GP2: 4%; 6.6%; 5.3%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Blonde, 2002[51]	RCT	GP1: Metformin Varied Start: 500 mg, Max: 2000 mg GP2: Glyburide Fixed Start: 10mg	Def: Mild or moderate, Fsg<=60mg/dl + symptomatic GP1: 1 (<1) GP2: 3 (1.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence GP1: (4.6); (12.4); (2) GP2: (3); (5.5); (0)	
Marre, 2002[52]	RCT	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Glibenclamide Varied Start: 5mg, Max: 20mg	Def: Symptoms or labs GP1: Serious: 1 (1.0), Mild or moderate: 0 GP2: Serious: 1 (1.0), Mild or moderate: 7					
Garber, 2002[53]	RCT	GP1: Metformin Varied Start: 500 mg (increase by 1 tablet at weeks 4, 6, 8 if patients meet criteria), Max: 2000mg GP2: Glyburide Varied Start: 2.5 mg (increase by 1 tablet at weeks 4, 6, 8 if patients meet criteria), Max: 10mg	Def: Mild or moderate GP1: 0 GP2: 10				Def: Nausea + vomiting + diarrhea + dyspepsia GP1: IR: 43 GP2: IR: 24	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Charpentier, 2001[59]	RCT	GP1: Metformin Fixed Start: 850mg tid GP2: 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 GP1: Serious: 0, Mild or moderate: 8 GP2: Serious: 3, Mild or moderate: 17				Def: Diarrhea GP1: 7% GP2: 1%	
DeFronzo, 1995[58]	RCT	GP1: Metformin Varied Start: 500mg, Max: 2500mg GP2: Glyburide Varied Start: 10 mg /day in two divided doses, Max: 20mg per day in 2 divided doses	Def: Mild or moderate GP1: 4 (2) GP2: 6 (3)				Def: Nausea + diarrhea GP1: (1.4) GP2: (1)	
Hermann, 1994[56]	RCT	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Glyburide Varied Start: 3.5mg, Max: 10.5mg	Def: Serious GP1: 8 (21) GP2: 12 (35)				Def: Nausea + diarrhea + dyspepsia and digestive GP1: (63) GP2: (32)	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Maru, 2005[158]	Cohort	GP1: Metformin NR GP2: Sulfonylurea NR			Def: CHF/clinical diagnosis + validated a small sample via questionnaires to GP to confirm the diagnosis + oxmis and read codes similar to ICD-9 codes GP1: IR: 18.8/1000 person-years GP2: IR: 26.6/1000 person-years			
Nichols, 2005[159]	Cohort	GP1: Metformin NR GP2: Sulfonylurea NR			Def: Medical record for CHF + ICD-9 code for CHF + clinical diagnosis + first record GP1: IR: 10.5 (6.7-16.2) GP2: IR: 13.8 (11.4-16.6)			
Rajagopalan, 2005[166]	Cohort	GP1: Metformin NR GP2: Any drug in SU class NR		Def: visit with ICD9 code liver failure or hepatitis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 0.8% incidence GP2: 1% incidence				

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2008[170]	RCT	GP1: Metformin Varied, glucose: < 140 Start dose: 500g, Max: 2g GP2: Glyburide Varied, glucose: < 140 Start dose: 2.5mg, Max: 15mg				Def: Fractures (NS) Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: Incidence: 1.2/100 patient yrs GP2: Incidence: 1.15/100 patient yrs		
Chien, 2007[47]	RCT	GP1: Metformin Varied, glucose: <140 mg/dL Start dose: 1000 mg/day, Max: 2000 mg/day, Mean: 1910 mg/day D: 4 wks GP2: Glyburide Varied, glucose: <140 mg/dL Start dose: 10 mg/day, Max: 20 mg/day, Mean: 19 mg/day D: 4 wks				Def: Right metacarpal bone fracture Collection: passive Timing/frequency: Unspecified ITT: Yes GP1: 0 GP2: 1		

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Amador-Licona, 2000[54]	RCT	GP1: Metformin 850 mg (dose was adjusted to reach adequate metabolic control for 3 weeks) GP2: Glibenclamide 5 mg (dose was adjusted to reach adequate metabolic control for 3 weeks)					Def: Diarrhea + Diffuse abdominal pain GP1: 4 (14.3) GP2: NR	
Goldstein, 2003[50]	RCT	GP1: Metformin Varied Start: 500 mg (tirated to patient glucose response), Max: 2000 mg GP2: Glipizide Varied Start: 30 mg (tirated to patient glucose response), Max: 30 mg					Def: Diarrhea GP1: 17.3% GP2: 13.1%	
Metformin vs DPP-IV Inhibitors								
Williams-Herman, 2009[63]	RCT	GP1: Metformin Fixed Mean: 1000mg or 2000mg GP2: Sitagliptin Fixed Mean: 100mg	Def: Collection: Active Timing/frequency: Unspecified ITT: No GP1: 2 (1) GP2: 2 (1)				Def: Nausea; Diarrhea; Abd pain; Vomiting; Nausea/Vomiting Collection: NR Timing/frequency: Unspecified ITT: No GP1: 3%; 7%; 4%; 0%; 20% for 1000mg and 10%; 12%; 6%; 3%; 31% for 2000mg GP2: 1%; 4%; 5%; 1%; 20%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Goldstein, 2007[64]	RCT	GP1: Metformin Varied, prespecified target Start: 500mg, Max: 2000mg GP2: Sitagliptin Varied, prespecified target Start: 50mg, Max: 100mg	GP1: 3 GP2: 1					
Metformin vs Meglitinides								
Lund, 2007[160]	RCT	GP1: Metformin Varied, prespecified target Start: 500 mg/day, Max: 2000 mg/day, Mean: 1629 mg D: 12 dys GP2: Repaglinide Varied, prespecified target Start: 1 mg/day, Max: 6 mg/day, Mean: 4.72 mg D: 12 dys	Collection: Active Timing/frequency: Specified ITT: Yes GP1: Serious: 1, Mild or moderate: 22 GP2: Serious: 1, Mild or moderate: 45				Def: NR Collection: Active Timing/frequency: Specified ITT: Yes GP1: 65.7% GP2: 42.7%	
Horton, 2004[66]		GP1: Metformin Fixed Start: 500mg GP2: Nateglinide Fixed Start: 120 qac	Def: mild/moderate, plasma glucose <2.8mmol/l Collection: Active Timing/frequency: Specified ITT: Yes GP1: 1 GP2: 2				Def: Diarrhea Collection: Active Timing/frequency: Specified ITT: Yes GP1: 20.2% GP2: 3.8%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Moses, 1999[68]	RCT	GP1: Metformin NR GP2: Repaglinide Fixed Start: 0.5 mg, Max: 4.0 mg D: 12-28 dys	Def: mild or moderate Collection: Passive Timing/frequency: Unspecified ITT: No GP1: 1 GP2: 3					
Derosa, 2003[67]	RCT	GP1: Metformin Varied Start: 500 mg bid (1500-2500 during 8 week titration period then fixed), Max: 2500 mg/day GP2: Repaglinide Varied Start: 0.5 mg bid (2-4 mg per day during 8 week titration period then fixed), Max: 4 tid	Def: mild or moderate GP1: 0 GP2: 0				Def: Nausea + diarrhea (withdrawn due to) GP1: 3.6% GP2: 0%	
Horton, 2000[65]	RCT	GP1: Metformin Fixed Start: 500mg GP2: Nateglinide Fixed Start: 120 mg tid	Def: mild or moderate GP1: 19 GP2: 22				Def: Nausea + diarrhea (withdrawn due to) GP1: 3.4% GP2: 0.6%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin vs Metformin + Thiazolidinedione								
Kawai, 2008[175]	Non-randomized	GP1: Metformin NR Start: 500-750 mg/day, Max: 750mg GP2: Metformin + Pioglitazone NR; Fixed Start: 500-750 mg/day, Max: 750mg; NR	Def: Mild, moderate and severe Collection: NR Timing/frequency: Unspecified ITT: No GP1: 0 GP2: 0					
Kaku, 2009[70]	RCT	GP1: Metformin Varied Start: 500mg, Max: 750mg GP2: Metformin + Pioglitazone Varied Start: 500mg, Max: 750mg; Start: 15mg, Max: 30mg D: NR; 16 wks	Def: Mild or moderate GP1: 0 GP2: 1				Def: abd pain and constipation GP1: 2.3% GP2: 2.4%	
Scott, 2008[71]	RCT	GP1: Metformin Fixed Start: >1500mg D: 10 wks GP2: Metformin + Rosiglitazone Fixed Start: >1500mg; Start: 8mg, Mean: 8mg D: 10 wks	Def: mild or moderate Collection: NR Timing/frequency: Unspecified GP1: 2 GP2: 1				Def: diarrhea, nausea, abdominal pain, vomiting Collection: NR Timing/frequency: Unspecified ITT: No GP1: 9% GP2: 7%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rosenstock, 2006[39]	RCT	GP1: Metformin Varied, mean daily glucose <= 6.1 mmol/l Start: 500mg, Max: 2000mg, Mean: 1847 D: 32 wks GP2: Metformin + Rosiglitazone Varied, mean daily glucose <= 6.1 mmol/l Start: 500mg, Max: 2000mg, Mean: 1799; Start: 2mg, Max: 8mg, Mean: 7.2mg D: 32 wks	Def: self reported mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 14 GP2: 19				Def: Diarrhoea, nausea, vomiting Dyspepsia Collection: Active Timing/frequency: Specified ITT: Yes GP1: 51% GP2: 47%	
Stewart, 2006[129]	RCT	GP1: Metformin Varied, prespecified Start: 500, Max: 3000, Mean: 2627.9 D: 20 wks GP2: Metformin + Rosiglitazone Varied, prespecified Start: 500, Max: 2000, Mean: 1812.2; Start: 4, Max: 8, Mean: 6.8 D: 18 wks; 16 wks	Def: Mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 10 (4) GP2: 17 (7)				Def: Diarrhea GP1: 18% GP2: 8%	
Jones, 2003[147]	RCT	GP1: Metformin Fixed Max: 2.5g GP2: Metformin + Rosiglitazone Fixed; Varied, prespecified target Max: 2.5g; Max: 8mg	Def: Symptomatic hypoglycemia GP1: All: (0.4), Obese: (1.7) GP2: All: (2.1), Obese: (1.9)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Weissman, 2005[72]	RCT	GP1: Metformin Varied Start: 500mg bid, Max: 1000mg bid GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 12mg	Def: Mild or moderate GP1: 4 (1) GP2: 4 (1)				Def: Withdrawn due to GI GP1: 6.8% GP2: 3.1%	
Bailey, 2005[73]	RCT	GP1: Metformin Varied Start: 2500mg, Max: 3000mg D: 24 wks GP2: Metformin + Rosiglitazone Fixed; Varied Start: 2000mg; Start: 4mg, Max: 8mg D: 24 wks	GP1: Serious: 0, Mild or moderate: 1 GP2: Serious: 0, Mild or moderate: 3				Def: diarrhea and abdominal pain GP1: 5.4% GP2: 3.2%	Def: acute cholecystitis, serious cholelithiasis and cholestatic jaundice Collection: Active Timing/frequency: Specified ITT: Yes GP1: 1 GP2: 0
Fonseca, 2000[76]	RCT	GP1: Metformin Fixed Start: 2500mg GP2: Metformin + Rosiglitazone Fixed Start: 2500mg; Start: 4-8mg/day	Def: mild or moderate GP1: 2 GP2: 5					
Einhorn, 2000[75]	RCT	GP1: Metformin NR GP2: Metformin + Pioglitazone NR; Fixed NR; 30mg	GP1: 1 (0.6) GP2: 1 (0.6)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Gomez-Perez, 2002[74]	RCT	GP1: Metformin Fixed Start: 2.5g/day GP2: Metformin+Rosiglitazone Fixed Start: 2.5g/day; Start: 2-4mg bid					Def: Nausea + vomiting + diarrhea + flatulence and abdominal pain GP1: 15.4% GP2: 16.8%	
Metformin vs Metformin + Sulfonylurea								
Nauck, 2009[78]	RCT	GP1: Metformin Varied Start: 2000mg, Max: 2000mg GP2: Metformin + Glimepiride Varied; Fixed Start: 2000mg, Max: 2000mg; Start: 1mg, Max: 4mg D: NR; 3 wks	Def: Serious Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 0 GP2: 0				Def: nausea, vomiting, and diarrhea Collection: NR Timing/frequency: NR ITT: NR GP1: 17% GP2: 17%	Def: acute pancreatitis Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 0 GP2: 1

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Feinglos, 2005[77]	RCT	GP1: Metformin Fixed Start: > or = 1000/day mg GP2: Metformin + Glipizide Fixed Start: > or = 1000/day mg; 2.5mg	Def: Finger stick glucose <60 mg/dl w/ symptoms or finger stick glucose <50 mg/dl w/o symptoms or fpg<55 mg/dl w/o symptoms GP1: Serious: 0, Mild or moderate: 2 (3.3) GP2: Serious: 0, Mild or moderate: 9 (14.8)					
Garber, 2003[49]	RCT	GP1: Metformin Varied Start: 500 mg (adjusted to patient response), Max: 2000 mg GP2: Metformin + Glyburide Varied Start: 250 mg (adjusted to patient response), Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Def: Mild or moderate GP1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) GP2: Symptomatic: 59 (39.1), Fingerstick: 19 (11.2)				Def: Abd pain; nausea + vomiting; Diarrhea GP1: 6.1%; 10.4%; 18.3% GP2: 4.1%; 4.7%; 7.6%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Tosi, 2003[28]	RCT	GP1: Metformin Varied Start: 500 mg, Max: 3000mg GP2: Metformin + Glibenclamide Varied Start: 502 mg, Max: 2000; Start: 2.5 mg, Max: 10mg	GP1: Severe: 2 (10.5), Mild or moderate: 1 (5) GP2: NR				Def: Diarrhea + constipation + discomfort and abdominal pain and anorexia GP1: 10.5% GP2: 2.6%	
Blonde, 2002[51]	RCT	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + Glyburide Varied Start: 500mg, Max: 2000mg; Start: 5 mg, Max: 20mg	Def: Fsg<=60mg/dl + symptomatic GP1: Mild or moderate: 1 (<1) GP2: Mild or moderate: 22 (6.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence GP1: 4.6%; 12.4%; 2% GP2: 3.7%; 6.8%; 2.5%	
Blonde, 2002[51]	RCT	GP1: Metformin Varied Start: 500mg, Max: 2000mg GP2: Metformin + Glyburide Varied Start: 500mg, Max: 2000mg; Start: 2.5 mg, Max: 10mg	Def: Fsg<=60mg/dl + symptomatic total GP1: Mild or moderate: 1 (<1) GP2: Mild or moderate: 22 (6.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence GP1: 4.6%; 12.4%; 2% GP2: 5%; 10%; 6.3%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Marre, 2002[52]	RCT	GP1: Metformin Varied Start: 500 mg, Max: 2000mg GP2: Metformin + Glibenclamide Varied Start: 500 mg, Max: 2000mg; Start: 2.5 mg, Max: 10mg	Def: Symptoms or labs GP1: Serious: 1 (1.0), Mild or moderate: 0 GP2: Serious: 0, Mild or moderate: 11(10.9)				Def: Not specified GP1: 14.4% GP2: 6.9%	
Marre, 2002[52]	RCT	GP1: Metformin Varied Start: 500 mg, Max: 2000mg GP2: Metformin + Glibenclamide Varied Start: 501 mg, Max: 2000; Start: 2.5 mg, Max:10	Def: Symptoms or labs GP1: Serious: 1 (1.0), Mild or moderate: 0 GP2: Serious: 2 (1.9), Mild or moderate: 12					
Garber, 2002[53]	RCT	GP1: Metformin Varied Start: 500 mg (increase by 1 tablet at weeks 4, 6, 8 if patients meet some criteria), Max: 2000mg GP2: Metformin + glyburide Varied Start: 250mg; Start: 1.25 mg (increase by 1 tablet at weeks 4, 6, 8 if patients meet some criteria)	Def: Mild or moderate GP1: NR GP2: 18 (11.4)				Def: Nausea + vomiting + diarrhea + dyspepsia GP1: IR - 43 GP2: IR - 32	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Garber, 2002[53]	RCT	GP1: Metformin Varied Start: 500 mg (increase by 1 tablet at weeks 4, 6, 8 if patients meet some criteria), Max: 2000mg GP2: Metformin + glyburide Varied Start: 500mg; Start: 2.5mg (increase by 1 tablet at weeks 4, 6, 8 if patients meet some criteria)	Def: Mild or moderate GP1: NR GP2: 61 (37.7)				Def: Nausea + vomiting + diarrhea + dyspepsia GP1: IR - 43 GP2: IR - 38	
Charpentier,2001[59]	RCT	GP1: Metformin Fixed Start: 850 mg tid GP2: Metformin + Glimepiride Fixed Start: 850 mg tid; Start: 1 mg (either fixed or increased stepwise to 2, 4, 6 mg od depending on clinical symptoms of hypoglycemia)	Def: Clinical symptoms GP1: Serious: 0 (0), Mild or moderate: 8 (11) GP2: Serious: 2 (1.4), Mild or moderate: 30				Def: diarrhea GP1: 7% GP2: 3%	
DeFronzo, 1995[58]	RCT	GP1: Metformin Varied Start: 500 mg, Max: 2500mg GP2: Metformin + glyburide Varied Start: 500 mg, Max: 2500; Start: 10 mg, Max: 20mg	Def: Mild or moderate GP1: 4 (2) GP2: 38 (18)				Def: Nausea + diarrhea GP1: 1.4% GP2: 0.9%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hermann, 1994[56]	RCT	GP1: Metformin Varied Start: 1000mg, Max: 3000mg GP2: Metformin + Glyburide Varied Start: 500mg, Max: 3000mg; Start: 1.75mg, Max: 14mg	Def: Mild or moderate GP1: 8 (21) GP2: 24 (33)					
Chien, 2007[47]	RCT	GP1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean dose: 1910 mg/day D: 4 wks GP2: Metformin + Glyburide Varied, glucose: <140 mg/dL Start: 1000 mg/day, Max: 2000 mg/day, Final mean dose: 1680 mg/day; Start: 5 mg/day, Max: 10 mg/day, Final mean dose: 8.4 mg/day D: 4 wks	Def: Collection: Passive Timing/frequency: Unspecified ITT: Yes GP1: 0 GP2: 4			Def: Right metacarpal bone fracture Collection: passive Timing/frequency: Unspecified ITT: Yes GP1: 0 GP2: 0	Def: diarrhea, dry mouth, increased apetite, GI disease Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 32% GP2: 7.7%; 26.9%	
Nichols, 2005[159]	Cohort	GP1: Metformin NR GP2: Metformin+unspecified sulfonylurea NR			Def: Medical record for CHF + ICD-9 code for CHF + clinical diagnosis + first record GP1: IR: 10.5 (6.7-16.2) GP2: IR: 13.4 (11.6-15.5)			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Goldstein, 2003[50]	RCT	GP1: Metformin Varied Start: 500 mg (tirated to patient glucose response), Max: 2000 mg GP2: Metformin + glipizide Varied Start: 500, Max: 2000 mg; Start: 5 mg, Max: 20mg (tirated to patient glucose response)					Def: Diarrhea GP1: 17.3% GP2: 18.4%	
Metformin vs Metformin + DPP-IV inhibitors								
Williams-Herman, 2009[63]	RCT	GP1: Metformin Fixed Mean: 1000mg bid GP2: Metformin + Sitagliptin Fixed Mean: 500mg bid; Mean: 50mg bid	Def: Mild or moderate Collection: Active Timing/frequency: Unspecified ITT: No GP1: 2 (1) GP2: 4 (2)				Def: Nausea; vomiting; diarrhea; abdominal pain; Nausea/Vomiting Collection: NR Timing/frequency: Unspecified ITT: No GP1: 3%; 0%; 7%; 4%; 31% GP2: 5%; 2%; 9%; 3%; 26%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Williams-Herman, 2009[63]	RCT	GP1: Metformin Fixed Mean: 1000mg bid GP2: Metformin + Sitagliptin Fixed Mean: 1000mg bid; Mean: 50mg bid	Def: Mild or moderate Collection: Active Timing/frequency: Unspecified ITT: No GP1: 2 (1) GP2: 5 (3)				Def: Nausea; vomiting; diarrhea; abdominal pain; Nausea/Vomiting Collection: NR Timing/frequency: Unspecified ITT: No GP1: 3%; 0%; 7%; 4%; 31% GP2: NR; 4%; 13%; 4%; 29%	
Scott, 2008[71]	RCT	GP1: Metformin Fixed Start: >= 1500 mg/day GP2: Metformin + Sitagliptin Fixed Start: >= 1500 mg/day; Start: 100mg/day	Def: Mild or moderate Collection: NR Timing/frequency: Unspecified ITT: No GP1: 2 (2) GP2: 1 (1)				Def: diarrhea, nausea, abdominal pain, vomiting Collection: NR Timing/frequency: Unspecified ITT: No GP1: 9% GP2: 1%	
Raz, 2008[79]	RCT	GP1: Metformin Fixed Start: >= 1500 mg/day GP2: Metformin + Sitagliptin Fixed Start: >= 1500 mg/day; Start: 100mg/day	Def: Mild or moderate Collection: NR Timing/frequency: Unspecified ITT: No GP1: 0 GP2: 1 (1)			Def: Limb fracture Collection: NR Timing/frequency: Unspecified ITT: No GP1: 1 GP2: 0	Def: abdominal pain, nausea, vomiting, or diarrhea Collection: NR Timing/frequency: Unspecified ITT: No GP1: 7.4% GP2: 10.4%	Def: Neoplasms Collection: NR Timing/frequency: Unspecified ITT: No GP1: 3 GP2: 0

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Goldstein, 2007[64]	RCT	GP1: Metformin Fixed Start: 500mg or 1000mg bid GP2: Metformin + Sitagliptin Fixed Start: 500mg or 1000mg bid; Start: 50mg bid	Def: Mild or moderate GP1: 3 GP2: 6					
Charbonnel, 2006[80]	RCT	GP1: Metformin Varied, HgbA1c: between 7 and 10 Start: >=1500 mg D: 19 wks GP2: Metformin + Sitagliptin Varied; Fixed Start: >=1500 mg; Mean: 100mg D: 19 wks	Def: Mild or moderate GP1: 5 (2.1) GP2: 6 (1.3)				Def: abdominal pain, nausea, vomiting, or diarrhea Collection: NR Timing/frequency: Unspecified ITT: No GP1: 10.5% GP2: 11.9%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin vs Metformin + Meglitinides								
Horton, 2004[66]	RCT	GP1: Metformin Fixed Start: 500mg tid GP2: Metformin + Nateglinide Fixed Start: 500mg tid; Start: 120mg ac	Def: Mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: Symptomatic: 11 (0.6), Confirmed <= 2.8mmol/l: 1 (1.0) GP2: Symptomatic: 26 (29.2), Confirmed <= 2.8mmol/l: 3 (3.4)				Def: Diarrhea Collection: Active Timing/frequency: Specified ITT: Yes GP1: 20.2% GP2: 16.9%	
Marre, 2002[81]	RCT	GP1: Metformin Fixed Start: 1000mg bid GP2: Metformin + Nateglinide Fixed Start: 1000mg bid; Start: 60mg ac	Def: Mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: Symptomatic: 6 (3.9), Confirmed: 1 (0.7) GP2: Symptomatic: 13 (8.4), Confirmed: 0					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Marre, 2002[81]	RCT	GP1: Metformin Fixed Start: 1000mg bid GP2: Metformin + Nateglinide Fixed Start: 1000mg bid; Start: 120mg ac	Def: Mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: Symptomatic: 6 (3.9), Confirmed: 1 (0.7) GP2: Symptomatic: 25 (15.6), Confirmed: 5 (3.1)					
Moses, 1999[68]	RCT	GP1: Metformin NR GP2: Metformin + Repaglinide NR; Varied, glucose: 4.4-7.8 mmol/l NR; Start: 0.5mg, Max: 4mg	Def: Mild or moderate Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 0 GP2: 9 (33.3)					
Thiazolidinedione vs Thiazolidinedione								
Hussein, 2004[164]	Cohort	GP1: Rosiglitazone Fixed Start: 15-45mg GP2: Pioglitazone Fixed Start: 4-8mg	Def: Mild or moderate Collection: Passive Timing/frequency: Unspecified GP1: 11 (11) GP2: 18 (17) GP1-GP2: p: NSG		Def: Pulmonary edema Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 3 GP2: 2			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rajagopalan, 2005[166]	Cohort	GP1: Rosiglitazone NR GP2: Pioglitazone NR		Def: visit with ICD9 code liver failure or hepatitis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 0.4% incidence GP2: 0.5% incidence				
Thiazolidinedione vs Sulfonylurea								
Jain, 2006[85]	RCT	GP1: Pioglitazone Varied, glucose: FPG (69-141mg/dl) Start: 15mg, Max: 45mg, Median: 45mg GP2: Glyburide Varied, glucose: FPG:69-141mg/dl Start: 5mg, Max: 15, Median: 10	Def: Mild or moderate Collection: Active Timing/frequency: Unspecified ITT: Yes GP1: 11 (4.4) GP2: 61 (24.3)			Def: Ankle Collection: Active Timing/frequency: No ITT: Yes GP1: (0) GP2: (0.8)	Def: diarrhea Collection: active Timing/frequency: Unspecified ITT: Yes GP1: 6% GP2: 6.4%	Def: stage IV colon ca Collection: active Timing/frequency: Unspecified ITT: Yes GP1: 0 GP2: 2 (0.8)
Yamanouchi, 2005[40]	RCT	GP1: Pioglitazone Fixed Start: 30mg for women and 45mg for men GP2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 after 1 month in 8 cases. Rest on 1 mg	GP1: Serious: 0 (0), Mild or moderate: 0 (0) GP2: Serious: 0 (0), Mild or moderate: 1 (2.7)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Tan, 2004[90]	RCT	GP1: Pioglitazone Varied Start: 30 mg, Max: 45mg GP2: Glibenclamide Varied Start: 1.75 mg, Max: 10.5mg	Def: Symptoms or self monitored bg < 50mg/dl GP1: 4 (4) GP2: 32 (29)					
Hanefeld, 2007[84]	RCT	GP1: Rosiglitazone Fixed Start: 4mg GP2: Glibenclamide Varied Start: 2.5, Max: 15	Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 1 (0.5) GP2: Serious: 2, Mild or moderate: 23				Def: Unspecified Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 11 (5.5) GP2: 7 (3.4)	
Hanefeld, 2007[84]	RCT	GP1: Rosiglitazone Fixed Start: 8mg GP2: Glibenclamide Varied Start: 2.5, Max: 15 D: 12 wks	Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 3 (1.6) GP2: Serious: 2, Mild or moderate: 23				Def: Unspecified Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 5 (2.6) GP2: 7 (3.4)	
St John Sutton, 2002[123]	RCT	GP1: Rosiglitazone Fixed Start: 4mg GP2: Glyburide Varied Start: NR (titrated 1st 8 weeks then fixed), Max: 20 mg/day	Def: Signs and symptoms0 (0) withdrawn for GP10 (0) serious for GP10 (0) withdrawn for GP23 (3.0) serious for GP27 (7.1) total for GP2 GP1: Serious: 0 (0) GP2: Serious: 3 (3.0), Mild or moderate: 4		Def: NR GP1: 1 (1.0) GP2: 0 (0)			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Asche, 2008[162]	Cohort	GP1: Thiazolidinedione NR GP2: Any in the Sulfonylurea class NR	Def: Mild or moderate Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 12 (1.7) GP2: 55 (2.6)		Collection: NR Timing/Frequency: Unspecified ITT: NR GP1: 18 (2.6) GP2: NR			
Kahn, 2006[30]	RCT	GP1: Rosiglitazone Varied, glucose: <140mg/dl Start: 4mg, Max: 8mg GP2: Glyburide Varied, glucose: <140mg/dl Start: 2.5, Max: 15	Def: Self reported events Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: Serious events: 1 (0.1), Mild or moderate events: 142 (9.8) GP2: Serious events: 8 (0.6), Mild or moderate events: 557 (38.7)		Def: investigator reported events Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: All: 22 (1.5), Serious: 12 (0.8) GP2: All: 9 (0.6), Serious: 3 (0.2), p relative to GP1: <= 0.05		Def: nausea, vomiting, diarrhea, abdominal discomfort GP1: 23% GP2: 21.9%	
Agarwal, 2005[151]	RCT	GP1: Pioglitazone Varied, glucose: 140, HgbA1c: 8 Start: 15mg D: 16 wks GP2: Glipizide Varied, glucose: 140, HgbA1c: 8 Start: 5mg D: 16 wks	GP1: 2 GP2: 3		GP1: 2 GP2: 2			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Karter, 2005[167]	Cohort	GP1: Pioglitazone NR GP2: Any sulfonylurea NR			Def: ICD-9-CM codes for primary discharge diagnosis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: HR relative to GP2: 1.28 (0.85-1.92), p: 0.2 GP2:			
Rajagopalan, 2005[166]	Cohort	GP1: Rosiglitazone NR GP2: Sulfonylurea NR		Def: visit with ICD9 code liver failure or hepatitis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 0.4% incidence GP2: 1% incidence				
Rajagopalan, 2005[166]	Cohort	GP1: Pioglitazone NR GP2: Sulfonylurea NR		Def: visit with ICD9 code liver failure or hepatitis Collection: Passive Timing/frequency: Unspecified ITT: NR GP1: 0.5% incidence GP2: 1% incidence				

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Thiazolidinedione vs. Meglitinides								
Jovanovic, 2004[93]	RCT	GP1: Pioglitazone Fixed Start: 30mg GP2: Repaglinide Varied Start: 0.5 mg if hba1c<8 or 1 mg if hba1c>8 (titrated up for 12 weeks then fixed for 12 weeks), Max: 4 mg per meal	Def: Severe: needed assistance, Mild or moderate: <50mg/dl GP1: Severe: 0, Mild or moderate: 2 (3) GP2: Severe: 0, Mild or moderate: 5 (8)				Def: Diarrhea GP1: 3% GP2: 5%	
Raskin, 2004[92]	RCT	GP1: Rosiglitazone Varied Start: 2 mg bid (12 week dose titration then 12 week maintenance), Max: 4 mg bid GP2: Repaglinide Varied Start: 0.5 mg per meal if HbA1c<=8 or 1 mg if >8 (12 week dose titration and 12 week maintenance), Max: 4 mg per meal	GP1: Severe: 0, Mild or moderate: 1 (2) GP2: Severe: 0, Mild or moderate: 4 (6)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2008[170]	RCT	GP1: Rosiglitazone Varied, glucose: <140 Start dose: 4mg, Max: 8mg GP2: Glyburide Varied, glucose: <140 Start dose: 2.5mg, Max: 15mg				Def: Fractures (NS) Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 1.86/100 patient years GP2: 1.15/100 patient years HR GP1 vs GP2: 1.61 (1.14-2.28), p: 0.0069		
Sulfonylurea vs DPP-IV inhibitors								
Scott, 2007[94]	RCT	GP1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks GP2: Sitagliptin Fixed Start: 5mg bid to 50mg bid	Def: Mild or moderate GP1: 21 (17.1) GP2: 0-4 (1.6-4.1)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Sulfonylurea vs Meglitinides								
Jibran,2006[95]	RCT	GP1: Glibenclamide Varied, fasting glucose < 130 mg/dl, PP < 175 mg/dl Start: 5 mg, Max: 15 mg GP2: Repaglinide Varied, fasting glucose < 130 mg/dl, PP < 175 mg/dl Start: 0.5 mg TDS, Max: 1.5 mg TDS	Def: Mild, moderate or severe GP1: 0 GP2: 0					
Vakkilainen, 2002[102]	RCT	GP1: Glibenclamide Varied Start: 5mg, Max: 10mg GP2: Nateglinide Fixed Start: 120mg tid	GP1: 3 (12.5) GP2: 0					
Madsbad, 2001[97]	RCT	GP1: Glipizide Varied Start: 5mg, Max: 15mg GP2: Repaglinide Varied Start: 0.5 mg, Max: 4.0 tid	Def: Severe GP1: 0 GP2: 0					
Landgraf, 1999[98]	RCT	GP1: Glibenclamide Varied Start: 1.75, 3.5, 7.0, 10.5 mg, Max: 10.5mg GP2: Repaglinide Varied Start: 0.5, 1.0, 2.0, 4.0 mg, Max: 4.0 tid	Def: Mild or moderate GP1: 9 (9.0) GP2: 9 (9.6)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Marbury, 1999[100]	RCT	GP1: Glyburide Varied Start: 2.5 mg, Max: 15mg GP2: Repaglinide Varied Start: 0.5 mg, Max: 12 mg	GP1: Severe: 2, Mild or moderate: 35 GP2: Severe: 5, Mild or moderate: 54					
Wolffenbuttel, 1999[99]	RCT	GP1: Glyburide Varied Start: 1.75 mg (titration for 6-8 weeks then stabilized dose for 12 months), Max: 10.5mg GP2: Repaglinide Varied Start: 1.5 mg (titration for 6-8 weeks then stabilized dose for 12 months), Max: 12.0 mg	Def: Mild or moderate GP1: 13 GP2: 26					
Wolffenbuttel, 1993[101]	RCT	GP1: Glibenclamide Varied Start: 5mg, Max: 15mg GP2: Repaglinide Varied Start: 0.5 mg, Max: 4 tid	GP1: Severe: 0, Mild or moderate: 1 GP2: Severe: 0, Mild or moderate: 0					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + Thiazolidinedione vs Metformin + Sulfonylurea								
Derosa, 2009[36]	RCT	GP1: Metformin+Pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3mos GP2: Metformin+Glimepiride Fixed; Varied, prespecified target dose Start: 850mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NA; 3mos	Def: Severe GP1: 0 GP2: 1					
Hamann, 2008[103]	RCT	GP1: Metformin+Rosiglitazone Varied, glucose: 6.1mmol/l Max: 2g/day; Start: 4mg/day, Max: 8mg/day D: 12 wks GP2: Metformin+Sulfonylurea Varied, glucose: 6.1mmol/l Max: 2g/day; Start: 5mg/day, Max: 15mg/day D: 12 wks	Def: Mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 18 GP2: 90				Collection: Active Timing/frequency: Specified ITT: Yes GP1: 13% GP2: 18%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Comaschi, 2007[109]	RCT	GP1: Metformin+Pioglitazone Varied Max: 3g/day; Start: 15mg, Max: 30mg D: NR, 22 wks GP2: Metformin+Sulfonylurea Varied, HgbA1c: 7.50% Start: 400mg, Max: 3g/day; Start: 2.5 D: 22 wks	Def: Mildor moderate GP1: 0 GP2: 1					
Bakris, 2006[105]	RCT	GP1: Metformin+Rosiglitazone Varied; Varied, glucose: <= 6.6mmol/L Unclear; Start: 4mg/day D: 3 wks GP2: Metformin+Glyburide Varied; Varied, glucose: <= 6.6mmol/L Unclear; Start: 5mg/day D: 3 wks	Def: mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 2 GP2: 22					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Umpierrez, 2006[106]	RCT	GP1: Metformin+Pioglitazone NR; Varied, glucose: <120, HgbA1c: <8.0 Start: 1.54gday, Max: 1.57gday; Start: 30mg/day, Max: 45mg/day GP2: Metformin+Glimepiride NR; Varied, glucose: <120mg/dL Start: 1.47gday, Max: 1.49gday; Start: 2mg/day, Max: 8mg/day D: NR, 6 wks	Def: mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 10 GP2: 32				Def: Diarrhea Collection: Active Timing/frequency: Specified ITT: Yes GP1: 4.7% GP2: 6%	
Garber, 2006[108]	RCT	GP1: Metformin+Rosiglitazone Varied Start: 1500 or 2000 depending on dose of metformin prior to study mg (esc), Max: 2000; Start: 4 mg, Max: 8 GP2: Metformin+Glibenclamide Varied Start: 1000 mg, Max: 2000; Start: 5 mg , Max: 10	GP1: Severe: 0, Mild or moderate: 2 GP2: Severe: 7, Mild or moderate: 53				Def: Diarrhea + abdominal pain + other GI symptoms GP1: 10%; (Diarrhea 3%; Abd pain 4%) GP2: 11% (Diarrhea 6%; Abd pain 6%)	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hanefeld, 2006[163]	RCT	GP1: Metformin+Pioglitazone Fixed; Varied Mean: 1900mg/day; Start: 30mg/day, Max: 45mg/day GP2: Metformin+Glibenclamide NR; Varied Mean: 1900mg/day; Start: 3.5mg/day, Max: 5mg/day	Def: Severe Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 5 GP2: 34					
Yang, 2003[114]	RCT	GP1: Metformin + Sulfonylurea Fixed GP2: Rosiglitazone + Sulfonylurea Fixed		Def: AST or ALT 3 x ULN Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 0 GP2: 0				
Derosa, 2005[133]	RCT	GP1: Metformin+Rosiglitazone Fixed Start: 1500 mg; Start: 4 mg GP2: Metformin + glimeperide Fixed Start: 1500 mg; Start: 2 mg					Def: Transient flatulence GP1: 4.2% GP2: 2.1%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + Thiazolidinedione vs Metformin + Meglitinides								
Raskin, 2009[110]	RCT	GP1: Metformin+Rosiglitazone Varied, prespecified target dose Start: 1000 mg, Max: 2500 mg; Start: 4mg, Max: 8mg D: 4 wks GP2: Metformin+Repaglinide Varied Start: 1000 mg, Max: 2500 mg; Start: 4mg, Max: 10mg D: 4 wks	Def: Collection: Active Timing/frequency: Specified ITT: NR GP1: Severe: 0, Mild or moderate: 19 GP2: Severe: 0, Mild or moderate: 73		GP1: 2 GP2: 0			
Metformin + Thiazolidinedione vs Metformin + DPP-IV inhibitors								
Scott, 2008[71]	RCT	GP1: Metformin+Rosiglitazone Fixed Start: > 1500 mg; Mean: 8mg D: 10 wks GP2: Metformin+Sitagliptin Fixed Start: > 1500 mg; Mean: 100mg D: 10 wks	Def: mild or moderate Collection: NR Timing/frequency: Unspecified ITT: No GP1: 1 GP2: 1				Def: Diarrhea, nausea, abdominal pain, vomiting Collection: NR Timing/frequency: Unspecified ITT: No GP1: 7% GP2: 1%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + Thiazolidinedione vs Thiazolidinedione+ Sulfonylurea								
Comaschi, 2007[109]	RCT	GP1: Metformin+Pioglitazone Varied Max: 3g/day; Start: 15mg/dl, Max: 30mg/dl D: NR; 22 wks GP2: Pioglitazone+ Sulfonylurea Varied, HgbA1c: 7.50%; Varied Start: 15mg/dl, Max: 30mg/dl; Unclear D: 22 wks; NR	Def: mild or moderate GP1: 0 GP2: 0					
Rosak, 2006[150]	Cohort	GP1: Metformin+Rosiglitazone NR Unclear; Start: 4mg, Max: 8mg GP2: Rosiglitazone+ Sulfonylurea Varied Start: 4mg, Max: 8mg; NR	Def: Severe Collection: Active Timing/frequency: Specified ITT: Yes GP1: 2 GP2: 12		Def: investigator reported Collection: Active Timing/frequency: Specified ITT: Yes GP1: incidence rate: 0.06%, 0.13/100 py GP2: incidence rate: 0.24%, 0.47/100 py			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Derosa, 2005[107]	RCT	GP1: Metformin + Rosiglitazone Fixed Start dose: 500mg po tid, Max: 500mg po tid; Start dose: 4mg po qday, Max: 4mg po qday GP2: Metformin + Glimeperide Fixed Start dose: 500mg po tid, Max: 500mg po tid; Start dose: 2mg po qday, Max: 2mg po qday		Def: Transiently elevated LFT to 1.5 times upper limit of normal Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 3 events out of 48 participants GP2: NR				
Metformin + Sulfonylurea vs Metformin + Meglitinides								
Schwarz, 2008[125]	RCT	GP1: Metformin+Glyburide Varied, glucose: <120mg/dL Start: 500mg, Max: 2000mg; Start: 1.25mg, Max: 10mg D: 12 wks GP2: Metformin+Nateglinide Varied, glucose: <120mg/dL Start: 500mg, Max: 2000mg; Start: 360mg, Max: 360mg D: 12 wks	Def: Severe Collection: Active Timing/frequency: Specified ITT: Yes GP1: 1 GP2: 0				Def: Diarrhea Collection: Active Timing/frequency: Specified ITT: Yes GP1: 20% GP2: 22.9%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Gerich, 2005[112]	RCT	GP1: Metformin+Glyburide Varied, glucose: FPG >=6.7 Start: 500mg po qda, Max: 2000mg po daily, Mean: 1105mg daily; Start: 1.25 mg po qday, Max: 10mg daily, Mean: 5.1mg daily D: 12 wks GP2: Metformin+Nateglinide Varied, glucose: FPG >=6.7; Fixed Start: 500mg po qday, Max: 2000mg daily, Mean: 1459mg daily; Start: 120mg po qac, Mean: 357mg daily D: 12 wks	Def: Severe Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: 38 GP2: 18					
Metformin + Sulfonylurea vs Metformin + DPP-IV inhibitors								
Nauck, 2007[113]	RCT	GP1: Metformin+Glipizide Varied; Varied, glucose: <6.1mmol/l NR; Start: 5mg/day, Max: 20mg/day D: NR, 18 wks GP2: Metformin+Sitagliptin Varied; Fixed NR	Def: Severe Collection: Active Timing/frequency: Specified ITT: Yes GP1: 7 GP2: 1				Def: Diarrhea, abdominal pains, nausea, vomiting Collection: Active Timing/frequency: Specified ITT: Yes GP1: 69 GP2: 70	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + Sulfonylurea vs Metformin + Premixed insulin								
Malone, 2003[118]	RCT	GP1: Metformin+Glibenclamide Varied; Varied, glucose: fasting and pre-meal goal <7mmol.L, 2-hour post-prandial goal <10mmol/L Max: 2550mg/day, Mean: 1968mg/day; Mean: 14.2mg/day D: 4 wks GP2: Metformin+Lispro 75/25 Varied; Varied, glucose: fasting and premeal glc <7mmol/L and 2-h post-prandial glc <10mmol/L Max: 2550mg/day; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks	Def: Symptomatic or BG <3.5mmol/l Timing/frequency: Unspecified ITT: NR GP1: (1) GP2: (1.3)					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kvapil, 2006[119]	RCT	GP1: Metformin+Glibenclamide Fixed; Varied Mean: 1660; Start: 1.75, Max: 10.5, Mean: 6.58 +/-4.18 GP2: Metformin+Aspart 70/30 Fixed; Varied, glucose: 5 to 8mmol/L Mean: 1660; Start: 0.2U/kg, Mean: 0.30 +/-0.12, Start: BID, Final: BID	Collection: NR Timing/frequency: Unspecified ITT: Yes GP1: Severe: 0, Mild or moderate: 9 GP2: Severe: 0, Mild or moderate: 13					
Metformin + Sulfonylurea vs Thiazolidinedione+ Sulfonylurea								
van der Meer, 2009[116]	RCT	GP1: Metformin+Glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks GP2: Pioglitazone+Glimepiride Fixed, Varied Start: 15mg, Max: 30mg; NR D: 2 wks; NR			GP1: 0 GP2: 0			

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Seufert, 2008[117]	RCT	GP1: Metformin + Sulfonylurea Fixed Max: 2550mg/day, Mean: 2081mg/day; NR D: 12 wks GP2: Pioglitazone + Sulfonylurea Fixed Max: 45, Mean: 37 mg; NR D: 12 wks	Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 50 GP2: 36				Def: Diarrhea Collection: NR Timing/frequency: Unspecified ITT: NR GP1: 14.4% GP2: 3.4%	
Hanefeld, 2004[115]	RCT	GP1: Metformin + Sulfonylurea Varied; Fixed Start: 850 mg (12 week titration and 40 week maintenance), Max: 2550 mg; NR GP2: Pioglitazone + Sulfonylurea Varied; Fixed Start: 15 mg (12 week titration 40 week maintenance), Max: 45 mg; NR	Def: Serious GP1: 0 GP2: 0				Def: Diarrhea GP1: 12.2% GP2: 23.4%	
Yang, 2003[114]	RCT	GP1: Metformin+SU Fixed Start: 1000 mg; NR GP2: Rosiglitazone+SU Fixed Start: 4mg; NR					Def: Diarrhea GP1: NR GP2: 2 cases of diarrhea	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin+Basal insulin vs Metformin+Premixed insulin								
Raskin, 2007[121]	RCT	GP1: Metformin+Glargine Fixed; Varied, glucose: 4.4 - 6.1mmol/L before before breakfast and dinner NR; Start: 12 U /day QD, Mean: 0.57 IU/kg QD GP2: Metformin+Aspart 70/30 Fixed; Varied, glucose: 4.4 - 6.1 mmol/L NR; Start: 12 IU/day BID, Mean: 0.91 IU/kg	Def: mild or moderate Collection: Active Timing/frequency: Specified ITT: Yes GP1: 11 GP2: 33					

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Robbins, 2007[120]	RCT	GP1: Metformin+Glargine Fixed; Varied, glucose: <6.7mmol/l Start: 500mg twice daily, Max: 1000mg twice daily, Mean: 1636 mg; Mean: 0.6 U/kg Start: QD, Final: QD GP2: Metformin+Insulin lispro 50/50 Fixed; Varied, glucose: <6.7mmol/l Start: 500mg twice a day, Max: 1000mg twice daily, Mean: 1641 mg; Mean: 0.7 U/kg Start: NR, Final: TID	Def: Collection: Active Timing/frequency: Specified ITT: Yes GP1: Severe: 2, Mild or moderate: 75 GP2: Severe: 3, Mild or moderate: 79				Def: Diarrhea Collection: Active Timing/frequency: Specified ITT: Yes GP1: 5.7% GP2: 6.4%	

Table 12. Comparative safety of diabetes medications

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Malone, 2004[137]	RCT	GP1: Metformin+Glargine Fixed; Varied, glucose: 90 to 126mg/dL Start: 1500mg, Max: 2550mg; Mean: 0.57 U/kg Start: QD, Final: QD GP2: Metformin+Lispro 75/25 Varied; Varied, glucose: 90 to 126mg/dL Start: 1500mg, Max: 2550mg; Mean: 0.62 U/kg Start: BID, Final: BID	Def: Collection: Active Timing/frequency: Specified ITT: Yes GP1: Severe: 0, Mild or moderate: 40 GP2: Severe: 0, Mild or moderate: 57		Collection: Active Timing/frequency: Specified ITT: Yes GP1: 0 GP2: 1			

D=Duration; def=Definition; dys=days; fsg=Fasting serum glucose; GP=group; HR=Hazard ratio; ICD= International classification disease; IR=Incident rates; ITT=Intention to treat; mg/day=milligram per day; mg/Dl= milligrams/deciliter; mg=milligram; mmol/l= millimoles per liter; NR=Not reported; NSG= non significant; od=once a day; SU= Sulfonylurea; tid=twice a day; wks=weeks