Draft Comparative Effectiveness Review

Number XX

Diabetes Medications for Adults with Type 2 Diabetes: An Update Focused on Monotherapy and Add-On Therapy to Metformin

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

This information is distributed solely for the purposes of predissemination peer review. It has not been formally disseminated by the Agency for Healthcare Research and Quality. The findings are subject to change based on the literature identified in the interim and peer-review/public comments and should not be referenced as definitive. It does not represent and should not be construed to represent an Agency for Healthcare Research and Quality or Department of Health and Human Services (AHRQ) determination or policy.

Contract No. [Redacted]

Prepared by:
[Redacted]

Investigators:
[Redacted]

AHRQ Publication No. xx-EHCxxx
<Month Year>

This report is based on research conducted by an Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxx). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: <Authors>. Diabetes Medications for Adults with Type 2 Diabetes: An Updated Focused on Monotherapy and Add-On Therapy to Metformin. (Prepared by the <EPC Name> Evidence-based Practice Center under Contract No. <##>.) AHRQ Publication No. XX-EHCXXX-EF. Rockville, MD: Agency for Healthcare Research and Quality. <Month Year>. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

David Meyers, M.D.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elisabeth Kato, M.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Karen Lee, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

[Redacted]

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:
[Redacted]

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:
[Redacted]

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:
[Redacted]

Diabetes Medications for Adults with Type 2 Diabetes: An Update Focused on Monotherapy and Add-On Therapy to Metformin

Structured Abstract

Objectives. The objective of this updated systematic review was to evaluate the comparative effectiveness and safety of monotherapy and metformin-based combination therapy comparisons most relevant to patients, clinicians, payers, and other decisionmakers.

Data sources. We searched MEDLINE®, Embase™, and the Cochrane Central Register of Controlled Trials (CENTRAL) for English language articles. We used the search developed for the prior review (2011) with the date restrictions of April 2009 through July 2014. We also evaluated unpublished data from the Food and Drug Administration medical reviews.

Review methods. Two reviewers independently reviewed titles, abstracts and full text articles to identify studies that assessed intermediate outcomes (e.g., hemoglobin A1c [HbA1c]), long-term clinical outcomes (e.g., all-cause mortality), and safety (e.g., hypoglycemia) for monotherapy (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors) or metformin-based combination therapy (metformin plus any other class) comparisons of interest . Two reviewers sequentially extracted data from the included articles using standardized protocols and evaluated study risk of bias independently.

Results. We included 229 studies. Cardiovascular mortality was 37 to 50 percent lower with MET vs SU monotherapy; cardiovascular morbidity was also lower for metformin versus SU. All-cause mortality and cardiovascular morbidity were similar for metformin compared to pioglitazone. All-cause mortality was also similar for metformin vs. MET plus a DPP-4 inhibitor and MET plus an SGLT-2 inhibitor. The evidence was of low strength or insufficient for congestive heart failure, cancer, lactic acidosis, and microvascular outcomes. For intermediate outcomes, most monotherapies had similar HbA1c reductions (1 absolute percentage point) except for metformin which lowered HbA1c by 0.4 absolute percentage point more than DPP-4 inhibitors. Metformin-based combinations lowered HbA1c by 0.7 to one absolute percentage point more than metformin monotherapy. Medications had varied and modest effects on weight with between-group differences of around 1 to 5 kg. Metformin, GLP-1 agonists, and SGLT-2 inhibitors were generally associated with weight loss while SUs and TZDs were associated with weight gain. Combination comparisons had HbA1c and weight effects consistent with monotherapy results. SGLT-2 inhibitors reduced systolic blood pressure by 3-5 mm Hg compared to most other drugs. For safety outcomes, rates of pancreatitis were similar for metformin and the combination of MET plus a DPP-4 inhibitor. SGLT-2 inhibitors increased the risk of genital mycotic infections, but not urinary tract infections, for the comparisons evaluating this. Sulfonylureas alone or in combination with metformin increased the risk of hypoglycemia vs. other comparisons. SGLT-2 inhibitors had a lower risk of hypoglycemia than metformin. Metformin was associated with more gastrointestinal adverse events than the other drugs except GLP-1 agonists which had about a 1.5 higher risk of nausea/vomiting vs. metformin.

Conclusions. Although the comparative long-term benefits and harms of most diabetes medications remain unclear, the evidence supports use of metformin as a first-line agent due to its beneficial effects on intermediate and long-term outcomes along with its relative safety, especially in light of its benefits over sulfonylureas for cardiovascular outcomes. This review provides comprehensive evidence on the benefits and differential harms of diabetes medications to facilitate personalized treatment choices for clinicians and their patients as well as to support decisionmaking for payers and regulators.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Rationale for Update of Review on Comparative Effectiveness of Diabetes Medications 2
Scope and Key Questions 6
Key Questions 6
Methods 9
Topic Refinement and Review Protocol 9
Literature Search Strategy 9
Search Strategy 9
Study Selection 9
Data Extraction 11
Risk of Bias Assessment of Individual Studies 12
Data Synthesis 12
Reporting Bias Assessment 13
Strength of the Body of Evidence 13
Applicability 15
Results 16
Results of Literature Searches 16
Key Question 1a and 1b: Intermediate Outcomes 17
Study Design and Population Characteristics 17
Risk of Bias 18
Key Points and Evidence Grades 19
The Evidence About Hemoglobin A1c 22
The Evidence About Weight 49
The Evidence About Systolic Blood Pressure 71
The Evidence About Heart Rate 81
Key Question 2a and 2b: Long-Term Clinical Outcomes 87
Study Design and Population Characteristics 87
Risk of Bias 87
Key Points and Evidence Grades 88
The Evidence About All-Cause Mortality 89
The Evidence About Cardiovascular Mortality 109
The Evidence About Cardiovascular and Cerebrovascular Morbidity 119
The Evidence About Retinopathy 136
The Evidence About Nephropathy 138
The Evidence About Neuropathy 144
Key Question 3a and 3b: Safety 146

Study Design and Population Characteristics 146
Risk of Bias 146
Key Points and Evidence Grades 147
The Evidence About Hypoglycemia 150
The Evidence About Gastrointestinal Side Effects 186
The Evidence About Cancer 208
The Evidence About Congestive Heart Failure 217
The Evidence About Liver Injury 224
The Evidence About Lactic Acidosis 228
The Evidence About Pancreatitis 230
The Evidence About Severe Allergic Reactions 237
The Evidence About Macular Edema or Decreased Vision 240
The Evidence About Urinary Tract Infections 242
The Evidence About Impaired Renal Function 248
The Evidence About Genital Mycotic Infections 253
The Evidence About Fracture 260
The Evidence About Volume Depletion 262
Key Question 4: Subgroups 267
Subgroups Defined by Age 267
Subgroups Defined by Sex 268
Subgroups Defined by Race/Ethnicity 268
Subgroups Defined by Body Mass Index 268
Discussion 269
Key Findings in Context 269
Intermediate Outcomes 269
Long-Term Clinical Outcomes 272
Adverse Events 275
Subgroups 279
Applicability 280
Implications for Clinical and Policy Decisionmaking 280
Limitations of the Comparative Effectiveness Review Process 281
Limitations of the Evidence Base 282
Research Gaps 283
Methodological Gaps and Suggested Improvements 285
Conclusions 286
References 287
Abbreviations 310

Tables

Table A. Study inclusion criteria ES-4
Table B. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for selected intermediate outcomes ES-9
Table C. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for selected long-term clinical outcomes ES-11
Table D. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for selected safety outcomes ES-14
Table 1. Characteristics of medications included in this report 3
Table 2. Priority Medication Comparisons Included for Each Key Question 8
Table 3. Inclusion and exclusion criteria 10
Table 4. Optimal information size for one arm and classification of dichotomous outcomes for optimal information size 14
Table 5. Pooled mean between-group difference in HbA1c comparing metformin with a combination of metformin plus a thiazolidinedione stratified by baseline HbA1c and dosing differences 27
Table 6. Strength of evidence domains for monotherapy comparisons in terms of hemoglobin A1c among adults with type 2 diabetes 45
Table 7. Strength of evidence domains for metformin-based combination comparisons in terms of hemoglobin A1c among adults with type 2 diabetes 47
Table 8. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a sulfonylurea stratified by baseline weight 53
Table 9. Strength of evidence domains for monotherapy comparisons in terms of weight among adults with type 2 diabetes 68
Table 10. Strength of evidence domains for metformin-based combination comparisons in terms of weight among adults with type 2 diabetes 69
Table 11. Strength of evidence domains for monotherapy comparisons in terms of systolic blood pressure among adults with type 2 diabetes 79
Table 12. Strength of evidence domains for metformin-based combination comparisons in terms of systolic blood pressure among adults with type 2 diabetes 80
Table 13. Strength of evidence domains for monotherapy comparisons in terms of heart rate among adults with type 2 diabetes 85
Table 14. Strength of evidence domains for metformin-based combination comparisons in terms of heart rate among adults with type 2 diabetes 86
Table 15. Observational studies comparing metformin with thiazolidinediones on all-cause mortality 91
Table 16. Randomized controlled trials comparing metformin with sulfonylureas on all-cause mortality 91
Table 17. Observational studies comparing metformin with sulfonylureas on all-cause mortality 92
Table 18. Randomized controlled trials or arms of randomized controlled trials excluded from the meta-analysis comparing metformin with a combination of metformin plus a DPP-4 inhibitor on all-cause mortality 98

Table 19. Randomized controlled trials comparing sulfonylureas with GLP-1 agonists on all-cause mortality 101
Table 20. Randomized controlled trials comparing a combination of metformin plus sitagliptin with a combination of metformin plus a GLP-1 agonist on all-cause mortality 105
Table 21. Strength of evidence domains for monotherapy comparisons in terms of all-cause mortality among adults with type 2 diabetes 106
Table 22. Strength of evidence domains for metformin-based combination comparisons in terms of all-cause mortality among adults with type 2 diabetes 108
Table 23. Randomized controlled trials comparing metformin with thiazolidinediones on cardiovascular mortality 109
Table 24. Observational studies comparing metformin with sulfonylureas on cardiovascular mortality 110
Table 25. Randomized controlled trials comparing metformin with DPP-4 inhibitors on cardiovascular mortality 111
Table 26. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cardiovascular mortality 115
Table 27. Strength of evidence domains for monotherapy comparisons in terms of cardiovascular mortality among adults with type 2 diabetes 117
Table 28. Strength of evidence domains for metformin-based combination comparisons in terms of cardiovascular mortality among adults with type 2 diabetes 118
Table 29. Randomized controlled trials comparing metformin with rosiglitazone on cardiovascular morbidity 119
Table 30. Randomized controlled trials comparing metformin with pioglitazone on cardiovascular morbidity 120
Table 31. Retrospective cohort studies comparing metformin with rosiglitazone on cardiovascular morbidity 120
Table 32. Retrospective cohort studies comparing metformin to pioglitazone on cardiovascular morbidity 120
Table 33. Randomized controlled trials comparing metformin with sulfonylureas on cardiovascular morbidity 121
Table 34. Retrospective cohort studies comparing metformin with sulfonylureas on cardiovascular morbidity 122
Table 35. Nested case-control study comparing metformin with sulfonylureas on hospitalization for incidence myocardial infarction 122
Table 36. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on cardiovascular morbidity 126
Table 37. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on nonfatal stroke 126
Table 38. Studies comparing rosiglitazone with sulfonylureas on cardiovascular morbidity 127
Table 39. Studies comparing pioglitazone with sulfonylureas on cardiovascular morbidity 128
Table 40. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea to a combination of metformin plus a DPP-4 inhibitor on cardiovascular morbidity 130

Table 41. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea to a combination of metformin plus a DPP-4 inhibitor on cerebrovascular morbidity 130
Table 42. Strength of evidence domains for monotherapy comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes 133
Table 43. Strength of evidence domains for combination therapy comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes 135
Table 44. Strength of evidence domains for monotherapy comparisons in terms of retinopathy among adults with type 2 diabetes 137
Table 45. Retrospective cohort studies comparing metformin with sulfonylureas on nephropathy 139
Table 46. Strength of evidence domains for monotherapy comparisons in terms of nephropathy among adults with type 2 diabetes 142
Table 47. Strength of evidence domains for metformin-based combination comparisons in terms of nephropathy among adults with type 2 diabetes 143
Table 48. Strength of evidence domains for monotherapy comparisons in terms of neuropathy among adults with type 2 diabetes 145
Table 49. Strength of evidence domains for metformin-based combination comparisons in terms of neuropathy among adults with type 2 diabetes 145
Table 50. Randomized controlled trials comparing metformin with thiazolidinediones on hypoglycemia 150
Table 51. Additional studies comparing metformin with sulfonylureas on hypoglycemia 152
Table 52. Randomized controlled trials comparing metformin with GLP-1 agonists on hypoglycemia 155
Table 53. Additional randomized controlled trials comparing metformin with a combination of metformin plus a sulfonylurea on hypoglycemia 157
Table 54. Randomized controlled trials comparing metformin with a combination of metformin plus a GLP-1 agonist on hypoglycemia 162
Table 55. Randomized controlled trials comparing thiazolidinediones with DPP-4 inhibitors on hypoglycemia 164
Table 56. Randomized controlled trials comparing sulfonylureas with DPP-4 inhibitors on hypoglycemia 165
Table 57. Randomized controlled trials comparing sulfonylureas with GLP-1 agonists on hypoglycemia 166
Table 58. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a premixed insulin on hypoglycemia 173
Table 59. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist on hypoglycemia 175
Table 60. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a basal insulin on hypoglycemia 176
Table 61. Randomized controlled trials comparing a combination of metformin plus a GLP-1 agonist with a combination of metformin plus a basal insulin on hypoglycemia 177
Table 62. Randomized controlled trials comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin on hypoglycemia 178
Table 63. Strength of evidence domains for monotherapy comparisons in terms of hypoglycemia among adults with type 2 diabetes 180

Table 64. Strength of evidence domains for metformin-based combination comparisons in terms of hypoglycemia among adults with type 2 diabetes 183
Table 65. Studies comparing metformin with sulfonylureas on gastrointestinal adverse events 187
Table 66. Randomized controlled trials comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea on gastrointestinal adverse events 201
Table 67. Strength of evidence domains for monotherapy comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes 205
Table 68. Strength of evidence domains for metformin-based combination comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes 207
Table 69. Retrospective cohort studies comparing metformin with sulfonylureas on cancer 208
Table 70. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on cancer 209
Table 71. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on cancer 210
Table 72. Randomized controlled trials comparing a combination of metformin with a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cancer 212
Table 73. Strength of evidence domains for monotherapy comparisons and cancer outcomes among adults with type 2 diabetes 215
Table 74. Strength of evidence domains for combination therapy comparisons and cancer among adults with type 2 diabetes 216
Table 75. Studies comparing metformin with thiazolidinediones on congestive heart failure ... 217
Table 76. Studies comparing metformin with sulfonylureas on congestive heart failure 218
Table 77. Randomized controlled trials comparing metformin with a combination of metformin plus a thiazolidinedione on congestive heart failure 218
Table 78. Observational studies comparing thiazolidinediones with sulfonylureas on congestive heart failure 219
Table 79. Strength of evidence domains for monotherapy comparisons in terms of congestive heart failure among adults with type 2 diabetes 222
Table 80. Strength of evidence domains for metformin-based combination comparisons in terms of congestive heart failure among adults with type 2 diabetes 223
Table 81. Randomized controlled trials comparing metformin with thiazolidinediones on liver injury 224
Table 82. Randomized controlled trials comparing metformin with sulfonylureas on liver injury 225
Table 83. Randomized controlled trials comparing metformin with DPP-4 inhibitors on liver injury 225
Table 84. Randomized controlled trials comparing thiazolidinediones with sulfonylureas on liver injury 226
Table 85. Strength of evidence domains for monotherapy comparisons in terms of liver injury among adults with type 2 diabetes 227
Table 86. Strength of evidence domains for metformin-based combination comparisons in terms of liver injury among adults with type 2 diabetes 227
Table 87. Strength of evidence domains for monotherapy comparisons in terms of lactic acidosis among adults with type 2 diabetes 229

Table 88. Strength of evidence domains for metformin-based combination comparisons in terms of lactic acidosis among adults with type 2 diabetes 229
Table 89. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on pancreatitis 231
Table 90. Randomized controlled trials comparing metformin with a combination of metformin plus a GLP-1 agonist on pancreatitis 232
Table 91. Strength of evidence domains for monotherapy comparisons in terms of pancreatitis among adults with type 2 diabetes 235
Table 92. Strength of evidence domains for metformin-based combination comparisons in terms of pancreatitis among adults with type 2 diabetes 236
Table 93. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on severe allergic reactions 237
Table 94. Strength of evidence domains for monotherapy comparisons in terms of severe allergic reactions among adults with type 2 diabetes 239
Table 95. Strength of evidence domains for metformin-based combination comparisons in terms of severe allergic reactions among adults with type 2 diabetes 239
Table 96. Strength of evidence domains for monotherapy comparisons in terms of macular edema or decreased vision among adults with type 2 diabetes 241
Table 97. Definitions of urinary tract infections used in randomized controlled trials comparing metformin with a combination of metformin and SGLT-2 inhibitor 243
Table 98. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor on urinary tract infections 245
Table 99. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor on urinary tract infections 246
Table 100. Strength of evidence domains for monotherapy comparisons in terms of urinary tract infections among adults with type 2 diabetes 247
Table 101. Strength of evidence domains for metformin-based combination comparisons in terms of urinary tract infections among adults with type 2 diabetes 247
Table 102. Randomized controlled trials comparing metformin with SGLT-2 inhibitors on impaired renal function 248
Table 103. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on impaired renal function 249
Table 104. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor on impaired renal function 250
Table 105. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor on impaired renal function 251
Table 106. Strength of evidence domains for monotherapy comparisons in terms of impaired renal function among adults with type 2 diabetes 252
Table 107. Strength of evidence domains for metformin-based combination comparisons in terms of impaired renal function among adults with type 2 diabetes 252
Table 108. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on genital infections 255

Table 109. Randomized controlled trials comparing DPP-4 inhibitors with SGLT-2 inhibitors on genital infections 256
Table 110. Randomized controlled trials comparing a combination with metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor on genital infections 258
Table 111. Strength of evidence domains for monotherapy comparisons in terms of genital mycotic infections among adults with type 2 diabetes 259
Table 112. Strength of evidence domains for metformin-based combination comparisons in terms of genital mycotic infections among adults with type 2 diabetes 259
Table 113. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of fracture among adults with type 2 diabetes 261
Table 114. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on volume depletion 263
Table 115. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor on volume depletion . 264
Table 116. Strength of evidence domains for monotherapy comparisons in terms of volume depletion among adults with type 2 diabetes 266
Table 117. Strength of evidence domains for metformin-based combination comparisons in terms of volume depletion among adults with type 2 diabetes 266

Figures

Figure A. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons ES-7
Figure B. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons ES-8
Figure C. Pooled odds ratios of all-cause mortality and strength of evidence for monotherapy and metformin-based combination comparisons ES-10
Figure D. Pooled odds ratios of mild/moderate hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons ES-12

Figure 1. Analytic framework 5
Figure 2. Summary of the search (number of articles) 17
Figure 3. Summary of the risk of bias of randomized controlled trials evaluating intermediate outcomes 19
Figure 4. Pooled mean between-group difference in hemoglobin A1c comparing metformin with thiazolidinediones 23
Figure 5. Pooled mean between-group difference in hemoglobin A1c comparing metformin with DPP-4 inhibitors 24
Figure 6. Mean between-group difference in hemoglobin A1c comparing metformin with GLP-1 agonists 26
Figure 7. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a sulfonylurea 28
Figure 8. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a DPP-4 inhibitor 29
Figure 9. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a SGLT-2 inhibitor 30
Figure 10. Pooled mean between-group difference in hemoglobin A1c comparing thiazolidinediones with sulfonylureas 32

Figure 11. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea..... 35
Figure 12. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a DPP-4 inhibitor 36
Figure 13. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration 37
Figure 14. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor 38
Figure 15. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a GLP-1 agonist..... 40
Figure 16. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor41
Figure 17. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist ... 42
Figure 18. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin 44
Figure 19. Pooled mean between-group difference in weight comparing metformin with DPP-4 inhibitors 50
Figure 20. Mean between-group difference in weight comparing metformin with GLP-1 agonists 51
Figure 21. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a thiazolidinedione 52
Figure 22. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a sulfonylurea 53
Figure 23. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration 54
Figure 24. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a SGLT-2 inhibitor..... 55
Figure 25. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a GLP-1 agonist 56
Figure 26. Pooled mean between-group difference in weight comparing thiazolidinediones with sulfonylureas 57
Figure 27. Pooled mean between-group difference in weight comparing sulfonylureas with GLP-1 agonists 58
Figure 28. Pooled mean between-group difference in weight comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea..... 60
Figure 29. Pooled mean between-group difference in weight comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a DPP-4 inhibitor ... 61
Figure 30. Pooled mean between-group difference in weight comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration..... 62
Figure 31. Pooled mean between-group difference in weight comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor..... 63
Figure 32. Pooled mean between-group difference in weight comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist..... 65

Figure 33. Pooled mean between-group difference in weight comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin..... 67
Figure 34. Pooled mean between-group difference in systolic blood pressure comparing metformin with SGLT-2 inhibitors 72
Figure 35. Pooled mean between-group difference in systolic blood pressure comparing metformin with a combination of metformin plus a SGLT-2 inhibitor 73
Figure 36. Pooled mean between-group difference in systolic blood pressure comparing metformin with a combination of metformin plus a GLP-1 agonist..... 74
Figure 37. Pooled mean between-group difference in systolic blood pressure comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor..... 76
Figure 38. Pooled mean between-group difference in systolic blood pressure comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor..... 77
Figure 39. Pooled mean between-group difference in heart rate comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor..... 83
Figure 40. Summary of the risk of bias of randomized controlled trials evaluating long-term clinical outcomes 88
Figure 41. Pooled odds ratio of all-cause mortality comparing metformin with pioglitazone..... 90
Figure 42. Pooled odds ratio of all-cause mortality comparing metformin with DPP-4 inhibitors 93
Figure 43. Pooled odds ratio of all-cause mortality comparing metformin with SGLT-2 inhibitors 94
Figure 44. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus rosiglitazone 95
Figure 45. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus a sulfonylurea 96
Figure 46. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus a DPP-4 inhibitor..... 97
Figure 47. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus a SGLT-2 inhibitor, stratified by study duration..... 99
Figure 48. Pooled odds ratio of all-cause mortality comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor..... 102
Figure 49. Pooled odds ratio of all-cause mortality comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor..... 103
Figure 50. Pooled odds ratio cardiovascular mortality comparing metformin with a combination of metformin plus rosiglitazone..... 111
Figure 51. Pooled odds ratio cardiovascular mortality comparing metformin with a combination of metformin plus a DPP-4 inhibitor 112
Figure 52. Pooled odds ratio cardiovascular mortality combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor..... 114
Figure 53. Pooled odds ratio of cardiovascular morbidity comparing metformin with a combination of metformin plus rosiglitazone..... 124
Figure 54. Pooled odds ratio of cardiovascular morbidity comparing metformin with a combination of metformin plus a DPP-4 inhibitor 125
Figure 55. Summary of the risk of bias of randomized controlled trials evaluating safety..... 147

Figure 56. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with sulfonylureas 151
Figure 57. Pooled odds ratio of symptomatic hypoglycemia comparing metformin with DPP-4 inhibitors 153
Figure 58. Pooled odds ratio of any hypoglycemia comparing metformin with SGLT-2 inhibitors 154
Figure 59. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a thiazolidinedione 156
Figure 60. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with combination of metformin plus a sulfonylurea 157
Figure 61. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor 158
Figure 62. Pooled odds ratio of severe hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor 159
Figure 63. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor 160
Figure 64. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a SGLT-2 inhibitor 161
Figure 65. Pooled odds ratio of any hypoglycemia comparing thiazolidinediones with sulfonylureas 163
Figure 66. Pooled odds ratio of any hypoglycemia comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea 168
Figure 67. Pooled odds ratio of hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration and severity of hypoglycemia 170
Figure 68. Pooled odds ratio of mild or moderate hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor* 171
Figure 69. Odds ratio of hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a GLP-1 agonist, stratified by study duration and severity of hypoglycemia 172
Figure 70. Odds ratio of hypoglycemia comparing a combination of metformin plus a SGLT-2 inhibitor with a combination of metformin plus a DPP-4 inhibitor, stratified by severity of hypoglycemia 174
Figure 71. Pooled odds ratio of gastrointestinal adverse events comparing metformin with thiazolidinediones 186
Figure 72. Odds ratio of gastrointestinal adverse events comparing metformin with DPP-4 inhibitors 188
Figure 73. Odds ratio of gastrointestinal adverse events comparing metformin with SGLT-2 inhibitors 189
Figure 74. Odds ratio of gastrointestinal adverse events comparing metformin with GLP-1 agonists 190
Figure 75. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a thiazolidinedione 191
Figure 76. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a sulfonylurea* 192

Figure 77. Pooled odds ratio of abdominal pain or nausea comparing metformin with a combination of metformin plus a DPP-4 inhibitor 193
Figure 78. Pooled odds ratio of any gastrointestinal-related adverse event comparing metformin with a combination of metformin plus a DPP-4 inhibitor..... 194
Figure 79. Pooled odds ratio of diarrhea comparing metformin with a combination of metformin plus a DPP-4 inhibitor..... 195
Figure 80. Pooled odds ratio of vomiting comparing metformin with a combination of metformin plus a DPP-4 inhibitor..... 196
Figure 81. Pooled odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a SGLT-2 inhibitor..... 197
Figure 82. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a GLP-1 agonist 198
Figure 83. Odds ratio of gastrointestinal adverse events comparing thiazolidinediones with sulfonylureas 199
Figure 84. Pooled odds ratio of gastrointestinal adverse events comparing sulfonylureas with GLP-1 agonists..... 200
Figure 85. Odds ratio of gastrointestinal adverse events comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor 202
Figure 86. Odds ratio of gastrointestinal adverse events comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist..... 203
Figure 87. Pooled odds ratio of cancer events comparing the combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist 213
Figure 88. Pooled odds ratio of congestive heart failure events comparing metformin with a combination of metformin plus a DPP-4 inhibitor 219
Figure 89. Pooled odds ratio of congestive heart failure events comparing thiazolidinediones with sulfonylureas 220
Figure 90. Pooled odds ratio of urinary tract infections comparing metformin with SGLT-2 inhibitors 243
Figure 91. Pooled odds ratio of urinary tract infections comparing metformin with a combination of metformin plus a SGLT-2 inhibitor..... 244
Figure 92. Pooled odds ratio of genital or mycotic infections comparing metformin with SGLT-2 inhibitors 253
Figure 93. Pooled odds ratio of genital or mycotic infections comparing metformin with a combination of metformin plus a SGLT-2 inhibitor..... 254
Figure 94. Pooled odds ratio of genital or mycotic infections comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor..... 257
Figure 95. Pooled odds ratio of volume depletion comparing metformin with a combination of metformin plus a SGLT-2 inhibitor 262
Figure 96. Pooled odds ratio of volume depletion comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor..... 264
Figure 97. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons 270
Figure 98. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons 271
Figure 99. Pooled odds ratios of all-cause mortality and strength of evidence for monotherapy and metformin-based combination comparisons 274

Figure 100. Pooled odds ratios of hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons 276

Appendixes

Appendix A. Literature Search Strategy
Appendix B. Forms
Appendix C: Excluded Articles
Appendix D: Evidence Tables
Appendix E: Grey Literature
Appendix F: Reference

Executive Summary

Background

Condition and Therapeutic Strategies

Type 2 diabetes affects 9.3 percent of the US population or 29.1 million people.[1] Estimates of diabetes incidence that include laboratory-diagnosed diabetes, in addition to self-report, are even higher than those reported by the US Centers for Disease Control and Prevention.[2] Diabetes and its complications are a substantial public health burden as they contribute significantly to mortality, morbidity, and health care costs.[1] Complications of longstanding diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy, and end-stage kidney disease. Diabetes also contributes importantly to macrovascular complications including coronary artery disease, peripheral arterial disease, and carotid artery disease and increases the risk of cardiovascular-related death nearly two-fold.[3] Lifestyle modification and pharmacologic therapy are the cornerstones of the management of hyperglycemia for type 2 diabetes to reduce diabetes complications.[4-6]

When beginning medical treatment, patients usually begin with one of five drug classes that have all been approved by the Food and Drug Administration (FDA) for use as monotherapy, although several guidelines recommend use of metformin when not contraindicated as first-line therapy after lifestyle modifications.[4, 5] These include metformin, 2nd generation sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Clinical guidelines, including those of the American Diabetes Association, recommend monitoring glycosylated hemoglobin (HbA1c) to determine the need for changing the medication dose or adding another agent to improve glycemic control.[5] If needed, clinicians typically add an additional medication, or may add insulin. Clinicians also monitor other intermediate outcomes, including weight and short-term and long-term safety and adverse effects of the drugs, which vary by drug class, with the goal of improving long-term clinical outcomes.

The Effective Health Care (EHC) Program of the Agency for Healthcare Research and Quality (AHRQ) has published two prior systematic reviews comparing monotherapies and medication combinations for adults with type 2 diabetes.[7, 8] Since January 2010, the last date of literature included in the past review, one new medication class (SGLT-2 inhibitors, with three new medications) and several new DPP-4 inhibitors and GLP-1 agonists have been approved by the FDA. Additional data on previously-approved medications have also emerged since then which could change the balance of benefit and risk attributable to these drugs or could alter the strength of evidence about some of the drug comparisons previously reviewed.[9-12] Given the ever-increasing literature about type 2 diabetes medications and the recent approval of many new medications, an updated systematic review evaluating the effects of these medications on intermediate and long-term effectiveness and safety outcomes will be valuable to clinicians, patients, investigators, guideline developers, and payers.

Scope and Key Questions

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[8] We are focusing on priority head-to-head drug comparisons, identified, a priori, as clinically relevant comparisons for which there are evidence gaps. Given the unique and

emerging safety concerns of some of these medications, we have included additional safety outcomes in the review including impaired renal function, urinary tract infections, genital infections, volume depletion, and bone fractures for studies that include a comparison with SGLT-2 inhibitors, and systolic blood pressure and heart rate as intermediate outcomes for studies including either SGLT-2 inhibitors or GLP-1 agonists.

The key questions that we address in this review are as follows:

Key Question 1a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications for the intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 agonists)?

Key Question 1b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of metformin-based combinations of FDA-approved diabetes medications for the intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 agonists)?

Key Question 2a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the monotherapy FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 2b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the metformin-based combinations of FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 3a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the monotherapy FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 3b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of metformin-based combinations of FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 4: Do the comparative safety and effectiveness of these treatments differ across subgroups defined by the age, sex, race/ethnicity, and body mass index (BMI) of adults with type 2 diabetes?

Methods

Topic Refinement and Review Protocol

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[8] We recruited a Technical Expert Panel (TEP) to review a draft of the protocol and a summary of the revisions from the 2011 review. The TEP included endocrinologists, general internists, biostatisticians, and diabetes experts from government agencies. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the Key Questions. With the feedback from the TEP and the Agency for Healthcare Research and Quality (AHRQ) representatives, we finalized and posted the protocol. (www.effectivehealthcare.ahrq.gov).

Literature Search Strategy

Search Strategy

We searched MEDLINE®, Embase™, and the Cochrane Central Register of Controlled Trials (CENTRAL). We ran the search developed for the 2011 review with the date restrictions of April 2009 through July 2014 (see Appendix A). The expanded search included medical subject headings (MeSH) and text words for all of the new medications included in this updated report, without date restrictions.

Study Selection

Two independent reviewers conducted title scans, and advanced articles if either one thought it relevant. The abstract review phase was designed to identify studies reporting the effectiveness or safety of the medications and medication combinations of interest. Abstracts were reviewed independently by two investigators. Differences between investigators regarding the inclusion or exclusion of abstracts were resolved through consensus adjudication. Full articles underwent another independent parallel review regarding their appropriateness for inclusion. Selection criteria for studies are provided in Table A.

Table A. Study inclusion criteria

PICOTS	Inclusion criteria
Population	• We included studies of adult humans with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes.
Interventions	• We included studies that evaluated a diabetes medication of interest or drug combination of interest.
Comparisons	• We included studies that evaluated a comparison of interest
Outcomes*	• We included studies addressing the following intermediate outcomes for KQ1: ▪ Hemoglobin A1c ▪ Weight ▪ Systolic blood pressure ▪ Heart rate • We included studies addressing the following long-term clinical outcomes for KQ2: ▪ All-cause mortality ▪ Cardiovascular and cerebrovascular morbidity and mortality ▪ Retinopathy ▪ Nephropathy ▪ Neuropathy • We included studies addressing the following safety outcomes for KQ3: ▪ Liver injury ▪ Impaired renal function ▪ Lactic acidosis ▪ Pancreatitis ▪ Hypoglycemia ▪ Gastrointestinal side effects ▪ Congestive heart failure ▪ Cancer ▪ Macular edema or decreased vision ▪ Fractures ▪ Urinary tract infections ▪ Genital mycotic infections ▪ Volume depletion • KQ4 included studies considering any of the above outcomes.
Type of study	• For KQ1, we included only RCTs. • For KQ2 and KQ3, we included RCTs, non-randomized experimental studies with a comparison group, and high-quality observational studies with a comparison group. • We included randomized trials utilizing a crossover design with some exceptions. • Published in English
Timing and setting	We included studies in which the observed intervention or exposure period was more than 3 months

KQ = Key Question; RCT = randomized controlled trial
*not every outcome was assessed for each comparison

Data Extraction

Reviewers extracted information on the general study characteristics, study participants characteristics, interventions, comparisons, the method of ascertainment of safety outcomes, and the outcome results, including measures of variability. We also collected data on outcomes for the subgroups of interest, which were defined by age, sex, race/ethnicity, and BMI.

Risk of Bias Assessment of Individual Studies

Two independent reviewers assessed risk of bias. We assessed the risk of bias in individual RCTs using the Jadad criteria consistent with the prior report.[13] We used the Downs and Black tool for assessment of internal validity for non-randomized trials and observational studies.[14] We included only medium or high-quality observational studies as determined by assessment of each study's risk of bias. The Downs and Black tool was applied to the observational studies that had

been included in the prior report;[8] some of the previously included observational studies were excluded due to methodological deficiencies.

Data Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies, including those from the prior evidence reports. We conducted meta-analyses when there were sufficient data (at least three trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose). We included in the quantitative pooling those study arms with drug doses and study durations most commonly reported. We tested the heterogeneity among the trials considered for quantitative pooling using a chi-squared test using a significance level of alpha less than or equal to 0.10, and also examined heterogeneity among studies with an I-squared statistic.[15] We pooled the mean difference between groups using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity (I-squared <50%),[16] and the profile likelihood estimate when statistical heterogeneity was high.[17] For dichotomous outcomes, we calculated pooled odds ratios using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity[16] or the profile likelihood estimate in settings of high heterogeneity (I-squared >50%).[17] Sensitivity analyses included sequential study elimination to assess for influential studies. Stratification and meta-regression (only if 10 or more studies were included in the meta-analysis) were done to identify and describe sources of heterogeneity and their effects on outcomes when substantial heterogeneity was identified.

Strength of the Body of Evidence

At the completion of the review, two reviewers sequentially graded the evidence addressing the Key Questions by adapting an evidence grading scheme recommended in the Guide for Conducting Comparative Effectiveness Reviews.[18] We generated evidence grades about each intervention comparison for each outcome (Table A) for which there was at least one RCT or three observational studies. We assessed the study limitations, consistency, directness, precision, and reporting bias.

We classified evidence pertaining to the Key Questions into four categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion).

Applicability

We assessed the applicability of the evidence in terms of the degree to which the study populations, interventions, outcomes, timing and settings were typical of the treatment of individuals with type 2 diabetes who are receiving treatment in a usual care setting, such as outpatient treatment by internists, family physicians, and endocrinologists.

Results

For the Executive Summary, results are presented by Key Question and focus on evidence for which there was moderate or high strength of evidence. We also highlight some key areas for which there was low-strength or insufficient evidence. The full results of this synthesis, including detailed results on all evidence, are in the body of the full report.

Results of Literature Searches

We included 166 publications in our previous review. After excluding all studies that no longer had a comparison or an outcome of interest and cohort studies that did not meet our quality criteria, we included 104 of these studies from the prior review (published in 107 articles) in the update.

We also retrieved 16,251 unique citations from our updated literature search. After reviewing titles, abstracts, and full text, we included 115 new studies (published in 142 new articles). Ten of the new publications were either extensions or additional analyses of studies included in the previous review. Overall, we included 229 studies, published in 249 articles.

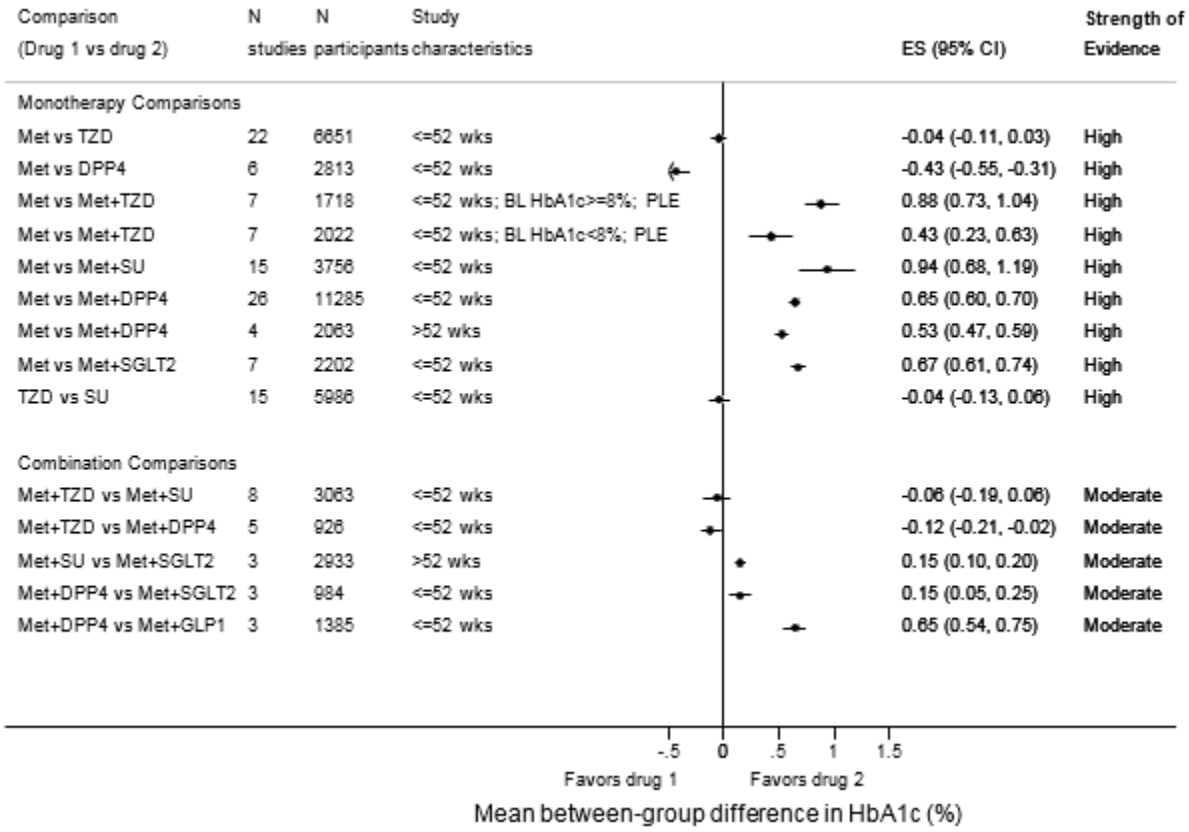
Key Question 1a and 1b. Comparative Effectiveness of Monotherapy and Metformin-based Combinations for Intermediate Outcomes

Of the 205 RCTs (reported in 211 articles) identified for Key Question 1, ninety-five percent were less than one year long. Only nine percent of these trials reported having received no industry support, and 20% did not report on this at all. Study participants were generally overweight or obese and had a baseline HbA1c between 7 and 9%.

Hemoglobin A1c

We found that most diabetes medications as monotherapy (metformin, thiazolidinediones, and sulfonylureas) reduced HbA1c to a similar degree after 3 or more months of treatment (Figure A). In the 2011 report,[8] metformin versus sulfonylurea was graded as high showing no significant between-group differences in HbA1c; therefore, it was not updated in this report. Metformin was more effective in reducing HbA1c than the DPP-4 inhibitors as monotherapy (by about 0.4 absolute percentage points). Two-drug combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, metformin plus SGLT-2 inhibitors and metformin plus DPP-4 inhibitors) were generally more effective in reducing HbA1c than was metformin monotherapy (by about 1 absolute percentage point) (Figure A). For the combination comparisons, the combination of metformin plus a GLP-1 agonist reduced HbA1c more than metformin plus DPP-4 inhibitors by 0.65% (all differences for HbA1c represents absolute percentage points). Otherwise, most combination therapy comparisons with moderate strength of evidence had either no significant or no clinically meaningful between-group differences (<0.3%) in HbA1c between arms (Figure A). Although we included comparisons with the GLP-1 agonists, we graded the evidence for most of these comparisons as insufficient or low; therefore, we were limited in our ability to draw firm conclusions about their effectiveness.

Figure A. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in HbA1c); GLP1 = glucagon-like peptide-1 agonists; HbA1c = hemoglobin A1c; Met = metformin; PLE = profile likelihood estimate; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; wks = weeks

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

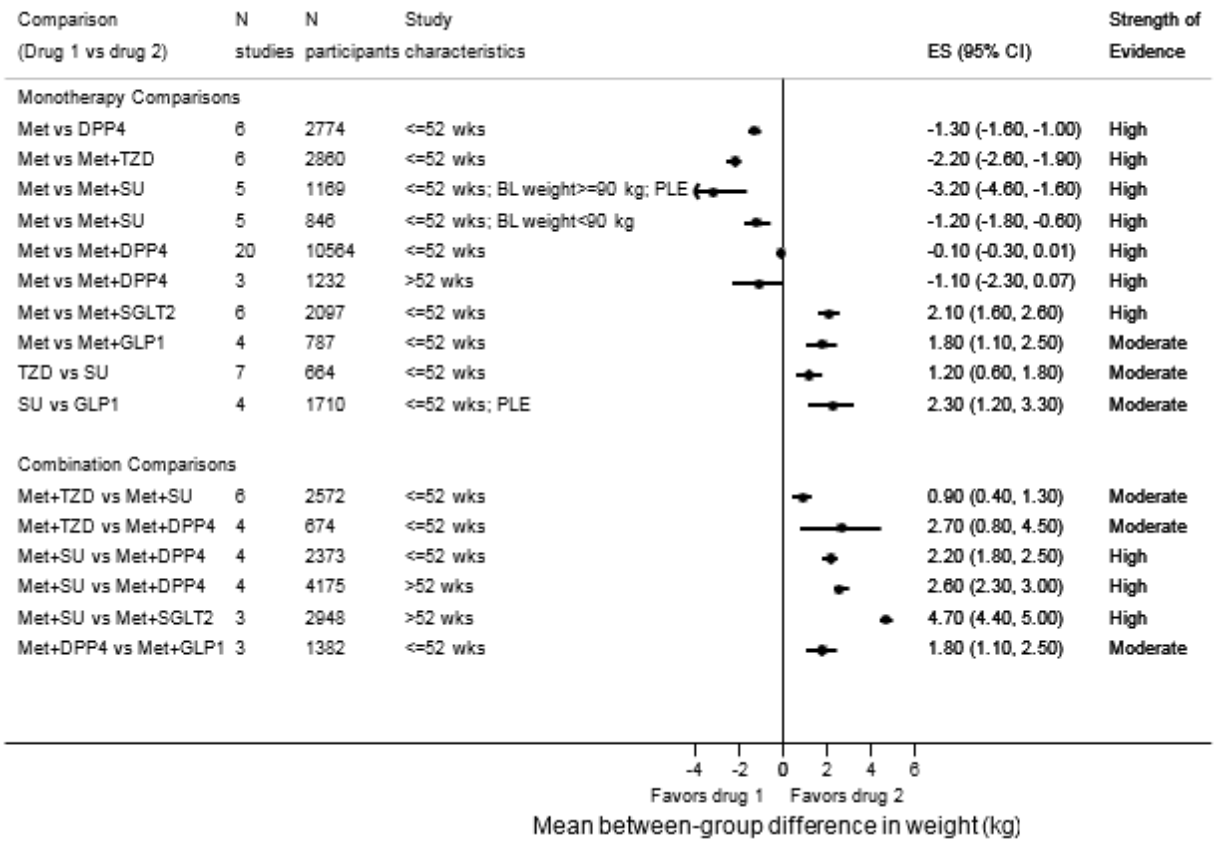
Weight

As expected, monotherapy and combination medication comparisons generally showed significant between-group differences when comparing medications expected to increase weight (sulfonylureas, thiazolidinediones) with medications expected to maintain or decrease weight (metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors). Figure B shows the data where meta-analyses were able to be conducted. We report between-group differences in the text below regarding results where meta-analyses were unable to be performed. In the 2011 report, comparisons of metformin versus thiazolidinedione and metformin versus sulfonylurea were found to favor metformin by about 2.5 kg, with high strength of evidence; therefore, these comparisons were not updated. DPP-4 inhibitors and GLP-1 agonists both decreased weight more than thiazolidinediones, (range in between-group differences of 2.5 kg and 3.5 kg respectively).

Several monotherapy and metformin-based combination medications were compared where both arms had medications expected to maintain or decrease weight or both arms had medications expected to increase weight, with varying effects. Metformin decreased weight more than DPP-4 inhibitors, while sulfonylureas caused slightly less weight gain than

thiazolidinediones. There was moderate strength of evidence that SGLT-2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors (between-group differences of around 1.4 kg and 2.7 kg, respectively). When compared with metformin plus a DPP-4 inhibitor, the combinations of metformin plus a GLP-1 agonist and metformin plus a SGLT-2 inhibitor were favored by about 1.8 kg and 2.5 kg respectively. Metformin plus a sulfonylurea had more favorable weight effects than the combination of metformin plus a premixed or basal insulin (range in mean between-group differences of -0.5 kg to -1.7 kg), with moderate strength of evidence.

Figure B. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons



Basal = basal insulin; BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in weight); GLP1 = glucagon-like peptide-1 agonists; kg = kilograms; Met = metformin; PLE = profile likelihood estimate; premixed = premixed insulin; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; wks = weeks

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Systolic Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were only evaluated for the newer medications SGLT-2 inhibitors and GLP-1 agonists due to suspected effects of these newer medications on these clinical outcomes based on prior literature.[19, 20] The SGLT-2 inhibitors consistently reduced systolic blood pressure by 3-5 mmHg in all comparisons where there were sufficient numbers of studies (Table B). Also, metformin plus a GLP-1 agonist yielded a greater reduction in systolic blood pressure by about 3 mmHg compared with metformin alone (Table B).

For heart rate, only two comparisons had sufficient data to grade the evidence as more than insufficient or low. These comparisons had no or small differences (<2 bpm) between groups. When there were differences in outcomes among comparisons rated as having a low strength of evidence, they were less than 3 beats per minute (Table B).

Table B. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for selected intermediate outcomes

Outcome	Conclusions	Strength of Evidence
Systolic blood pressure	Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than: • Metformin alone: pooled between-group difference, 4.9 mmHg (95% CI, 2.4 to 6.3 mmHg). • Metformin plus SU: pooled between-group difference, 5.1 mmHg (95% CI, 4.2 mmHg to 5.9 mmHg).	High
	Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin + a DPP-4 inhibitor: pooled between-group difference, 4.1 mmHg (95% CI, 3.6 mmHg to 4.6 mmHg).	Moderate
	SGLT-2 inhibitors reduced systolic blood pressure more than metformin: pooled between-group difference, 2.8 mmHg (95% CI, 2.6 mmHg to 3.0 mmHg).	Moderate
	Metformin plus a GLP-1 agonist reduced systolic blood pressure more than metformin: pooled between-group difference, 3.1 mmHg (95% CI, 1.4 to 4.9 mmHg).	Moderate
Heart rate	Increases in heart rate were minimal and similar for metformin and GLP-1 agonist monotherapy.	Moderate
	Combination therapy with metformin plus a SGLT-2 inhibitor resulted in less of an increase in heart rate than metformin plus a sulfonylurea: pooled between group difference in heart rate, 1.5 bpm; 95% CI, 0.6 bpm to 2.3 bpm.	Moderate

bpm=beats per minute; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists; mmHg=millimeters of mercury; SGLT-2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea

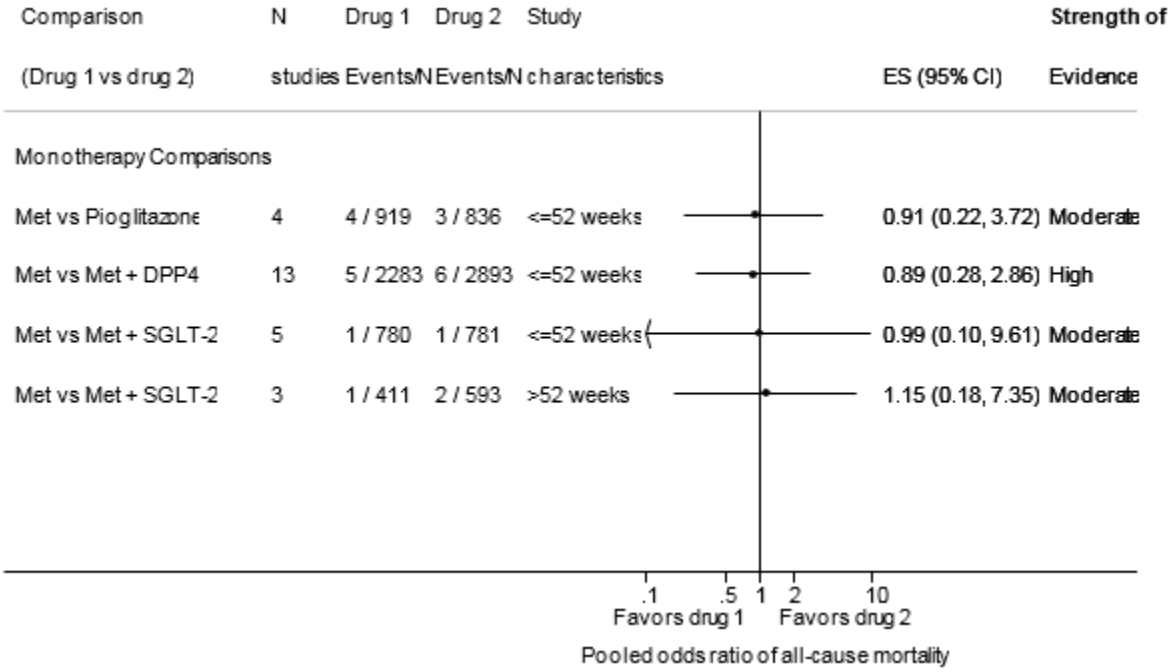
Key Question 2a and 2b. Comparative Effectiveness of Monotherapy and Metformin-based Combination Therapy for Long-Term Clinical Outcomes

Of 132 studies (reported in 134 publications) identified for Key Question 2, ninety-seven were RCTs and 32 were observational (mainly retrospective cohort) studies. Of the 97 trials, thirty-four of these were at least one year in duration, and notably, no trial specified a long-term outcome as its primary outcome. Mean/median follow up of the observational studies ranged from 6 months to 8 years, and 13 of the observational studies were designed to evaluate cardiovascular outcomes.

All-Cause Mortality

Most studies reporting on all-cause mortality lasted less than 12 months and had few events. We found moderate or high strength of evidence that metformin monotherapy, pioglitazone monotherapy and the combinations of metformin plus a DPP-4 inhibitor and metformin plus an SGLT-2 inhibitor were associated with similar all-cause mortality (Figure C). Otherwise, all evidence for all-cause mortality was of low strength or insufficient.

Figure C. Pooled odds ratios of all-cause mortality and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (odds ratio); Met = metformin; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea
The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Cardiovascular Mortality

Most studies reporting on cardiovascular mortality were 12 months or shorter and did not have many events. We found high strength of evidence that metformin yielded a 37 to 50 percent lower risk of cardiovascular mortality when compared to a sulfonylurea monotherapy (Table C). Otherwise, all evidence for cardiovascular mortality was of low strength or insufficient. Notably, we were unable to identify evidence supporting strong conclusions regarding the comparative effect on cardiovascular mortality associated with rosiglitazone.

Cardiovascular Morbidity

Most studies reporting on cardiovascular morbidity were 12 months or shorter and did not have many events. Consistent with our findings on cardiovascular mortality, we found moderate strength of evidence that metformin was associated with less cardiovascular morbidity than a sulfonylurea monotherapy (Table C). We also found moderate strength of evidence that cardiovascular morbidity was similar for metformin and pioglitazone monotherapy. Otherwise, all evidence for cardiovascular mortality was of low strength or insufficient. We were unable to identify evidence supporting strong conclusions regarding the comparative effect on cardiovascular morbidity associated with rosiglitazone.

Retinopathy, Nephropathy, and Neuropathy

While we found more evidence than in the prior report, few studies evaluated these outcomes; all evidence was of low strength or insufficient for these outcomes.

Table C. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for selected long-term clinical outcomes

Outcome	Conclusions	Strength of Evidence
Cardiovascular mortality	Metformin monotherapy had 37-50% lower risk of cardiovascular mortality compared with SU monotherapy.	High
Cardiovascular morbidity	Metformin monotherapy was associated with less cardiovascular morbidity than SU monotherapy (range of risk differences with metformin as the reference reported across three RCTs, -10.1% to +0.4%; range of adjusted HRs reported across five observational studies, 1.06 to 3.22).	Moderate
	Cardiovascular morbidity was similar for metformin and pioglitazone monotherapy (no events in two of three RCTs; range of adjusted HRs with metformin as the reference reported in observational studies, 1.0 to 1.15).	Moderate

HR = hazard ratio; RCT = randomized controlled trial; SU = sulfonylurea

Key Question 3a and 3b. Comparative Safety of Monotherapy and Metformin-based Combinations

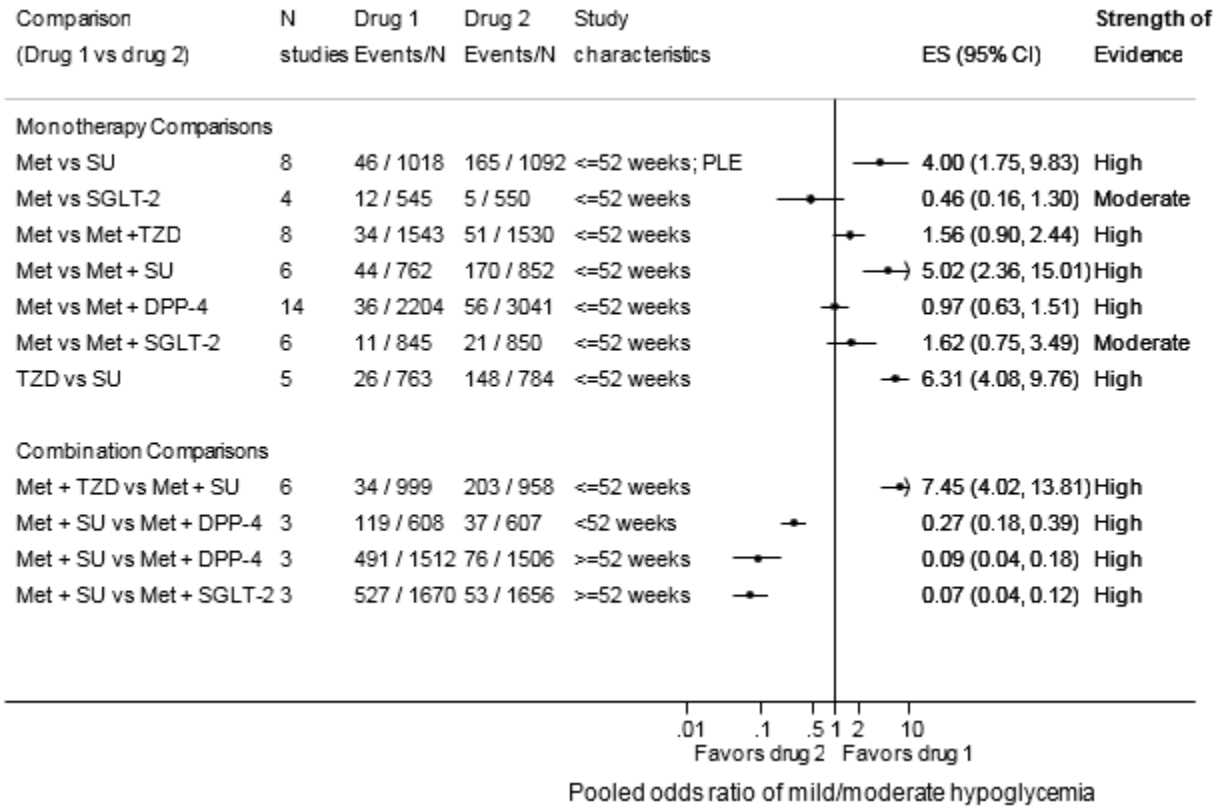
Of 189 studies identified for Key Question 3, one hundred sixty-eight were RCTs and eight were observational (mainly retrospective cohort) studies. Mean or median follow up of the observational studies ranged from 3 months to 5 years.

Hypoglycemia

Sulfonylurea alone and in combination with metformin had a higher risk of mild, moderate or total hypoglycemia compared to all other monotherapies and metformin-based combinations for which we identified evidence (Figure D). Compared to metformin monotherapy, only metformin plus a sulfonylurea had a significantly higher rate of hypoglycemia. When compared with metformin plus a basal insulin, metformin plus a GLP-1 agonist had less hypoglycemia risk and metformin plus a premixed insulin had a modestly higher risk of hypoglycemia.

For severe hypoglycemia, we found moderate to high strength of evidence that sulfonylureas had about a 1.5-fold increase in the risk of severe hypoglycemia compared with metformin or thiazolidinedione monotherapy. Similarly, in combination with metformin, sulfonylureas had a greater risk of severe hypoglycemia when compared with the combination of metformin plus DPP-4 inhibitors or SGLT-2 inhibitors (moderate strength of evidence). We also found moderate strength of evidence that metformin plus DPP-4 inhibitors had similarly few to no severe hypoglycemia events compared with metformin monotherapy or metformin plus a thiazolidinedione.

Figure D. Pooled odds ratios of mild/moderate hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (odds ratio); Met = metformin; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinediones
The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Gastrointestinal Side Effects

Metformin and GLP-1 agonists were associated with higher risk of gastrointestinal side effects than were all other medications with sufficient studies for comparison, regardless of whether they were used as monotherapy or combination (Table D). Metformin plus a GLP-1 agonist had more GI side effects than other metformin-based combinations. Nausea and vomiting were more common with GLP-1 agonists compared with metformin, but diarrhea was similar between the groups.

Congestive Heart Failure

We found low strength of evidence that the risk of congestive heart failure was 1.4 fold greater with thiazolidinediones compared to sulfonylureas or metformin. There were no long-term trials and only a few observational studies of medium quality that could provide an assessment of the comparative safety of diabetes medications on congestive heart failure.

Cancer

While we found much more evidence than in the prior report, few studies evaluated cancer risk, and all of the evidence was of low strength or insufficient. Notably, we did not identify

evidence to support strong conclusions regarding the comparative cancer risk for pioglitazone or the GLP-1 agonists.

Pancreatitis

We found moderate strength of evidence that metformin monotherapy and metformin plus a DPP-4 inhibitor were associated with similar risks of pancreatitis (Table D); pancreatitis was rare in the studies of this comparison. All other evidence on pancreatitis, including that for DPP-4 inhibitor comparisons and the GLP-1 comparisons, was of low strength or insufficient.

SGLT-2 Inhibitor-Specific Outcomes

We evaluated the comparative effectiveness of SGLT-2 inhibitors for specific adverse events of interest: urinary tract infections, genital mycotic infections, renal function impairment, fractures, and volume depletion. We found high strength of evidence that the combination of metformin plus a SGLT-2 inhibitor increased the odds of a genital mycotic infection approximately 3-fold compared to metformin monotherapy and 6-fold compared to the combination of metformin plus a sulfonylurea (Table D). We also found moderate strength of evidence that SGLT-2 inhibitors increased the odds of genital mycotic infection 4-fold compared to metformin monotherapy. Moderate to high strength of evidence suggested no increased risk of urinary tract infections for SGLT-2 inhibitors alone or in combination with metformin compared to metformin monotherapy or metformin plus a sulfonylurea. The evidence was of low strength or insufficient for the other SGLT-2 inhibitor-specific safety outcomes.

Other Outcomes

The evidence on the outcomes of liver injury, lactic acidosis, severe allergic reactions, and macular edema and decreased vision was of low strength or insufficient. We could not make any solid conclusions about these outcomes.

Table D. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for selected safety outcomes

Outcome	Conclusions	Strength of Evidence
GI	Metformin was associated with more frequent GI adverse events than DPP-4 inhibitor monotherapy • Pooled OR 2.6; 95% CI, 1.2 to 5.5 for diarrhea • Pooled OR 2.7; 95% CI, 1.1 to 6.6 for nausea	High
	The rates of GI adverse events were similar for: • TZD vs. SU monotherapy • Metformin vs. metformin plus a DPP-4 inhibitor (diarrhea) • Metformin plus SU vs. metformin plus DPP-4 inhibitor	High
	Metformin was associated with more frequent GI adverse events than • TZD monotherapy: o Pooled OR 0.29; 95% CI, 0.24 to 0.35 for diarrhea o Pooled OR 0.62; 95% CI, 0.49 to 0.78 for nausea • SU monotherapy: o Pooled OR 0.41; 95% CI, 0.28 to 0.59 for diarrhea o Pooled OR 0.57; 95% CI, 0.40 to 0.81 for abdominal pain o Pooled OR 0.45; 95% CI, 0.31 to 0.65 for nausea and vomiting • Metformin plus SU: o Pooled OR 0.66; 95% CI, 0.34 to 1.28 for diarrhea	Moderate
	The occurrence of diarrhea was similar for metformin and GLP-1 agonist monotherapy, but vomiting was more frequent for GLP-1 agonist vs. metformin monotherapy: pooled OR, 0.45; 95% CI, 0.31 to 0.65 for nausea and vomiting.	Moderate
	Metformin plus a GLP-1 agonist was associated with about a 2-fold higher risk of GI adverse events than: • Metformin plus a DPP-4 inhibitor • Metformin plus a TZD	Moderate
	The rates of GI adverse events were similar for metformin monotherapy and • Metformin plus a SGLT-2 inhibitor (diarrhea) • Metformin plus a DPP-4 inhibitor (nausea)	Moderate
	The rates of GI adverse events were similar for the combination of metformin plus SU compared with metformin plus TZD.	Moderate
Pancreatitis	The rates of pancreatitis were similar for metformin compared to combination therapy with metformin and DPP-4 inhibitor.	Moderate
UTI	The rates of UTIs were similar for metformin plus SGLT-2 inhibitors and metformin monotherapy.	High
	The rates of UTIs were similar for: • metformin and SGLT-2 inhibitors • metformin plus a SGLT-2 inhibitor compared with metformin plus SU	Moderate
Genital mycotic infections	The rates of genital mycotic infections were higher with metformin plus SGLT-2 inhibitors compared with • Metformin monotherapy: o pooled OR, 3.0; 95% CI, 1.22 to 7.2 for females o pooled OR, 2.7; 95% CI, 0.8 to 9.0 for males • Metformin plus SU: o pooled OR, 6.1; 95% CI, 4.0 to 9.2	High
	The rates of genital mycotic infections were higher with SGLT-2 inhibitors compared with • Metformin monotherapy: o pooled OR, 4.1; 95% CI, 2.0 to 8.3 • Metformin plus DPP-4 inhibitors	Moderate

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GI=gastrointestinal; GLP-1 = glucagon-like peptide-1 agonists; OR=odds ratio; SGLT-2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; UTI = urinary tract infection

Key Question 4. Subgroups

We found little evidence on the comparative effectiveness and safety of diabetes medications in predefined subgroups defined by age, sex, race/ethnicity, or BMI. Most of the evidence on subgroups was for the outcome of HbA1c and did not show differential effects of the included comparisons by age, sex, race/ethnicity, or BMI.

Discussion

Key Findings in Context

Intermediate Outcomes

Our results on the intermediate outcomes of hemoglobin A1c and weight are generally consistent with existing literature.[8, 19-23] This report builds on prior work by adding more information regarding the metformin-based combination comparisons and comparisons with the newer medications. HbA1c is unequivocally linked to microvascular disease,[24-26] making it a good proximal outcome to measure. Consistent with the 2011 report, most monotherapies were similarly effective in reducing HbA1c with the exception of DPP-4 inhibitors which had a smaller effect relative to metformin (Figure A). While metformin versus GLP-1 agonists and metformin versus SGLT-2 inhibitors also showed no clear between-group differences in HbA1c, they were graded as low strength of evidence since the three studies in each comparison were imprecise and inconsistent. In this update, we found inconsistent findings in the studies of GLP-1 agonists. It may be that the individual GLP-1 agonists have different effects on HbA1c. A 2011 Cochrane systematic review showed small between-group differences in HbA1c, around 0.3%, in the effect of different GLP-1 agonists.[20]

Combination therapy with metformin generally reduced HbA1c by 0.7 to 1 absolute percentage point compared to metformin monotherapy. While several moderate strength of evidence combination comparisons were significantly favored over the comparator combination (Figure 97), most between-group differences were small (<0.3%) with questionable clinical relevance. Only one combination comparison with moderate strength of evidence was favored by greater than 0.3% over any other combination comparison: the combination of metformin plus a GLP-1 agonist reduced HbA1c more than metformin plus a DPP-4 inhibitor. Two prior network meta-analyses[21, 22] showed that most metformin combination comparisons had similar reductions in HbA1c. However, the direct comparisons evaluated in this report are more precise than the indirect comparisons found in the network meta-analyses.

Weight gain was small to moderate in the trials in which participants gained weight; even in the longest trials, weight gain was less than 5 kg. However, even small amounts of weight gain (5 percent to 10 percent of body weight) may be associated with increased insulin resistance.[27] Drug effects on weight may impact the choice of the drug added for second-line combination therapy in a patient not well controlled on a single agent. As monotherapy and in combination with metformin, thiazolidinediones and sulfonylureas are associated with weight gain, DPP-4 inhibitors with weight maintenance, and SGLT-2 inhibitors and GLP-1 agonists are associated with weight loss.[8, 19, 20, 28] Our systematic review builds on prior work by adding more direct comparative data about metformin combination comparisons, which further confirm the known weight effects of the individual medications.

Systolic blood pressure and heart rate were evaluated for the newer classes of medications, the SGLT-2 inhibitors and GLP-1 agonists, due to suspected effects of these medications based on prior literature.[19, 20] Blood pressure control is important in adults with diabetes.[29-32] The United Kingdom Prospective Diabetes Study (UKPDS) showed that for every 10 mmHg decrease in systolic blood pressure, there is a 15% decrease in diabetes-related deaths.[30] Our findings on modest systolic blood pressure reductions of 3 to 5 mmHg with SGLT-2 inhibitors, compared to many other agents, are consistent with other reviews[19] on these agents (Table B). Our review builds on this prior work by evaluating direct comparisons of specific medication classes as comparators, as opposed to lumping all active comparators together. This is especially important since thiazolidinediones and GLP-1 agonists also have been associated with decreases in systolic blood pressure by 3 to 5 mmHg.[7, 20] Also, metformin plus a GLP-1 agonist had a greater reduction in systolic blood pressure compared with metformin alone (pooled between-group difference, 3.1 mmHg; 95% confidence interval [CI], 1.4 to 4.9 mmHg), with moderate strength of evidence. While the clinical relevance of these small differences is unclear, a change of 3 to 5 mmHg is about half the effect of a low sodium diet (around 7 to 11 mmHg) and about one-third the effect of blood pressure medications (around 10 to 15 mmHg).[33, 34]

Increased heart rate is associated with increased mortality.[35] However, whether heart rate is an independent predictor of long-term clinical outcomes such as mortality is less clear.[36] We also wanted to determine if the benefits from blood pressure reduction might be offset by a concomitant increase in heart rate. We did not identify any prior systematic reviews that have evaluated this outcome for the diabetes comparisons of interest. Only two comparisons had sufficient data to grade the evidence as more than insufficient or low. Surprisingly, SGLT-2 inhibitors in combination with metformin were found to decrease heart rate by 1.5 bpm (95% CI, 0.6 bpm to 2.3 bpm) when compared with metformin plus a sulfonylurea; metformin and GLP-1 agonists showed no differences in heart rate between groups. Therefore, these early findings support minimal to no effects on heart rate and no increase in heart rate for the newer medications.

Long-term Outcomes

Most of the evidence on long-term outcomes came from RCTs which were generally 12 months or shorter in duration and had few events; combined with small sample sizes, these studies were underpowered to evaluate long-term outcomes; notably, none of the RCTs specified a long-term outcome as a primary outcome. This report builds substantially on our prior results for metformin versus sulfonylurea monotherapy.[8] Metformin was associated with a 37 to 50 percent lower risk of cardiovascular mortality compared to sulfonylurea monotherapy, with consistent findings on cardiovascular morbidity (Table C). This adds to published evidence on cardiovascular mortality with sulfonylureas.[37] We found moderate strength of evidence that metformin and pioglitazone monotherapy were associated with similar all-cause mortality and cardiovascular morbidity, but we did not otherwise find evidence to support substantial conclusions about the comparative effectiveness of thiazolidinediones on cardiovascular risk (Figure C).

We found little evidence supporting conclusions regarding most of the newer classes of drugs (DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors) and clinical outcomes. Metformin and the combination of metformin plus a DPP-4 inhibitor were associated with similar all-cause mortality as were metformin and the combination of metformin plus an SGLT-2 inhibitor.

Existing literature has not evaluated this outcome for these comparisons of add-on therapy to metformin.

The scant evidence on the comparative effectiveness of diabetes medications and microvascular outcomes (retinopathy, nephropathy, and neuropathy) precludes any substantive conclusions.

Safety Outcomes

For the outcomes of hypoglycemia and GI side effects, we confirmed the elevated risk of hypoglycemia associated with sulfonylureas compared other drug classes (Figure D), including for severe hypoglycemia. We added to the literature base on SGLT-2 inhibitors by providing more evidence showing that SGLT-2 inhibitors may have less risk of hypoglycemia than metformin, although both medications had low absolute rates of hypoglycemia. We also found that when compared with metformin plus basal insulin, metformin plus a GLP-1 agonist had less hypoglycemia risk. This is especially important when considering which injectable medication to add as second line therapy. Finally, our findings suggest that DPP-4 inhibitors do not increase risk of severe hypoglycemia when added to metformin compared with metformin monotherapy or metformin plus a thiazolidinedione (i.e., non-insulin and non-insulin secretagogue medications).

We also confirmed prior findings that metformin induces more GI events than thiazolidinediones, sulfonylureas and DPP-4 inhibitors (Table B). We identified new evidence about GLP-1 agonists and SGLT-2 inhibitors: metformin plus a GLP-1 agonist was associated with more GI side effects compared to metformin plus a thiazolidinedione or metformin plus a sulfonylurea. GLP-1 agonists were also associated with more vomiting, but similar rates of diarrhea, when compared to metformin monotherapy. Surprisingly, the combinations of metformin plus DPP-4 inhibitors did not have worse GI events than metformin monotherapy or metformin combinations despite the DPP-4 inhibitors known side effects of nausea.[38] SGLT-2 inhibitors did not increase GI events when added to metformin.

We found about a 1.4-fold increased risk of heart failure with the thiazolidinedione class of medications (low strength of evidence), when compared with metformin or sulfonylureas, which was also reported in two recent meta-analyses.[39, 40] We excluded the RECORD study for this outcome due to the active comparator being *either* sulfonylurea or metformin in the analysis instead of a single active comparator. RECORD showed that the combination of thiazolidinediones and another agent (sulfonylurea or metformin) was associated with a significant doubling in the risk of heart failure in comparison to the combination of sulfonylurea and metformin (61/2220 versus 29/2227, risk ratio (RR), 2.1; 95% CI, 1.35 to 3.27).[41] Both thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage 3 or Stage 4) according to product labels.[42, 43]

We had low or insufficient strength of evidence for most other medication comparisons for heart failure, including the newer agents. The SAVOR-TIMI 53 trial,[44] mentioned above, was excluded from our systematic review of head-to-head comparisons of diabetes medications since it compared saxagliptin with placebo. Hospitalization for heart failure was reported in 289/8280 (3.5%) in the saxagliptin arm versus 228/8212 (2.8%) in the matching placebo arm, with a HR of 1.27 (95% CI, 1.07 to 1.51). Due to this finding, the FDA has requested trial data from the manufacturer to analyze whether there might be an increased risk of heart failure with saxagliptin.[45] Further research directly comparing DPP-4 inhibitors with other active

comparators on heart failure outcomes will be critical for determining the comparative safety of these medications on heart failure risk.

We found little evidence to substantiate firm conclusions about pancreatitis for the incretin therapies, which include DPP-4 inhibitors and GLP-1 agonists. Rates of pancreatitis were similar for metformin monotherapy and metformin plus a DPP-4 inhibitor. Notably, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction (SAVOR TIMI) 53 trial, not included in this review, found 17 cases of definite acute pancreatitis in the saxagliptin monotherapy arm compared to nine in the placebo arm over 2.1 years (P =0.17).[44]

We found little evidence about cancer risk. Reviews and meta-analyses published since the 2011 report show that metformin decreases the risk of many types of cancer[46, 47] and suggest that pioglitazone[48] increases the risk of bladder cancer slightly, but we could not include many of the studies supporting those conclusions in our review because of our stringent inclusion criteria for observational studies. While animal studies raise concern about the risk of cancer with incretin therapies, we found little evidence about cancer risk in humans.

SGLT-2 inhibitors increased the risk of genital mycotic infections substantially. Our findings that SGLT-2 inhibitors did not increase the risk of urinary tract infections are in conflict with one review[19] but in agreement with another.[49] The evidence on SGLT-2 inhibitor comparisons regarding fractures, renal impairment, and volume depletion were not conclusive.

Evidence on other adverse events including liver injury, lactic acidosis, macular edema/decreased vision, and severe allergic reactions was not conclusive in this report. Similarly, the evidence on the comparative effectiveness of diabetes medications in subgroups defined by age, sex, race/ethnicity, and BMI was generally inconclusive.

Implications

This update provides additional evidence supporting metformin as the first-line medication therapy to treat type 2 diabetes when tolerated, and supports a number of treatment options that can be added to metformin based on patient preferences. Not only is metformin favored on many intermediate outcomes including HbA1c and weight, we found more conclusive evidence to support a greater benefit on cardiovascular morbidity and mortality with metformin over sulfonylureas. This is consistent with several current guidelines such as the American College of Physicians (ACP) and American Diabetes Association (ADA) which recommend metformin as a first-line treatment choice. We did not find large differences in HbA1c-lowering effects of the diabetes medications studied except for DPP-4 inhibitors which were not as effective.

Weight effects of the medications varied and this may be a valid consideration when choosing a medication to add to metformin. Similarly, each class of medications has differing common side effects (e.g., hypoglycemia, GI side effects) which may impact treatment choice; the evidence on rare, serious side effects is less clear. Overall, after first-line therapy with metformin, patient preferences and medication costs are likely to continue to drive selection of and adherence to the diabetes medications.

Limitations of the Review Process

A few key limitations to our review deserve mention. To focus on comparative effectiveness, we did not include placebo-controlled studies and instead evaluated head-to-head comparisons. We also excluded studies in which participants could take non-study drugs for treating diabetes (“background” medications) in which results were not stratified by medication. We used this

exclusion to avoid interactions between medications. This was especially important because of our goal of evaluating two-drug combinations. Using these criteria, we excluded some well-known trials,[50, 51] since investigators did not stratify their results to allow reporting on the head-to-head comparisons of interest. We also used strict selection criteria for observational studies, mainly based on the control of confounding factors. In this way, we included observational studies with the most valid results to support conclusions. Finally, we did not evaluate patient-reported outcomes such as quality of life; future research is needed to identify ideal measures to assess patient-reported outcomes in diabetes.

Applicability

Using the PICOTS (Population, Intervention, Comparisons, Outcomes, Timing, Setting) framework, the evidence in this report is generally applicable to the population of US adults with type 2 diabetes with a few notable concerns. Compared to the general population with diabetes,[52] populations in the included studies were slightly younger, included fewer elderly adults (e.g., often excluded persons >75 years of age), had fewer significant co-morbid conditions, and were less racially and ethnically diverse. Regarding the interventions, the majority of studies were less than two years long, but in usual care, patients with diabetes are on medications for decades. While many of the longer duration studies were consistent with the short-term findings, more studies lasting greater than 2 years are needed to better understand the durability of the differences reported in shorter-term studies.

Research Gaps

Using the PICOTS framework, we identified several important gaps in the evidence and highlight the major ones below:

- Studies often excluded older adults, racial/ethnic minorities, and persons with co-morbid conditions such as significant renal, cardiovascular and hepatic impairment.
- Studies rarely reported specified *a priori* subgroups of interest such as older adults, racial/ethnic minorities, sex, or BMI.
- RCTs evaluating intermediate outcomes of glycemic control, weight, and blood pressure for GLP-1 agonist comparisons as monotherapy and in combination with metformin versus specific diabetes medication comparators were rarely included.
- We did not identify any RCTs which had all-cause mortality, cardiovascular mortality, cardiovascular morbidity, or adverse events as a primary outcome.
- The evidence base is completely lacking in studies on microvascular outcomes.
- RCTs for long-term clinical outcomes and rare safety events were underpowered (characterized by small sample sizes, study duration generally 12 months or less, and low event rates).
- Studies were lacking for specific safety concerns related to specific drugs (e.g., congestive heart failure [CHF] and thiazolidinediones; liver injury and thiazolidinediones; lactic acidosis and metformin; pancreatitis with DPP-4 inhibitors and GLP-1 agonists; macular edema and thiazolidinediones; hypovolemia, renal impairment and fractures for SGLT-2 inhibitors).
- Few studies on intermediate outcomes, long-term outcomes or harms lasted more than two years whereas patients take diabetes medications for decades.

- Few studies compared metformin plus insulin with other specific metformin-based combinations. The comparison of metformin plus insulin versus metformin plus a GLP-1 agonist is particularly relevant for all outcomes when deciding on an add-on injectable to metformin.

Based on these gaps, we make the following recommendations by outcome for future research:

Intermediate Outcomes

- Longer duration RCTs (>4 years) of all diabetes medication comparisons to determine if short-term comparative effects are durable.
- RCTs evaluating the GLP-1 agonists as monotherapy and in combination with metformin are needed. If adding GLP-1 agonists to different background medications, then RCTs should conduct stratified randomization by background medication and evaluate effects by background medication in their analysis. See methodologic gaps below.
- RCTs evaluating intermediate outcomes for metformin plus the addition of insulin with other metformin-based combinations, and in particular metformin plus a GLP-1 agonist would be useful for patients and clinicians contemplating an add-on injectable to metformin.

Long-term Outcomes

- Longer duration RCTs and higher quality observational studies (>2 years) of all diabetes medication comparisons for retinopathy, nephropathy, and neuropathy.
- Longer duration RCTs and higher quality observational studies (>2 years) of all diabetes medication comparisons where all-cause mortality, cardiovascular mortality, and cardiovascular morbidity are the primary outcomes.

Safety Outcomes

- Higher-quality observational studies are needed for most safety outcomes (i.e. CHF, cancer, pancreatitis, hypovolemia, liver injury, lactic acidosis, macular edema/decreased vision, renal impairment, and severe allergic reactions).
- To answer specific safety concerns related to specific drug classes, we also recommend the following more focused approach:
  - For CHF and macular edema, more studies are needed which directly compare thiazolidinediones with specific classes of diabetes medications directly.
  - For CHF, more studies are needed which directly compare DPP-4 inhibitors with specific classes of diabetes medications directly.
  - For pancreatitis, more studies are needed which directly compare DPP-4 inhibitors and GLP-1 agonists with other specific classes of diabetes medications directly.
  - For bladder cancer, more studies are needed which directly compare pioglitazone directly to other medications, and for thyroid cancer, more studies are needed which compare the GLP-1 agonists directly to other drugs.
  - For hypovolemia, renal impairment, and fractures, more studies are needed which directly compare SGLT-2 inhibitors with specific classes of diabetes medications directly.

Subgroups

- Studies which include older adults, racial/ethnically diverse populations, and adults with comorbid conditions (such as renal impairment, hepatic impairment, and cardiovascular

conditions) will allow investigators to conduct subgroup analyses on areas of interest, which is especially important for long-term and safety outcomes.

- Studies with an a priori plan to investigate differences by important subgroups of interest (i.e., age, race, sex, and BMI) are needed.

Methodological Gaps and Suggested Improvements

Key methodological issues which severely limited our ability to draw conclusions from the existing evidence on the comparative effectiveness of diabetes medications include the following: lack of reporting on randomization methods for RCTs, allocation concealment, blinding, and withdrawals; inconsistent definitions and ascertainment of long-term and safety outcomes; inconsistent reporting of safety and long-term outcomes in each study arm; and lack of appropriate accounting for confounding for observational studies. Based on these methodological gaps, we make the following recommendations for future research:

- Consistent adverse event and long-term outcome reporting for all arms in a study, with predefined outcomes and definitions, and a description of methods for ascertainment of outcomes
- Consistent reporting of the number of deaths and other adverse events in each study arm, even if there were none
- Consistent reporting of between-group comparisons of changes from baseline, as well as measures of dispersion to improve interpretation of findings
- Use of clinically-relevant, standardized definitions for microvascular outcomes (e.g., incident nephropathy based on eGFR and urine albumin:creatinine ratios).
- Use of clinically-relevant, standardized definitions for safety outcomes (e.g., liver injury >3x the upper limit of normal) and active ascertainment of these outcomes.
- For randomized trials:
  - Consistent reporting of the steps taken to ensure randomization, allocation concealment, and double blinding
  - Focusing on retention of participants and followup of withdrawn participants if possible, especially for deaths and rare safety events (e.g., cancer)
  - If allowing more than one background medication, then stratifying randomization by background medication
- High-quality observational studies, including post-marketing studies, are needed to strengthen the evidence base, especially given the resource-intense nature of adequately-powered RCTs to evaluate long-term and safety outcomes.
- For observational studies:
  - Consistent reporting of details of the treatment type, dose, timing and duration of use of the medication, when available
  - Appropriate control for confounders (including confounding by indication), such as the use of propensity scores
  - Comparison of one medication directly with another medication (e.g., as opposed to thiazolidinediones versus non-thiazolidinediones).
- Consistent reporting on which medications are allowed as “background” medications and stratification of results by the combination therapy (for studies allowing use of “background” medications).

Conclusions

Although the comparative long-term benefits and harms of most diabetes medications remain unclear, the evidence continues to support the beneficial effects of metformin on intermediate and long-term outcomes, along with its relative safety. In this report, we provide comprehensive information comparing the benefits and minor and serious harms of diabetes medications. This can facilitate personalized treatment choices for clinicians and their patients as well as support decisionmaking by payers and regulators. This may be especially important as newer, costly medications come off patent and become more accessible to patients.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014 [cited 2015 February 26]; Available from: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
2. Nichols GA, Schroeder EB, Karter AJ, Gregg EW, Desai J, Lawrence JM, et al. Trends in diabetes incidence among 7 million insured adults, 2006-2011: the SUPREME-DM project. Am J Epidemiol. 2015 Jan 1;181(1):32-9.
3. Standards of medical care in diabetes-2014. Diabetes Care. 2014;37(SUPPL.1):S14-S80.
4. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
5. (7) Approaches to glycemic treatment. Diabetes Care. 2015 Jan;38 Suppl:S41-8.
6. Garber A, Abrahamson M, Barzilay J, Blonde L, Bloomgarden Z, Bush M, et al. American association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. Endocrine Practice. 2013;19(SUPPL. 2):1-48.
7. Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S, et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Comparative Effectiveness Review No 8 (Prepared by the Johns Hopkins Evidence-based Practice Center under Contract No 290-02-0018). Rockville, MD: Agency for Healthcare Research and Quality; 2007.
8. Bennett WL, Wilson LM, Bolen S, Maruthur N, Singh S, Chatterjee R, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Rockville MD2011.
9. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012 Nov;55(11):2929-37.
10. Lu CJ, Sun Y, Muo CH, Chen RC, Chen PC, Hsu CY. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013;36(2):145-51.
11. Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013 Aug;166(2):240-9 e1.
12. Mamtani R, Haynes K, Bilker WB, Vaughn DJ, Strom BL, Glanz K, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst. 2012 Sep 19;104(18):1411-21.

13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12.

14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998 Jun;52(6):377-84.

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.

16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88.

17. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Ann Intern Med. 2014 Feb 18;160(4):267-70.

18. Owens DK, Lohr KN, Atkins D, Treadwell JR, Reston JT, Bass EB, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23.

19. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-74.

20. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [serial on the Internet]. 2011; (10): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006423.pub2/abstract.

21. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: A network meta-analysis. Diabetes, Obesity and Metabolism. 2012;14(9):810-20.

22. McIntosh B, Cameron C, Singh SR, Yu C, Ahuja T, Welton NJ, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med. 2011;5(1):e35-48.

23. Goring S, Hawkins N, Wygant G, Roudaut M, Townsend R, Wood I, et al. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis. Diabetes Obes Metab. 2014 May;16(5):433-42.

24. Schellhase KG, Koepsell TD, Weiss NS. Glycemic control and the risk of multiple microvascular diabetic complications. Fam Med. 2005 Feb;37(2):125-30.

25. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med. 1997 Nov 1;127(9):788-95.

26. 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. 1998 Sep 12;352(9131):837-53.

27. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000 Aug;106(4):473-81.

28. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [serial on the Internet]. 2008; (2): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006739.pub2/abstract.

29. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991 Jun 26;265(24):3255-64.

30. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998 Sep 12;317(7160):703-13.

31. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000 Aug 12;321(7258):412-9.

32. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med. 2000 Jan 24;160(2):211-20.

33. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001 Jan 4;344(1):3-10.

34. Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, et al. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005 Jul;18(7):935-42.

35. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011 Dec 21;306(23):2579-87.

36. Singh N. Diabetes, heart rate, and mortality. J Cardiovasc Pharmacol Ther. 2002 Apr;7(2):117-29.

37. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: A meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism. 2013;15(10):938-53.

38. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: Systematic review and meta-analysis. BMJ (Online). 2012;344(7850):17.

39. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007 Sep 29;370(9593):1129-36.

40. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007 Sep 12;298(10):1189-95.

41. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 2009 Jun 5.

42. GlaxoSmithKline. Highlights of Prescribing Information: Avandia (rosiglitazone maleate) tablets. 2014 [cited 2015 March 2]; Available from: http://us.gsk.com/products/assets/us_avandia.pdf.

43. Takeda Pharmaceuticals America. Highlights of Prescribing Information: Actos (pioglitazone) tables for oral use. 2013 [cited 2015 March 2]; Available from: http://general.takedapharm.com/content/file/pi.pdf?applicationcode=8a9c4571-a123-4477-91deb9cafe7d07e3&filetypecode=actospi.

44. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.

45. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR). 2014 [cited 2015 March 2]; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm385287.htm.

46. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One. 2013;8(8):e71583.

47. Zhang ZJ, Bi Y, Li S, Zhang Q, Zhao G, Guo Y, et al. Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis. Am J Epidemiol. 2014 Jul 1;180(1):11-4.

48. Ferwana M, Firwana B, Hasan R, Al-Mallah MH, Kim S, Montori VM, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. Diabet Med. 2013 Sep;30(9):1026-32.

49. Kawalec P, Mikrut A, Lopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2014 May;30(4):269-83.

50. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.

51. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 2009 Jan;32(1):84-90.

52. Wong HK, Ong KL, Cheung CL, Cheung BM. Utilization of glucose, blood pressure, and lipid lowering medications among people with type II diabetes in the United States, 1999-2010. Ann Epidemiol. 2014 Jul;24(7):516-21 e1.

Introduction

Background

Type 2 diabetes currently affects 9.3 percent of the US population or 29.1 million people.[1] The proportion of affected individuals in the US varies greatly by race and ethnicity, with 16 percent of American Indian/ Alaska Natives, 13 percent of non-Hispanic black Americans and Hispanic Americans, 9 percent of Asian Americans, and 7 percent of non-Hispanic white Americans afflicted with diabetes, the vast majority of which is type 2 diabetes.[2] Within these racial categories, rates also vary substantially within sub-populations (e.g., South Asian-Americans and East Asian-Americans).[2] Estimates of diabetes incidence that include laboratory-diagnosed diabetes, in addition to self-report, are higher than those reported by the US Centers for Disease Control and Prevention.[3] Encouragingly, most reports in the US and Europe suggest that the incidence of disease has *not* been rising over the past decade.[4] Similarly, the age at diagnosis has been relatively stable at 55 years in non-Hispanic whites, and 49 years in non-Hispanic blacks and Hispanics.[5]

Diabetes and its complications are a substantial public health burden as they contribute significantly to mortality, morbidity, and health care costs.[1, 6] Costs related to diabetes were approximately $245 billion in 2012.[1] Complications of longstanding diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy, and end-stage kidney disease. Diabetes is the most prevalent cause of new-onset blindness and new-onset end-stage renal disease in adults in the U.S. Diabetes also contributes importantly to macrovascular complications including coronary artery disease, peripheral arterial disease, and carotid artery disease and increases the risk of cardiovascular-related death nearly two-fold.[7]

Lifestyle modification and pharmacologic therapy are the cornerstones of the management of hyperglycemia for type 2 diabetes.[8] Results from randomized controlled trials have established that the risk of microvascular complications, particularly retinopathy, can be reduced with glycemic control in patients with type 2 diabetes.[9, 10] However, studies in the past decade have suggested, however, that using diabetes medications to achieve *intensive* glycemic control [hemoglobin A1c (HbA1c) less than 7%] does not have benefits on cardiovascular morbidity and mortality[11, 12] and may harm patients, including those with important co-morbid conditions.[13] Recent work also suggests that the effects of intensive glucose lowering may vary across racial and ethnic groups.[14] These mixed results on the benefits and safety of glycemic control through pharmacologic therapy suggest the need for further research, including investigation of the long-term impact of glucose lowering therapies.

Even if there is resolution of the question about intensity of control, clinicians and other stakeholders are left with the question regarding the choice of the optimal agent for glucose lowering. Given the ever-increasing literature about type 2 diabetes medications and the recent approval of many new medications, an updated systematic review evaluating the effects of these medications on intermediate and long-term effectiveness and safety outcomes will be valuable to clinicians, patients, investigators, guideline developers, and payers. In this era of intensive direct-to-consumer marketing of new drugs, clinicians need a trustworthy source of comprehensive information about the comparative effectiveness and safety of medications. This review seeks to inform diverse clinicians about treatment options for their patients; this includes family practitioners, general internists, nurse practitioners, physician assistants, nurses, pharmacists, endocrinologists, cardiologists, nephrologists, and others. Guideline developers may also find this review to be informative for clinical practice guideline preparation. Patients and patient

advocates will find the information valuable when making decisions about treatment options. Finally, investigators will be able to use the results of this review to identify gaps in the literature and formulate original research questions to fill these knowledge gaps.

Rationale for Update of Review on Comparative Effectiveness of Diabetes Medications

The Effective Health Care (EHC) Program of the Agency for Healthcare Research and Quality (AHRQ) has published two systematic reviews comparing monotherapies and medication combinations for adults with type 2 diabetes.[15, 16] In 2007, the AHRQ published its first systematic review, including 216 studies, on this topic.[15] This review concluded that most U.S. Food and Drug Administration (FDA)-approved diabetes medications had similar effects on reducing HbA1c, and most drugs, except for metformin and acarbose, caused at least modest increases in body weight. The sulfonylurea class was associated with an increased risk of hypoglycemia, metformin with gastrointestinal problems, and the thiazolidinediones with heart failure. Importantly, the literature was too sparse to support any conclusions about differential effects of the oral diabetes medications on all-cause mortality, cardiovascular mortality and morbidity, and microvascular complications. When asked by AHRQ to update that review in 2011, we identified an additional 140 randomized controlled trials and 26 observational studies.[16] We found that most medications lowered HbA1c by 1 absolute percentage point, on average, but metformin was more effective for HbA1c-lowering than the dipeptidyl-peptidase 4 (DPP-4) inhibitors, a newer class of diabetes medications approved since the initial report. The two-drug combinations largely all had similar effects on HbA1c reduction. Compared with metformin, thiazolidinediones and sulfonylureas contributed to more weight gain. Sulfonylureas had a four-fold higher risk of mild/moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a five-fold increased risk of hypoglycemia when compared with metformin plus thiazolidinediones. The risk of congestive heart failure was higher with thiazolidinediones than with sulfonylureas, and the risk of bone fractures was higher with thiazolidinediones than with metformin. Thus, the evidence continued to support use of metformin as a first line agent based on its HbA1c and weight effects and side effect profile, and the risk of adverse effects was the main determinant of the risk-benefit balance for the two-drug combinations.

Despite the addition of important evidence on the HbA1c-lowering and adverse effects of the FDA-approved diabetes at that time, data on the then recently-approved medication classes (glucagon-like peptide-1 (GLP-1) agonists and DPP-4 inhibitors) were sparse, and data on long-term outcomes for both older and newer medications were still lacking.[17, 18] Based on these prior systematic reviews, metformin has strong evidence to support its use as an initial pharmacologic treatment for most patients with type 2 diabetes;[7] however, the evidence base regarding therapies for patients with intolerance or contraindications to metformin or when monotherapy is insufficient continues to evolve.

Since January 2010, one new medication class [the sodium-glucose co-transporter 2 (SGLT-2) inhibitors, with three new medications] and several new DPP-4 inhibitors and GLP-1 agonists have been approved by the FDA. Additional data on previously-approved medications have also emerged since 2010 which could change the balance of benefit and risk attributable to these drugs or could alter the strength of evidence about some of the drug comparisons previously reviewed.[19-22] Including insulin, there are 10 medication classes with approval by the FDA for

treatment of type 2 diabetes. We have included most, although not all, in this updated systematic review.

Table 1. Characteristics of medications included in this report

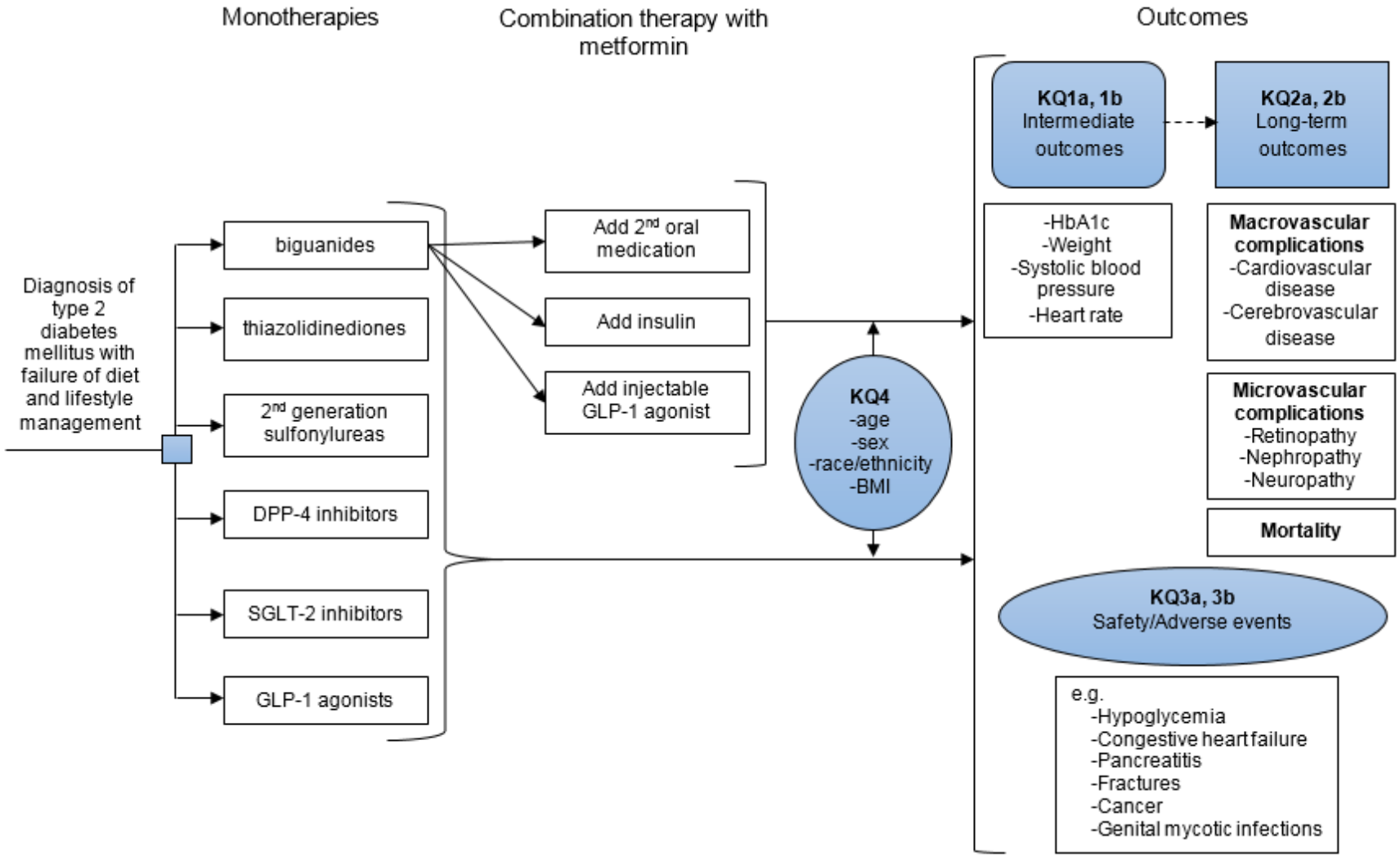
Class	Drug	Trade name	Dosing
Biguanides	Metformin	Glucophage®, Glucophage XR®	Oral: 500 to 2550 mg divided doses (qd to tid) Max dose: 2550 mg; 2000 mg for XR
Thiazolidinediones	Pioglitazone	Actos®	Oral: 15 to 30 mg qd Max dose: 45 mg qd
	Rosiglitazone	Avandia®	Oral: 4 to 8 mg qd or 2 to 4 mg bid Max dose: 8 mg qd or 4 mg qd with insulin or sulfonylurea
Sulfonylureas	Glimepiride	Amaryl®	Oral: 1 to 8 mg qd Max dose: 8 mg qd
	Glipizide	Glucotrol®, Glucotrol XL®	Oral: 5 to 15 mg qd or 5 to 20 mg bid Max dose: 20 mg bid, 20 mg qd for XL
	Glyburide or glibenclamide	DiaBeta®, Glynase® PresTab®, Micronase®	Oral: 2.5 to 20 mg qd or bid Max dose: 20 mg qd
DPP-4 inhibitors	Alogliptin	Nesina®	Oral: 6.25 to 25 mg qd Recommended dose: 25 mg qd
	Linagliptin	Tradjenta®	Oral: 5 mg qd Recommended dose: 5 mg qd
	Saxagliptin	Onglyza®	Oral: 2.5 to 5 mg qd Recommended dose: 2.5 or 5 mg qd
	Sitagliptin	Januvia®	Oral: 25 to 100 mg qd Recommended dose: 100 mg qd
SGLT-2 inhibitors	Canagliflozin	Invokana®	Oral: 100 to 300 mg Max dose: 300 mg
	Dapagliflozin	Farxiga®	Oral: 5 to 10 mg qd Max dose: 10 mg qd
	Empagliflozin	Jardiance®	Oral: 10 to 25 mg qd Max dose: 25 mg qd
GLP-1 agonists	Albiglutide injection	Tanzeum®	SC injection: 30 mg qw Max dose: 50 mg qw
	Dulaglutide injection	Trulicity®	SC injection: 0.75 to 1.5 mg/0.5 mL Max dose: 1.5 mg/0.5 mL
	Exenatide injection	Byetta®	SC injection: 5 to 10 mcg SC bid
	Liraglutide injection	Victoza®	SC injection: 1.6 to 1.8 mg SC qd
Basal insulin	NPH insulin	Humulin N®, Novolin N®	NA
	Insulin detemir	Levemir®	NA
	Insulin glargine	Lantus®	1 to 80 units daily
Premixed insulin	50% NPH and 50% regular insulin	Humulin® 50/50	NA
	70% NPH and 30% regular insulin	Humulin® 70/30 Novolin® 70/30	NA
	50% lispro protamine suspension and 50% lispro	Humalog Mix® 50/50	NA
	75% lispro protamine suspension and 25% lispro	Humalog Mix® 75/25	NA
	70% aspart protamine suspension and 30% aspart	NovoLog Mix® 70/30	NA

bid = twice daily; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; mcg = microgram; mg = milligrams; mL = milliliter; NA = not applicable; NPH = neutral protamine Hagedorn; qd = once daily; qw = once weekly; SC = subcutaneous; SGLT-2 = sodium-glucose co-transporter-2; tid = three-times daily; XL = extended release; XR = extended release

Analytic Framework

Our analytic framework describes the decisions that patients and their providers face when managing type 2 diabetes pharmacologically (Figure 1). It highlights the comparisons and outcomes of interest that correspond to each of the key questions in our review. When beginning medical treatment, patients usually begin with one of five drug classes (Table 1), which have all been FDA-approved for monotherapy. These include biguanides, thiazolidinediones, 2nd generation sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 agonists. Clinical guidelines of the American Diabetes Association recommend monitoring HbA1c to determine the need for changing the medication dose or adding another agent to improve glycemic control.[23] If the HbA1c is not adequately controlled, clinicians typically add an additional oral diabetes medication, or may add insulin or a noninsulin injectable medication like a GLP-1 agonist. Clinicians also monitor other intermediate outcomes such as weight and short-term and long-term safety and adverse effects of the drugs, which vary by drug class. Finally, the ultimate goal is to improve long-term outcomes.

Figure 1. Analytic framework



BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; KQ=key question; NPH = neutral protamine Hagedorn; SGLT-2 inhibitor = sodium-glucose co-transporter 2

Scope and Key Questions

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[16] In this review, we have chosen to focus on head-to-head drug comparisons for which there are evidence gaps (see Table 2). We have included a new FDA-approved class of oral diabetes medications, the SGLT-2 inhibitors, including empagliflozin, dapagliflozin, and canagliflozin. We have included new DPP-4 inhibitors approved since the last review, linagliptin and alogliptin; as well as GLP-1 agonists approved since the last review, albiglutide and dulaglutide.

Given the unique and emerging safety concerns of some of these medications, we have included additional safety outcomes in the review including impaired renal function, urinary tract infections, genital infections, volume depletion, and bone fractures for studies that include a comparison with SGLT-2 inhibitors, and systolic blood pressure and heart rate as intermediate outcomes for studies including either SGLT-2 inhibitors or GLP-1 agonists.

We have chosen to exclude meglitinides as interventions of interest as they are uncommonly used in current clinical practice (<1% of hypoglycemic prescriptions).[24, 25] We evaluated meglitinides in our two earlier systematic reviews and found that this class has similar effects on HbA1c and similar rates of hypoglycemia as sulfonylureas. The 2011 update included little new information on meglitinides, and we expected to find little additional evidence for this class of medication.

Similarly, we are no longer reporting on lipid levels as intermediate outcomes of interest. LDL targets are no longer universally the primary factor guiding the use of cholesterol-lowering therapy. Current guidelines suggest that 10-year global cardiovascular disease (CVD) risk should be used to determine statin usage and intensity, and this global risk score does not actually include low-density lipoprotein cholesterol.[26] Furthermore, triglycerides and high-density lipoprotein are not usual targets of cholesterol therapy. Statin usage is recommended for all patients age 40 and over with diabetes in the US.[27] Based on these new approaches to lipids, we did not feel that evidence of the impact of diabetes medications on lipid levels would be substantially informative to clinical care to warrant inclusion in this report.

Key Questions

Key Question 1a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications (see Table 2) for the intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 agonists)?

Key Question 1b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications (see Table 2) for the intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 agonists)?

Key Question 2a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications (see Table 2) for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 2b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications (see Table 2) for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 3a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the specified monotherapy FDA-approved diabetes medications (see Table 2) regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 3b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the specified metformin-based combinations of FDA-approved diabetes medications (see Table 2) regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 4: Do the comparative safety and effectiveness of these treatments differ across subgroups defined by the age, sex, race/ethnicity, and body mass index (BMI) of adults with type 2 diabetes?

Table 2. Priority Medication Comparisons Included for Each Key Question

	Main Intervention	Comparisons
Monotherapy as main intervention	Metformin	• Thiazolidinediones* • Sulfonylureas† • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 agonists • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT-2 inhibitor • Combination of metformin plus GLP-1 agonist
	Thiazolidinedione	• Sulfonylureas • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 agonists
	Sulfonylurea	• DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 agonists
	DPP-4 inhibitor	• SGLT-2 inhibitors • GLP-1 agonists
	SGLT-2 inhibitor	• GLP-1 agonists
Combination therapy as main intervention	Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 agonist or basal insulin)	• Combination of metformin plus (sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 agonist or basal insulin or premixed insulin)

DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; GLP-1 agonist = glucagon-like peptide-1 receptor agonist; SGLT-2 inhibitor = sodium-glucose co-transporter 2

* For studies comparing thiazolidinediones with metformin, we review only the outcomes of HbA1c, long-term outcomes, and select safety outcomes given the **high strength of evidence** from our prior evidence report for other outcomes (specifically fracture and weight).[16]

† For studies comparing sulfonylureas with metformin, we review only the long-term outcomes and cancer given the **high strength of evidence** on the other outcomes from our prior CER.[16]

Methods

Topic Refinement and Review Protocol

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[16] We recruited a Technical Expert Panel (TEP) to review a draft of the protocol and a summary of the revisions from the 2011 review (see the Scope and Key Questions section from the Introduction). The TEP included endocrinologists, general internists, biostatisticians, and representatives from government agencies. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the Key Questions. With the feedback from the TEP and the Agency for Healthcare Research and Quality (AHRQ) representatives, we finalized the protocol and posted it on AHRQ Effective Health Care Program's Web site (www.effectivehealthcare.ahrq.gov).

Literature Search Strategy

Search Strategy

The 2011 review searched the following databases for the dates listed: MEDLINE® (1966 to April 2010), Embase™ (1974 to April 2010), and the Cochrane Central Register of Controlled Trials (CENTRAL). Per AHRQ's guidance, our new search dates overlapped the prior search by more than 1 year.[28] We ran the search developed for the 2011 review with the date restrictions of April 2009 through July 2014 (see Appendix A).

An additional expanded search included medical subject headings (MeSH) and text words for all of the new medications included in this updated report. The expanded search did not have any date restrictions.

We handsearched the reference lists of all newly included articles and relevant systematic reviews. Additionally, we searched ClinicalTrials.gov to identify relevant registered trials. We also reviewed the Food and Drug Administration (FDA) Web site for any unpublished additional studies relevant to the topic as part of our grey literature search. We provided an opportunity for manufacturers of interventions to submit unpublished data as well.

Study Selection

Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers needed to indicate that the study was ineligible. If the reviewers disagreed, the article was advanced to the next level, which was abstract review.

The abstract review phase was designed to identify studies reporting the effectiveness or safety of the medications and medication combinations of interest. Abstracts were reviewed independently by two investigators and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 3). Differences between investigators regarding the inclusion or exclusion of abstracts were tracked and resolved through consensus adjudication.

Articles promoted on the basis of the abstract review underwent another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion were tracked and resolved through consensus adjudication.

Table 3. Inclusion and exclusion criteria

PICOTS	Inclusion criteria	Exclusion criteria
Population	• We included studies of adult humans with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes.	• We excluded studies of patients with type 1 diabetes, impaired glucose tolerance, metabolic syndrome, maturity onset diabetes of youth, and gestational diabetes. • We excluded studies if they included only pregnant women or subjects less than or equal to 17 years of age. • We excluded studies where everyone was required to have at least one of the following comorbid conditions: ESLD, ESRD, cancer, new onset diabetes after organ transplant, or a recent cardiovascular event within the 3 months prior to study start.
Interventions	• We included studies that evaluated a diabetes medication of interest or drug combination of interest (see Table 2).	• We excluded studies that did not specify the adjunctive medications, such as those stating use of "any oral hypoglycemic" or if the study listed several possible medications without stratification of the results by treatment.
Comparisons	• We included studies that evaluated a comparison of interest (see Table 2).	• We excluded studies that did not have a comparison group or that used a placebo comparison or non-pharmacological comparison. • We excluded intraclass head-to-head comparisons.
Outcomes*	• We included studies addressing the following intermediate outcomes for KQ1: ▪ Hemoglobin A1c^ ▪ Weight† ▪ Systolic blood pressure‡ ▪ Heart rate‡ • We included studies addressing the following long-term clinical outcomes for KQ2: ▪ All-cause mortality ▪ Cardiovascular and cerebrovascular morbidity and mortality ▪ Retinopathy ▪ Nephropathy ▪ Neuropathy • We included studies addressing the following safety outcomes for KQ3: ▪ Liver injury^ ▪ Impaired renal function§ ▪ Lactic acidosis^ ▪ Pancreatitis^ ▪ Hypoglycemia^ ▪ Gastrointestinal side effects^ ▪ Congestive heart failure^ ▪ Cancer ▪ Macular edema or decreased vision^ ▪ Fractures§ ▪ Urinary tract infections§ ▪ Genital mycotic infections§ ▪ Volume depletion§ • KQ4 included studies considering any of the above outcomes.	

Type of study	• For KQ1, we included only RCTs. • For KQ2 and KQ3, we included RCTs, non-randomized experimental studies with a comparison group, and high-quality observational studies with a comparison group. • We included randomized trials utilizing a crossover design with some exceptions.[‖]	• We excluded studies not written in English[¶] and excluded articles with no original data. • We excluded meeting abstracts.
Timing and setting		• We excluded studies in which the observed intervention or exposure period was less than 3 months, 12 weeks, or 90 days.

ESLD = end-stage liver disease; ESRD = end-stage renal disease; KQ = Key Question; RCT = randomized controlled trial
* Of note, some outcomes could be classified as either safety or long-term clinical outcomes (e.g., myocardial infarction and cancer).
^ We did not evaluate this outcome for metformin vs. sulfonylurea comparisons as the evidence was high from the prior report.
[†] We did not evaluate this outcome for metformin vs. thiazolidinedione or metformin vs. sulfonylurea comparisons as the evidence was high from the prior report.
[‡] We evaluated this outcome only for comparisons that included a GLP-1 agonist or a SGLT-2 inhibitor.
[§] We evaluated this outcome only for comparisons that included a SGLT-2 inhibitor.
[‖] For crossover randomized trials, we abstracted data on all outcomes at the end of the first period prior to the crossover. If data were not presented at the end of the first period, then we excluded the article for the following outcomes where we would be unable to draw conclusions about causality: long-term outcomes (KQ2), fractures, cancer, intermediate outcomes in studies where there was a washout period of less than 3 months; and safety outcomes in studies where the washout period was less than a month except for hypoglycemia, gastrointestinal side effects, and liver injury.
[¶] We decided to include non-English language articles through the full text article review phase of the updated search and assess the volume and content of these articles along with workload to determine if abstracting data from these articles would add value to the review.

Data Extraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We used standardized forms from the previous reviews as templates for data extraction and pilot tested them for the new medications and outcomes. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

We double-reviewed all data abstracted from the studies. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. A third reviewer audited a random sample of articles to ensure consistency in the data abstraction of the articles. Reviewers were not be masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers extracted information on the general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, race, weight/body mass index, hemoglobin A1c levels, and duration of diabetes), interventions (e.g., initial, maximum, and mean doses, frequency of use, duration of use, and permissibility of treatment intensification with additional therapies), comparisons, the method of ascertainment of safety outcomes, and the outcome results, including measures of variability. We also collected data on outcomes for the subgroups of interest, which were age, sex, race/ethnicity, and body mass index (BMI).

For continuous outcomes, we extracted the mean difference between groups and a measure of dispersion. If the between-group difference was not reported, we calculated the point estimate of the difference using the mean difference from baseline for each group. If the mean difference from baseline was not reported, we calculated this from the baseline and final values for each

group.[29] If there were no measures of dispersion for the mean difference from baseline for each group, we calculated the variance using the standard deviation of the baseline and final values, assuming a correlation between baseline and final values of 0.5.

We entered all information from the article review process into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada). Reviewers entered comments into the system whenever applicable. The DistillerSR database was used to maintain the data and to create detailed evidence tables and summary tables. Data will later be uploaded into the Systematic Review Data Repository.

Risk of Bias Assessment of Individual Studies

Two independent reviewers assessed study quality. We assessed the risk of bias in individual randomized controlled trials (RCTs) using the Jadad criteria consistent with the prior report.[30] We used the Downs and Black tool for assessment of risk of bias for non-randomized trials and observational studies.[31] Given that observational studies with a high risk of bias add little value to a systematic review of effectiveness,[32] we included only medium- and high-quality observational studies as determined by assessment of each study's risk of bias. For inclusion, we required that observational studies account for the following potential confounders: age, sex, either race or socioeconomic status, and co-morbid conditions (either quantified with a co-morbidity scale or index, or by inclusion of other medical conditions or medications used by the patient, or with valid methods to adjust for confounding by indication or restricted to one race or age group making adjustment unnecessary). If the study met both the confounding and losses to follow up criteria, the observational study was considered eligible for inclusion in the review. The Downs and Black tool and other inclusion criteria for nonrandomized trials and observational studies were also applied to the non-randomized trials and observational studies that had been included in the prior report.[16]

Data Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies, including those from the prior evidence reports. We included the results of individual studies included in the prior report as well as the newly-identified studies. We conducted meta-analyses when there were sufficient data (at least three trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose). For trials having more than one dosing arm, we chose the arm for inclusion that had dosing most consistent with the other trials considered for inclusion in the meta-analysis. When more than one followup interval was reported, we used the data from the followup most similar to the other trials.

We tested the heterogeneity among the trials considered for quantitative pooling using a standard chi-squared test using a significance level of alpha less than or equal to 0.10. We also examined heterogeneity among studies with an I-squared statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. We considered a value greater than 50 percent to indicate substantial heterogeneity.[33] We pooled the mean difference between groups using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity (I-squared <50%).[34] We pooled studies using the profile likelihood estimate when we detected high statistical heterogeneity (I-squared >50%).[35] When data were not sufficient or appropriate to combine in a meta-analysis, we summarized the outcomes by

reporting the ranges of values for mean differences from baseline or mean differences between groups, when available.

Since we anticipated that most drugs would have similar physiologic effects within a class, we combined studies of unique medications within classes when reporting outcomes *except* where known differences exist (such as the effects of pioglitazone and rosiglitazone on cardiovascular outcomes). If we saw substantial heterogeneity (I-squared >50%) in pooled estimates for any outcome, we stratified studies by medication within a class and repeated the pooled analyses and recalculated measures of heterogeneity. Additionally, when there were at least 10 studies for a given comparison and outcome and evidence of statistical heterogeneity, we attempted to determine other reasons for heterogeneity by evaluating study-level characteristics, such as baseline values of the outcome, study duration, quality measures, or dosing differences between study arms using metaregression techniques. We also conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimates.

For the outcome of hypoglycemia, we conducted separate analyses for: (a) severe hypoglycemia and (b) mild or moderate hypoglycemia. The categories were based on the definitions of hypoglycemia provided in the studies. For hypoglycemia and all other dichotomous outcomes, we calculated pooled odds ratios using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity[34] or the profile likelihood estimate in settings of high heterogeneity.[35]

Reporting Bias Assessment

We assessed reporting biases in the included RCTs as follows:[36]

1) Publication bias was evaluated by:

a) Using the Begg and Mazumdar[37] and the Egger[38] test to quantitatively assess for publication bias when there were at least 10 studies for a given comparison and outcome pair
b) Comparing ClinicalTrials.gov entries and actual publications for evidence of absence of published literature
c) Comparing FDA medical and statistical reviews and actual publications for evidence of absence of published literature.

2) Selective Outcomes Reporting bias was evaluated by comparing differences in reporting on the outcomes of hemoglobin A1c (HbA1c), hypoglycemia, and all-cause mortality in the actual publications to the FDA medical and statistical reviews.

3) Selective Analysis Reporting bias was evaluated by assessing the precision of outcome data reporting by determining the number of studies which reported on an outcome of interest (e.g., HbA1c) but did not report a precise measure of dispersion completely or at all. We assessed this for the outcomes of HbA1c, hypoglycemia, and all-cause mortality. For dichotomous outcomes (hypoglycemia and all-cause mortality), we evaluated the number of studies reporting both the n of events and the n at risk for the event (i.e., numerator and denominator for risk). We reviewed this for the studies included for the update only.

Strength of the Body of Evidence

At the completion of our review, two reviewers sequentially graded the available evidence addressing the Key Questions by adapting an evidence grading scheme recommended by the

Guide for Conducting Comparative Effectiveness Reviews.[39] We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome. We assessed the study limitations, consistency, directness, precision, and reporting bias.

We assessed the study limitations of individual studies using the tools described in the Risk of Bias of Individual Studies section. We started with the assumption that randomized controlled trials would have "low" study limitations and observational studies would have "medium" study limitations. We downgraded the study limitations score based on the items in the quality assessment tools.

We rated the body of evidence as "consistent" if at least 75% of the studies showed the same direction of effect. We rated the consistency of comparison-outcome dyads for which there was only a single study as "unknown." All other bodies of evidence were rated as "inconsistent."

We rated the bodies of evidence for all outcomes as "direct" except for heart rate and liver injury. We rated the bodies of evidence for heart rate as "indirect" because the association between heart rate and clinically important outcomes such as mortality is less strong in adults with diabetes.[40] We rated the bodies of evidence for the outcome of liver injury as "indirect" since most of the studies used liver injury enzyme elevation as the indicator of injury.

If we conducted a meta-analysis for a body of evidence, we relied on the results of the meta-analysis to rate precision and used the designated minimally important differences as a point of reference for precision. For continuous outcomes, we rated the body of evidence as "imprecise" if one-half of the width of the confidence interval for the meta-analysis was wider than the minimally important difference. We defined the minimally important difference to be 0.3% for HbA1c, 1 kg for weight, and 3 mmHg for systolic blood pressure. If there was no meta-analysis, we rated precision by evaluating the narrowness of the confidence intervals or the magnitude of the *P*-value. For dichotomous outcomes, we evaluated precision using the optimal information size for that outcome. If the total sample size across both arms of the studies was greater than the optimal information size, then we rated the body of evidence as "precise." Otherwise, it was rated as "imprecise." We estimated rough optimal information sizes using the Mantel Hanzel model for relative odds and incorporating the approximate baseline rate of the outcome and the desired minimum detectable relative odds (Table 4).[41]

Table 4. Optimal information size for one arm and classification of dichotomous outcomes for optimal information size

	"Low" detectable OR, 1.05	**"Medium" detectable OR, 1.5**	**"High" detectable OR, 2.0**
"Low" baseline risk, 0.01	654,548 (All-cause mortality, cardiovascular mortality, cardiovascular morbidity, cancer, diabetic nephropathy)	8,364 (Liver injury, pancreatitis, severe allergic reaction, renal impairment, congestive heart failure, microalbuminuria, volume depletion)	2,597
"Medium" baseline risk, 0.15	51,168 (Severe hypoglycemia)	690 (Urinary tract infections, genital infections)	225
"High" baseline risk, 0.3	31,296	446 (Hypoglycemia)	153 (Gastrointestinal events)

OR = odds ratio

We rated reporting bias by evaluating publication bias, selective outcomes reporting bias, and selective analysis reporting bias (described in the Reporting Bias Assessment section). If any of

these domains was rated as “suspected,” then we rated the body of evidence as having “suspected” reporting bias. Otherwise, we rated reporting bias as “undetected.”

We classified evidence pertaining to the Key Questions into four categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion). We provided a conclusion regarding if a given drug was favored over another (or if neither was favored) when the evidence permitted this.

We graded the evidence separately for the RCTs and the observational studies.[39] The final evidence grade and conclusion was typically based on the RCT grade and could be strengthened by evidence from the observational studies. We noted differences between RCT and observational evidence in the text when present.

Applicability

We discussed the applicability of studies in terms of the degree to which the study population (e.g., age, sex, race/ethnicity, and co-morbid conditions), interventions (e.g., dose, frequency, rescue therapy, duration of exposure), outcomes (e.g., outcome definition and reporting), and settings are typical of the treatment of individuals with type 2 diabetes who are receiving treatment in a usual care setting (conceived as outpatient treatment by internists, family physicians, and endocrinologists).

Results

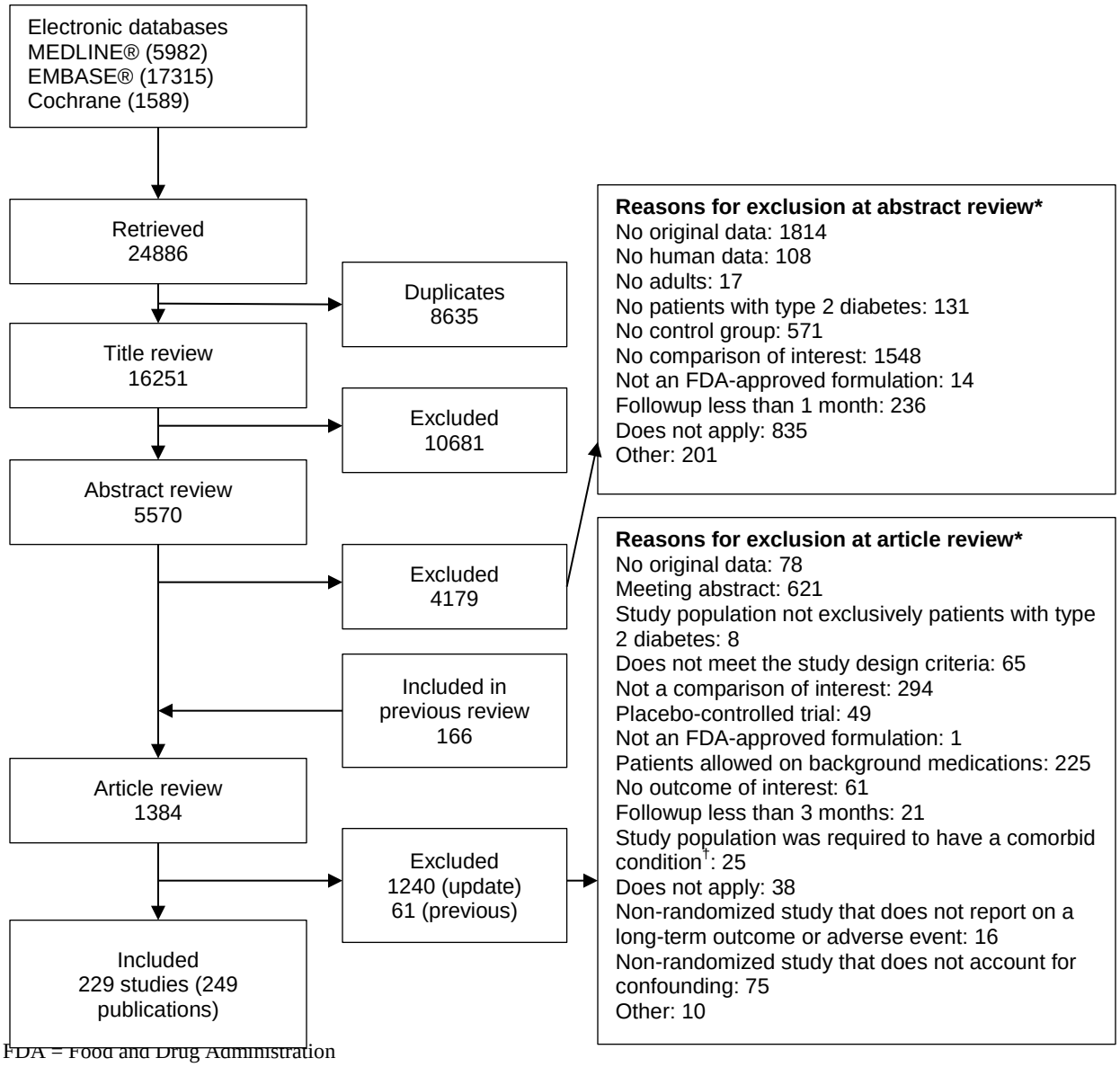
Results of Literature Searches

We included 166 publications in our previous review. After excluding studies without a comparison or an outcome relevant to this update, and cohort studies not meeting our revised quality criteria, we included 104 studies (published in 107 articles) in this update.

We retrieved 16,251 unique citations from our updated literature search (Figure 2). After reviewing titles, abstracts, and full text, we included 115 new studies (published in 142 new articles). Ten of the new publications were either extensions or additional analyses of studies included in the previous review.

In total, we include in this review 229 studies, published in 249 articles.

Figure 2. Summary of the search (number of articles)



FDA = Food and Drug Administration
* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
† Comorbid condition restrictions were end-stage renal disease, end-stage liver disease, cancer, new onset diabetes after transplant, or a cardiovascular event within 3 months (e.g., acute coronary syndrome, acute myocardial infarction, post-coronary artery bypass graft surgery, or with drug-eluting stents)

Key Question 1a and 1b: Intermediate Outcomes

Study Design and Population Characteristics

Two hundred and five randomized controlled trials (RCTs) (reported in 211 articles) evaluated intermediate clinical outcomes for adults with type 2 diabetes, and met our inclusion criteria (Appendix D, Tables 1 to 4). All trials were parallel arm RCTs except one which also used a crossover design[42] and one which also used a factorial design.[43] About half the trials answering Key Question 1 occurred partly or exclusively in the United States (US) (n = 37), Italy

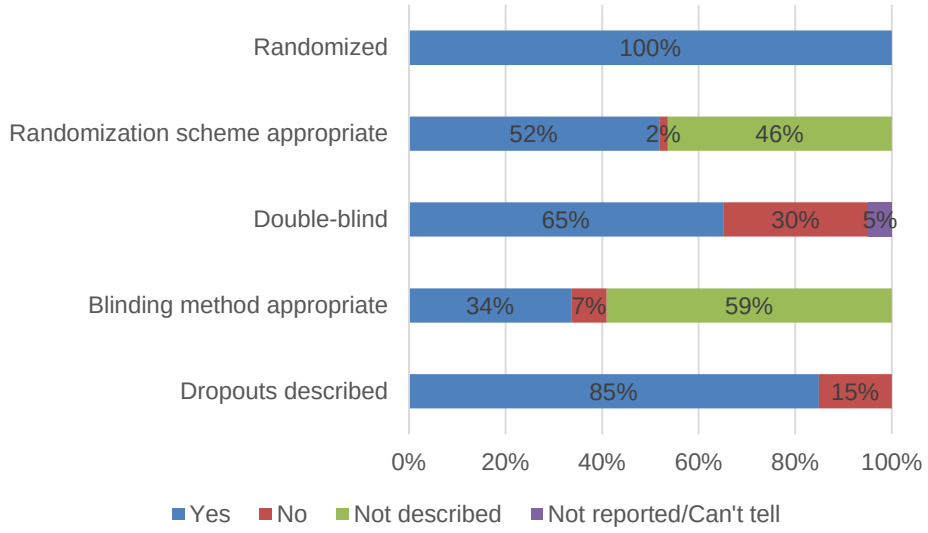
(n = 19), and/or were multi-national (n = 67); the rest of the trials occurred in developed or newly industrialized countries. These RCTs lasted from 12 weeks to 5.5 years; however, most studies (95%) lasted less than a year and only four studies lasted more than 2 years (including the well-known Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD), and A Diabetes Outcome Progression Trial (ADOPT)).[44-47] Only 9% of studies (n=19) reported receiving no pharmaceutical support, while about 20% of RCTs (n = 38) did not describe whether or not they received pharmaceutical support. The number of studies not reporting on pharmaceutical support has dropped from 25% of the studies included in the last diabetes medication comparative effectiveness report[16] to only 5% of the newly included 87 studies in this update. The use of rescue therapy was not reported in 43 of the 91 studies included (47.2%), was not allowed in 19 studies (20.9%), and was allowed in 29 studies (31.9%). In the studies where rescue therapy was allowed, 11 studies did not specify which medications were used, and when reported, the medications varied greatly.

Study participants were mainly middle-aged, overweight, or obese adults who had had diabetes between 3 to 7 years. The exclusion criteria were generally similar for most trials: significant renal, cardiovascular, and hepatic disease. About half the trials (58%) excluded older subjects (generally over 75 to 80 years old). Almost all the studies reported a diverse gender mix among the participants. About 29% of the RCTs did not report race/ethnicity. In this update, the percent not reporting race/ethnicity had increased from 20% of the 119 studies in the prior report[16] to 40% of the 86 studies in the newly included studies. When race was reported, most subjects were Caucasian but between 10% and 20% of the enrolled population was of other races in these studies. The mean baseline HbA1c among study subjects varied from 6 to 12 absolute percentage points, with most subjects having a mean baseline HbA1c between 7 and 9 absolute percentage points.

Risk of Bias

All of the studies included in this section were described as randomized (Figure 3). Fifty-two percent described their randomization scheme and another 65 percent were described as being double-blinded. About one-third (34 percent) of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of trials (85 percent) described the withdrawals and dropouts.

Figure 3. Summary of the risk of bias of randomized controlled trials evaluating intermediate outcomes



Key Points and Evidence Grades

Hemoglobin A1c

Monotherapy Comparisons

- Most oral diabetes medications had similar efficacy in achieving reductions in hemoglobin A1c (HbA1c), with absolute reduction by around 1 absolute percentage point compared with baseline values.
  - The strength of evidence was graded high that metformin was similar to sulfonylurea (pooled between-group difference of 0.1 percent; 95% confidence interval [CI], -0.1% to 0.3%) in the prior report. Therefore, we did not update this comparison for HbA1c in this review.
  - The strength of evidence (SOE) was also graded as high that metformin was similar to thiazolidinedione with a pooled between-group difference of -0.02% (95% CI, -0.10% to 0.07%).
  - Thiazolidinediones performed similarly to sulfonylureas with a pooled between-group difference of -0.04% (95% CI, -0.13% to 0.06%).
  - The strength of evidence was graded as low or insufficient for the monotherapy comparisons with the newer classes of sodium-glucose cotransporter (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, and will warrant further study.
- The one exception was that metformin had a greater reduction in HbA1c compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, with a pooled between-group difference of -0.4% (95% CI, -0.5% to -0.3%). (SOE: High)
- All combination therapies were better at reducing HbA1c than monotherapy regimens, with between-group differences of around 0.7 to 1 absolute percentage points. (SOE: Moderate or High)

Metformin-Based Combination Comparisons

- The combination of metformin plus GLP-1 agonists reduced HbA1c more than metformin plus DPP-4 inhibitors, with a pooled between-group difference of -0.65% (95% CI, -0.75% to -0.54%). (SOE: Moderate)
- Most other combination therapy comparisons had either no significant or no clinically meaningful (<0.3%) between-group differences in HbA1c between arms.
- The evidence was graded as moderate for the following comparisons: metformin plus a thiazolidinedione versus metformin plus a sulfonylurea, metformin plus a thiazolidinedione versus metformin plus a DPP-4 inhibitor, metformin plus a sulfonylurea versus metformin plus an SGLT-2 inhibitor, and metformin plus a DPP-4 inhibitor versus metformin plus an SGLT-2 inhibitor.

Weight

Monotherapy Comparisons

- Metformin had greater weight reductions than thiazolidinediones (pooled mean between-group difference of -2.6 kg; 95% CI, -4.1 kg to -1.2 kg) or sulfonylureas (pooled mean between-group difference of -2.7 kg; 95% CI, -3.5 kg to -1.9 kg) in the 2011 report with high strength of evidence. Therefore, we did not update these two comparisons in this report.
- Metformin had greater weight reduction than DPP-4 inhibitors (pooled mean between-group difference, -1.3 kg; 95% CI, -1.6 kg to -1.0 kg). (SOE: High)
- SGLT-2 inhibitors had greater weight reduction when compared with metformin or DPP-4 inhibitors (between-group differences ranging from 1.3 kg to 2.7 kg). (SOE: Moderate for both comparisons)
- DPP-4 inhibitors and GLP-1 agonists both decreased weight more than thiazolidinediones (range in between-group differences of 2.3 kg and 3.5 kg). (SOE: Moderate for both comparisons)
- GLP-1 agonists decreased weight more than sulfonylureas (pooled mean between-group difference, -2.3 kg; 95% CI, -3.3 kg to -1.2 kg). (SOE: Moderate)
- Sulfonylureas caused slightly less weight gain when compared with thiazolidinediones (between-group difference of -1.2 kg; 95% CI, -1.8 kg to -0.6 kg). (SOE: Moderate)
- Metformin monotherapy reduced weight more than the combination of metformin plus a thiazolidinedione (pooled mean between-group difference, -2.2 kg; 95% CI, -2.6 kg to -1.9 kg) or metformin plus a sulfonylurea (pooled mean between-group difference, -2.2 kg, 95% CI, -3.4 kg to -1.0 kg). (SOE: High for both comparisons)
- When compared with metformin, the combination of metformin plus
  - SGLT-2 inhibitor had greater weight reduction (pooled mean between-group difference, 2.1 kg; 95% CI, 1.5 kg to 2.6 kg). (SOE: High)
  - GLP-1 agonist had greater weight reduction (pooled mean between-group difference, 1.8 kg; 95% CI, 1.1 kg to 2.5 kg). (SOE: Moderate)
- Metformin monotherapy had no significant differences in weight when compared with the combination of metformin plus DPP-4 inhibitors (pooled mean between-group difference, -0.1 kg; 95% CI, -0.3 kg to 0.01 kg). (SOE: High)

Metformin-Based Combination Comparisons

- The combinations of metformin plus a sulfonylurea, metformin plus a GLP-1 agonist, and metformin plus a DPP-4 inhibitor all had a more favorable effect on weight compared with metformin plus a thiazolidinedione (range in between-group differences, 0.9 kg to 5.1 kg). (SOE: Moderate for all comparisons)
- When compared with the combination of metformin plus a sulfonylurea, the combination of metformin plus
  - DPP-4 inhibitors had more favorable effects on weight (pooled mean between-group difference, 2.2 kg; 95% CI, 1.8 kg to 2.5 kg). (SOE: High)
  - SGLT-2 inhibitors had more favorable effects on weight (pooled mean between-group difference, 4.7 kg; 95% CI, 4.4 kg to 5.0 kg). (SOE: High)
  - GLP-1 agonist had more favorable effects on weight (range in mean between-group differences, 2.4 kg to 12.3 kg). (SOE: Moderate)
  - Premixed insulin or basal insulin had **less** favorable effects on weight (range in mean between-group differences, -0.5 kg to -1.7 kg). The strength of evidence is low for both comparisons due to the small number of studies. However, taken together the strength of evidence would be moderate favoring metformin plus sulfonylurea over metformin plus a premixed or long-acting insulin.
- When compared with metformin plus a DPP-4 inhibitor,
  - The combination of metformin plus a GLP-1 agonist has greater reductions in weight (pooled mean between-group difference, 1.8 kg; 95% CI, 1.1 kg to 2.5 kg). (SOE: Moderate)
  - The combination of metformin plus SGLT-2 inhibitors had greater reductions in weight (between-group differences of around 2.5 kg). (SOE: Moderate)

Systolic Blood Pressure (For Comparisons That Include SGLT-2 Inhibitors or GLP-1 Agonists)

Monotherapy Comparisons

- SGLT-2 inhibitors had a greater reduction in systolic blood pressure compared with metformin, with a pooled between-group difference of 2.8 mmHg (95% CI, 2.6 mmHg to 3.0 mmHg). (SOE: Moderate)
- The strength of evidence was graded low or insufficient for the following comparisons:
  - SGLT-2 inhibitors versus DPP-4 inhibitors, and
  - GLP-1 agonists versus metformin, thiazolidinediones, sulfonylureas, and DPP-4 inhibitors.
- Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin alone, with a pooled between-group difference of 4.9 mmHg (95% CI, 2.4 to 6.3 mmHg). (SOE: High)
- Metformin plus a GLP-1 agonist reduced systolic blood pressure more than metformin alone, with a pooled between-group difference of 3.1 mmHg (95% CI, 1.4 to 4.9 mmHg). (SOE: Moderate)

Metformin-Based Combination Comparisons

- Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin plus a sulfonylurea (pooled between-group difference, 5.1 mmHg; 95% CI, 4.2 mmHg to

5.9 mmHg) or metformin plus a DPP-4 inhibitor (pooled between-group difference, 4.1 mmHg; 95% CI, 3.6 mmHg to 4.6 mmHg). (SOE: High and Moderate respectively)

Heart Rate (For Comparisons That Include SGLT-2 Inhibitors or GLP-1 Agonists)

Monotherapy Comparisons

- Metformin compared with a GLP-1 agonist yielded no differences in heart rate between arms. (SOE: Moderate)
- There was low or insufficient evidence for all metformin combination therapies compared with metformin alone.

Metformin-Based Combination Comparisons

- Combination therapy with metformin plus a SGLT-2 inhibitor resulted in less increase in heart rate compared with metformin plus a sulfonylurea (pooled between group difference in heart rate, 1.5 bpm; 95% CI, 0.6 bpm to 2.3 bpm). (SOE: Moderate)

The Evidence About Hemoglobin A1c

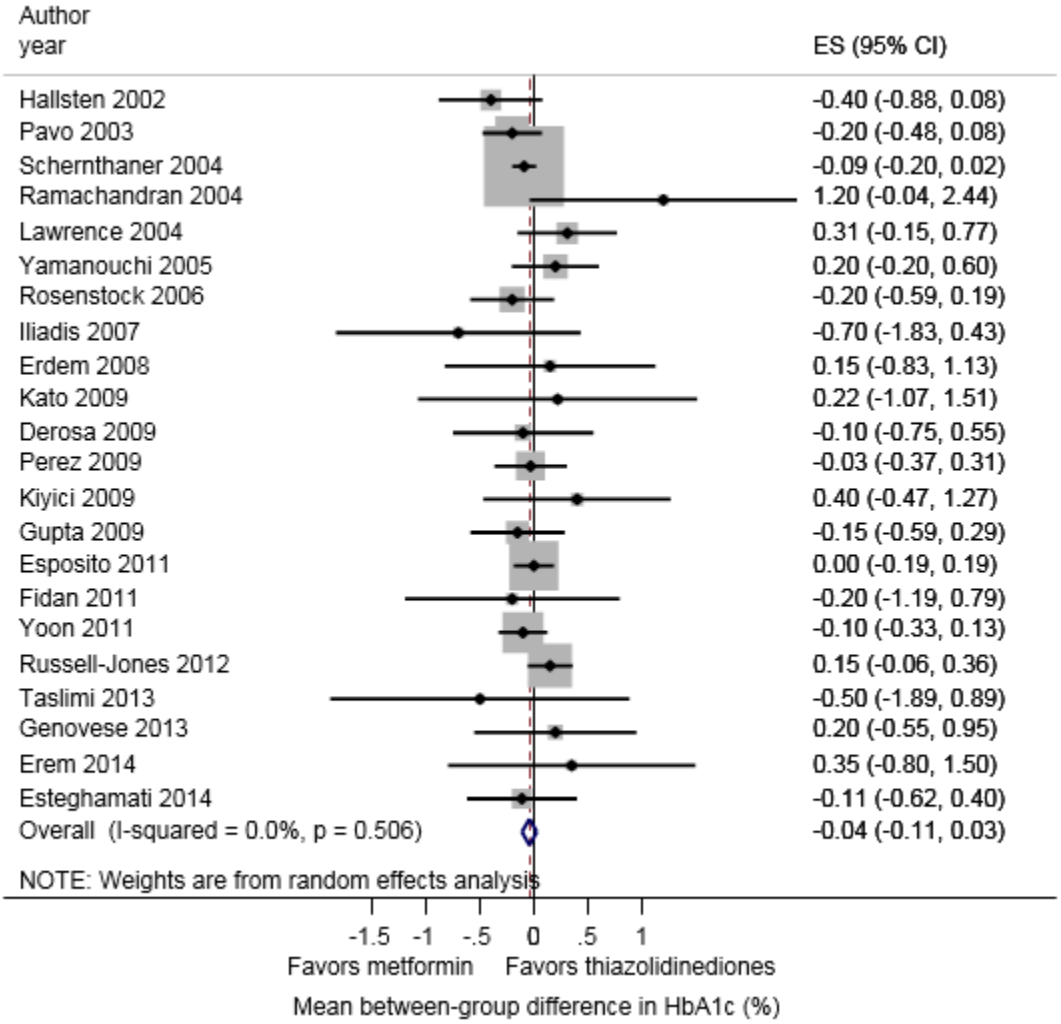
Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Twenty-two RCTs lasting around a year or less directly compared metformin with a thiazolidinedione, showing no between-group differences in HbA1c, with a pooled between-group difference of -0.04% (95% CI, -0.11% to 0.03%) (Figure 4).[48-69] We tested the relative effect of each individual study to the combined point estimate. No single study influenced the pooled results. No substantial heterogeneity was identified.

We excluded three studies from the meta-analysis, one with a median study duration of 4 years,[45] one which reported median HbA1c instead of means,[70] and one study where the mean difference between groups could not be calculated.[71] The 4-year double-blind RCT (known as the ADOPT study) was designed to compare long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for adults with type 2 diabetes.[45] The authors found a statistically significant but small difference between groups favoring rosiglitazone (mean difference between groups 0.1%; 95% CI, 0.05% to 0.2%). Of note, the HbA1c decreased in all groups for the first 6 months, and then increased in all groups over the rest of the study. The other two short duration RCTs excluded from the meta-analysis were consistent with the pooled results. One study reported no between-group differences in median HbA1c.[70] The second study was missing the number in each arm needed to calculate the between-group difference. Since this was an RCT, we calculated the between-group difference with the assumption of equal numbers in each arm which showed no statistically significant differences between-groups in HbA1c.[71] (SOE: High; Neither drug favored)

Figure 4. Pooled mean between-group difference in hemoglobin A1c comparing metformin with thiazolidinediones



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus Sulfonylureas

In the prior report, we graded the evidence as high showing no differences in HbA1c between-groups for this comparison. Therefore, we did not re-evaluate this comparison for HbA1c.

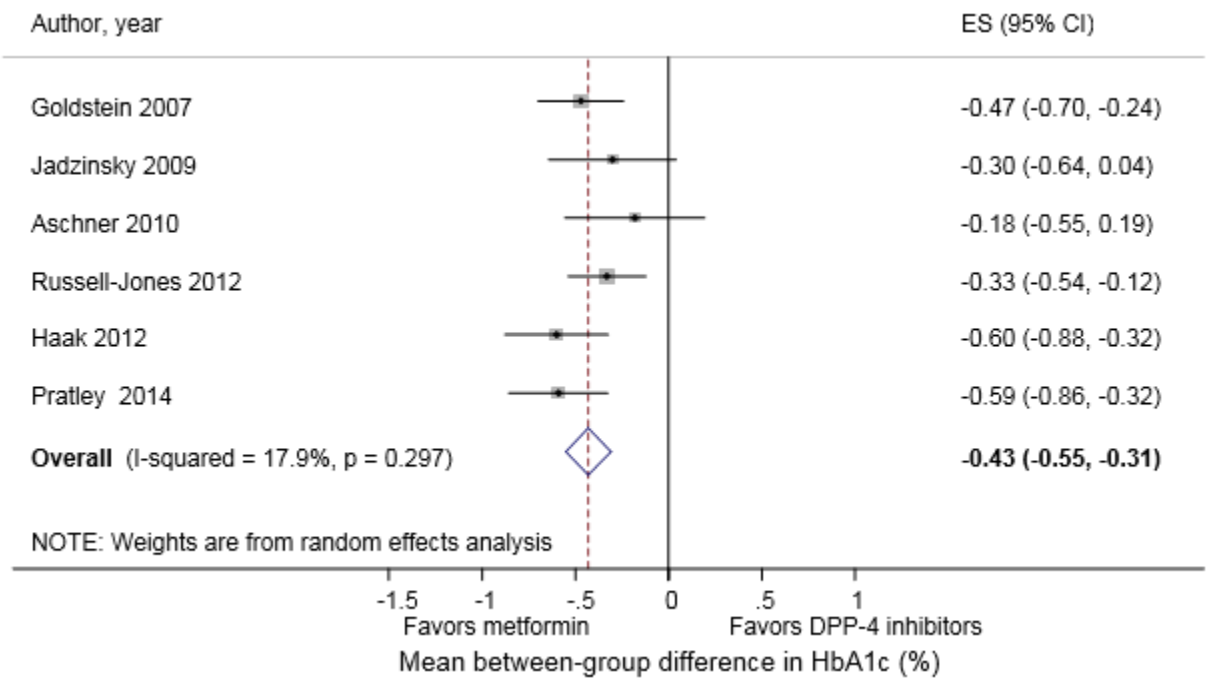
Metformin Versus DPP-4 Inhibitors

Six short duration RCTs (reported in nine articles) compared metformin with DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin and saxagliptin).[66, 72-79] These studies reported greater reductions in HbA1c with metformin, with a pooled between-group difference in HbA1c of -0.4% (95% CI, -0.5% to -0.3%) (Figure 5). No single study strongly influenced the meta-analysis results. In the three studies using both low and high metformin dosages compared with

the maximum dose DPP-4 inhibitor, we included the maximum dose metformin arm to make the drug dosages most comparable in the meta-analysis. The lower dose metformin arms (1000 mg) compared with maximum dose DPP-4 showed no statistically significant between-group differences in HbA1c.[76-78]

Two RCTs (in five articles) were reported as extension studies.[72, 73, 75, 77, 79] The shorter duration studies were included in the meta-analysis since their study durations were more similar to the other studies in the meta-analysis. The first RCT comparing metformin 1000 mg twice daily with sitagliptin 100 mg daily reported HbA1c at 24 weeks,[72] 54 weeks,[73] and 104 weeks.[77] The between-group difference in HbA1c of -0.5% favored metformin over sitagliptin at both 24 and 54 weeks of followup. At week 104, there was no significant difference between-groups in HbA1c, but there was high and differential losses to followup among the arms (74% loss to followup in the sitagliptin arm and 48% in the metformin arm). The second 76-week study[79] was an RCT initially reported at 24 weeks comparing metformin up to 1000 mg twice daily with saxagliptin 10 mg daily. In this study, the between-group difference of -0.3 in HbA1c non-significantly favored metformin at 24 weeks[75] and statistically significantly favored metformin at 76 weeks (mean difference between-groups in HbA1c, -0.2%; 95% CI, -0.5% to -0.03%),[79] which is consistent with the meta-analysis results. (SOE: High; Metformin favored)

Figure 5. Pooled mean between-group difference in hemoglobin A1c comparing metformin with DPP-4 inhibitors



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus SGLT-2 Inhibitors

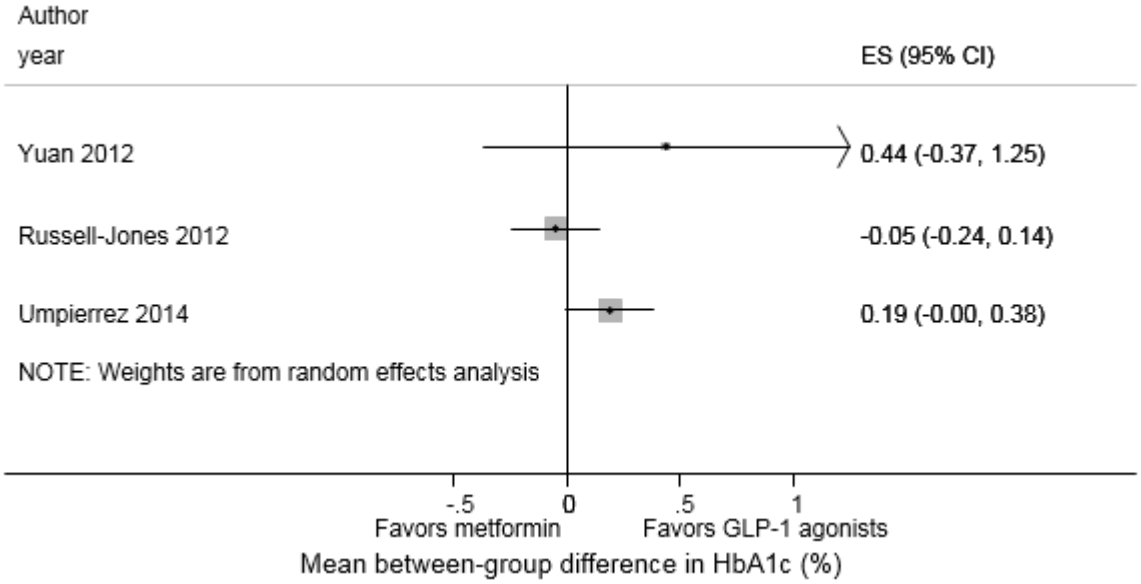
Three short duration and one longer duration RCTs (reported in three articles) compared metformin with an SGLT-2 inhibitor, showing no consistent between-group differences in

HbA1c among the studies.[80-82] We did not combine these studies in a meta-analysis due to dosing and study duration differences. Two of the short duration studies reported in one article compared metformin XR titrated to 2000 mg with dapagliflozin 5 mg in one study, and compared metformin XR titrated to 2000 mg with dapagliflozin 10 mg in the second study.[80] Both studies, lasting 24 weeks, reported no significant between-group differences in HbA1c.[80] The study comparing metformin XR to the lower dose dapagliflozin arm of 5 mg had a mean difference between-groups in HbA1c which favored metformin by 0.16% although non-significantly, while the study comparing metformin XR to the higher dose dapagliflozin arm of 10 mg did not favor either arm. The third study comparing a lower dose of metformin XR of 1500 mg daily with dapagliflozin 10 mg daily for 12 weeks favored the dapagliflozin arm, with a calculated mean difference between-groups in HbA1c of 0.12% (95% CI, 0.08% to 0.16%).[81] The 90-week RCT comparing metformin 1000 mg twice daily with empagliflozin 10 mg daily and 25 mg daily, reported no significant differences between groups in HbA1c.[82] (SOE: Low; Neither drug favored)

Metformin Versus GLP-1 Agonists

Three studies lasting a year or less compared metformin versus a GLP-1 agonist, with no consistent between-group differences in HbA1c (Figure 6).[66, 83, 84] We did not combine the studies in a meta-analysis due to study duration and dosing differences. Each study compared metformin at 1500 mg or higher to a GLP-1 agonist (exenatide twice daily in one study, exenatide weekly in a second study, and dulaglutide weekly in a third study) lasting 24 to 52 weeks in duration. Only one had a borderline significant result favoring dulaglutide 1.5 mg weekly over metformin titrated to 2000 mg daily after 52 weeks, with a calculated mean between group difference in HbA1c of 0.2% (95% CI, 0.0% to 0.4%).[83] This same study also had a lower-dose dulaglutide arm at 0.75 mg weekly which showed no significant difference in HbA1c when compared with metformin titrated to 2000 mg daily.[83] (SOE: Low; Neither drug favored)

Figure 6. Mean between-group difference in hemoglobin A1c comparing metformin with GLP-1 agonists



CI = confidence interval; GLP-1 = glucagon-like peptide-1; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Fourteen studies lasting less than a year compared metformin with the combination of metformin plus a thiazolidinedione (eight studies with rosiglitazone and six studies with pioglitazone)[48, 52, 60, 85-95] and showed a greater improvement in HbA1c with the combination therapy in all the studies. The pooled between-group difference for all the studies combined had marked heterogeneity, but the metaregression and stratified meta-analysis results show consistent superiority of combination therapy (Table 5). The baseline HbA1c and dosing differences between arms were significant sources of heterogeneity. Studies with higher baseline HbA1c (HbA1c $\geq$ 8%) had greater between-group differences than studies with lower baseline HbA1c (HbA1c < 8%). Studies with smaller dosing differences between study arms had smaller between-group differences in HbA1c than studies with larger dosing differences between arms. The one long study,[96] with 80 weeks of followup, compared metformin titrated to 2000 mg daily with metformin plus rosiglitazone titrated to 8/2000 mg daily. In that study, with around 5% loss to followup, the adjusted mean difference in HbA1c between groups favored combination therapy by 0.5%, consistent with the results in the shorter studies. (SOE: High; Combination of metformin plus a thiazolidinedione favored)

Table 5. Pooled mean between-group difference in HbA1c comparing metformin with a combination of metformin plus a thiazolidinedione stratified by baseline HbA1c and dosing differences

Variables	N of studies	WMD (95% CI)	I^2	Summary
Baseline HbA1c <8%	7	0.43% (0.23% to 0.63%)	79%	Favored metformin + thiazolidinedione
Baseline HbA1c >=8%	7	0.88% (0.73% to 1.04%)	18%	Favored metformin + thiazolidinedione
Small dosing differences between study arms*	4	0.25% (0.16% to 0.34%)	0%	Favored metformin + thiazolidinedione
Large dosing differences between study arms*	10	0.79% (0.64% to 0.95%)	57%	Favored metformin + thiazolidinedione

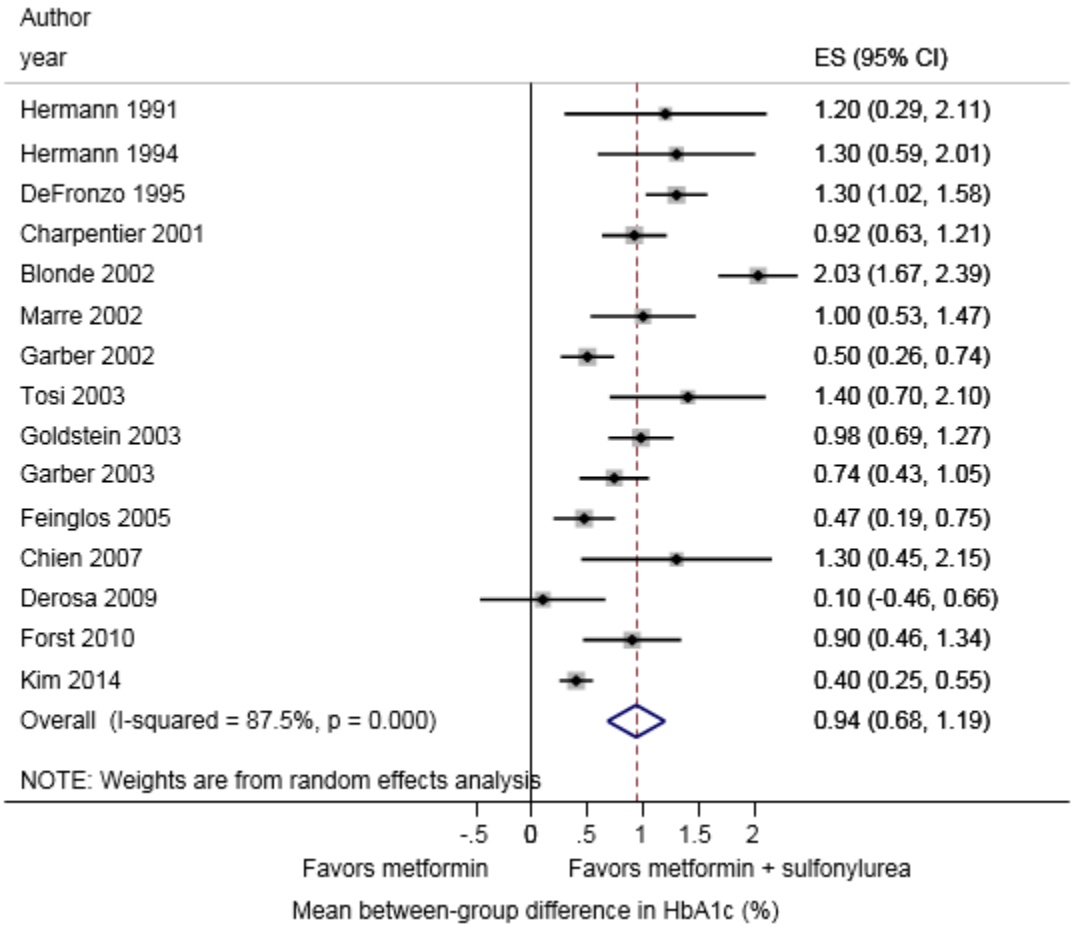
CI = confidence interval; HbA1c = hemoglobin A1c; WMD = weighted mean difference
*Studies were grouped together that had similar between-group differences in study dosing between arms. This led to two categories: those studies with smaller and larger between-group differences in drug dosing. We used the random effects point estimate for the weighted mean difference of the large dosing differences since profile likelihood estimate results would not converge.

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Fifteen RCTs lasting less than a year compared metformin with the combination of metformin plus a second-generation sulfonylurea, with all of the studies favoring the combination arm over monotherapy (pooled between-group difference, 0.9%; 95% CI, 0.7% to 1.2%) (Figure 7).[42, 48, 97-109]

No single study markedly influenced the results. Meta-regression was conducted due to substantial heterogeneity, but none of the *a priori* variables were found to be significant including study duration, dosing differences, appropriate randomization, double blinding, baseline HbA1c or whether the study reported on withdrawals and dropouts. The study by Blonde et al. showed the greatest between-group differences; this study used a high dose combination and started with the highest baseline HbA1c compared with other studies.[100] The study with the smallest between-group difference underdosed the metformin arm substantially in the metformin plus sulfonylurea arm.[48] Three of the six dose-response studies showed a dose-response gradient favoring greater reductions in HbA1c with a higher dose combination than with a lower dose combination.[100, 101, 103] One crossover study initially showed a difference between groups at the first crossover and then a negative rebound effect when changing the combination to monotherapy.[42] One study by Ahren et al. was excluded from the meta-analysis since the study duration was longer than the other studies.[110] This study lasting 104 weeks compared metformin at ≥ 1500 mg daily to the combination of metformin at ≥ 1500 mg daily plus glimepiride (up to 4 mg daily), and showed a between-group difference in HbA1c of 0.63% favoring the combination arm which was consistent with the results of the shorter studies included in the meta-analysis. (SOE: High; Combination of metformin plus a sulfonylurea favored)

Figure 7. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a sulfonylurea



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

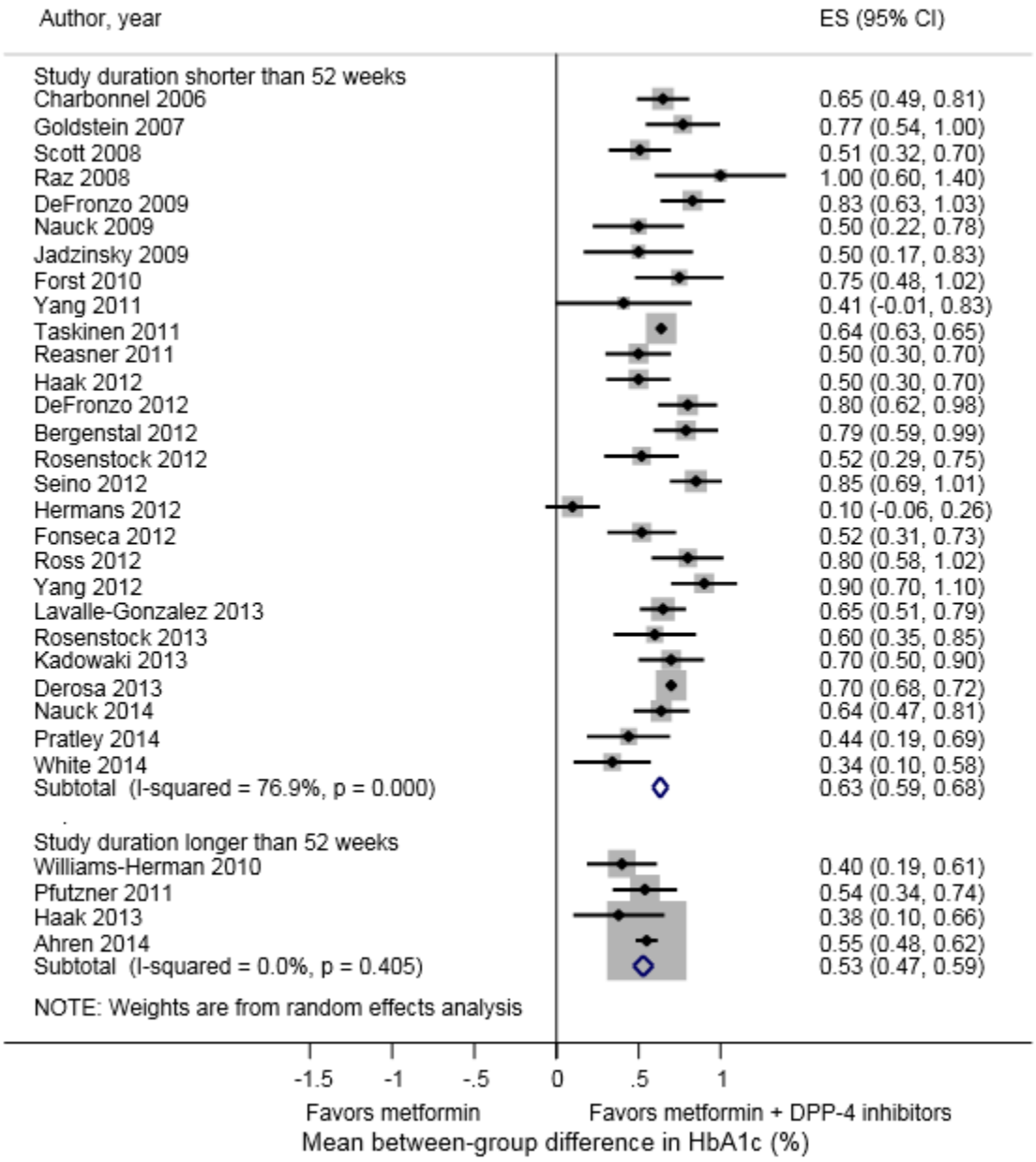
Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Twenty-six RCTs lasting a year or less directly compared metformin with the combination of metformin plus a DPP-4 inhibitor – all favoring the combination arm, with a pooled between-group difference of 0.65% (95% CI, 0.60% to 0.70%) (Figure 8).[46, 72, 75, 76, 78, 87, 95, 108, 111-128] No single study markedly influenced the results, and no substantial heterogeneity was identified.

Two short studies were not included in the meta-analysis due to dosing differences in one study and median HbA1c being reported in the other study.[129, 130] The one RCT with dosing differences compared uptitration of metformin to 2500 mg in the metformin monotherapy arm while the combination arm metformin dose was only uptitrated to 1500 mg with addition of the DPP-4 inhibitor; therefore, this study had a smaller between-group difference than the other studies. The 12-week study[130] reporting median HbA1c described a non-significant between-group difference in median HbA1c of 0.9% (p=0.1) favoring the combination arm of metformin (>1000 mg daily) plus sitagliptin (100 mg daily) over metformin alone (>1000 mg daily).

Four longer studies (two of which were extension studies) lasting 76 to 104 weeks also compared metformin with a metformin plus a DPP-4 inhibitor, with consistent results to the shorter studies.[77, 79, 110, 131] All four of the studies favored the combination arm, with a pooled between-group difference in HbA1c of 0.53% (95% CI, 0.47% to 0.59%) (Figure 8). No single study markedly influenced the results, and no substantial heterogeneity was found. (SOE: High; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 8. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a DPP-4 inhibitor



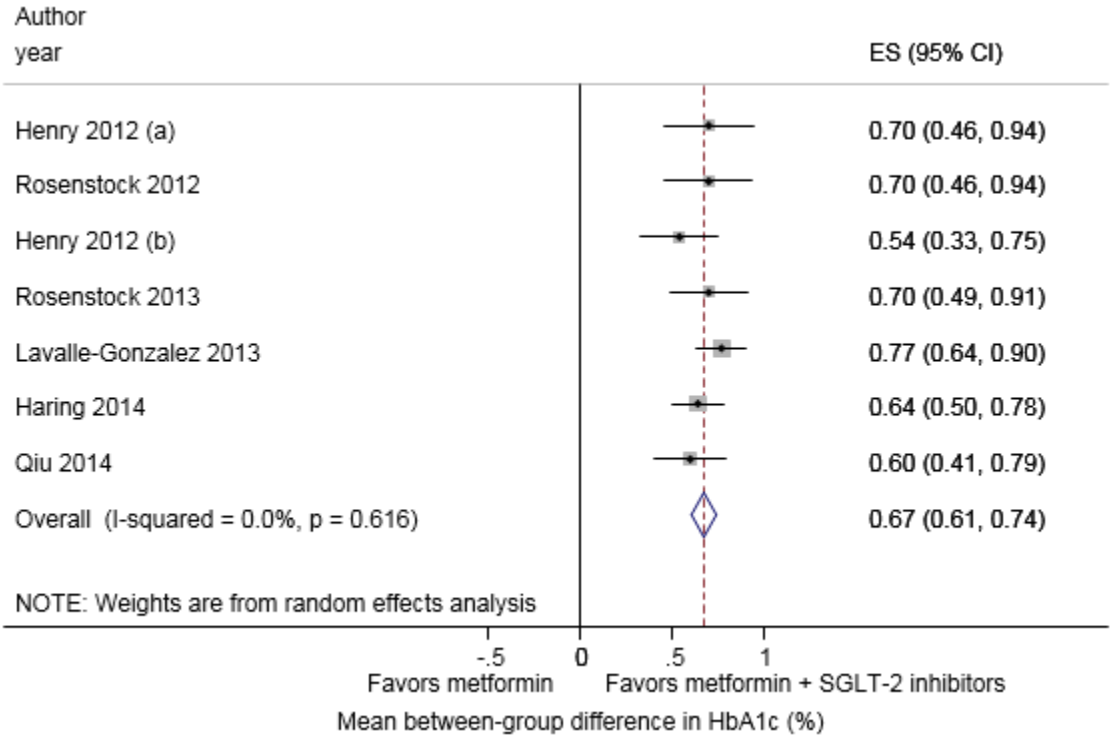
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Seven RCTs (reported in six articles) lasting less than a year compared metformin alone with metformin plus an SGLT-2 inhibitor, with all studies favoring the combination arm (pooled between-group difference in HbA1c, 0.67%; 95% CI, 0.61% to 0.74%) (Figure 9).[80, 122, 125, 127, 132, 133] No single study markedly influenced the results, and no substantial heterogeneity was identified. Consistent with the meta-analysis results, two additional RCTs lasting 102 weeks had statistically significant between-group differences in HbA1c of 0.4% and 0.8% favoring the combination arms.[134, 135] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 9. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Four short RCTs lasting less than a year and one RCT lasting 2 years compared metformin with metformin plus a GLP-1 agonist (albiglutide, liraglutide, dulaglutide, and exenatide), with all studies significantly favoring the combination arm over the monotherapy arm (range in between-group differences in HbA1c of 0.5% to 1.3%).[110, 128, 136-138] We did not combine these studies in a meta-analysis due to differences in baseline HbA1c, study duration, and drug dosing. The two studies with lower mean baseline HbA1c of 6.3% and 7.2% had between-group differences in HbA1c of 0.5%[137, 138] while the three studies with higher mean baseline HbA1c of

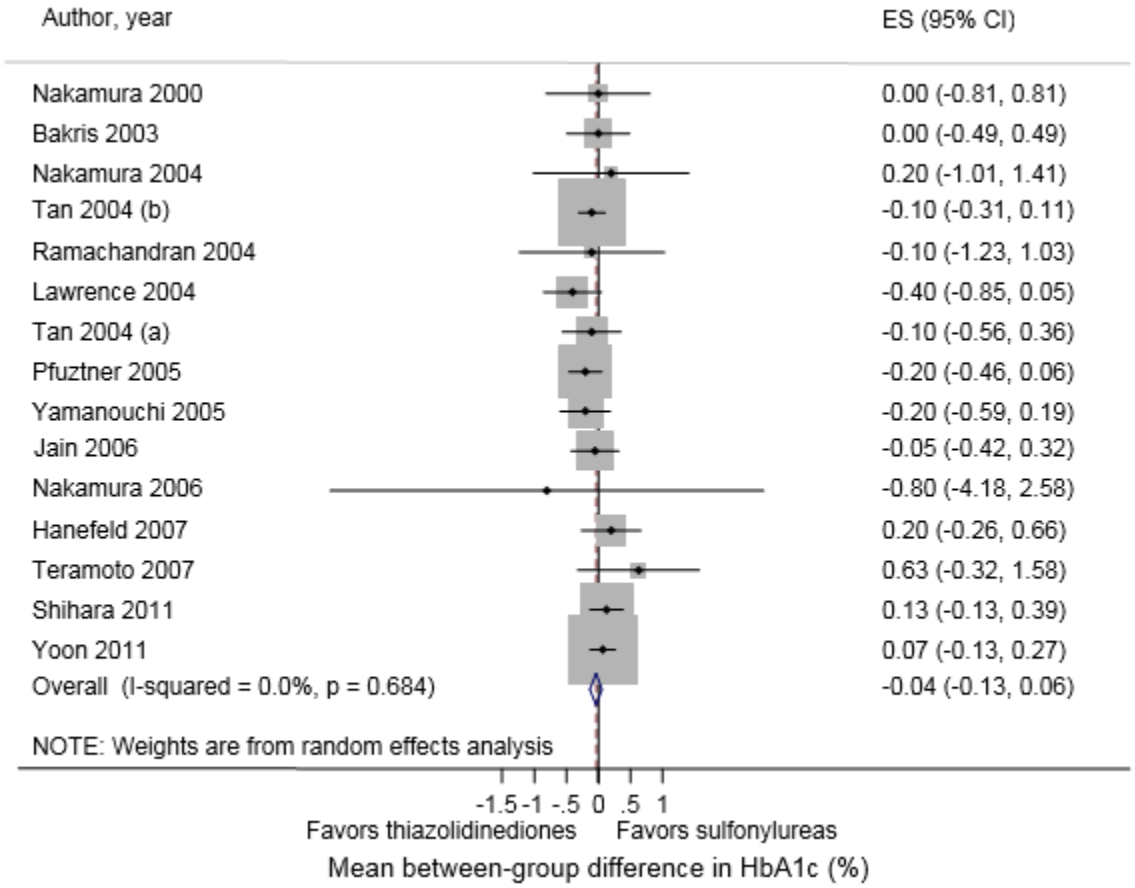
around 8.0% had between-group differences in HbA1c ranging from 0.8% to 1.3%.[110, 128, 136] (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

Thiazolidinediones Versus Sulfonylureas

Thiazolidinediones (pioglitazone and rosiglitazone) and second-generation sulfonylureas (glibenclamide, glimepiride, and glyburide) had similar effects on HbA1c in 15 short duration RCTs, with a pooled mean difference between groups of -0.04% (95% CI, -0.13% to 0.06%) (Figure 10).[53, 54, 56, 67, 139-149] In a sensitivity analysis, we found no single study influenced the results , and there was no substantial heterogeneity between studies. We excluded one short duration RCT from the meta-analysis since it did not report a number for analysis in each arm.[71] This open label 12-week RCT compared rosiglitazone titrated to 4-8 mg daily with glipizide titrated to 5-15 mg daily, and reported a greater reduction in HbA1c in the thiazolidinedione arm (-0.9%) compared with the glipizide arm (-0.3%).[71]

We excluded the ADOPT study from the meta-analysis due to its long duration (median followup of 4 years).[45] As mentioned previously, this double-blind RCT evaluated the long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults. The between-group difference between rosiglitazone and glyburide favored rosiglitazone after 4 years (mean difference between-groups, -0.4%; 95% CI, -0.5% to -0.3%). Of note, glyburide reduced HbA1c more than rosiglitazone initially. The HbA1c then rose higher in the glyburide arm than in the rosiglitazone arm after 1.5 years. (SOE: High; Neither drug favored in the short-term. SOE: Insufficient; Unable to determine effect in the long-term.)

Figure 10. Pooled mean between-group difference in hemoglobin A1c comparing thiazolidinediones with sulfonylureas



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

Three RCTs lasting less than 26 weeks compared pioglitazone with the DPP-4 inhibitors alogliptin and sitagliptin with no clear between-group differences in HbA1c (range in between-group differences of -0.48% to 0.23%).[43, 66, 150] We did not combine the studies due to dosing differences among the studies. The one RCT with maximal dosing in both arms (pioglitazone titrated to 45 mg daily in one arm and sitagliptin 100 mg daily in the other arm) favored pioglitazone over sitagliptin (between group difference in HbA1c of -0.5%; 95% CI -0.7% to -0.3%).[66] The other two RCTs used maximum dose DPP-4 inhibitors compared with moderately-dosed pioglitazone at 30 mg daily and reported no significant between-group differences in HbA1c.[43, 150] (SOE: Insufficient; Unable to determine effect)

Thiazolidinediones Versus GLP-1 Agonists

One double-blind moderately-sized RCT compared pioglitazone titrated to 45 mg daily with exenatide 2 mg weekly.[66] After 26 weeks, the calculated between-group difference in HbA1c

favored pioglitazone by -0.2% (95% CI, -0.4% to 0.0%).[66] (SOE: Insufficient; Unable to determine effect)

Sulfonylureas Versus DPP-4 Inhibitors

Three RCTs lasting 54 weeks or less compared a sulfonylurea (glipizide or glimepiride) with a DPP-4 inhibitor (sitagliptin or linagliptin) with no clear between-group differences in HbA1c.[151-153] We did not combine these studies in a meta-analysis due to dosing differences and study population differences. Two RCTs non-significantly favored sulfonylureas over the DPP-4 inhibitor arms (between-group differences in HbA1c of -0.22% and -0.28%).[151, 153] The third RCT enrolled patients with moderate or severe renal insufficiency at baseline and compared glipizide (mean dose 7.7 mg) with sitagliptin at 25 or 50 mg daily depending on the participant's renal function.[152] This study showed no significant differences in HbA1c between-groups.[152] (SOE: Insufficient; Unable to determine effect)

Sulfonylureas Versus GLP-1 Agonists

Four RCTs (reported in five articles) compared sulfonylureas directly with a GLP-1 agonist (all studies using liraglutide).[154-158] Three of the four studies favored liraglutide over sulfonylureas.[154, 155, 157, 158] We did not combine these trials in a meta-analysis due to dosing differences between studies. Only two of the four studies used approximately equipotent dosing in the two arms. The first reported no statistically significant differences between the two arms.[156] The second RCT favored the GLP-1 arm, with a between-group difference in HbA1c of 0.6% (95% CI, 0.4% to 0.8%) at 52 weeks and 0.3% (95% CI, 0.2% to 0.4%) at the 104-week followup.[157, 158] The two other RCTs lasting 24 and 52 weeks significantly favored the liraglutide arm by 0.5% each,[154, 155] yet both of these studies used relatively lower doses in the sulfonylurea arm compared with the liraglutide arm making it difficult to discern drug differences versus dosing differences.[154, 155] (SOE: Insufficient; Unable to determine effect)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Only one double-blind moderately-sized RCT lasting 24 weeks compared the DPP-4 inhibitor sitagliptin at 100 mg daily with the SGLT-2 inhibitor empagliflozin at 10 mg and 25 mg daily.[159] The lower dose empagliflozin arm showed no significant between-group differences in HbA1c when compared with sitagliptin 100 mg daily. The higher dose empagliflozin 25 mg arm was favored slightly but not significantly over sitagliptin 100 mg, with a between-group difference in HbA1c of 0.01% (95% CI, -0.03% to 0.3%).[159] (SOE: Insufficient; Unable to determine effect)

DPP-4 Inhibitors Versus GLP-1 Agonists

One RCT compared a DPP-4 inhibitor with a GLP-1 agonist with a significant between-group difference in HbA1c favoring the GLP-1 agonist.[66] This double blind, moderately-sized RCT compared sitagliptin at 100 mg daily with exenatide 2 mg weekly for 26 weeks, with a calculated between-group difference in HbA1c of 0.3% (95% CI, 0.07% to 0.49%) favoring exenatide.[66] (SOE: Insufficient; Unable to determine effect)

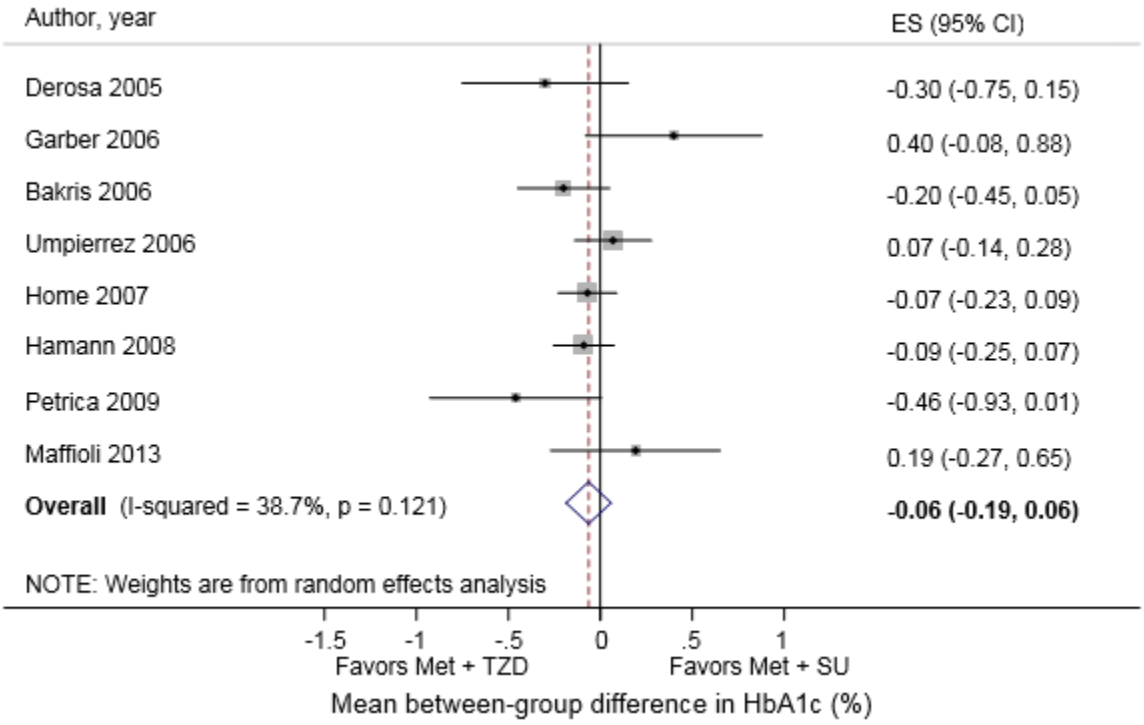
Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Eight comparably-dosed RCTs lasting less than a year directly compared the combination of metformin plus a thiazolidinedione with metformin plus a sulfonylurea, showing a pooled between-group difference in HbA1c of -0.06% (95% CI, -0.19% to 0.06%) (Figure 11).[160-167] No single study markedly influenced the results, and no substantial heterogeneity was found. We excluded four studies from the meta-analysis due to dosing concerns within the studies.[48, 168-170] Two studies used lower doses in the metformin plus sulfonylurea arms than the comparator arms, and found between-group differences in HbA1c favoring the metformin plus thiazolidinedione arms (-0.3% in both studies).[48, 168] Two additional studies used submaximal sulfonylurea in the metformin plus sulfonylurea arm, with one of the two studies then favoring the metformin plus thiazolidinedione arm. A sensitivity analysis including these four studies in the meta-analysis shows no marked differences in the pooled estimate and confidence interval but more heterogeneity.

In the meta-analysis, we included the 18 month results from the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) study since the study duration was comparable to the other included studies.[161] The RECORD study was a multicenter open label RCT evaluating 4447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[44, 161] The investigators randomly assigned subjects to the addition of rosiglitazone or to a combination of metformin and sulfonylurea, and the primary endpoint was cardiovascular hospitalization or cardiovascular death. They reported glycemic control at a mean of 18 months and 5.5 years after study start.[44, 161] The between-group difference in HbA1c of -0.07% was small and not significant in the 516 subjects with 18-month followup.[161] In the article reporting on the mean followup of 5.5 years in 2222 subjects, the between-group difference in HbA1c of -0.29% significantly favored metformin plus rosiglitazone over metformin plus sulfonylurea.[44] (SOE: Moderate; Neither drug combination favored)

Figure 11. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea

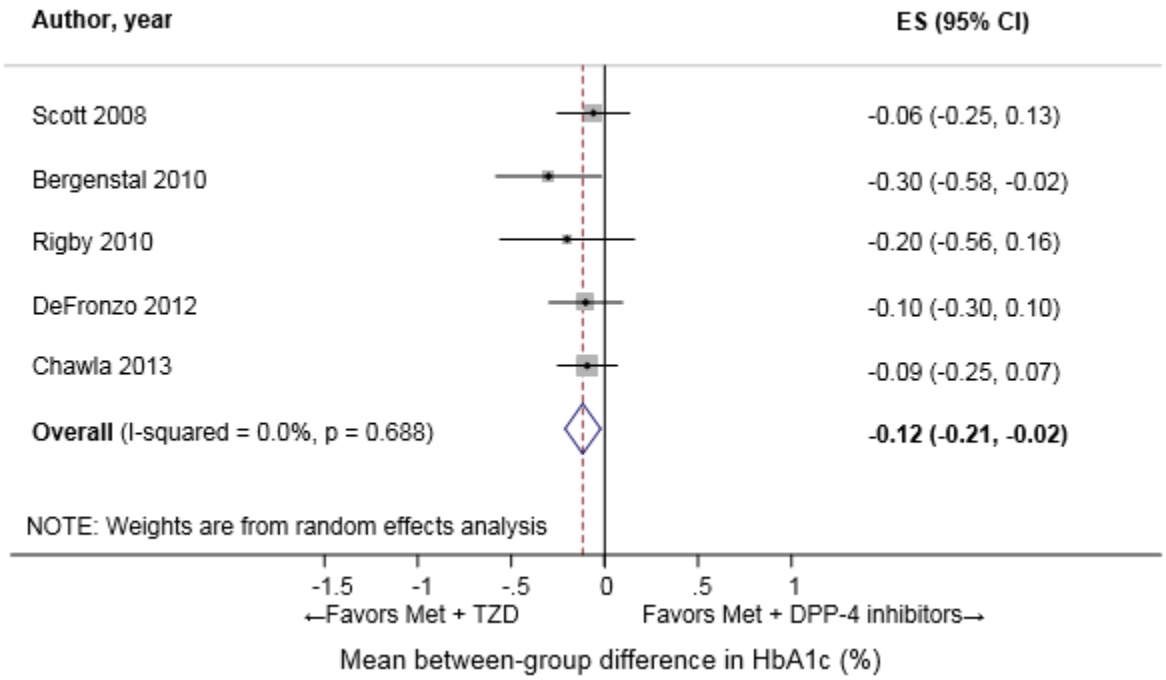


CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SU = sulfonylurea; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Five short RCTs compared metformin plus rosiglitazone with the combination of metformin plus sitagliptin, slightly favoring the metformin plus thiazolidinedione arms (pooled between-group difference in HbA1c, -0.12%; 95% CI, -0.21% to -0.02%) (Figure 12).[87, 95, 171-173] No substantial heterogeneity was identified in the meta-analysis. Removing the study by Bergenstal et al.[173] changed the confidence interval to become non-significant (95% CI with Bergenstal et al. removed, -0.19 to 0.006). This study[173] was not qualitatively different than the other studies, so we included it in the overall meta-analysis. This meta-analysis may underestimate the effect of metformin plus thiazolidinedione over metformin plus DPP-4 inhibitors since two of the studies used lower drug doses in the metformin plus thiazolidinedione arms.[171, 172] (SOE: Moderate; Combination of metformin plus a thiazolidinedione favored)

Figure 12. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

Two short RCTs, with adequate dosing in both arms, compared metformin plus thiazolidinediones (pioglitazone and rosiglitazone) with metformin plus a GLP-1 agonist (exenatide) and had conflicting results.[173, 174] The 20-week RCT comparing a combination of metformin and rosiglitazone with the combination of metformin and exenatide showed no significant between-group differences in HbA1c (between-group difference, -0.1%; $P = 0.7$).[174] The 26-week RCT comparing the combination of metformin and pioglitazone with the combination of metformin and weekly exenatide favored the metformin plus exenatide arm (mean difference in HbA1c, 0.3%; 95 CI, 0.05% to 0.55%).[173] (SOE: Insufficient; Unable to determine effect)

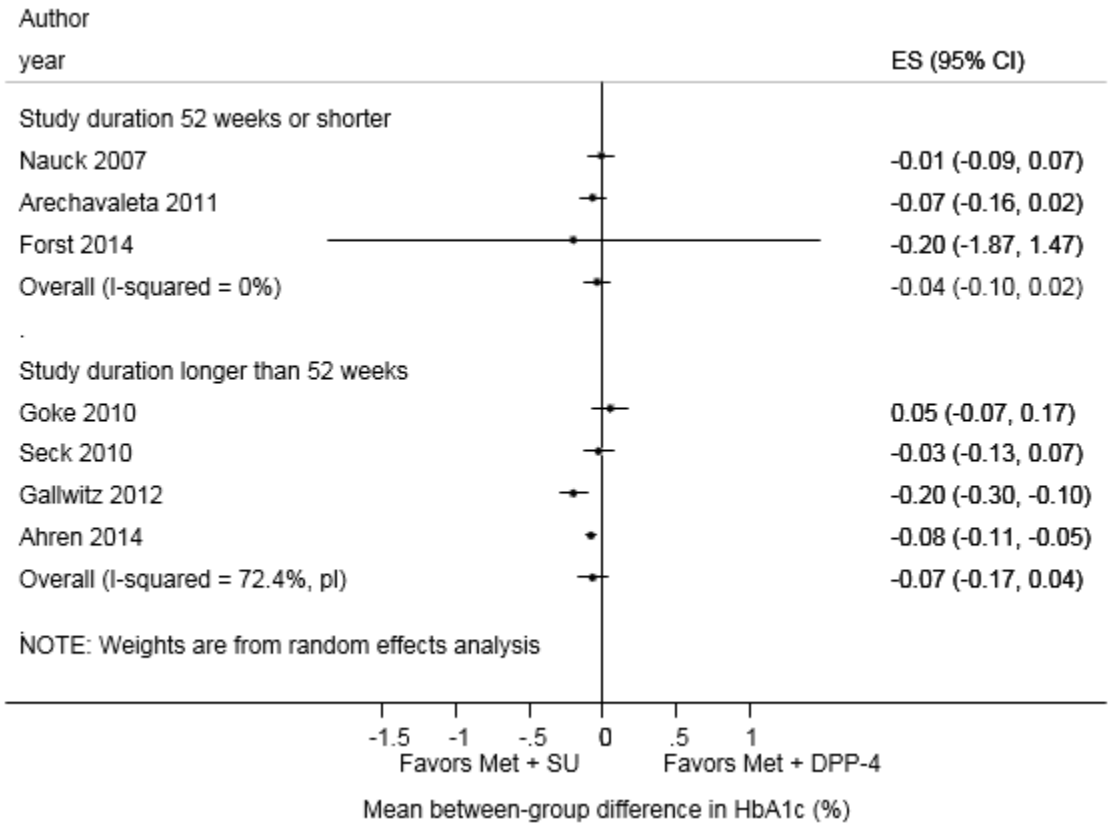
Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Seven studies (reported in eight articles) compared the combination of metformin plus sulfonylurea with metformin plus a DPP-4 inhibitor. We combined three RCTs lasting a year or less comparing metformin plus a sulfonylurea with metformin plus a DPP-4 inhibitor, showing no significant between-groups differences in HbA1c (pooled between-group difference, -0.04%; 95 CI, -0.10% to 0.02%) (Figure 13).[175-177] However, all three RCTS underdosed the metformin plus sulfonylurea arms using a moderate dose of sulfonylurea while using the maximum dose of

the DPP-4 inhibitors. No single study strongly influenced the meta-analysis results and no substantial heterogeneity was found. One additional short RCT was excluded from the meta-analysis since we were unable to calculate a measure of variability.[108] This study reported a mean change from baseline in HbA1c that significantly favored the metformin plus sulfonylurea arm over the metformin plus DPP-4 inhibitor arm of -0.2%, despite low dosing of the sulfonylurea.

Four longer studies lasting 104 weeks also compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor, showing no significant pooled between-group difference in HbA1c (-0.07%; 95% CI, -0.17% to 0.04%) (Figure 13).[110, 178-180] However, all four RCTs titrated the sulfonylurea to a moderate dose compared to using fixed maximum doses of DPP-4 inhibitors. One of the longer studies was an extension of a study included in the meta-analysis of the shorter studies.[177] Removing the study by Goke et al.[179] changed the pooled estimate to significantly favor the metformin plus sulfonylurea arm over the metformin plus DPP-4 inhibitor arm; however, this study was not clearly different than the other studies and was retained in the meta-analysis. (SOE: Low; Neither drug combination favored)

Figure 13. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration

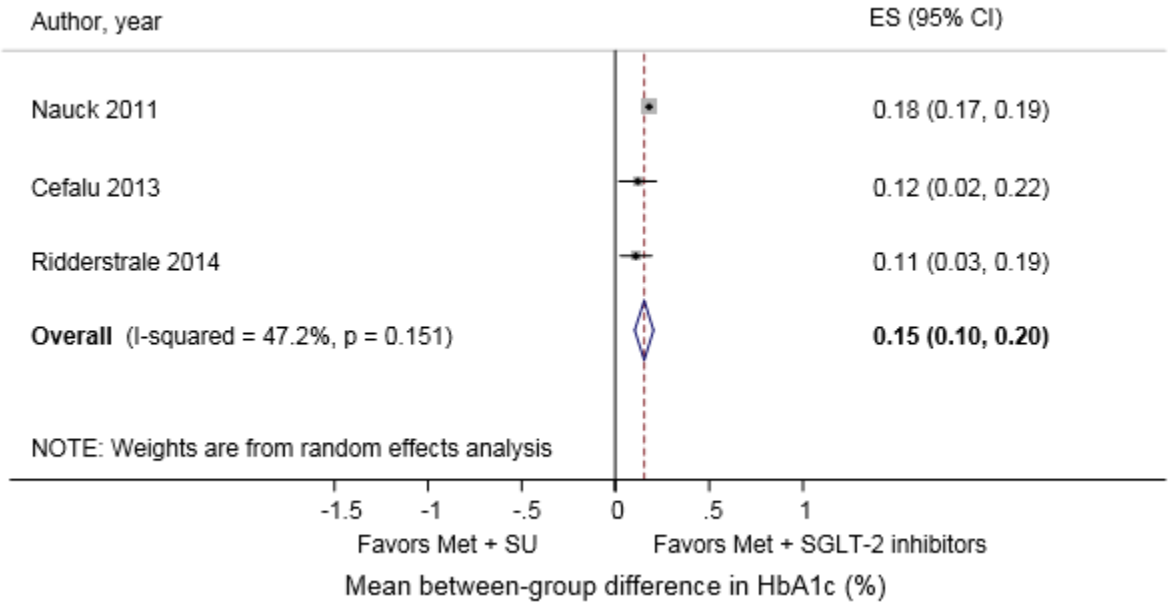


CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; pl = profile likelihood estimate; SU = sulfonylurea
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

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

Three RCTs lasting 1 to 2 years compared the combination of metformin plus sulfonylurea with the combination of metformin plus a SGLT-2 inhibitor (empagliflozin, dapagliflozin, or canagliflozin).[181-183] All three favored the combination of metformin plus an SGLT-2 inhibitor with a pooled between-group difference in HbA1c of 0.15% (95% CI, 0.10% to 0.20%) (Figure 14).[181-183] No single study markedly influenced the results, and no substantial heterogeneity was identified. While all three studies used the maximum fixed dose of the SGLT-2 inhibitor, the sulfonylurea arms were all uptitrated to a moderate dose (mean glimepiride dose of 3 mg in one study, mean glimepiride dose of 5.6 mg in a second study and a mean glipizide dose of 16 mg in the third study). One of the three studies also compared the combination of metformin plus a lower dose SGLT-2 inhibitor arm of canagliflozin 100 mg daily with the combination of metformin plus glimepiride (mean dose of 5.6 mg daily), reporting no significant between-group differences in HbA1c of 0.01%.[181] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 14. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

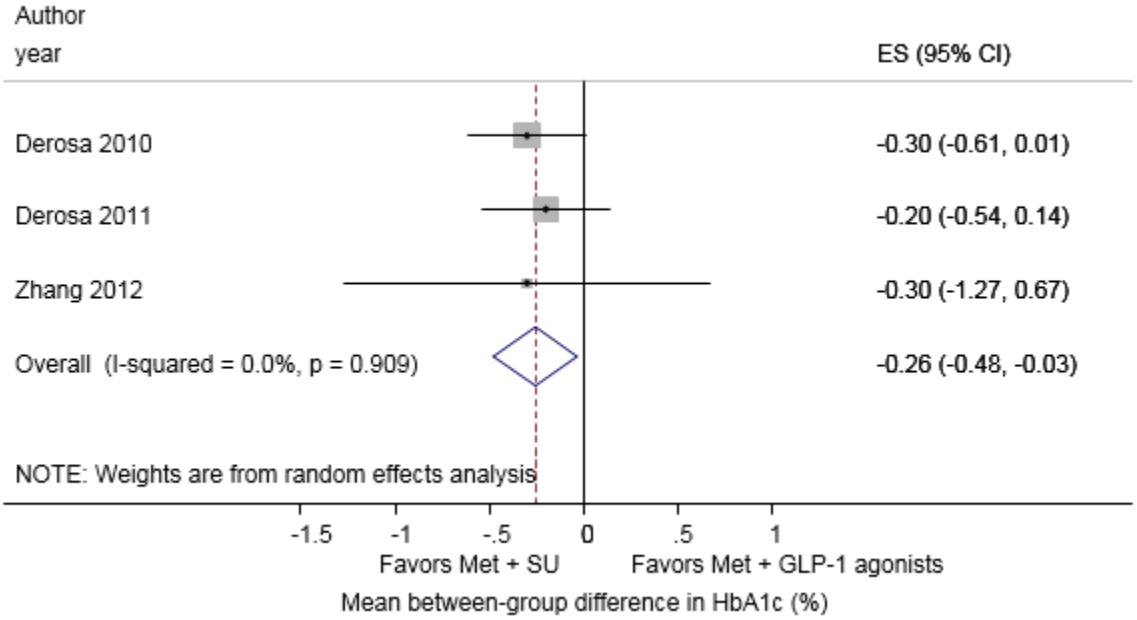
Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Six RCTs compared metformin plus sulfonylurea with metformin plus a GLP-1 agonist, with conflicting results.[110, 184-188] While no clear source of heterogeneity was identified, intraclass differences could be part of the reason for the conflicting results. Three short duration RCTs lasting a year or less compared metformin plus sulfonylurea with metformin plus exenatide, all

favoring the combination of metformin plus sulfonylurea despite submaximal doses of sulfonylureas being compared with maximal doses of daily exenatide (pooled between-group difference in HbA1c, -0.26%; 95% CI, -0.48% to -0.03%) (Figure 15).[184, 186, 188] No single study strongly influenced the results, and no substantial heterogeneity was identified. An additional longer duration RCT excluded from the meta-analysis due to dosing and study duration differences compared metformin plus low dose glimepiride (mean daily dose: 2 mg) with metformin plus high dose exenatide (mean daily dose: 17 micrograms) with about a 75% loss to followup among the treatment groups over 48 months. The primary outcome was time to treatment failure. They also evaluated HbA1c using a mixed model repeated measures analysis at different time points, and reported no significant between-group differences at 1 year. At 2 years, they report a significant between-group difference in HbA1c, favoring the metformin plus exenatide group by 0.2% which was maintained at 3 years.[185]

Three RCTs also compared metformin plus a sulfonylurea with metformin plus other types of GLP-1 agonists (albiglutide or liraglutide), with conflicting results.[110, 187, 188] These were excluded from the meta-analysis due to dosing, drug type, and study duration differences. The first 16-week RCT compared metformin plus glimepiride (titrated to 4 mg daily) with similar dosed metformin plus liraglutide (titrated to 1.8 micrograms daily), favoring the combination of metformin plus sulfonylurea (mean between-group difference, -0.3%; 95% CI, -0.34% to -0.27%).[187] Another 16-week RCT comparing metformin plus sulfonylurea (titrated to 4 mg daily) with metformin plus liraglutide (titrated to 1.8 micrograms daily) showed no significant between-group differences in HbA1c of 0.06% (95% CI, -0.11% to 0.23%).[188] The 104-week RCT with about 10% loss to followup compared metformin plus submaximal dose glimepiride (titrated to 4 mg daily) with the combination of metformin plus maximum dose albiglutide (titrated to 50 mg weekly), favoring the metformin plus albiglutide arm (mean between-group difference in HbA1c, 0.3%; 95% CI, 0.1% to 0.5%).[110] (SOE: Low; Combination of metformin plus exenatide favored; SOE: Insufficient; Unable to determine effect for combination of metformin plus other GLP-1 agonists)

Figure 15. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; GLP-1 = glucagon-like peptide-1; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

One small open-label RCT lasting 48 weeks compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a basal insulin, showing no significant differences between-groups in HbA1c of 0.1% (95% CI, -0.5% to 0.7%).[189] Patients were kept on their prior metformin doses and were randomized to uptitration of glimepiride (mean daily dose of 4 mg) versus uptitration of insulin glargine (mean daily dose of 23 units). Uptitration was stopped after reaching fasting plasma glucose titration goals.[189] (SOE: Insufficient; Unable to determine effect)

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

Two 16-week RCTs compared metformin plus glibenclamide with the combination of metformin plus a premixed insulin analogue – insulin aspart 70/30 in one study and insulin lispro 75/25 in the other study, with different results.[190, 191] These differences may have been due to differences in dosing of the medications. The RCT[190] that showed no significant between-group differences in HbA1c (-0.11%, p = 0.238) reported their mean total dose for each combination arm, while the other RCT which significantly favored the metformin plus premixed insulin analogue (insulin aspart 70/30) arm over the metformin plus sulfonylurea arm (between-group difference of 0.46%, p = 0.027) did not clearly report mean total or maximum doses.[191] Another

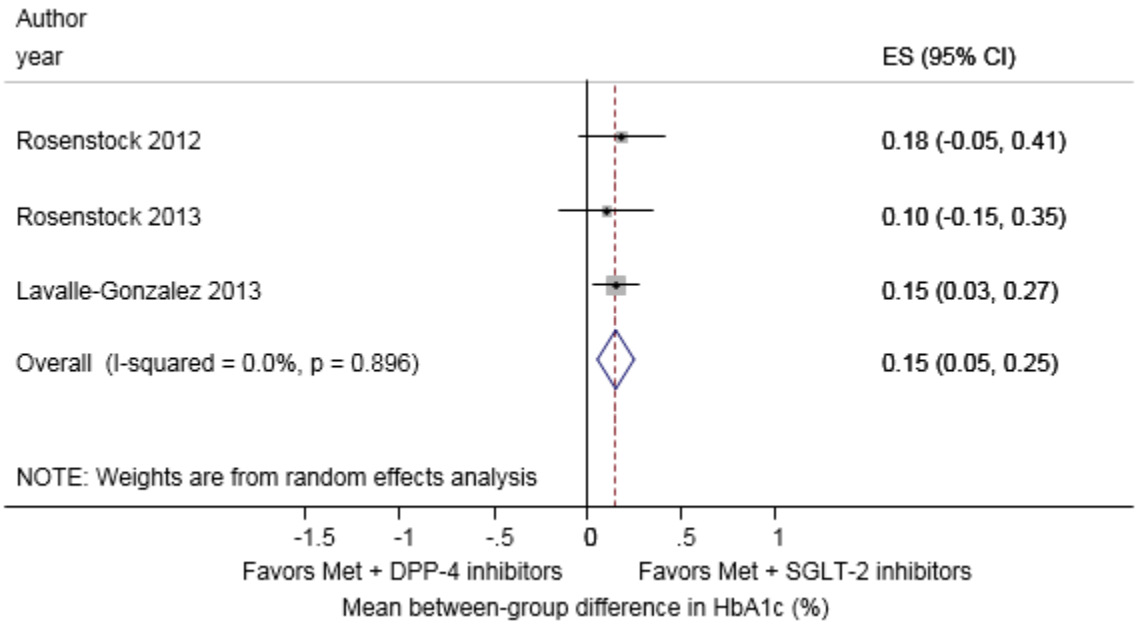
possible difference may have been the type of premixed insulin analogue. (SOE: Insufficient; Unable to determine effect)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Three short, sufficiently-dosed RCTs lasting a year or less compared the combination of metformin plus a DPP-4 inhibitor (all sitagliptin) with the combination of metformin plus an SGLT-2 inhibitor (canagliflozin or empagliflozin). The studies significantly favored the combination of metformin plus an SGLT-2 inhibitor (pooled between-group difference in HbA1c, 0.15%; 95% CI, 0.05% to 0.25%) (Figure 16).[122, 125, 127] Removal of the study by Lavalle-Gonzalez et al.[127] made the pooled estimate effects borderline non-significant. However, this study[127] is qualitatively similar to the other studies and should be retained. No substantial heterogeneity was found in the meta-analysis.

One longer RCT lasting 90 weeks comparing metformin plus sitagliptin with metformin plus empagliflozin at maximum doses was consistent with the shorter studies' pooled results, favoring slightly the metformin plus empagliflozin arm (mean between-group difference in HbA1c, 0.2%; 95% CI, 0.0% to 0.5%).[82] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 16. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor

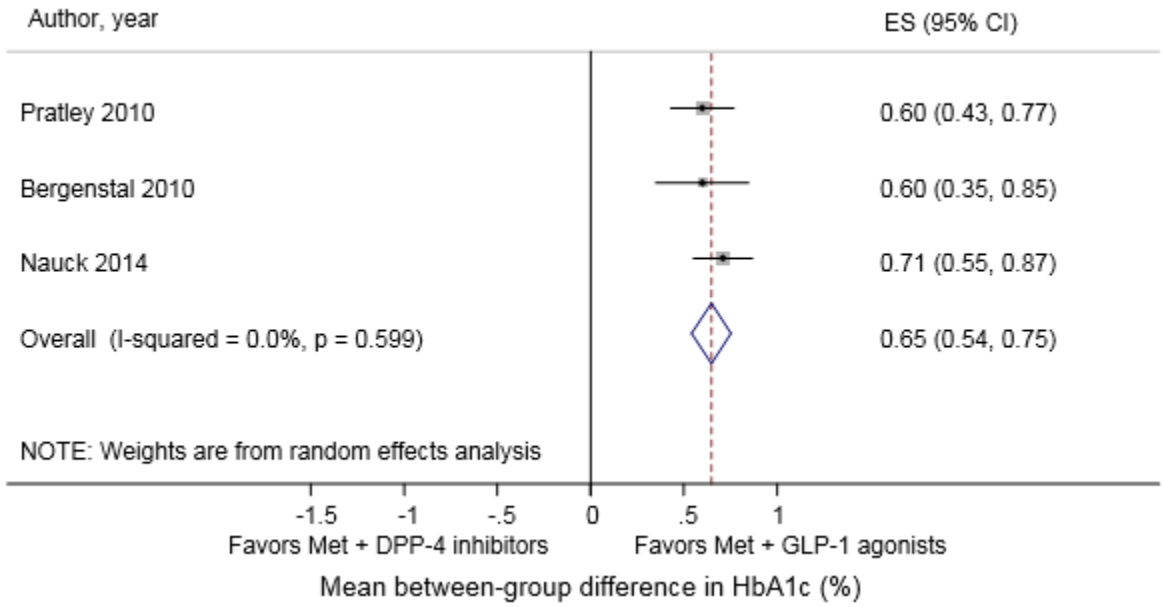


CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Three adequately-dosed RCTs lasting a year or less compared the combination of metformin plus sitagliptin with the combination of metformin plus a GLP-1 agonist (liraglutide or exenatide). All three RCTs significantly favored the combination of metformin plus a GLP-1 agonist (pooled between-group difference in HbA1c, 0.65%; 95% CI, 0.54% to 0.75%) (Figure 17).[128, 173, 192] No single study markedly influenced the meta-analysis results, and no substantial heterogeneity was identified. One longer study lasting 104 weeks compared metformin plus sitagliptin with metformin plus albiglutide, significantly favoring the metformin plus albiglutide arm by 0.4% consistent with the shorter studies' pooled results.[110] (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

Figure 17. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; Met = metformin
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

One moderately-sized 24-week RCT compared metformin plus sitagliptin 100 mg daily with metformin plus insulin glargine titrated to 0.5 units per kg, significantly favoring the metformin plus insulin glargine arm with a mean between-group difference in HbA1c of 0.59% (95% CI, 0.42% to 0.76%).[193] (SOE: Low; Combination of metformin plus a basal insulin favored)

Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

Two RCTs (reported in three articles) compared metformin plus a GLP-1 agonist with metformin plus a basal insulin, showing no between-group differences in HbA1c.[47, 194, 195] One small 56-week RCT compared the combination of metformin and exenatide (titrated to a maximum of 20 micrograms daily) with the combination of metformin and glargine insulin, showing similar reductions in HbA1c (between-group difference of -0.1%).[195] The exenatide combination arm had about 25% of their subjects on higher than the maximum recommended dose of exenatide. This study was reported in another article with a 3-year followup showing no significant between-group differences in HbA1c of -0.3% ($P = 0.186$).[47] The other short duration 26-week RCT comparing metformin plus exenatide (2 mg weekly) with metformin plus glargine insulin showed no significant between-group difference in HbA1c of -0.1% (95% CI, -0.28% to 0.08%).[194] (SOE: Low; Neither drug combination favored)

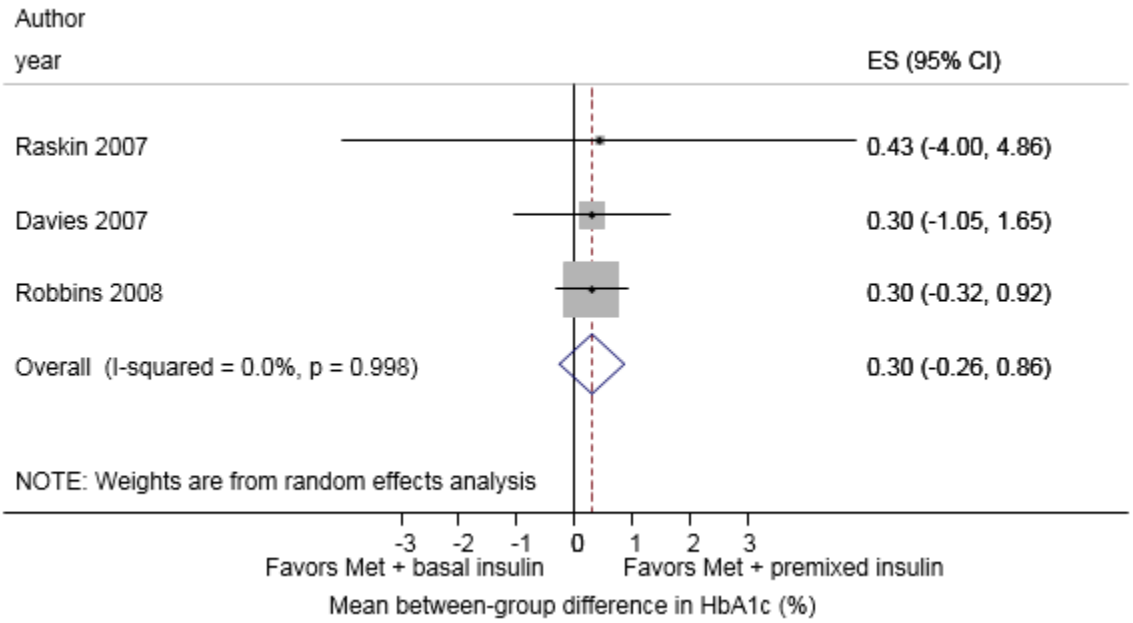
Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One moderately-sized RCT lasting 104 weeks compared the combination of metformin plus exenatide (titrated to 20 micrograms) with the combination of metformin plus premixed insulin (titrated to glucose target, mean dose 28 units), showing no significant between-group difference in HbA1c of 0.14% (95% CI, -0.003% to 0.29%).[196] (SOE: Insufficient; Unable to determine effect)

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

Three RCTs directly compared the combination of metformin plus basal insulin with the combination of metformin plus premixed insulin, showing no between-group differences in HbA1c (pooled between-group difference, 0.3%; 95% CI, -0.3% to 0.9%) (Figure 18).[197-199] No single study strongly influenced the results, and no substantial heterogeneity was found. (SOE: Insufficient; Unable to determine effect)

Figure 18. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Strength of Evidence for Hemoglobin A1c

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 6 and Table 7 and summarized in the key points. All studies were RCTs. Study limitations for most comparisons were low or medium with only one comparison having high study limitations due to lack of blinding and lack of description of withdrawals and dropouts. Where quality influences results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias using the Begg's and Egger's tests in any of the comparisons for HbA1c. We also did not find any evidence of publication bias or reporting bias in the grey literature review which would change the overall conclusions. The grey literature was consistent with our findings for each of the comparisons except for two comparisons (metformin versus DPP-4 inhibitors and metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitors) where each had one study with conflicting results. These two studies under-dosed one of the study arms, making it more likely that conflicting results were from differing doses as opposed to publication bias. Only three studies did not report a measure of dispersion; therefore, we were able to combine most of the studies in meta-analyses where appropriate.

Table 6. Strength of evidence domains for monotherapy comparisons in terms of hemoglobin A1c among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD	25 (7281)	Medium	Consistent	Direct	Precise	Undetected	High	Neither drug favored
Metformin vs. SU*	NA	NA	NA	NA	NA	NA	High	Neither drug favored
Metformin vs. DPP-4 inhibitors	6 (6700)	Low	Consistent	Direct	Precise	Undetected	High	Metformin favored; small effect
Metformin vs. SGLT-2 inhibitors	3 (1633)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. GLP-1 agonists	3 (1089)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. Metformin + TZD	15 (6090)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin +TZD favored; medium effect
Metformin vs. Metformin + SU	17 (5210)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SU favored; large effect
Metformin vs. Metformin + DPP-4 inhibitors	32 (21692)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin + DPP-4 inhibitor favored; medium effect
Metformin vs. Metformin + SGLT-2 inhibitors	9 (5778)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitor favored; medium effect
Metformin vs. Metformin + GLP-1 agonists	5 (2556)	Medium	Inconsistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 agonist; medium effect
TZD vs. SU	17 (6212)	Medium	Consistent	Direct	Precise	Undetected	High (for short-term); Insufficient (long-term)	Neither drug favored in short-term; 1 longer term study favored TZD with a small effect
TZD vs. DPP-4 inhibitors	3 (1686)	Low	Inconsistent	Direct	Imprecise	Suspected[†]	Insufficient[†]	Unable to determine
TZD vs. GLP-1 agonists	1 (820)	Low	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
SU vs. DPP-4 inhibitors	3 (1271)	Low	Inconsistent	Direct	Imprecise	Suspected[‡]	Insufficient[‡]	Unable to determine
SU vs. GLP-1 agonists	4 (2056)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient[§]	Unable to determine
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
DPP-4 inhibitors vs. GLP-1 agonists	1 (820)	Low	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We did not re-evaluate hemoglobin A1c for the comparison of metformin with sulfonylureas because we previously rated this comparison as having high strength of evidence.[16]

We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of

available evidence.
† For thiazolidinediones versus DPP-4 inhibitors, we graded the strength of evidence as insufficient since there was only one comparably-dosed study which used maximum doses in each arm. We suspected reporting bias since one study was found in the grey literature which favored thiazolidinediones while two of the three published studies showed no significant difference between-groups in hemoglobin A1c but underdosed the thiazolidinedione arms compared to the DPP-4 inhibitor arms.
‡For sulfonylureas versus DPP-4 inhibitors, we graded the strength as insufficient since two of the three studies minimally favored sulfonylureas while one study did not favor either medication. Two additional studies found in the grey literature minimally favored sulfonylurea. Probably sulfonylurea is mildly favored overall. We will be able to form a more formative opinion by the final report since these two studies will be included in the updated search we will do between the draft and final report.
§ For sulfonylurea versus GLP-1 agonist, only two comparably-dosed studies were identified and each showed different results. The two non-comparably-dosed studies favored the GLP-1 agonist.

Table 7. Strength of evidence domains for metformin-based combination comparisons in terms of hemoglobin A1c among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin +SU	14 (3294)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Neither drug combination favored
Metformin + TZD vs. metformin +DPP-4 inhibitors	5 (2413)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + TZD favored; small effect
Metformin + TZD vs. metformin +GLP-1 agonists	2 (604)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin +DPP-4 inhibitors	7 (5453)	Medium	Consistent	Direct	Precise	Undetected	Low	Neither drug combination favored
Metformin + SU vs. metformin +SGLT-2 inhibitors	3 (3815)	Low	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitor favored; small effect
Metformin + SU vs. metformin +GLP-1 agonists	7 (4375)	Medium	1. Consistent for Met+SU vs Met+exenatide 2. Inconsistent for Met+SU vs Met+other GLP-1 agonist	Direct	Precise	Undetected	Low for #1 and insufficient for #2	1. Metformin + exenatide favored; small effect 2. Unable to determine
Metformin + SU vs. metformin + basal insulin	1 (75)	High	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + premixed insulin	2 (827)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + DPP-4 inhibitors vs. metformin +SGLT-2 inhibitors	4 (2889)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitor favored; small effect
Metformin + DPP-4 inhibitors vs. metformin +GLP-1 agonists	4 (3322)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 agonist favored; moderate effect
Metformin + DPP-4 inhibitors vs. metformin + basal insulin	1 (515)	Medium	Unable to determine	Direct	Precise	Undetected	Low	Metformin + basal insulin favored; moderate effect

Metformin + GLP-1 agonists vs. metformin + basal insulin	2 (390)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
Metformin + GLP-1 agonists vs. metformin + premixed insulin	1 (363)	High	Unable to determine	Direct	Precise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	3 (530)	Medium	Consistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

The Evidence About Weight

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

In the prior report, we graded the evidence as high[16] that metformin was significantly favored, with weight gain in the thiazolidinedione arms and weight loss in the metformin arms. Therefore, we did not re-evaluate this comparison for weight. (SOE: High; Metformin favored)

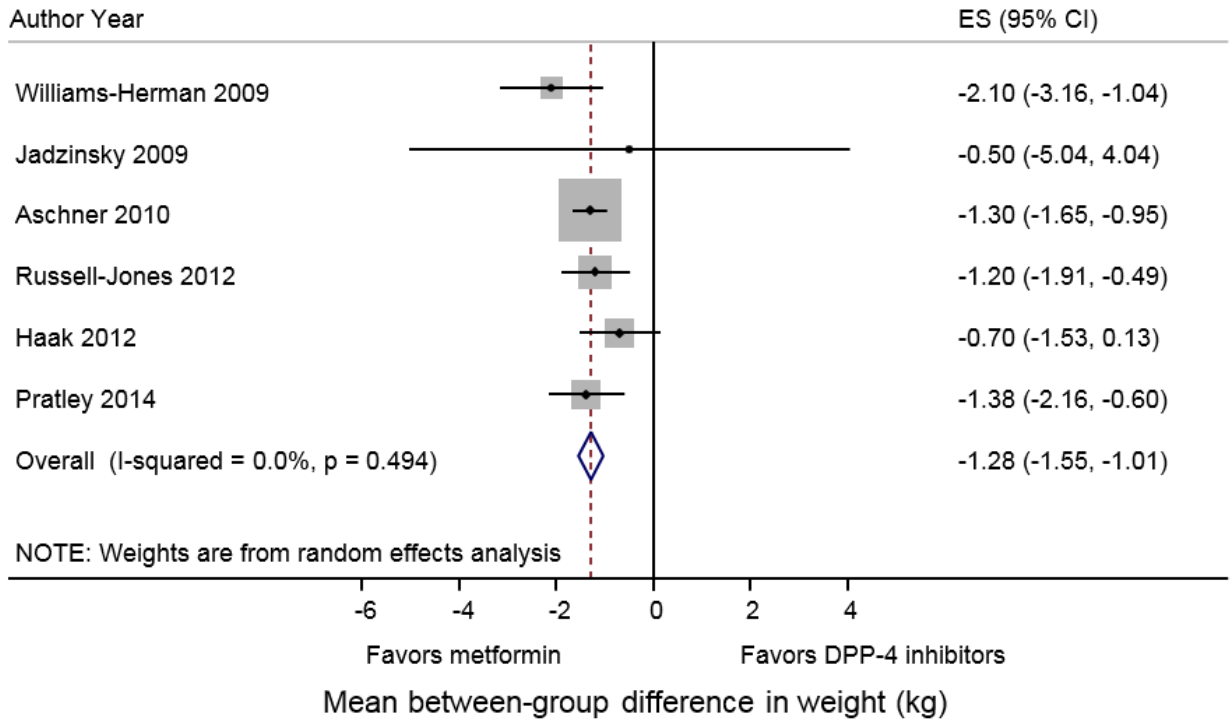
Metformin Versus Sulfonylureas

In the prior report, we graded the evidence as high[16] that metformin was significantly favored, with weight gain in the sulfonylurea arms and mild weight loss in the metformin arms. Therefore, we did not re-evaluate this comparison for weight. (SOE: High; Metformin favored)

Metformin Versus DPP-4 Inhibitors

Six short RCTs, reported in nine articles, compared metformin with DPP-4 inhibitors, reporting greater reductions in weight with metformin (pooled between-group difference, -1.3 kg; 95% CI, -1.6 kg to -1.0 kg) (Figure 19).[66, 72-79] No substantial heterogeneity was found in the meta-analysis, and no single study markedly influenced the results. Two RCTs (in three articles) were reported as extension studies.[73, 77, 79] The extension studies lasting 76 weeks and 104 weeks all favored metformin over the DPP-4 inhibitors (between-group differences of -0.7 kg to -2.9 kg), consistent with the meta-analysis results from the shorter studies. Three RCTs had a lower dose and higher dose metformin arm.[76-78] The higher dose metformin arms in two of the studies which compared metformin with alogliptin and sitagliptin both showed greater reductions in weight than the lower dose metformin arms.[76, 77] The third RCT comparing a low dose and high dose metformin arm with linagliptin did not show this dose response.[78] (SOE: High; Metformin favored)

Figure 19. Pooled mean between-group difference in weight comparing metformin with DPP-4 inhibitors



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus SGLT-2 Inhibitors

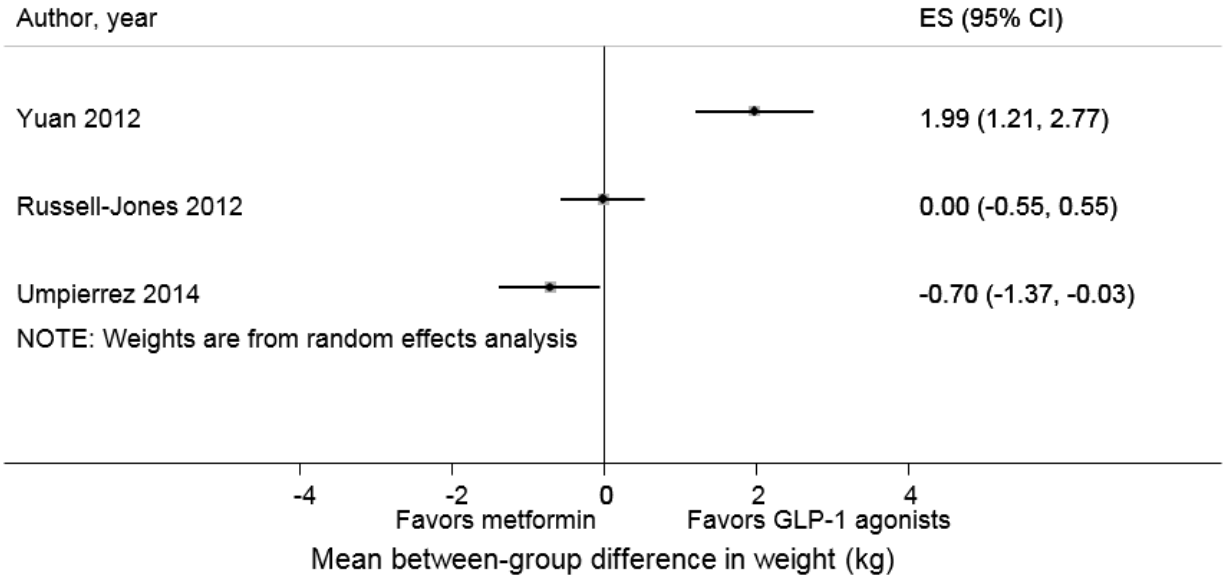
Two 24-week (reported in the same article) and one 90-week RCT compared metformin with an SGLT-2 inhibitor (dapagliflozin or empagliflozin), showing greater reductions in weight with the SGLT-2 inhibitors (range of between-group differences in weight of -1.3 kg to -1.4 kg).[80, 82] These between-group differences were statistically significant in two of the three RCTs.[80] (SOE: Moderate; SGLT-2 inhibitors favored)

Metformin Versus GLP-1 Agonists

Three studies lasting a year or less compared metformin with a GLP-1 agonist, with conflicting effects on weight (Figure 20).[66, 83, 84] We did not combine the studies in a meta-analysis due to study duration and dosing differences. Each of the three studies, lasting 24 to 52 weeks, compared metformin at 2000 to 2500 mg with a GLP-1 agonist at maximum doses (exenatide 20 micrograms daily in one study, exenatide 2 mg weekly in a second study, and dulaglutide 1.5 mg weekly in a third study). The first comparably-dosed 26-week RCT of metformin titrated to 2500 mg daily compared with a fixed dose of 2 mg of exenatide weekly reported a mean between-group difference in weight of 0 kg (95% CI, -0.6 kg to 0.6 kg).[66] The second 26-week RCT compared metformin titrated to 2000 mg with exenatide 20 micrograms daily.[84] This RCT reported a mean between-group difference of 2.0 kg, favoring the GLP-1 agonist arm (95% CI, 1.2 kg to 2.8 kg).[84] The last 52-week RCT compared metformin titrated to 2000 mg with dulaglutide of 1.5 mg weekly, and reported a mean between-group difference in

weight favoring the metformin arm of -0.7 kg (95% CI, -1.4 kg to -0.03 kg).[83] (SOE: Insufficient; Unable to determine)

Figure 20. Mean between-group difference in weight comparing metformin with GLP-1 agonists

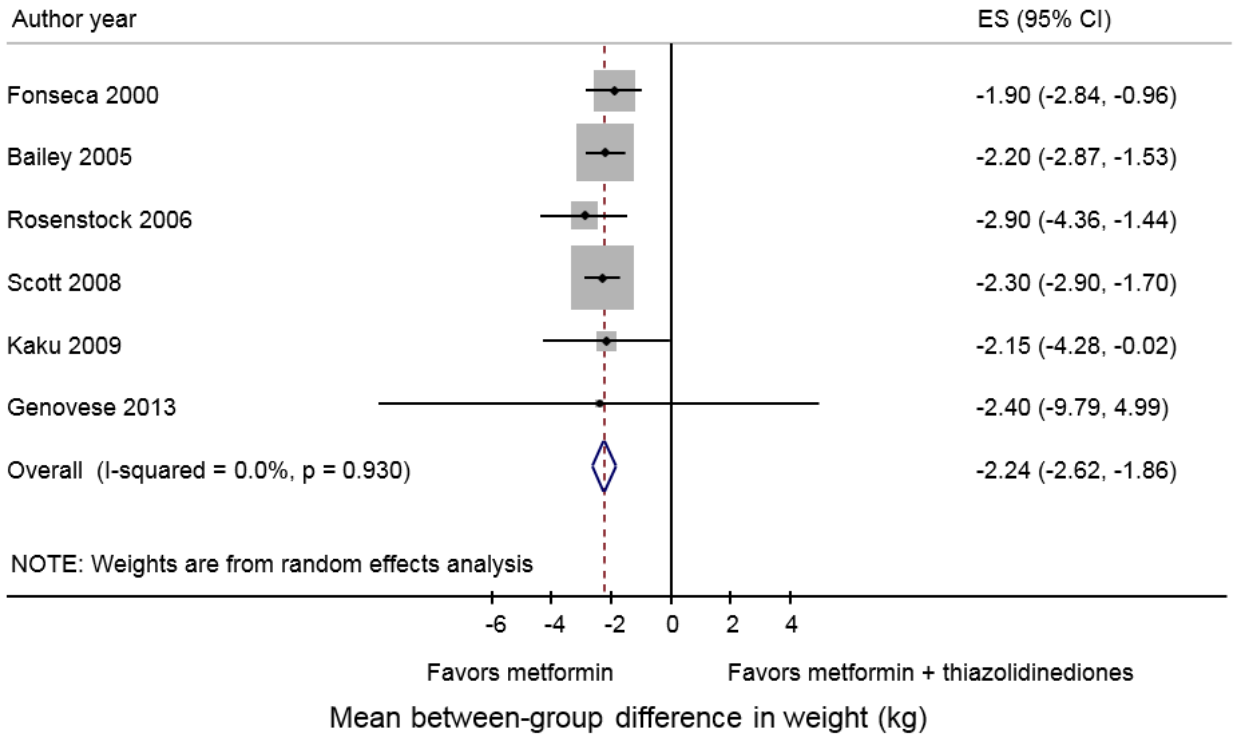


CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

We combined six studies which directly compared metformin monotherapy with the combination of metformin plus a thiazolidinedione (mostly rosiglitazone), showing a pooled between-group difference in weight of -2.2 kg (95% CI, -2.6 kg to -1.9 kg) favoring metformin (Figure 21).[52, 86, 87, 89, 92, 94] There was no significant heterogeneity between studies, and no single study markedly affected the results. All six studies showed that the metformin arms had weight loss while the combination arms had weight gain. Four studies were excluded from the meta-analysis due to insufficient quantitative data to combine the studies[60, 85, 95] or due to study duration differences.[96] All four of these studies reported modest weight gain in the combination arms which was consistent with the studies included in the meta-analysis.[60, 85, 95, 96] (SOE: High; Metformin favored)

Figure 21. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a thiazolidinedione

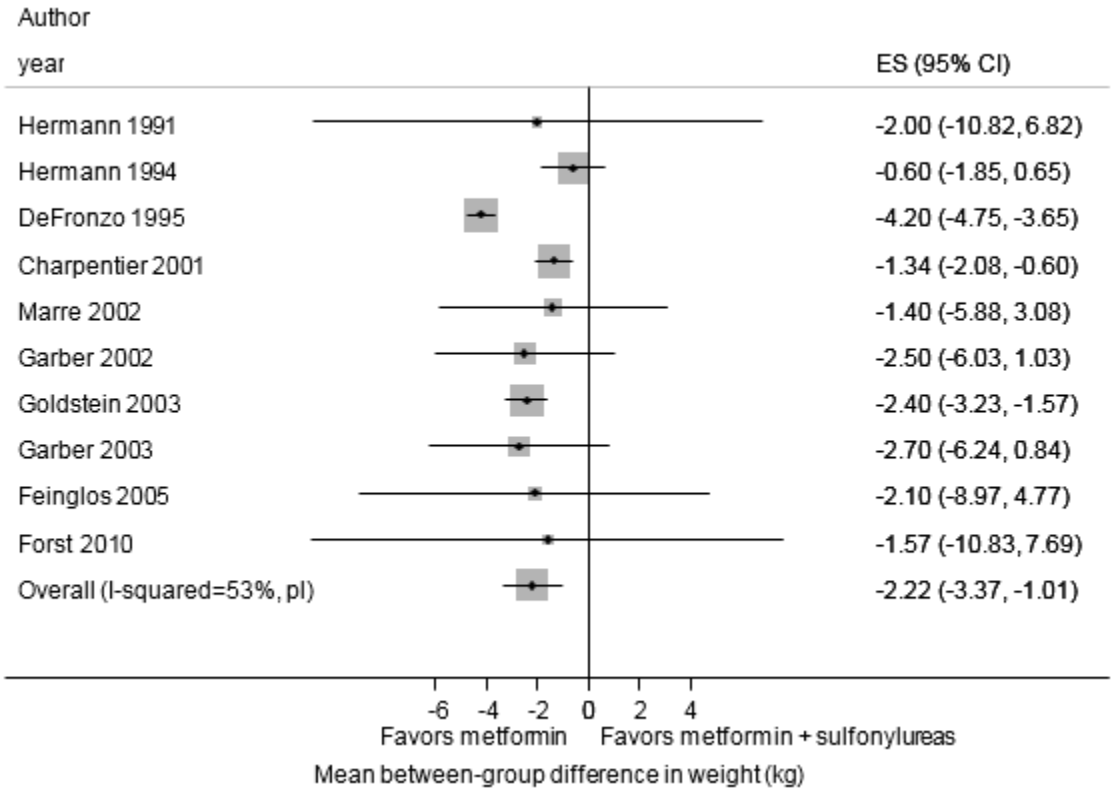


CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Ten short RCTs compared metformin with the combination of metformin plus a second-generation sulfonylurea favoring metformin monotherapy, with a pooled between-group difference of -2.2 kg (95% CI -3.4 kg to -1.0 kg) (Figure 22).[97-99, 101-106, 108] No single study markedly influenced the results. While heterogeneity existed, all studies favored the metformin arm over the combination arm with minimal between-group differences among the studies. In metaregression, baseline weight was identified as a significant source of heterogeneity; dosing differences, double blinding, study duration, and appropriate randomization were not identified as significant. Baseline weight explained 55% of the between-study heterogeneity (adjusted r-squared = 55%). We present the stratified meta-analyses in Table 8. One 104-week study was excluded from the meta-analysis due to its long duration.[110] The mean between-group difference in weight favored the metformin monotherapy arm, non-significantly, by 2.2 kg.[110] (SOE: High; Metformin favored)

Figure 22. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a sulfonylurea



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Table 8. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a sulfonylurea stratified by baseline weight

Variables	N of studies	WMD (95% CI)	I^2	Summary
Baseline weight ≥ 90 kg*	5	-3.2 kg (-4.6 kg to -1.6 kg)	56%	Favors metformin
Baseline weight < 90 kg	5	-1.2 kg (-1.8 kg to -0.6 kg)	0%	Favors metformin

CI = confidence interval; kg = kilogram; WMD = weighted mean difference
* Analysis was calculated using a profile likelihood estimate.

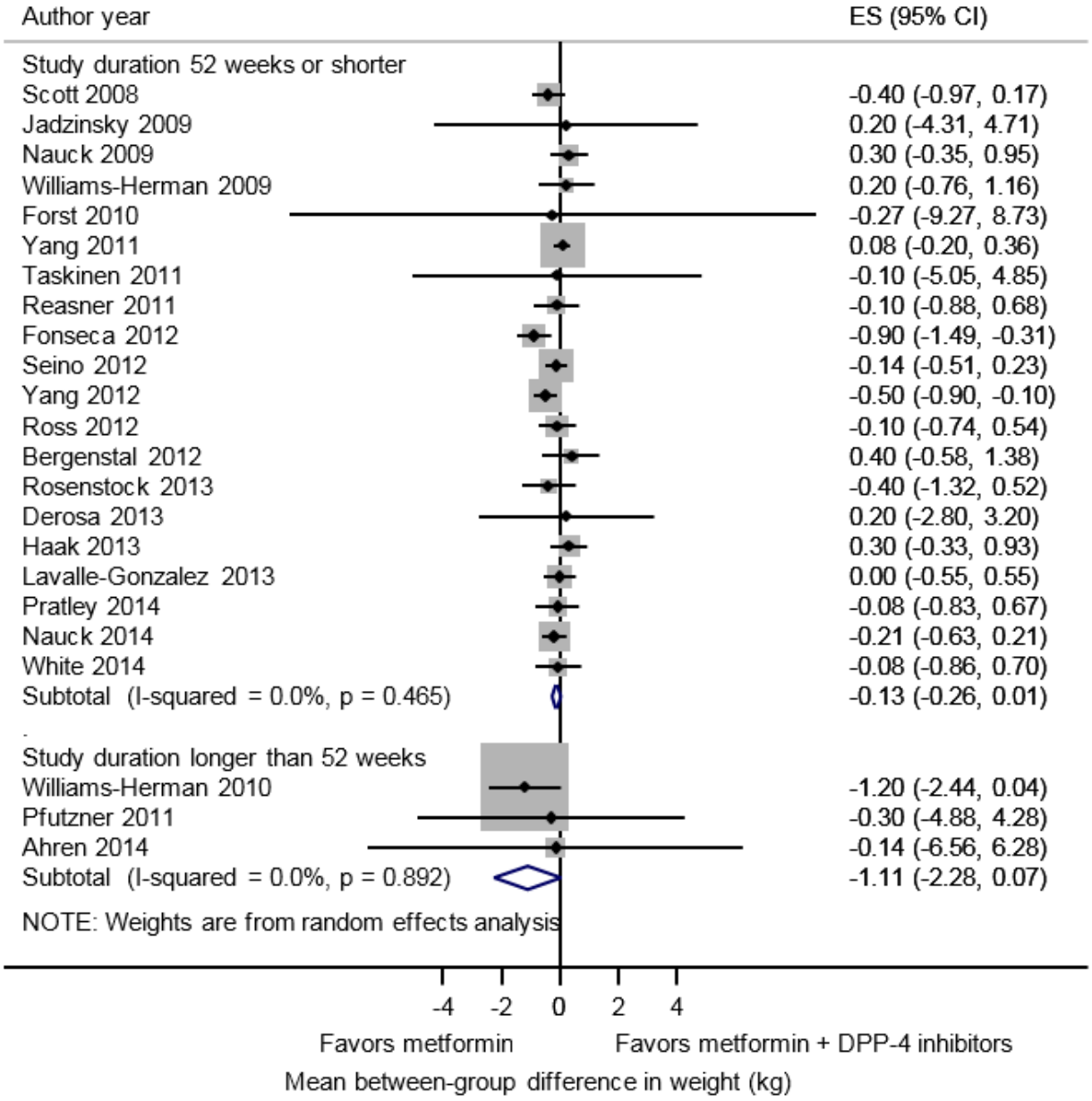
Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

We combined twenty RCTs lasting a year or less comparing metformin with the combination of metformin plus a DPP-4 inhibitor, with a pooled between-group difference of -0.1 kg (95% CI, -0.3 kg to 0.01 kg) (Figure 23).[46, 73, 75, 76, 78, 87, 108, 114-117, 119-124, 126-128] No substantial heterogeneity was found. In a standard sensitivity analysis, several studies removal significantly changed the pooled estimate to favor metformin monotherapy slightly. However, there were no clear qualitative differences to prompt removal of any of these studies. Six studies with similar results to the other studies were excluded from the short duration meta-analysis due to absence of data needed to quantitatively combine the studies.[95, 112, 113, 118, 125, 130]

We also pooled three longer studies (two of which were extension studies) lasting 76 to 104 weeks that compared metformin with a metformin plus a DPP-4 inhibitor. Consistent with the short studies, these trials showed no significant difference in weight (pooled between-group

difference in weight, 1.1 kg; 95% CI, -2.3 kg to 0.07 kg) (Figure 23).[77, 79, 110] No single study markedly influenced the results, and no substantial heterogeneity was found. (SOE: High; Neither favored)

Figure 23. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration



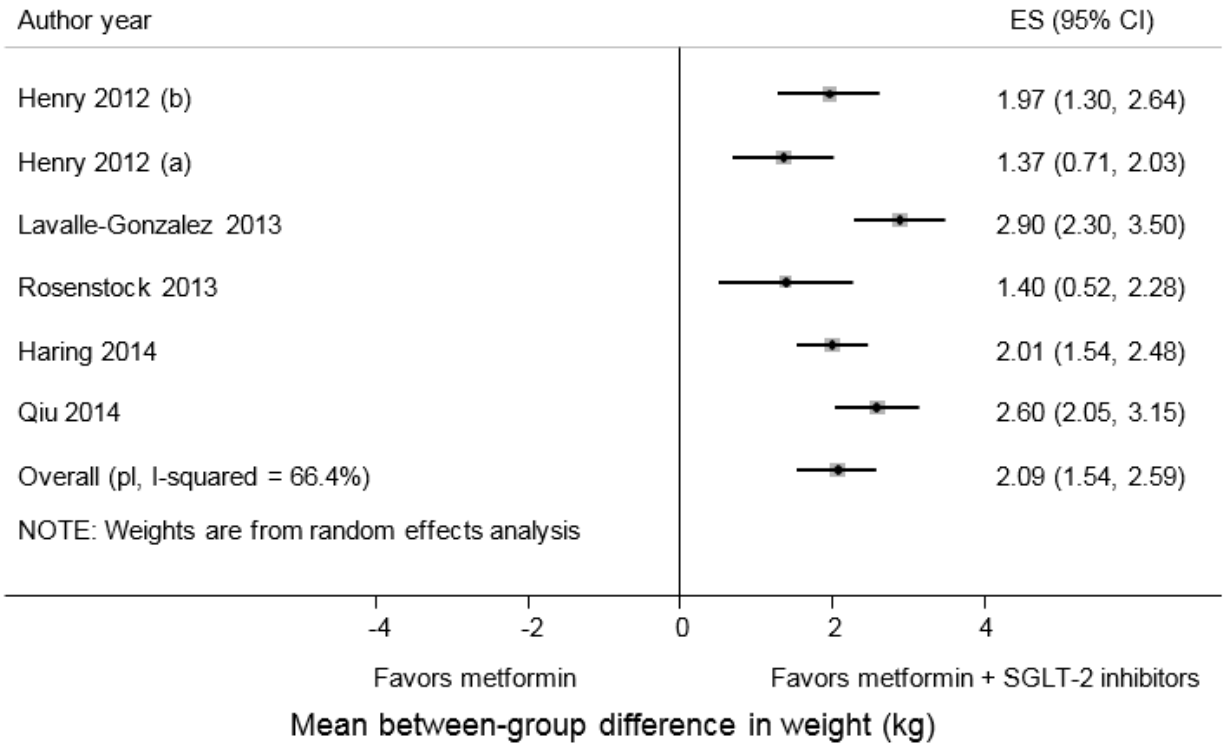
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Six RCTs (reported in five articles) lasting 26 weeks or less compared metformin alone with the combination of metformin plus an SGLT-2 inhibitor, with greater weight reductions in the combination arm (pooled between-group difference in weight, 2.1 kg; 95% CI, 1.5 kg to 2.6 kg) (Figure 24).[80, 122, 127, 132, 133] No single study markedly influenced the results. There was substantial statistical heterogeneity among the studies, yet the individual between-group differences were similar among the studies. One additional short RCT was excluded since it only reported percent change in weight, but it also favored the combination of metformin plus an SGLT-2 inhibitor.[125] Two 102-week RCTs were excluded from the meta-analysis due to study duration differences.[134, 135] These longer RCTs also significantly favored the combination of metformin plus an SGLT-2 inhibitor, with the range in between-group differences in weight of 2.4 kg to 3.1 kg. The between-group differences in weight were maintained in these longer studies when compared with the shorter studies. (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 24. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a SGLT-2 inhibitor



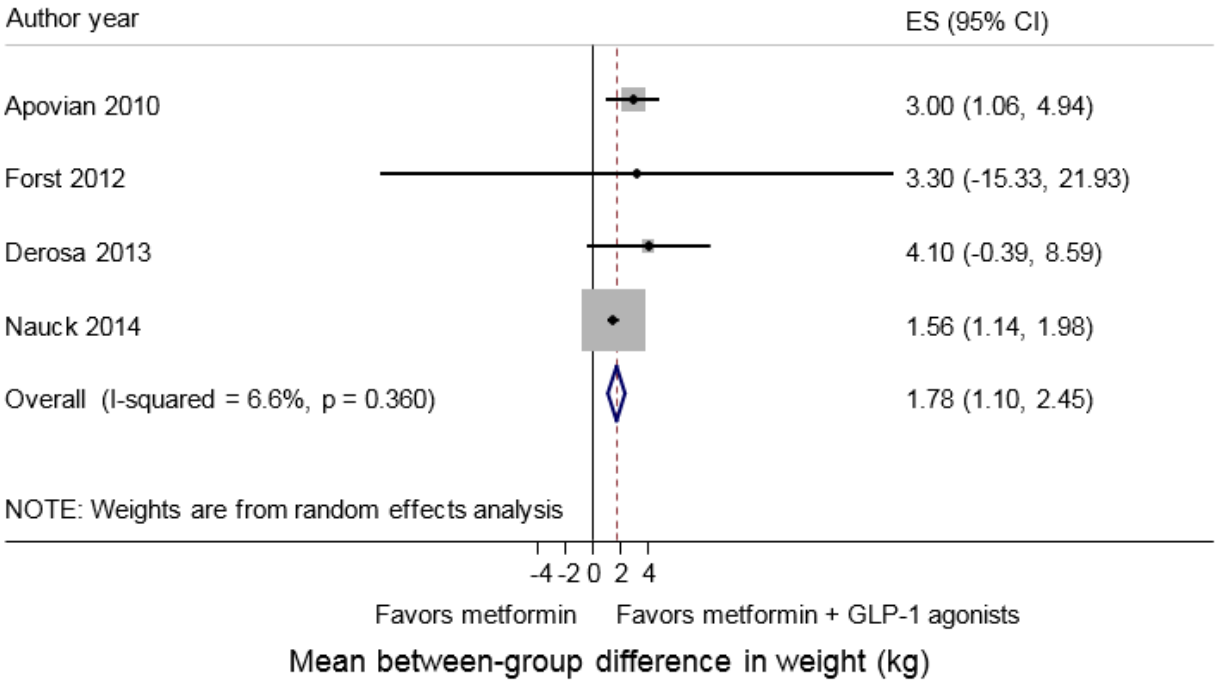
CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; pl = profile likelihood estimate; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Four RCTs lasting 48 weeks or less compared metformin with the combination of metformin plus a GLP-1 agonist, with all four studies showing greater weight reduction in the combination metformin plus GLP-1 agonist arm (pooled between-group difference, 1.8 kg; 95% CI, 1.1 kg to

2.5 kg) (Figure 25).[128, 136-138] No one study strongly influenced the pooled results, and no substantial heterogeneity was identified. The one short study which had two dosing arms of the combination showed a smaller between-group difference in weight when comparing the metformin monotherapy arm to the lower dose combination arm versus the higher dose combination arm.[128] One 104-week RCT excluded from the meta-analysis showed a non-significant greater weight reduction in the combination arm of 0.2 kg.[110] (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

Figure 25. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus Sulfonylureas

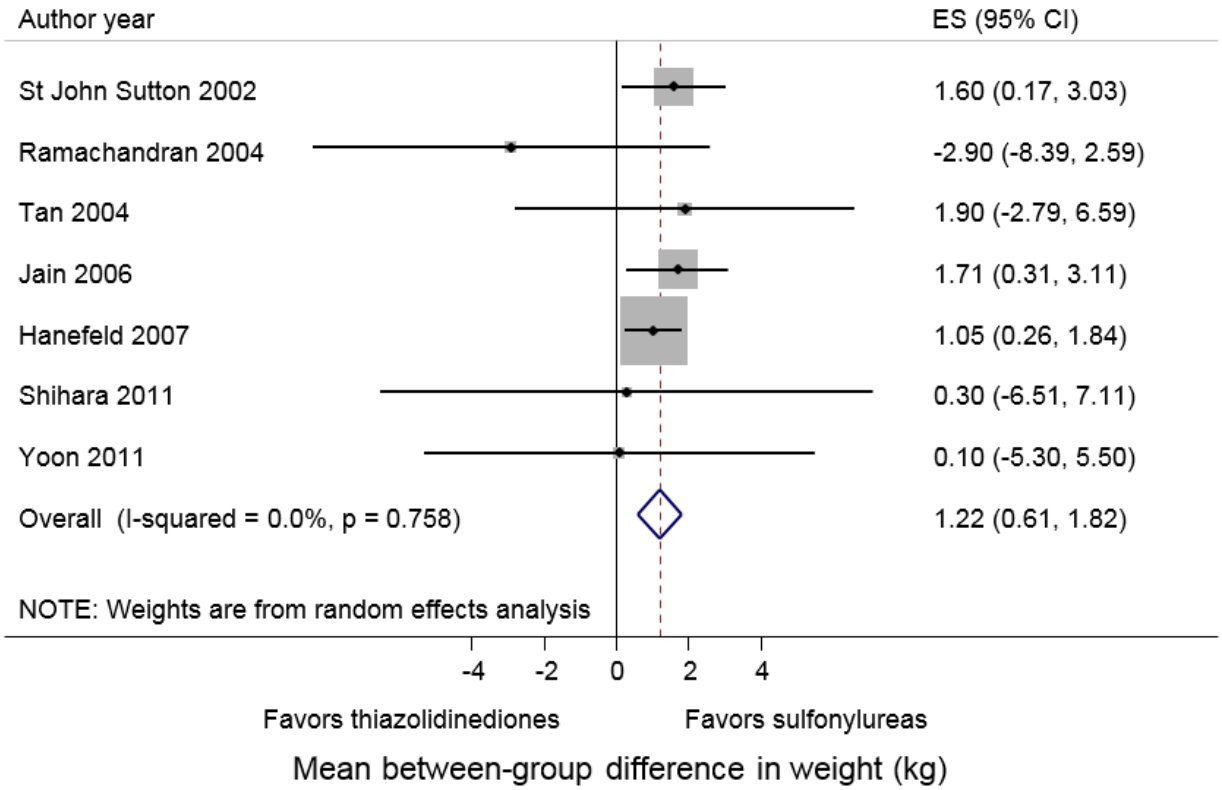
Seven studies lasting a year or less compared a thiazolidinedione to a second-generation sulfonylurea, showing higher weight gain in the thiazolidinedione arms, with a pooled between-group difference of 1.2 kg (95% CI, 0.6 kg to 1.8 kg) (Figure 26).[54, 67, 140, 141, 146, 149, 200] No single study markedly influenced the results, and no substantial heterogeneity was found.

One study showed a dose response relationship between rosiglitazone and weight; patients treated with rosiglitazone (4 mg per day) gained 1.8 kg and those treated with 8 mg per day gained 3.0 kg over 52 weeks compared with the glibenclamide arm which gained 1.9 kg.[140]

We excluded two RCTs from the meta-analysis due to their longer durations of 3 to 4 years.[45, 201] Both RCTs had results consistent with the meta-analysis. As mentioned previously, the ADOPT study evaluated the long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for adults with type 2 diabetes, with weight as a secondary outcome.[45] The between-group difference between rosiglitazone and glyburide was

consistent with the results of the meta-analysis of the shorter studies favoring sulfonylureas after approximately 5 years of followup (mean between-group difference, 2.5 kg; 95% CI, 2.0 kg to 3.1 kg). Of note, individuals in the glyburide arm gained weight over the first year and then stabilized, while those in the rosiglitazone arm had continued weight gain throughout the study. The second large 3-year multicenter study comparing pioglitazone with glibenclamide showed a 5.2 kg weight gain in the pioglitazone-treated group and a 0.9 kg weight gain in the glibenclamide-treated group.[201] (SOE: Moderate; Sulfonylurea favored)

Figure 26. Pooled mean between-group difference in weight comparing thiazolidinediones with sulfonylureas



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

Two 26-week RCTs compared thiazolidinediones with DPP-4 inhibitors; both studies significantly favored DPP-4 inhibitors with a mean between-group difference of 2.3 kg and 2.5 kg.[66, 150] The thiazolidinedione arms increased weight by around 1.8 kg while the DPP-4 inhibitor arms decreased weight by around 0.5 kg. (SOE: Moderate; DPP-4 inhibitors favored)

Thiazolidinediones Versus GLP-1 Agonists

One double-blind moderately-sized RCT compared pioglitazone titrated to 45 mg daily with exenatide 2 mg weekly.[66] After 26 weeks, the calculated between-group difference in weight favored exenatide by 3.5 kg (95% CI, 2.8 kg to 4.2 kg).[66] The pioglitazone arm increased weight

by 1.5 kg and the exenatide arm decreased weight by 2 kg. (SOE: Moderate; GLP-1 agonists favored)

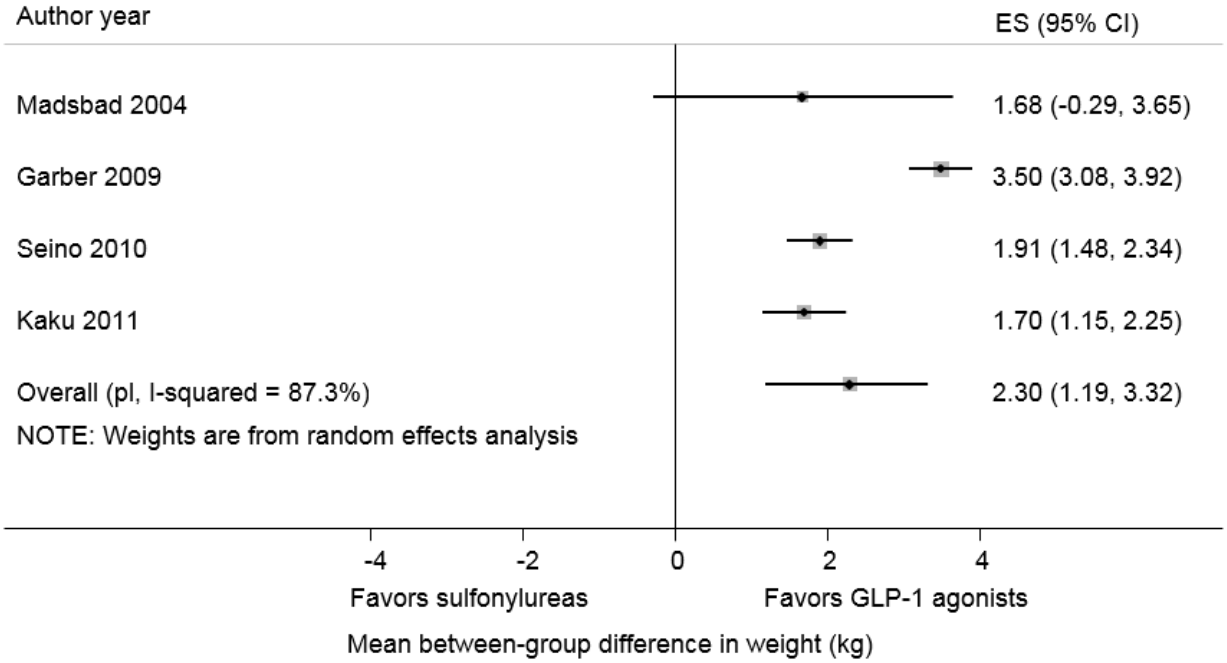
Sulfonylureas Versus DPP-4 Inhibitors

Three RCTs lasting 54 weeks or less compared a sulfonylurea (glipizide or glimepiride) with a DPP-4 inhibitor (sitagliptin or linagliptin) and favored the DPP-4 inhibitor arms (range in mean between-group differences of 0.9 kg to 1.8 kg).[151-153] This difference was significant in two of the three studies; one study did not provide sufficient data to assess.[153] We did not combine these studies due to dosing and study population differences. Sulfonylureas increased weight by about 1.2 kg and the DPP-4 inhibitors decreased weight by around 0.4 kg in these studies. (SOE: Low; DPP-4 inhibitors favored)

Sulfonylureas Versus GLP-1 Agonists

Four RCTs comparing sulfonylureas directly with liraglutide showed greater weight gain with a sulfonylurea (pooled mean between-group difference, 2.3 kg; 95% CI, 1.2 kg to 3.3 kg) (Figure 27).[154-157] No single study strongly influenced the results. Substantial heterogeneity was found. Potential sources of heterogeneity were dosing differences, study duration differences, and differences in baseline weight. The one study with the largest between-group difference in weight[157] lasted at least 24 weeks longer than the other two studies, used medications titrated to the maximum dose in both arms, and started with a higher baseline BMI. (SOE: Moderate; GLP-1 agonists favored)

Figure 27. Pooled mean between-group difference in weight comparing sulfonylureas with GLP-1 agonists



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram; pl = profile likelihood estimate

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One double-blind, moderately-sized 24-week RCT compared the DPP-4 inhibitor, sitagliptin at 100 mg daily, with the SGLT-2 inhibitor, empagliflozin at 10 mg and 25 mg daily. The results significantly favored the empagliflozin arms (calculated mean between-group difference of 2.5 kg and 2.7 kg for the low dose and high dose empagliflozin arms respectively).[159] The sitagliptin arm maintained weight while the empagliflozin arms decreased weight over the 24 weeks. (SOE: Moderate; SGLT-2 inhibitors favored)

DPP-4 Inhibitors Versus GLP-1 Agonists

One RCT compared a DPP-4 inhibitor with a GLP-1 agonist and reported a significant between-group difference in weight favoring the GLP-1 agonist.[66] This double-blind RCT compared sitagliptin at 100 mg daily with exenatide 2 mg weekly for 26 weeks, with greater weight reduction in the exenatide arm (calculated mean between-group difference in weight, 1.2 kg; 95% CI, 0.5 kg to 1.9 kg).[66] (SOE: Low; GLP-1 agonists favored)

Metformin-Based Combination Comparisons

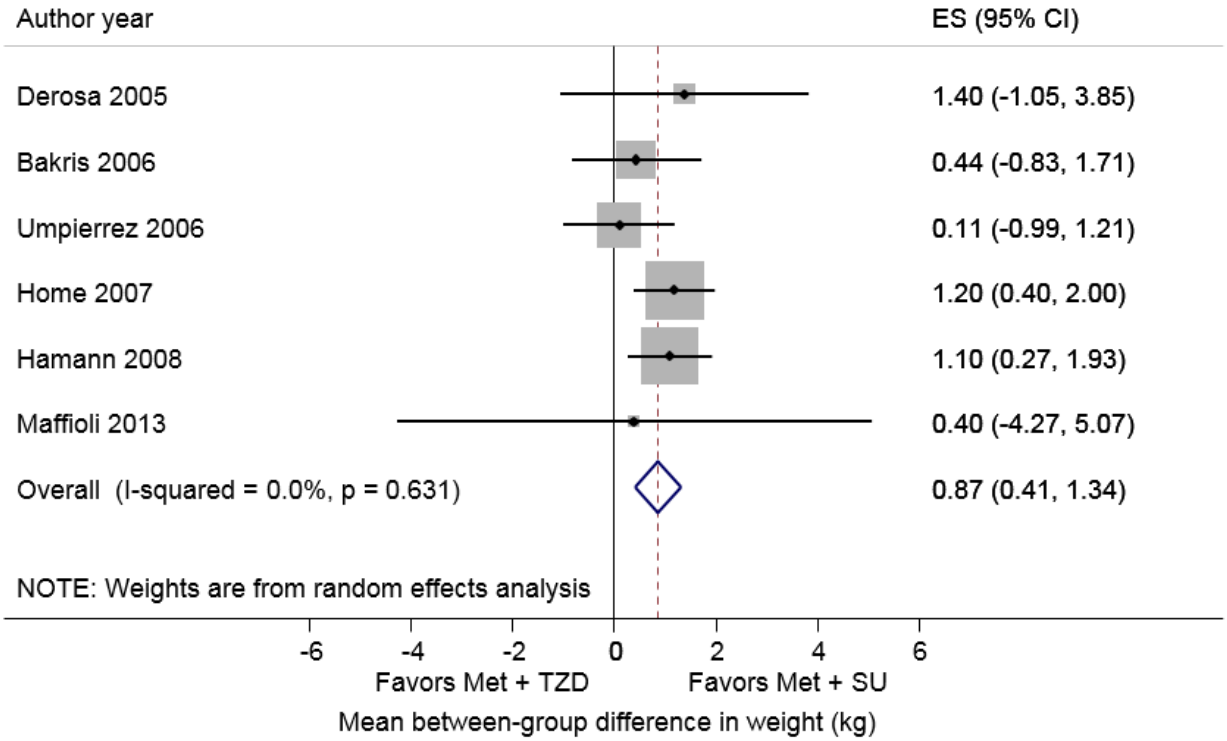
Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

We combined six comparably-dosed studies lasting less than a year that directly compared metformin plus a thiazolidinedione with metformin plus a sulfonylurea.[160-163, 166, 202] The pooled mean between-group difference favored the combination of metformin plus sulfonylurea by 0.9 kg (95% CI, 0.4 kg to 1.3 kg) (Figure 28). No one study markedly influenced the results, and no substantial heterogeneity was found.

In the meta-analysis, we included the short-term results from the large RECORD study.[161] The RECORD study was a multicenter, open-label RCT evaluating 4447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[44, 161] Body weight increased significantly with rosiglitazone plus metformin compared with sulfonylurea plus metformin, with a mean between-group difference of 1.2 kg (95% CI, 0.4 kg to 2.0 kg) after 18 months.[161] The mean between-group difference increased to 3.8 kg after 5 years of followup.[44]

We excluded three short RCTs from the meta-analysis since the dosing was not comparable with the other studies.[165, 169, 170] One[165] used a lower dose of metformin in the metformin plus sulfonylurea arm compared with a higher dose of metformin in the metformin plus thiazolidinedione arm. The two other short RCTs used low doses of a sulfonylurea in the metformin plus sulfonylurea arm.[169, 170] As a sensitivity analysis, we included these three RCTs in the meta-analysis and noted no meaningful change in results (pooled mean between-group difference in weight`, 0.8 kg.[165, 169, 170] (SOE: Moderate; Combination of metformin plus a sulfonylurea favored)

Figure 28. Pooled mean between-group difference in weight comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea



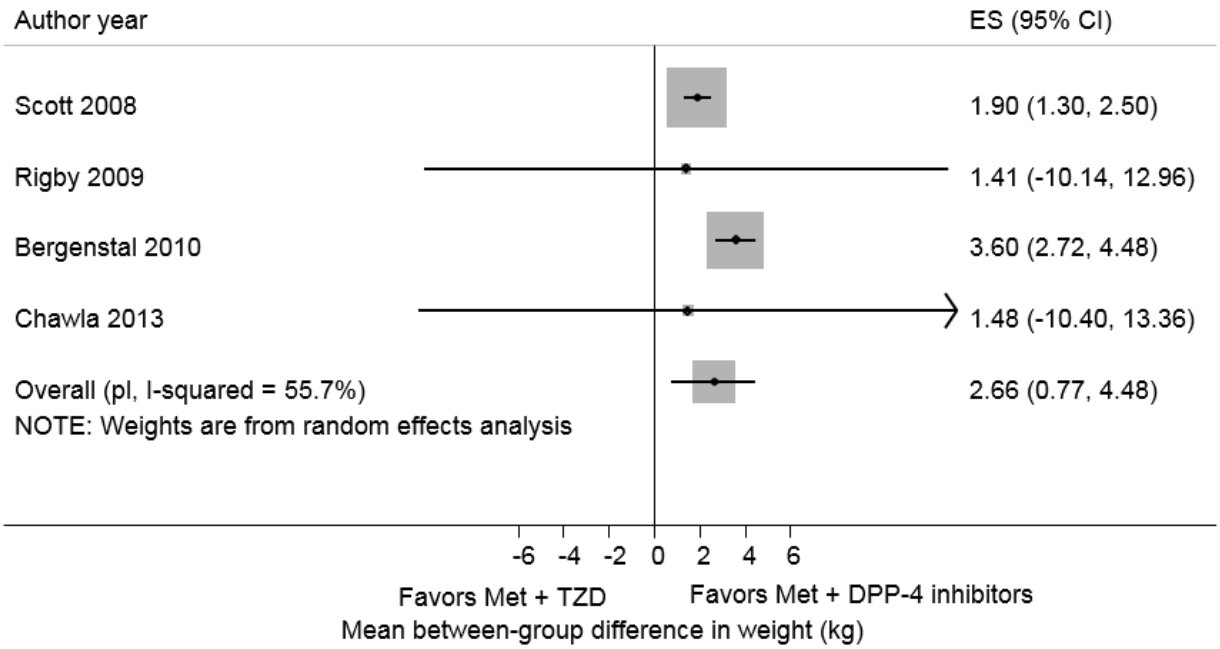
CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; kg = kilogram; SU = sulfonylurea; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Four short duration RCTs compared metformin plus a thiazolidinedione with the combination of metformin plus a DPP-4 inhibitor, favoring the combination of metformin plus a DPP-4 inhibitor (pooled mean between-group difference, 2.7 kg; 95% CI, 0.8 kg to 4.5 kg) (Figure 29).[87, 171-173] The patients in the metformin plus DPP-4 inhibitor arms had a mean weight loss while the patients in the metformin plus thiazolidinedione arms had a mean weight gain. No single study markedly influenced the results. Substantial heterogeneity was identified; however, all four studies favored the metformin plus DPP-4 inhibitor arms by 1.4 to 3.6 kg. We were unable to quantitatively explore heterogeneity due to the small numbers of studies, but there were differences in baseline weight and drug types.

One additional short duration RCT comparing metformin plus pioglitazone with metformin plus alogliptin was excluded from the meta-analysis since it did not have sufficient quantitative data.[95] The study reported a decrease weight of 0.7 kg in the metformin plus alogliptin arms but only stated qualitatively that there was an increase in weight in the metformin plus pioglitazone arm, consistent with the direction of weight change in the other four studies.[95] (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 29. Pooled mean between-group difference in weight comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; kg = kilogram; pl = profile likelihood estimate; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

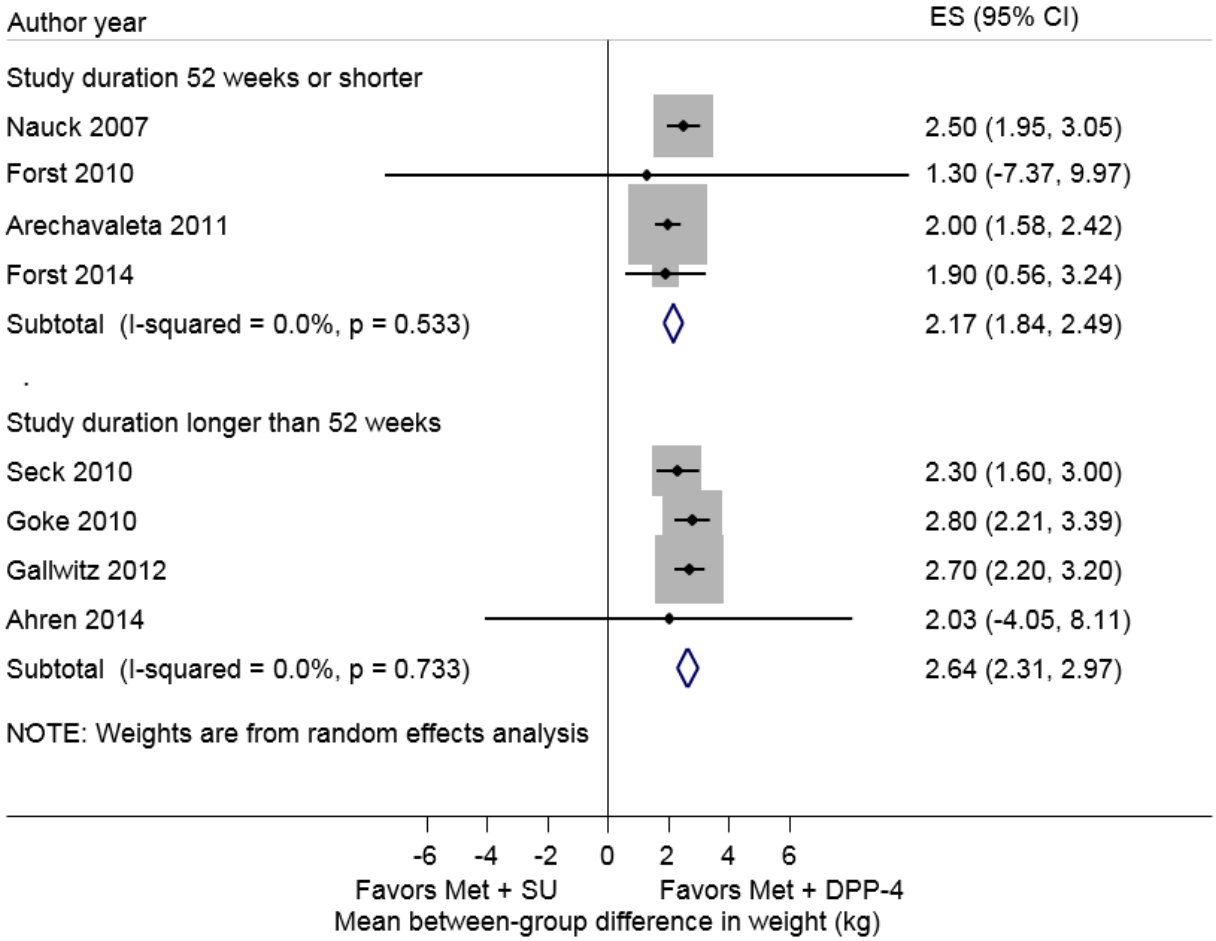
Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

Two short, comparably-dosed RCTs compared metformin plus thiazolidinediones (pioglitazone and rosiglitazone) with metformin plus a GLP-1 agonist (exenatide).[173, 174] Both studies significantly favored the combination of metformin plus a GLP-1 agonist (range in mean between-group differences in weight, 2.7 kg to 5.1 kg). Both studies had weight gain in the metformin plus thiazolidinedione arms and weight loss in the metformin plus GLP-1 agonist arms. (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

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

Seven RCTS (reported in eight articles) compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor.[108, 110, 175-180] Both the shorter (under a 1 year) and longer (2-year) studies favored the metformin plus DPP-4 inhibitor arms (Figure 30). The metformin plus sulfonylurea arms all had weight gain while the metformin plus DPP-4 inhibitor arms all had weight loss. The four RCTs lasting 1 year or less had a pooled between-group difference in weight of 2.2 kg (95% CI, 1.8 kg to 2.5 kg)[108, 175-177] and the four RCTs lasting 2 years had a pooled between-group difference of 2.6 kg (95% CI, 2.3 kg to 3.0 kg).[110, 178-180] No single study markedly influenced the results, and no substantial heterogeneity was identified in either meta-analysis. (SOE: High; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 30. Pooled mean between-group difference in weight comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration

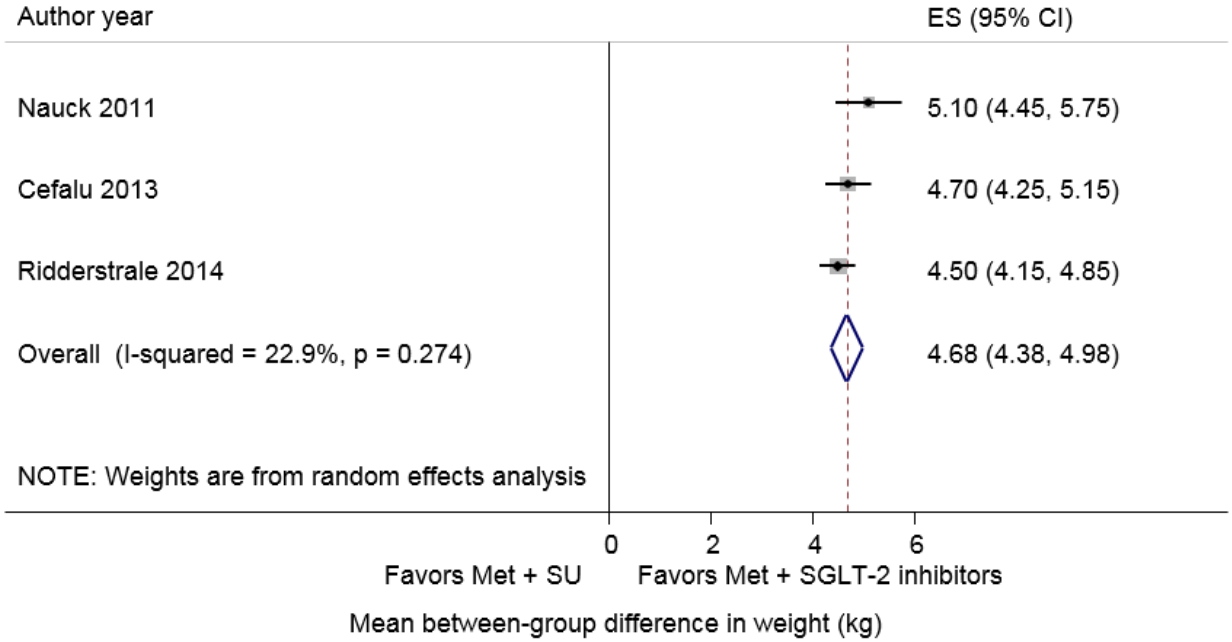


CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; Met = metformin; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Three RCTs lasting 52 to 104 weeks compared the combination of metformin plus a sulfonylurea (glimepiride or glipizide) with the combination of metformin plus an SGLT-2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin).[181-183] The combination of metformin plus an SGLT-2 inhibitor was strongly favored (pooled mean between-group difference in weight, 4.7 kg; 95% CI, 4.4 kg to 5.0 kg) (Figure 31). No single study markedly influenced the results, and no substantial heterogeneity was found. One of the RCTs which had a lower and higher dose metformin plus canagliflozin arm demonstrated a small dose-response effect in weight reduction, with a smaller mean between-group difference in weight in the lower dose arm of 4.4 kg versus 4.7 kg in the higher dose arm.[181] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 31. Pooled mean between-group difference in weight comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; Met = metformin; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Four RCTs (three lasting less than 1 year and one lasting 2 years) compared metformin plus sulfonylurea with metformin plus a GLP-1 agonist.[110, 186-188] These favored the combination of metformin and GLP-1 agonist (range in mean between-group differences, 2.4 kg to 12.3 kg). All four RCTs showed weight loss with the combination of metformin and GLP-1 agonists and weight gain with the combination of metformin and sulfonylureas. We did not combine these studies in a meta-analysis due to differences in drug dosing, drug type, and study duration.

One RCT compared metformin plus a sulfonylurea with three different dosing arms of metformin plus liraglutide. The arms with lower doses of liraglutide had smaller between-group differences in weight relative to the higher dose arm.[187] (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

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

One small, open-label RCT lasting 48 weeks compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a basal insulin, favoring metformin plus sulfonylurea although not significantly (mean between-group difference in weight, -1.7 kg; 95% CI, -3.1 kg to -0.3 kg).[189] Patients were kept on their prior metformin doses and were randomized to uptitration of glimepiride (mean daily dose of 4 mg) versus uptitration of insulin glargine (mean daily dose of 23 units) until a fasting plasma glucose target was reached. Individuals in

the metformin plus sulfonylurea arm had no change in weight while those in the metformin plus insulin glargine arm gained weight. (SOE: Low; Combination of metformin plus a sulfonylurea favored)

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

Two short RCTs compared metformin plus glibenclamide with the combination of metformin plus a premixed insulin analogue: insulin aspart 70/30 in one study and insulin lispro 75/25 in the other study.[190, 191] Both studies favored the metformin plus sulfonylurea arms (range in between-group differences, -0.7 kg to -0.5 kg). One of the two studies showed a statistically significant difference. There was not a mean decrease in weight in any of the study arms.

Of note, if we combine the three studies comparing metformin plus sulfonylurea with metformin plus a premixed or basal insulin (adding in the study described in the prior comparison), metformin plus sulfonylurea is favored with a weighted mean between-group difference in weight of -0.67 kg (95% CI, -0.83 kg to -0.51 kg). No single study influenced the results and no substantial heterogeneity was identified. Since premixed and basal insulins may have similar effects on weight, it may be reasonable to combine these categories. (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Four RCTs compared metformin plus a DPP-4 inhibitor with the combination of metformin plus an SGLT-2 inhibitor.[82, 122, 125, 127] All four studies significantly favored the combination of metformin plus an SGLT-2 inhibitor. We did not combine these studies due to differences in study duration and reporting of the outcome. The first 12-week RCT reported a mean percent change in weight of -0.6% in the metformin plus DPP-4 arm versus -3.4% in the metformin plus SGLT-2 inhibitor arm.[125] The second 12-week RCT reported a mean between-group difference in weight of 1.8 kg (95% CI, 1.9 kg to 2.7 kg).[122] The two longer RCTs, lasting 52 to 90 weeks, reported mean between-group differences of 2.9 kg and 3.6 kg, favoring the metformin plus SGLT-2 inhibitor arms.[82, 127] Two of the three studies with a lower dose and higher dose combination of metformin plus SGLT-2 inhibitor arm demonstrated a dose-response effect in weight reduction, with smaller between-group differences in the lower dose arms and larger between-group differences in the higher dose arms.[82, 127] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

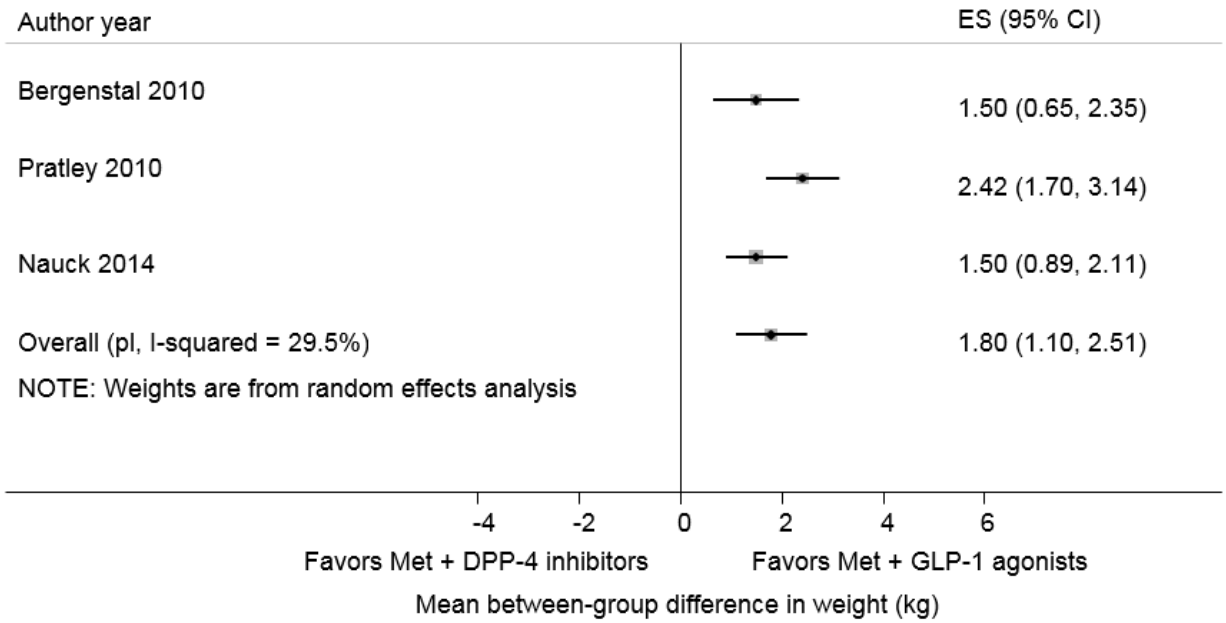
We combined three short RCTs comparing the combination of metformin plus a DPP-4 inhibitor with the combination of metformin plus a GLP-1 agonist.[128, 173, 192] All three studies significantly favored the combination of metformin plus a GLP-1 agonist (pooled mean between-group difference, 1.8 kg, 95% CI, 1.1 kg to 2.5 kg) (Figure 32). Individuals in both arms lost weight but the metformin plus GLP-1 agonist decreased weight more than the metformin plus DPP-4 treatment. No single study markedly influenced the results. Moderate heterogeneity was identified although studies and point estimates were relatively similar.

The two studies with both low dose and high dose arms of the GLP-1 agonist showed smaller between-group differences in weight for the lower dose arms (between-group differences for

lower dose arms of 1.9 kg and 1.1 kg compared with the higher dose arm of 2.5 kg and 1.5 kg).[128, 192]

One 104-week RCT reported a non-significant between-group difference in weight of 0.4 kg (95% CI, -4.7 kg to 5.4 kg).[110] (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

Figure 32. Pooled mean between-group difference in weight comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram; Met = metformin; pl = profile likelihood estimate
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

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

One 24-week RCT compared metformin plus sitagliptin 100 mg daily with metformin plus insulin glargine titrated to 0.5 units per kg. The RCT significantly favored the metformin plus DPP-4 arm with a mean between-group difference in weight of -1.5 kg (95% CI, -2.1 kg to -0.9 kg).[193] The metformin plus DPP-4 arm decreased weight while the metformin plus insulin glargine arm increased weight. (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Combination of Metformin Plus a GLP1-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

Two RCTs (reported in three articles) compared metformin plus a GLP-1 agonist with metformin plus a basal insulin, with both significantly favoring the combination of metformin plus GLP-1 agonists (mean between-group differences in weight of -4.6 kg and -7.8 kg).[47, 194, 195] Both studies showed decreased weight in the metformin plus GLP-1 agonist arms and weight gain in the metformin plus basal insulin arms. The 56-week RCT compared the combination of

metformin and exenatide with the combination of metformin and insulin glargine, showing statistically significant weight loss with the metformin plus exenatide treated group compared with the metformin plus insulin glargine treated group (between group difference of -4.6 kg, $P < 0.0001$).[195] Of note, the exenatide combination arm had about 25% of their subjects on higher than the FDA-approved highest recommended dose of exenatide. Weight returned to baseline 12 weeks after discontinuation of treatment in both arms. This study was also extended to 3 years and reported a higher between-group difference in weight over time (-7.8 kg).[47] The other short 26-week RCT was more comparably-dosed, with metformin plus exenatide (2 mg weekly) compared with metformin plus glargine insulin (titrated based on blood sugars). This RCT showed a mean between-group difference of -4.7 kg.[194] (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

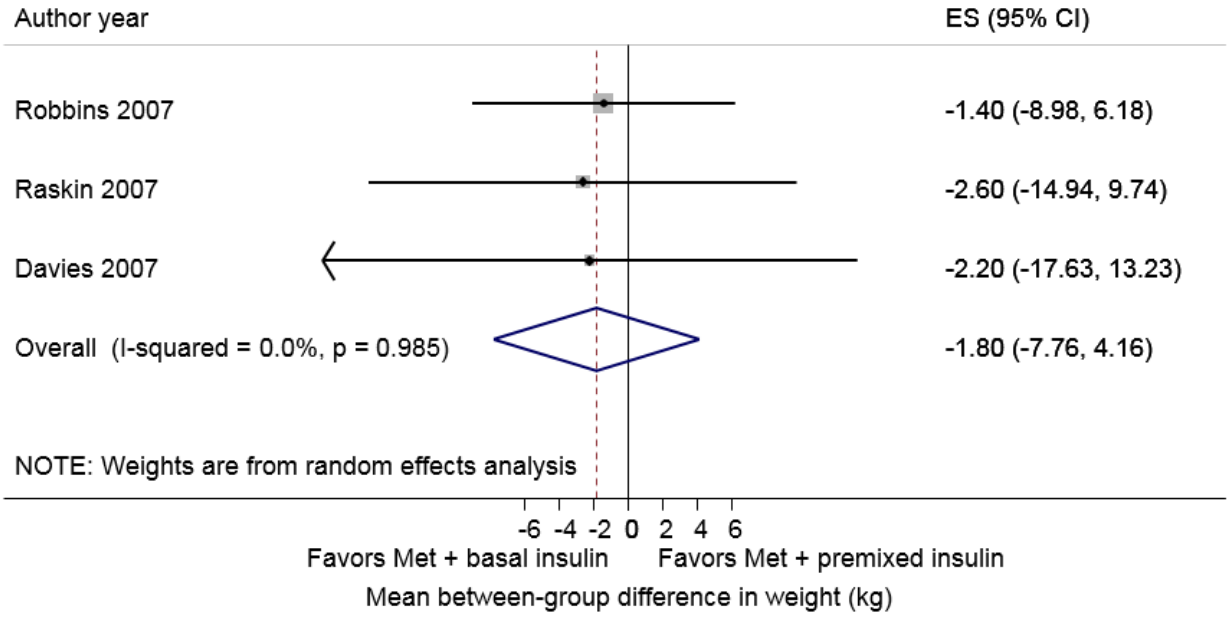
Combination of Metformin Plus a GLP1-1 Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One moderately-sized RCT lasting 104 weeks compared the combination of metformin plus exenatide (titrated to 20 micrograms) with the combination of metformin plus premixed insulin (titrated to glucose target, mean dose 28 units).[196] The RCT significantly favored metformin plus exenatide (mean between-group difference in weight, -5.1 kg; 95% CI, -5.7 kg to -4.5 kg). The metformin plus GLP-1 agonist arm decreased weight while the metformin plus premixed insulin arm increased weight. (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

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

Three RCTs directly compared the combination of metformin plus basal insulin with the combination of metformin plus premixed insulin, showing no between-group differences in weight (pooled mean between-group difference, -1.8 kg; 95% CI, -7.8 kg to 4.2 kg) (Figure 33).[197-199] No single study strongly influenced the results, and no substantial heterogeneity was found. (SOE: Low; Neither treatment favored)

Figure 33. Pooled mean between-group difference in weight comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; Met = metformin

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Strength of Evidence for Weight

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 9 and Table 10 and summarized in the key points. All studies were RCTs. Study limitations for most comparisons were low or medium with only one comparison having high study limitations due to lack of blinding and lack of description of withdrawals and dropouts. Where quality influences results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias in any of the comparisons for weight. We also did not find any evidence of publication bias or reporting bias in the grey literature review. Ten studies did not report a measure of dispersion; however, addition of these studies would not have importantly changed our conclusions or the strength of evidence assessment. We considered weight a direct outcome since patients care about weight independent of its cardiovascular effects. Several of the comparisons were downgraded due to imprecision. The comparisons were considered imprecise mainly due to the small and not clinically relevant between-group differences in weight of 2 pounds or less.

Table 9. Strength of evidence domains for monotherapy comparisons in terms of weight among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD*	NA	NA	NA	NA	NA	NA	High	Metformin favored
Metformin vs. SU*	NA	NA	NA	NA	NA	NA	High	Metformin favored
Metformin vs. DPP-4 inhibitors	6 (6700)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; small effect
Metformin vs. SGLT-2 inhibitors	3 (1903)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	SGLT-2 inhibitors favored; small effect
Metformin vs. GLP-1 agonists	3 (1089)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + TZD	10 (5102)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; small effect
Metformin vs. metformin + SU	11 (3692)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; small effect
Metformin vs. metformin + DPP-4 inhibitors	27 (21,406)	Medium	Consistent	Direct	Precise	Undetected	High	Neither treatment favored
Metformin vs. metformin + SGLT-2 inhibitors	9 (5778)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; small effect
Metformin vs. metformin + GLP-1 agonists	5 (2556)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 agonists favored; small effect
TZD vs. SU	9 (6766)	Medium	Inconsistent	Direct	Precise	Undetected	Moderate	SU favored; small effect
TZD vs. DPP-4 inhibitors	2 (1475)	Low	Consistent	Direct	Precise	Undetected	Moderate	DPP-4 inhibitors favored; small effect
TZD vs. GLP-1 agonists	1 (820)	Low	Unknown	Direct	Precise	Undetected	Moderate	GLP-1 agonists favored; small to moderate effect
SU vs. DPP-4 inhibitors	3 (1271)	Low	Consistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored; small effect
SU vs. GLP-1 agonists	4 (1157)	Medium	Consistent	Direct	Precise	Undetected	Moderate	GLP-1 agonists favored; small effect
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Direct	Precise	Undetected	Moderate	SGLT-2 inhibitors favored; small effect
DPP-4 inhibitors vs. GLP-1 agonists	1 (820)	Low	Unknown	Direct	Imprecise	Undetected	Low	GLP-1 agonists favored; small effect

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We did not re-evaluate weight for the comparisons of metformin with thiazolidinediones and metformin with sulfonylureas because we previously rated these comparisons as having high strength of evidence.[16] We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 10. Strength of evidence domains for metformin-based combination comparisons in terms of weight among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin +SU	9 (2928)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SU favored; small effect
Metformin + TZD vs. metformin +DPP-4 inhibitors	5 (2413)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + DPP-4 inhibitors favored; small effect
Metformin + TZD vs. metformin +GLP-1 agonists	2 (604)	Low	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 agonists favored; small to moderate effect
Metformin + SU vs. metformin +DPP-4 inhibitors	7 (6039)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + DPP-4 inhibitors favored, small effect
Metformin + SU vs. metformin +SGLT-2 inhibitors	3 (3815)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored, moderate effect
Metformin + SU vs. metformin +GLP-1 agonists	4 (3304)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + GLP-1 agonists favored, small to moderate effect
Metformin + SU vs. metformin + basal insulin	1 (75)	Medium	Unknown	Direct	Precise	Undetected	Low**	Metformin + SU favored; small effect
Metformin + SU vs. metformin + premixed insulin	2 (819)	Medium	Consistent	Direct	Imprecise	Undetected	Low**	Metformin + SU favored; small effect
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	4 (2889)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitors favored, small to moderate effect
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	4 (3322)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 agonists favored; small effect
Metformin + DPP-4 inhibitors vs. metformin + basal insulin	1 (515)	Medium	Unknown	Direct	Precise	Undetected	Low	Metformin + DPP-4 inhibitors favored, small effect
Metformin + GLP-1 agonists vs. metformin + basal insulin	2 (459)	Medium	Consistent	Direct	Precise	Undetected	Low	Metformin + GLP-1 agonists favored; moderate effect
Metformin + GLP-1 agonists vs. metformin + premixed insulin	1 (363)	High	Unknown	Direct	Precise	Undetected	Low	Metformin + GLP-1 agonists favored, moderate effect
Metformin + basal insulin vs. metformin + premixed	3 (530)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored

insulin								

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

** While each of these comparisons are rated low strength of evidence due to low numbers of studies, this would move to moderate if all three studies were combined in a row of metformin plus sulfonylurea vs metformin plus premixed or basal insulin since all 3 studies were consistent, direct, precise, study limitations were medium, and reporting bias was undetected. Since premixed and basal insulins may have similar effects on weight, it may be reasonable to combine these categories.

The Evidence About Systolic Blood Pressure

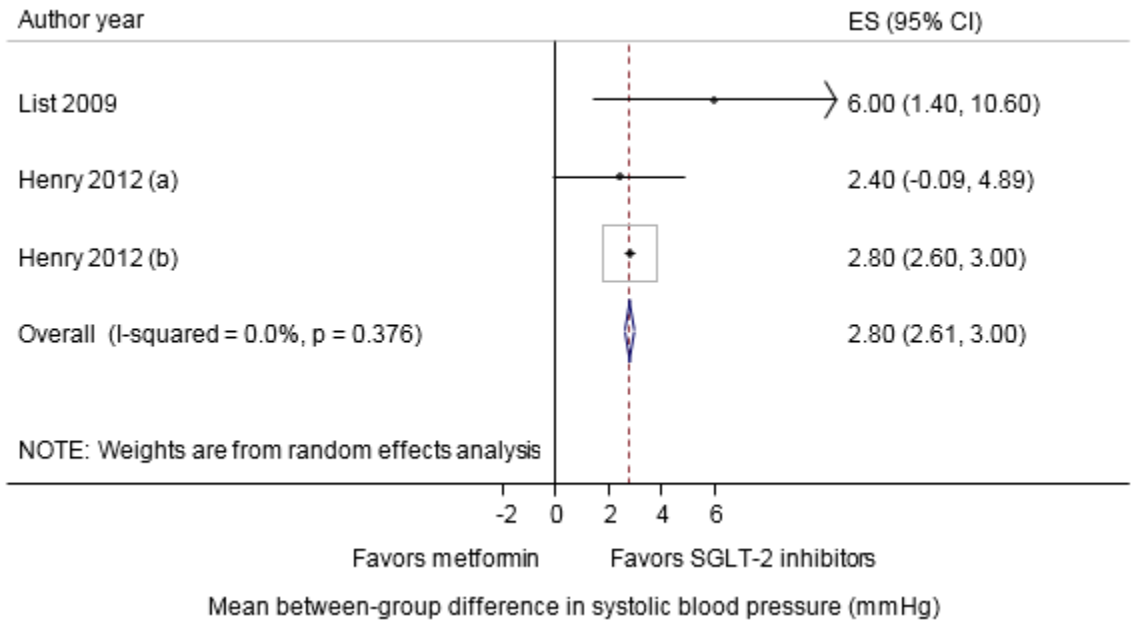
Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

We combined three short RCTs (reported in two articles) directly comparing metformin with a SGLT-2 inhibitor, favoring SGLT-2 inhibitors in systolic blood pressure reduction.[80, 81] Each study compared metformin with dapagliflozin,[80, 81] resulting in a pooled mean between-group difference in systolic blood pressure of 2.8 mmHg (95% CI, 2.6 mmHg to 3.0 mmHg) favoring SGLT-2 inhibitors over metformin (Figure 34). The metformin arms decreased mean systolic blood pressure by 0.4 mmHg to 1.8 mmHg while the SGLT-2 inhibitors arms decreased mean systolic blood pressure by 4.0 mmHg to 6.4 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

We excluded one study from the meta-analysis given its length.[82] This trial was a randomized, open-label, 78-week extension of two shorter trials of empagliflozin. There was a non-significant between-group difference in systolic blood pressure of 3.7 mmHg (95% CI, -1.3 mmHg to 8.7 mmHg).[82] The metformin arm increased the mean systolic blood pressure by 2 mmHg while empagliflozin 10 mg increased mean systolic blood pressure by 0.1 mmHg and empagliflozin 25 mg decreased mean systolic blood pressure by 1.7 mmHg. (SOE: Moderate; SGLT-2 inhibitors favored)

Figure 34. Pooled mean between-group difference in systolic blood pressure comparing metformin with SGLT-2 inhibitors



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus GLP-1 Agonists

Two RCTs compared metformin with a GLP-1 agonist with inconclusive results.[66, 83] The first study was a 52-week RCT which compared two doses of dulaglutide with metformin; there was 20% loss to follow up in all arms. The RCT reported a non-significant between-group difference in systolic blood pressure of 1.7 mmHg (95% CI, -0.7 mmHg to 4.1 mmHg) with dulaglutide 0.75 mg weekly and 0.9 mmHg (95% CI, -1.5 mmHg to 3.3 mmHg) with dulaglutide 1.5 mg weekly. The metformin arm increased mean systolic blood pressure by 1.0 mmHg while the dulaglutide arms increased mean systolic blood pressure by 0.1 mmHg to 2.7 mmHg.[83] The second study was a 26-week RCT which showed a systolic blood pressure reduction of 1.3 mmHg with exenatide, but did not provide systolic blood pressure results for the metformin arm.[66] (SOE: Low; Neither drug favored)

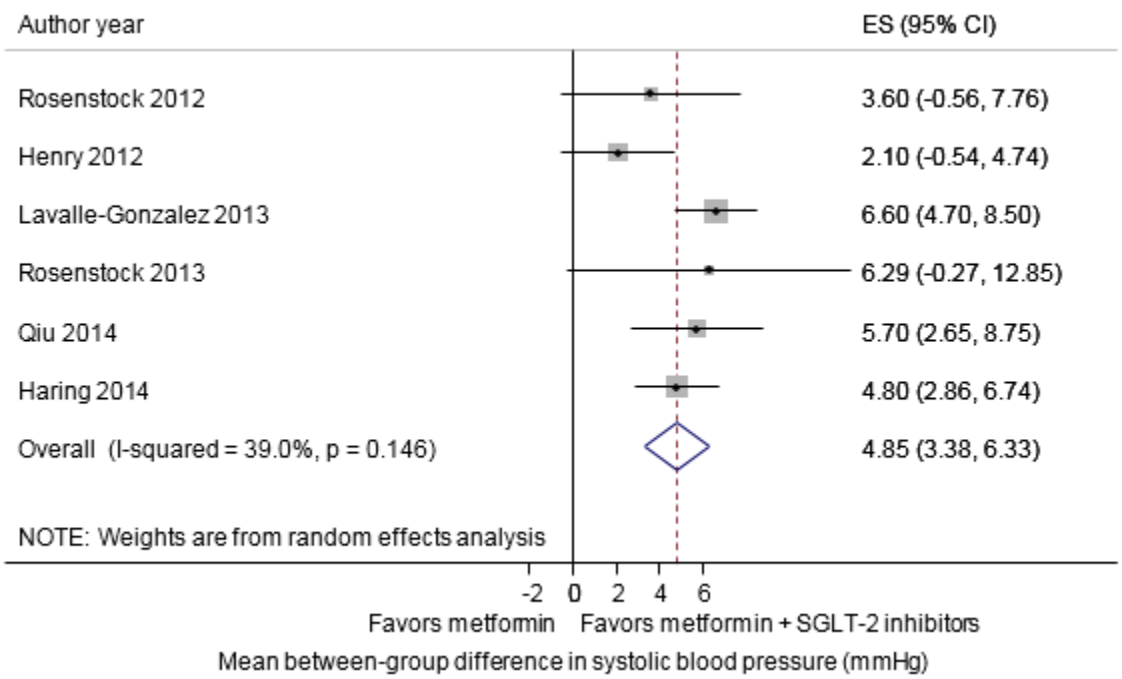
Metformin Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Six RCTs (reported in five articles) lasting less than a year compared metformin to a combination of metformin and a SGLT-2 inhibitor. All studies favored the combination arm (pooled mean between-group difference in systolic blood pressure, 4.9 mmHg; 95% CI, 3.4 mmHg to 6.3 mmHg) (Figure 35).[122, 125, 127, 132, 133] The metformin arms did not have consistent effects on the change in mean systolic blood pressure, which ranged from -2.2 mmHg to 3.3 mmHg. However, the SGLT-2 inhibitor combination arms consistently decreased mean systolic blood pressure by 2.4 mmHg to 8.5 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

Two 102-week studies compared metformin with a combination of metformin and a SGLT-2 inhibitor, and favored neither arm.[134, 135] One was a 102-week RCT which compared metformin (at least 1500 mg daily) with a metformin plus two different doses of dapagliflozin. This RCT showed a non-significant between-group difference in systolic blood pressure of 2.6 mmHg (95% CI, -1.6 mmHg to 6.8 mmHg) for the combination with 5mg of dapagliflozin and 1.8 mmHg (95% CI, -2.6 mmHg to 6.2 mmHg) for the combination with 10mg of dapagliflozin.[135] The metformin arm increased mean systolic blood pressure by 1.5 mmHg while the dapagliflozin arms decreased mean systolic blood pressure by 0.3 mmHg to 1.1 mmHg. There was a high loss to followup in this study (47% in the metformin arm and 30% to 40% in the combination arms). The other study was a 102-week RCT with over 20% loss to follow up in both arms. This RCT compared metformin at the dosage prior to enrollment with metformin plus dapagliflozin 10 mg daily, and showed a non-significant between-group difference in systolic blood pressure of 2.4 mmHg (95% CI, -1.5 mmHg to 6.3 mmHg).[134] The metformin arm increased mean systolic blood pressure by 1.1 mmHg while the metformin plus SGLT-2 inhibitor arm decreased mean systolic blood pressure by 1.3 mmHg.

One 24-week RCT was excluded from the meta-analysis due to differences in medication dosing for the SGLT-2 inhibitor arm. In this study, metformin was compared with metformin plus 5mg of dapagliflozin showing a between-group difference in systolic blood pressure of 1.1 mmHg (95% CI, -1.4 mmHg to 3.6 mmHg) with both arms decreasing mean systolic blood pressure.[80] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 35. Pooled mean between-group difference in systolic blood pressure comparing metformin with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2

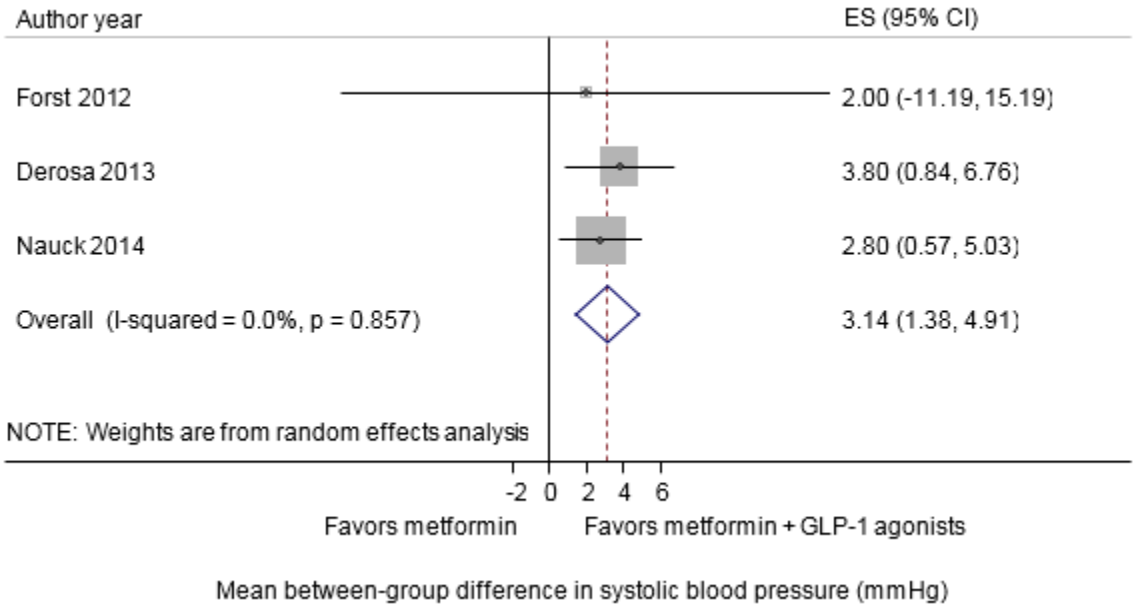
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Three short RCTs lasting less than a year compared metformin with a combination of metformin plus a GLP-1 agonist. The pooled analysis showed a between-group difference in systolic blood pressure of 3.1 mmHg (95% CI, 1.4 mmHg to 4.9 mmHg), favoring the combination arm over the monotherapy arm (Figure 36).[128, 136, 137] These studies used different combinations of metformin plus a GLP-1 agonist (liraglutide, dulaglutide, and exenatide). The metformin arms did not show consistent effects with the mean change in systolic blood pressure ranging from -3.0 mmHg to 1.1 mmHg; the GLP-1 agonist arms consistently decreased mean systolic blood pressure by 1.7 mmHg to 6.8 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

We excluded the 104-week RCT from the meta-analysis due to its long duration.[110] Consistent with the meta-analysis results, this study reported a significant between-group difference in systolic blood pressure of 3.2 mmHg (95% CI, 0.03 mmHg to 6.4 mmHg) favoring the combination arm.[110] The metformin arm increased mean systolic blood pressure by 2.2 mmHg while the metformin plus liraglutide arm decreased mean systolic blood pressure by 1 mmHg. There were high losses to follow up, 30% to 40%, among both arms in this study. (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored)

Figure 36. Pooled mean between-group difference in systolic blood pressure comparing metformin with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; GLP-1 = glucagon-like peptide-1; ES = effect size (mean between-group difference in the change from baseline); mmHg = millimeters mercury
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus GLP-1 Agonists

One RCT compared pioglitazone to exenatide over 26 weeks, reporting a non-significant between-group difference in systolic blood pressure of 0.4 mmHg (95% CI, -2.1 mmHg to 2.9 mmHg).[66] (SOE: Low; Neither drug favored)

Sulfonylureas Versus GLP-1 Agonists

One 104-week RCT compared glimepiride with liraglutide, and showed a non-significant between-group difference in systolic blood pressure of 0.9 mmHg (95% CI, -1.5 mmHg to 3.2 mmHg) with 1.2 mg of liraglutide and 1.9 mmHg (95% CI, -0.5 mmHg to 4.2 mmHg) with 1.8 mg of liraglutide.[158] Participants in all arms had a mean decrease in systolic blood pressure. There was high loss to follow up, 50% to 60%, among all arms. (SOE: Low; Neither drug favored)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One double-blind, 24-week RCT compared sitagliptin 100 mg daily to empagliflozin 10 mg and 25 mg daily. This RCT reported significant between-group differences in systolic blood pressure of 3.4 mmHg (95% CI, 1.2 mmHg to 5.7 mmHg) with 10mg of empagliflozin and 4.2 mmHg (95% CI, 2.0 mmHg to 6.5 mmHg) with 25mg of empagliflozin, favoring the SGLT-2 inhibitor over the DPP-4 inhibitor.[159] The DPP-4 inhibitor increased mean systolic blood pressure by 0.5 mmHg while the empagliflozin decreased mean systolic blood pressure by 2.9 to 3.7 mmHg. (SOE: Low; SGLT-2 inhibitors favored)

DPP-4 Inhibitors Versus GLP-1 Agonists

One 26-week RCT compared sitagliptin 100 mg daily with exenatide 2 mg weekly, reporting a non-significant between-group difference in systolic blood pressure of 0.5 mmHg (95% CI -2.0 mmHg to 3.0 mmHg).[66] The DPP-4 inhibitor decreased mean systolic blood pressure by 1.8 mmHg while the GLP-1 agonist decreased mean systolic blood pressure by 1.3 mmHg. (SOE: Low; Neither drug favored)

Metformin-Based Combination Comparisons

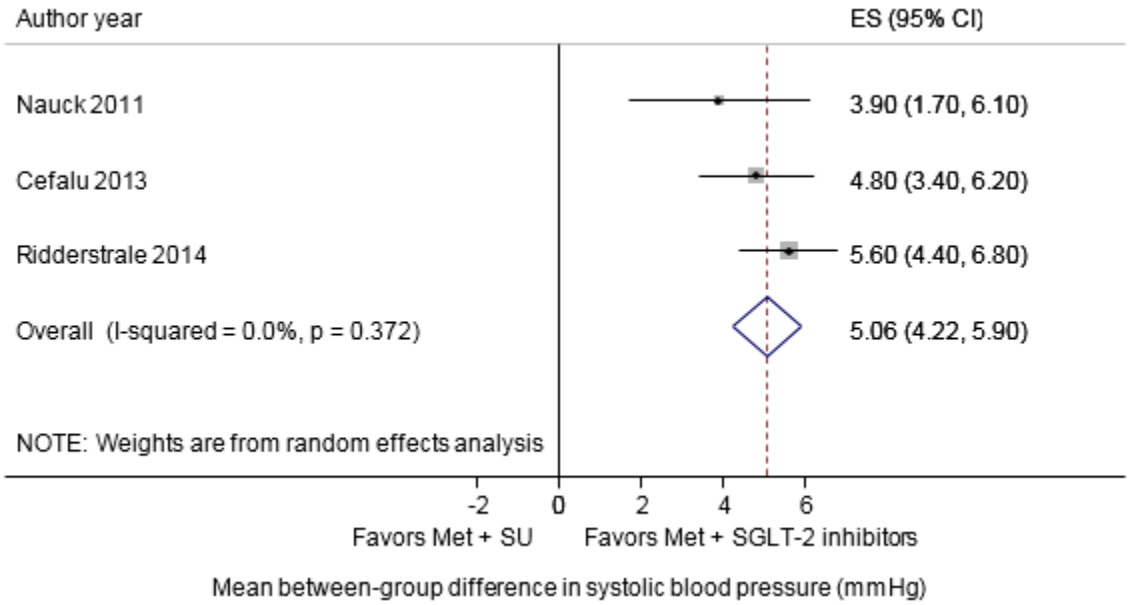
Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

One 26-week RCT compared metformin plus pioglitazone with metformin plus weekly exenatide, reporting a non-significant between-group difference in systolic blood pressure of 2.0 mmHg (95% CI, -0.8 mmHg to 4.8 mmHg).[173] The metformin plus pioglitazone combination decreased mean systolic blood pressure by 1.6 mmHg while the metformin plus exenatide combination decreased mean systolic blood pressure by 3.6 mmHg. (SOE: Low; Neither combination favored)

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

Three RCTs over a year in duration compared metformin plus a sulfonylurea with metformin plus a SGLT-2 inhibitor (canagliflozin, empagliflozin, and dapagliflozin).[181-183] The pooled between-group difference in systolic blood pressure was 5.1 mmHg (95% CI, 4.2 mmHg to 5.9 mmHg) (Figure 37), favoring combinations with a SGLT-2 inhibitor for lowering blood pressure. Metformin with a sulfonylurea increased mean systolic blood pressure by 0.2 mmHg to 2.5 mmHg, while metformin with a SGLT-2 inhibitor decreased mean systolic blood pressure by 2.7 mmHg to 4.6 mmHg. No substantial heterogeneity was found, and no single study markedly influenced the results. (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 37. Pooled mean between-group difference in systolic blood pressure comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Four RCTs comparing metformin plus a sulfonylurea with metformin plus a GLP-1 agonist reported systolic blood pressure, favoring the combination of metformin plus a GLP-1 agonist for lowering blood pressure.[110, 184, 185, 187] These were not combined in a meta-analysis due to differences in the duration, and absence of sufficient data.[185] One 16-week RCT compared metformin plus glimepiride with metformin plus exenatide and showed a non-significant between-group difference in systolic blood pressure of 2.0 mmHg (95% CI, -12.5 mmHg to 16.5 mmHg) with both combinations decreasing mean systolic blood pressure.[184]

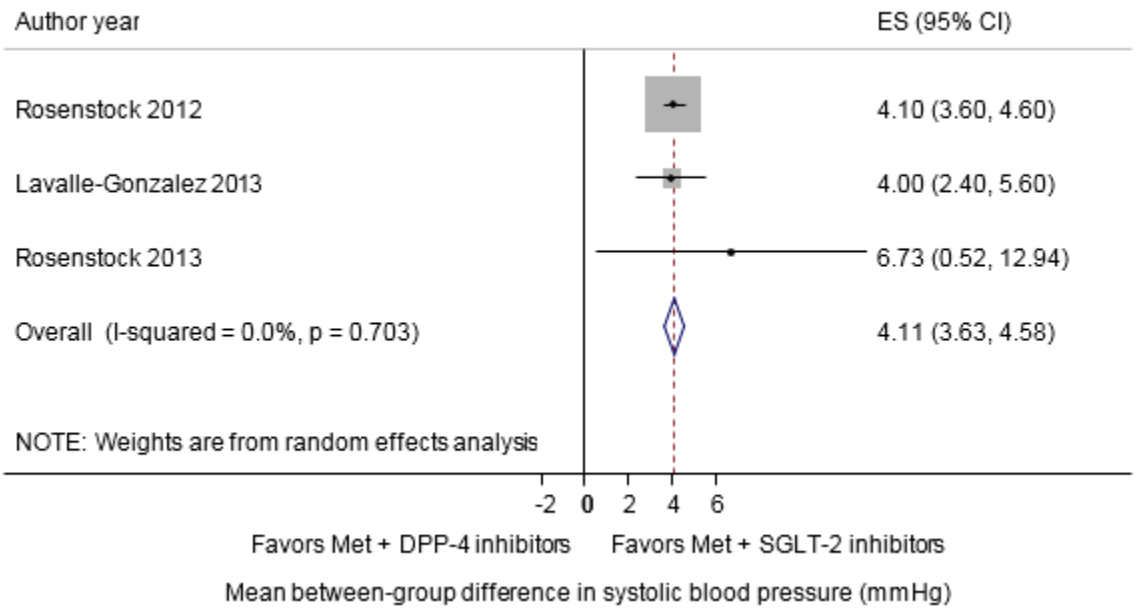
One 16-week RCT compared metformin plus glimepiride with metformin plus liraglutide showing a significantly greater reduction in systolic blood pressure, by more than 3 mmHg, with the liraglutide combination arms compared with 0.91 mmHg in the glimepiride combination arm ($P < 0.05$).[187] There was a differential loss to followup with 46% to 59% in the higher liraglutide dose arms compared with 16% in the metformin plus sulfonylurea arm. One 104-week RCT compared metformin plus glimepiride with metformin plus albiglutide showing a significant between-group difference in systolic blood pressure favoring the GLP-1 agonist combination by 2.5 mmHg (95% CI, 0.3 mmHg to 4.7 mmHg).[110] The metformin plus glimepiride increased mean systolic blood pressure by 1.5 mmHg while the metformin plus albiglutide arm decreased mean systolic blood pressure by 1.0 mmHg. (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

We pooled three short duration RCTs comparing metformin plus a DPP-4 inhibitor versus metformin plus a SGLT-2 inhibitor.[122, 125, 127] The pooled results showed a between-group difference in systolic blood pressure of 4.1 mmHg (95% CI, 3.6 mmHg to 4.6 mmHg) (Figure 38), favoring metformin plus SGLT-2 inhibitors. The DPP-4 inhibitor combinations decreased mean systolic blood pressure by 0.7 mmHg to 1.8 mmHg, while the SGLT-2 inhibitor combinations decreased mean systolic blood pressure by 4.7 mmHg to 8.5 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

We excluded one 104-week RCT from the meta-analysis due to its long duration.[82] The trial compared metformin plus sitagliptin with metformin plus empagliflozin. The trial showed a between-group difference in systolic blood pressure of 5.1 mmHg (95% CI, 1.0 mmHg to 9.2 mmHg) with metformin plus 10 mg of empagliflozin and 4.8 mmHg (95% CI, 0.7 mmHg to 8.9 mmHg) with metformin plus 25 mg of empagliflozin, favoring the combination arm with a SGLT-2 inhibitor.[82] These results were consistent with the results from the meta-analysis. The metformin plus sitagliptin arm increased mean systolic blood pressure by 1.8 mmHg while the metformin plus empagliflozin arms decreased mean systolic blood pressure by 3 mmHg to 3.3 mmHg. (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 38. Pooled mean between-group difference in systolic blood pressure comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Four RCTs comparing metformin plus a DPP-4 inhibitor with metformin plus a GLP-1 agonist showed no clear differences between-groups.[110, 128, 173, 192] We did not combine these RCTs in a meta-analysis because of differences in drug type and study duration.

One 26-week RCT compared metformin plus sitagliptin with metformin plus exenatide and showed a between-group difference in systolic blood pressure of 4.0 mmHg (95% CI, 1.5 mmHg to 6.5 mmHg) favoring the combination arm with GLP-1 agonists. The metformin plus DPP-4 inhibitor arm increased mean systolic blood pressure by 0.2 mmHg while the metformin plus GLP-1 agonist arm decreased mean systolic blood pressure by 3.6 mmHg.[173] A 26-week RCT compared metformin plus sitagliptin with metformin plus liraglutide showing a non-significant between-group difference in systolic blood pressure of 0.4 mmHg (95% CI, -2.0 mmHg to 2.7 mmHg) with metformin plus1.2 mg of liraglutide and 0.2 mmHg (95% CI, -2.1 mmHg to 2.6 mmHg) with metformin plus1.8 mg of liraglutide.[192] All arms decreased mean systolic blood pressure.

Among the newest studies, one 52-week RCT compared metformin plus sitagliptin with metformin plus dulaglutide and showed a non-significant between-group difference in systolic blood pressure of 0 mmHg (95% CI, -1.9 mmHg to 1.9 mmHg) with 0.75 mg of dulaglutide weekly and 0.3 mmHg (95% CI, -1.6 mmHg to 2.2 mmHg) with 1.5 mg of dulaglutide weekly.[128] All arms decreased mean systolic blood pressure. One 104-week RCT compared metformin plus sitagliptin with metformin plus albiglutide and showed a non-significant between-group difference in systolic blood pressure of 1.2 mmHg (95% CI, -1.1 mmHg to 3.5 mmHg).[110] The metformin plus DPP-4 inhibitor arm increased mean systolic blood pressure by 0.2 mmHg while the metformin plus GLP-1 agonist arm decreased mean systolic blood pressure by 1.0 mmHg. (SOE: Low; Neither combination favored)

Strength of Evidence for Systolic Blood Pressure

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 11 and Table 12 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We were unable to assess publication bias given the limited number of studies for each comparison for systolic blood pressure. We also did not find any evidence of publication bias or reporting bias in the grey literature review. We considered this outcome direct since systolic blood pressure is strongly linked with important long-term clinical outcomes.[203-205]

Table 11. Strength of evidence domains for monotherapy comparisons in terms of systolic blood pressure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SGLT-2 inhibitors	4 (1651)	Medium	Consistent	Direct	Precise	Undetected	Moderate	SGLT-2 inhibitors favored; Small effect
Metformin vs. GLP-1 agonists	2 (820)	Low	Inconsistent	Direct	Precise	Undetected	Low	Neither drug favored
Metformin vs. metformin + SGLT-2 inhibitors	9 (4478)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; Moderate effect
Metformin vs. metformin + GLP-1 agonists	4 (2362)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + GLP-1 agonists favored; Moderate effect
TZD vs. GLP-1 agonists	1 (820)	Low	Unknown	Direct	Precise	Undetected	Low	Neither drug favored
SU vs. GLP-1 agonists	1 (746)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither drug favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Direct	Imprecise	Undetected	Low	SGLT-2 inhibitors favored; Moderate effect
DPP-4 inhibitors vs. GLP-1 agonists	1 (820)	Low	Unknown	Direct	Precise	Undetected	Low	Neither drug favored

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 12. Strength of evidence domains for metformin-based combination comparisons in terms of systolic blood pressure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin + GLP-1 agonists	1 (514)	Low	Unknown	Direct	Precise	Undetected	Low	Neither combination favored
Metformin + SU vs. metformin + SGLT-2 inhibitors	3 (3815)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; Moderate effect
Metformin + SU vs. metformin + GLP-1 agonists	4 (3049)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 agonists favored; Small effect
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	4 (2853)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitors favored; Moderate effect
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	4 (3322)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither combination favored

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Heart Rate

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Two RCTs compared metformin with SGLT-2 inhibitors and showed no differences in heart rate between the arms.[81, 82] One 12-week RCT compared metformin with dapagliflozin showing a non-significant between-group difference in heart rate of 2.1 beats per minute (bpm) (95% CI, -1.3 bpm to 5.5 bpm) with 5 mg of dapagliflozin and 1.1 bpm (95% CI, -2.4 bpm to 4.7 bpm) with 10 mg of dapagliflozin. The metformin arm increased mean heart rate by 1.1 bpm, while the SGLT-2 inhibitor arms decreased mean heart rate by 0.03 bpm to 1 bpm.[81] The other 90-week RCT compared metformin and empagliflozin and reported that "reductions in blood pressure were not associated with increases in heart rate."[82] (SOE: Low; Neither drug favored)

Metformin Versus GLP-1 Agonists

Two RCTs compared metformin with a GLP-1 agonist and showed no clear differences in heart rate between the arms.[66, 83] One RCT, with 20% loss to follow up, compared metformin with two doses of dulaglutide over 52 weeks. There was a non-significant between-group difference in heart rate of 0.5 bpm (95% CI, -1.1 bpm to 2.1 bpm) with 0.75 mg of dulaglutide weekly and 0.7 bpm (95% CI, -0.9 bpm to 2.3 bpm) with 1.5 mg of dulaglutide weekly. All arms had an increase in mean heart rate.[83] One 26-week RCT compared metformin with exenatide and showed a non-significant between-group difference in heart rate of 1.2 bpm (95% CI, -0.5 bpm to 2.9 bpm). The metformin arm had a mean heart rate increase of 0.3 bpm while the GLP-1 agonist arm had an increase of 1.5 bpm.[66] (SOE: Moderate; Neither drug favored)

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

Three RCTs comparing metformin to a combination of metformin plus a SGLT-2 inhibitor had inconsistent results.[125, 132, 134] We did not combine the studies in a meta-analysis due to differences in study duration.

One 12-week RCT compared metformin to metformin plus canagliflozin. Compared to metformin, the between-group difference in heart rate was 1.9 bpm lower (95% CI, 1.5 bpm to 2.3 bpm) with metformin plus 100 mg of canagliflozin, 1.1 bpm (95% CI, 0.7 bpm to 1.5 bpm) lower with metformin plus 200 mg of canagliflozin, and 3.4 bpm (95% CI, 3.0 bpm to 3.8 bpm) lower with metformin plus 300 mg of canagliflozin.[125] In this study, the mean heart rate increased by 1.7 bpm in the metformin arm and decreased by 1.7 bpm in the metformin plus 300 mg of canagliflozin arm.

One 18-week RCT compared metformin with metformin plus canagliflozin and reported a between-group difference in heart rate of 0.9 bpm with 100 mg of canagliflozin daily and 1.4 bpm with 300mg of canagliflozin daily. Metformin caused no increase in mean heart rate while metformin plus canagliflozin increased mean heart rate.[132]

A 102-week RCT, with over 20% loss to follow up, compared metformin to metformin plus 10 mg of dapagliflozin, and showed a non-significant between-group difference in heart rate of 0.1 bpm (95% CI, -2.8 bpm to 3.0 bpm). Both arms increased mean heart rate slightly.[134] (SOE: Low; Neither drug favored)

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Two RCTs compared metformin to a combination of metformin plus a GLP-1 agonist with conflicting results.[110, 128] The 104-week RCT compared metformin to metformin plus albiglutide and showed a non-significant between-group difference in heart rate of 1.0 bpm (95% CI, -1.2 bpm to 3.2 bpm) favoring metformin.[110] A 26-week RCT compared metformin to metformin plus dulaglutide and showed a between-group difference in heart rate of 2.8 bpm (95% CI, 1.1 bpm to 4.5 bpm) favoring metformin. There was high loss to followup of at least 60% in all arms in this study.[128] (SOE: Insufficient; Unable to determine effect)

Thiazolidinediones Versus GLP-1 Agonists

One double-blind, 26-week RCT compared pioglitazone titrated to 45 mg daily with exenatide 2 mg weekly and showed a between-group difference in heart rate of 3.2 bpm (95% CI, 1.3 bpm to 5.0 bpm).[66] In this study, the pioglitazone arm decreased mean heart rate by 1.7 bpm while the GLP-1 agonist arm increased mean heart rate by 1.5 bpm. (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus GLP-1 Agonists

One 104-week RCT compared glimepiride with liraglutide, 1.2 mg and 1.8 mg, and showed a non-significant between-group difference in heart rate of 1.4 bpm (95% CI, -0.2 bpm to 2.9 bpm) for the lower dose and 0.2 bpm (95% CI, -1.3 bpm to 1.8 bpm) for the higher dose, favoring glimepiride.[158] The sulfonylurea arm increased the mean heart rate by 0.6 bpm while the liraglutide arms increased mean heart rate between 0.9 bpm to 2.0 bpm. There was high loss to followup of 50% to 60% among all arms in this study. (SOE: Low; Neither drug favored)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One 24-week RCT compared 100 mg of sitagliptin to empagliflozin, 10 mg and 25 mg, and showed a non-significant between-group difference in heart rate of 0.2 bpm (95% CI, -1.5 bpm to 1.9 bpm) with 10 mg of empagliflozin and 0.5 bpm (95% CI, -2.2 bpm to 1.2 bpm) with 25 mg of empagliflozin, favoring empagliflozin.[159] The DPP-4 inhibitor arm increased mean heart rate by 0.2 bpm, while lower dose empagliflozin increased mean heart rate by 0.02 bpm and the higher dose decreased mean heart rate by 0.25 bpm. (SOE: Low; Neither drug favored)

DPP-4 Inhibitors Versus GLP-1 Agonists

One 26-week RCT compared sitagliptin with exenatide and showed a non-significant between-group difference in heart rate of 1.0 bpm (95% CI, -0.9 bpm to 2.9 bpm). Both arms increased mean heart rate.[66] (SOE: Low; Neither drug favored)

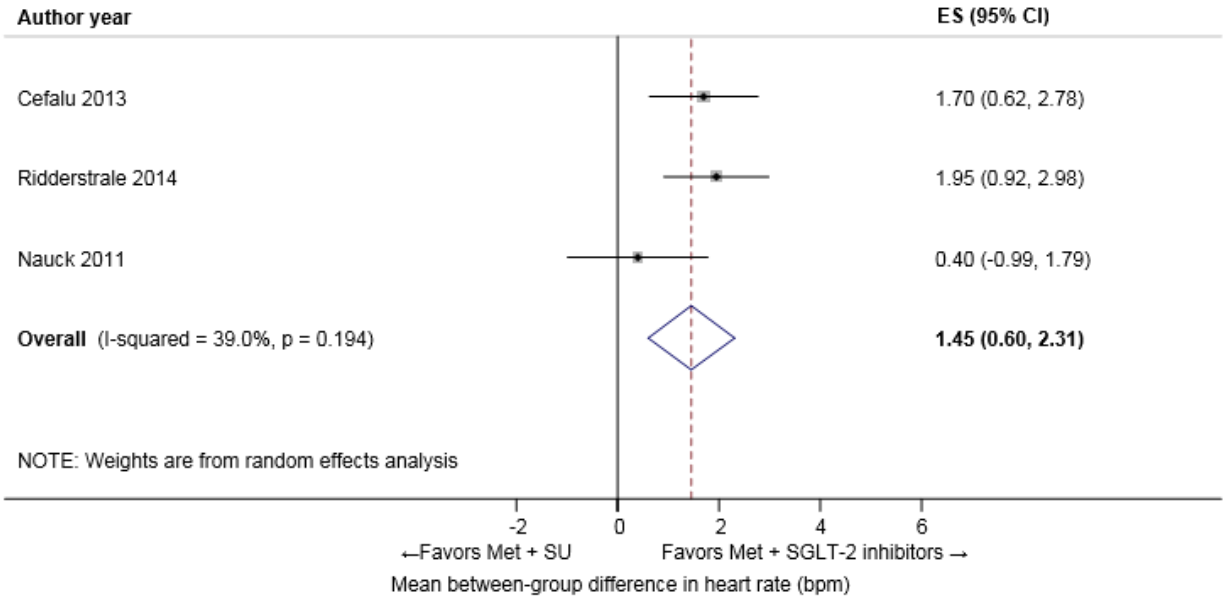
Metformin-Based Combination Comparisons

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

We pooled three RCTs over a year in duration that compared metformin plus a sulfonylurea with metformin plus a SGLT-2 inhibitor.[181-183] The pooled between-group difference in heart rate was 1.5 bpm (95% CI, 0.6 bpm to 2.3 bpm) (Figure 39). The metformin plus sulfonylurea arms increased mean heart rate between 0.3 bpm to 0.6 bpm, while the metformin plus SGLT-2 inhibitor arms decreased mean heart rate between 0.1 bpm to 1.4 bpm. No substantial

heterogeneity was identified, and no single study markedly influenced the results. (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 39. Pooled mean between-group difference in heart rate comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



bpm = beats per minute; CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Two RCTs compared metformin plus a sulfonylurea with metformin plus a GLP-1 agonist with conflicting results.[110, 185] One RCT, with 75% losses to followup, reported that mean heart rate increased by 1.2 bpm ($P = 0.024$) with metformin plus exenatide, but not with metformin plus glimepiride (0.6 bpm; $P = 0.28$) with no differences between groups at any time.[185] One 104-week RCT, with 30% loss to followup, compared metformin plus glimepiride with metformin plus albiglutide, and showed a between-group difference of 1.8 bpm (95% CI, 0.2 bpm to 3.4 bpm) favoring the metformin with glimepiride treatment.[110] The sulfonylurea combination decreased mean heart rate by 0.5 bpm, while the GLP-1 agonist combination increased mean heart rate by 1.3 bpm. (SOE: Insufficient; Unable to determine effect)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Two RCTs compared metformin plus a DPP-4 inhibitor to metformin plus a SGLT-2 inhibitor and showed no clear differences between groups in heart rate.[82, 125] One 12-week RCT compared metformin plus sitagliptin with three dose strengths of metformin plus canagliflozin. The RCT showed a non-significant between-group difference in heart rate of 1.5 bpm (95% CI, 1.2 bpm to 1.8 bpm) with 100 mg of canagliflozin, 2.3 bpm (95% CI, 2.0 bpm to 2.6 bpm) with

200 mg of canagliflozin, and 0.0 bpm (95% CI, -0.4 bpm to 0.4 bpm) with 300 mg of canagliflozin.[125] The DPP-4 inhibitor with metformin decreased mean heart rate by 1.7 bpm while 100 mg of canagliflozin with metformin decreased mean heart rate by 0.2 bpm, 200 mg increased mean heart rate by 0.6 bpm, and 300 mg decreased mean heart rate by 1.7 bpm. One 90-week RCT compared metformin plus sitagliptin to metformin plus empagliflozin and found no increase in heart rate accompanying blood pressure reduction.[82] (SOE: Low; Neither combination favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Three RCTs compared metformin plus a DPP-4 inhibitor with metformin plus a GLP-1 agonist.[110, 128, 192] These studies were not combined in a meta-analysis due to differences in study duration.

The two short studies significantly favored the combination of metformin plus a DPP-4 inhibitor. One 26-week RCT compared metformin plus sitagliptin with metformin plus liraglutide and showed a between-group difference in heart rate of 3.0 bpm (95% CI, 1.4 bpm to 4.5 bpm) with 1.2 mg of liraglutide and 4.6 bpm (95% CI, 3.0 bpm to 6.1 bpm) with 1.8 mg of liraglutide. The DPP-4 inhibitor combination decreased mean heart rate by 0.64 bpm while the GLP-1 combinations increased mean heart rate by 2.3 bpm and 3.9 bpm.[192] A 52-week RCT, with over 60% loss to followup, compared metformin plus sitagliptin to metformin plus dulaglutide, showing a between-group difference in heart rate of 2.4 bpm (95% CI, 1.0 bpm to 3.8 bpm) with 0.75 mg of dulaglutide weekly and 2.7 bpm (95% CI, 1.3 bpm to 4.1 bpm) with 1.5 mg of dulaglutide weekly. The DPP-4 inhibitor combination decreased mean heart rate by 0.3 bpm, while the GLP-1 combinations increased mean heart rate by 2.1 and 2.4 bpm.[128]

The 104-week RCT, with over 30% loss to follow up, compared metformin plus sitagliptin to metformin plus albiglutide and showed a non-significant between-group difference in heart rate of 0.5 bpm (95% CI, -1.2 bpm to 2.2 bpm). Both arms increased mean heart rate slightly.[110] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Strength of Evidence for Heart Rate

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 13 and Table 14 and summarized in the key points. All studies were RCTs. Study limitations for all comparisons were low or medium. Where quality influenced the study results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We were unable to assess publication bias given the limited number of studies for each comparison for heart rate. We also did not find any evidence of publication bias or reporting bias in the grey literature review. We considered this outcome indirect since there is limited evidence directly linking heart rate to mortality or other clinical outcomes, including among adults with diabetes.

Table 13. Strength of evidence domains for monotherapy comparisons in terms of heart rate among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SGLT-2 inhibitors	2 (1048)	Medium	Consistent	Indirect	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. GLP-1 agonists	2 (820)	Low	Consistent	Indirect	Precise	Undetected	Moderate	Neither drug favored
Metformin vs. metformin + SGLT-2 inhibitors	3 (912)	Low	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. metformin + GLP-1 agonists	2 (2147)	Low	Inconsistent	Indirect	Imprecise	Undetected	Insufficient	Unable to determine
TZD vs. GLP-1 agonists	1 (820)	Low	Unknown	Indirect	Precise	Undetected	Low	TZD favored; Small effect
SU vs. GLP-1 agonists	1 (746)	Medium	Unknown	Indirect	Precise	Undetected	Low	Neither drug favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Indirect	Precise	Undetected	Low	Neither drug favored
DPP-4 inhibitors vs. GLP-1 agonists	1 (820)	Low	Unknown	Indirect	Precise	Undetected	Low	Neither drug favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 14. Strength of evidence domains for metformin-based combination comparisons in terms of heart rate among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + SU vs. metformin +SGLT-2 inhibitors	3 (3815)	Low	Consistent	Indirect	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitor favored; Small effect
Metformin + SU vs. metformin +GLP-1 agonists	2 (2078)	Medium	Inconsistent	Indirect	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	2 (1110)	Medium	Consistent	Indirect	Imprecise	Undetected	Low	Neither combination favored
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	3 (2808)	Medium	Inconsistent	Indirect	Precise	Undetected	Low	Metformin + DPP-4 inhibitor favored; Small effect

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Key Question 2a and 2b: Long-Term Clinical Outcomes

Study Design and Population Characteristics

One hundred and thirty-two studies, in 134 publications, reported on the comparative effectiveness of oral diabetes medications on long-term outcomes of interest (Appendix D, Tables 5 to 9). Thirty studies occurred in North America, 33 in Europe, 14 in Asia, and all others were multi-continent studies.

Ninety-seven studies were RCTs, with durations from 12 weeks to 8.5 years. Thirty-four of the RCTs lasted for at least one year. All studies specified intermediate, not long-term, outcomes as their primary outcome (see Key Question 1), but then also reported the incidence of one or more long-term outcomes (e.g., mortality), usually as an adverse event. Two studies used a cross-over design.[206, 207] Ninety RCTs reported support from a pharmaceutical company. Twenty-five of the 74 (33.8%) RCTs identified in this update did not report on rescue therapy; rescue therapy was allowed in 26 studies (35.2%) and was not allowed in 23 studies (31%).

We also included 31 retrospective cohort studies and 1 case-control study; duration of followup ranged from six months to eight years. These studies analyzed data from 12 unique cohorts, including five studies from Danish national databases;[208-212] one from the Saskatchewan Health Database.[213] Thirteen of the observational studies were designed to explicitly evaluate cardiovascular outcomes.[120, 208-212, 214-220] Six observational studies reported support from a pharmaceutical company.

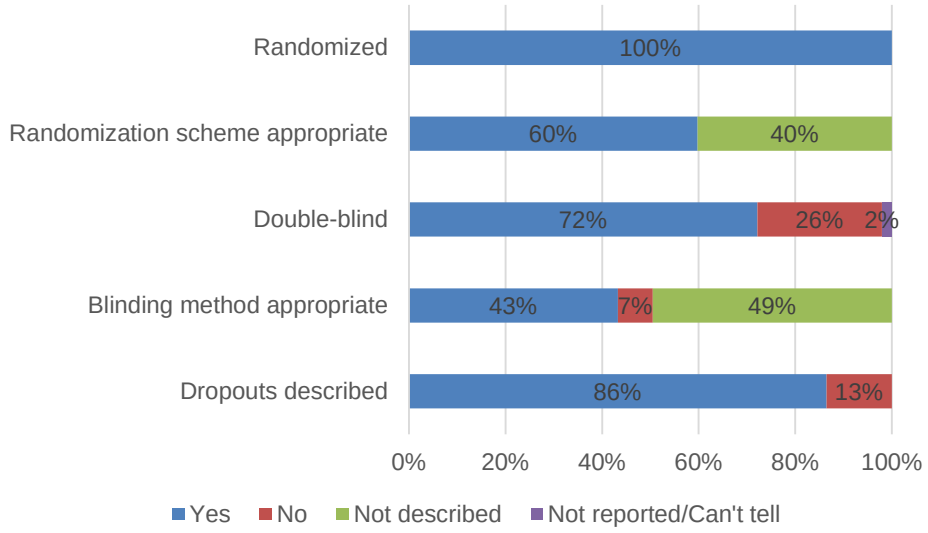
The mean age of participants ranged from 48 years to 75 years, with the majority of studies reporting a mean age in the upper 50s. Participants were about 50% female. Fifty-two studies did not report race or ethnicity. In the studies that reported race, the majority of the participants were Caucasians. Two RCTs reported greater than 25 percent African American participants,[87, 221] and two studies reported 70 to 80 percent Hispanic participants.[90, 171] Most trials excluded people with coexisting illness, such as renal, cardiovascular, or liver disease.

Risk of Bias

Ninety-seven RCTs were included in this section, all of which were described as randomized (Figure 40). Sixty percent described their randomization scheme and another 72 percent were described as being double-blinded. Forty-three percent of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of trials (86 percent) described the withdrawals and dropouts.

Of the 17 observational studies included in this section, 100 percent reported characteristics of subjects and tests of interest, 94 percent reported actual probability values, and 82 percent described the measurement of outcomes of interest. All studies described and adjusted for confounding factors and conducted statistical analyses. All of the observational studies described the number of participants who were lost to follow-up after the start of the period of observation.

Figure 40. Summary of the risk of bias of randomized controlled trials evaluating long-term clinical outcomes



Key Points and Evidence Grades

All-Cause Mortality

- Studies reporting on all-cause mortality generally had few deaths and followup durations of 12 months or less and therefore, had limited power for this outcome.
- Short-term (12 months or less) all-cause mortality rates were similar for metformin and pioglitazone monotherapy (pooled OR for metformin versus pioglitazone, 0.91; 95% CI, 0.22 to 3.72). (SOE: Moderate)
- All-cause mortality rates were similar for the combination of metformin plus a DPP-4 inhibitor and metformin monotherapy (pooled OR for studies 52 or less weeks in duration, pooled OR, 0.89; 95% CI, 0.28 to 2.86). (SOE: High)
- All-cause mortality rates were similar for the combination of metformin plus an SGLT-2 inhibitor and metformin monotherapy for both short- and long-term studies (pooled OR for studies 52 weeks or greater in duration, 1.15; 95% CI, 0.18 to 7.35 and pooled OR for studies less than 52 weeks in duration, 0.99; 95% CI, 0.10 to 9.61). (SOE: Moderate)

Cardiovascular Mortality

- Studies reporting on cardiovascular mortality generally had few cardiovascular deaths and follow up durations less than 12 months and therefore, had limited power for this outcome.
- Sulfonylurea monotherapy was associated with increased cardiovascular mortality compared with metformin monotherapy (relative risk range 1.6 to 2.0 from individual RCTs). (SOE: High)
- Even though there is much concern about the cardiovascular effects of diabetes medications as evidenced by the FDA labeling stating a lack of known lower macrovascular risk for any diabetes medication, all other evidence on the comparative

effectiveness of the included diabetes medications on cardiovascular mortality was of low strength or insufficient.

Cardiovascular and Cerebrovascular Disease Morbidity

- Studies reporting on cardiovascular and cerebrovascular morbidity generally had few events and follow up durations less than 12 months and therefore, had limited power for this outcome.
- Metformin monotherapy was favored over sulfonylurea monotherapy for cardiovascular morbidity (range of risk differences with metformin as the reference reported across three RCTs, -10.1% to +0.4%; range of adjusted HRs reported across five observational studies, 1.06 to 3.22). (SOE: Moderate)
- Cardiovascular morbidity was similar for metformin and pioglitazone monotherapy (no events in two of three RCTs; range of adjusted HRs with metformin as the reference reported in observational studies, 1.0 to 1.15). (SOE: Moderate).
- Even though there is much concern about the cardiovascular effects of diabetes medications as evidenced by the FDA labeling stating a lack of known lower macrovascular risk for any diabetes medication, all other evidence on the comparative effectiveness of the included diabetes medications on cardiovascular morbidity was of low strength or insufficient.

Retinopathy, Nephropathy, and Neuropathy

- The evidence was low or insufficient for all comparisons.

The Evidence About All-Cause Mortality

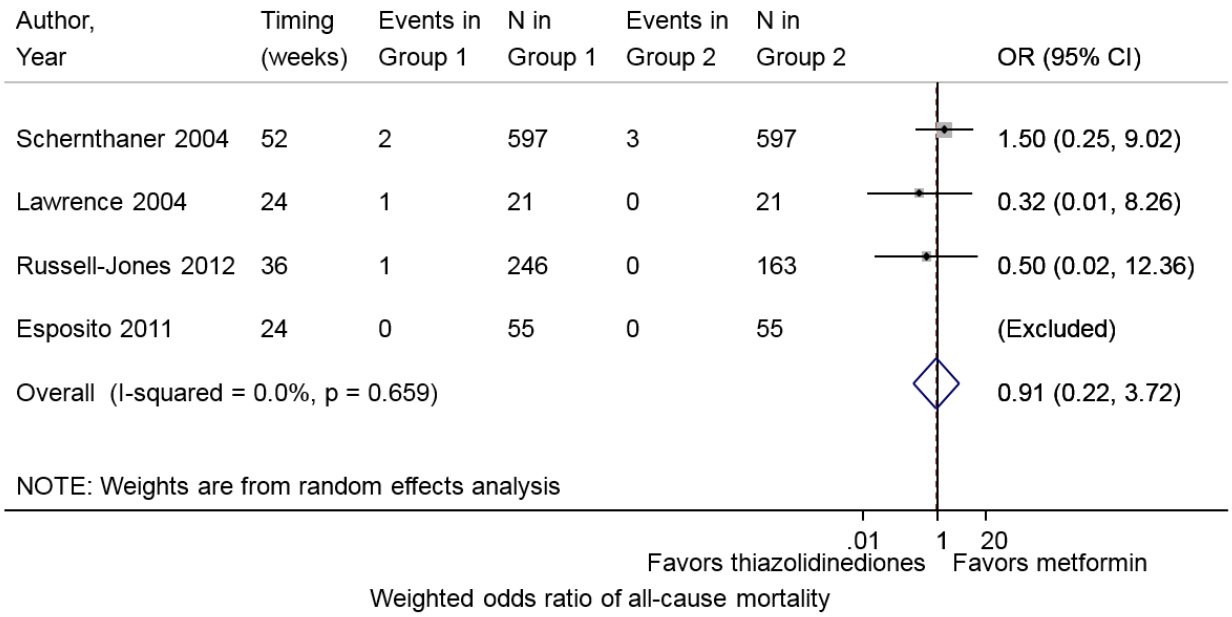
Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Randomized Controlled Trials

Four RCTs lasting 24 to 52 weeks compared the effects of metformin with pioglitazone and found similar risks of all-cause mortality in the metformin and pioglitazone arms with a total of seven deaths across the studies (pooled OR for metformin versus pioglitazone, 0.91; 95% CI, 0.22 to 3.72) (Figure 41).[55, 56, 66, 69] We found no evidence of statistical heterogeneity. Omission of any single study did not change the conclusions. Deaths were not described in the pioglitazone arm of one study, so we imputed “0” events in this arm for the meta-analysis.[69]

Figure 41. Pooled odds ratio of all-cause mortality comparing metformin with pioglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = thiazolidinediones; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Two RCTs compared the effects of metformin with rosiglitazone on all-cause mortality.[45, 52] The A Diabetes Outcome Progression Trial (ADOPT) trial randomized participants from 488 different centers in the United States, Canada, and Europe to rosiglitazone, metformin, or glyburide.[45] Death rates were similar in the metformin (31/1454; 2.1%) and rosiglitazone (34/1456; 2.3%) arms (median followup 4.0 years).[45] The second trial was 32 weeks in duration and reported no deaths in the metformin or rosiglitazone arm.[52]

Observational Studies

Two retrospective cohort studies compared the effects of initiating thiazolidinediones and metformin (Table 15).[222, 223] One study found no difference in all-cause mortality for metformin and thiazolidinediones.[222] The second study found a significantly increased risk of all-cause mortality among women but not men for rosiglitazone versus metformin.[223] (SOE: Moderate for pioglitazone; Neither treatment favored for pioglitazone) (SOE: Low; Neither treatment favored for rosiglitazone)

Table 15. Observational studies comparing metformin with thiazolidinediones on all-cause mortality

Author, year	Population	Mean followup	Results
Pantalone, 2009[222]	Cleveland Clinic electronic health record system N not reported	Not reported	HR for rosiglitazone, 1.33, 95% CI, 0.93 to 1.91 HR for pioglitazone, 1.08, 95% CI, 0.78 to 1.51 Reference = metformin
Wheeler, 2013[223]	Veterans Health Administration 2004-2009 n=132,306 (metformin) n=3753 (rosiglitazone)	1.7 years (metformin) 1.4 years (rosiglitazone)	HR for 185,360 men, 1.19; 95% CI, 0.95 to 1.49 HR for 7,812 women, 4.36; 95% CI, 1.34 to 14.20 Reference = metformin *P* interaction for gender = 0.034

CI = confidence interval; HR = hazard ratio

Metformin Versus Sulfonylureas

Randomized Controlled Trials

Six RCTs compared the effects of metformin and a sulfonylurea on all-cause mortality (Table 16).[45, 66, 98, 99, 106, 107] Two of these RCTs were long trials (followup, 2.8 years to 4.1 years). One reported more than double the risk of death for the glipizide versus metformin arm[66] whereas the other RCT found no difference in the risk of death between glyburide and metformin.[45] The other four RCTs lasted less than 30 weeks.[98, 99, 106, 107] Three of these reported no deaths in either arm;[98, 99, 107] the fourth reported one death in the metformin arm and none in the sulfonylurea arm.[106]

Table 16. Randomized controlled trials comparing metformin with sulfonylureas on all-cause mortality

Author, year	Mean followup	Number of deaths (%): metformin versus sulfonylurea	Estimate of the measure of association (95% CI) (metformin as reference group)
Russell-Jones, 2012[66]	2.8 years	7/156 (4.5) versus 14/148 (9.5)	RR, 2.1* (0.9 to 5.1)
Kahn, 2006[45]	4.1 years (median)	31/1454 (2.1) versus 31/1441 (2.2)	RR, 1.0* (0.6 to 1.7)
Chien, 2007[107]	4 weeks	0/17 (0.0) versus 0/17 (0.0)	NR
Garber, 2003[98]	16 weeks	0/164 (0.0) versus 0/151 (0.0)	NR
Goldstein, 2003[99]	18 weeks	0/76 (0.0) versus 0/84 (0.0)	NR
DeFronzo, 1995[106]	29 weeks	1/210 (0.5) versus 0/209 (0.0)	NR

CI = confidence interval; NR= not reported; RR = relative risk
* Calculated for this report from values published in study

Observational Studies

We identified seven retrospective cohort studies based on four cohorts (Veteran's Health Administration, n=2;[223, 224] Cleveland Clinic electronic health record, n=2;[222, 225] Danish National Patient Health Registry, n=2;[208, 212] and the Health Service Database of Lombardy, n=1[226]) comparing the effects of metformin with a sulfonylurea on all-cause mortality. All studies reported an increased risk of death for a sulfonylurea versus metformin (Table 17). (SOE: Low; Metformin favored)

Table 17. Observational studies comparing metformin with sulfonylureas on all-cause mortality

Author, year	Population	Followup	Number of deaths (%): metformin versus sulfonylurea	Adjusted Results
Kahler, 2007[224]	Veterans' Health Administration Diabetes Epidemiology Cohort	3 years	82 / 2988 (2.7%) versus 1005 / 19,053 (5.3%)	OR, 0.87; 95% CI, 0.68 to 1.10 Reference = sulfonylurea
Wheeler, 2013[223]	Veterans' Health Administration	222,258 p-years (metformin) 47,604 p-years (glipizide) 48,238 p-years (glibenclamide)	2107 / 13,2306 versus 1121 / 28,957 (glipizide) and 912 / 28,156 (glibenclamide)	HR for glipizide, 1.55; 95% CI, 1.43 to 1.67 HR for glibenclamide, 1.38; 95% CI, 1.27 to 1.5 Reference = sulfonylurea
Pantalone, 2009[222]	Cleveland Clinic EHR	8 years	NR	HR, 0.54; 95% CI, 0.46 to 0.64 Reference = sulfonylurea
Pantalone, 2012[225]*	Cleveland Clinic EHR	2.2 years (median)	NR / 12,774 (metformin) NR / 4,325 (glipizide) NR / 4,279 (glyburide) NR / 2,537 (glibenclamide)	HR for glipizide, 1.64; 95% CI, 1.39 to 1.94 HR for glyburide, 1.59; 95% CI, 1.35 to 1.88 HR for glibenclamide, 1.68; 95% CI, 1.37 to 2.06 Reference = metformin
Schramm, 2011[212]	National Patient Registry (Denmark) Previous MI	3.3 years (median)	213 / 2906 versus 141 / 660 (glipizide) 737 / 3894 (glimepiride) 265 / 1168 (glibenclamide)	HR for glipizide, 1.53; 95% CI, 1.23 to 1.89 HR for glimepiride, 1.3; 95% CI, 1.11 to 1.51 HR for glibenclamide, 1.47; 95% CI, 1.22 to 1.76 Reference = metformin
	National Patient Registry (Denmark) No previous MI	91.5 weeks	1548 / 43340 versus 947 / 6965 (glipizide) 4081 / 36,313 (glimepiride) 1546 / 12,495 (glibenclamide)	HR for glipizide, 1.27; 95% CI,1.17 to 1.38 HR for glimepiride, 1.32; 95% CI, 1.24 to 1.4 HR for glibenclamide, 1.19; 95% CI, 1.11 to 1.28 Reference = metformin
Andersson, 2010[208]	National Patient Registry (Denmark) – patients with admission for heart failure (1997-2006)	844 days	239 / 688 (35%) versus 2344 / 3615 (65%)	HR, 0.85; 95% CI, 0.75 to 0.98; *P* = 0.02) Reference = sulfonylurea
Corrao, 2011[226]	Health Services Database of Lombardy	Mean followup 4.8 to 5.1 years	NR / 21,810 versus NR / 48,627	HR, 1.37; 95% CI, 1.26 to 1.49 Reference = metformin

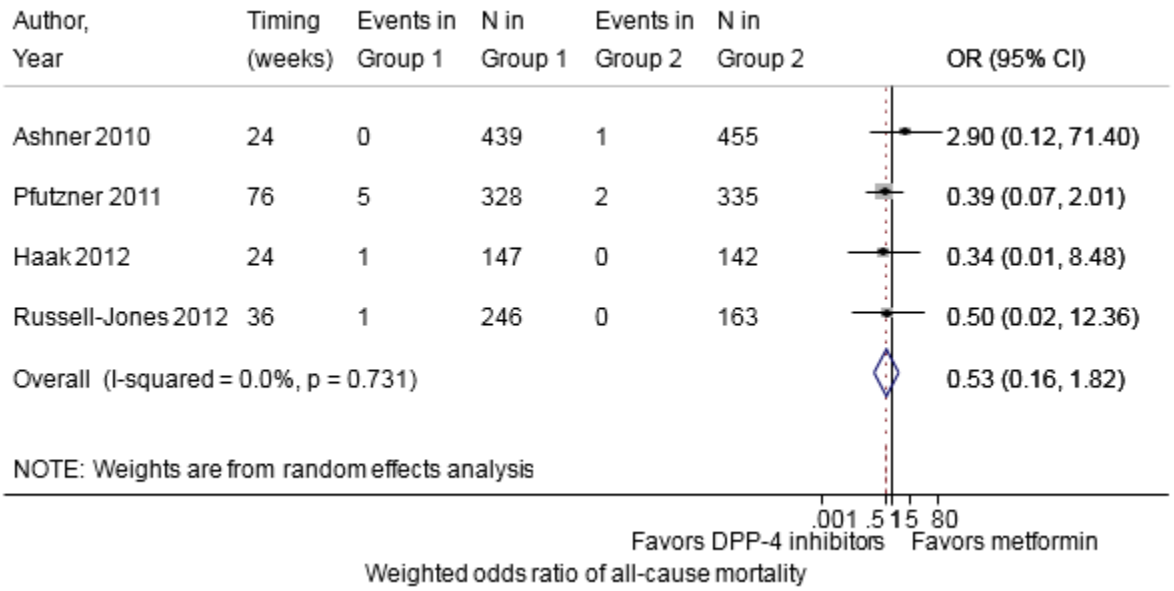
CI = confidence interval; EHR = electronic health record; HR = hazard ratio; MI = myocardial infarction; NR = not reported; OR = odds ratio
* This study population may overlap with Pantalone, 2009.[222]

Metformin Versus DPP-4 Inhibitors

Five RCTs compared the effects of metformin with sitagliptin on all-cause mortality. Meta-analysis of the four RCTs with the most similar durations (24 to 76 weeks) showed no difference in all-cause mortality for metformin compared with DPP-4 inhibitors based on a total of 10 deaths across the studies (pooled OR, 0.53; 95% CI, 0.16 to 1.82) (Figure 42).[66, 74, 78, 79] We did not find evidence of statistical heterogeneity. One of these RCTs did not report on deaths in the DPP-4 inhibitor arm, and we imputed "0" for this arm.[66] The fifth RCT compared three metformin arms with sitagliptin 100 mg over 104 weeks. Two deaths were reported in the arm which started on placebo and was switched to metformin at 24 weeks; one death was reported in the metformin arm using 1000 mg as its maximum dose; and no deaths were reported in the metformin arm using 2000 mg as its maximum dose.[77] No deaths occurred in the sitagliptin arm.[77]

A single retrospective cohort study from the Danish National Patient Registry reported on mortality for metformin (3,024/83,528) and sitagliptin (49/1,228) with mean followup of 0.9 to 1.8 years. The adjusted risk ratio (RR) for metformin versus sitagliptin was 1.25 (95% CI, 0.92 to 1.71; $P = 0.15$).[211] (SOE: Low; Neither treatment favored)

Figure 42. Pooled odds ratio of all-cause mortality comparing metformin with DPP-4 inhibitors



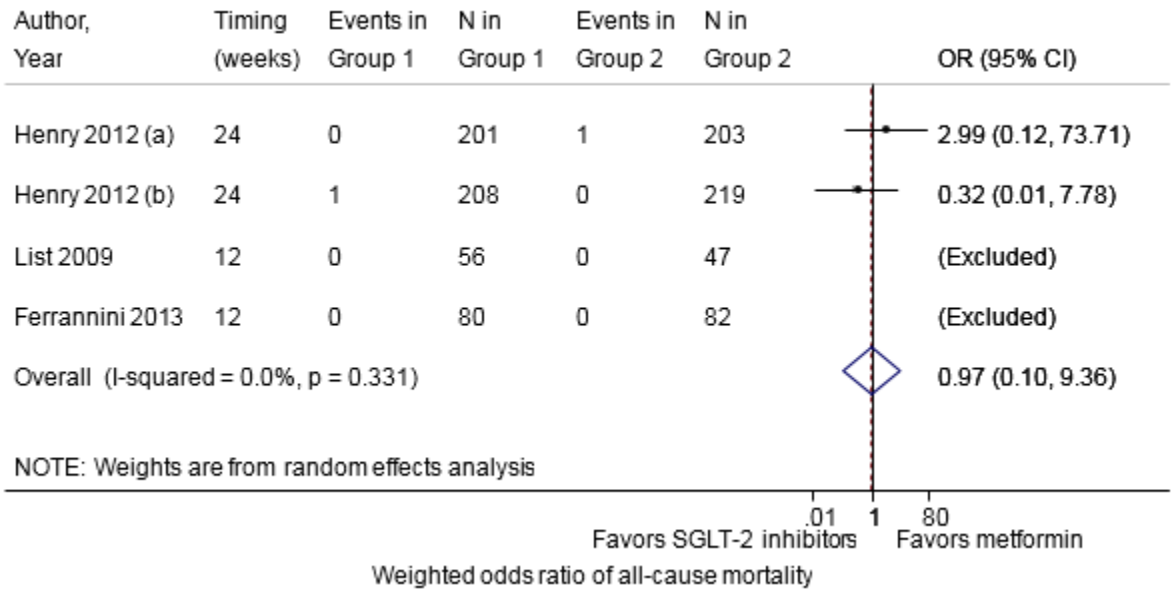
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = dipeptidyl peptidase-4 inhibitors; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus SGLT-2 Inhibitors

Four (reported in three articles) short-term RCTs (12 to 24 weeks in duration) compared the effects of metformin to SGLT-2 inhibitors on all-cause mortality and found no difference for

metformin versus SGLT-2 inhibitors (pooled OR, 0.97; 95% CI, 0.10 to 9.36) (Figure 43).[80, 81, 227] Only two deaths were reported in the studies (one death in the metformin arm of one study[80] and one death in the SGLT-2 arm of another[80]). We did not observe significant statistical heterogeneity (I^2 = 0.0%). Removal of any one study did not change the inference for this finding. (SOE: Low; Neither favored)

Figure 43. Pooled odds ratio of all-cause mortality comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

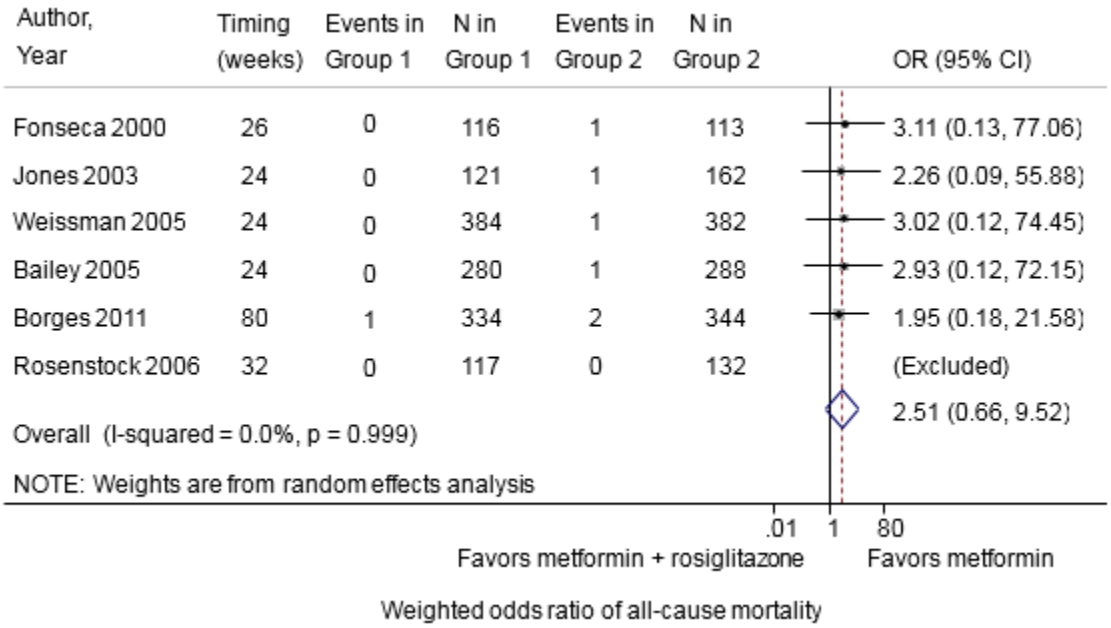
Metformin Versus GLP-1 Agonists

Two RCTs compared all-cause mortality between metformin and GLP-1 agonists.[66, 83] In one RCT lasting 52 weeks, there were no deaths in the metformin or dulaglutide arms.[83] In the other RCT, lasting 36 weeks, one death was reported in the metformin arm, and deaths were not described in the exenatide arm.[66] (SOE: Low; Neither favored)

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Six articles reported the results of seven RCTs (duration ranging from 24 to 80 weeks) on the effects of metformin versus metformin plus rosiglitazone on all-cause mortality.[52, 88, 89, 92, 96, 228] The combined OR comparing metformin plus rosiglitazone to metformin was 2.51 (95% CI, 0.66 to 9.52; I^2 = 0.0%) (Figure 44), showing a non-significant increased risk of death with metformin plus rosiglitazone (six deaths) compared with metformin monotherapy (one death). Removal of any one study did not impact the effect size or confidence interval of the combined estimate substantially. (SOE: Low; Metformin monotherapy favored over combination of metformin plus rosiglitazone)

Figure 44. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus rosiglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus rosiglitazone; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

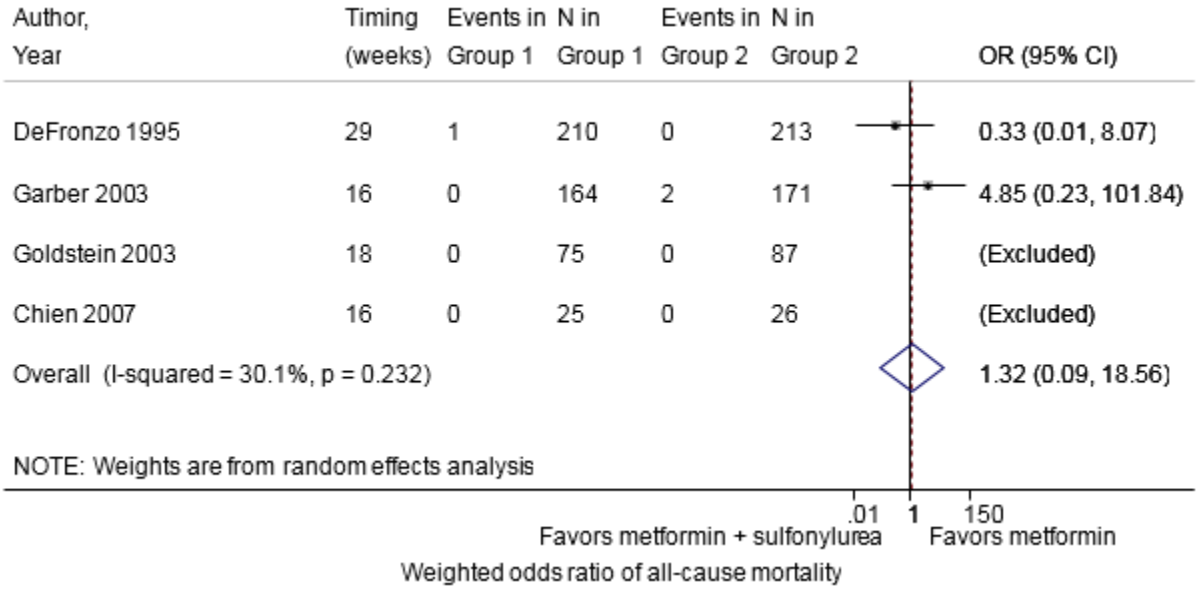
A single 24-week RCT compared the effects of metformin (n=103) to metformin plus pioglitazone (n=110) reported on all-cause mortality; no deaths occurred in either arm.[94] (SOE: Insufficient; Unable to draw a conclusion for combination of metformin plus pioglitazone)

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Randomized Controlled Trials

Four RCTs ranging from 16 to 29 weeks compared the effects of metformin with the combination of metformin plus a sulfonylurea on all-cause mortality with a total of three deaths reported.[98, 99, 106, 107] There was no significant difference for metformin plus a sulfonylurea versus metformin (pooled OR, 1.32; 95% CI, 0.09 to 18.56; I^2 = 30.1%) (Figure 45). Although removal of one study did change the direction of the combined estimate (pooled OR, 0.33),[98] removal of a single study did not change the width of the confidence interval substantially. (SOE: Low; Neither treatment favored)

Figure 45. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus a sulfonylurea

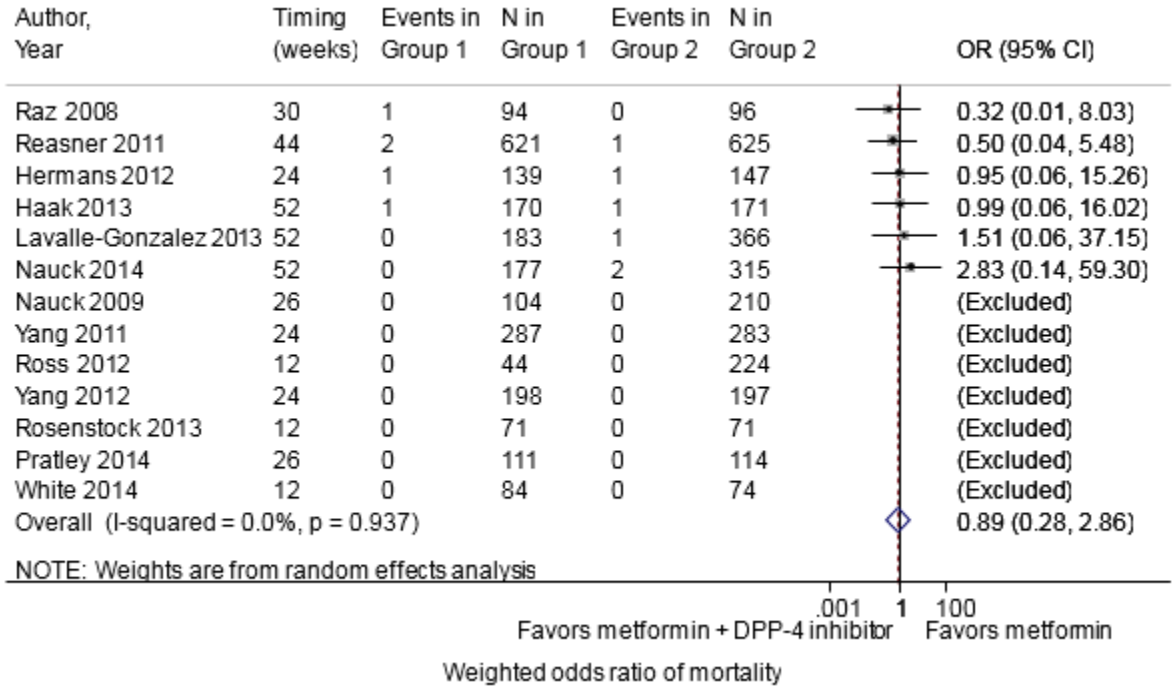


CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sulfonylurea; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Sixteen RCTs (published in 17 articles) comparing metformin plus a DPP-4 inhibitor to metformin monotherapy reported on all-cause mortality.[76-79, 111, 114, 115, 117, 118, 120-123, 127-129, 131] For studies 52 weeks or less in duration, the pooled OR indicated no difference in mortality rates for metformin plus DPP-4 inhibitor versus metformin (pooled OR, 0.89; 95% CI, 0.28 to 2.86) (Figure 46).[76, 78, 111, 114, 115, 117, 120-123, 127-129, 131] We did not find evidence of statistical heterogeneity (I^2 = 0.0%). Removal of any one study did not change the direction of effect or inference, and there was no evidence of publication bias statistically (*P* = 0.80) using Harbord's modified test. Three studies did not report on event rates in the metformin arm, and we imputed "0" events for these studies.[115, 127, 128]

Figure 46. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Four RCTs included additional arms with lower doses than the arms from these RCTs that were included in the meta-analysis. Results from these arms did not differ from those of the meta-analysis (Table 18).[76, 78, 123, 131]

We excluded one of the short-term RCTs from the meta-analysis because it underdosed the study drugs substantially; this 12-week study reported no deaths in either arm (Table 18).[118]

Two RCTs were not included in the meta-analysis because their durations were much longer than in the other trials.[77, 79] Their results were not substantially different from those reported above, and dose of medication did not appear to significantly affect results (Table 18).[77, 79] (SOE: High; Neither favored)

Table 18. Randomized controlled trials or arms of randomized controlled trials excluded from the meta-analysis comparing metformin with a combination of metformin plus a DPP-4 inhibitor on all-cause mortality

Author, year	Followup (weeks)	Metformin dose in monotherapy arm	Metformin dose in combination arm	DPP-4 inhibitor dose in combination arm	Number of deaths / N (%) in metformin arm	Number of deaths / N (%) in metformin + DPP-4 inhibitor arm
Kadowaki, 2013[118]	12	96% of participants on ≤750mg	94% of participants on ≤750mg	Sitagliptin 50 mg	0/72 (0)	0/77 (0)
Pratley, 2014[76]	26	1000 mg	1000 mg	Alogliptin 25 mg	0/109 (0)	0/106 (0)
		1000 mg	2000 mg	Alogliptin 25 mg	0/109 (0)	0/114 (0)
		2000 mg	1000 mg	Alogliptin 25 mg	0/111 (0)	0/106 (0)
		2000 mg*	2000 mg	Alogliptin 25 mg	0/111 (0)	0/114 (0)
Haak, 2013[131]	52	2000 mg	1000 mg	Linagliptin 5 mg	1/170 (0.6)	2/225 (0.9)
		2000 mg*	2000 mg	Linagliptin 5 mg	1/170 (0.6)	1/171 (0.6)
Haak, 2012[78]	24	1000 mg	1000 mg	Linagliptin 5 mg	0/144 (0)	0/143 (0)
		1000 mg	2000 mg	Linagliptin 5 mg	0/144 (0)	0/143 (0)
		2000 mg	1000 mg	Linagliptin 5 mg	1/147 (0.7)	0/143 (0)
		2000 mg	2000 mg	Linagliptin 5 mg	1/147 (0.7)	0/143 (0)
Nauck, 2009[123]	26	Mean 1868 mg	Mean 1837 mg	Alogliptin 12.5 mg	0/104 (0)	1/213 (0.5)
		Mean 1868 mg*	Mean 1846 mg	Alogliptin 25 mg	0/104 (0)	0/210 (0)
Pfutzner, 2011[79]	76	2000 mg	2000 mg	Saxagliptin 5 mg	5/328 (1.5)	1/320 (0.3)
		2000 mg	2000 mg	Saxagliptin 10 mg	5/328 (1.5)	2/323 (0.6)
Williams-Herman, 2010[77]	104	2000 mg	1000 mg	Sitagliptin 100 mg	2/176 (1.1)	1/190 (0.6)
		1000 mg	1000 mg	Sitagliptin 100 mg	1/182 (0.5)	1/190 (0.6)
		1000 mg	2000 mg	Sitagliptin 100 mg	1/182 (0.5)	1/182 (0.5)
		2000 mg	1000 mg	Sitagliptin 100 mg	0/182 (0)	1/190 (0.6)
		2000 mg	2000 mg	Sitagliptin 100 mg	0/182 (0)	1/182 (0.5)

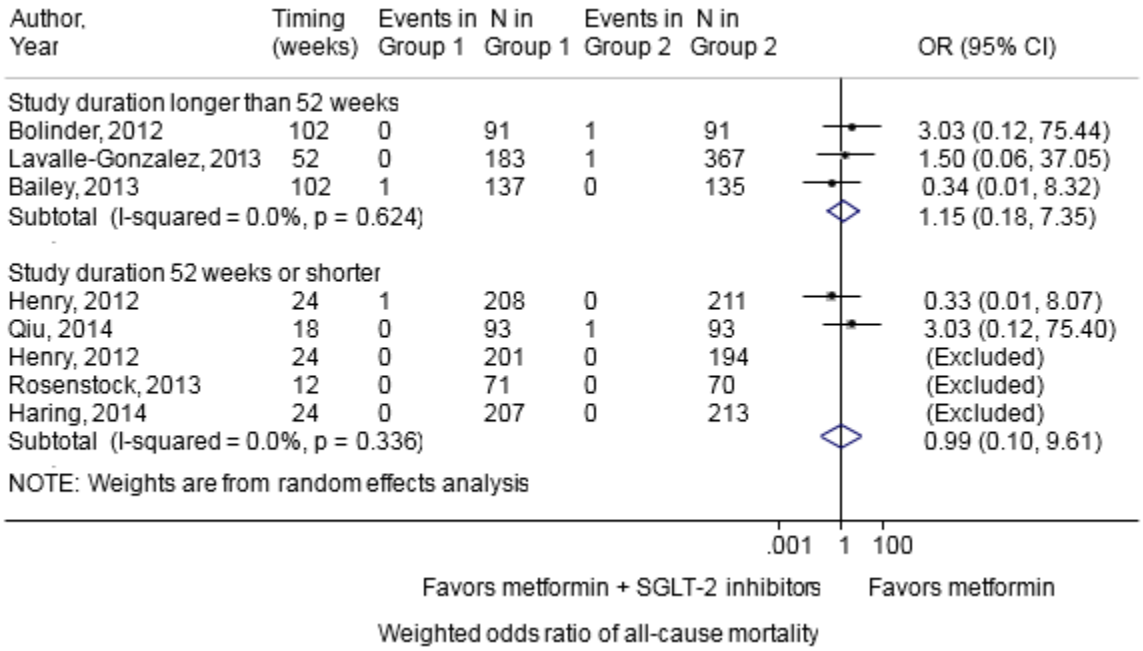
DPP-4 = dipeptidyl peptidase-4; mg = milligrams
*arm included in the meta-analysis

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

Eight RCTs (in seven articles) compared metformin monotherapy with metformin plus an SGLT-2 inhibitor and reported on mortality (five deaths).[80, 122, 127, 132-135] Five of these were short trials (duration range, 12 to 24 weeks), including two trials described by Henry, et al;[80] no difference in mortality was seen between arms. The combined OR for all-cause mortality for metformin plus SGLT-2 inhibitor versus metformin was 0.99 (95% CI, 0.10 to 9.61) (Figure 47).[80, 122, 132, 133] We did not find statistical heterogeneity (I^2 = 0.0%). Removal of any one study did not change the overall inference. Two of these RCTs did not report on events in the metformin arm, and we imputed "0" events in these arms.[132, 133]

Three of the RCTs were longer (range, 52 to 102 weeks). The OR for all-cause mortality for metformin plus SGLT-2 inhibitor versus metformin was 1.15 (95% CI, 0.18 to 7.35) (Figure 47).[127, 134, 135] We did not find evidence of statistical heterogeneity (I^2 = 0.0%).

Figure 47. Pooled odds ratio of all-cause mortality comparing metformin with a combination of metformin plus a SGLT-2 inhibitor, stratified by study duration



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Five of the eight RCTs comparing metformin with metformin plus a SGLT-2 inhibitor had multiple different dosing arms; event rates were low and did not appear to vary by dose.[122, 127, 132, 133, 135] (SOE: Moderate: Neither favored)

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

A single RCT compared metformin with the combination of metformin plus two doses of dulaglutide (two dulaglutide arms: 0.75 mg and 1.5 mg weekly) and reported on all-cause mortality at 52 weeks. No deaths were reported in the metformin monotherapy arm (0/177); one death was reported in the metformin plus 1.5 mg of dulaglutide weekly arm (1/304); and no deaths were observed in the 0.75 mg of dulaglutide weekly arm (0/302) over 52 weeks.[128] (SOE: Low; Neither treatment favored)

Thiazolidinediones Versus Sulfonylureas

Randomized Controlled Trials

Three RCTs compared thiazolidinediones with sulfonylureas and reported on mortality. The ADOPT trial reported a similar number of deaths in the rosiglitazone arm compared with the glyburide arm (2.3% versus 2.2%, respectively) over a median of 4.1 years.[45] Another trial

(N=598) reported no deaths in either the rosiglitazone (4 mg and 8 mg arms) or sulfonylurea arms at 52 weeks.[140] A 56-week trial reported two deaths in the glyburide arm (2/251; 0.8%) and no deaths in the pioglitazone arm (0/251).[141]

Observational Studies

Two retrospective cohort studies compared the effects of thiazolidinediones with sulfonylureas on all-cause mortality.[222, 223] In the cohort from the Cleveland Clinic (N=20,450), individuals initiating pioglitazone had a significantly lower risk of death compared with those initiating a sulfonylurea (adjusted HR, 0.59; 95% CI, 0.43 to 0.81). Those initiating rosiglitazone did not have a statistically significant lower risk of death compared with those initiating a sulfonylurea (adjusted HR, 0.73; 95% CI, 0.51 to 1.02). Followup time was not specified.[222] In the Veterans' Hospital Administration cohort, glipizide and glibenclamide were each compared separately with rosiglitazone.[223] Event rates were 1,104/28,202 (over 46,627 person-years); 899/27,376 (over 47,190 person-years); and 85/3,653 (over 5,140 person-years) for glipizide, glibenclamide, and rosiglitazone, respectively.[223] Compared with rosiglitazone, the adjusted RR for glipizide was 1.26 (95% CI, 1.00 to 1.58), and the adjusted RR for glibenclamide was 1.09 (95% CI, 0.87 to 1.38).[223] (SOE: Low; Pioglitazone favored over sulfonylureas) (SOE: Low; Neither rosiglitazone nor sulfonylureas favored)

Thiazolidinediones Versus DPP-4 Inhibitors

Two RCTs compared pioglitazone with sitagliptin and reported on mortality.[43, 66] The 12-week RCT (N=106) reported no deaths in either arm.[43] The 36-week RCT (N=326) did not report on deaths in the pioglitazone or sitagliptin arm although it did report on deaths in other study arms.[66] Of note, Russell-Jones 2012, et al did not use an intention-to-treat approach and had greater than 13% losses to followup across arms.[66] (SOE: Low; Neither favored)

Thiazolidinediones Versus GLP-1 Agonists

A single RCT with 36 weeks of followup did not report on deaths in the pioglitazone (n=163) or exenatide (n=248) arm although it did report on deaths in other study arms.[66] (Not graded)

Sulfonylureas Versus DPP-4 Inhibitors

A single RCT reported seven and three deaths over 58 weeks in the glipizide (7/212, 3.3%) and sitagliptin (3/210, 1.4%) arms, respectively.[152] The authors did not use an ITT approach for mortality, and losses to followup were greater than 19% for both arms.[152] (SOE: Low; DPP-4 inhibitors favored)

Sulfonylureas Versus GLP-1 Agonists

Two RCTs compared sulfonylureas with liraglutide and reported on all-cause mortality.[155, 158] Liraglutide doses varied across the trials, and death rates were low in both trials (Table 19).[155, 158] (SOE: Low; Neither treatment favored)

Table 19. Randomized controlled trials comparing sulfonylureas with GLP-1 agonists on all-cause mortality

Author, year	Followup (weeks)	Sulfonylurea (dose*)	Liraglutide (dose*)	Number of deaths / N (%) in the sulfonylurea arm	Number of deaths / N (%) in the liraglutide arm
Kaku, 2011[155]	52	Glibenclamide (fixed at 1.25 to 2.5 mg)	Liraglutide (max 0.9 mg)	NR/132	1/268 (0.4)
Garber, 2011[158]	104	Glimepiride (max 8 mg)	Liraglutide (max 1.2 mg)	1/248 (0.4)	0/251 (0)
		Glimepiride (max 8 mg)	Liraglutide (max 1.8 mg)	1/248 (0.4)	1/247 (0.4)

GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams
* All doses were titrated, unless otherwise stated.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Two RCTs compared sitagliptin with a SGLT-2 inhibitor (followup 24 to 26 weeks).[159, 229] No deaths occurred in one study (N=670),[159] and one death was reported in the sitagliptin arm of the other study (no deaths in the SGLT-2 inhibitor arms; N=495).[229] Neither study used an intention-to-treat approach for mortality, and losses to followup ranged from 3 to 13% across the arms of the trials.[159, 229] (SOE: Low; Neither treatment favored)

DPP-4 Inhibitors Versus GLP-1 Agonists

A single RCT compared sitagliptin (n=163) with exenatide (n=248) and did not report on deaths in either arm although it did report on deaths in other study arms.[66] (SOE: Insufficient; Unable to draw a conclusion)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two multinational RCTs[160, 162] directly compared the effect of the combination of metformin plus rosiglitazone with the combination of metformin plus a sulfonylurea. One study (N=596) reported two deaths in each arm over 52 weeks of treatment,[160] and the other reported a fatal myocardial infarction in the metformin plus rosiglitazone arm and no deaths in the metformin plus sulfonylurea arm (N=514) at 32 weeks.[162] (SOE: Low; Neither metformin plus rosiglitazone nor metformin plus a sulfonylurea favored)

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

A single RCT compared the combination of metformin plus pioglitazone with the combination of metformin plus sitagliptin and reported one death in the metformin plus sitagliptin arm (1/172) and did not report on deaths in the metformin plus pioglitazone arm (n=172) at 26 weeks.[173] (SOE: Insufficient; Unable to draw a conclusion)

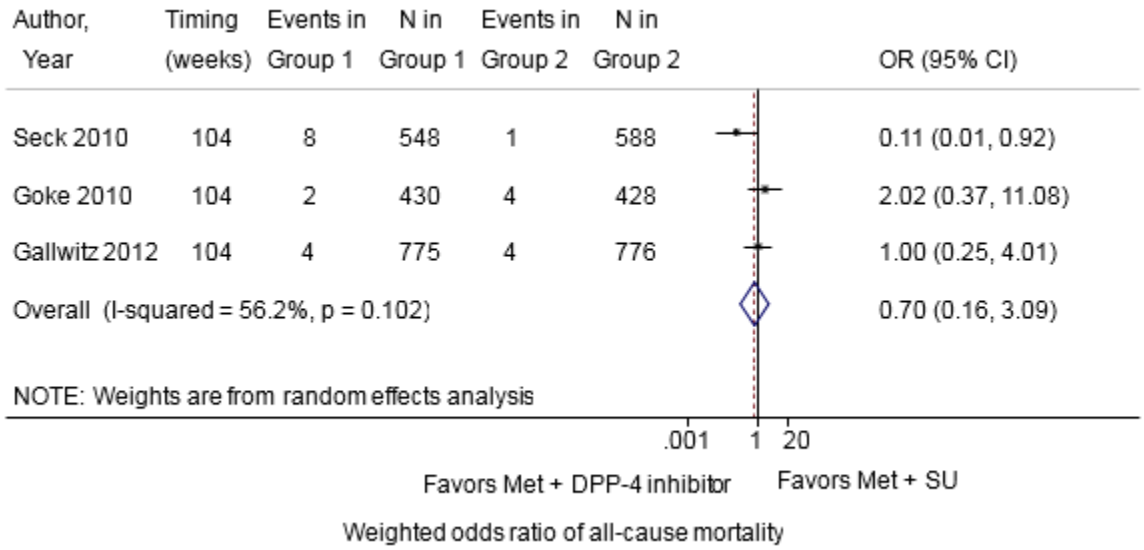
Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

A single RCT compared the combination of metformin plus pioglitazone (n=172) with the combination of metformin plus weekly exenatide (n=170) at 26 weeks but only provided data on deaths in a third arm (metformin plus sitagliptin).[173] Given the reporting in the metformin plus sitagliptin arm, we may infer that there were no deaths in the metformin plus pioglitazone and metformin plus exenatide arms, but this information was not reported.[173] (SOE: Insufficient; Unable to draw a conclusion)

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

Three RCTs compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor and found no significant reduction in mortality for metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea at two years (pooled OR, 0.70; 95% CI, 0.16 to 3.09) (Figure 48).[178-180] We found evidence of significant statistical heterogeneity (I^2 = 56.2%).

Figure 48. Pooled odds ratio of all-cause mortality comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include a fourth RCT evaluating this comparison because of its brief followup (30 weeks) compared with those in the meta-analysis. The investigators reported one death in the metformin plus sulfonylurea arm (1/519) and no deaths in the metformin plus sitagliptin arm (0/516).[175]

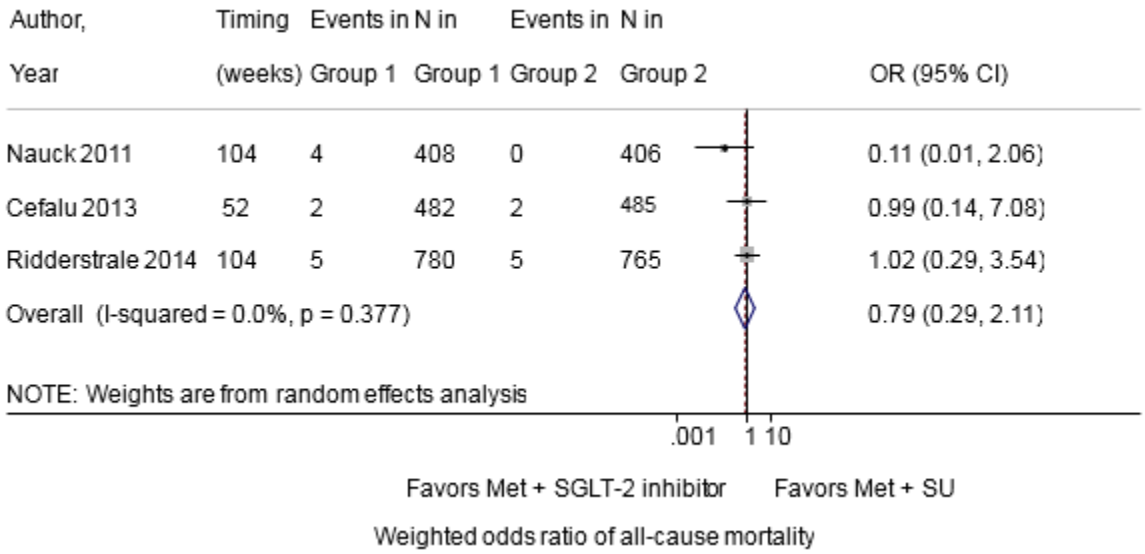
A single retrospective cohort study in the Danish National Registry reported a significantly decreased risk of death among metformin plus DPP-4 inhibitor users (n=11,138) versus

metformin plus sulfonylurea users (n=25,092) with median follow up of 2.1 years (adjusted rate ratio, 0.65; 95% CI, 0.54 to 0.8).[210] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

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

Results from three RCTs (duration 52 to 104 weeks) suggested that metformin plus SGLT-2 inhibitors did not significantly affect the risk of death relative to metformin plus sulfonylurea (pooled OR, 0.79; 95% CI, 0.29 to 2.11) (Figure 49).[181-183] We did not find any evidence of statistical heterogeneity (I^2 = 0.0%), and removal of any one study did not change the inference of no difference between arms. One of the RCTs also evaluated metformin plus canagliflozin at a dose lower than that included in the meta-analysis (300 mg daily). The RCT reported no deaths in the lower-dose canagliflozin arm (100 mg daily) at 52 weeks.[181] Of note, two[181, 183] of three studies did not use an intention-to-treat approach and had greater than 15% losses to followup across arms. (SOE: Low; Neither favored)

Figure 49. Pooled odds ratio of all-cause mortality comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

A single RCT compared the combination of metformin plus glimepiride (n=508) with the combination of metformin plus exenatide (n=510) and reported five deaths in each arm (assumed 48 months of followup).[185]

A single retrospective cohort study in the Danish National Registry did not find a significantly decreased risk of death among metformin plus GLP-1 agonist users (n=4,345)

versus metformin plus sulfonylurea users (n=25,092) over median follow up of 2.1 years (adjusted rate ratio, 0.77; 95% CI, 0.51 to 1.17).[210] (SOE: Low; Neither favored)

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

A single retrospective cohort study in the Danish National Registry found a significantly increased risk of death among metformin plus basal insulin users (n=6,858) versus metformin plus sulfonylurea users (n=25,092) over median follow up of 2.1 years (adjusted rate ratio, 1.95; 95% CI, 1.7 to 2.25).[210] (Not graded)

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

Two multinational RCTs (N=938) compared the effect of the combination of metformin plus a sulfonylurea with the combination of metformin plus a premixed insulin (insulin aspart 70/30 in one study and insulin lispro 75/25 in the other). Each trial reported one death in the metformin plus premixed insulin arms and no deaths in the metformin plus sulfonylurea arms at 16 weeks.[190, 191] (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Two RCTs compared metformin plus sitagliptin with metformin plus an SGLT-2 inhibitor and reported on mortality.[122, 127] A small (N=212), 12-week trial reported no deaths in any arm (metformin plus sitagliptin, metformin plus empagliflozin 10 mg, and metformin plus empagliflozin 25 mg).[122] A second trial with 52 weeks of followup reported one death in the metformin plus sitagliptin arm (1/366), one death in the metformin plus canagliflozin 300 mg arm (1/367), and no deaths in the metformin plus canagliflozin 100 mg arm (0/368).[127] (SOE: Low; Neither favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Two RCTs compared the combination of metformin plus sitagliptin with metformin plus a GLP-1 agonist and reported few deaths. In the study with longer followup (52 weeks), the death rate was twice as high in the metformin plus DPP-4 inhibitor arm versus the metformin plus GLP-1 agonist arm based on a total of three deaths.[128] The other trial did not report on events in the metformin plus GLP-1 agonist arm, and reported a rate similar to that in the other trial for the metformin plus DPP-4 inhibitor arm (Table 20).[173] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Table 20. Randomized controlled trials comparing a combination of metformin plus sitagliptin with a combination of metformin plus a GLP-1 agonist on all-cause mortality

Author, year	Follow up	Number of deaths/N (%) in the metformin + sitagliptin arm	Number of deaths/N (%) in the metformin + GLP-1 agonist arm
Nauck, 2014[128]	26 weeks	0/315 (0)	Dulaglutide 0.75 mg: 0/302 (0) Dulaglutide 1.5 mg: 0/304 (0)
	52 weeks	2/315 (0.6)	Dulaglutide 0.75 mg: 0/302 (0) Dulaglutide 1.5 mg: 1/304 (0.3)
Bergenstal, 2010[173]	26 weeks	1/172 (0.6)	Exenatide 2 mg weekly: NR/170

GLP-1 = glucagon-like peptide-1; mg = milligrams; NR = not reported

Combination of Metformin Plus a GLP1-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

A single RCT (N=321) compared metformin plus exenatide with metformin plus insulin glargine and reported no deaths in either arm at 26 weeks.[194] (SOE: Insufficient; Unable to draw a conclusion)

Strength of Evidence for All-Cause Mortality

We found high strength of evidence that neither metformin nor the combination of metformin plus DPP-4 inhibitors were favored for short-term all-cause mortality and moderate strength of evidence for a few additional metformin-based monotherapy comparisons (see Key Points, Table 21, and Table 22). We found low or insufficient strength of evidence for all other comparisons, including all combination comparisons, evaluating all-cause mortality.

Most evidence on this outcome came from RCTs that we found to be at low or medium risk of bias. Notably, none of the RCTs were designed to evaluate all-cause mortality. Observational studies had medium risk of bias and tended to support RCT findings. For the comparison of rosiglitazone and sulfonylurea monotherapy, two RCTs suggested no treatment difference for all-cause mortality, but the observational studies including 79,681 participants favored rosiglitazone over sulfonylurea monotherapy. Evidence was generally consistent across monotherapy comparisons with less consistency for combination therapy comparisons, in part because of the smaller number of studies for these comparisons. The RCT evidence on mortality was substantially underpowered and imprecise because of few studies and small sample sizes with few events.

Our evaluation of publication bias was generally limited by the small number of studies. However, we suspect there may be reporting bias for two of the comparisons: sulfonylureas versus DPP-4 inhibitors and metformin plus a sulfonylurea versus metformin plus a DPP-4 inhibitor. For the monotherapy comparison, we identified in the published literature a single moderately-sized RCT which suggested that DPP-4 inhibitors were favored over sulfonylureas for all-cause mortality. We found two additional unpublished studies with results consistent with the findings in the one published RCT. For the combination therapy comparison, we identified four RCTs and one observational study which suggested that metformin plus DPP-4 inhibitors were favored over metformin plus a sulfonylurea; however results among the RCTs were inconsistent. We identified an additional unpublished study supporting that the combination of metformin plus a DPP-4 inhibitor is favored over that of metformin plus a sulfonylurea. In both of these cases, the evidence could have been strengthened if these results had been published.

Table 21. Strength of evidence domains for monotherapy comparisons in terms of all-cause mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. pioglitazone	RCTs: 4 (1755) Observational: 1 (NR)	Low Medium	Consistent Unknown	Direct Direct	Imprecise N/A	Undetected N/A	Moderate	Neither treatment favored Pooled OR for metformin versus pioglitazone, 0.91; 95% CI, 0.22 to 3.72
Metformin vs. rosiglitazone	RCTs: 2 (3224) Observational: 2 (193,172)	Low Medium	Inconsistent Consistent	Direct Direct	Imprecise Precise	Undetected N/A	Low	Neither treatment favored
Metformin vs. SU	RCTs: 6 Observational: 7 (50,802)	Low Medium	Inconsistent Consistent	Direct Direct	Imprecise Imprecise	Undetected N/A	Low	Metformin favored
Metformin vs. DPP-4 inhibitors	RCTs: 5 (4,792) Observational: 1 (84,756)	Low Medium	Inconsistent Unknown	Direct Direct	Imprecise Imprecise	Undetected N/A	Low	Neither treatment favored
Metformin vs. SGLT-2 inhibitors	RCTs: 4 (2,041)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. GLP-1 agonists	RCTs: 2 (820)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored Incomplete reporting on death
Metformin vs. metformin + pioglitazone	RCT: 1 (213)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + rosiglitazone	RCTs: 7 (3242)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin monotherapy favored
Metformin vs. metformin + SU	RCTs: 4 (971)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. metformin + DPP-4 inhibitors	RCTs: 17 (11,434)	Low	Consistent	Direct	Precise	Undetected	High	Neither treatment favored Pooled OR for metformin plus DPP-4 inhibitor versus metformin, 0.89; 95% CI, 0.28 to 2.86
Metformin vs. metformin	RCTs: 8	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Neither treatment

+ SGLT-2 inhibitors	(4668)							favored <52 weeks: Pooled OR for metformin plus SGLT-2 inhibitor versus metformin, 0.99; 95% CI, 0.10 to 9.61 ≥52 weeks: Pooled OR for metformin plus SGLT-2 inhibitor versus metformin, 1.15; 95% CI, 0.18 to 7.35
Metformin vs. metformin + GLP-1 agonists	RCT: 1 (1098)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Rosiglitazone vs. SU	RCTs: 2 (3,484) Observational: 2 (79,681)	Low Medium	Consistent Inconsistent	Direct Direct	Imprecise Precise	Undetected N/A	Low	Neither treatment favored
Pioglitazone vs. SU	RCT: 1 (502) Observational: 1 (20,450)	Low Medium	Unknown Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Pioglitazone favored
Pioglitazone vs. DPP-4 inhibitors	RCTs: 2 (1031)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
SU vs. DPP-4 inhibitors	RCT: 1 (426)	Medium	Unknown	Direct	Imprecise	Suspected	Low	DPP-4 inhibitors favored
SU vs. GLP-1 agonists	RCTs: 2 (1157)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	RCTs: 2 (1486)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
DPP-4 inhibitors vs. GLP-1 agonists	RCT: 1 (820)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 22. Strength of evidence domains for metformin-based combination comparisons in terms of all-cause mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + rosiglitazone vs. metformin + SU	RCTs: 2 (1110)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + pioglitazone vs. metformin + DPP-4 inhibitors	RCT: 1 (514)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pioglitazone vs. metformin + GLP-1 agonists	RCT: 1 (514)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + DPP-4 inhibitors	RCTs: 4 (3445) Observational: 1 (47433)	Low Medium	Inconsistent Unknown	Direct Direct	Imprecise Precise	Suspected N/A	Low	Metformin + DPP-4 inhibitors favored
Metformin + SU vs. metformin + SGLT-2 inhibitors	RCTs: 3 (3815)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + SU vs. metformin + GLP-1 agonists	RCT: 1 (1069) Observational: 1 (29,437)	High Medium	Unknown Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Neither treatment favored
Metformin + SU vs. metformin + premixed insulin	RCTs: 2 (938)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	RCTs: 2 (1779)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	RCTs: 2 (1612)	Low	Consistent	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitors favored
Metformin + GLP-1 agonists vs. metformin + basal insulin	RCT: 1 (321)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Cardiovascular Mortality

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Three RCTs compared metformin with thiazolidinediones and did not find differences in cardiovascular mortality. Two of the RCTs were small, lasted less than one year, and did not report any cardiovascular deaths (Table 23).[45, 56, 63] Studies were not combined due to different lengths of followup. (SOE: Low; Neither favored)

Table 23. Randomized controlled trials comparing metformin with thiazolidinediones on cardiovascular mortality

Author, year	Followup	Number of events/N (%) in the metformin arm	Number of events/N (%) in the thiazolidinedione arm
Lawrence, 2004[56]	24 weeks	0/20	0/20 (pioglitazone)
Erem, 2014[63]	48 weeks	0/19	0/19 (pioglitazone)
Kahn, 2006[45]	4 years (median)	2/1454 (0.1%)	1/1456 (0.1%) (rosiglitazone)

Metformin Versus Sulfonylureas

Two longer-term RCTs compared metformin with sulfonylureas and reported on cardiovascular mortality.[45, 214] The multi-national ADOPT trial (N=2895) reported a slightly higher incidence of cardiovascular mortality in the glyburide arm versus the metformin arm with median followup of 4 years, with two fatal myocardial infarctions in the metformin arm and three in the sulfonylurea arm (0.2% versus 0.1%).[45] The smaller RCT was conducted in China and also reported a higher risk of cardiovascular mortality in the sulfonylurea arm (11/148, 7.4%) compared with the metformin arm (7/156, 4.5%) over 144 weeks (2.8 years).[214] We calculated the risk ratio of cardiovascular mortality comparing sulfonylurea with metformin to be 1.66 (95% CI, 0.66 to 4.16).

Three retrospective cohort studies analyzing two cohorts compared metformin with a sulfonylurea, and all found a higher risk of cardiovascular mortality for sulfonylurea users versus metformin users (Table 24).[208, 212, 213] (SOE: High; Metformin favored)

Table 24. Observational studies comparing metformin with sulfonylureas on cardiovascular mortality

Author, year	Cohort	Metformin, N	Sulfonylurea, N	Median followup	Adjusted HR (95% CI) for cardiovascular mortality
Johnson, 2005[213]	Saskatchewan Health database	923	2138	4.6 to 5.6 years	0.76 (0.58 to 1.00) Reference: sulfonylurea
Schramm, 2011[212]	Danish National Patient Register	Prior MI 2,906 No prior MI 43,340	Prior MI Glibenclamide: 1,168 Glipizide: 660 Glimepiride: 3,894 No prior MI Glibenclamide: 12,495 Glipizide: 6,965 Glimepiride: 36,313	3.3 years	Prior MI Glibenclamide: 1.5 (1.22 to 1.84) Glipizide: 1.63 (1.28 to 2.07) Glimepiride: 1.32 (1.11 to 1.57) No prior MI Glibenclamide: 1.14 (1.03 to 1.25) Glipizide: 1.25 (1.12 to 1.4) Glimepiride: 1.28 (1.18 to 1.38) Reference: metformin
Andersson, 2010[208]	Danish National Patient Register – Incident admission for heart failure*	688	3615	844 days	0.79 (0.65 to 0.96) Reference: sulfonylurea

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction
*unclear if this population was included in Schramm, 2011[212]

Metformin Versus DPP-4 Inhibitors

Three RCTs compared metformin with DPP-4 inhibitors and reported on cardiovascular mortality (Table 25). These studies varied in duration and did not consistently report on events. Therefore, we did not combine them in a meta-analysis. Cardiovascular mortality was rare and appeared to be more frequent in the metformin than DPP-4 inhibitor arms when reported.[77-79] The longest study did not report on this outcome for these monotherapy arms – only for the combination therapy arms (see below).[77] (SOE: Low; DPP-4 inhibitors favored)

Table 25. Randomized controlled trials comparing metformin with DPP-4 inhibitors on cardiovascular mortality

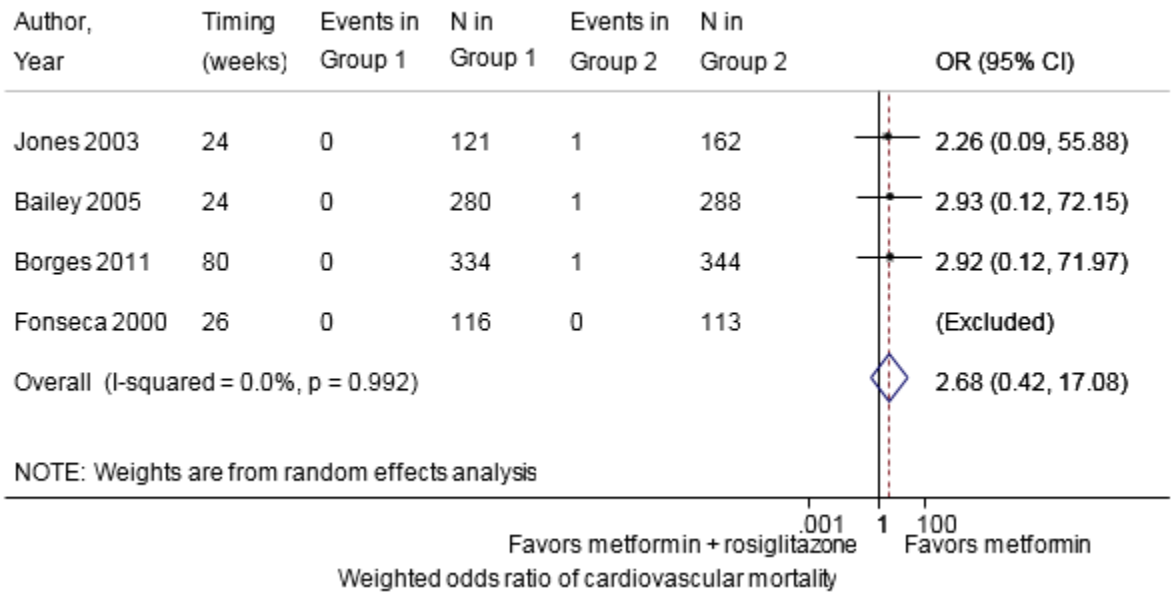
Author, year	Outcome	Followup (weeks)	Metformin dose: Number of events/N (%)	DPP-4 inhibitor dose: Number of events/N (%)
Haak, 2012[78]	Fatal MI	24	1000 mg: 0/142 (0.0%) 2000 mg: 1/147 (0.7%)	Linagliptin 5 mg: 0/142 (0.0%)
Pfutzner, 2011[79]	Sudden death, cardiac arrest, coronary arteriosclerosis, cardiac failure, acute MI	76	2000 mg: 3/328 (0.9%)	Saxagliptin 10 mg: 1/335 (0.3%)
Williams-Herman, 2010[77]	Sudden cardiac death or worsening CHD	104	1000 mg: NR/182 2000 mg: NR/182	Sitagliptin 100 mg: NR/179

CHD = coronary heart disease; DPP-4 = dipeptidyl peptidase-4; mg = milligrams; MI = myocardial infarction; NR = not reported

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Five RCTs reported in four articles[89, 92, 96, 228] compared metformin with metformin plus rosiglitazone and found non-significant increased odds of cardiovascular mortality for the combination of metformin plus rosiglitazone versus metformin monotherapy (pooled OR, 2.68; 95% CI, 0.42 to 17.08) (Figure 50). Three of the studies reported a single cardiovascular death in the metformin plus rosiglitazone arm, and all studies reported no cardiovascular deaths in the metformin monotherapy arms. The results of the 80-week study[96] did not differ from those of the shorter studies.[89, 92, 228] We did not find evidence of statistical heterogeneity (I^2 = 0.0%), and removal of any one study from the meta-analysis did not change the inference.

Figure 50. Pooled odds ratio cardiovascular mortality comparing metformin with a combination of metformin plus rosiglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus rosiglitazone; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

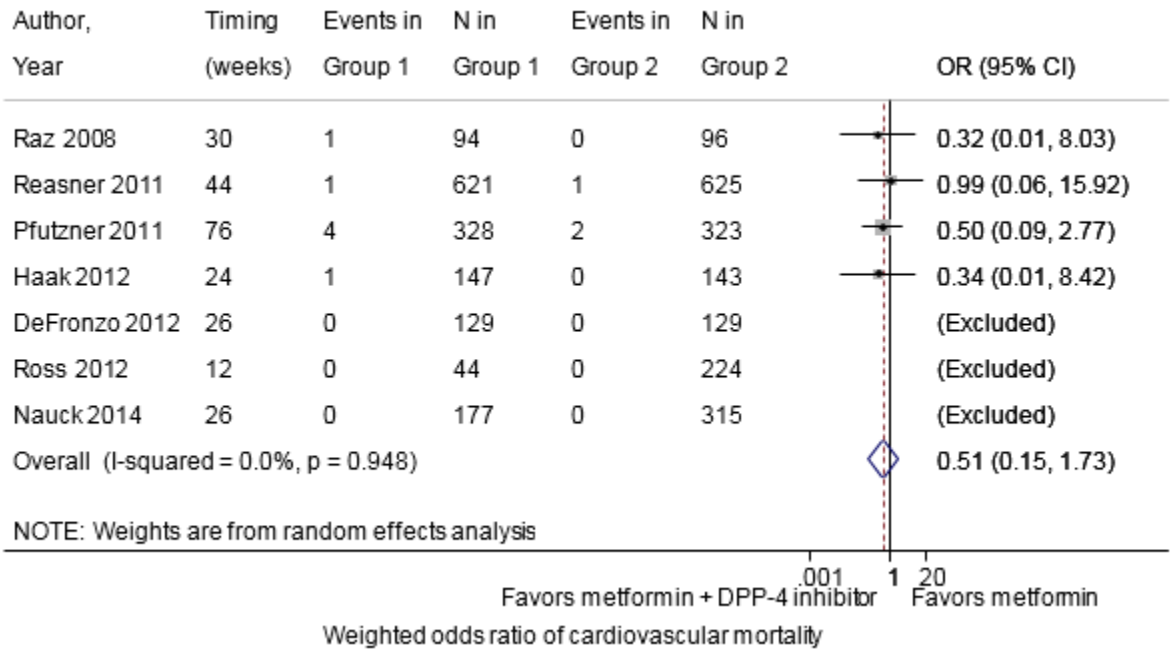
A single 26-week RCT compared metformin monotherapy with metformin plus pioglitazone (15, 30, and 45 mg arms) and reported one event of sudden cardiac death in the metformin plus pioglitazone 45 mg arm. The study did not report on sudden cardiac death for the other arms.[95]

Of note, two of the RCTs had substantial losses to followup (38% to 45% in one study[96] and 12% to 18% in the other[95]). This, along with a lack of reporting on the intention-to-treat population, limits our conclusions. (SOE: Low; Metformin monotherapy favored over combination of metformin plus rosiglitazone) (SOE: Insufficient; Unable to draw a conclusion for combination of metformin plus pioglitazone)

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

Results from six RCTs comparing metformin with the combination of metformin plus a DPP-4 inhibitor showed a non-significant decreased risk of cardiovascular mortality for the metformin plus DPP-4 inhibitor arms versus metformin based on 10 deaths across the trials (pooled OR, 0.51; 95% CI, 0.15 to 1.73) (Figure 51). We did not find evidence of statistical heterogeneity, and removal of any one study did not change the inference from the meta-analysis.[78, 79, 111, 114, 121, 128] Cerebrovascular deaths were not reported on in the metformin plus saxagliptin arm in Pfutzner 2011, et al, and we assumed that no events occurred in that arm for the meta-analysis.[79] Three of the RCTs included in the meta-analysis also had additional arms with lower dosages and did not report on events in those arms.[78, 79, 95]

Figure 51. Pooled odds ratio cardiovascular mortality comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a DPP-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

An additional longer RCT (104 weeks) reported one cardiovascular death in the metformin plus sitagliptin arm and did not report on cardiovascular deaths in the metformin monotherapy arms.[77] (SOE: Low; Combination of metformin plus DPP-4 inhibitors favored)

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

One RCT (N=546) compared metformin with the combination of metformin plus dapagliflozin at different doses (2.5, 5.0, and 10.0 mg) and reported two cardiovascular deaths in the metformin plus 2.5-mg dapagliflozin arm at 102 weeks and did not report on deaths in the other arms.[135] (SOE: Insufficient; Unable to draw a conclusion)

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

A single 26-week RCT compared metformin with metformin plus dulaglutide at two different doses (0.5 mg and 1.5 mg per week) and reported one fatal stroke in the metformin plus dulaglutide 1.5 mg/week (1/304) arm and no events in the metformin (0/177) or metformin plus dulaglutide 0.75 mg/week (0/302) arm.[128] (SOE: Low; Neither treatment favored)

Thiazolidinediones Versus Sulfonylureas

The ADOPT trial compared rosiglitazone with glyburide over four years and reported two fatal myocardial infarctions in the rosiglitazone arm (2/1446, 0.1%) and three fatal myocardial infarctions in the glyburide arm (3/1441, 0.2%) resulting in a calculated risk ratio of 0.66 (95% CI, 0.11 to 3.97).[45] (SOE: Low; Neither treatment favored)

Sulfonylureas Versus DPP-4 Inhibitors

Two small RCTs compared a sulfonylurea with a DPP-4 inhibitor (duration 52 to 58 weeks) and reported mixed results on fatal myocardial infarction.[151, 152] The high-quality study reported one fatal myocardial infarction in the linagliptin arm (1/151) and none in the sulfonylurea arm (0/151),[151] and the other study reported two events in the sulfonylurea arm (2/212) and did not report on fatal myocardial infarctions in the sitagliptin arm (n=211).[152] The lower-quality study did not use an intention-to-treat analysis for fatal myocardial infarction and had large losses to followup (19.8% and 22.3% in the sulfonylurea and DPP-4 inhibitor arms, respectively).[152] (SOE: Low; Neither treatment favored)

Metformin-Based Combination Comparisons

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

A single, five-arm, 26-week RCT (N=1,554) compared metformin plus pioglitazone (arms with doses of 15 mg, 30 mg, and 45 mg) with metformin plus alogliptin (12.5-mg and 25-mg arms) and reported on sudden cardiac death.[95] The investigators reported one sudden cardiac death in the metformin plus pioglitazone 45-mg arm (1/129) and did not report on this outcome in the other arms. (SOE: Insufficient; Unable to determine effect)

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

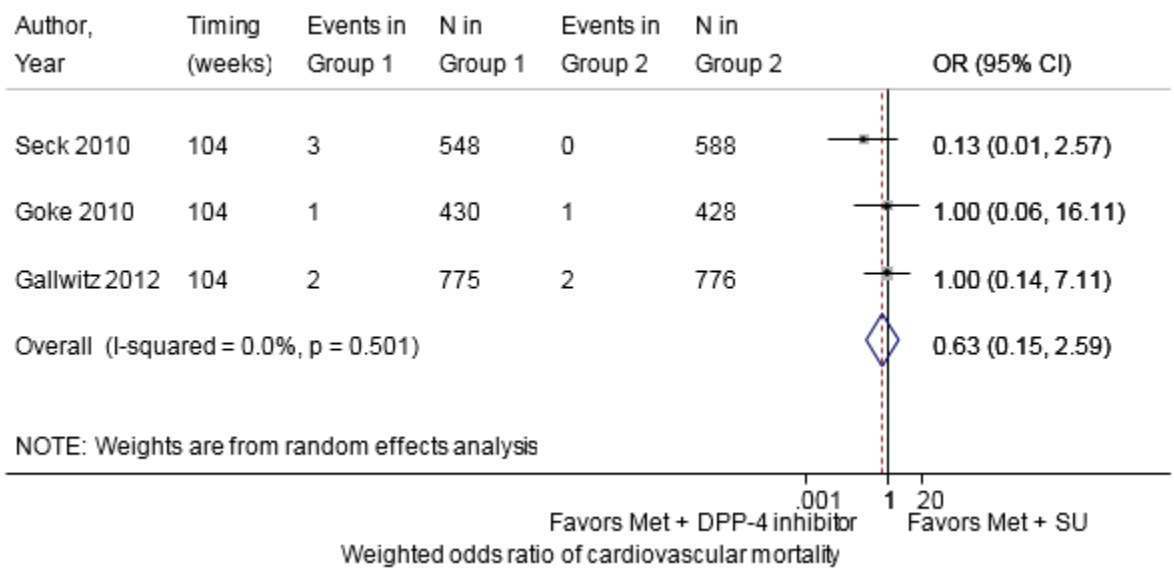
Four RCTs addressed cardiovascular/cerebrovascular mortality for this comparison.

Three RCTs with 104 weeks of followup found few (zero to three) fatal cardiovascular events across the arms for metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea (pooled OR, 0.63; 95% CI, 0.15 to 2.59) (Figure 52). We did not find evidence of statistical heterogeneity (I^2 = 0.0%).[178-180] Removal of a single study did not change the inference of the meta-analysis. Of note, definitions of cardiovascular mortality varied slightly across the studies included in this meta-analysis (Table 26).

Two RCTs (N=1893; duration, 30 weeks and 104 weeks) addressed fatal stroke specifically for this comparison and reported one event in the metformin plus sulfonylurea arms and did not report on this outcome for the metformin plus DPP-4 inhibitor arms.[175, 179]

A single retrospective cohort study (N=36,230) from the Danish Patient Register reported a significantly lower risk of cardiovascular mortality with a median of 2.1 years of followup for metformin plus DPP-4 inhibitor users versus metformin plus sulfonylurea users (adjusted rate ratio, 0.57; 95% CI, 0.4 to 0.8).[210] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 52. Pooled odds ratio cardiovascular mortality combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 26. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cardiovascular mortality

Author, year	Followup (weeks)	Definition of fatal cardiovascular event	Number of events / N (%) in the metformin plus sulfonylurea arm	Number of events / N (%) in the metformin plus DPP-4 inhibitor arm	Included in meta-analysis
Seck, 2010[180]*	104	Sudden cardiac death, fatal MI	3/548	0/588 (0)	Yes
Goke, 2010[179]	104	Composite CVD mortality outcome (cardiac failure, MI)	1/430	1/428	Yes
Gallwitz, 2012[178]	104	Composite CVD mortality outcome (sudden cardiac death, fatal MI, and fatal stroke)	2/775	2/776	Yes
Goke, 2010[179]	104	Fatal stroke	1/430	NR/428	No; did not report on events in both arms
Arechavaleta, 2011[175]	30	Fatal stroke	1/519	NR/516	No; short-term duration and did not report on events in both arms

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; MI = myocardial infarction
*104-week followup of Nauck 2007, et al[177]

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

A single 104-week RCT reported one cardiovascular death in the metformin plus glipizide arm (1/408) and no cardiovascular deaths in the metformin plus dapagliflozin arm (0/406).[182] (SOE: Low; Combination of metformin plus a SGLT-2 inhibitor favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

A single retrospective cohort study (N=29,437) from the Danish Patient Register reported a non-significant lower risk of cardiovascular mortality with a median of 2.1 years of followup for metformin plus GLP-1 agonist users versus metformin plus sulfonylurea users (adjusted rate ratio, 0.89; 95% CI, 0.47 to 1.68).[210] (Not graded)

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

A single retrospective cohort study (N=29,437) from the Danish Patient Register reported a significantly increased risk of cardiovascular mortality with a median of 2.1 years of followup for metformin plus basal insulin users versus metformin plus sulfonylurea users (adjusted rate ratio, 1.57; 95% CI, 1.23 to 2.01).[210] (Not graded)

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

A single 16-week open-label RCT (N=341) randomized participants with poorly controlled diabetes on metformin alone to the addition of glibenclamide or twice daily insulin aspart 70/30 and reported no deaths in the metformin plus glibenclamide arm and one fatal myocardial infarction in the metformin plus premixed insulin arm.[191] (SOE: Low; Combination of metformin plus sulfonylurea favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

A single 26-week, open-label RCT (N=665) randomized participants with poorly controlled diabetes on metformin alone to the addition of oral sitagliptin (100 mg) or one of two doses of daily subcutaneous injections of liraglutide (1.2 mg or 1.8 mg) and reported one fatal cardiac arrest in the metformin plus sitagliptin arm and none in the metformin plus liraglutide arms.[192]

A single 26-week RCT (N=921) reported on fatal stroke for metformin plus sitagliptin versus metformin plus dulaglutide at two doses (0.75 mg/week and 1.5 mg/week). The investigators reported one fatal stroke in the metformin plus dulaglutide 1.5-mg/week arm and no events in the other arms.[128] (SOE: Insufficient; Unable to determine effect)

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

A single 32-week, open-label, cross-over study (N=597) randomized participants to metformin plus insulin glargine or metformin plus insulin lispro 75/25 twice daily and reported one fatal myocardial infarction in the metformin plus insulin lispro 75/25 arm and no events in the metformin plus glargine arm.[207] (SOE: Insufficient; Unable to determine effect)

Strength of Evidence for Cardiovascular Mortality

Although we identified one comparison for which there was high strength of evidence, evidence was generally of low strength or insufficient for cardiovascular mortality (see Key Points, Table 27 and Table 28). Most evidence on cardiovascular mortality came from RCTs lasting 12 months or less, and none of the RCTs were designed to evaluate all-cause mortality. We did identify observational studies which strengthened the evidence for a few comparisons (metformin versus sulfonylurea and metformin plus a sulfonylurea versus metformin plus DPP-4 inhibitors). About one-half of the available evidence on monotherapy comparisons and more than one-half of that on combination comparisons was at medium or high risk of bias. Most evidence from monotherapy comparisons was consistent while we often only found one study for a given combination comparison making consistency indeterminate. Sample size and low event rates in RCTs limited precision of the evidence on cardiovascular mortality, and the small number of studies limited our ability to assess publication bias. Finally, we did not identify unpublished studies which looked at comparisons for which we had no published studies.

Table 27. Strength of evidence domains for monotherapy comparisons in terms of cardiovascular mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. pioglitazone	RCTs: 2 (120)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. rosiglitazone	RCT: 1 (2940)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. SU	RCTs: 2 (4664) Observational: 3 (115,105)	Low Medium	Consistent Consistent	Direct Direct	Imprecise Precise	Undetected Undetected	High	Metformin favored; RR 1.6 to 2.0 from RCTs for SU vs. metformin
Metformin vs. DPP-4 inhibitors	RCTs: 3 (3,188)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored
Metformin vs. metformin + rosiglitazone	RCTs: 5 (2,167)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin vs. metformin + pioglitazone	RCT: 1 (1,554)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin+DPP-4 inhibitor	RCTs: 7 (6,673)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitors favored; OR 0.55 (0.17 to 1.76)
Metformin vs. metformin + SGLT-2 inhibitor	RCT: 1 (546)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Events not reported on in three arms
Metformin vs. metformin + GLP-1 agonist	RCT: 1 (1098)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
TZD vs. SU	RCT: 1 (2,987)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
SU vs. DPP-4 inhibitors	RCT: 2 (653)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither treatment favored Events not reported for all arms

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 28. Strength of evidence domains for metformin-based combination comparisons in terms of cardiovascular mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor	RCT: 1 (1554)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Events not reported on in four arms
Metformin + SU vs. metformin + DPP-4 inhibitors	RCTs: 4 (4580) Observational: 1 (36,620)	Low Medium	Consistent Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Metformin + DPP-4 inhibitors favored; Combined OR 0.69 (0.17 to 2.86)
Metformin + SU vs. metformin + SGLT-2 inhibitor	RCT: 1 (814)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin + SGLT-2 inhibitors favored
Metformin + SU vs. metformin + premixed insulin	RCT: 1 (341)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + SU favored
Metformin + DPP-inhibitor vs. metformin + GLP-1 agonist	RCTs: 2 (1,763)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	RCT: 1 (597)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Cardiovascular and Cerebrovascular Morbidity

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Randomized Controlled Trials

Two RCTs compared metformin with rosiglitazone and reported on cardiovascular morbidity.[45, 52] Event rates did not differ by treatment; we did not combine these studies in a meta-analysis because of variation in duration of followup (Table 29).

Table 29. Randomized controlled trials comparing metformin with rosiglitazone on cardiovascular morbidity

Author, year	Enrolled N	Followup	Outcome	Number of events / N (%) for metformin vs. rosiglitazone
Kahn*, 2006[45]	4360	4 years (median)	Non-fatal myocardial infarction Stroke	21/1454 (1.4) vs. 25/1456 (1.7) 19/1454 (1.3) vs. 16/1456 (1.1)
Rosenstock, 2006[52]	468	32 weeks	Not defined ischemic heart disease	2/154 (1) vs. 1/159 (1)

* ADOPT Study

Three small RCTs less than one year in duration compared metformin with pioglitazone and reported very few events.[56, 63, 64] We did not perform a meta-analysis given the absence of events in two of the three studies (Table 30).

Table 30. Randomized controlled trials comparing metformin with pioglitazone on cardiovascular morbidity

Author, year	Enrolled N	Followup	Outcome	Number of events / N (%) for metformin vs. pioglitazone
Erem, 2014[63]	57	48 weeks	Nonfatal MI	0/19 (0) vs. 0/9 (0)
Lawrence, 2004[56]	60	24 weeks	Nonfatal CVD morbidity/MI	0/20 (0) vs. 0/20 (0)
Genovese, 2013[64]	58	16 weeks	Discontinuation due to myocardial ischemia	1/29 (3.4) vs. NR/29

CVD = cardiovascular disease; MI = myocardial infarction; NR = not reported

Observational Studies

Three retrospective cohort studies[222, 230, 231] compared metformin with rosiglitazone and reported mixed results (Table 31). One reported no increased risk of ischemic heart disease for rosiglitazone versus metformin[222] and the other two suggested an increased risk of cardiovascular morbidity.[230, 231] (SOE: Low; Neither metformin nor rosiglitazone favored)

Table 31. Retrospective cohort studies comparing metformin with rosiglitazone on cardiovascular morbidity

Author, year	Population (N)	Followup	Outcome	Adjusted HR (95% CI)
Pantalone, 2009[222]	Cleveland Clinic electronic health record system (11,515)	8 years	Ischemic heart disease	0.96 (0.76 to 1.21) Reference = metformin
Hsiao, 2009[230]	Taiwan National Health Insurance – newly-diagnosed diabetes (48,537)	6 years	Myocardial infarction Angina pectoris Transient ischemic attack Stroke	2.09 (1.36 to 3.24) 1.79 (1.39 to 2.30) 2.57 (1.33 to 4.96) 1.61 (0.72 to 3.62) Reference = metformin
Brownstein, 2010[231]	United States (34,252)	7 years	Hospitalization for acute MI	3.0 (2.4 to 3.7) Reference = metformin

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction

The same three retrospective cohort studies compared metformin with pioglitazone[222, 230, 231] and found no significant difference in cardiovascular disease risk between groups (Table 32). Of note, participants in the Taiwan National Health Insurance database study prescribed pioglitazone were more likely to have a history of cardiovascular disease than those prescribed metformin.[230] (SOE: Moderate; neither metformin nor pioglitazone favored)

Table 32. Retrospective cohort studies comparing metformin to pioglitazone on cardiovascular morbidity

Author, year	Population (N)	Followup	Outcome	Adjusted HR (95% CI)
Pantalone, 2009[222]	Cleveland Clinic electronic health record system (11944)	8 years	Ischemic heart disease	1.11 (0.91 to 1.34) Reference = metformin
Hsiao, 2009[230]	Taiwan National Health Insurance – newly-diagnosed diabetes (473,483)	6 years	Myocardial infarction Angina pectoris	1.0 (0.26 to 3.89) 1.15 (0.6 to 2.21) Reference = metformin

CI = confidence interval; HR = hazard ratio

Metformin Versus Sulfonylureas

Randomized Controlled Trials

Three RCTs[45, 103, 214] compared metformin with sulfonylureas and reported on cardiovascular morbidity with two of the three favoring metformin (Table 33). Rates of non-fatal myocardial infarction and stroke were similar in the metformin and sulfonylurea arms of the multinational ADOPT Study.[45] Rates were higher for sulfonylurea versus metformin in the RCT conducted in a predominantly-male Chinese population with an established diagnosis of coronary heart disease (history of acute myocardial infarction or angiographic evidence of coronary artery stenosis >50%).[214] The third RCT was small and short (6 months) and found higher rates of undefined cardiovascular morbidity in the sulfonylurea than metformin arm.[103]

Table 33. Randomized controlled trials comparing metformin with sulfonylureas on cardiovascular morbidity

Author, year	Followup	Outcome	Number of events / N (%) for metformin vs. sulfonylurea
Kahn, 2006[45]	4 years (median)	Non-fatal MI	21/1454 (1.4) vs. 15/1441 (1.0)
		Stroke	19/1454 (1.3) vs. 17/1441 (1.2)
Hong, 2013[214]	2.8 years	Non-fatal MI confirmed by medical records	5/156 (3.2) vs. 6/148 (4.1)
		Non-fatal stroke confirmed by medical records	10/156 (6.4) vs. 15/148 (10.1)
		Arterial revascularization by PTCA or by coronary artery bypass graft confirmed by medical records	21/156 (13.5) vs. 25/148 (16.9)
		CVD morbidity composite outcome*	39/156 (25.0) vs. 52/148 (35.1)
		New critical cardiac arrhythmia confirmed by medical record	30/156 (19.2) vs. 27/148 (18.2)
		New or worsening angina confirmed by medical record	77/156 (49.4) vs. 71/148 (48.0)
		New peripheral vascular disease events confirmed by medical record	1/156 (0.6) vs. 6/148 (4.1)
Hermann, 1994[103]	6 months	Unclear – CVD morbidity/CHD	2/25 (5) vs. 3/21 (9)

CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty

* Including nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization by PTCA or by coronary artery bypass graft, death from a cardiovascular cause, and death from any cause, obtained and confirmed by medical record

Observational Studies

Five retrospective cohort studies[212, 222, 226, 232, 233] and one case-control study[209] reported on cardiovascular morbidity for metformin and sulfonylurea use (Table 34 and Table 35. All but one[222] study reported increased incident cardiovascular morbidity among sulfonylurea versus metformin users.[209, 212, 222, 226, 232, 233] This risk extended to populations without a history of cardiovascular disease at baseline.[212, 226] (SOE: Moderate; Metformin favored)

Table 34. Retrospective cohort studies comparing metformin with sulfonylureas on cardiovascular morbidity

Author, year	Population (N)	Followup	Outcome	Adjusted HR (95% CI)
Pantalone, 2009[222]	Cleveland Clinic EHR system (17863)	8 years	Incident ischemic heart disease by ICD-9 code	0.94 (0.85 to 1.05) Reference = sulfonylurea
Hung, 2013[232]	Taiwan National Health Insurance Research Database (N=925)	Median 3.1 to 3.8 years	Composite cardiovascular outcome based on ICD-9 codes	0.31 (0.24 to 0.4) Reference = sulfonylurea
Roumie, 2012[233]	Veterans Administration database linked to Medicare files (N= 253,690)	0.61 to 0.78 years	Hospitalization for acute MI, stroke, or death	1.21 (1.13 to 1.29)* Reference = metformin
			Acute MI and stroke	1.15 (1.06 to 1.25)* Reference = metformin
Schramm, 2011[212]	Danish Patient Register (N=107,806)	Median 3.3 years	Composite of MI, stroke and cardiovascular death based on ICD-10 codes	Prior MI 1.29 (1.09 to 1.52)† 1.46 (1.2 to 1.78)‡ 1.29 (1.12 to 1.49)§ No prior MI 1.12 (1.04 to 1.21)† 1.17 (1.07 to 1.28)‡ 1.21 (1.14 to 1.29)§ Reference = metformin
Corrao, 2011[226]	Health Service Databases Lombardy (N=70,437)	Mean 4.8 to 5.1 years	Composite of death from any cause or first hospitalization for MI, cerebrovascular disease, or coronary artery bypass graft based on ICD-9	1.15 (1.08 to 1.21) Reference = metformin

CI = confidence interval; EHR = electronic health record; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction
*33% to 39% data missing on hemoglobin A1c (covariate in model)
† glibenclamide
‡glipizide
§glimepiride

Table 35. Nested case-control study comparing metformin with sulfonylureas on hospitalization for incidence myocardial infarction

	Population Followup	Cases	Controls	Adjusted OR (95% CI)
Horsdal, 2011[209]	Danish National Patient Registry Median 6 months	First-time hospitalization for non-fatal MI (N=10,616)	Age- and gender-matched patients with diabetes and no history of MI (N=90,697)	0.86 (0.78 to 0.95) Reference = sulfonylurea

CI = confidence interval; MI = myocardial infarction; OR = odds ratio

Metformin Versus DPP-4 Inhibitors

Two RCTs compared metformin with DPP-4 inhibitor monotherapy and reported on cardiovascular morbidity. One small, 26-week RCT of low quality reported one nonfatal myocardial infarction in the alogliptin arm (1/112) and did not report on events in the metformin arms (n=109 and 111 for the 1000-mg and 2000-mg arms, respectively). This study noted that it evaluated nonfatal stroke but did not report these outcomes.[76] This study did not use an intention-to-treat approach for cardiovascular morbidity and had greater than 17% losses to followup in

both arms.[76] A second larger and longer (76 weeks) RCT of higher quality reported that 2.1% of participants in the metformin arm (n=328) experienced an acute cardiovascular adverse event (otherwise unspecified) and did not report on this outcome in the saxagliptin arm (n=335).[79]

A single retrospective cohort study from the Danish National Patient Registry (N=84,756) reported a non-significant increase in cardiovascular risk (composite outcome: all-cause mortality, acute myocardial infarction, and stroke) for sitagliptin versus metformin over mean followup of 0.9 to 1.8 years (adjusted RR, 1.22; 95% CI, 0.92 to 1.61).[211] (SOE: Insufficient; Unable to determine effect)

Metformin Versus SGLT-2 Inhibitors

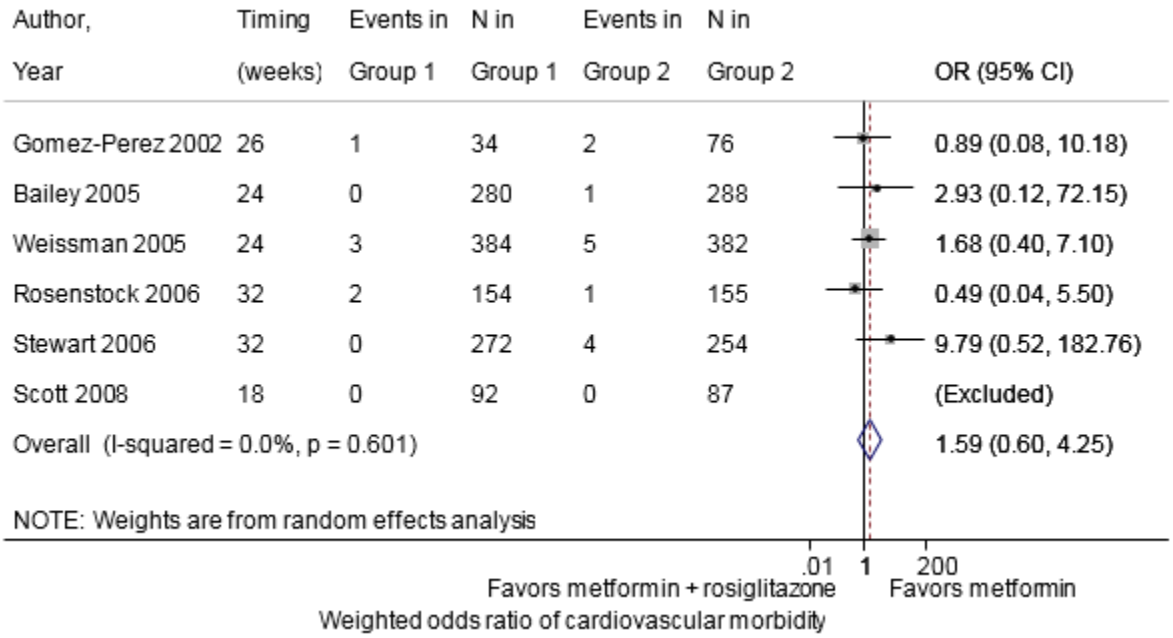
A single 12-week RCT reported one episode of Prinzmetal angina in the metformin arm (1/80) and did not report on events in the empagliflozin 10–mg (n=81) or empagliflozin 25–mg (n=82) arms.[227] This study did not use an intention-to-treat approach and did not report on withdrawals.[227] (SOE: Insufficient; Unable to determine effect)

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Six short-term (18 to 32 weeks) RCTs found a non-significant increase in cardiovascular morbidity for metformin plus rosiglitazone versus metformin (pooled OR, 1.59; 95% CI, 0.60 to 4.25) (Figure 53).[52, 87-90, 234] The removal of any one study did not change the inference of the meta-analysis.

Another longer RCT (80 weeks of followup) reported four ischemic events (4/344, 1.7%) and five cerebrovascular events (5/344) in the metformin plus rosiglitazone arm compared with four ischemic events (4/334, 1.2%) and three cerebrovascular events (3/334) in the metformin arm.[96] Of note, the text of article contradicts results in table (reported here); text reports five ischemic events in the metformin arm.[96] (SOE: Low; Metformin favored over combination of metformin plus rosiglitazone)

Figure 53. Pooled odds ratio of cardiovascular morbidity comparing metformin with a combination of metformin plus rosiglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus rosiglitazone; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

A single 26-week RCT compared metformin to metformin plus pioglitazone (dosed at 15, 30, and 45 mg in separate arms) and reported one nonfatal stroke in the metformin arm (1/129) and did not report on this outcome for the metformin plus pioglitazone arms (n=388).[95] (SOE: Insufficient; Unable to determine effect for combination of metformin plus pioglitazone)

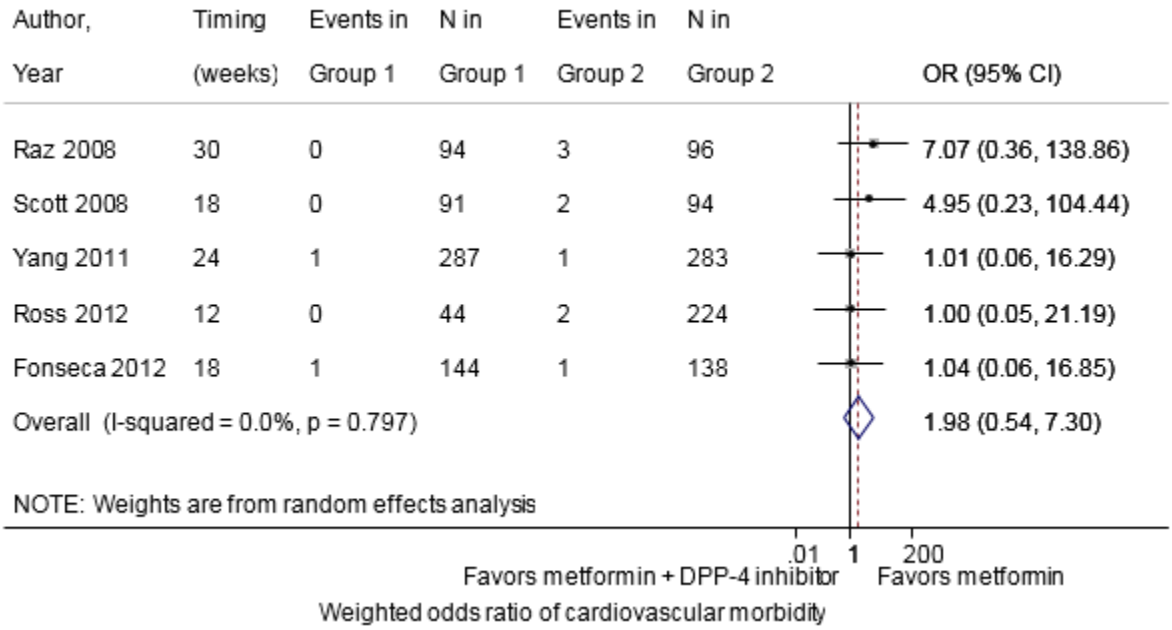
Metformin Versus a Combination of Metformin Plus a Sulfonylurea

One 6-month RCT,[103] which was a good although older study, reported rates of 5% and 14% for unspecified cardiovascular events in the metformin versus combination metformin plus sulfonylurea arm, respectively.[103] (SOE: Low; Metformin favored)

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

Five short RCTs compared the combination of metformin plus a DPP-4 inhibitor with metformin monotherapy and found no significant difference in cardiovascular morbidity based on 11 events across studies (pooled OR, 1.98; 95% CI, 0.54 to 7.30) (Figure 54).[87, 111, 115, 116, 121] We did not find statistical evidence of heterogeneity, and removal of any one study did not change the inference of this meta-analysis.

Figure 54. Pooled odds ratio of cardiovascular morbidity comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4;Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include one RCT (N=651) in the meta-analysis because of its longer duration (76 weeks). The investigators reported a rate of 2.1% for acute cardiovascular adverse events in the metformin arm, 0.3% in the metformin plus saxagliptin 5-mg arm, and did not report this rate in the metformin plus saxagliptin 10-mg arm.[79]

We did not include three additional RCTs in the meta-analysis because of a lack of reporting of events in at least one arm precluding estimation of an OR (Table 36). Cardiovascular morbidity did not appear to differ by arm based on the limited results reported.[76, 120, 131]

Table 36. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on cardiovascular morbidity

Author, year	Followup (weeks)	Outcome	Number of events / N (%) for metformin vs. metformin + DPP-4 inhibitor
Raz, 2008[111]	30	Acute MI	Results presented in Figure 54
Yang, 2011[115]	24	Acute myocardial ischemia or MI	Results presented in Figure 54
Scott, 2008[87]	18	Acute CV event	Results presented in Figure 54
Fonseca, 2012[116]	18	Acute CV events (myocardial ischemia or MI	Results presented in Figure 54
Ross, 2012[121]	12	Acute MI	Results presented in Figure 54
Pfutzner, 2011[79]	76	Acute CV events	NR/328 (2.1) Metformin + saxagliptin 5 mg: NR/320 (0.3) Metformin + saxagliptin 10 mg: NR/323 (NR)
Haak, 2013[131]	52	Nonfatal MI	1/170 (0.6) Metformin 2000 mg + linagliptin: NR /171 Metformin 1000 mg + linagliptin: 3/225 (1.3)
		Unstable angina	NR/170 (0.6) Metformin 2000 mg + linagliptin: 2/171 (1.2) Metformin 1000 mg + linagliptin: 2/225 (0.9)
White, 2014[120]	12	Nonfatal MI	NR/86 1/74 (1.4)
Pratley*, 2014[76]	26	Nonfatal MI	Metformin 2000 mg: NR/111 Metformin 1000 mg: NR/109 Metformin 2000 mg + alogliptin: NR/114 Metformin 1000 mg + alogliptin: NR/106

CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; mg = milligrams; MI = myocardial infarction; NR = not reported
* included in table even though did not report on outcome for any of the arms because study did provide results for alogliptin monotherapy arm implying that there were likely no nonfatal myocardial infarctions in the other arms

Three RCTs comparing metformin with metformin plus a DPP-4 inhibitor reported on nonfatal stroke but did not report on events in all arms (Table 37).[76, 95, 131] Nonfatal strokes were uncommon and did not appear to vary by arm based on limited reporting of results on this outcome. (SOE: Low; Neither treatment favored)

Table 37. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on nonfatal stroke

Autor, year	Followup (weeks)	Number of events / N (%) for metformin vs. metformin + DPP-4 inhibitor
Haak, 2013[131]	52	1/170 (0.6) Metformin 2000 mg + linagliptin: NR/171 Metformin 1000 mg + linagliptin: 1/225 (0.4)
DeFronzo, 2012[95]	26	1/129 (0.8) Metformin + alogliptin 12.5 mg: NR/128 Metformin + alogliptin 25 mg: NR/129
Pratley, 2014[76]	26	Metformin 2000 mg: NR/111 Metformin 1000 mg: NR/109 Metformin 2000 mg + alogliptin: NR/114 Metformin 1000 mg + alogliptin: NR/106

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; NR = not reported

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

A single 24-week RCT (N=182) compared the effects of metformin with metformin plus dapagliflozin on cardiovascular morbidity without prespecifying this as an adverse event. This study reported that two participants (2/91, 2.2%) developed angina pectoris in the metformin plus dapagliflozin arm and that there were no events in the metformin arm.[134] The investigators

also reported one transient ischemic attack in the metformin plus dapagliflozin arm (1/91) and did not report on this outcome in the metformin arm.[134] (SOE: Low; Metformin favored)

Thiazolidinediones Versus Sulfonylureas

Two RCTs[45, 200] and two retrospective cohort studies[230, 231] compared the effects of sulfonylureas and rosiglitazone on cardiovascular morbidity (Table 38). A single RCT[141] and two retrospective cohort studies compared the effects of sulfonylureas and pioglitazone on this outcome (Table 39).[222, 230] (SOE: Low; Sulfonylureas favored over rosiglitazone) (SOE: Low; Neither sulfonylureas nor pioglitazone favored)

Table 38. Studies comparing rosiglitazone with sulfonylureas on cardiovascular morbidity

Author, year Study design	Population (N)	Followup	Outcome	Results
Kahn, 2006[45] RCT	ADOPT Study (4360)	4.1 years (median)	Nonfatal MI Stroke	Rosiglitazone: 1.7%; SU: 1.0% Rosiglitazone: 1.3%; SU: 1.2%
St John Sutton, 2002[200] RCT	N=351	52 weeks	Cardiac-related adverse events	Rosiglitazone: 15.4%; SU: 12.1%
Pantalone, 2009[222] Retrospective cohort	Cleveland Clinic electronic health record system (8506)	8 years	Incident ischemic heart disease by ICD-9 code	Adjusted HR 0.90; 95% CI, 0.71 to 1.14 Reference = SU
Hsiao, 2009[230] Retrospective cohort	Taiwan National Health Insurance – newly-diagnosed diabetes (99744)	6 years	MI Stroke Transient ischemic attack Angina pectoris	Adjusted HR 1.49; 95% CI, 0.99 to 2.24 Adjusted HR 1.45; 95% CI, 0.69 to 3.05 Adjusted HR 1.90; 95% CI,1.02 to 3.57 Adjusted HR 1.46; 95% CI, 1.15 to 1.85 Reference = SU
Brownstein, 2010[231] Retrospective cohort	Research Patient Data Registry (34,252)	7 years	Hospitalization for MI	Adjusted RR, 1.3; 95% CI, 1.0 to 1.6 Reference = SU

ADOPT = A Diabetes Outcome Progression Trial; CI = confidence interval; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction; RCT = randomized controlled trial; SU = sulfonylurea; RR = rate ratio

Table 39. Studies comparing pioglitazone with sulfonylureas on cardiovascular morbidity

Author, year Study design	Population (N)	Followup	Outcome	Results
Jain, 2006[141] RCT	N=502	56 weeks	CHD, MI and chest pain	Pioglitazone: 1%; glyburide: 3%
Pantalone, 2009[222] Retrospective cohort	Cleveland Clinic electronic health record system (8935)	8 years	Incident ischemic heart disease by ICD-9 code	Adjusted HR 1.04; 95% CI, 0.86 to 1.26 Reference = SU
Hsiao, 2009[230] Retrospective cohort	Taiwan National Health Insurance – newly-diagnosed diabetes (98146)	6 years	MI Stroke Transient ischemic attack Angina pectoris	Adjusted HR 0.72; 95% CI, 0.19 to 2.77 Adjusted HR 0.59; 95% CI, 0.06 to 6.03 Adjusted HR 1.28; 95% CI, 0.34 to 4.86 Adjusted HR 0.91; 95% CI, 0.47 to 1.74 Reference=SU

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction; RCT = randomized controlled trial; SU = sulfonylurea

Sulfonylureas Versus DPP-4 Inhibitors

Two RCTs (52 to 58 weeks duration) compared the effects of sulfonylureas with DPP-4 inhibitors on cardiovascular morbidity and found mixed results.[151, 152] One study reported one nonfatal myocardial infarction in one participant in the sulfonylurea arm (1/76, 1.3%) and no events in the linagliptin arm (0/151, 0.0%).[151] The other study reported 11 vascular events in the sulfonylurea arm (11/212, 5.2%) and eight events in the sitagliptin arm (8/210, 3.8%).[152] The dose of glimepiride was low in one study (4 mg),[151] and the dose of sitagliptin was low in the other study.[152] The study by Arjona Ferreira et al did not use an intention-to-treat approach and had greater than 20% losses to followup across arms.[152] (SOE: Low; DPP-4 inhibitors favored)

Sulfonylureas Versus GLP-1 Agonists

Two RCTs compared the effects of sulfonylurea with liraglutide on cardiovascular morbidity and reported slightly higher rates of cardiovascular events in the sulfonylurea arms compared with the liraglutide arms. In one study (104 weeks), 14 of 248 (6%) participants experienced a cardiac disorder in the sulfonylurea arm, and eight of 251 (3%) and 11 of 246 (5%) experienced a cardiac disorder in the liraglutide 1.2-mg and 1.8-mg arms, respectively.[158] One participant had a nonfatal myocardial infarction thought to be related to the study drug in each of the sulfonylurea and liraglutide 1.2-mg and 1.8-mg arms.[158] The other RCT (N=200) was 52 weeks and reported higher rates of vascular (7.6% versus 6.3%) and cardiac (10.6% versus 6.3%) disorders in the sulfonylurea arm compared with the liraglutide arm.[155] Of note, Kaku 2012, et al, used low doses of glibenclamide (1.25 to 2.5 mg/day) and liraglutide (0.9 mg/day).[155] (SOE: Low; GLP-1 agonists favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two RCTs compared metformin plus pioglitazone to metformin plus a sulfonylurea and reported mixed results on cardiovascular morbidity.[168, 170] One trial (N=288) with submaximally-dosed pioglitazone (30 mg/day) reported three events (coronary heart disease, carotid artery stenosis, and peripheral artery disease) at 24 weeks in the metformin plus sulfonylurea arm and did not report on events in the metformin plus pioglitazone arm.[170] The other RCT (N=250) reported one acute myocardial infarction at 24 weeks in the metformin plus pioglitazone arm versus no events on the metformin plus sulfonylurea arm.[168] (SOE: Insufficient; Unable to determine effect)

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

Two RCTs compared metformin plus pioglitazone to metformin plus a DPP-4 inhibitor at 26 weeks and reported on cerebrovascular events.[95, 173] One reported a cerebrovascular accident in each arm,[173] and the other did not report on cerebrovascular events in the combination therapy arms (reported events for monotherapy as discussed above).[95] Bergenstal 2010 et al, also reported three cardiovascular events (unstable angina, n=1; coronary artery occlusion, n=2) in the metformin plus pioglitazone group and no events in the metformin plus sitagliptin group.[173] This RCT did not use an intention-to-treat approach and had differential and large losses to followup (13% in metformin plus DPP-4 inhibitor arm and 21% in metformin plus pioglitazone arm).[173] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored over metformin plus pioglitazone)

Two RCTs compared metformin plus rosiglitazone with metformin plus sitagliptin (duration 16 to 18 weeks) and reported on cardiovascular and cerebrovascular morbidity.[87, 171] The trial evaluating cardiovascular events reported none in the metformin plus rosiglitazone arm (0/87) and two coronary artery disease events in the metformin plus sitagliptin arm (2/94).[87] The other trial (N=169) reported a transient ischemic attack in each arm.[171] (SOE: Insufficient; Unable to determine effect for the combination of metformin plus rosiglitazone)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

One RCT (N=325) compared metformin plus pioglitazone to metformin plus exenatide at 26 weeks and reported one cerebrovascular accident and three cardiac events (unstable angina and coronary artery occlusions) in the metformin plus pioglitazone arms and no events in the metformin plus exenatide arm.[173] (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

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

Of three 104-week RCTs comparing metformin plus sulfonylurea to metformin plus a DPP-4 inhibitor, one reported an increased risk of a composite cardiovascular outcome for metformin

plus sulfonylurea versus metformin plus DPP-4 inhibitor, and the others suggested no difference in cardiovascular morbidity (Table 40).[177-180]

One of these RCTs reported higher cerebrovascular event rates for metformin plus sulfonylurea compared with metformin plus DPP-4 inhibitors while the other RCT reporting on this outcome only reported a single event (Table 41).[178, 179]

Of note, sulfonylurea doses were submaximal in these RCTs. (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Table 40. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea to a combination of metformin plus a DPP-4 inhibitor on cardiovascular morbidity

Author, year	Followup	Outcome	Number of events / N (%) for metformin + sulfonylurea vs. metformin + DPP-4 inhibitor
Nauck, 2007[177, 180]	104 weeks N=1172	MI	1/588 (0.2) vs. 0/584 (0)
Gallwitz, 2012[178]	104 weeks	Nonfatal MI	10/775 vs. 6/776 Unadjusted RR, 0.6; 95% CI, 0.22 to 1.64 Reference = metformin + sulfonylurea
		Composite: CV death, MI, stroke, or admission to hospital due to unstable angina	26/775 vs. 12/776 Unadjusted RR, 0.46; 95% CI, 0.23 to 0.91 Reference = metformin + sulfonylurea
		Admission to hospital due to unstable angina	3/775 vs. 3/776 Unadjusted RR, 1.0; 95% CI, 0.2 to 4.93 Reference = metformin + sulfonylurea
Goke, 2010[179]	104 weeks	Not defined	Qualitative statement: "The incidences of CV AEs…were low and similar between treatment groups."

AE = adverse event; CI = confidence interval; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; MI = myocardial infarction; RR = risk ratio

Table 41. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea to a combination of metformin plus a DPP-4 inhibitor on cerebrovascular morbidity

Author, year	Followup	Outcome	Number of events / N (%) for metformin + sulfonylurea vs. metformin + DPP-4 inhibitor
Gallwitz, 2012[178]	104 weeks	Cerebral infarction	4/775 vs. 0/776 (0)
		Nonfatal stroke*	11/775 vs. 3/776 Unadjusted RR, 0.27; 95% CI, 0.08 to 0.97 Reference = metformin + sulfonylurea
Goke, 2010[179, 235]	104 weeks	Transient ischemic attack	1/430 vs. NR/428

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; NR = not reported; RR = risk ratio
*This outcome appears to include stroke and transient ischemic attacks

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Two short-term (26-week) RCTs (N=991) suggested no difference in cardiovascular morbidity for this comparison.[173, 192] One reported no cardiovascular events in either arm (defined as unstable angina or coronary artery occlusion), and the other reported "cardiac disorders" in one participant in the metformin plus sitagliptin and the metformin plus liraglutide 1.8-mg arm.[173, 192]

One of these trials reported on cerebrovascular accidents and reported one event in the metformin plus sitagliptin arm and no events in the metformin plus exenatide arm.[173] (SOE: Low; Neither favored)

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

A single RCT (N=501) reported that five participants experienced cardiovascular events (carotid artery occlusion, angina pectoris, and unstable angina) in the metformin plus insulin glargine arm and two participants experienced cardiovascular events (nonfatal acute myocardial infarction and angina pectoris) in the metformin plus sitagliptin arm at 25 weeks.[193] Of note, events had to be considered "serious" to be reported.[193] This study did not use an intention-to-treat analysis and had moderate, differential losses to followup across arms (5% for sitagliptin and 9% for insulin glargine).[193] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Combination of Metformin Plus a GLP1-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

A single, small (N=69) RCT compared metformin plus exenatide (mean 0.6 mg daily) with metformin plus insulin glargine (mean 33.7 units daily) and reported that one participant in the metformin plus insulin arm experienced a cerebrovascular incident at 168 weeks of followup; events were not reported for the metformin plus exenatide arm.[47] (SOE: Insufficient; Unable to determine effect)

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

In a 16-week cross-over study, 105 participants with newly-diagnosed type 2 diabetes were randomly assigned to metformin plus insulin glargine versus metformin plus insulin lispro 75/25 twice daily.[206] During an 8-week lead-in period, participants received neutral protamine Hagedorn (NPH) insulin at night, and the metformin dose was titrated. One participant experienced a myocardial infarction during the lead-in period, one participant experienced chest pain during treatment with premixed insulin; the investigators did not report if this event occurred before or after the crossover.[206] (SOE: Insufficient; Unable to determine effect)

Strength of Evidence for Cardiovascular and Cerebrovascular Morbidity

We did not find any high strength of evidence for cardiovascular and cerebrovascular morbidity. Most evidence was low or insufficient because of a paucity of studies reporting on these outcomes (see Key Points, Table 42, and Table 43). Notably, none of the RCTs were designed to evaluate cardiovascular outcomes, and they tended to be short in duration (less than 12 months), and event rates were low. We identified a mixture of RCT and observational study evidence for these outcomes for the monotherapy comparisons, but only RCTs for combination comparisons. Most of the evidence was at medium or high risk of bias; common study limitations included lack of reporting on randomization and masking procedures and lack of an intention-to-treat approach combined with substantial losses to followup. The consistency of this evidence was limited by the small number of studies and differences in definitions. While observational studies offer the opportunity for precision given their larger sizes in some cases,

most evidence was still imprecise since we did not identify that many high-quality observational studies. Notably, observational studies did not tend to corroborate RCT findings.

We did suspect publication bias for a few comparisons. For metformin versus DPP-4 inhibitor monotherapy, two published RCTs did not provide sufficient evidence for a conclusion; the unpublished study was too short to add much to the strength of evidence and contradicted the published RCTs. We identified three published and one unpublished RCT comparing the combination of metformin plus a sulfonylurea to metformin plus a DPP-4 inhibitor; the published evidence was inconsistent but suggested that the DPP-4 inhibitor-based therapy was favored. However, the unpublished study was moderate in size and had opposite findings emphasizing the low strength of this evidence. Finally, we identified one published and one unpublished study of metformin plus a basal insulin versus metformin plus a premixed insulin. The published study did not report on events in both arms whereas the unpublished study suggested an increased risk of cardiovascular morbidity (consistent with the reporting of an event in the metformin plus premixed arm in the published RCT). Therefore, the unpublished study could have led to a higher grade for the strength of this evidence which might have supported a conclusion about this comparison.

Table 42. Strength of evidence domains for monotherapy comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. rosiglitazone	RCTs: 2 (4828)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
	Observational: 3 (94,304)	Medium	Inconsistent	Direct	Precise	N/A		
Metformin vs. pioglitazone	RCTs: 3 (158)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Neither treatment favored
	Observational: 3 (65,152)	Medium	Consistent	Direct	Precise	N/A		
Metformin vs. SU	RCT: 3 (4808)	Low	Inconsistent	Direct	Imprecise	Undetected	Moderate	Metformin favored
	Observational: 6 (545,686)	Medium	Consistent	Direct	Precise	N/A		
Metformin vs. DPP-4 inhibitors	RCT: 2 (2,090)	Medium	Inconsistent	Direct	Imprecise	Suspected	Insufficient	Unable to determine
	Observational: 1 (84,756)	Medium	Unknown	Direct	Precise	N/A		
Metformin vs. SGLT-2 inhibitors	RCT: 1 (408)	High	Unknown	Direct	Imprecise	N/A	Insufficient	Unable to determine
Metformin vs. metformin + rosiglitazone	RCTs: 7 (3136)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin vs. metformin + pioglitazone	RCTs: 1 (1,554)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + SU	RCT: 1 (110)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin vs. metformin + DPP-4 inhibitor	RCTs: 10 (4045)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored Inadequate reporting of events in all arms
Metformin vs. metformin + SGLT-2 inhibitor	RCT: 1 (182)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored
Rosiglitazone vs. SU	RCT: 2 (4711)	Medium	Consistent	Direct	Imprecise	Undetected	Low	SU favored
	Observational: 3 (142,502)	Medium	Inconsistent	Direct	Precise	N/A		
Pioglitazone vs. SU	RCT: 1 (502)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
	Observational: 2 (107,081)	Medium	Inconsistent	Direct	Precise	N/A		
SU vs. DPP-4 inhibitors	RCTs: 2 (653)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitor

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
								favored
SU vs. GLP-1 agonists	RCTs: 2 (1157)	High	Consistent	Direct	Imprecise	Undetected	Low	GLP-1 agonist favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 43. Strength of evidence domains for combination therapy comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin + SU	RCTs: 2 (538)	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor	RCTs: 2 (2068)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitor favored
Metformin + rosiglitazone vs. metformin + DPP-4 inhibitor	RCTs: 2 (350)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pioglitazone vs. metformin + GLP-1 agonist	RCT: 1 (325)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 agonist favored
Metformin + SU vs. metformin + DPP-4 inhibitor	RCTs: 3 (2410)	Low	Inconsistent	Direct	Imprecise	Suspected	Low	Metformin + DPP-4 inhibitor favored
Metformin + DPP-4 inhibitor vs. metformin + GLP-1 agonist	RCTs: 2 (1179)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + DPP-4 inhibitor vs. metformin + basal insulin	RCTs: 1 (501)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitor favored
Metformin + GLP-1 agonist vs. metformin + basal insulin	RCTs: 1 (69)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Did not report on events in both arms
Metformin + basal insulin vs. metformin + premixed insulin	RCTs: 1 (105)	Medium	Unknown	Direct	Imprecise	Suspected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Retinopathy

Monotherapy Comparisons

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

Two RCTs (N=437) compared low-dose metformin with low-dose metformin plus a DPP-4 inhibitor at 12 weeks and reported on retinopathy.[118, 126] Each trial reported one case of retinopathy in the metformin monotherapy arm. One of the RCTs reported one case of retinopathy in the metformin plus DPP-4 inhibitor arm (alogliptin 12.5 mg) and no cases in in the metformin plus alogliptin 25 mg arm.[126] The other RCT reported no cases in the metformin plus sitagliptin arm.[118] (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Agonists

A single RCT (N=400) compared rates of retinopathy at 52 weeks in participants randomized to submaximally dosed glibenclamide or submaximally dosed liraglutide. Nine (9/132, 6.8%) and 16 (16/268, 6%) participants were diagnosed with retinopathy as a "treatment-emergent adverse event" during this study in the sulfonylurea and GLP-1 agonist arms, respectively.[155] The study did not report on baseline rates of retinopathy.[155] Losses to follow up were greater than 15% in each arm, and the investigators did not use an intention-to-treat approach for this analysis.[155] (SOE: Low; Neither favored)

Strength of Evidence for Retinopathy

We identified three RCTs (and no observational studies) evaluating retinopathy, and one study was of poor quality.[155] Therefore, evidence is mainly insufficient for this outcome (see Key Points and Table 44).

Table 44. Strength of evidence domains for monotherapy comparisons in terms of retinopathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. metformin + DPP-4 inhibitors	RCTs: 2 (N=437)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored
SU vs. GLP-1 agonists	RCT: 1 (411)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of evidence.

The Evidence About Nephropathy

We included the following nephropathy outcomes: categorical definitions of new or progressive nephropathy, changes in urine albumin, and changes in estimated glomerular filtration rate.

Studies of comparisons including an SGLT-2 inhibitor are described in the section on renal insufficiency in this report (see Key Question 3 – renal insufficiency).

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

One RCT and two retrospective cohort studies evaluated this outcome and found mixed results.[55, 236, 237]The 12-month RCT (N=1,194) reported a significant decrease in the urine albumin-to-creatinine ratio for participants randomized to the pioglitazone arm compared with the metformin arm (19% versus 1% reduction; $P = 0.002$).[55]

The smaller retrospective cohort study of 1,271 patients in the US (Baylor Health Care System, Dallas, TX and Christiana Care Health System, Newark, DE) evaluated nephropathy defined as new albuminuria or new estimated glomerular filtration rate (eGFR) rate below 60 mL/min/1.73 $m^2$and found no significant difference between metformin users and thiazolidinedione users for either outcome (adjusted HR, 1.00 and 1.04 for thiazolidinedione versus metformin) with median followup of 2.8 to 3.2 years.[237]

The large, although short, retrospective cohort study from the Veterans Health Administration (N=93,577) with median follow up of 0.7 to 0.9 years also found no significant difference in nephropathy for thiazolidinedione versus metformin users. The adjusted HR for the composite outcome of a GFR event (persistent decline of 25% or greater from baseline eGFR) or end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2or first inpatient or outpatient code for dialysis or related procedures or renal transplant) was 0.92 (95% CI, 0.71 to 1.18).[236] (SOE: Insufficient; Unable to determine)

Metformin Versus Sulfonylureas

One small (N=51) 3-month RCT reported that microalbuminuria decreased significantly with metformin ($P = 0.008$) and increased non-significantly with glibenclamide ($P = 0.09$). GFR was stable in the metformin arm ($P = 0.46$) and increased in the sulfonylurea arm ($P = 0.04$).[238] The study did not provide statistical comparisons between groups.

Three retrospective cohort studies in the US suggested a decreased risk of nephropathy among metformin versus sulfonylurea users (Table 45).[236, 237, 239] Two of the studies were from the Veterans Health Administration, and it is not clear if the study populations overlapped.[236, 239] (SOE: Low; Metformin favored)

Table 45. Retrospective cohort studies comparing metformin with sulfonylureas on nephropathy

Author, year	Population	Followup	Outcome Definition	HR (95% CI)
Hung, 2013[239]	Veterans Health Administration VA Mid-South VISN 9 Data Warehouse (N=13,238) Incident medication users	Approximately 1 year	Composite of GFR event or ESRD*	All: 0.85 (0.72 to 1.01) Urine protein measures at baseline: 0.78 (0.64 to 0.97) Reference = sulfonylurea
Hung, 2012[236]	Veterans Health Administration N=93,577 Did not appear to exclude incident users	0.7 to 0.9 years (median)	Composite of GFR event or ESRD*	1.2 (1.13 to 1.28) Reference = metformin
Masica, 2013[237]	1,271 participants from an electronic health record database in the US (Baylor Health Care System, Dallas, TX) and Christiana Care Health System, Newark, DE)	Median follow up of 2.8 to 3.2 years	Microalbuminuria or worse	Urine protein measures available: 1.27 (0.93 to 1.74) Reference = metformin
			eGFR ≥60 ml/min/1.73m^2 at first measurement and an eGFR <60 ml/min/1.73m^2 during follow-up	eGFR available: 1.41 (1.05 to 1.91) Reference = metformin

CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; ml/min/1.73m^2 = milliliters per minute per 1.73 meters squared; VA = Veterans Affairs; VISN = Veterans Integrated Service Network

* GFR event= persistent 25% or greater decline from the baseline eGFR; ESRD: eGFR <15 mL/minute/1.73m2 or first code for dialysis or related procedure or renal transplant

Thiazolidinediones Versus Sulfonylureas

Five small RCTs provided mixed results on the effect of thiazolidinediones and sulfonylureas on nephropathy outcomes, and all studies reported on albuminuria as the outcome.[44, 142-144, 148] Four trials found less albuminuria in patients receiving pioglitazone compared with a sulfonylurea;[44, 142, 143, 148] only one reported a significant difference.[142]

One trial compared rosiglitazone and glyburide at 12 months and found no statistically significant difference in the urinary albumin-to-creatinine ratio, and progression to microalbuminuria did not differ between groups.[144]

A retrospective cohort study using a small US database reported a non-significant increased risk of nephropathy (incident albuminuria) among sulfonylurea versus thiazolidinedione users who had a measure of urine protein (adjusted HR, 1.27; 95% CI, 0.93 to 1.74).[237] (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus DPP-4 Inhibitors

A single RCT analyzed changes in eGFR and urine albumin-to-creatinine ratio from baseline among 277 participants randomized to glipizide or sitagliptin and reported small, similar changes from baseline over 54 weeks. The eGFR decreased slightly in both arms (-3.3 to -3.9 ml/min/1.73m^2 for glipizide and sitagliptin, respectively) and urine albumin-to-creatinine ratio increased slightly in both arms (0.1 and 0.06 for glipizide and sitagliptin, respectively).[152] Of

note, approximately 20% of participants were lost to followup in each arm (423 participants originally randomized), and the investigators did not conduct an intention-to-treat analysis, thereby limiting conclusions.[152] (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Agonists

A single RCT (N=745) reported similar cumulative incidences of 6%, 5% and 5% of "renal and urinary disorders" at 104 weeks in those randomized to glimepiride 8 mg, liraglutide 1.2 mg, and liraglutide 1.8 mg.[158] (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two RCTs compared metformin plus rosiglitazone with metformin plus a sulfonylurea. Evaluation of the urine albumin-to-creatinine ratio favored the combination of metformin plus rosiglitazone.[162, 167] One small RCT (N=34) with 48 weeks of followup reported a negligible decrease in urine albumin-to-creatinine ratio in the metformin plus thiazolidinedione arm (-0.77 mg/g) and a small increase (12.23 mg/g) in the metformin plus sulfonylurea arm.[167] The larger trial (N=389) reported a greater, although non-significant, reduction in the urine albumin-to-creatinine ratio with the combination of metformin plus a thiazolidinedione versus metformin plus a sulfonylurea arm at 32 weeks.[162]

The smaller RCT also reported a negligible decrease in eGFR in the metformin plus thiazolidinedione arm (-1.48 ml/min/1.73m^2) and an increase in eGFR in the metformin plus sulfonylurea group (9.97 ml/min/1.73m^2); the study did not provide a statistical comparison of the between-group difference.[167] This very small trial reported more than 20% losses to followup across arms and did not use an intention-to-treat analysis for nephropathy.[167] (SOE: Low; Combination of metformin plus a thiazolidinedione favored)

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

A single RCT (N=514) with 26 weeks of followup reported on percent change in urine albumin-to-creatinine ratio for the combination of metformin plus pioglitazone and the combination of metformin plus sitagliptin and found similar changes from baseline in both arms: -4% (95% CI, -17% to 12.1%) for metformin plus pioglitazone and -6.9% (95% CI, -20 to unclear but greater than 0) for metformin plus sitagliptin.[173] This study had 13% and 21% losses to followup in the sitagliptin- and pioglitazone-based arms, respectively, and did not use an intention-to-treat analysis for this outcome.[173] (SOE: Low; Neither treatment favored)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

A single RCT (N=514) with 26 weeks of followup reported on percent change in urine albumin-to-creatinine ratio for the combination of metformin plus pioglitazone and the combination of metformin plus exenatide and found a reduction in urine albumin-to-creatinine from baseline for the metformin plus exenatide arm and no change for the metformin plus pioglitazone arm: -4% (95% CI, -17% to 12%) for metformin plus pioglitazone and -16% (95% CI, -28% to -2%) for metformin plus exenatide.[173] This study had approximately 20% losses to

followup both arms and did not use an intention-to-treat analysis for this outcome.[173] (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

A small RCT conducted in 42 participants with baseline microalbuminuria compared change in 24-hour urine albumin over 16 weeks for metformin plus sub-maximally dosed glimepiride and metformin plus exenatide and reported a significant reduction in urine albumin in the metformin plus exenatide arm (-42 mg/day; *P* for change for baseline <0.01) compared to the metformin plus glimepiride arm (5 mg/day; *P* for change from baseline >0.05; calculated between group difference, -37 mg/day; *P* for between-group difference <0.001).[184] This small study had more than 20% losses to followup across arms and did not use an intention-to-treat analysis.[184] (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

A single RCT (N=514) with 26 weeks of followup reported on percent change in urine albumin-to-creatinine ratio for the combination of metformin plus sitagliptin and the combination of metformin plus exenatide. The trial found a reduction in urine albumin-to-creatinine from baseline for the metformin plus exenatide arm (-16%; 95% CI, -28 to -2%) but not for the metformin plus sitagliptin arm (-6.9%; 95% CI, -20 to unclear but greater than 0).[173] This study had approximately 20% losses to followup in both arms and did not use an intention-to-treat analysis for this outcome.[173] (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

Strength of Evidence for Nephropathy

We found low or insufficient strength of evidence on nephropathy outcomes for all comparisons of interest as described in the Key Points, and Table 46 and Table 47.

The evidence on nephropathy was limited by the lack of studies. For RCTs, major study limitations included small sample sizes and high rates of withdrawals (>20%), without use of an intention-to-treat approach. We could usually not determine consistency because of a lack of studies, and the evidence on all comparisons was imprecise due to insufficient sample size. We did not detect reporting bias. However, the small number of studies limited our ability to assess publication bias. Many of the studies did not provide measures of dispersion for nephropathy outcomes, but we did not believe that this was actually a source of selective analysis reporting bias as much as a reflection of a lack of a focus on reporting of these outcomes given that they were not primary outcomes.

Table 46. Strength of evidence domains for monotherapy comparisons in terms of nephropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD	RCT: 1 (1194) Observational: 2 (94,848)	Low Medium	Unknown Inconsistent	Direct Direct	Precise Imprecise	Undetected N/A	Insufficient	Unable to determine
Metformin vs. SU	RCT: 1 (51) Observational: 3 (108,356)	High Medium	Unknown Consistent	Indirect Direct	Imprecise Precise	Undetected N/A	Low	Metformin favored
TZD vs. SU	RCTs: 5 (375) Observational: 2 (1271)	High Medium	Consistent Unknown	Direct Direct	Imprecise Imprecise	Undetected N/A	Low	TZD favored
SU vs. DPP-4 inhibitors	RCT: 1 (423)	High	Unknown	Indirect	Imprecise	Undetected	Low	Neither treatment favored
SU vs. GLP-1 agonists	RCT: 1 (746)	Medium	Unknown	Indirect	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; N/A = not applicable; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Studies of comparisons including an SGLT-2 inhibitor are graded in the section on renal insufficiency in this report.

Table 47. Strength of evidence domains for metformin-based combination comparisons in terms of nephropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin + SU	RCT: 2 (433)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + TZD vs. metformin + GLP-1 agonist	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 favored
Metformin + SU vs. metformin + GLP-1 agonist	RCT: 1 (42)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 favored
Metformin + DPP-4 inhibitor vs. metformin + GLP-1 agonist	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Studies of comparisons including an SGLT-2 inhibitor are graded in the section on renal insufficiency in this report.

The Evidence About Neuropathy

For the neuropathy analyses, we included studies where newly developed neuropathy was reported for each treatment group. Four short trials reported on neuropathy as an adverse outcome.[90, 111, 123, 168]

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

A single RCT compared the effects of metformin with alogliptin on undefined neuropathy. At 26 weeks of followup, one participant developed unspecified neuropathy in each of the alogliptin arms [12.5 mg (n=213) and 25 mg (n=210) arms]); neuropathy was not reported on in the metformin arm.[123] (SOE: Insufficient; Unable to determine effect)

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

In a single RCT of 26 weeks duration, one withdrawal due to undefined neuropathy occurred in the metformin arm (n=34); no events were reported on in the two metformin plus rosiglitazone arms (n=35 and n=36).[90] (SOE: Insufficient; Unable to determine effect)

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

One RCT reported the occurrence of undefined diabetic neuropathy as 2.1% among participants in the metformin arm (n=94) and 4.2% in the metformin plus sitagliptin arm (n=96) at 30 weeks.[111] (SOE: Low; Metformin favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

In a 6-month trial, neuropathy was described but was not a pre-specified outcome.[168] One of 103 participants in the metformin plus thiazolidinedione arm developed neuropathy, and none of the 80 participants in the metformin plus sulfonylurea arm developed neuropathy.[168] (SOE: Low; Neither favored)

Strength of Evidence for Neuropathy

The evidence grading for neuropathy is summarized in Table 48 and Table 49.

Table 48. Strength of evidence domains for monotherapy comparisons in terms of neuropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. DPP-4 inhibitors	RCT: 1 (527)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Results not reported for all arms
Metformin vs. metformin + TZD	RCT: 1 (105)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Results not reported for all arms
Metformin vs. metformin + DPP-4 inhibitor	RCT: 1 (190)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 49. Strength of evidence domains for metformin-based combination comparisons in terms of neuropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin + SU	RCT: 1 (183)	High	Unknown	Indirect	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Key Question 3a and 3b: Safety

Study Design and Population Characteristics

We included 189 studies describing adverse effects for the comparisons of interest (Appendix D, Tables 10 to 13). We included 101 articles from our prior 2011 review[16] and identified an additional 88 studies for this update. Four of the newly included studies were updates of earlier studies.[77, 79, 158, 180] The majority were RCTs (85 from the previous report, 83 more for the update). Few studies were designed explicitly to evaluate adverse events; of the 22 studies designed to evaluate the adverse events specified in Key Question 3, most focused on cancer,[240-242] renal toxicity[236, 239] and general safety and tolerability.[243-246] Thirty-seven of 83 (45%) RCTs did not report on the use of rescue therapy; rescue therapy was allowed in 31 studies (37%) and was not allowed in 14 studies (18%).

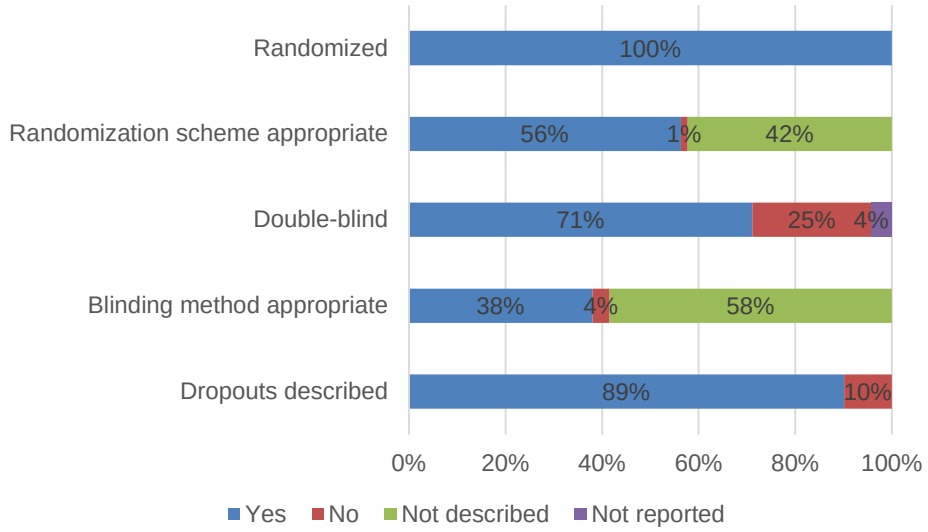
The mean age of participants ranged from approximately 40 years to 81 years, with the majority of studies reporting a mean age in the upper 50's. Participants were about 50% female. Sixty-nine studies did not report race or ethnicity. In the studies that reported race, the majority of the participants were Caucasians. No study included more than 25% African American participants; two studies included more than 70% Hispanic participants;[90, 171] and six studies included more than 70% Asian participants.[67, 84, 124, 154, 240 5251, 247]

Risk of Bias

We included 189 trials in this section**.** All of the trials were described as randomized (Figure 55). Fifty-six percent described their randomization scheme and another 71 percent were described as being double-blinded. Thirty-eight percent of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of trials (89 percent) described the withdrawals and dropouts.

Of the eight observational studies included in this section, 100 percent reported characteristics of subjects and tests of interest. All studies reported actual probability values and also described their measurement of the outcomes of interest. All studies described and adjusted for confounding factors and conducted statistical analyses. Eighty-six percent of studies described the number of participants who were lost to follow-up after the start of the period of observation.

Figure 55. Summary of the risk of bias of randomized controlled trials evaluating safety



Key Points and Evidence Grades

Hypoglycemia

Mild, Moderate, or Total Hypoglycemia

Unless otherwise noted, results on hypoglycemia refer to the number of participants experiencing hypoglycemia and not the number of events.

- Metformin monotherapy was favored over the following (SOE: High):
  - Sulfonylurea monotherapy for mild-moderate hypoglycemia (pooled OR for sulfonylurea versus metformin, 4.00; 95% CI, 1.75 to 9.83)
  - The combination of metformin plus a thiazolidinedione (pooled OR for metformin plus a thiazolidinedione versus metformin monotherapy, 1.56; 95% CI, 0.99 to 2.44)
  - The combination of metformin plus a sulfonylurea (pooled OR, 5.02; 95% CI, 2.36 to 15.0).
- The risks of mild-moderate and total hypoglycemia were similar for metformin monotherapy and the combination of metformin plus a DPP-4 inhibitor (SOE: High).
  - Pooled OR for metformin plus a DPP-4 inhibitor versus metformin monotherapy:
    - Mild-moderate hypoglycemia: 0.97; 95% CI, 0.63 to 1.51
    - Total hypoglycemia: 0.92; 95% CI, 0.43 to 1.97
- Hypoglycemia risk was higher for the combination of metformin plus an SGLT-2 inhibitor compared with metformin monotherapy (pooled OR, 1.62; 95% CI, 0.75 to 3.49). (SOE: Moderate)
- Sulfonylurea monotherapy increased risk of total hypoglycemia compared with thiazolidinedione monotherapy (pooled OR 6.31; 95% CI, 4.08 to 9.76). (SOE: High)
- SGLT-2 inhibitor monotherapy was associated with lower risk of hypoglycemia compared with metformin monotherapy (pooled OR, 0.46; 95% CI, 0.16 to 1.30). This did not reach statistical significance due to the low absolute event rate. (SOE: Moderate)

- DPP-4 inhibitor monotherapy was favored over sulfonylurea monotherapy (range of relative risks, 0.096 to 0.50 from individual studies for sulfonylurea versus DPP-4 inhibitor monotherapy). (SOE: Moderate)
- Mild-moderate hypoglycemia was approximately 2.5 times more common with sulfonylurea monotherapy than with GLP-1 agonist monotherapy. (SOE: Moderate)
- When compared with metformin plus a sulfonylurea, metformin plus an SGLT-2 inhibitor had 93% less risk of mild or moderate hypoglycemia. (SOE: High)
- When compared with metformin plus sulfonylurea, several combinations had 70% to 90% less risk of mild, moderate or total hypoglycemia: metformin plus a thiazolidinedione, metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 agonist. (SOE: High or Moderate for all comparisons)
- When compared with metformin plus basal insulin, metformin plus a GLP-1 agonist had between 35% and 88% less risk of mild or moderate hypoglycemia risk. (SOE: Moderate)
- Moderate grade evidence showed a 6% to 30% lower risk of hypoglycemia when metformin is combined with a basal insulin rather than a premixed insulin.

Severe Hypoglycemia

- Only the sulfonylurea comparisons convincingly demonstrated about a 1.5 times higher risk of severe hypoglycemia in the sulfonylurea arms compared with nonsulfonylurea medications: sulfonylurea versus metformin, sulfonylurea versus thiazolidinediones, metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitors, and metformin plus sulfonylurea versus metformin plus DPP-4 inhibitors. (SOE: Moderate or High)
- Only two comparisons had sufficient evidence to show no between-group differences in severe hypoglycemia: the combination of metformin plus thiazolidinediones versus metformin plus DPP-4 inhibitors and metformin monotherapy versus metformin plus a DPP-4 inhibitor. (SOE: Moderate)

Gastrointestinal Side Effects

- Gastrointestinal (GI)-related adverse events are more common with:
  - Metformin than with DPP-4 inhibitors (OR 2.6 and 2.7 for nausea and diarrhea favoring DPP-4 inhibitors). (SOE: High)
  - Metformin than thiazolidinediones (between 1.3 to 3.3 fold higher risk). (SOE: Moderate)
  - Metformin than sulfonylureas (between 1.8 to 2.4 fold higher risk). (SOE: Moderate)
- GI-related adverse events are equally common with:
  - Thiazolidinediones and sulfonylureas (SOE: High)
  - Metformin and GLP-1 agonists for diarrhea; however metformin is favored over GLP-1 agonists for nausea and vomiting which had 1.5 times increased odds with GLP-1 agonists (SOE: Moderate)
- GI-related adverse events are more common by about 2-fold with:
  - Metformin plus a GLP-1 agonist than metformin plus a DPP-4 inhibitor (SOE: Moderate)
  - Metformin plus a GLP-1 agonist than metformin plus a thiazolidinedione (SOE: Moderate)
- GI-related adverse events are equally common with:

- Metformin monotherapy and metformin plus a DPP-4 inhibitor (SOE: Low for any GI-related adverse event; Moderate for nausea; High for diarrhea)
- Metformin plus a sulfonylurea and metformin plus a DPP-4 inhibitor (SOE: High)
- Metformin monotherapy and combination therapy with metformin plus a SGLT-2 inhibitor (diarrhea) (SOE: Moderate)
- Metformin plus a thiazolidinedione and metformin plus a sulfonylurea (SOE: Moderate)

Cancer

- Type of cancer was not designated *a priori* in most of the studies reporting on cancer; thus the following conclusions apply to any cancer unless specified.
- Even though the FDA has issued warnings regarding increased bladder cancer risk with pioglitazone, we found low or insufficient strength of evidence on TZD-based comparisons and cancer outcomes.
- Despite FDA warnings of a possible increased risk of thyroid cancer with GLP-1 agonists, we found low or insufficient evidence on GLP-1 agonist-based comparisons and cancer outcomes.

Congestive Heart Failure

- Thiazolidinediones alone increase the risk of heart failure by 1.4 fold when compared with sulfonylureas or metformin. (SOE: Low)

Pancreatitis

- Rates of pancreatitis were similar between metformin and the combination of metformin plus a DPP-4 inhibitor. (SOE: Moderate)
- Despite FDA warnings regarding an increased risk of pancreatitis with GLP-1 agonists and DPP-4 inhibitors, we found low or insufficient evidence on the comparative safety of these drug classes for this outcome.

Urinary Tract Infections (For Comparisons That Include SGLT-2 Inhibitors)

- The rates of UTIs were similar between metformin and SGLT-2 inhibitors. (SOE: Moderate)
- The rates of UTIs were similar between metformin plus SGLT-2 inhibitors compared with metformin alone (SOE: High) or in combination with a sulfonylurea. (SOE: Moderate)

Genital Mycotic Infections (For Comparisons That Include SGLT-2 Inhibitors)

- The rates of genital mycotic infections were higher with SGLT-2 inhibitors compared with metformin alone (pooled OR, 4.1; 95% CI, 2.0 to 8.3) or the combination of metformin and DPP-4 inhibitors. (SOE: Moderate)
- The rates of genital mycotic infections were higher with metformin plus SGLT-2 inhibitors compared with metformin alone (pooled OR, 3.0; 95% CI, 1.22 to 7.2 for

females and pooled OR, 2.7; 95% CI, 0.8 to 9.0 for males) or in combination with sulfonylureas (pooled OR, 6.1; 95% CI, 4.0 to 9.2). (SOE: High)

Other Serious Adverse Events

- There was no moderate or high strength of evidence for the following adverse events: Liver Injury, Lactic Acidosis, Severe Allergic Reactions, Macular Edema/Decreased Vision, Impaired Renal Function (For SGLT-2 inhibitors), Fractures (For SGLT-2 inhibitors), and Volume Depletion (For SGLT-2 inhibitors). Therefore, we were unable to draw any firm conclusions regarding the diabetes medication comparisons and these safety outcomes.

The Evidence About Hypoglycemia

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Five RCTs addressed hypoglycemia for metformin versus thiazolidinediones finding no consistent differences in hypoglycemia by arm (Table 50).[45, 63, 64, 66, 67] We were unable to conduct a meta-analysis because of differences in the definitions of hypoglycemia and lengths of followup. (SOE: Low; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 50. Randomized controlled trials comparing metformin with thiazolidinediones on hypoglycemia

Author, year	Followup	Metformin (dose*)	TZD (dose*)	Definition of hypoglycemia	Results† (Metformin vs TZD)
Kahn, 2006[45]	4 years	Metformin (max 2000 mg)	Rosiglitazone (max 8 mg)	Total (self-reported)	168/1454 (11.6%) vs 142/1456 (9.8%)
Yoon, 2011[67]	48 weeks	Metformin (max 2000 mg; mean 1234.2 mg)	Rosiglitazone (max 8 mg; mean 5.9 mg)	Total (signs or symptoms)	4/114 (3.5%) vs 8/117 (6.8%)
Erem, 2014[63]	48 weeks	Metformin (max 2000 mg)	Pioglitazone (max 45 mg)	Total (not specified)	0/19 (0%) vs 0/19 (0%)
Russell-Jones, 2012[66]	26 weeks	Metformin (max 2500 mg)	Pioglitazone (max 45 mg)	Severe‡ Total (signs or symptoms)	0/246 (0%) vs 0/163 (0%) 10/246 (4.1%) vs 6/163 (3.7%)
Genovese, 2013[64]	16 weeks	Metformin (max 2550 mg)	Pioglitazone (max 45 mg)	Total (not specified)	0 episodes among 26 patients vs 4 episodes among 24 patients

Max = maximum; mg = milligram; TZD = thiazolidinedione
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.
‡ Severe hypoglycemia was defined as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after glucose administration, or documented blood glucose less than 3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness.

Metformin Versus Sulfonylureas

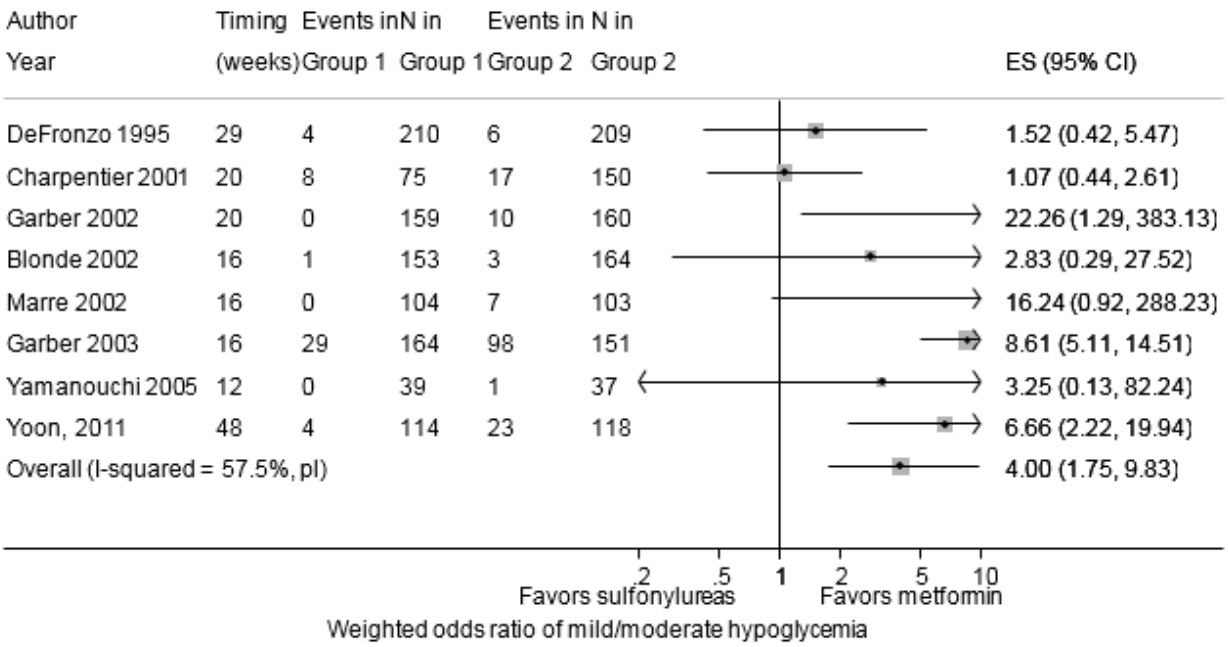
Fifteen studies addressed this comparison (14 RCTs and one observational study).[45, 53, 67, 98, 100-103, 105-107, 214, 248-250] Meta-analysis of the 10 RCTs deemed sufficiently homogeneous for quantitative synthesis showed a significantly increased risk of mild to moderate hypoglycemia

for sulfonylureas versus metformin (pooled OR, 4.07; 95% CI, 1.73 to 9.58). Omission of Garber 2003[98] most affected the point estimate of the random-effects meta-analysis, presumably reflecting the precision of its estimate.

We found evidence of high statistical heterogeneity (I-squared of 67%); a meta-regression did not find significant influence of study characteristics on the estimate. The profile likelihood method yielded a similar result (pooled OR for sulfonylurea versus metformin, 4.00; 95% CI, 1.75 to 9.83) (Figure 56). Exclusion of any one study did not change this inference.

We did not include seven studies in the meta-analysis because of differences in hypoglycemia definitions,[103, 214] in study duration,[45, 249] in how hypoglycemic events were reported,[249] and in study design.[250] There were also two studies that were excluded due to no events in either arm.[107, 248] Results of the studies not included in the meta-analyses were generally consistent with the findings of the meta-analysis (Table 51). (SOE: High; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Metformin favored for severe hypoglycemia)

Figure 56. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with sulfonylureas



CI = confidence interval; Group 1 = metformin; Group 2 = sulfonylureas; OR = odds ratio; pl = profile likelihood estimate
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Table 51. Additional studies comparing metformin with sulfonylureas on hypoglycemia

Author, year Study design	Followup	Metformin (dose*)	SU (dose*)	Definition of hypoglycemia	Results† (Metformin vs SU)
Hong, 2013[214] RCT	36 months	Metformin (max 1500 mg; mean 1400 mg)	Glipizide (max 30 mg; mean 28.3 mg)	Severe (required assistance and/or PG < 56 mg/dL [3.1 mmol/L])	3/156 (1.9%) vs 4/148 (2.7%)
Hermann, 1994[103] RCT	24 weeks	Metformin (max 3000 mg)	Glyburide (max 14 mg)	Severe (based on clinical findings or available BG)	8/38 (21.1%) vs 12/34 (35.3%); *P* = 0.18
Derosa, 2004[248] RCT	48 weeks	Metformin (max 3000 mg)	Glimepiride (max 4 mg)	Mild-moderate (not specified)	0/75 (0%) vs 0/73 (0%)
Chien, 2007[107] RCT	16 weeks	Metformin (max 2000 mg; mean 1910 mg)	Glyburide (max 20 mg; mean 19 mg)	Mild-moderate (symptomatic or BG < 60 mg/dL)	0/25 (0%) vs 0/23 (0%)
Kahn, 2006[45] RCT	4 years	Metformin (max 2000 mg)	Glyburide (max 15 mg)	Total (self-reported)	168/1454 (11.6%) vs 557/1441 (38.7%)
Wright, 2006[249] RCT	6 years	Metformin (max 2550 mg)	Glyburide (max 20 mg)	Mild to severe (not just transient symptoms)	Mean annual percentage 0.3% among 290 patients vs 1.2% among 1418 patients
Weir, 2011[250] Retrospective cohort	3 months	Metformin (NR)	Glyburide (NR)	Total (presented to an emergency room or hospital with an admission diagnosis of hypoglycemia)	Among patients with normal renal function 27/572 (4.7%) vs 53/193 (27.5%) Among patients with impaired renal function 29/580 (5.0%) vs 109/444 (24.5%)

BG = blood glucose; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimoles per liter; PG = plasma glucose; RCT = randomized controlled trial; SU = sulfonylurea
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.

Metformin Versus DPP-4 Inhibitors

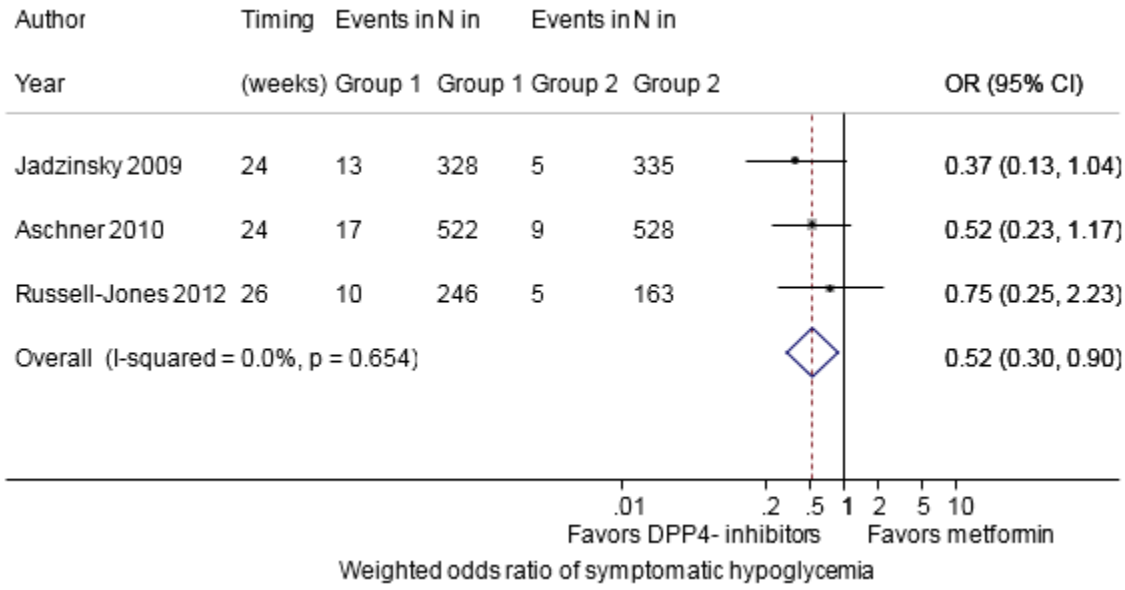
Six RCTs (reported in seven publications) compared metformin with DPP-4 inhibitors and reported on hypoglycemia.[66, 74-79]

Meta-analysis of the short-term, sufficiently-homogeneous RCTs favored DPP-4 inhibitors over metformin for symptomatic hypoglycemia (pooled OR, 0.52; 95% CI, 0.30 to 0.90) (Figure 57).[66, 74, 75] Consistent with these findings, longer-term followup from two studies also revealed less hypoglycemia in the DPP-4 inhibitor arms compared with the metformin arms.[77, 79] Of note, differences in hypoglycemia rates across the arms were not as clear when the definition of hypoglycemia required biochemical confirmation.[66, 76]

Rates of severe hypoglycemia were low in the studies reporting on this. Of four short RCTs (24 to 26 weeks), two reported no severe hypoglycemia in either arm.[66, 76] One study reported a single event in the metformin arm and none in the DPP-4 inhibitor arm,[78] and the other study reported two events in the DPP-4 inhibitor arm and did not report on severe hypoglycemia in the metformin arm.[74] Of two RCTs with long-term followup (76 to 104 weeks), one reported no severe hypoglycemia events,[79] and the other reported three events of severe hypoglycemia in the metformin monotherapy arms (n=2 for metformin 1000 mg and n=1 for metformin 2000 mg daily) and none in the DPP-4 inhibitor arm.[77]

Three of the six RCTs did not use an intention-to-treat approach, and withdrawals were high in all three of these studies[75-77] with two excluding data from persons initiating rescue therapy.[75, 76] (SOE: Low; DPP-4 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 57. Pooled odds ratio of symptomatic hypoglycemia comparing metformin with DPP-4 inhibitors



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = dipeptidyl peptidase-4; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

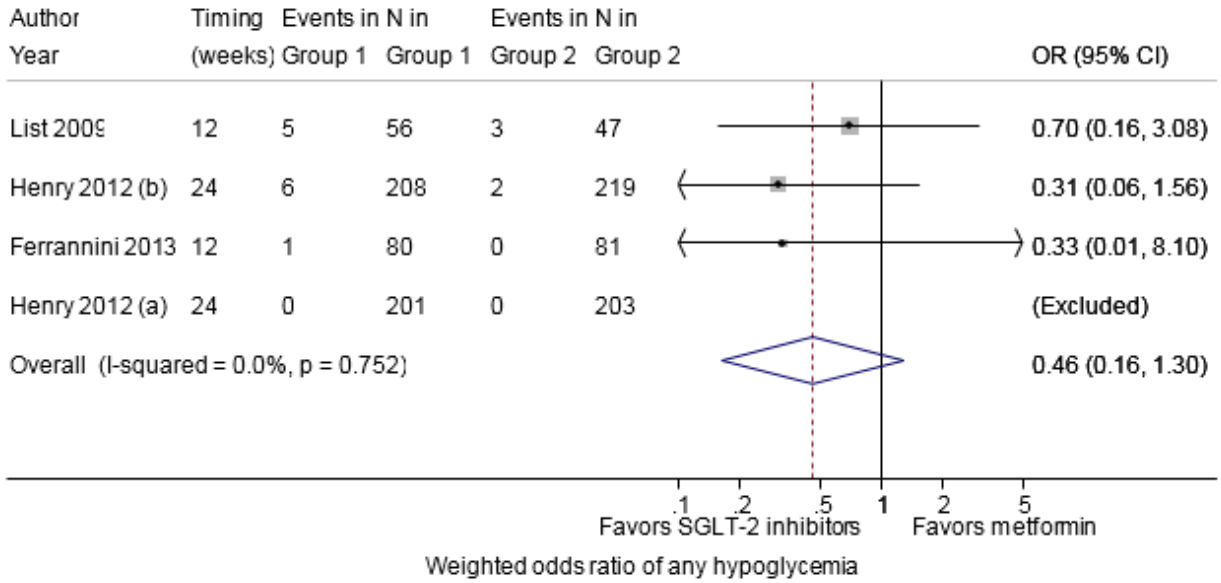
Metformin Versus SGLT-2 Inhibitors

Four RCTs (reported in three articles) compared metformin with SGLT-2 inhibitors and reported on total hypoglycemia.[80, 81, 227] The meta-analysis favored SGLT-2 inhibitors versus metformin for any hypoglycemia although the combined result was not statistically significant (Figure 58).

In a 2013 RCT, Ferrannini et al.,[82] an extension of one of the included studies[227] with 78 weeks of followup, found slightly higher rates of hypoglycemia in the metformin (3.6%) versus empagliflozin arms (10 mg, 0.9%; 25 mg, 1.8%); we did not include this study in the meta-analysis because of its longer duration.

Two studies reported no events of severe hypoglycemia.[80] (SOE: Moderate; SGLT-2 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 58. Pooled odds ratio of any hypoglycemia comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus GLP-1 Agonists

Three RCTs compared metformin with GLP-1 agonists (duration 26 to 52 weeks) (Table 52).[66, 83, 84] For mild hypoglycemia, there appeared to be more patients with events in the GLP-1 agonist arm than the metformin arm. No study reported severe hypoglycemia events. For total hypoglycemia, one study[83] reported comparable proportions of patients with that outcome in the two arms. Some of the heterogeneity may be due to dosing differences across studies. (SOE: Low; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 52. Randomized controlled trials comparing metformin with GLP-1 agonists on hypoglycemia

Author, year	Followup (weeks)	Metformin (dose*)	GLP-1 agonist (dose*)	Definition of hypoglycemia	Results† (Metformin vs GLP-1 agonist)
Russell-Jones, 2012[66]	26	Metformin (max 2500 mg)	Exenatide (fixed at 2.0 mg weekly)	Mild-moderate (signs or symptoms associated with BG < 3.0 mmol/L (either self-treated or resolved independently))	0/246 (0%) vs 5/248 (2.0%)
				Severe‡	0/246 (0%) vs 0/248 (0%)
				Total (signs or symptoms)	10/246 (4.1%) vs 13/248 (5.2%)
Umpierrez, 2014[83]	52	Metformin (max 2000 mg or ≥ 1500 mg depending on tolerability), 268	Dulaglutide (fixed at 0.75 mg weekly)	Total (signs or symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L])	34/268 (12.7%) vs 30/270 (11.1%)
				Severe (required third party assistance)	0/268 (0%) vs 0/270 (0%)
Umpierrez, 2014[83]	52	Metformin (max 2000 mg or ≥ 1500 mg depending on tolerability), 268	Dulaglutide (fixed at 1.5 mg weekly)	Total (signs or symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L])	34/268 (12.7%) vs 33/269 (12.3%)
				Severe (required third party assistance)	0/268 (0%) vs 0/269 (0%)
Yuan, 2012[84]	26	Metformin (max 2000 mg), 26	Exenatide (max 2.0 mg), 33	Mild (not specified)	1/26 (3.8%) vs 4/33 (12.1%)
				Severe (required third party assistance or hospital treatment)	0/26 (0%) vs 0/33 (0%)

BG = blood glucose; GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams; mg/dL = milligram per deciliter; mmol/L = millimole per liter; PG = plasma glucose

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Severe hypoglycemia was defined as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after glucose administration, or documented blood glucose less than 3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness.

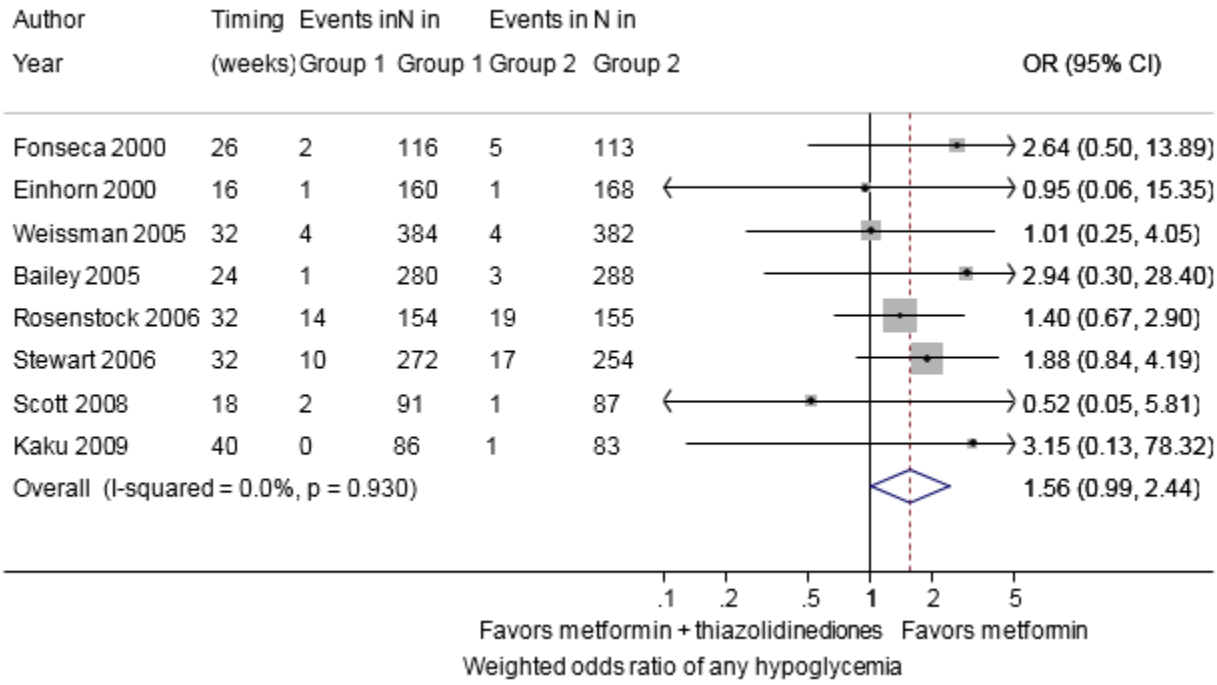
Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

More patients experienced hypoglycemia in the combination arm than in the metformin-alone arm. We combined eight sufficiently-homogeneous RCTs and found increased odds of mild or moderate hypoglycemia for metformin plus thiazolidinedione versus metformin alone (pooled OR, 1.56; 95% CI, 0.99 to 2.44) (Figure 59).[52, 86-89, 91, 92, 234] We did not find evidence of statistical heterogeneity.

We did not include two RCTs in this meta-analysis because of heterogeneity in length of followup. One compared metformin (titrated to a maximum of 2000 mg daily) with metformin plus rosiglitazone (titrated to a maximum of 8 mg/2000 mg daily) at 80 weeks, and reported 10 total hypoglycemia events in the metformin-alone arm (3% of patients), and 20 hypoglycemia events in the metformin-rosiglitazone arm (6% of patients).[96] The other compared metformin

(fixed at 1700 mg daily) with metformin and rosiglitazone (fixed at 4 mg/500 mg daily), reporting no total hypoglycemia events in either arm at 24 weeks.[93] This difference is probably attributable to dosing heterogeneity. (SOE: High, Metformin favored for mild, moderate, total hypoglycemia)

Figure 59. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a thiazolidinedione



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus thiazolidinedione; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

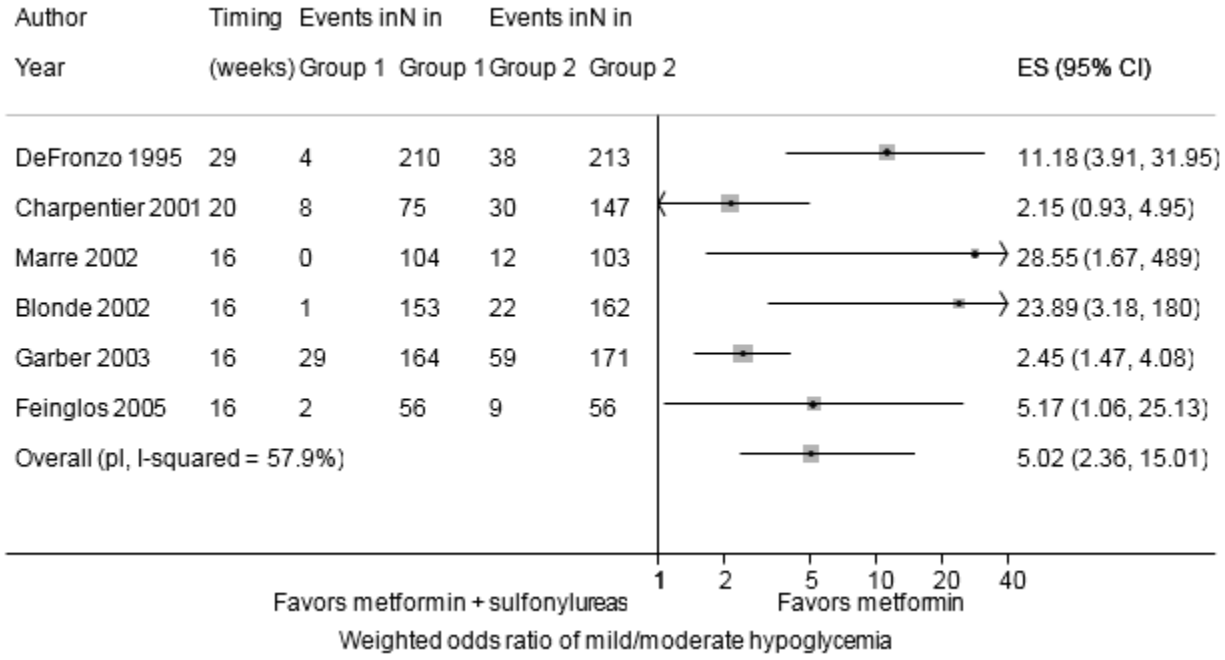
Metformin Versus a Combination of Metformin Plus a Sulfonylurea

For this comparison, metformin is favored to metformin plus sulfonylurea for the adverse event of mild/moderate hypoglycemia.

The seven studies reporting mild or moderate hypoglycemia were pooled.[97, 98, 100, 101, 105-107] The estimated odds ratio comparing metformin plus a sulfonylurea with metformin for mild or moderate hypoglycemia was 5.21 (95% CI, 2.38 to 11.4), favoring metformin. Exclusion of any one study did not change the inference. Due to the significant heterogeneity (I-squared 63.5%) a profile-likelihood estimate was also generated (Figure 60). The weighted odds ratio was 5.02 (95% CI, 2.36 to 15.0), favoring metformin.

Three RCTs published since the last version of this report were too heterogeneous to be pooled due to differences in classification of hypoglycemia.[108-110] (Table 53). Additionally, Chien was excluded from the meta-analysis due to absence of events in both arms.[107] (SOE: High; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 60. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with combination of metformin plus a sulfonylurea



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus sulfonylurea; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 53. Additional randomized controlled trials comparing metformin with a combination of metformin plus a sulfonylurea on hypoglycemia

Author, year	Followup (weeks)	Metformin (dose*)	SU (dose*)	Definition of hypoglycemia	Results† (Metformin vs SU)
Ahren, 2014[110]	104	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + glimepiride (max 4 mg)	Mild-moderate (Asymptomatic, but PG ≤ 3.9 mmol/L)	1/101 (1.0%) vs 3/307 (1.0%)
				Mild-moderate (Symptomatic and PG ≤ 3.9 mmol/L)	4/101 (4.0%) vs 55/307 (17.9%)
				Severe (required third party assistance)	0/101 (0%) vs 0/307 (0%)
Kim, 2014[109]	26	Metformin (max 2500 mg)	Metformin (max 2000 mg) + glimepiride (fixed at 1-8 mg)	Total (symptomatic)	4/108 (3.7%) vs 39/100 (0.4%)
				Severe (not specified)	0/108 (0%) vs 0/100 (0%)
Forst, 2010[108]	12	Metformin (fixed)	Metformin (fixed) + glimepiride (max 3 mg)	Total (not specified)	0/71 (0%) vs 3/65 (4.6%)

max = maximum; mg = milligrams; mmol/L = millimole per liter; PG = plasma glucose; SU = sulfonylurea
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.

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

There was little difference between arms in the outcomes of mild, severe, or total hypoglycemia in the studies for this comparison.

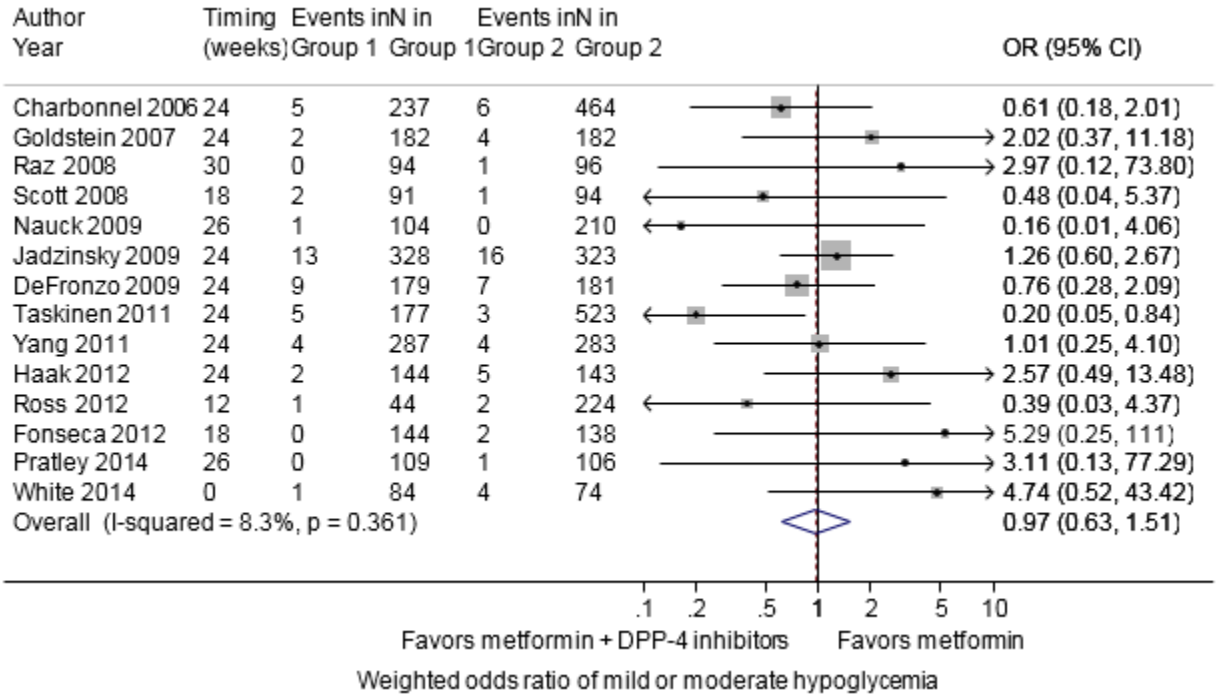
We included 25 studies for this comparison (29 publications). Six RCTs were from our prior report; two RCTs were published extensions of those prior studies; and we identified 19 additional studies for this comparison for hypoglycemia.

Mild Hypoglycemia

Two long-term (followup >=52 weeks) studies reported on mild hypoglycemia. One reported hypoglycemia events in 1% of patients in the metformin arm compared with 1.3% of patients in the metformin plus sitagliptin arm.[110] The other reported 4.8 events per person-year in the metformin arm compared with 0.1 events per person-year in the metformin plus sitagliptin arm.[128]

Fourteen studies reported on mild hypoglycemia with short-term followup (Figure 61).[72, 75, 76, 78, 87, 111-113, 116, 117, 120, 121, 124, 251] I-squared was 8.3%. The weighted odds ratio for mild or moderate hypoglycemia was 0.97 (95% CI, 0.63 to 1.51), favoring neither the metformin nor metformin plus DPP-4 inhibitor arm.

Figure 61. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

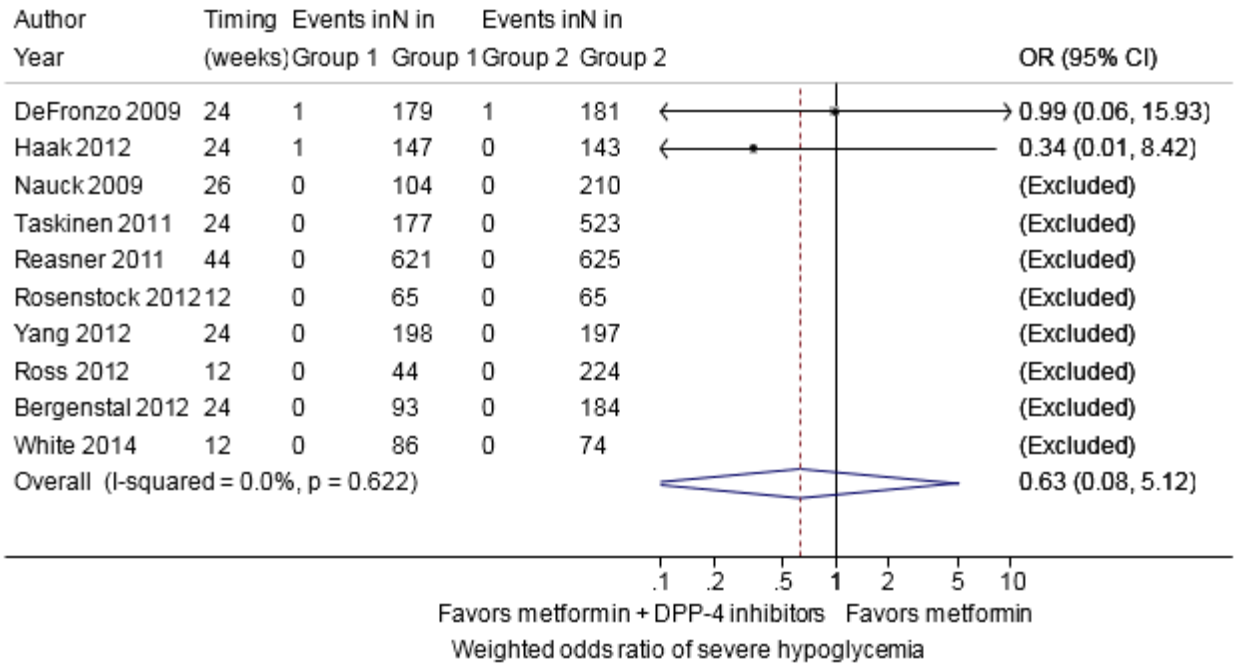
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Severe Hypoglycemia

Nine new studies and one old study reported severe hypoglycemia with short term (<52 week) followup.[46, 78, 113, 114, 117, 120, 121, 124, 125, 251] (Figure 62). The weighted odds ratio of severe hypoglycemia favored neither arm (OR, 0.63; 95% CI, 0.08, 5.12) with eight studies not contributing to the pooling because of no events in either arm.

Two long-term (>=52 weeks) studies reported on severe hypoglycemia. Pfutzner, 2011[79] reported no severe hypoglycemic events in the metformin arm and one event in the metformin plus DPP-4 inhibitor arm. Williams-Herman, 2010[77] reported no severe hypoglycemic events in either arm.

Figure 62. Pooled odds ratio of severe hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

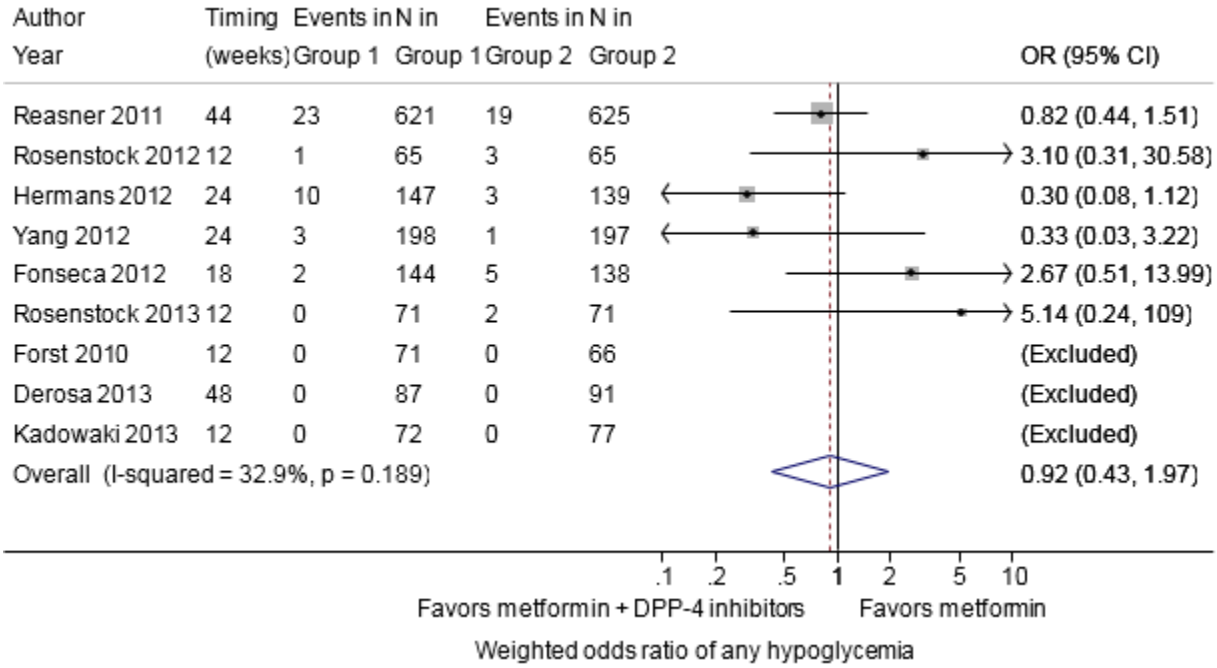
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Total Hypoglycemia

There were nine new studies reporting total hypoglycemic events with short term (<52 week) followup.[108, 114, 116-119, 122, 125, 129] The pooled odds ratio was 0.92; 95% CI, 0.43, 1.97, favoring neither arm (Figure 63).

There were two studies reporting total hypoglycemic events at greater than a year followup. One described 20 total hypoglycemic events in the metformin arm (6.1%), compared with 15 in the metformin plus saxagliptin arm (4.7%) at 76 weeks.[79] The other found, at 52 weeks, that 2.9% of patients had hypoglycemia events in the metformin arm, 4.9% of patients had events in the fixed linagliptin combination arm, and 6.4% of patients had events in the titrated linagliptin combination arm.[131] (SOE: High; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Neither favored for severe hypoglycemia)

Figure 63. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

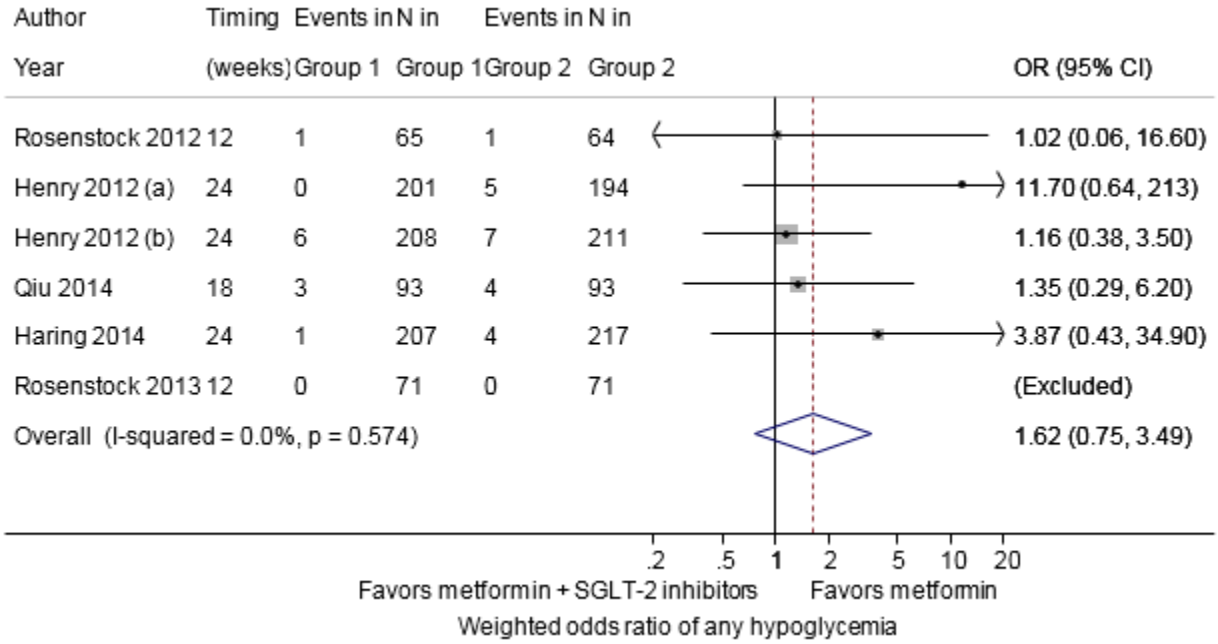
Six studies (published in five articles) reported on total hypoglycemic events with short-term followup.[80, 122, 125, 132, 133] The weighted odds ratio was 1.62 (95% CI, 0.75, 3.49), showing no significant between-group differences (Figure 64).

One study reported on total hypoglycemic events with long-term followup (78 weeks) and reported similar rates of total hypoglycemia in the monotherapy and combination arms: two patients of 56 in the metformin arm (3.6%), three patients of 166 in the arm receiving 10 mg of empagliflozin (1.8%), and four patients of 166 in the arm receiving 25 mg of empagliflozin (2.4%).[82]

One 52-week study reported on mild hypoglycemia events and reported four events in both the metformin arm (4.4%) and the metformin plus dapagliflozin combination arm (4.4%).[134]

Five studies (published in four articles) reported on severe hypoglycemia events with followup less than one year, and none of these studies reported any severe events.[80, 125, 132, 133] One study reported no severe hypoglycemic events with more than 52 weeks follow-up.[135] (SOE: Moderate; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 64. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Three studies assessed this comparison,[110, 128, 136] favoring neither arm consistently, with heterogeneity likely due to differences in followup time, dosing, and hypoglycemia definitions (Table 54). Two of these studies did not use an intention-to-treat approach and had large losses to followup.[110, 136] (SOE: Low; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 54. Randomized controlled trials comparing metformin with a combination of metformin plus a GLP-1 agonist on hypoglycemia

Author, year	Followup (weeks)	Metformin (dose*)	Metformin + GLP-1 agonist (dose*)	Definition of hypoglycemia	Results† (Metformin vs metformin + GLP-1 agonist)
Ahren, 2014[110]	104	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + albiglutide (max 50 mg weekly)	Mild-moderate (Asymptomatic, but PG ≤ 3.9 mmol/L) Mild-moderate (Symptomatic and PG ≤ 3.9 mmol/L) Severe (required third party assistance)	1/101 (1%) vs 4/302 (1.3%) 4/101 (4.0%) vs 9/302 (3.0%) 0/101 (0%) vs 0/302 (0%)
Nauck, 2014[128]	52	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed at 0.75 mg/week)	Mild-moderate (Signs and symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L]) Severe (required third party assistance)	2/177 (1.1%)‡ vs 16/302 (5.3%) 0/177 (0%)‡ vs 0/302 (0%)
Nauck, 2014[128]	52	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed at 1.5 mg/week)	Mild-moderate (Signs and symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L]) Severe (required third party assistance)	2/177 (1.1%)‡ vs 31/304 (10.2%) 0/177 (0%)‡ vs 0/304 (0%)
Derosa, 2013[136]	48	Metformin (mean 2500 mg)	Metformin (mean 2500 mg) + exenatide (max 20 mcg)	Total (FPG < 60 mg/dL)	0/85 (0%) vs 0/86 (0%)

FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; mcg = micrograms; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; PG = plasma glucose; vs = versus
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.
‡ Incidence of hypoglycemia at 26 weeks. Incidence is not available for this arm at 52 weeks. In the trial, patients were switched from a combination of metformin and placebo to a combination of metformin and sitagliptin.

Thiazolidinediones Versus Sulfonylureas

Nine RCTs compared thiazolidinedione with sulfonylurea monotherapy and reported on hypoglycemia.[45, 53, 67, 140, 141, 146, 149, 200, 252]

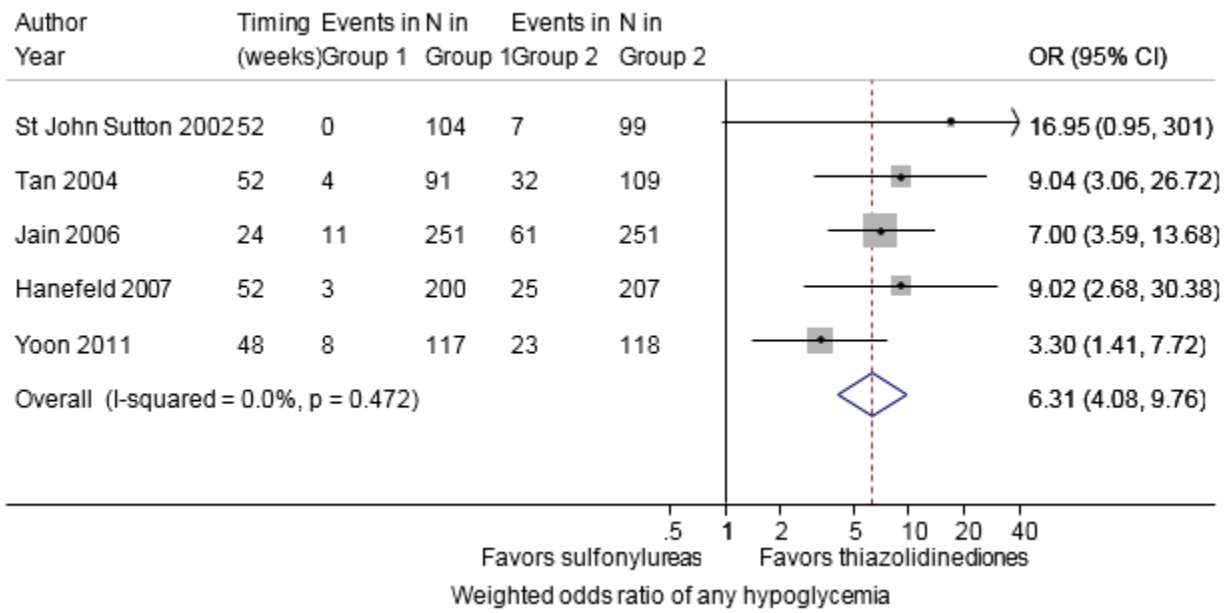
Results from the meta-analysis of five sufficiently-homogeneous RCTs 52 or fewer weeks in duration showed that the risk of total hypoglycemia was higher for sulfonylurea compared with thiazolidinedione monotherapy (pooled OR for sulfonylurea compared with thiazolidinedione monotherapy, 6.31, 95% CI, 4.08 to 9.76) (Figure 65).

We did not include one short-term (16 weeks) study in the meta-analysis because it reported on the number of events and not number of participants experiencing events; this study reported two events of hypoglycemia in the thiazolidinedione arm and three events in the sulfonylurea arm.[252] We excluded another short-term (24 weeks) RCT from the meta-analysis because its mean daily dose of glimepiride (1.5 mg/day) was much lower than the dosing of sulfonylureas in the other studies included in the meta-analysis. This study still found higher rates of

hypoglycemia (blood glucose < 60 mg/dL) in the sulfonylurea (7/95, 7.4%) than thiazolidinedione (5/96, 5.2%) arm.[149]

The longer study, ADOPT, also found higher rates of total hypoglycemia for the sulfonylurea (557/1441, 38.7%) arm compared with the thiazolidinedione (142/1456, 9.8%) arm. This study also found more severe hypoglycemia in the sulfonylurea (8/1441, 0.6%) arm compared with the thiazolidinedione (1/1456, 0.1%) arm. One of the short-term studies reported that two participants experienced severe hypoglycemia in the sulfonylurea arm but did not report on this outcome for the thiazolidinedione arm.[140] (SOE: High; Thiazolidinediones favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Thiazolidinediones favored for severe hypoglycemia)

Figure 65. Pooled odds ratio of any hypoglycemia comparing thiazolidinediones with sulfonylureas



CI = confidence interval; Group 1 = thiazolidinediones; Group 2 = sulfonylureas; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

Three studies evaluated hypoglycemia for this comparison (Table 55).[43, 66, 150] This comparison appears to favor neither arm; heterogeneity in the results is likely due to differences in length of follow up, definition of hypoglycemia, and type of DPP-4 inhibitor. (SOE: Low; Neither favored for mild, moderate, total, or severe hypoglycemia)

Table 55. Randomized controlled trials comparing thiazolidinediones with DPP-4 inhibitors on hypoglycemia

Author, year	Followup (weeks)	TZD (dose*)	DPP-4 inhibitor (dose*)	Definition of hypoglycemia	Results† (TZD vs DPP-4 inhibitor)
Alba, 2013[43]	12	Pioglitazone (fixed at 30 mg)	Sitagliptin (fixed at 100 mg)	Total (all reports of hypoglycemia; no glucose measurement required)	2/54 (3.7%) vs 0/52 (0%)
Rosenstock, 2010[150]	26	Pioglitazone (fixed at 30mg)	Alogliptin (fixed at 25 mg)	Severe (required third party assistance)	0/163 (0%) vs 0/164 (0%)
Russell-Jones, 2012[66]	26	Pioglitazone (max 45 mg)	Sitagliptin (fixed at 100 mg)	Severe‡ Total (signs or symptoms)	6/163 (3.7%) vs 5/163 (3.1%) 0/163 (0%) vs 0/163 (0%)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; TZD = thiazolidinedione
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.
‡ Severe hypoglycemia was defined as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after glucose administration, or documented blood glucose less than 3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness.

Thiazolidinediones Versus GLP-1 Agonists

One RCT addressed this outcome, with results favoring the thiazolidinedione arm.[66] At 26 weeks, zero among the 163 participants in the pioglitazone arm had mild hypoglycemia, but 5 of 248 did in the exenatide arm. (SOE: Low; Thiazolidinediones favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Sulfonylureas Versus DPP-4 Inhibitors

Comparisons for both mild and severe hypoglycemia favored the DPP-4 inhibitor arms over sulfonylureas. Four RCTs examined hypoglycemia with this comparison, and differences in followup length precluded a meta-analysis (Table 56). (SOE: Moderate; DPP-4 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; DPP-4 inhibitors favored for severe hypoglycemia)

Table 56. Randomized controlled trials comparing sulfonylureas with DPP-4 inhibitors on hypoglycemia

Author, year	Followup (weeks)	SU (dose*)	DPP-4 inhibitor (dose*)	Definition of hypoglycemia	Results† (SU vs DPP-4 inhibitor)
Arjona Ferreira, 2013[152]	58	Glipizide (max 20 mg; mean 7.7 mg)	Sitagliptin (fixed at 50 mg for those with moderate renal insufficiency and 25 mg for those with severe renal insufficiency)	Severe (required third party assistance or medical intervention or exhibited markedly depressed level of consciousness, loss of consciousness, or seizure) Total (signs and/or symptoms)	6/212 (2.8%) vs 3/210 (1.4%) 36/212 (17%) vs 13/210 (6.2%); *P* < 0.001
Gupta, 2013[253]	24	Glimepiride (max 4 mg)	Sitagliptin (max 200 mg)	Total (not specified)	11 episodes among 71 patients vs 3 episodes among 77 patients
Barnett, 2012[151]	34	Glimepiride (max 4 mg)	Linagliptin (fixed at 5 mg)	Mild-moderate (Symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/]) Severe (required third party assistance)	5/64 (7.8%) vs 3/137 (2.2%) 0/64 (0%) vs 0/137 (0%)
Scott, 2007[153]	12	Glipizide (max 20 mg)	Sitagliptin (fixed at 25 mg)	Total (self-report and glucose measurements)	21/123 (17.1%) vs 5/123 (4.1%)
Scott, 2007[153]	12	Glipizide (max 20 mg)	Sitagliptin (fixed at 50 mg)	Total (self-report and glucose measurements)	21/123 (17.1%) vs 5/123 (4.1%)
Scott, 2007[153]	12	Glipizide (max 20 mg)	Sitagliptin (fixed at 100 mg)	Total (self-report and glucose measurements)	21/123 (17.1%) vs 2/122 (1.6%)

DPP-4 = dipeptidyl peptidase-4; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; PG = plasma glucose; SU = sulfonylurea
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.

Sulfonylureas Versus GLP-1 Agonists

GLP-1 agonists were favored over sulfonylureas for mild to moderate hypoglycemia (Table 57). Five studies assessed this outcome, and could not be pooled due to heterogeneity in outcome definitions and follow-up length. No study reported any events of severe hypoglycemia. (SOE: Moderate; GLP-1 agonists favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 57. Randomized controlled trials comparing sulfonylureas with GLP-1 agonists on hypoglycemia

Author, year	Followup (weeks)	SU (dose*)	GLP-1 agonist (dose*)	Definition of hypoglycemia	Results† (SU vs GLP-1 agonist)
Garber, 2011[158]	104	Glimepiride (max 8mg)	Liraglutide (max 1.2 mg)	Mild-moderate (did not require assistance, BG < 56 mg/dL [3.1 mmol/L]) Severe (required third-party assistance)	64/248 (25.8%) vs 30/251 (12%) 0/248 (0%) vs 0/251 (0%)
Garber, 2011[158]	104	Glimepiride (max 8 mg)	Liraglutide (max 1.8 mg)	Mild-moderate (did not require assistance, BG < 56 mg/dL [3.1 mmol/L]) Severe (required third-party assistance)	64/248 (25.8%) vs 25/247 (10.1%) 0/248 (0%) vs 1/247 (0.4%)‡
Kaku, 2011[155]	52	Glibenclamide (fixed at 1.25 -2.5 mg)	Liraglutide (max 0.9 mg)	Mild-moderate (self-treated) Severe (required third party assistance)	1.10 events per patient-year vs 0.19 events per patient-year 0/132 (0%) vs 0/268 (0%)
Madsbad, 2004[156]	12	Glimepiride (max 4 mg)	Liraglutide (Fixed (0.60 mg))	Mild-moderate (BG < 2.8 mmol/L)	4/26 (15.4%) vs 1/30 (3.3%)
Madsbad, 2004[156]	12	Glimepiride (max 4 mg)	Liraglutide (Fixed (0.75 mg))	Mild-moderate (BG < 2.8 mmol/L)	4/26 (15.4%) vs 0/28 (0%)
Seino, 2010[154]	24	Glibenclamide (max 2.5 mg)	Liraglutide (max 0.9 mg)	Mild-moderate (symptoms) Mild-moderate (symptoms and BG < 3.1 mmol/L) Severe (required third party assistance)	45/132 (34.1%) vs 36/268 (13.4%) 29/132 (22%) vs 22/268 (8.2%) 0/132 (0%) vs 0/268 (0%)

BG = blood glucose; GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; SU = sulfonylurea
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.
‡ Event in the context of insulin infusion as part of a "sub-study" procedure.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One study assessed hypoglycemia for this comparison.[159] The study compared sitagliptin with empagliflozin at 24 weeks, with one of 223 patients in the sitagliptin arm (<1%) with any hypoglycemia, one of 224 patients in the 10 mg empagliflozin arm, and one of 223 patients in the 25 mg empagliflozin arm. No patients experienced severe hypoglycemia. (SOE: Low; Neither favored for mild, moderate, total, or severe hypoglycemia)

DPP-4 Inhibitors Versus GLP-1 Agonists

One study assessed hypoglycemia for this comparison, favoring sitagliptin.[66] Investigators compared sitagliptin with exenatide at 26 weeks. There were five patients of 163 in the sitagliptin arm with any hypoglycemia, and 13 of 248 in the exenatide arm; zero patients of 163

in the sitagliptin arm had mild hypoglycemia, and five of 248 did in the exenatide arm; and no patients had severe hypoglycemia in either arm. (SOE: Low; DPP-4 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

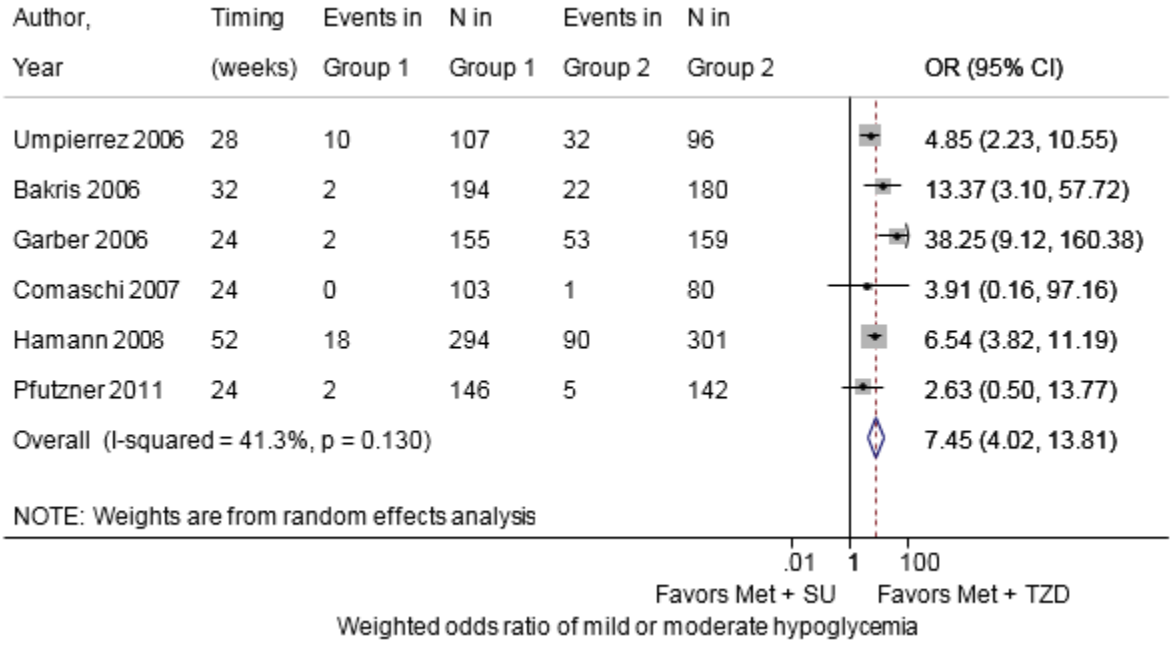
Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Six short-duration RCTs reporting on mild or moderate hypoglycemia compared the combination of metformin plus a thiazolidinedione with metformin plus a sulfonylurea, showing higher risk of hypoglycemia in the metformin plus sulfonylurea arm (pooled OR, 7.5; 95% CI, 4.0 to 13.8) (Figure 66).[160, 162, 163, 165, 168, 170] The trial by Hamann et al. was designed so that patients were withdrawn from the study if they did not reach an efficacy target after 8 weeks of treatment.[160] The rates of hypoglycemia were high as medications were titrated up to efficacy, although the relative odds of hypoglycemia in the two arms was comparable to the other studies. No single study strongly influenced the results of the meta-analysis and no substantial heterogeneity was identified.

One study reported on severe hypoglycemia, showing results consistent with the mild to moderate hypoglycemia outcome.[165] In Garber et al., seven of 159 patients had severe hypoglycemic events in the metformin with sulfonylurea arm and none did in the metformin with thiazolidinedione arm.[165] This study included patients with high baseline HbA1c and had a higher proportion of Asian patients than most studies (12% Asian). (SOE: High; Combination of metformin plus a thiazolidinedione favored for mild, moderate, or total hypoglycemia) (SOE: Low; Combination of metformin plus a thiazolidinedione favored for severe hypoglycemia)

Figure 66. Pooled odds ratio of any hypoglycemia comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea



CI = confidence interval; Group 1 = combination of metformin plus thiazolidinedione; Group 2 = combination of metformin plus a sulfonylurea; Met = metformin; OR = odds ratio; SU = sulfonylurea; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Three studies (two RCTs and one observational study) compared the combination of metformin plus a thiazolidinedione with metformin plus a DPP-4 inhibitor, showing no clear differences between-groups in hypoglycemia risk.[171, 173, 254] One low quality study randomized 56 patients to metformin and rosiglitazone and 56 to metformin and sitagliptin. One patient in the rosiglitazone group withdrew for hypoglycemia but it is not clearly reported how many in each group experienced hypoglycemia.[171] One study compared mild hypoglycemia in a metformin plus pioglitazone arm with a metformin plus sitagliptin arm at 26 weeks.[173] There was one patient with an event in the metformin plus pioglitazone arm and five patients with events in the metformin plus sitagliptin arm. This study also evaluated severe hypoglycemia, finding no events in either arm. A prospective cohort study also assessed severe hypoglycemia; no patients with these events were recorded.[254] (SOE: Low; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Neither favored for severe hypoglycemia)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

Two short RCTs compared metformin plus a thiazolidinedione with metformin plus a GLP-1 agonist, showing little differences between-groups in hypoglycemia risk. The first 20-week study randomized 45 patients to metformin and rosiglitazone and 45 to metformin and exenatide at comparable doses.[174] No patients receiving metformin plus rosiglitazone reported hypoglycemia

while two patients receiving metformin plus exenatide did, although this difference was not statistically significant.[174] There were no severe hypoglycemic events in this study. The second 26-week study randomized 325 patients to either metformin and pioglitazone or metformin and exenatide at comparable doses.[173] They reported one patient with mild hypoglycemia in the metformin plus pioglitazone arm, and two patients with mild hypoglycemia in the metformin plus exenatide arm. They also reported that no patients had severe hypoglycemia in either arm. (SOE: Low; Neither favored for mild, moderate, total, or severe hypoglycemia)

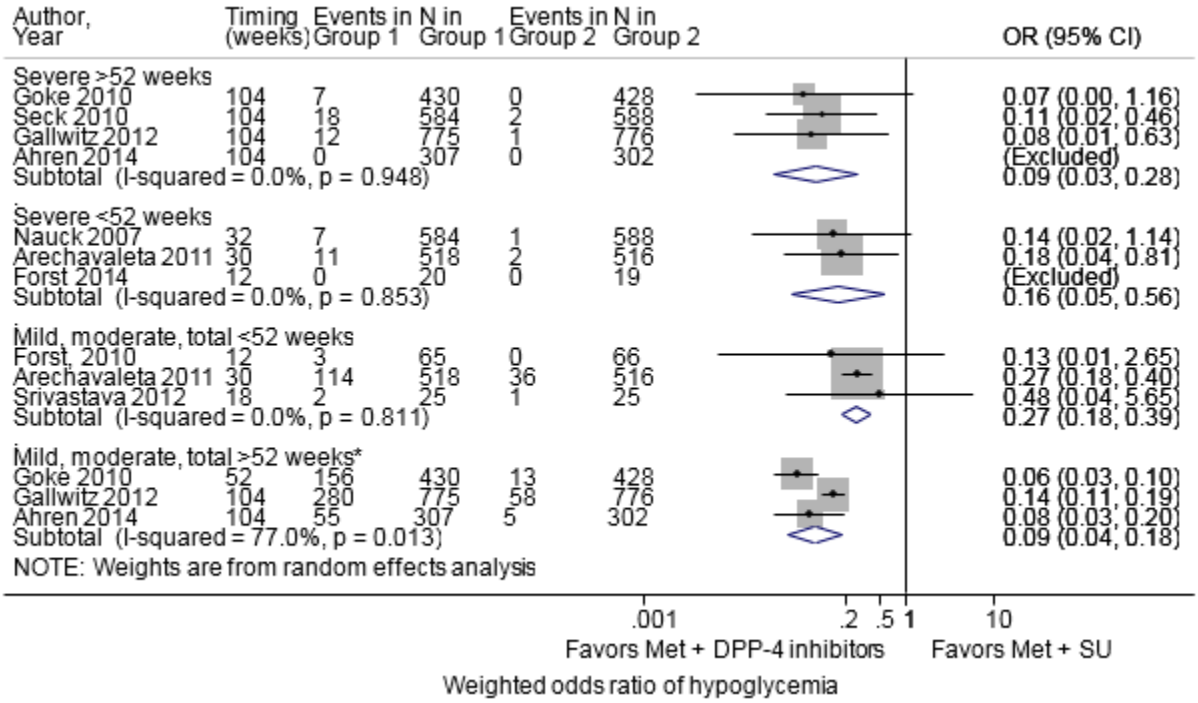
Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Nine studies of this comparison found more patients with severe and non-severe hypoglycemia in the metformin plus sulfonylurea arms compared with the metformin plus DPP-4 inhibitor arms (Figure 67).[108, 110, 175-180, 255]

Four studies lasting over a year reported on the outcome of severe hypoglycemia, favoring metformin plus a DPP-4 inhibitor over metformin plus a sulfonylurea (pooled OR, 0.09; 95% CI, 0.03 to 0.28).[110, 178-180] Similarly, three studies lasting less than a year reported on the outcome of severe hypoglycemia, favoring metformin plus a DPP-4 inhibitor over metformin plus a sulfonylurea (pooled OR, 0.16; 95% CI, 0.05 to 0.56).[175-177]

Three additional studies were pooled for a meta-analysis of hypoglycemia (defined as mild, moderate, or total) with follow up less than 52 weeks. The pooled odds ratio was 0.27 (95% CI, 0.18 to 0.39), favoring metformin plus a DPP-4 inhibitor.[108, 175, 255] Three longer studies with followup greater than 52 weeks reported on mild, moderate, or total hypoglycemia, with all three studies reporting significantly less hypoglycemia in the metformin plus DPP-4 inhibitor arms compared with the metformin plus sulfonylurea arms (pooled OR, 0.09; 95% CI, 0.04 to 0.18).[110, 178, 179] For all meta-analyses, no single study markedly influenced the results. Only one meta-analysis had substantial heterogeneity, yet the point estimates were fairly similar among these studies. (SOE: High; Combination of metformin plus a DPP-4 inhibitor favored for mild, moderate, total, or severe hypoglycemia)

Figure 67. Pooled odds ratio of hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration and severity of hypoglycemia



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU - sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
* The profile likelihood estimate provided a similar result.

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

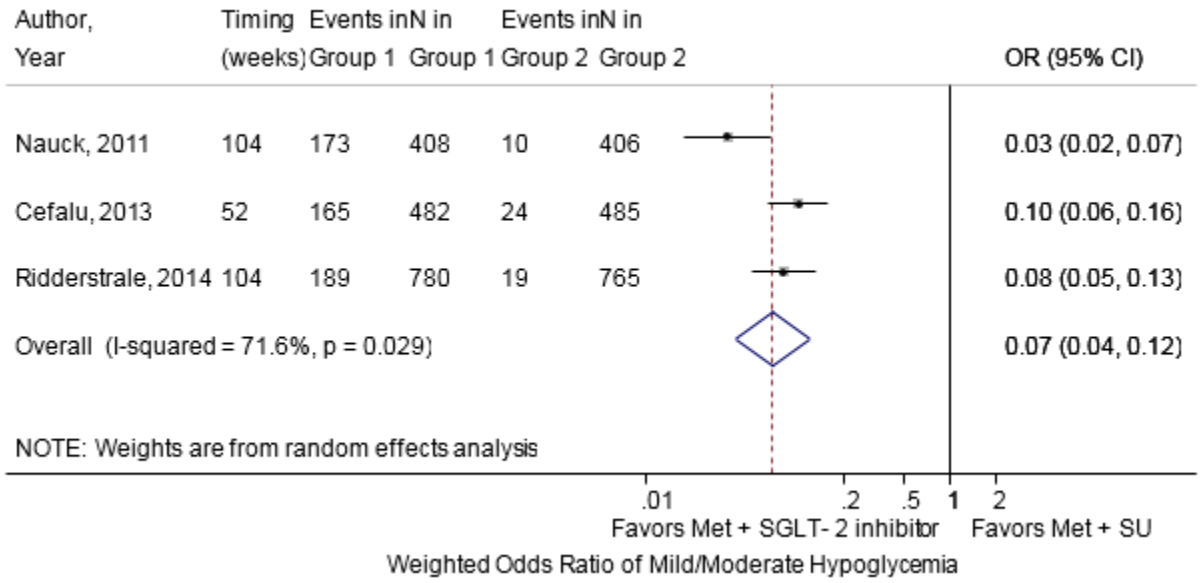
For the combined outcome of mild or total hypoglycemia, and for severe hypoglycemia, this comparison favored the metformin plus SGLT-2 inhibitor combinations over the combination of metformin and a sulfonylurea.

Three studies were pooled assessing mild or total hypoglycemia for this comparison.[181-183] The weighted odds ratio was 0.07 (95% CI, 0.03 to 0.13), favoring metformin plus SGLT-2 inhibitor combinations. There was substantial heterogeneity for this meta-analysis (I-squared = 71.6%); however, point estimates were fairly similar among the trial (Figure 68). Two of the three studies used equipotent drug dosing between the treatment arms.[181, 182] One study mildly underdosed the metformin plus sulfonylurea arm (mean glimepiride dose of 2.7 mg) in comparison with the SGLT-2 inhibitor arm.[183] No single study strongly influenced the meta-analysis results.

Two of these trials also assessed severe hypoglycemia for this comparison.[181, 182] As above, the combination of metformin plus an SGLT-2 inhibitor was favored in both studies. The first RCT assessed severe hypoglycemia at 52 weeks in 965 randomized patients.[181] There were 15 patients with a severe hypoglycemic event in the metformin plus sulfonylurea arm and two patients in the metformin plus SGLT-2 inhibitor arm. The second RCT assessed severe

hypoglycemia at 104 weeks in 814 randomized patients.[182] Severe hypoglycemic events were reported in 7% of patients in the metformin plus sulfonylurea arm and 1.7% of patients in the metformin plus SGLT-2 inhibitor arm. (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored for severe hypoglycemia)

Figure 68. Pooled odds ratio of mild or moderate hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor*



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea

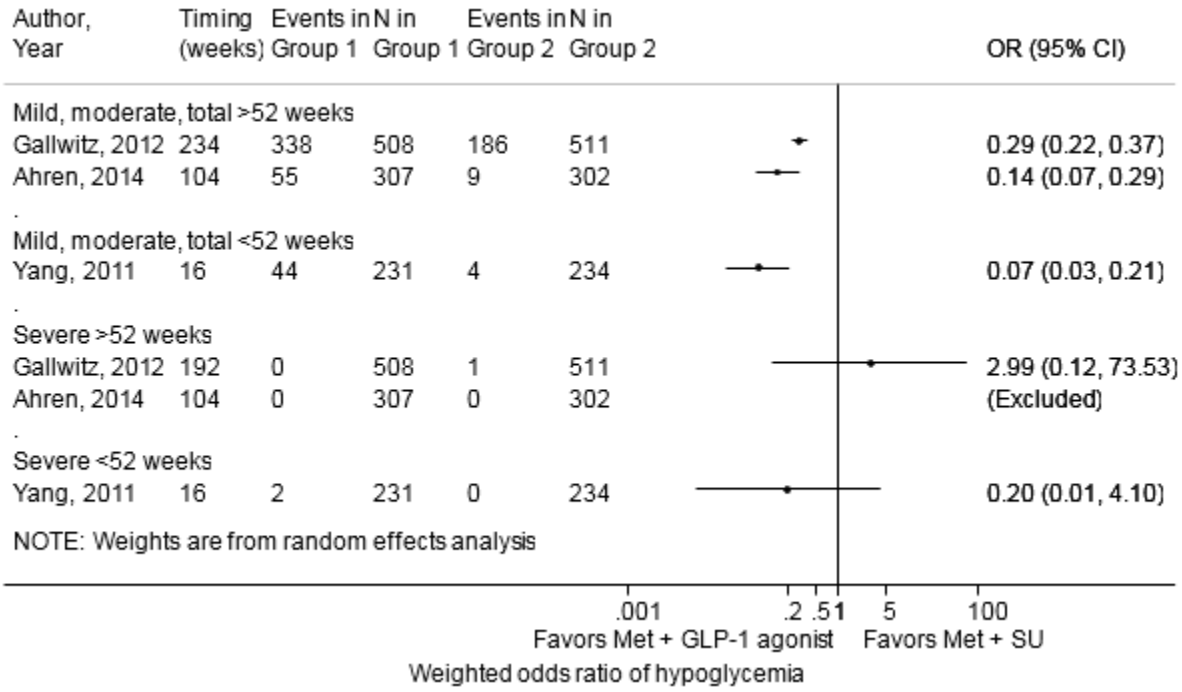
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

* The profile likelihood estimate provided a similar result.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Three RCTs compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a GLP-1 agonist, showing a lower risk of total/mild/moderate hypoglycemia with the combination of metformin plus a GLP-1 agonist and no clear differences between groups in severe hypoglycemia risk (Figure 69).[110, 185, 187] No meta-analysis could be conducted for this comparison due to differences in study duration and hypoglycemia definitions. In all studies, glimepiride was the sulfonylurea given in combination with metformin. (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored for mild, moderate, or total hypoglycemia) (SOE: Low, Neither favored for severe hypoglycemia)

Figure 69. Odds ratio of hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a GLP-1 agonist, stratified by study duration and severity of hypoglycemia



CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a glucagon-like peptide-1 agonist; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

One study addressed this comparison, favoring metformin and insulin glargine. This 48-week RCT compared metformin and glimepiride with metformin and insulin glargine.[189] While patients continued on the same pre-study dose of metformin of around 1500 mg, both the sulfonylurea and the insulin glargine were titrated to reach blood sugar targets. Nineteen patients out of 30 (63%) in the metformin plus glimepiride arm had mild hypoglycemia compared with 10 out of 34 (29%) in the metformin plus insulin glargine arm. No severe hypoglycemia events occurred in either treatment arm. (SOE: Low; Combination of metformin plus basal insulin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither arm favored for severe hypoglycemia)

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

Two RCTs compared metformin plus sulfonylurea with metformin plus a premixed insulin, showing no clear differences between groups in hypoglycemia risk (Table 58).[190, 191] (SOE: Low; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Insufficient; Unable to draw a conclusion for severe hypoglycemia)

Table 58. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a premixed insulin on hypoglycemia

Author, year	Followup	Comparison	Outcome	Results
Malone, 2003[190]	16 weeks	Metformin + glargine versus metformin + lispro 75/25	Nocturnal	(N = 597 in trial) Greater number of participants with nocturnal hypoglycemia (p < 0.01) with metformin plus sulfonylurea than metformin plus insulin.
			Severe	Comparable number with severe hypoglycemia (p=0.10)
Kvapil, 2006[191]	16 weeks	Metformin + glibenclamide versus metformin + aspart 70/30	Mild or moderate	9/114 versus 13/108; RR = 1.5 (95% CI, 0.7 to 3.4)

CI = confidence interval; RR = relative risk

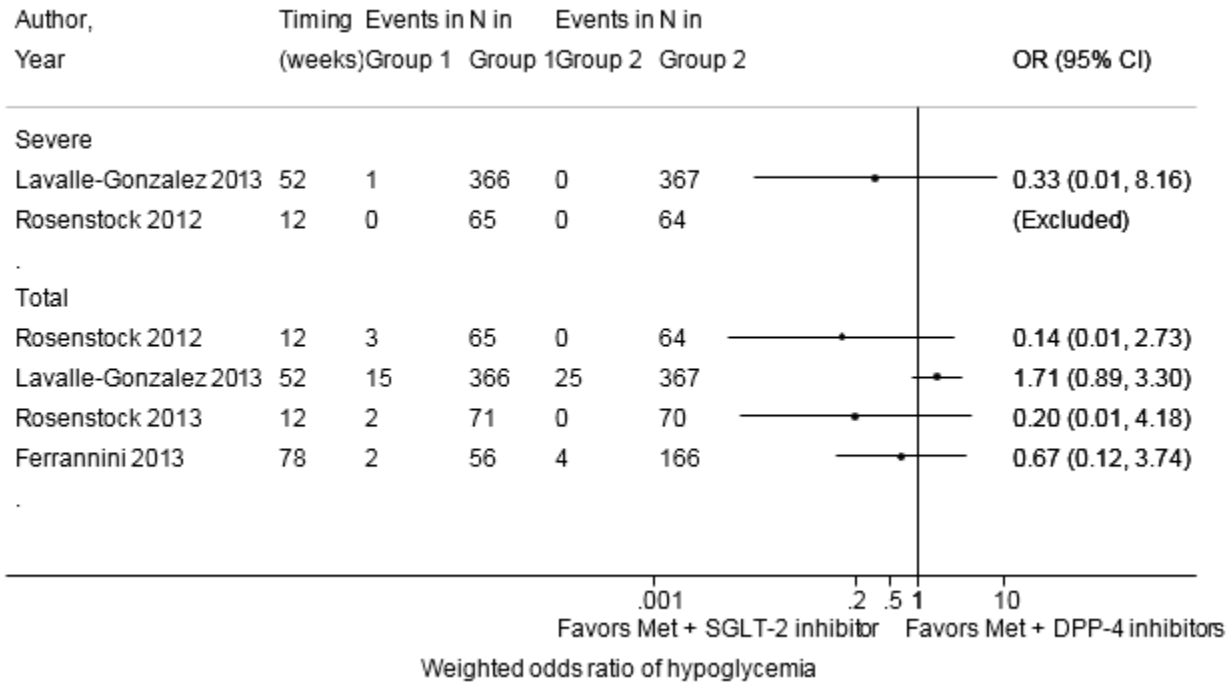
Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Four studies considered hypoglycemia for this comparison, showing no clear between-group differences in hypoglycemia risk (Figure 70). Two RCTs with equipotent doses in each arm showed no significant between-group differences in severe hypoglycemia risk.[125, 127]

One 52-week RCT[127] randomized 714 patients to metformin plus sitagliptin or metformin plus canagliflozin, finding 4.1% of patients in the metformin plus sitagliptin arm with any hypoglycemic event, compared with 6.8% of patients in the metformin plus canagliflozin arm. A 78-week lower quality RCT[82] found 3.6% of patients with any hypoglycemic event in the metformin plus sitagliptin arm, 1.8% of patients with such events in the low-dose metformin plus empagliflozin arm, and 2.4% of patients in the high-dose metformin plus empagliflozin arm.

Two shorter RCTs assessed total hypoglycemia with followup at 12 weeks, showing a non-significant greater risk of total hypoglycemia in the metformin plus DPP-4 inhibitor arms.[122, 125] (SOE: Low; Neither arm favored for mild, moderate, total, or severe hypoglycemia)

Figure 70. Odds ratio of hypoglycemia comparing a combination of metformin plus a SGLT-2 inhibitor with a combination of metformin plus a DPP-4 inhibitor, stratified by severity of hypoglycemia



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Three studies reported on hypoglycemia for this comparison, showing no clear between-group differences in hypoglycemia risk (Table 59).[110, 128, 173] All three studies compared metformin plus sitagliptin, but each of the studies used a different GLP-1 agonist in the metformin plus GLP-1 agonist comparator arm (albiglutide, exenatide, and dulaglutide). None of the three studies had any severe hypoglycemia in either arm. For mild to moderate hypoglycemia, there are conflicting results with two of the three studies favoring the metformin plus DPP-4 inhibitor arms. This may be due to different types of GLP-1 agonists although there may be unidentified sources of heterogeneity too. (SOE: Low; Neither arm favored for mild, moderate, total, or severe hypoglycemia)

Table 59. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist on hypoglycemia

Author, year	Followup (weeks)	Metformin + DPP-4 inhibitor (dose*)	Metformin + GLP-1 agonist (dose*)	Definition of hypoglycemia	Results† (Metformin + DPP-4 inhibitor vs metformin + GLP-1 agonist)
Ahren, 2014[110]	104	Metformin (fixed at ≥ 1500 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed at ≥ 1500 mg) + albiglutide (max 50 mg weekly)	Mild-moderate (asymptomatic, but BG ≤ 3.9 mmol/L)	4/302 (1.3%) vs 4/302 (1.3%)
				Mild-moderate (symptomatic and BG ≤ 3.9 mmol/L)	5/302 (1.7%) vs 9/302 (3%)
				Severe (required third party assistance)	0/302 (0%) vs 0/302 (0%)
Bergenstal, 2010[173]	26	Metformin (fixed, mean 1583 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed, mean 1504 mg) + exenatide (fixed at 2 mg weekly)	Mild-moderate (symptomatic and BG < 3 mmol/L)	5/166 (3%) vs 2/160 (1.3%)
				Severe‡	0/166 (0%) vs 0/160 (0%)
Nauck, 2014[128]	52	Metformin (fixed at ≥ 1500 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed 0.75 mg weekly)	Mild-moderate (signs, symptoms and/or BG ≤ 70 mg/dL)	15/315 (4.8%) vs 16/302 (5.3%)
				Severe (required third party assistance)	0/315 (0%) vs 0/302 (0%)
		Metformin (fixed at ≥ 1500 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed 1.5 mg weekly)	Mild-moderate (signs, symptoms and/or BG ≤ 70 mg/dL)	15/315 (4.8%) vs 31/304 (10.2%)
				Severe (required third party assistance)	0/315 (0%) vs 0/304 (0%)

BG = blood glucose; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Severe hypoglycemia was defined as a loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L.

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

One RCT assessed hypoglycemia for this comparison, finding more hypoglycemic events in the metformin plus insulin arm (Table 60).[193] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 60. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a basal insulin on hypoglycemia

Author, year	Followup (weeks)	Metformin + DPP-4 inhibitor (dose*)	Metformin + basal insulin (dose*)	Definition of hypoglycemia	Results† (Metformin + DPP-4 inhibitor vs metformin + basal insulin)
Aschner, 2012[193]	24	Metformin (baseline dose 1835 mg) + sitagliptin (fixed at 100 mg)	Metformin (baseline dose 1852 mg) + insulin glargine (max 0.5 U/kg)	Severe (severe symptomatic) Total (symptomatic and BG ≤ 3.9 mmol/L)	1/264 (0.4%) vs 3/237 (1.3%) 28/264 (10.6%) vs 86/237 (36.3%)

BG = blood glucose; DPP-4 = dipeptidyl peptidase-4; max = maximum; mg = milligrams; mmol/L = millimole per liter; U/kg = units per kilogram

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

Three RCTs (reported in four articles) compared metformin plus basal insulin with the combination of metformin plus exenatide, with lower risk of mild or moderate hypoglycemia in the metformin plus exenatide arms in all three studies (Table 61).[47, 194, 195, 256] One of the three RCTs (reported in two articles) initially reported their 56-week followup data and later their 168-week followup data.[47, 195] Twenty-five percent of the patients in the metformin plus exenatide arm were taking above maximally-approved doses of exenatide,[47, 195] yet the patients in the metformin plus insulin arm still had greater hypoglycemia than the metformin plus exenatide arm. The two RCTs which reported on severe hypoglycemia showed no between-group differences in severe hypoglycemia.[194, 256] (SOE: Moderate; Combination of metformin plus a GLP-1 agonist favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 61. Randomized controlled trials comparing a combination of metformin plus a GLP-1 agonist with a combination of metformin plus a basal insulin on hypoglycemia

Author, year	Followup (weeks)	Metformin + GLP-1 agonist (dose*)	Metformin + basal insulin (dose*)	Definition of hypoglycemia	Results† (Metformin + GLP-1 agonist vs metformin + basal insulin)
Davies, 2013[256]	26	Metformin (fixed at ≥ 1000 mg) + exenatide (fixed at 2 mg weekly)	Metformin (fixed at ≥ 1000 mg) + insulin detemir (mean initial dose 0.21 IU/kg; mean end dose 20.8 IU, end dose 0.51 IU/kg)	Mild-moderate (symptoms that were self-treated or resolved on their own, with documented BG < 3.0 mmol/L) Severe hypoglycemia‡	0/33 (0%) vs 1/29 (3.4%) 0/33 (0%) vs 0/29 (0%)
Bunck, 2011[47] Bunck, 2009[195]	168	Metformin (fixed at pre-enrollment dose) + exenatide + (max 60 ug)	Metformin (fixed at pre-enrollment dose) + insulin glargine (mean 33.7 IU)	Mild-moderate (BG < 3.0 mmol/L)	7/36 (19.4%) vs 9/33 (27.3%) at 168 weeks 3/36 (8.3%) vs 8/33 (24.2%) at 56 weeks
Diamant, 2010[194]	84	Metformin (continued stable dose) + exenatide (fixed at 2 mg weekly)	Metformin (continued stable dose) + insulin glargine (started at 10 IU then titrate to glycemic goal of 4-5.5 mmol/L)	Mild-moderate (symptoms and BG < 3.0 mmol/L and was either self-treated or resolved independently) Severe hypoglycemia‡	13/164 (7.9%) vs 51/157 (32.5%) 1/164 (0.6%) vs 1/157 (0.6%)

BG = blood glucose; GLP-1 = glucagon-like peptide-1; IU = international units; IU/kg = international units per kilogram; mg = milligrams; mmol/L = millimole per liter;
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.
‡ Any hypoglycemic episode with symptoms consistent with hypoglycemia that led to loss of consciousness or seizure, with prompt recovery in response to glucagon or glucose administration, or documented hypoglycemia [blood glucose <3.0mmol] necessitating assistance of another person

Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One study assessed this comparison, showing less hypoglycemia in the metformin plus GLP-1 agonist arm compared with the metformin plus premixed insulin arm. This 26-week RCT found an incidence of first hypoglycemic episodes of 8.0% in the metformin plus exenatide group versus 20.5% in the metformin plus insulin aspart 70/30 group.[196] No severe hypoglycemia was reported. (SOE: Low; Combination of metformin plus a GLP-1 agonist favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

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

Five trials examined the comparison of metformin plus basal insulin to metformin plus a mix of long- and short-acting insulin, consistently favoring the former (Table 62).[197-199, 206, 207] Due to the heterogeneity of these trials (I-squared = 78.8%) they were not pooled in a meta-analysis. The heterogeneity may be due to the difference in followup times, insulin preparations, and insulin dosing. (SOE: Moderate; Combination of metformin plus a basal insulin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither arm favored for severe hypoglycemia)

Table 62. Randomized controlled trials comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin on hypoglycemia

Author, year	Comparison	Outcome	Results	RR and comments (combination metformin and another insulin as reference group)
Malone, 2004[206]	Metformin + glargine versus metformin + lispro 75/25	Mild or moderate at 32 weeks	40/101 versus 57/100 (87 versus 181 events)	RR = 0.69 (95% CI 0.5 to 0.9), both arms of cross-over pooled
		Severe at 32 weeks	None	NA
Malone, 2005[207]	Metformin + glargine versus metformin + lispro 75/25	Mild or moderate at 32 weeks	0.44 versus 0.61 events/patient/30 days	P = 0.47; more daytime hypoglycemia with lispro 75/25 but less nocturnal hypoglycemia
		Severe at 32 weeks	None	NA
Raskin, 2007[198]	Metformin + glargine versus metformin + aspart 70/30	Mild or moderate at 28 weeks	11/78 versus 33/79 (23 versus 121 events)	RR = 0.34 (95% CI 0.2 to 0.6)
Robbins, 2007[197]	Metformin + glargine versus metformin + lispro 50/50	Mild or moderate at 24 weeks	75/158 versus 79/157	RR = 0.94 (95% CI 0.8 to 1)
		Severe at 24 weeks	2/158 versus 3/157	RR = 0.66 (95% CI 0.1 to 4)
Davies, 2007[199]	Metformin + NPH versus metformin + NPH/regular 70/30	Mild or moderate	7/29 versus 8/27	RR = 0.81 (95% CI 0.34 to 1.9); a poorly conducted trial

CI = confidence interval; NA = not available; NPH = neutral protamine Hagedorn; RR = relative risk

Strength of Evidence for Hypoglycemia

As noted in the Key Points and Table Hypo 14 and Table 64, we found moderate or high strength of evidence for many of the monotherapy comparisons evaluating hypoglycemia and also found a number of combination comparisons with high or moderate strength of evidence. We found several comparisons of interest for which there was no or minimal evidence, especially among the combination comparisons. Study limitations for most comparisons were low or medium with only two comparisons having high study limitations due to lack of blinding, lack of description of withdrawals and dropouts, or high losses to followup. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. When we found low strength of evidence for hypoglycemia, this tended to occur in the setting of fair to poor study quality and inconsistency for monotherapy comparisons, and was related more to insufficient data in the combination comparisons. We generally found consistency among studies

if there were more than three studies for a given comparison. Most evidence on hypoglycemia was precise for monotherapy comparisons; there was less precision when there were fewer studies, as in the combination comparisons. We did not find any evidence of publication bias using the Begg's and Egger's test for the comparisons with greater than ten studies. We did identify a few unpublished studies that could have influenced our rating of the evidence. A single unpublished study found more hypoglycemia in a DPP-4 inhibitor arm than in the comparator metformin arm; this was not consistent with our meta-analysis findings for this comparison. This did not change our conclusions for this comparison due to the small effect. Also, we identified two additional studies of the comparison of sulfonylurea to DPP-4 inhibitor monotherapy which were consistent with the published studies; the addition of this evidence may have allowed us to rate the strength of evidence as high for this comparison.

Table 63. Strength of evidence domains for monotherapy comparisons in terms of hypoglycemia among adults with type 2 diabetes

Comparison	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD	Mild, moderate, total	5 (4,197)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Metformin favored
	Severe	1 (409)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. SU	Mild, moderate, total	RCTs: 14 (7,332)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; combined OR for mild-moderate hypoglycemia for SU vs. metformin, 4.00; 95% CI, 1.75 to 9.83
		Observational: 1 (1789)	Medium	Unknown	Direct	Precise	n/a		
	Severe	2 (376)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin favored
Metformin vs. DPP-4 inhibitors	Mild, moderate, total	6 (6,710)	High	Consistent for symptomatic hypoglycemia	Direct	Precise	Suspected	Low	DPP-4 inhibitor favored
	Severe	6 (6,710)	High	Inconsistent	Direct	Imprecise	Suspected	Low	Neither favored
Metformin vs. SGLT-2 inhibitors	Mild, moderate, total	5 (2,700)	Medium	Consistent	Direct	Precise	Undetected	Moderate	SGLT-2 inhibitors favored; combined OR for SGLT-2 vs. metformin, 0.46; 95% CI, 0.16 to 1.30
	Severe	2 (831)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. GLP-1 agonists	Mild, moderate, total	3 (1360)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin favored
	Severe	3 (1360)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. Metformin + TZD	Mild, moderate, total	10 (3,906)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; combined OR for metformin plus TZD vs. metformin, 1.56; 95% CI, 0.99 to 2.44
Metformin vs. Metformin + SU	Mild, moderate, total	12 (3,732)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; pooled OR for metformin + SU vs. metformin, 5.02; 95% CI, 2.36 to 15.01
	Severe	2 (544)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

Metformin vs. Metformin + DPP-4 inhibitors	Mild, moderate, total	25 (17,011)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored; pooled OR for metformin + DPP-4 inhibitor vs. metformin: Mild-moderate, 0.97; 95% CI, 0.63 to 1.51 Total, 0.92; 95% CI: 0.43 to 1.97
	Severe	11 (5,369)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Neither favored; pooled OR for metformin + DPP-4 inhibitor vs. metformin, 0.63; 95% CI, 0.08 to 5.12
Metformin vs. Metformin + SGLT-2 inhibitors	Mild, moderate, total	9 (5,778)	Low	Consistent	Direct	Precise	Undetected	Moderate	Metformin favored: pooled OR for metformin + SGLT-2 inhibitor vs. metformin, 1.62; 95% CI, 0.75 to 3.49
	Severe	6 (2,534)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. Metformin + GLP-1 agonists	Mild, moderate, total	3 (2,318)	High	Inconsistent	Direct	Precise	Undetected	Low	Metformin favored
	Severe	2 (1,186)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. SU	Mild, moderate, total	8 (6,212)	Low	Consistent	Direct	Precise	Undetected	High	TZD favored Total hypoglycemia Pooled OR for SU vs. TZD: 6.31; 95% CI, 4.08 to 9.76
	Severe	2 (3,304)	Low	Consistent	Direct	Precise	Undetected	Moderate	TZD favored
TZD vs. DPP-4 inhibitors	Mild, moderate, total	3 (1,686)	Low	Inconsistent	Direct	Precise	Undetected	Low	Neither favored
	Severe	2 (653)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. GLP-1 agonists	Mild, moderate, total	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	TZD favored
	Severe	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
SU vs. DPP-4	Mild,	4 (1,065)	Medium	Consistent	Direct	Precise	Undetected	Moderate	DPP-4 favored

inhibitors	moderate, total								
	Severe	2 (623)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	DPP-4 favored
SU vs. GLP-1 agonists	Mild, moderate, total	5 (2,467)	Medium	Consistent	Direct	Precise	Undetected	Moderate	GLP-1 favored for mild-moderate hypoglycemia;
	Severe	3 (1546)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	Mild, moderate, total	1 (670)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
	Severe	1 (670)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
DPP-4 inhibitors vs. GLP-1 agonists	Mild, moderate, total	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	DPP-4 favored
	Severe	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

CI = confidence interval; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; OR = odds ratio; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

Table 64. Strength of evidence domains for metformin-based combination comparisons in terms of hypoglycemia among adults with type 2 diabetes

Comparison	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin + SU	Mild, moderate, total	7 (975)	Medium	Consistent	Direct	Imprecise	Undetected	High	Metformin + TZD favored: Pooled OR, for metformin + SU compared to metformin +TZD, 7.5; 95% CI, 4.0 to 13.8
	Severe	1 (314)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 inhibitors	Mild, moderate, total	2 (603)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
	Severe	RCT 1 (491) Observational study 1 (83)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Neither favored
Metformin + TZD vs. metformin + GLP-1 agonists	Mild, moderate, total	2 (415)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
	Severe	2 (415)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
Metformin + SU vs. metformin + DPP-4 inhibitors	Mild, moderate, total	9 (6,039)	Medium	Consistent	Direct	Imprecise	Undetected	High	Metformin + DPP4-inhibitors favored
	Severe	6 (4,717)	Medium	Consistent	Direct	Imprecise	Undetected	High	Metformin + DPP-4 inhibitors favored
Metformin + SU vs. metformin + SGLT-2 inhibitors	Mild, moderate, total	3 (3,815)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored compared to metformin and SU, 0.07 95% CI, 0.03 to 0.13 for mild and total hypoglycemia
	Severe	2 (1,779)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + SGLT-2 inhibitors favored
Metformin + SU vs. metformin +	Mild, moderate, total	3 (2,557)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 inhibitor favored

GLP-1 agonists									
	Severe	3 (2,557)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + basal insulin	Mild, moderate, total	1 (75)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + insulin favored
	Severe	1 (75)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + SU vs. metformin + premixed insulin	Mild, moderate, total	2 (827)	Medium	Consistent	Direct	Imprecise	Suspected	Low	Neither arm favored
	Severe	1 (597)	High	Unknown	Direct	Imprecise	Suspected	Insufficient	Unable to draw a conclusion
Metformin + DPP-4 inhibitors vs. metformin +SGLT-2 inhibitors	Mild, moderate, total	4 (2,889)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither arm favored
	Severe	2 (1,359)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	Mild, moderate, total	3 (1,851)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Neither arm favored
	Severe	3 (1,851)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + DPP-4 inhibitors vs. metformin + basal insulin	Mild, moderate, total	1 (515)	Medium	Unknown	Direct	Precise	Undetected	Low	Metformin + DPP-4 inhibitor favored
	Severe	1 (515)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + GLP-1 agonists vs. metformin + basal insulin	Mild, moderate, total	3 (452)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + GLP-1 agonist favored
	Severe	2 (383)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + GLP-1 agonists vs.	Mild, moderate, total	1 (363)	High	N/A	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 agonist favored

metformin + premixed insulin									
	Severe	1 (363)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + basal insulin vs. metformin + premixed insulin	Mild, moderate, total	5 (530)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + basal insulin favored
	Severe	3 (613)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

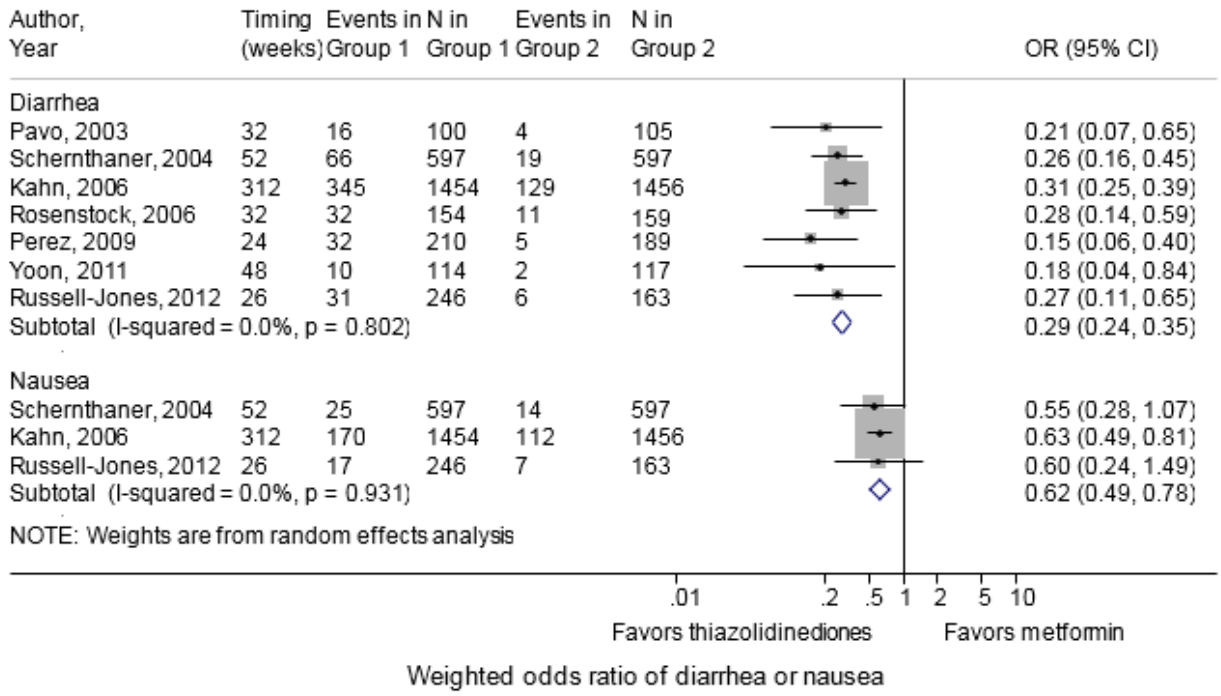
The Evidence About Gastrointestinal Side Effects

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Eight RCTs compared GI adverse events between metformin and either pioglitazone or rosiglitazone.[45, 52, 55, 57, 60, 63, 66, 67] GI adverse events were more common with metformin compared with thiazolidinediones in the majority of RCTs, except for dyspepsia where the number of events were comparable for both treatments. More people had diarrhea and had nausea with metformin than thiazolidinediones (Figure 71). There was little heterogeneity between these studies and no overly influential studies. (SOE: Moderate; Thiazolidinediones favored for diarrhea and nausea)

Figure 71. Pooled odds ratio of gastrointestinal adverse events comparing metformin with thiazolidinediones



CI = confidence interval; Group 1 = metformin; Group 2 = thiazolidinediones; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus Sulfonylureas

Twelve RCTs compared GI adverse events between metformin and a second-generation sulfonylurea.[45, 67, 98-100, 102, 103, 105-107, 238, 248] GI adverse events tended to be more common with metformin than with sulfonylurea (Table 65). Based on meta-analyses, there were fewer GI adverse events with sulfonylureas than metformin for the outcomes of diarrhea (OR, 0.41; 95% CI, 0.28 to 0.59; I-squared, 47.5%; seven studies), abdominal pain (OR, 0.57; 95% CI, 0.40 to 0.81; I-squared, 35.1%; four studies), nausea and vomiting (OR, 0.45; 95% CI, 0.31 to 0.65; I-

squared, 0%; three studies) and any GI adverse event (OR, 0.48; 95% CI, 0.37 to 0.62; I-squared, 22.0%; six studies). (SOE: Moderate; Sulfonylureas favored)

Table 65. Studies comparing metformin with sulfonylureas on gastrointestinal adverse events

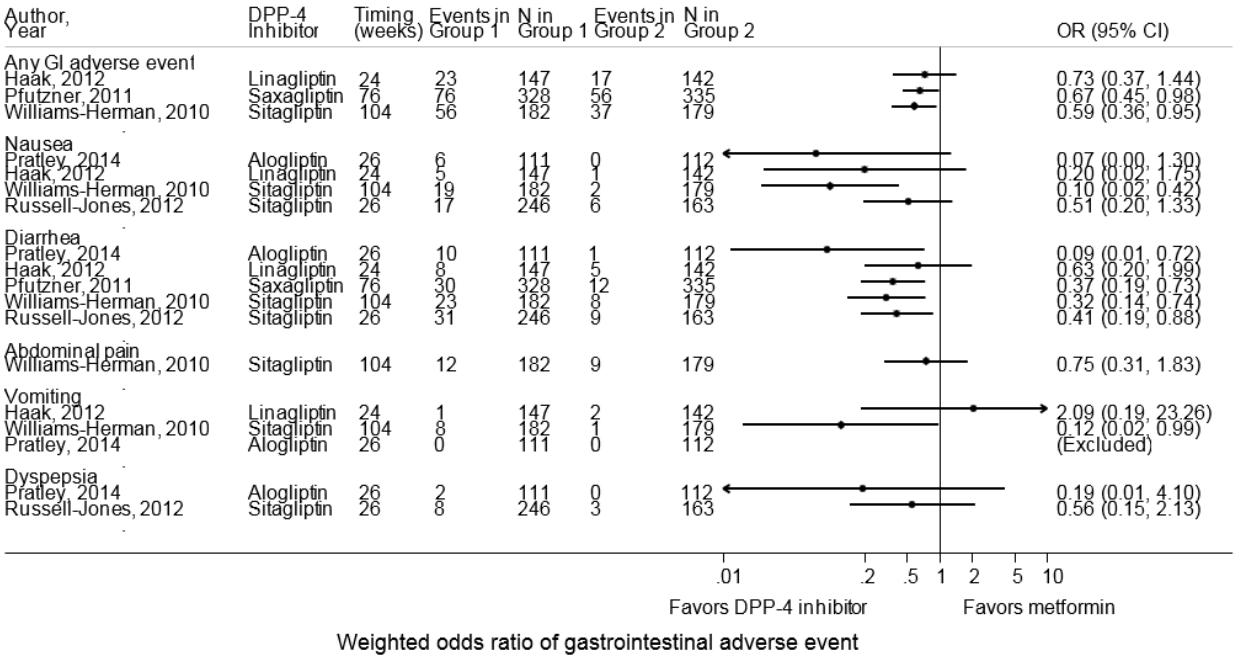
Author, year	Outcome	Event rates (metformin versus sulfonylureas)
Hermann, 1994[103]	Any GI outcome Abdominal pain Diarrhea Nausea Withdrawal for GI symptoms	63% (24/38) versus 32% (11/34) 18% (7/38) versus 6% (2/34) 50% (19/38) versus 0 (0/34) 24% (9/38) versus 9% (3/34) 14% versus 0%
DeFronzo, 1995[106]	Nausea and diarrhea	1.4% (3/210) versus 1.0% (2/209)
Amador-Licona, 2000[238]	Diarrhea and abdominal pain	14.3% (4/28) for metformin; event rates are not reported for sulfonylurea
Charpentier, 2001[105]	Diarrhea	7% (5/75) versus 1% (1/150)
Blonde, 2002[100]	Nausea and vomiting Dyspepsia/heartburn Flatulence	12.4% (19/153) versus 5.5% (9/164) 4.6% (7/153) versus 3% (5/164) 2% (3/153) versus 0% (0/164)
Garber, 2002[102]	 Any GI outcome Diarrhea Nausea/vomiting Abdominal pain Dyspepsia	Metformin (n = 159); glyburide (n = 160) 43% versus 24% 15.1% versus 4.4% 6.3% versus 0.6% 5% versus 3.1% 5% versus 2.5%
Garber, 2003[98]	Nausea/vomiting Abdominal pain Diarrhea	10.4% (17/164) versus 6.6% (10/151) 6.1% (10/164) versus 4% (6/151) 18% (30/164) versus 5.3% (18/151)
Goldstein, 2003[99]	Diarrhea	17.3% (13/75) versus 13.1% (11/84)
Derosa, 2004[248]	Nausea and diarrhea	2.4% (2/75) versus 0% (0/73)
Kahn, 2006[45]	Combined GI events Nausea Vomiting Diarrhea Abdominal discomfort	38% (557/1454) versus 22% (316/1441) 11.7% (170/1454) versus 6.9% (99/1441) 5.8% (84/1454) versus 3.1% (45/1441) 23.7% (345/1454) versus 9.9% (142/1441) 15.4% (224/1454) versus 11.3% (163/1441)
Chien, 2007[107]	Combined GI events	32% (8/25) versus 13% (3/23)
Yoon, 2011[67]	Diarrhea Discomfort, pain, nausea or vomiting	8.8% (10/114) versus 3.4% (4/118) 8.8% (10/114) versus 8.5% (10/118)

GI = gastrointestinal

Metformin Versus DPP-4 Inhibitors

Six RCTs compared metformin with a DPP-4 inhibitor and reported on GI adverse events.[66, 74, 76-79] Metformin had more GI adverse events compared with each of the DPP-4 inhibitors (Figure 72). One trial identified solely in ClinicalTrials.gov had results consistent with the published studies (NCT01076088). We combined the three studies with similar study durations and dosages for nausea and diarrhea. We did not combine “any” GI adverse event outcomes since study durations were not sufficiently similar. Based on meta-analyses, there were fewer nausea outcomes for DPP-4 inhibitors compared with metformin (pooled OR, 2.7; 95% CI, 1.1 to 6.6; I-squared, 4%; three studies) and fewer diarrhea outcomes (pooled OR, 2.6, 95% CI, 1.2 to 5.5; I-squared, 25%; three studies). The excluded longer studies were consistent with the findings favoring DPP-4 inhibitors over metformin (Figure 72). (SOE: High; DPP-4 inhibitors favored)

Figure 72. Odds ratio of gastrointestinal adverse events comparing metformin with DPP-4 inhibitors



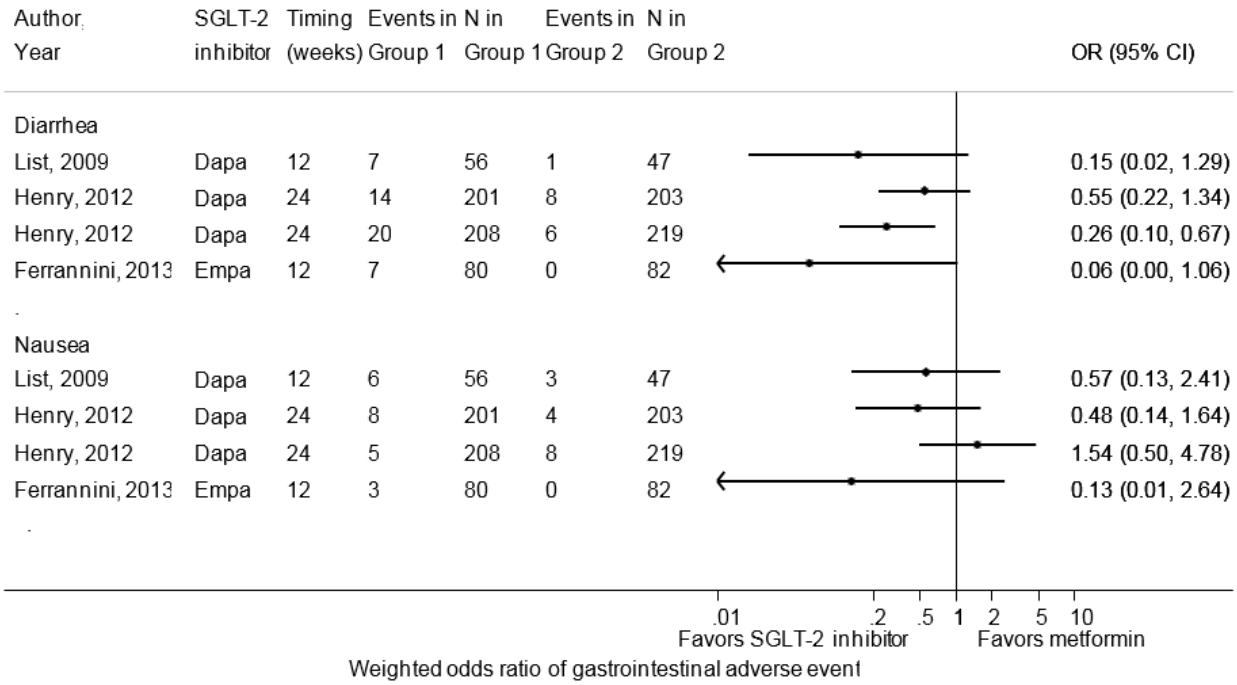
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = dipeptidyl peptidase-4 inhibitors; OR = odds ratio

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus SGLT-2 Inhibitors

Three trials (published in two articles) compared metformin with dapagliflozin.[80, 81] One trial compared metformin with empagliflozin,[227] Diarrhea and nausea tended to be more common with metformin than with the SGLT-2 inhibitors (Figure 73). We did not pool the trials due to dosage differences. (SOE: Low; SGLT-2 inhibitors favored for diarrhea and nausea)

Figure 73. Odds ratio of gastrointestinal adverse events comparing metformin with SGLT-2 inhibitors

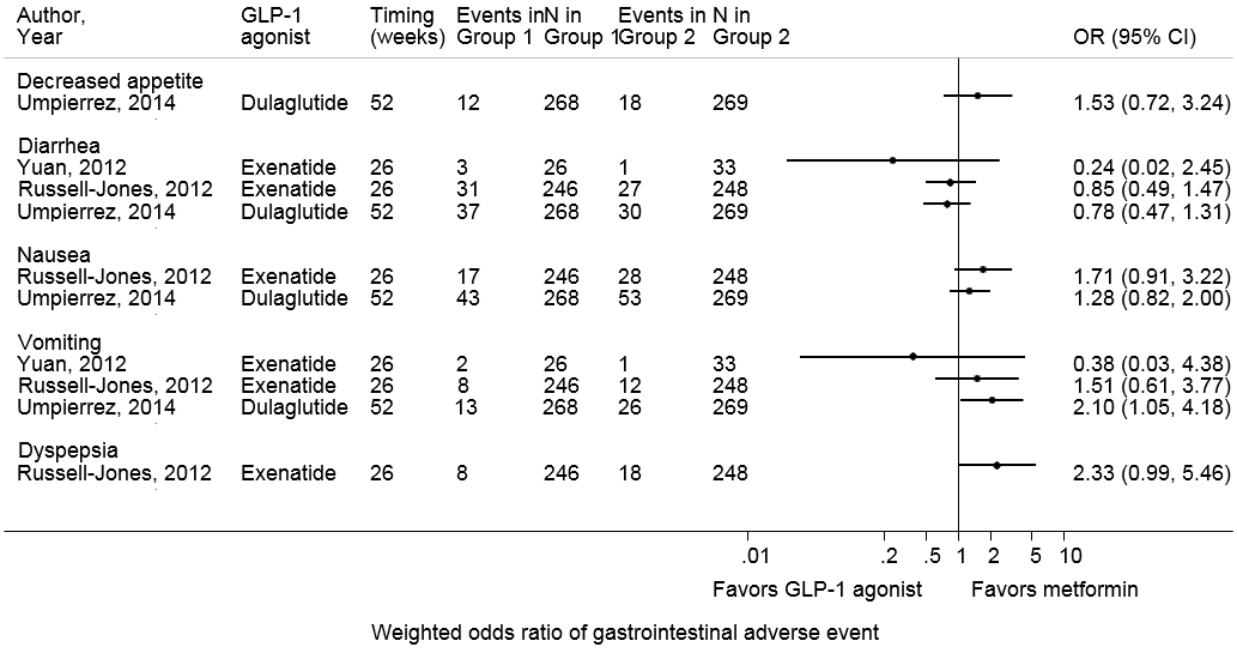


CI = confidence interval; Dapa = dapagliflozin; Empa = empagliflozin, Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus GLP-1 Agonists

Two trials compared metformin with exenatide.[66, 84] One trial compared metformin with once-weekly subcutaneously injected 0.75 mg or 1.5 mg of dulaglutide.[83] Diarrhea non-significantly differed between metformin and GLP-1 agonists (OR, 0.78; 95% CI, 0.54 to 1.14; I-squared, 0%; three studies). However, nausea (OR, 1.28 and 1.71), vomiting (pooled OR, 1.73; 95% CI, 1.01 to 2.95; I-squared 0%; three studies) and dyspepsia (OR, 2.33) were more common with the GLP-1 agonists (Figure 74). (SOE: Low; GLP-1 agonists favored for diarrhea; SOE: Moderate; Metformin favored for nausea)

Figure 74. Odds ratio of gastrointestinal adverse events comparing metformin with GLP-1 agonists



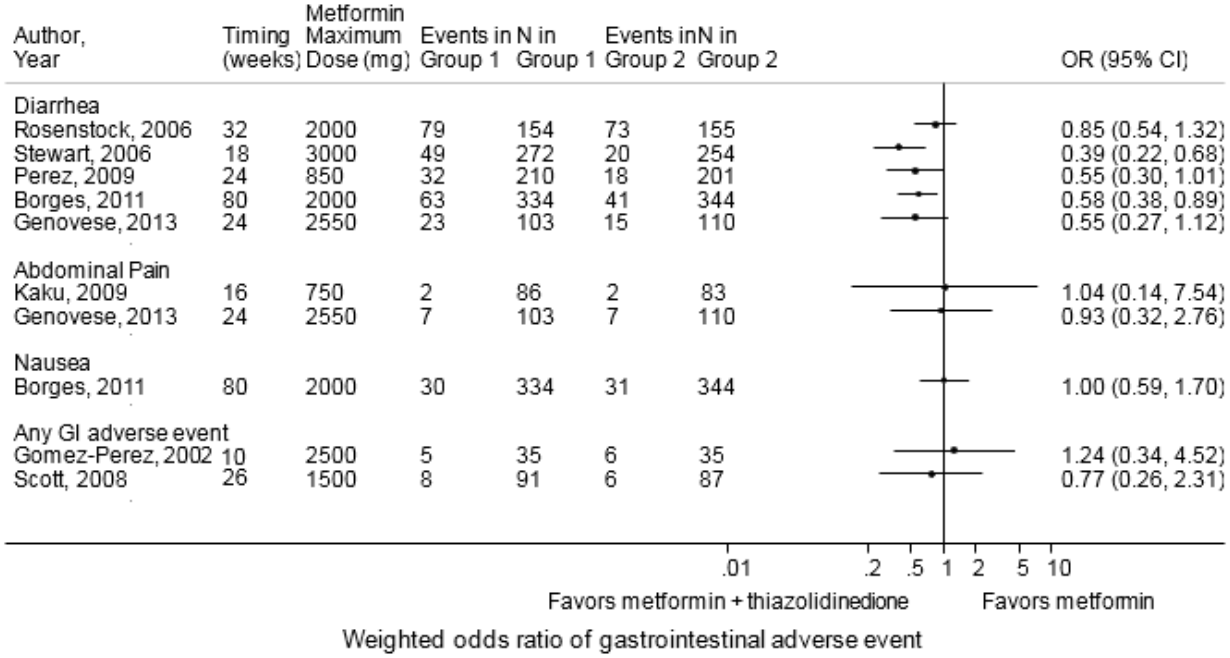
CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = metformin; Group 2 = glucagon-like peptide-1 agonists; OR = odds ratio

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Ten RCTs compared the rates of GI adverse events with metformin to a combination of metformin and a thiazolidinedione. Diarrhea tended to be more common among the metformin monotherapy group (OR, 0.59; 95% CI, 0.45 to 0.76; I-squared, 16.4%; five studies), with no consistent differences in other GI-related adverse events (Figure 75).[52, 60, 86-90, 94, 96, 234] Dose of metformin was generally similar in both arms within trials and differences in dose between trials did not appear to impact the GI adverse events. (SOE: Low; Combination of metformin plus a thiazolidinedione favored for diarrhea; neither favored for other GI-related outcomes)

Figure 75. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a thiazolidinedione

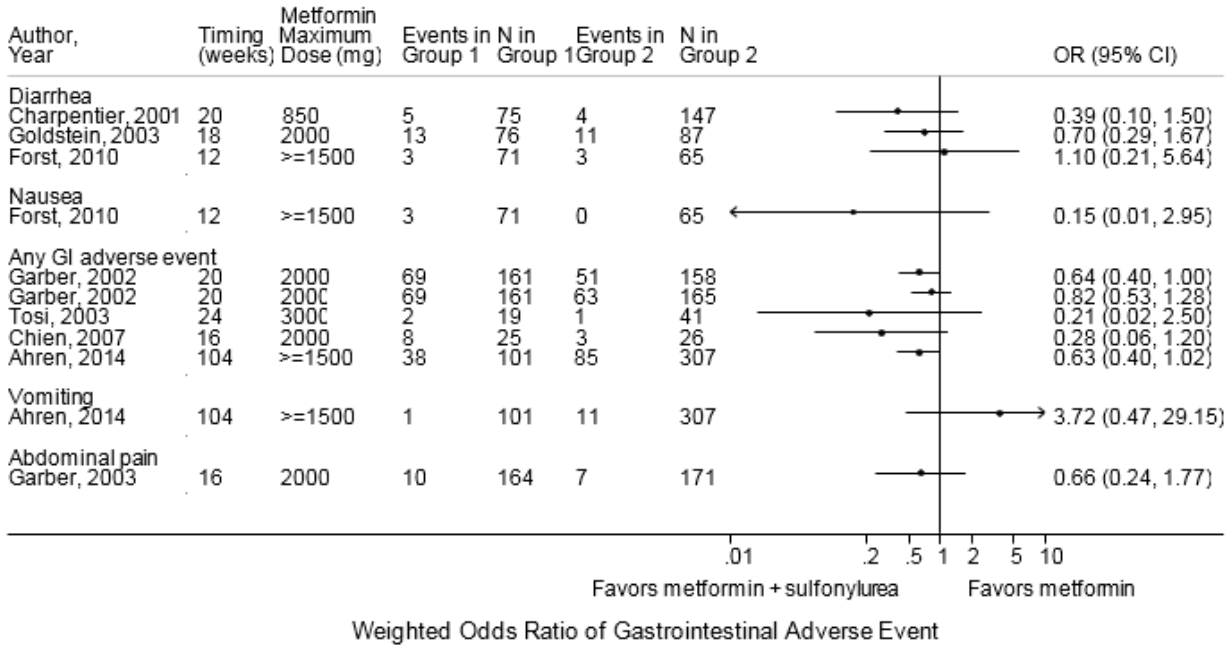


CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a thiazolidinedione; mg = milligrams; OR = odds ratio
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Twelve RCTs examined GI adverse events comparing metformin to metformin plus a second-generation sulfonylurea.[42, 98-100, 102, 103, 105-110] GI-related adverse events may be more common with monotherapy than with combination therapy (Figure 76). For the outcomes with at least 3 studies, the pooled OR were 0.66 (95% CI, 0.34 to 1.28; I-squared, 0%; three studies) for diarrhea. We did not combine the four studies reporting on any GI adverse event due to differences in study duration and dosing differences. Two of the studies used lower doses of metformin with combination therapy compared with monotherapy.[42, 98] Studies that reported on combinations of adverse events that did not conform with the definition of “any” adverse event, which were diarrhea, nausea, vomiting or pain, are not included in the summary figure. (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Figure 76. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a sulfonylurea*



CI = confidence interval; GI = gastrointestinal; Group 1 = metformin; Group 2 = combination of metformin plus a sulfonylurea; mg = milligrams; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

*Studies with more than one dosing arm under the same gastrointestinal outcome are reported twice in the figure to demonstrate effects of different dosing arms

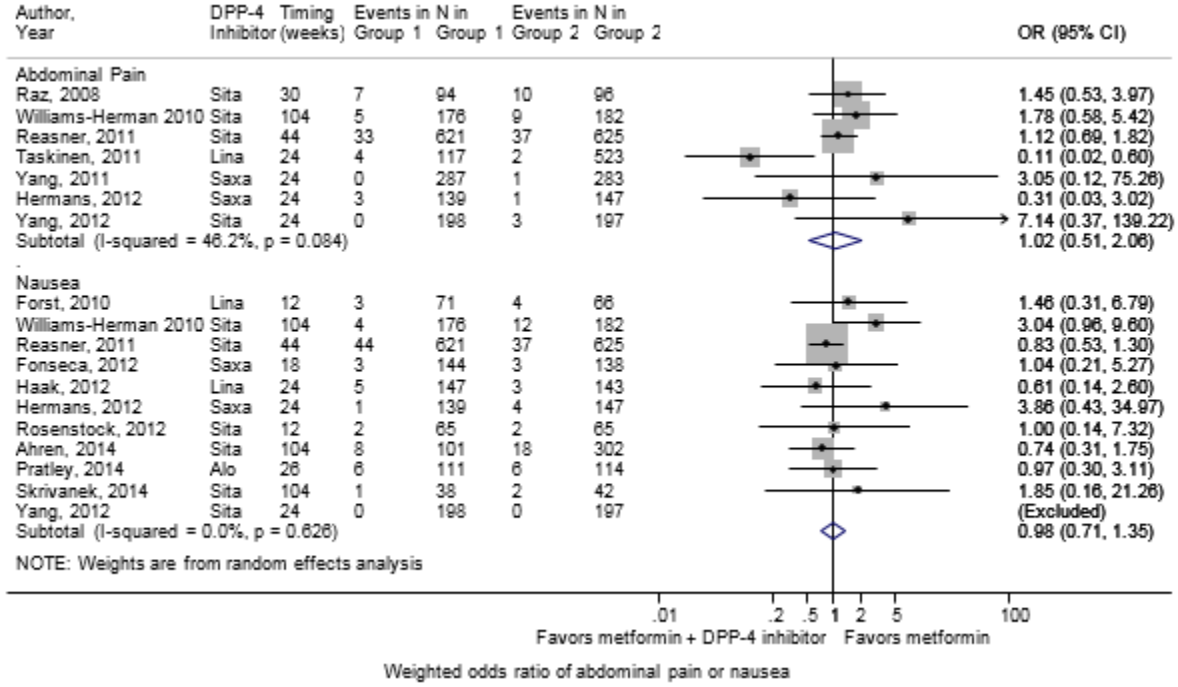
Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three RCTs compared metformin with metformin plus alogliptin.[76, 123, 126] Four RCTs compared metformin with metformin plus linagliptin.[78, 108, 121, 124] Six RCTs compared GI adverse events between metformin and metformin plus saxagliptin.[79, 113, 115, 116, 120, 129] Twelve RCTs compared GI adverse events between metformin and metformin plus sitagliptin.[77, 87, 110-112, 114, 117, 118, 122, 125, 128, 247]

There were inconsistent findings for GI-related adverse events depending on the outcome examined. There was no difference between groups for abdominal pain, nausea, and any GI-related adverse event (Figure 77 and Figure 78). Diarrhea tended to occur more often with metformin monotherapy, although there was no statistically significant difference (Figure 79). Vomiting tended to occur less often with metformin monotherapy, although there were no statistically significant differences (Figure 80).

Two trials were identified solely in ClinicalTrials.gov (NCT00960076; NCT01076088). One found less diarrhea with metformin monotherapy compared with metformin combined with saxagliptin (3.5% vs 5.8%). The other trial (NCT01076088) reported similar numbers of individuals with GI-related adverse events in the metformin monotherapy group (9 people reported diarrhea; 4 reported nausea) and the metformin plus sitagliptin group (4 diarrhea; 8 nausea). (SOE: Low for any GI-related adverse event, Moderate for nausea, High for diarrhea; Neither favored for all outcomes)

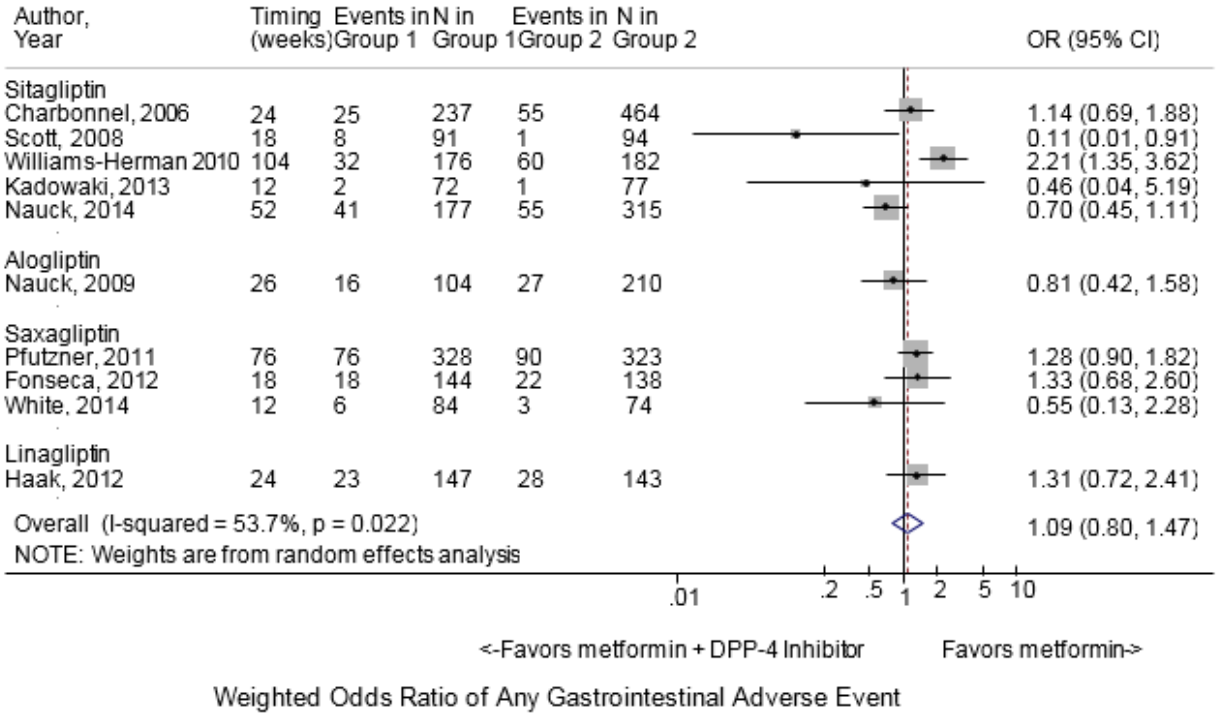
Figure 77. Pooled odds ratio of abdominal pain or nausea comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

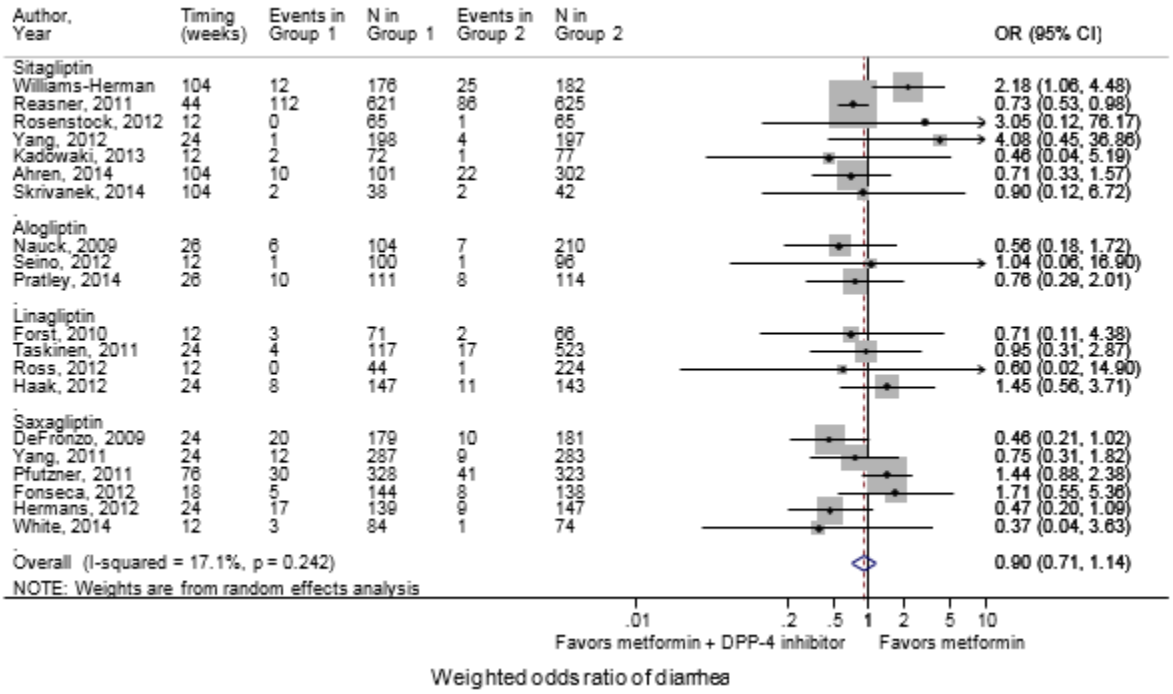
Figure 78. Pooled odds ratio of any gastrointestinal-related adverse event comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

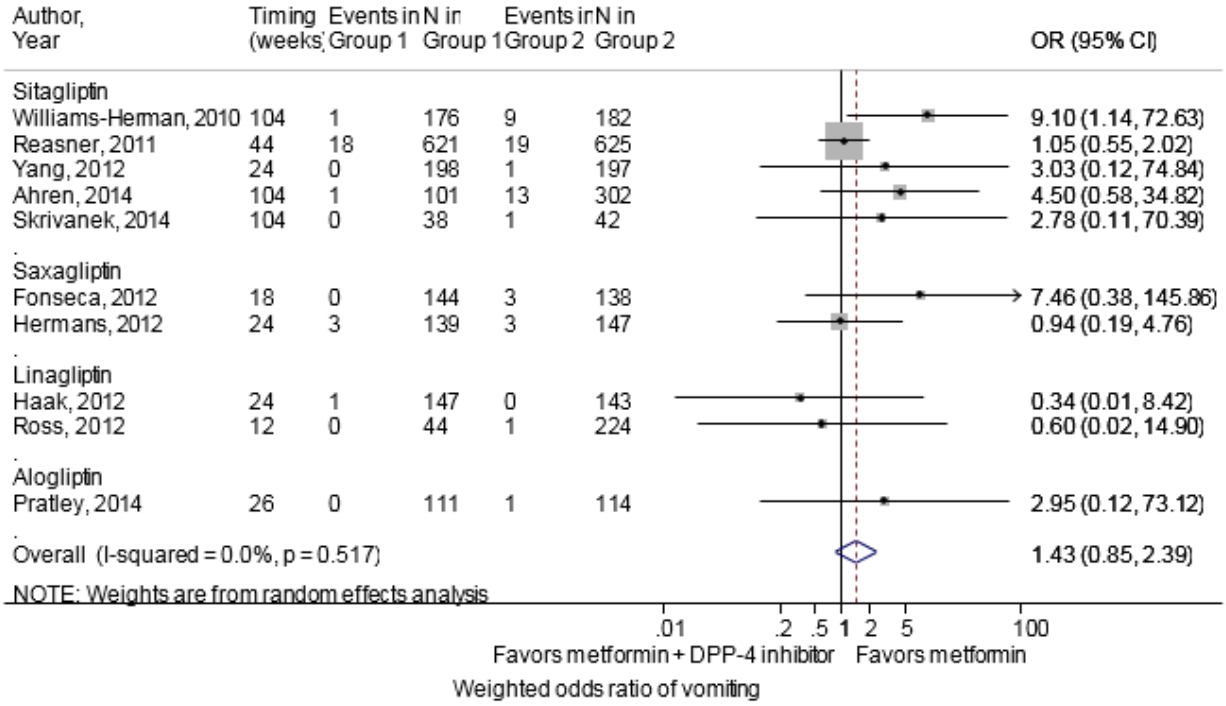
Figure 79. Pooled odds ratio of diarrhea comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 80. Pooled odds ratio of vomiting comparing metformin with a combination of metformin plus a DPP-4 inhibitor



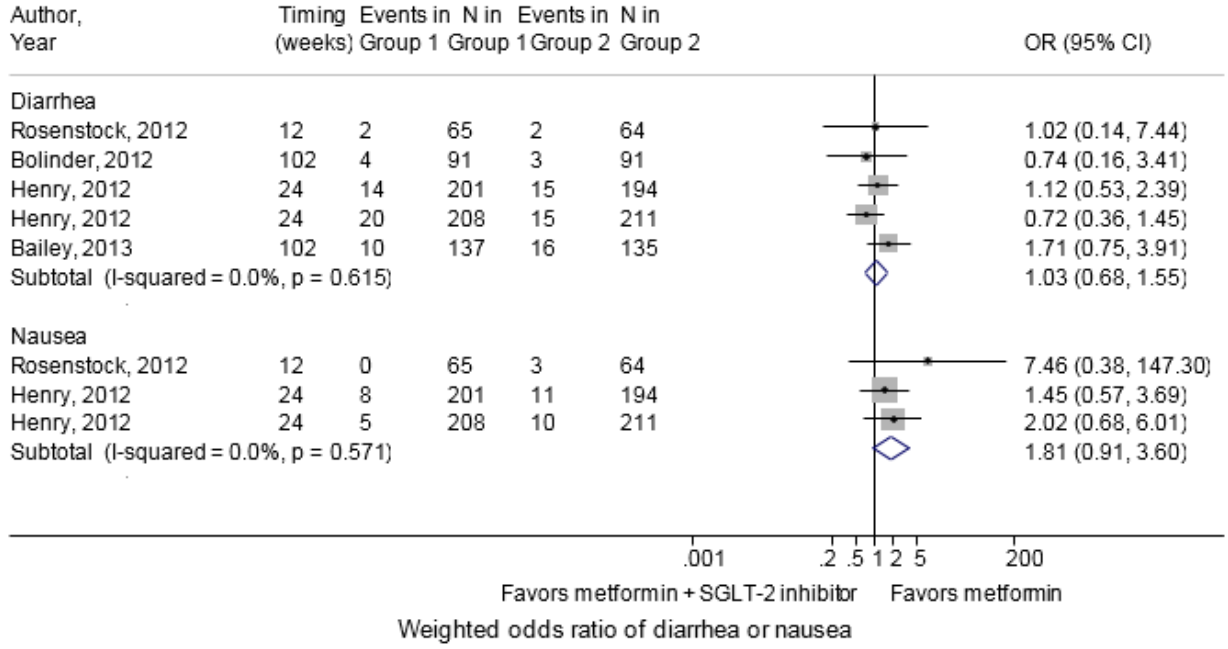
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

One RCT compared diarrhea and nausea with metformin to metformin combined with canagliflozin.[125] Four RCTs (published in three articles) compared diarrhea and nausea with metformin to metformin combined with dapagliflozin.[80, 134, 135] One RCT compared metformin to metformin combined with empagliflozin.[122] There were no consistent differences in diarrhea between arms. Nausea tended to be more common with combination therapy, although the finding was not statistically significant (Figure 81). (SOE: Moderate; Neither favored for diarrhea, metformin favored for nausea)

Figure 81. Pooled odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a SGLT-2 inhibitor

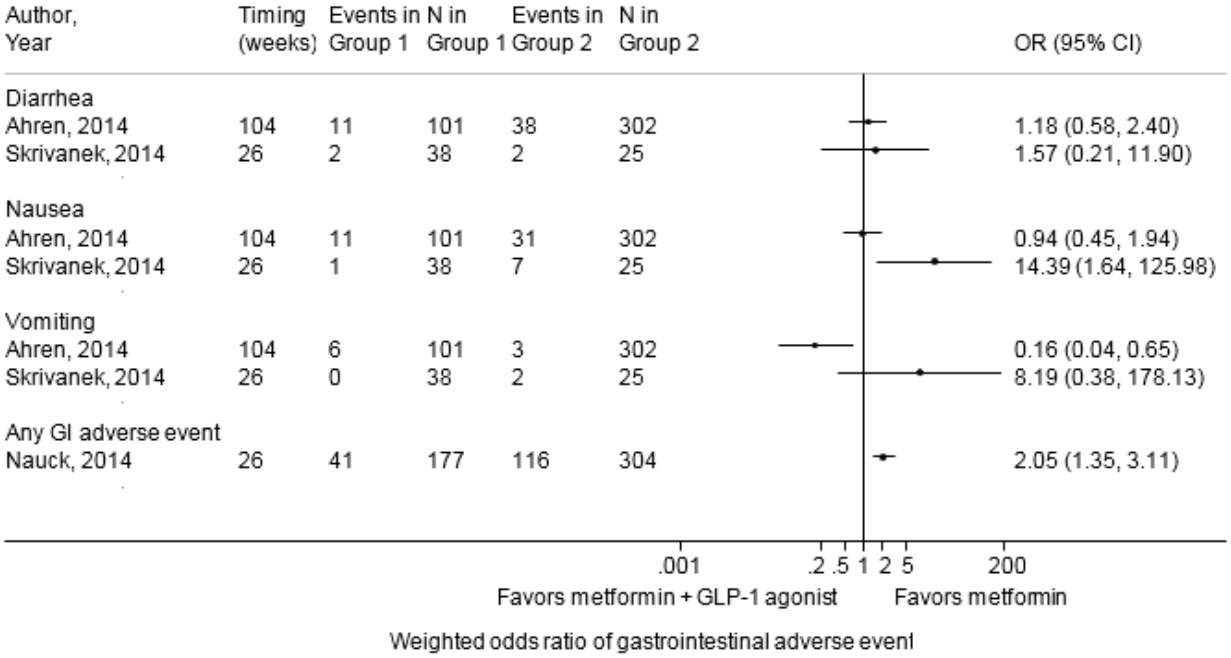


CI = confidence interval; Group 1 = metformin; Group 2 = metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Three RCTs compared metformin to metformin plus a GLP-1 agonist.[110, 128, 247] Metformin plus a GLP-1 agonist showed no clear differences between groups in GI-related adverse events compared with metformin alone, except in the study using alogliptin where there were two-fold more adverse GI events in the combination arm (Figure 82).[128] (SOE: Low; Neither favored)

Figure 82. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a GLP-1 agonist

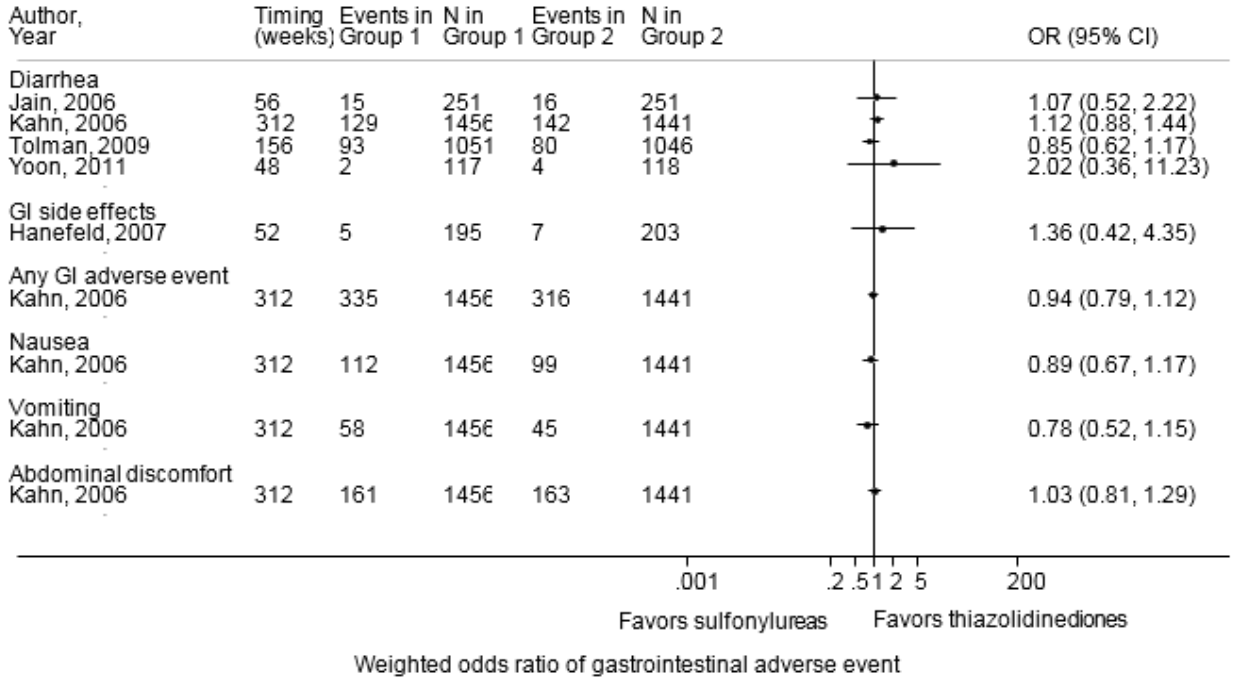


CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = metformin; Group 2 = metformin plus a glucagon-like peptide-1 agonist; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Thiazolidinediones Versus Sulfonylureas

Five RCTs compared diarrhea occurrence with pioglitazone or rosiglitazone to either glyburide, glibenclamide or glimepiride and showed no differences between treatments (Figure 83).[45, 67, 140, 141, 201] Studies of diarrhea were not combined in a meta-analysis diarrhea due to differences in study duration. (SOE: High; Neither favored)

Figure 83. Odds ratio of gastrointestinal adverse events comparing thiazolidinediones with sulfonylureas



CI = confidence interval; Group 1 = thiazolidinediones; Group 2 = sulfonylureas; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Thiazolidinediones Versus DPP-4 Inhibitors

Two trials compared pioglitazone with sitagliptin with no meaningful difference between treatments for GI-related adverse events.[43, 66]

One trial identified solely in ClinicalTrials.gov (NCT01183013) reported no cases of diarrhea or vomiting in any of the 134 participants receiving pioglitazone 45 mg daily or the 130 participants receiving linagliptin 5 mg daily. (SOE: Low; Neither favored)

Thiazolidinediones Versus GLP-1 Agonists

One trial compared pioglitazone with exenatide for outcomes of diarrhea, dyspepsia, nausea and vomiting.[66] Exenatide-treated participants tended to have more diarrhea, dyspepsia and nausea than those receiving pioglitazone.

A trial identified from ClinicalTrials.gov (NCT01147627) reported significantly more GI-related adverse events with exenatide compared with pioglitazone (37/142 versus 1/136 for nausea; 15/142 versus 1/136 for vomiting; 6/142 versus 4/136 for diarrhea). (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus DPP-4 Inhibitors

One RCT compared glipizide (n=212) with sitagliptin (n=210).[152] At 58 weeks, the trial authors stated that there were no significant differences between treatments for outcomes of abdominal pain, diarrhea and vomiting, but that sitagliptin-treated participants had statistically significantly less nausea ($P = 0.025$), although the number or percent of individuals with nausea was not reported.

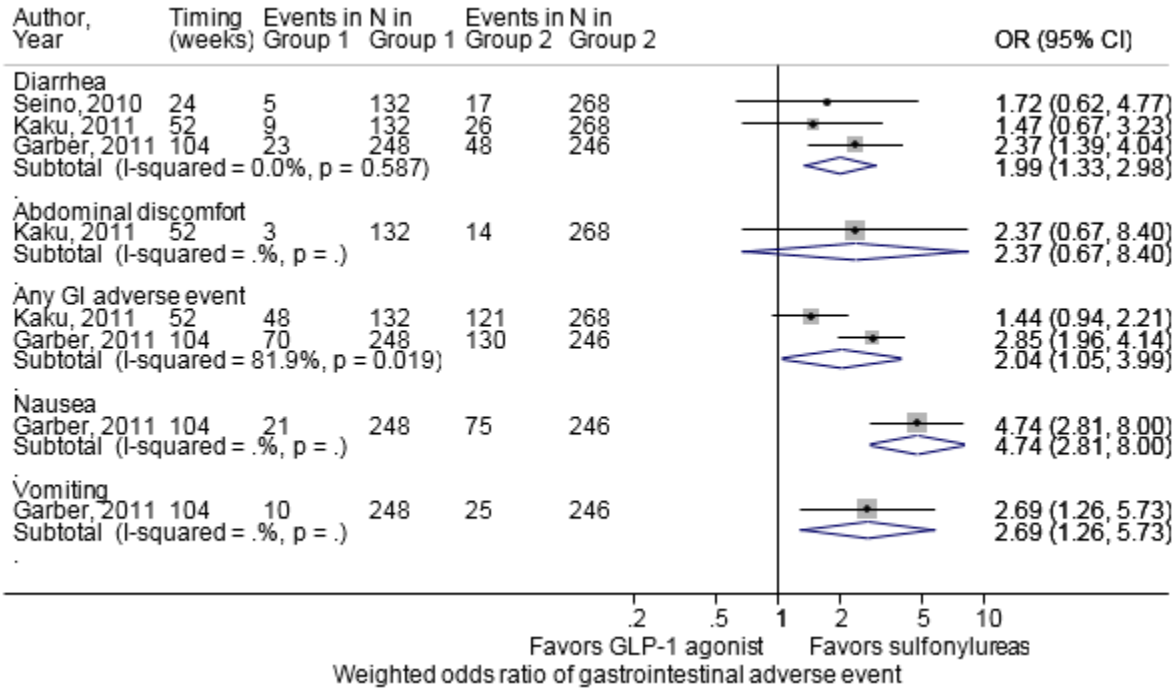
One RCT compared glimepiride with linagliptin.[151] By 34 weeks, 9 percent of individuals on each drug had an unspecified GI-related adverse event.

One trial was identified only in ClinicalTrials.gov (NCT01006603). A comparable number of GI-related adverse events occurred with glimepiride and with saxagliptin (19/359 verses 15/359 for diarrhea; 8/359 versus 4/359 for nausea). (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Agonists

Three RCTs compared GI-related adverse events between glibenclamide and liraglutide.[154, 155, 158] GI-related adverse events were more common with GLP-1 agonists (Figure 84). (SOE: Low; Sulfonylureas favored)

Figure 84. Pooled odds ratio of gastrointestinal adverse events comparing sulfonylureas with GLP-1 agonists



CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = sulfonylureas; Group 2 = glucagon-like peptide-1 agonists; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

DPP-4 Inhibitors Versus GLP-1 Agonists

One RCT compared sitagliptin to exenatide.[66] At 26 weeks, there tended to be more diarrhea (5.5% vs 10.9%), dyspepsia (1.8% vs 7.3%), nausea (3.7% vs 11.3%), and vomiting (1.8% vs 4.8%) with exenatide than sitagliptin. (SOE: Low; DPP-4 inhibitors favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Five RCTs examined GI adverse events between metformin plus a thiazolidinedione and metformin plus a sulfonylurea with little difference in GI-related adverse events between groups (Table 66).[160, 163, 165, 166, 257] (SOE: Moderate; Neither favored)

Table 66. Randomized controlled trials comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea on gastrointestinal adverse events

Author, year	Outcome	Event rates (metformin plus thiazolidinedione versus metformin plus sulfonylurea)
Derosa, 2005[257]	Flatulence	4.2% (2/48) versus 2.1% (1/47)
Garber, 2006[165]	Combined GI events Diarrhea Abdominal pain	10% (16/155) versus 11% (18/159) 3% (5/155) versus 6% (10/159) 4% (6/155) versus 6% (10/159)
Umpierrez, 2006[163]	Diarrhea	4.7% (5/104) versus 6% (6/96) (no difference)
Hamann, 2008[160]	Combined GI events	13% (38/294) versus 18% (54/301)
Maffioli, 2013[166]	Withdrawal due to nausea	1% (1/86) versus 1% (1/84)

GI = gastrointestinal

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

Three RCTs compared GI adverse events in the combination of metformin plus pioglitazone or rosiglitazone versus the combination metformin plus sitagliptin.[87, 172, 173] Diarrhea and nausea tended to be more common with sitagliptin in one trial,[173] but there was only one occurrence of each (4%) in the sitagliptin group (and none reported in the pioglitazone group) in the other trial.[172] In the third trial, six out of 87 patients in the metformin plus rosiglitazone arm and one out of 94 patients in the metformin plus sitagliptin arm experienced a GI- related adverse event, a difference that was close to statistically significant.[87] (SOE: Low; Neither favored)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

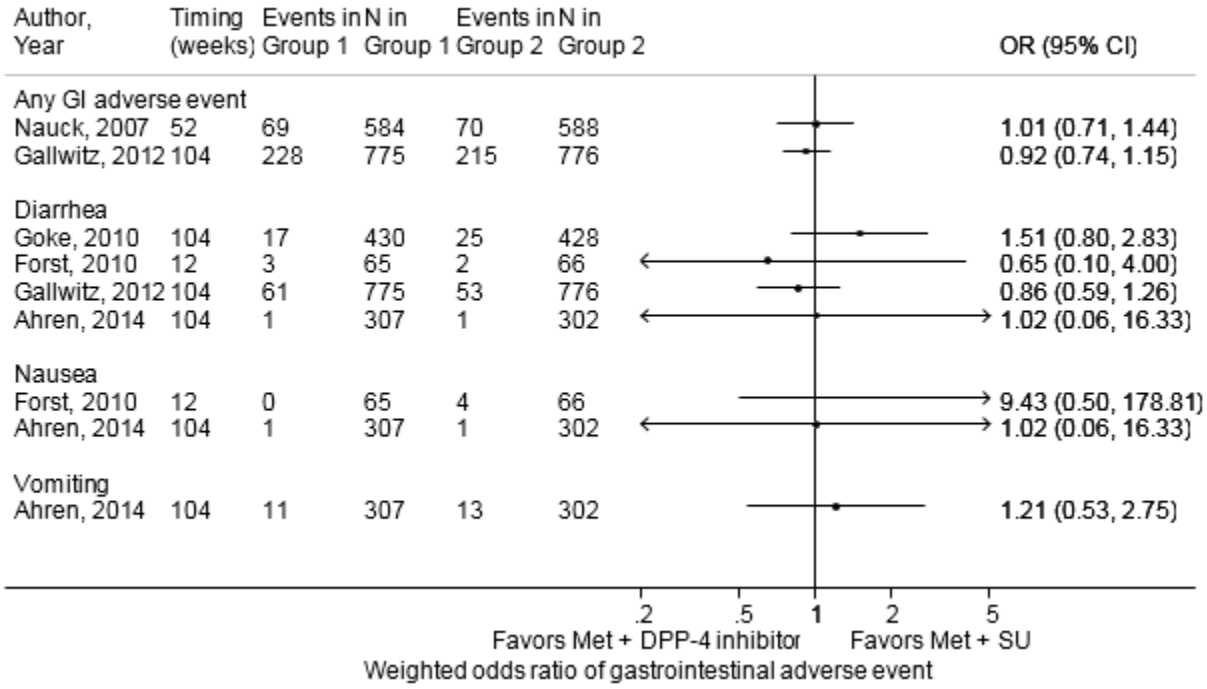
One RCT compared diarrhea, nausea, and vomiting in the combination of metformin plus pioglitazone versus the combination metformin plus exenatide at 26 weeks.[173] There was more diarrhea (7% vs 18%), nausea (5% vs 24%), and vomiting (3% vs 11%) in the group receiving exenatide; all differences are statistically significant. (SOE: Moderate; Combination of metformin plus a thiazolidinedione favored)

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

Five RCTs compared diarrhea, abdominal pain, nausea, vomiting, and unspecified adverse events with metformin plus glipizide or glimepiride to metformin plus linagliptin, sitagliptin, or saxagliptin with no difference between treatments (Figure 85).[108, 110, 177-179] The OR for the three trials with similar study duration reporting on diarrhea was 0.98 (95% CI, 0.67 to 1.42; I-squared, 11%).[110, 178, 179] No single study strongly influenced the results, and no substantial heterogeneity was identified.

One trial was identified in ClinicalTrials.gov (NCT00856284) that randomized 869 people to metformin plus 5 mg of glipizide and 378 to metformin plus 25 mg of alogliptin. Metformin plus alogliptin had more GI-related adverse events (32 nausea, 1 severe vomiting, 60 diarrhea), than metformin plus glipizide (20 nausea and 63 diarrhea). No severe diarrhea was described in either group. (SOE: High; Neither favored)

Figure 85. Odds ratio of gastrointestinal adverse events comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = a combination of metformin plus a sulfonylurea; Group 2 = a combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

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

Two RCTs compared diarrhea and nausea with metformin plus glipizide or glimepiride to metformin plus dapagliflozin or empagliflozin.[182, 183] There was little difference between treatments.

One trial identified from ClinicalTrials.gov (NCT01368081) reported no significant difference in the number of individuals with diarrhea with metformin plus sulfonylurea (5 of 63) and metformin plus empagliflozin (4 of 65). (SOE: Low; Neither favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Three RCTs compared metformin plus glibenclamide or glimepiride to metformin plus albiglutide or exenatide for diarrhea, nausea, or vomiting with a similar and low incidence of adverse events in one trial of exenatide (diarrhea: 1/65 versus 2/63; vomiting: 1/65 versus 1/63;),[188] but a greater percentage of individuals with GI-related adverse events with exenatide in

another trial (diarrhea: 7% vs 12%; nausea: 2% vs 29%; vomiting: 2% vs 9%).[185] Diarrhea and nausea were more common with albiglutide (diarrhea: 7 vs 10/person-year; nausea: 4 vs 10/person-year; unspecified adverse events: 85 vs 110/person-year; vomiting: 4% vs 6%).[110] (SOE: Low; Combination of metformin plus a sulfonylurea favored)

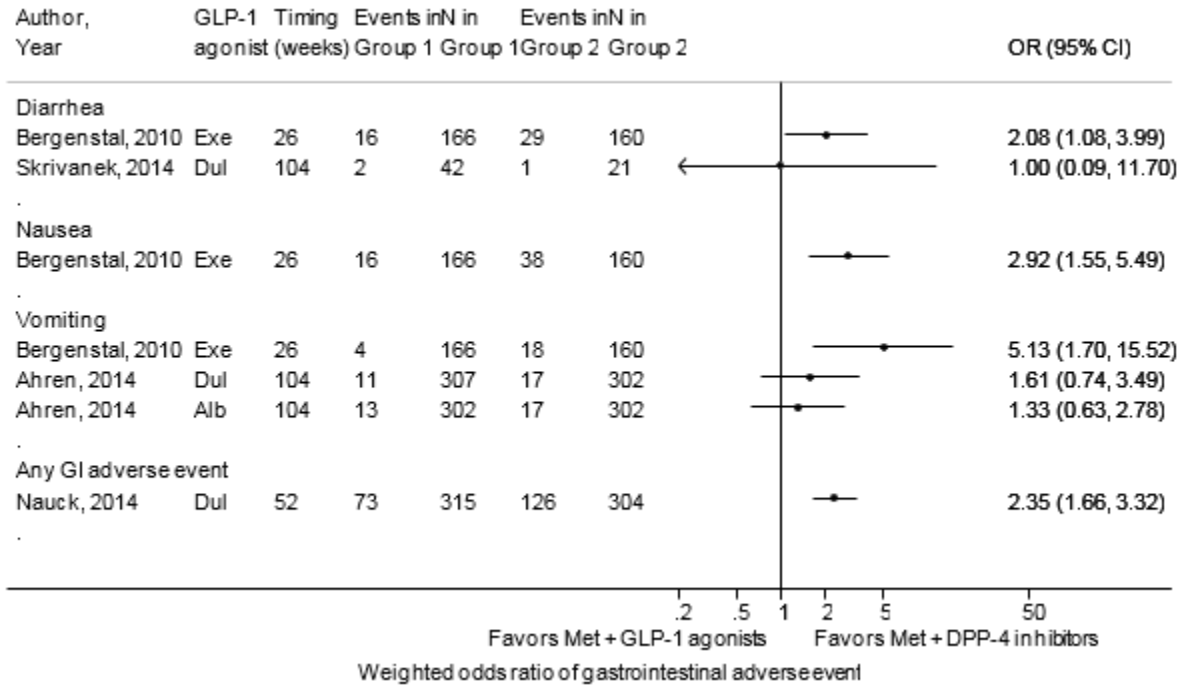
Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Two trials compared metformin plus sitagliptin to metformin plus different doses of canagliflozin or empagliflozin.[122, 125] Diarrhea and nausea were reported for the canagliflozin comparisons and dyspepsia was reported for the empagliflozin comparisons. There were no clear differences in GI-related side effects for either medication. (SOE: Low; Neither favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Four trials reported on GI-related adverse events comparing metformin plus sitagliptin to metformin plus albiglutide, dulaglutide, or exenatide.[110, 128, 173, 247] There were more GI-related adverse events with GLP-1 agonists in two of the four trials (Figure 86). (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 86. Odds ratio of gastrointestinal adverse events comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Group 1 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Group 2 = combination of metformin plus a glucagon-like peptide-1 agonist; Met = metformin; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

One trial compared abdominal distention, diarrhea, nausea, vomiting, and the composite of these outcomes with metformin plus exenatide to metformin plus insulin glargine at 168 weeks.[47] There were more occurrences of GI-related adverse events for the composite outcome in the group receiving exenatide (43% versus 16%) and no difference in vomiting between the groups (10% versus 8%). Abdominal distention, diarrhea, and nausea were only reported for exenatide (5%, 5%, and 38%), preventing a comparison between groups. (SOE: Low; Combination of metformin plus a basal insulin favored)

Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One trial compared diarrhea, dyspepsia, nausea and vomiting with metformin plus exenatide to metformin plus insulin aspart 70/30 at 26 weeks.[196] There was no difference in diarrhea between the treatments (11% versus 8%). Differences between groups for the other outcomes could not be evaluated because they were only reported for exenatide (6% dyspepsia; 19% nausea; 10% vomiting). (SOE: Insufficient; Unable to determine effect)

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

One RCT compared diarrhea incidence with metformin in a combination regimen with either insulin glargine or with lispro and neither arm was favored.[197]

One trial was reported only in ClinicalTrials.gov (NCT01068652). Of the 200 people who received metformin plus insulin detemir, 13 had diarrhea compared with 15 of 203 in the metformin plus biphasic insulin aspart 30 group. (SOE: Low; Neither favored)

Strength of Evidence for Gastrointestinal Side Effects

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 67 and Table 68 and summarized in the key points. All studies were RCTs. Study limitations for most comparisons in the strength of evidence table were graded as low or medium with only two comparisons graded as having high study limitations due to lack of description of randomization or blinding or failure to describe withdrawals or dropouts. In general, we did not find strong relative differences in outcomes by study quality. We did not find any evidence of publication bias comparing results published in peer-reviewed journals to results published on ClinicalTrials.gov. We considered GI side effects a direct outcome because they were measured directly. The most common reasons for downgrading the evidence were imprecision, inconsistency and study limitations.

Table 67. Strength of evidence domains for monotherapy comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD	8 (6,250)	Medium	Consistent	Direct	Precise	Undetected	Moderate	TZD favored for diarrhea and nausea
Metformin vs. SU	12 (6094)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	SU favored for GI-related adverse events
Metformin vs. DPP-4 inhibitors	6 (5,842)	Low	Consistent	Direct	Precise	Undetected	High	DPP-4 inhibitors favored
Metformin vs. SGLT-2 inhibitors	4 (2,041)	Medium	Consistent	Direct	Imprecise	Undetected	Low	SGLT-2 inhibitors favored for diarrhea and nausea
Metformin vs. GLP-1 agonists	3 (879)	Low	Inconsistent	Direct	Imprecise for diarrhea; Precise for nausea/ vomiting	Undetected	Low for diarrhea; Moderate for nausea/ vomiting	GLP-1 agonists favored for diarrhea; Metformin favored for nausea
Metformin vs. metformin + TZD	10 (3,878)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + TZD favored for diarrhea; Neither favored for other GI-related outcomes
Metformin vs. metformin + SU	12 (4,317)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored for GI-related adverse events
Metformin vs. metformin + DPP-4 inhibitors	25 (13,685)	Low	Inconsistent	Direct	Imprecise	Undetected	Low for any GI-related adverse event; Moderate for nausea; High for diarrhea	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors	6 (2,918)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Neither favored for diarrhea, Metformin favored for nausea
Metformin vs. metformin + GLP-1 agonists	3 (2,377)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. SU	5 (6,432)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored
TZD vs. DPP-4 inhibitors	2 (1,031)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored

Comparison	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
TZD vs. GLP-1 agonists	1 (820)	Low	Not applicable	Direct	Not evaluated	Undetected	Low	TZD favored
SU vs. DPP-4 inhibitors	2 (653)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
SU vs. GLP-1 agonists	3 (1,568)	High	Consistent	Direct	Precise	Undetected	Low	SU favored
DPP-4 inhibitors vs. GLP-1 agonists	1 (820)	Low	Not applicable	Direct	Not evaluated	Undetected	Low	DPP-4 inhibitors favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

Table 68. Strength of evidence domains for metformin-based combination comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin +SU	5 (1,382)	Low	Consistent	Direct	Precise	Undetected	Moderate	Neither favored
Metformin + TZD vs. metformin +DPP-4 inhibitors	3 (747)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + TZD vs. metformin +GLP-1 agonists	1 (514)	Low	Not applicable	Direct	Imprecise	Undetected	Moderate	Metformin + TZD favored
Metformin + SU vs. metformin +DPP-4 inhibitors	5 (4,964)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored
Metformin + SU vs. metformin +SGLT-2 inhibitors	2 (2,363)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin +GLP-1 agonists	3 (2,018)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	2 (946)	Medium	Not applicable	Direct	Not evaluated	Undetected	Low	No difference
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	4 (2,891)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + DPP-4 inhibitors favored
Metformin + GLP-1 agonists vs. metformin + basal insulin	1 (69)	Medium	Not applicable	Direct	Imprecise	Undetected	Low	Basal insulin favored
Metformin + GLP-1 agonists vs. metformin + premixed insulin	1 (363)	High	Not applicable	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	1 (317)	Medium	Not applicable	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

The Evidence About Cancer

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

A single retrospective cohort study from the England Cancer Registry reported no difference in non-melanoma cancer risk for thiazolidinediones (N=31,372) versus metformin (N=109,708) users (adjusted RR, 0.96; 95% CI, 0.81 to 1.13, *P* not reported) over 4 years of followup.[241] (Not graded)

Metformin Versus Sulfonylureas

Three retrospective cohort studies compared cancer outcomes for metformin and sulfonylurea users (Table 69).[208, 240, 241] Two studies reported no difference between metformin and sulfonylurea users.[208, 241] The other only provided results stratified by statin use, indicating a possible interaction with statin use.[240] (SOE: Low; Neither favored)

Table 69. Retrospective cohort studies comparing metformin with sulfonylureas on cancer

Author, year	Population	Followup	Outcome	Results
van Staa, 2012[241]	England Cancer Registry [n=68,209 (sulfonylurea); n=109,708 (metformin)]	4-5 years	Non-melanoma cancer	HR 1.03; 95% CI, 0.91 to 1.17 Reference=metformin
Andersson, 2010[208]	Danish Patient Registry Patients with heart failure (N=5,852)	10 years	Death from cancer	HR 1.01; 95% CI, 0.72 to 1.43 Reference=sulfonylurea
Lehman, 2012[240]	Veterans Health Administration [n=533 (metformin-statin); n=2404 (sulfonylurea-statin); n=175 (metformin-no statin); n=1,930 (sulfonylurea-no statin)]	270.4 weeks	Incident prostate cancer	Statin users HR 0.69; 95% CI, 0.5 to 0.92, *P* = 0.01 Reference=sulfonylurea Non users of statins HR 2.15; 95% CI, 1.83 to 2.52, *P* < 0.0001 Reference=sulfonylurea

CI = confidence interval; HR = hazard ratio

Metformin Versus DPP-4 Inhibitors

Two RCTs of metformin plus placebo (N=510) versus a DPP-4 inhibitor plus placebo (N=514) evaluated cancer outcomes.[77, 79] Each reported a single cancer event; one death due to pancreatic neoplasm/sepsis[79] and one occurrence of esophageal cancer[77] in the metformin arms. Neither study reported on cancer in the DPP-4 inhibitor arm.[77, 79] Followup ranged from 76[79] to 104 weeks.[77] (SOE: Low; Neither favored)

Metformin Versus SGLT-2 Inhibitors

A single RCT (N=404) of metformin plus placebo versus dapagliflozin plus placebo with 24 weeks of followup reported on occurrence of cancer.[80] The RCT reported no bladder cancer in either arm and a single case of breast cancer in the SGLT-2 arm; breast cancer was not reported on in the metformin arm.[80] (SOE: Insufficient; Unable to determine effect)

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

A single RCT compared metformin (N=101) with metformin plus glimepiride (N=307) and reported no cases of thyroid cancer in either arm at 104 weeks.[110] Of note, withdrawal rates were greater than 30% across arms, and the investigators did not use an intention-to-treat analysis. (SOE: Insufficient; Unable to determine effect)

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

Six RCTs compared metformin with metformin plus a DPP-4 inhibitor.[77, 79, 110, 111, 123, 128] We did not combine these studies in a meta-analysis because of lack of consistent ascertainment of and reporting on cancer outcomes; and when reported, heterogeneous definitions of cancer outcomes (Table 70). Three studies had more than 1 year of followup.[77, 79, 110] Of these, the RCT with active ascertainment reported two cases of thyroid cancer in the metformin plus DPP-4 inhibitor arm (0.7%) and none in the metformin arm (0.0%) at 104 weeks.[110] Results were mixed across the other studies, with many arms not reporting on cancer outcomes. (SOE: Insufficient; Unable to determine effect)

Table 70. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on cancer

Author, year	Followup (weeks)	Outcome	Active/Passive Ascertainment	Metformin Events/n (%)	Metformin + DPP-4 inhibitor Events/n (%)
Nauck, 2009[123]	26	Discontinuation because of prostate cancer	Passive	NR/104	Alogliptin 12.5 mg: 1/213 (0.5) Alogliptin 25 mg: NR/210
		Discontinuation because of endometrial cancer	Passive	NR/104	Alogliptin 12.5 mg: 1/213 (0.5) Alogliptin 25 mg: NR/210
Nauck, 2014[128]*	26	Thyroid cancer	NR	0/177 (0)	0/315 (0)
Raz, 2008[111]	30	Cases of cancer	Active	3/94 (3)	0/96 (0)
Pfutzner, 2011[79]	76	Death due to pancreatic neoplasm/sepsis	NR	1/328 (0.3)	Saxagliptin 5 mg: NR/320 Saxagliptin 10 mg: NR/323
Ahren, 2014[110]	104	Thyroid cancer	Active	0/101 (0)	2/302 (0.7)
Williams-Herman, 2010[77]	104	Esophageal cancer	NR	Metformin 1000 mg: 1/182 (0.5) Metformin 2000 mg: NR/182	Metformin 2000 mg + sitagliptin 100 mg: NR/182 Metformin 1000 mg + sitagliptin 100 mg: NR/190

DPP-4 = dipeptidyl peptidase-4; mg = milligram; NR = not reported
*Cancer outcome at 52 weeks not reported in the metformin arm and none reported in the MET+DPP-4 arm

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

Four RCTs compared metformin with metformin plus an SGLT-2 inhibitor and reported on cancer outcomes (Table 71).[80, 132, 134, 135] Reporting of cancer was incomplete for many studies, and studies did not report on whether there was active ascertainment for cancer outcomes. Therefore, we did not perform a meta-analysis for this comparison (Table 71). Cancer outcomes

were rare but appeared to occur at similar rates in the treatment arms; most studies were small and less than 1 year in duration. (SOE: Low; Neither favored)

Table 71. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on cancer

Author, year	Followup (weeks)	Outcome	Active/Passive Ascertainment	Metformin Events/n (%)	Metformin + SGLT-2 inhibitor Events/n (%)
Qiu, 2014[132]	18	Colon cancer	NR	NR/93	Canagliflozin 100 mg: NR/93 Canagliflozin 300 mg: 1/93 (1.1)
Henry, 2012[80]	24	Bladder malignancy	NR	0/201 (0)	0/194 (0)
Bolinder, 2012[134]	50	Prostatic cancer or prostatic adenoma	NR	1/91 (1.1)	1/91 (1.1)
		Basal cell carcinoma	NR	1/91 (1.1)	NR/91
		Breast cancer leading to discontinuation	NR	0/91 (0)	1/91 (1.1)
Bailey, 2013[135]	102	Unspecified adverse event (lung cancer)	NR	1/137 (0.7)	Dapagliflozin 2.5 mg: NR/137 Dapagliflozin 5 mg: 1/137 (0.7) (bladder cancer) Dapagliflozin 10 mg: 1/135 (0.7) (breast cancer)

mg = milligram; NR = not reported; SGLT-2 = sodium-glucose co-transporter-2

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Two RCTs compared metformin with metformin plus a GLP-1 agonist and reported on cancer outcomes.[110, 128] One trial did active surveillance for thyroid cancer and reported one case of follicular thyroid cancer in the metformin plus albiglutide arm (1/302, 0.3%) and no cases (0/101, 0.0%) in the metformin arm at 104 weeks.[110] The 52-week RCT reported no cases of thyroid cancer in the metformin plus dulaglutide arms (metformin plus dulaglutide 0.75 mg/week, n=302; metformin plus dulaglutide 1.5 mg/week, n=304) and did not report on thyroid cancer in the metformin arm (n=177).[128] (SOE: Low; Neither favored)

Thiazolidinediones Versus Sulfonylureas

A 56-week, multi-center trial in the US, including Puerto Rico, reported two events of stage IV colon cancer (2/251, 0.8%) in the sulfonylurea arm and none in the thiazolidinedione arm (0/251, 0.0%).[141] (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus DPP-4 Inhibitors

Two RCTs compared sulfonylurea with DPP-4 inhibitor monotherapy and reported on cancer outcomes collected through passive ascertainment.[151, 152] One 52-week RCT reported one case of colon cancer in the glimepiride arm (1/76, 1.3%) and did not report on cancer in the linagliptin arm (n=151).[151] The other RCT compared glipizide with sitagliptin among participants with at least moderate renal insufficiency and reported five cases of cancer in the sitagliptin arm (5/210, 2.3%) and none in the sulfonylurea arm (0/212, 0.0%) over 58 weeks of follow up.[152] In that

study, cancer cases were chronic myeloid leukemia in a participant with baseline leukocytosis, breast cancer diagnosed after 4 days of sitagliptin initiation, lung cancer in a participant with 40 pack-years of smoking, a pancreatic mass, and a case of polycythemia vera in a participant with a germline JAK-2 mutation.[152] (SOE: Insufficient; Unable to determine effect)

Sulfonylureas Versus GLP-1 Agonists

One RCT compared glimepiride with liraglutide and reported on cancer outcomes with 104 weeks of followup, but did not report if ascertainment was active.[158] Two cases of breast cancer occurred in the liraglutide 1.8 mg arm (2/251, 0.8%) and two cases of thyroid tumors (one benign thyroid neoplasm and one papillary thyroid cancer) in the liraglutide 1.2 mg arm (1/247, 0.4%); cancer outcomes were not reported on in the sulfonylurea arm (N=248).[158] These events were reported if they were considered to be possibly related to the trial drug.[158] (SOE: Insufficient; Unable to determine effect)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

One 24-week RCT compared the combination of moderately-dosed metformin plus pioglitazone with the combination of moderately-dosed metformin plus glimepiride and reported on cancer outcomes, but whether ascertainment was active was not reported.[170] A single case of prostate cancer occurred in the metformin plus glimepiride arm (1/142, 0.7%), and cancer was not reported on in the metformin plus pioglitazone arm (n=146).[170] More than 20% of participants withdrew from each arm.[170] (SOE: Insufficient; Unable to determine effect)

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

A single 26-week RCT compared the combination of metformin plus pioglitazone with the combination of metformin plus sitagliptin and reported on cancer outcomes; the method of ascertainment was not described.[173] A single case of papillary thyroid cancer occurred in the metformin plus sitagliptin arm (1/166, 0.6%), and no events were reported in the metformin plus pioglitazone arm (0/165, 0.0%).[173] More participants withdrew from the metformin plus pioglitazone arm (21%) than the metformin plus sitagliptin arm, and the investigators did not use an intention-to-treat analysis for this outcome.[173] (SOE: Insufficient; Unable to determine effect)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

A single 26-week RCT compared the combination of metformin plus pioglitazone with the combination of metformin plus weekly exenatide and reported on cancer outcomes; the method of ascertainment was not described.[173] No cases of thyroid cancer were reported in either arm (metformin plus pioglitazone: 0/165, 0.0% and metformin plus exenatide: 0/160, 0.0%).[173] (SOE: Insufficient; Unable to determine effect)

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

Three RCTs with 104 weeks of followup compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor and reported on cancer outcomes (Table 72).[110, 178, 179] Cancer incidence was slightly higher in the metformin plus DPP-4 arms than the metformin plus sulfonylurea arms in these 2-year trials. More than 20% of participants withdrew from these studies, but two used an intention-to-treat analysis.[178, 179] (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Table 72. Randomized controlled trials comparing a combination of metformin with a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cancer

Author, year	Outcome	Active/Passive Ascertainment	ITT analysis	Metformin + SU Events/n (%)	Metformin + DPP-4 inhibitor Events/n (%)
Ahren, 2014[110]	Thyroid cancer	Active	No	0/307 (0.0%)	2/302 (0.7%)
Gallwitz, 2012[178]	Prostate, breast, and colon cancer*	NR	Yes	7/775 (0.9%)	10/776 (1.3%)
Goke, 2010[179]	Acute myeloid leukemia	NR	Yes	NR/430	1/428 (0.2%)

DPP-4 = dipeptidyl peptidase-4; ITT = intention-to-treat; NR = not reported; SU = sulfonylurea
* Unclear if ascertained for specific types of cancer

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

A single RCT compared the combination of metformin plus an sulfonylurea with the combination of metformin plus an SGLT-2 inhibitor and reported on malignancies over 104 weeks using passive ascertainment.[182] The authors reported more cases of cancer (prostate cancer, n=3; breast cancer, n=1; gastric cancer, n=1; and pancreatic cancer, n=2) in the metformin plus dapagliflozin arm (7/406, 1.7%) than in the metformin plus glipizide arm (prostate cancer, basal cell skin cancer, and lung cancer; 3/408, 0.7%).[182] (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

Two RCTs compared the combination of metformin plus glimepiride with the combination of metformin plus a GLP-1 agonist and reported on cancer outcomes.[110, 185] Both trials reported thyroid cancer events in the metformin plus GLP-1 agonist arm.[110, 185] In the study by Ahren 2014, the investigators actively ascertained for thyroid cancer with 104 weeks of followup and found no thyroid cancer in the metformin plus glimepiride arm (0/307, 0.0%) and one case in the metformin plus albiglutide arm (1/302, 0.3%).[110] In the other trial (maximum followup of 3 years) which did not report on the method of ascertainment of cancer outcomes, the authors reported three cases of thyroid cancer (3/511, 0.6%) in the metformin plus exenatide arm and did not report on thyroid cancer for the metformin plus sulfonylurea arm. In that trial, the authors also reported a single case of breast cancer in the metformin plus sulfonylurea arm (1/508, 0.2%) and did not report on breast cancer for the metformin plus exenatide arm.[185] (SOE: Low; Combination of metformin plus a sulfonylurea favored for thyroid cancer)

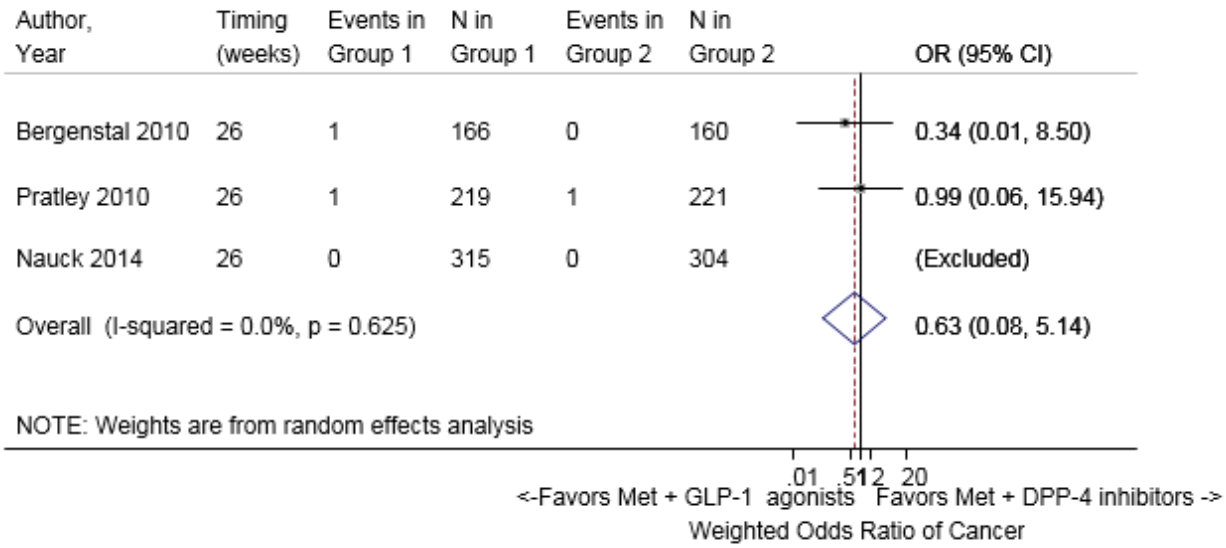
Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

Three RCTs with 26 weeks of followup compared the combination of metformin plus a GLP-1 agonist with the combination of metformin plus a DPP-4 inhibitor and found no difference in thyroid cancer events (combined OR, 0.63; 95% CI, 0.08 to 5.14) (Figure 87).[128, 173, 192] We did not find evidence of statistical heterogeneity (I^2=0.0%), and event rates were low. None of these short-term studies reported active ascertainment of thyroid cancer, and one did not provide results for the intention-to-treat population.[173]

One of the above RCTs continued followup for 52 weeks and reported no cases of thyroid cancer in either arm.[128] A fourth RCT lasting 104 weeks in duration actively ascertained thyroid cancer and reported two events in the metformin plus DPP-4 arm and one event in the metformin plus GLP-1 agonist arm; the authors did not evaluate this outcome in the intention-to-treat population.[110]

Withdrawal rates were high across the study arms (range 13% to 77%) with most arms having more than 30% loss to followup.[110, 128, 173, 192] (SOE: Low; Combination of metformin plus a GLP-1 agonist favored)

Figure 87. Pooled odds ratio of cancer events comparing the combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

A single 25-week RCT compared the combination of metformin plus sitagliptin with the combination of metformin plus insulin glargine and reported two cases of cancer (Kaposi's sarcoma and prostate cancer) in the metformin plus sitagliptin arm (2/264, 0.8%) and none in the metformin plus insulin glargine arm (0/237, 0.0%).[193] (SOE: Low; Combination of metformin plus a basal insulin favored)

Strength of Evidence for Cancer

We found low or insufficient strength of evidence on cancer outcomes for all comparisons of interest as described in the Key Points and Table 73 and Table 74.

The major limitation of the evidence on cancer for the diabetes medication comparisons under study was the lack of studies. For RCTs, major study limitations included high rates of withdrawals (>20%) combined with lack of an intention-to-treat approach and lack of active ascertainment (or reporting on) of cancer outcomes. We could usually not determine consistency because of a lack of studies (i.e., one study available for a given comparison); otherwise, evidence was often inconsistent based on a few studies for each comparison. The evidence on all comparisons was imprecise due to insufficient sample size for cancer outcomes.

We found evidence of publication bias for the comparison of sulfonylurea monotherapy and DPP-4 inhibitor monotherapy; two unpublished studies favored sulfonylurea. Combined with the two published RCTs which showed inconsistent results, these results would move our evidence grade from “insufficient” to “low” for this comparison and suggest that sulfonylurea monotherapy is favored over DPP-4 inhibitors. We found two additional unpublished studies of comparisons for which there were no published studies: thiazolidinedione vs. DPP-4 inhibitors and metformin plus basal insulin vs. metformin plus premixed insulin.

Finally, most evidence for the comparisons of interest included studies that did not report on cancer events in all arms; while this limited our ability to synthesize quantitatively, we did not believe that this was actually a source of selective analysis reporting bias, as much as a reflection of a lack of a focus on active ascertainment and reporting of cancer outcomes.

Table 73. Strength of evidence domains for monotherapy comparisons and cancer outcomes among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SU	Observational: 3 (120,602)	Medium risk of bias	Inconsistent	Direct	Imprecise	NA	Low	Neither favored
Metformin vs. DPP-4 inhibitors	RCTs: 2 (1,014)	Low risk of bias	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. SGLT-2 inhibitors	RCT: 1 (404)	Medium risk of bias	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + SU	RCT: 1 (1049)	High risk of bias	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + DPP-4 inhibitors	RCTs: 6 (5271)	Low risk of bias	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine 4 RCTs did not report on events in all arms
Metformin vs. metformin + SGLT-2 inhibitors	RCTs: 4 (1610)	Low risk of bias	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + GLP-1 agonists	RCTs: 2 (2147)	High risk of bias	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. SU	RCT: 1 (502)	Medium risk of bias	Unknown	Direct	Imprecise	Undetected	Low	TZD favored
SU vs. DPP-4 inhibitors	RCTs: 2 (653)	Low risk of bias	Inconsistent	Direct	Imprecise	Suspected	Insufficient	Unable to determine
SU vs. GLP-1 agonists	RCT: 1 (746)	Medium risk of bias	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; NA = not applicable; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 74. Strength of evidence domains for combination therapy comparisons and cancer among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + pio vs. metformin + SU	RCT: 1 (305)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pio vs. metformin + DPP-4 inhibitors	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pio vs. metformin + GLP-1 agonists	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + DPP-4 inhibitors	RCTs: 3 (3,459)	Medium	Consistent	Direct	Imprecise	Suspected	Low	Metformin + SU favored
Metformin + SU vs. metformin + SGLT-2 inhibitors	RCT: 1 (408)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin + SU favored
Metformin + SU vs. metformin + GLP-1 agonists	RCT: 2 (2,078)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored for thyroid cancer
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 agonists	RCT: 4 (3,107)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 agonists favored, OR 0.63; 95% CI, 0.08 to 5.14
Metformin + DPP-4 inhibitor vs. metformin + basal insulin	RCT: 1 (515)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + basal insulin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; pio = pioglitazone; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Congestive Heart Failure

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Three randomized trials[45, 63, 69] and two observational studies[222, 230] examined heart failure for this comparison (Table 75). We did not conduct a meta-analysis due to differences in study duration and design. The two RCTs lasting less than a year showed no events of heart failure in either arm.[63, 69] The third RCT, the ADOPT study,[45] had over 1,400 subjects in each arm with a median duration of treatment of 4 years. In this study, the investigators compared metformin with rosiglitazone on the primary outcome of time to monotherapy failure. While the study was not powered to detect differences in cardiovascular events and excluded patients with heart failure at baseline, there was no statistically significant difference between the incidence of investigator reported heart failure in these two arms (22/1456 for rosiglitazone versus 19/1454 for metformin).[45]

Two observational studies also compared metformin with thiazolidinediones.[222, 230] Both studies reported point estimates suggesting harm from thiazolidinediones compared with metformin, but results were only close to statistically significant for the comparison of pioglitazone versus metformin in one of the two studies (Table 75).[222] (SOE: Low; Metformin favored)

Table 75. Studies comparing metformin with thiazolidinediones on congestive heart failure

Author, year	Study design	Comparison	Heart failure incidence (metformin as reference group)
Kahn, 2006[45]	RCT	Rosiglitazone versus metformin	22/1456 versus 19/1454 versus
Erem, 2014[63]	RCT	Pioglitazone versus metformin	0/19 versus 0/19
Esposito, 2011[69]	RCT	Pioglitazone versus metformin	0/55 versus 0/55
Pantalone, 2009[222]	Observational study	Rosiglitazone versus Metformin	HR, 1.16 (95% CI, 0.78 to 1.73)
		Pioglitazone versus metformin	HR, 1.38 (95% CI, 1.00 to 1.90)
Hsiao, 2009[230]	Observational study	Rosiglitazone versus metformin	HR, 1.30 (95% CI, 0.89 to 1.89)
		Pioglitazone versus metformin	HR, 1.54 (95% CI, 0.65 to 3.64)

CI = confidence interval; HR = hazard ratio for TZDs with metformin as references group; RCT = randomized controlled trial

Metformin Versus Sulfonylureas

Two studies (one RCT and one observational study) reported on the risk of heart failure events with metformin compared with the sulfonylureas, with both point estimates favoring metformin over sulfonylureas (Table 76).[214, 222] The 144-week RCT compared metformin with glipizide in adults with diabetes and a history of coronary artery disease, and reported a small non-significant greater number of events in the glipizide arm (10/148) compared to the metformin arm (9/156).[214] Rescue therapy was insulin and was initiated in about 20% of each arm. The larger retrospective observational study (N=20,450) compared metformin with sulfonylurea in patients within one health care system in the United States from 1998 to 2006.[222] After adjusting for differences in baseline patient characteristics (e.g., gender, race, age, smoking status, and medications), sulfonylureas were associated with a greater risk of heart failure than metformin.[222] (SOE: Low; Metformin favored)

Table 76. Studies comparing metformin with sulfonylureas on congestive heart failure

Author, year	Study design	Comparison	Heart failure incidence (metformin as reference group)
Hong, 2013[214]	RCT	Metformin versus glipizide	HR, 0.82 (95% CI, 0.31 to 2.13)
Pantalone, 2009[222]	Observational study	Metformin versus sulfonylurea (unspecified drug type)	HR, 0.76 (95% CI, 0.64 to 0.91)

CI = confidence interval; HR = hazard ratio for metformin with sulfonylureas as the reference group; RCT = randomized controlled trial

Metformin Versus DPP-4 Inhibitors

One RCT lasting 26 weeks compared metformin with alogliptin with no heart failure events in either arm.[76] (SOE: Low; Neither favored)

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Three RCTs lasting from 26 to 80 weeks compared metformin alone with the combination of metformin plus a thiazolidinedione, showing a small non-significant greater number of heart failure events in the metformin plus thiazolidinedione arms in two of the three studies (Table 77).[85, 95, 96] (SOE: Low; Metformin favored)

Table 77. Randomized controlled trials comparing metformin with a combination of metformin plus a thiazolidinedione on congestive heart failure

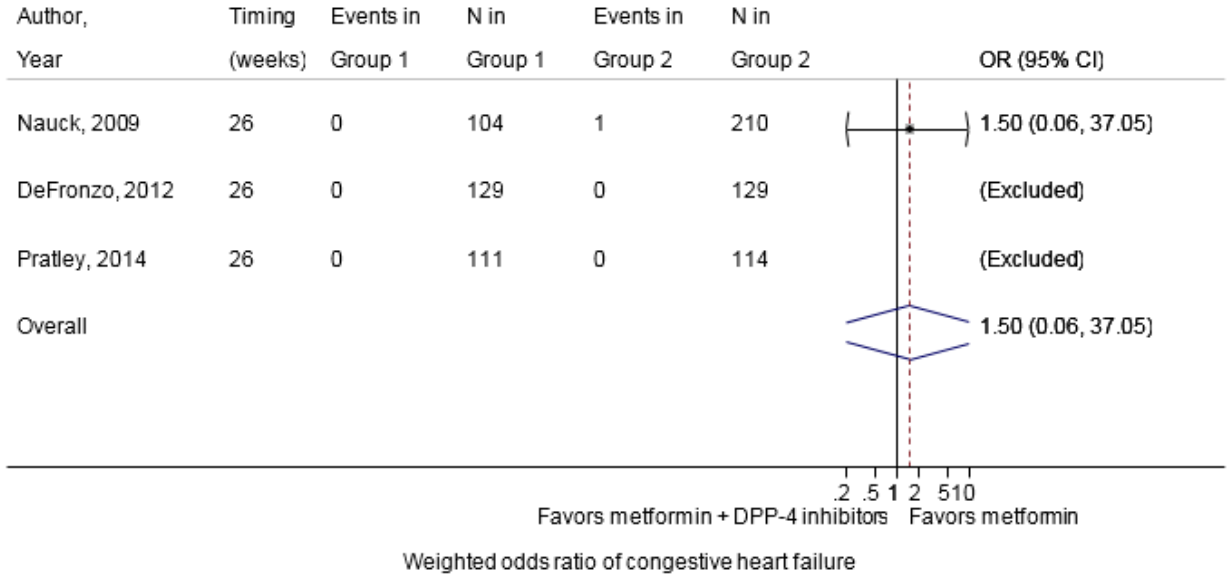
Author, year	Study design	Comparison	Heart failure incidence
Leiter, 2005[85]	RCT	Metformin versus metformin plus rosiglitazone	0/78 versus 0/158
Borges, 2011[96]	RCT	Metformin versus metformin plus rosiglitazone	0/334 versus 1/344
DeFronzo, 2012[95]	RCT	Metformin versus metformin plus pioglitazone	NR/129 versus 1/129

RCT = randomized controlled trial

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

Three 26-week RCTs compared metformin alone with the combination of metformin plus a DPP-4 inhibitor, showing no significant increased risk of heart failure in either arm.[76, 95, 123] One RCT reported no events in either arm.[76] One RCT reported no events in the combination arm, but did not report on events in the metformin monotherapy arm.[95] The third RCT reported one event in the combination arm and did not report on events in the metformin monotherapy arm.[123] We combined these three RCTs in a meta-analysis using zero events for the arms where no data was reported, and found no significant increased risk of heart failure between groups (pooled OR, 1.5; 95% CI, 0.06 to 37.05) (Figure 88).[76, 95, 123] (SOE: Low; Neither favored)

Figure 88. Pooled odds ratio of congestive heart failure events comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus Sulfonylureas

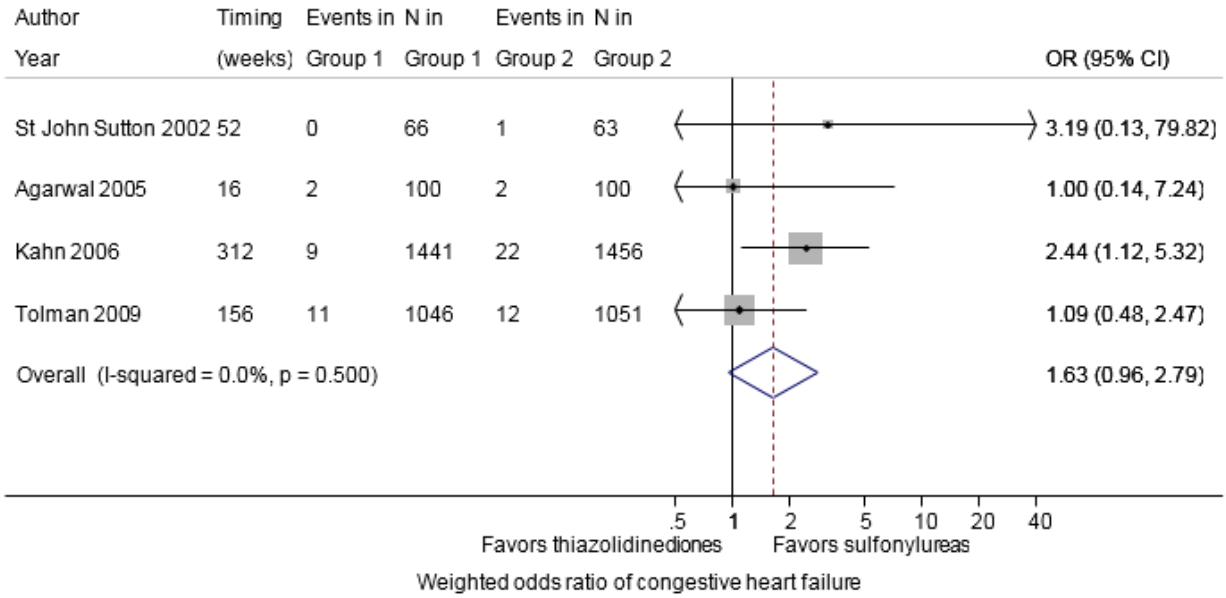
Four trials[44, 45, 200, 201] and two observational studies[222, 230] examined heart failure outcomes for this comparison (Table 78), finding no clear between-group differences. A meta-analysis of the four RCTs[44, 45, 200, 201] showed an increased risk of congestive heart failure with thiazolidinediones compared with second-generation sulfonylureas which did not reach statistical significance (pooled OR, 1.62; 95% CI, 0.95 to 2.76) (Figure 89). There was no evidence of statistical heterogeneity among the included studies ($I^2 = 0\%$). Consistent with the meta-analysis of the RCTs, the two observational studies also showed increased risk of heart failure which did not reach statistical significance in three of the four thiazolidinedione arms compared with the sulfonylurea arms.[222, 230] (SOE: Low; Sulfonylureas favored)

Table 78. Observational studies comparing thiazolidinediones with sulfonylureas on congestive heart failure

Author, year	Study design	Comparison	Heart failure incidence (sulfonylurea as reference)
Pantalone, 2009[222]	Observational study	Rosiglitazone versus sulfonylurea	HR, 0.88 (95% CI, 0.60 to 1.31), p = 0.55
		Pioglitazone versus sulfonylurea	HR, 1.05 (95% CI, 0.77 to 1.43), p = 0.76
Hsiao, 2009[230]	Observational study	Rosiglitazone versus sulfonylurea	HR, 1.22 (95% CI, 0.86 to 1.74), p = 0.26
		Pioglitazone versus sulfonylurea	HR, 1.37 (95% CI, 0.58 to 3.20), p = 0.46

CI = confidence interval; HR = hazard ratio

Figure 89. Pooled odds ratio of congestive heart failure events comparing thiazolidinediones with sulfonylureas



CI = confidence interval; Group 1 = sulfonylureas; Group 2 = thiazolidinediones; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

One 26-week RCT compared pioglitazone with alogliptin, reporting no heart failure events in either arm.[150] (SOE: Low; Neither drug favored)

Sulfonylureas Versus DPP-4 Inhibitors

One 58-week RCT comparing glipizide with sitagliptin reported four out of 212 patients having heart failure events in the glipizide arm compared with none out of 210 patients in the sitagliptin arm.[152] The only rescue therapy was insulin which was initiated in about 10% of participants in each arm. (SOE: Low; DPP-4 inhibitors favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

One 24-week RCT comparing metformin plus pioglitazone with metformin plus glipizide reported two out of 146 patients with heart failure events in the metformin plus pioglitazone arm and did not report whether there were any events in the 142 patients in the metformin plus glipizide arm.[170] (SOE: Insufficient; Unable to determine effect)

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

One 26-week RCT comparing different doses of metformin plus pioglitazone with different doses of metformin plus alogliptin reported two heart failure events in the 258 patients in the

metformin plus pioglitazone arms and did not report on heart failure events in the metformin plus alogliptin arms.[95] (SOE: Insufficient; Unable to determine effect)

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

In an RCT that compared a combination of insulin glargine daily plus metformin with a combination of insulin lispro 75/25 plus metformin, hospitalization due to heart failure was reported in a single patient on the insulin lispro 75/25 and metformin combination.[206] (SOE: Insufficient; Unable to determine effect)

Strength of Evidence for Congestive Heart Failure

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 79 and Table 80 and summarized in the key points. Most studies were RCTs, although five medium quality observational studies were included. Study limitations for all comparisons were low or medium. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. However, many comparisons only had one or two studies making these comparisons based on quality difficult. We did not find any evidence of publication bias in any of the comparisons for congestive heart failure. We also did not find any evidence of publication bias or reporting bias in the grey literature review. Three studies reported events in one arm only; therefore, we were unable to draw firm conclusions from those studies. While this raises concerns for reporting bias, we expect arms with reporting on this outcome are likely to be the arms where more events occurred. For instance, two of the three studies reported the congestive heart failure events in the thiazolidinedione arms. However, this inconsistent reporting remains problematic when aiming to compare specific medication effects on adverse events and long-term outcomes such as congestive heart failure.

Table 79. Strength of evidence domains for monotherapy comparisons in terms of congestive heart failure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD	RCTs: 3 (4530)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored
	Observational studies: 2 (493,933)	Medium	Consistent	Direct	Imprecise			
Metformin vs. SU	RCT: 1 (304)	Low	Consistent with observational study	Direct	Imprecise	Undetected	Low	Metformin favored
	Observational study: 1 (20,450)	Medium	Consistent with RCT	Direct	Precise			
Metformin vs. DPP-4 inhibitors	RCT: 1 (784)	Medium	Unable to determine	Direct	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. metformin + TZD	RCT: 3 (2947)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin vs. metformin + DPP-4 inhibitors	RCT: 3 (2865)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug arm favored
TZD vs. SU	RCTs: 4 (11,130)	Low	Consistent	Direct	Imprecise	Undetected	Low	SU favored
	Observational studies: 2 (493,933)	Medium	Consistent	Direct	Imprecise			
TZD vs. DPP-4 inhibitors	RCT: 1 (655)	Low	Unable to determine	Direct	Imprecise	Undetected	Low	Neither drug favored
SU vs. DPP-4 inhibitors	RCT: 1 (426)	Low	Unable to determine	Direct	Imprecise	Undetected	Low	DPP-4 inhibitor favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 80. Strength of evidence domains for metformin-based combination comparisons in terms of congestive heart failure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin + SU	RCT: 1 (305)	Medium	Unable to determine	Direct	Imprecise	Suspected†	Insufficient	Unable to determine
Metformin + TZD vs. metformin + DPP-4 inhibitors	RCT: 1 (1554)	Medium	Unable to determine	Direct	Imprecise	Suspected†	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	RCT: 1 (105)	Medium	Unable to determine	Direct	Imprecise	Suspected†	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

† Reporting bias was listed as suspected for each of these comparisons since they did not report events in one of the study arms; however, the arm where the event was not reported is often in the drug arm where one might anticipate that there is likely to be no events.

The Evidence About Liver Injury

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Three RCTs comparing metformin with thiazolidinediones reported on liver injury. Two studies compared metformin with pioglitazone,[55, 63] and one compared metformin with rosiglitazone.[67] Followup and liver injury definitions varied across studies, and results were mixed. All studies targeted at least 2,000 mg daily in their metformin arms, and doses of thiazolidinediones varied (Table 81). The longer studies were of poorer quality and did not find differences in liver injury between arms. The shortest and largest RCT was a high-quality trial which used the highest doses of the drugs (metformin 2,550 daily maximum dose and pioglitazone 45 mg daily maximum dose) and found more liver injury in the metformin than pioglitazone arm. (SOE: Low; Neither favored)

Table 81. Randomized controlled trials comparing metformin with thiazolidinediones on liver injury

Author, year	Study size (total N)	Followup	TZD	Definition of liver injury	Metformin Events/N (%)	TZD Events/N
Yoon, 2011[67]	349	48 weeks	Rosiglitazone 5.9 mg daily (mean)	Abnormal liver function not defined	0/114 (0)	1/117 (0.85%)
Erem, 2014[63]	60	48 weeks	Pioglitazone started at 15 mg daily (most participants on ≤30 mg daily at end)	Liver enzymes > 2 times ULN	0/13 (0)	0/12 (0)
Schernthaner, 2004[55]	1,199	26 weeks	Pioglitazone started at 30 mg daily; 45 mg daily (maximum)	Liver enzymes > 3 times ULN	2.2%	0.9%

mg = milligrams; TZD = thiazolidinedione; ULN = upper limit normal

Metformin Versus Sulfonylureas

Two RCTs with long-term followup compared metformin with sulfonylureas and reported on liver injury.[45, 67] Neither study provided a specific definition of liver injury, and both studies used sub-maximal doses of the sulfonylurea and comparable doses of metformin (titration to maximum of 2,000 mg daily). One study found similar rates of liver injury in the two arms,[45] and the other study reported more liver abnormalities in the sulfonylurea arm (Table 82).[67] (SOE: Low; Neither favored)

Table 82. Randomized controlled trials comparing metformin with sulfonylureas on liver injury

Author, year	Study size (total N)	Followup	SU	Definition of liver injury	Metformin Events/N (%)	SU Events/N
Kahn, 2006[45] ADOPT Study	4360	Not reported*	Glyburide; started 2.5 mg; maximum 15 mg	Not defined	NR/1341 (1.1)	NR/1441 (0.8)
Yoon, 2011[67]	349	48 weeks	Glimepiride 4.5 mg daily (mean)	Abnormal liver function not defined	0/114 (0)	5/118 (4.24%); *P* = 0.05

ADOPT = A Diabetes Outcome Progression Trial; mg = milligrams; NR = not reported; SU = sulfonylurea
*Study was 6.1 years in duration, but follow up for this outcome not reported

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

Three RCTs compared metformin with the combination of metformin plus a DPP-4 inhibitor.[115, 121, 131] Followup and liver injury definitions varied (Table 83). In the longest study (52 weeks), both treatments were associated with similar rates of hepatic adverse events (not specified), at a dose of metformin 1,000 mg/day.[131] In the shorter studies (12 to 24 weeks), which used higher doses of metformin (1,500 mg/day), events were rare.[115, 121] (SOE: Low; Neither favored)

Table 83. Randomized controlled trials comparing metformin with DPP-4 inhibitors on liver injury

Author, year	Study size (total N)	Followup	DPP-4 inhibitor	Definition of liver injury	Metformin Events/N (%)	DPP-4 inhibitor Events/N
Haak, 2013[131]	567	52 weeks	Linagliptin 5 mg daily	Unspecified hepatic adverse events	13 /170 (7.6%)	11/171 (6.4%)
Ross, 2012[121]	491	12 weeks	Linagliptin 5 mg daily	Unspecified elevation of liver enzymes	0/44 (0%)	2/224 (0.9%)
Yang, 2011[115]	570	24 weeks	Saxagliptin 5 mg daily	Abnormal liver function	0/142 (0%)	1/146 (0.6%)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams

Thiazolidinediones Versus Sulfonylureas

Three RCTs comparing thiazolidinediones with sulfonylureas reported on liver injury.[45, 67, 201] Followup and liver injury definitions varied (Table 84).

One study reported an non-significant increased risk of liver injury for sulfonylurea versus submaximal rosiglitazone,[67] and the other two RCTs did not find substantial differences in livery injury between arms.[45, 201] Of note, the highest-quality, largest and longest study reported no liver toxicity in either arm.[45] (SOE: Low; Neither favored)

Table 84. Randomized controlled trials comparing thiazolidinediones with sulfonylureas on liver injury

Author, year	Study size (total N)	Followup	TZD	SU	Definition of liver injury	TZD Events/N (%)	SU Events/N
Kahn, 2006[45] ADOPT Study	4360	Not reported*	Rosiglitazone 8 mg (maximum)	Glyburide 15 mg daily (maximum)	Not defined	0/1456 (0%)	0/1441 (0%)
Yoon, 2011[67]	349	48 weeks	Rosiglitazone 5.9 mg daily (mean)	Glimepiride 4.5 mg daily (mean)	Abnormal liver function not defined	1/117 (0.85%)	5/118 (4.2%); *P* = 0.05
Tolman, 2009[201]	2120	24 weeks	Pioglitazone 45 mg daily (maximum)	Glyburide 15 mg daily (maximum)	Liver enzymes > 3 times ULN with confirmation	0/1051 (0%)	4/1046 (0.4%) *P* =0.06

ADOPT = A Diabetes Outcome Progression Trial; mg = milligrams; SU = sulfonylurea; TZD = thiazolidinedione; ULN = upper limit of normal

*Study was 6.1 years in duration, but followup time for this outcome was not reported

Sulfonylureas Versus GLP-1 Agonists

One RCT examined liver injury (defined as hepatobiliary disorders) as an adverse event for this comparison.[155] Seven of 132 participants treated with submaximally-dosed glibenclamide (fixed dose of 1.25 to 2.5 mg daily) developed liver injury at 52 weeks compared with 11 participants of 268 treated with liraglutide titrated to a maximum of 0.9 mg daily (5.3% versus 4.1%).[155] (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two RCTs compared the combination of metformin plus a thiazolidinedione with the combination of metformin plus a sulfonylurea and reported on liver injury.[164, 170] One trial reported no cases of liver injury (defined as “hepatic failure”) in the metformin plus pioglitazone arm (0/146; 0%) and one case in the metformin plus glimepiride arm (1/142; 0.7%) at 24 weeks.[170] A smaller 48-week trial reported no cases of liver injury (defined as liver enzymes values greater than three times the upper limit of normal) in the metformin plus rosiglitazone (0/48) or metformin plus glimepiride (0/47) arms.[164] (SOE: Insufficient; Unable to determine effect)

Strength of Evidence for Liver Injury

We found low strength of evidence for the monotherapy comparisons for which there was evidence on liver injury and insufficient evidence for all combination therapy comparisons for this outcome (Table 85 and 86). The evidence was limited by a small number of studies with a high risk of bias based on assessment of randomization, masking, and withdrawals. Studies addressing liver injury were generally small and did not use maximal dosing of medications, especially for the non-metformin arms. Also, heterogeneity in definitions of liver injury (or lack of reporting specific definitions) limited the strength of evidence and our ability to make conclusions.

Strength of Evidence for Liver Injury

Table 85. Strength of evidence domains for monotherapy comparisons in terms of liver injury among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. TZD	3 (1608)	High	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither favored
Metformin vs. SU	2 (4709)	High	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + DPP-4 inhibitors	3 (1628)	Low	Consistent	Indirect	Imprecise	Undetected	Low	Neither favored
TZD vs. SU	3 (6829)	Medium	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither favored
SU vs. GLP-1 agonists	1 (400)	High	Unknown	Indirect	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 86. Strength of evidence domains for metformin-based combination comparisons in terms of liver injury among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin +SU	2 (723)	High	Inconsistent	Indirect	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Lactic Acidosis

Monotherapy Comparisons

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

We identified two RCTs (18 and 16 weeks) reporting the rates of lactic acidosis for metformin and the combination of metformin and a sulfonylurea. These RCTs reported no cases of lactic acidosis in any of the treatment arms.[99, 100] (SOE: Low; Neither favored)

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

One 12-week RCT reported that increased lactic acid blood levels were more frequent in participants treated with metformin alone (3/100; 3%) than in those treated with the combined regimen of metformin with alogliptin (1/96; 1%); the study did not provide a statistical comparison of these rates.[126] Of note, metformin doses were very small in this study (500 to 750 mg daily). (SOE: Insufficient; Unable to determine effect)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

One 24-week RCT compared the rates of lactic acidosis between the combination of metformin and pioglitazone and the combination of metformin and glimepiride. One case of lactic acidosis was reported in the 142 participants (0.7%) receiving metformin plus glimepiride and none were reported in the 146 participants (0%) who received metformin plus pioglitazone.[170] Of note, the participant with lactic acidosis was noted to have had multiple serious adverse events including heart failure, liver failure, renal failure, and electrolyte disturbances. (SOE: Low; Combination of metformin plus a thiazolidinedione favored)

Strength of Evidence for Lactic Acidosis

Few studies addressed lactic acidosis, and evidence was of low strength or insufficient when present (Table 87 and Table 88). Studies for this evidence base were mainly at medium or high risk of bias and were small and brief in duration; thus the evidence was imprecise and consistency unknown. One of the four studies addressing lactic acidosis only reported on elevated blood levels of lactic acidosis and not on the clinical syndrome of lactic acidosis.

Table 87. Strength of evidence domains for monotherapy comparisons in terms of lactic acidosis among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. Metformin + SU	2 (886)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. Metformin + DPP-4 inhibitors	1 (288)	Low	Unknown	Indirect	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SU = sulfonylurea

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 88. Strength of evidence domains for metformin-based combination comparisons in terms of lactic acidosis among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin +SU	1 (288)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + TZD favored

SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Pancreatitis

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

A 26-week trial compared metformin 1,000 mg daily (n=109), metformin 2,000 mg daily (n=111), and alogliptin 25 mg daily (n=112) and actively ascertained for pancreatitis finding no cases of pancreatitis in these arms.[76] (SOE: Low; Neither favored)

Metformin Versus GLP-1 Agonists

A 52-week RCT that compared metformin with dulaglutide reported no cases of pancreatitis (defined as a lipase increase higher than three times upper limit) in any of the 268 participants receiving metformin or the 269 participants receiving dulaglutide.[83] (SOE: Low; Neither favored)

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Only one RCT compared the incidence of pancreatitis with metformin to the combination of metformin plus a sulfonylurea.[110] There were no cases of pancreatitis, at 104 weeks of followup, among the 100 participants who received monotherapy or the 302 participants who received combined therapy. Criteria of pancreatitis was enzymatic elevation at three times the upper limit plus clinical symptoms. (SOE: Low; Neither favored)

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

We identified nine RCTs comparing the incidence of pancreatitis with metformin to the combination of metformin plus a DDP-4 inhibitor.[46, 76, 110, 120, 121, 126, 128, 131, 247] Definitions of pancreatitis and duration of followup differed across studies (Table 89). Three RCTs did not describe active ascertainment of pancreatitis,[46, 131, 247] and three had substantial losses to followup.[46, 76, 110] Pancreatitis was rare, with any events in only two of the nine studies. In one study, rates of pancreatitis were similar (0.6%) across arms at 52 weeks,[128] and in the other study, two events (0.9%) occurred in the DPP-4 inhibitor combination arm and none in the metformin monotherapy arm at 26 weeks. (SOE: Moderate; Neither favored)

Table 89. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on pancreatitis

Author, year	Study size (total N)	Followup	DPP-4 inhibitor	Definition of pancreatitis	Metformin Events/N (%)	DPP-4 inhibitor Events/N
Nauck, 2014[128]	1098	52 weeks	Sitagliptin 100 mg daily	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	1/177 (0.6%)	2/315 (0.6%)
Ahren, 2014[110]	1049	104 weeks	Sitagliptin 100 mg daily	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	0/100	0/299
Bergenstal, 2012[46]	666	156 weeks	Sitagliptin 100 mg daily	Unspecified	0/93	0/184
Skrivanek, 2014[247]	230	26 weeks	Sitagliptin 100 mg daily	Unspecified elevation of enzymes	0/38	0/42
Pratley, 2014[76]	784	26 weeks	Alogliptin 25 mg daily	Unspecified elevation of enzymes	0/222	2/220 (0.9%) 1 case confirmed
Seino, 2012[126]	288	12 weeks	Alogliptin 12.5 or 25 mg daily	Unspecified	0/100	Alogliptin 12.5 mg: 0/92 Alogliptin 25 mg: 0/96
Haak, 2013[131]	567	52 weeks	Linagliptin 5 mg	Clinical diagnosis	0/170	0/396
Ross, 2012[121]	491	12 weeks	Linagliptin 5 mg	Unspecified	0/44	0/447
White, 2014[120]	160	12 weeks	Saxagliptin 5 mg	Unspecified	0/78	0/66

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; ULN = upper limit of normal

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

Three RCTs compared the incidence of pancreatitis with metformin and the combination of metformin plus a GLP-1 agonist (Table 90).[110, 128, 247] The longest study actively ascertained for pancreatitis but had substantial losses to followup. Two cases of pancreatitis were reported in the metformin plus GLP-1 agonist arm of this study with none in the metformin monotherapy arm.[110] In the other studies, one reported no pancreatitis in either arm at 26 weeks, but did not report on active ascertainment,[247] and the other saw a single case in the metformin monotherapy arm followed to 52 weeks, with active ascertainment for pancreatitis.[128] (SOE: Low; Neither favored)

Table 90. Randomized controlled trials comparing metformin with a combination of metformin plus a GLP-1 agonist on pancreatitis

Author, year	Study size (total N)	Followup	GLP-1 agonist	Definition of pancreatitis	Metformin Events/N (%)	DPP-4 inhibitor Events/N
Skrivanek, 2014[247]	230	26 weeks	Dulaglutide 0.75, 1.0, and 1.5 mg weekly	Unspecified elevation of enzymes	0/38	0.75 mg: 0/21 1.0 mg: 0/10 1.5 mg: 0/25
Nauck, 2014[128]	1098	52 weeks	Dulaglutide 0.75 and 1.5 mg weekly	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	1/177 (0. 5%)	0.75 mg: 0/302 1.5 mg: 0/304
Ahren, 2014[110]	1049	104 weeks	Albiglutide 50 mg weekly (maximum)	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	0/100	2/296 (0.7%)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; mg = milligrams; ULN = upper limit of normal

Sulfonylureas Versus DPP-4 Inhibitors

We identified one RCT comparing the incidence of pancreatitis between sulfonylurea and DPP-4 inhibitors.[151] There were no cases of pancreatitis in any of the 76 participants receiving glimepiride or the 151 participants receiving linagliptin. The definition of pancreatitis was unspecified. (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Agonists

Two RCTs compared sulfonylureas with GLP-1 agonists and reported on pancreatitis.[154, 157] One trial reported two cases of pancreatitis in the liraglutide arm (2/498; 0.4%) and no cases in the glimepiride arm (0/248; 0%) at 104 weeks.[157] A 24-week trial reported no cases of pancreatitis in the liraglutide (n=272) or glibenclamide (n=139) arms.[154] The criteria for a diagnosis of pancreatitis was unspecified in both studies. (SOE: Low; Sulfonylureas favored)

DPP-4 Inhibitors Versus GLP-1 Agonists

A 26-week RCT that compared liraglutide (n = 446) with sitagliptin (n = 219) reported no episodes of pancreatitis.[192] The definition of pancreatitis was unspecified. (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

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

The 26-week DURATION-2 RCT reported two cases of pancreatitis in the 165 participants who were treated with the metformin plus pioglitazone combination compared with none of the 166 participants who received the metformin plus sitagliptin combination.[173] Pancreatitis was not actively ascertained and criteria for diagnosis were unspecified; this study had differential losses to followup across the arms (metformin plus thiazolidinedione, 21% and metformin plus DPP-4 inhibitor, 13%). (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Agonist

The DURATION-2 RCT described above also had an additional arm with 160 participants who received metformin plus weekly exenatide, and none were reported to have pancreatitis during the study.[173] Again, two of 165 participants had pancreatitis in the metformin plus thiazolidinedione arm; pancreatitis was not actively ascertained and criteria for diagnosis were unspecified. This study had large losses to followup across the arms (21% in both the metformin plus thiazolidinedione and metformin plus exenatide arms).[173] (SOE: Low; Neither favored)

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

We identified two RCTs which compared the incidence of pancreatitis for the combination of metformin plus a sulfonylurea to the combination of metformin plus a DPP-4 inhibitor.[178, 179] Both trials reported that one participant in the metformin plus sulfonylurea arm had pancreatitis during the study (0.1% and 0.2% of participants) and that no participants in the metformin plus DPP-4 arms had pancreatitis. Neither study actively ascertained for pancreatitis and did not provide definitions for this outcome; losses to followup were substantial in both studies. (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

We identified two relevant RCTs.[185, 187] A 104-week RCT comparing metformin plus glimepiride (N=508) versus metformin plus exenatide (N = 511) reported one case of pancreatitis in each arm (0.2% in each arm).[185] A 16-week RCT comparing metformin plus glimepiride (N=231) versus metformin plus liraglutide (N = 467) reported no cases of pancreatitis in either arm.[187] Studies did not report active ascertainment of pancreatitis, and the criteria for pancreatitis diagnosis were unspecified. (SOE: Low; Neither favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

The 26-week DURATION-2 RCT reported no cases of pancreatitis in either the metformin plus weekly exenatide (n=160) or metformin plus sitagliptin arm (n=166). Pancreatitis was not actively ascertained, and criteria for diagnosis of pancreatitis were unspecified. This study had differential losses to followup across the arms (metformin plus GLP-1 agonist, 21% and metformin plus DPP-4 inhibitor, 13%).[173] (SOE: Low; Neither favored)

Combination of Metformin Plus a GLP-1 Agonist Versus a Combination of Metformin Plus a Basal Insulin

One 52-week RCT reported that one patient on metformin plus exenatide developed pancreatitis (1/36, 2.7%) and did not report on this outcome for the metformin plus insulin glargine arm (0/33, 0%).[195] The 3-year followup of this study which had significant losses to followup reported no additional pancreatitis after the 52 week report.[47] The study did not report active ascertainment or provide criteria for pancreatitis. It is also unclear if an intention-to-treat approach was taken.[47, 195] (SOE: Low; Combination of metformin plus a basal insulin favored)

Strength of Evidence for Pancreatitis

With the exception of one comparison, we found low-strength or insufficient evidence for most monotherapy and combination comparisons for pancreatitis (Table 91 and Table 92). The evidence was mainly limited by a lack of studies. All evidence came from RCTs but tended to be at medium to high risk of bias, mainly because of the availability of only a few fair- to poor-quality studies for each comparison. Consistency tended to be indeterminate because of a lack of more than one study for many comparisons. All evidence was direct although active ascertainment and definitions were not usually provided in studies. The small number of studies and their small sample sizes contributed to the evidence being imprecise for all comparisons for which we had studies. We did not detect reporting bias for pancreatitis but had few studies to evaluate publication bias.

Table 91. Strength of evidence domains for monotherapy comparisons in terms of pancreatitis among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. DPP-4 inhibitors	1 (784)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. GLP-1 agonists	1 (495)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. Metformin + SU	1 (1049)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. Metformin + DPP-4 inhibitors	9 (5333)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Neither treatment favored
Metformin vs. Metformin + GLP-1 agonists	3 (2377)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
SU vs. DPP-4 inhibitors	1 (227)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
SU vs. GLP-1 agonists	2 (1210)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	SU favored
DPP-4 inhibitors vs. GLP-1 agonists	1 (661)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

Table 92. Strength of evidence domains for metformin-based combination comparisons in terms of pancreatitis among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + TZD vs. metformin +DPP-4 inhibitors	1 (491)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitor favored
Metformin + TZD vs. metformin +GLP-1 agonists	1 (491)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + SU vs. metformin +DPP-4 inhibitors	2 (2410)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitors favored
Metformin + SU vs. metformin +GLP-1 agonists	2 (2481)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + DPP-4 inhibitors vs. metformin +GLP-1 agonists	1 (491)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + GLP-1 agonists vs. metformin + basal insulin	1 (69)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin plus basal insulin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

The Evidence About Severe Allergic Reactions

Monotherapy Comparisons

Metformin Versus GLP-1 Agonists

A single 52-week RCT (N=495) that compared metformin with dulaglutide reported no systemic hypersensitivity reaction in either arm.[83] (SOE: Low; Neither favored)

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

Four RCTs compared the incidence of severe allergic reactions between metformin and the combination of metformin plus a DDP-4 inhibitor (Table 93).[115, 120, 121, 131] Heterogeneity in definitions of severe allergic reactions and duration of followup precluded a meta-analysis. Three of the four RCTs reported slightly higher rates of hypersensitivity reaction events in the metformin plus DPP-4 inhibitor versus the metformin monotherapy arms.

The longest RCT was a 54-week extension study[131] in which the arms included participants from the initial 6-month study[78] and participants who were re-randomized for the extension study. Among participants who were newly randomized for the 54-week extension study, hypersensitivity reactions occurred in 0% of the metformin 2,000 mg arm, 0% of the metformin 1,000 mg plus linagliptin 5 mg arm, and in 1.7% of the metformin 2,000 mg plus linagliptin 5 mg arm. (SOE: Low; Metformin favored)

Table 93. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on severe allergic reactions

Author, year	Sample size (total N)	Followup	DPP-4 inhibitor	Definition of severe allergic reaction	Active Asc.	Metformin Events/N (%)	DPP-4 inhibitor Events/N (%)
Haak, 2013[131]	567	54 weeks	Linagliptin 5 mg	Hypersensitivity reactions (e.g., angioedema, anaphylaxis)	Yes	1/170 (0.6%)*	2/171 (1.2%)*
				Severe cutaneous reactions	Yes	0/170	0/171
White, 2014[120]	160	12 weeks	Saxagliptin 5 mg	Hypersensitivity reactions	NR	0/78	0/66
Yang, 2011[115]	570	24 weeks	Saxagliptin 5 mg	Hypersensitivity reactions	Yes	0/287	3/283 (1.1%)
Ross, 2012[121]	491	12 weeks	Linagliptin	Hypersensitivity reactions (angioedema, anaphylaxis, angioedema-like)	Yes	0/44	5 mg: 1/224 (0.4%) 2.5 mg: 0/223

Asc = ascertainment; DPP-4 = dipeptidyl peptidase-4; mg = milligrams

* Data are shown for the metformin 2000 mg monotherapy arm and the metformin 2000 mg plus linagliptin 5 mg combination arm; there were no events reported in the metformin 1000 mg plus linagliptin combination arm

Metformin-Based Combination Comparisons

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

A single 52-week RCT compared metformin plus glipizide with metformin plus saxagliptin and reported on hypersensitivity adverse events.[179] The authors reported a hypersensitivity adverse event in one participant in the metformin plus saxagliptin arm and in two participants in the metformin plus glipizide arm. One of the events in the metformin plus glipizide arm was noted to be related to ciprofloxacin. This study did not provide information on the method of ascertainment or definition of hypersensitivity. This RCT also had high rates of discontinuation based partly on increasingly-strict glycemic control criteria for maintaining eligibility in the study.[179] (SOE: Low; Neither favored)

Strength of Evidence for Severe Allergic Reactions

We identified evidence for three comparisons for the outcome of allergic reactions (Table 94 and Table 95). The published studies were on comparisons that included GLP-1 agonists and DPP-4 inhibitors. All evidence was low or insufficient for this outcome. Because of the limited numbers of studies and their samples sizes, evidence was imprecise. We did not detect reporting bias, but our assessment of this was also limited by the small number of studies.

Table 94. Strength of evidence domains for monotherapy comparisons in terms of severe allergic reactions among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. GLP-1 agonists	1 (495)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + DPP-4 inhibitors	4 (1788)	Low	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists

Table 95. Strength of evidence domains for metformin-based combination comparisons in terms of severe allergic reactions among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + SU vs. metformin +DPP-4 inhibitors	1 (858)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SU = sulfonylurea

The Evidence About Macular Edema or Decreased Vision

Monotherapy Comparisons

Sulfonylureas Versus GLP-1 Agonists

One 104-week RCT compared glimepiride with liraglutide at two different doses (1.2 and 1.8 mg) and reported on decreased vision.[158] At the end of the study, the incidence of decreased vision was comparable in all arms, with 7% of the glimepiride participants (n=248) having decreased vision compared with 6% of the liraglutide participants (n=251 for liraglutide-1.2 mg and n=247 at liraglutide-1.8 mg). (SOE: Low; Neither favored)

Strength of Evidence for Macular Edema or Decreased Vision

We identified one study for this outcome. Therefore, the evidence on this outcome was insufficient due to a lack of studies (Table 96).

Table 96. Strength of evidence domains for monotherapy comparisons in terms of macular edema or decreased vision among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
SU vs. GLP-1 agonists	1 (746)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

GLP-1 agonists = glucagon-like peptide-1 agonists; SU = sulfonylurea

The Evidence About Urinary Tract Infections

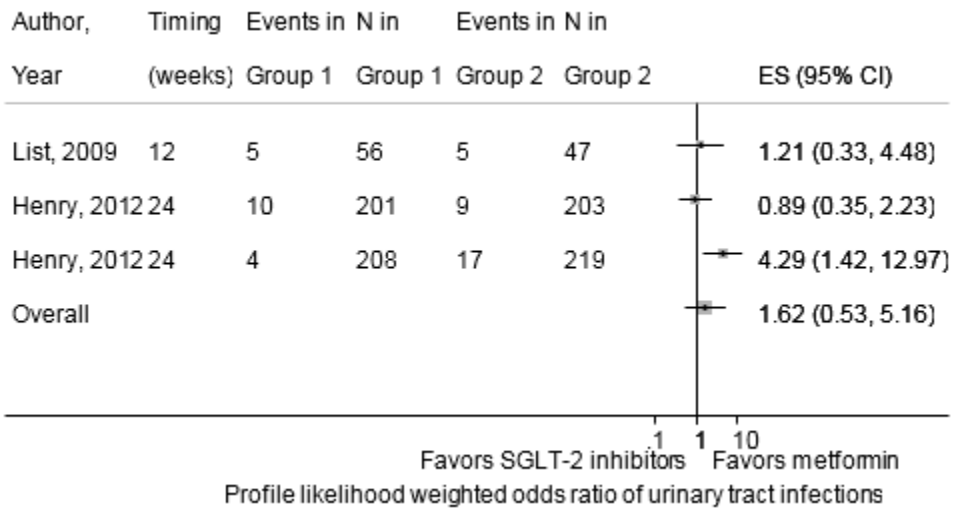
Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Three short RCTs (published in two articles), 12 to 24 weeks in duration, compared dapagliflozin with metformin and reported on UTIs.[80, 81] Since ORs did not appear to vary by gender in these short-term studies, we present results for men and women combined. We found significant statistical heterogeneity using a random effects meta-analysis (pooled OR, 1.64; 95% CI, 0.61 to 4.39; I-squared = 58.3%). Exclusion of any one study did not change the inference of the meta-analysis. We found a similar non-significant increased odds for SGLT-2 inhibitors versus metformin for UTIs (pooled OR, 1.6; 95% CI, 0.5 to 5.2 (Figure 90) using the profile likelihood method. One of the RCTs used a lower dose of dapagliflozin of 5 mg[80] relative to the 10 mg in the other two RCTs.

We did not include one RCT in the meta-analysis because it was much longer (78 weeks) than the other three studies.[82] This study compared metformin to 10 mg of empagliflozin and 25 mg of empagliflozin and reported similar overall incidences of UTIs with both doses of empagliflozin. UTI rates among men receiving 25 mg of empagliflozin (4/57; 7.0%) were non-significantly higher than among those receiving 10 mg of empagliflozin (0/49; 0%) and metformin (0/28; 0%), and approached UTI rates among women (empagliflozin 10 mg: 4/57 (7.0%), empagliflozin 25 mg: 3/52 (5.8%), and metformin: 2/28 (7.1%)).[82] (SOE: Moderate; Neither favored)

Figure 90. Pooled odds ratio of urinary tract infections comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

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

Six RCTs (published in five articles) compared metformin with the combination of metformin plus an SGLT-2 inhibitor. The four shorter RCTs suggested no difference in risk of UTIs for metformin plus SGLT-2 inhibitors versus metformin (pooled OR, 1.2; 95% CI, 0.7 to 2.0) (Figure 91).[80, 122, 125, 132, 133] No single study markedly influenced the results, and we did not find evidence of substantial statistical heterogeneity ($I^2 = 0.0\%$). One study also reported that no events of urosepsis or pyelonephritis occurred in either arm.[133] The definitions for UTIs varied across studies (Table 97).

Table 97. Definitions of urinary tract infections used in randomized controlled trials comparing metformin with a combination of metformin and SGLT-2 inhibitor

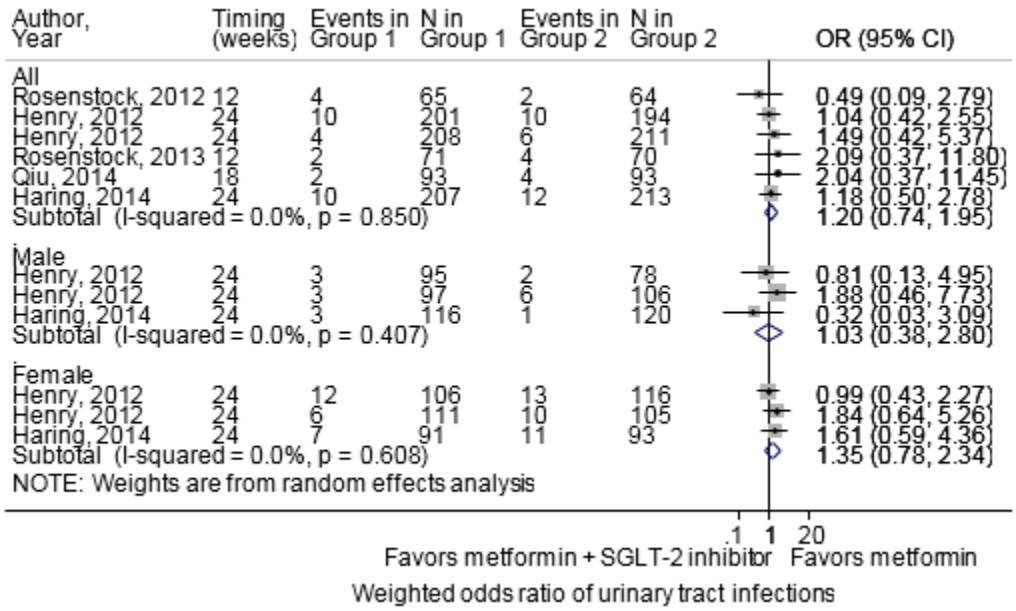
Author, year	Definition of UTI outcome (actively ascertained unless otherwise noted)
Bailey, 2013[135]	UTI (does not include events suggestive of UTI)
Rosenstock, 2012[125]	UTI, not otherwise specified
Henry, 2012[80]	Events suggestive of UTI
Bolinder, 2012[134]	MedDRA definition of UTI
Rosenstock, 2013[122]	UTI, not otherwise specified
Qiu, 2014[132]	UTI, not otherwise specified
Haring, 2014 (a)[133]	MedDRA definition for UTI
Henry, 2012 (b)[80]	Based on a predefined list of signs, symptoms and other events suggestive of UTI

MedDRA = Medical Dictionary for Regulatory Activities; UTI = urinary tract infection

Meta-analyses stratified by gender, available in few studies, did not demonstrate clear gender differences for UTIs for this comparison.[80, 133] Women had non-significantly increased rates of

UTIs for the combination of metformin plus an SGLT-2 inhibitor versus metformin (pooled OR, 1.4; 95% CI, 0.8 to 2.3 for women and pooled OR, 1.0; 95% CI, 0.4 to 2.8 for men).

Figure 91. Pooled odds ratio of urinary tract infections comparing metformin with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include two moderately-sized RCTs (total sample size, 182 to 546) in the meta-analysis because they were longer (102 weeks).[134, 135] One compared metformin with metformin plus dapagliflozin and reported UTI rates of 5.8% and 11.9% in the metformin and dapagliflozin arms, respectively.[135] The other had similar UTI rates across arms (metformin, 4.4% and dapagliflozin, 3.3%).[134] Of note, the former had very high losses to followup with 47% losses in the metformin arm compared with 30% to 40% in the other arms.[135] (SOE: High; Neither favored)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One 24-week RCT compared 100 mg of sitagliptin with 10 mg and 25 mg of empagliflozin and reported UTI events separately by gender.[159] UTI occurrences among men were similar in those receiving sitagliptin (4/141; 3%) versus 10 mg of empagliflozin (3/142; 2%) and 25 mg of empagliflozin (2/144; 1%).[159] UTI events were non-significantly lower in women receiving sitagliptin (7/82; 9%) versus 10 mg of empagliflozin (12/82; 15%) and 25 mg of empagliflozin (10/78; 13%). The study did not test for an interaction by gender. (SOE: Low; Neither favored in men, DPP-4 inhibitors favored in women)

Metformin-Based Combination Comparisons

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

Three RCTs compared metformin plus a sulfonylurea with metformin plus an SGLT-2 inhibitor and reported inconsistent results regarding UTIs (Table 98).[181-183] We did not combine these studies in a meta-analysis because of the heterogeneity in the definition of UTI and study durations. A 52-week RCT found a similar incidence of UTIs with metformin plus glimepiride versus metformin plus 100 mg or 300 mg of canagliflozin.[181] A second 104-week RCT found more UTIs in the metformin plus dapagliflozin arm compared to the metformin plus glipizide arm.[182] This study also reported a 3% incidence of kidney infections, defined as pyelocystitis and pyelonephritis, in the metformin plus glipizide arm compared with no cases in the metformin plus dapagliflozin arm.[182] The third trial, also 104 weeks long, reported higher UTI rates among females in both arms compared with males; the study did not find a difference in UTI rates across arms within gender.[183] (SOE: Moderate; Neither favored)

Table 98. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor on urinary tract infections

Author, year	Definition of UTI Outcome*	Results Events/N (%)
Cefalu, 2013[181]	Cystitis, pyelonephritis chronic, and UTI	Metformin + glimepiride: 22/482 (5%) Metformin + canagliflozin 100 mg: 31/483 (6%) Metformin + canagliflozin 300 mg: 31/485 (6%)
Nauck, 2011[182]	Events suggestive of UTI	Metformin + glipizide: 37/408 (9.1%) Metformin + dapagliflozin: 55/406 (13.5%)
Ridderstrale, 2014[183]	MedDRA definition of UTI (passive ascertainment)	Female Metformin + glimepiride: 81/359 (23%) Metformin + empagliflozin: 74/333 (22%) Male Metformin + glimepiride: 21/421 (5%) Metformin + empagliflozin: 31/432 (7%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; UTI = urinary tract infections
* Outcomes are actively ascertained unless otherwise noted.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Four RCTs compared metformin plus DPP-4 with metformin plus an SGLT-2 inhibitor and reported inconsistent results (Table 99). We did not combine them due to differences in study duration.[82, 122, 125, 127]

One 78-week RCT of low quality compared metformin plus sitagliptin to metformin plus 10 mg and 25mg of empagliflozin and reported UTI rates stratified by sex. This study found a higher UTI rate among females in the metformin plus 25mg of empagliflozin arm compared with metformin plus sitagliptin arm, but higher rates of UTIs among males in the metformin plus sitagliptin arm.[82] A medium-quality 52-week RCT compared metformin plus sitagliptin to metformin plus canagliflozin at doses of 100 mg and 300 mg and reported slightly lower UTI rates in the highest-dose canagliflozin (300 mg) arm and slightly higher rates in the lower-dose canagliflozin (100 mg) arm; results were not stratified by sex.[127]

The two short-term studies also conflicted. One medium-quality study reported a higher UTI rate with metformin plus 200 mg of canagliflozin compared with the other arms.[125] The other high-quality short-term RCT found similar UTI rates with metformin plus sitagliptin and

metformin plus empagliflozin arms with a slightly higher rate in the highest-dose empagliflozin arm.[122] The quality of the studies was graded as medium risk of bias because of failure to report clearly on the randomization scheme. (SOE: Low; Neither favored)

Table 99. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor on urinary tract infections

Author, year	Followup	Definition of UTI Outcome*	Results Events/N (%)
Rosenstock, 2012[125]	12 weeks	UTI, not otherwise specified	Metformin + sitagliptin 100 mg: 1/65 (2%) Metformin + canagliflozin 100 mg: 2/64 (3%) Metformin + canagliflozin 200 mg: 6/65 (9%) Metformin + canagliflozin 300 mg: 2/64 (3%)
Rosenstock, 2013[122]	12 weeks	UTIs, including cystitis, excluding signs and symptoms	Metformin + sitagliptin 100 mg: 4.2% Metformin + empagliflozin 10 mg: 4.2% Metformin + empagliflozin 25 mg: 5.7%
Lavalle-Gonzalez, 2013[127]	52 weeks	UTI, not otherwise specified	Metformin + sitagliptin 100 mg: 23/366 (6.3%) Metformin + canagliflozin 100 mg: 29/368 (7.9%) Metformin + canagliflozin 300 mg: 18/367 (4.9%)
Ferrannini, 2013[82]	78 weeks	MedDRA definition of UTI	Female Metformin + sitagliptin 100 mg: 4/27 (14.8%) Metformin + empagliflozin 10 mg: 13/83 (15.7%) Metformin + empagliflozin 25 mg: 18/78 (23.1%) Male Metformin + sitagliptin 100 mg: 3/29 (10.3%) Metformin + empagliflozin 10 mg: 2/83 (2.4%) Metformin + empagliflozin 25 mg: 3/88 (3.4%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; UTI = urinary tract infections
* Outcomes are actively ascertained unless otherwise noted.

Strength of Evidence for Urinary Tract Infections

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 100 and Table 101 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. Although evidence of gender differences in UTI rates was limited, the data suggests that there may be higher rates of UTIs among females (particularly noted in the comparisons of metformin versus metformin plus SGLT2). In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias in any of the comparisons for UTI. We also did not find any evidence of publication bias or reporting bias in the grey literature review. The grey literature was consistent with our findings in the metformin plus SU vs. metformin plus SGLT2 comparison with one unpublished study that found no UTIs in either arm.

Table 100. Strength of evidence domains for monotherapy comparisons in terms of urinary tract infections among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SGLT-2 inhibitors	4 (2,292)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors	8 (3,835)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored in men DPP-4 inhibitors favored in women

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors
* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 101. Strength of evidence domains for metformin-based combination comparisons in terms of urinary tract infections among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + SU vs. metformin + SGLT-2 inhibitors	3 (3,815)	Low risk of bias	Inconsistent	Direct	Precise	Suspected	Moderate	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	4 (2,889)	Medium risk of bias	Inconsistent	Direct	Precise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione
* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Impaired Renal Function

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Three RCTs compared metformin with SGLT-2 inhibitors and reported on impaired renal function (Table 102).[81, 82, 227] We did not combine the results of these RCTs in a meta-analysis because they varied greatly in their definitions of impaired renal function.

Two trials evaluated the change in estimated glomerular filtration rate (eGFR) and found no substantial differences between the arms.[81, 82]

One 12-week trial (N=408) evaluated incident microalbuminuria, change in the urine albumin-to-creatinine ratio, and incident diabetic nephropathy.[227] The investigators did not find substantial differences in urine albumin-to-creatinine ratio across arms, and those in the low-dose empagliflozin arm had more incident microalbuminuria and diabetic nephropathy compared with the metformin and high-dose empagliflozin arm. (SOE: Low; Neither favored)

Table 102. Randomized controlled trials comparing metformin with SGLT-2 inhibitors on impaired renal function

Author, year	Followup	Definition of Impaired Renal Function*	Results
List, 2009[81]	12 weeks	eGFR	NR for any arm Qualitative statement of no difference across groups
Ferrannini, 2013[82]	90 weeks	eGFR (ml/min/1.73 m^2)	Metformin vs. empagliflozin 10 mg: between-group difference from baseline to final, 0.13 (95% CI, -4.5 to 4.7) Metformin vs. empagliflozin 25 mg: between-group difference from baseline to final, 2.66 (95% CI, -1.8 to 7.1)
Ferrannini, 2013[227]	12 weeks	Microalbuminuria, not further defined	Metformin: 1.3% Empagliflozin 10 mg: 3.7% Empagliflozin 25 mg: 0%
	12 weeks	Diabetic nephropathy (unclear if actively ascertained)	Metformin: 1.3% Empagliflozin 10 mg: 2.5% Empagliflozin 25 mg: 1.2%
	12 weeks	Urinary albumin to creatinine ratio (mg/mmol)	Metformin vs. empagliflozin 10 mg: between-group difference from baseline to final, 0.08 mg/mmol Metformin vs. empagliflozin 25 mg: between-group difference 0.6 mg/mmol

CI = confidence interval; eGFR = estimated glomerular filtration rate; mg = milligrams; mg/mmol = milligrams per millimole; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported
* Outcomes are actively ascertained unless otherwise noted.

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

Five RCTs comparing metformin with a combination of metformin plus SGLT-2 inhibitor reported on albuminuria and eGFR (Table 103).[122, 132-135] One 12-week RCT evaluated albuminuria comparing metformin with metformin plus empagliflozin and stated that treatment with empagliflozin did not significantly change measures of creatinine clearance compared with sitagliptin, and did not change markers of glomerular function (microalbumin).[122]

Two 102-week trials evaluated renal impairment or failure as a categorical outcome with conflicting results.[134, 135] One found no events of renal impairment in either arm,[134] and the other RCT did not find a clear pattern of differences across arms.[135]

Two trials evaluated eGFR and found no substantial differences between the arms.[132, 133] (SOE: Low; Neither favored)

Table 103. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on impaired renal function

Author, year	Followup	Definition of Impaired Renal Function*	Results
Rosenstock, 2013[122]	12 weeks	Creatinine clearance, microalbuminuria	NR for any arm Qualitative statement of no difference across groups
Qiu, 2014[132]	18 weeks	eGFR	% reduction in eGFR Metformin: 0.3% Metformin + canagliflozin 50 mg twice daily: 0.7% Metformin + canagliflozin 150 mg twice daily: 3.8%
Haring, 2014[133]	24 weeks	eGFR (ml/min/1.73 m^2)	Metformin vs. metformin + empagliflozin 10 mg: between-group difference from baseline to final, 0.9 (95% CI, -1.5 to 3.3) Metformin vs. metformin + empagliflozin 25 mg: between-group difference from baseline to final, 2.7 (95% CI, 0.6 to 4.8)
Bailey, 2013[135]	102 weeks	Renal impairment or failure, not otherwise specified	Metformin: 2/137 (1.5%) Metformin + dapagliflozin 2.5 mg: 6/137 (4.4%) Metformin + dapagliflozin 5 mg: 4/137 (2.9%) Metformin + dapagliflozin 10 mg: 2/135 (1.5%)
Bolinder, 2012[134]	102 weeks	MedDRA definition of renal impairment, renal failure	Metformin: 0/91 (0%) Metformin + dapagliflozin 10 mg: 0/91 (0%)

CI = confidence interval; eGFR = estimated glomerular filtration rate; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported
* Outcomes are actively ascertained unless otherwise noted.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Two RCTs comparing DPP-4 inhibitors with SGLT-2 inhibitors evaluated change in eGFR and showed no differences between arms.[159, 229] One 26-week RCT compared sitagliptin with canagliflozin showing a between-group difference in change from baseline eGFR of 4.2 ml/min/1.73 m^2 (95% CI, 3.2 to 11.6 ml/min/1.73 m^2) with 150 mg of canagliflozin 150 mg and 4.3 ml/min/1.73 m^2 (95% CI, -2.8 to 11.4 ml/min/1.73 m^2) with 300 mg of canagliflozin with all arms lowering eGFR.[229] One 24-week RCT compared sitagliptin with empagliflozin showing a non-significant between-group difference in eGFR of 1.1 ml/min/1.73 m^2 (95% CI, -1.2 to 3.5 ml/min/1.73 m^2) with empagliflozin 10 mg and 0.5 ml/min/1.73 m^2 (95% CI, -1.7 to 2.6 ml/min/1.73 m^2) with 25 mg of empagliflozin 25 mg, with all arms increasing eGFR.[159] (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

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

Three RCTs compared the effects of metformin plus a sulfonylurea to metformin plus a SGLT-2 inhibitor on renal impairment or failure, changes in eGFR, and albuminuria (Table 104).[181-183] One 104-week trial evaluated total renal impairment and failure showing a higher incidence of events with metformin plus SGLT-2 inhibitors.[182] Three trials evaluated changes in eGFR with inconsistent results.[181-183] Two trials evaluated albuminuria showing no differences between arms.[181, 183] (SOE: Low; Neither favored)

Table 104. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor on impaired renal function

Author, year	Followup	Definition of Impaired Renal Function*	Results	Notes
Cefalu, 2013[181]	52 weeks	eGFR (ml/min/1.73 m^2)	Metformin + glimepiride vs. metformin + canagliflozin 100 mg: between-group difference, 1.3 ml/min/1.73 m^2 Metformin + glimepiride vs. metformin + canagliflozin 300 mg: between-group difference, 3.4 ml/min/1.73 m^2	Subjects meeting eGFR withdrawal criteria: n=1 in glimepiride arm, n=4 in canagliflozin 100 mg arm, and n=7 for canagliflozin 300 mg arm Unclear if included in analysis
Ridderstrale, 2014[183]	104 weeks	eGFR (ml/min/1.73 m^2)	Metformin + glipizide vs. metformin + empagliflozin 25 mg; between-group difference, 3.5 (95% CI, 2.2 to 4.8)	
Nauck, 2011[182]	104 weeks	Decreased eGFR	Metformin + glipizide: 3/408 (0.7%) Metformin + dapagliflozin: 1/406 (0.2%)	
Nauck, 2011[182]	104 weeks	Total renal impairment (calculated creatinine renal clearance decreased, renal impairment, blood creatinine increased, decreased eGFR, acute renal failure)	Metformin + glipizide: 14/408 (3.4%) Metformin + dapagliflozin: 24/406 (5.9%)	Includes 13 patients in dapagliflozin group and 6 patients in the glipizide group who discontinued due to "calculated creatinine renal clearance decreased"
Cefalu, 2013[181]	52 weeks	Urine albumin-to-creatinine ratio (mg/g)	Metformin + glimepiride vs. metformin + canagliflozin 100 mg: between-group difference, 7.1 mg/g (95% CI, -8.0 to 22.1 mg/g) Metformin plus glimepiride vs. metformin plus canagliflozin 300 mg: between-group difference, 14.2 mg/g (95% CI -1.8 to 30.1 mg/g)	
Ridderstrale, 2014[183]	104 weeks	Urine albumin-to-creatinine ratio (mg/g)	Metformin + glimepiride vs. metformin + empagliflozin 25 mg: between-group difference, 1.9 mg/g (95% CI, -5.1 to 8.9 mg/g)	Subgroup with no albuminuria at baseline

CI = confidence interval; eGFR = estimated glomerular filtration rate; mg = milligrams; mg/g = milligrams per gram; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported
* Outcomes are actively ascertained unless otherwise noted.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Three RCTs compared metformin plus a DPP-4 inhibitor with metformin plus an SGLT-2 inhibitor on renal outcomes (Table 105).[82, 122, 127] Two trials evaluated changes in eGFR showing no differences.[82, 127] One 12-week RCT compared metformin plus sitagliptin and metformin plus

empagliflozin and found no significant differences between arms.[122] (SOE: Low; Neither favored)

Table 105. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor on impaired renal function

Author, year	Followup	Definition of Impaired Renal Function*	Results
Ferrannini, 2013[82]	90 weeks	eGFR (ml/min/1.73 m^2)	Metformin + sitagliptin vs. metformin + empagliflozin 10 mg: between-group difference, 4.1 (95% CI, 0.3 to 8.6) Metformin + sitagliptin vs. metformin + empagliflozin 25 mg: between-group difference, 2.8 (95% CI, -1.5 to 7.1)
Lavalle-Gonzalez, 2013[127]	52 weeks	Decreased eGFR	Metformin + sitagliptin vs. metformin + canagliflozin 100 mg: between-group difference, 1.0% Metformin + sitagliptin vs. metformin + canagliflozin 300 mg: between-group difference, 0.9%
Rosenstock, 2013[122]	12 weeks	Creatinine clearance, microalbuminuria	NR for any arm Qualitative statement of no difference across groups

CI = confidence interval; eGFR = estimated glomerular filtration rate; mg = milligrams; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported
* Outcomes are actively ascertained unless otherwise noted.

Strength of Evidence for Impaired Renal Function

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 106 and Table 107 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. We did not have adequate information to grade precision for metformin plus DPP-4 inhibitors versus metformin plus SGLT2 inhibitors because only two of the three studies reported quantitative data. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias in any of the comparisons for renal outcomes. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 106. Strength of evidence domains for monotherapy comparisons in terms of impaired renal function among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SGLT-2 inhibitors	3 (1,456)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors	5 (2,140)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	2 (1,394)	Medium	Consistent	Direct	Precise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors
* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 107. Strength of evidence domains for metformin-based combination comparisons in terms of impaired renal function among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + SU vs. metformin + SGLT-2 inhibitors	3 (3,815)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	3 (2,438)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea
* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

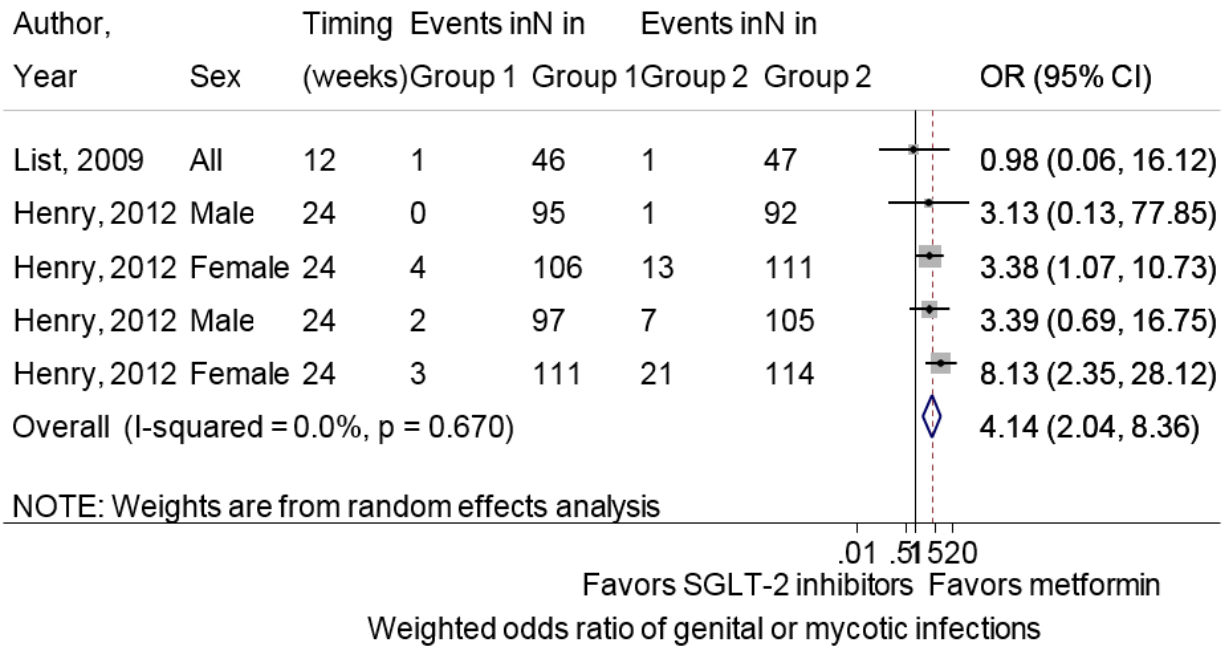
The Evidence About Genital Mycotic Infections

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Three medium to high quality short RCTs (reported in two articles) compared metformin with SGLT-2 inhibitors reporting more genital infections with the SGLT-2 inhibitor arm (pooled OR, 4.1; 95% CI, 2.0 to 8.3) (Figure 92).[80, 81] ORs did appear to vary by gender. No single study markedly influenced the results, and we did not find significant statistical heterogeneity (I^2 = 0.0%).

Figure 92. Pooled odds ratio of genital or mycotic infections comparing metformin with SGLT-2 inhibitors



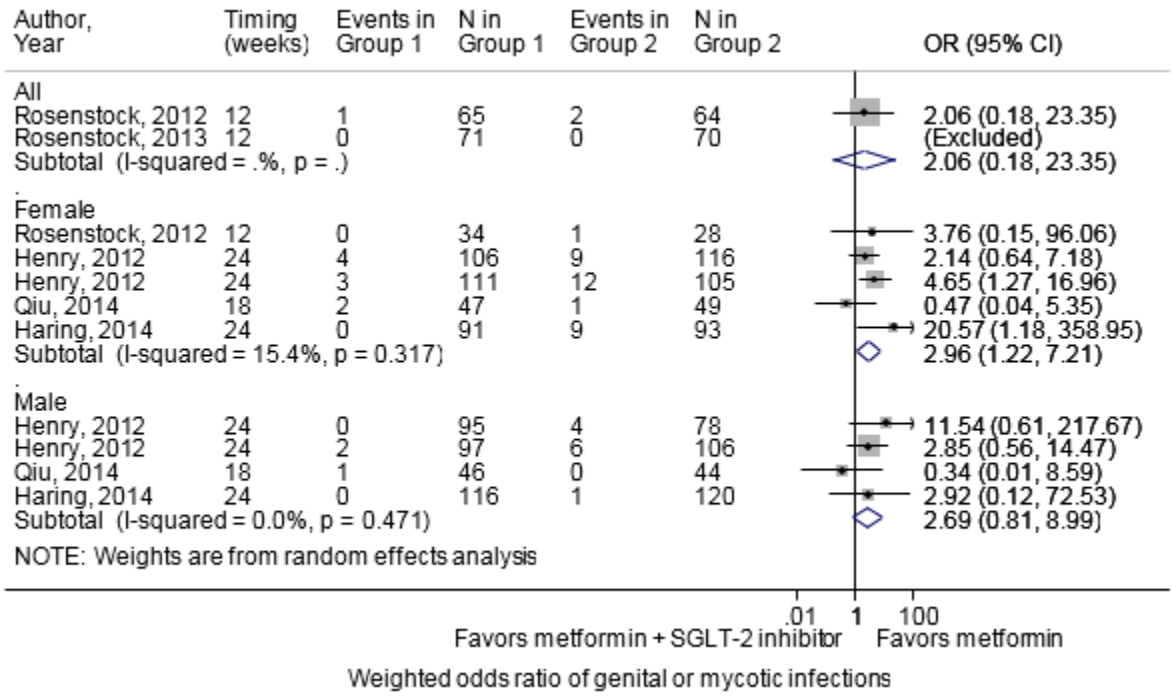
CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include a low quality 78-week RCT in the meta-analysis due to differences in study duration.[82] This study compared metformin with empagliflozin, reporting slightly higher rates of genital infections among females for SGLT-2 inhibitor therapy [1/28 (3.6%) with metformin versus 3/57 (5.3%) with metformin plus low-dose empagliflozin and 3/52 (5.8%) with metformin plus high-dose empagliflozin], and possibly more genital infections among males with SGLT-2 inhibitors [0/28 (0%) with metformin versus 2/49 (4.1%) with metformin plus low dose empagliflozin and 3/57 (5.3%) with metformin plus high- dose empagliflozin]. (SOE: Moderate; Metformin favored)

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

Five RCTs (reported in four articles) compared metformin with metformin plus a SGLT-2 inhibitor for genital infection events suggesting increased odds of genital infections for combination therapy over metformin monotherapy but no clear differences by gender: combined OR, 3.0 (95% CI, 1.22 to 7.2) for women and combined OR, 2.7 (95% CI, 0.8 to 9.0) for men (Figure 93).[80, 125, 132, 133] No single study markedly influenced the results, and we did not find significant statistical heterogeneity (I^2 = 15.4% for women and I^2 = 0.0% for men). An additional 12-week RCT did not provide sex-stratified analyses so it was not included in the meta-analysis.[122] This study reported more genital infection events in one of the groups receiving empagliflozin compared with the other two arms (metformin plus sitagliptin 100 mg: 0%, metformin plus empagliflozin 10 mg: 9.9%, metformin plus empagliflozin 25 mg: 0%).

Figure 93. Pooled odds ratio of genital or mycotic infections comparing metformin with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We excluded two RCTs from the meta-analysis due to their longer durations.[134, 135] Their results are included in Table 108. (SOE: High; Metformin favored)

Table 108. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on genital infections

Author, year	Followup	Genital Infection Outcome*	Results (metformin versus metformin + SGLT-2 inhibitor)
Rosenstock, 2012[125]	12 weeks	Symptomatic of genital infections	Metformin: 1/65 (2%) Metformin + canagliflozin 100 mg: 4/64 (6%) Metformin + canagliflozin 200 mg: 2/65 (3%) Metformin + canagliflozin 300 mg: 2/64 (3%)
Rosenstock, 2013[122]	12 weeks	MedDRA definition	Metformin: 0% Metformin + empagliflozin 10 mg: 9.9% Metformin + empagliflozin 25 mg: 0%
Qiu, 2014[132]	18 weeks	Males: balanitis candida and genital infection fungal. Females: vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis	Males Metformin: 1/46 (2.2%) Metformin + canagliflozin 100 mg: 1/40 (2.5%) Metformin + canagliflozin 300 mg: 0/44 (0%) Females Metformin: 2/47 (4.3%) Metformin + canagliflozin 100 mg: 6/53 (11.3%) Metformin + canagliflozin 300 mg: 1/49 (2.0%)
Henry, 2012 (a)[80]	24 weeks	Events suggestive of vulvovaginitis, balanitis, and related genital infection	Males Metformin: 0% Dapagliflozin 5 mg: 5.1% Females Metformin: 3.8% Dapagliflozin 5 mg: 7.8%
Haring, 2014[133]	24 weeks	MedDRA definition	Males Metformin: 0/116 (0%) Metformin + empagliflozin 10 mg: 1/125 (0.8%) Metformin + empagliflozin 25 mg: 1/120 (0.8%) Females Metformin: 0/91 (0%) Metformin + empagliflozin 10 mg: 7/92 (7.6%) Metformin + empagliflozin 25 mg: 9/93 (9.7%)
Henry, 2012 (b)[80]	24 weeks	Based on a predefined list of signs, symptoms and other events suggestive of genital infection	Males Metformin: 2/97 (2.1%) Metformin + dapagliflozin 10 mg: 6/106 (5.7%) Females Metformin: 3/111 (2.7%) Metformin + dapagliflozin 10 mg: 12/105 (11.4%)
Bolinder, 2012[134]	102 weeks	Genital infections	Metformin: 1/91 (1.1%) Metformin + dapagliflozin 10 mg: 2/91 (2.2%)
Bailey, 2013[135]	102 weeks	Events suggestive of genital infection	Metformin: 7/137 (5.1%) Metformin + dapagliflozin 2.5 mg: 16/137 (11.7%) Metformin + dapagliflozin 5 mg: 20/137 (14.6%) Metformin + dapagliflozin 10 mg: 17/135 (12.6%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams
* Outcomes are actively ascertained unless otherwise noted.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Two RCTs (24 to 26 weeks) compared outcomes from use of 100 mg of sitagliptin daily to an SGLT-2 inhibitor, by gender.[159, 229] Both trials reported higher rates of genital infections among both women and men with use of SGLT-2 inhibitors compared with sitagliptin, with some of the comparisons statistically significant (Table 109).[159, 229] (SOE: Low; DPP-4 inhibitors favored)

Table 109. Randomized controlled trials comparing DPP-4 inhibitors with SGLT-2 inhibitors on genital infections

Author, year	Medication dose	Women Events/N (%)	Men Events/N (%)
Stenlof, 2014[229]	Sitagliptin 100 mg Canagliflozin 100 mg Canagliflozin 300 mg	1/155 (1.2) 3/170 (3) 3/170 (3.2)	0/155 (0) 3/170 (3) 5/170 (6.5)
Roden, 2013[159]	Sitagliptin 100 mg Empagliflozin 10 mg Empagliflozin 25 mg	1/82 (1) 3/82 (4) 7/79 (9)	1/141 (1) 4/142 (3) 2/144 (1)

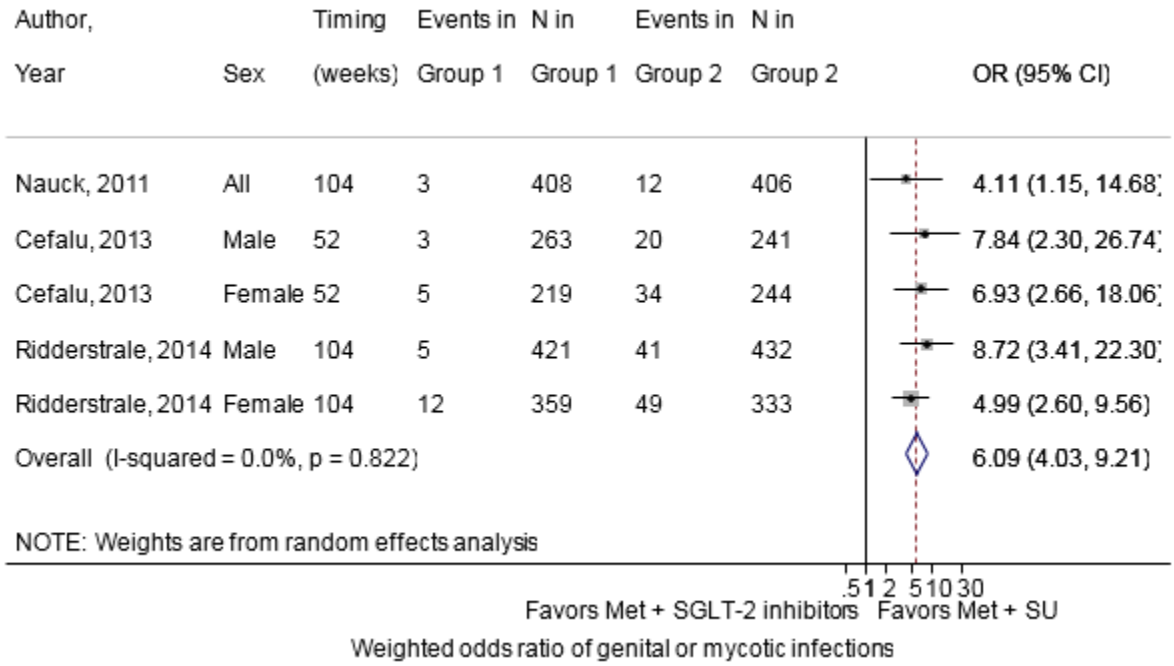
mg = milligrams

Metformin-Based Combination Comparisons

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

Three RCTs compared metformin plus a sulfonylurea with metformin plus a SGLT-2 inhibitor (pooled OR, 6.1; 95% CI, 4.0 to 9.2) (Figure 94) favoring metformin plus a sulfonylurea for this outcome of genital infections.[181-183] Two of the studies were 52 weeks long (comparing metformin with metformin with canagliflozin), and one study was 104 weeks long (comparing metformin with metformin with dapagliflozin). No single study markedly influenced the results, and we did not find significant statistical heterogeneity (I^2 = 0.0%). (SOE: High; Combination of metformin plus a sulfonylurea favored)

Figure 94. Pooled odds ratio of genital or mycotic infections comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Four RCTs compared metformin plus DPP-4 with metformin plus SGLT-2 showing more genital infection events with the SGLT-2 inhibitor arms.[82, 122, 125, 127] Two of the studies stratified outcomes by gender (Table 110).[82, 127] (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored)

Table 110. Randomized controlled trials comparing a combination with metformin plus a DPP-4 inhibitor with a combination of metformin plus a SGLT-2 inhibitor on genital infections

Author, year	Followup (weeks)	Medication dose	Women Events/N (%)	Men Events/N (%)	Total Events/N (%)*	Comments
Rosenstock, 2012[125]	12 weeks	Metformin + sitagliptin	1/27 (3.7)	NR	NR	
		Metformin + canagliflozin 100 mg	2/28 (7.1)	NR	NR	
		Metformin + canagliflozin 200 mg	4/32 (12.5)	NR	NR	
		Metformin + canagliflozin 300 mg	1/28 (3.6)	NR	NR	
Rosenstock, 2013[122]	12 weeks	Metformin + sitagliptin	NR	NR	2/71 (2.8)	
		Metformin + empagliflozin 10 mg	NR	NR	7/71 (9.9)	
		Metformin + empagliflozin 25 mg	NR	NR	0/70 (0)	
Lavalle-Gonzalez, 2013[127]	52 weeks	Metformin + sitagliptin	5/194 (2.6)	2/172 (1.2)	NR	ITT analysis not performed
		Metformin + canagliflozin 100 mg	22/194 (11.3)	9/174 (5.2)	NR	
		Metformin + canagliflozin 300 mg	20/202 (9.9)	4/165 (2.4)	NR	
Ferrannini, 2013[82]	78 weeks	Metformin + sitagliptin	0/29 (0)	0/27 (0)	NR	ITT analysis not performed
		Metformin + empagliflozin 10 mg	2/83 (2.4)	3/83 (3.6)	NR	
		Metformin + empagliflozin 25 mg	3/88 (3.4)	3/78 (3.8)	NR	

DPP-4 = dipeptidyl peptidase-4; ITT = intention-to-treat; mg = milligrams; NR = not reported; SGLT-2 = sodium-glucose co-transporter-2

* Results for both genders provided if sex-stratified results not reported

Strength of Evidence for Genital Mycotic Infections

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 111 and Table 112 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias in any of the comparisons for genital infections. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 111. Strength of evidence domains for monotherapy comparisons in terms of genital mycotic infections among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SGLT-2 inhibitors	4 (2,292)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin favored; Pooled OR, 4.1 (95% CI, 2.0 to 8.3)
Metformin vs. metformin + SGLT-2 inhibitors	8 (3,835)	Low	Consistent	Direct	Precise	Undetected	High	Metformin favored; Pooled OR, 3.0 (95% CI, 1.22 to 7.2) for females and 2.7 (95% CI, 0.8 to 9.0) for males
DPP-4 inhibitors vs. SGLT-2 inhibitors	2 (1,394)	Medium	Consistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored

CI = confidence interval; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; OR = odds ratio; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors
* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 112. Strength of evidence domains for metformin-based combination comparisons in terms of genital mycotic infections among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + SU vs. metformin + SGLT-2 inhibitors	3 (3,815)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin + SU favored; Pooled OR, 6.1 (95% CI, 4.0 to 9.2)
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	4 (2,889)	Medium	Consistent	Direct	Imprecise (n for metformin insufficient)	Undetected	Moderate	Metformin + DPP-4 inhibitors favored

CI = confidence interval; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; OR = odds ratio; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea
* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Fracture

Monotherapy Comparisons

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

Two RCTs compared metformin with metformin plus SGLT-2 showing no differences in fractures.[134, 135] One 102-week RCT compared metformin with metformin plus dapagliflozin showing similar incidences in fractures [2/137 (1.5%) for metformin versus 2/137 (1.5%) for dapagliflozin 2.5 mg, 2/137 (1.5%) for dapagliflozin 5 mg, and 3/135 (2.2%) for dapagliflozin 10 mg]. There was a high loss to followup in this study with 47% in the metformin arm compared with 30% to 40% in the other arms.[135] Another 102-week RCT compared metformin with metformin plus 10 mg of dapagliflozin and reported one fracture in each treatment arm (n=91 for both arms).[258] (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

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

Two studies compared metformin plus a SGLT-2 inhibitor with metformin plus a GLP-1 agonist showing no differences in fracture risk.[182, 183] One 104-week RCT compared metformin plus glipizide with metformin plus dapagliflozin showing similar incidences in fractures [9/408 (2.2%) for metformin plus glipizide versus 6/406 (1.5%) for metformin plus dapagliflozin].[182] Another 104-week RCT compared metformin plus glimepiride to metformin plus empagliflozin showing similar incidences of fractures in both arms (2%).[183] (SOE: Low; Neither favored)

Strength of Evidence for Fracture

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 113 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low. We did not find any evidence of publication bias in any of the comparisons for fractures. A single unpublished trial reported no fractures in either arm (NCT01368081) which is consistent with the other studies. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 113. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of fracture among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. metformin + SGLT-2 inhibitors	2 (728)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + SGLT-2 inhibitors	2 (2,363)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

The Evidence About Volume Depletion

Monotherapy Comparisons

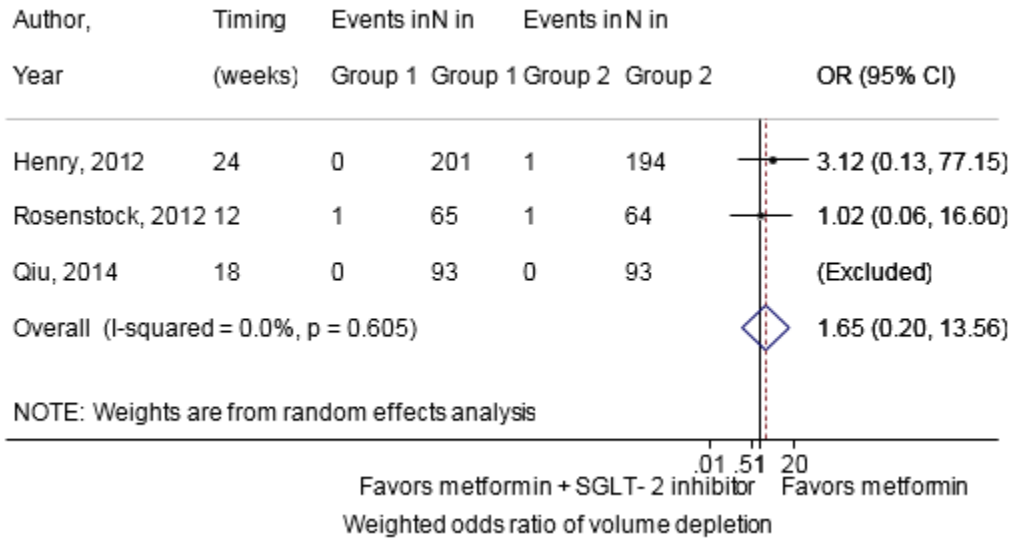
Metformin Versus SGLT-2 Inhibitors

Two moderately-sized, short RCTs compared metformin with SGLT-2 inhibitors and reported inconsistent results.[80, 81] One 12-week RCT comparing metformin with dapagliflozin reported a higher incidence of hypotensive events with metformin (4% for metformin versus 0% for dapagliflozin 5 mg and 10 mg).[81] One 24-week RCT comparing metformin with dapagliflozin 5 mg reported significantly more events of hypotension or syncope with dapagliflozin [0/201 (0%) for metformin versus 4/203 (2%) for dapagliflozin 5 mg].[80] (SOE: Low; Conflicting results)

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

Three short-duration RCTs comparing metformin with metformin plus SGLT-2 inhibitor reported on volume depletion events with varying definitions in each study. Volume depletion events were rare and there was no difference in event rates between groups (pooled OR, 1.6; 95% CI, 0.2 to 13.6) (Figure 95).[80, 125, 132] Two of the trials compared metformin to metformin plus 300 mg of canagliflozin daily,[125, 132] while one trial compared metformin to metformin plus 5mg of dapagliflozin daily.[80] No single study markedly influenced the results, and we did not detect substantial heterogeneity (I^2 = 0.0%).

Figure 95. Pooled odds ratio of volume depletion comparing metformin with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not combine two of the RCTs in the meta-analysis due to differences in study duration.[134, 135] Their results are in Table 114. (SOE: Low; Neither favored)

Table 114. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on volume depletion

Author, year	Followup	Definition of Volume Depletion Outcome	Results (Metformin versus metformin + SGLT2 inhibitor)	Comments
Rosenstock, 2012[125]	12 weeks	Adverse events possibly related to hypovolemia (dizziness, dizziness postural, heart rate increased, tachycardia, and urine output decreased)	Metformin: 1/65 (2%) Metformin + canagliflozin 100 mg: 4/64 (6%) Metformin + canagliflozin 200 mg: 3/65 (5%) Metformin + canagliflozin 300 mg: 1/64 (2%)	Included in meta-analysis
Henry, 2012[80]	24 weeks	Hypotension or syncope	Metformin: 0/201 (0%) Dapagliflozin 5 mg: 1/194 (0.5%)	No ITT analysis performed Included in meta-analysis
Qiu, 2014[132]	18 weeks	Orthostatic hypotension, postural dizziness	Metformin: 0/93 (0%) Metformin + canagliflozin 100 mg: 0/93 (0%) Metformin + canagliflozin 300 mg: 0/93 (0%)	Included in meta-analysis
Bolinder, 2012[134]	102 weeks	Hypotension	Metformin: 0/91 (0%) Metformin + dapagliflozin 10 mg: 0/91 (0%)	Unclear if ITT analysis performed High losses to follow up
Bailey, 2013[135]	102 weeks	MedDRA definition for hypotension, dehydration, or hypovolemia	Metformin: 2/137 (1.5%) Metformin + dapagliflozin 2.5 mg: 0/137 (0%) Metformin + dapagliflozin 5 mg: 3/137 (2.2%) Metformin + dapagliflozin 10 mg: 2/135 (1.5%)	High losses to follow up

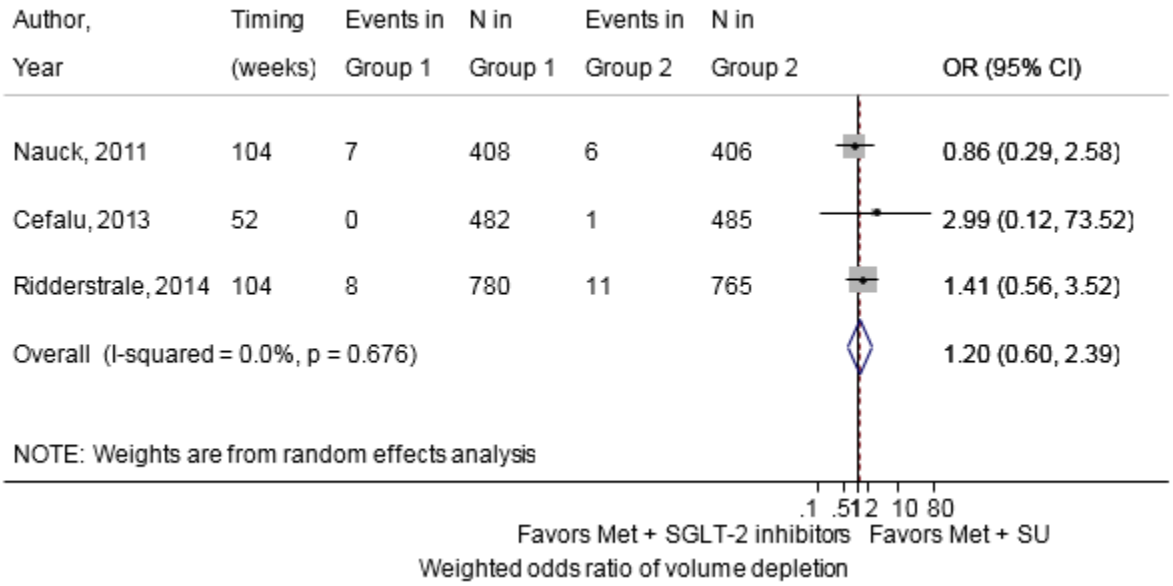
ITT = intention-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; SGLT-2 = sodium-glucose co-transporter-2

Metformin-Based Combination Comparisons

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

Three RCTs compared metformin plus a sulfonylurea to metformin plus a SGLT-2 inhibitor and described volume depletion events with varying definitions in each study. The evidence suggested little difference between arms (pooled OR for metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitor, 1.2; 95% CI, 0.6 to 2.4) (Figure 96 and Table 115).[181-183] No single study markedly influenced the results, and we did not detect substantial heterogeneity (I^2 = 0.0%). (SOE: Low; Neither favored)

Figure 96. Pooled odds ratio of volume depletion comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 115. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a SGLT-2 inhibitor on volume depletion

Author, year	Followup	Definition of Volume Depletion Outcome	Results Events/N (%)
Cefalu, 2013[181]	52 weeks	Orthostatic hypotension	Metformin + glimepiride: 0/482 (0%) Metformin + canagliflozin 100 mg: 1/483 (0.2%) Metformin + canagliflozin 300 mg: 1/485 (0.2%)
Nauck, 2011[182]	104 weeks	Hypotension, dehydration, hypovolemia	Metformin + glimepiride: 8/780 (1%) Metformin + empagliflozin 25 mg: 11/765 (1%)
Ridderstrale, 2014[183]	104 weeks	MedDRA definition	Metformin + glipizide: 7/408 (1.7%) Metformin + dapagliflozin 10 mg: 6/406 (1.5%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Two RCTs compared metformin plus DPP-4 with metformin plus SGLT-2 inhibitor and showed no clear differences in volume depletion outcomes.[125, 127] Both studies reported active ascertainment of the outcome. One 52-week RCT comparing metformin plus sitagliptin to metformin plus 100mg of canagliflozin and 300 mg of canagliflozin reported similar incidences in orthostatic hypotension (0% to 0.3% across all three arms).[127] One 12-week RCT comparing metformin plus sitagliptin with metformin plus canagliflozin reported slightly more events related to hypovolemia in the arms receiving the lower doses of canagliflozin [1/65 (2%) for metformin plus sitagliptin versus 4/64 (6%) for metformin plus canagliflozin 100 mg, 3/65 (5%) for metformin plus canagliflozin 200 mg, 1/64 (2%) for metformin plus canagliflozin 300 mg].[125] (SOE: Low; Neither favored)

Strength of Evidence for Volume Depletion

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 116 and Table 117 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low. Where quality influences results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias in any of the comparisons for volume depletion. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 116. Strength of evidence domains for monotherapy comparisons in terms of volume depletion among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin vs. SGLT-2 inhibitors	2 (992)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Conflicting results from 2 RCTs
Metformin vs. metformin + SGLT-2 inhibitors	5 (2,061)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Table 117. Strength of evidence domains for metformin-based combination comparisons in terms of volume depletion among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
Metformin + SU vs. metformin + SGLT-2 inhibitors	3 (3,815)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	2 (1,735)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence.

Key Question 4: Subgroups

Although forty studies reported on the comparative effectiveness and safety for sub-populations relevant to Key Question 4 (Appendix D, Table 14), few studies had sufficient power to assess comparative effectiveness or safety by subgroup. The evidence favoring one medication over another across subgroups is unclear.

We included 33 RCTs and six cohort studies that addressed this key question. The majority of these trials (n=19) evaluated subgroup effects on the outcome of HbA1c.[72, 75, 76, 87, 95, 108, 110, 111, 114, 118, 120, 123, 150, 152, 177, 178, 191, 259, 260] RCTs also included subgroup results on weight gain,[134, 228, 261] nephropathy,[252] hypoglycemia,[175, 179] and fractures.[263] The cohort studies' included subgroup results for mortality,[223, 233, 264] cardiovascular events,[232, 233] and kidney disease progression.[236]

We were unable to draw conclusions about the differential effects of medications in the specified sub-populations because of the small number of studies available for any one outcome for the included comparisons.

Subgroups Defined by Age

Hemoglobin A1c

Sixteen RCTs, out of the 19 reporting on subgroups for this outcome, did not find differences in the effects of diabetes medications on HbA1c by age.[72, 74, 76, 87, 95, 108, 110, 111, 114, 118, 120, 123, 150, 152, 178, 260]

Cardiovascular Mortality and Morbidity

We included two retrospective cohort studies which reported on cardiovascular outcomes by age. One study compared in metformin users, glimepiride users, and glyburide users.[232] Metformin and glimepiride use were both associated with lower risk of nonfatal CVD events compared with glyburide use among older participants (>51 years old) (Adjusted HR for metformin vs. glyburide, HR, 0.28; 95% CI, 0.20 to 0.39) In the younger age group, metformin was also associated with a decreased risk of cardiovascular events (adjusted HR for metformin vs. glyburide, 0.39; 95% CI, 0.21 to 0.73). Another retrospective cohort study compared metformin with sulfonylureas and found no difference in the incidence of death or cardiovascular events across age groups.[233]

Hypoglycemia

Two RCTs evaluating the risk of hypoglycemia by age reported no differences by age for the combination of metformin and a sulfonylurea versus the combination of metformin and a DPP-4 inhibitor.[175, 179]

Kidney Function Decline

A retrospective cohort study compared the effect of metformin, rosiglitazone and sulfonylureas on kidney function and found no differences by age for kidney disease progression.[236]

Subgroups Defined by Sex

Hemoglobin A1c

Fifteen RCTs examined the impact of sex on glycemic control (HbA1c) for the comparisons of interest and found no differences by sex.[72, 74, 76, 87, 95, 108, 110, 111, 114, 118, 120, 123, 150, 152, 262]

Weight

One trial reported a greater weight reduction among men compared with women for the combination of metformin plus dapagliflozin vs. metformin: the mean decrease at 24 weeks attributable to the addition of dapagliflozin was 2.76 kg for men vs. 1.22 kg for women, *P* for interaction = 0.048).[134]

Long-Term Clinical Outcomes

The two retrospective cohort studies described above comparing the effect of metformin and different sulfonylureas on cardiovascular risk, found no association between treatments and cardiovascular outcomes by sex.[232, 233] However, a retrospective cohort of new monotherapy users found that compared with those on metformin, women on rosiglitazone had a higher risk of death (RR, 6.21; 95% CI, 1.22 to 19.65) than men (RR, 1.76; 95% CI, 1.41 to 2.18).[223]

Hypoglycemia

One study compared the combination of metformin and glimepiride with the combination of metformin and sitagliptin and found no differences by gender for this outcome.[175]

Fractures

A retrospective analysis of the ADOPT trial found that women treated with rosiglitazone experienced an increased risk of fracture relative to those treated with metformin or glyburide (HR, 1.57 and 1.61, respectively); the investigators did not find an increased risk of fracture among men in this study with a median of 4 years of followup.[263]

Subgroups Defined by Race/Ethnicity

Hemoglobin A1c

Eleven RCTs examined the impact of race on HbA1c reduction, and found no differences by race for the comparisons studied.[74, 76, 95, 108, 110, 114, 120, 123, 150, 152, 178]

Kidney Function Decline

A single retrospective cohort evaluating the effects of metformin, glyburide, and glimepiride on progression of chronic kidney disease found no differences by race for this outcome.[236]

Subgroups Defined by Body Mass Index

Hemoglobin A1c

Fourteen RCTs found no differences by baseline BMI on the effects of diabetes medications on HbA1c reduction for the comparisons studied.[72, 74, 76, 87, 95, 108, 110, 114, 118, 123, 150, 152, 178, 262]

Discussion

This systematic review addresses the comparative effectiveness and safety of diabetes medications used most frequently in the United States as monotherapy and compares add-on therapy to metformin (combination therapies) with each other. This review updates and adds to two previous comparative effectiveness reviews (CER) published in 2007[15] and 2011[16] by focusing on the head-to-head comparisons of medications that should be of greatest relevance to clinicians and their patients (Table 2), particularly those for which evidence was previously lacking. We broadened the scope by including seven new Food and Drug Administration (FDA)-approved medications including one new medication class, the sodium-glucose co-transporter-2 (SGLT-2) inhibitors. We identified 115 new studies, which included 96 trials and 19 observational studies that have been published since we completed our 2011 review. Our comprehensive review of the newer medication classes in comparison with other medications and comparisons of combination therapies is an important contribution to the literature because it is the first to address this many comparisons for a wide range of outcomes in patients with type 2 diabetes mellitus.

Key Findings in Context

Intermediate Outcomes

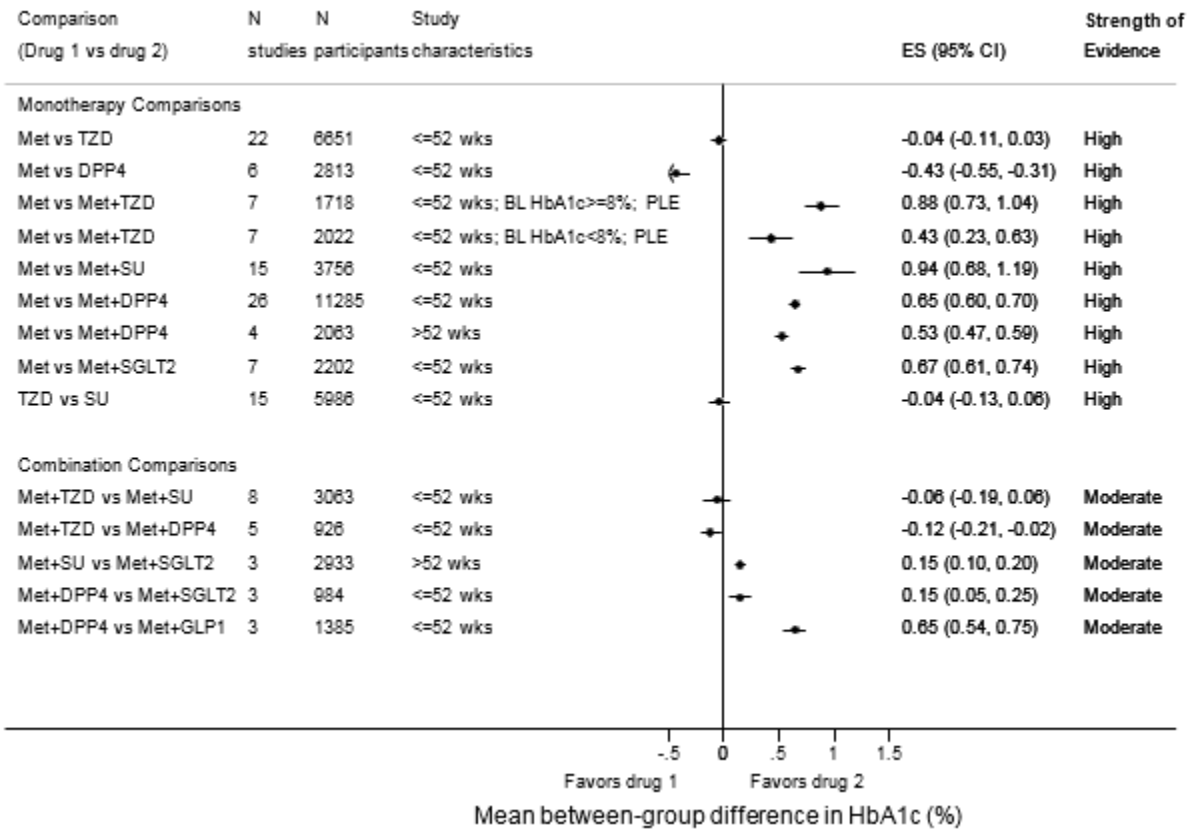
Hemoglobin A1c

HbA1c is unequivocally linked to microvascular disease,[10, 265, 266] making it a good proximal outcome to measure. Consistent with the prior 2011 report,[16] most oral diabetes medications (thiazolidinediones, sulfonylureas, and metformin) had similar efficacy in achieving reductions in HbA1c as monotherapy (Figure 97). The one exception was that metformin had a greater reduction in HbA1c compared with DPP-4 inhibitors, consistent with the prior report.[16] In the last report,[16] metformin versus sulfonylurea was graded as high showing no significant between-group differences in HbA1c; therefore, it was not updated in this report. While metformin versus GLP-1 agonists and metformin versus SGLT-2 inhibitors also showed no clear between-group differences in HbA1c, they were graded as low strength of evidence since the three studies in each comparison were imprecise and inconsistent. In this update, we found inconsistent findings in the studies of GLP-1 agonists. It may be that the individual GLP-1 agonists have different effects on HbA1c. A 2011 Cochrane systematic review showed small between-group differences in HbA1c, around 0.3%, in the effect of different GLP-1 agonists.[267] The strength of evidence was graded as insufficient for the other monotherapy comparisons with the newer classes of SGLT-2 inhibitors and GLP-1 agonists, and will warrant further study.

All metformin combination therapies were better at reducing HbA1c than metformin monotherapy regimens, with between-group differences of around 0.7 to 1 absolute percentage points (Figure 97). While several moderate strength of evidence combination comparisons were significantly favored over the comparator combination (Figure 97), most between-group differences were small (<0.3%) with questionable clinical relevance. Only one combination comparison with moderate strength of evidence was favored by >0.3% over any other combination comparison: the combination of metformin plus a GLP-1 agonist reduced HbA1c more than metformin plus a DPP-4 inhibitor. Two prior network meta-analyses[268, 269] showed that most metformin combination comparisons had similar reductions in HbA1c. However, the

direct comparisons evaluated in this report are more precise than indirect comparisons found in network meta-analyses.

Figure 97. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in HbA1c); GLP1 = glucagon-like peptide-1 agonists; HbA1c = hemoglobin A1c; Met = metformin; PLE = profile likelihood estimate; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; wks = weeks

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

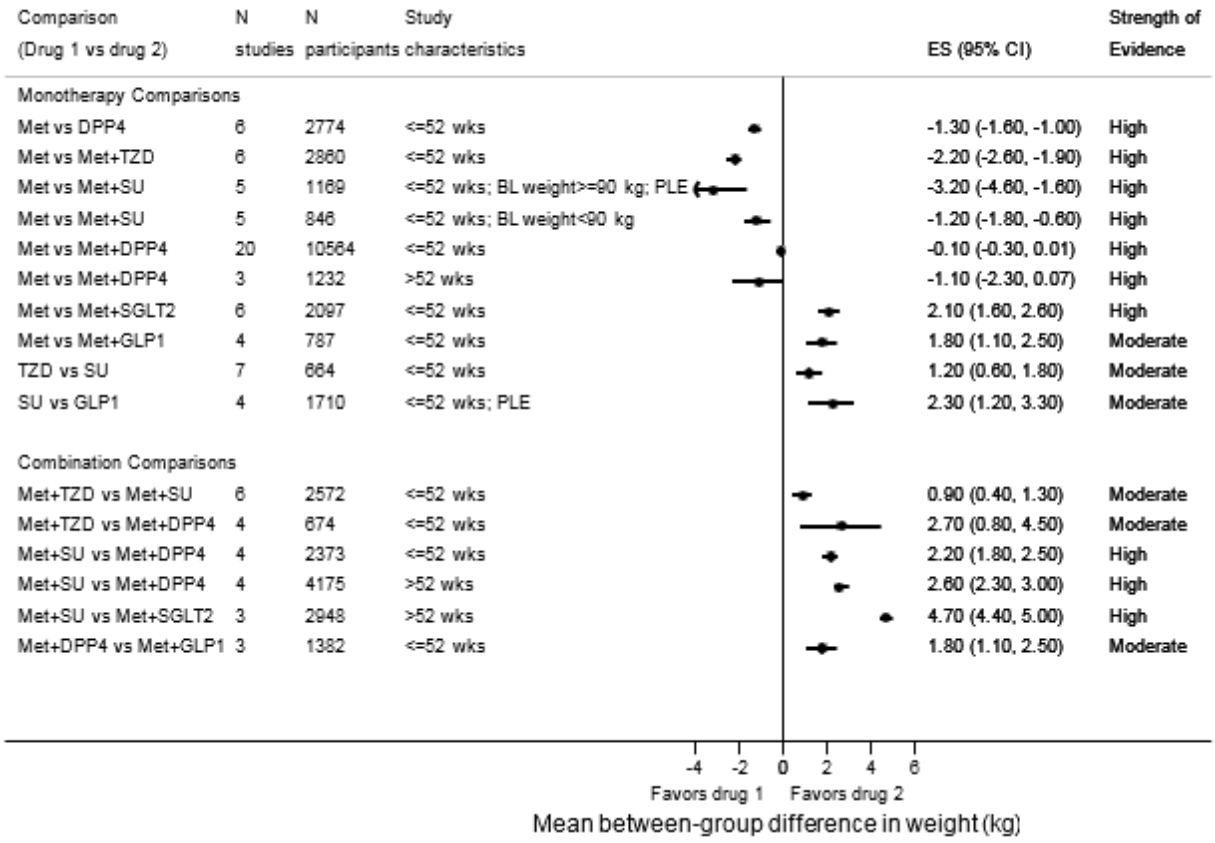
Weight

Monotherapy and combination medication comparisons generally showed significant between-group differences when comparing medications anticipated to increase weight (sulfonylurea, thiazolidinediones) with medications expected to maintain or decrease weight (metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors) (Figure 98). In the prior report, metformin versus thiazolidinedione and metformin versus sulfonylureas were found to favor metformin with differences of 2.5 kg, with high strength of evidence; therefore, these comparisons were not updated. Several monotherapy comparisons demonstrated weight changes in the same direction. Metformin decreased weight more than DPP-4 inhibitors, while sulfonylureas caused slightly less weight gain than thiazolidinediones. SGLT-2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors.(Figure 98). Compared with metformin plus a DPP-4 inhibitor, the combinations of metformin plus GLP-1 agonist and metformin plus SGLT-2 inhibitors were favored. The strength of evidence is moderate favoring

metformin plus a sulfonylurea over metformin plus a premixed or long-acting insulin (between-group difference ranging from 0.5 kg to 1.7 kg).

Notably, weight gain was small to moderate in the trials in which participants gained weight; even in the longest trials, weight gain was less than 5 kg. However, even small amounts of weight gain (5 percent to 10 percent of body weight) may be associated with increased insulin resistance.[270] Drug effects on weight may impact the choice of the drug added for second-line combination therapy in a patient not well controlled on a single agent. Our findings about diabetes medications effects on weight are similar to other prior systematic reviews.[16, 267, 271] As monotherapy and in combination with metformin, thiazolidinediones and sulfonylurea are associated with weight gain, DPP-4 inhibitors with weight maintenance, and SGLT-2 inhibitors and GLP-1 agonists are associated with weight loss.[16, 267, 271, 272] Our systematic review builds on prior work by adding more direct comparative data about metformin combination comparisons, which further confirm the known weight effects of the individual medications.

Figure 98. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons



Basal = basal insulin; BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in weight); GLP1 = glucagon-like peptide-1 agonists; kg = kilograms; Met = metformin; PLE = profile likelihood estimate; premixed = premixed insulin; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; wks = weeks

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Systolic Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were evaluated for the newer classes of medications, the SGLT-2 inhibitors and GLP-1 agonists due to suspected effects of these medications based on prior literature.[267, 271] Blood pressure control is important in adults with diabetes.[203, 273-275] The United Kingdom Prospective Diabetes Study (UKPDS) showed that for every 10 mmHg decrease in systolic blood pressure, there is a 15% decrease in diabetes-related deaths.[274] Consistent with a prior systematic review on SGLT-2 inhibitors,[271] the SGLT-2 inhibitors consistently reduced systolic blood pressure in all comparisons where there were sufficient numbers of studies (significant between-group differences of 3 to 5 mmHg when compared with other diabetes medications which have no effect on blood pressure). Our review builds on this prior work by evaluating direct comparisons of specific medication classes as comparators, as opposed to lumping all active comparators together. This is especially important since thiazolidinediones and GLP-1 agonists also have been associated with decreases in systolic blood pressure by 3 to 5 mmHg.[15, 267] Also, metformin plus a GLP-1 agonist had a greater reduction in systolic blood pressure compared with metformin alone (pooled between-group difference, 3.1 mmHg; 95% confidence interval [CI], 1.4 to 4.9 mmHg), with moderate strength of evidence. While the clinical relevance of these small differences is unclear, a change of 3-5 mmHg is about half the effect of a low sodium diet (around 7-11 mmHg) and about one-third the effect of blood pressure medications (around 10-15 mmHg).[276, 277]

Increased heart rate is associated with increased mortality.[278] However, whether heart rate is an independent predictor of long-term clinical outcomes such as mortality is less clear.[40] We opted to evaluate heart rate for the newer medications SGLT-2 inhibitors and GLP-1 agonists given its association with mortality. In addition, we wanted to see if the benefits from blood pressure reduction might be offset by a concomitant increase in heart rate. We did not identify any prior systematic reviews that have evaluated this outcome for the diabetes comparisons of interest. Only two comparisons had sufficient data to grade the evidence as more than insufficient or low. Surprisingly, SGLT-2 inhibitors in combination with metformin were found to decrease heart rate by 1.5 bpm (95% CI, 0.6 bpm to 2.3 bpm) when compared with metformin plus a sulfonylurea; metformin and GLP-1 agonists showed no differences in heart rate between groups. Therefore, these early findings support minimal to no effects on heart rate and no increase in heart rate for the newer medications.

Long-Term Clinical Outcomes

Compared to the prior report,[16] the evidence on long-term outcomes of mortality, cardiovascular mortality, and cardiovascular morbidity was strengthened for many comparisons although most of this evidence was of low strength (Table 119). We were also able to report stronger evidence about some comparisons for which there had only been low-strength evidence. The evidence regarding cardiovascular mortality was generally stronger than that for cardiovascular morbidity because of more uniformity in outcome definitions and more consistent reporting of events. The evidence regarding treatment effect on microvascular outcomes remains largely insufficient. Overall, the evidence base on long-term clinical outcomes was limited by the low number of studies evaluating the same comparisons, lack of RCTs designed to evaluate these outcomes, short duration of RCTs, the lack of uniform reporting on these outcomes in all study arms, and a lack of high-quality observational studies, as may be needed for adequate power to detect rare outcomes. Most notably, none of the included RCTs were designed to evaluate these long-term outcomes.

All-Cause Mortality, Cardiovascular Mortality, and Cardiovascular Morbidity

This report builds substantially on our prior results for metformin versus sulfonylurea monotherapy.[16] We found high strength of evidence that metformin was associated with a 37% to 50% lower risk of cardiovascular mortality compared with sulfonylureas, and metformin was also favored over sulfonylurea monotherapy for cardiovascular morbidity (moderate strength of evidence [SOE]). Our findings on sulfonylurea monotherapy enhance findings from meta-analyses published in 2012 and 2013 which relied more heavily on observational data or did not evaluate metformin versus sulfonylurea monotherapy specifically.[279, 280]

We evaluated pioglitazone and rosiglitazone separately when they were compared with other drug classes for all-cause mortality and cardiovascular outcomes given concerns about cardiovascular risk and mortality associated with rosiglitazone raised previously[281] and acted upon by the FDA through substantial restrictions on prescribing and dispensing of this medication in 2010.[282, 283] The strength of evidence increased from the prior report for many of the thiazolidinedione comparisons. Compared to metformin monotherapy, pioglitazone was associated with similar rates of all-cause mortality (moderate SOE) and cardiovascular morbidity (moderate SOE).

We had little evidence on the combination of metformin plus a sulfonylurea or metformin plus a thiazolidinedione. In The Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) Trial, 4,447 participants with diabetes were randomized to a rosiglitazone-based combination (with either metformin or sulfonylurea) or to the combination of metformin plus a sulfonylurea.[44] We excluded this study from this outcome assessment because it did not stratify results by a comparison of interest. This trial did not find a difference between rosiglitazone-based two-drug therapy and metformin plus a sulfonylurea for the primary endpoint, which was cardiovascular hospitalization or death. After 5.5 years, all-cause mortality, cardiovascular death, and stroke were slightly higher in the metformin plus sulfonylurea arm, and myocardial infarction rates were slightly (non-statistically significantly) higher in the rosiglitazone combination therapy arm. Of note, the FDA commissioned an independent re-adjudication and analysis of the data from RECORD and subsequently (in 2013) lifted their restrictions on rosiglitazone usage.[284]

We identified many new studies evaluating all-cause mortality and cardiovascular outcomes for DPP-4 inhibitor comparisons, but most of this evidence was of low strength. High strength of evidence did show that metformin and the combination of metformin plus a DPP-4 inhibitor were associated with similar short-term all-cause mortality (Figure 99). We also identified unpublished evidence that may have increased our grading of the strength of evidence from low to moderate for DPP-4 inhibitor-based therapy vs. sulfonylurea-based therapy. An unpublished study suggested a reduction in all-cause mortality for DPP-4 inhibitor vs. sulfonylurea monotherapy, and another unpublished study suggested that the combination of metformin plus a DPP-4 inhibitor was associated with a lower all-cause mortality and cardiovascular morbidity compared to the combination of metformin plus a sulfonylurea.

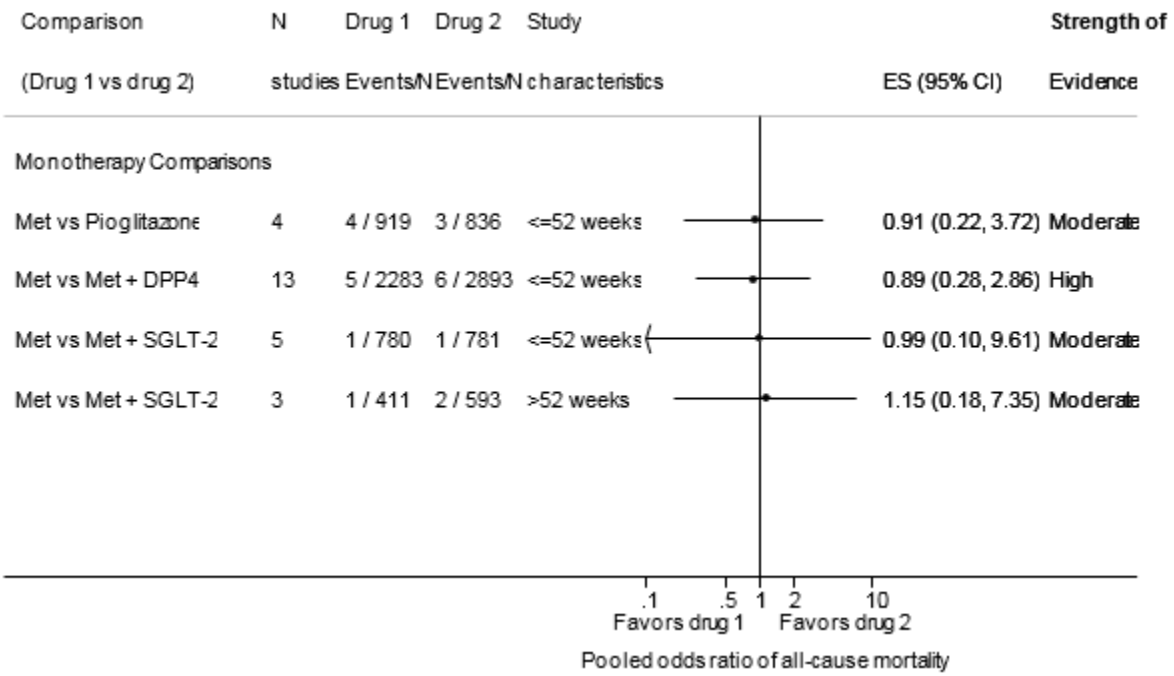
Several meta-analyses published since the 2011 report have evaluated DPP-4 inhibitors and all-cause mortality and cardiovascular outcomes; they tended to combine comparators (active, placebo, or both) against DPP-4 inhibitors so were not conclusive about specific drug comparisons. These reviews have generally found that DPP-4 inhibitors are similar to other agents, considered in aggregate, for all-cause mortality and associated with lower cardiovascular mortality and morbidity – based on mainly non-statistically significant findings. Outside of these

meta-analyses, since the prior report, the large Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 RCT randomized 16,492 high-risk patients with diabetes to saxagliptin or placebo and continued prior diabetes medications per routine clinical care.[285] Over a median of 2.1 years, there was no difference in the primary endpoint (cardiovascular death, myocardial infarction, and stroke) or in cardiovascular mortality between arms. The risk of death from any cause was non-significantly higher for the saxagliptin versus placebo arm (hazard ratio [HR], 1.11; 95% CI, 0.96 to 1.27; *P* =0.15); the absolute risk difference for all-cause mortality was 0.3% for saxagliptin versus placebo. Unlike the meta-analyses that compared DPP-4 inhibitors to any drug, this placebo-controlled study did not suggest a cardiovascular benefit for DPP-4 inhibitors.

The evidence remains largely insufficient or of low strength regarding mortality and cardiovascular benefits or harms associated with GLP-1 agonists. A recent meta-analysis suggested no difference in mortality rates for GLP-1 agonists compared with other agents but did not make explicit monotherapy or combination comparisons.[286]

Regarding the newest class of medications, the SGLT-2 inhibitors, we found moderate strength of evidence that all-cause mortality was similar for the combination of metformin plus an SGLT-2 inhibitor compared with metformin monotherapy. Our findings build on a recent systematic review which only evaluated monotherapy comparisons for SGLT-2 inhibitors.[271] The evidence on cardiovascular mortality and morbidity for SGLT-2 inhibitor comparisons was limited.

Figure 99. Pooled odds ratios of all-cause mortality and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (odds ratio); Met = metformin; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea
The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Retinopathy, Nephropathy, and Neuropathy

While we found more evidence on microvascular outcomes compared to the 2011 report,[16] all evidence was of low strength or inconclusive, thereby limiting substantial conclusions. We did not identify any other evidence syntheses of these microvascular outcomes published since the prior report.

Adverse Events

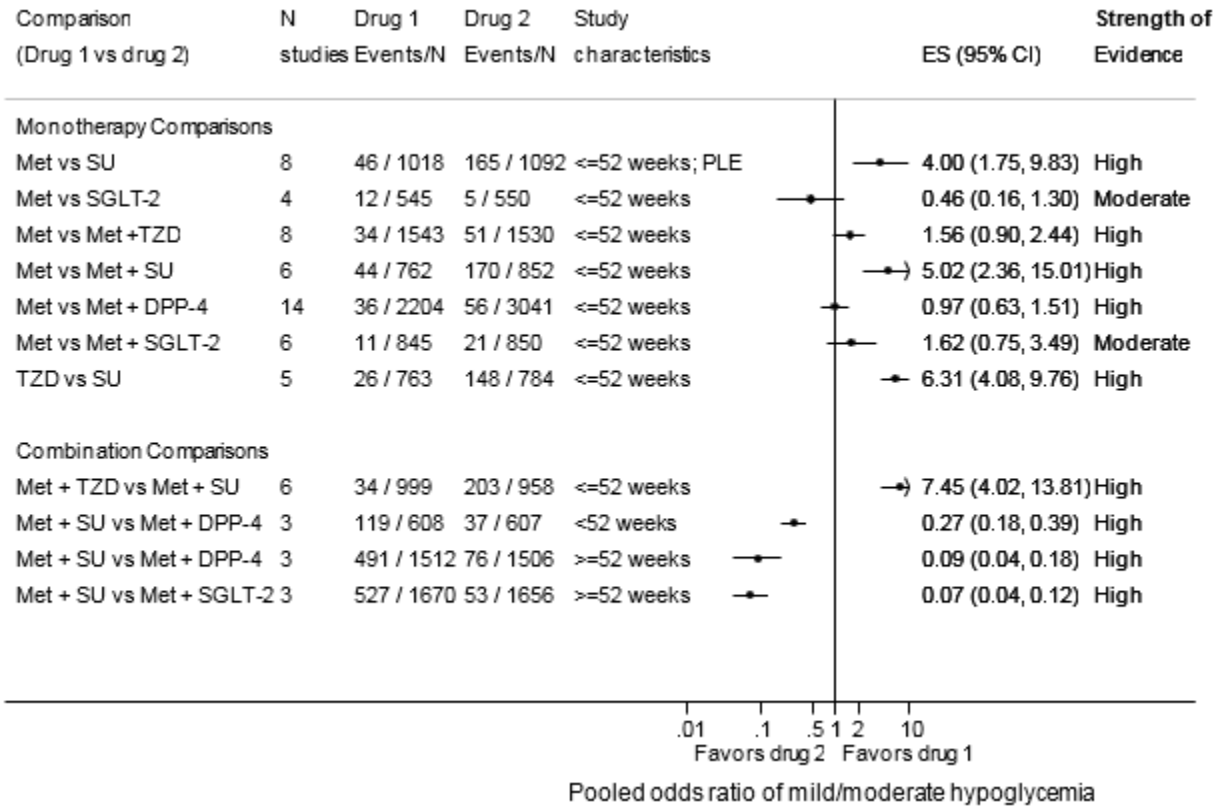
Hypoglycemia

We confirmed the elevated risk of mild, moderate, or total hypoglycemia associated with sulfonylureas, either alone or in combination, compared with both the older and newer hypoglycemic agents (Figure 100). Of the combination comparisons, we also confirmed that metformin plus premixed insulin had higher hypoglycemia risk than metformin plus basal insulin. We added new information related to severe hypoglycemia. We found moderate to high strength of evidence that sulfonylureas had about 1.5 times increased risk of severe hypoglycemia when compared with metformin or thiazolidinedione monotherapy. Similarly, in combination with metformin, sulfonylureas had a greater risk of severe hypoglycemia when compared with the combination of metformin plus DPP-4 inhibitors or SGLT-2 inhibitors. We also found moderate strength of evidence that metformin plus DPP-4 inhibitors had similarly few to no severe hypoglycemia events when compared with metformin monotherapy or metformin plus a thiazolidinedione.

For the newer medications (SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors), we added to the evidence base by summarizing data showing that SGLT-2 inhibitors may have 54% less risk of hypoglycemia than metformin, although absolute event rates were small in both arms. This is consistent with a high quality systematic review of the SGLT-2 inhibitors which also shows a non-significant lower risk of hypoglycemia in the SGLT-2 inhibitor arms compared with active comparators, although excluding sulfonylureas.[271] We also found that when compared with metformin plus basal insulin, metformin plus a GLP-1 agonist had less hypoglycemia risk. This is especially important when considering which injectable medication to add as second line therapy.

Prior systematic reviews of individual classes of newer agents had sparse data on hypoglycemia when compared with active comparators, although the newer classes were generally found to have rare hypoglycemia events.[267, 271, 287] While we found more studies comparing metformin combinations with metformin plus sulfonylurea, there were still few studies on the newer medication classes as monotherapy and in combination with metformin.

Figure 100. Pooled odds ratios of hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (odds ratio); Met = metformin; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinediones
The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Gastrointestinal Side Effects

Metformin and GLP-1 agonists as monotherapy and in combination had about a two-fold increased risk of gastrointestinal (GI) events when compared with most other comparators, with moderate to high strength of evidence. Several medications had similar rates of GI events with moderate or high strength of evidence: thiazolidinedione versus sulfonylurea, metformin plus a sulfonylurea versus metformin plus a DPP-4 inhibitor, metformin plus a thiazolidinedione versus metformin plus a sulfonylurea, metformin plus a sulfonylurea versus metformin plus a SGLT-2 inhibitor, metformin monotherapy versus metformin plus a SGLT-2 inhibitor, and metformin monotherapy versus metformin plus a DPP-4 inhibitor.

We confirmed findings of the 2011 report[16] showing that metformin had a greater risk of GI events than thiazolidinediones, sulfonylureas, or DPP-4 inhibitors. We also report new findings showing GLP-1 agonists have higher risk of GI events when compared with thiazolidinediones and sulfonylureas, both as monotherapy or when used in combination with metformin. Our data confirm the GLP-1 comparative findings from a prior Cochrane systematic review,[267] and adds information about specific combination comparisons and specific types of GI events. Of note, GLP-1 agonists also had higher risk of nausea and vomiting than metformin but no significant difference in diarrhea. Surprisingly, the combinations of metformin plus DPP-4 inhibitors did not have worse GI events than metformin monotherapy or metformin combinations despite the DPP-4 inhibitors known side effects of nausea.[287] Lastly, we report new findings that SGLT-2

inhibitors showed no increased risk of GI events when compared in combination with metformin against metformin plus sulfonylureas or compared with metformin monotherapy.

Cancer

The evidence about cancer was generally insufficient because of a lack of studies, and the existing evidence was of low strength. Most published studies for the comparisons did not report on cancer events in all arms which limited our ability to synthesize the evidence quantitatively and to draw conclusions.

Reviews and meta-analyses published since the 2011 report show that metformin decreases the risk of many types of cancer[288, 289] and suggest that pioglitazone[290] increases the risk of bladder cancer slightly, but we did not include many of the studies supporting those conclusions because of our stringent inclusion criteria for observational studies. We excluded the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) Study[291] since it did not evaluate a comparison of interest. This trial found a higher rate of bladder cancer in the pioglitazone versus placebo arm which did not persist in the 5.8-year followup study that included only 74% of the original study population, the majority of whom did not take pioglitazone after the randomized period.[292]

However, our review adds low strength of evidence for many comparisons, mainly on comparisons of GLP-1 agonists and DPP-4 inhibitors. Evidence on these therapies and cancer outcomes is of particular interest given the preclinical evidence linking incretins (the GLP-1 agonists and DPP-4 inhibitors) to cancer. The FDA prescribing information for the GLP-1 agonists,[293, 294] liraglutide and albiglutide, includes a warning regarding the potential for a link between these agents and medullary thyroid cancer based on data in mice and rats.[295] The evidence that we identified on the incretin-based therapies and cancer was of low strength and conflicted.

Congestive Heart Failure

We found low strength of evidence of about a 1.4-fold increased risk of heart failure with the thiazolidinedione class of medications, when compared with metformin or sulfonylureas, which was also reported in two recent meta-analyses.[296, 297] There were no long-term trials and only a few observational studies of medium quality that could provide a comparative assessment of safety of diabetes medications on congestive heart failure. Both thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage 3 or Stage 4) according to product labels.[298, 299] Our strength of evidence on this outcome dropped to low strength of evidence in this update (from moderate in the prior review) since we excluded lower quality observational studies and also excluded the RECORD study for this outcome due to the active comparator being *either* sulfonylurea or metformin instead of a single active comparator. RECORD showed that the combination of thiazolidinediones and another agent (sulfonylurea or metformin) was associated with a significant doubling in the risk of heart failure in comparison to the combination of sulfonylurea and metformin (61/2220 versus 29/2227, risk ratio (RR), 2.1; 95% CI, 1.35 to 3.27).[44]

We had low or insufficient strength of evidence for most other medication comparisons for heart failure, including the newer agents. The SAVOR-TIMI 53 trial,[285] mentioned above, was excluded from our systematic review of head-to-head comparisons of diabetes medications since it compared saxagliptin with placebo. Hospitalization for heart failure was reported in 289/8280 (3.5%) in the saxagliptin arm versus 228/8212 (2.8%) in the matching placebo arm, with a HR of

1.27 (95% CI, 1.07 to 1.51). Due to this finding, the FDA has requested trial data from the manufacturer to analyze whether there might be an increased risk of heart failure with saxagliptin.[300] Further research directly comparing DPP-4 inhibitors with other active comparators on heart failure outcomes will be critical for determining the comparative safety of these medications on heart failure risk.

Liver Injury

Similar to the 2011 report, we found little evidence on liver injury. Compared to the prior report, we downgraded the available evidence for metformin versus thiazolidinedione monotherapy (from moderate to low) and downgraded the evidence for thiazolidinedione versus sulfonylurea monotherapy (from high to low). Notably, there is are FDA warnings of post-marketing cases of hepatic failure for both alogliptin and pioglitazone, but we found low or insufficient strength of evidence for TZD- and DPP-4 inhibitor-based comparisons and liver injury.

Lactic Acidosis

Even though there is continued concern about an increased risk of lactic acidosis with metformin, we found low or insufficient evidence on the comparative safety of metformin-based therapy and lactic acidosis. Consistent with the prior report[16] and an updated Cochrane review on this topic,[301] we did not find an increased risk of lactic acidosis with metformin based on the low strength of evidence identified.

Pancreatitis

Compared to the prior report, we identified many more studies on pancreatitis but found low strength of evidence for most comparisons. An exception is the finding that metformin and the combination of metformin plus a DPP-4 inhibitor are associated with similar rates of pancreatitis. The DPP-4 inhibitors and GLP-1 agonists were of most interest for this outcome given the spontaneous reports to the FDA of pancreatitis associated with these agents. We excluded some of the Liraglutide Effect and Action in Diabetes (LEAD) RCTs from this report because they did not evaluate comparisons of interest;[302] seven participants exposed to liraglutide and one exposed to a sulfonylurea were diagnosed with pancreatitis across the six LEAD trials.[303] In the SAVOR TIMI 53 trial, definite acute pancreatitis occurred in 17 participants in the saxagliptin arm and nine in the placebo arm (P =0.17), and the authors concluded that there was no increased risk of pancreatitis for saxagliptin versus placebo.[285] In addition to these key trials, systematic reviews and recent observational studies, with some exceptions,[304] have not found an increased risk of pancreatitis with incretins compared with other therapy.[305-308]

Severe Allergic Reactions

In the prior report, we did not find evidence on severe allergic reactions. However, the issue of hypersensitivity reactions with diabetes medications has become more prominent with the uptake of DPP-4 inhibitors[309] and GLP-1 agonists.[310-312] In March, 2012, the FDA added a warning about the risk of hypersensitivity reactions with DPP-4 inhibitors.[313] Although still of low strength, we found the strongest evidence (based on four RCTs) that the addition of a DPP-4 inhibitor to metformin increases the risk of hypersensitivity reactions over metformin monotherapy alone. Prior data on the risk of hypersensitivity reactions with DPP-4 inhibitors has been mixed.[309] Of note, over a median followup of 2.1 years, the SAVOR-TIMI 53 trial

(described above) found similar rates of hypersensitivity reactions for saxagliptin compared with placebo.[285]

Macular Edema and Decreased Vision

We have not found conclusive evidence in the prior or this report on these outcomes. A concern regarding the risks of macular edema with the thiazolidinediones persists and is based primarily on observational studies.[314-316] Seven compared with three participants in the rosiglitazone and active comparator arms, respectively, developed macular edema in the RECORD trial (described above), although there were more than 2000 treated in each arm.[44]

Adverse Events Specific to SGLT-2 Inhibitors

Our findings of an increased risk of genital mycotic infections for SGLT-2 inhibitors compared to other agents are consistent with recent reviews of this topic.[271, 317] The existing systematic reviews did not evaluate comparative effectiveness but instead grouped comparators together for synthesis.

In contrast to one of these recent systematic reviews of SGLT-2 monotherapy,[271] we did not find an increased risk of urinary tract infection (except for low-strength evidence in women for SGLT-2 inhibitor monotherapy relative to DPP-4 inhibitors) or volume depletion events. That review also found evidence of increased risk of hypotension for SGLT-2 inhibitor monotherapy, while we had low strength of evidence on volume depletion events. We also evaluated fracture risk and renal insufficiency associated with SGLT-2 inhibitors given the issues raised about these adverse events in Vasilakou et al 2013; in that review, the authors did not make conclusions about these outcomes as their data were limited. Similarly, we did not identify substantial evidence on these outcomes either. The other large systematic review evaluated the combination of metformin plus SGLT-2 inhibitors and the combination of metformin plus DPP-4 inhibitors; this review did not find an increase in the risk of UTI and did not report on fractures or renal insufficiency.[317]

Subgroups

The limited evidence on subgroups was for the outcome of HbA1c and did not show differential effects of the included comparisons on glycemic control by age, sex, race/ethnicity, or BMI. Otherwise, the evidence on the comparative effectiveness of diabetes medications in subgroups defined by age, sex, race/ethnicity, and BMI was generally inconclusive. This is especially unfortunate for the age and race/ethnicity sub-populations because of the known disparities in diabetes prevalence and diabetes outcomes for these groups. Older Americans suffer disproportionately from diabetes with over 25% of persons 65 years or older having diabetes compared to 16.2% of persons ages 45 to 64, and there is concern about the safety of medications (and polypharmacy) in older adults.[1, 8] Also, compared to non-Hispanic white adults in the US, diabetes is 20% more common in Asian Americans, 70% more common in Hispanics and non-Hispanic blacks, and twice as common in American Indians/Alaska Natives.[1] Racial and ethnic minorities are also more likely to suffer from diabetes complications including diabetic end-stage renal disease,[318] retinopathy,[319] amputations, hospitalization for cardiovascular outcomes,[320] and diabetes-related mortality.[321] Finally, racial and ethnic minorities are less likely to have controlled diabetes (HbA1c <7%), but are more likely to be on oral treatment only for diabetes.[322]

Applicability

The applicability of these studies depends largely on the similarity of the study populations to the U.S. population with type 2 diabetes and the similarity of the interventions to usual clinical care (e.g., comparability of the drug interventions including dosing and duration of exposure to drugs). The included studies generally had populations, interventions, outcomes, and settings applicable to U.S. adults with type 2 diabetes with a few notable exceptions as described below.

Study population differences are the most pronounced threat to applicability. Study participants were mainly middle-aged (mean age in the mid 50s), overweight or obese adults who had diabetes for 3 to 7 years at the start of the studies. This is similar to the U.S. population with type 2 diabetes which has a mean age of 60.5 years and a mean BMI of 33 kg/m2 (23.5% overweight, 65.3% obese).[323] Most studies excluded older people over the age of 75 or 80 years and excluded people with significant renal, hepatic, and cardiovascular disease, and other significant co-morbid conditions, making these studies less applicable given that 52% of US adults with diabetes are over the age of 60, and just over 25% have a history of cardiovascular disease.[323] When race was reported in the included studies, most subjects were Caucasian although about 10 to 20 percent of study participants were often other races. These studies are therefore less applicable to people of different races and ethnicities who make up about 40 percent of the US population with diabetes, and importantly, these groups have greater diabetes burden than Caucasians (i.e., African Americans, Hispanics, Asian Americans and American Indians).[1, 323]

Characteristics of the interventions could also impact applicability, and most studies used dosing, frequency, and monitoring comparable to usual care. One possible threat to applicability relates to the duration of drug exposure, especially for glycemic control. The vast majority of RCTs lasted for two years or less. In usual care, patients with diabetes are on medications for over 10 years and are on multiple medications which impact adherence and side effects. Also, the glycemic response to medications may degrade over time; retained insulin sensitivity may allow insulin sensitizers (like metformin) to work longer as monotherapy than medications that are not insulin sensitizers. Also, in roughly one-third of the included trials, rescue therapy was used if participants did not meet specific glycemic goals, and participants were often censored from the study at that time. Thus, the final results of these studies do not reflect what will occur with the clinical usage of the studied medications.

We had few concerns regarding applicability of the trial settings to usual care. While many trials did not take place exclusively in the United States, they did occur in similar settings. About half the trials occurred partly or exclusively in the United States, Italy, and/or were multinational; the rest of the trials occurred in developed or newly industrialized countries. However, few of the trials (about 25 percent) reported on the setting of recruitment, such as primary care or specialty care, so we cannot definitively comment on how like this is to usual care.

Implications for Clinical and Policy Decisionmaking

This update provides additional evidence supporting metformin as the first-line medication therapy to treat type 2 diabetes when tolerated, and supports a number of treatment options for add-on to metformin based on patient preferences. Not only is metformin favored on many intermediate outcomes including HbA1c and weight, we found more conclusive evidence to support a greater benefit on cardiovascular morbidity and mortality with metformin over

sulfonylureas. This is consistent with several current guidelines such as the American College of Physicians[324] and American Diabetes Association[23] guidelines which recommend metformin as a first-line treatment choice. The American Association of Clinical Endocrinologists[325] guideline also lists metformin as one of its first-line choices for treatment of type 2 diabetes, but allows more flexibility in the choice of first-line therapy.

As the newer medications (DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 agonists) remain on the market, become available as generics, and have additional data on comparative efficacy (for long-term outcomes) and safety, these newer medications may be preferred by patients. They have some unique effects on weight loss, specifically the SGLT-2 inhibitors and GLP-1 agonists, and may offer the convenience of a once weekly injection over daily medication. However, the SGLT-2 inhibitors clearly increase the risk of genital mycotic infections compared to other agents, and GLP-1 agonists cause GI side effects. Therefore, the continued emphasis in guidelines about accounting for patient preferences when choosing therapy will be critical, as well as explaining benefits and potential harms accurately to patients in clinical practice.

In terms of cost, pioglitazone is the newest agent that has a generic. The first patent for Byetta expires in December 2016 and Januvia will have a patent expiry in 2017. If generics are available soon after, this will give patients and clinicians more valid options for therapy. Clinically, the choice of therapy still depends a lot on patients' out-of-pocket costs which are influenced by generic availability, insurance status, prescription coverage, and tier of medication. For drugs with comparable effectiveness and safety, particularly in the short-term, out-of-pocket costs drive clinical decisions more than small differences in the outcomes included in this report. Similarly, the decision by insurers to include a product as a preferred product, such as for lower tier placement, has more to do with negotiated prices than with small differences in clinical outcomes.

In summary, we did not find large differences in HbA1c-lowering effects of the diabetes medications studied except for DPP-4 inhibitors which are not as effective. Weight effects of the medications are differential, and there is only evidence on cardiovascular mortality to support metformin over sulfonylureas. Each class of drug has different common side effects (e.g., hypoglycemia, GI side effects), and the evidence on rare, serious side effects is less clear. Therefore, factors such as patient preferences and costs are likely to continue to drive selection of and adherence to the diabetes medications.

Limitations of the Comparative Effectiveness Review Process

Several important limitations to our updated systematic review deserve mention. Because this was an update of a comprehensive review published in 2007 and an update in 2011, we focused our update *a priori* on studies with active control comparators, which are most relevant for clinical practice. Placebo-controlled trials had been included in the original 2007 review, but excluded in the 2011 update. In general, the majority of placebo-controlled trials are short. However, the exclusion of placebo-controlled trials has implications for the review, including the inability to evaluate rare outcomes using indirect comparisons. To conclude from an active-control study that one medication is more effective than another requires prior knowledge that the active-control drug has been studied previously and is known to be more effective than placebo. Because the 2007 review had included placebo-controlled trials, we know that many drugs were more effective than placebo for the intermediate outcomes for many drug comparisons. However, this assumption may be less valid for the newer medications, where

evidence on comparisons with placebo from other systematic reviews, such as the Cochrane Reviews, will be also be helpful in making conclusions.

In addition, our inclusion criteria required that all studies fit into one or more of the pre-specified comparisons of interest (Table 2), which identified specific drug-drug or two-drug comparisons. For example, studies that included any number of "background medications" were excluded. Our rationale was to avoid attributing outcomes to the medication of interest when it was truly due to the background medication. This was especially important because of our goal of evaluating two-drug combinations. Applying the inclusion criteria, which required pre-specified comparisons of interest, had several implications. This criteria required the exclusion of several large trials,[9-12, 291, 326-330] some of which evaluated HbA1c lowering strategies rather than individual medications, as well as some smaller trials and observational studies.

Of note, the RECORD study was included for the intermediate outcomes but excluded from this updated review for the long-term and safety outcomes since it did not stratify these outcomes by comparisons of interest. While excluding this study for these outcomes lowered our evidence grade strength for CHF, it did not change the overall conclusion. Another unintended consequence of requiring these pre-specified comparisons of interest was that some of the recent studies of exenatide[331-334] and liraglutide[251, 335-337] as add-on therapy to metformin did not fit our inclusion criteria.

We also had strict criteria for including only medium- to high-quality observational studies to make the data from these studies more useful in drawing conclusions. For instance, we required observational studies to have accounted for confounding by age, gender, race/socioeconomic status, and co-morbid conditions. The article could have used propensity score methodologies or other appropriate methods to account for differences between groups. In addition, they could restrict to one race or socioeconomic status and still be included. By excluding observational studies with a higher risk of bias, we included only observational studies that could provide the most valid results for drawing our conclusions. This resulted in the exclusion of many observational studies of harms, which could have strengthened the evidence base, but this was necessary to reduce confounding by indication in these studies.

We selected key questions focused on intermediate and long-term clinical outcomes through a topic refinement at the beginning of this process, which involved input from stakeholders on the Technical Expert Panel. Diabetes care is a rapidly growing and very extensive field, and we note the omission of key outcomes. For example, we did not collect information about patient-reported outcomes, such as medication adherence and barriers to adherence, health-related quality of life, or treatment satisfaction. These outcomes are important because they may mediate the efficacy of treatment outcome, and also have significant value to patients and clinicians. Future reviews with methodologies designed to capture many different study designs, including qualitative studies, and use of a wide range of measures, are needed to address these outcomes. Although we assessed the mean difference in HbA1c between intervention groups in Key Question 1, we did not include the durability of HbA1c changes over time as an outcome, which may best be addressed using long-term well-designed observational studies.

Limitations of the Evidence Base

A major limitation of the evidence on long-term clinical outcomes and rare adverse events was the absence of RCTs designed to look at these outcomes specifically. Most RCTs evaluating these outcomes were underpowered based on size and duration (generally 12 months or less),

and as a result, event rates were low. Often, no events (e.g., deaths) would occur in either arm in a given RCT.

Limitations within the included studies presented challenges to how we reported study outcomes and impacted our ability to combine them in meta-analyses. For example, several studies failed to report the significance of between-group differences and the measures of dispersion, thereby hindering efforts to estimate effect size across trials for intermediate outcomes. For the long-term clinical and safety outcomes, many studies would report an event in one arm but not in the comparator arm, making it challenging to compare medications. Some trials under-dosed comparison medications, limiting our ability to draw conclusions about efficacy. Authors of randomized trials often did not describe their method of randomization and often did not describe double-blinding, making it difficult to appropriately assess risk of bias of individual studies. Finally, many included trials were industry-sponsored, raising the possibility of publication bias and other forms of bias, such as selective reporting of outcomes. While publication bias and reporting bias generally were not found, publication bias analyses have limited power due to the small numbers of studies for any given comparison.

Additional limitations of the evidence base on long-term and safety outcomes include the following: lack of reporting on or lack of active ascertainment of safety outcomes, lack of reporting on or lack of an intention-to-treat approach, and short duration. Also, many studies had large rates of withdrawals; even if they described them, they often did not use a valid method for accounting for missing data. Also, once we applied selection criteria to account for confounding by basic factors, we did not identify many observational studies on the long-term and rare outcomes. Therefore, high-quality observational studies, including post-marketing studies, are needed to strengthen the evidence base, especially given the resource-intense nature of adequately-powered RCTs to evaluate these outcomes.

Research Gaps

Using the PICOTS framework, we identified several important gaps in the evidence and highlight the major ones below:

- Studies often excluded older adults, racial/ethnic minorities, and persons with co-morbid conditions such as significant renal, cardiovascular and hepatic impairment.
- Studies rarely reported specified *a priori* subgroups of interest such as older adults, racial/ethnic minorities, sex, or BMI.
- RCTs evaluating intermediate outcomes of glycemic control, weight, and blood pressure for GLP-1 agonist comparisons as monotherapy and in combination with metformin versus specific diabetes medication comparators were rarely included.
- We did not identify any RCTs which had all-cause mortality, cardiovascular mortality, cardiovascular morbidity, or adverse events as a primary outcome.
- The evidence base is completely lacking in studies on microvascular outcomes.
- RCTs for long-term clinical outcomes and rare safety events were underpowered (characterized by small sample sizes, study duration generally 12 months or less, and low event rates).
- Studies were lacking for specific safety concerns related to specific drugs (e.g., CHF and thiazolidinediones; liver injury and thiazolidinediones; lactic acidosis and metformin; pancreatitis with DPP-4 inhibitors and GLP-1 agonists; macular edema and thiazolidinediones; hypovolemia, renal impairment and fractures for SGLT-2 inhibitors).

- Few studies on intermediate outcomes, long-term outcomes or harms lasted more than two years whereas patients take diabetes medications for decades.
- Few studies compared metformin plus insulin with other specific metformin-based combinations. The comparison of metformin plus insulin versus metformin plus a GLP-1 agonist is particularly relevant for all outcomes when deciding on an add-on injectable to metformin.

Based on these gaps, we make the following recommendations by outcome for future research:

Intermediate Outcomes

- Longer duration RCTs (>4 years) of all diabetes medication comparisons to determine if short-term comparative effects are durable.
- RCTs evaluating the GLP-1 agonists as monotherapy and in combination with metformin are needed. If adding GLP-1 agonists to different background medications, then RCTs should conduct stratified randomization by background medication and evaluate effects by background medication in their analysis. See methodologic gaps below.
- RCTs evaluating intermediate outcomes for metformin plus the addition of insulin with other metformin-based combinations, and in particular metformin plus a GLP-1 agonist would be useful for patients and clinicians contemplating an add-on injectable to metformin.

Long-term Outcomes

- Longer duration RCTs and higher quality observational studies (>2 years) of all diabetes medication comparisons for retinopathy, nephropathy, and neuropathy.
- Longer duration RCTs and higher quality observational studies (>2 years) of all diabetes medication comparisons where all-cause mortality, cardiovascular mortality, and cardiovascular morbidity are the primary outcomes.

Safety Outcomes

- Higher-quality observational studies for most safety outcomes are needed (i.e., CHF, cancer, pancreatitis, hypovolemia, liver injury, lactic acidosis, macular edema/decreased vision, renal impairment, and severe allergic reactions).
- To answer specific safety concerns related to specific drug classes, we also recommend the following more focused approach:
    - For CHF and macular edema, more studies are needed which directly compare thiazolidinediones with specific classes of diabetes medications directly.
    - For CHF, more studies are needed which directly compare DPP-4 inhibitors with specific classes of diabetes medications directly.
    - For pancreatitis, more studies are needed which directly compare DPP-4 inhibitors and GLP-1 agonists with other specific classes of diabetes medications directly.
    - For bladder cancer, more studies are needed which directly compare pioglitazone directly to other medications, and for thyroid cancer, more studies are needed which compare the GLP-1 agonists directly to other drugs.
    - For hypovolemia, renal impairment, and fractures, more studies are needed which directly compare SGLT-2 inhibitors with specific classes of diabetes medications directly.

Subgroups

- Studies which include older adults, racial/ethnically diverse populations, and adults with comorbid conditions (such as renal impairment, hepatic impairment and cardiovascular conditions) will allow investigators to conduct subgroup analyses on areas of interest, which is especially important for long-term and safety outcomes.
- Studies with an a priori plan to investigate differences by important subgroups of interest (i.e., age, race, sex, and BMI) are needed.

Methodological Gaps and Suggested Improvements

Key methodological issues which severely limited our ability to draw conclusions from the existing evidence on the comparative effectiveness of diabetes medications include the following: lack of reporting on randomization methods for RCTs, allocation concealment, blinding, and withdrawals; inconsistent definitions and ascertainment of long-term and safety outcomes; inconsistent reporting of safety and long-term outcomes in each study arm; and lack of appropriate accounting for confounding for observational studies.

Based on these methodological gaps, we make the following recommendations for future research:

- Consistent adverse event and long-term outcome reporting for all arms in a study, with predefined outcomes and definitions, and a description of methods for ascertainment of outcomes
- Consistent reporting of the number of deaths and other adverse events in each study arm, even if there were none
- Consistent reporting of between-group comparisons of changes from baseline, as well as measures of dispersion to improve interpretation of findings
- Use of clinically-relevant, standardized definitions for microvascular outcomes (e.g., incident nephropathy based on eGFR and urine albumin:creatinine ratios).
- Use of clinically-relevant, standardized definitions for safety outcomes (e.g., liver injury >3x ULN) and active ascertainment of these outcomes.
- For randomized trials:
  - Consistent reporting of the steps taken to ensure randomization, allocation concealment, and double blinding
  - Focusing on retention of participants and followup of withdrawn participants if possible, especially for deaths and rare safety events (e.g., cancer)
  - If allowing more than one background medication, then stratifying randomization by background medication.
- High-quality observational studies, including post-marketing studies, are needed to strengthen the evidence base, especially given the resource-intense nature of adequately-powered RCTs to evaluate long-term and safety outcomes.
- For observational studies:
  - Consistent reporting of details of the treatment type, dose, timing and duration of use of the medication, when available
  - Appropriate control for confounders (including confounding by indication), such as the use of propensity scores
  - Comparison of one medication directly with another medication (e.g., as opposed to thiazolidinedione versus non-thiazolidinedione).

- Consistent reporting on which medications are allowed as “background” medications and stratification of results by the combination therapy (for studies allowing use of “background” medications).

Conclusions

Although the comparative long-term benefits and harms of most diabetes medications remain unclear, the evidence supports use of metformin as a first-line agent due to its beneficial effects on intermediate and long-term outcomes (cardiovascular mortality benefit for metformin versus sulfonylureas in particular) along with its relative safety. Comparisons of metformin combinations showed little to no difference in HbA1c reduction, but some combinations reduced weight and some increased risk for hypoglycemia and other adverse events. Each class of drug is clearly associated with some common side effects (e.g., hypoglycemia, GI side effects), and the evidence on serious, but rare, safety events remains unclear. In the face of this uncertainty, we provide comprehensive information in this report about the benefits and harms of diabetes medications which can facilitate personalized treatment choices by patients and their clinicians, as well as support decisionmaking for payers and regulators, especially as newer medications come off patent and become more accessible.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014 [cited 2015 February 26]; Available from: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
2. Lee JW, Brancati FL, Yeh HC. Trends in the prevalence of type 2 diabetes in Asians versus whites: results from the United States National Health Interview Survey, 1997-2008. Diabetes Care. 2011 Feb;34(2):353-7.
3. Nichols GA, Schroeder EB, Karter AJ, Gregg EW, Desai J, Lawrence JM, et al. Trends in diabetes incidence among 7 million insured adults, 2006-2011: the SUPREME-DM project. Am J Epidemiol. 2015 Jan 1;181(1):32-9.
4. Maruthur NM. The growing prevalence of type 2 diabetes: increased incidence or improved survival? Current diabetes reports. 2013 Dec;13(6):786-94.
5. Centers for Disease Control and Prevention. Diabetes Public Health Resource: Incidence ang Age at Diagnosis. 2013 [cited 2015 January 27]; Available from: http://www.cdc.gov/diabetes/statistics/incidence_national.htm.
6. Economic costs of diabetes in the U.S. In 2007. Diabetes Care. 2008 Mar;31(3):596-615.
7. Standards of medical care in diabetes-2014. Diabetes Care. 2014;37(SUPPL.1):S14-S80.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
9. 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. 1998 1998 Sep 12;352(9131):854-65.
10. 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. 1998 Sep 12;352(9131):837-53.
11. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39.
12. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.
13. Papademetriou V, Lovato L, Doumas M, Nylen E, Mottl A, Cohen RM, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. Kidney Int. 2014 Sep 17.
14. Saremi A, Schwenke DC, Bahn G, Ge L, Emanuele N, Reaven PD. The effect of intensive glucose lowering therapy among major racial/ethnic groups in the Veterans Affairs Diabetes Trial. Metabolism. 2015 Feb;64(2):218-25.
15. Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S, et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Comparative Effectiveness Review No 8 (Prepared by the Johns Hopkins Evidence-based Practice Center under Contract No 290-02-0018). Rockville, MD: Agency for Healthcare Research and Quality; 2007.

16. Bennett WL, Wilson LM, Bolen S, Maruthur N, Singh S, Chatterjee R, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Rockville MD2011.

17. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007 Sep 18;147(6):386-99.

18. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011 May 3;154(9):602-13.

19. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012 Nov;55(11):2929-37.

20. Lu CJ, Sun Y, Muo CH, Chen RC, Chen PC, Hsu CY. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013;36(2):145-51.

21. Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013 Aug;166(2):240-9 e1.

22. Mamtani R, Haynes K, Bilker WB, Vaughn DJ, Strom BL, Glanz K, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst. 2012 Sep 19;104(18):1411-21.

23. (7) Approaches to glycemic treatment. Diabetes Care. 2015 Jan;38 Suppl:S41-8.

24. Turner LW, Nartey D, Stafford RS, Singh S, Alexander GC. Ambulatory treatment of type 2 diabetes in the U.S., 1997-2012. Diabetes Care. 2014 Apr;37(4):985-92.

25. Raebel MA, Xu S, Goodrich GK, Schroeder EB, Schmittdiel JA, Segal JB, et al. Initial antihyperglycemic drug therapy among 241 327 adults with newly identified diabetes from 2005 through 2010: a surveillance, prevention, and management of diabetes mellitus (SUPREME-DM) study. Ann Pharmacother. 2013 Oct;47(10):1280-91.

26. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-S45.

27. (8) Cardiovascular disease and risk management. Diabetes Care. 2015 Jan;38 Suppl:S49-57.

28. Tsertsvadze A, Maglione M, Chou R, Garritty C, Coleman C, Lux L, et al. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1208-15.

29. Higgins JPT, S. G. Cochrane handbook for systemic reviews of interventions Version 5.1.0. 2011 [cited Oxford, England]; Available from: http://handbook.cochrane.org/.

30. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12.

31. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998 Jun;52(6):377-84.

32. Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press; 2011 [cited 2014 July 9]; Available from: books.nap.edu/openbook.php?record_id=13059&page=81.

33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.

34. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88.

35. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Ann Intern Med. 2014 Feb 18;160(4):267-70.

36. Balshem H, Stevens A, Ansari M, Norris S, Kansagara D, Shamliyan T, et al. Finding Grey Literature Evidence and Assessing for Outcome and Analysis Reporting Biases When Comparing Medical Interventions: AHRQ and the Effective Health Care Program

Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville MD2008.

37. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 Dec;50(4):1088-101.

38. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34.

39. Owens DK, Lohr KN, Atkins D, Treadwell JR, Reston JT, Bass EB, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23.

40. Singh N. Diabetes, heart rate, and mortality. J Cardiovasc Pharmacol Ther. 2002 Apr;7(2):117-29.

41. Dupont WD, Plummer WD, Jr. Power and sample size calculations. A review and computer program. Control Clin Trials. 1990 Apr;11(2):116-28.

42. Tosi F, Muggeo M, Brun E, Spiazzi G, Perobelli L, Zanolin E, et al. Combination treatment with metformin and glibenclamide versus single-drug therapies in type 2 diabetes mellitus: a randomized, double-blind, comparative study. Metabolism. 2003 2003 Jul;52(7):862-7.

43. Alba M, Ahren B, Inzucchi SE, Guan Y, Mallick M, Xu L, et al. Sitagliptin and pioglitazone provide complementary effects on postprandial glucose and pancreatic islet cell function. Diabetes Obes Metab. 2013 Dec;15(12):1101-10.

44. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 2009 Jun 5.

45. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 2006 Dec 7;355(23):2427-43.

46. Bergenstal RM, Forti A, Chiasson JL, Woloschak M, Boldrin M, Balena R. Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). Diabetes Ther. 2012 Dec;3(1):13.

47. Bunck MC, Corner A, Eliasson B, Heine RJ, Shaginian RM, Taskinen MR, et al. Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care. 2011 Sep;34(9):2041-7.

48. Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, et al. Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism. 2009 2009 Apr 22.

49. Gupta AK, Smith SR, Greenway FL, Bray GA. Pioglitazone treatment in type 2 diabetes mellitus when combined with portion control diet modifies the metabolic syndrome. Diabetes Obes Metab. 2009 2009 Apr;11(4):330-7.

50. Erdem G, Dogru T, Tasci I, Bozoglu E, Muhsiroglu O, Tapan S, et al. The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008 2008 Nov;82(2):214-8.

51. Iliadis F, Kadoglou NP, Hatzitolios A, Karamouzis M, Alevizos M, Karamitsos D. Metabolic effects of rosiglitazone and metformin in Greek patients with recently diagnosed type 2 diabetes. In Vivo. 2007 2007 Nov-Dec;21(6):1107-14.

52. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2006 2006 Nov;8(6):650-60.

53. Yamanouchi T, Sakai T, Igarashi K, Ichiyanagi K, Watanabe H, Kawasaki T. Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes. Diabet Med. 2005 2005 Aug;22(8):980-5.

54. Ramachandran A, Snehalatha C, Salini J, Vijay V. Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes--a study in Indians. J Assoc Physicians India. 2004 2004 Jun;52:459-63.

55. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. J Clin Endocrinol Metab. 2004 2004 Dec;89(12):6068-76.

56. Lawrence JM, Reid J, Taylor GJ, Stirling C, Reckless JP. Favorable effects of pioglitazone and metformin compared with gliclazide on lipoprotein subfractions in overweight patients with early type 2 diabetes. Diabetes Care. 2004 2004 Jan;27(1):41-6.

57. Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab. 2003 2003 Apr;88(4):1637-45.

58. Hallsten K, Virtanen KA, Lonnqvist F, Sipila H, Oksanen A, Viljanen T, et al. Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes. 2002 2002 Dec;51(12):3479-85.

59. Kiyici S, Ersoy C, Kaderli A, Fazlioglu M, Budak F, Duran C, et al. Effect of rosiglitazone, metformin and medical nutrition treatment on arterial stiffness, serum MMP-9 and MCP-1 levels in drug naive type 2 diabetic patients. Diabetes Research and Clinical Practice. [doi: DOI: 10.1016/j.diabres.2009.07.004]. 2009 2009/10//;86(1):44-50.

60. Perez A, Zhao Z, Jacks R, Spanheimer R. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin. 2009 Dec;25(12):2915-23.

61. Kato T, Sawai Y, Kanayama H, Taguchi H, Terabayashi T, Taki F, et al. Comparative study of low-dose pioglitazone or metformin treatment in Japanese diabetic patients with metabolic syndrome. Exp Clin Endocrinol Diabetes. 2009 Nov;117(10):593-9.

62. Esteghamati A, Ghasemiesfe M, Mousavizadeh M, Noshad S, Nakhjavani M. Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes. J Diabetes Investig. 2014 May 4;5(3):327-32.

63. Erem C, Ozbas HM, Nuhoglu I, Deger O, Civan N, Ersoz HO. Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2014 May;122(5):295-302.

64. Genovese S, De Berardis G, Nicolucci A, Mannucci E, Evangelista V, Totani L, et al. Effect of pioglitazone versus metformin on cardiovascular risk markers in type 2 diabetes. Adv Ther. 2013 Feb;30(2):190-202.

65. Taslimi S, Esteghamati A, Rashidi A, Tavakkoli HM, Nakhjavani M, Kebriaee-Zadeh A. Treatment with pioglitazone is associated with decreased preprandial ghrelin levels: a randomized clinical trial. Peptides. 2013 Feb;40:89-92.

66. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzalez JG, Chan M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012 Feb;35(2):252-8.

67. Yoon KH, Shin JA, Kwon HS, Lee SH, Min KW, Ahn YB, et al. Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in korean drug-naive type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study. Diabetes Metab J. 2011 Feb;35(1):26-33.

68. Fidan E, Onder Ersoz H, Yilmaz M, Yilmaz H, Kocak M, Karahan C, et al. The effects of rosiglitazone and metformin on inflammation and endothelial dysfunction in patients with type 2 diabetes mellitus. Acta Diabetol. 2011 Dec;48(4):297-302.

69. Esposito K, Maiorino MI, Di Palo C, Gicchino M, Petrizzo M, Bellastella G, et al. Effects of pioglitazone versus metformin on circulating endothelial microparticles and progenitor cells in patients with newly diagnosed type 2 diabetes--a randomized controlled trial. Diabetes Obes Metab. 2011 May;13(5):439-45.

70. Turkmen Kemal Y, Guvener Demirag N, Yildirir A, Atar A, Dogruk Unal A, Biyiklioglu Z. Effects of rosiglitazone on plasma brain natriuretic peptide levels and myocardial performance index in patients with type 2 diabetes mellitus. Acta Diabetol. 2007 2007 Sep;44(3):149-56.

71. Gupta RK, Rehan HS, Rohatagi A, Bhatacharjee J, Chopra D. The effect of glipizide, metformin and rosiglitazone on nontraditional cardiovascular risk factors in newly diagnosed patients with type 2 diabetes mellitus. International journal of diabetes in developing countries [serial on the Internet]. 2010; (3): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/971/CN-00797971/frame.html.

72. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care. 2007 2007 Aug;30(8):1979-87.

73. Williams-Herman D, Johnson J, Teng R, Luo E, Davies MJ, Kaufman KD, et al. Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. Curr Med Res Opin. 2009 2009 Mar;25(3):569-83.

74. Aschner P, Katzeff HL, Guo H, Sunga S, Williams-Herman D, Kaufman KD, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes Obes Metab. 2010 Mar;12(3):252-61.

75. Jadzinsky M, Pfutzner A, Paz-Pacheco E, Xu Z, Allen E, Chen R. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009 2009 Jun;11(6):611-22.

76. Pratley RE, Fleck P, Wilson C. Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naive patients with type 2 diabetes: a randomized, double-blind, 6-month study. Diabetes Obes Metab. 2014 Jul;16(7):613-21.

77. Williams-Herman D, Johnson J, Teng R, Golm G, Kaufman KD, Goldstein BJ, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab. 2010 May;12(5):442-51.

78. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012 Jun;14(6):565-74.

79. Pfutzner A, Paz-Pacheco E, Allen E, Frederich R, Chen R. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011 Jun;13(6):567-76.

80. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012 May;66(5):446-56.

81. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009 Apr;32(4):650-7.

82. Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013;36(12):4015-21.

83. Umpierrez G, Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Efficacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3). Diabetes Care. 2014 May 19.

84. Yuan GH, Song WL, Huang YY, Guo XH, Gao Y. Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study. Chin Med J (Engl). 2012 Aug;125(15):2677-81.

85. Leiter LA, Harris SB, Chiasson J-L, Edwards L, O'Neill MC, Van Daphne M. Efficacy and safety of Rosiglitazone as monotherapy or in combination with metformin in primary care settings. Can J Diabetes. 2005 2005;29(4):384-92.

86. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. Curr Med Res Opin. 2009 2009 May;25(5):1111-9.

87. Scott R, Loeys T, Davies MJ, Engel SS. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008 2008 Sep;10(10):959-69.

88. Weissman P, Goldstein BJ, Rosenstock J, Waterhouse B, Cobitz AR, Wooddell MJ, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin. 2005 2005 Dec;21(12):2029-35.

89. Bailey CJ, Bagdonas A, Rubes J, McMorn SO, Donaldson J, Biswas N, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. 2005 2005 Oct;27(10):1548-61.

90. Gomez-Perez FJ, Fanghanel-Salmon G, Antonio Barbosa J, Montes-Villarreal J, Berry RA, Warsi G, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. Diabetes Metab Res Rev. 2002 2002 Mar-Apr;18(2):127-34.

91. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. Clin Ther. 2000 2000 Dec;22(12):1395-409.

92. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA. 2000 2000 Apr 5;283(13):1695-702.

93. Kadoglou NP, Kapelouzou A, Tsanikidis H, Vitta I, Liapis CD, Sailer N. Effects of rosiglitazone/metformin fixed-dose combination therapy and metformin monotherapy on serum vaspin, adiponectin and IL-6 levels in drug-naive patients with type 2 diabetes. Exp Clin Endocrinol Diabetes. 2011 Feb;119(2):63-8.

94. Genovese S, Passaro A, Brunetti P, Comaschi M, Cucinotta D, Egan CG, et al. Pioglitazone Randomised Italian Study on Metabolic Syndrome (PRISMA): effect of pioglitazone with metformin on HDL-C levels in Type 2 diabetic patients. J Endocrinol Invest. 2013 Sep;36(8):606-16.

95. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1615-22.

96. Borges JL, Bilezikian JP, Jones-Leone AR, Acusta AP, Ambery PD, Nino AJ, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naive type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011 Nov;13(11):1036-46.

97. Feinglos M, Dailey G, Cefalu W, Osei K, Tayek J, Canovatchel W, et al. Effect on glycemic control of the addition of 2.5 mg glipizide GITS to metformin in patients with T2DM. Diabetes Res Clin Pract. 2005 2005 May;68(2):167-75.

98. Garber AJ, Donovan DSJ, Dandona P, Bruce S, Park JS. Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. J Clin Endocrinol Metab. 2003 2003 Aug;88(8):3598-604.

99. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. Clin Ther. 2003 2003 Mar;25(3):890-903.

100. Blonde L, Rosenstock J, Mooradian AD, Piper BA, Henry D. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. Diabetes Obes Metab. 2002 2002 Nov;4(6):368-75.

101. Marre M, Howlett H, Lehert P, Allavoine T. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in Type 2 diabetic patients inadequately controlled on metformin. Diabet Med. 2002 2002 Aug;19(8):673-80.

102. Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab. 2002 2002 May;4(3):201-8.

103. Hermann LS, Schersten B, Bitzen PO, Kjellstrom T, Lindgarde F, Melander A. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care. 1994 1994 Oct;17(10):1100-9.

104. Hermann LS, Bitzen PO, Kjellstrom T, Lindgarde F, Schersten B. Comparative efficacy of metformin and glibenclamide in patients with non-insulin-dependent diabetes mellitus. Diabete Metab. 1991 1991 May;17(1 Pt 2):201-8.

105. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med. 2001 2001 Oct;18(10):828-34.

106. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995 1995 Aug 31;333(9):541-9.

107. Chien HH, Chang CT, Chu NF, Hsieh SH, Huang YY, Lee IT, et al. Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. J Chin Med Assoc. 2007 2007 Nov;70(11):473-80.

108. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med. 2010 Dec;27(12):1409-19.

109. Kim HS, Kim DM, Cha BS, Park TS, Kim KA, Kim DL, et al. Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea. Journal of Diabetes Investigation. 2014((Kim H.-S.) Department of Internal Medicine Keimyung University School of Medicine Daegu Korea).

110. Ahren B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, et al. HARMONY 3: 104-Week Randomized, Double-Blind, Placebo- and Active-Controlled Trial Assessing the Efficacy and Safety of Albiglutide Compared With Placebo, Sitagliptin, and Glimepiride in Patients With Type 2 Diabetes Taking Metformin. Diabetes Care. 2014 Jun 4.

111. Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin. 2008 2008 Feb;24(2):537-50.

112. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006 2006 Dec;29(12):2638-43.

113. DeFronzo RA, Hissa MN, Garber AJ, Luiz Gross J, Yuyan Duan R, Ravichandran S, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care. 2009 Sep;32(9):1649-55.

114. Reasner C, Olansky L, Seck TL, Williams-Herman DE, Chen M, Terranella L, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011 Jul;13(7):644-52.

115. Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract. 2011 Nov;94(2):217-24.

116. Fonseca V, Zhu T, Karyekar C, Hirshberg B. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. Diabetes Obes Metab. 2012 Apr;14(4):365-71.

117. Yang W, Guan Y, Shentu Y, Li Z, Johnson-Levonas AO, Engel SS, et al. The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes. J Diabetes. 2012 Sep;4(3):227-37.

118. Kadowaki T, Tajima N, Odawara M, Nishii M, Taniguchi T, Ferreira JC. Addition of sitagliptin to ongoing metformin monotherapy improves glycemic control in Japanese patients with type 2 diabetes over 52 weeks. J Diabetes Investig. 2013 Mar 18;4(2):174-81.

119. Derosa G, Carbone A, D'Angelo A, Querci F, Fogari E, Cicero AF, et al. Variations in inflammatory biomarkers following the addition of sitagliptin in patients with type 2 diabetes not controlled with metformin. Intern Med. 2013;52(19):2179-87.

120. White JL, Buchanan P, Li J, Frederich R. A randomized controlled trial of the efficacy and safety of twice-daily saxagliptin plus metformin combination therapy in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy. BMC Endocr Disord. 2014;14(1):17.

121. Ross SA, Rafeiro E, Meinicke T, Toorawa R, Weber-Born S, Woerle HJ. Efficacy and safety of linagliptin 2.5?mg twice daily versus 5?mg once daily in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, placebo-controlled trial. Curr Med Res Opin [serial on the Internet]. 2012; (9): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/674/CN-00859674/frame.html.

122. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab [serial on the Internet]. 2013; (12): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/648/CN-00915648/frame.html.

123. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2009 Jan;63(1):46-55.

124. Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011 Jan;13(1):65-74.

125. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012 Jun;35(6):1232-8.

126. Seino Y, Miyata Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. Diabetes Obes Metab. 2012 Oct;14(10):927-36.

127. Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013 Dec;56(12):2582-92.

128. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5). Diabetes Care. 2014 Apr 17.

129. Hermans MP, Delibasi T, Farmer I, Lohm L, Maheux P, Piatti P, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. Curr Med Res Opin. 2012 Oct;28(10):1635-45.

130. Aaboe K, Knop FK, Vilsboll T, Deacon CF, Holst JJ, Madsbad S, et al. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2010 Apr;12(4):323-33.

131. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. Int J Clin Pract. 2013 Dec;67(12):1283-93.

132. Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. Journal of Clinical and Translational Endocrinology. 2014;1(2):54-60.

133. Haring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, et al. Empaglif lozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37(6):1650-9.

134. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012 Mar;97(3):1020-31.

135. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11:43.

136. Derosa G, Cicero AF, Franzetti IG, Querci F, Carbone A, Ciccarelli L, et al. Effects of exenatide and metformin in combination on some adipocytokine levels: a comparison with metformin monotherapy. Can J Physiol Pharmacol. 2013 Sep;91(9):724-32.

137. Forst T, Michelson G, Ratter F, Weber MM, Anders S, Mitry M, et al. Addition of liraglutide in patients with Type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function. Diabet Med. 2012 Sep;29(9):1115-8.

138. Apovian CM, Bergenstal RM, Cuddihy RM, Qu Y, Lenox S, Lewis MS, et al. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. Am J Med. 2010 May;123(5):468 e9-17.

139. Teramoto T, Yamada N, Shirai K, Saito Y. Effects of pioglitazone hydrochloride on Japanese patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2007 2007 Apr;14(2):86-93.

140. Hanefeld M, Patwardhan R, Jones NP. A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. Nutr Metab Cardiovasc Dis. 2007 2007 Jan;17(1):13-23.

141. Jain R, Osei K, Kupfer S, Perez AT, Zhang J. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy. 2006 2006 Oct;26(10):1388-95.

142. Nakamura T, Matsuda T, Kawagoe Y, Ogawa H, Takahashi Y, Sekizuka K, et al. Effect of pioglitazone on carotid intima-media thickness and arterial stiffness in type 2 diabetic nephropathy patients. Metabolism. 2004 2004 Oct;53(10):1382-6.

143. Nakamura T, Ushiyama C, Shimada N, Hayashi K, Ebihara I, Koide H. Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. J Diabetes Complications. 2000 2000 Sep-Oct;14(5):250-4.

144. Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI. Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens. 2003 2003 Jan;17(1):7-12.

145. Pfutzner A, Marx N, Lubben G, Langenfeld M, Walcher D, Konrad T, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol. 2005 2005 Jun 21;45(12):1925-31.

146. Tan MH, Johns D, Strand J, Halse J, Madsbad S, Eriksson JW, et al. Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with Type 2 diabetes. Diabet Med. 2004 2004 Aug;21(8):859-66.

147. Tan M, Johns D, Gonzalez Galvez G, Antunez O, Fabian G, Flores-Lozano F, et al. Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, parallel-group trial. Clin Ther. 2004 2004 May;26(5):680-93.

148. Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Koide H. Effect of pioglitazone on urinary liver-type fatty acid-binding protein concentrations in diabetes patients with microalbuminuria. Diabetes Metab Res Rev. 2006 2006 Sep-Oct;22(5):385-9.

149. Shihara N, Kitaoka M, Inagaki N, Kadowaki T, Koumoto S, Satoh J, et al. Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: A comparative study. J Diabetes Investig. 2011 Oct 7;2(5):391-8.

150. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care. 2010 Nov;33(11):2406-8.

151. Barnett AH, Patel S, Harper R, Toorawa R, Thiemann S, von Eynatten M, et al. Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. Diabetes Obes Metab. 2012 Dec;14(12):1145-54.

152. Arjona Ferreira JC, Marre M, Barzilai N, Guo H, Golm GT, Sisk CM, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care. 2013 May;36(5):1067-73.

153. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007 2007 Jan;61(1):171-80.

154. Seino Y, Rasmussen MF, Nishida T, Kaku K. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. Curr Med Res Opin. 2010 May;26(5):1013-22.

155. Kaku K, Rasmussen MF, Nishida T, Seino Y. Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes. J Diabetes Investig. 2011 Nov 30;2(6):441-7.

156. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care. 2004 2004 Jun;27(6):1335-42.

157. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009 2009 Feb 7;373(9662):473-81.

158. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):348-56.

159. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes and Endocrinology [serial on the Internet]. 2013; (3): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/599/CN-00915599/frame.html.

160. Hamann A, Garcia-Puig J, Paul G, Donaldson J, Stewart M. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone. Exp Clin Endocrinol Diabetes. 2008 2008 Jan;116(1):6-13.

161. Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med. 2007 2007 Jun;24(6):626-34.

162. Bakris GL, Ruilope LM, McMorn SO, Weston WM, Heise MA, Freed MI, et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006 2006 Oct;24(10):2047-55.

163. Umpierrez G, Issa M, Vlajnic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. Curr Med Res Opin. 2006 2006 Apr;22(4):751-9.

164. Derosa G, Gaddi AV, Piccinni MN, Ciccarelli L, Salvadeo S, Peros E, et al. Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome. Pharmacotherapy. 2005 2005 May;25(5):637-45.

165. Garber A, Klein E, Bruce S, Sankoh S, Mohideen P. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2006 2006 Mar;8(2):156-63.

166. Maffioli P, Fogari E, D'Angelo A, Perrone T, Derosa G. Ultrasonography modifications of visceral and subcutaneous adipose tissue after pioglitazone or glibenclamide therapy combined with rosuvastatin in type 2 diabetic patients not well controlled by metformin. Eur J Gastroenterol Hepatol. 2013 Sep;25(9):1113-22.

167. Petrica L, Petrica M, Vlad A, Dragos Jianu C, Gluhovschi G, Ianculescu C, et al. Nephro- and neuroprotective effects of rosiglitazone versus glimepiride in normoalbuminuric patients with type 2 diabetes mellitus: a randomized controlled trial. Wien Klin Wochenschr. 2009;121(23-24):765-75.

168. Comaschi M, Demicheli A, Di Pietro C, Bellatreccia A, Mariz S. Effects of pioglitazone in combination with metformin or a sulfonylurea compared to a fixed-dose combination of metformin and glibenclamide in patients with type 2 diabetes. Diabetes Technol Ther. 2007 2007 Aug;9(4):387-98.

169. Schondorf T, Musholt PB, Hohberg C, Forst T, Lehmann U, Fuchs W, et al. The fixed combination of pioglitazone and metformin improves biomarkers of platelet function and chronic inflammation in type 2 diabetes patients: results from the PIOfix study. J Diabetes Sci Technol. 2011 Mar;5(2):426-32.

170. Pfutzner A, Schondorf T, Tschope D, Lobmann R, Merke J, Muller J, et al. PIOfix-study: effects of pioglitazone/metformin fixed combination in comparison with a combination of metformin with glimepiride on diabetic dyslipidemia. Diabetes Technol Ther. 2011 Jun;13(6):637-43.

171. Rigby SP, Handelsman Y, Lai YL, Abby SL, Tao B, Jones MR. Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. Endocr Pract. 2010 Jan-Feb;16(1):53-63.

172. Chawla S, Kaushik N, Singh NP, Ghosh RK, Saxena A. Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. J Pharmacol Pharmacother. 2013 Jan;4(1):27-32.

173. Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010 Aug 7;376(9739):431-9.

174. DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Maggs D, Glass LC. Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. Diabetes Care. 2010 May;33(5):951-7.

175. Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2011 Feb;13(2):160-8.

176. Forst T, Anastassiadis E, Diessel S, Loffler A, Pfutzner A. Effect of linagliptin compared to glimepiride on postprandial glucose metabolism, islet cell function, and vascular function parameters in patients with type 2 diabetes mellitus on ongoing metformin treatment. Diabetes Metab Res Rev. 2014 Jan 23.

177. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007 2007 Mar;9(2):194-205.

178. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012 Aug 4;380(9840):475-83.

179. Goke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract. 2010 Nov;64(12):1619-31.

180. Seck T, Nauck M, Sheng D, Sunga S, Davies MJ, Stein PP, et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract. 2010 Apr;64(5):562-76.

181. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013 Sep 14;382(9896):941-50.

182. Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011 Sep;34(9):2015-22.

183. Ridderstrale M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. The Lancet Diabetes and Endocrinology. 2014((Ridderstrale M., mtrd@steno.dk) Steno Diabetes Center, Gentofte, Denmark).

184. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. Kidney Blood Press Res. 2012;35(6):483-8.

185. Gallwitz B, Guzman J, Dotta F, Guerci B, Simo R, Basson BR, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet. 2012 Jun 16;379(9833):2270-8.

186. Derosa G, Putignano P, Bossi AC, Bonaventura A, Querci F, Franzetti IG, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. Eur J Pharmacol. 2011 Sep;666(1-3):251-6.

187. Yang W, Chen L, Ji Q, Liu X, Ma J, Tandon N, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). Diabetes Obes Metab. 2011 Jan;13(1):81-8.

188. Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Ragonesi PD, Querci F, et al. Exenatide versus glibenclamide in patients with diabetes. Diabetes Technol Ther. 2010 Mar;12(3):233-40.

189. Moon JS, Ha KS, Yoon JS, Lee HW, Lee HC, Won KC. The effect of glargine versus glimepiride on pancreatic beta-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. Acta Diabetol. 2014 Apr;51(2):277-85.

190. Malone JK, Beattie SD, Campaigne BN, Johnson PA, Howard AS, Milicevic Z. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? Diabetes Res Clin Pract. 2003 2003 Dec;62(3):187-95.

191. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab. 2006 2006 Jan;8(1):39-48.

192. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010 Apr 24;375(9724):1447-56.

193. Aschner P, Chan J, Owens DR, Picard S, Wang E, Dain MP, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet. 2012 Jun 16;379(9833):2262-9.

194. Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010 Jun 26;375(9733):2234-43.

195. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 2009 May;32(5):762-8.

196. Gallwitz B, Bohmer M, Segiet T, Molle A, Milek K, Becker B, et al. Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. Diabetes Care. 2011 Mar;34(3):604-6.

197. Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther. 2007 2007 Nov;29(11):2349-64.

198. Raskin PR, Hollander PA, Lewin A, Gabbay RA, Bode B, Garber AJ. Basal insulin or premix analogue therapy in type 2 diabetes patients. Eur J Intern Med. 2007 2007 Jan;18(1):56-62.

199. Davies MJ, Thaware PK, Tringham JR, Howe J, Jarvis J, Johnston V, et al. A randomized controlled trial examining combinations of repaglinide, metformin and NPH insulin. Diabet Med. 2007 2007 Jul;24(7):714-9.

200. St John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care. 2002 2002 Nov;25(11):2058-64.

201. Tolman KG, Freston JW, Kupfer S, Perez A. Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. Drug Saf. 2009;32(9):787-800.

202. Derosa G, Cicero AF, Gaddi AV, Ciccarelli L, Piccinni MN, Salvadeo S, et al. Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial. Clin Ther. 2005 2005 Sep;27(9):1383-91.

203. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000 Aug 12;321(7258):412-9.

204. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1565-76.

205. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27;165(12):1410-9.

206. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004 2004 Dec;26(12):2034-44.

207. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabet Med. 2005 2005 Apr;22(4):374-81.

208. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jorgensen CH, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010 Dec;53(12):2546-53.

209. Horsdal HT, Sondergaard F, Johnsen SP, Rungby J. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. Pharmacoepidemiol Drug Saf. 2011 Apr;20(4):331-7.

210. Mogensen UM, Andersson C, Fosbol EL, Schramm TK, Vaag A, Scheller NM, et al. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a combination of metformin and sulphonylurea in type 2 diabetes mellitus - a retrospective nationwide study. Diabetes Obes Metab. 2014 May 14.

211. Scheller NM, Mogensen UM, Andersson C, Vaag A, Torp-Pedersen C. All-cause mortality and cardiovascular effects associated with the DPP-IV inhibitor sitagliptin compared with metformin, a retrospective cohort study on the Danish population. Diabetes, Obesity and Metabolism. 2014;16(3):231-6.

212. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011 Aug;32(15):1900-8.

213. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. Diabet Med. 2005 2005 Apr;22(4):497-502.

214. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11.

215. Vaccaro O, Masulli M, Bonora E, Del Prato S, Giorda CB, Maggioni AP, et al. Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: impact on cardiovascular events. A randomized controlled trial. Nutr Metab Cardiovasc Dis. 2012 Nov;22(11):997-1006.

216. Sullivan D, Forder P, Simes J, Whiting M, Kritharides L, Merrifield A, et al. Associations between the use of metformin, sulphonylureas, or diet alone and cardiovascular outcomes in 6005 people with type 2 diabetes in the FIELD study. Diabetes Res Clin Pract. 2011 Nov;94(2):284-90.

217. Evans JM, Doney AS, AlZadjali MA, Ogston SA, Petrie JR, Morris AD, et al. Effect of Metformin on mortality in patients with heart failure and type 2 diabetes mellitus. Am J Cardiol. 2010 Oct 1;106(7):1006-10.

218. Sillars B, Davis WA, Hirsch IB, Davis TM. Sulphonylurea-metformin combination therapy, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. Diabetes Obes Metab. 2010 Sep;12(9):757-65.

219. Hsiao FY, Tsai YW, Wen YW, Chen PF, Chou HY, Chen CH, et al. Relationship between cumulative dose of thiazolidinediones and clinical outcomes in type 2 diabetic patients with history of heart failure: a population-based cohort study in Taiwan. Pharmacoepidemiol Drug Saf. 2010 Aug;19(8):786-91.

220. Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med. 2010 May;122(3):16-27.

221. Raskin P, Lewin A, Reinhardt R, Lyness W. Twice-daily dosing of a repaglinide/metformin fixed-dose combination tablet provides glycaemic control comparable to rosiglitazone/metformin tablet. Diabetes Obes Metab. 2009 2009 May 19.

222. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009 2009 Jun;46(2):145-54.

223. Wheeler S, Moore K, Forsberg CW, Riley K, Floyd JS, Smith NL, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013 Jun 25.

224. Kahler KH, Rajan M, Rhoads GG, Safford MM, Demissie K, Lu SE, et al. Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. Diabetes Care. 2007 2007 Jul;30(7):1689-93.

225. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012 Sep;14(9):803-9.

226. Corrao G, Romio SA, Zambon A, Merlino L, Bosi E, Scavini M. Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011 Mar;67(3):289-99.

227. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2013;15(8):721-8.

228. Jones TA, Sautter M, Van Gaal LF, Jones NP. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. Diabetes Obes Metab. 2003 2003 May;5(3):163-70.

229. Stenlof K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin. 2014 Feb;30(2):163-75.

230. Hsiao FY, Huang WF, Wen YW, Chen PF, Kuo KN, Tsai YW. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: a retrospective cohort study of over 473,000 patients using the National Health Insurance database in Taiwan. Drug Saf. 2009 2009;32(8):675-90.

231. Brownstein JS, Murphy SN, Goldfine AB, Grant RW, Sordo M, Gainer V, et al. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care. 2010 2010 Mar;33(3):526-31.

232. Hung YC, Lin CC, Wang TY, Chang MP, Sung FC, Chen CC. Oral hypoglycaemic agents and the development of non-fatal cardiovascular events in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2013 Nov;29(8):673-9.

233. Roumie CL, Hung AM, Greevy RA, Grijalva CG, Liu X, Murff HJ, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2012 Nov 6;157(9):601-10.

234. Stewart MW, Cirkel DT, Furuseth K, Donaldson J, Biswas N, Starkie MG, et al. Effect of metformin plus roziglitazone compared with metformin alone on glycaemic control in well-controlled Type 2 diabetes. Diabet Med. 2006 2006 Oct;23(10):1069-78.

235. Goke B, Gallwitz B, Eriksson JG, Hellqvist A, Gause-Nilsson I. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. Int J Clin Pract. 2013 Apr;67(4):307-16.

236. Hung AM, Roumie CL, Greevy RA, Liu X, Grijalva CG, Murff HJ, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int. 2012 Apr;81(7):698-706.

237. Masica AL, Ewen E, Daoud YA, Cheng D, Franceschini N, Kudyakov RE, et al. Comparative effectiveness research using electronic health records: impacts of oral antidiabetic drugs on the development of chronic kidney disease. Pharmacoepidemiol Drug Saf. 2013 Apr;22(4):413-22.

238. Amador-Licona N, Guizar-Mendoza J, Vargas E, Sanchez-Camargo G, Zamora-Mata L. The short-term effect of a switch from glibenclamide to metformin on blood pressure and microalbuminuria in patients with type 2 diabetes mellitus. Arch Med Res. 2000 2000 Nov-Dec;31(6):571-5.

239. Hung AM, Roumie CL, Greevy RA, Liu X, Grijalva CG, Murff HJ, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. Pharmacoepidemiol Drug Saf. 2013 Jun;22(6):623-31.

240. Lehman DM, Lorenzo C, Hernandez J, Wang CP. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. Diabetes Care. 2012 May;35(5):1002-7.

241. van Staa TP, Patel D, Gallagher AM, de Bruin ML. Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. Diabetologia. 2012 Mar;55(3):654-65.

242. Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, Viberti G. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia. 2010 Sep;53(9):1838-45.

243. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. Postgrad Med. 2014 Jan;126(1):7-17.

244. Nyirjesy P, Zhao Y, Ways K, Usiskin K. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. Curr Med Res Opin. 2012 Jul;28(7):1173-8.

245. Davidson JA. Tolerability of saxagliptin in patients with inadequately controlled type 2 diabetes: results from 6 phase III studies. J Manag Care Pharm. 2014 Feb;20(2):120-9.

246. Rosenstock J, Gross JL, Aguilar-Salinas C, Hissa M, Berglind N, Ravichandran S, et al. Long-term 4-year safety of saxagliptin in drug-naive and metformin-treated patients with Type 2 diabetes. Diabet Med. 2013 Dec;30(12):1472-6.

247. Skrivanek Z, Gaydos BL, Chien JY, Geiger MJ, Heathman MA, Berry S, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Apr 25.

248. Derosa G, Franzetti I, Gadaleta G, Ciccarelli L, Fogari R. Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: comparison between glimepiride and metformin. Diabetes Nutr Metab. 2004 2004 Jun;17(3):143-50.

249. Wright AD, Cull CA, Macleod KM, Holman RR. Hypoglycemia in Type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications. 2006 2006 Nov-Dec;20(6):395-401.

250. Weir MA, Gomes T, Mamdani M, Juurlink DN, Hackam DG, Mahon JL, et al. Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. Nephrol Dial Transplant. 2011 Jun;26(6):1888-94.

251. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 2009 Jan;32(1):84-90.

252. Agarwal R, Saha C, Battiwala M, Vasavada N, Curley T, Chase SD, et al. A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy. Kidney Int. 2005 2005 Jul;68(1):285-92.

253. Gupta A, Ahmad Ansari N, Yadav N. Comparative efficacy and safety of sitagliptin and Glimepiride in patients of newly diagnosed type 2 diabetes mellitus. International Journal of Pharmaceutical Sciences Review and Research. 2013;23(2):137-41.

254. Lee YK, Song SO, Kim KJ, Cho Y, Choi Y, Yun Y, et al. Glycemic Effectiveness of Metformin-Based Dual-Combination Therapies with Sulphonylurea, Pioglitazone, or DPP4-Inhibitor in Drug-Naive Korean Type 2 Diabetic Patients. Diabetes Metab J. 2013 Dec;37(6):465-74.

255. Srivastava S, Saxena GN, Keshwani P, Gupta R. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. J Assoc Physicians India. 2012 Mar;60:27-30.

256. Davies M, Heller S, Sreenan S, Sapin H, Adetunji O, Tahbaz A, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care. 2013 May;36(5):1368-76.

257. Derosa G, Gaddi AV, Ciccarelli L, Fogari E, Ghelfi M, Ferrari I, et al. Long-term effect of glimepiride and rosiglitazone on non-conventional cardiovascular risk factors in metformin-treated patients affected by metabolic syndrome: a randomized, double-blind clinical trial. J Int Med Res. 2005 2005 May-Jun;33(3):284-94.

258. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes, Obesity and Metabolism. 2014;16(2):159-69.

259. Chou HS, Palmer JP, Jones AR, Waterhouse B, Ferreira-Cornwell C, Krebs J, et al. Initial treatment with fixed-dose combination rosiglitazone/glimepiride in patients with previously untreated type 2 diabetes. Diabetes Obes Metab. 2008 2008 Aug;10(8):626-37.

260. Perez-Monteverde A, Seck T, Xu L, Lee MA, Sisk CM, Williams-Herman DE, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naive patients with type 2 diabetes. Int J Clin Pract. 2011 Sep;65(9):930-8.

261. Kawai T, Funae O, Shimada A, Tabata M, Hirata T, Atsumi Y, et al. Effects of pretreatment with low-dose metformin on metabolic parameters and weight gain by pioglitazone in Japanese patients with type 2 diabetes. Intern Med. 2008 2008;47(13):1181-8.

262. 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 Prospective Diabetes Study Group. Ann Intern Med. 1998 1998 Feb 1;128(3):165-75.

263. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 2008 May;31(5):845-51.

264. Horsdal HT, Johnsen SP, Sondergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study. Diabetologia. 2008 2008 Apr;51(4):567-74.

265. Schellhase KG, Koepsell TD, Weiss NS. Glycemic control and the risk of multiple microvascular diabetic complications. Fam Med. 2005 Feb;37(2):125-30.

266. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med. 1997 Nov 1;127(9):788-95.

267. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [serial on the Internet]. 2011; (10): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006423.pub2/abstract.

268. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: A network meta-analysis. Diabetes, Obesity and Metabolism. 2012;14(9):810-20.

269. McIntosh B, Cameron C, Singh SR, Yu C, Ahuja T, Welton NJ, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med. 2011;5(1):e35-48.

270. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000 Aug;106(4):473-81.

271. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-74.

272. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [serial on the Internet]. 2008; (2): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006739.pub2/abstract.

273. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991 Jun 26;265(24):3255-64.

274. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998 Sep 12;317(7160):703-13.

275. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med. 2000 Jan 24;160(2):211-20.

276. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001 Jan 4;344(1):3-10.

277. Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, et al. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005 Jul;18(7):935-42.

278. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011 Dec 21;306(23):2579-87.

279. Phung OJ, Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med. 2013 Oct;30(10):1160-71.

280. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: A meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism. 2013;15(10):938-53.

281. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71.

282. U.S. Food and Drug Administration. FDA Drug Safety Communication: Updated Risk Evaluation and Mitigation Strategy (REMS) to Restrict Acces to Rosiglitazone-containing Medicines including Avandia, Avandamet, and Avandaryl. 2013 [cited 2015 February 26]; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm.

283. U.S. Food and Drug Administration. FDA significantly restricts access to the diabetes drug Avandia. 2010 [cited 2015 February 26]; Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm.

284. U.S. Food and Drug Administration. FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. 2013 [cited 2015 February 25]; Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM381108.pdf.

285. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.

286. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: A meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism. 2014;16(1):38-47.

287. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: Systematic review and meta-analysis. BMJ (Online). 2012;344(7850):17.

288. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One. 2013;8(8):e71583.

289. Zhang ZJ, Bi Y, Li S, Zhang Q, Zhao G, Guo Y, et al. Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis. Am J Epidemiol. 2014 Jul 1;180(1):11-4.

290. Ferwana M, Firwana B, Hasan R, Al-Mallah MH, Kim S, Montori VM, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. Diabet Med. 2013 Sep;30(9):1026-32.

291. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.

292. Erdmann E, Song E, Spanheimer R, van Troostenburg de Bruyn AR, Perez A. Observational follow-up of the PROactive study: a 6-year update. Diabetes Obes Metab. 2014 Jan;16(1):63-74.

293. U.S. Food and Drug Administration. Highlights of Prescribing Information: Victoza (liraglutide [rDNA origin] injection, solution for subcutaneous use. 2011 [cited 2015 March 2]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf.

294. U.S. Food and Drug Administration. Highlights of Prescribing Information: Tanzeum (albiglutide) for injection, for subcutaneous use. 2014 [cited 2015 March 2]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125431s000lbl.pdf.

295. U.S. Food and Drug Administration. Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis. 2011 [cited 2015 February 25]; Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm; .

296. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007 Sep 29;370(9593):1129-36.

297. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007 Sep 12;298(10):1189-95.

298. GlaxoSmithKline. Highlights of Prescribing Information: Avandia (rosiglitazone maleate) tablets. 2014 [cited 2015 March 2]; Available from: http://us.gsk.com/products/assets/us_avandia.pdf.

299. Takeda Pharmaceuticals America. Highlights of Prescribing Information: Actos (pioglitazone) tables for oral use. 2013 [cited 2015 March 2]; Available from: http://general.takedapharm.com/content/file/pi.pdf?applicationcode=8a9c4571-a123-4477-91deb9cafe7d07e3&filetypecode=actospi.

300. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR). 2014 [cited 2015 March 2]; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm385287.htm.

301. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010(4):CD002967.

302. Sethi BK, Viswanathan V, Kumar A, Chatterjee S, Chandalia HB. Liraglutide in Clinical Practice: Insights from LEAD Programme. Supplement to JAPI. 2010 June 2010;58:18-22.

303. Franks AS, Lee PH, George CM. Pancreatitis: a potential complication of liraglutide? Ann Pharmacother. 2012 Nov;46(11):1547-53.

304. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med. 2013 Apr 8;173(7):534-9.

305. Li L, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. BMJ. 2014;348:g2366.

306. Chou HC, Chen WW, Hsiao FY. Acute pancreatitis in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors: a population-based nested case-control study. Drug Saf. 2014 Jul;37(7):521-8.

307. Thomsen RW, Pedersen L, Moller N, Kahlert J, Beck-Nielsen H, Sorensen HT. Incretin-Based Therapy and Risk of Acute Pancreatitis: A Nationwide Population-Based Case-Control Study. Diabetes Care. 2015 Jan 29.

308. Wang T, Wang F, Gou Z, Tang H, Li C, Shi L, et al. Using real-world data to evaluate the association of incretin-based therapies with risk of acute pancreatitis: a meta-analysis of 1,324,515 patients from observational studies. Diabetes Obes Metab. 2015 Jan;17(1):32-41.

309. Karagiannis T, Boura P, Tsapas A. Safety of dipeptidyl peptidase 4 inhibitors: A perspective review. Therapeutic Advances in Drug Safety. 2014;5(3):138-46.

310. U.S. Food and Drug Administration. Highlights of Prescribing Information: Byetta (exenatide) Injection. 2014 [cited 2015 March 2]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021773s036lbl.pdf

311. U.S. Food and Drug Administration. Highlights of Prescribing Information: Victoza (liraglutide). 2013 [cited 2015 March 2]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf

312. U.S. Food and Drug Administration. Summary Review: 125469Orig1s000. 2013 [cited 2015 March 2]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000SumR.pdf

313. U.S. Food and Drug Administration. Janumet (sitagliptin/metformin HCl) tablets. 2013 [cited 2015 February 25]; Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm196610.htm.

314. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med. 2012 Jul 9;172(13):1005-11.

315. Silva PS, Cavallerano JD, Sun JK, Aiello LM, Aiello LP. Effect of systemic medications on onset and progression of diabetic retinopathy. Nature Reviews Endocrinology. 2010;6(9):494-507.

316. Singh S, Segal JB. Thiazolidinediones and macular edema. Archives of Internal Medicine. 2012;172(13):1011-3.

317. Kawalec P, Mikrut A, Lopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2014 May;30(4):269-83.

318. United States Renal Data System. 2012 Atlas of CKD & ESRD. 2012 [cited 2015 March 2]; Available from: http://www.usrds.org/atlas12.aspx.

319. Centers for Disease Control and Prevention. Diabetic Retinopathy. 2015 [cited 2015 March 2]; Available from: http://www.cdc.gov/visionhealth/pdf/factsheet.pdf

320. Centers for Disease Control and Prevention. New Diabetes Atlas. 2014 [cited 2015 February 27]; Available from: http://www.cdc.gov/diabetes/data/.

321. The Henry J. Kaiser Family Foundation. Number of Diabetes Deaths per 100,000 Population by Race/Ethnicity. 2015 [cited 2015 February 27]; Available from: http://kff.org/other/state-indicator/diabetes-death-rate-by-raceethnicity/

322. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann Intern Med. 2014 Apr 15;160(8):517-25.

323. Wong HK, Ong KL, Cheung CL, Cheung BM. Utilization of glucose, blood pressure, and lipid lowering medications among people with type II diabetes in the United States, 1999-2010. Ann Epidemiol. 2014 Jul;24(7):516-21 e1.

324. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.

325. Garber A, Abrahamson M, Barzilay J, Blonde L, Bloomgarden Z, Bush M, et al. American association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. Endocrine Practice. 2013;19(SUPPL. 2):1-48.

326. Turner R, Murchison L, Wright AD, Oakley N, Kohner E, Hayes R, et al. 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. Ann Intern Med. 1998 1998;128(3):165-75.

327. 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. 1985 1985 Aug;34(8):793-8.

328. 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. 1995 1995 Jan 14;310(6972):83-8.

329. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.

330. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA. 2008 Apr 2;299(13):1561-73.

331. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004 Nov;27(11):2628-35.

332. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005 May;28(5):1092-100.

333. Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, et al. 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 Jul;8(4):436-47.

334. Zinman B, Hoogwerf BJ, Duran Garcia S, Milton DR, Giaconia JM, Kim DD, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2007 Apr 3;146(7):477-85.

335. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009 Jul 4;374(9683):39-47.

336. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009 Mar;26(3):268-78.

337. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009 Jul;32(7):1224-30.

Abbreviations

ADOPT = A Diabetes Outcome Progression Trial
AHRQ = Agency for Healthcare Research and Quality
BMI = body mass index
CER = comparative effectiveness reviews
CI = confidence interval
CVD = cardiovascular disease
DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors
EHC = Effective Health Care
FDA = Food and Drug Administration
GI = gastrointestinal
GLP-1 agonists = glucagon-like peptide-1 agonists
HbA1c = hemoglobin A1c
HR = hazard ratio
LEAD = Liraglutide Effect and Action in Diabetes
MeSH = medical subject headings
OR = odds ratio
PROactive = PROspective pioglitAzone Clinical Trial In macroVascular Events
RCT = randomized controlled trial
RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes
RR = risk ratio
SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction
SGLT-2 inhibitors = sodium glucose co-transporter 2 inhibitors
SOE = Strength of evidence
TEP = technical expert panel
UKPDS = United Kingdom Prospective Diabetes Study
UTI = urinary tract infection