AHRQ Comparative Effectiveness Review Surveillance Program

CER #27:
Oral Diabetes Medications for Adults with Type 2 Diabetes: An Update

Original release date: March 2011

Surveillance Report: December 2013

Key Findings:

- For Key Question 1, conclusions on comparative effectiveness of oral diabetes agents are considered out of date due to a newly approved drug class and new evidence on previously reviewed drug classes.
- For Key Question 2, conclusions regarding cardiovascular morbidity and mortality are considered out of date due to new data on rosiglitazone.
- For Key Question 3, conclusions regarding other adverse events are possibly out of date.
- For Key Question 4, the conclusion that there is insufficient evidence on this question is probably still valid.

Summary Decision

This CER's priority for updating is **High**

Authors:

Priyanka Desai, MSPH, CPH
Christel Villarivera, MS
Nicolas Stettler, MD, MSCE

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

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

Subject Matter Experts

Wendy Bennett, MD, MPH

Johns Hopkins University

Shari Bolen, MD, MPH

Johns Hopkins University

Silvio Inzucchi, MD

Yale School of Medicine

Helena W. Rodbard, M.D., F.A.C.P., M.A.C.E.

Endocrine and Metabolic Consultants

Lisa Wilson, ScM

Johns Hopkins University

Contents

Oral Diabetes Medications for Adults with Type 2 Diabetes: An Update

1. Introduction

Comparative Effectiveness Review (CER) #27, Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update, was released in March 2011.[1] The CER underwent surveillance in December 2013. At that time, we contacted experts involved in the original CER to gather their expert opinions on whether, based on their knowledge of the recent scientific literature, the conclusions of the 2011 update were still valid and whether the CER needed to be updated again. We also conducted an independent electronic literature search update. Furthermore, we conducted searches of the US Food and Drug Administration (FDA), Health Canada, and UK Medicines and Healthcare Regulatory Agency (MHRA) databases for safety alerts on medications. The drug classes included in this surveillance assessment are listed below.

Drug Class	Mechanism	Example Drugs
Biguanide	Suppresses glucose production by the liver	▪ Metformin
Thiazolidinedione	Activates nuclear receptor that contributes to glucose and insulin metabolism	▪ Rosiglitazone ▪ Pioglitazone
Sulfonylurea	Enhances secretion of insulin	▪ Glyburide ▪ Glibenclamide ▪ Glipizide ▪ Glimepiride
Dipeptidyl peptidase-4 (DPP-4) inhibitor	Inhibits glucagon release, stimulates insulin secretion	▪ Sitagliptin ▪ Saxagliptin
Glucagon-like peptide-1 (GLP-1) agonist	Inhibits glucagon release, stimulates insulin secretion	▪ Exenatide ▪ Liraglutide
Meglitinides	Enhances insulin secretion	▪ Repaglinide ▪ Nateglinide
Sodium-glucose co-transporter-2 (SGLT-2) inhibitors	Increases urinary secretion of glucose	▪ Canagliflozin

2. Methods

2.1 Literature Searches

We used the search strategy employed for the original CER and modified the strategy to include sodium-glucose co-transporter-2 (SGLT-2) inhibitors, the most recent drug classes approved as an oral anti-diabetes agent. We conducted a limited literature search, which included the five major medical journals (Annals of Internal Medicine, Journal of the American Medical Association, British Medical Journal, Lancet, and the New England Journal of Medicine), as well

as these the following specialty journals related to diabetes:: Diabetes Medicine, Diabetes Care, Diabetes, Obesity and Metabolism, and Diabetes Research and Clinical Practice. Our search covered the time period of December 2010 to December 2013; the original CER update searched through December 2010.

2.2 Study selection

We applied the same inclusion and exclusion criteria as the original CER, which required studies to include active comparators. However, at the suggestion of our experts, we did not apply these criteria to studies that discussed a new drug class (e.g., SGLT-2inhibitors) in order to have a broader body of evidence to assess. Studies discussing SGLT-2 inhibitors were included regardless of whether they included an active comparator. We screened the titles and abstracts and obtained full text copies of publications accordingly.

2.3 Expert Opinion

We shared the conclusions of the original report with seven experts in the field, including the original project leaders and four original technical expert panel members, for their assessment of the need to update the report and their recommendations of any relevant new studies. Five subject matter experts responded. Appendix C shows the questionnaire matrix used.

2.4 Check for qualitative and quantitative signals

After abstracting details and findings for each new included study into an evidence table, we assessed whether the new findings provided a "signal" according to the Ottawa Method and used the RAND Method to determine whether these signals suggested the need for an update. The criteria to define a "signal" or need for update are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating

2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

We constructed a summary table that included the key questions, the original conclusions, the findings of the new literature search, expert assessments, and any FDA or MHRA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as probably still valid with or without a need to update based on new evidence.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 211 titles on the use of oral diabetes agents in type 2 diabetes. After title and abstract review, we further reviewed the full text of 71 journal articles on oral diabetes agents. The remaining titles were rejected because they clearly did not meet inclusion criteria for any of the review questions

Of the 71 articles that underwent full text screening, 28 were rejected because they did not meet the inclusion criteria of the original report (e.g., duration less than three months, no active comparator) or examined therapies not available in the US. We did not have resources to apply formal quality ratings to each study; we, however, used our best judgment focusing on variables such as method of randomization, allocation, blinding, and methods of adverse events ascertainment for cohort studies.

The 43 remaining articles were abstracted into an evidence table (Appendix B) for this assessment.[4-46]

3.2 Expert Opinion

Three of the CER authors completed the questionnaire matrix. Their responses are summarized in Table 1 below. In addition, two technical expert panel members provided overall comments on the CER. The experts noted that the availability of a new class of oral diabetes drug indicates that the conclusions in the CER would need to be updated to reflect newly available data. In addition, the experts indicated that additional data may be available on drug classes included in the original CER. One expert felt strongly that the CER was out of date due to new evidence. In summary, the experts felt that the while some of the conclusions on the comparative effectiveness of the oral diabetes agents may still be valid, the CER needs to be updated to reflect the availability of evidence on a new drug class and new drug combinations.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the Scientific Resource Center (SRC) regarding the need for update.

Forty-three studies were abstracted. Forty of these studies were randomized controlled trials (RCTs); the remaining three were retrospective cohort studies. The majority of studies (22) included the use of metformin in combination with another therapy. Three studies discussed the use of the SGLT-2 (canagliflozin), a recently approved class of agents not included in the 2011 update recommendation, in subjects with type 2 diabetes.

Our search of FDA, Health Canada, and MHRA databases identified several warnings related to the safety of some oral diabetes agents. From 2010-2011, both the FDA and MHRA issued

warnings about increased cardiovascular risks associated with rosiglitazone (thiazolidinedione). The FDA thus previously mandated that providers must enroll in the *Avandia-Rosiglitazone Medicines Access Program* to prescribe rosiglitazone. However, as of November 2013, it appears that prescribing and dispensing restrictions will be modified based on new evidence. The FDA, Health Canada, and MHRA have also issued warnings related to the use of pioglitazone. Data suggests that pioglitazone is associated with an increased risk of bladder cancer and that the combination of pioglitazone with insulin may cause cardiac failure. The FDA is also evaluating new evidence regarding increased risk of pancreatitis with GLP-1 analogs or DPP-4 inhibitors.

Overall, the results of our limited literature search support expert opinion that there is new evidence available on oral diabetes agents. Our literature search found several studies that included the use of SGLT-2 inhibitors as well as several studies that discussed the use of combination therapies not currently discussed in the CER. Thus, we have classified this CER as a **high** priority for update.

Table 1: Summary Table

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
Key Question #1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of treatment options for the intermediate outcomes of glycemic control (in terms of HbA1c), weight, or lipids?					
HbA1c	None (new evidence)	New studies include novel combinations of multiple drug classes such as GLP-1 or DPP-4 plus metformin and sulfonylureas, metformin plus thiazolidinedione and DPP-4 inhibitors, or thiazolidinedione and DPP-4 inhibitors.[5-7, 10,11, 27] In addition, a study of SGLT-2 plus metformin suggests that SGLT-2 plus metformin may outperform other combination therapies.[38]	New FDA-Approved Drugs, 2011-2013: Bydureon (exeantide synthetic), Duetact (pioglitazone hydrochloride and glimepiride), Janumet XR (sitagliptin and metformin HCl extended-release), Jentadueto (linagliptin plus metformin hydrochloride), Juvisync (sitagliptin and simvastatin), Invokana (canagliflozin).	Experts noted that additional data on new and existing drug classes is available.	Conclusions should be updated to reflect new evidence.
	Metformin and second-generation sulfonylureas showed similar changes in HbA1c, with a pooled between-group difference of 0.07% (95% CI -0.12% to 0.26%) for studies lasting longer than 3 months but usually less than 1 year in duration. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Combination therapies were better than monotherapy regimens at reducing HbA1c, with an absolute difference of about 1%. In comparisons of metformin versus metformin plus thiazolidinediones, and metformin versus metformin plus sulfonylureas, the combination therapy was favored for HbA1c reduction. (High)	Multiple studies support conclusion that combination therapies, including metformin in combination with another agent, are superior to monotherapy.[4,8,9,12,17-18, 25, 29, 31, 32, 34, 38, 42]	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	When compared with DPP-4 inhibitors, metformin had a greater reduction in HbA1c, with a pooled between-group difference of -0.4% (95% CI -0.5% to -0.2%). (Moderate)	No new studies identified on DPP-4 monotherapy in literature scan.	No issues identified.	Three experts feel that new evidence on DPP4 inhibitors should be evaluated.	Conclusion possibly out of date based on expert opinion.

* Regulatory agency warnings are not listed if they are unrelated to the efficacy of the drug. Data related to adverse events is listed in Key Questions 2 and 3.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	Comparisons of metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone showed similar reductions in HbA1c, with an absolute reduction in HbA1c of around 1% as compared with baseline values, with trials lasting 1 year or less. (Moderate)	No new studies identified on listed comparisons.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin plus DPP-4 inhibitor was favored over metformin alone for HbA1c reduction. (Moderate)	New evidence supports conclusion.[12-13, 17, 18, 34]	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin plus thiazolidinedione had a similar efficacy in reducing HbA1c as the combination of metformin plus sulfonylurea. (Moderate)	No new studies identified on listed comparisons.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of pioglitazone plus sulfonylurea was minimally favored over metformin plus pioglitazone, by an absolute difference of 0.03%. (Low)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin plus a premixed insulin analogue was minimally favored over metformin plus basal insulin, by an absolute difference of 0.30% to 0.43%. (Low)	No new studies identified comparing premixed and basal insulin. Three new studies comparing combinations of metformin and insulin with active comparators.[10,14, 21]	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
Body weight	Metformin maintained or decreased weight to a greater extent than did thiazolidinediones (pooled between-group difference of -2.6 kg, 95% CI -4.1 kg to -1.2 kg), the combination of metformin plus a thiazolidinedione (pooled between-group difference of -2.2 kg, 95% CI -2.6 kg to -1.9 kg), or the combination of metformin plus a sulfonylurea (pooled between-group	One new study support conclusion comparing metformin versus metformin plus thiazolidinediones.[8] One new study supports conclusion that metformin decreased weight to a greater extent that metformin plus sulfonylurea.[42] New studies support conclusion that thiazolidinediones are associated with weight gain and that metformin	No issues identified.	Three experts feel that there is some new relevant evidence on newer agents.	Conclusion probably still valid, but should be updated with new data.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	difference of -2.3 kg, 95% CI -3.3 kg to -1.2 kg). Thiazolidinediones alone or in combination were associated with weight gain. (High)	decreases body weight to a greater extent in comparison. [22, 31,32,39]			
	Metformin maintained or decreased weight to a greater extent than did sulfonylureas, with a pooled between-group difference of -2.7 kg (95% CI -3.5 kg to -1.9 kg). (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Sulfonylureas and the meglitinides had similar effects on body weight. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	GLP-1 agonists decreased weight to a greater extent than did sulfonylureas (pooled between-group difference of -2.5 kg, 95% CI -3.8 kg to -1.1 kg). (Moderate)	One new study supports conclusion.[24]	No issues identified.	Three experts feel that newer GLP-1 agonist studies might change point estimate although direction would still be similar.	Conclusion probably still valid, but should be updated with new data.
	Metformin plus sulfonylurea had a more favorable effect on weight than did either the combinations of a thiazolidinedione plus sulfonylurea (pooled between-group difference of -3.2 kg, 95% CI -5.2 kg to -1.1 kg) or metformin plus a thiazolidinedione (pooled between-group difference of -0.9 kg, 95% CI -1.3 kg to -0.4 kg). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin decreased weight to a greater extent than did DPP-4 inhibitors (pooled between-group difference of -1.4 kg, 95% CI -1.8 kg to -1.0 kg). (Moderate)	No new studies identified comparing metformin monotherapy to DPP-4 inhibitors monotherapy.	No issues identified.	Three experts feel that some newer DPP4 inhibitor studies need to be incorporated.	Conclusion probably still valid, but should be updated with new data.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	Metformin had no significantly different effect on weight than did the combination of metformin plus DPP-4 inhibitors (pooled between-group difference of −0.2 kg, 95% CI −0.7 kg to 0.2 kg). (Moderate)	New studies identified comparing metformin to metformin plus DPP-4 inhibitors indicate reductions in body weight may be similar.[12,17,18]	No issues identified.	Three experts feel that some newer DPP4 inhibitor studies need to be incorporated.	Conclusion probably still valid, but should be updated with new data.
	Metformin plus GLP-1 agonists decreased weight to a greater extent than did several combination therapies (metformin plus sulfonylurea, metformin plus thiazolidinedione, metformin plus basal insulin, or metformin plus DPP-4 inhibitor). (Low)	New studies identified indicate that GLP-1 agonists may reduce body weight when in combination with metformin or other agents.[16,19,22, 24-26, 39, 42]	No issues identified.	Three experts feel that some newer GLP-1 antagonist studies need to be incorporated.	Conclusion probably still valid, but should be updated with new data.
	Metformin plus DPP-4 inhibitors decreased weight to a greater extent than did two standard combinations, metformin plus thiazolidinedione or metformin plus sulfonylurea. (Low)	One new study supports conclusion that metformin plus DPP-4 inhibitors decrease weight to a greater extent than metformin plus sulfonylurea. [20]	No issues identified.	Three experts feel that some newer DPP4 inhibitor studies need to be incorporated.	Conclusion probably still valid, but should be updated with new data.
LDL cholesterol	Metformin decreased LDL to a greater extent than did sulfonylureas, which generally had little effect on LDL, with a pooled between-group difference of −10.1 mg/dL (95% CI −13.3 mg/dL to −7.0 mg/dL). (High)	No new studies identified comparing metformin and sulfonylurea monotherapy. However, new studies identified on comparisons between various combination therapies.	No issues identified.	Three experts feel that the conclusion is still valid	Conclusion probably still valid.
	The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did metformin monotherapy (pooled between-group difference of 14.5 mg/dL, 95% CI 13.3 mg/dL to 15.7 mg/dL),. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin decreased LDL cholesterol to a greater extent than did pioglitazone, which increased LDL cholesterol, with a pooled between-group difference in LDL of −14.2	No new studies identified comparing metformin and pioglitazone monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	mg/dL (95% CI −15.3 mg/dL to −13.1 mg/dL). (Moderate)				
	Metformin decreased LDL cholesterol to a greater extent than did rosiglitazone, with a pooled between-group difference in LDL of −12.8 mg/dL (95% CI −24.0 mg/dL to −1.6 mg/dL). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin decreased LDL to a greater extent than did DPP-4 inhibitors, with a pooled between-group difference of −5.9 mg/dL (95% CI −9.7 mg/dL to −2.0 mg/dL). (Moderate)	No new studies identified comparing metformin and DPP-4 inhibitor monotherapy. However, new study identified on combination DPP-4 and metformin compared to metformin monotherapy.[12]	No issues identified.	Three experts feel that some newer DPP-4 inhibitor studies need to be incorporated.	Conclusion probably still valid, but should be updated with new data.
	The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did a combination of metformin and a second-generation sulfonylurea, with a pooled between-group difference in LDL of 13.5 mg/dL (95% CI 9.1 mg/dL to 17.9 mg/dL). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
HDL cholesterol	Metformin increased HDL to a lesser extent than did pioglitazone, with a pooled between group difference of −3.2 mg/dL (95% CI −4.3 mg/dL to −2.1 mg/dL). (High)	No new studies identified comparing metformin and pioglitazone monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Sulfonylureas were similar to metformin in terms of changes in HDL. (High)	No new studies identified comparing metformin and sulfonylurea monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin and rosiglitazone increased HDL to a greater extent than did metformin monotherapy (pooled between-group difference 2.8 mg/dL, 95% CI 2.2 mg/dL to 3.5 mg/dL). (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Rosiglitazone increased HDL to a lesser extent than did pioglitazone (pooled	No new studies identified.	No issues identified.	Three experts feel that the conclusion	Conclusion probably

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	between-group difference of −2.3 mg/dL, 95% CI −3.5 mg/dL to −1.2 mg/dL). (Moderate)			is still valid.	still valid.
	Rosiglitazone alone was similar to metformin in terms of changes in HDL. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Pioglitazone increased HDL to a greater extent than did sulfonylureas (pooled between-group difference of 4.3 mg/dL, 95% CI 1.9 mg/dL to 6.6 mg/dL). (Moderate)	No new studies identified comparing sulfonylurea monotherapy and pioglitazone monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin and pioglitazone increased HDL by about 5 mg/dL relative to the combination of metformin and a sulfonylurea. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin and rosiglitazone increased HDL to a greater extent than did the combination of metformin and a sulfonylurea (pooled between-group difference 2.7 mg/dL, 95% CI 1.4 mg/dL to 4.1 mg/dL). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin and DPP-4 inhibitors had similar effect on HDL as did metformin monotherapy (pooled between-group difference was 0.5 mg/dL, 95% CI −1.5 mg/dL to 2.5 mg/dL). (Moderate)	Two new studies support conclusion.[12, 18]	No issues identified.	Three experts feel that new evidence should be incorporated.	Conclusion probably still valid, but should be updated with new data.
	The combination of pioglitazone with another medication was favored for the following comparisons: pioglitazone plus metformin versus metformin monotherapy, metformin plus pioglitazone versus metformin plus sulfonylurea, and pioglitazone plus sulfonylurea versus metformin plus sulfonylurea, with a range of between-group differences from 3.1	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	mg/dL to 10.5 mg/dL. (Low)				
Triglycerides	Pioglitazone decreased TG to a greater extent than did metformin (pooled between-group difference −27.2 mg/dL, 95% CI −30.0 mg/dL to −24.4 mg/dL). (High)	No new studies identified comparing metformin and pioglitazone monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin monotherapy decreased TG to a greater extent than did the combination of metformin and rosiglitazone, with a pooled between-group difference in TG of −14.5 mg/dL (95% CI −15.7 mg/dL to −13.3 mg/dL). (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin decreased TG to a greater extent than did rosiglitazone, which increased TG, with a pooled between-group difference of −26.9 mg/dL (95% CI −49.3 mg/dL to −4.5 mg/dL). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin decreased TG to a greater extent than did sulfonylureas (pooled between-group difference −8.6 mg/dL, 95% CI −15.6 mg/dL to −1.6 mg/dL). (Moderate)	No new studies identified comparing metformin and sulfonylurea monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion still valid.
	The combination of metformin plus rosiglitazone and the combination of metformin plus sulfonylurea had similar effects on TG. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin and pioglitazone decreased TG to a greater extent than did the combination of metformin and a sulfonylurea, with between-group differences ranging from −10 mg/dL (p = 0.30) to −24.9 mg/dL (p = 0.045). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Sulfonylureas and meglitinides had similar effects on TG (pooled between-group difference 0.2 mg/dL, 95% CI −3.8 mg/dL to 4.2 mg/dL). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, and neuropathy?					
All-cause mortality	Compared to sulfonylureas, metformin was associated with a slightly lower risk of all-cause mortality in observational studies, but the results were inconsistent between trials and observational studies, and all had a moderate risk of bias. (Low)	One new retrospective cohort study indicates that metformin has less all-cause mortality than sulfonylureas.[30,33]	No issues identified.	Three experts feel that the conclusion should be updated with new supporting data.	Conclusion probably still valid, but should be updated with new data.
	Many RCTs were of short duration (less than 1 year) and had few deaths, limiting the precision of the results. (Low)	Majority of new studies are of short duration.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	No studies addressed several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, comparisons with an insulin preparation, and the majority of combination therapy comparisons. (Insufficient)	No new studies identified.	No issues identified.	Three experts feel that larger studies, not identified in literature scan, have been published that address these questions but did not specify which studies.	Conclusion possibly out of date.
Cardiovascular disease mortality	Metformin was associated with a slightly lower risk of cardiovascular mortality than was a second-generation sulfonylurea, but the results were imprecise and had a moderate risk of bias. (Low)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The risk of cardiovascular mortality was similar between metformin and each of the thiazolidinediones as monotherapy, with high imprecision of results, inconsistencies, and a moderate risk of bias. (Low)	No new studies identified.	Avandia (rosiglitazone)Previous (2010-2011) FDA and MHRA warnings of cardiovascular risks (elevated risk of heart attack) modified. Providers are no longer required to enroll in *Avandia-Rosiglitazone Medicines Access Program* to prescribe (November 2013).	Three experts feel that the conclusion is less clinically relevant since thiazolidinediones are not used as frequently.	Conclusion probably still valid, but should be updated with new data.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	Metformin alone was slightly favored over a combination of metformin and rosiglitazone in terms of lower risk of fatal myocardial infarction, with consistent direction of the results but high imprecision. (Low)	No new studies identified.	Avandia (rosiglitazone)- Previous (2010-2011) FDA and MHRA warnings of cardiovascular risks (elevated risk of heart attack) modified. Providers are no longer required to enroll in *Avandia-Rosiglitazone Medicines Access Program* to prescribe (November 2013).	Three experts feel that the conclusion is still valid.	Conclusion probably still valid, but should be updated with new data.
	No studies addressed several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons. (Insufficient)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
Cardiovascular and cerebrovascular morbidity (nonfatal myocardial infarction and stroke)	A comparison of the risk of cardiovascular morbidity between metformin and thiazolidinedione as monotherapy was inconclusive, with high imprecision and inconsistency in the direction of the findings. (Low)	No new studies identified.	Avandia (rosiglitazone)- Previous (2010-2011) FDA and MHRA warnings of cardiovascular risks (elevated risk of heart attack) modified. Providers are no longer required to enroll in *Avandia-Rosiglitazone Medicines Access Program* to prescribe (November 2013).	Three experts feel that the conclusion is less clinically relevant since thiazolidinediones are not used as frequently.	Conclusion probably still valid, but should be updated with new data.
	Metformin alone was slightly favored over a combination of metformin and rosiglitazone in terms of a lower risk of non-fatal ischemic heart disease, with a consistent direction of the results but high imprecision and a failure to reach statistical significance. The pooled odds ratio (OR) for combined fatal and non-fatal ischemic heart	No new studies identified.	Avandia (rosiglitazone)- Previous (2010-2011) FDA and MHRA warnings of cardiovascular risks (elevated risk of heart attack) modified. Providers are no longer required to enroll in *Avandia-Rosiglitazone Medicines Access*	Three experts feel that the conclusion is still valid.	Conclusion probably still valid, but should be updated with new data.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	disease events was 0.43, 95% CI 0.17 to 1.10. The range of rates for non-fatal ischemic heart disease for the comparison group, metformin, ranged from 0 to 2.9%. (Low)		*Program* to prescribe (November 2013).		
	No studies addressed several comparisons, including most DPP-4 inhibitors and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons. (Insufficient)	No new studies identified.	Pioglitazone and insulin-MHRA warning of cases of cardiac failure when pioglitazone is used in with insulin, especially in patients with cardiac risk factors (2011).	Three experts feel that larger studies on newer agents are available. The studies were not specified.	Conclusion is possibly out of date.
Microvascular outcomes (retinopathy, nephropathy, neuropathy)	Pioglitazone was more effective than metformin in reducing the urinary albumin-to-creatinine ratio (15% and 19% decrease in 2 trials), likely indicating less nephropathy. (Moderate)	No new studies identified.	No issues identified.	Experts do not know if conclusion is still valid.	Conclusion probably still valid.
	Three comparisons were included for the outcome of neuropathy, but studies were at high risk for bias, with low sample sizes and poorly defined outcomes. (Low)	No new studies identified.	No issues identified.	Experts do not know if conclusion is still valid	Conclusion probably still valid.
	No studies addressed the outcome of retinopathy. (Insufficient)	No new studies identified.	No issues identified.	Experts do not know if conclusion is still valid.	Conclusion probably still valid.
Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the treatment options in terms of the adverse events and side effects?					
Hypoglycemia	The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with metformin, with a pooled OR of 4.6 (95% CI 3.2 to 6.5). The range of rates for mild to moderate hypoglycemia in the metformin group was 0 to 17.7%, with a median rate of 0%. (High)	No new studies identified comparing metformin and sulfonylurea monotherapy.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with thiazolidinediones, with a pooled OR of 3.9 (95% CI 3.0 to 4.9). The range of rates for mild to moderate hypoglycemia in the thiazolidinedione group was 0 to 92.1%, with a median rate of 4.4%. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The risk of hypoglycemia with metformin plus sulfonylurea exceeds the risk of metformin plus thiazolidinediones, with a pooled OR of 5.8 (95% CI 4.3 to 7.7). The range of rates for mild to moderate hypoglycemia in the metformin plus thiazolidinediones group ranged from 0 to 9.3%, with a median rate of 1.3%. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The risk of hypoglycemia with sulfonylurea exceeds the risk with DPP-4 inhibitors (20 events versus none in a single study). (Moderate)	Two new studies supports conclusion.[15,43]	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid, but should be updated with new data.
	The risk of hypoglycemia was similar between metformin and thiazolidinediones. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The risk of hypoglycemia with metformin plus sulfonylurea exceeded the risk with metformin alone, with an OR range of 0.6 to 9.3. (Moderate)	One new study supports conclusion.[42]	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid, but should be updated with new data.
	The risk of hypoglycemia was modestly higher for meglitinides than for metformin, with an OR of 3.0 (95% CI 1.8 to 5.2). The range of rates for mild to moderate hypoglycemia in the metformin group ranged	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	from 0 to 24%, with a median rate of 3.7%. (Moderate)				
	The risk of hypoglycemia was higher for metformin plus a thiazolidinedione than for metformin alone, with an OR of 1.6 (95% CI 1.0 to 2.4). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 9.1%, with a median rate of 1.4%. (Moderate)	One new study supports conclusion.[8]	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid, but should be updated with new data.
	The combination of metformin and DPP-4 inhibitor had similar risk of hypoglycemia as that of metformin alone. (Moderate)	Multiple new studies support conclusions.[12, 17,18, 34]	No issues identified.	Three experts feel that the conclusion is probably still valid, but new evidence should be added.	Conclusion probably still valid, but should be updated with new data.
	The combination of metformin with a sulfonylurea had a higher risk of hypoglycemia than metformin with GLP-1 agonist. (Moderate)	Two new studies support conclusion.16,42	No issues identified.	Three experts feel that the conclusion is probably still valid, but new evidence should be added.	Conclusion probably still valid, but should be updated with new data.
	Metformin combined with basal insulin had a modestly lower risk of hypoglycemia when compared to metformin combined with premixed insulin, with the RR ranging from 0.34 to 0.94 in 5 trials. (Moderate)	No new studies identified comparing premixed and basal insulin.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
Gastrointestinal (GI) side effects	Metformin was associated with twice as many GI adverse events, most commonly diarrhea, nausea, and vomiting, as were thiazolidinediones. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The rates of GI adverse effects were similar for thiazolidinediones and sulfonylureas. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin was associated with more frequent GI adverse events than were DPP-4 inhibitors.	No new studies identified.	No issues identified.	Three experts feel that the conclusion	Conclusion probably

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	(Moderate)			is probably still valid, but new evidence (not identified in literature scan) should be added. The studies were not specified.	still valid, but should be updated with new data.
	Metformin was associated with twice as many GI adverse event rates as were second-generation sulfonylureas. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	Metformin monotherapy was associated with more frequent GI adverse events than were either the combination of metformin plus a sulfonylurea or metformin plus a thiazolidinedione, if the metformin component was of a lower dose than in the metformin monotherapy arm. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The combination of metformin and sulfonylurea was associated with slightly more frequent GI adverse events than were seen with a combination of a thiazolidinedione and a sulfonylurea. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
Congestive heart failure	The risk of CHF was higher for thiazolidinediones than for sulfonylureas (OR 1.68, 95% CI 0.99 to 2.85). (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	No long-term trials assessed the comparative effects of the DPP-4 inhibitors and GLP-1 agonists on the risk of heart failure. (Insufficient)	No new studies identified.	No issues identified.	Three experts feel that more data is available. The studies were not specified.	Conclusion probably still valid, but should be updated with new data..

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
Cholecystitis and pancreatitis	Two comparisons were included for the outcome of cholecystitis, and one comparison was included for the outcome of pancreatitis, with unclear conclusions. (Low)	No new studies identified.	Incretin mimetic drugs (GLP-1 analogs, DPP-4 inhibitors)-FDA evaluating unpublished findings by a that suggest an increased risk of pancreatitis in type 2 diabetes patients treated with incretin mimetics (2013) . DPP-4 inhibitors-MHRA warning on risk of acute pancreatitis. Victoza (liraglutide)-FDA warning on risk of acute pancreatitis (2011).	Three experts feel that more data is available. The studies were not specified.	Conclusion probably out of date.
Lactic acidosis	The risk of lactic acidosis was similar for metformin and sulfonylurea alone and for the two in combination. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion still valid.
Macula edema	Only one trial reported on macular edema. The evidence was insufficient for all comparisons. (Insufficient)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
Cancer	Few studies addressed the outcome of cancer. (Insufficient)	One retrospective cohort study found that metformin users were at a lower risk for cancer mortality.[33] One retrospective cohort study found that metformin was associated with a lower risk of cancer than sulfonylureas. [40]	Incretin mimetic drugs (GLP-1 analogs, DPP-4 inhibitors)-FDA evaluating unpublished findings by a that suggest pre-cancerous cellular changes in type 2 diabetes patients treated with incretin mimetics (2013) . Actos (pioglitazone)-FDA label warning on increased risk of bladder cancer (2011) and Health Canada and MHRA warning on increased risk of bladder cancer (2012). Victoza (liraglutide)-FDA warning on risk of thyroid C-cell tumors (2011).	Three experts feel that more studies may be available.	Conclusion probably out of date.
Liver injury	The risk of liver injury was similar for thiazolidinediones and sulfonylureas. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The rates of liver injury were similar between thiazolidinediones and metformin. (Moderate)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
Fractures	The risk of fracture was higher for thiazolidinediones than for metformin. In one large RCT the RR was 1.57 (95% CI 1.13 to 2.17) and women in the thiazolidinedione arm had a higher fracture risk than men. The fracture rate was 4.1% in the reference (metformin) arm. (High)	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.
	The risk of fracture was higher for combination therapy with a thiazolidinedione than for metformin plus sulfonylurea, with higher risk in women than in men. In one large RCT, the RR was 1.57 (95% CI 1.26 to 1.97) for the rosiglitazone combination	No new studies identified.	No issues identified.	Three experts feel that the conclusion is still valid.	Conclusion probably still valid.

Conclusions From CER Executive Summary		SRC Literature Search	FDA / Health Canada / MHRA (UK)*	Expert Opinion EPC Investigator, Other Experts	Conclusion from SRC
	therapy arm, as compared to the combination of metformin plus sulfonylurea arms. The fracture rate in the reference (metformin + sulfonylurea) arm was 1.6%. (High)				
Key Question 4: Do the safety and effectiveness of these treatment options (see list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular, and cerebrovascular outcomes?					
	No conclusions.	No new studies identified.	No issues identified.		Conclusion probably still valid.

References

1. Bennett WL, Wilson LM, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. http://www.effectivehealthcare.ahrq.gov/ehc/products/155/644/type-2-diabetes-medications-report-130911.pdf

2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.

3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. PMID 17638714.

4. Forst T, Uhlig-Laske B, Ring A, 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;27(12):1409-19.

5. Liutkus J, Rosas Guzman J, Norwood P, et al. A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin. Diabetes Obes Metab. 2010;12(12):1058-65.

6. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med. 2011;28(11):1352-61.

7. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab. 2011;13(12):1088-96.

8. Borges JL, Bilezikian JP, Jones-Leone AR, 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-naïve type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011;13(11):1036-46.

9. Kaku K, Itayasu T, Hiroi S, Hirayama M, Seino Y. Efficacy and safety of alogliptin added to

pioglitazone 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. 2011;13(11):1028-35.

10. Bell DS, Dharmalingam M, Kumar S, Sawakhande RB. Triple oral fixed-dose diabetes polypill versus insulin plus metformin efficacy demonstration study in the treatment of advanced type 2 diabetes (TrIED study-II). Diabetes Obes Metab. 2011;13(9):800-5.

11. Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011;13(7):653-61.

12. Reasner C, Olansky L, Seck TL, 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;13(7):644-52.

13. Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011;13(6):567-76.

14. Hollander P, Raslova K, Skjøth TV, Råstam J, Liutkus JF. Efficacy and safety of insulin detemir once daily in combination with sitagliptin and metformin: the TRANSITION randomized controlled trial. Diabetes Obes Metab. 2011;13(3):268-75.

15. Arechavaleta R, Seck T, Chen Y, 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;13(2):160-8.

16. Yang W, Chen L, Ji Q, 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;13(1):81-8.

17. Taskinen MR, Rosenstock J, Tamminen I, 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;13(1):65-74.

18. 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;94(2):217-24.

19. Petrica L, Vlad A, Petrica M, et al. Pioglitazone delays proximal tubule

dysfunction and improves cerebral vessel endothelial dysfunction in normoalbuminuric people with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2011;94(1):22-32.

20. Seck TL, Engel SS, Williams-Herman DE, et al. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide. Diabetes Res Clin Pract. 2011;93(1):e15-7.

21. Gallwitz B, Böhmer M, Segiet T, 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;34(3):604-6.

22. Best JH, Rubin RR, Peyrot M, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. Diabetes Care. 2011;34(2):314-9.

23. Gram J, Henriksen JE, Grodum E, et al. Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study. Diabetes Care. 2011;34(1):27-33.

24. Garber A, Henry RR, Ratner R, et al. 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;13(4):348-56.

25. Forst T, Michelson G, Ratter F, 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;29(9):1115-8.

26. Derosa G, Franzetti IG, Querci F, et al. Exenatide plus metformin compared with metformin alone on β-cell function in patients with Type 2 diabetes. Diabet Med. 2012;29(12):1515-23.

27. Violante R, Oliveira JH, Yoon KH, et al. A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin. Diabet Med. 2012;29(11):e417-24.

28. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012;14(6):565-74.

29. Seino Y, Miyata Y, Hiroi S, et al. 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;14(10):927-36.

30. Pantalone KM, Kattan MW, Yu C, 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;14(9):803-9.

31. Yoon KH, Steinberg H, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and pioglitazone in patients with type 2 diabetes: a 54-week study. Diabetes Obes Metab. 2012;14(8):745-52.

32. Wainstein J, Katz L, Engel SS, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. Diabetes Obes Metab. 2012;14(5):409-18.

33. Bo S, Ciccone G, Rosato R, et al. Cancer mortality reduction and metformin: a retrospective cohort study in type 2 diabetic patients. Diabetes Obes Metab. 2012;14(1):23-9.

34. Derosa G, Carbone A, Franzetti I, et al. Effects of a combination of sitagliptin plus metformin vs metformin monotherapy on glycemic control, β-cell function and insulin resistance in type 2 diabetic patients. Diabetes Res Clin Pract. 2012;98(1):51-60.

35. Gallwitz B, Rosenstock J, Rauch T, 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;380(9840):475-83.

36. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2012;157(9):601-10.

37. Pratley RE, Nauck MA, Bailey T, et al. Efficacy and safety of switching from the DPP-4 inhibitor sitagliptin to the human GLP-1 analog liraglutide after 52 weeks in metformin-treated patients with type 2 diabetes: a randomized, open-label trial. Diabetes Care. 2012;35(10):1986-93.

38. Rosenstock J, Aggarwal N, Polidori D,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;35(6):1232-8.

39. Russell-Jones D, Cuddihy RM, Hanefeld 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;35(2):252-8.

40. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. Diabetes Care. 2012;35(1):119-24.

41. Takihata M, Nakamura A, Tajima K, et al. Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial. Diabetes Obes Metab. 2013;15(5):455-62.

42. Nauck M, Frid A, Hermansen K, et al. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. Diabetes Obes Metab. 2013;15(3):204-12.

43. Rathmann W, Kostev K, Gruenberger JB, et al. Treatment persistence, hypoglycaemia and clinical outcomes in type 2 diabetes patients with dipeptidyl peptidase-4 inhibitors and sulphonylureas: a primary care database analysis. Diabetes Obes Metab. 2013;15(1):55-61.

44. Cefalu WT, Leiter LA, Yoon KH, 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;382(9896):941-50.

45. Yale JF, Bakris G, Cariou B, Yue D, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15(5):463-73.

46. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15(4):372-82.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 12/01/2010-12/31/2013

LANGUAGE:
English

SEARCH STRATEGY:

(((((("diabetes mellitus, type 2"[majr] OR (diabet*[tiab] AND ("non-insulin dependent"[tiab] OR type-2[tiab] OR "type II"[tiab] OR "type 2"[tiab]))) AND ("thiazolidinediones"[majr] OR "glipizide"[mh] OR "glyburide"[majr] OR "metformin"[majr] OR "acarbose"[majr] OR thiazolidinedione*[tiab] OR pioglitazone[tiab] OR rosiglitazone[tiab] OR sulfonylurea*[tiab] OR sulphonylurea*[tiab] OR glipizide[tiab] OR glyburide[tiab] OR glimepiride[tiab] OR glibenclamide[tiab] OR biguanide*[tiab] OR metformin[tiab] OR "insulin secretagogues"[tiab] OR meglitinide*[tiab] OR repaglinide[tiab] OR nateglinide[tiab] OR "alpha-glucosidase inhibitors"[tiab] OR "alpha-glucosidase inhibitor"[tiab] OR acarbose[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[mh] OR sitagliptin*[tiab] OR saxagliptin*[tiab] OR dpp-4[tiab] OR dpp-iv[tiab] OR bromocriptine[majr] OR bromocriptine[tiab] OR colesevelam[tiab] OR "Glucagon-Like Peptide 1"[majr] OR liraglutide[tiab] OR exenatide[tiab] OR "Sodium-Glucose Transport Proteins"[majr] OR "sglt2" OR "sglt1"[tiab] OR "sodium-glucose cotransporter-2"[tiab] OR "sodium-glucose cotransporter-1"[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT (letter[pt] OR comment[pt] OR editorial[pt]))) AND ("Ann Intern Med"[Journal] OR BMJ[Journal] OR JAMA[Journal] OR Lancet[Journal] OR "N Engl J Med"[Journal] OR "Diabet Med"[Journal] OR "Diabetes Care"[Journal] OR "Diabetes Obes Metab"[Journal] OR "Diabetes Res Clin Pract"[Journal]) AND (("2010/12/01"[PDat] : "2013/12/31"[PDat]) AND Humans[Mesh]))) AND ("controlled clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "comparative study"[Publication Type] OR "case control studies"[MeSH Terms] OR "cohort studies"[MeSH Terms])

NUMBER OF RESULTS: 211

Appendix B. Evidence Table

Author, Year	Intervention	Comparator(s)	Study Design	N, Population	Duration	Primary Outcome(s)	Findings
Forst, 2010[4]	Metformin with linagliptin (1, 5 or 10 mg once daily)	Metformin with placebo, Metformin with glimepiride (1–3 mg once daily)	RCT	333 patients with type 2 diabetes with inadequate glycemic control treated with metformin (alone or in combination)	12 weeks	Change from baseline HbA1c	Average placebo-corrected lowering in HbA1c levels of 0.40% (+/- 0.14); 4.4 mmol/mol (+/- 1.5) for 1 mg linagliptin, 0.73% (+/- 0.14); 8.0 mmol/mol (+/- 1.5) for 5 mg, and 0.67% (+/- 0.14); 7.3 mmol/mol (1.5) for 10 mg. Differences between linagliptin and placebo were statistically significant. (1 mg, P < 0.01; 5 mg and 10 mg, P < 0.0001). No hypoglycemic events for linagliptin or placebo. Three patients (5%) receiving glimepiride experienced hypoglycemia.
Liutkus, 2010[5]	Exenatide with thiazolidinedione and metformin	Placebo with thiazolidinedione and metformin	RCT	165 subject suboptimally controlled with thiazolidinediones with (157) or without (8) metformin	26 weeks	Change from baseline HbA1c	Exenatide reduced HbA1c more than placebo [−0.84% (s.e. 0.20) vs. −0.10% (0.23), treatment difference −0.74% (0.16), p < 0.001)]. Approximately 71% of subjects had reduction in HbA1c and body weight with exenatide compared to 54% with placebo. Adverse events (exenatide vs. placebo) were nausea (12% vs. 2%, p = 0.037), vomiting (8% vs. 0%, p = 0.031) and headache (4% vs. 4%). Incidence of hypoglycemia was not significantly different between groups.
Owens, 2011[6]	Linagliptin (5 mg once daily) with metformin and sulphonylurea	Placebo with metformin and sulphonylurea	RCT	1058 patients with type 2 diabetes being treated with metformin and sulphonylureas	24 weeks	Change from baseline HbA1c	Linagliptin placebo-corrected HbA1c adjusted mean change from baseline was -7 mmol/mol (-0.62%) [95% CI -8 to -6 mmol/mol; P < 0.0001]. More participants with baseline HbA1c >= 7.0% achieved an HbA1c <7.0% with linagliptin compared with placebo (29.2% vs. 8.1%, P < 0.0001). No significant weight changes. Mean values of triglyceride were above the normal reference range at baseline (236 mg/dl placebo; 234 mg/dl linagliptin) and at last value on treatment with respect to baseline only in the placebo group (mean change from baseline)12 mg/dl). The mean changes from baseline to the last value on treatment for total cholesterol, HDL cholesterol and LDL cholesterol were similar in both treatment groups. Symptomatic hypoglycemia occurred in 16.7 and 10.3% of the linagliptin and placebo groups, respectively.
Bosi, 2011[7]	Metformin (>= 1500 mg or maximum tolerated dose and pioglitazone (30 mg) with alogliptin (25 mg)	Metformin (>= 1500 mg or maximum tolerated dose and pioglitazone (30 mg) with pioglitazone (15 mg)	RCT	969 patients with type 2 diabetes with an HbA1c >= 7.0	52 weeks	Change from baseline HbA1c at 26 and 52 weeks	Intervention arm showed superior glycemic control versus comparator at week 52 [least squares (LS) mean change from baseline in HbA1c, −0.70 vs. −0.29%; p < 0.001]. At week 52, intervention resulted in greater change from baseline in HbA1c regardless of baseline HbA1c (p < 0.001). Two severe events of hypoglycemia in intervention arm.

Borges, 2011[8]	Avandamet® (rosiglitazone/ metformin)	Metformin	RCT	688 drug naïve patients with type 2 diabetes	18 months	Change in baseline HbA1c	Avandamet was better than metformin in achieving statistically significant reductions in HbA1c ($p < 0.0001$) and fasting plasma glucose ($p < 0.001$). A week 80 decrease of 3.37 kg in the metformin group and an increase of 1.42 kg in the Avandamet group were observed. HDL cholesterol increased and triglycerides decreased from baseline to week 80 in both groups with no significant differences. Total cholesterol and LDL cholesterol decreased from baseline to week 80 in the metformin group. Increase in total cholesterol in the Avandamet group with little change in LDL cholesterol. The treatment differences for the change in total cholesterol ($p = 0.0006$) and LDL cholesterol ($p = 0.0056$) to week 80 were statistically significantly different with Avandamet compared to metformin.
Kaku, 2011[9]	Alogliptin (12.5 or 25 mg once daily) added to pioglitazone (15 or 30 mg/day)	Piogliatzone (15 or 30 mg/day) with placebo	RCT	339 type 2 diabetes patients with inadequate glycaemic control	12 weeks	Change in HbA1c from baseline to week 12	Change from baseline in HbA1c at 12 weeks was significantly greater with alogliptin 12.5 mg added to pioglitazone and alogliptin 25 mg added to pioglitazone than with placebo added to pioglitazone (−0.91 and −0.97% vs. −0.19%; $p < 0.0001$). Change in LDL-cholesterol (mg/dl): pioglitazone, 0.1 (20.4); alogliptin 12.5 mg, −2.5 (18.1); alogliptin 25 mg −4.0 (18.4) Change in HDL-cholesterol(mg/dl) : −0.8 (9.6); −1.4 (8.0); −2.4 (8.2) Change in triglycerides (mg/dl): 7.6 (79.3); −7.8 (54.9); −6.8 (56.8).
Bell, 2011[10]	Polypill containing 1 or 2 mg glimepiride, 500 mg sustained-release metformin, and 15 mg pioglitazone, once daily	Insulin 70/30 mix and 500 mg sustained-release metformin, twice daily	RCT	101 insulin-naïve subjects with inadequately controlled type 2 diabetes	12 weeks	Change in HbA1c	Lower HbA1c with polypill (−1.33% vs. −0.83%; $p = 0.059$). A greater number of subjects achieved a decrease in HbA1c of greater than 1.0% for the polypill (72.5% vs. 22%; $p = 0.0001$). Both options equally and significantly reduced fasting and postprandial glucose levels ($p = 0.05$). Weight gain was greater with the insulin and metformin (2.69 vs. 0.92 kg; $p = 0.223$). Polypill mean change in LDL -9.41, triglycerides -42.04, and HDL +2.15. Insulin/metformin mean change in LDL -17.35, triglycerides -26.40, and HDL +6.52.

Gomis, 2011[11]	Linagliptin (5 mg) and pioglitazone (30 mg)	Pioglitazone (30 mg) and placebo	RCT	389 individuals with uncontrolled diabetes (HbA1c 7.5-11%)	24 weeks	Change in HbA1c	Adjusted mean change in HbA1c with the initial combination of linagliptin/pioglitazone was −1.06% (±0.06), and −0.56% (±0.09) for placebo/pioglitazone. The difference in adjusted mean HbA1c in the linagliptin group compared with placebo was −0.51% (95% CI −0.71, −0.30; p < 0.0001). Mild hypoglycemic episodes occurred only in 1.2% of the linagliptin/ pioglitazone patients. Mean values for total cholesterol, HDL cholesterol and LDL cholesterol were within the normal reference range at baseline and end of treatment. Mean triglycerides above the normal reference range was seen for linagliptin plus pioglitazone at baseline (228 mg/dl), and for placebo plus pioglitazone at baseline (236 mg/dl) and end of treatment (219 mg/dl). However, mean values decreased with respect to baseline in both groups (−35 mg/dl linagliptin plus pioglitazone;−18 mg/dl placebo plus pioglitazone). No clinically significant changes in renal function.
Reasner, 2011[12]	Sitagliptin and metformin 50/500 mg	Metformin 500 mg	RCT	1250 drug-naïve, type 2 diabetes patients	18 weeks	Mean HbA1c reductions from baseline	Mean change from baseline HbA1c was −2.4% for sitagliptin/metformin and −1.8% for metformin alone (p < 0.001). More patients treated with sitagliptin/metformin had an HbA1c value <7% (p < 0.001) versus metformin alone. Baseline body weight was reduced by 1.6 kg in each group. Both treatments were generally well tolerated with a low and similar incidence of hypoglycemia. Abdominal pain (1.1 and 3.9%; p = 0.002) and diarrhea (12.0 and 16.6%; p = 0.021) occurred significantly less with sitagliptin/metformin versus metformin alone. The sitagliptin/metformin and metformin monotherapy groups showed small improvements from baseline in total cholesterol (TC) [−4.2% (95% CI: −5.7, −2.8) vs. −3.8% (95% CI: −5.2, −2.3), respectively], HDL-C [4.8% (95% CI: 3.3, 6.3) vs. 5.8% (95% CI: 4.3, 7.3), respectively], TG [−8.4% (95% CI: −12.4, −4.4) vs. −2.1% (95% CI: −6.3, 2.1), respectively] and non-HDL-C [−5.6% (95% CI: −7.6, −3.7) vs. −5.4% (95% CI: −7.3, −3.4), respectively]. Small decreases in low-density lipoprotein cholesterol (LDL-C) observed for both treatment groups [−1.3% (95% CI: −3.8, 1.2) vs. −4.2% (95% CI: −6.8, −1.7)]. The mean percent changes from baseline in LDL-C, TC, HDL-C, TG and non- HDL-C were similar between the two groups, with the exception of a significantly greater between-group reduction in TG seen with sitagliptin/metformin compared with metformin monotherapy (p = 0.049).
Pfutzner, 2011[13]	Saxagliptin 5 mg + 500 mg metformin, saxagliptin 10 mg + 500 mg metformin	Saxagliptin 10 mg + placebo or 500 mg metformin + placebo	RCT	1306 treatment-naïve type 2 diabetes patients	76 weeks	Change in HbA1c	Adjusted mean change from baseline HbA1c (95% CI) for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin were −2.31 (−2.44, −2.18), −2.33 (−2.46, −2.20), −1.55 (−1.70, −1.40) and −1.79% (−1.93, −1.65), respectively (post hoc and nominal p < 0.0001 vs. metformin and saxagliptin monotherapies for saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin). Adverse event rates were similar; hypoglycemic events occurred at a low frequency.

Hollander, 2011[14]	Insulin determir, sitagliptin, and metformin (IDet + SITA + MET)	Sitagliptin, metformin, and sulphonylurea (SITA + MET ± SU)	RCT (open-label)	217 insulin naïve subjects	26 weeks	Change in HbA1c, BMI	HbA1c decreased by 1.44% in the IDet + SITA + MET group versus 0.89% in SITA + MET ± SU, $p < 0.001$. 45% of the subjects in the IDet + SITA + MET arm achieved HbA1c ≤7% compared with 24% in the SITA + MET ± SU arm, [adjusted OR 3.2, 95% CI (1.65 to 6.19), $p = 0.001$]. Small decreases in weight and BMI were observed in both arms, with no significant differences. There was no significant difference between treatments in the rate of minor hypoglycemia (rate ratio IDet + SITA + MET : SITA + MET ± SU 0.97, 95% CI (0.35 to 2.74), $p = 0.96$) or overall hypoglycemia (rate ratio 0.98, 95% CI (0.48 to 2.02), $p = 0.96$).
Arechavaleta, 2011[15]	Sitagliptin	Glimepiride	RCT	1035 subjects with an A1c of 6.5-9% while on a stable does of metformin	30 weeks	Change in HbA1c	The least squares (LS) mean change in HbA1c from baseline was −0.47% with sitagliptin and −0.54% with glimepiride, with a between-group difference (95% CI) of 0.07% (−0.03, 0.16). Hypoglycemia was reported at 7% in the sitagliptin group and 22% in the glimepiride group ($p < 0.001$). Relative to baseline, sitagliptin was associated with a mean weight loss (−0.8 kg), and glimepiride was associated with a mean weight gain (1.2 kg), ($p < 0.001$). The LS mean percent change from baseline (95% CI) for HDL-C was 4.4% (1.8, 7.0) in the sitagliptin group and 0.9% (−1.7, 3.5) in the glimepiride group, resulting in a between group difference of 3.5% (0.6, 6.5) favoring sitagliptin. The median percent change from baseline (95% CI) in TG was −5.3% (−9.0, −1.6) in the sitagliptin group and 2.1% (−1.7, 5.9) in the glimepiride group, resulting in a between-group difference of −6.1% (−10.4, −1.7), also favouring sitagliptin. No meaningful between-group differences in total cholesterol [−0.8% (−2.9, 1.3)], LDL-C [2.3% (−1.9, 6.5)] or non-HDL-C [−1.2% (−4.3, 1.8)].
Yang, 2011[16]	Liraglutide, metformin	Glimepiride, metformin	RCT	929 subjects with type 2 diabetes	16 weeks	Change in HbA1c	Treatment with liraglutide 1.2 and 1.8 mg resulted in mean HbA1c reduction of 1.36% points and 1.45% points, respectively. While glimepiride resulted in reduction of 1.39% points. No significant difference was shown in the percentage of subjects reaching a HbA1c <7% or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride. Liraglutide was associated with a 1.8–2.4 kg mean weight reduction; glimepiride was associated with a 0.1 kg mean weight gain. Two subjects in the glimepiride group reported major hypoglycemia, none reported in the liraglutide groups. Liraglutide was associated with about 10-fold lower incidence of minor hypoglycemia than glimepiride. Gastrointestinal disorders were the most common adverse events (AEs) for liraglutide, but were transient.
Taskinen, 2011[17]	Linagliptin add-on to metformin	Metformin with placebo	RCT	701 subjects with type 2 diabetes and inadequate glycemic control	24 weeks	Change in HbA1c	Linagliptin showed significant reductions vs. placebo in adjusted mean changes from baseline of HbA1c (−0.49 vs. 0.15%), FPG (−0.59 vs. 0.58 mmol/l), $p < 0.0001$. Hypoglycemia occurred in three patients (0.6%) treated with linagliptin and five patients (2.8%) in the placebo group. Body weight did not change significantly in both groups (−0.5 kg placebo, −0.4 kg linagliptin).

Yang, 2011[18]	Saxagliptin (5 mg) added to metformin	Metformin with placebo	RCT	570 Asian patients with type diabetes on stable metformin >= 1500 mg/day	24 weeks	Change in HbA1c	Saxagliptin plus metformin provided significant adjusted mean decreases versus metformin alone (p<= 0.0052) in HbA1c (0.78% versus 0.37%). More saxagliptin-treated patients achieved a HbA1c < 7.0% (46.5% versus 30.5%; p = 0.0001). The proportion of patients experiencing adverse events (e.g., diarrhea, UTI, hyperlipidemia, excluding hypoglycemia) was similar for saxagliptin plus metformin (42.8%) versus metformin alone (40.8%). Hypoglycemic events were reported in 1.4% of patients in each group. Reductions in body weight/BMI were similar. No clinically meaningful changes in lipid profiles were observed between the treatment groups.
Petricia, 2011[19]	Pioglitazone with metformin	Glimepiride(sulfonylureas) with metformin	RCT	68 normoalbuminuric type 2 diabetes patients	1 year	Renal and cerebral protective effects	Differences between groups regarding ADMA, urinary beta2-microglobulin, urinary alpha1-microglobulin, parameters of inflammation, serum creatinine, GFR, UACR, the cerebral hemodynamic indices. Significant correlations were between alpha 1-microglobulin-UACR (R2 = 0.143; P = 0.001) and GFR (R2 = 0.081; P = 0.01); beta2-microglobulin-UACR (R2 = 0.241; P = 0.0001) and GFR (R2 = 0.064; P = 0.036); ADMA–GFR (R2 = 0.338; P = 0.0001), parameters of inflammation, HbA1c, duration of DM, cerebral indices.
Seck, 2011[20]	Sitagliptin added to metformin	Glipizide added to metformin	RCT (post hoc analysis of data)	1,172 subjects with inadequate glycemic control on metformin monotherapy	52 weeks	Change in HbA1c and body weight	Both treatment arms provided similar degrees of glycemic efficacy in subjects at 1 year; however, significantly more patients in the sitagliptin group achieved an A1C reduction of >0.5% without hypoglycemia and without an increase in body weight.
Galliwitz, 2011[21]	Exenatide added to metformin	Premixed insulin 70/30 added to metformin	RCT (open-label)	354 subjects with type 2 diabetes treated with metformin	26 weeks	Change HbA1c, hypoglycemic events	Exenatide was non-inferior to insulin for A1C control (least squares [LS] mean change −1.0 vs. −1.14%; difference [95% CI] 0.14 [−0.003 to 0.291]) and associated with a lower risk for hypoglycemia (8.0 vs. 20.5%, P < 0.05). LS mean weight decreased by 4.1 kg with exenatide and increased by 1.0 kg with insulin (P < 0.001). A total of 39.2 (exenatide) vs. 20.8% (insulin) of patients reached the composite end point of A1C <7.0%, no weight gain, and no hypoglycemia (P < 0.001; post hoc analysis).
Best, 2011[22]	Exenatide	Sitagliptin or pioglitazone	RCT	491 subjects with type 2 diabetes	26 weeks	Weight related quality of life	Exenatide showed greater improvements in A1C (−1.55 vs. −0.92% for sitagliptin and −1.23% for pioglitazone; P < 0.05 for both) and fasting plasma glucose (−1.8 vs. −0.9 mmol/L for sitagliptin and –1.5 for pioglitazone; P < 0.05 for exenatide vs. sitagliptin). Significantly greater reduction in weight for exenatide (−2.3 kg) compared with sitagliptin (−0.8 kg) and pioglitazone, who gained weight (+2.8 kg) (P < 0.05 for both). There was no major hypoglycemia. The incidence of minor hypoglycemia was similar (1.3, 3.0, and 0.6% of patients who received exenatide, sitagliptin, and pioglitazone, respectively).

Gram, 2011[23]	NPH insulin	NPH insulin and metformin NPH insulin and rosiglitazone NPH insulin with metformin and rosiglitazone Insulin aspart Insulin aspart and metformin Insulin aspart and rosiglitazone Insulin aspart and metformin and rosiglitazone	RCT (partially placebo controlled)	371 patients with type 2 diabetes on at least oral anti-glycemic treatment	2 years	Change in HbA1c	A1C decreased in all study groups. Triple therapy, with any insulin, resulted in the greatest reduction in A1C compared with any insulin plus placebo (−1.14 ± 0.13%, P < 0.001), any insulin plus rosiglitazone (−0.50 ± 0.14%, P < 0.001), and any insulin plus metformin (−0.45 ± 0.14%, P < 0.001). Insulin aspart was associated with an increase in body weight of 1.6 ± 0.6 kg (P = 0.009) compared with NPH insulin, rosiglitazone with an increase of 2.3 ± 0.6 kg (P < 0.001) compared with non-rosiglitazone treatment, and metformin with a decrease in body weight of 2.8 ± 0.6 kg (P < 0.001) compared with non-metformin treatment. Metformin decreased A1C compared with placebo (−0.60 ± 0.10%, P < 0.001), as did rosiglitazone (−0.55 ± 0.10%, P < 0.001).
Garber, 2011[24]	Liraglutide (1.2 mg or 1.8 mg)	Glimepiride (8 mg)	RCT	746 type 2 diabetes populations	2 years	Change in HbA1c, body weight	For completers: HbA1c reductions were −0.6% with glimepiride versus −0.9% with liraglutide 1.2 mg (95% CI: −0.71 to −0.02; p = 0.0376) and −1.1% with liraglutide 1.8 mg (95% CI: −0.88 to −0.21; p = 0.0016). In the ITT population, HbA1c reductions were −0.3% with glimepiride versus −0.6% with liraglutide 1.2 mg (95% CI: −0.54 to −0.08; p = 0.0076) and −0.9% with liraglutide 1.8 mg (95% CI: −0.83 to −0.38; p < 0.0001). Over 2 years, rates of minor hypoglycemia were significantly lower with liraglutide 1.2 mg and 1.8 mg compared with glimepiride (p < 0.0001). For both ITT and completer populations, liraglutide was more effective in reducing weight.
Forst, 2012[25]	Liraglutide added to metformin	Metformin monotherapy	RCT	44 patients on a stable dosage of metformin	12 weeks	Change in HbA1, vascular effects (laboratory markers characterizing vascular and endothelial function)	HbA1c declined from 45 +/- 4 mmol⁄mol (6.3 +/- 0.4%; mean +/- sd) to 40 +/- 3 mmol⁄mol (5.8 +/- 0.3%) during liraglutide treatment. The microvascular response to flicker light increased from 7.0 +/- 15.1 to 15.4 +/- 11.5% after 6 weeks and to 11.1+/- 9.9% after 12 weeks. No change could be observed for high-sensitivity C-reactive protein, monocyte chemotactic protein 1, vascular cell adhesion molecule or arterial stiffness parameters.

Derosa, 2012[26]	Exenatide added to metformin	Metformin with placebo	RCT	174 patients with poor glycemic control instructed to take metformin for 6-10 months	12 months	Glycemic control, insulin resistance, and beta-cell function variables	Decrease in HbA1c with both placebo+ metformin (P < 0.01) and exenatide + metformin (P < 0.001) compared with baseline. Exenatide + metformin were superior to placebo + metformin in reducing HbA1c at 12 months (P < 0.05). Significant decrease of waist circumference, and hip circumference after 12 months (P < 0.01, and P < 0.05, respectively) with exenatide + metformin, but not with placebo + metformin. At 12 months the body weight and BMI values obtained with exenatide + metformin were lower than those obtained with placebo + metformin (P < 0.01 for both)
Violante, 2012[27]	Exenatide plus placebo, and metformin (SWITCH)	Exenatide, stigaliptin, and metformin (ADD)	RCT	255 patients inadequately controlled on stigaliptin plus metformin	20 weeks	Change in HbA1c	Greater reduction (P = 0.012) in HbA1c [least-squares mean (se)] for patients in the ADD group {-7 mmol⁄mol [])0.68%] [0.9 (0.08)]}, compared with those in the SWITCH group {-4 mmol⁄ mol [-0.38%] [1.0 (0.09)]} and a greater proportion (P = 0.027) of patients in the ADD group (41.7%) reached < 7.0% (< 53 mmol ⁄ mol) HbA1c target, compared with those in the SWITCH group (26.6%) by week 20.
Haak, 2012[28]	Linagliptin 2.5 mg twice daily + either low (500 mg) or high (1000 mg) dose metformin	Linagliptin 5 mg once daily, metformin 500 mg or 1000 mg bid or placebo	RCT (partial open-label)	791 patients with type 2 diabetes	24 weeks	Change in HbA1c	The placebo-corrected mean change in HbA1c was −1.7% (−2.0, −1.4) for linagliptin + high-dose metformin, −1.3% (−1.6, −1.1) for linagliptin + low-dose metformin, −1.2% (−1.5, −0.9) for high-dose metformin, −0.8% (−1.0, −0.5) for low-dose metformin and −0.6 (−0.9, −0.3) for linagliptin (all p < 0.0001). In the open-label arm, the mean change in HbA1c from baseline (11.8%) was −3.7%. Hypoglycemia occurred at a similar low rate with linagliptin + metformin (1.7%) as with metformin alone (2.4%). Adverse event rates were comparable across treatment arms. No clinically significant changes in body weight were noted.
Seino, 2012[29]	Algoliption (12.5 or 25 mg) added to metformin	Metformin monotherapy	RCT	288 Japanese patients with type 2 diabetes	12 weeks	Change in HbA1c	Dosages of alogliptin+metformin produced significantly greater changes from baseline in HbA1c than metformin monotherapy (with changes in LS means−0.55 and−0.64% vs. 0.22%, respectively; p<0.0001). Incidences of adverse effects were comparable between groups, with no increases in hypoglycemia. Minor increase in body weight in the alogliptin 12.5mg+metformin group (mean rise 0.17 ± 1.38 kg) versus minor decreases in the other two groups (not clinically significant). Fasting triglyceride, mg/dl: alogliptin 12.5 mg,−6.6 (±140.19) ; alogliptin 25mg , −23.1 (±117.01); metformin monotherapy, −10.3 (±118.04) Fasting HDL-C, mg/dl; alogliptin 12.5mg, −2.0 (±8.24), alogliptin 25 mg, −1.2 (±7.09), metformin monotherapy, −0.5 (±7.69). Fasting LDL-C, mg/dl alogliptin 12.5 mg, −4.3 (±20.26). alogliptin 25 mg, −0.5 (±21.09); metformin monotherapy, −5.3 (±21.07)
Patanlone, 2012[30]	Sulfonylureas (glipizide, glyburide, glimepiride)	Metformin	Retrospective cohort	23, 915 type 2 diabetes patients on monotherapy	4 years	Mortality risk	Increase in overall mortality risk was observed in the entire cohort with glipizide (HR 1.64; 95% CI 1.39–1.94), glyburide (HR 1.59; 95% CI 1.35–1.88), and glimepiride (HR 1.68; 95% CI 1.37–2.06) versus metformin; however, in those patients with documented CAD, a statistically significant increase in overall mortality risk was only found with glipizide (HR 1.41; 95% CI 1.07–1.87) and glyburide (HR 1.38; 95% CI 1.04–1.83) versus metformin.

Yoon, 2012[31]	Stiagliptin and pioglitazone	Pioglitazone monotherapy	RCT	317 patients with type 2 diabetes	54 weeks	Change in HbA1c	Mean reduction in HbA1c was −2.4% with the combination of sitagliptin 100 mg and pioglitazone 45 mg versus −1.9% with pioglitazone monotherapy [between-group difference (95% CI) = −0.5% (−0.8, −0.3)] Safety and tolerability of initial treatment with the combination of sitagliptin and pioglitazone and pioglitazone monotherapy were similar. Increases in body weight from baseline were observed in both treatment groups at week 54: 4.8 and 4.1 kg in the combination and monotherapy groups, respectively [between-group difference (95% CI) = 0.7 kg (−0.7, 2.1)]. In both treatment groups, there were clinically meaningful, similar reductions in TGs (change vs. pioglitazone, -1.1) and increases in HDL-C from baseline at week 54 (change vs. pioglitazone, -4.1). Neither treatment group exhibited meaningful changes from baseline in LDL-C
Wainstein, 2012[32]	Sitagliptin and metformin	Pioglitazone (TZD) monotherapy	RCT	527, treatment naïve type 2 diabetes patients	32 weeks	Change in HbA1c	LS mean changes in HbA1c were −1.9 and −1.4% for sitagliptin/metformin and pioglitazone, respectively ($p < 0.001$). Greater proportion of patients had an HbA1c of <7% at week 32 with sitagliptin/metformin vs. pioglitazone (57% vs. 43%, $p < 0.001$). Sitagliptin/metformin led to weight loss (−1.4 kg), while pioglitazone led to weight gain (3.0 kg) ($p < 0.001$). Higher incidences of diarrhea (15.3% vs. 4.3%, $p < 0.001$), nausea (4.6% vs. 1.2%, $p = 0.02$) and vomiting (1.9% vs. 0.0%, $p = 0.026$), and a lower incidence of oedema (1.1% vs. 7.0%, $p < 0.001$), were observed with sitagliptin/metformin. The between-group difference in hypoglycemia was not statistically significant (8.4 and 4.3% with sitagliptin/metformin and pioglitazone, $p = 0.055$) Fasting total cholesterol, triglycerides and LDL-C were essentially unchanged from baseline with sitagliptin/metformin, while total cholesterol and LDL-C increased and triglycerides decreased after treatment with pioglitazone. HDL-C increased with both treatments, with pioglitazone treatment resulting in a greater increase.
Bo, 2012[33]	Metformin	Sulphonylureas, insulin	Retrospective cohort	3685 type 2 diabetes patients without cancer at baseline	4.5 years	All-cause and cancer mortality	All-cause- and cancer-related deaths occurred in: 9.2 and 1.6% of metformin users, 13.1 and 3.0% of sulfonylureas users.. Metformin users were at a lower risk of cancer mortality (adjusted HR 0.73, $p<0.001$ vs. 0.97 $p=0.69$ for sulfonylureas). All-cause mortality (adjusted HR): Metformin-0.91 ($p <0.001$), sulfonylureas-0.95 ($p=0.11$)
Derosa, 2012[34]	Stiagliptin and metformin	Metformin and placebo	RCT	178 drug naïve type 2 diabetics	12 months	Glycemic control	Improvement of HbA1c and PPG at 6 ($p < 0.05$), 9 ($p < 0.01$) and 12 months ($p < 0.001$) with sitagliptin + metformin, and at 9 ($p < 0.05$), and 12 months ($p < 0.01$) with placebo + metformin. Sitagliptin+ metformin were more effective than placebo + metformin in reducing HbA1c, and PPG at 12 months ($p < 0.05$. A Similar decrease of body weight and BMI was observed with both treatments at 12 months ($p < 0.05$ for both), without any differences between the two groups. No patients had hypoglycemia (fasting plasma glucose < 60 mg/dl).

Gallwitz, 2012[35]	Linagliptin (5 mg) added to metformin	Glimpiride (sulphonylureas) added to metformin	RCT	1552 type 2 diabetes patients on stable metformin	2 years	Change in HbA1c	Reductions in adjusted mean HbA(1c) (baseline 7·69% [SE 0.03] in both groups) were similar in the linagliptin (-0.16% [SE 0.03]) and glimepiride groups (-0.36% [0.03]; difference 0.20%, 97.5% CI 0.09-0.30). Fewer participants had hypoglycemia (7% vs. 36%, p<0·0001) or severe hypoglycemia (<1% vs 2%) with linagliptin compared with glimepiride. Linagliptin was associated with significantly fewer cardiovascular events (12 vs 26 patients; relative risk 0.46, 95% CI 0.23-0.91, p=0.0213).
Roumie, 2012[36]	Sulfonylurea	Metformin	Retrospective cohort	253,690 patients receiving regular VHA care	1 year	Composite outcome of hospitalization for acute myocardial infarction or stroke, or death	Crude rates of the composite outcome were 18.2 per 1000 person-years in sulfonylurea users and 10.4 per 1000 person-years in metformin users (adjusted incidence rate difference, 2.2 [95% CI, 1.4 to 3.0] more CVD events with sulfonylureas per 1000 person-years; adjusted hazard ratio [aHR], 1.21 [CI, 1.13 to 1.30]). Using adjusted rate differences, estimated 2.2 (CI, 1.4 to 3.0) more CVD events or deaths and 1.2 (CI, 0.5 to 2.1) more CVD events per 1000 person-years of sulfonylurea compared with metformin use.
Partley, 2012[37]	Liraglutide (1.2 or 1.8 mg/day) added to metformin	Sitagliptin (100 mg/day) added to metformin	RCT, cross-over	665 subjects with type 2 diabetes	78 weeks	Change in HbA1c	Cross-over: 52 weeks of sitagliptin changed HbA1c by −0.9% from baseline, but additional decreases occurred after switching to liraglutide (1.2 mg/day, −0.2%, P = 0.006; 1.8 mg/day, −0.5%, P = 0.0001). Significant weight reductions occurred after switching to liraglutide for 26 weeks: from 92.8 ± 20.6 kg by −1.6 ± 0.4 kg for liraglutide 1.2 mg/day and from 91.6 ± 18.7 kg by −2.5 ± 0.4 kg for liraglutide 1.8 mg/day (both P < 0.0001). Liraglutide only: Liraglutide (1.2 and 1.8 mg/day) reduced HbA1c (baseline, 8.4% ± 0.8% and 8.4% ± 0.7%, respectively) by −0.9% ± 0.1% and −1.3% ± 0.1%; and body weight (baseline, 93.7 ± 18.4 and 94.6 ± 18.1 kg, respectively) by −2.6 kg and −3.1 kg, respectively.
Rosenstock, 2012[38]	Canagliflozin (50, 100, 200, or 300 mg twice daily) add-on to metformin	Sitagliptin (100 mg, DPP-4) with metformin, Placebo with metformin	RCT	451 type 2 diabetics on metformin monotherapy	12 weeks	Change in HbA1c	Reductions in A1C from baseline (7.6-8.0%) to week 12: -0.79, -0.76, -0.70, -0.92, and -0.95% for canagliflozin 50, 100, 200, 300 mg QD and 300 mg BID, respectively, versus -0.22% for placebo (all P < 0.001) and -0.74% for sitagliptin. Non-dose-dependent increase in symptomatic genital infections with canagliflozin (3-8%) versus placebo and sitagliptin (2%). Urinary tract infections were reported without dose dependency in 3-9% of canagliflozin, 6% of placebo, and 2% of sitagliptin arms. Increase in HDL cholesterol (significant with canagliflozin 300 mg BID, P = 0.001), a slight reduction in the ratio of total cholesterol to HDL cholesterol, and a significant reduction in triglycerides with canagliflozin 300-mg QD and BID doses compared with placebo (P = 0.025 and 0.001, respectively). Slight increases in LDL cholesterol with canagliflozin 300 mg BID, with no notable changes observed at the once-daily doses of canagliflozin. Overall incidence of hypoglycemia was low. Canagliflozin was associated with reductions in body weight from baseline; −2.3 to −3.4% (−2.0 to −2.9 kg) at week 12. Reductions in the placebo and sitagliptin groups were −1.1% (−0.8 kg) and −0.6% (−0.4 kg) from baseline.

Russell-Jones, 2012[39]	Exenatide and placebo	Metformin with placebo, pioglitazone (TZD) with placebo, sitagliptin (TZD)+D61 with placebo	RCT	820 suboptimally treated type 2 diabetes patients	26 weeks	Change in HbA1c	HbA(1c) reductions (%) at with exenatide versus metformin, pioglitazone, and sitaglipin were -1.53 vs. -1.48 (P = 0.620), -1.63 (P = 0.328), and -1.15 (P < 0.001), respectively. Weight changes (kg) were -2.0 vs. -2.0 (P = 0.892), +1.5 (P < 0.001), and -0.8 (P < 0.001), respectively. Adverse events: exenatide- nausea (11.3%) and diarrhea (10.9%); metformin- diarrhea (12.6%) and headache (12.2%); pioglitazone- nasopharyngitis (8.6%) and headache (8.0%); and SIT, nasopharyngitis (9.8%) and headache (9.2%). Minor hypoglycemia was rare.
Ruiter, 2012[40]	Metformin	Sulfonylurea	Retrospective cohort	2.5 million individuals in the Netherlands since 1986 in the Dutch National Medicare Register	10 years	Cancer risk	Use of metformin was associated with a lower risk of cancer in general (hazard ratio 0.90 [95% CI 0.88-0.91]) compared with use of sulfonylurea derivatives.
Takihata, 2013[41]	Sitagliptin (50 mg/day)	Pioglitazone (TZA, 15 mg/day)	RCT	130 type 2 diabetes patients inadequately controlled on metformin and/or sulphonylurea	24 weeks	Change in HbA1c	Mean changes in the HbA1c level from baseline were -0.86 ± 0.63% stigaliptin versus -0.58 ± 0.68% pioglitazone (p = 0.024). Hypoglycemia (2 patients, 3.4% vs. 2 patients, 3.5%), gastrointestinal symptoms (3 patients, 5.2% vs. 1 patient, 1.8%) and pretibial edema (0 patients, 0% vs. 39 patients, 68.4%, p < 0.001) were observed for 24 weeks.
Nauck, 2013[42]	Glimepiride and metformin or liraglutide and metformin	Metformin monotherapy	RCT	1091 type 2 diabetes patients	26 weeks	Change in HbA1c	HbA1c decreased with liraglutide (0.4% with 0.6 mg, 0.6% with 1.2 and 1.8 mg) versus 0.3% increase with metformin monotherapy (p < 0.0001). HbA1c decrease with liraglutide was non-inferior to 0.5% decrease with glimepiride. Liraglutide experienced significant weight loss (2.1, 3.0 and 2.9 kg with 0.6, 1.2 and 1.8 mg, respectively) compared to weight gain (0.7 kg) with glimepiride (p < 0.0001). Weight loss with liraglutide 1.2 and 1.8 mg was greater than with metformin monotherapy (1.8 kg; p = 0.0185 and p = 0.0378 for 1.2 and 1.8 mg, respectively). Minor hypoglycemia was <5.0% in all liraglutide groups, significantly less than with glimepiride (24.0%; p < 0.0001). Gastrointestinal events were more common in liraglutide than with glimepiride or metformin monotherapy.
Rathman n, 2013[43]	DPP-4	Sulphonylureas	Retrospective cohort	19,184 DPP-4 and 31,110 sulphoynlurea users	2 years	Treatment persistence, hypoglycaemia, macrosvascular outcomes	DDP-4 (non-persistence: 39%) were associated with a lower risk of discontinuation compared to SU (49%) [adjusted hazard ratio (HR): 0.74; 95% CI: 0.71–0.76]. Hypoglycemia (≥1) was documented in 0.18% patients with DPP-4 and in 1.00% with SU [odds ratio (OR): 0.21; 95%CI: 0.08–0.57]. Hypoglycemia was significantly associated with incident macrovascular complications (HR: 1.6; 95% CI: 1.1–2.2). Risk of macrovascular events was 26% lower in DPP-4 than in SU users.

Cefalu, 2013[44]	Canagliflozin	Glimepiride	RCT	1452 patients with type 2 diabetes	52 weeks	Change in HbA1c	In lowering HbA1c, canagliflozin 100 mg was non-inferior to glimepiride (least-squares mean difference -0·01% [95% CI -0·11 to 0·09]), and canagliflozin 300 mg was superior to glimepiride (-0·12% [-0·22 to -0·02]). 39 (8%) patients had serious adverse events in the glimepiride group versus 24 (5%) in the canagliflozin 100 mg group and 26 (5%) in the 300 mg group. In the canagliflozin 100 mg and 300 mg groups versus the glimepiride group, there were a greater number of genital mycotic infections (women: 26 [11%] and 34 [14%] vs five [2%]; men: 17 [7%] and 20 [8%] vs three [1%]), urinary tract infections (31 [6%] for both canagliflozin doses vs 22 [5%]), and osmotic diuresis-related events (pollakiuria: 12 [3%] for both doses vs one [<1%]; polyuria: four [<1%] for both doses vs two [<1%]).
Yale, 2013[45]	Canagliflozin	Placebo	RCT	269 subjects with type 2 diabetes and stage 3 chronic kidney disease	26 weeks	Change in HbA1c	Canagliflozin 100 and 300 mg reduced HbA1c from baseline compared with placebo at week 26 (-0.33, -0.44 and -0.03%; $p < 0.05$). Adverse events rates were similar for canagliflozin 100 and 300 mg and placebo (78.9, 74.2 and 74.4%). Slightly higher rates of urinary tract infections and adverse events related to osmotic diuresis and reduced intravascular volume were observed with canagliflozin 300 mg. Canagliflozin 100 and 300 mg provided reductions from baseline in body weight over 26 weeks, placebo was associated with a slight increase in body weight. Differences in LS mean percent changes (95% CI) relative to placebo at week 26 were –1.6% (–2.3, –0.8) and –1.8% (–2.6, –1.0) for canagliflozin 100 and 300 mg, respectively, corresponding to absolute changes of –1.4 and –1.6 kg, respectively. Canagliflozin 100 and 300 mg increased high-density lipoprotein cholesterol (HDL-C) compared with placebo (LS mean percent changes of 4.0, 3.0 and 1.5%, respectively). An increase in triglycerides (LS mean percent changes of 11.9, 6.2 and 7.9%, respectively) and a decrease in low-density lipoprotein cholesterol (LDL-C; LS mean percent changes of –1.0, 6.4 and 6.3%, respectively) were seen with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo. There was no difference in non–HDL-C between the canagliflozin 300 mg and placebo groups (LS mean percent changes of 2.8 and 3.8%, respectively).
Stenlof, 2013[46]	Canagliflozin	Placebo	RCT	584 subjects with inadequately controlled diabetes	26 weeks	Change in HbA1c	HbA1c significantly reduced from with canagliflozin 100 and 300 mg compared with placebo (-0.77, -1.03 and 0.14%, respectively; $p < 0.001$ for both). Reductions from baseline in body weight were observed with canagliflozin 100 and 300 mg compared with placebo ($p < 0.001$). Canagliflozin 100 and 300 mg provided LS mean percent changes of −2.2% (−1.9 kg) and −3.3% (−2.9 kg), respectively (relative to placebo). Significant increases in HDL-C were observed with canagliflozin 100 and 300 mg compared with placebo at week 26 [differences in LS mean changes of 6.8% ($p < 0.001$) and 6.1% ($p < 0.01$), respectively]. Modest, increases from baseline in LDL-C were seen with canagliflozin 100 and 300 mg (2.9 and 7.1%, respectively) compared with placebo (1.0%).

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: CER 27: Oral Diabetes Medications for Adults with Type 2 Diabetes: An Update (2011)

Name of Person Completing the Form: _____

Conclusions From CER Executive Summary		Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question #1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of treatment options for the intermediate outcomes of glycemic control (in terms of HbA1c), weight, or lipids?				
HbA1c	Metformin and second-generation sulfonylureas showed similar changes in HbA1c, with a pooled between-group difference of 0.07% (95% CI -0.12% to 0.26%) for studies lasting longer than 3 months but usually less than 1 year in duration. (High)	☐	New Evidence:	☐
	Combination therapies were better than monotherapy regimens at reducing HbA1c, with an absolute difference of about 1%. In comparisons of metformin versus metformin plus thiazolidinediones, and metformin versus metformin plus sulfonylureas, the combination therapy was favored for HbA1c reduction. (High)	☐	New Evidence:	☐
	When compared with DPP-4 inhibitors, metformin had a greater reduction in HbA1c, with a pooled between-group difference of -0.4% (95% CI -0.5% to -0.2%). (Moderate)	☐	New Evidence:	☐
	Comparisons of metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone		New Evidence:	

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	versus rosiglitazone showed similar reductions in HbA1c, with an absolute reduction in HbA1c of around 1% as compared with baseline values, with trials lasting 1 year or less. (Moderate)	☐		☐
	Metformin plus DPP-4 inhibitor was favored over metformin alone for HbA1c reduction. (Moderate)	☐	New Evidence:	☐
	The combination of metformin plus thiazolidinedione had a similar efficacy in reducing HbA1c as the combination of metformin plus sulfonylurea. (Moderate)	☐	New Evidence:	☐
	The combination of pioglitazone plus sulfonylurea was minimally favored over metformin plus pioglitazone, by an absolute difference of 0.03%. (Low)	☐	New Evidence:	☐
	The combination of metformin plus a premixed insulin analogue was minimally favored over metformin plus a basal insulin, by an absolute difference of 0.30% to 0.43%. (Low)	☐	New Evidence:	☐
Body weight	Metformin maintained or decreased weight to a greater extent than did thiazolidinediones (pooled between-group difference of -2.6 kg, 95% CI -4.1 kg to -1.2 kg), the combination of metformin plus a thiazolidinedione (pooled between-group difference of -2.2 kg, 95% CI -2.6 kg to -1.9 kg), or the combination of metformin plus a sulfonylurea (pooled between-group difference of -2.3 kg, 95% CI -3.3 kg to -1.2 kg). Thiazolidinediones alone or in combination were associated with weight gain. (High)	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Metformin maintained or decreased weight to a greater extent than did sulfonylureas, with a pooled between-group difference of -2.7 kg (95% CI -3.5 kg to -1.9 kg). (High)	☐	New Evidence:	☐
Sulfonylureas and the meglitinides had similar effects on body weight. (High)	☐	New Evidence:	☐
GLP-1 agonists decreased weight to a greater extent than did sulfonylureas (pooled between-group difference of -2.5 kg, 95% CI -3.8 kg to -1.1 kg). (Moderate)	☐	New Evidence:	☐
Metformin plus sulfonylurea had a more favorable effect on weight than did either the combinations of a thiazolidinedione plus sulfonylurea (pooled between-group difference of -3.2 kg, 95% CI -5.2 kg to -1.1 kg) or metformin plus a thiazolidinedione (pooled between-group difference of -0.9 kg, 95% CI -1.3 kg to -0.4 kg). (Moderate)	☐	New Evidence:	☐
Metformin decreased weight to a greater extent than did DPP-4 inhibitors (pooled between-group difference of -1.4 kg, 95% CI -1.8 kg to -1.0 kg). (Moderate)	☐	New Evidence:	☐
Metformin had no significantly different effect on weight than did the combination of metformin plus DPP-4 inhibitors (pooled between-group difference of −0.2 kg, 95% CI −0.7 kg to 0.2 kg). (Moderate)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	Metformin plus GLP-1 agonists decreased weight to a greater extent than did several combination therapies (metformin plus sulfonylurea, metformin plus thiazolidinedione, metformin plus basal insulin, or metformin plus DPP-4 inhibitor). (Low)	☐	New Evidence:	☐
	Metformin plus DPP-4 inhibitors decreased weight to a greater extent than did two standard combinations, metformin plus thiazolidinedione or metformin plus sulfonylurea. (Low)	☐	New Evidence:	☐
LDL cholesterol	Metformin decreased LDL to a greater extent than did sulfonylureas, which generally had little effect on LDL, with a pooled between-group difference of −10.1 mg/dL (95% CI −13.3 mg/dL to −7.0 mg/dL). (High)	☐	New Evidence:	☐
	The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did metformin monotherapy (pooled between-group difference of 14.5 mg/dL, 95% CI 13.3 mg/dL to 15.7 mg/dL),. (High)	☐	New Evidence:	☐
	Metformin decreased LDL cholesterol to a greater extent than did pioglitazone, which increased LDL cholesterol, with a pooled between-group difference in LDL of −14.2 mg/dL (95% CI −15.3 mg/dL to −13.1 mg/dL). (Moderate)	☐	New Evidence:	☐
	Metformin decreased LDL cholesterol to a greater extent than did rosiglitazone, with a pooled between-group difference in LDL of −12.8 mg/dL (95% CI −24.0 mg/dL to −1.6 mg/dL). (Moderate)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	Metformin decreased LDL to a greater extent than did DPP-4 inhibitors, with a pooled between-group difference of −5.9 mg/dL (95% CI −9.7 mg/dL to −2.0 mg/dL). (Moderate)	☐	New Evidence:	☐
	The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did a combination of metformin and a second-generation sulfonylurea, with a pooled between-group difference in LDL of 13.5 mg/dL (95% CI 9.1 mg/dL to 17.9 mg/dL). (Moderate)	☐	New Evidence:	☐
HDL cholesterol	Metformin increased HDL to a lesser extent than did pioglitazone, with a pooled between group difference of −3.2 mg/dL (95% CI −4.3 mg/dL to −2.1 mg/dL). (High)	☐	New Evidence:	☐
	Sulfonylureas were similar to metformin in terms of changes in HDL. (High)	☐	New Evidence:	☐
	The combination of metformin and rosiglitazone increased HDL to a greater extent than did metformin monotherapy (pooled between-group difference 2.8 mg/dL, 95% CI 2.2 mg/dL to 3.5 mg/dL). (High)	☐	New Evidence:	☐
	Rosiglitazone increased HDL to a lesser extent than did pioglitazone (pooled between-group difference of −2.3 mg/dL, 95% CI −3.5 mg/dL to −1.2 mg/dL). (Moderate)		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	☐		☐
Rosiglitazone alone was similar to metformin in terms of changes in HDL. (Moderate)	☐	New Evidence:	☐
Pioglitazone increased HDL to a greater extent than did sulfonylureas (pooled between-group difference of 4.3 mg/dL, 95% CI 1.9 mg/dL to 6.6 mg/dL). (Moderate)	☐	New Evidence:	☐
The combination of metformin and pioglitazone increased HDL by about 5 mg/dL relative to the combination of metformin and a sulfonylurea. (Moderate)	☐	New Evidence:	☐
The combination of metformin and rosiglitazone increased HDL to a greater extent than did the combination of metformin and a sulfonylurea (pooled between-group difference 2.7 mg/dL, 95% CI 1.4 mg/dL to 4.1 mg/dL). (Moderate)	☐	New Evidence:	☐
The combination of metformin and DPP-4 inhibitors had similar effect on HDL as did metformin monotherapy (pooled between-group difference was 0.5 mg/dL, 95% CI −1.5 mg/dL to 2.5 mg/dL). (Moderate)	☐	New Evidence:	☐
The combination of pioglitazone with another medication was favored for the following comparisons: pioglitazone plus metformin versus metformin		New Evidence:	

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	monotherapy, metformin plus pioglitazone versus metformin plus sulfonylurea, and pioglitazone plus sulfonylurea versus metformin plus sulfonylurea, with a range of between-group differences from 3.1 mg/dL to 10.5 mg/dL. (Low)	☐		☐
Triglycerides	Pioglitazone decreased TG to a greater extent than did metformin (pooled between-group difference −27.2 mg/dL, 95% CI −30.0 mg/dL to −24.4 mg/dL). (High)	☐	New Evidence:	☐
	Metformin monotherapy decreased TG to a greater extent than did the combination of metformin and rosiglitazone, with a pooled between-group difference in TG of −14.5 mg/dL (95% CI −15.7 mg/dL to −13.3 mg/dL). (High)	☐	New Evidence:	☐
	Metformin decreased TG to a greater extent than did rosiglitazone, which increased TG, with a pooled between-group difference of −26.9 mg/dL (95% CI −49.3 mg/dL to −4.5 mg/dL). (Moderate)	☐	New Evidence:	☐
	Metformin decreased TG to a greater extent than did sulfonylureas (pooled between-group difference −8.6 mg/dL, 95% CI −15.6 mg/dL to −1.6 mg/dL). (Moderate)	☐	New Evidence:	☐
	The combination of metformin plus rosiglitazone and the combination of metformin plus sulfonylurea had similar effects on TG. (Moderate)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	The combination of metformin and pioglitazone decreased TG to a greater extent than did the combination of metformin and a sulfonylurea, with between-group differences ranging from −10 mg/dL (p = 0.30) to −24.9 mg/dL (p = 0.045). (Moderate)	☐	New Evidence:	☐
	Sulfonylureas and meglitinides had similar effects on TG (pooled between-group difference 0.2 mg/dL, 95% CI −3.8 mg/dL to 4.2 mg/dL). (Moderate)	☐	New Evidence:	☐
Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, and neuropathy?				
All-cause mortality	Compared to sulfonylureas, metformin was associated with a slightly lower risk of all-cause mortality in observational studies, but the results were inconsistent between trials and observational studies, and all had a moderate risk of bias. (Low)	☐	New Evidence:	☐
	Many RCTs were of short duration (less than 1 year) and had few deaths, limiting the precision of the results. (Low)	☐	New Evidence:	☐
	No studies addressed several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, comparisons with an insulin preparation, and the majority of combination therapy comparisons. (Insufficient)	☐	New Evidence:	☐
r di se	Metformin was associated with a slightly lower risk of cardiovascular mortality than was a second-generation sulfonylurea, but the results were		New Evidence:	

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	imprecise and had a moderate risk of bias. (Low)	☐		☐
	The risk of cardiovascular mortality was similar between metformin and each of the thiazolidinediones as monotherapy, with high imprecision of results, inconsistencies, and a moderate risk of bias. (Low)	☐	New Evidence:	☐
	Metformin alone was slightly favored over a combination of metformin and rosiglitazone in terms of lower risk of fatal myocardial infarction, with consistent direction of the results but high imprecision. (Low)	☐	New Evidence:	☐
	No studies addressed several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons. (Insufficient)	☐	New Evidence:	☐
	A comparison of the risk of cardiovascular morbidity between metformin and thiazolidinedione as monotherapy was inconclusive, with high imprecision and inconsistency in the direction of the findings. (Low)	☐	New Evidence:	☐
ok)	Metformin alone was slightly favored over a combination of metformin and rosiglitazone in terms of a lower risk of non-fatal ischemic heart disease, with a consistent direction of the results but high imprecision and a failure to reach statistical significance. The pooled odds ratio (OR) for combined fatal and non-fatal ischemic heart disease events was 0.43, 95% CI 0.17 to 1.10. The range of rates for non-fatal ischemic heart disease for the comparison group, metformin, ranged from 0 to 2.9%. (Low)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	No studies addressed several comparisons, including most DPP-4 inhibitors and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons. (Insufficient)	☐	New Evidence:	☐
Microvascular outcomes (retinopathy, nephropathy, neuropathy)	Pioglitazone was more effective than metformin in reducing the urinary albumin-to-creatinine ratio (15% and 19% decrease in 2 trials), likely indicating less nephropathy. (Moderate)	☐	New Evidence:	☐
	Three comparisons were included for the outcome of neuropathy, but studies were at high risk for bias, with low sample sizes and poorly defined outcomes. (Low)	☐	New Evidence:	☐
	No studies addressed the outcome of retinopathy. (Insufficient)	☐	New Evidence:	☐
Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the treatment options in terms of the adverse events and side effects?				
Hypoglycemia	The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with metformin, with a pooled OR of 4.6 (95% CI 3.2 to 6.5). The range of rates for mild to moderate hypoglycemia in the metformin group was 0 to 17.7%, with a median rate of 0%. (High)	☐	New Evidence:	☐
	The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with thiazolidinediones, with a pooled OR of 3.9 (95% CI 3.0 to 4.9). The range of rates for mild to moderate hypoglycemia in the thiazolidinedione group was 0 to 92.1%, with a median rate of 4.4%. (High)	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
The risk of hypoglycemia with metformin plus sulfonylurea exceeds the risk of metformin plus thiazolidinediones, with a pooled OR of 5.8 (95% CI 4.3 to 7.7). The range of rates for mild to moderate hypoglycemia in the metformin plus thiazolidinediones group ranged from 0 to 9.3%, with a median rate of 1.3%. (High)	☐	New Evidence:	☐
The risk of hypoglycemia with sulfonylurea exceeds the risk with DPP-4 inhibitors (20 events versus none in a single study). (Moderate)	☐	New Evidence:	☐
The risk of hypoglycemia was similar between metformin and thiazolidinediones. (Moderate)	☐	New Evidence:	☐
The risk of hypoglycemia with metformin plus sulfonylurea exceeded the risk with metformin alone, with an OR range of 0.6 to 9.3. (Moderate)	☐	New Evidence:	☐
The risk of hypoglycemia was modestly higher for meglitinides than for metformin, with an OR of 3.0 (95% CI 1.8 to 5.2). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 24%, with a median rate of 3.7%. (Moderate)	☐	New Evidence:	☐
The risk of hypoglycemia was higher for metformin plus a thiazolidinedione than for metformin alone, with an OR of 1.6 (95% CI 1.0 to 2.4). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 9.1%, with a median rate of 1.4%. (Moderate)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	The combination of metformin and DPP-4 inhibitor had similar risk of hypoglycemia as that of metformin alone. (Moderate)	☐	New Evidence:	☐
	The combination of metformin with a sulfonylurea had a higher risk of hypoglycemia than metformin with GLP-1 agonist. (Moderate)	☐	New Evidence:	☐
	Metformin combined with a basal insulin had a modestly lower risk of hypoglycemia when compared to metformin combined with a premixed insulin, with the RR ranging from 0.34 to 0.94 in 5 trials. (Moderate)	☐	New Evidence:	☐
Gastrointestinal (GI) side effects	Metformin was associated with twice as many GI adverse events, most commonly diarrhea, nausea, and vomiting, as were thiazolidinediones. (High)	☐	New Evidence:	☐
	The rates of GI adverse effects were similar for thiazolidinediones and sulfonylureas. (High)	☐	New Evidence:	☐
	Metformin was associated with more frequent GI adverse events than were DPP-4 inhibitors. (Moderate)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	Metformin was associated with twice as many GI adverse event rates as were second-generation sulfonylureas. (Moderate)	☐	New Evidence:	☐
	Metformin monotherapy was associated with more frequent GI adverse events than were either the combination of metformin plus a sulfonylurea or metformin plus a thiazolidinedione, if the metformin component was of a lower dose than in the metformin monotherapy arm. (Moderate)	☐	New Evidence:	☐
	The combination of metformin and sulfonylurea was associated with slightly more frequent GI adverse events than were seen with a combination of a thiazolidinedione and a sulfonylurea. (Moderate)	☐	New Evidence:	☐
Congestive heart failure	The risk of CHF was higher for thiazolidinediones than for sulfonylureas (OR 1.68, 95% CI 0.99 to 2.85). (Moderate)	☐	New Evidence:	☐
	No long-term trials assessed the comparative effects of the DPP-4 inhibitors and GLP-1 agonists on the risk of heart failure. (Insufficient)	☐	New Evidence:	☐

Conclusions From CER Executive Summary		Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Cholecystitis and pancreatitis	Two comparisons were included for the outcome of cholecystitis, and one comparison was included for the outcome of pancreatitis, with unclear conclusions. (Low)	☐	New Evidence:	☐
Lactic acidosis	The risk of lactic acidosis was similar for metformin and sulfonylurea alone and for the two in combination. (Moderate)	☐	New Evidence:	☐
Macula edema	Only one trial reported on macular edema. The evidence was insufficient for all comparisons. (Insufficient)	☐	New Evidence:	☐
Cancer	Few studies addressed the outcome of cancer. (Insufficient)	☐	New Evidence:	☐
Liver injury	The risk of liver injury was similar for thiazolidinediones and sulfonylureas. (High)	☐	New Evidence:	☐
	The rates of liver injury were similar between thiazolidinediones and metformin. (Moderate)	☐	New Evidence:	☐

	Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Fractures	The risk of fracture was higher for thiazolidinediones than for metformin. In one large RCT the RR was 1.57 (95% CI 1.13 to 2.17) and women in the thiazolidinedione arm had a higher fracture risk than men. The fracture rate was 4.1% in the reference (metformin) arm. (High)	☐	New Evidence:	☐
	The risk of fracture was higher for combination therapy with a thiazolidinedione than for metformin plus sulfonylurea, with higher risk in women than in men. In one large RCT, the RR was 1.57 (95% CI 1.26 to 1.97) for the rosiglitazone combination therapy arm, as compared to the combination of metformin plus sulfonylurea arms. The fracture rate in the reference (metformin + sulfonylurea) arm was 1.6%. (High)	☐	New Evidence:	☐
Key Question 4: Do the safety and effectiveness of these treatment options (see list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular, and cerebrovascular outcomes?				
	No conclusions.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Are there new data that could inform the key questions that might not be addressed in the conclusions?			