Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Diabetes Medications for Adults With Type 2 Diabetes: An Update*

Draft review available for public comment from April 29, 2015 to May 27, 2015.

Research Review Citation: Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, Wilson LM, Chu Y, Iyoha E, Maruthur NM. Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 16-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	The report is encyclopedic in its wealth of knowledge, but my concern is that the presentation to the average clinician is not clear on the issues of greatest importance regarding metformin and sulfonylurea therapy: 1) Risk of using metformin in mild-moderated CKD 2) Effect size of cardiovascular risks of SU vs. metformin	Thank you for taking the time to review our report. We welcome the opportunity to clarify these important issues. Regarding point 1, we have added more detail about metformin and CKD to the Discussion and ES. We have added text on the Implications section of the Discussion to address the issue of non-metformin monotherapy in the setting of contraindications or intolerance of metformin as well as add-on therapy to metformin. Ultimately, there is no right answer, and we have clarified that we do not have much evidence on long-term effects on mortality/CVD outcomes or rare adverse events and that there are otherwise differential effects of many of the medications on weight, hypoglycemia, and GI side effects. For point 2, we have added absolute risk differences for long-term mortality and cardiovascular outcomes in the Results, Discussion, and Executive Summary to provide better clinical context for these results.
TEP Reviewer #1	Introduction	Appropriate	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #1	Methods	Clearly stated and standards noted	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #1	Results	The AHRQ report is up to date as of this writing- though major findings on the cardiovascular safety of the DPP-IV inhibitor class will be formally announced at the American Diabetes Association Meeting on June 9th 2015 and will need to be incorporated when published	Thank you. We have added the published results from TECOS to the Discussion.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Discussion/ Conclusion	The Evidence About Cardiovascular MortalityPage 153/154 of 1080 Effective Health Care. Metformin is the preferred medication for diabetes management. It is possible that metformin conveys cardiovascular (CV) benefit not seen in any other class of medication. The pertinent question is how to frame SU risk--which is best studied, against metformin, the gold standard. My concern is that the discussion, while factually accurate, does not in that section note that the ADOPT study arguably is the largest/longest study, and that the rates of fatal MI (0.2% versus 0.1%) is small. The Chinese study is of greater concern, but its applicability to other races/ethnicity is uncertain. Retrospective cohort studies and large data base studies are clearly of lesser validity with respect to effect size. Bottom line: The effect size of risk of SU vs. Metformin, in my opinion, needs to have a better formulated qualitative discussion.	We appreciate the opportunity to enhance our qualitative reporting and discussion of these important results; please see the substantial changes that we have made in the Results section which have been carried over to the Discussion and Executive Summary. Regarding the framing of sulfonylureas, we were unable to draw conclusions about these long-term outcomes for metformin compared with other medications so we can't really make specific claims about metformin being "beneficial" versus the sulfonylureas being "harmful." In the absence of being able to assign a label of beneficial or harmful, we have just used relative terms which could be interpreted either way. On the point of ADOPT as a most important trial, we have pointed out major issues with ADOPT and compared it with the Chinese study in the Results section. Even though ADOPT was large and long, losses to followup were massive and differential (more in the sulfonylurea arm), and even followup durations were differential across the arms (shorter duration in the sulfonylurea arm). Also, while the Chinese study was conducted in a Chinese population, the more important difference was that the participants had established cardiovascular disease; we do not have evidence that a Chinese population itself is so different from others that we cannot generalize to other populations to some extent. We compared the studies using relative and absolute measures because of differences in baseline risk. Regarding the absolute difference of 0.1% seen in ADOPT, this would translate to a number need to harm of 1,000 which is actually a small number given the number of potential patients who could be exposed.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1 (continued)	Discussion/ Conclusion (continued)		Finally, we used the observational studies only to support our interpretation of RCT findings and focused on their relative findings (adjusted HRs); we agree that observational studies are prone to confounding by indication. However, the observational studies used sophisticated methodologies such as propensity scores to try and deal with this issue.
TEP Reviewer #1	Clarity and Usability	As noted above, the major controversial issues in anti-glycemic agents in my mind (Metformin in CKD and SU CV risk) are not clearly delineated. There are many other comparisons that need to be made in choosing second agents after metformin, or 1st agents if metformin is not tolerated (CKD would certainly be of concern for SU use as well). However, CV morbidity and morality dominates from my perspective, and this needs more clarity	We have reframed the Discussion/Executive Summary to address these issues. Specifically, we have added sections to the Discussion and Executive Summary on the issue of monotherapy in the presence of contraindications to/intolerance of metformin and evidence on metformin use in chronic kidney disease. The former specifically addresses the relative long-term effectiveness (cardiovascular disease outcomes) and safety of the alternatives to metformin.
Peer Reviewer #1	General	This report will be of great use to clinicians and other audiences in summarizing the state of the current literature as well as the gaps in knowledge. Key questions are relevant and timely.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #1	Introduction	Introduction is comprehensive and clear	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #1	Methods	No concerns with search strategy or methods. The executive summary should note that the unpublished literature was also assessed.	We have added to the Methods section of the Executive Summary that we searched ClinicalTrials.gov and the Food and Drug Administration Web site.
Peer Reviewer #1	Results	Given the complexity of the key questions and the multitude of comparisons, the results are logically organized and well presented. The writing is clear, and key messages are clearly stated.	Thank you for taking the time to review our report. We appreciate your feedback!

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	Major findings are clearly stated, and ambiguities in the literature are noted as well. The limitations are thoughtfully expressed. The relative lack of reporting bias is reassuring, and each individual section carefully assesses it. This issue (lack of bias) could receive more emphasis in the conclusion since it is so often a concern about systematic reviews that are largely based on industry- sponsored trials.	We have made this important issue of industry sponsorship more prominent in the Discussion (Limitations of the Evidence Base).
Peer Reviewer #1	Clarity and Usability	The report is well organized. Its massive length is endemic to these reports. While this diminishes usability, the major points can easily be found while the details are available for those with special interests in particular areas.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #2	General	The reason that I gave this an overall "good" is that the questions and methods were great, the report is very clear and the limitations defined, but the conclusions are very limited due to the limitations of the available data.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #2	Introduction	well done	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #2	Methods	Only suggestiion re: methods is to be more explicit on how strength of individual comparisons was judged. Some labeled moderate seemed to have few events and little power to distinguish.	Thank you for this very important comment. We agree that much of the evidence on comparisons for long-term and safety outcomes was underpowered. After further discussions with the Technical Expert Panel and other peer reviewers, we have added an additional stipulation to our approach to evidence grading. If the evidence on a comparison for a given outcome is imprecise (underpowered), we will not exclude harm/benefit with moderate or high strength of evidence. We have clarified this in the Methods.
TEP Reviewer #2	Results	The results were clear	Thank you for taking the time to review our report. We appreciate your feedback!

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	Future research was clear. Research gaps might have started with an overarching statement about the very limited number of head to head comparisons available and the short durations of f/u. I might have commented on the lack of studies comparing drugs used in combination with SU. These would have been valuable with regard to hypoglycemia and weight gain to see which combinations might have more adverse effects together with SU. I think it is very unlikely that future long term outcomes will include comparisons of effects on microvascular outcomes, yet this bullet precedes the more important bullet about CVD and mortality.	We have changed the research gaps to a table to make it more clear to the reader and have added something about timing and moved the bullet on macrovascular outcomes prior to microvascular outcomes. We did not include sulfonylurea-based combinations except for metformin; therefore, we did not include a statement regarding the sulfonylurea-based combinations here.
TEP Reviewer #2	Clarity and Usability	I think the slides presented on today's TEP call gave a quick overview of results. Perhaps they could be presented as "key findings". Even the executive summary is quite long and one has to wade through a table of contents listing all the tables and figures to get to it.	We have created an appendix (Appendix G) that has all of the Key Points. AHRQ publishes the Executive Summaries as stand-alone documents. That will eliminate the need for any reader to have to wade through a table of contents.
TEP Reviewer #3	General	Need better clarity on whether comparative studies that include insulin are included -- they are not referred to in the introduction or in the main initial figures (figure A/B), yet they are used as examples in the text intermittently	We have added to the Executive Summary a table on drug comparisons (see Table A). We only evaluated metformin plus long-acting or premixed insulins with metformin plus another medication of interest since these are the more commonly used insulins for second-line therapy in combination with metformin. They are not in the figures because the figures highlight moderate and high strength of evidence and pooled meta-analyses only. I have added text to the Discussion and Executive Summary to make it clear why certain items are in text only and not in related figures throughout.
TEP Reviewer #3	General	Need clarity on time point of outcome comparison -- this is not clear (6 months? 52 weeks? 2 years? etc.)	We have added text describing study duration throughout the executive summary and discussion. This is already explicitly stated in the results sections under each comparison.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	General	Need better alignment of conclusions with design and results -- the paper is laid out as looking at intermediate outcomes (a1c etc) then long-term, then conclusions primarily focus on longterm safety. this is misleading, primarily since most of the data strength currently is in intermediate outcomes and only now (since 2008, with most study outcomes pending) is there renewed interest in long-term issues. suggest outlining results/conclusions in same fashion as proposed methods (intermediate, then long-term, then safety).	We have realigned all sections to follow the order of Key Questions.
TEP Reviewer #3	General	Need to recognize that the conclusions one can draw really depend on the length of study a drug has been studied for in a given trial. not fair to say that trials are inadequate, when long-term safety was not the intended outcome of many of the trials.	We appreciate this point. Data from randomized controlled trials are generally inadequate to answer many of the safety questions. We do want this to be clear since that is the evidence that we have. However, we have revised our Discussion to indicate the importance of realizing that randomized controlled trials cannot answer all of these questions and that observational methods need to be refined and used.
TEP Reviewer #3	Abstract	results need to align with methods (intermediate outcomes first…)	We have made this change.
TEP Reviewer #3	Executive Summary	need clarity on what categories of drugs are included or not included how does length of time factor (length of time on market or of studies) figures or text do not clarify at what timepoint data is being collected or compared	We have added a table of medication comparisons to the Executive Summary (see Table A of the Executive Summary). We have also added more text throughout on study duration as well as a figure (Figure A of the Executive Summary) to demonstrate study duration by key question. The Executive Summary results figures do list whether pooled analyses were <52 weeks or longer study duration.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Executive Summary: ES-19	studies often excluded older adults, racial/ethnic minorities -- this is not true. studies do not exclude racial/ethnic minorities, but rather enrollment may not be representative of all the racial/etnic minorities.	Actually, many studies do exclude older adult populations. Although studies may not have explicit exclusions based on race/ethnicity, we saw underrepresentation of racial and ethnic minority populations across the studies we evaluated. We have documented this in our study population characteristics tables and paragraph in the text in our results that describe the studies. We have added a sentence on this in the Executive Summary study characteristics description for the intermediate outcomes.
TEP Reviewer #3	Executive Summary: ES-20:	more studies are needed.... not sure this is the proper framework - -recommending studies to specifically study bladder cancer with tzds vs others, for example. many of these sporadic safety concerns have been from spontaneous case report or reporting to the FDA rather than concerns borne out of prospective RCTS. rather than forcing a recommendation to do more studies to compare different agents against each other for possible side effects (do we really want a comparative effectiveness bladder cancer study?) might be more useful to recommend longer-term prospective (e.g. observational) studies as a whole to systematically assess for safety signals. the phrasing of 'more studies are needed' is a turn-off and needs more contextual phrasing, espcially for drugs that are already waning in use. it may not be that more studies are needed, but rather certain type of studies would help define and characterize risk that we really haven't had to date in this field. figures-- currently they do not include insulin comparisons, but text does?	We agree and have dedicated substantial space in the Discussion and Executive Summary on the importance of observational studies to answering these important safety questions. We did not intend to imply that randomized controlled trials should be done for these questions (e.g., comparative safety of pioglitazone for bladder cancer). We have also revised the Future Research Needs to reflect this.
TEP Reviewer #3	Executive Summary: ES-10:	cv morbidity/mortality -- text would benefit from adding clarification of length of studies and intended purpose of studies (is cv data a primary or secondary outcome)	We have added this detail to the text and noted that no trial had a macrovascular or microvascular outcome as its primary outcome.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Executive Summary:	cancer section only hones in on pioglitazone and GLP-1 agonists. not clear why -- the text phrasing is not clear and does not provide context. in addition, there was a lot of hoopla previously on insulin and cancer risk, but none of this is explored	We removed references to specific drug classes from the Results of the Executive Summary. In the Discussion of the Executive Summary, we did briefly review the literature on cancer for the medications included in this report. We appreciate the point about insulin but did not discuss it because it was not a medication of focus for this report. We only included insulin as add-on to metformin and had very little evidence on this.
TEP Reviewer #3	Executive Summary: ES-14: Table D --	this is purely for safety, but legend includes effectiveness; like the figure representation better (may take up more space but these are easier to comprehend rather than text/table) at places, there is some editorializing, which should probably be kept to a minimum - eg. page 35, line 28-29 'surprisingly' ; page 36 line 19-20 'this is especially important when considering what second line injectable to use' (dangerous to promote or put down one class so openly, especially when newer insulins are approved that may have different data). -p 42 onwards, e.g. -- sections comparing insulin, but insulin not part of primary table of comparison (table 2) or main figures -- need to pick one or the other -- sounds like enough data to include insulin as one of the combination comparators.	We agree. We removed the word safety from the title for Table D. We have added a figure for GI events and removed the table to make it easier to view results. We have removed the word surprisingly and the sentence about especially important to consider. Premixed and basal insulins are part of combination comparisons in Table A. We did not have sufficient strength of evidence to include the insulin comparisons in the figures. We have added this to the text due to clinical interest.
TEP Reviewer #3	Methods	At several stages there are 'two reviewers' listed -- should you include initials of the two reviewers whenever it is mentioned, or clarify that it is a separate two reviewers from the other steps? -as above -- insuln used for comparison in text but selectively; -length of time should factor into analysis, as this effects viable outcomes to assess and compare and strength of evidence pertaining to a specific med	We added a sentence to the Study Selection section of the Methods stating, "All of the review authors participated in the study selection." We added statements to the Data Synthesis section about how we handled short- and long-term studies in the analysis.
TEP Reviewer #3	Results	Critiques as above	We appreciate your feedback. We have addressed your comments, as noted above.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	as above -- future research specifically asking for more studies directly comparing very specific side effects is the wrong direction, i believe (e.g. need head to head studies with pioglitazone on bladder cancer), but rather a broader approach of prospectively collecting in standardized approach events of special interest across studies. writing team might want to review their recommendations for future research and reconsider the very specific recommendations.	We definitely appreciate the concern that outcomes assessment should be standardized for all of the safety outcomes. In highlighting the research gaps and future research needs, we focused on what are the current gaps (e.g., effects of pioglitazone on bladder cancer vs. other drugs). Based on your suggestion, we have broadened the recommendation on the need for standardized approaches to all safety events - current and future. We have also emphasized the importance of observational studies to address safety questions.
TEP Reviewer #3	Clarity and Usability	OK	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #4	General	Embedded; the labels for the figures are much better in the main paper than in the ES	Thank you. We have revised the labels in the Executive Summary figures to be clearer.
TEP Reviewer #4	Introduction	Good	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #4	Methods	Good. Would be helpful to understand why insulin included	Insulin was only included as an add-on to metformin.
TEP Reviewer #4	Results	Very complex, detailed. I can't imagine how you could have done it better (except for 2 reports which wasn't in your purview)	We appreciate the time it took for you to review this lengthy report. AHRQ is experimenting with alternative report formats, including having multiple reports for large reviews. Perhaps this is something AHRQ could consider for future updates.
TEP Reviewer #4	Discussion/ Conclusion	Good. Future research section is clear	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #4	Clarity and Usability	As above, this should have been 2 (at least) reports. However, given the volume of information, I can't imagine how you would have done one report differently than this. I am afraid it might be of limited usability given its volume	We appreciate the time it took for you to review this lengthy report. AHRQ is experimenting with alternative report formats, including having multiple reports for large reviews. Perhaps this is something AHRQ could consider for future updates.
TEP Reviewer #4	ES-6 HbA1c section	Do you mean the evidence was graded "high"? ?high quality	We added the words "strength of evidence" after the word high for clarity.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Table B	Since this is a summary of intermediate outcomes able, it would be good to include HbA1c in my view.	We thought the figure was a better summary for hemoglobin A1c and only put in table intermediate outcomes without a figure. We have changed the Table B (now Table C) heading to say systolic blood pressure and heart rate and deleted selected intermediate outcomes.
TEP Reviewer #4	Figure D	This is difficult. Met associated with much less hypoglycemia, it is drug 1 and the Or is 4.0 and the legend states "Favors drug 1". I think this needs to be created more clearly. i would change the legend to say "More hypoglycemia and less hypoglycemia."	Thank you for this suggestion. We have changed the legend for the hypoglycemia figure to say, "Fewer events with drug 2/drug 1."
TEP Reviewer #4	ES-12 Gastro-intestinal side effects	typically….. Describe the common Se's (diarrhea, etc)	Our figure denotes types of gastrointestinal adverse events in the meta-analyses. We decided to let the new gastrointestinal figure relay that information.
TEP Reviewer #4	ES-13 Pancreatitis	what about metformin monotherapy? is it associated with pancreatitis?	Based on feedback from the technical expert panel and peer reviewers, regrading of the evidence led to no moderate strength of evidence on pancreatitis. Therefore, we no longer have a separate section on this in the Executive Summary Results. Regarding the question of metformin and pancreatitis, we did not have conclusive evidence on metformin compared with another drug. We did not evaluate metformin compared with placebo in this report.
TEP Reviewer #4	ES-15 Discussion	showing ……	We added results of existing literature at end of sentence in the Executive Summary Discussion. We now say, "Our results on the intermediate outcomes of hemoglobin A1c and weight are generally consistent with existing literature showing that most diabetes medications reduce A1c similarly as monotherapy and that individual weight effects differ by medication class."

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	ES-15 Discussion	That is a lot i think (esp for women)	We have edited this sentence in the Discussion to say, "However, even small TO MODERATE amounts of weight gain (5 percent to 10 percent of body weight) may be associated with increased insulin resistance." Our edits are shown here in all capital letters.
TEP Reviewer #4	ES-17 Discussion	i would make this paragraph only about hypoglycemia (take "GI side effects" out of first sentence	We have made this change.
TEP Reviewer #4	ES-17 Discussion	side effects	We have changed the word "events" to side effects or adverse events after the word gastrointestinal.
TEP Reviewer #4	ES-17 Discussion	I think readers will want to know which ones	Since we conducted interclass comparisons, we discuss results as class effects unless we found an effect by drug type.
TEP Reviewer #4	ES-17 Discussion	i am assuming you couldn't fiugre out which and stratify by comparator	Correct, we have added text to clarify at end of the sentence. We now say, "We did not include the Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) Trial here because it did not report on macrovascular outcomes stratified by specific medication combinations of interest; a re-analysis of data from this study led to the FDA lifting its restrictions on the use of rosiglitazone."
TEP Reviewer #4	ES-17 Discussion	important finding	Thanks. We agree.
TEP Reviewer #4	ES-18 Discussion	really? did you report this in 2011? this seems important to highlight to me if true since i would guess most people don't know this. i think you could elaborate a little also if you trust the findings	We have made a change to indicate that we didn't find anything conclusive in the prior report (2011). We now state under Safety Outcomes in the Executive Summary Discussion, "Similar to the 2011 report, we found little evidence about cancer risk."
TEP Reviewer #4	ES-18 Implications	? Important	Revisions of this section have led to removal of that sentence in its past form.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	ES-18 Implications	the way this is written and the first sentence I mentioned above has the appearance of equating these SE's. I think that hypoglycemia is way more important in terms of the implications. i recommend somehow fixing this. I also am hoping that the long terms risks of hypoglycemia are discussed more in the full text. it is a huge issue	We have revised the Implications section of the Executive Summary substantially and hope that this does not lead the reader to conclude that the adverse events are equivalent. We did not feel comfortable going as far as ranking them since preferences and risk for adverse effects do vary. We focused on this aspect of the differential patterns of adverse effects with different medications. We also added that severe hypoglycemia is especially clinically-relevant (see Executive Summary Discussion and Discussion of main report). We agree that long-term risk of hypoglycemia is extremely important since patients will take medications for years. Unfortunately, most studies reporting on hypoglycemia (and generally for the entire report) were less than 2 years in duration. We have added text to the Discussion to clarify this issue for adverse events, including hypoglycemia.
TEP Reviewer #4	Introduction, pg 2	do you evaluate this outcome?	Please see the Methods chapter in the report. We evaluate fracture risk for the SGLT-2 inhibitors only.
TEP Reviewer #4	Introduction, pg 3	i am assuming you say which/why later	Yes, we provide a rationale in the Scope and Key Questions section under the Introduction chapter. We list the medications and comparisons of interest in Table 2 and Table A of the Executive Summary.
TEP Reviewer #4	Introduction, Table 1	i don't understand why there is NA in all of these columns	There is no maximum dose for these insulins in Table 1. We have added a footnote to the table to explain that further.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Introduction, Analytic Framework	do you think you need to say here that most guidelines recommend Metformin or that there are important reasons when possible to begin with Metformin? this makes it look like all choices are OK/equivalent. same with the analytic framework	The analytic framework allows us to question the supposition that metformin is the best first line agent. We do compare monotherapy in this report. We thought having the analytic framework focused primarily on metformin as first-line therapy would be too narrow. We added a sentence about guidelines to the Introduction chapter and under the Scope and Key Questions section. We also already discuss the guidelines in the Discussion and Executive Summary under Implications.
TEP Reviewer #4	Introduction, Figure 1	really nice AF	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #4	Introduction, Scope and Key Questions	i was surprised to see insulin included with this as I initially thought that it was an update of the 2011 review on oral meds. i think you might want to add a sentence or 2 here about why you included insulin and how you chose which insulin regimens to include	The 2011 report also had insulin in combination with metformin since the report was evaluating second-line therapy as add-on to metformin.
TEP Reviewer #4	Results, Results of Literature Searches	the number of references you had to review and papers is incredible! great job!	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #4	Results, KQ2, Key Points and Evidence Grades, All-Cause Mortality	above you discuss cancer outcomes with metformin yet this isn't addressed. Ishould it be mentioned? this report is long and i don't recall you saying why cancer outcomes not eval (and can't go back easily given the review format0	We apologize for the confusion. We did specify that we evaluated cancer outcomes for all comparisons in our protocol and Methods and reported on this in the Results section. The evidence was of low-strength or insufficient as stated in the Discussion. However, we wanted to put the lack of results in context but discussing what is currently know about cancer risk with the medications of interest.
Peer Reviewer #2	General	The report might be improved by drawing more explicit connections between the comparisons and key questions that were part of the design of this review and the stepped-treatment guidelines published by various professional groups.	We did add a sentence about how metformin is recommended as first line therapy in most guidelines under introduction and under scope. We also discuss guidelines in our discussion and executive summary under implications.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Introduction	"Same as general comment."	We did add a sentence about how metformin is recommended as first line therapy in most guidelines under introduction and under scope. We also discuss guidelines in our discussion and executive summary under implications.
Peer Reviewer #2	Methods	The inclusion and exclusion criteria are explained and seem reasonable. They do lead to the exclusion of some RCTs that relied on placebo controls, and which are widely referenced in discussions of how best to treat diabetic patients.	This is true. We have discussed this issue in our limitations section of the report. We have also brought up relevant trials in our discussion section where appropriate.
Peer Reviewer #2	Results	The results are clearly organized and encyclopedic in scope and content. The results are presented clearly. Most results were presented as relative risks. For those outcomes with the richest evidence base, presentation of absolute risk differences and number needed to treat might be useful. There may be sufficient evidence to do this only for the metformin-SU comparison and perhaps the dual therapies involving met-SU vs met-other.	We have added absolute risk differences to the Results sections and Executive Summary for all-cause mortality and cardiovascular outcomes. We also highlight the absolute risk difference and number needed to treat for the comparison for which we had the best quantitative data (metformin versus sulfonylurea) in the Discussion of the report.
Peer Reviewer #2	Discussion/ Conclusion	The discussion and conclusions were clear and reasonable. The gaps identified by the authors are so numerous that I wonder whether they could perhaps be a little more directive by suggesting priorities for which specific outcomes should be tackled first. In this context, discussion of how such a study might be designed and how large it would need to be, and how long it should be continued would also be helpful. From an RCT perspective, a few large, well-designed trials of sufficient duration would probably be more informative than a score of smaller/shorter studies.	We have rewritten this section to highlight the most important gaps with the goal of prioritizing the needed research for the reader. Regarding the specifics of randomized controlled trials, consistent with your comment below, we have added detailed text on the need for observational studies and particular methodologic issues that need to be addressed in such studies. We make the point (as you do below) that it is actually just not feasible to do randomized controlled trials to answer all of the questions about long-term clinical and safety outcomes.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion/ Conclusion	I was also struck by the paucity of high quality evidence on many major clinical outcomes and how difficult and expensive it will be to design appropriate RCTs to generate this evidence. It seems to me that this may be a situation where, like it or not, observational studies are probably all we're likely to have for many years to come. Discussion about how observational studies could be designed and conducted to help fill this evidence gap would be most useful. I thought the current discussion was rather weak and vague in this regard. Since diabetes is a progressive disease and its treatment dynamic and changing over time, observational databases would need to have large numbers with low drop-out and long follow-up, perhaps relying on MSM or other techniques to capture the changing therapies.	Per the comment above, we have added a section to the Future Research Needs on observational studies and how to design them. This includes a discussion of the methodologic issues that you pointed out.
Peer Reviewer #2	Clarity and Usability	The report is well-organized. What impressed me most was how weak the evidence base is for virtually all clinical outcomes.	Yes, we agree. The state of the evidence base is quite weak.
Peer Reviewer #3	General	Is the report clinically meaningful? The report strengthens and adds to the evidence comparing of specific diabetes medication monotherapies and specific combination therapies on intermediate outcomes (HbA1c and weight, particularly) and safety outcomes. Some of this, however, is difficult to clinically interpret because relative risks may be high yet absolute differences are clinically minimally. Some context around this issue would be valuable. This also applies in general to clinically meaningful differences between treatment regimens. For example, while a weight difference of approximately 5lbs is observed for a variety of treatment regimen comparison, the clinical effect of this amount of weight change is limited among patients with diabetes who are mostly overweight and obese already. Furthermore, costs and patient preferences will also come into the clinical decision-making process. A broader context within which to interpret the findings would be helpful.	We have added risk differences throughout the Results sections for mortality, and cardiovascular outcomes, and safety outcomes where most relevant. The Discussion of the Executive Summary and main report also includes information on the absolute differences. We have also discussed the clinical relevance of weight effects and patient preferences in the Discussion, including the Implications of the Discussion of the main report and Implications of the Executive Summary.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207
Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	Are the target population and audience explicitly defined? Yes. But, a limited evidence-base prevents the authors from adequately assessing comparisons within demographic and comorbid subpopulations.	Thank you. We agree.
Peer Reviewer #3	General	Are the Key Questions appropriate and explicitly stated? Yes. The Key Questions are well-constructed.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Introduction	The Introduction and Rationale are focused and well done. Lines 38 and 39 discuss the need for better evidence on the effects of intensive glucose control and medications (cardiovascular and safety outcomes) within specific co-morbid subpopulations. It would be good to highlight some of these key co-morbid populations (i.e CKD, CHD), especially given that most studies either do not report on these populations or exclude them even though they represent a substantial proportion of the type 2 diabetes population. This is eventually a take home message for researchers that more studies examining the effects of specific diabetes therapies within these populations is urgently needed.	We discuss this under Study Characteristics and under Future Research in the Discussion and Executive Summary.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207
Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	Many of the selected outcomes (intermediate, long-term, and safety) are important for clinical consideration. This is not as clear for weight, especially given the amount of difference we are talking about. It might be useful to add more to the Intro (or perhaps the Discussion) to put this amount of weight difference in clinical context. Here is a reference to a Look Ahead analysis examining this issue: Benefits of modest weight loss in improving cardiovascular risk factors in overweight andobese individuals with type 2 diabetes. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L; Look AHEAD Research Group. Diabetes Care. 2011 Jul;34(7):1481-6. doi: 10.2337/dc10-2415. Epub 2011 May 18.	We did not want to discuss the controversy regarding weight change and effects on mortality and morbidity as this could be long and would divert from the comparative effects discussion. We did add data on how important weight change is to patients regardless of their effects on longer-term outcomes to emphasize the importance weight plays when choosing diabetes medications for the consumer. We have added this to the Discussion of the main report and in the Executive Summary Discussion.
Peer Reviewer #3	Introduction	More context about clinically meaningful change/differences in heart rate would also be helpful…whether in the Intro or in the Discussion. In fact, this is a general consideration, what difference is clinically meaningful taking into account absolute event rates and the amount of difference between the outcome of interest. This is important because unless these are substantial other factors such as patient preference and costs will likely drive clinical decisions.	We did describe this in the Discussion of the main report as well as the Executive Summary Discussion.
Peer Reviewer #3	Introduction	Line 36 has an extra 'however'.	Thanks for noting this. We have removed the redundant "however."
Peer Reviewer #3	Methods	Are the inclusion and exclusion criteria justifiable? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Methods	Are the search strategies explicitly stated and logical? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Methods	Are the definitions or diagnostic criteria for the outcome measures appropriate? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	Line 27-28: What was the basis for determining minimally important differences for A1c, weight, and SBP?	We have added to the Methods chapter under the Strength of the Body of Evidence section: "While there are no strict definitions of what might be considered clinically relevant differences, we used minimally important differences that clinical experts suggested are clinically relevant and that are supported, in part, in the literature."
Peer Reviewer #3	Methods	Are the statistical methods appropriate? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Results	Is the amount of detail presented in the results section appropriate? 'Key Points and Evidence Grade' section beginning on p.19: • The main convention is discussing 'reductions' and a negative difference between groups. This is not used consistently but should be to make reading and interpretation easier. For example, with the monotherapy, the last bullet (Line 54-6) does not include the (-) when talking about the reduction difference between-group but all the previous bullets do. This is particularly the case with the weight key points (p20-1).	We have changed this for clarity to the reader in the Key Points.
Peer Reviewer #3	Results	Are the characteristics of the studies clearly described? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Results	Are the key messages explicit and applicable? As suggested in e-mails after last weeks' presentation, it would be useful to have some figures detailing the length of studies since this appears to be a major limitation for many aspects of this review. Essentially, by selection criteria definition almost all analyses were for studies 3-12 months in length since longer studies were truncated to align with the duration of the majority of studies. Study duration is a critical and important issue that merits highlighting.	We have added a figure (Figure A in the Executive Summary and Figure 3 in the Results chapter) that shows the study duration for the randomized controlled trials. We also added a section to the Results section, Study Duration of the Randomized Controlled Trials, that describes the length of followup.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Are the Figures, tables, and appendices adequate and descriptive? The figures and tables are well done. Figure B in the Executive Summary (pES-8), and the preceding text, talk about the comparison of MET+SU vs either premixed insulin or basal insulin, however these comparisons are not in the Figure. The Figure B notes suggest it should be in the Figure.	We have removed from Figure B footnote. We have explained in the text about these comparisons.
Peer Reviewer #3	Results	I particularly like the Strength of Evidence Summary Tables such as Table 6 (p45-6), Table 7 (p47-8), etc. In the 'Summary' column of these tables effects are described as small, medium/moderate, and large but there is no definition of these. This should be included in the notes at the bottom of the table or, better yet, use the actual definitions in this column.	Thanks. We have changed these to actual results throughout when there were sufficient data to present quantitative findings.
Peer Reviewer #3	Results	Figure 62 (p159) has several excluded studies. While I understand these are excluded from the weighted pooled analyses because they do not contribute any events, it may be good to include this statement in the Figure footnotes.	We added a footnote, "Studies were excluded because they did not contribute any events," whenever there was a study that was excluded from the meta-analysis because they did not contribute any events. For Figure 62 (now Figure 63) specifically, we decided not to conduct a meta-analysis because there were so few studies reporting any events.
Peer Reviewer #3	Results	Many of the Key Questions could not be addressed because of study limitations. While these are described in the text, it would be nice to have a summary table of the 'Research Gaps', perhaps in the PICOT framework. In the Executive Summary and the Main Report, it would be nice to label the PICOT section related to each identified research gap. Similarly, a Summary Table of Method Gaps and Suggested Improvements would be nice.	We have reorganized the Research Gaps using the PICOT framework and placed them with the Future Research Needs in a table.
Peer Reviewer #3	Results	Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? No.	Thank you for taking the time to review our report. We appreciate your feedback!

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/ Conclusion	Are the implications of the major findings clearly stated? The major findings are clearly stated. But, the implications are more difficult to ascertain because the clinical relevance in terms of amount of difference between treatment regimens, especially absolute versus relative, and other non-evidence-based factors like patient or provider preference and cost are not taken into account. While these may be beyond the scope of the review, it would be useful to include some intention-to-treat information to provide context regarding the clinical and policy implications of the results.	We have added substantial text to the Implications section based on this comment and others. Regarding differences between treatments, we wanted to avoid redundancy in reporting numbers but do have absolute risk differences in the earlier part of the Discussion in which we discuss Key Findings. We have emphasized the importance of preference and cost as well.
Peer Reviewer #3	Discussion/ Conclusion	pES-17-8: The full name of the SAVOR study should be listed in the last paragraph on pES-17 and removed from the first paragraph of pES-18.	Thank you for pointing this out to us. The SAVOR TIMI 53 trial is spelled out the first time it is mentioned.
Peer Reviewer #3	Discussion/ Conclusion	Are the limitations of the review/studies described adequately? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Discussion/ Conclusion	In the discussion, did the investigators omit any important literature? When discussing the clinical and policy decision implications, the authors indicate that ultimately costs will drive patient/provider decision making. It would be good to include some references about this because these few lines on p281 get to the pragmatic use of the reports' findings (i.e the findings are important but their use may be overwhelmed by cost issues).	We removed some discussion of costs since it is not clear that costs are the primary driver. We have discussed patient preference as well as cost briefly as potential drivers.
Peer Reviewer #3	Discussion/ Conclusion	Is the future research section clear and easily translated into new research? See above.	We appreciate your feedback. We have addressed your comments, as noted above.
Peer Reviewer #3	Clarity and Usability	Is the report well structured and organized? Yes.	Thank you for taking the time to review our report. We appreciate your feedback!
Peer Reviewer #3	Clarity and Usability	Are the main points clearly presented? Yes, the main findings are clearly presented. Although, as noted above, more context to inform practical use of the findings would be nice and a table to present research gaps and future recommendations would be helpful.	We have reorganized the Research Gaps using the PICOT framework and placed them with the Future Research Needs in a table. We have also revised the Implications section in the main report and Executive Summary considerably to provide more context for use of the findings.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Clarity and Usability	Can the conclusions be used to inform policy and or practice decisions? See prior comments.	We appreciate your feedback. We have addressed your comments, as noted above.
Peer Reviewer #4	General	The authors are to be congratulated on outstanding work of very high quality. This report provides a very high-quality review of relevant evidence with respect to the impact of various glucose-lowering monotherapies and combination therapies on relevant and important patient outcomes such as mortality, major CV events, microvascular complications of diabetes, and selected safety outcomes relevant to particular classes of medications. Most of the results are presented, appropriately, as odds ratios or hazard ratios (with confidence limits) for mortality, CV mortality, and similar outcomes. Foe A1c, weight, BP and pulse, among others, the pooled mean between-group differences are presented. These metrics are useful but see comments below.	Thank you for taking the time to review our report. We appreciate your feedback!

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207
Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	Fro mortality and CV event outocmes, it would be very helpful to supplement data on OR or Hazard Rations (HR) with data on absolute risk difference (AR), which could be communicated as number needed to treat over specified periods of time. The practical challenges of using AR are numerous, because the difference in rates may differ substantially across particular studies, and there may be some differences in the definitons of certin evnets across studies. However, the presentation of such data are CRUCIAL from the perspective of clinical application of the findings of the report, and very helpful in terms of communicating these reustls to patients in a way that may, in a comprehensible way, inform patient preferences for specific treatment options. I urge the authors o fthis report to accept this challenge and find ways to meaningfully communicate to readers of this report not only the ration of rates, but also the difference in rates of certain non-continuous outcomes (ranging form mortality to mycotic genital infections). This is a major point.	We agree that absolute differences are very important to interpreting our results and have incorporated between-group risk differences to the Executive Summary and to the Results section of the report. Risk differences are also discussed in the Discussion of the main report and Executive Summary when most relevant.
Peer Reviewer #4	General	There are few conclusions based on subgroup analyses, which is unfortunate. It is unlikely that the risks and benefits of many of the therapies of interest are the same in various age strata. However, the authors of the report are constrained by available, data. IN future reports, it would be most helpful to select studies in future reports that targeted particular subgorups.	It is unfortunate we do not have more subgroup analyses. For a study to be most useful on differences by subgroup, one would want to compare results within a specific subgroup to those without the condition within the same study. In future, other alternatives could be discussed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	With respect to subgforup analyses, it is noted that reports limited to patients with certain comorbid conditions (presumably including coronary heart disease, and CHF) were not included in the review. I suggest that such studies be included in future reviews, because it is of great clinical importance to understand the risks and benefits of certain treatments and treatment combinations on CV outcomes and events. It is likely that medications with some CV risk may be most easily identified when assessing the impact on that treatment on those most susceptible to CV events, namely, patients with high CV risk, or those who have previously had an established diagnosis of CV disease. This is a major point.	We only excluded 25 studies due to this exclusion (see Figure 2). The data from these studies would not have influenced the results. We did include studies for many comorbidities such as mild to moderate chronic kidney disease or coronary artery disease. There were insufficient studies under each comparison and each outcome to definitively determine differences among these studies and studies without the comorbid condition. However, that was not part of the analytic plan due to difficulties in comparing a study with all one subgroup to studies without the subgroup given the different settings and interventions which can also influence or confound the findings.
Peer Reviewer #4	General	The criteria used to rank quality of cohort studies may be outdated. The main requirement for inclusion of such studies appears to have been an analysis plan that adjusts for age, race/ethnicity, and sex. However, such adjustment may not assure valid conclusions. A more sophisticated and updated method to evaluate the validity of observational studies is needed. Such a method may need to consider inclusion criteria, use of propensity scores, and modern statistical methods such as marginal structural models or instrumental variables analysis. This seems to me to be a somewhat major issue for future reports.	We actually used age, race/SES, sex, AND comorbidity/confounding by indication as needed adjustment to be included in the review. Once included, we also rated the quality of the observational studies using the well validated Downs and Black scale. The observational studies were therefore moderate to high quality. None were considered low quality using the Downs and Black criteria. This is discussed in the Methods under risk of bias assessment, and the quality of the observational studies are described under risk of bias paragraphs in the results as well as where appropriate under the comparisons of interest. We have also added a section to the Research Gaps/Future Research Needs of the Discussions on the need for high-quality observational studies and have made suggestions regarding the design of such studies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	In addition to expanding subgroup analysis to include those with CHD and separately those with CHF, I would also suggest that conclusions be stratified based on length of study follow-up for outcomes such as mortality, CV mortality, or CV events. This is a major suggestion.	We have stratified conclusions on long-term vs. short-term studies when possible (i.e., when evidence present to do so) for mortality and cardiovascular disease outcomes. We have also summarized evidence in the Results section separately for the long- and short-term studies for these outcomes. We did not prespecify coronary heart disease and congestive heart failure as subgroups for analysis when we finalized the protocol for our report in 2014. While this was not part of our systematic review protocol and therefore not done systematically, we have generally pointed out when studies restricted to these populations or pointed out when results stratified by these variables were available.
TEP Reviewer #5	General	Yes, the report is clinically meaningful. The target populations and key questions are approriate. It's no fault of the authors that the data in some important areas is so sparse!	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Introduction	Well done.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Methods	The methods appeared quite strong!	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Results	In general, yes. I was eager for more data on results by individual drugs in a class (see uploaded review).	We separated into individual drugs when there was sufficient differences in results to suggest differences in that outcome by individual drug. For GLP-1 agonists, for example, we often did not combine studies due to potential differences in the individual drugs. We described these studies in the text. We did separately evaluate rosiglitazone and pioglitazone for the longer-term outcomes due to known differences by drug in that outcome. We have added to the methods and also the limitations regarding this issue.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Discussion/ Conclusion	The implications could have deleved more deeply into questions important to clincains (and guideline developers). What's the second choice for monotherpay if metformin can't be used (CKD, for example) or isn't tolerated? What are the specific pros and cons of the choice of a second drug to add to metformin when greater control of hemoglobin A1c is desired?	We agree that these are very important issues. We have added text on the Implications section of the Discussion to address the issue of non-metformin monotherapy in the setting of contraindications or intolerance of metformin as well as add-on therapy to metformin. Ultimately, there is no right answer, and we have clarified that we do not have much evidence on long-term effects on mortality or cardiovascular disease outcomes or rare adverse events and that there are otherwise differential effects of many of the medications on weight, hypoglycemia, and gastrointestinal side effects. Overall, the data presented here allow guideline groups to discuss the benefits or harms of the medications and make choices for second-line therapy. Translational products to communicate these benefits and risks may add clarity on some of these issues.
TEP Reviewer #5	Clarity and Usability	Obviously, the report is long and difficult to plow through, although the executive summary and key tables are very helpful. The document is organized so that when a "deep dive" is desired, the right section can be found fairly easily.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Executive Summary	ES-1 Given the proliferation of new medications for people with diabetes, readers would benefit from a Table listing the drug classes, a brief indication of the mechanism of each class, and the generic and Brand names of the FDA-approved members of the class, at least those drugs available as of the end date of the review.	We have added Table 2 from the main report to the Executive Summary which now includes generic drug names (this is Table A in the Executive Summary). Due to space constraints in the executive summary, we did not add anything more in this section. We did add main mechanism of action to Table 1 in the report. This table also lists the generic and brand names of the medications.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Executive Summary	Figure A is key. In general, the take-aways are that based on A1c effect, metformin as monotherapy is about equivalent to TZD (and SU based on the previous review). Adding a member of any class to metformin decreases A1c by about 0.5-1.0% with high SOE. The combinations are pretty equivalent (statistically significant differences are of dubious clinical significance), except that in 3 trials, Met+DPP1 was not as good as Met+GLP1 (an injectable). Moderate SOE.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Executive Summary	Figure B. Weight favors Met over DPP4 (and TZD and SU in previous review). GLP1 beats SU. Adding GLP1 or SGLT2 to Met increases weight loss. Absolute differences are ~2 Kg. Adding DPP4 or SGLT2 to Met beats Met+SU. Met+SGLP2 beats Met+SU by ~ 5 Kg. High SOE.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Executive Summary	Table B. Met+SGLP2 reduces systolic blood pressure more than Met or Met+SU, by ~5 mm Hg, High SOE; and more than Met+DPP4, by ~4 mm Hg, Moderate SOE. Met+GLP1 reduces systolic BP more than Met, by ~ 3 mm Hg, Moderate SOE.	Thank you for taking the time to review our report. We appreciate your feedback!
TEP Reviewer #5	Executive Summary	The lack of long-term data from RCTs on cardiovascular mortality is disappointing, but supports the approach of examining higher-quality observational studies. In Figure C, the confidence intervals appear too broad to support a moderate and particularly a high SOE of equivalent total mortality. Do I misinterpret?	We appreciate this comment. We have regraded the evidence and have refined our approach regarding excluding benefit or harm. After further discussions with the Technical Expert Panel and other peer reviewers, we have added an additional stipulation to our approach to evidence grading. If the evidence on a comparison for a given outcome is imprecise (underpowered), we will not conclude that the comparators are similar in effect with moderate or high strength of evidence. We have clarified this in the Methods. The comparison in question is no longer rated as "moderate."
TEP Reviewer #5	Executive Summary	Cardiovascular mortality and morbidity/Table C. Given the lower risk with Met than SU, a "pertinent negative" to mention is the lack of evidence for higher cardiovascular mortality/morbidity with Met+SU than Met monotherapy, or Met+other agents.	Thank you. We have added this to the Executive Summary Results as a pertinent negative.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Executive Summary	Figure D. The higher RRs of hypoglycemia with SU alone or in combinations, as are the absolute risks of ~15-20% in relatively short-tem studies. Was there any evidence that this finding is not a class effect, but depends on the SU agent (for example, glipizide versus glyburide)? This question is important, as it bears on the best drug to add to Met if better A1c control is eeded.	We did not find evidence of an intraclass effect and have discussed this in the Discussion of the main report and added text about this in the Executive Summary.
TEP Reviewer #5	Executive Summary	ES-12. Any evidence on differences in GI side effects with different formulations of metformin (immediate vs delayed release, for example)?	This was not a comparison of interest for this review. It could be considered at a separate time.
TEP Reviewer #5	Executive Summary	ES-15. Weight effect summary: TZD and SU associated with weight gain, DPP4 inhibitors with weight maintenance, and GLP1 agonists and SGLT2 inhibitors with weight loss. Regarding injectable medications, presumably SGLT2 associated with weight loss, but presumably basal insulin with weight gain?	Yes, we agree. We have added that insulin is associated with weight gain.
TEP Reviewer #5	Executive Summary	ES-16. Regarding SBP, given the relative effectiveness of glucose-lowering therapy, low sodium diet, and antihypertensives, there's an argument to simply manage SBP separately with antihypertensive drugs proven to reduce MIs and strokes.	We agree with this completely reasonable argument. The reason for evaluating effects on systolic blood pressure is that reductions in systolic blood pressure could be a reason why one drug may or may not have a longer-term mortality benefit. The question is whether these small differences in systolic blood pressure have any long-term effect on mortality and morbidity in the presence of an antihypertensive medication. We don't really know the answer to that. We have added a sentence in the Discussion and Executive Summary on this issue.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207
Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Executive Summary	ES-16. Regarding long-term outcomes and the choice of a second drug to add if MET is inadequate, I take it there are no data on MET vs MET+SU vs MET+any other agent on CV mortality or morbidity? This concern about increasing CV mortality may be an important reason for a clinician deciding to prescribe newer, high-priced medication as a second drug.	We agree that this is important. However, we did not find moderate or high strength of evidence for other comparisons to substantiate a conclusion regarding the "best" add-on to metformin. We had some low strength of evidence on metformin plus a sulfonylurea versus metformin plus a DPP-4 inhibitor that suggested a benefit of metformin plus a DPP-4 inhibitor over metformin plus sulfonylurea but more evidence is needed (discussed in the Discussion of the main report). We think it is still unclear whether sulfonylureas just have less benefit vs increased risk since we do not have placebo-controlled trials in this report, and we would be cautious in advocating use of newer meds with less data as add-on over older meds.
TEP Reviewer #5	Executive Summary	ES-18. Implications section is relatively weak. Needs discussion of advantages/disadvantages of choice of a second agent after Met, particularly focusing on hyperglycemia and CV morbidity and mortality.	Thank you for suggesting ways to improve this important section. We assumed that this comment referred to **hypoglycemia** and not hyperglycemia (in addition to cardiovascular disease morbidity and mortality). We have revised the Implications sections of the Discussions in the main report and Executive Summary substantially based on this and other comments.
TEP Reviewer #5	Executive Summary	ES-18. Limitations. Were head-to-head comparisons of agents within a class excluded, or were there just none of those comparisons? Are there tables later in the paper showing which SU agents were used in the trials documenting more hypoglycemia and CV mortality and morbidity? Knowing which SUs were associated with these safety concerns would be helpful in udging whether it's likely a class effect.	We appreciate this comment. We did not evaluate intraclass comparisons formally (as specified in our protocol) but did look at agents within a class as a source of potential heterogeneity when relevant. We did not see an intraclass effect for sulfonylurea therapy and hypoglycemia. We do note which sulfonylurea is under study in the Results sections (in tables or text depending on number of studies).
TEP Reviewer #5	Executive Summary	ES 19-20. I like the research recommendations!	Thank you for taking the time to review our report. We appreciate your feedback!

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Introduction	Page 3/Table 1. The Table is really helpful and should be in the executive summary. What is meant by "basal" insulin in this context? Should the search have found studies comparing adding basal insulin to Met versus other 2nd drugs (especially the injectable GLP-1 agonists)? Table 2 suggests yes. Taking injections is a big step for many patients, and it would be helpful if there were evidence comparing the benefits and harms of adding either of the injectables to Met.	Yes, we did study this important comparison of metformin plus GLP-1 agonists to metformin plus basal insulin. See table of medication comparisons (Table 2). We have added text on this to the Executive Summary and Discussion given the clinical interest in these medication comparisons.
TEP Reviewer #5	Methods	Page 13. So class effect for therapeutic effect and side effects was "assumed until proven otherwise?" Since tests of heterogeneity can have low power, the reviewer wonders about the wisdom of that approach. As noted above, for some analyses, particularly for SUs, differences within the class (for example, hypoglycemia risk with glyburide versus glipizide) would be important to examine in detail if possible.	We did not rely solely on statistical heterogeneity. If we felt something was clinically sufficiently different due to a known or potential drug class difference, then we evaluated or discussed it separately. Glyburide was found to have more hypoglycemia than glipizide from our first systematic review in 2007 by 3%, but we did not find consistent evidence of larger between-group differences in hypoglycemia for these medications compared with other sulfonylureas. Therefore, we did combine these in with other sulfonylurea studies for this outcomes.
TEP Reviewer #5	Results, KQ1	Page 18. What's a "rescue medicine" in this context?	We added in parentheses (i.e., the addition of another diabetes medication if not controlled on the study medications). This edit was made to the Study Design and Population Characteristics paragraph of the Key Question 1 Results section.
TEP Reviewer #5	Results, KQ1	Page 31. The differences in relative effect in the ADOPT study emphasize the need for longer-term data on comparisons.	We agree that longer data are important. However, ADOPT had over 50% loss to followup and was funded by the manufacturer of rosiglitazone. We have added more on the need for longer-term data in the Executive Summary and Discussion.
TEP Reviewer #5	Results, KQ1	Page 43. So in response to a question above, 2 RCTs showed no dramatic benefit of Met+GLP-1 agonist versus Met+basal insulin on A1c, though low SOE.	Correct, we have added this to the text in the Executive Summary and Discussion and Key Points for clarity to the reader.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results, KQ1	Page 65. So in 2 RCTs Met+GLP1 agonist beat Met+basal insulin on weight, by ~5 Kg, low SOE.	Correct, we have added this to the text in the Executive Summary and Discussion and Key Points for clarity to the reader.
TEP Reviewer #5	Results, KQ2	Page 89. So the FDA labeling appears appropriate given the low/insuffcent SOE for the comparisons on CV mortality, right? Why the "however?"	We were pointing out that despite the importance of cardiovascular outcomes (emphasized by the fact that the U.S. Food and Drug Administration has made a note about this for all diabetes medications), we did not find a good evidence base to substantiate conclusions.
TEP Reviewer #5	Results, KQ2	Page 91. So in the 2 RCTs with a reasonable amount of person-time, the glyburide study showed an RR point estimate of 1.0 for overall mortality and the glipizide study showed an RR of 2.1? That would seem to challenge the theory of a class effect. The observational studies are more suggestive of a class effect, but of course are not as strong methodologically.	We appreciate this point but do not believe that we can comment much on if there is an agent-specific rather than class effect. In the absence of that ability, we have summarized the findings of sulfonylureas together. While the relative risk was 1.0 in ADOPT, the absolute risk difference was 0.1% (indicating a slightly higher risk in the sulfonylurea versus metformin arm, number needed to treat of 1,000 which is important given the number of potential people to be exposed). The two randomized controlled trials with long-term followup were very different (aside from the sulfonylurea used): ADOPT had a healthier population (newly diagnosed diabetes, no treatment) while the other trial enrolled patients with diabetes for a longer duration (based on baseline characteristics) and required a history of coronary heart disease. Therefore, baseline risks were different in the trials. Also, losses to followup were at least twice as high in ADOPT vs. the other randomized controlled trial. Combined with the information from the observational studies, we felt most comfortable with summarizing this as evidence metformin versus sulfonylureas as a class and not specific sulfonylureas.
TEP Reviewer #5	Results, KQ2	Page 92. Note glibenclamide and glyburide are the same drug, right? Needs a table footnote.	Thank you for mentioning this. We made a note of this in Table 2, where the drugs are first described.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results, KQ2	Page 95. Too bad there's not more evidence for Met versus Met+SU on overall mortality!	Yes, we agree!
TEP Reviewer #5	Results, KQ2	Page 109. ES-11 notes a 37-50% reduction in CV mortality on Met versus SU with high SOE. That seems hard to reconcile with the data on pages 109-110. Looks like those RRRs come from the observational studies? The confidence intervals from the RRs in the two RCTs are quite broad.	We have regraded the evidence for KQ2 and have rated the evidence as moderate in strength for the comparison of metformin versus sulfonylurea. We have clarified that these are relative risk reductions from randomized controlled trials when used and also provide risk differences from the randomized controlled trials. We used the observational studies to support our conclusions from trial data.
TEP Reviewer #5	Results, KQ3	Page 151/Figure 156. Provide the names of the specific drugs, as in Table 51 on the next page. Do the data suggest a class effect? I note in Table 1, only one study compared Met versus glipizide, and the rates of severe hypoglycemia were similar.	There was substantial statistical heterogeneity in the metformin versus sulfonylurea hypoglycemia meta-analysis (now shown in Figure 56). Unfortunately, we don't have enough studies to explore the source of heterogeneity statistically. Since we don't know the source of heterogeneity, we decided to display potential sources (such as specific drug name, dose, followup duration, and hypoglycemia definition) in Table 57.
TEP Reviewer #5	Results, KQ3	Page 157. Same issue, provide the names of specific drugs.	We decided to present this information in Table 63.
TEP Reviewer #5	Results, KQ3	Page 165. Well, the SU versus DPP-4 inhibitor RCTs do suggest a higher risk of hypoglycemia, even with glipizide. Agree with moderate SOE.	Thanks for your careful review.
TEP Reviewer #5	Results, KQ3	Page 170. Seems confirmatory to data on page 165, but would name SU drugs in Figure 167.	There were only two types of sulfonylureas used by the studies included in Figure 67: glipizide and glimepiride. We used a footnote to designate which studies used which type of sulfonylurea.
TEP Reviewer #5	Results, KQ3	Page 187. Any evidence of a difference in GI side effects depending on use of immediate versus extended release metformin in these or following comparisons?	We did not do sub-analyses based on release formulation of metformin.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Discussion/ Conclusion	Page 269: Is it worth pointing out that while A1c may be linked to microvascular disease, it isn't well linked to macrovascualr disease, the bigger killer. Too narrow a focus on A1c and not enough focus on BP, lipids, perhaps aspirin may be counter-productive. In that same paragraph, the discussion on the possibility of heterogeneity of effects within a class could use xpansion.	We agree about the link to macrovascular disease is less well established. We think the second part is important but off topic off for this report. In terms of heterogeneity expansion, see my comment related to heterogeneity within a class above. I think this is mainly relevant for the GLP-1 agonists currently and not other medications for A1c where most individual drugs had similar effects within class. This was determined by clinically looking at the data as well as statistical heterogeneity.
TEP Reviewer #5	Discussion/ Conclusion	Page 273: To the reviewer's eye, the comparison of Met versus SU on overall mortality still seems to depend heavily on observational studies (pages 91-92).	We regraded the evidence and found low (instead of moderate) strength of evidence for long-term all-cause mortality for metformin versus sulfonylurea based on two longer RCTs and seven observational studies. After further discussions with the Technical Expert Panel and other peer reviewers, we have added an additional stipulation to our approach to evidence grading. If the evidence on a comparison for a given outcome is imprecise (underpowered), we will not conclude that the comparators have similar effects with moderate or high strength of evidence. We have clarified this in the Methods.
TEP Reviewer #5	Discussion/ Conclusion	Page 281. Yes, cost will be an issue to tackle as we move to developing guidelines based on these data!	Yes, we agree.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer GlaxoSmithKline	Methods	The following was prepared in response to your request for public comment for the draft comparative effectiveness review titled "Diabetes Medications for Adults with Type 2 Diabetes: An Update Focused on Monotherapy and Add-On Therapy to Metformin". Consider including studies in which patients received other background medications in addition to metforminto represent dual therapy, triple therapy, and add on to insulin which is aligned with the American Diabetes Association recommendations for the treatment of type 2 diabetes mellitus. Please consider the following publications for Tanzeum (albiglutide): 1.Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia 2014;57:2475–2484. 2.Rosenstock J, Fonseca VA, Gross JL, et at. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care 2014;37(8):2317-2325. 3.Pratley RE, Nauck MA, Barnett AH, et al, for the HARMONY 7 Study Group. Once-weekly albiglutide vs once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomized, open-label, multicenter, noninferiority phase 3 study. Lancet Diabetes Endocrinol 2014;2(4):289-297. 4.Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study . Diabetes Care 2014;37:2723-2730.	Thank you for these suggestions. The Weissman article was included in our updated search, but excluded during our full text review because the study allowed participants to take background medications. The Rosenstock article was excluded during our full text review because it does not have a drug comparison of interest. The Pratley article was excluded during the full text review because it had a head-to-head comparison. The Leiter article was excluded because patients were allowed to continue their background medications. The Reusch article was included in our updated search, but was excluded because there was no comparison of interest.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer GlaxoSmithKline (continued)	Methods (continued)	5.Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled, trial in patients with type 2 diabetes mellitus not controlled on pioglitazone with or without metformin. Diabetes Obes Metab 2014;16(12):1257-1264. 6.Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year inpeople with type 2 diabetes currently taking metformin and glimepiride: Harmony 5. Diabetes Obes Metab 2014. Published online December 10, 2014.	
Public Reviewer GlaxoSmithKline	Results	The lost to follow-up for Ahren et al (reference 110) is reported as various percentages throughout the results section. Please consider revising to match Figure 1 of the publication.	Throughout the report, we tried to consistently state that there was a 30 to 40 percent loss to followup in the Ahren study.
Public Reviewer GlaxoSmithKline	Results	Page 74, 2nd paragraph of draft report - reference 110 is for the comparison of metformin versus metformin + albiglutide and the paragraph states liraglutide.	We have corrected this error.
Public Reviewer GlaxoSmithKline	Results	Page 84 of the draft report - in the 3rd paragraph under the comparison of metformin + DPP4 versus metformin versus GLP-1, it states that there was a non-significant between difference in heart rate between metformin + sitagliptin versus metformin + abiglutide. No statistical analysis was performed on heart rate for this comparison.	Thank you for noting this. Many studies do not report all the measures we use to summarize the results, but they provide sufficient information for us to derive these measures. We describe in the Methods chapter, in the Data Synthesis section, how we derived the summary results.
Public Reviewer GlaxoSmithKline	Results	Page 99 of draft report - consider adding all cause mortality is reported in Ahren et al (reference 110) to the following comparisons: metformin versus metformin + GLP-1, metformin + sulfonylurea versus metformin + GLP-1, and metformin + DPP4 versus metformin + GLP-1.	Thank you for mentioning this. We have updated the mortality section to include the results from the Ahren 2014 study.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer GlaxoSmithKline	Results	Page 109 and 119 of draft report - consider including information on cardiovascular mortality and cardiovascular events for the following comparisons: metformin versus metformin + GLP-1, metformin + sulfonylurea versus metformin + GLP-1, metformin + DPP4 versus metformin + GLP-1. Please see study summary at http://www.GlaxoSmithKline-clinicalstudyregister.com/study/112753#rs.	We have included this information in the Grey Literature section and discussed it with the strength of evidence when relevant.
Public Reviewer GlaxoSmithKline	Results	Page 202 and 203 - for comparison of metformin + sulfonylurea versus metformin + GLP-1, the GI events presented for Ahren et al (reference 110) are different than the publication. Please consider revising the data to include the information presented in Table 1 and text of the publication.	We have corrected the report to match page 2145 of the manuscript (vomiting) and the appendix so that all items are reported as percent.
Public Reviewer GlaxoSmithKline	Results	Page 233 of draft report - consider adding pancreatitis data from Ahren et al (reference 110) to the comparison of metformin + sulfonylurea versus metformin + GLP-1.	We added pancreatitis data from Ahren on metformin plus a sulfonylurea versus metformin plus a GLP-1 agonist. Thanks for catching it.
Public Reviewer GlaxoSmithKline	Results	Page 237 of draft report - consider adding data on systemic allergic reactions from Ahren et al (reference 110) to the following comparisons: metformin versus metformin + GLP-1, metformin + sulfonylurea versus metformin + GLP-1, and metformin + DPP4 versus metformin + GLP-1.	We did not add this outcome here because Ahren only reports injection site reaction. The outcomes we included in the report were severe allergic reactions. Thanks for your comment.
Public Reviewer GlaxoSmithKline	Figures	Please consider adding the length of the studies evaluated in the figures included in the result section.	For the Executive Summary figures, we have noted if the studies are 1 year or shorter or provided the exact range of study duration if the studies are longer than 1 year. For the figures in the main body of the report, we feel that the study durations are adequately described in the text.
Public Reviewer GlaxoSmithKline	Figures	Figure 82 - GI events presented for Ahren et al (reference 110) are different than the publication. Please consider revising the data to include the information presented in Table 1 and text of the publication.	We corrected this to match page 2145 of the manuscript (vomiting) and the appendix so that all items are reported as percent.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer GlaxoSmithKline	Figures	Figure 86 - diarrhea and nausea are also presented in the publication for Ahren et al (reference 110). Please consider revising the data to include the information presented in Table 1 of the publication. In addition, Skrivanek et al should be the publication for dulaglutide under vomiting, not Ahren et al.	We corrected this to match page 2145 of the manuscript (vomiting) and the appendix so that all items are reported as percent. We also fixed the labeling issue.
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	Page ES1 The sentence ...guidelines recommend use of metformin when not contraindicated as firstline therapy after lifestyle modifications is we believe incomplete. Please alter it to read ...guidelines recommend use of metformin after lifestyle modifications when not contraindicated as firstline therapy or if metformin is not tolerated due to GI side effects.	Ok, we have added or intolerant to that sentence in the Executive Summary.
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	The text states that five classes of antihyperglycemic agents have been approved for monotherapy and then lists six. Please revise.The list of agents approved as firstline treatments includes 2nd generation sulfonylureas. This is potentially misleading as many taxonomies include three generations of sulfonylureas. We recommend deleting the term 2nd generation here and elsewhere in the review.	We have changed this to six classes. We did not include first generation sulfonylureas in the systematic review. Table 1 indicated which sulfonylureas were included. We have changed anywhere which has second to second or third generation sulfonylurea.
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	Page ES12 The text states that the risk of congestive heart failure was 1.4fold greater with TZDs. However the number 1.4 does not appear in the Results section page 217 which explicitly states that no metaanalysis was performed. Please explain in detail how an effect size was calculated in the absence of a metaanalysis and whether this difference was statistically significant.	We have changed this to represent the range in calculated OR of 1.2 to 1.6 for the studies. We have also further given details regarding the results found for congestive heart failure.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	As noted below under Methods in this report the EPC repeatedly draws conclusions in the absence of a statistically significant difference often in the absence of an analysis. We consider this to be a serious breach of sound methodology. Please revise.	Judgements can be made in the absence of statistical significance but are often low strength of evidence. Most of the low strength of evidence was therefore not highlighted in the executive summary. Low strength of evidence means there is low confidence in the results. We followed the GRADE workgroup regarding strength of evidence - see our methods on this well documented method for grading the evidence. We double checked that we were consistent in this approach throughout the report.
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	Page ES17 The phrase ...despite the DPP4 inhibitors known side effects of nausea. is inappropriate for two reasons. First in a systematic review studies that meet inclusion criteria are subjected to rigorous quality analysis before their results are interpreted. To state the conclusions of a study that does not meet inclusion criteria and has not been assessed for quality defeats the purpose of conducting a systematic review. To make matters worse the study cited Karagiannis et al. does not support the conclusion that DPP4 inhibitors cause nausea. Rather it supports the conclusion of the current review that DPP4 inhibitors did not have worse GI events than metformin. From the abstract of Karagiannis et al. Incidence of nausea diarrhoea and vomiting was higher in patients receiving metformin or a GLP1 agonist than in those receiving a DPP4 inhibitor. Please remove the phrase and the Karagiannis reference.	We have deleted the phrase and reference.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	Pages ES1718 The discussion of safety outcomes includes a discussion of the RECORD and SAVOR TIMI trials which are not otherwise included in the review. While a systematic review may be justified in mentioning recent controversial and interesting studies in order to provide context it is inappropriate for a systematic evidence review to present the results of a trial that has not been assessed for quality and for which strength of evidence is not rated. Moreover to present the results for a single outcome without providing context by discussing the primary outcomes of the trial contributes significantly to publication bias. Finally the implication that the results of this trial may apply to other DPP4 inhibitors is speculative. Please refrain from presenting data from studies that do not meet inclusion criteria. If the RECORD and SAVOR TIMI trials must be mentioned please state explicitly that they have not been assessed for quality that the EPC may be introducing publication bias into their analysis by failing to discuss their complete results and that the extent to which their results are applicable to the results of the current review is unknown. Please also be advised that the results of the TECOS cardiovascular safety trial Clinicaltrials.gov ID NCT00790205 will be available sometime in June. If it is considered vital to provide context by mentioning recent important studies that do not meet inclusion criteria TECOS should probably be discussed as well subject to the same caveats mentioned above.	We actually did include the RECORD study for the intermediate outcomes so we did assess study quality. We did not report it for the congestive heart failure outcome data since it combined metformin and sulfonylureas. We do feel it is appropriate to discuss in the context of congestive heart failure although have removed the actual data and just discussed the findings. As we discuss the context of the different medications and their effects, it is important to discuss controversial issues. We have edited the section on DPP-4 inhibitors and congestive heart failure to discuss recent large placebo-controlled trials that came out after we wrote the draft report.
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	Page ES18 The sentence We did not find large differences in HbA1clowering effects of the diabetes medications studied except for DPP4 inhibitors which were not as effective. is misleading because it implies that DPP4 inhibitors are less effective than all comparators when in fact they were only found to be less effective than metformin. Please amend the sentence to read ...were not as effective as metformin.	We did have the words "relative to metformin" there.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Richard Chapell, Merck Co. Inc.	Executive Summary	Page ES18 Please note the recent FDA warning that SGLT2 inhibitors may be associated with increased risk of ketoacidosis.	Thank you. We have included this in the Discussion of the Executive Summary and main report.
Public Reviewer Richard Chapell, Merck Co. Inc.	Introduction	Page 20 The discussion of burden of illness only describes longterm complications of hyperglycemia. Please also include acute complications eg volume depletion weight loss as reasons to treat hyperglycemia.	Jodi, I think that he is referring to the absence of acute complications (DKA, HNKK) as a reason to treat DM. Public health wise, the long-term things matter most. Here is what I suggest, "We agree that the acute complications of diabetes are also important but have focused on long-term complications to maintain brevity while highlighting the most important complications from a public health perspective."
Public Reviewer Kathleen GansBrangs, Astrazeneca	Executive Summary	Executive Summary Please carry through comments made to corresponding sections in the body of the document e.g. Results section.Discussion Please carry through comments made to corresponding sections in the body of the document e.g. Results section.	We have tried to make all the corresponding edits.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Executive Summary	Full Report Recommend replacing GLP1 agonist with GLP1 receptor agonist GLP1 RA for all instances.	We have made this edit throughout the report.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Executive Summary	ES 9 to ES 10 AllCause Mortality CV Mortality cV Morbidity Please carry through comments made to corresponding Results section of the document regarding SAVOR.PP	We have discussed SAVOR TIMI, TECOS, and EXAMINE in the Executive Summary Discussion and Discussion section. We do not have text on these studies, which were not eligible for inclusion in the systematic review, in the Results.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Executive Summary	ES 1718 The report notes in 2 places there is a critical gap regarding the comparative safety of DPP4is in the context of heart failure. Please see attached report describing a postauthorization safety study using observational insurance claims data to compare the risk of heart failure with DPP4i vs. SU and saxagliptin vs. sitagliptin. Source NonInterventional Study Primary Report Study Comparing Risk of Hospitalization for Heart Failure Between Dipeptidyl Peptidase4 Inhibitors and Sulfonylureas	This report was interesting but was excluded since there was no stratification by background medication.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Executive Summary	p. ES18 first paragraph. Please carry through comments made to corresponding Results section of the document regarding SAVOR	We have tried to make all the corresponding edits.
Public Reviewer Richard Chapell, Merck Co. Inc.	Methods	Page 12 We note that the Jadad criteria were used to assess study quality. We have found this method to be limited in scope and uninformative. As stated in the AHRQ methods guide while the Jadad method remains popular other criteria may be more useful. Please consider an alternative method in future reports.	When we conducted the initial review in 2006-2007, the Jadad criteria was considered one of the better quality assessment tools. We agree that better quality assessment tools have been developed since then. However, we are unable to reassess the quality of the included randomized controlled trials given our budget and time restrictions.
Public Reviewer Richard Chapell, Merck Co. Inc.	Methods	Throughout the document e.g. Pages 144 212 213 217 219 232 244 and many others conclusions are reported as supported by a low strength of evidence despite a lack of statistical significance. In some cases no statistics were performed. In at least one instance page ES12 Congestive Heart Failure an effect size is reported despite no metaanalysis having been performed. Often conclusions are based on the results of a single study. In our opinion this constitutes insufficient evidence rather than a low strength of evidence. A single study cannot be said to be consistent and a difference that is not statistically significant cannot be reasonably described as precise. Magnitude of effect which AHRQ considers an optional domain when assessing strength of evidence is of some importance in this situation as well. If a difference is too small to be considered clinically significant the result does not favor either treatment. Lack of a statistically significant effect may support a conclusion of No Difference especially if a metaanalysis has been performed. Please explicitly state the EPCs decision rules for distinguishing levels of evidence and ensure that they are consistently applied throughout the document. If the evidence does not support the conclusion that results are different please refrain from stating such a conclusion.	Judgements can be made in the absence of statistical significance but are often low strength of evidence. Most of the low strength of evidence was therefore not highlighted in the executive summary. Low strength of evidence means there is low confidence in the results. We followed the GRADE workgroup regarding strength of evidence - see our methods on this well documented method for grading the evidence. We double checked that we were consistent in this approach throughout the report. For congestive heart failure, we tried to make sure we wrote "about" in front of the 1.4 fold increased risk. We have changed this to a range in odds ratio.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Page 19 Conclusions rated as supported by High strength of evidence in the previous report were not revisited in the current report. However the recent AHRQ white paper on the predictive value of evidence grades for the stability of effect estimates concluded that the predictive value is quite low. Please consider revisiting these comparisons.	While this is a very interesting paper, it is preliminary and based on a limited sample; therefore the EPC program will continue to use the current methods until there is sufficient data to warrant a change.
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Page 39 44 Here as well as several other places in the review sulfonylurea dosages are described as submaximal or underdosed. This was probably done out of fear of hypoglycemia. Clinical opinion differs as to the maximal safe dosage of sulfonylureas and the safety of these agents varies with patient characteristics. Please consider qualifying statements using the term submaximal by stating that they were the maximum dose considered safe in that specific clinical setting.	We have removed the word underdosed and changed to moderate doses. Occasionally, we did use submaximal doses which we feel accurately depicts the dosing. We agree that there are reasons why a sulfonylurea may not be titrated to the maximal dose such as concerns for hypoglycemia. In this report, we are just describing dosing comparisons of the studies and not speculating on reasons why dosing might have been chosen for individual studies.
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Note for example that cardiovascular morbidity a known sequel to hypoglycemia was higher among patients receiving sulfonylureas plus metformin than the comparators listed in Table 40 despite sulfonylurea doses described as submaximal.Page 111 Table 25 states that the number of patients experiencing sudden cardiac death in the study by WilliamsHerman et al. 2010 was not reported. However the text of the article states unambiguously that five patients died over the course of the study and lists the cause of death for each. Basic arithmetic therefore leads one to conclude that no patients in the groups listed in Table 25 died of sudden cardiac death or worsening CHD. Please amend Table 25 accordingly	We have made edits to the table that is now Table 30 in the report.
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Page 112 The word cerebrovascular is used when the author probably intended to say cardiovascular.	Thank you for noticing this. We have made the edit.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Page 116 The text states that none of the RCTs were designed to evaluate allcause mortality when the subject of the paragraph is cardiovascular mortality. Please evaluate whether a pasting error was made.	Thank you. We have made this edit.
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Page 128 Please note that the study by Arjona Ferreira et al enrolled patients with moderate to severe kidney disease. The dose of sitagliptin was therefore not low but entirely appropriate for this patient group. Please revise the text to make this clear.	Thank you. We have edited the text.
Public Reviewer Richard Chapell, Merck Co. Inc.	Results	Page 178 Apparent pasting error Table Hypo 14	Thank you for mentioning this. This error has been fixed.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 24. Paragraph 1 above figure 5. Ref. 79 does not show mean difference between groups in the publicationPP 2425. Consider adding a figure showing the metformin comparison with SGLT2is similar to the figures for the other comparisons.	We did not show figures for those analyses without pooled results for the intermediate outcomes. We were unable to pool results due to differences in study dosing and duration among the studies. These comparisons have tables and text which display the results.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	P 30.Metformin Versus a Combination of Metformin Plus a SGLT2 Inhibitor. Bailey et al. also assessed Farxiga as an addon to Metformin compared to placebo and metformin. Consider adding data from this reference. Ref Bailey C Gross JL Pieters A et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin a randomised doubleblind placebocontrolled trial. Lancet. 201037522232233.	We have added this. We included the longer study originally but have added the shorter duration results to text as well. It does not alter the findings from this section.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 30 Metformin Versus a Combination of Metformin Plus a GLP1 Agonist A Byetta study Defronzo et al. Effect of exenatide on glycemic control and weight over 30 weeks in metformintreated patients with type 2 diabetes. Diabetes care. 200528510921100 evaluated HbA1c changes with MetByetta vs Metplacebo. Suggest to add study results to this analysis. All subjects in this study continued their current dose of metformin when assigned to placebo or Byetta arms.Suggest report be modified to mention that HbA1C changes were assessed as a secondary endpoint in references 136 and 138.	We do not comment on whether a study reported something as primary or secondary outcome since this will not influence whether we put the results in a meta-analysis or not.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Pg 32. Thiazolidinediones Versus DPP4 Inhibitors. Hollander at al. evaluated Saxagliptin added to TZD to assess efficacy at week 24. Consider adding this reference.Ref Hollander P et al. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. J Clin Endocrinol Metab. 2009 Dec941248109. doi 10.1210jc.20090550.	We did not evaluate the comparison of thiazolidinediones plus a DPP-4 inhibitor versus thiazolidinedione alone for this update.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Epub 2009 Oct 28Page 3233 TZD vs. GLP1 agonists. Based on DURATION4 publication the HbA1c difference between the Bydureon and Pioglitazone arms should be changed to 0.1 Bydureon had a 1.53 and Pioglitazone had a 1.63 reduction.Page 33 SUs vs. GLP1 agonists. The term equipotent dosing is incorrect. Recommend changing to maximum doses Page 33 last paragraph Between group difference in HbA1c is 0.38 1.53 for Bydureon 1.15 for sitagliptin based on DURATION 4 publication cited in this section.DPP4 inhibitors vs GLP1 RA	We agree. We have changed the between-group difference from 0.2 to 0.1 for thiazolidinediones versus GLP-1 agonists. We changed to comparably dosed for sulfonylureas versus GLP-1 agonists. For DPP-4 inhibitors versus GLP-1 agonists, we have changed the between group difference to 0.4 (rounding up to keep at one digit).
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 36 Combination of metformin plus TZD vs. a combination of metformin and a GLP1 RA. First sentence in paragraph recommend change language in parentheses to pioglitazone or rosiglitazone to prevent implication that both arms were included in both studies.	We have made this edit.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 39 second paragraph line 7Incorrect reference Reference 188 is related to exenatide current text in report is regarding liraglutide.	We have removed this sentence and reference from that section.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Pages 39-40Summary of Met SU vs Met GLP1 states SOE Low Combination of metformin plus exenatide favored SOE Insufficient Unable to determine effect for combination of metformin plus other GLP1 agonists but the following Figure 15 seems to be showing the opposite. Please clarifyreconcile.	We have clarified in the figure that these are exenatide only.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 41 Combination of Metformin Plus a DPP4 Inhibitor Versus a Combination of Metformin Plus a SGLT2 InhibitorConsider adding publication and appropriate data.Ref Rosenstock J Hansen L Zee P et al. Dual Addon Therapy in Type 2 Diabetes Poorly Controlled With etformin Monotherapy A Randomized DoubleBlind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. Diabetes Care 201538376383. DOI 10.2337dc141142	The Rosenstock 2015 study was captured in our updated search and is now included in our review. Thanks for mentioning this study.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 43 Combination of Metformin Plus a GLP1 Agonist Versus a Combination of Metformin Plus a Basal Insulin 1st paragraph line 4. Please correct inaccurate dosing informatino Maximum dose of exenatide in this study was 20 mcg TID.	We excluded this study since it used above FDA approved dosage.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 43 Combination of Metformin Plus a GLP1 Agonist Versus a Combination of Metformin Plus a Basal Insulin 1st paragraph line 9Correction of treatment difference reported in reference 194 DURATION 3 study p. 2237 0.18 95 CI 0.34 to 0.02 p0.031.	We had used our calculated mean difference and measure of variability which was similar. We have changed this to the reported value which is more accurate.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 43 Combination of Metformin Plus a GLP1 Agonist Versus a Combination of Metformin Plus a Premixed InsulinIncorrect study duration. Study duration should be 26 weeks instead of 104 weeks.	We have changed the study duration to 26 weeks.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 45 Table 6 Metformin vs MetforminGLP1 agonistsRecommend adding Defronzo et al.	We have added this article.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 46In Table 6 how were large effect medium effect determined What are the criteria and the definition for effect size Please clarify in final report.	In our strength of evidence tables, we decided to add actual results when we have conducted a meta-analysis and have deleted the small, medium, and large effect comments.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Pages 4748In Table 7 how were small effect medium effect determined What are the criteria and the definition for effect size Please clarify in final report.	In our strength of evidence tables, we decided to add actual results when we have conducted a meta-analysis and have deleted the small, medium, and large effect comments.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 50 Metformin Versus GLP1 Agonists Line 5Change dosing regimen from 20mcg daily to 10 mcg BID.	Ok, we have changed this.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 55-56 Metformin Versus a Combination of Metformin Plus a GLP1 Agonist effect on weightA Byetta study Defronzo et al. Effect of exenatide on glycemic control and weight over 30 weeks in metformintreated patients with type 2 diabetes. Diabetes care. 200528510921100 evaluated HbA1c changes with MetByetta vs Metplacebo. Suggest to add study results to this analysis. All subjects in this study continued their current dose of metformin when assigned to placebo or Byetta arms.	We have added this article. Thank you for mentioning it.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 61 Combination of metformin plus TZD vs. a combination of metformin plus a GLP1 RA Line 4Change the range of weight differences from 2.75.1 to 4.35.1 based on Table 1 of reference 174 Page 64 line 2For Met SU vs. Met basal insulin it states SOE Low Combination of metformin plus a sulfonylurea favored but the small study cited in the text states the difference was nonsignificant	We double checked this data. The Bergenstal article reports a between-group difference of 5.1 kg. The lower range was 2.7 kg in the other article. We were reporting the range in between-group differences from the two articles not just the range in differences within one article. For metformin plus a sulfonylurea versus metformin plus basal insulin, this was statistically significant. We have removed the words not statistically significant since this wording may have led to the confusion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 64 Combination of Metformin Plus a DPP4 Inhibitor Versus a Combination of Metformin Plus a SGLT2 InhibitorConsider adding publication and appropriate data.Ref Rosenstock J Hansen L Zee P et al. Dual Addon Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy A Randomized DoubleBlind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. Diabetes Care 201538376383. DOI 10.2337dc141142	The Rosenstock 2015 study was captured in our updated search and is now included in our review. Thanks for mentioning this study.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 66 Combination of Metformin Plus a GLP11 Agonist Versus a Combination of Metformin Plus a Premixed Insulin Line 1Change duration of the study to 26 weeks see reference 196 page 604	We have changed this to 26 weeks.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Pages 68-70In table 9 how is effect size defined small moderate Please clarify in final report.	In our strength of evidence tables, we decided to add actual results when we have conducted a meta-analysis and have deleted the small, medium, and large effect comments.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Page 77 Combination of Metformin Plus a DPP4 Inhibitor Versus a Combination of Metformin Plus a SGLT2 Inhibitor Paragraph 1Consider adding publication.Ref Rosenstock J Hansen L Zee P et al. Dual Addon Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy A Randomized DoubleBlind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. Diabetes Care 201538376383. DOI 10.2337dc141142	The Rosenstock 2015 study was captured in our updated search and is now included in our review. Thanks for mentioning this study.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	p. 94 MET vs. GLP1 AgonistsDrug listed as exenatide should be exenatideextended release or exenatide once weekly consistent with product labeling. Consider adding clarification DURATION4 was a 26week study with a 10week followup 36 weeks listed as study duration in narrative.	We have noted that exenatide was once weekly. We are only reporting the total followup time for each of the studies. Many studies had additional followup periods. To comment on each one of these would add length, but not substance, to the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Ref 173 p. 100 TZD vs GLP1 Agonists Drug listed as exenatide should be exenatideextended release or exenatide once weekly consistent with product labeling Consider adding clarification DURATION4 was a 26week study with a 10week followup 36 weeks listed as study duration.	We have noted that exenatide was once weekly. We are only reporting the total followup time for each of the studies. Many studies had additional followup periods. To comment on each one of these would add length, but not substance, to the report.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Ref 173 p. 102 Combo of METTZD vs. Combo of METGLP1A Drug listed as exenatide should be exenatideextended release or exenatide once weekly consistent with product labeling.	We already state that it was weekly exenatide. We didn't make any edits based on this comment.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Results	Text mentions death only reported in SITAMET arm but does not mention mention cause of death. Consider including cause uncontrolled hypertension in the sita arm Ref 173 Please note AE is represented numerically in Table 20 p. 105 for allcause mortality but not necessarily CV mortality. Please consider clarification. SITAMET occurrence of cerebrovascular accident n1 1 and 1 serious AE which was fatal uncontrolled hypertension mentioned abovePioglitazoneMET coronary artery occlusion n2 1 unstable angina n1 1 acute renal failure n1	Thank you for these suggestions. We were reporting on all-cause mortality in the section referred to regarding metformin plus DPP-4 inhibitor vs. metformin plus TZD. Therefore, we did not list specific causes of death. We did report on pre-specified non-fatal CVD outcomes per our protocol.
Public Reviewer Richard Chapell, Merck Co. Inc.	Discussion/ Conclusion	Page 281 Again. DPP4 inhibitors are misleadingly described as less effective. Please revise the sentence to say less effective than metformin.	It does say less effective than metformin.
Public Reviewer Richard Chapell, Merck Co. Inc.	Discussion/ Conclusion	Pages 281282 Another important limitation of the review process is that important subgroups may not have been assessed in the included trials. For example placebocontrolled studies have shown that SGLT2 inhibitors are less effective among elderly patients and those with renal impairment compared to their effects on more healthy patients Bode et al. 2013 Yale et al.2013 Kohan et al. 2014. The included trials do not capture this observation. Please add a discussion of this limitation to the report.	We have addressed the possibility of exclusion of trials based on our selection criteria in the section on limitations of the review process.
Public Reviewer Richard Chapell, Merck Co. Inc.	Discussion/ Conclusion	Page 283 Again medication is described as underdosed when the dosage was appropriate for the specific situation. Please revise the text to include this caveat.	We have changed this wording.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Richard Chapell, Merck Co. Inc.	Discussion/ Conclusion	Page 283 The discussion implies without evidence that industrysponsored studies are more prone to bias. In fact industrysponsored studies that are part of regulatory submissions are subject not just to peer review but to intensive scrutiny by the FDA and other regulatory agencies. For this reason they are actually much less vulnerable to bias. Simply put poorly designed performed or reported studies are bad for business. For a discussion of the evidence underlying these assertions please see Del Parigi 2012. Please consider revising the discussion of sources of bias so that it does not unnecessarily impugn the pharmaceutical industry.Bode et al. Hospital Practice 2013 412 7284Del Parigi Current Medical Research and Opinion 2012 2325Yale et al. Diabetes Obesity and Metabolism 2013 15 463473 Kohan et al. Kidney International 2014 85 962971	We have expanded on our discussion of this to indicate that an intrinsic conflict of interest does exist for industry-sponsored studies; that some study limitations identified that could be influenced by such a conflict; but that we can cannot conclude that there is in fact bias and that the limitations listed are important regardless of sponsorship.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Discussion/ Conclusion	Page 278 Recommend more fully describing the pancreatic results from reference 285 in the text. Specifically by going beyond direct acute pancreatitis.Pancreatitis occurred infrequently and the number of patients with acute or chronic pancreatitis was similar in the two groups 24 patients 0.3 in the saxagliptin group and 21 patients 0.3 in the placebo group P 0.77. Definite or possible acute pancreatitis occurred in 22 patients 0.3 in the saxagliptin group and in 16 patients 0.2 in the placebo group P 0.42 definite acute pancreatitis in 17 patients 0.2 and 9 patients 0.1 in the two groups respectively P 0.17 and chronic pancreatitis in 2 patients 0.1 and 6 patients 0.1 respectively P 0.18. There were 5 cases of pancreatic cancer in the saxagliptin group and 12 in the placebo group P 0.095.Page 283 Recommend editing the sentence toFinally many included trials were industrysponsored raising the possibility of publication bias and other forms of bias such as selective reporting of outcomes.We believe reporting requirements of clinical trials have substantially decreased the risk of reporting bias. Moreover it is possible that if meaningful publication bias still exists there could be less publication bias among industry sponsored studies.	We appreciate these concerns. We report on acute pancreatitis as it is clearly an incidental or new event. The reported results are consistent with additional data from EXAMINE and TECOS which also show that the incidence of pancreatitis was higher for the DPP-4 inhibitor arms with the same between-group difference of 0.1%. This translates to a number needed to harm which is 1,000, and we contend that this is indeed relevant given the number of people who may be exposed. Please see our response to the above comment regarding discussion of industry sponsorship.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	References	Page 287Please consider including the following references as evidence about allcause mortality CV mortality and morbidity and congestive heart failureBannister CA Holden SE JenkinsJones S et al. Can people with type 2 diabetes live longer than those without A comparison of mortality in people initiated with metformin or sulfonylurea monotherapy and matched nondiabetic controls. Diabetes Obes Metab 2014161111651173. doi 10.1111dom.12354.Forst T Hanefeld M Jacob S et al. Association of sulphonylurea treatment with allcause and cardiovascular mortality a systematic review and metaanalysis of observational studies. Diab Vasc Dis Res. 2013104302314. doi 10.11771479164112465442.Hung YC Lin CC Wang TY et al. Oral hypoglycemic agents and the development of nonfatal cardiovascular events in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2013298673679. doi 10.1002dmrr.2444.Kheirbek RE Alemi F and Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. J Manag Care Pharm 2013199740744.Kim SC Glynn RJ Liu J et al. Dipeptidyl peptidase4 inhibitors do not increase the risk of cardiovascular events in type 2 diabetes a cohort study. Acta Diabetol. 201451610151023. doi 10.1007s0059201406632.Li Y Hu Y Ley SH et al. Sulfonylurea use and incident cardiovascular disease among patients with type 2 diabetes prospective cohort study among women. Diabetes Care2014371131063113. doi 10.2337dc141306.Liang H Vallarino C Joseph G et al. Increased risk of subsequent myocardial infarction in patients with type 2 diabetes a retrospective cohort study using the U.K. General Practice Research Database. Diabetes Care 201437513291337. doi 10.2337dc131953.Mogensen UM Andersson C Fosbol EL et al.	Thank you for suggesting these studies. Most of these studies were either included in our original search or in our updated search. The Hung 2013 study is included in our review. The remaining articles were independently reviewed by two investigators and excluded. Bannister 2014, Morgan 2014, and Yu 2015 were excluded because they were non-randomized studies that did not account for confounding for all the prespecified variables. Forst 2013 and Monami 2013 were excluded because they were not original studies. Kheirbek 2013 and Velez 2015 were excluded because they did not either stratify their randomization or their analysis by background medications. Kim 2014, Li 2014, and Mogenson 2015 were excluded because they did not have a comparison of interest. Liang 2014 was not included in our search. This study does not evaluate diabetes medications for adults with type 2 diabetes, so it was not expected to have been captured in the search.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca (continued)	References (continued)	Sulfonylurea in combination with insulin is associated with increased mortality compared with a combination of insulin and metformin in a retrospective Danish nationwide study. Diabetologia 20155815058. doi 10.1007s001250143372z.Monami M. Metformin may not reduce cardiovascular risk or allcause mortality. Evid Based Med. 2013182e13. doi 10.1136eb2012100836.Morgan CL Mukherjee J JenkinsJones S. et al. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP4 inhibitors association with major adverse cardiovascular events and allcause mortality. Diabetologia 20155815058. doi 10.1007s001250143372z.Velez M Peterson EL Wells K et al. Association of antidiabetic medications targeting the glucagonlike peptide 1 pathway and heart failure events in patients with diabetes. J Card Fail 201521128. doi 10.1016j.cardfail.2014.10.012.Yu OH Filion KB Azoulay L et al. Incretinbased drugs and the risk of congestive heart failure. Diabetes Care 2015382277284. doi 10.2337dc141459.	
Public Reviewer Kathleen GansBrangs, Astrazeneca	Abbreviations	Recommend replacing GLP1 agonist with GLP1 receptor agonist GLP1 RA for all instances	We have made this edit throughout the report.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	pp. 79 80 85 86For tables 11 12 13 14 how is effect size defined	In our strength of evidence tables, we decided to add actual results when we have conducted a meta-analysis and have deleted the small, medium, and large effect comments.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 108Table 22Summary column for the row Metformin DPP4 inhibitors vs. metformin GLP1 agonists reflects the opposite conclusion of text corresponding to that section on page 104. Please reconcile.pp. 126 130 139 209 Tables 36 40 41 45 70Please consider adding Author Year and Followup information to the empty cells in the tables	We have confirmed that our conclusion in the strength of evidence table (now Table 27) matches our text in that section. For the other tables, we have fixed the formatting so that the cells do not appear to be empty.

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 210 Table 71Verify data from Bolinder 2012 reference 134 cannot locate data presented in table regarding bladder prostate breast cancers and basal cell carcinoma in the publication.	The Bolinder 2012 study was published in several articles. The cancer data was reported in Bolinder J et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes, Obesity, and Metabolism 2014 (16):159-169.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 210 Table 71Include additional information regarding Bailey malignancy data such as below One patient on dapagliflozin 5 mg with a history of hematuria that predated randomization experienced a bladder transitional cell cancer. One patient on dapagliflozin 10 mg was diagnosed with breast cancer within the first year of enrollment.Page 210 Table 71Include additional information regarding Bailey malignancy data such as below One patient on dapagliflozin 5 mg with a history of hematuria that predated randomization experienced a bladder transitional cell cancer. One patient on dapagliflozin 10 mg was diagnosed with breast cancer within the first year of enrollment.	Thank you for this suggestion. We did not feel that the factors pointed out were sufficient to necessitate a qualification of these events.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 212 Table 72Verify malignancy data from Goke 2010 could not locate cancer incidence in publication which is listed in the table.	The Goke 2010 study was published in multiple articles. The cancer data was reported in Goke B, et al. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. Int J Clin Pract 2013. 67(4):307-316.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 218Table 76Header for the last column states Heart failure incidence metformin as reference group but the footnote for the table states HR hazard ratio for metformin with sulfonylureas as the reference groupComment the reported HR and the concluding statement on page 217 SOE Low Metformin favored suggest that the footnote is correct and the header should be corrected to match the footnote.	We have fixed this. Thanks.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	P245 Table 98For Nauck 2011 reference 182 this is the 52week data. Please use Nauck 2014 for 104week data. Nauck MA Del Prato S DuranGarcia S Rohwedder K Langkilde AM Sugg J et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as addon therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab. 20141611111120.	We have replaced Nauck 2011 with Del Prato 2015 which reports on the 208-week extension results.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	P249 Table 103Change Bolinder 2012 to Bolinder 2014P249 Table 103Update reference 134 Bolinder J Ljunggren O Johansson L Wilding J LangKilde AM Sjostrom CD et al. Dapagliflozin maintains glycemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabtes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014162159169.	We have updated this reference.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	P249 Table 103For Bolinder Ref 134 change Metformin dapagliflozin 10 mg 091 0 to Metformin dapagliflozin 10 mg 391 3.3	We have corrected this error.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 250 Table 104 Chance Nauck 2011 to Nauck 2014.	We have replaced Nauck 2011 with Del Prato 2015 which reports on the 208-week extension results.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 255 Table 108 row 5 Column 4 Change to Study 1Males Metformin 0Metformin dapagliflozin 5 mg 5.1Females Metformin 3.8Metformin dapagliflozin 5 mg 7.8	We have corrected this error.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 255 Table 108 Change to Males Metformin 2.1Metformin Dapagliflozin 10 mg 5.7Females Metformin 2.7Metformin Dapagliflozin 10 mg 11.4	This is reflected in the table. No change is necessary.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 255 Table 108 Change to Bolinder 2014	We have corrected this error.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 257 Figure 94 Change Nauck 2011 to Nauck 2014	We have replaced Nauck 2011 with Del Prato 2015 which reports on the 208-week extension results.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 264 Table 115Change Nauck 2011 to Nauck 2014	We have corrected this error.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Tables	Page 264 Table 115 The data needs to be reversed	We have corrected this error.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 26 Fig 6 Appears to be a misrepresentation of study results by RussellJones et al 2012 DURATION 4. This study showed that Bydureon had a greater reduction in A1c than metformin 1.53 vs 1.48. This difference was not found to be statistically significant but did favor Bydureon. The box should be placed on the opposite side of zero for this study. Effect size should be changed to 0.05.	Thank you for bringing this to our attention. We have fixed the graph to show the correct results for Russell-Jones et al 2012.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Pg 30 Figure 9.Bailey et al. also assessed Farxiga as an addon to Metformin compared to placebo and metformin. Consider adding data from this reference. Ref Bailey C Gross JL Pieters A et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin a randomised doubleblind placebocontrolled trial. Lancet. 201037522232233.	We have added this study.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Pg. 158 Figure 61 and ReferenceRemove reference 120 to White 2014 and associated data in Figure 61 data is for Saxagliptin 2.5 BID MET not indication Recommend utilizing similar definition of hypoglycemia throughout the report confirmed hypoglycemia that is reported in papers ie Jadzinsky DeFronzo more similar to definition of hypoglycemia in other publications vs reported hypoglycemia which is used here	Based on methodology used throughout the report, we left the White 2014 study in the meta-analysis because we felt that is was similar enough (in terms of the dosing and definition of hypoglycemia) to the other studies to pool.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 159 Figure 63Recommend delete Rosenstock 2013 reference 122 this is a SGLT2 study under the DPP4 inhibitor section	The Rosenstock 2013 study also included an arm where patients received sitagliptin, which is a DPP-4 inhibitor. We have decided to keep this study in this section.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 159 Figure 63Recommend delete Rosenstock 2012 reference 125 this is a SGLT2 study under the DPP4 inhibitor section	The Rosenstock 2012 study also included an arm where patients received sitagliptin, which is a DPP-4 inhibitor. We have decided to keep this study in this section.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 159 Figure 63Recommend addition of Jadzinsky 2009 data is from 24 week study 52 week addition of DeFronzo 2009 data is from 24 week study 52 week	This data was included in the mild to moderate hypoglycemia meta-analysis because none of the events were severe.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 159 Figure 62 DeFronzo 2009 Recommend verifying data with publication All events were of mild or moderate intensity and did not require treatment or medical intervention	Per our methods with the prior report, we considered confirmed hypoglycemia with blood glucose <50 to be severe. Removal of this study from qualitative or quantitative analysis would not change the inference.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 159 Figure 63Recommend delete Rosenstock 2013 reference 122 this is a SGLT2 study under the DPP4 inhibitor section	The Rosenstock 2013 study also included an arm where patients received sitagliptin, which is a DPP-4 inhibitor. We have decided to keep this study in this section.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 161 Figure 64Recommend verifying calculated OR and 95 CI of Henry 2012 a data	We have confirmed the data for the Henry 2012 a data. There were no events among 201 participants in the metformin arm and 5 events among the 194 participants in the metformin plus dapagliflozin arm. The odds ratio and 95% confidence interval are automatically calculated by the Stata program.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 170 Figure 67Update Goke 2010 data this was a study of 52 week duration and data in chart for both severe and mildmoderate hypoglycemia should match the data reported in the publication. Please verify and update accordingly.	We have updated the figure with the correct reference.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 171 Figure 68Verify Nauck reference. Nauck 2011 reported 52 Week data Nauck 2014 reported 104 week data	We have fixed this reference.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 189 Figure 73Clarify difference in 2 Henry 2012 studies as done previously with marking a or b after the study reference Henry 2012 listed twice under Diarrhea and Nausea	We added a and b to the figure.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 194 Figure 78Figure 80Consider listing all studies that were mentioned in above introductory paragraph including Ref 75 Jadzinsky	All studies that reported on the outcomes of interest as a percent of patients are included. We are only including the longest followup duration for each study. Therefore, we have included the results reported in Pfutzner 2011, which is the 52-week extension of the Jadzinsky 2009 paper.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	Page 202 Figure 85Verify Goke 2010 data in Figure publication includes different values	We corrected values to match Table 3.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	P243 Figure 90Henry et al 2012 included 3 treatment arms in each study. Study 1 included DAPA 5 mgMET DAPA 5 mg PBO MET PBO. Study 2 included DAPA 10 mg MET DAPA 10 mg PBO MET PBO. In Figure 90 only 2 of the treatment arms are listed. Suggest including results for all 3 treatment arms to present full scope of the data. Accordingly suggest presenting all three treatment arms when introducing the study.	Only two treatment arms from each study were included in Figure 90 because we are comparing metformin versus SGLT-2 inhibitor. The metformin plus dapagliflozin arm was not included because this is a different comparison and is reported on in the section comparing metformin with metformin plus a SGLT-2 inhibitor.
Public Reviewer Kathleen GansBrangs, Astrazeneca	Figures	P243 Figure 90For List et al 2009 the number of events in Group 1 metformin was 6 not 5. Page 264 Figure 96 Change Nauck 2011 to Nauck 2014	We have corrected the error for number of events in Group 1 Metformin. We have corrected the error in Figure 96.
Public Reviewer Joseph Vassalotti, National Kidney Foundation	General	Recent observational studies a Cochrane metaanalysis and the KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD suggest the safety of metformin for patients with eGFR 3060. This is in contrast with the metformin package insert recommendations to avoid metformin when serum creatinine is above 1.5 mgdL in men or 1.4 mgdL in women. NKF recommends the FDA consider revising this package insert accordingly to allow more individuals with CKD to benefit from this first line agent.	We agree that there are analyses which suggest safety of metformin in these populations. We did not include many of these observational studies due to the use of background medications which did not allow specific medication comparisons of interest. We have added more to our discussion and executive summary discussion under lactic acidosis related to this material. We are unable to make recommendations to the FDA or others as part of the report; however, the FDA could review our report discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Joseph Vassalotti, National Kidney Foundation	General	One of the potential reasons for limited evidence to support metformin impact on nephropathy outcomes is the exclusion of CKD patients in studies of the drug.Rachmani R Slavachevski I Levi Z Zadok B Kedar Y Ravid M. Metformin in patients with type 2 diabetes mellitus reconsideration of traditional contraindications. Eur J Intern Med. Oct 2002137428433.Salpeter SR Greyber E Pasternak GA Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 20104 CD002967.Nye HJ Herrington WG. Metformin the safest hypoglycaemic agent in chronic kidney disease Nephron Clin Pract. 2011 1184c380383. Pilmore HL. Review metformin potential benefits and use in chronic kidney disease. Nephrology Carlton. Jun 2010154412418. Lipska KJ Bailey CJ Inzucchi SE. Use of metformin in the setting of mildtomoderate renal insufficiency. Diabetes Care. Jun 201134614311437. Inker LA Astor BC Fox CH et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis.63713735.National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD 2012 update. Am J Kidney Dis. 201260850886.Lipska KL Bailey CL Inzucchi SE. Use of metformin in the setting of mildtomoderate renal insufficiency. Diabetes Care. 20113414311437	This is true. Our future research section describes the need for studies with these populations.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Rebha Monga, Janssen Scientific Affairs LLC.	General	Thank you for the opportunity to provide comments on the following draft report Diabetes Medications for Adults with Type 2 Diabetes An Update Focused on Monotherapy and AddOn Therapy to Metformin. For your consideration the following phase 3 clinical trial has been published and may be of importance to your report Leiter LA Yoon KH Arias P et al. Canagliflozin provides durable glycemicimprovements and body weight reduction over 104 weeks versus glimepiridein patients with type 2 diabetes on metformin a randomized doubleblindphase 3 study. Diabetes Care. 2015383355364.	Thank you for this suggestion. This study was included in our updated search and is now included in our review.
Public Reviewer ACP	General	1) This is an important review on a major topic of interest to ACP as it updates our prior guideline.	Thank you for taking the time to review our report. We appreciate your feedback!
Public Reviewer ACP	General	It is important to emphasize when outcomes are intermediate (this includes blood pressure, lipids, possibly weight and definitely most of the measures of neuropathy, retinopathy and nephropathy-many of these are physio/biochemical NOT clinical outcomes), especially in the absence of evidence on clinical outcomes (all-cause mortality, fatal and nonfatal cardiovascular events, hospitalizations, end stage renal disease) a. As a recent example: sitagliptin improves a1c and does not worsen weight but a recent article in NEJM shows that it has NO effect on mortality or cardiovascular outcomes versus through 4 years among 14,000 patients. Please incorporate this study (also for pancreatitis-results were NS but there was a 2x increase in acute pancreatitis).	We did designate blood pressure and weight as intermediate outcomes. We only included studies evaluating actual clinical outcomes of retinopathy and neuropathy for these outcomes. In the case of nephropathy, we did include studies with evidence on eGFR and albuminuria and after much discussion, decided to label this as "direct" evidence. We do feel that eGFR and albuminuria are relevant clinical measures in themselves and even though we would have preferred diabetic nephropathy and ESRD as the most relevant clinical outcomes, we included these as nephropathy outcomes. We found little evidence on these anyway so our inclusion of these outcomes that certainly could be considered intermediate did not affect our findings/conclusions. We will include TECOS trial in discussion. It does not meet our inclusion criteria.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016

Commentator & Affiliation	Section	Comment	Response
Public Reviewer ACP	General	There have been several studies published subsequent to the SAVOR-TIMI 53 trial (reference 44 in the ES) addressing the concern of CHF and saxagliptin. Can you please address this issue in the report?	We agree. These were not yet available when we wrote the draft report. We have added discussion of the three placebo-controlled randomized controlled trials (EXAMINE, TECOS, and SAVOR-TIMI-53) in the Discussion and Executive Summary and also the two randomized controlled trials on linagliptin which are pending (CAROLINA and CARMELINA).
Public Reviewer ACP	Key Question 2	Most of the "long term" outcomes are NOT long-term. They should be deleted from long-term outcomes. i. The first line is: "Most studies reporting on all-cause mortality lasted less than 12 months and had few events." Further, they found moderate strength evidence that the drugs had similar all-cause mortality (in the long-term results section). The studies do not provide data on long-term outcomes. Instead they provide sparse data on short-term harms, which is how the report should read.	We appreciate this concern and changed the title of that section to "All-Cause Mortality and Macrovascular and Microvascular Outcomes." We have also emphasized when the evidence is short-term (<2 years of followup) and long-term (≥2 years) throughout the results. In the Executive Summary, we specified the duration of the studies when we were making a key point with high or moderate strength of evidence. Given that there is not a clear definition of when an outcome would be considered a short-term harm vs. a long-term benefit/risk, we did not make a further distinction qualifying outcomes as harms or benefits.
Public Reviewer ACP	Key Question 2	ii. A recent follow-up of the VA trial (in NEJM) shows a reduction in combined fatal and nonfatal CHD outcomes at 10 years plus of about 8 per 1000 person years. The P-value was 0.04 and they did not correct for multiple testing (2nd reporting of the data), the 95% upper limit of CI goes to 0.99. This includes individuals hospitalized for new or worsening CHF (the largest number of outcomes), some diagnosed only on the basis of an EF < 40. There was no reduction in fatal MI or all-cause mortality (HR overall mortality= 1.05).	This study compared high intensity with low intensity; it was not a head-to-head comparison of drugs.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer ACP	Key Question 2	b. Disagree with several of the SOE ratings: For all-cause mortality (figure C) the events are rare, the confidence intervals are very wide, and there is "indirectness". The mortality findings at less than 52 weeks provide little information on long-term mortality. At best they could be rated as low to moderate quality, but possibly insufficient. c. Same with cardiovascular morbidity	Per the response above, we have revamped our framing of these results considerably – with special attention to delineating long-term and short-term results. We did consider death, cardiovascular disease mortality, and cardiovascular disease events as direct evidence as part of our methodology. Imprecision was accounted for in our strength of evidence ratings.
Public Reviewer ACP	Key Question 2	d. Same with retinopathy, nephropathy and neuropathy i. The measures are almost always biochemical, physiologic or screening DM eye exams in asymptomatic individuals. Follow-up is too short to show clinical benefits and when trials have looked at long-term clinical outcomes, they found that after 10 years any benefit due to intensive therapy is small at best in the combined outcome of cardiovascular outcomes (fatal, nonfatal CHD, all-cause mortality, CHF, angina hospitalizations etc), but not in the individual outcomes especially for retinopathy/nephropathy/neuropathy.	We found low or insufficient for all of the microvascular outcomes.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Commentator & Affiliation	Section	Comment	Response
Public Reviewer ACP	Discussion	5) Discussion of evidence gaps confuses intermediate and long-term outcomes: For intermediate they suggest longer duration RCTs (and then state > 4 years), while for long-term outcomes they suggest longer duration RCTs and observational studies, but then say > 2 years. Why the time discrepancy? Why include observational studies for long-term but not for intermediate? Also, long term is NOT < 52 weeks if looking at effectiveness in DM care (all trials show no difference in the major clinical outcomes through 5-7 years).	This was a typo. It should have been >2 years for both intermediate and long term. We have corrected this. Recommendations for observational studies for longer term outcomes can be made since we included observational studies. We did not include observational studies for A1c and weight since this had not been done in the first and second reports. At that time, the large number of RCTs made the research team less interested in potentially lower quality observational studies. We agree that long term is not <52 weeks. This terminology has been used for the last report. It may not be possible to change the key question terminology which has already been vetted by the Technical Expert Panel and public from this report and the last report. However, we have changed the discussion and headers to state macrovascular, microvascular outcomes and mortality. We have also added in study duration to make it more clear what the length of followup was for these outcomes.
Public Reviewer ACP	General	6) Do we want to eventually wade into screening in this report and/or at least put this into context of treatment with patients with DM detected earlier in the course of disease vs. later in the course of disease?	This was not one of our key questions, and would need to be addressed in a separate report since we did not evaluate screening. We discussed this with the TEP in terms of subgroup analyses, but we decided not to evaluate this in order to restrict scope and we felt there would be less data on this by subgroup. In addition, other investigators at another EPC had looked at this in newly diagnosed patients without seeing any substantial differences in intermediate outcomes. Most studies had adults with diabetes in the 5-7 year range. We do describe the study characteristics in the results.

Source: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2207

Published Online: April 19, 2016