Article details: 2013-0073	
Title	Sulphonylurea monotherapy versus metformin in patients with type 2 diabetes: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses
Authors	Bianca Hemmingsen, Jeppe Schroll, Søren Lund, Jørn Wetterslev, Christian Gluud, Allan Vaag, David Sonne, Lars Lundstrøm, Thomas Almdal,
Reviewer 1	**Christianne Roumie**
Institution	Vanderbilt University Medical Center, Internal medicine
General comments	This is a very well done and through meta analysis done by the authors. I have only a few comments 1. The highlight I believe of this paper is the concept of the trial sequential analysis which serves as an analytic tool to determine if each analysis has obtained enough patients in order to detect an effect on a particular outcome. While the use of this tool is important and I believe the only novel aspect of this analysis it is not highlighted in a way to help the reader see that all the analyses are "underpowered" except for the analysis of weight change. 2. Similarly the authors point out the flaws in observational studies however all of the observational studies referenced meet the number of patients required to detect cardiovascular disease noted in his trial sequential analysis The study by Schramm et al had > 105,000 patients The study by Roumie et al had > 250000 patients and the study by Pantelone was by his definition underpowered at 23000. the authors also neglects to mention the study by Tzoulaki. Some mention of the observational studies in the discussion may be warranted because I do not believe that there will be a clinical trial of More than 55000 patients funded to study the effects of metformin versus sul on CVD. 3. In the discussion there should be further mention of why this meta analysis is warranted given the meta analysis of Bolen et al and bennett Et al. both of which were designed to answer the same question. How does this meta analysis add to the literature?
Reviewer 2	**Kristian Filion**
Institution	McGill University, Medicine
General comments	GENERAL COMMENTS: In this systematic review and meta-analysis, Hemmingsen and colleagues compare sulphonylurea monotherapy to metformin in patients with type 2 diabetes. Overall, this study is well done and methodologically rigorous. My main criticism is that this work has already been published as a Cochrane Review (acknowledged by the authors on page 26 of the manuscript), limiting its potential contribution to the literature. SPECIFIC COMMENTS: 1. The literature search, conducted in August 2011, is already 2 years old. This greatly limits the contribution of this work to the literature. 2. Caution should be used when interpreting the cardiovascular mortality results. With a RR of 1.47 and 95% CI 0.54 to 4.01, available data are inconclusive. Rather than focusing entirely on whether or not the results are statistically significant, an interpretation of the limits of the 95% CI would be more informative. 3. The exclusion of zero-event trials is problematic. These trials had similar event rates in the two groups and their inclusion would move the point estimate towards the null. At the very least, they should be included in sensitivity analyses.
Author response	To the Editors of Canadian Medical Association Open Re: "Sulphonylurea monotherapy versus metformin in patients with type 2 diabetes: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses" (Manuscript no. CMAJOpen-2013-0073). Dear Editors, Thank you very much for the highly relevant comments from the editorial meeting and from the reviewers as well as for the opportunity to revise our submitted manuscripts as indicated above.

Enclosed, please find a list below with explicit references to the manuscript as well as a response to each of the individual comments by the reviewers. All changes are marked with red color through out the revised manuscript.

We look forward to receive comments from the editors or the reviewers and we will be happy to supply any further information or answer any further questions/comments raised by the editors or the reviewers to the revised manuscript.

On behalf of all authors

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Copy to Bernd Richter (The Coordinating Editor of the Cochrane Metabolic and Endocrine Disorders Group) and Gavin Stewart (Associate Editor of the Cochrane Library).

Re: "Sulphonylurea monotherapy versus metformin in patients with type 2 diabetes: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses" (Manuscript no. CMAJOpen-2013-0073).

Response to each of the individual comments raised by the reviewers:

1. Please update your search strategy, and if necessary, the results of your meta-analysis. It appears the databases were searched to August 2011.

Authors reply
According to correspondence with Gordon Giddings, Medical Editorial Fellow, CMAJ ,we have done a cursory search and mentions this briefly in the discussion section of our paper. In the previous submission we had already discussed the trial by Hong et al. which was published after our search and what the inclusion of the data from the trial do the results of our meta-analysis.

We have performed a search on Medline for randomized clinical trials comparing sulphonylurea versus metformin monotherapy. We have not been able to identified any other trials with relevance for our systematic review besides the trial from Hong et al., which is already mentioned. However, we do now explicit tell the reader that it is the only trial published since the search in August 2011(page 30, line 12 to page 31, line 14):

"The literature search for the current meta-analysis included trials until 2011. A cursory update of the search thorough Medline in December 2013 did only identify one randomized clinical trial of relevance of our systematic review. This randomized clinical trial by Hong et al. included about 300 Chinese patients with type 2 diabetes and existing coronary artery disease and indicated a significant benefit in favour of metformin compared with glipizide for the primary composite cardiovascular outcome after around 3 years.(53) Notably, the primary outcome was not reported after 3 years, but after a median follow up of about 5 years – i.e., about two years after the trial medication was stopped. This trial was published after the database search of our present systematic review was finalised and has therefore not been included in our systematic review. Implementing the patient-important data from Hong et al. into our meta-analysis did not change the significance of the effect estimates for the primary outcomes or for non-fatal myocardial infarction, although the composite outcome of non-fatal macrovascular complications did no longer reach statistical significance (relative risk 0.86, 95% confidence interval 0.49 to 1.50 with sulphonylurea versus metformin). The discrepancy of the result of this relatively small trial and our current meta-analysis comprising substantially more number of patients underscores the need for further randomized trials with low risk of bias, and, in particular, in broader populations, to clarify the benefits and harms of sulphonylurea versus metformin in patients with type 2 diabetes."

	2. We would prefer to see the information of trials with zero events included in your meta-analysis. Please present results with these trials included. Authors reply: We have now added a sensitivity analysis (page 6, line 23 to page 7, line 3): "Sensitivity analyses for all dichotomous outcomes including trials with zero events are performed in this abbreviated version of the systematic review, but not in the current version of the Cochrane review." For each of the dichotomous outcomes the relative risk and the confidence interval including zero events trials are reported (e.g., page 14, line 21 to page 15, line 3): "All-cause mortality was not significantly influenced by the interventions (relative risk 0.98, 95% confidence interval 0.61 to 1.58; 8 trials, 3768 participants; I2=0%, P=0.68; fig 2; including trials with zero events; relative risk 0.98, 95% confidence interval 0.62 to 1.56)." 3. Please structure the abstract into 4 main sections: a. Background: Provide the context for the study. Explain the problem or issue (the reason you decided to conduct your study) in the first sentence. State the objective of your study (the question you set out to answer) in the second sentence. b. Methods: Include 4 elements: setting, patients, study type or design, and key measurements or outcomes. c. Results: Provide data for the key measurements. Describe the data in absolute and relative terms, if applicable. Give confidence intervals for differences where appropriate, or other measures of statistical significance. d. Interpretation: Begin with a sentence that answers your research question (What did the study show?). The second sentence should be a brief statement about implications for practice or research (What do the findings mean?). Avoid speculation and generalization. Authors reply We have now changed the structure of the abstract as recommended. 4. Please structure the Interpretation section (discussion) into the following 4 main categories: Main findings; explanation and comparison with other studies; limitations; and conclusions and implications for practice and future research Authors reply We have now changed the structure of the interpretation section as recommended. 5. Please list the highest degree(s) held by each author. CMAJ publishes up to one professional degree (e.g. MD) and one additional academic degree (e.g. PhD) Authors reply We have now added one professional degree and one academic degree for each author, whenever possible. 6. Please use plain numbers in parentheses for your references and do not use automatic numbering of field codes as these do not carry over well into our publishing software. Our manuscript editors will convert these into the CMAJ's usual reference numbering format once the manuscript is laid out for publication. Authors reply We have now made the recommended changes. 7. Please include a copy of a completed PRISMA checklist with your revision. Authors reply A completed PRISMA checklist is enclosed. Reviewer 1 Comments to the Author

	This is a very well done and through meta analysis done by the authors. I have only a few comments Authors reply We thank the reviewer for this positive comment. 1. The highlight I believe of this paper is the concept of the trial sequential analysis which serves as an analytic tool to determine if each analysis has obtained enough patients in order to detect an effect on a particular outcome. While the use of this tool is important and I believe the only novel aspect of this analysis it is not highlighted in a way to help the reader see that all the analyses are "underpowered" except for the analysis of weight change Authors reply We have now made the high risk of random error explicit to the reader (page 25, line 3-6): "Besides having a high risk of bias, our results also have a high risk of random errors, as the trial sequential analysis showed lack of data for all outcomes, except for weight change." 2. Similarly the authors point out the flaws in observational studies however all of the observational studies referenced meet the number of patients required to detect cardiovascular disease noted in his trial sequential analysis The study by Schramm et al had > 105,000 patients The study by Roumie et al had > 250000 patients and the study by Pantelone was by his definition underpowered at 23000. the authors also neglects to mention the study by Tzoulaki. Some mention of the observational studies in the discussion may be warranted because I do not believe that there will be a clinical trial of More than 55000 patients funded to study the effects of metformin versus sul on CVD. Authors reply We do now mention the study by Tzoulaki et al. Besides, we do now explicit describe that the mentioned observational studies have a large sample size (page 28, line 8-10): "The data from the observational studies are based on a large number of patients, but should be evaluated with caution. (52)" 3. In the discussion there should be further mention of why this meta analysis is warranted given the meta analysis of Bolen et al and bennett et al. both of which were designed to answer the same question. How does this meta analysis add to the literature? Authors reply Bolen et al did not include studies published after January 2006. Therefore, the landmark study, the 'A Diabetes Outcome Progression Trial' (ADOPT) investigating time to treatment failure of glibenclamide, metformin and rosiglitazone during about four years in 4360 drug-naive patients with T2DM and published in December 2006, was not included. The study by Bennett et al only included eight trials published in English. Neither Bolen et al. nor Bennett et al. assessed the risk of bias as recommended by the Cochrane Library. Reviewer 2 Comments to the Author GENERAL COMMENTS: In this systematic review and meta-analysis, Hemmingsen and colleagues compare sulphonylurea monotherapy to metformin in patients with type 2 diabetes. Overall, this study is well done and methodologically rigorous. My main criticism is that this work has already been published as a Cochrane Review (acknowledged by the authors on page 26 of the manuscript), limiting its potential contribution to the literature. Authors reply We thank the reviewer for the positive comments regarding the quality of our

	systematic review. The reason for making an abbreviated version of the Cochrane Review is to provide an abbreviated version of the most clinical relevant comparison of the Cochrane Review, which consist of 497 pages. SPECIFIC COMMENTS: 1. The literature search, conducted in August 2011, is already 2 years old. This greatly limits the contribution of this work to the literature. Authors reply Authors reply According to correspondence with Gordon Giddings, Medical Editorial Fellow, CMAJ ,we have done a cursory search and mentions this briefly in the discussion section of our paper. In the previous submission we had already discussed the trial by Hong et al. which was published after our search and what the inclusion of the data from the trial do the results of our meta-analysis. We have performed a search on Medline for randomized clinical trials comparing sulphonylurea versus metformin monotherapy. We have not been able to identified any other trials with relevance for our systematic review besides the trial from Hong et al., which is already mentioned. However, we do now explicit tell the reader that it is the only trial published since the search in August 2011 (page 30, line 12 to page 31, line 14): "The literature search for the current meta-analysis included trials until 2011. A cursory update of the search thorough Medline in December 2013 did only identify one randomized clinical trial of relevance of our systematic review. This randomized clinical trial by Hong et al. included about 300 Chinese patients with type 2 diabetes and existing coronary artery disease and indicated a significant benefit in favour of metformin compared with glipizide for the primary composite cardiovascular outcome after around 3 years.(53) Notably, the primary outcome was not reported after 3 years, but after a median follow up of about 5 years – i.e., about two years after the trial medication was stopped. This trial was published after the database search of our present systematic review was finalised and has therefore not been included in our systematic review. Implementing the patient-important data from Hong et al. into our meta-analysis did not change the significance of the effect estimates for the primary outcomes or for non-fatal myocardial infarction, although the composite outcome of non-fatal macrovascular complications did no longer reach statistical significance (relative risk 0.86, 95% confidence interval 0.49 to 1.50 with sulphonylurea versus metformin). The discrepancy of the result of this relatively small trial and our current meta-analysis comprising substantially more number of patients underscores the need for further randomized trials with low risk of bias, and, in particular, in broader populations, to clarify the benefits and harms of sulphonylurea versus metformin in patients with type 2 diabetes." 2. Caution should be used when interpreting the cardiovascular mortality results. With a RR of 1.47 and 95% CI 0.54 to 4.01, available data are inconclusive. Rather than focusing entirely on whether or not the results are statistically significant, an interpretation of the limits of the 95% CI would be more informative. Authors reply We have now made a comment about the confidence intervals (page 24, line 2-4): "Moreover, trial sequential analysis demonstrated that the amount of evidence was insufficient to draw firm conclusions for mortality or any of the vascular outcomes. Besides, the confidence intervals were broad, making the data inconclusive." 3. The exclusion of zero-event trials is problematic. These trials had similar event rates in the two groups and their inclusion would move the point estimate towards the null. At the very least, they should be included in sensitivity analyses. Authors reply: We have now added a sensitivity analysis (page 6, line 23 to page 7, line 3): "Sensitivity analyses for all dichotomous outcomes including trials with zero events are performed in this abbreviated version of the systematic review, but not in the current

	version of the Cochrane review." For each of the dichotomous outcomes the relative risk and the confidence interval including zero events trials are reported (e.g., page 14, line 21 to page 15, line 3): "All-cause mortality was not significantly influenced by the interventions (relative risk 0.98, 95% confidence interval 0.61 to 1.58; 8 trials, 3768 participants; I2=0%, P=0.68; fig 2; including trials with zero events; relative risk 0.98, 95% confidence interval 0.62 to 1.56)."