PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Medicine. The paper was subsequently accepted for publication at BMJ Medicine.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sodium-glucose co-transporter-2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes: a systematic review and meta-analysis
AUTHORS	Li, Sheyu; Zou, Xinyu; Shi, Qingyang; Olav Vandvik, Per; Mao, Yunhe; Agarwal, Arnav; Ponte, Belen; Zeng, Xiaoxi; Guyatt, Gordon; Yang, Qinbo; Luo, Xianghang; Xu, Chang; Fu, Ping; Tian, Haoming; Agoritsas, Thomas

VERSION 1 - REVIEW

REVIEWER NAME	Christian W. Mende
REVIEWER AFFILIATION	University of California at San Diego
REVIEWER CONFLICT OF INTEREST	Speaker for Boehringer Ingelheim , Lilly , AstraZenica
DATE REVIEW RETURNED	30-May-2024

GENERAL COMMENTS	This is a well done review, but there are many other similar published articles and it has really no new findings . I would like additional comments of SGLT2 inhib and effects on nephrolithiasis, acute kidney disease (AKD in addition to AKI), new onset of gout ,and effect on magnesium (if available from the analysis)

REVIEWER NAME	Reviewer 2
REVIEWER AFFILIATION	
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	30-May-2024

GENERAL COMMENTS	1) The search date is as of July 2023. It is recommended to update the search to obtain potential articles published recently; 3) The author used Mantel Haenszel to merge RCT data, but this method itself cannot handle heterogeneity issues well; When heterogeneity is significant, the DerSimonian Laird random effects model may be more appropriate; 4) Some studies have reported single arm zero events, and it is recommended that the author supplement the correction issue for zero events in statistical analysis; 5) In the full text screening stage, it is recommended that the author supplement the attachment, list the excluded literature and corresponding reasons, to make it transparent; 6) Some RCTs have a follow-up time of up to 100+weeks, while others only have a follow-up time of

	20+weeks. The death cases observed during the follow-up time are bound to be different. It is recommended to add results based on time as a subgroup

REVIEWER NAME	Sarah Cook
REVIEWER AFFILIATION	Imperial College London
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	30-May-2024

GENERAL COMMENTS	This is a systematic review looking at a range of health outcomes among people with chronic kidney disease using SGLT-2 Inhibitors compared to non use (regardless of whether they also have diabetes). In total 13 randomised controlled trials (RCTS) were included. There is a strong rationale for the study and it is an important topic for a systematic review. The findings are of clinical importance. The methods are well described and appropriate from what was reported. There were two points where more clarification is needed 1) What was the justification for the outcomes included? The title does not include an outcomes and within the abstract the study objective was given as “to examine efficacy and safety” which could potentially cover any outcome and did not fit well with the outcomes reported. In the main manuscript the full list of eligible outcomes was included within the eligibility criteria section however it would be good here to explain the justification for how this list of outcomes was selected and clarify if there was an a priori list of outcomes of interest or whether any outcomes found in published RCTs were included. 2) There was some inconsistency in the reporting of whether SGLT-2's were associated with any adverse outcomes. In the abstract and summary box an increased risk of genital infection, diabetic ketoacidosis and symptomatic hypovolaemia was reported but in the main results section in the manuscript reported SGLT2 inhibitors probably have little or no effect on these outcomes (page 15 lines 48 -59). Minor comments: Table 1- for the columns Age, eGFR and UACR it would be good to clarify mean (SD)/ median (IQR) as appropriate Figure 2 – The text within the figure was very small within the pdf version of the manuscript making this difficult to read

REVIEWER NAME	Marcus Säemann
REVIEWER AFFILIATION	Clinic Ottakring
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	30-May-2024

GENERAL COMMENTS	In their manuscript, Zhou et al. perform a meta-analysis and systematic review on SGLT-2i in CKD with/without diabetes mellitus employing 13 trials. Respective meta-analyses of SGLT-2i also in CKD are hitherto very abundant; especially a similar analysis has been carried out by Reyes-Farias (PLoS One. 2023 Nov 29;18(11):e0295059) with 14 trials recently with similar even identical HRs such as for renal outcomes (HR 0.69, significant). Further recent meta-analyses come to the same conclusion (e.g. Mavrakanas et al., Sci Rep. 2023 Sep 23;13(1):15922, Zhou et al et al., Curr Pharm Des. 2023;29(21):1659-1670 and Shiau et al., Int Urol Nephrol. 2024 Apr;56(4):1359-1381). Hence, one of the main conclusions, that SGLT-2i beneficially affect CKD patients irrespective of diabetes status and offer renal as well as cardiovascular outcomes has been documented and published many times already (those analyses with only diabetes patients and SGLT-2i naturally outweigh the analyses with also non-diabetes patients with CKD and/or HF). While absolute effects of SGLT-2i vary at the individual level, how should the presented data inform about individual clinical decision making beyond what is already known? Overall I do not see the unique point of this manuscript. In principal, the effects of SGLT-2i on analyzed primary outcomes should be specified in the title and abstract, e.g. cv- and kidney outcomes and also with regard to safety. Throughout the manuscript there are many shortcomings with regard to grammar and style, hence it should be corrected by a native speaker. For example: p. 7 " So far, …represented the core aspect,…" p.7 "SGLT-2i, such as dapagliflozin … are initially diabetes treatment medications…". Initially? p. 7 "While CKD affects….are needed for these population." P 7/8 "…regarding SGLT2 inhibitors for all CKD population with an eGFR…" P 8: "…general practitioners, internists and nephrologist…"

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Comment 1:

This is a well-done review, but there are many other similar published articles and it has really no new findings. I would like additional comments of SGLT2 inhibitors and effects on nephrolithiasis, acute kidney disease (AKD in addition to AKI), new onset of gout, and effect on magnesium (if available from the analysis).

Response 1: Thanks for the comment. The systematic review was conducted based on the PICOS predefined in the protocol. Besides kidney failure, kidney-related death, and AKI requiring dialysis,

other kidney-related outcomes (e.g., nephrolithiasis, new onset of gout and acute kidney disease) are beyond the scope of our study.

Reviewer 2:

Comment 1:

The search date is as of July 2023. It is recommended to update the search to obtain potential articles published recently.

Response 1: Thanks for the comment. We updated the literature search up to 15 June 2024 and included one *post-hoc* analysis providing new information for kidney failure and kidney-related death. we revised the flow diagram (Figure 1) and manuscript accordingly. It now reads:

- *We searched OVID Medline, Embase, and Cochrane Central Register of Controlled Trials from inception to 15 June 2024.*
- *List of included reports and excluded studies during full-text screening are listed in Appendix 6.*
- *…four (25,898 participants) reported kidney-related death.*[5,8,9,32]
- *Nine trials involving 28,221 participants reported kidney failure…*

Comment 2:

The author used Mantel Haenszel to merge RCT data, but this method itself cannot handle heterogeneity issues well; When heterogeneity is significant, the DerSimonian Laird random effects model may be more appropriate

Response 2: Thanks for the comment. We performed a sensitivity analysis using DerSimonian-Laird method with Hartung-Knapp adjustment and found consistent results (Appendix 13.7). We revised the manuscript accordingly. It now reads:

- *…6) conducting a random effects meta-analysis with DerSimonian-Laird method and Hartung-Knapp adjustment.*

Comment 3:

Some studies have reported single arm zero events, and it is recommended that the author supplement the correction issue for zero events in statistical analysis

Response 3: Thanks for the comment. Continuity correction of 0.5 was used in studies with zero cell frequencies. We revised the manuscript accordingly. It now reads:

- *Continuity correction of 0.5 was used in studies with zero events.*

Comment 4:

In the full text screening stage, it is recommended that the author supplement the attachment, list the excluded literature and corresponding reasons, to make it transparent

Response 4: Thanks for the kind reminder. Appendix 6 listed excluded studies and reasons during full-text screening. We revised manuscript accordingly. It now reads:

- *List of included reports and excluded studies during full-text screening are listed in Appendix 6.*

Comment 5:

Some RCTs have a follow-up time of up to 100+weeks, while others only have a follow-up time of 20+weeks. The death cases observed during the follow-up time are bound to be different. It is recommended to add results based on time as a subgroup

Response 5: Thanks for the comment. To solve the concern regarding inconsistent follow-up duration of included trials, we performed a meta-regression by median follow-up duration, indicating no interaction effects (as detailed in Appendix 11). We revised the manuscript accordingly. It now reads:

- *A meta-regression by median follow-up duration was added due to the concern of various follow-up duration across studies.*
- *The relative effects were consistent according to diabetes status, heart failure status, eGFR level, and follow-up duration (Appendices 9 and 11).*

Reviewer 3:

Comment 1:

What was the justification for the outcomes included? The title does not include an outcomes and within the abstract the study objective was given as “to examine efficacy and safety” which could potentially cover any outcome and did not fit well with the outcomes reported.

In the main manuscript the full list of eligible outcomes was included within the eligibility criteria section however it would be good here to explain the justification for how this list of outcomes was selected and clarify if there was an a priori list of outcomes of interest or whether any outcomes found in published RCTs were included.

Response 1: Thanks for the comment. As a guideline-informing evidence synthesis, this systematic review rated the importance of the outcomes in accordance with the judgement of the guideline panel, including nine critical outcomes and four important ones. We added more information of the outcomes and absolute effects in the abstract and main text. It now reads:

- *To examine patient-important cardiovascular, kidney, and safety outcomes of sodium-glucose co-transporter-2 (SGLT2) inhibitors in risk stratified adults with chronic kidney disease (CKD) regardless of diabetes status.*
- *The guideline panel judged all-cause death, cardiovascular death, kidney-related death, kidney failure, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, acute kidney injury (AKI) requiring dialysis, and lower limb amputation as critical outcomes; bone fracture, genital infection, diabetic ketoacidosis (DKA), and symptomatic hypovolaemia as important outcomes. Eligible studies reported on at least one of the outcomes.*

Comment 2:

There was some inconsistency in the reporting of whether SGLT-2's were associated with any adverse outcomes. In the abstract and summary box an increased risk of genital infection, diabetic ketoacidosis and symptomatic hypovolaemia was reported but in the main results section in the manuscript reported SGLT2 inhibitors probably have little or no effect on these outcomes (page 15 lines 48-59).

Response 2: Thanks for the comment. We interpreted the results in the relative and absolute terms, respectively. In the absolute term, in accordance with GRADE approach, this systematic review interprets the effects using minimal important difference (MID) as the threshold.[1] When point estimates of the absolute risk reduction prove between the positive and negative MIDs, we interpret the difference to be little or no effect. The thresholds for each outcome were provided in Notes of Figure 2 and Appendix 5.

Comment 3:

Table 1- for the columns Age, eGFR and UACR it would be good to clarify mean (SD)/ median (IQR) as appropriate

Response 3: Thanks for the comment. As the note of Table 1 shows, data is presented as mean (standard deviation, SD) or median (interquartile range, IQR) unless otherwise specified.

Comment 4:

Figure 2 – The text within the figure was very small within the pdf version of the manuscript making this difficult to read

Response 4: Thanks for the kind reminder. We revised the figures accordingly.

Reviewer 4:

Comment 1:

In principal, the effects of SGLT-2i on analyzed primary outcomes should be specified in the title and abstract, e.g. cv- and kidney outcomes and also with regard to safety.

Response 1: Thanks for the comment. More information of the outcomes was added in the abstract. It now reads:

- *To examine patient-important cardiovascular, kidney, and safety outcomes of sodium-glucose co-transporter-2 (SGLT2) inhibitors in risk stratified adults with chronic kidney disease (CKD) regardless of diabetes status.*

Comment 2:

Throughout the manuscript there are many shortcomings with regard to grammar and style, hence it should be corrected by a native speaker.

Response 2: Thanks for the comment. We revised the manuscript accordingly.

Reference

1. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. *J Clin Epidemiol*. 2021;137:163–75. doi:10.1016/j.jclinepi.2021.03.026

VERSION 2 – REVIEW

REVIEWER NAME	Perera, Rafael
REVIEWER AFFILIATION	University of Oxford, Primary Care Health Sciences

REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	06-Aug-2024

GENERAL COMMENTS	bmjmed-2024-001009: Sodium-glucose co-transporter-2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes: a systematic review and meta-analysis Stats Review: The current manuscript presents evidence of the effects of SGLT2 inhibitors on multiple (patient-relevant) outcomes based on a systematic review of the published RCTs of this class of drugs for people with CKD. Their finding, which is consistent with previous reviews, is that this class has a positive effect reducing mortality (multiple causes) and other similar outcomes, while delivering a small increase in potential harms. The reporting of the Review is comprehensive and mostly complete; there are some very minor points that I would suggest are considered by the authors, although these should not affect the overall findings but should provide further clarity in their reporting. • Regarding their fully contextualised interpretation of the findings, the use of thresholds to define MIDs is useful. These are presented in Appendix 5, but it is unclear how they were derived. Also, some basic explanation as to this fully contextualised approach with reference to the thresholds in the Appendix would be particularly useful in the Methods section. This will aid in understanding the interpretations presented in the Results section. • The Introduction/Background section mainly presents that guidance for the use of SGLT2 has been provided for populations with eGFRs >=20, while for the review, the target/reported population has eGFRs >=30. Please explain the rationale for this in the Background or in the Methods and consider how your findings can affect guidelines given this constraint. • The continuity correction of 0.5 is valid in studies where 'one arm' has zero events, not when the whole study has zero events. Please adjust your reporting accordingly. • The sensitivity analyses, excluding those trials that stopped early, mainly show a similar point estimate effect across the different outcomes. However, for All-cause death, the point estimate in the sensitivity analysis is considerably closer to the null (with 95% CI on either side of no effect). This suggests a potential bias, at least for this outcome. This is not mentioned anywhere and would be worth commenting on in the Discussion section. On this same point, the 'Fragility Index' of this outcome is 9. It is unclear if this is low/high enough that it warrants mentioning. • In a couple of places, 'these population' is used. I believe 'population' is singular. Please correct. • For the reporting of the 'Safety outcomes', please provide the values equivalent to the 95%CI, not only the point estimate, as you have done for the previous outcomes.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Stats Review:

The current manuscript presents evidence of the effects of SGLT2 inhibitors on multiple (patient-relevant) outcomes based on a systematic review of the published RCTs of this class of drugs for people with CKD. Their finding, which is consistent with previous reviews, is that this class has a positive effect reducing mortality (multiple causes) and other similar outcomes, while delivering a small increase in potential harms. The reporting of the Review is comprehensive and mostly complete; there are some very minor points that I would suggest are considered by the authors, although these should not affect the overall findings but should provide further clarity in their reporting.

Comment 1:

• Regarding their fully contextualised interpretation of the findings, the use of thresholds to define MIDs is useful. These are presented in Appendix 5, but it is unclear how they were derived. Also, some basic explanation as to this fully contextualised approach with reference to the thresholds in the Appendix would be particularly useful in the Methods section. This will aid in understanding the interpretations presented in the Results section.

Response 1: We agree that some basic explanation of the fully contextualised approach and how the thresholds were derived will aid in understanding our study. We revised the Methods section. It now reads:

> – Imprecision was judged using outcome-specific minimal important differences informed by panel discussions and existing literature (see Appendix 5).[24] Final assessments of certainty were fully contextualised, considering all outcomes together and aligned with judgements of the guideline panel.

Comment 2:

• The Introduction/Background section mainly presents that guidance for the use of SGLT2 has been provided for populations with eGFRs >=20, while for the review, the target/reported population has eGFRs >=30. Please explain the rationale for this in the Background or in the Methods and consider how your findings can affect guidelines given this constraint.

Response 2: Thanks for your comments. This systematic review included all adults with CKD and did not restrict their baseline eGFR levels. We also conducted subgroup analyses between patients with eGFR ≥ or < 30 ml/min per 1.73m².

Comment 3:

• The continuity correction of 0.5 is valid in studies where 'one arm' has zero events, not when the whole study has zero events. Please adjust your reporting accordingly.

Response 3: Thanks for your correction. The continuity correction in this meta-analysis was only for trials with zero events in a single arm. This analysis did not include trials with zero events in both arms. To avoid any confusion, we revised the manuscript and it now reads:

– Continuity correction of 0.5 was used in studies with zero events in at least one of the arms (trials with zero events in all arms were excluded).

Comment 4:

• The sensitivity analyses, excluding those trials that stopped early, mainly show a similar point estimate effect across the different outcomes. However, for All-cause death, the point estimate in the sensitivity analysis is considerably closer to the null (with 95% CI on either side of no effect). This suggests a potential bias, at least for this outcome. This is not mentioned anywhere and would be worth commenting on in the Discussion section. On this same point, the 'Fragility Index' of this outcome is 9. It is unclear if this is low/high enough that it warrants mentioning.

Response 4: Thanks for the comments. We acknowledge that the relative effect estimate of all-cause death but not other benefit outcomes in the sensitivity analyses is indeed closer to the null than that of the primary analysis. However, given the certainty of evidence has already been rated down once for serious imprecision, we judged uncertainty related to early termination was already accounted for with overall moderate certainty evidence and did not warrant downgrading twice. We tried fragility index to aid in the interpretation of robustness, but we also agree that there is no generally acceptable threshold for high or low fragility index. To avoid confusion, we revised risk of bias section and the first bullet of the limitation as following:

– Sensitivity analyses excluding trials stopped early for benefit showed smaller effects for all-cause death; effects for other outcomes were similar to those in the primary analysis. Given certainty was already rated down for serious imprecision for all-cause death based on wide confidence intervals and small event rates, we judged uncertainty related to early termination was already accounted for with overall moderate certainty evidence and did not rate down further for risk of bias as a result. Similarly, given no indication of treatment effect overestimation for other outcomes, we did not rate risk of bias as high.

– First, four large-scale kidney outcome trials, which accounted for 83% of study population, were terminated early; we acknowledge the possibility of treatment overestimation with stopping early, and therefore warrants longer-term surveillance in real-world practice.[36]

Comment 5:

• In a couple of places, 'these population' is used. I believe 'population' is singular. Please correct.

Response 5: Thanks for the reminder. We revised the manuscript to avoid such mistakes.

Comment 6:

• For the reporting of the 'Safety outcomes', please provide the values equivalent to the 95%CI, not only the point estimate, as you have done for the previous outcomes.

Response 6: Thanks for the comment. We revised the manuscript accordingly. It now reads:

> – SGLT2 inhibitors probably have little or no effect on AKI requiring dialysis (9 fewer per 1000 patients, 95% CI 14 fewer to 1 fewer), fracture (2 more per 1000 patients, 95% CI 10 fewer to 15 more), lower limb amputation (2 more per 1000 patients, 95% CI 4 fewer to 10 more), genital infection (27 more per 1000 patients, 95% CI 17 more to 39 more), ketoacidosis (4 more per 1000 patients, 95% CI 1 more to 9 more), and symptomatic hypovolaemia (32 more per 1000 patients, 95% CI 17 more to 49 more) over five years (low certainty for lower limb amputation; moderate certainty for other outcomes).