PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Systematic Review and Meta-Analysis of the Effect of SGLT-2 Inhibitors in Microvascular Outcomes in Patients with Type 2 Diabetes: A Review Protocol
AUTHORS	Dorsey-Treviño, Edgar Gerardo; Contreras-Garza, Belinda; González-González, JG; Alvarez-Villalobos, Neri; Salcido-Montenegro, Alejandro; Díaz González-Colmenero, Alejandro; Farrell, Ann; González-Nava, Victoria; Rodríguez-Tamez, Giselle; Montori, Victor; Rodriguez-Gutierrez, R

VERSION 1 – REVIEW

REVIEWER	Norman Waugh Professor of public health medicine and health technology assessment, University of Warwick, UK
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	BMJ Open paper 2017-020692 General comments There are already a lot of reviews of the SGLT2 inhibitors (the flozins), so do we need yet another one? The review proposed by Dorsey-Trevino and colleagues seeks a new angle – microvascular outcomes. Unfortunately most trials of the flozins are short-term, usually 26 weeks, so they cannot provide data on microvascular outcomes. Indeed if they did, they might be seriously misleading due to the “glycaemic re-entry” problem with effects on retinopathy. There are a few longer studies, of a year, but even those are too short to report on retinopathy etc. So intermediate indicators would have to be used as outlined on page 8, and the authors would have to justify how well those relate to proper outcomes. In practice, I doubt if most of the flozins trials would report most of these. However, it’s traditional in protocols for systematic reviews (especially in Cochrane ones) to be idealistic rather than realistic, and to specify what is wanted rather than what you expect to get. But I think the review will find little of what is sought. Specific comments The title mentions SGLT-2 inhibitors but names only three. So either it should be changed to “effect of dapagliflozin, empagliflozin and canagliflozin”, or the review should be extended to cover the other flozins. Ertugliflozin was approved by FDA last year. Sotagliflozin is close to approval by FDA. There are published trials of luseogliflozin, ipragliflozin and tofogliflozin which we included in a BMJ Open review back in 2015 (Shyangdan DS,Uthman OA, Waugh N.SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. BMJ Open2016;6:e009417. doi:10.1136).

	There are 11 authors listed which seems a lot, but their contributions are listed on page 13. The English needs some tidying up. Introduction Page 5. The authors say that the review by Rodriguez-Gutierrez and Montori (who are amongst the authors of this protocol) reported no effect of tight control (HbA1c <7%) but they don't say what that is compared to. I don't have the full paper but the abstract gives no details of what was meant by tight control nor what it was compared to. I suggest they also refer to the very good review by Boussageon et al 2011 BMJ 2011;343:d4169 doi: 10.1136/bmj.d4169 which came to similar but not identical conclusions – tight control reduced microalbuminuria a bit. Page 5, line 87. The flozins are not one of the most used classes. Page 5, line 89, HbA1c reduction of around 1%. That depends on baseline HbA1c, which flozin is used, and where in the treatment pathway flozins are used. Our NMA found HbA1c reduction of over 1% for canagliflozin, in some scenarios, but not for other flozins. Similarly weight loss varies according to baseline BMI. The authors will need to consider heterogeneity in their analyses. Some trials were done in patients with baseline HbA1c only 7.5%. Another point to note is that trials randomised people to 100mg or 300 mg canagliflozin from the start, but licences say people should start on 100mg and only increase to 300mg if the drug is tolerated but has insufficient effect. Those who don't respond enough to 100mg may not get as big an effect on 300mg as was seen in the trials. Page 6, line 94. All the references cited are on nephropathy. That is affected by blood pressure control, and the flozins have effects on BP which may not be applicable to e.g. retinopathy risk. Dapagliflozin 5mg – is that used now? Possibly in East Asians? If so, heterogeneity will be an issue. Page 6, line 111. A minimum of 4 weeks is far far too short. I doubt if any useful data on mincrovascular outcomes would be available in studies under 12 months. Page 7, line 118. Who is NAV? Neri Alvarez-Villlobos? Page 7, line 119 – searching from earliest inception of databases doesn't seem worthwhile when the flozins are a recent discovery. Page 7, search strategy. I suggest adding ClinicalTrials.Gov which may show some unpublished trials, or trials that don't report what they set out to report. It will also show what is underway at present, such as long-term extension studies. Page 9, missing data. It's probably worth contacting authors but the data will usually be held by the drug manufacturers, who really run the trials and do the analyses. So I would suggest contacting the manufacturers as well. Page 10, risk of bias assessment. Will a quality threshold be used to exclude studies? Even if only in a sensitivity analysis. In practice, nearly all studies will have been run by the manufacturers, and quality as assessed by Cochrane RoB will appear good. The biases will be in choice of comparators, and possibly in representativeness of recruits. We often see trials done in dozens of centres, each of

	which recruits only a few patients. These have been described by Godlee et al as “marketing trials”. Page 10, lines 189-192, seem to be getting away from microvascular outcomes. Page 10, lines 198 – 199. When considering meta-analysis, need to consider heterogeneity. We looked at this in a review for NICE (Johnston R, Uthman O, Cummins E, Clar C, Royle P, Colquitt J et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment 2017/21/ number 2) and the results varied according to which trials were included. Will meta-analysis be discarded if I squared is over 50%? Page 12, line 228, spelling of PRISMA. Page 14, line 271, first author Mb? I had a look at registrations on PROSPERO and there are two that seem to overlap with this one – Hemmingson et al CRD 42016045570 from the Cochrane CMED team, and one on renal outcomes only, CRD42018085405. (PROSPERO is supposed to reduce duplication of reviews but it doesn’t even prevent duplication of registrations of overlapping protocols.) Comments The guidance from BMJ Open for reviewers of protocols for reviews is that few changes can be made. Which makes me wonder what the point of reviews is. Hopefully, reviewers may sometimes make useful suggestions. My main comment is that this review should cover all the flozins trials that may have data on microvascular outcomes, but that I would not expect many trials to have such data. So the review by Dorsey-Trevino and colleagues might find little to report – but that is of value in itself, if a new class of drugs for diabetes comes into use without evidence that they reduce the specific complications of diabetes. The flozins are being pushed/hyped because of EMPA-REG OUTCOME, but the mechanism underlying the slight reduction on CVD outcomes in that trial was probably not via glycaemic control, but via a diuretic effect. Comment to editor. The protocol has been entered on PROSPERO. I have raised before with BMJ Open editors, the question of whether giving details on PROSPERO reduces the value of publication in a journal – does it represent dual publication? However the authors have given only brief details on PROSPERO so I think publication of a fuller version is justified. Someone should take a critical look at the value of PROSPERO.

REVIEWER	K. Melissa Hallow University of Georgia
REVIEW RETURNED	30-Jan-2018

GENERAL COMMENTS	The manuscript contains a lot of typos, grammatical errors, and unclear language. The authors may need to have a native English-speaker assist them in updating the manuscript. Abstract line 38: Actually the bulk of CV benefit with SGLT2 inhibition appears to be from reduced Heart failure hospitalization and improved renal function. Non-fatal MI and non-fatal stroke were not changed in the EMPA-REG study. Authors should update this sentence.

REVIEWER	Natalie Mordi

	University of Dundee, Scotland, United Kingdom
REVIEW RETURNED	04-Feb-2018

GENERAL COMMENTS	The authors describe the protocol for systematic review and meta-analysis via electronic databases to analyse the effect of SGLT2 inhibitors on microvascular outcomes. The authors clearly state the outcomes of interest whilst recognise the study's limitations and have accounted for heterogenicity Unfortunately the grammar is poor throughout, particularly in the abstract with spelling mistakes e.g. "across some of the [mayor] RCTs." Overall would benefit from review by a native English speaker.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)´ Comments:

Reviewer 1:

Comment #1: The title mentions SGLT-2 inhibitors but names only three. So either it should be changed to “effect of dapagliflozin, empagliflozin and canagliflozin”, or the review should be extended to cover the other flozins.

Response:
The three we mentioned are the most commonly used in clinical practice; however, we agree that there are more flozins that are equally important, so we will include all of them to avoid losing valuable information.

The manuscript now reads as follows:

We will search for RCTs that compare any of the SGLT-2 inhibitors with any other active treatment or placebo assessing microvascular outcomes in either their primary or secondary outcomes.

Comment #2: Introduction Page 5. The authors say that the review by Rodriguez-Gutierrez and Montori (who are amongst the authors of this protocol) reported no effect of tight control (HbA1c <7%) but they don’t say what that is compared to. I don’t have the full paper but the abstract gives no details of what was meant by tight control nor what it was compared to. I suggest they also refer to the very good review by Boussageon et al 2011 BMJ 2011;343:d4169 doi: 10.1136/bmj.d4169 which came to similar but not identical conclusions – tight control reduced microalbuminuria a bit.

Response:

We thank the reviewer for this comment. The comparison was tight (HbA1c <7%) vs conventional glycemic control (HbA1c <8.0-8.5) regarding patient-important outcomes. We have also included the Boussageon et al. reference and a couple more SR that are consistent with these findings. While we focused on patient-important outcomes, we also found that tight glycemic control reduced some surrogate outcomes such as microalbuminuria.

The references included now reads as follows:

Hemmignsen et al., Cochrane 2013,

Coca et al., Annals 2012

Boussageon, BMJ 2013

Kelly et al., Annals 2009

Rodríguez-Gutiérrez R et al., Circ Cardiovasc Qual Outcomes 2016

The manuscript now reads as follows:

Consistent with other studies, a recent systematic review reported no effect of tight glycemic control (HbA1c <7.0%) when compared to conventional glycemic control (HbA1c 8.0-8.5%) regarding patient-important microvascular outcomes (e.g., end-stage renal disease, blindness, clinical neuropathy) in patients with type 2 diabetes (3–7). Still, there is a positive, however, inconsistent effect regarding surrogate markers (e.g., microalbuminuria, photocoagulation)(7). Other strategies, such as lipid lowering drugs (e.g., fibrates), antiplatelet agents, smoking cessation, blood pressure control including angiotensin-converting enzyme inhibitors, and lifestyle modifications, in most cases as a multifactorial intervention, have been reported to have a positive effect; however, mostly over surrogate markers
.

Comment #3: Page 5, line 87. The flozins are not one of the most used classes.

Response:

Following the recommendation of the reviewer we changed this sentence.

The manuscript now reads as follows:

To date, there are at least 10 classes of antihyperglycemic medications with different mechanisms of action, efficacy, adverse events, costs, and convenience(8,9) Sodium glucose co-transporter 2 (SGLT-2) inhibitors are one of the novel classes of antihyperglycemic drugs and as a group are positioning themselves as a promising therapeutic class in current diabetes treatment(10–12).

Comment #4: Page 5, line 89, HbA1c reduction of around 1%. That depends on baseline HbA1c, which flozin is used, and where in the treatment pathway flozins are used. Our NMA found HbA1c reduction of over 1% for canagliflozin, in some scenarios, but not for other flozins. Similarly weight loss varies according to baseline BMI. The authors will need to consider heterogeneity in their analyses. Some trials were done in patients with baseline HbA1c only 7.5%.

Response:
That is why we initially included the word “around” but it is probably confusing. Hence, we thank the reviewer for the comment and have made the changes accordingly.

The manuscript now reads as follows:

Previous systematic reviews have demonstrated their effectiveness in reducing hemoglobin A1c (HbA1c), body weight, blood pressure(13–15)

Comment #5: Another point to note is that trials randomized people to 100 mg or 300 mg canagliflozin from the start, but licenses say people should start on 100 mg and only increase to 300 mg if the drug is tolerated but has insufficient effect. Those who don't respond enough to 100 mg may not get as big an effect on 300 mg as was seen in the trials.

Response:
CANVAS Trial used this approach and while dose effect may play a role it seems that regarding efficacy and outcomes it is not big enough to conclude that only one dose or another can be used or is efficacious. Depending on the final RCTs we have we will try to do a sensitivity analysis exploring this issue.

The manuscript now reads as follows:

If possible, we will also try to analyze different drug doses. Also, we will conduct the following sensitivity analysis: patients with long-term versus recent diabetes diagnosis and patients with arterial hypertension as comorbidity versus patients without hypertension.

Comment #6: Page 6, line 94. All the references cited are on nephropathy. That is affected by blood pressure control, and the flozins have effects on BP which may not be applicable to e.g. retinopathy risk.

Response:

While it is true that most of the SGLT-2 inhibitor trials involving microvascular outcomes focus on renal outcomes, there are a few others that evaluate different microvascular outcomes. For instance, Ott C, Jumar A, Striepe K, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol. 2017;16:26. This is reference 19 and it evaluates retinal outcomes

Comment #7: Dapagliflozin 5 mg – is that used now? Possibly in East Asians? If so, heterogeneity will be an issue.

Response:

We are planning to include studies that evaluate any SGLT-2 at any dose, and the recommended starting dose by the FDA is 5 mg of dapagliflozin once daily. We might find none if it is really not used in a clinical trial, however, for now we do not know for sure. This issue, about different doses is common to all SR that are similar to ours- for instance statin or antihypertensive medications.

Comment #8: Page 6, line 111. A minimum of 4 weeks is far far too short. I doubt if any useful data on microvascular outcomes would be available in studies under 12 months.

Response:
We agree, 4 weeks is a very short period for the evaluation of microvascular damage; however, as there could be some studies with this short follow-up period that evaluate surrogate markers such as albuminuria, we didn't want to risk valuable information for our systematic review and hence, we decided to establish 4 weeks as the minimum amount of time for inclusion of the study. It is probable that in short-follow up studies we will find no data and we will end up with longer studies.

Comment #9: Page 7, line 118. Who is NAV? Neri Alvarez-Villlobos?

Response:

Indeed, he is an experienced librarian who has received extensive training in performing search strategies in several systematic reviews performed at the KER Unit at the Mayo Clinic in Rochester, Minnesota.

Comment #10: Page 7, line 119 – searching from earliest inception of databases doesn't seem worthwhile when the flozins are a recent discovery.

Response:
We agree with this; however, quality assessment (risk of bias) of systematic reviews asks to be compliant with this. While it is more work in the end we can assure that we will not miss any article.

Comment #11: Page 7, search strategy. I suggest adding ClinicalTrials.Gov which may show some unpublished trials, or trials that don't report what they set out to report. It will also show what is underway at present, such as long-term extension studies.

Response:
We thank the reviewer for this suggestion. In ClinicalTrials.gov, we will find unfinished trials in which data (estimates) will not be available and hence will not be useful for our purpose to determine the effect of SGLT-2 inhibitors regarding microvascular outcomes.

Comment #12: Page 9, missing data. It's probably worth contacting authors but the data will usually be held by the drug manufacturers, who really run the trials and do the analyses. So I would suggest contacting the manufacturers as well.

Response:
We agree and thank the reviewer for this suggestion, we will try to contact manufacturers as well.

The manuscript now reads as follows:

If any data is either not clear, missing or presented in an unextractable form from the full-text, an email will be sent to either the corresponding author or the drug manufacturer to clarify the situation. After a lapse of 10 days a second email will be sent to non-responders. If the second attempt is unsuccessful, other authors will be contacted. If none of the authors or the manufacturers respond, we will exclude the study. Every author and manufacturer contact will be documented.

Comment 13: Page 10, risk of bias assessment. Will a quality threshold be used to exclude studies? Even if only in a sensitivity analysis. In practice, nearly all studies will have been run by the manufacturers, and quality as assessed by Cochrane RoB will appear good. The biases will be in choice of comparators, and possibly in representativeness of recruits. We often see trials done in dozens of centres, each of which recruits only a few patients. These have been described by Godlee et al as "marketing trials".

Response:
No, we will not exclude studies because of bias, instead we will include all of them and then grade the overall quality of the evidence. The results of the bias assessment for each study will be accessible on the final manuscript. By doing this readers will have a wide picture of the type of studies included in terms of bias assessment and have their particular tone/ weight to the conclusions.

Comment #14: Page 10, lines 189-192, seem to be getting away from microvascular outcomes.

Response:

We thank the reviewer for the observation. Yet, we will not study any cardiovascular outcome. However, it might be interesting, in case we find this kind of articles, to have a sensitivity analysis of microvascular outcomes in primary vs secondary cardiovascular prevention as it is plausible that patients will not have the same outcomes.

This section in the manuscript now reads as follows:

Sensitivity analysis
To explain possible inconsistencies between studies we will conduct the following subgroup analysis: patients with long-term versus recent diabetes diagnosis and trials of primary versus secondary cardiovascular prevention.

Comment #15: Page 10, lines 198 – 199. When considering meta-analysis, need to consider heterogeneity. We looked at this in a review for NICE (Johnston R, Uthman O, Cummins E, Clar C, Royle P, Colquitt J et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment 2017/21/ number 2) and the results varied according to which trials were included. Will meta-analysis be discarded if I squared is over 50%?

Response:
Not necessarily, this is why we have prespecified to carry out a sensitivity analysis. This sensitivity analysis can help us understand heterogeneity and hence, in these cases, a meta-analysis can be carried out.

Comment #16: Page 12, line 228, spelling of PRISMA.

Response:
We thank the reviewer for acknowledging this.

The manuscript now reads as follows:

95% CI: 95% confidence interval; OR: odds ratio; SGLT-2: sodium glucose cotransporter 2; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis Protocols; CENTRAL: Cochrane Central Register of Controlled Trials, WHO: The World Health Organization; ICTRP: International Clinical Trials Registry Platform; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; RCT: Randomized Clinical Trial.

Comment #17: Page 14, line 271, first author Mb?

Following the reviewer observation, we have corrected this error.

The manuscript now reads as follows:

Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, et al. Pharmacologic Management of Type 2 Diabetes. Can J Diabetes. 2016;40(3):193–5

Comment #18: My main comment is that this review should cover all the flozins trials that may have data on microvascular outcomes, but that I would not expect many trials to have such data.

Response:

As previously mentioned, we will include all trials that evaluate any SGLT-2 inhibitor that has been FDA approved and that hence, is used in clinical practice and has an impact on patient care.

Reviewer 2

Comment #1: The manuscript contains a lot of typos, grammatical errors, and unclear language. The authors may need to have a native English-speaker assist them in updating the manuscript.

Response:
We thank the reviewer for the comment. Following this recommendation, the entire manuscript has been carefully reviewed by an international certified expert in medical writing.

Comment #2: Abstract line 38: Actually the bulk of CV benefit with SGLT2 inhibition appears to be from reduced Heart failure hospitalization and improved renal function. Non-fatal MI and non-fatal stroke were not changed in the EMPA-REG study. Authors should update this sentence.

Response:

Following the reviewers commend we modified this section.

The manuscript now reads as follows:

Sodium glucose cotransporter 2 (SGLT-2) inhibitors are a relatively new drug-class of antidiabetic medications. Several trials and systematic reviews have demonstrated their beneficial effect on some macrovascular outcomes.

Reviewer 3:

Comment: Unfortunately, the grammar is poor throughout, particularly in the abstract with spelling mistakes e.g. "across some of the [mayor] RCTs." Overall would benefit from review by a native English speaker.

Response:
As stated before, we thank the reviewer for the comment. Following his recommendation, the whole manuscript has been carefully reviewed by an international certified expert in medical writing.

VERSION 2 – REVIEW

REVIEWER	Norman Waugh University of Warwick, UK
REVIEW RETURNED	10-Mar-2018

GENERAL COMMENTS	Revisions have improved this protocol and I have few comments. The term “antidiabetic” to describe drugs is perhaps not as good as "glucose-lowering". I note some of my comments not accepted. There is no point in searching the databases from their inception, or any mention of checking Clinical.Trials.gov for ongoing trials. Line 59 “overcome across studies” should be "vary amongst studies"? Outcome should be outcomes L75 “a control” – delete “a”. Missing data. It seems harsh and undesirable to omit complete

	studies if author or company does not reply, because only some items may be missing. L66 assess with 2 ss L62 outcomes are L71-72. Isn't AMD the leading cause of blindness? L73 "is a foremost" doesn't make sense L78 says "a recent systematic review" but then lists 4 references. L92 talks of "previous systematic reviews" but reference 16 was not a review. L216 "conduction of review" not right – just say "this review".

REVIEWER	Dr Natalie Mordi British Heart Foundation, Clinical Research Fellow, University of Dundee, Scotland
REVIEW RETURNED	20-Mar-2018

GENERAL COMMENTS	The manuscript is much improved. The authors now intend to review all SGLT2i (not just cana/dapa/empagliflozin). A number of issues that were identified on the original manuscript from the reviewers have been addressed. The issue of 4 weeks being such a short time period to include any meaningful data on microvascular outcomes remains, but I appreciate that there needs to be a lower cut off.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments:

Reviewer 1:

Revisions have improved this protocol and I have few comments.

Comment #1: The term "antidiabetic" to describe drugs is perhaps not as good as "glucose-lowering".

Response: We agree that the term "glucose-lowering" is more appropriate and change it accordingly.

Comment #2: I note some of my comments not accepted. There is no point in searching the databases from their inception, or any mention of checking Clinical.Trials.gov for ongoing trials.

Response: We took in consideration all of your comments and really appreciated them, however, we decided to search in databases from their inception as quality assessment (risk of bias) of systematic reviews asks to be compliant with this. We acknowledge we will do more work, but at the end the important thing is that no article will be missed, and we will be able to assess the complete body of evidence. On the other hand, we considered unnecessary to evaluate ClinicalTrial.gov for ongoing trial as data results (estimates) will not be available and hence will not be useful for our purpose to

determine the effect of SGLT-2 inhibitors regarding microvascular outcomes. However, if we take long to have the results of our study we might have to update our search.

Comment #3: Line 59 “overcome across studies” should be "vary amongst studies"? Outcome should be outcomes.

Response: We have followed your suggestion and change it accordingly.

The manuscript now reads as follows:

One limitation of this systematic review is that data availability and heterogeneity of outcomes definitions may vary amongst studies.

Comment #4: L75 “a control” – delete “a”.

Response: We checked the manuscript several times and we couldn´t find the “a”.

The manuscript reads as follows:

Different strategies had been adopted to decrease this risk- the paradigm that tight glucose control (i.e. independently of the drug used), will result in a decreased risk of the microvascular complications has been recently dispelled.

Comment #5: Missing data. It seems harsh and undesirable to omit complete studies if author or company does not reply, because only some items may be missing.

Response: Studies will only be omitted if major data (i.e. mean, median, standard deviation, interquartile range, odds ratio, effect sizes, number of participants, etc.) related to our primary or secondary outcomes are not clear, unextractable, or otherwise not explicitly stated. If minor data is missing in the study this will not prevent us from analyzing the study. However, we understand this could originate confusions among readers. Hence, we have rephrased the statement.

The manuscript now reads as follows.

If major data (mean, median, standard deviation, interquartile range, odds ratio, effect sizes, number of participants, etc.) regarding our primary or secondary outcomes is not clear, missing or presented in a form that is either un-extractable from the full-text an email will be send to the corresponding author to clarify the situation.

Comment #6: L66 assess with 2 ss

Response: We have corrected this mistake

The manuscript now reads as follows:

One strength of this review is that this will be the first systematic review and meta-analysis designed to specifically assess the body of evidence regarding the effectiveness of SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes.

Comment #7: L62 outcomes are

Response: This mistake has been properly addressed.

The manuscript now reads as follows:

A third limitation of this systematic review is that patient-important outcomes are scarcely reported in 20% of trials, therefore, data may not be enough to draw precise conclusions.

Comment #8: L71-72. Isn't AMD the leading cause of blindness?

Response: In fact, cataracts accounts as the leading cause of blindness worldwide followed by glaucoma, AMD and diabetic retinopathy (Pascolini D and Mariotti SP. Global estimates of visual impairment: 2010. BMJ 2010). Nonetheless, diabetes plays a major role in the onset and development in 3 of these diseases. Therefore, we consider diabetes to be one of the leading causes of blindness worldwide.

Comment #9: L73 "is a foremost" doesn't make sense

Response: We thank the reviewer for the observation and changed the word in order to have a better understanding.

The manuscript now reads follows:

Therefore, decreasing the risk of the aforementioned microvascular diabetes complications is a priority for any diabetes therapeutic intervention and represents a major concern for any healthcare system.

Comment #10: L78 says “a recent systematic review” but then lists 4 references.

Response: The manuscript has been corrected for this mistake and we now list just reference number 3.

The manuscript now reads as follows:

Recently, a systematic review has reported no effect of tight glycemic control (HbA1c <7.0%) regarding patient-important microvascular outcomes (e.g. end-stage renal disease, blindness, clinical neuropathy)[3].

Comment #11: L92 talks of “previous systematic reviews” but reference 16 was not a review.

Response: The systematic reviews we are referring to are references 9 to 11. Reference 16 was placed in the next statement along with references 13 to 19 in which we talk about several trials elucidating the effect of the SGLT-2 inhibitors on microvascular outcomes

Comment #12: L216 “conduction of review” not right – just say “this review”.

Response: We thank the reviewer and have change accordingly.

The manuscript now reads as follows:

We anticipate this review will provide highly relevant information for clinicians, policy- and guideline-makers that will benefit from a summary of the best available evidence regarding the effect, in

patients with type 2 diabetes, of SGLT-2 inhibitors over microvascular complications to counsel their patients and make higher quality recommendations, accordingly

Reviewer 2:

The manuscript is much improved. The authors now intend to review all SGLT2 (not just cana/dapa/empagliflozin). A number of issues that were identified on the original manuscript from the reviewers have been addressed.

Comment #1: The issue of 4 weeks being such a short time period to include any meaningful data on microvascular outcomes remains, but I appreciate that there needs to be a lower cut-off.

Response: We thank and agree with the reviewer comment.