BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020692
Article Type:	Protocol
Date Submitted by the Author:	20-Nov-2017
Complete List of Authors:	Dorsey-Treviño, Edgar Gerardo; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Contreras-Garza, Belinda; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division González-González, JG; Hospital University "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León, Endocrinology; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Research Unit Alvarez-Villalobos, Neri; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Research Unit Salcido-Montenegro, Alejandro; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Díaz González-Colmenero, Alejandro; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Farrell, Ann; Mayo Clinic, Mayo Medical Library González-Nava, Victoria; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Rodríguez-Tamez, Giselle; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Montori, Victor; Mayo Clinic, Knowledge and Evaluation Research Unit Rodriguez-Gutierrez, R; Universidad Autónoma de Nuevo León, Endocrinology Division; Mayo Clinic, Knowledge and Evaluation Research Unit
Keywords:	SGLT-2, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Diabetic retinopathy < DIABETES & ENDOCRINOLOGY, Diabetic neuropathy < DIABETES & ENDOCRINOLOGY, Peripheral Vascularization, DIABETES & ENDOCRINOLOGY

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:

Edgar Gerardo Dorsey-Treviño [1*] (dorsey.trevino@gmail.com)

Belinda Maricela Contreras-Garza [1*] (belinda.garza@hotmail.com)

José Gerardo González-González [1,4] (jgerardo@meduanl.com)

Neri Álvarez-Villalobos [2,4] (villalobos.neri@mayo.edu)

Alejandro Salcido-Montenegro [1] (alex.salcido.montenegro@gmail.com)

Alejandro Díaz González-Colmenero [1] (alejandrodgc@hotmail.com)

Ann M. Farrell [5] (farrell@mayo.edu)

Victoria González-Nava [1] (victoriagnzz@gmail.com)

Giselle Rodríguez-Tamez[1] (gisirdz_94@hotmail.com)

Victor M. Montori [2,3] (montori.victor@mayo.edu)

René Rodríguez-Gutiérrez [1,2,3] (rodriguezgutierrez.rene@mayo.edu)

* EGDT and BMCG contributed equally.

Institutional Affiliations:

[1]Endocrinology Division, Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, 64460, México.

[2]Knowledge and Evaluation Research Unit in Endocrinology, Mayo Clinic, Rochester, MN, 55905, USA.

[3]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Medicine, Mayo Clinic, Rochester, MN, 55905, USA.

[4]Research Unit, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, 64460, México.

[5]Mayo Medical Library, Mayo Clinic, Rochester, MN, USA

Corresponding Author:

René Rodríguez-Gutiérrez MD, MSc

Endocrinology Division, Universidad Autónoma de Nuevo León

Francisco I. Madero y Av. Gonzalitos s/n, Mitras Centro, Monterrey, Nuevo León, México 64460.

Telephone: 8114749146

E-mail: rodriguezgutierrez.rene@mayo.edu

Word Count: 1840

ABSTRACT

Introduction: Sodium glucose cotransporter 2 (SGLT-2) inhibitor are a relatively new class of drug which mechanism of action differs from other antidiabetic drugs. Several trials and systematic reviews have proved its beneficial effect on macrovascular complications such as myocardial infarction and stroke. Their effect on microvascular been reported in several individual trials to be positive, however, across some of the mayor RCTs their effect appears to be inconsistent and imprecise and remains in great extent uncertain. Therefore, we report the protocol of an ongoing systematic review and meta-analysis aimed to determine the effect of SGLT-2 inhibitors regarding patient-important and surrogate microvascular outcomes in adult patients with type 2 diabetes.

Methods and Analysis: The following electronic databases will be searched for relevant articles: Ovid MEDLINE, EMBASE, Web of Science, and Scopus. A narrative synthesis of the findings from the included studies will be provided, considered type of intervention, target population characteristics, type of outcome and intervention content. If the studies are sufficiently homogeneous, a quantitative synthesis approach will be taken.

Ethics and Dissemination: The results of the systematic review will be disseminated via publication in a peer-reviewed journal regardless of outcome and will be presented at relevant conferences. The data we will use do not include individual patient data, so ethical approval is not required

Systematic Review Registration: PROSPERO registration number: CRD 42017076460

Key Words: SGLT-2 Inhibitors, Microvascular, Nephropathy, Retinopathy, Neuropathy, Peripheral Vascularization, Systematic Review, Type 2 Diabetes

STRENGTHS AND LIMITATIONS

- One limitation of this systematic review is that data availability and heterogeneity of outcome definitions may overcome across studies.
- Another limitation is that outcome from microvascular complications will be mostly from secondary outcomes.
- A third limitation of this systematic review is that patient-important outcomes is scarcely reported in 20% of trials, therefore, data may not be enough to draw precise conclusions.
- One strength of this review is that this will be the first systematic review and meta-analysis designed to specifically asses the body of evidence regarding the effectiveness of SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes.

INTRODUCTION

Globally, diabetes represents the leading cause of end-stage renal disease/chronic renal disease, blindness, clinical peripheral neuropathy, and amputations[1,2]. Therefore, decreasing the risk of the aforementioned microvascular diabetes complications is a foremost for any diabetes therapeutic intervention and represents a priority for any healthcare system. 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. A recent systematic review 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]. Still, there is a positive, however, inconsistent effect regarding surrogate markers (e.g. microalbuminuria, photocoagulation)[3]. Other strategies, such as lipid lowering (e.g. fibrates), antiplatelet agents, smoking cessation, blood pressure control including angiotensin-converting enzyme inhibitors, and life-style modification, in most cases, as a multifactorial intervention have been reported to have a positive effect, however, mostly over surrogate markers.

To date, there are at least 10 classes of anti-hyperglycemic medications with different mechanism of action, efficacy, adverse events, costs, and convenience[4,5]. The sodium glucose co-transporter 2 (SGLT-2) inhibitors (e.g. dapagliflozon, empagliflozin, and canagliflozin) are one of the novel and most used class of anti-hyperglycemic medications[6–8]. Previous systematic reviews have demonstrated their effectiveness in reducing hemoglobin A1c (HbA1c) in around 1%, body weight (1.2 – 2.5 kg), blood pressure (3.5 – 4.4 mmHg systolic and 1–2.2 mmHg diastolic)[9–11] and the risk mayor

cardiovascular outcomes, including mortality[12]. Their effect on microvascular patient important outcomes and intermediate (i.e. surrogate) markers has been reported in several individual trials to be positive, however, across some of the mayor RCTs their effect appears to be inconsistent and imprecise and remains in great extent uncertain[13–19].

Therefore, we plan to conduct a systematic review and meta-analysis to determine the effect of SGLT-2 inhibitors regarding patient-important and surrogate microvascular outcomes in adult patients with type 2 diabetes.

METHODS AND ANALYSIS

Study Design

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA-P) (Supplementary File)[20].

Eligibility Criteria

We will search only for RCTs that include the comparison of any SGLT-2 inhibitor (e.g. canagliflozin, dapagliflozin, or empagliflozin), among doses that were approved by the FDA and/or EMA (canagliflozin 100 – 300 mg/24hrs, empagliflozin 10 – 25 mg/24hrs, and dapagliflozin 5 – 10 mg/24hrs), with any other active treatment or placebo, which are assessing among their primary or secondary outcomes their effectiveness regarding microvascular outcomes. We will also include any follow-up, sub-analysis, or post-hoc analyses from the original trial assessing these same outcomes. We will consider studies enrolling adults (18 years or older) with type 2 diabetes defined by any recognized standard diagnosis criteria, regardless of its evolution time, and with a minimum of ≥4 weeks of treatment for diabetes. We will exclude patients with any other diagnosis of diabetes (type

1 diabetes, MODY, iatrogenic, gestational diabetes, drug-induced diabetes, or any other pancreas disease related). There will be no language restriction and we will exclude studies with missing data despite author contact.

Study identification

The search strategy will be designed by two experienced librarians (AF and NAV) with input from the study's principal investigators (NAV and RRG). A comprehensive search will be conducted to find eligible articles in several databases from each database's earliest inception to October 2017. These databases will include Ovid MEDLINE, EMBASE, Web of Science, and Scopus. Controlled vocabulary supplemented with keywords will be used to search for studies evaluating the effect of SGLT-2 inhibitors regarding diabetes microvascular complications. The design and conduction of the search strategy will be finished around October 2017. After we complete the data extraction phase, we will conduct a second search using the same criteria mentioned above to update any missing trial published between the months of data extraction. We will consult experts in the field and the references from each included trial to identify studies missed by our search strategy.

Selection of studies

Reviewers working independently and in duplicate will review all abstracts and selected full-text manuscripts for eligibility. Prior to formal abstract screening, a pilot, between reviewers, will be carried out to clarify any misunderstandings and ensure adequate comprehension. Two reviewers working independently and in duplicate will screen all titles and abstracts of the selected articles to assess eligibility. In this phase we will be highly

sensitive and therefore whenever reviewers disagree, the article will be included into the the full-text phase. Disagreements at full-text screening will be resolved by consensus. Reasons for non-eligibility will be documented by the reviewers. Chance-adjusted inter-rater agreement for the title/abstract screening and the full-text will be calculated using the Kappa statistics[21]. Before and after both screening phases the total number of included and excluded articles will be documented, including reasons for exclusion.

Outcome of interest

Microvascular outcomes (i.e. nephropathy, retinopathy, peripheral neuropathy, and peripheral vascular disease) will be assessed. Also, we will assess patient-important outcomes for any of the complication mentioned before. For this protocol we defined microvascular complications and patient-important outcomes as:

Nephropathy- Surrogates: doubling of the serum creatinine, macroalbuminuria, and microalbuminuria. Patient-important outcomes: end stage renal disease (ESRD) defined as need for continuous renal replacement therapy or renal transplant, chronic renal disease stage ≥III or renal death.

Retinopathy- Surrogates: Changes from baseline of retinal neovascularization, cataract extraction, event reported in general as retinopathy, retinal photocoagulation, and treatment with intravitreal agents. Patient-important outcomes: diabetes related blindness, vitreous hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion.

Peripheral Neuropathy- Surrogates: changes from baseline of tendon reflexes, and electrophysiological parameters such as nerve conduction velocity and sensory conduction

velocity. Patient-important outcomes: (pain, numbness), sensory loss (touch, vibration, and quality of life).

Peripheral vascular disease: Surrogate: Abnormal ankle-brachial index and/or arterial Doppler ultrasonography. Patient-important outcomes: prolonged wound healing, ulcers, or amputation.

Data Collection Process

Two reviewers working independently will collect data for all the eligible articles. To standardized data extraction a web-based data extraction form will be designed including information about type of study, baseline patient characteristics, drug being studied, and effectiveness regarding microvascular complications. Two or more reviewers working independently and in duplicate will conduct a pilot phase to assess any disagreement; disagreements will be discussed and resolved by consensus. If any disagreement cannot be resolved by consensus, a third reviewer will arbitrate the final decision. If necessary, modifications on the form will be effectuated based on the feedback of the reviewers to get optimal calibration. Data collection will take place around November-December 2017.

Missing Data

If any data 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. After a lapse of 10 days a second email will be sent to the non-responders. If the second attempt is unsuccessful, other authors will be contacted. If none of the authors respond exclude the study. Every author contact will be documented.

Risk of Bias in Individual Studies and Quality Assessment

Two review authors working independently and in duplicate will use the Cochrane risk of bias tool to assess the quality of RCTs based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). For any follow-up, sub-analysis, or post-hoc analysis we will assess the bias of the original study. We will also evaluate the overall quality of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[22]. Disagreement will again be resolved by consensus or if not possible, by arbitration of a third reviewer. Risk of bias in individual studies will be assessed around November-December 2017.

Subgroup analysis

To explain possible inconsistencies across study results, we will conduct the following subgroup analysis: patients with long-term versus recent diabetes diagnosis, primary cardiovascular prevention versus secondary cardiovascular prevention.

Summary measures and data Synthesis

A narrative synthesis of the findings from the included studies will be provided, considered type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). When more than one study provide data on the same outcome measure, using the same type of intervention and comparator, a cumulative meta-analysis will be performed. Statistical analyses will be performed using Review Manager v 5.3. and results

pooled following random-effects models in order to best address the heterogeneity in population characteristics across studies. Chi-squared test and the I-squared statistic will be used to assess heterogeneity between studies. A Chi-square cut-off value of P<0.10 and an I-squared value >50% will be considered as indicative of considerable heterogeneity not explained by chance. To explore causes of inconsistency and subgroup-treatment interactions, we developed protocol pre-specified subgroup analyses (mentioned earlier).

DISCUSSION

We anticipate that the conduction of this systematic 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. Also, this information might be important in those patients in whom a new anti-diabetic medication is needed. At this point, patients and clinicians will carefully have to consider the benefits aside glucose reduction in light of the potential risks of each drug class.

Several limitations can be foreseen of this review for instance data availability and heterogeneity of outcome definitions may overcome across studies. Probably most of the included trials will have as primary objective glucose measures (i.e. HbA1c) or macrovascular complications, hence, data for microvascular outcomes will stem mostly from secondary endpoints. Also, as patient-important outcomes are evaluated by less than 20% of trials, data of RCTs evaluating patient-important outcomes may not be enough to have precision regarding their effect. However, this will be the first systematic review and meta-analysis designed to specifically assess the body of evidence regarding the effect of

SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes. In addition, the review will be based on an extensive and systematic literature search and will represent the best estimate of effect from the available body evidence.

Abbreviations.

95% CI: 95% confidence interval, OR: odds ratio, SGLT-2: sodium glucose cotransporter 2, PRIMSA-P: Preferred Reporting Items for Systematic Review and Meta-analysis, 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

DECLARATIONS.

Acknowledgements.

None

Ethics approval and consent to participate

Not applicable.

Competing interest

The authors declare that they have no competing interest.

Funding

None.

Authors' contributions

RRG, EGDT and BMCG designed and wrote the protocol. EGDT, ASM, VGN, GRT, ADGC, JGGG, VMM and RRG made substantial contribution and revision to it. NAV and ASM working with AMF will design the search strategy for this review. EGDT, BMCG, ASM, VGN, GRT, and ADGC will undertake data collection. EGDT and NAV will perform the statistical analysis of data. RRG, EGDT, and BMCG will interpret the results and write the final manuscript. JGGG and VMM will work as 2nd reviewer and 3rd reviewer respectively. The definitive version of this protocol reflects the contribution of all authors. All authors read and approved the final manuscript.

References.

1. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular Complications of Impaired Glucose Tolerance. Diabetes. 2003;52(12):2867–73.

2. Centers for Disease Control Prevention. Diabetes Report Card 2012 [Internet]. Centers for Disease Control and Prevention, US Department of Health and Human Services. 2014. Available from: www.cdc.gov/diabetes/library/reports/congress.html

3. Rodríguez-Gutiérrez R, Montori VM. Glycemic control for patients with type 2 diabetes mellitus: Our evolving faith in the face of evidence. Circ Cardiovasc Qual Outcomes. 2016;9(5):504–12.

4. Rodbard H, Jellinger P, Davidson J, Einhorn D, Garber A, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An

Algorithm for Glycemic Control. Endocr Pract [Internet]. 2009;15(6):540–59. Available from: http://journals.aace.com/doi/abs/10.4158/EP.15.6.540

5. Cheng AYY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J diabetes. 2013;37:S1–3.

6. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes Care. 2015;38(1):140–9.

7. Mb AH, Harper W, Main A, Retnakaran R, Rn DS, Woo V, et al. Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update. Can J Diabetes. 2016;40(3):193–5.

8. Qaseem A, Barry MJ, Humphrey LL, Forciea MA, Fitterman N, Boyd C, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: A clinical practice guideline update from the American college of physicians. Ann Intern Med. 2017;166(4):279–90.

9. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. J Am Soc Hypertens [Internet]. 2014;8(4):262–75. Available from: http://dx.doi.org/10.1016/j.jash.2014.01.007

10. Zhang Q, Dou J, Lu J. Combinational therapy with metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes: Systematic review and

meta-analyses. Diabetes Res Clin Pract [Internet]. 2014;105(3):313–21. Available from: http://dx.doi.org/10.1016/j.diabres.2014.06.006

11. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes A Systematic Review and Meta-analysis. Ann Intern Med [Internet]. 2013;159(April):262. Available from: annals.org/article.aspx?doi=10.7326/0003-4819-159-4-201308200-00007

12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med [Internet]. 2015;373(22):2117–28. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1504720

13. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects. J Am Soc Nephrol [Internet]. 2017;28(1):368–75. Available from: http://www.jasn.org/lookup/doi/10.1681/ASN.2016030278

14. Kohan DE, Fioretto P, Johnsson K, Parikh S, Ptaszynska A, Ying L. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J Nephrol. 2016;29(3):391–400.

15. Ott C, Jumar A, Striepe K, Friedrich S, Karg M V., Bramlage P, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol [Internet]. 2017;16(1):26. Available from: http://cardiab.biomedcentral.com/articles/10.1186/s12933-017-0510-1

16. Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587–97.

17. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):610–21.

18. Cherney D, Lund SS, Perkins BA, Groop P-H, Cooper ME, Kaspers S, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia [Internet]. 2016;59(9):1860–70. Available from: http://link.springer.com/10.1007/s00125-016-4008-2

19. Dziuba J, Alperin P, Racketa J, Iloeje U, Goswami D, Hardy E, et al. Modeling effects of SGLT-2 inhibitor dapagliflozin treatment versus standard diabetes therapy on cardiovascular and microvascular outcomes. Diabetes, Obes Metab [Internet]. 2014 Jul 1 [cited 2017 Oct 8];16(7):628–35. Available from: http://doi.wiley.com/10.1111/dom.12261

20. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev [Internet]. 2015;4(1):1. Available from: http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1

21. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, Guyatt G. Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). CMAJ. 2004;171(11):1369–73.

22. Murad MH, Montori VM, Ioannidis JPA, Jaeschke R, Devereaux PJ, Prasad K, et al. How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care. JAMA [Internet]. 2014;312(2):171. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.5559

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

A Systematic Review and Meta-Analysis of the Effect of SGLT-2 Inhibitors on Microvascular Outcomes in Patients with Type 2 Diabetes: A Review Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020692.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Mar-2018
Complete List of Authors:	Dorsey-Treviño, Edgar Gerardo; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Contreras-Garza, Belinda; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division González-González, JG; Hospital University "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León, Endocrinology; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Research Unit Alvarez-Villalobos, Neri; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Research Unit Salcido-Montenegro, Alejandro; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Díaz González-Colmenero, Alejandro; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Farrell, Ann; Mayo Clinic, Mayo Medical Library González-Nava, Victoria; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Rodríguez-Tamez, Giselle; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Montori, Victor; Mayo Clinic, Knowledge and Evaluation Research Unit Rodriguez-Gutierrez, R; Universidad Autónoma de Nuevo León, Endocrinology Division; Mayo Clinic, Knowledge and Evaluation Research Unit
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice
Keywords:	SGLT-2, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Diabetic retinopathy < DIABETES & ENDOCRINOLOGY, Diabetic neuropathy < DIABETES & ENDOCRINOLOGY, Peripheral Vascularization, DIABETES & ENDOCRINOLOGY

A Systematic Review and Meta-Analysis of the Effect of SGLT-2 Inhibitors on Microvascular Outcomes in Patients with Type 2 Diabetes: A Review Protocol

Authors:

Edgar Gerardo Dorsey-Treviño [1*] (dorsey.trevino@gmail.com)

Belinda Maricela Contreras-Garza [1*] (belinda.garza@hotmail.com)

José Gerardo González-González [1,4] (jgerardo@meduanl.com)

Neri Álvarez-Villalobos [2,4] (neri_alex@hotmail.com)

Alejandro Salcido-Montenegro [1] (alex.salcido.montenegro@gmail.com)

Alejandro Díaz González-Colmenero [1] (alejandrodgc@hotmail.com)

Ann M. Farrell [5] (farrell@mayo.edu)

Victoria González-Nava [1] (victoriagnzz@gmail.com)

Giselle Rodríguez-Tamez[1] (gisirdz_94@hotmail.com)

Victor M. Montori [2,3] (montori.victor@mayo.edu)

René Rodríguez-Gutiérrez [1,2,3] (rodriguezgutierrez.rene@mayo.edu)

* EGDT and BMCG contributed equally.

Institutional Affiliations:

[1]Endocrinology Division, Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, 64460, México.

[2]Knowledge and Evaluation Research Unit in Endocrinology, Mayo Clinic, Rochester, MN, 55905, USA.

[3]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Medicine, Mayo Clinic, Rochester, MN, 55905, USA.

[4]Research Unit, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, 64460, México.

[5]Mayo Medical Library, Mayo Clinic, Rochester, MN, USA

Corresponding Author:

René Rodríguez-Gutiérrez MD, MSc

Endocrinology Division, Universidad Autónoma de Nuevo León

Francisco I. Madero y Av. Gonzalitos s/n, Mitras Centro, Monterrey, Nuevo León, México 64460.

e-mail: rodriguezgutierrez.rene@mayo.edu

Keywords: SGLT-2 inhibitors, type 2 diabetes, microvascular outcomes

Abstract.

Introduction: 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. Their effect on microvascular outcomes has been reported as positive in several trials, however, their effect remains uncertain. Therefore, we report the protocol of a systematic review and meta-analysis aimed at determining the effect of SGLT-2 inhibitors regarding patient-important and surrogate microvascular outcomes in patients with type 2 diabetes.

Methods and Analysis: A comprehensive search will be conducted to find eligible articles from each database's earliest inception to November 2017. These databases will include Ovid MEDLINE, EMBASE, Web of Science, and Scopus. We will search for randomized controlled trials (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. Reviewers working independently and in duplicate will review all abstracts, and full-text manuscripts for eligibility, and will systematically extract the data and will assess the risk of bias in the included studies. Random-effects models will also be used.

Ethics and Dissemination: The results of the systematic review will be disseminated via publication in a peer-reviewed journal regardless of outcome and will be presented at relevant conferences. The data we will use do not include individual patient data, so ethical approval is not required.

Systematic Review Registration: PROSPERO registration number: CRD 42017076460

Key Words: SGLT-2 Inhibitors, Microvascular, Nephropathy, Retinopathy, Neuropathy, Peripheral Vascularization, Systematic Review, Type 2 Diabetes

STRENGTHS AND LIMITATIONS

- One limitation of this systematic review is that data availability and heterogeneity of outcome definitions may overcome across studies.
- Another limitation is that outcome from microvascular complications will be mostly from secondary outcomes.
- A third limitation of this systematic review is that patient-important outcomes is scarcely reported in 20% of trials, therefore, data may not be enough to draw precise conclusions.
- One strength of this review is that this will be the first systematic review and meta-analysis designed to specifically asses the body of evidence regarding the effectiveness of SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes.

Introduction

Globally, diabetes represents the leading cause of end-stage renal disease/chronic renal disease, blindness, clinical peripheral neuropathy, and amputations(1,2). Therefore, decreasing the risk of the aforementioned microvascular complications is a foremost in any diabetes therapeutic intervention and represents a priority for any healthcare system. Different strategies involving a rigorous glycemic control have been adopted to try to reduce this risk. Nonetheless, the paradigm of tight glycemic control (i.e. independently of the drug used) resulting in a decreased risk of microvascular complications has recently been dispelled. 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 life-style modifications, in most cases as a multifactorial intervention, have been reported to have a positive effect, however, mostly over surrogate markers.

To date, there are at least 10 classes of anti-hyperglycemic medications with different mechanism 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 anti-hyperglycemic drugs and as a group are positioning themselves as a promising therapeutic class in current diabetes treatment(10–12). Previous systematic reviews have demonstrated

their effectiveness in reducing hemoglobin A1c (HbA1c), body weight , blood pressure(13–15) and the risk of major cardiovascular outcomes, including mortality(16). Their effect on microvascular patient-important outcomes and intermediate (surrogate) markers has been reported in several individual trials as positive, however, among some of the major RCTs their effect appears to be inconsistent and imprecise and remains to a great extent, uncertain(17–23).

Therefore, we plan to conduct a systematic review and meta-analysis to determine the effect of SGLT-2 inhibitors on patient-important and surrogate microvascular outcomes in adult patients with type 2 diabetes.

Methods and Analysis

Study Design

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA-P)(24).

Eligibility Criteria

We will search for RCTs that compare any of the SGLT-2 inhibitors with any other active treatment or placebo evaluating microvascular outcomes in either their primary or secondary outcomes. We will also include any follow-up, sub-analysis, or post-hoc analyses from the original trial assessing these same outcomes. We will consider studies enrolling adults (18 years or older) with type 2 diabetes defined by any recognized standard diagnostic criteria, regardless of evolution time, and with a minimum of ≥4 weeks of intervention. We will exclude patients with any other type of diabetes (type 1 diabetes, MODY, iatrogenic, gestational diabetes, drug-induced diabetes, or any other pancreas-

related disease). There will be no language restriction and studies with missing data despite author and manufacturer contact will be excluded.

Study identification

The search strategy will be designed by two experienced librarians (AF and NAV) with input from the study's principal investigators. A comprehensive search will be conducted to find eligible articles in several databases from each database's earliest inception to November 2017. These databases will include Ovid MEDLINE, EMBASE, Web of Science, and Scopus. Controlled vocabulary supplemented with keywords will be used to search for studies evaluating the effect of SGLT-2 inhibitors on diabetes microvascular complications. The design and conduction of the search strategy will be finished around November 2017. After we complete the data extraction phase, we will conduct a second search using the same criteria mentioned above to update any missing trial published during the months of data extraction. We will consult experts in the field and review the references from each included trial to identify studies missed by our search strategy.

Selection of studies

Reviewers working independently and in duplicate will review all abstracts and select full-text manuscripts for eligibility. Prior to formal abstract screening, a pilot, between reviewers, will be carried out to clarify any misunderstandings and ensure adequate comprehension. Two reviewers working independently and in duplicate will screen all titles and abstracts of the selected articles to assess eligibility. In this phase we will be highly sensitive and therefore whenever reviewers disagree, the article will be included in the full-text phase. Disagreements at full-text screening will be resolved by consensus. Reasons for

non-eligibility will be documented by the reviewers. Chance-adjusted inter-rater agreement for the title/abstract screening and the full-text will be calculated using the Kappa statistic(25). Before and after both screening phases the total number of included and excluded articles will be documented, including reasons for exclusion. Selection of studies will be carried out from January to February 2018

Outcomes of interest

Microvascular outcomes (i.e. nephropathy, retinopathy, peripheral neuropathy, and peripheral vascular disease) will be assessed. Also, we will assess patient-important outcomes for any of the complication mentioned before. For this protocol we defined microvascular complications and patient-important outcomes as:

Nephropathy surrogates: doubling of serum creatinine, macroalbuminuria, and microalbuminuria. Patient-important outcomes: end-stage renal disease (ESRD) defined as the need for continuous renal replacement therapy or renal transplant, chronic renal disease stage ≥III or renal death.

Retinopathy surrogates: Changes from baseline of retinal neovascularization, cataract extraction, event reported in general as retinopathy, retinal photocoagulation, and treatment with intravitreal agents. Patient-important outcomes: diabetes related blindness, vitreous hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion.

Peripheral neuropathy surrogates: Changes from baseline of tendon reflexes, and electrophysiological parameters such as nerve conduction velocity and sensory conduction velocity. Patient-important outcomes: (pain, numbness), sensory loss (touch, vibration, and quality of life).

Peripheral vascular disease surrogate: Abnormal ankle-brachial index and/or arterial Doppler ultrasonography. Patient-important outcomes: prolonged wound healing, ulcers, or amputation.

Data Collection Process

Two reviewers working independently will collect data from all the eligible articles. To standardized data extraction a web-based data extraction form will be designed that includes information about type of study, baseline patient characteristics, drug being studied, and effectiveness regarding microvascular complications. Two or more reviewers working independently and in duplicate will conduct a pilot phase to assess any disagreement; disagreements will be discussed and resolved by consensus. If any disagreement cannot be resolved by consensus, a third reviewer will arbitrate the final decision. If necessary, modifications on the form will be effectuated based on the feedback of the reviewers to get optimal calibration. Data collection will take place around March – April 2018.

Missing Data

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.

Risk of Bias in Individual Studies and Quality Assessment

Two authors working independently and in duplicate will use the Cochrane risk of bias tool to assess the quality of RCTs based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). For any follow-up, sub-analysis, or post-hoc analysis we will assess the bias of the original study. We will also evaluate the overall quality of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)(26). Disagreement will again be resolved by consensus or if not possible, by arbitration of a third reviewer. Risk of bias in individual studies will be assessed around March – April 2018.

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. 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.

Summary measures and data synthesis

A narrative synthesis of the findings from the included studies will be provided, considering the type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). When more than one study provide data on the same outcome

measure, using the same type of intervention and comparator, a cumulative meta-analysis will be performed. Statistical analyses will be performed using Review Manager v 5.3. and results will be pooled following random-effects models in order to best address the heterogeneity in population characteristics across studies. The Chi-squared test and the I-squared statistic will be used to assess heterogeneity between studies. A Chi-square cutoff value of $P<0.10$ and an I-squared value >50% will be considered as indicative of considerable heterogeneity not explained by chance. To explore causes of inconsistency and subgroup-treatment interactions, we developed protocol pre-specified subgroup analyses (mentioned earlier).

Patient and Public Involvement

Patients and public will not be involved in this study.

Discussion

We anticipate that the conduction of this systematic review will provide highly relevant information for clinicians, policy- and guideline-makers, who will benefit from a summary of the best available evidence regarding the effect of SGLT-2 inhibitors on microvascular complications in patients with type 2 diabetes to counsel their patients and make higher quality recommendations, accordingly. Also, this information might be important for those patients in whom a new antidiabetic drug is needed. At this point, patients and clinicians will carefully have to consider the benefits aside from glucose reduction in light of the potential risks of each drug class.

Several limitations can be foreseen of this review for instance data availability and heterogeneity of outcome definitions may overcome across studies. Probably most of the

included trials will have as a primary objective glucose measures (i.e. HbA1c) or macrovascular complications; hence, data for microvascular outcomes will stem mostly from secondary endpoints. Also, as patient-important outcomes are evaluated by less than 20% of trials, data from RCTs evaluating patient-important outcomes may not be enough to determine their effect precisely. However, this will be the first systematic review and meta-analysis designed to specifically assess the body of evidence regarding the effect of SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes. In addition, the review will be based on an extensive and systematic literature search and will represent the best estimate of effect from the available body of evidence.

Abbreviations.

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; 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.

Declarations.

Ethics and Dissemination

The results of the systematic review will be disseminated via publication in a peer-reviewed journal regardless of outcome and will be presented at relevant conferences. The data we will use do not include individual patient data, so ethical approval is not required.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interest

The authors declare that they have no competing interest.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

RRG (guarantor), EGDT and BMCG designed and wrote the protocol. EGDT, BMCG, ASM, VGN, GRT, ADGC, JGGG, VMM and RRG made substantial contribution and revision to it. NAV and ASM working with AMF will design the search strategy for this review. EGDT, BMCG, ASM, VGN, GRT, and ADGC will undertake data collection. EGDT and NAV will perform the statistical analysis of data. RRG, EGDT, and BMCG will interpret the results and write the final manuscript. JGGG and VMM will work as 2nd reviewer and 3rd reviewer respectively. The definitive version of this protocol reflects the contribution of all authors. All authors read and approved the final manuscript.

Acknowledgments

We thank Dr. Sergio Lozano for the language revision of the manuscript.

References.

1. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular Complications of Impaired Glucose Tolerance. Diabetes. 2003;52(12):2867–73.

2. Centers for Disease Control Prevention. Diabetes Report Card 2012 [Internet]. Centers for Disease Control and Prevention, US Department of Health and Human Services. 2014. Available from: www.cdc.gov/diabetes/library/reports/congress.html

3. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane database Syst Rev [Internet]. 2011 Jun 15 [cited 2018 Feb 16];(6):CD008143. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21678374

4. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: Systematic review and meta-analysis [Internet]. Vol. 172, Archives of Internal Medicine. NIH Public Access; 2012 [cited 2018 Feb 16]. p. 761–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22636820

5. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ [Internet]. 2011 Jul 26 [cited 2018 Feb 16];343(jul26 1):d4169–d4169. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21791495

6. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: Glucose control and cardiovascular disease in type 2 diabetes [Internet]. Vol. 151, Annals of Internal Medicine. 2009 [cited 2018 Feb 16]. p. 394–403. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19620144

7. Rodríguez-Gutiérrez R, Montori VM. Glycemic control for patients with type 2 diabetes mellitus: Our evolving faith in the face of evidence. Circ Cardiovasc Qual Outcomes [Internet]. 2016;9(5):504–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27553599

8. Rodbard H, Jellinger P, Davidson J, Einhorn D, Garber A, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control. Endocr Pract [Internet]. 2009;15(6):540–59. Available from: http://journals.aace.com/doi/abs/10.4158/EP.15.6.540

9. Cheng AYY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J diabetes. 2013;37:S1–3.

10. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes Care. 2015;38(1):140–9.

11. 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.

12. Qaseem A, Barry MJ, Humphrey LL, Forciea MA, Fitterman N, Boyd C, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: A clinical practice guideline update from the American college of physicians. Ann Intern Med. 2017;166(4):279–90.

13. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. J Am Soc Hypertens [Internet]. 2014;8(4):262–75. Available from: http://dx.doi.org/10.1016/j.jash.2014.01.007

14. Zhang Q, Dou J, Lu J. Combinational therapy with metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes: Systematic review and meta-analyses. Diabetes Res Clin Pract [Internet]. 2014;105(3):313–21. Available from: http://dx.doi.org/10.1016/j.diabres.2014.06.006

15. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes A Systematic Review and Meta-analysis. Ann Intern Med [Internet]. 2013;159(April):262. Available from: annals.org/article.aspx?doi=10.7326/0003-4819-159-4-201308200-00007

16. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med [Internet]. 2015 Nov 26 [cited 2017 Oct 16];373(22):2117–28. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1504720

17. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V.

Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects. J Am Soc Nephrol [Internet]. 2017;28(1):368–75. Available from: http://www.jasn.org/lookup/doi/10.1681/ASN.2016030278

18. Kohan DE, Fioretto P, Johnsson K, Parikh S, Ptaszynska A, Ying L. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J Nephrol. 2016;29(3):391–400.

19. Ott C, Jumar A, Striepe K, Friedrich S, Karg M V., Bramlage P, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol [Internet]. 2017;16(1):26. Available from: http://cardiab.biomedcentral.com/articles/10.1186/s12933-017-0510-1

20. Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587–97.

21. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):610–21.

22. Cherney D, Lund SS, Perkins BA, Groop P-H, Cooper ME, Kaspers S, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia [Internet]. 2016;59(9):1860–70. Available from:

http://link.springer.com/10.1007/s00125-016-4008-2

23. Dziuba J, Alperin P, Racketa J, Iloeje U, Goswami D, Hardy E, et al. Modeling effects of SGLT-2 inhibitor dapagliflozin treatment versus standard diabetes therapy on cardiovascular and microvascular outcomes. Diabetes, Obes Metab [Internet]. 2014 Jul 1 [cited 2017 Oct 8];16(7):628–35. Available from: http://doi.wiley.com/10.1111/dom.12261

24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev [Internet]. 2015;4(1):1. Available from: http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1

25. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, Guyatt G. Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). CMAJ. 2004;171(11):1369–73.

26. Murad MH, Montori VM, Ioannidis JPA, Jaeschke R, Devereaux PJ, Prasad K, et al. How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care. JAMA [Internet]. 2014;312(2):171. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.5559

372

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5 and 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	N/A

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	N/A
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020692.R2
Article Type:	Protocol
Date Submitted by the Author:	29-May-2018
Complete List of Authors:	Dorsey-Treviño, Edgar Gerardo; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Contreras-Garza, Belinda; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division González-González, JG; Hospital University "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León, Endocrinology; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Research Unit Alvarez-Villalobos, Neri; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Research Unit Salcido-Montenegro, Alejandro; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Díaz González-Colmenero, Alejandro; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Farrell, Ann; Mayo Clinic, Mayo Medical Library González-Nava, Victoria; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Rodríguez-Tamez, Giselle; Hospital University "Dr. José E. González" Universidad Autónoma de Nuevo León, Endocrinology Division Montori, Victor; Mayo Clinic, Knowledge and Evaluation Research Unit Rodriguez-Gutierrez, R; Universidad Autónoma de Nuevo León, Endocrinology Division; Mayo Clinic, Knowledge and Evaluation Research Unit
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice
Keywords:	SGLT-2, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Diabetic retinopathy < DIABETES & ENDOCRINOLOGY, Diabetic neuropathy < DIABETES & ENDOCRINOLOGY, Peripheral Vascularization, DIABETES & ENDOCRINOLOGY

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:

Edgar Gerardo Dorsey-Treviño [1*] (dorsey.trevino@gmail.com)

Belinda Maricela Contreras-Garza [1*] (belinda.garza@hotmail.com)

José Gerardo González-González [1,4] (jgerardo@meduanl.com)

Neri Álvarez-Villalobos [2,4] (villalobos.neri@mayo.edu)

Alejandro Salcido-Montenegro [1] (alex.salcido.montenegro@gmail.com)

Alejandro Díaz González-Colmenero [1] (alejandrodgc@hotmail.com)

Ann M. Farrell [5] (farrell@mayo.edu)

Victoria González-Nava [1] (victoriagnzz@gmail.com)

Giselle Rodríguez-Tamez[1] (gisirdz_94@hotmail.com)

Victor M. Montori [2,3] (montori.victor@mayo.edu)

René Rodríguez-Gutiérrez [1,2,3] (rodriguezgutierrez.rene@mayo.edu)

* EGDT and BMCG contributed equally.

Institutional Affiliations:

[1]Endocrinology Division, Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, 64460, México.

[2]Knowledge and Evaluation Research Unit in Endocrinology, Mayo Clinic, Rochester, MN, 55905, USA.

[3]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Medicine, Mayo Clinic, Rochester, MN, 55905, USA.

[4]Research Unit, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, 64460, México.

[5]Mayo Medical Library, Mayo Clinic, Rochester, MN, USA

Corresponding Author:

René Rodríguez-Gutiérrez MD, MSc

Endocrinology Division, Universidad Autónoma de Nuevo León

Francisco I. Madero y Av. Gonzalitos s/n, Mitras Centro, Monterrey, Nuevo León, México 64460.

Telephone: 8114749146

E-mail: rodriguezgutierrez.rene@mayo.edu

Word Count: 1735

Competing Interests: None

ABSTRACT

Introduction: Sodium glucose cotransporter 2 (SGLT-2) inhibitors are a relatively new class of drug which mechanism of action differs from other glucose-lowering drugs. Several trials and systematic reviews have proved its beneficial effect on macrovascular complications such as myocardial infarction and stroke. Their effect on microvascular been reported in several individual trials to be positive, however, across some of the mayor RCTs their effect appears to be inconsistent and imprecise and remains in great extent uncertain. Therefore, we report the protocol of an ongoing systematic review and meta-analysis aimed to determine the effect of SGLT-2 inhibitors regarding patient-important and surrogate microvascular outcomes in adult patients with type 2 diabetes.

Methods and Analysis: The following electronic databases will be searched for relevant articles: Ovid MEDLINE, EMBASE, Web of Science, and Scopus. A narrative synthesis of the findings from the included studies will be provided, considered type of intervention, target population characteristics, type of outcome and intervention content. If the studies are sufficiently homogeneous, a quantitative synthesis approach will be taken.

Ethics and Dissemination: The results of the systematic review will be disseminated via publication in a peer-reviewed journal regardless of outcome and will be presented at relevant conferences. The data we will use do not include individual patient data, so ethical approval is not required

Systematic Review Registration: PROSPERO registration number: CRD 42017076460

Key Words: SGLT-2 Inhibitors, Microvascular, Nephropathy, Retinopathy, Neuropathy, Peripheral Vascularization, Systematic Review, Type 2 Diabetes

STRENGTHS AND LIMITATIONS

- One limitation of this systematic review is that data availability and heterogeneity of outcomes definitions may vary among studies.
- Another limitation is that outcomes from microvascular complications will be mostly from secondary outcomes.
- 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.
- 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.

INTRODUCTION

Globally, diabetes represents the leading cause of end-stage renal disease/chronic renal disease, blindness, clinical peripheral neuropathy, and amputations[1,2]. 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. 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. 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]. Still, there is a positive, however, inconsistent effect regarding surrogate markers (e.g. microalbuminuria, photocoagulation).[3] Other strategies, such as lipid lowering (e.g. fibrates), antiplatelet agents, smoking cessation, blood pressure control including angiotensin-converting enzyme inhibitors, and life-style modification, in most cases, as a multifactorial intervention have been reported to have a positive effect, however, mostly over surrogate markers.

To date, there are at least 10 classes of anti-hyperglycemic medications with different mechanism of action, efficacy, adverse events, costs, and convenience[4,5]. The sodium glucose co-transporter 2 (SGLT-2) inhibitors (e.g. dapagliflozin, empagliflozin, and canagliflozin) are one of the novel and most used class of anti-hyperglycemic medications[6–8]. Previous systematic reviews have demonstrated their effectiveness in reducing hemoglobin A1c (HbA1c) in around 1%, body weight (1.2 – 2.5 kg), blood pressure (3.5 – 4.4 mmHg systolic and 1–2.2 mmHg diastolic)[9–11] and the risk of major

cardiovascular outcomes, including mortality[12]. Their effect on microvascular patient important outcomes and intermediate (i.e. surrogate) markers has been reported in several individual trials to be positive, however, across some of the mayor RCTs their effect appears to be inconsistent and imprecise and remains in great extent uncertain[13–19].

Therefore, we plan to conduct a systematic review and meta-analysis to determine the effect of SGLT-2 inhibitors regarding patient-important and surrogate microvascular outcomes in adult patients with type 2 diabetes.

METHODS AND ANALYSIS

Study Design

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA-P) (Supplementary File)[20].

Eligibility Criteria

We will search only for RCTs that include the comparison of any SGLT-2 inhibitor (e.g. canagliflozin, dapagliflozin, or empagliflozin), among doses that were approved by the FDA and/or EMA (canagliflozin 100 – 300 mg/24hrs, empagliflozin 10 – 25 mg/24hrs, and dapagliflozin 5 – 10 mg/24hrs), with any other active treatment or placebo, which are assessing among their primary or secondary outcomes their effectiveness regarding microvascular outcomes. We will also include any follow-up, sub-analysis, or post-hoc analyses from the original trial assessing these same outcomes. We will consider studies enrolling adults (18 years or older) with type 2 diabetes defined by any recognized standard diagnosis criteria, regardless of its evolution time, and with a minimum of ≥4 weeks of treatment for diabetes. We will exclude patients with any other diagnosis of diabetes (type

1 diabetes, MODY, iatrogenic, gestational diabetes, drug-induced diabetes, or any other pancreas disease related). There will be no language restriction and we will exclude studies with missing data despite author contact.

Study identification

The search strategy will be designed by two experienced librarians (AF and NAV) with input from the study's principal investigators (NAV and RRG). A comprehensive search will be conducted to find eligible articles in several databases from each database's earliest inception to October 2017. These databases will include Ovid MEDLINE, EMBASE, Web of Science, and Scopus. Controlled vocabulary supplemented with keywords will be used to search for studies evaluating the effect of SGLT-2 inhibitors regarding diabetes microvascular complications. The design and conduction of the search strategy will be finished around October 2017. After we complete the data extraction phase, we will conduct a second search using the same criteria mentioned above to update any missing trial published between the months of data extraction. We will consult experts in the field and the references from each included trial to identify studies missed by our search strategy.

Selection of studies

Reviewers working independently and in duplicate will review all abstracts and selected full-text manuscripts for eligibility. Prior to formal abstract screening, a pilot, between reviewers, will be carried out to clarify any misunderstandings and ensure adequate comprehension. Two reviewers working independently and in duplicate will screen all titles and abstracts of the selected articles to assess eligibility. In this phase we will be highly

sensitive and therefore whenever reviewers disagree, the article will be included into the full-text phase. Disagreements at full-text screening will be resolved by consensus. Reasons for non-eligibility will be documented by the reviewers. Chance-adjusted inter-rater agreement for the title/abstract screening and the full-text will be calculated using the Kappa statistics[21]. Before and after both screening phases the total number of included and excluded articles will be documented, including reasons for exclusion.

Outcomes of Interest

Microvascular outcomes (i.e. nephropathy, retinopathy, peripheral neuropathy, and peripheral vascular disease) will be assessed. Also, we will assess patient-important outcomes for any of the complication mentioned before. For this protocol we defined microvascular complications and patient-important outcomes as:

Nephropathy- Surrogates: doubling of the serum creatinine, macroalbuminuria, and microalbuminuria. Patient-important outcomes: end stage renal disease (ESRD) defined as need for continuous renal replacement therapy or renal transplant, chronic renal disease stage ≥III or renal death.

Retinopathy- Surrogates: Changes from baseline of retinal neovascularization, cataract extraction, event reported in general as retinopathy, retinal photocoagulation, and treatment with intravitreal agents. Patient-important outcomes: diabetes related blindness, vitreous hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion.

Peripheral Neuropathy- Surrogates: changes from baseline of tendon reflexes, and electrophysiological parameters such as nerve conduction velocity and sensory conduction

velocity. Patient-important outcomes: (pain, numbness), sensory loss (touch, vibration, and quality of life).

Peripheral vascular disease: Surrogate: Abnormal ankle-brachial index and/or arterial Doppler ultrasonography. Patient-important outcomes: prolonged wound healing, ulcers, or amputation.

Data Collection Process

Two reviewers working independently will collect data for all the eligible articles. To standardized data extraction a web-based data extraction form will be designed including information about type of study, baseline patient characteristics, drug being studied, and effectiveness regarding microvascular complications. Two or more reviewers working independently and in duplicate will conduct a pilot phase to assess any disagreement; disagreements will be discussed and resolved by consensus. If any disagreement cannot be resolved by consensus, a third reviewer will arbitrate the final decision. If necessary, modifications on the form will be effectuated based on the feedback of the reviewers to get optimal calibration. Data collection will take place around November-December 2017.

Missing Data

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. After a lapse of 10 days a second email will be sent to the non-responders. If the second attempt is unsuccessful, other

authors will be contacted. If none of the authors respond exclude the study. Every author contact will be documented.

Risk of Bias in Individual Studies and Quality Assessment

Two review authors working independently and in duplicate will use the Cochrane risk of bias tool to assess the quality of RCTs based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). For any follow-up, sub-analysis, or post-hoc analysis we will assess the bias of the original study. We will also evaluate the overall quality of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[22]. Disagreement will again be resolved by consensus or if not possible, by arbitration of a third reviewer. Risk of bias in individual studies will be assessed around November-December 2017.

Subgroup analysis

To explain possible inconsistencies across study results, we will conduct the following subgroup analysis: patients with long-term versus recent diabetes diagnosis, primary cardiovascular prevention versus secondary cardiovascular prevention.

Summary measures and data Synthesis

A narrative synthesis of the findings from the included studies will be provided, considered type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous

outcomes). When more than one study provide data on the same outcome measure, using the same type of intervention and comparator, a cumulative meta-analysis will be performed. Statistical analyses will be performed using Review Manager v 5.3. and results pooled following random-effects models in order to best address the heterogeneity in population characteristics across studies. Chi-squared test and the I-squared statistic will be used to assess heterogeneity between studies. A Chi-square cut-off value of $P<0.10$ and an I-squared value >50% will be considered as indicative of considerable heterogeneity not explained by chance. To explore causes of inconsistency and subgroup-treatment interactions, we developed protocol pre-specified subgroup analyses (mentioned earlier).

Patient and Public Involvement

No patients or public were involved in the study.

DISCUSSION

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. Also, this information might be important in those patients in whom a new anti-diabetic medication is needed. At this point, patients and clinicians will carefully have to consider the benefits aside glucose reduction in light of the potential risks of each drug class.

Several limitations can be foreseen of this review for instance, data availability and heterogeneity of outcome definitions may vary among studies. Probably most of the

included trials will have as primary objective glucose measures (i.e. HbA1c) or macrovascular complications, hence, data for microvascular outcomes will stem mostly from secondary endpoints. Also, as patient-important outcomes are evaluated by less than 20% of trials, data of RCTs evaluating patient-important outcomes may not be enough to have precision regarding their effect. However, this will be the first systematic review and meta-analysis designed to specifically assess the body of evidence regarding the effect of SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes. In addition, the review will be based on an extensive and systematic literature search and will represent the best estimate of effect from the available body evidence.

Abbreviations.

95% CI: 95% confidence interval, OR: odds ratio, SGLT-2: sodium glucose cotransporter 2, PRIMSA-P: Preferred Reporting Items for Systematic Review and Meta-analysis, 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

DECLARATIONS.

Acknowledgements.

None

Ethics approval and consent to participate

Not applicable.

Competing interest

The authors declare that they have no competing interest.

Funding

None.

Authors' contributions

RRG, EGDT, and BMCG designed and wrote the protocol. EGDT, ASM, VGN, GRT, ADGC, JGGG, VMM and RRG made substantial contribution and revision to it. NAV and ASM working with AMF will design the search strategy for this review. EGDT, BMCG, ASM, VGN, GRT, and ADGC will undertake data collection. EGDT and NAV will perform the statistical analysis of data. RRG, EGDT, and BMCG will interpret the results and write the final manuscript. JGGG and VMM will work as 2nd reviewer and 3rd reviewer respectively. The definitive version of this protocol reflects the contribution of all authors. All authors read and approved the final manuscript.

References.

1. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular Complications of Impaired Glucose Tolerance. Diabetes. 2003;52(12):2867–73.

2. Centers for Disease Control Prevention. Diabetes Report Card 2012 [Internet]. Centers for Disease Control and Prevention, US Department of Health and Human Services. 2014. Available from: www.cdc.gov/diabetes/library/reports/congress.html

3. Rodríguez-Gutiérrez R, Montori VM. Glycemic control for patients with type 2

diabetes mellitus: Our evolving faith in the face of evidence. Circ Cardiovasc Qual Outcomes [Internet]. 2016;9(5):504–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27553599

4. Rodbard H, Jellinger P, Davidson J, Einhorn D, Garber A, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control. Endocr Pract [Internet]. 2009;15(6):540–59. Available from: http://journals.aace.com/doi/abs/10.4158/EP.15.6.540

5. Cheng AYY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J diabetes. 2013;37:S1–3.

6. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes Care. 2015;38(1):140–9.

7. 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.

8. Qaseem A, Barry MJ, Humphrey LL, Forciea MA, Fitterman N, Boyd C, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: A clinical practice guideline update from the American college of physicians. Ann Intern Med. 2017;166(4):279–90.

9. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects

of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. J Am Soc Hypertens [Internet]. 2014;8(4):262–75. Available from: http://dx.doi.org/10.1016/j.jash.2014.01.007

10. Zhang Q, Dou J, Lu J. Combinational therapy with metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes: Systematic review and meta-analyses. Diabetes Res Clin Pract [Internet]. 2014;105(3):313–21. Available from: http://dx.doi.org/10.1016/j.diabres.2014.06.006

11. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes A Systematic Review and Meta-analysis. Ann Intern Med [Internet]. 2013;159(April):262. Available from: annals.org/article.aspx?doi=10.7326/0003-4819-159-4-201308200-00007

12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med [Internet]. 2015 Nov 26 [cited 2017 Oct 16];373(22):2117–28. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1504720

13. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects. J Am Soc Nephrol [Internet]. 2017;28(1):368–75. Available from: http://www.jasn.org/lookup/doi/10.1681/ASN.2016030278

14. Kohan DE, Fioretto P, Johnsson K, Parikh S, Ptaszynska A, Ying L. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J Nephrol.

2016;29(3):391–400.

15. Ott C, Jumar A, Striepe K, Friedrich S, Karg M V., Bramlage P, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol [Internet]. 2017;16(1):26. Available from: http://cardiab.biomedcentral.com/articles/10.1186/s12933-017-0510-1

16. Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587–97.

17. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):610–21.

18. Cherney D, Lund SS, Perkins BA, Groop P-H, Cooper ME, Kaspers S, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia [Internet]. 2016;59(9):1860–70. Available from: http://link.springer.com/10.1007/s00125-016-4008-2

19. Dziuba J, Alperin P, Racketa J, Iloeje U, Goswami D, Hardy E, et al. Modeling effects of SGLT-2 inhibitor dapagliflozin treatment versus standard diabetes therapy on cardiovascular and microvascular outcomes. Diabetes, Obes Metab [Internet]. 2014 Jul 1 [cited 2017 Oct 8];16(7):628–35. Available from:

http://doi.wiley.com/10.1111/dom.12261

20. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev [Internet]. 2015;4(1):1. Available from: http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1

21. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, Guyatt G. Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). CMAJ. 2004;171(11):1369–73.

22. Murad MH, Montori VM, Ioannidis JPA, Jaeschke R, Devereaux PJ, Prasad K, et al. How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care. JAMA [Internet]. 2014;312(2):171. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.5559

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5 and 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	N/A

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	N/A
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.