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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

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

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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 assess the body of evidence regarding the effectiveness of SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes.

68 INTRODUCTION

69 Globally, diabetes represents the leading cause of end-stage renal disease/chronic
70 renal disease, blindness, clinical peripheral neuropathy, and amputations[1,2]. Therefore,
71 decreasing the risk of the aforementioned microvascular diabetes complications is a
72 foremost for any diabetes therapeutic intervention and represents a priority for any
73 healthcare system. Different strategies had been adopted to decrease this risk- the paradigm
74 that tight glucose control (i.e. independently of the drug used), will result in a decreased
75 risk of the microvascular complications has been recently dispelled. A recent systematic
76 review reported no effect of tight glycemic control (HbA1c <7.0%) regarding patient-
77 important microvascular outcomes (e.g. end-stage renal disease, blindness, clinical
78 neuropathy)[3]. Still, there is a positive, however, inconsistent effect regarding surrogate
79 markers (e.g. microalbuminuria, photocoagulation)[3]. Other strategies, such as lipid
80 lowering (e.g. fibrates), antiplatelet agents, smoking cessation, blood pressure control
81 including angiotensin-converting enzyme inhibitors, and life-style modification, in most
82 cases, as a multifactorial intervention have been reported to have a positive effect, however,
83 mostly over surrogate markers.

84 To date, there are at least 10 classes of anti-hyperglycemic medications with
85 different mechanism of action, efficacy, adverse events, costs, and convenience[4,5]. The
86 sodium glucose co-transporter 2 (SGLT-2) inhibitors (e.g. dapagliflozon, empagliflozin,
87 and canagliflozin) are one of the novel and most used class of anti-hyperglycemic
88 medications[6–8]. Previous systematic reviews have demonstrated their effectiveness in
89 reducing hemoglobin A1c (HbA1c) in around 1%, body weight (1.2 – 2.5 kg), blood
90 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 \geq 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

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

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

161 **Data Collection Process**

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

171 **Missing Data**

172 If any data is not clear, missing or presented in a form that is either un-extractable from the
173 full-text an email will be send to the corresponding author to clarify the situation. After a
174 lapse of 10 days a second email will be sent to the non-responders. If the second attempt is
175 unsuccessful, other authors will be contacted. If none of the authors respond exclude the
176 study. Every author contact will be documented.

177 Risk of Bias in Individual Studies and Quality Assessment

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

188 Subgroup analysis

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

192 Summary measures and data Synthesis

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

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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

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

226 **Abbreviations.**

227 95% CI: 95% confidence interval, OR: odds ratio, SGLT-2: sodium glucose cotransporter
228 2, PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis,
229 CENTRAL: Cochrane Central Register of Controlled Trials, WHO: The World Health
230 Organization ICTRP: International Clinical Trials Registry Platform, GRADE: Grading of
231 Recommendations Assessment, Development, and Evaluation, RCT: Randomized Clinical
232 Trial

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236 **Ethics approval and consent to participate**

237 Not applicable.

238 **Competing interest**

239 The authors declare that they have no competing interest.

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3 242 **Authors' contributions**

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6 243 RRG, EGDT and BMCG designed and wrote the protocol. EGDT, ASM, VGN, GRT,
7
8 244 ADGC, JGGG, VMM and RRG made substantial contribution and revision to it. NAV and
9
10 245 ASM working with AMF will design the search strategy for this review. EGDT, BMCG,
11
12 246 ASM, VGN, GRT, and ADGC will undertake data collection. EGDT and NAV will
13
14 247 perform the statistical analysis of data. RRG, EGDT, and BMCG will interpret the results
15
16 248 and write the final manuscript. JGGG and VMM will work as 2nd reviewer and 3rd reviewer
17
18 249 respectively. The definitive version of this protocol reflects the contribution of all authors.
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21 250 All authors read and approved the final manuscript.
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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 prioritisation 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 inconsistency (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 (note 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

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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

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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

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

33 Abstract.

34 **Introduction:** Sodium glucose cotransporter 2 (SGLT-2) inhibitors are a relatively new
35 drug-class of antidiabetic medications. Several trials and systematic reviews have
36 demonstrated their beneficial effect on some macrovascular outcomes. Their effect on
37 microvascular outcomes has been reported as positive in several trials, however, their effect
38 remains uncertain. Therefore, we report the protocol of a systematic review and meta-
39 analysis aimed at determining the effect of SGLT-2 inhibitors regarding patient-important
40 and surrogate microvascular outcomes in patients with type 2 diabetes.

41 **Methods and Analysis:** A comprehensive search will be conducted to find eligible articles
42 from each database's earliest inception to November 2017. These databases will include
43 Ovid MEDLINE, EMBASE, Web of Science, and Scopus. We will search for randomized
44 controlled trials (RCTs) that compare any of the SGLT-2 inhibitors with any other active
45 treatment or placebo assessing microvascular outcomes in either their primary or secondary
46 outcomes. Reviewers working independently and in duplicate will review all abstracts, and
47 full-text manuscripts for eligibility, and will systematically extract the data and will assess
48 the risk of bias in the included studies. Random-effects models will also be used.

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

53 **Systematic Review Registration:** PROSPERO registration number: CRD 42017076460

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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.

70 Introduction

71 Globally, diabetes represents the leading cause of end-stage renal disease/chronic
72 renal disease, blindness, clinical peripheral neuropathy, and amputations(1,2). Therefore,
73 decreasing the risk of the aforementioned microvascular complications is a foremost in any
74 diabetes therapeutic intervention and represents a priority for any healthcare system.
75 Different strategies involving a rigorous glycemic control have been adopted to try to
76 reduce this risk. Nonetheless, the paradigm of tight glycemic control (i.e. independently of
77 the drug used) resulting in a decreased risk of microvascular complications has recently
78 been dispelled. Consistent with other studies, a recent systematic review reported no effect
79 of tight glycemic control (HbA1c <7.0%) when compared to conventional glycemic control
80 (HbA1c 8.0-8.5%) regarding patient-important microvascular outcomes (e.g. end-stage
81 renal disease, blindness, clinical neuropathy) in patients with type 2 diabetes (3–7). Still,
82 there is a positive, however, inconsistent effect regarding surrogate markers (e.g.
83 microalbuminuria, photocoagulation)(7). Other strategies, such as lipid lowering drugs (e.g.
84 fibrates), antiplatelet agents, smoking cessation, blood pressure control including
85 angiotensin-converting enzyme inhibitors and life-style modifications, in most cases as a
86 multifactorial intervention, have been reported to have a positive effect, however, mostly
87 over surrogate markers.

88 To date, there are at least 10 classes of anti-hyperglycemic medications with
89 different mechanism of action, efficacy, adverse events, costs, and convenience(8,9)
90 Sodium glucose co-transporter 2 (SGLT-2) inhibitors are one of the novel classes of anti-
91 hyperglycemic drugs and as a group are positioning themselves as a promising therapeutic
92 class in current diabetes treatment(10–12). Previous systematic reviews have demonstrated

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3 93 their effectiveness in reducing hemoglobin A1c (HbA1c), body weight , blood pressure(13–
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5 94 15) and the risk of major cardiovascular outcomes, including mortality(16). Their effect on
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8 95 microvascular patient-important outcomes and intermediate (surrogate) markers has been
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10 96 reported in several individual trials as positive, however, among some of the major RCTs
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12 97 their effect appears to be inconsistent and imprecise and remains to a great extent,
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14 98 uncertain(17–23).

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18 99 Therefore, we plan to conduct a systematic review and meta-analysis to determine
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20 100 the effect of SGLT-2 inhibitors on patient-important and surrogate microvascular outcomes
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22 101 in adult patients with type 2 diabetes.

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25 102 **Methods and Analysis**

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28 103 **Study Design**

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31 104 This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-
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33 105 analysis (PRISMA-P)(24).

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36 106 **Eligibility Criteria**

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38 107 We will search for RCTs that compare any of the SGLT-2 inhibitors with any other active
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40 108 treatment or placebo evaluating microvascular outcomes in either their primary or
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42 109 secondary outcomes. We will also include any follow-up, sub-analysis, or post-hoc
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44 110 analyses from the original trial assessing these same outcomes. We will consider studies
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46 111 enrolling adults (18 years or older) with type 2 diabetes defined by any recognized standard
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48 112 diagnostic criteria, regardless of evolution time, and with a minimum of ≥4 weeks of
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50 113 intervention. We will exclude patients with any other type of diabetes (type 1 diabetes,
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52 114 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

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3 137 non-eligibility will be documented by the reviewers. Chance-adjusted inter-rater agreement
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5 138 for the title/abstract screening and the full-text will be calculated using the Kappa
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7 139 statistic(25). Before and after both screening phases the total number of included and
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10 140 excluded articles will be documented, including reasons for exclusion. Selection of studies
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12 141 will be carried out from January to February 2018
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15 142 **Outcomes of interest**

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18 143 Microvascular outcomes (i.e. nephropathy, retinopathy, peripheral neuropathy, and
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20 144 peripheral vascular disease) will be assessed. Also, we will assess patient-important
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22 145 outcomes for any of the complication mentioned before. For this protocol we defined
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24 146 microvascular complications and patient-important outcomes as:

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28 147 Nephropathy surrogates: doubling of serum creatinine, macroalbuminuria, and
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30 148 microalbuminuria. Patient-important outcomes: end-stage renal disease (ESRD) defined as
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32 149 the need for continuous renal replacement therapy or renal transplant, chronic renal disease
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34 150 stage \geq III or renal death.
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39 151 Retinopathy surrogates: Changes from baseline of retinal neovascularization, cataract
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41 152 extraction, event reported in general as retinopathy, retinal photocoagulation, and treatment
42
43 153 with intravitreal agents. Patient-important outcomes: diabetes related blindness, vitreous
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45 154 hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion.
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49 155 Peripheral neuropathy surrogates: Changes from baseline of tendon reflexes, and
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51 156 electrophysiological parameters such as nerve conduction velocity and sensory conduction
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53 157 velocity. Patient-important outcomes: (pain, numbness), sensory loss (touch, vibration, and
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55 158 quality of life).
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159 Peripheral vascular disease surrogate: Abnormal ankle-brachial index and/or arterial
160 Doppler ultrasonography. Patient-important outcomes: prolonged wound healing, ulcers, or
161 amputation.

162 **Data Collection Process**

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

173 **Missing Data**

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

180 **Risk of Bias in Individual Studies and Quality Assessment**

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3 181 Two authors working independently and in duplicate will use the Cochrane risk of bias tool
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5 182 to assess the quality of RCTs based on the following domains: random sequence generation
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7 183 (selection bias), allocation concealment (selection bias), blinding (performance bias and
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9 184 detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting
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11 185 bias). For any follow-up, sub-analysis, or post-hoc analysis we will assess the bias of the
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13 186 original study. We will also evaluate the overall quality of evidence for each outcome using
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15 187 the Grading of Recommendations Assessment, Development, and Evaluation
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17 188 (GRADE)(26). Disagreement will again be resolved by consensus or if not possible, by
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19 189 arbitration of a third reviewer. Risk of bias in individual studies will be assessed around
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21 190 March – April 2018.

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26 191 **Sensitivity analysis**

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28 192 To explain possible inconsistencies between studies we will conduct the following
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30 193 subgroup analysis: patients with long-term versus recent diabetes diagnosis and trials of
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32 194 primary versus secondary cardiovascular prevention. If possible, we will also try to analyze
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34 195 different drug doses. Also, we will conduct the following sensitivity analysis: patients with
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36 196 long-term versus recent diabetes diagnosis and patients with arterial hypertension as
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38 197 comorbidity versus patients without hypertension.

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42 198 **Summary measures and data synthesis**

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45 199 A narrative synthesis of the findings from the included studies will be provided,
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47 200 considering the type of intervention, target population characteristics, type of outcome and
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49 201 intervention content. We will provide summaries of intervention effects for each study by
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51 202 calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for
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53 203 continuous outcomes). When more than one study provide data on the same outcome
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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

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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.

247 **Consent for publication**

248 Not applicable.

249 **Availability of data and material**

250 Not applicable.

251 **Competing interest**

252 The authors declare that they have no competing interest.

253 **Funding**

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

256 **Authors' contributions**

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

265 **Acknowledgments**

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

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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- (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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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

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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

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34 **Competing Interests:** None

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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

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

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

142 **Outcomes of Interest**

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

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

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

155 Peripheral Neuropathy- Surrogates: changes from baseline of tendon reflexes, and
156 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

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

180 **Risk of Bias in Individual Studies and Quality Assessment**

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

191 **Subgroup analysis**

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

195 **Summary measures and data Synthesis**

196 A narrative synthesis of the findings from the included studies will be provided, considered
197 type of intervention, target population characteristics, type of outcome and intervention
198 content. We will provide summaries of intervention effects for each study by calculating
199 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

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2
3 222 included trials will have as primary objective glucose measures (i.e. HbA1c) or
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5 223 macrovascular complications, hence, data for microvascular outcomes will stem mostly
6
7 224 from secondary endpoints. Also, as patient-important outcomes are evaluated by less than
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10 225 20% of trials, data of RCTs evaluating patient-important outcomes may not be enough to
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12 226 have precision regarding their effect. However, this will be the first systematic review and
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14 227 meta-analysis designed to specifically assess the body of evidence regarding the effect of
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16 228 SGLT-2 inhibitors in patients with type 2 diabetes regarding microvascular outcomes. In
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18 229 addition, the review will be based on an extensive and systematic literature search and will
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21 230 represent the best estimate of effect from the available body evidence.
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25 231 **Abbreviations.**
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28 232 95% CI: 95% confidence interval, OR: odds ratio, SGLT-2: sodium glucose cotransporter
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30 233 2, PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis,
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32 234 CENTRAL: Cochrane Central Register of Controlled Trials, WHO: The World Health
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34 235 Organization ICTRP: International Clinical Trials Registry Platform, GRADE: Grading of
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36 236 Recommendations Assessment, Development, and Evaluation, RCT: Randomized Clinical
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39 237 Trial
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42 238 **DECLARATIONS.**
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48 240 None
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51 241 **Ethics approval and consent to participate**
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55 242 Not applicable.
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243 **Competing interest**

244 The authors declare that they have no competing interest.

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246 None.

247 **Authors' contributions**

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

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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.**

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