PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effects of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: protocol for a systematic review with meta-analysis of randomised trials
AUTHORS	Storgaard, Heidi; Gluud, Lise; Christensen, Mikkel; Knop, Filip; Vilsbøll, Tina

VERSION 1 - REVIEW

REVIEWER	Dario Giugliano Second University of Naples, Italy
REVIEW RETURNED	29-Apr-2014

GENERAL COMMENTS	The main limitation of this protocol is represented by the lack of acknowledgment of previous meta-analyses on this topic. The authors acknowledged the existence of previous systematic reviews by quoting in lines 24 to 29 of page 5 the following: "Unlike previous systematic reviews, we plan to include focus on trials assessing on STLG-2i in doses that are recommended for clinical practice." However, they did not mention any of these previous systematic reviews and meta-analyses (a rapid inspection at PubMed let me know at least 4 recent meta-analyses on dapagliflozin only). The authors must detail how their protocol is different from the previous ones, why there is a need for another meta-analysis, and what their meta-analysis will add to knowledge.

REVIEWER	Peter Rossing Steno Diabetes Center Denmark participated in expert group meetings for Astra Zeneca/V`BMS Boehringer Ingelheim Eli LIlly, and Janssen
REVIEW RETURNED	07-May-2014

GENERAL COMMENTS	The paper is a protocol for a metaanalysis, thus no data are presented but a detailed plan for the analysis of the efficacy and safety of SGLT2 inhibitors. In the abstract it is stated that cholesterol is a secondary outcome, in the text LDL cholesterol is only metioned and I suggest the whole lipid profile total, HDL, LDL cholesterol and triglyceride is evaluated kidney blood tests? does that include effects on fex potassium and sodium Ca++ and uric acid which could be relevant in addition to creatinine, furthermore for drug acting on the kidney assessment of

	effect on urinary albumin would be of interest to the extend available it is stated that approved agents (or almost) in clinical relevant doses are used, however recommended doses differ in different countries and several drugs are approved or almost approved in Japan that are not included, either it should be specified what is meant (in which countries) or more drugs and doses will have to be looked at it should be specified when "safety" is mentioned as an outcome that some are of special interest like hypoglycaemia, hypotension, UTI and genital infections it is not clear if the analyses will be stratified based on treatment combinations, or baseline characteristics like age, hba1c, BMI, BP, GFR, gender, active compound or others? Before starting this the authors should be aware of the recently published metaanalysis in the same journal, which should be quoted: BMJ Open. 2012 Oct 18;2(5). pii: e001007. doi: 10.1136/bmjopen-2012-001007. Print 2012. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. Clar C1, Gill JA, Court R, Waugh N. I will leave it for the editorial office to decide if a protocol for a metaanalysis is within the scope of the journal

REVIEWER	Castaneda, Francisco Herzberg Hospital Germany
REVIEW RETURNED	11-May-2014

GENERAL COMMENTS	The manuscript “The effects of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: protocol for a systematic review with meta-analysis of randomised trials” (Manuscript ID: bmjopen-2014-005378) does not provide any significant substantial information to that included in at least three recent published meta-analyses regarding the role of sodium-glucose co-transporter 2 inhibitors in the treatment of type 2 diabetic patients. Additionally, the inclusion of clinically relevant doses restricts the number of studies that can be included in the proposed meta-analysis. Therefore, the main aim of the study, which is to contribute to the knowledge regarding the beneficial and harmful effects of SGLT2 inhibitors, as stated by the author, cannot be achieved with the information currently included or potentially available for the proposed protocol. Thus, my recommendation is to reject this paper from publication in the BMJ Open journal. The proposed protocol for a systematic review with meta-analysis of randomized trials on the effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors in patients with type 2 diabetes as proposed needs some important considerations and major revisions: 1. To increase external validity, the authors plan to include only trials with clinically relevant daily doses of SGLT2 inhibitors (canagliflozin 300 mg, dapagliflozin 10 mg and empagliflozin 25 mg). The definition of “clinically relevant doses” must be defined and explained. In the case of dapagliflozin, the dosages ranging from 2.5 to 10 mg have already been reported in the literature. The use of 10 mg as clinically relevant daily doses, as postulated in the present study, must be explained and corroborated with references.

	2. The other important point that needs to be considered and discussed is the inclusion criteria. For example the duration of the intervention, which is key to this report, needs to be included. 3. As mentioned in “Strength and limitations of this study” the inclusion of clinical trials represents an important limitation of the present study that needs to be considered. Additionally, the authors need to consider revising the purpose of the proposed protocol for systematic-review taking into account at least three of the most recent and very complete systematic-reviews on SGLT2 inhibitors that have been published between 2012 and 2014.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 – Dr. Dario Giugliano, University of Naples, Italy

1. The main limitation of this protocol is represented by the lack of acknowledgment of previous meta-analyses on this topic. The authors acknowledged the existence of previous systematic reviews by quoting in lines 24 to 29 of page 5 the following: "Unlike previous systematic reviews, we plan to include focus on trials assessing on STLG-2i in doses that are recommended for clinical practice." However, they did not mention any of these previous systematic reviews and meta-analyses (a rapid inspection at PubMed let me know at least 4 recent meta-analyses on dapagliflozin only).

Answer:
We have now included references regarding previous meta-analyses on SGLT-2i (references 19-24 in the manuscript) and have emphasized how our meta-analysis differs from these (see below).

1. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med 2013;159:262–74.

2. Berhan A, Barker A. Sodium glucose co-transport 2 inhibitors in the treatment of type 2 diabetes mellitus: a meta-analysis of randomized double-blind controlled trials. BMC Endocr Disord 2013;13:58.

3. Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2.

4. Goring S, Hawkins N, Wygant G, et al. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis. Diabetes Obes Metab 2014;16:433–42.

5. Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflo -zin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab Published Online First: 26 April 2014.

6. Musso G, Gambino R, Cassader M, et al. A novel approach to control hyper -glycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: syste-matic review and meta-analysis of randomized trials. Ann Med 2012;44:375–93.

2. The authors must detail how their protocol is different from the previous ones, why there is a need for another meta-analysis, and what their meta-analysis will add to knowledge

Answer:
Unlike previous meta-analyses, we have narrowed our analyses down to focus on 'clinically relevant' trials, i.e., trials assessing doses that we use in clinical practice, clinical relevant compounds and with sufficient follow up. This approach means that smaller trials, which often focus on surrogate outcomes or dose finding trials will not be included in our main assessment. We believe that this approach will give the evidence-based clinician a clearer and more useful answer Doses that are not clinical relevant may under- or overestimate beneficial and potential harmful effects of SGLT-2i. These considerations have now been added in the manuscript (page 4). Furthermore, unlike previous reviews, we plan to include unpublished as well as published data. The unpublished data will be retrieved through correspondence with companies producing the SGLT2i (dapagliflozin; AstraZeneca and Bristol-Myers Squibb, canagliflozin; Janssen, empagliflozin; Boehringer Ingelheim and Eli Lilly).The fact that we will be able to retrieve unpublished data (regarding e.g. blood pressure, cholesterol, liver enzymes and side-effects) reduce the risk of reporting biases (i.e., selective reporting of outcome with a positive result).

Reviewer 2 – Dr. Peter Rossing, Steno Diabetes Center, Denmark

1. In the abstract it is stated that cholesterol is a secondary outcome, in the text LDL cholesterol is only metioned and I suggest the whole lipid profile total, HDL, LDL cholesterol and triglyceride is evaluated

Answer:
Excellent suggestion this has now been included

2. kidney blood tests? does that include effects on fex potassium and sodium Ca++ and uric acid which could be relevant in addition to creatinine, furthermore for drug acting on the kidney assessment of effect on urinary albumin would be of interest to the extend available

Answer:
Excellent suggestion this has now been included

3. It is stated that approved agents (or almost) in clinical relevant doses are used, however recommended doses differ in different countries and several drugs are approved or almost approved in Japan that are not included, either it should be specified what is meant (in which countries) or more drugs and doses will have to be looked at

Answer:
Important point raised by the reviewer. We now specify that we evaluate doses that are those currently recommended by the European Medicines Agency (EMA) (reference 17, 24 and 25 in the manuscript) and Food and Drug Administration (FDA).

1. Forxiga, INN-dapagliflozin - WC500136024.pdf.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002322/WC500136024.pdf

2. Invokana, INN-canagliflozin - WC500156456.pdf.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002649/WC500156456.pdf

3. Jardiance, INN-Empagliflozin - anx_128562_en.pdf.
http://ec.europa.eu/health/documents/community-register/2014/20140522128562/anx_128562_en.pdf

4. it should be specified when "safety" is mentioned as an outcome that some are of special interest like hypoglycaemia, hypotension, UTI and genital infections

Answer:
As suggested by the reviewer this has now been clarified in the manuscript.

5. it is not clear if the analyses will be stratified based on treatment combinations, or baseline characteristics like age, hba1c, BMI, BP, GFR, gender, active compound or others?

Answer:
We plan to perform subgroup and meta-regression analyses based on treatment combinations as well as baseline patient characteristics. We have clarified this in the methods section.

6. Before starting this the authors should be aware of the recently published metaanalysis in the same journal, which should be quoted: BMJ Open. 2012 Oct 18;2(5). pii: e001007. doi: 10.1136/bmjopen-2012-001007. Print 2012. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. Clar C1, Gill JA, Court R, Waugh N.

Answer:
Please see our response to reviewer no. 1. As suggested by both reviewers already published meta-analyses have now been included in the manuscript (ref.19-24)

Reviewer – 3 Dr. Francisco Castaneda, Herzberg Hospital, Germany

1. The manuscript “The effects of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: protocol for a systematic review with meta-analysis of randomised trials” (Manuscript ID: bmjopen-2014-005378) does not provide any significant substantial information to that included in at least three recent published meta-analyses regarding the role of sodium-glucose co-transporter 2 inhibitors in the treatment of type 2 diabetic patients.

Answer:
Please see our reply above regarding (Reviewer 1 point 2)

2. Additionally, the inclusion of clinically relevant doses restricts the number of studies that can be included in the proposed meta-analysis. Therefore, the main aim of the study, which is to contribute to the knowledge regarding the beneficial and harmful effects of SGLT2 inhibitors, as stated by the author, cannot be achieved with the information currently included or potentially available for the proposed protocol.

Answer:
When performing a meta-analysis, the decision to lump trials across several different doses and

treatment durations or to split the analyses based on pre-specified criteria is difficult. The combination of several different treatment regimens may be considered to increase the external validity. Based on our baseline knowledge in the area, we estimate that we will be able to include at least 20 trials. Several trials are large and have a low risk of bias. We therefore believe that the information that we will be able to generate based on our review, will provide sufficiently strong evidence to provide important knowledge to clinical practitioners.

3. To increase external validity, the authors plan to include only trials with clinically relevant daily doses of SGLT2 inhibitors (canagliflozin 300 mg, dapagliflozin 10 mg and empagliflozin 25 mg). The definition of “clinically relevant doses” must be defined and explained. In the case of dapagliflozin, the dosages ranging from 2.5 to 10 mg have already been reported in the literature. The use of 10 mg as clinically relevant daily doses, as postulated in the present study, must be explained and corroborated with references.

Answer::
Please see our reply above regarding (Reviewer 2, point 3).

4. The other important point that needs to be considered and discussed is the inclusion criteria. For example the duration of the intervention, which is key to this report, needs to be included.

Answer:
Important point raised by the reviewer and we do apologies for omitting this central issue. Duration has now been included (page 5).

5. As mentioned in “Strength and limitations of this study” the inclusion of clinical trials represents an important limitation of the present study that needs to be considered.

Answer:
As suggested by the reviewer we have clarified this section in the manuscript

6. Additionally, the authors need to consider revising the purpose of the proposed protocol for systematic-review taking into account at least three of the most recent and very complete systematic-reviews on SGLT2 inhibitors that have been published between 2012 and 2014.

Answer:
Please see our response to reviewer 1, point 2.