

April 10, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 33261-review.doc).

Title: Effects of glucose-lowering agents on ischemic stroke

Authors: Konstantinos Avgerinos, Konstantinos Tziomalos

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 33261

The manuscript has been improved according to the suggestions of reviewers. All changes are shown in red in the revised text:

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewers.

Reviewer 03461082

This manuscript addresses an important topic. However, in reviewing the literature, the authors misinterpret results of some trials, and also are mixing up results from different trials (e.g., there was a retinopathy signal with semaglutide - not empagliflozin). Furthermore, as the topic is T2DM, you should not include the DCCT and EDIC results. The written English could also be improved as many of the sentences starts similarly. A few suggestions has been given directly as comments to the paper which, at least in my view, could help to strengthen this paper further.

We thank this Reviewer for stating that "This manuscript addresses an important topic." We scrutinized the review and corrected previous misinterpretations as suggested. We removed the references to DCCT and EDIC results. We also tried to improve the written English. We also addressed all comments that were made directly in the paper.

Reviewer 00506298

The Avgerinos et al review aimed to summarize the evidence on the effects of antidiabetic agents on the incidence of ischemic stroke. This is an interesting manuscript from a clinical practice point of view. However, before the article will publish in the WJD, authors should clarify one point and attend a recommendation in order to improve the paper:

1. Why the insulin was not included in the study?

We thank this reviewer for stating "This is an interesting manuscript from a clinical practice point of view." Regarding insulin, we added a paragraph in page 7 where we mention "In the UKPDS, treatment with insulin had no effect on the risk of ischemic stroke^[9]. There is no other RCT that evaluated the effects of insulin on the risk of ischemic stroke in patients with T2DM." Insulin is also discussed in the context of studies that evaluated the effects of strict glycemic control on the risk of ischemic stroke. We also briefly comment on the efficacy and safety of insulin in page 6.

2. I recommend that authors do a table summarize the effect of the different agents on ischemic stroke.

We added a table that summarizes the effect of different agents on ischemic stroke.

Reviewer 00507108

A difficult subject to review. How long do the patients have to be on a particular therapy to attribute the stroke to the therapy. Most patients are on more than one therapy as time goes by, hence difficult to assess the impact of the newest treatment on the stroke.

The introduction makes the point that rising blood sugar correlates with increasing stroke risk from normal glycaemia through pre-diabetes. The statement that some, but not all, glucose lowering agents reduce the risk of ischaemic stroke- no ref given and the statement suggests that the agent, not the glucose lowering, reduces the risk of stroke.

We removed from the "INTRODUCTION" (page 3, second paragraph), the statement "Accumulating data suggest that some, but not all, glucose-lowering agents reduce the risk of ischemic stroke in patients with T2DM."

The introduction seems to confuse cardiovascular data with ischaemic stroke data. It would be better if the introduction stuck to ischaemic stroke . That isn't the title after all.

We now refer only to ischemic stroke.

Ref 18 for example is a good review but what did it say about ischaemic stroke.

Reference 18 (page 4, second paragraph) suggests that there was no effect of tight glycemic control on the risk of non-fatal stroke compared with less strict control.

The section on the different glucose lowering agents seems out of place. Efficacy and safety are outside the remit of the title and probably well known at the superficial level given to the readers of the article?

The section "GLUCOSE-LOWERING AGENTS: EFFICACY AND SAFETY" was written in order to give quickly a picture of how effective each agent is in glucose lowering and what is the side effect profile of each drug. With these in mind and in conjunction with the possible effect of each agent on ischemic stroke (which is described in later sections in the paper), the reader can balance the advantages and disadvantages of each antidiabetic agent.

The UKPDS reference 8 does not specify what type of stroke and many patients had another drug added to help to normalise the hyperglycaemia I think. Again Ref 9 does not define the type of stroke.?

It is true that these studies (reference 8 and 9) specify strokes as fatal and non-fatal, without further classification into ischemic or hemorrhagic. But, since the majority of strokes are ischemic, they provide some data on the effect of intensive glucose management on ischemic stroke (page 3, third paragraph).

The sulphonylurea section should make it clear that ref 61 refers to carotid artery Ref 32 refers to fractures.

In the chapter "EFFECTS OF GLUCOSE-LOWERING AGENTS ON ISCHEMIC STROKE-sulfonylureas" (page 7, second paragraph), after the statement "Moreover, glimepiride had a less favorable effect than pioglitazone", we added the statement "on carotid intima media thickness (CIMT)"(reference 61).

In the chapter "GLUCOSE-LOWERING AGENTS: EFFICACY AND SAFETY-thiazolidinediones"(page 5, third paragraph),reference 32 is already mentioned in the statement "Both rosiglitazone and pioglitazone are also associated with weight gain, edema, heart failure, bone fractures and urinary bladder cancer".

In the Pioglitazone section and in the conclusion the authors refer to unfavourable safety profile but ref to a Cochrane review in 2015 does not support this statement for pioglitazone.

In the chapter "GLUCOSE-LOWERING AGENTS: EFFICACY AND SAFETY-thiazolidinediones"(page 5, third paragraph), after the statement "Both rosiglitazone and pioglitazone are also associated with weight gain, edema, heart failure, bone fractures and urinary bladder cancer", we added the statement "although for pioglitazone a systematic review of 2015 showed no difference in side effects when compared to placebo" (we added a new reference).

In the "CONCLUSIONS" chapter (page 11, second paragraph), we removed the statement "but its unfavorable safety profile limits its use".

A difficult task to review the effects of glucose lowering agents on ischaemic stroke. The conclusion might allude to the difficulties and focus on ischaemic stroke rather than cardiovascular events.

In the "CONCLUSIONS" chapter (page 11, second paragraph) after the statement "Moreover, semaglutide is the only agent that reduced the risk of ischemic stroke in a placebo-controlled trial, although it increased the retinopathy risk." we added the statement "Empagliflozin, on the contrary, might increase the incidence of stroke."

We also, removed the statement "sulfonylureas and DPP-4 inhibitors have a neutral effect on cardiovascular morbidity and might be less attractive options in this high-risk population." and instead we added "sulfonylureas and DPP-4 inhibitors have a neutral effect on ischemic stroke. For linagliptin, a DPP-4 inhibitor, trials are ongoing, although basic research showed encouraging results."

Reviewer 00506397

Avgerinos and Tziomalos outline an excellent survey of published studies that deal with the topic of treatment of diabetes mellitus (DM) with a variety of glucose lowering drugs and their impact on the frequency and severity of ischemic stroke. Based on the findings of this survey, the authors concluded that strict glycemic control does not appear to reduce ischemic stroke. Significantly, the use of newer glucose-lowering agents (glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitor) had salutary effect on ischemic stroke in patients with DM. These benefits partly appear to due to the favorable effects of these agents on body weight and blood pressure.

We thank this reviewer for stating "Avgerinos and Tziomalos outline an excellent survey of published studies that deal with the topic of treatment of diabetes mellitus (DM) with a variety of glucose lowering drugs and their impact on the frequency and severity of ischemic stroke."

I have following suggestions to improve this presentation:

1. The authors should revise the Abstract and Core Tip sections to be more lucid with respect to stating more poignantly that the effect of newer diabetic medications on ischemic stroke is independent of strict glucose control.

We revised both the Abstract and Core Tip accordingly.

2. The literature that supports this contention need to be discussed more elaborately. Thus, the sections on DPP-4 inhibitors and SGLT-2 inhibitors need to be considerable expanded to provide more nuanced view of these drugs and their effects that do not involve glycemic control but appetite and weight. The authors need to discuss the limitations and caveats of these studies.

In the chapter "EFFECTS OF GLUCOSE-LOWERING AGENTS ON ISCHEMIC STROKE-DPP-4 inhibitors"(page 9,first paragraph) we added the statement "Of note, a study in mice showed that linagliptin-mediated neuroprotection is glucose-independent and likely involves GLP-1." Also in the "CONCLUSIONS" we added the statement "For linagliptin, a

DPP-4 inhibitor, trials are ongoing, although basic research showed encouraging results", to show the need for further clinical investigation. In the chapter "EFFECTS OF GLUCOSE-LOWERING AGENTS ON ISCHEMIC STROKE-DPP-4 inhibitors"(page 10, second paragraph) after the statement "the reduction in cardiovascular death rates appeared to be mostly due to the reduction in body weight, blood pressure and possibly a diuretic effect of empagliflozin in patients with heart failure", we added the statement "which shows that favorable outcomes regarding ischemic strokes were independent of glucose lowering"

3. A Summary Table showing a comparison glycemic and non-glycemic effects of various medications and their effect on the ischemic stroke should be presented to provide a succinct overview of this important Review.

Again, we thank this Reviewer for stating that our Review is important. We added an appropriate table showing a comparison of glycemic and non-glycemic effects of various medications and their effect on the ischemic stroke.

Reviewer 00506390

General Comments:

1. The review has a very interesting and relevant topic, especially with the prevalence of Diabetes and Ischemic Stroke. The manuscript is generally well written with only a few issues that should be addressed to strengthen this review.

We thank this reviewer for stating tghat "The review has a very interesting and relevant topic, especially with the prevalence of Diabetes and Ischemic Stroke. The manuscript is generally well written."

2. In the section: "Glucose-lowering agents: efficacy and safety," many generic drugs are referenced without specifying which actual class they belong. Please indicate which drug class each drug belongs. This will make the manuscript much clearer when reading, especially to those without a strong background in the various generic drug names. A suggestion would be to insert a simple table with each described drug in their respective drug class for reference.

In the chapter "GLUCOSE-LOWERING AGENTS: EFFICACY AND SAFETY", whenever the drug class of each drug is not implied by the subtitle, we added an explanation of the class to which it belongs. Moreover, we added a table with the drug classes and their main representative drugs, together with their effect on ischemic stroke and their efficacy in lowering the glucose in diabetics.

3. Please review for formatting issues. There were some minor formatting issues (i.e., spacing within spacing within section titles) throughout the manuscript.

We corrected the formatting issues.

Specific Comments:

1. Page 7: Para 2 "Sulfonylureas": The authors state "Moreover, glimepiride....which is marker of subclinical..." This statements seems to indicate that one of the drugs is a marker for subclinical atherosclerosis, which I am unfamiliar with a drug being a marker of disease. Please restructure and clarify this statement to the appropriate message.

In chapter "EFFECTS OF GLUCOSE-LOWERING AGENTS ON ISCHEMIC STROKE-sulfonylureas"(page 7, second paragraph), we corrected the statement "Moreover, glimepiride had a less favorable effect than pioglitazone which is marker of subclinical atherosclerosis and a risk factor for ischemic stroke", to "Moreover, glimepiride had a less favorable effect than pioglitazone on carotid intima media thickness (CIMT) which

is marker of subclinical atherosclerosis and a risk factor for ischemic stroke" by adding the statement "on carotid intima media thickness (CIMT)".

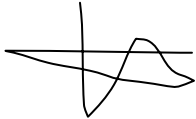
2. Page 7: Para 3 "Thiazolidinediones": The authors refer to the PROACTIVE trial and state both the primary endpoints and secondary endpoints of the study. However, the authors state three of the same endpoints as both primary and secondary. Did the authors mean the primary endpoints were between groups and the secondary were used for comparison within groups? If so, please clarify.

In this study, three endpoints (all-cause mortality, non-fatal myocardial infarction, and stroke) were part of both the primary and secondary composite endpoint.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,



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