

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 33261

**Title:** Effects of glucose-lowering agents on ischemic stroke

**Reviewer's code:** 03461082

**Reviewer's country:** Norway

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-02-12

**Date reviewed:** 2017-02-13

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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 start similarly. A few suggestions have been given directly as comments to the paper which, at least in my view, could help to strengthen this paper further.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 33261

**Title:** Effects of glucose-lowering agents on ischemic stroke

**Reviewer's code:** 00506298

**Reviewer's country:** Spain

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-02-27

**Date reviewed:** 2017-02-28

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 33261

**Title:** Effects of glucose-lowering agents on ischemic stroke

**Reviewer's code:** 00506397

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-02-27

**Date reviewed:** 2017-03-02

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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. 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. 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



## BAISHIDENG PUBLISHING GROUP INC

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

<http://www.wjgnet.com>

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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. 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.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 33261

**Title:** Effects of glucose-lowering agents on ischemic stroke

**Reviewer's code:** 00507108

**Reviewer's country:** Ireland

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-02-27

**Date reviewed:** 2017-03-10

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
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## COMMENTS TO AUTHORS

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. 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. Ref 18 for example is a good review but what did it say about ischaemic stroke. 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 UKPDS reference 8 does not specify what type of stroke and many patients had another drug added to help to normalise the



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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

<http://www.wjgnet.com>

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hyperglycaemia I think. Again Ref 9 does not define the type of stroke.? The sulphonylurea section should make it clear that ref 61 refers to carotid artery Ref 32 refers to fractures. In the Pioglitazone section and in the conclusion the authors refer to unfavourable safety profile but ref to a Cocherane review in 2015 does not support this statement for pioglitazone. 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.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 33261

**Title:** Effects of glucose-lowering agents on ischemic stroke

**Reviewer's code:** 00506390

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-02-27

**Date reviewed:** 2017-03-14

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
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<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
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		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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



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<http://www.wjgnet.com>

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Please restructure and clarify this statement to the appropriate message. 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.