

November 2, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5387-review.doc).

Title: Antidiabetic treatment and stroke severity and outcome

Authors: Dimitra Magkou, Konstantinos Tziomalos

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 5387

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 00506122

The manuscript by Magkou et al provides an interesting and updated account of the beneficial application of anti-diabetic treatment in patients suffering from stroke.

We thank this Reviewer for these positive comments.

Major points

1. The mechanism underlying the beneficial effects of DPP-4 in stroke reduction should be described.

We mention in our manuscript (page 7, second paragraph) "This neuroprotective effect of linagliptin appears to be glucose-lowering-independent since the reduction in blood glucose levels was smaller during treatment with linagliptin compared with glimepiride. In addition, linagliptin also prevented neuronal death in non-diabetic mice even though it did not affect glucose levels, further supporting a glucose-lowering-independent neuroprotective effect. Similar results have been reported very recently with another DPP-4 inhibitor, alogliptin." We also mention (page 8, first paragraph) "Several alternative mechanisms besides glucose lowering may underpin the beneficial effects of linagliptin in the setting of acute stroke. First, treatment with linagliptin results in increased blood GLP-1 levels and pretreatment with exendin-4, a GLP-1 agonist, was shown to reduce stroke volume and neurological deficit in animal stroke models. Antiapoptotic, antiinflammatory and antioxidant actions as well as stimulation of the proliferation of neural stem cells and attenuation of microglial activation appear to contribute to these neuroprotective effects. Interestingly, administration of exendin-4 in non-diabetic animals immediately after stroke also reduces stroke volume and improves outcome through similar mechanisms without affecting glucose levels. These effects appear to be GLP-1 receptor-mediated, since they are not observed in GLP-1 receptor knockout (-/-) mice. Moreover, GLP-1 readily crosses the blood-brain barrier and GLP-1 receptors are expressed in brain neurons in humans. In addition, both ischemia and treatment with exendin-4 up-regulate the expression of GLP-1 receptors in pyramidal neurons. Given the putative neuroprotective effects of GLP-1, this increased expression might represent a defense mechanism against ischemic damage". Finally, we mention (page 8, last paragraph) "A second possible pathway through which linagliptin might exert its neuroprotective effects is the increased bioavailability of other bioactive DPP-4 substrates. Indeed, DPP-4 has many other substrates except GLP-1, some of which appear to exert

neurotrophic or neuroprotective effects. The latter include glucose-dependent insulintropic polypeptide, pituitary adenylate cyclase-activating polypeptide and stromal cell-derived factor 1a, which were reported in preclinical models to promote synaptic plasticity, neurogenesis and neuronal differentiation, to inhibit apoptosis and to reduce stroke size.”

2. A table summarizing the agents and major findings of the studies that are described in the text will improve the manuscript and make it more accessible to readers.

We added a relevant Table.

Reviewer 00500972

This is a well written manuscript commenting on a recent preclinical paper suggesting favorable effects of linagliptin on stroke.

We thank this Reviewer for these positive comments.

1. The paper should include a more critical assessment of the preclinical effects in light of the recent larger published CV outcome trials with Saxagliptin and Alogliptin where no favorable effect on overall CV or stroke were observed.

We thank this Reviewer for raising this important point. We mention in the Abstract “Despite these preclinical findings suggesting neuroprotective effects of DPP-4 inhibitors in acute stroke, it is still unclear whether these actions will also be observed in humans. Of note, two recent large randomized, placebo-controlled studies did not show any effect of DPP-4 inhibitors on cardiovascular events, including stroke. Several other ongoing trials are evaluating the effects of DPP-4 inhibitors on cardiovascular morbidity or mortality. These studies also provide a major opportunity to assess whether patients treated with this class of antidiabetic agents will suffer from less severe strokes and whether their outcome after stroke will be more favorable.” We also mention in the text (page 9, third paragraph) “Despite these promising preclinical findings suggesting neuroprotective effects of DPP-4 inhibitors in acute stroke, it is still unclear whether these actions will also be observed in humans. Interestingly, a recent randomized double-blind study showed that the addition of linagliptin to metformin reduces the risk of non-fatal stroke more than the addition of glimepiride despite comparable decreases in HbA_{1c}. Preliminary data also suggest similar reductions in stroke risk with other DPP-4 inhibitors. However, these studies was neither planned nor powered to assess the effects of DPP-4 inhibitors on cardiovascular events. On the other hand, two recent large randomized, placebo-controlled studies did not show any benefit of DPP-4 inhibitors on cardiovascular events, including stroke. Several other ongoing trials are evaluating the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality. These studies also provide a major opportunity to assess whether patients treated with this class of antidiabetic agents will suffer from less severe strokes and whether their outcome after stroke will be more favorable.”

2. In light hereof the authors are encouraged to be more cautious e.g. when suggesting that these preclinical observations have important clinical implications.

We changed the statement “might have important clinical implications” to “appear promising” in both the Abstract and in the text.

3. When demonstrating an effect vs. glimepiride this may not mean that there is a positive effect in itself - the observation could due to a negative effect of glimepiride, and some comment on whether a similar effect would have been seen vs. metformin in mice is suggested.

We added in the text (page 9, second paragraph) “Another possible explanation of the different effects of linagliptin and glimepiride on stroke volume is that glimepiride

exerts detrimental effects rather than that linagliptin is protective. Indeed, several recent studies suggested that patients treated with sulfonylureas have increased cardiovascular morbidity compared with patients treated with metformin. Therefore, it would be of interest to compare the effects of prior treatment of DPP-4 inhibitors with prior treatment with metformin in experimental models of stroke or in patients who suffer a stroke."

Reviewer 00102794

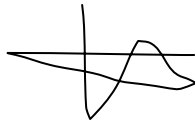
Very well written paper. I have no specific comments or suggestions. I think it's publishable as is.

We thank this Reviewer for these positive comments.

3 References and typesetting were corrected.

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

Sincerely yours,

A handwritten signature in black ink, consisting of a series of loops and a horizontal line, representing the name Konstantinos TZIOMALOS.

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