July 2, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: esps-10775-review.doc).

Title: Type 2 diabetes is associated with worse functional outcome of ischemic stroke

Author: Konstantinos Tziomalos, Marianna Spanou, Stella D. Bouziana, Maria Papadopoulou, Vasilios Giampatzis, Stavroula Kostaki, Vasiliki Dourliou, Maria Tsopozidi, Christos Savopoulos, Apostolos I Hatzitolios

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 10775

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers
<u>**Reviewer 00043561**</u>
I carefully read the manuscript by Tziomalos et al. They present valuable data regarding the outcome expectations for T2DM patients after having an ischemic stroke. Such studies are important especially when they come from different populations.
We thank this Reviewer for stating that we "present valuable data regarding the outcome expectations for T2DM patients after having an ischemic stroke." and that "Such studies are important especially when they come from different populations."

However, subjects with diabetes have different risk profiles according to the duration as well as severity of the disease. Therefore, I need to point on some points that could be improved in the manuscript. 1. The article needs some classified evaluations regarding the severity of diabetes, based on HbA1c categories, presence of complications, and disease duration. As an example, I see there were no differences between the diabetics and non-diabetics regarding established CKD, but weren't there also no differences with respect to proteinuria? Do we know whether presence of proteinuria does not affect outcome? 2. This may also be true for the disease duration. The authors could easily examine whether disease duration of longer than 10 years could have a worse outcome or not. 3. HbA1c values above 9% versus below 9% would also worth evaluation regarding the study outcomes. 4. These analyses could be performed by binary logistics using multiple models. In such case, we could still discuss whether the study sample was sufficient or not but this would be only a limitation. In its present form, the study lacks some major answers for the readers of the journal.
We thank this Reviewer for these constructive comments. We added in the Results (page 8) a paragraph where we mention "We also evaluated whether T2DM duration and glycemic control were associated with stroke severity and outcome. At admission, the NIHSS score did not differ between patients with T2DM duration > 10 years (n = 64, 41.3% of patients with T2DM), patients with T2DM duration ≤ 10 years and patients without T2DM (8.8±9.0, 7.7±8.2 and 8.6±9.2, respectively;

p = NS) or between patients with T2DM and HbA$_{1c}$ > 9% (n = 28, 18.1% of patients with T2DM), patients with T2DM and HbA$_{1c}$ ≤ 9% and patients without T2DM (8.4±9.8, 10.6±9.5 and 8.6±9.2, respectively; p = NS). In univariate analysis, the duration of hospitalization, the mRS score at discharge and the rates of adverse outcome at discharge did not differ between patients with T2DM duration > 10 years, patients with T2DM duration ≤ 10 years and patients without T2DM. In multivariate analysis, both patients with T2DM duration > 10 years and patients with T2DM duration ≤ 10 years had higher risk for adverse outcome than patients without T2DM (RR 2.66, 95% CI 1.17-6.08 and RR 2.60, 95% CI 1.05-7.49, respectively; p = 0.030). The risk for adverse outcome did not differ between patients with T2DM duration > 10 years and patients with T2DM duration ≤ 10 years. In contrast, in-hospital mortality rates did not differ between patients with T2DM duration > 10 years, patients with T2DM duration ≤ 10 years and patients without T2DM in either univariate or multivariate analysis. The duration of hospitalization, the mRS score at discharge and the rates of adverse outcome at discharge and in-hospital mortality also did not differ between patients with T2DM and HbA$_{1c}$ > 9%, patients with T2DM and HbA$_{1c}$ ≤ 9% and patients without T2DM in either univariate or multivariate analysis." Regarding proteinuria, we did not evaluate urinary albumin excretion in all patients and therefore we added a limitations section in the Discussion (page 10, last paragraph) where we state "Since we did not evaluate urinary albumin excretion in all patients, we were not able to evaluate the effects of albuminuria on stroke severity or outcome."

<u>Reviewer 00506294</u>

The manuscript entitled: "Type 2 diabetes is associated with worse functional outcome of ischemic stroke" has been done to assess whether ischemic stroke severity and outcome is more adverse in patients with type 2 diabetes mellitus. The authors studied prospectively 482 patients 40.2% males, aged 78.8±6.7 years, 155 with type 2 diabetes and studied them with complete methodology. Stroke severity was evaluated with the National Institutes of Health Stroke Scale score at admission. The outcome was assessed with the Rankin scale score at discharge and with in-hospital mortality. They also studied adverse outcome and the length of hospitalization. The main findings of the study are that the severity of ischemic stroke does not appear to differ between patients with type 2 diabetes and those without type 2 diabetes, but type 2 diabetes independently portends more adverse functional outcome at discharge in this population. This is an important conclusion and accordingly, management of hyperglycemia might have beneficial effects in patients with acute ischemic stroke, but this is not yet completely established.

We thank this Reviewer for her/his positive comments.

<u>Reviewer 00504772</u>

In this manuscript, the authors tried to analyze the effects of T2DM on the severity of stroke and stroke outcomes. They concluded that T2DM does not affect stroke severity but is an independent factor associated with worse functional outcome at discharge. The research is highly clinical relevant.

We thank this Reviewer for stating that "The research is highly clinical relevant."

However I have following concerns. 1. Please describe the criteria that were used for patient enrollment.

We mention in the Materials and Methods (page 5, first paragraph) "We prospectively studied all patients who were admitted in our Department with acute ischemic stroke between September 2010 and June 2013".

2. The locations of the stroke were not indicated, which may influence the functional outcomes. The paper showed all patients underwent CT at admission, a second CT was performed if clinically indicated. CT scan alone may not be enough, because most of ischemic stroke do not show changes in CT at admission.

Unfortunately, we did not systemically record the location of the stroke in our patients. This is partly because many patients did not have any abnormalities in the CT at admission, in agreement with the comments of this Reviewer. Accordingly, we added in the Limitations section of the Discussion (page 10, last paragraph) "The location of stroke, which may influence the functional outcome, was not systemically recorded." However, the severity of stroke was assessed with the NIHSS score at admission in all patients and we believe that the NIHSS is an accurate surrogate marker of stroke location and that it accurately reflects stroke severity.

3. The authors did not mention what treatments were given to these patients.

We added in the Materials and Methods section (page 5, last paragraph) "All patients without atrial fibrillation were treated with aspirin; clopidogrel was given to patients intolerant to aspirin. Patients who were on aspirin prior stroke were switched to clopidogrel and vice versa. Patients with atrial fibrillation were treated with low-molecular weight heparin. All patients were given a statin. Antihypertensive agents were discontinued during the acute phase of stroke except beta-blockers. Most patients with T2DM were treated with insulin during the acute phase of stroke. No patient underwent thrombolysis."

4. The mRS score may not be a good method to evaluate outcomes of these patients, because stroke patients were discharged 7 days later. NIHSS may be a better way for the evaluation.

We added in the Results (page 7, second paragraph) "The NIHSS score at discharge was also comparable in patients with and without T2DM (6.2±6.4 and 6.0±6.2, respectively; p = NS)."

Reviewer 00113121

The authors present a systematic study with the aim to estimate the clinical profile and prognosis of stroke in patients with diabetes mellitus. Of the 482 acute ischemic stroke patients included in the analysis, 155 (32.2%) had diabetes mellitus, and diabetes mellitus was associated with worse functional outcome at discharge. The study is potentially interesting but can be improved if the following considerations are addressed: 1. It would be interesting to know the frequency of the different ischemic stroke subtypes (lacunar, atherothrombotic, cardioembolic, infarcts of unusual etiology and infarcts of unknown etiology) in the study sample.

We thank this Reviewer for stating that "The study is potentially interesting". Since imaging of the intra- or extracranial arteries was not performed in all patients, we cannot determine the frequency of the different stroke subtypes in our population. We mention this in the Limitations section in the Discussion (page 10, last paragraph), where we state "Magnetic resonance imaging is not available in our institution and imaging of the intra- or extracranial arteries was not performed in all patients. Therefore, we cannot determine the frequency of the different stroke subtypes in our population."

2. Lacunar infarcts are the ischemic stroke subtype with a better functional prognosis (Expert Rev Neurother 2014;14:261-76); In the discussion, it should be noted that, although diabetic patients with stroke have poorer short term functional prognosis, the subgroup of diabetic patients with lacunar infarction shows better functional prognosis (J Neurol. 2005 Feb;252(2):156-62). The inclusion and comment of these two references is recommended.

We thank this Reviewer for this important comment. We now cite these two important references and we mention in the Limitations section of the Discussion (page 10, last paragraph) "Although diabetic patients had poorer short-term functional prognosis in our population, previous studies showed that the subgroup of diabetic patients with lacunar infarction shows better outcome. However, magnetic resonance imaging is not available in our institution and imaging of the intra- or extracranial arteries was not performed in all patients. Therefore, we cannot determine the frequency of the different stroke subtypes in our population."
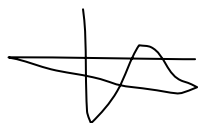
3. A recently published study on impact of female gender on prognosis in type 2 diabetic patients with ischemic stroke should be also commented in the Discussion (Eur Neurol 2006; 56; 6-12).
We now comment on this interesting study in the Discussion (page 9, second paragraph) and we state "Indeed, among patients with T2DM who suffer an ischemic stroke, women have less favorable prognosis than men."

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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