June 09, 2020

Prof. Enrique Fisman

Editor-in-Chief

*Cardiovascular Diabetology*

Dear Editor:

Please find enclosed our manuscript entitled “Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial,” which we request you to consider for publication as an *Original Investigation* in *Cardiovascular Diabetology*.

For the first time, we have studied the effects of an SGLT2 inhibitor, empagliflozin in human patients with type 2 diabetes mellitus and acute myocardial infarction (AMI) in a 6-month double-blind, randomized, placebo-controlled trial. We evaluated changes in heart rate variability, such as the 5 minutes average NN interval and the low-frequency to high-frequency ratio from baseline to 24 weeks as the primary endpoint and changes in other sudden cardiac death surrogate-markers such as heart rate turbulence from baseline to 24 weeks as the secondary endpoints. The empagliflozin-allocated group exhibited significant suppression in the heart rate variability and heart rate turbulence as cardiac sympathetic hyperactivity, but not placebo group. We propose that the decrease in cardiac sympathetic hyperactivity associated with empagliflozin may contribute to the prevention of cardiovascular events including sudden cardiac death observed in patients with type 2 diabetes and AMI treated with SGLT2 inhibitors.

We believe that this is the first trial to provide randomized clinical data in humans demonstrating that empagliflozin might be suppressed the cardiac sympathetic hyperactivity. Based on the findings of our study, we suggest that early SGLT2 inhibitor administration to AMI patients is not only safe but also effective.

The EMBODY trial was registered by the UMIN in November 2017 (ID: 000030158). <https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034442>.

This manuscript has not been published elsewhere and is not under consideration by another journal. We have approved the manuscript and agree with submission to *Cardiovascular Diabetology.* One author has received honorariums and research grants from Boehringer Ingelheim. This trial is funded by Boehringer Ingelheim and Eli Lilly and Company. The funding agencies had no role in designing or conducting the trial.

We believe that the findings of this study are relevant to the scope of your journal and will be of interest to its readership. The manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by scientists whose native language is not English. We have no conflicts of interest to declare.

We look forward to hearing from you at your earliest convenience.

Sincerely,

Wataru Shimizu

Department of Cardiovascular Medicine, Nippon Medical School

1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-0022, Japan

Phone No: +81-3-3822-2131

Fax No: -81-3-5814-6050

Email address: wshimizu@nms.ac.jp