UNIVERSITY OF PUERTO RICO, UNIVERSIDAD DE PUERTO RICO
MEDICAL SCIENCES CAMPUS, RECINTO DE CIENCIAS MÉDICAS
SCHOOL OF MEDICINE, ESCUELA DE MEDICINA

Department of Physiology
Departamento de Fisiología

June 15, 2015

Eduardo H Garin, MD
Editor-in-chief
World Journal of Diabetes
Professor
Department of Diabetes
University of Florida
Gainesville, FL 32610

RE: Manuscript #18617

Dear Dr. Garin:

Please find enclosed the revised version of our manuscript entitled, "Simvastatin, Atorvastatin, and Pravastatin Equally Improve the Hemodynamic Status of Diabetic Rats". Our responses below to the reviewer's recommendations are indicated in red type in the manuscript.

Please note that the manuscript title was changed to comply with the 12 word limit.

Answers to Reviewer #1:

Point #1: **There are some spelling mistakes in the text. I recommend accepting this manuscript with minor revision.**

A spellcheck was performed on the manuscript and the spelling mistakes were corrected.

Answers to Reviewer #2:

Point #1: The all statins were dissolved in corn oil. Pravastatin is water-soluble-statin and should be dissolved in water not corn oil.

Page 4, last line, we substitute the word "dissolved" with "suspended". In the revised manuscript, the new sentence reads: "The statins were suspended in corn oil and administered by gavage at a dose of 10 mg/kg/day".

The latter reflects the fact that although pravastatin is not soluble in corn oil, the animal received the desired dose because the suspension was administered by gavage.

Point #2: In the present study, statins did not modify plasma cholesterol levels in either diabetic or CT rats. It would be better to add the data about plasma triglyceride, HDL and FFA.

Total cholesterol was evaluated because it has been associated with CV complications in diabetes. The use of statins at a low dose, which is sub-optimal to reduce cholesterol levels, allowed us to assess the effect of these drugs on the CV system independently of the benefits derived from cholesterol reduction.

We agree with the reviewer's comment regarding the value of data on triglycerides, HDL, and FFA. Although worthy of future experiments, gathering the necessary data is beyond the scope of the current study.

Point #3: In table 3 and Table 4, is there no change between Diabetic+statins and CT+statins when compared to age-matched CT?

Following the reviewer's suggestion, we have added the statistical comparison between treated diabetic and CT rats in both Table 3 and Table 4.

Point #4: Whereas SBP was also higher in diabetic rats, it was significantly reduced by all three statins. It would be better to discuss the pathophysiological mechanisms in greater detail.

The following paragraph was added on page 12, at the end of the first paragraph of the Discussion.

In addition, although the etiology of hypertension is largely unknown, oxidative stress, endothelial dysfunction, and structural alterations of the vasculature have been associated with hypertensive pathophysiology. Thus, the reduction of oxidative stress and vascular remodeling, together with the improved endothelial dysfunction observed following statin treatment, may underlie the reduced SBP found in diabetic rats.

Point #5: STZ mice are diabetic model of Type-1 diabetes. Similar results are also obtained in Type-2 diabetic model? Some comments would be helpful.

As pointed out on page 13 in the second paragraph of the Discussion, the STZ-diabetic rat model is widely used in experimental studies because it replicates both type 1 diabetes and poorly-controlled Type 2 diabetes. Although the etiology of Type 1 and Type 2 diabetes is different, oxidative stress is high in both conditions. The CV benefits after statin administration observed in the current study appear to be related to improved vascular function that is secondary to reduced oxidative stress. Thus, it is plausible to postulate that Type 2 diabetics also may benefit from statin treatment.

The following sentences were added in the last paragraph of the Discussion (page 13).

"Although the etiology of Type 1 and Type 2 diabetes is different, in both conditions oxidative stress is high. Thus, it is plausible to postulate that Type 2 diabetics also may benefit from statin treatment."

Answers to Reviewer #3:

No changes were requested.

We hope that we have adequately addressed the concerns of the reviewers. Thank you, once again, for considering our manuscript for publication in *World Journal of Diabetes.*

Sincerely yours,

María José Crespo, PhD, FAHA
Professor