Format for ANSWERING REVIEWERS

July 15, 2015

Dear Editor,

Please find enclosed the edited manuscript in word format (14813-Review)

Title: Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research

Author: Benjamin M Leon, Thomas M Maddox

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 14813

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

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer:

(1) Reviewer suggestion: Page 4 line 26, the authors describe the technique used in the cited articles as: Doppler strain analysis of peak systolic velocity. However, in these papers Tissue Doppler Imaging rather than strain analysis has been used. The systolic function was evaluated by strain technique in other studies (Ng AC et al. Circulation. 2010;122:2538-44. Ernande L et al. J Am Soc Echocardiogr. 2010; 23: 1266-72. Ng AC et al. Am J Cardiol. 2009;104:1398-401).
Revision: "Subtle abnormalities in systolic function have also been observed in patients with DM using tissue Doppler imaging and Doppler strain analysis of peak systolic velocity."

(2) Reviewer suggestion: In the section focusing on treatment of arterial hypertension it should be mentioned the possible metabolic differences among antihypertensive drugs.
Revision: "While different antihypertensive agents used to treat hypertension have varying metabolic effects, many studies, including the ALLHAT trail, found no significant difference in the risk of coronary heart disease, nonfatal myocardial infarction, total mortality, or other clinical complications attributable to the initial antihypertensive drug therapy used to treat diabetic patients. This would suggest that metabolic differences between the various antihypertensive agents do not play a major role in the subsequent development of CVD in patients with DM."

(3) Reviewer suggestion: In the section dedicated to lipid lowering treatment the possible LDL targets should be better described.
Revision: "Dyslipidemia is both common in patients with DM and associated with increased risk of CVD. Health providers are encouraged to identify and aggressively treat patients with dyslipidemia

to help diminish their risk of subsequent CV events. The current recommendation for treating dyslipidemia in diabetic patients varies by age and is in line with recognition that treatment with fixed-dose statins, rather to specific LDL target levels, is the validated approach from clinical trials. Accordingly, diabetic patients who are under the age of 40 are recommended to take a high-intensity statin if they have clinical evidence of atherosclerotic CVD or a LDL-C greater than 189 mg/dl. All diabetic patients over the age of 40 are encouraged to begin statin therapy. Patients over 40 with an estimated 10-year ASCVD risk greater than 7.5% are treated with a high-intensity statin, and patients with a 10-year ASCVD risk less than 7.5% are treated with a moderate-intensity statin."

(4) Reviewer suggestion: The results of the recent trial IMPROVE-IT in the subgroup of diabetic patients should be added.
Revision: "Some trials have also investigated if additional CV benefit can be achieved in patients with DM by combining a statin with other lipid-lowering therapies. For example, the IMPROVE-IT trial found that the combination of ezetimibe (a cholesterol absorption inhibitor) with simvastatin was superior to simvastatin alone in reducing CV events for diabetic patients with acute coronary syndrome (ACS)."

(5) Reviewer suggestion: The other thing is that since you assess the CV field some brief remarks on prevention/early diagnosis would improve the paper. I mean, when a patient is diagnosed as diabetic, what are the next steps regarding the CV área (stress test, statins, aspirin?..)
Revision: "As CVD is the most prevalent cause of mortality and morbidity in patients with DM, effective treatment is critical to lower the subsequent risk of CV events, particularly MI, CAD, stroke and CHF in diabetics. Suboptimal glycemic control, obesity, hypertension, dyslipidemia and autonomic dysfunction are common CV risk factors among diabetic patients, placing them at heightened risk of CV complications. Therapy that is targeted to modify these risk factors can improve CV outcomes, but this can be a challenging to achieve. The guidelines pertaining to these risk factors typically vary from the guidelines for non-diabetic patients and the recommendations often change or differ depending on what organization publishes them. In addition, the research on how these different risk factors affect the CV risk profile of diabetics can be unclear, and at times, contradictory. The purpose of this section is to provide the most recent guidelines for the treatment of glycemic control, hypertension, dyslipidemia and autonomic dysfunction in patients with DM, and also describe the research that pertains to each of these topics."

(6) Reviewer suggestion: In "Treatment", the author discussed glycemic control, treatment of obesity, hypertension, and dyslipidemia. Would you please add some information about the treatment of diabetic cardiomyopathy, cardiovascular autonomic neuropathy…as mentioned in "CY Risk Factors and CV Disease".
Revision: "CAN is a common complication of diabetes and places patients with DM at increased risk of CV related morbidity and mortality. The autonomic dysfunction commonly found in diabetic patients is associated with a high risk of cardiac arrhythmias and sudden death, as well as other serious CV sequelae including silent myocardial ischemia, diabetic cardiomyopathy, stroke, and both intraoperative and perioperative cardiovascular instability. Some of the most common clinical manifestations of CAN include heart rate variability (variability in the instantaneous beat-to-beat intervals), resting tachycardia, exercise intolerance, orthostatic hypotension and abnormal blood pressure regulation.

Early treatment of autonomic dysfunction can slow the pathogenesis and complications of CAN. Some studies have shown that tight glycemic control may play an important role in reducing the incidence of CAN in patients with DM. For example, the DCCT demonstrated that patients with better glycemic control, as measured by Hba1c, had significantly lower risk of developing autonomic dysfunction according to a CAN index. While the effect of glycemic control on CAN in patients with T2DM have been less conclusive, some trials, including the Steno-2 study found that improving glucose control and other CV risk factors reduced the prevalence of CAN in T2DM patients. Lifestyle interventions that focus on improving exercise endurance and promote weight loss have also improved autonomic dysfunction. Pharmacological therapy including ACE inhibitors, angiotensin receptor blockers and aldose reductase inhibitors also appear to help slow the progression of CAN. In addition, IGF-1, ACE inhibitors and beta-blockers appear to be beneficial in the treatment of diabetic cardiomyopathy by slowing ventricular hypertrophy and normalizing the calcium homeostasis in diabetic cardiomyocytes. Further studies are necessary, however, to validate what the best pharmacological treatment is for diabetic patients with CAN."

(7) Reviewer suggestion: In "Future directions in the treatment of DM", the author only talked about glycemic control and CVD benefit. What about the other risk factors?
Revision: "Further research is also necessary to determine what the best treatment is to decrease the risk and severity of cardiomyopathy and CAN in patients with DM. Many studies have demonstrated that autonomic dysfunction and diabetic cardiomyopathy are disease processes that are not only common in patients with DM, but also place them at increased risk of subsequent CV complications. Lifestyle modification, tighter glycemic control and pharmacological agents appear to provide some benefit in slowing the progression of CAN and diabetic cardiomyopathy. However, few studies have investigated what specific therapy is most effective in treating these conditions, as well as what might be done to prevent the development of these disease processes altogether.

Additional research is also needed to better understand how traditional CV risk factors including dyslipidemia, obesity and blood pressure should be monitored and managed in diabetic patients. For example, combination therapy may be the best way to treat dyslipidemia, contrary to the current recommendation that focuses primarily on statin mono-therapy. More studies like IMPROVE-IT could help determine what therapy is most effective to manage dyslipidemia in diabetic patients. In addition, the role of HDL on CV health is complicated, and further investigation is necessary to determine if pharmacological agents designed to increase HDL can provide clinical benefit in diabetic patients. The effect of weight loss in patients with DM is also somewhat unclear as to if, and how much, weight loss is necessary to achieve clinically significant improvements in CV outcomes. Five percent weight loss may not be sufficient for diabetic patients with other CV risk factors and comorbidities. Further studies are needed to determine what amount of weight loss is needed attain CV benefit, and what the best treatment method is to reach that weight loss goal. Finally, follow-up regarding the new blood pressure guidelines, particularly in adults over 60 yo who now fall under the higher systolic BP threshold, will need to be closely monitored moving forward."

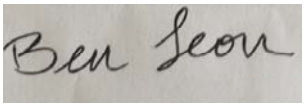
(8) Reviewer suggestion: What is you opinion about the relationship between HFpEF and diabetes?
Revision: "It is likely that many of the mechanisms that contribute to reductions in systolic and diastolic function seen in diabetic patients also place them at an increased risk of heart failure (HF). The prevalence of HF, particularly heart failure and preserved ejection fraction (HFpEF), is higher in diabetic patients (16-31%) than the general population (4-6%). While some of the difference may be

accounted for by traditional CV risk factors, DM may independently alter cardiac structure and function by promoting hypertrophy and fibrosis."

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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