Professor Dimitris Tousoulis MD, PhD

1st Cardiology Clinic, 'Hippokration' General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

e-mail: drtousoulis@hotmail.com

To:

World Journal of Diabetes

Athens, February 2023

Dear Editor-in-Chief,

We would like to thank you for the thoughtful evaluation of our review article entitled "**Diabetes Mellitus and Atrial Fibrillation-From Pathophysiology to Treatment**" and for the most welcome comments that helped us to improve the presentation of our article. We read the comments carefully and we tried to address them all; thus, we are now pleased to submit the revised version of the manuscript for consideration by the World Journal of Diabetes.

Below we provide a point-by-point response to all comments in a separate rebuttal letter. Specifically, please find listed below our point-by point response (in normal font) to the comments (in bold).

A potential publication of our work in your journal would be great honor for our study group.

We thank you for your time and consideration on our behalf.

Sincerely yours,

Professor Dimitris Tousoulis

Reviewer #1:

This interesting review presents the current evidence regarding the connection between diabetes and AF and discussing the therapeutic options. It is with significant importance for the treatment of cardiometabolic disease. The manuscript was well written. I have some suggestions for revision.

Reply: We would like to thank the reviewer for his/her overall impression on our manuscript. Please find below a point-by-point response to the issues raised.

1. A figure summarized the mechanisms between the association between DM and AF is needed. It is important for the readers to get the key messages from the review.

Reply: We agree with the reviewer that a figure is needed to better illustrate the mechanisms of AF development in DM. A diagram displaying the pathophysiology of this interaction has been created, in addition to the information provided in table 1.

Please see the new Figure 1.

2. It is important to summarize the biomarkers in the risk prediction and management of DM with AF. For example, adipokines are important in this field. Recently, some novel adipokines (PMID: 34790288; PMID: 32842761) had been reported in the risk prediction and management of cardiometabolic disease (e.g, diabetic cardiomyopathy).

Reply: We would like to thank the reviewer for this important remark. We proceeded to elaborate a bit more on biomarkers in the revised manuscript version. However, no specific studies have assessed those biomarkers in the specific subgroup of DM patients with respect to AF development.

Please see the revised "PATHOPHYSIOLOGY" section:

"A high oxidative stress burden can both result in and aggravate pre-existing inflammation and inflammatory markers such as C-reactive protein and tumor necrosis factor (TNF)-α, associated with left atrial dilatation and increased AF incidence[23-25]."

"We should also mention that the levels of myocardial fibrosis biomarkers, including ST2 and galectin-3, could indicate structural remodeling[25]."

"Other adipokines, such as secreted frizzled-related protein 5, may represent important biomarkers in the risk prediction and management of diabetic complications such as heart failure[48], since they are implicated in mitochondrial energetics, oxidative stress, and apoptosis pathways[49]. However, their role in AF has not been thoroughly assessed."

3. Even in patients with prediabetes, the risk of CVD and HF (PMID: 32669282; PMID: 33769672) was increased. Is it similar for AF？

Reply: As correctly stated by the revised, prediabetes is also associated with cardiovascular complications. This extends to AF patients, as seen in various studies. The review has been updated to reflect this information.

Please see the revised "AN ASSOCIATION BETWEEN AF AND T2DM" section:

"Interestingly, prediabetes, a condition that is also associated with heart failure[14], cardiovascular and all-cause mortality[15], may drive the development of AF[16]."

4. The authors had discussed that obesity and insulin resistance may play a link for DM and AF. Similar, nonalcoholic fatty liver disease is associated with increased risk of atrial fibrillation (PMID: 32279432). Is there an interaction?

Reply: We apologize for our negligence to stress the role of NAFLD in AF development. Since NAFLD is largely related to insulin resistance and obesity, it is also related to incident AF. This has now been addressed in the revised manuscript version.

Please see the revised "Glycemic parameters" section:

"Insulin resistance and adiposity are also considered main contributors to nonalcoholic fatty liver disease development, a condition that is linked to AF development[50]."

Reviewer #2:

1.It would be more appropriate to change the contents of Table 2 to those related to treatment

Reply: We would like to thank the reviewer for this comment. We followed the reviewer's recommendation and now Table 2 displays the impact of glucose lowering therapies in AF development.

Please see the revised Table 2.

2.Draw a figure to describe the pathophysiological mechanism of the relationship between DM and AF in detail

Reply: We agree with the reviewer that a figure is needed to better illustrate the mechanisms of AF development in DM. A diagram displaying the pathophysiology of this interaction has been created, in addition to the information provided in table 1.

Please see the new Figure 1.

3.The manuscript should talk about correlation of DM and AF first, then pathophysiological mechanism

Reply: We totally agree with the reviewer about the rearrangement of sections in our manuscript and we apologize for this mistake. According to his/her suggestion, this issue has been resolved in the revised manuscript version.

4.The structure of the pathophysiological mechanism is not very clear, because the correlation is bidirectional. Will AF patients develop into DM? What is the mechanism?

Reply: We thank the reviewer for this comment. While the bidirectional relationship between DM and AF could be hypothesized, there is no evidence in the literature suggesting

this (AF patients developing T2DM). An assumption has been added in the revised manuscript version.

Please see the revised "AN ASSOCIATION BETWEEN AF AND T2DM" section:

"While there is significant evidence pointing concerning the high rates of AF among individuals with T2DM, there is no data on the prevalence of T2DM among AF populations. Thus, the bidirectional relationship of those two entities could only be speculated at present."

Reviewer #3:

The topic of this article is very interesting, but there are still some issues that need to be clarified and further explain in the manuscript.

Reply: We would like to thank the reviewer for his/her overall impression on our manuscript. Please find below a point-by-point response to the issues raised.

1.the term of "DM" is type1 or 2?

Reply: The reviewer has raised an important concern. We have now indicated the type of DM (T2DM, T1DM) throughout the manuscript.

2.if the "DM" is type 2, how does the "glucose-lowering therapies " affect the ROS , or patients' HBA1C?

Reply: We thank the reviewer for this important comment. In the revised manuscript, we briefly state the main hypoglycemic mechanism of action of the mentioned drug categories, while also adding information regarding potential antioxidant effects, where they have been studied.

Please see the revised "Antidiabetic drugs" section:

"By inhibiting hepatic gluconeogenesis, opposing the action of glucagon, and increasing insulin sensitivity, it exerts its glucose-lowering action."

"Several mechanisms have been implicated, including the prevention of the structural and electrical remodeling of left atrium via attenuating intracellular reactive oxygen species, activation of 5′ adenosine monophosphate-activated protein kinase, improvement of calcium homeostasis, attenuation of inflammation, increase in connexin-43 gap junction expression, and restoration of small conductance calcium-activated potassium channels current[52]."

"Thiazolidinediones (TZD) increase insulin sensitivity by acting on adipose, muscle, and, to a lesser extent, liver to increase glucose utilization and decrease glucose production. Antioxidant effects may be additionally evident, through proliferator-activated receptor-γ agonism and stimulation of catalase[53]."

"On the other hand, sulfonylureas, a widely prescribed second-line hypoglycemic drug category that directly stimulates release of insulin from pancreatic beta cells, is not associated with a lower risk for AF[56]."

"Moving to novel antidiabetic agents, dipeptidyl peptidase-4 (DPP-4) inhibitors are glucose lower agents that inhibit DPP-4 activity in peripheral plasma, which prevents the inactivation of the incretin hormone glucagon-like peptide-1 (GLP1) in the peripheral circulation."

"Another new class of antidiabetic drugs, GLP1 receptor agonists, are a potent glucose-lowering option by stimulating glucose-dependent insulin release from the pancreatic islets. They exhibit many cardioprotective effects, including antioxidant responses through upregulation of antioxidant substances (catalase, glutathione peroxidase)[63]."

"Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower plasma glucose levels by blocking reabsorption of filtered glucose at the level of the kidneys. These agents have established cardioprotective effects[67, 68], which are dependent on numerous molecular mechanisms, including restoration of beneficial autophagy, antioxidant[63], anti-inflammatory[69, 70], and anti-fibrotic responses."

3. what is the possible direct mechanism of "glucose-lowering therapies " in AF?

Reply: The direct antiarrhythmic effects of glucose-lowering therapies are a topic of continuous research, with incompletely understood mechanisms. In the revised manuscript, we present such possible mechanisms where available.

Please see the revised "Antidiabetic drugs" section:

"Several mechanisms have been implicated, including the prevention of the structural and electrical remodeling of left atrium via attenuating intracellular reactive oxygen species, activation of 5′ adenosine monophosphate-activated protein kinase, improvement of calcium homeostasis, attenuation of inflammation, increase in connexin-43 gap junction expression, and restoration of small conductance calcium-activated potassium channels current[52]."

"They are also associated with a lower risk of new-onset AF, possibly due to their anti-fibrotic effect[54]"

"Experimental studies have been conducted to assess the anti-arrhythmic mechanisms of SGLT2 inhibitors. Shao et al. initially demonstrated the reversal of atrial structural and electrical remodeling induced by T2DM in rats following treatment with empagliflozin. This effect was possibly mediated by the peroxisome proliferator-activated receptor-c coactivator 1α/nuclear respiratory factor-1/mitochondrial transcription factor A signaling pathway[82]. Moreover, the administration of canagliflozin in an experimental model of rapid atrial pacing resulted in a diminished atrial refractory period reduction, suppressed AF inducibility, attenuated atrial interstitial fibrosis, and oxidative stress[83]. A decreased inducibility and duration of pacing-induced AF were also reported in a rat model of mitral regurgitation following treatment with dapagliflozin[84]."