

## Response to reviewers point by point

### ***Reviewer #1:***

This is a comprehensive review of the literature regarding the cardiac effects of hyperglycemia, hypoglycemia, and glycemic variability. The text is clear. The author reports both the epidemiological findings and the underlying biochemical mechanisms. To be accepted with minor changes For the authors: The authors are to be congratulated for this review. We liked the fact that they detailed the biochemical mechanisms for understanding how changes in blood glucose levels can affect cardiac function.

**Point 1-** Page 5: High glycemic variability appears to exert more detrimental effects than persistent hyperglycemia on the pathogenesis of diabetic complications [7, 8], and also has been associated with an increased risk of cardiac arrhythmias than those with good glycemic control [9]. Better to say “and has also been associated with an increased risk of cardiac arrhythmias compared to those with good glycemic control.”

**Author’s response:** We thank the Reviewer very much for this comment. We have revised the corresponding section according to the suggestion (Page 5, Line 82-83).

**Point 2-** Page 6: As for the overt DM, numerous studies have shown that diabetes is associated with an increased risk of AF and has been considered a risk factor for AF in healthy individuals and hospitalized patients[10, 15, 16]. Further develop that to such an extent that diabetes is included in the CHADVASC, CHARGE AF, CHEST, and MR DASH scores that assess the chances of developing AF in future years.

**Author’s response:** We thank the Reviewer very much for this valuable comment. We have added further discussion about the prediction value of diabetes in AF according to the suggestion in Page 6, Line 137-139 – “Diabetes is included in the CHA2DS2-VASc, CHARGE-AF, and MR DASH scores which have been established to predict the chances of developing AF [17, 18]”.

### ***Reviewer #2:***

In this review authors discuss about the various implications of glycemic control with cardiac arrhythmia. This is an interesting work and I congratulate the authors for their effort. I have the following recommendations:

**Point 1-** In methodology mention manuscript of which languages were used? Which all articles were included metanalysis, RCT, cohort studies, cross sectional studies, retrospective, prospective studies, case reports?

**Author’s response:** We thank the Reviewer very much for this comment. The literature search in this

review was restricted to English. No restriction of the study type was applied in this review, namely that relevant meta-analysis, RCT, cohort studies, cross sectional studies, retrospective, prospective studies, case reports were included. We have added further description about the search strategy in the Method section. In addition, we have added information about the included studies regarding the associations between hyperglycemia, hypoglycemia, and glycemic variability with arrhythmias in Supplemental Table 1-3, respectively.

**Point 2-** Mention what was included and what was excluded. How many people screened the articles? please change the time line to the duration of the first article to the November 2022 3. Include a section on result and mention: How many articles were found, mention types of articles, how many included and how many excluded.

**Author's response:** We appreciate the Reviewer for this comment. 1) We have clarified the inclusion and exclusion criteria in the Method section as follows: "Studies that focused on the associations between three dysglycemia domains with cardiac arrhythmias were included in this review, without study design restriction. Duplicate records and studies without full-text access were excluded." 2) Two reviewers screened the articles, and discrepancies were resolved by a third author. We have clarified this point in the Method section. 3) We have changed the time line to the duration of the first article (April 1975) to the November 2022. 4) A total of 1,929 records were identified, after excluding duplicates (n=509) and those irrelevant (n=1296), 124 studies were included in this review. We have added further description regarding the included studies in the Result section and Supplemental Table 1-3.

**Point 3-** Include the definitions of hyperglycemia, hypoglycemia and DM based on the blood sugar. Were they similar across all studies if not can mention in limitation 4. Was google scholar used? if not mention in limitation

**Author's response:** We thank the Reviewer very much for this comment. 1) In this review, hyperglycemia mainly includes impaired fasting blood glucose (IFG), impaired glucose tolerance (IGT), and overt diabetes. IFG was defined as a fasting plasma glucose (FPG) level between 110 and 125 mg/dL, according to the 2006 World Health Organization (WHO) guidelines. IGT was defined as FPG <126 mg/dL with 2-h plasma glucose after a 75-g oral glucose challenge of 140-199 mg/dL. Patients with DM were defined as those with a history of physician-confirmed diabetes or history of oral hypoglycemic agent or insulin use. Hypoglycemia is defined as blood glucose concentration less than 70 mg/dL. Glycemic variability refers to intraday or daily blood glucose fluctuation, and months or years of blood glucose fluctuation. At present, the definition of glycemic variability is very vague, and it is mainly measured by indicators such as mean blood glucose and standard deviation, J index and coefficient of variation, postprandial hyperglycemia and mean amplitude of glucose excursion. We have added the detailed definitions of these dysglycemic indexes in the Method section. 2) The definitions of the dysglycemic indexes are consistent in most of the included studies, whereas some minor difference existed in a few studies. We have added this point to the Limitation section. 3) Google scholar was not used in this Review. We have added this point to the Limitation section.

**Point 4-** Consider adding schematic images alike image one which is extremely good.

**Author's response:** We thank the reviewer for this comment. We have added a Graphic abstract figure to help communicate the key messages of our paper to readers.

#### **Editorial office's comments**

Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights.

**Author's response:** We thank the Editor very much for this comment. We have provided the PowerPoint version Figures according to the suggestion. The figures in this manuscript were generated in a de novo manner. We have add the "Copyright ©The Author(s) 2023" to the bottom right-hand side of the picture in PowerPoint.