Peer Review File

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Reviewer A

The authors provided a review regarding diabetes and cardiac surgery, and strategies for glycaemic control in patients undergoing cardiac surgery. The topic is of high interest, since diabetes is a key risk factor in developing a coronary artery disease. Furthermore, it has a high impact on the coronary morphology and long-term outcome, as highlighted in the guidelines on revascularization. The role of diabetes and glycaemic control strategies in patients undergoing cardiac surgery is in consideration of the high morbidity and mortality in these patients a topic of interest.

However, some major concerns appear, reading the review.

COMMENT 1:

- English language has to be improved throughout the manuscript

REPLY: Thank you for your revision. We have made some changes to write the manuscript in a more formal English

CHENGES IN THE TEXT: see parts in red in the text.

COMMENT 2:

- the first part is poorly written, redundant and misses some opportunities. The authors are writing countless times on a poor outcome of patients with diabetes. However, there description misses to dive into the details. Please rewrite the first part, and give detailed explanations and mechanisms, why and how diabetes is affecting which specific adverse outcome. Split this part into the respective sections.

REPLY: I agree with your comment and I have re-written the first part diving more deeply into the explanations and examples of how diabetes leads to worsen outcomes.

CHENGES IN THE TEXT: see lines 84-118

COMMENT 3:

- The Background and Objective of the Abstract should be more precisely articulated to clearly define the significance and necessity of this review.

REPLY: Agreed. I have added more paragraphs to explain the significance of diabetes in the postoperative recovery and also explained more extensively the need of a literature review.

CHENGES IN THE TEXT: see lines 84-118 and 128-132

COMMENT 4:

- Consistency in units is crucial. Please use either mmol/L or % uniformly, or preferably both, where applicable

REPLY: Thank you for pointing this out. I have written both units mmol/mol and %

CHENGES IN THE TEXT: see lines 201, 203, 216, 227, 232, 242, 255.

COMMENT 5:

- In line 175-178 the authors state

"So, for elective patients at least, there is a real opportunity to intervene prior to surgery and it could be argued that not doing so is putting patients at unnecessary risk of harm. But what exactly can be done? Furthermore, optimisation of glycaemic control during the perioperative period should be possible for all diabetic patients regardless of urgency."

-> this statement is worthless without data proving these lines. I agree, that a preoperative optimization is of high importance and will help the patients outcome. But what is the best time interval for which patient. Elective patients, urgent patients, patients with stable multivessel disease or valve stenosis/insufficiency, or NSTEMI, STEMI, endocarditis etc. When will the harm of waiting for treatment will be worse than the adverse outcome due to a badly treatened diabetes. The authors have to stress all available data on this issue, to proof their statement.

REPLY: This is a very good point but unfortunately in the literature we could not find studies looking at when the harm of waiting for surgery will carry more risks than the adverse outcome due to a poorly controlled diabetes. I have added in the text the lack of this information and the need for further studies looking at the best time interval.

CHENGES IN THE TEXT: line 264-272

COMMENT 6:

- Please include the publication years for the cited manuscripts in the tables

REPLY: good point thank you.

CHENGES IN THE TEXT: publication year of each manuscript added to the table.

COMMENT 7:

- Postaggression metabolism due to surgical stress is not even mentioned in the manuscript and has to be included and discussed. Glucose management in the early postoperative period is challenging due to the enhanced catabolic metabolism, even more challenging in patients with poorly managed diabetes at baseline. Unfortunately, the authors missed the opportunity to dig in the postoperative challenges and eventually phrasing a precise recommendation. However, in this review, the authors mainly leave the reader with a general phrase "to lower the HbA1c of the patient" (line 194)

REPLY: I agree that we missed to mention the implications of postaggression metabolism. I have now included it in the manuscript.

CHENGES IN THE TEXT: see lines 95-108

COMMENT 8:

- The authors state

"Empagliflozin and canagliflozin, both SGLT2 inhibitors, demonstrated a significant reduction in a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in the EMPA-REG OUTCOME trial and the CANVAS program, respectively in patient populations with type 2 diabetes and an increased cardiovascular risk [44]. It is thought the beneficial mechanism of action is driven by haemodynamic/metabolic mechanisms of action [46]."

-> In case of SGLT2 inhibitors a more detailed description of the molecular mechanisms is of need to understand the effects. In fact, SGLT2 inhibitors are now recommended with a Class I recommendation for patients with heart failure even in patients with no diabetes. This not fully understood beneficial effects of SGLT2 inhibitors remain not even mentioned by the authors. A more sophisticated description of the SGLT2 inhibitors is needed.

REPLY: I have now added a paragraph addressing the SGLT2 mechanism of action and its benefits in heart failure.

CHENGES IN THE TEXT: see lines 306-320

COMMENT 9:

- the authors state

"continuous glucose monitoring is now also increasingly available for patients with poorly controlled type 2 diabetes. Having this continuous data encourages patients to aim for improved glycaemic control [47]."

-> Unfortunately the consequence is missing. What to do with these data? Should the analysis of these data be part of the surgical department? What changes in the perioperative treatment? Are these data really assessed by the primary care physician?

REPLY: I have looked at the literature and added few lines in this regard

CHENGES IN THE TEXT: see lines 332-338

COMMENT 10:

- The authors state

"To help achieve these goals, some cardiac surgical centres have in-house preoperative optimization programmes to facilitate these efforts, as relying on patients primary care physicians and local hospitals can prove challenging due to capacity and competing requests. The model of having such a service in-house enables focused optimization and in the long run may potentially be cost effective for the cardiac surgical centre through reducing patient complications and postoperative length of stay."

-> Firstly, the key points of the in-house programmes mentioned should be introduced to fulfill the duty of this review. Secondly, the authors just speculate on probable outcomes. Are there any data driven by these centers. Even if not, it is key to state that data on their effect on the outcomes are currently missing. To state these phrases without any reliable data is worthless.

REPLY: I have added the key points of an in-house diabetic management program as well as evidences from the literature which showed that it plays a fundamental role in reducing postoperative complications and improving surgical outcomes.

CHENGES IN THE TEXT: see lines 365-401

Reviewer B

The manuscript is intriguing and timely and deals with a well known issue in the cardiac surgery setting. The manuscript is well written and methodological sound and summarized plainly current evidence on the topic. All in all it is worth of publication in the present form.

REPLY: Thank you.