Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-428

Reviewer A

Thank you for allowing me to review this interesting topic and manuscript. Authors are commended for an extensive review and certainly put in many hours into their work. This is an extremely important topic that is very relevant to the daily practice of every cardiac surgeon. The manuscript is worth publishing, however, several important points/revisions should be strongly considered first:

Comment 1: The manuscript is too long. Needs to be condensed. Many times authors discuss the same topic

Reply 1: We appreciate your constructive remark about the manuscript's length and repetition of topics in different chapters. We addressed this issue by reducing the overall number of words by almost 1000. We explained the necessity to repeat some discussions in Reply 9. The overall word count of the main part of the manuscript (without References and Tables) is now 5.326.

Comment 2: Page 2, line 44: results: the title of the manuscript is "management". The results should mention the "results" in your search in managing patients undergoing cardiac surgery and not just the incidence of bleeding. This is a fundamental point

Reply 2: We are grateful for this remark. Therefore, we rearranged this part of the abstract and rephrased the text about results to correspond with the title. Now, the whole "Results" section reads like this:
"From all reviewed studies, a total of 19 articles could be included evaluating the risk for bleeding in cardiac surgery related to DAPT or DOACs and 10 papers evaluating antithrombotic drug reversal or removal in the setting of cardiovascular surgery. Reported bleeding rates ranged between 18% and 41%. The variability of the reported data is remarkable. Idarucizumab is reported to provide optimal perioperative hemostasis in up to 93% of patients. It has been observed that andexanet alfa causes unresponsiveness to the anticoagulant effects of heparin. Antithrombotic removal by intraoperative hemoadsorption is found to be associated with a significant decrease in re-thoracotomy rate, overall procedure duration, administered transfusion volumes, chest-tube drainage, and length of hospitalization."

Comment 3: Page 2, lines 51-53: "Drug removal via hemoadsorption, however, seems to be 52 a safe and cost-effective option to reduce perioperative bleeding" This statement is not a result. This needs to be modified to show results of using

hemoadsorption and not a conclusion.

Reply 3: We are thankful for this remark. The sentence in question is deleted and this section rephrased (please refer to Reply 2).

Comment 4: Page 3, line 57: “Interestingly, bleeding-related 57 complications can be prevented by applying innovative intraoperative hemoadsorption”:
This sentence should be removed. This is a very strong conclusion that the results of this study did not prove.

Reply 4: This point is well-taken. We rephrased this sentence, and now it reads like this:
“Interestingly, bleeding-related complications seem to be effectively reduced by applying innovative intraoperative hemoadsorption techniques.”

Comment 5: Page 5, line 102: “The only one of these three drugs with a reversible antiplatelet effect is 103 ticagrelor (5).
I believe the reversal medication bentracimab is still not FDA approved. I would add the word “potential” and also mention that the drug is still under consideration by FDA and not approved yet.

Reply 5: Many thanks for this comment. It seems that our wording did not correspond well with what we were trying to say. Ticagrelor is the only oral platelet aggregation inhibitor that reversibly binds to $P2Y_{12}$-receptor on platelets. Clopidogrel and Prasugrel inhibit platelets irreversibly. This part elaborates on reversibility/irreversibility of the antiplatelet effect and it is not about the reversal agents. We changed this sentence accordingly:
“The only one of these three $P2Y_{12}$ receptor antagonists that reversibly binds to platelets is ticagrelor.”

Comment 6: Page 6, line 140: Why did you only include ticagrelor and not include other antiplatelet medications as aim of the study? You discussed them in other parts of your manuscript.

Reply 6: Thank you very much for this well-founded question. Clopidogrel and prasugrel are discussed in our manuscript only in the context of DAPT and mentioned if one or the other was investigated next to ticagrelor in any of the studies retrieved in our search. We included only ticagrelor due to the fact that because of the irreversible platelet inhibition effect of clopidogrel and prasugrel there are no specific solutions on the horizon for such cases – platelets inhibited by these two drugs are irreversibly inactivated and no antidote or removal strategy can make these platelets viable again. In contrast, ticagrelor may become “detached” from the platelet receptor, inactivated by antidote or adsorbed, and this way previously inhibited platelets may become activated for the efficient hemostasis. For all the above reasons we decided that it

would have been redundant to elaborate on the management of bleeding complications caused by active clopidogrel or prasugrel therapy because no specific solutions for these exist (nor there is a rationale for the future development in this field), but only standard transfusion protocols and the evaluation of these would go beyond the scope of this review. We hope that we sufficiently explained our reasons and that you will accept this part of the manuscript as it is. If this is not the case, we kindly ask you to instruct us about the preferred way to address this issue.

Comment 7: Page 12, line 274: "a group of authors of a very recent study"
Rephrase: In a review by Akhrass et al from Cleveland Clinic group…

Reply 7: We appreciate your suggestion. Where applicable, for consistency, we have changed the way how we refer to publications in the manuscript. Now several articles are cited with the first author's name and colleagues, including Akhrass et al.

8-Page 12, line 277-279: the authors in reference 27 mentioned that hemoadsorption could be promising in patients on antiplatelet medications. They did not mention DOAC. The study from Hassan et al was mainly patients on antiplatelet medications not DOAC. Please add after the word promising: for patients on antiplatelet medications.

Reply 8- We are very grateful you caught this discrepancy. We modified the sentence in question accordingly.

Comment 9: Page 19, line 450: Reversal agents…..
I would move this entire section to results, not in discussion.

Reply 9: We highly appreciate your suggestion. Unfortunately, as stated in the manuscript, the systematic literature search did not result in a satisfactory number of publications about the potential specific solutions used or proposed for the management of perioperative bleeding risk in patients on antithrombotic medications undergoing cardiac surgery. This is the reason why in the Results section we could only describe findings from the retrieved articles – and very few were about reversal agents. In order to "give them a fair chance", we decided to discuss all potential solutions in detail in the Discussion part in which we included also references previously known to authors.
We propose to leave this paragraph as it is to comply with the systematic review design principles. Otherwise, we would need to exclude all results retrieved outside of the systematic PubMed search, which would lead to extreme underrepresentation of antidotes and the impression of strong bias towards hemoadsorption.

Comment 10: Page 21, line 509: ..is the only reversible"
Again, not FDA approved yet. Add the word: potentially

Reply 10: We have to thank you again. Please see Reply 5. Appropriate correction of the text is done as follows:
"Ticagrelor (Brilique® or Brilinta®) is the only reversibly binding oral $P2Y_{12}$ inhibitor."

Comment 11: Page 22, line 528: authors already talked about hemoadsorption extensively. In result section. Need to condense and summarize.

Reply 11: Your constructive critique about the length and unnecessary comprehensiveness of our manuscript is highly appreciated. Please see explanation about why this section is not in the Results part in Reply 9. We condensed the whole paper (Reply 1) and also summarized this section.

Comment 12: Page 25, line 605: the manuscript is heavily biased towards hemoadsorption. This was mainly used for antiplatelet s and not DOACS. The authors cannot make such strong recommendations to use for all agents without solid proof. This HAS TO BE REVISED. This conclusion is a sales pitch to use hemoadsorption in situations beyond the scope of the title of manuscript which is urgent cardiac surgery

Reply 12: We are grateful for this remark. The difference in the robustness of literature between strategies, particularly in the absence of comparable outcome measures, must have influenced the overall "tone" of this review. We have now "softened" the claims in this regard and changed the Conclusion section as requested:
"The incidence of bleeding complications in patients on DAPT or DOACs undergoing urgent cardiac surgery is very high. As the proportion of surgical patients under antithrombotics rapidly grow, there is an increasing unmet clinical need. Reversal agents for DOACs have been launched in recent years, but their usefulness in the non-elective cardio-thoracic surgery setting remains very limited due to high cost or incompatibility with heparin-based anticoagulation for CPB. The reversal agent for ticagrelor is under development, preliminary results look promising, however, once approved, expected high price might limit its availability. In contrast, it seems that intraoperative hemoadsorption strategy is a well-established, universal, and cost-effective method to mitigate perioperative bleeding risk and improve clinical outcomes. It is still not approved by the U.S. Food and Drug Administration, so, currently, two multicenter RCTs are being conducted in the USA evaluating the effectiveness and safety of antithrombotic removal. Contemporary evidence suggests hemoadsorption as a method of choice in the management of perioperative bleeding risk in patients on antithrombotic medications undergoing CPB-assisted cardiac surgery."

Reviewer B

Uncontrollable massive bleeding that occurs when patients taking anticoagulants undergo emergency cardiac surgery without enough discontinuation is a major problem for any cardiac surgeon or anesthesiologist. It's also a very important issue in the patient's prognosis and medical economy.
While the use of antidote is not universal yet, the authors showed us one of solution and evidence, which is considered to be a highly meaningful paper.
To make it better understanding, please consider the additional statements and considerations below.

Comment 1: The more details of mechanism of adsorption including side effects, contraindicated cases and precautions.

Reply 1: Thank you very much for your suggestion. Relevant details about every of the described potential solutions are now given in the enclosed Pros & Cons table.

Comment 2: The extent to which antiplatelet/antithrombotic medication inhibit platelet function cannot be determined by measuring the number of platelets by collecting blood. Is there a paper showing how the coagulation ability changed before and after hemoadsorption, and the test results that can measure the coagulation ability such as ROTEM and TEG?

Reply 2: Wee highly appreciate this well-taken remark. In clinical practice, the level of antiplatelet effect is assessed by platelet function tests and the effect of any of the DOACs is assessed by measuring specific anti-Xa or anti-IIa activity by calibrated chromogenic assays. We agree with the reviewer's opinion that both ROTEM and TEG are important techniques to assess coagulation. To date no clinical study reported on the results of the afore mentioned tests in the context of hemoadsorption antithrombotic removal treatment. A couple of reports[1,2] suggested decreased anti-Xa activity immediately after hemoadsorption and one case report suggests hemoadsorption provided normal ROTEM result[3]. Nevertheless, the technique of ROTEM and TEG and their potential use also in combination with hemoadsorption has now been added into the revised version of the manuscript including an update of the references (please see lines 490 – 496).

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[1] Mendes, V., et al. (2021). "Cytosorb((R)) hemoadsorption of apixaban during emergent cardio-pulmonary bypass: a case report." Perfusion **36**(8): 873-875.

[2] Roed-Undlien, H., et al. (2022). "In Vitro Apixaban Removal By CytoSorb Whole Blood Adsorber: An Experimental Study." J Cardiothorac Vasc Anesth **36**(6): 1636-1644.

[3] Kruger, B., et al. (2021). "The effect of hemoadsorption on rivaroxaban blood plasma concentration in emergency cardiac surgery." Indian J Thorac Cardiovasc Surg **37**(6): 1-4.