

August 12th, 2019

Dr. Yan,

Thank you for the thoughtful reviews, and for providing us an opportunity to improve our work. Please find below the listed comments from each reviewer and the associated response (comments in *italic*, response in **bold**).

Reviewer #1: This review paper is of clinical importance and well written. It should be eligible for publication in this journal. I have some minor comments.

The clinical evidence regarding use of DTI in ECMO patients should be carefully and systematically reviewed in a table.

We have added three tables outlining the pharmacological properties of the discussed agents, as well as the clinical evidence which supports their use in ECMO patients.

After the occurrence of abbreviation of "direct thrombin inhibitors", please use the abbreviations. Similar errors should be carefully reviewed.

We have revised the manuscript to include the abbreviation where appropriate.

Reviewer #2: The authors of the manuscript (MS) review the incidence of heparin-induced thrombocytopenia (HIT) during ECMO, and review recent experience with the off-label use of direct thrombin inhibitors (DTIs) as heparin alternative agents.

This is a rather brief literature survey with no Figures / Tables.

We have revised the manuscript to include comprehensive tables outlining the pharmacology of commonly used DTI agents, as well as the clinical data supporting their use.

MINOR CONCERNS:

1. The pathophysiology of HIT and a comprehensive review of alternatives to heparin have been reviewed elsewhere (e.g. Salter et al., J Am Coll Cardiol 2016, PMID: 27230048).

We have revised the manuscript to include this reference in the discussion of HIT.

2. Additional contemporary references on HIT incidence and outcome associated with ECMO could be added, e.g. Choi et al., Ann Cardiothorac Surg 2019, PMID: 30854309; Kimmoun et al., Intensive Care Med 2018, PMID: 30136139, Glick et al., J Crit Care 2015, PMID: 26363901. Specifically, the retrospective study by Kimmoun et al. suggests that prevalence of HIT among

patients under VA-ECMO is extremely low at 0.36%. This is in contrast with your statement on P5 second para where you state that “complications to UFH are common” and “incidence of HIT is... 2.6%”. You acknowledge that these data do not originate from ECMO patients; study by Kimmoun et al. looked specifically at this population. The MS should be updated and revised accordingly.

Thank you for this suggestion. We have revised the manuscript to include more recent data on the incidence of HIT in ECMO patients, and corrected our previous statement.

3. Most larger studies do not show a significant difference in bleeding with use of heparin vs. DTIs. However, the key fact that “DTIs do not have target-specific antidote” is only briefly mentioned at P7 end of first para in your MS. This could be of concern should bleeding arise, specifically during insertion or removal of ECMO. An expanded comment on that would be appreciated (feel free to add comments to P15 bottom of page section on re-instating anticoagulation protocol with DTIs when failed to wean from ECMO after discontinuation of DTIs).

We have added a paragraph on bleeding management with DTIs.

4. This MS reviews literature from the adult population. For informative purposes, a reference to a recent review of heparin alternatives for ECMO in pediatric population should be included – Pollak et al., Pefusion 2018, PMID: 29788841.

We have added a statement regarding pediatric populations to the manuscript, along with the associated reference.

Reviewer #3: Well-written concise but very useful review of use of these alternative anticoagulants in ECMO. Should be very clinically helpful.

Thank you.