PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antithrombotic Therapy for Durable Left Ventricular Assist Devices: Protocol for a Systematic Review with Indirect Comparison/Network Meta-analysis
AUTHORS	Derzi, Simone Helena; Dewidar, Omar; Sabri, Hind; Tran, Diem; Wells, George

VERSION 1 – REVIEW

REVIEWER	Consolo, Filippo Università Vita Salute San Raffaele
REVIEW RETURNED	29-Nov-2023

GENERAL COMMENTS	Comments The study describes the design and protocols of a living systematic review with network meta-analysis and indirect comparison between current antithrombotic therapies in patients with durable LVADs. My comments are in the following: 1. The Authors declare lack of randomized trials that directly measure the effects of different antithrombotic regimens in the setting of LVAD support. However, the results of the ARIES study have been recently published (doi: 10.1001/jama.2023.23204). 2. In the introduction, the Authors missed to include references to relevant different studies in the field, including: a. the US- and EU-TRACE studies (probably the first reports on reduced/no antithrombotic therapy in patients with CF-LVADs, doi: 10.1016/j.healun.2015.06.018 and 10.1016/j.athoracsur.2016.07.072) b. previous studies that evaluated safety and efficacy of warfarin alone with contemporary LVADs, as a primary antithrombotic approach, following a bleeding event, or after the first 3mo of support (e.g., doi: 10.1002/ejhf.1468 and 10.1097/MAT.0000000000000859) c. the MAGENTUM-1 study that evaluated safety and efficacy of low-intensity anticoagulation (INR target 1.5–1.9) d. a recent paper in ASAIO J that synthesize contemporary clinical evidence on long-term outcomes with reduced anticoagulation in patients implanted with the HM3 and derive a new practical algorithm for rationale management of anticoagulation in these patients, for the prevention of primary bleeding events as well as post-event treatment strategy to avoid recurrence (doi: 10.1097/MAT.0000000000000859).

	I therefore suggest the Authors to revise the text according to the above referenced manuscripts. Also the protocol of the research strategy should be revised to ensure those studies will be included in the systematic review. 3. Discussion: I suggest the Authors to elaborate more on the significance and potential impact of the proposed study based on the current scenario and recent evidence (e.g., the HM3 is the only available implantable pump, and has very low thrombotic risk…, the results of the ARIES study indicate safety and efficacy of no-aspirin to reduce the risk of bleeding events) 4. Page 3, line 33: "Reference more recent studies like INTERMACS registry, ENDURANCE DT trial and MOMENTUM Trial". I think this is a typo coming from the drafting of the manuscript. 5. Please check for grammar errors (e.g., page 9 line 39: aim aims).

REVIEWER	Montisci, Andrea ASST Spedali Civili di Brescia
REVIEW RETURNED	08-Jan-2024

GENERAL COMMENTS	The topic is of high interest, in light of the recent results of the ARIES trial. I think that the study is worth performing and that the methodology is clearly described.

VERSION 1 – AUTHOR RESPONSE

Thank you for your valuable comments and feedback. My initial submission included a protocol drafted in 2020, shortly before Medtronic discontinued the Heartware device. I regret the oversight of not incorporating the most recent studies at this time. I have now updated the protocol accordingly. Please find the revised sections highlighted for your review.

1. "The Authors declare lack of randomized trials that directly measure the effects of different antithrombotic regimens in the setting of LVAD support. However, the results of the ARIES study have been recently published (doi: 10.1001/jama.2023.23204).
2. In the introduction, the Authors missed to include references to relevant different studies in the field, including:
   a. the US- and EU-TRACE studies (probably the first reports on reduced/no antithrombotic therapy in patients with CF-LVADs, doi: 10.1016/j.healun.2015.06.018 and 10.1016/j.athoracsur.2016.07.072)
   b. previous studies that evaluated safety and efficacy of warfarin alone with contemporary LVADs, as a primary antithrombotic approach, following a bleeding event, or after the first 3mo of support (e.g., doi: 10.1002/ejhf.1468 and 10.1097/MAT.0000000000000859)
   c. the MAGENTUM-1 study that evaluated safety and efficacy of low-intensity anticoagulation (INR target 1.5–1.9)
   d. a recent paper in ASAIO J that synthesize contemporary clinical evidence on long-term outcomes with reduced anticoagulation in patients implanted with the HM3 and derive a new practical algorithm for rationale management of anticoagulation in these patients, for the prevention of primary bleeding events as well as post-event treatment strategy to avoid recurrence (doi: 10.1097/MAT.0000000000000859).

I therefore suggest the Authors to revise the text according to the above referenced manuscripts. Also the protocol of the research strategy should be revised to ensure those studies will be included in the systematic review."

Response: We have included all the following studies into the Background section: ARIES study, US and EU-TRACE studies, Consolo et al., Lim et al., MAGENTUM-1. Moreover, our search strategy can capture all the studies included above. Please refer to the supplementary file for the detailed search criteria.

3. "Discussion: I suggest the Authors to elaborate more on the significance and potential impact of the proposed study based on the current scenario and recent evidence (e.g., the HM3 is the only available implantable pump, and has very low thrombotic risk…, the results of the ARIES study indicate safety and efficacy of no-aspirin to reduce the risk of bleeding events)."

Response: In the Discussion section, we have clarified our objective to synthesize the current evidence on antithrombotic therapy for LVAD patients. We acknowledge the significant insights from the recent ARIES study concerning the exclusion of aspirin in antithrombotic regimens of LVAD patients. However, it is important to note that this study does not cover patients with devices other than the HeartMate 3, for instance (and we still have alive patients with Heartmate 2 worldwide). Additionally, we aim to explore the effects on our primary and secondary outcomes in patients administered other therapies such as direct oral anticoagulants (DOACs), phosphodiesterase type 5 inhibitors and phenprocoumon.

4. "Page 3, line 33: "Reference more recent studies like INTERMACS registry, ENDURANCE DT trial and MOMENTUM Trial". I think this is a typo coming from the drafting of the manuscript."

Response: Typo was addressed.

5. "Please check for grammar errors (e.g., page 9 line 39: aim -> aims)."
Response: Grammar error addressed.

VERSION 2 – REVIEW

REVIEWER	Consolo, Filippo Università Vita Salute San Raffaele
REVIEW RETURNED	25-Mar-2024

GENERAL COMMENTS	Thanks for your revision I reiterate that citing the paper doi: 10.1097/MAT.0000000000000859 in the Introduction would provide the readers with a complete background on this topic and recent advancements (i.e., after Lim et al.)

VERSION 2 – AUTHOR RESPONSE

Dear Reviewer,

Thank you for your feedback.

The paper with DOI 10.1097/MAT.0000000000000859 is now described in greater detail in the introduction.