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Antithrombotic Therapy for Durable Left Ventricular Assist Devices: Protocol for a Systematic Review with Indirect Comparison/Network Meta-analysis

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Complete List of Authors:	Derzi, Simone Helena; University of Alberta, Anesthesiology; University of Ottawa Dewidar, Omar; Bruyere Research Institute, Center for Global Health Sabri, Hind; University of Ottawa Heart Institute Tran, Diem; University of Ottawa Heart Institute Wells, George ; University of Ottawa, School of Epidemiology and Public Health; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre
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Systematic Review Protocol

Title: Antithrombotic Therapy for Durable Left Ventricular Assist Devices: Protocol for a Systematic Review with Indirect Comparison/Network Meta-analysis

Registration: PROSPERO Registration Number CRD: . *Any modifications made to this protocol will be reported and justified in the publication of the final report.*

Authors:

Simone Derzi[b]	sderz86@uottawa.ca
Omar Dewidar[c,d]	odewi090@uottawa.ca
Hind Sabri[a]	hind.sabri.2015@gmail.com
Diem Tran[a,b]	dtran@ottawaheart.ca
George Wells[a,b]	gawells@ottawaheart.ca

Affiliations:

a) University of Ottawa Heart Institute, Ottawa, Ontario, Canada

b) School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

c) Temerty School of Medicine, University of Toronto, Toronto, Ontario, Canada

d) Bruyere Research Institute, University of Ottawa, Ontario, Canada

Correspondence: Simone Derzi
54 James Crescent
St. Albert, AB, Canada T8N 7S5
Phone: 1-587-736-1234
Sderz086@uottawa.ca

Contributions: GW, DT and SD conceived the project, and SD wrote the first draft of the manuscript. GW, DT, OD and SD contributed to the subsequent revisions to the manuscript. SD will lead the systematic review and network meta-analysis using the provided guidance. All authors commented on every version of the draft manuscript. All authors approved the final manuscript.

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ABSTRACT

Background

Left ventricular assist devices (LVADs) have emerged as a successful treatment option for patients with end-stage heart failure. Compared to the best medical therapy, LVADs improve survival and enhance functional capacity and quality of life. However, two major complications compromise this patient population's outcomes: thrombosis and bleeding. Despite technological innovations and better hemocompatibility, these devices alter the rheology, triggering the coagulation cascade and, therefore, require antithrombotic therapy. Current guidelines for antithrombotic therapy are primarily based on the results of device trials that did not randomize patients to a particular antithrombotic strategy. Anticoagulation and antiplatelet therapies represent the current standard of care. Still, inconsistency in the literature exists, especially whether antiplatelet therapy is required, whether direct oral anticoagulants can replace vitamin K antagonists and even whether phosphodiesterase type 5 inhibitors with their antithrombotic effects could be added to the regimen of anticoagulation.

Objective

To perform a living systematic review and network meta-analysis to assess different antithrombotic strategies in LVAD patients.

Methods/design

We will perform a living systematic review with network meta-analysis and indirect comparison between current antithrombotic therapies, which have and have not been compared directly within a trial. We plan to search electronic databases for relevant randomized controlled trials and comparative cohort studies. Two independent reviewers will assess the articles by title, abstract and full text; any disagreement will be resolved through discussion, and a third reviewer will be involved if necessary. The Cochrane Risk of Bias tool will be used to assess the risk of bias. We will then conduct a pairwise meta-analysis; if the assumption of transitivity is satisfied, we will proceed with network meta-analysis using Bayesian methodology.

1. INTRODUCTION

Heart failure is a global health crisis that appears to be on the rise, mainly due to the aging population(1). Despite the availability of effective medical treatments for heart failure, a considerable number of patients progress to the advanced stages known as congestive heart failure (CHF). For these individuals, cardiac transplantation is the optimal and conclusive treatment option. However, the chronic shortage of donor organs worldwide has led to a growing disparity between potential heart transplant recipients and available donor hearts. Consequently, left ventricular assist devices (LVADs) have emerged as a viable alternative not only to temporarily support heart function until a suitable heart becomes available (2), but also as a definitive therapy.

In 2001, the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated the effectiveness of the HeartMate XVE (Thoratec Corp, Pleasanton, CA), a pulsatile-flow LVAD, in reducing all-cause mortality compared to optimal medical therapy (52% of survival compared to 25% in the medical group, p=0.002)(3). Since then, LVADs have undergone considerable advancements, becoming smaller, more hemocompatible, silent and durable, making them increasingly suitable for long-term support.

Continuous-flow (CF) technology with minimal or no pulse physiology(4) was a key factor in the miniaturization of newer LVAD designs. Devices like HeartMate 3 (Abbott Laboratories, Abbott Park, IL) and Heartware HVAD (Medtronic, Minneapolis, MN) exemplify CF-LVADs that no longer rely on large pneumatic extracorporeal pumps for generating pulses. Subsequently, survival after LVAD implantation has improved significantly over the last decade. Reference more recent studies like INTERMACS registry, ENDURANCE DT trial and MOMENTUM Trial. However, this change in blood flow dynamics, characterized by laminar flow with reduced or absent pulsatility in CF-LVADs, is considered a major contributing factor to endothelial dysfunction, leading to potential occurrences of bleeding or thromboembolic events(5). Of note, in June 2021, Medtronic halted the worldwide distribution and sale of the Heartware HVAD device due to an elevated risk of neurological adverse events and mortality(6).

To prevent thrombotic events and minimize bleeding incidence, a careful antithrombotic management is necessary. In the past, pulsatile devices required only aspirin as antithrombotic therapy(3). Today, for newer CF-LVADs, the practice involves life-long anticoagulation with a vitamin k antagonist (VKA) along with concomitant antiplatelet agents, mainly based on non-randomized evidence(7,8).

More recently, as a result of enhanced blood compatibility of these devices, more conservative approaches to anticoagulation have been explored. Newer direct-acting oral anticoagulants (DOACs) have emerged as a potential substitute for anticoagulation among LVAD patients(9,10). Additionally, observations suggest that a lower dosage of aspirin (81 mg daily) achieves comparable antithrombotic

effects compared to the standard dose (325 mg)(11). Consequently, a range of worldwide antithrombotic protocols have been investigated, including those excluding aspirin(11), using reduced aspirin doses(12) adopting DOACs, and even utilizing phosphodiesterase type 5 inhibitors for their antithrombotic properties(13,14).

Due to the absence of direct comparisons between numerous antithrombotic regimens, there exists clinical equipoise concerning the most suitable antithrombotic therapy for LVAD patients. Meaningful advancements in antithrombotic treatment will likely emerge only through the implementation of well-designed randomized trials that directly measure the effects of different therapies. In the interim, an indirect comparison may offer additional insights into this crucial and current aspect of the lives of many LVAD patients worldwide.

2. OBJECTIVES

We plan to conduct a living systematic review and network meta-analysis (NMA) of comparative cohort studies and randomised controlled trials to assess the incidence of thrombotic events and bleeding between various antithrombotic regimes in patients implanted with left ventricular assist devices.

3. METHODS

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) Statement (15) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The review will be conducted in accordance with the guidance provided in The Cochrane Handbook of Systematic Review of Interventions and will be reported following the PRISMA Extension Statement for NMA (15). Any protocol modifications made during the conduct of the review will be described in the publication of the final report.

3.1. Search strategy

The search strategy was developed with the assistance of an experienced librarian in systematic reviews and network meta-analyses. The search strategy is described in *Appendix A*, and we systematically search the following electronic sources: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE).

We will exclusively examine studies published in English from 2016 to the present. Studies conducted prior to 2016 will be omitted since our primary concentration is on the evaluation of continuous flow devices. It is noteworthy that studies before 2016 typically involved the assessment of pulsatile flow devices, which have since become obsolete.
We will conduct searches on clinicaltrials.gov and clinicaltrialregister.eu to locate ongoing trials. Furthermore, we will find additional references by manually reviewing the citations of the included articles. Our database searches will be refreshed every two months until the time of publication.

3.2. Eligibility criteria

Population: Adult patients greater than 18 years old on continuous flow-LVAD support.

Index-note: Patients receiving vitamin K antagonist (INR goal between 2-3) with aspirin 325 mg.

Comparators: studies that compare alternative antithrombotic regimens, which involve:

- Vitamin K antagonists (at varying INR levels), either in combination with different aspirin doses or without.
- Direct thrombin inhibitors.
- Phosphodiesterase type 5 inhibitors.
- Aspirin.
- The absence of antithrombotic medications.

We will include any of these control interventions irrespective of dose and duration of administration.

Outcomes: Stroke, thromboembolic events and pump thrombosis are our primary outcomes; bleeding is our secondary outcome. We will define outcomes according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) study (16):
Ischemic stroke: "new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit";
Hemorrhagic stroke: "new acute neurologic deficit attributable to intracranial hemorrhage".
Pump thrombosis: “special case of major device malfunction and can be categorized as a suspected device thrombus or confirmed device thrombus.”
Bleeding: “Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone).”

Studies with either primary and/or secondary outcomes will be included.

Study designs: We will include randomized controlled trials and comparative cohort studies. The reasons for including non-randomized studies is that randomized trials often do not report rare adverse events or late-occurring adverse events.

3.3. Data management and study selection

All records identified by the search strategy will be uploaded to Covidence 2.0 software (17), and duplicates will be removed. Two independent reviewers (SD vs OD or HS) will screen studies for eligibility based on titles, abstracts, and full-texts using the eligibility criteria. Any discrepancies in the inclusion criteria will be resolved through discussion and consensus between the reviewers. If necessary, a third reviewer (DT) will be involved. We will use the discrepancies between the reviewers to calculate a kappa statistic and assess inter-reviewer reliability; a kappa statistic>0.6 will be considered acceptable

We will document the reasons for excluding full texts and present this information using Covidence to create a PRISMA flowchart.

3.4. Data collection process and data items

We will design a standardized data extraction form that will be piloted on 10% of included studies. Two reviewers will independently extract the data and any inconsistencies will be resolved through discussion, or with a third reviewer, if necessary. If we need further information or if the data appear to be insufficient, we will contact the authors. If not possible to reach the authors, we will discuss this limitation in the final manuscript.

Using the data extraction form, we will capture the following information: title, authors, journal, publication date, study period, number of participants, country, type of implanted device, study population characteristics, antithrombotic regimens, primary and secondary outcomes.

If necessary, our team will contact study authors to obtain additional information for our review.

3.5. Living systematic review

We will perform updates to our search every two months. At present, there is a range of antiplatelet and anticoagulation strategies being utilized, but there is a lack of studies directly comparing them. We are of the opinion that ongoing clinical trials focused on antithrombotic therapies have the potential to offer new perspectives that will enrich our network meta-analysis.

3.6. Network meta-analysis

Before proceeding with the network meta-analysis, we will assess if there are sufficient statistical data to evaluate their consistency and the assumption of transitivity.

According to this assumption, we can only examine these trials when we have closed loops, and it assumes that the distribution of the effect modifiers is comparable across treatments. For instance, if studies of warfarin and aspirin versus apixaban and aspirin, and warfarin-aspirin versus warfarin differ with respect to their effect modifiers, then it would not be appropriate to make an indirect comparison between apixaban-aspirin and warfarin-only regimen. See the diagram below:

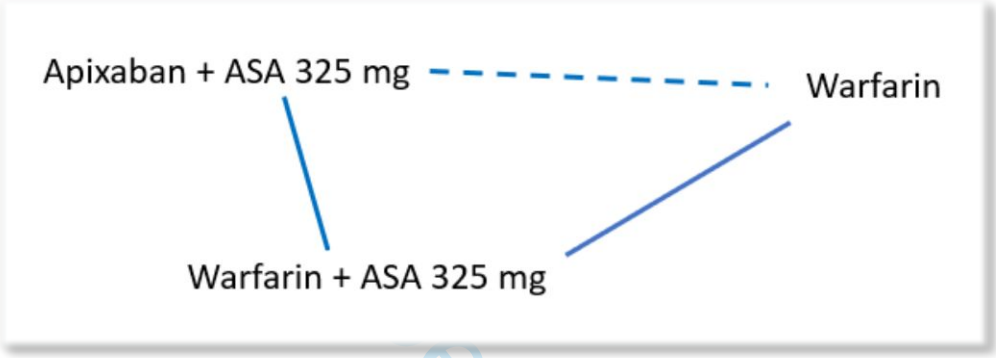

Figure 1. Dashed line indicates an indirect comparison.

If network meta-analysis is conducted, we will adopt a Bayesian approach and a random effects model for binomial and continuous outcomes assessing the effect estimate of each anticoagulation therapy.

Mean difference and odds ratios with 95% confidence intervals will be presented. Following unadjusted analysis, secondary analyses will be conducted to account for any imbalance in the distribution of effect modifiers, especially types of devices. Network meta-regression methods will be conducted to account for these differences.

3.7. Geometry of the network

The network diagram will provide a visual representation of the available evidence of each comparison between different antithrombotic regimen. Below, we show a draft of the possible network diagram for our future analysis.

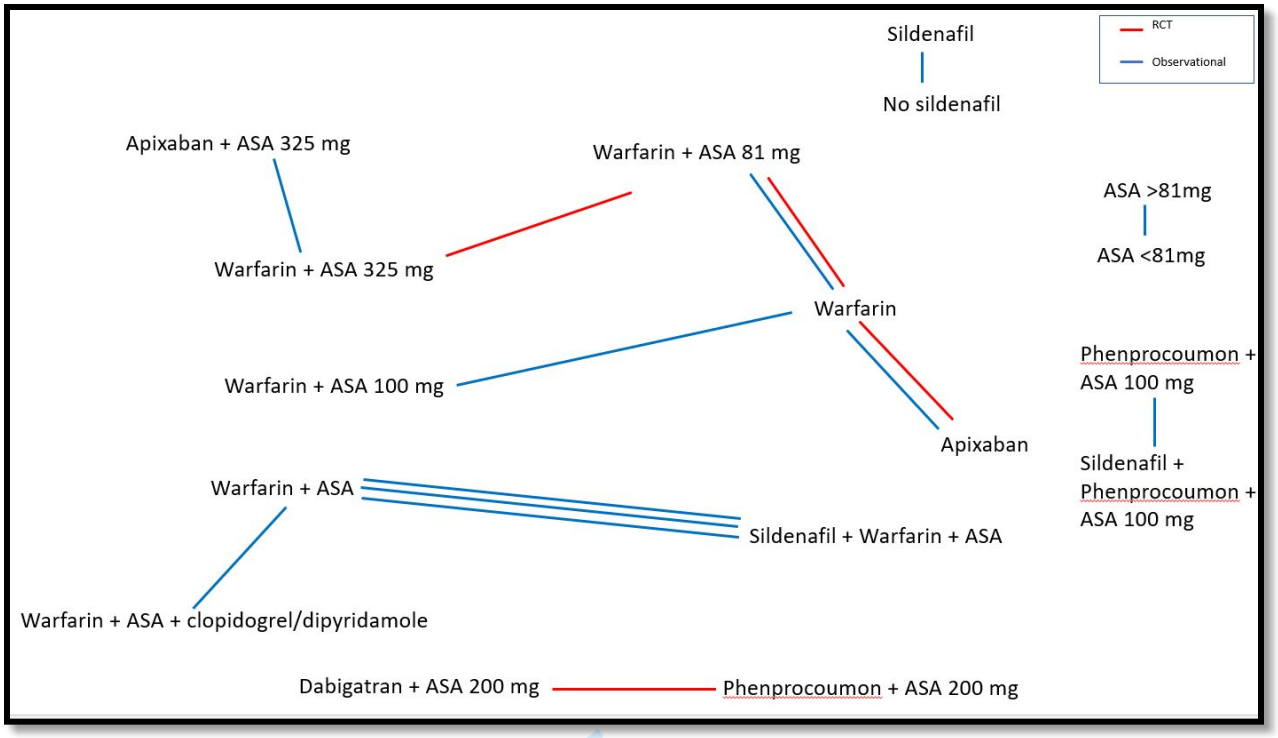

***Figure 2**: The network diagram illustrates several comparisons of various antithrombotic regimens employed in LVAD patients. It is essential to observe that the current standard of care involves the combination of warfarin and aspirin.*

3.8. Risk of bias in individual studies

To determine methodological validity, we will assess the risk of bias of the included studies at a study level using the Revised Cochrane Collaborations Risk-of-Bias (RoB 2) tool and ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions). Any discrepancies will be resolved through discussion until consensus is reached.

3.9. Summary measures

Primary outcome

Incidence of stroke and thromboembolic events will be reported as dichotomous outcomes occurring at any time after implantation of the LVAD until three years of follow-up. Relative risks with 95% confidence intervals will be calculated to compare the incidence of stroke between different antithrombotic regimens.

Secondary outcomes

Bleeding will be reported as dichotomous data.

3.10. Pairwise meta-analysis

We will conduct a pairwise meta-analysis using random-effects model. Statistical heterogeneity within pairwise comparisons will be evaluated by visual inspection of forest plots and I^2 measure. If there is a high amount of heterogeneity (I^2> 75%), then sources of heterogeneity will be examined through subgroup and sensitivity analyses.

3.11. Subgroup and sensitivity analyses

If the studies have high heterogeneity, subgroup analysis will be performed based on age, type of device and recalled devices from 2021.

Sensitivity analysis will be used to verify the reliability of results. According to the Cochrane Handbook, sensitivity analysis will be conducted in the three aspects of methodological quality, sample size, and statistical model. We will exclude studies with poor research quality, small sample size, and high risk of bias.

3.12. Assessment of inconsistency

Inconsistency in the data will be assessed by fitting inconsistency model scatterplots and using Cochran's *Q* test. A statistician with experience in systematic review and network meta-analysis will assist our team.

4. DISCUSSION

This systematic review and network meta-analysis aim to study the available direct and indirect evidence concerning the potential distinctions among various antithrombotic treatments in LVAD patients. While the utilization of LVAD therapy has been on the rise, changes to anticoagulation and antiplatelet drugs have only recently been introduced, deviating from the standard of care represented by the combination of warfarin and aspirin 325mg.

By conducting this network meta-analysis, we will be able to compare current antithrombotic therapies with the recently implemented ones, which have not been directly compared in head-to-head clinical trials.

Limitations

We recognize that the inherent heterogeneity and biases in observational studies could pose significant challenges when analyzing the data.

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APPENDIX A: SEARCH STRATEGY

MEDLINE

1.	(left ventricular assist device or LVAD*).ti,ab,kf.
2.	(Heartmate or Heartware or HVAD).ti,ab,kf.
3.	Heart-Assist Devices/
4.	1 or 2 or 3
5.	limit 4 to yr="2016-2023"
6.	(stroke or cerebrovascular accident or cva or thrombo* or cerebral thrombosis or thrombosis).ti,ab,kf.
7.	thrombosis/
8.	thromboembolism/
9.	exp stroke/
10.	6 or 7 or 8 or 9
11.	coumarins/
12.	exp anticoagulants/
13.	exp heparin/
14.	exp coumarins/
15.	(anticoagulation or anti-coagulation or anticoagulant* or antithrombotic or phytomenadione or doac or direct oral anticoagulants or fondaparinux or edoxaban or coumarin or dabigatran or apixaban or rivaroxaban or low molecular weight heparin or hirudin or enoxaparin or heparin or phosphodiesterase type 5 inhibitors or viagra or warfarin or ximelagatran or acetylsalicylic acid).ti,ab,tw,kf.
16.	aspirin/
17.	(vitamin adj3 antagonist*).mp.
18.	11 or 12 or 13 or 14 or 15 or 16 or 17
19.	5 and 10 and 18

EMBASE

1.	(left ventricular assist device or LVAD*).ti,ab,kf.
2.	(Heartmate or Heartware or HVAD).ti,ab,kf.
3.	exp left ventricular assist device/
4.	1 or 2 or 3
5.	(stroke or cerebrovascular accident or cva or thrombo* or cerebral thrombosis or thrombosis).ti,ab,kf.
6.	exp stroke/
7.	limit 4 to yr="2016-2023"
8.	5 or 6
9.	anticoagulant agent/ or fondaparinux/ or edoxaban/ or coumarin/ or dabigatran/ or rivaroxaban/ or low molecular weight heparin/ or hirudin/ or enoxaparin/ or heparin/ or phosphodiesterase type 5 inhibitors viagra/ or sildenafil/ or tadalafil/ or warfarin/ or ximelagatran/ or acetylsalicylic acid/
10.	exp anticoagulant agent/
11.	exp coumarin/
12.	(anticoagulation or anti-coagulation or anticoagulant* or antithrombotic or phytomenadione or doac or direct oral anticoagulants or fondaparinux or edoxaban or coumarin or dabigatran or apixaban or rivaroxaban or low molecular weight heparin or hirudin or enoxaparin or heparin or phosphodiesterase type 5 inhibitors or viagra or warfarin or ximelagatran or acetylsalicylic acid).ti,ab,tw,kf.
13.	(vitamin adj3 antagonist*).mp.
14.	9 or 10 or 11 or 12 or 13
15.	7 and 8 and 14

APPENDIX B: PRISMA NMA Checklist

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			3
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***3***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			4
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***5***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	13

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***7***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	8
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***9***
RESULTS†			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).
DISCUSSION		
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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Complete List of Authors:	Derzi, Simone Helena; University of Ottawa, Anesthesiology Dewidar, Omar; Bruyere Research Institute, Center for Global Health; University of Toronto Temerty Faculty of Medicine Sabri, Hind; University of Ottawa Heart Institute Tran, Diem; University of Ottawa Heart Institute; University of Ottawa School of Epidemiology and Public Health Wells, George ; University of Ottawa School of Epidemiology and Public Health; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre
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Antithrombotic Therapy for Durable Left Ventricular Assist Devices: Protocol for a Systematic Review with Indirect Comparison/Network Meta-analysis

Authors:

Simone Derzi[b]	sderz86@uottawa.ca
Omar Dewidar[c,d]	odewi090@uottawa.ca
Hind Sabri[a]	hind.sabri.2015@gmail.com
Diem Tran[a,b]	dtran@ottawaheart.ca
George Wells[a,b]	gawells@ottawaheart.ca

Affiliations:

a) University of Ottawa Heart Institute, Ottawa, Ontario, Canada

b) School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

c) Temerty School of Medicine, University of Toronto, Toronto, Ontario, Canada

d) Bruyere Research Institute, University of Ottawa, Ontario, Canada

Correspondence:

Simone Derzi

54 James Crescent

St. Albert, AB, Canada T8N 7S5

Phone: 1-587-736-1234

Sderz086@uottawa.ca

ABSTRACT

Background: Left ventricular assist devices (LVADs) have emerged as a successful treatment option for patients with end-stage heart failure. Compared to the best medical therapy, LVADs improve survival and enhance functional capacity and quality of life. However, two major complications compromise this patient population's outcomes: thrombosis and bleeding. Despite technological innovations and better hemocompatibility, these devices alter the rheology, triggering the coagulation cascade and, therefore, require antithrombotic therapy. Anticoagulation and antiplatelet therapies represent the current standard of care. Still, inconsistency in the literature exists, especially whether antiplatelet therapy is required, whether direct oral anticoagulants can replace vitamin K antagonists and even whether phosphodiesterase type 5 inhibitors with their antithrombotic effects could be added to the regimen of anticoagulation.

Methods and analysis: We will perform a living systematic review with network meta-analysis and indirect comparison between current antithrombotic therapies, which have and have not been directly compared within clinical trials and observational studies. We will systematically search the following electronic sources: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE). We will exclusively examine studies published in English from 2016 to the present. Studies conducted before 2016 will be omitted since our primary focus is evaluating continuous flow devices. Two independent reviewers will assess the articles by title, abstract and full text; any disagreement will be resolved through discussion, and a third reviewer will be involved if necessary. The Cochrane Risk of Bias tool will be used to assess the risk of bias. We will then conduct a pairwise meta-analysis; if the assumption of transitivity is satisfied, we will proceed with network meta-analysis using Bayesian methodology.

Ethics and dissemination: Formal ethical approval is not required as no primary data is collected. This systematic review and network meta-analysis will delineate the risks of stroke, thromboembolic events, pump thrombosis, gastrointestinal bleeding and mortality in patients equipped with LVADs who are subjected to various antithrombotic regimens. The findings will be disseminated via a peer-reviewed publication and presented at conference meetings. This will enhance clinical practice and guide future research on anticoagulation strategies within this distinct patient cohort.

Registration: PROSPERO CRD42023465288.

Strengths and limitations of this study:

- In LVAD patients, anticoagulation practices, particularly concerning aspirin dosage, exhibit significant global variability, potentially introducing heterogeneity into the study and complicating analysis.
- Variations in follow-up durations across studies, attributed to the absence of a standardized reporting protocol for major outcomes in LVAD patients, could affect outcome consistency.
- The evidence base is restricted to a limited set of clinical trials; therefore, our analysis will encompass both clinical trials and observational studies. We recognize that observational studies' inherent heterogeneity and biases could pose significant challenges when analyzing the data.

BACKGROUND AND RATIONALE

Heart failure is a global health crisis that appears to be on the rise, mainly due to the aging population(1). Despite the availability of effective medical treatments for heart failure, a considerable number of patients progress to advanced congestive heart failure (CHF) stages. For these individuals, cardiac transplantation is the optimal and conclusive treatment option. However, the chronic shortage of donor organs worldwide has led to a growing disparity between potential heart transplant recipients and available donor hearts. Consequently, left ventricular assist devices (LVADs) have emerged as a viable alternative not only to temporarily support heart function until a suitable heart becomes available (2) but also as a definitive therapy.

In 2001, the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated the effectiveness of the HeartMate XVE (Thoratec Corp, Pleasanton, CA), a pulsatile-flow LVAD, in reducing all-cause mortality compared to optimal medical therapy (52% of survival compared to 25% in the medical group, p=0.002)(3). Since then, LVADs have undergone considerable advancements, becoming smaller, more hemocompatible, silent and durable, making them increasingly suitable for long-term support.

Continuous-flow (CF) technology with minimal or no pulse physiology(4) was a key factor in the miniaturization of newer LVAD designs. Devices like HeartMate 3 (HM3) (Abbott Laboratories, Abbott Park, IL) and Heartware HVAD (Medtronic, Minneapolis, MN) exemplify CF-LVADs that no longer rely on large pneumatic extracorporeal pumps for generating pulses. Subsequently, survival after LVAD implantation has improved significantly over the last decade. However, this change in blood flow dynamics, characterized by laminar flow with reduced or absent pulsatility in CF-LVADs, is considered a major contributing factor to endothelial dysfunction, leading to potential occurrences of bleeding or thromboembolic events(5). Of note, in June 2021, Medtronic halted the worldwide distribution and sale of the Heartware HVAD device due to an elevated risk of neurological adverse events and mortality(6).

To prevent thrombotic events and minimize bleeding incidence, careful antithrombotic management is necessary. In the past, pulsatile devices required only aspirin as antithrombotic therapy(3). Until recently, for newer CF-LVADs, the practice involved life-long anticoagulation with a vitamin K antagonist (VKA) along with concomitant antiplatelet agents, mainly based on non-randomized evidence(7,8). The ARIES-HM3 trial(9), however, has recently challenged this approach by demonstrating that excluding aspirin from the antithrombotic regimen in patients with a fully magnetically levitated LVAD did not compromise safety and was associated with a reduction in bleeding events, with 74% of patients in the placebo group versus 68% in the aspirin group being alive and free of major nonsurgical hemocompatibility-related adverse events at 12 months. This aspirin avoidance led to a 34% reduction in nonsurgical bleeding events without an increase in stroke or other thromboembolic events. Similarly, the US-TRACE study observed 93.8% freedom from ischemic stroke and 92.7% from device thrombosis at one year among HeartMate II patients on reduced antithrombotic therapy, despite a subsequent bleeding event in 52% of cases(10). The European TRACE study further supports managing HeartMate II patients with a vitamin K antagonist without antiplatelet therapy could reduce the incidence of major bleeding without increasing thromboembolic events, including ischemic stroke and pump thrombosis, with an 81% freedom from bleeding and 96% freedom from ischemic stroke at 2 years(11).

These findings challenge the necessity of aspirin in antithrombotic regimens, especially with devices like the HM3, which have significantly reduced the incidence of pump thrombosis. An observational study reported no bleeding events among patients discharged without aspirin, contrasting with a 39% bleeding occurrence in patients treated with aspirin, suggesting the potential safety and efficacy of primary warfarin monotherapy after discharge(12). Another study contributed to this evolving narrative by proposing a novel algorithm for anticoagulation management in HM3 patients to prevent primary bleeding events and formulate a post-bleeding treatment strategy (13).

More recently, as a result of enhanced blood compatibility of these devices, more conservative approaches to anticoagulation have been explored. The MAGENTUM-1 study validated lower international normalized ratios (INR) levels without increasing the risk of adverse events (14). Newer direct-acting oral anticoagulants (DOACs) have emerged as a potential substitute for anticoagulation among LVAD patients (15,16). Additionally, observations suggest that a lower dosage of aspirin (81 mg daily) achieves comparable antithrombotic effects compared to the standard dose (325 mg)(17). Consequently, a range of worldwide antithrombotic protocols have been investigated, including those excluding aspirin (9,12,18), using reduced aspirin doses(17,19), adopting DOACs(15,16), and even utilizing phosphodiesterase type 5 inhibitors for their antithrombotic properties(20–22). Due to the absence of direct comparisons between numerous antithrombotic regimens, clinical equipoise exists concerning the most suitable antithrombotic therapy for LVAD patients. Meaningful advancements in antithrombotic treatment will likely emerge only by implementing well-designed randomized trials that

directly measure the effects of different treatments. In the interim, an indirect comparison may offer additional insights into this crucial and current aspect of the lives of many LVAD patients worldwide. Therefore, we plan to conduct a living systematic review and network meta-analysis (NMA) of comparative cohort studies and randomised controlled trials to assess the incidence of thrombotic events and bleeding between various antithrombotic regimes in patients implanted with left ventricular assist devices.

METHODS

This protocol is reported following the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) Statement (23) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The review will be conducted under the guidance of The Cochrane Handbook for Systematic Reviews of Interventions and will be reported following the PRISMA Extension Statement for NMA (23). Any protocol modifications will be described in the publication of the final report.

Types of studies

We will include randomized controlled trials and comparative cohort studies. The inclusion of non-randomized studies is justified by the predominance of observational studies over randomized trials in the literature, and the tendency of randomized trials to underreport rare or late-emerging adverse events.

Types of participants

Adult patients greater than 18 years old on continuous flow-LVAD support.

Types of interventions and comparators

Patients receiving vitamin K antagonist (INR goal between 2-3) with aspirin 325 milligrams will be the reference group (or comparator). As new interventions, we will include alternative antithrombotic regimens, such as:

- Vitamin K antagonists (at varying INR levels), either in combination with different aspirin doses or without.
- Direct thrombin inhibitors.
- Phosphodiesterase type 5 inhibitors.
- Factor Xa Inhibitors.
- The absence of antithrombotic medications.

We will include any of these interventions irrespective of dose and duration of administration.

Outcomes of interest

Stroke, thromboembolic events and pump thrombosis are our primary outcomes; bleeding and mortality are our secondary outcomes. We will define outcomes according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) study (24):

Ischemic stroke: "new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit";

Hemorrhagic stroke: "New acute neurologic deficit attributable to intracranial hemorrhage."

Pump thrombosis: "special case of major device malfunction and can be categorized as a suspected device thrombus or confirmed device thrombus."

Bleeding: "Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone)."

Studies with either primary and/or secondary outcomes will be included.

Search strategy and databases

The search strategy was developed with the assistance of an experienced librarian in systematic reviews and network meta-analyses. The search strategy is described in *Appendix A*, and we systematically search the following electronic sources: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE).

We will exclusively examine studies published in English from 2016 to the present. Studies conducted before 2016 will be omitted since our primary focus is evaluating continuous flow devices. It is noteworthy that studies before 2016 typically involved the assessment of pulsatile flow devices, which have since become obsolete.

We will conduct searches on clinicaltrials.gov and clinicaltrialregister.eu to locate ongoing trials. Furthermore, we will find additional references by manually reviewing the citations of the included articles. Our database searches will be refreshed every two months until publication.

Study selection

All records identified by the search strategy will be uploaded to Covidence 2.0 software (25), and duplicates will be removed. Two independent reviewers (SD vs OD or HS) will screen studies for eligibility based on titles, abstracts, and full texts using the eligibility criteria. Any discrepancies in the inclusion criteria will be resolved through discussion and consensus between the reviewers. If necessary, a third

reviewer (DT) will be involved. We will use the discrepancies between the reviewers to calculate a kappa statistic and assess inter-reviewer reliability; a kappa statistic>0.6 will be considered acceptable.

We will document the reasons for excluding full texts and present this information using Covidence to create a PRISMA flowchart.

Data extraction

We will design a standardized data extraction form that will be piloted on 10% of included studies. Two reviewers will independently extract the data, and any inconsistencies will be resolved through discussion or with a third reviewer, if necessary. If we need further information or the data appears insufficient, we will contact the authors. If it is impossible to reach the authors, we will discuss this limitation in the final manuscript.

Using the data extraction form, we will capture the following information: title, authors, journal, publication date, study period, number of participants, country, type of implanted device, study population characteristics, antithrombotic regimens, and primary and secondary outcomes.

If necessary, our team will contact study authors to obtain additional information for our review.

Living systematic review

We will perform updates to our search every two months. A range of antiplatelet and anticoagulation strategies are being utilized, but there is a lack of studies directly comparing them. We are of the opinion that ongoing clinical trials focused on antithrombotic therapies have the potential to offer new perspectives that will enrich our network meta-analysis.

Network meta-analysis

Before proceeding with the network meta-analysis, we will assess if sufficient statistical data exists to evaluate their consistency and the assumption of transitivity.

According to this assumption, we can only examine these trials when we have closed loops, and it assumes that the distribution of the effect modifiers is comparable across treatments. For instance, if studies of warfarin and aspirin versus apixaban and aspirin, and warfarin-aspirin versus warfarin differ with respect to their effect modifiers, then it would not be appropriate to make an indirect comparison between apixaban-aspirin and warfarin-only regimen (**Figure 1**).

If network meta-analysis is conducted, we will adopt a Bayesian approach and a random effects model for binomial and continuous outcomes, assessing the effect estimate of each anticoagulation therapy.

Mean differences and odds ratios with 95% confidence intervals will be presented. Following unadjusted analysis, secondary analyses will be conducted to account for any imbalance in the distribution of effect modifiers, especially types of devices. Network meta-regression methods will be conducted to account for these differences.

Geometry of the network

The network diagram will visually represent the available evidence of each comparison between different antithrombotic regimens. **Figure 2** shows a draft of the possible network diagram for our future analysis.

Risk of bias in individual studies

To determine methodological validity, we will assess the risk of bias of the included studies at a study level using the Revised Cochrane Collaborations Risk-of-Bias (RoB 2) tool and ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions). Any discrepancies will be resolved through discussion until a consensus is reached.

Summary measures

Primary outcome

Incidence of stroke and thromboembolic events will be reported as dichotomous outcomes occurring at any time after implantation of the LVAD until three years of follow-up. Relative risks with 95% confidence intervals will be calculated to compare the incidence of stroke between different antithrombotic regimens.

Secondary outcomes

Bleeding will be reported as dichotomous data**.**

Pairwise meta-analysis

We will conduct a pairwise meta-analysis using random-effects model. Statistical heterogeneity within pairwise comparisons will be evaluated by visual inspection of forest plots and I^2 measure. If there is a high amount of heterogeneity (I^2> 75%), then sources of heterogeneity will be examined through subgroup and sensitivity analyses.

Subgroup and sensitivity analyses

If the studies have high heterogeneity, subgroup analysis will be performed based on age, type of device and recalled devices from 2021.

Sensitivity analysis will be used to verify the reliability of the results. According to the Cochrane Handbook, sensitivity analysis will be conducted in the three aspects of methodological quality, sample size, and statistical model. We will exclude studies with poor research quality, small sample size, and high risk of bias.

Assessment of inconsistency

Inconsistency in the data will be assessed by fitting inconsistency model scatterplots and using Cochran's *Q* test. A statistician with experience in systematic review and network meta-analysis will assist our team.

Ethics and dissemination

This study is SR protocol collecting data from published literature and, therefore does not require institutional review board approval. Results from this SR and NMA will be published in a peer-reviewed journal.

Patient and public involvement

No patients or members of the public will be directly assessed. Only data already reported in the literature will be used in this study.

DISCUSSION

This systematic review and network meta-analysis is conducted against a backdrop of evolving LVAD technology and antithrombotic therapy. With the HM3 emerging as the only available implantable pump in many regions and its notably low risk of thrombosis, the implications of antithrombotic management have never been more pivotal. The HM3's technological advancements have reduced the incidence of pump thrombosis, shifting the focus toward managing bleeding risks. The ARIES study's findings are particularly relevant here(9), as they underscore the safety and efficacy of excluding aspirin from the

antithrombotic regimen, which could mark a paradigm shift in reducing bleeding events without increasing thromboembolic risks.

While we recognize the pivotal contributions of the ARIES study, particularly its insights into aspirin's role in the antithrombotic regimens for LVAD recipients, it's critical to underline that its findings predominantly pertain to those with the HeartMate 3 device. This focus leaves a gap in our understanding of therapy for individuals with other devices, such as the still-utilized HeartMate 2. Furthermore, our analysis seeks to broaden the scope of investigation by assessing the impact of various treatments—including direct oral anticoagulants (DOACs), phosphodiesterase type 5 inhibitors, and phenprocoumon—on both primary and secondary outcomes. This comprehensive approach is designed to offer a more nuanced understanding of antithrombotic therapy's efficacy and safety across the diverse spectrum of LVAD technologies and patient needs.

Authors' contributions

SD, OD, HS, DT, and GW contributed equally to this work. SD, DT, and GW conceived the idea and design for this systematic review. SD, OD, DT, and GW developed the methodology for the systematic review protocol. The contents of this manuscript were drafted by SD, OD, and GW with input from all members of the authorship team. The manuscript was reviewed by SD, OD, DT, HS and GW for important intellectual content. All authors read and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

None.

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Figure 1. The dashed line indicates an indirect comparison.

Figure 2: The network diagram depicts multiple comparisons among different antithrombotic regimens used in LVAD patients. Although warfarin combined with 325 mg of aspirin was the standard treatment until recently, there has been a trend towards more conservative strategies in current practice. RCT: randomized controlled trial. ASA: aspirin.

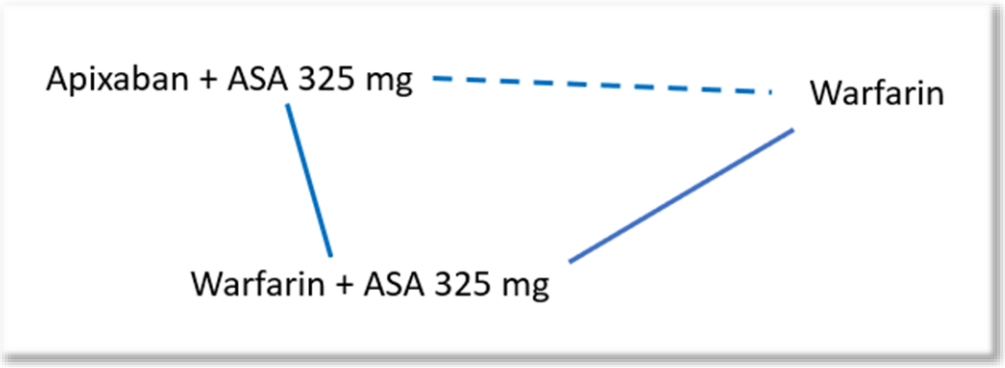

Figure 1. The dashed line indicates an indirect comparison.

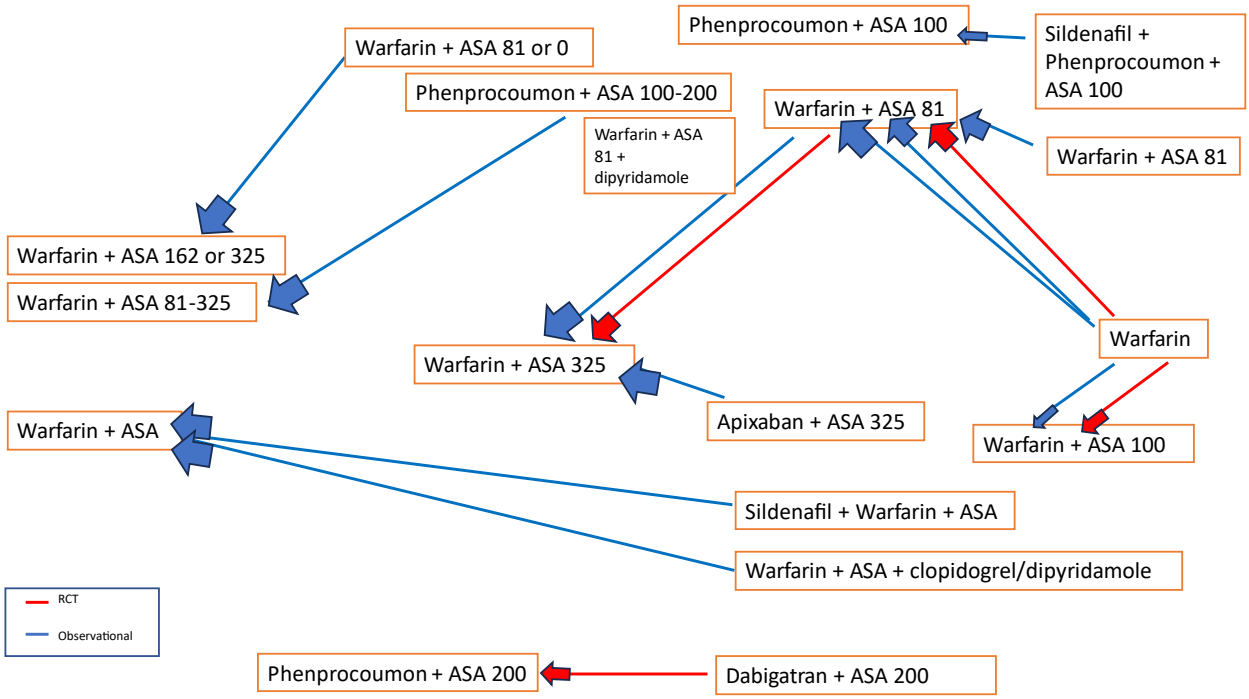

Figure 2: The network diagram depicts multiple comparisons among different antithrombotic regimens used in LVAD patients. Although warfarin combined with 325mg of aspirin was the standard treatment until recently, there has been a trend towards more conservative strategies in current practice.

SUPPLEMENTARY MATERIAL

APPENDIX A

Table 1 EMBASE search strategy

1. (left ventricular assist device or LVAD*).ti,ab,kf.
2. (Heartmate or Heartware or HVAD).ti,ab,kf.
3. exp left ventricular assist device/
4. 1 or 2 or 3
5. (stroke or cerebrovascular accident or cva or thrombo* or cerebral thrombosis or thrombosis).ti,ab,kf.
6. exp stroke/
7. limit 4 to yr="2016-2023"
8. 5 or 6
9. anticoagulant agent/ or fondaparinux/ or edoxaban/ or coumarin/ or dabigatran/ or rivaroxaban/ or low molecular weight heparin/ or hirudin/ or enoxaparin/ or heparin/ or phosphodiesterase type 5 inhibitors/ or viagra/ or sildenafil/ or tadalafil/ or warfarin/ or ximelagatran/ or acetylsalicylic acid/
10. exp anticoagulant agent/
11. exp coumarin/
12. (anticoagulation or anti-coagulation or anticoagulant* or antithrombotic or phytomenadione or doac or direct oral anticoagulants or fondaparinux or edoxaban or coumarin or dabigatran or apixaban or rivaroxaban or low molecular weight heparin or hirudin or enoxaparin or heparin or phosphodiesterase type 5 inhibitors or viagra or warfarin or ximelagatran or acetylsalicylic acid).ti,ab,tw,kf.
13. (vitamin adj3 antagonist*).mp.
14. 9 or 10 or 11 or 12 or 13
15. 7 and 8 and 14

Table 2 Medline search strategy

1. (left ventricular assist device or LVAD*).ti,ab,kf.
2. (Heartmate or Heartware or HVAD).ti,ab,kf.
3. Heart-Assist Devices/
4. 1 or 2 or 3
5. limit 4 to yr="2016-2023"
6. (stroke or cerebrovascular accident or cva or thrombo* or cerebral thrombosis or thrombosis).ti,ab,kf.
7. thrombosis/
8. thromboembolism/
9. exp stroke/
10. 6 or 7 or 8 or 9
11. coumarins/
12. exp anticoagulants/
13. exp heparin/
14. exp coumarins/
15. (anticoagulation or anti-coagulation or anticoagulant* or antithrombotic or phytomenadione or doac or direct oral anticoagulants or fondaparinux or edoxaban or coumarin or dabigatran or apixaban or rivaroxaban or low molecular weight heparin or hirudin or enoxaparin or heparin or phosphodiesterase type 5 inhibitors or viagra or warfarin or ximelagatran or acetylsalicylic acid).ti,ab,tw,kf.
16. aspirin/
17. (vitamin adj3 antagonist*).mp.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 5 and 10 and 18

APPENDIX B

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Performed
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Performed
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Performed
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Performed
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Performed
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Performed
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Performed
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Performed

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Performed
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Performed
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Performed
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Performed
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Performed
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Performed
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Performed
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Performed

BMJ Open

Antithrombotic Therapy for Durable Left Ventricular Assist Devices: Protocol for a Systematic Review with Indirect Comparison/Network Meta-analysis

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Antithrombotic Therapy for Durable Left Ventricular Assist Devices: Protocol for a Systematic Review with Indirect Comparison/Network Meta-analysis

Authors:

Simone Derzi[b]	sderz86@uottawa.ca
Omar Dewidar[c,d]	odewi090@uottawa.ca
Hind Sabri[a]	hind.sabri.2015@gmail.com
Diem Tran[a,b]	dtran@ottawaheart.ca
George Wells[a,b]	gawells@ottawaheart.ca

Affiliations:

a) University of Ottawa Heart Institute, Ottawa, Ontario, Canada

b) School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

c) Temerty School of Medicine, University of Toronto, Toronto, Ontario, Canada

d) Bruyere Research Institute, University of Ottawa, Ontario, Canada

Correspondence:

Simone Derzi

54 James Crescent

St. Albert, AB, Canada T8N 7S5

Phone: 1-587-736-1234

Sderz086@uottawa.ca

ABSTRACT

Background: Left ventricular assist devices (LVADs) have emerged as a successful treatment option for patients with end-stage heart failure. Compared to the best medical therapy, LVADs improve survival and enhance functional capacity and quality of life. However, two major complications compromise this patient population's outcomes: thrombosis and bleeding. Despite technological innovations and better hemocompatibility, these devices alter the rheology, triggering the coagulation cascade and, therefore, require antithrombotic therapy. Anticoagulation and antiplatelet therapies represent the current standard of care. Still, inconsistency in the literature exists, especially whether antiplatelet therapy is required, whether direct oral anticoagulants can replace vitamin K antagonists and even whether phosphodiesterase type 5 inhibitors with their antithrombotic effects could be added to the regimen of anticoagulation.

Methods and analysis: We will perform a living systematic review with network meta-analysis and indirect comparison between current antithrombotic therapies, which have and have not been directly compared within clinical trials and observational studies. We will systematically search the following electronic sources: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE). We will exclusively examine studies published in English from 2016 to the present. Studies conducted before 2016 will be omitted since our primary focus is evaluating continuous flow devices. Two independent reviewers will assess the articles by title, abstract and full text; any disagreement will be resolved through discussion, and a third reviewer will be involved if necessary. The Cochrane Risk of Bias tool will be used to assess the risk of bias. We will then conduct a pairwise meta-analysis; if the assumption of transitivity is satisfied, we will proceed with network meta-analysis using Bayesian methodology.

Ethics and dissemination: Formal ethical approval is not required as no primary data is collected. This systematic review and network meta-analysis will delineate the risks of stroke, thromboembolic events, pump thrombosis, gastrointestinal bleeding and mortality in patients equipped with LVADs who are subjected to various antithrombotic regimens. The findings will be disseminated via a peer-reviewed publication and presented at conference meetings. This will enhance clinical practice and guide future research on anticoagulation strategies within this distinct patient cohort.

Registration: PROSPERO CRD42023465288.

Strengths and limitations of this study:

- In LVAD patients, anticoagulation practices, particularly concerning aspirin dosage, exhibit significant global variability, potentially introducing heterogeneity into the study and complicating analysis.
- Variations in follow-up durations across studies, attributed to the absence of a standardized reporting protocol for major outcomes in LVAD patients, could affect outcome consistency.
- The evidence base is restricted to a limited set of clinical trials; therefore, our analysis will encompass both clinical trials and observational studies. We recognize that observational studies' inherent heterogeneity and biases could pose significant challenges when analyzing the data.

BACKGROUND AND RATIONALE

Heart failure is a global health crisis that appears to be on the rise, mainly due to the aging population(1). Despite the availability of effective medical treatments for heart failure, a considerable number of patients progress to advanced congestive heart failure (CHF) stages. For these individuals, cardiac transplantation is the optimal and conclusive treatment option. However, the chronic shortage of donor organs worldwide has led to a growing disparity between potential heart transplant recipients and available donor hearts. Consequently, left ventricular assist devices (LVADs) have emerged as a viable alternative not only to temporarily support heart function until a suitable heart becomes available (2) but also as a definitive therapy.

In 2001, the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated the effectiveness of the HeartMate XVE (Thoratec Corp, Pleasanton, CA), a pulsatile-flow LVAD, in reducing all-cause mortality compared to optimal medical therapy (52% of survival compared to 25% in the medical group, p=0.002)(3). Since then, LVADs have undergone considerable advancements, becoming smaller, more hemocompatible, silent and durable, making them increasingly suitable for long-term support.

Continuous-flow (CF) technology with minimal or no pulse physiology(4) was a key factor in the miniaturization of newer LVAD designs. Devices like HeartMate 3 (HM3) (Abbott Laboratories, Abbott Park, IL) and Heartware HVAD (Medtronic, Minneapolis, MN) exemplify CF-LVADs that no longer rely on large pneumatic extracorporeal pumps for generating pulses. Subsequently, survival after LVAD implantation has improved significantly over the last decade. However, this change in blood flow dynamics, characterized by laminar flow with reduced or absent pulsatility in CF-LVADs, is considered a major contributing factor to endothelial dysfunction, leading to potential occurrences of bleeding or thromboembolic events(5). Of note, in June 2021, Medtronic halted the worldwide distribution and sale of the Heartware HVAD device due to an elevated risk of neurological adverse events and mortality(6).

To prevent thrombotic events and minimize bleeding incidence, careful antithrombotic management is necessary. In the past, pulsatile devices required only aspirin as antithrombotic therapy(3). Until recently, for newer CF-LVADs, the practice involved life-long anticoagulation with a vitamin K antagonist (VKA) along with concomitant antiplatelet agents, mainly based on non-randomized evidence(7,8). The ARIES-HM3 trial(9), however, has recently challenged this approach by demonstrating that excluding aspirin from the antithrombotic regimen in patients with a fully magnetically levitated LVAD did not compromise safety and was associated with a reduction in bleeding events, with 74% of patients in the placebo group versus 68% in the aspirin group being alive and free of major nonsurgical hemocompatibility-related adverse events at 12 months. This aspirin avoidance led to a 34% reduction in nonsurgical bleeding events without an increase in stroke or other thromboembolic events. Similarly, the US-TRACE study observed 93.8% freedom from ischemic stroke and 92.7% from device thrombosis at one year among HeartMate II patients on reduced antithrombotic therapy, despite a subsequent bleeding event in 52% of cases(10). The European TRACE study further supports managing HeartMate II patients with a vitamin K antagonist without antiplatelet therapy could reduce the incidence of major bleeding without increasing thromboembolic events, including ischemic stroke and pump thrombosis, with an 81% freedom from bleeding and 96% freedom from ischemic stroke at 2 years(11).

These findings challenge the necessity of aspirin in antithrombotic regimens, especially with devices like the HM3, which have significantly reduced the incidence of pump thrombosis. An observational study reported no bleeding events among patients discharged without aspirin, contrasting with a 39% bleeding occurrence in patients treated with aspirin, suggesting the potential safety and efficacy of primary warfarin monotherapy after discharge(12). Another study added insight to this ongoing discussion by examining the effects of discontinuing aspirin in patients equipped with the HeartMate 3 LVAD(13). Initially, 43 patients—after excluding 7 who died before leaving the hospital—received a combination of aspirin and warfarin. Based on personalized evaluations, three patients chose to continue this combined treatment, while the remaining 40 switched to only warfarin. This change enabled the researchers to assess the safety and effectiveness of warfarin alone in managing the risks of blood clots and bleeding, with measures like INR and lactate dehydrogenase levels showing no significant changes after stopping aspirin. The study also tracked the performance of the LVAD, monitoring metrics such as blood pressure, pump speed, and flow to ensure the device worked well without aspirin(13).

More recently, as a result of enhanced blood compatibility of these devices, more conservative approaches to anticoagulation have been explored. The MAGENTUM-1 study validated lower international normalized ratios (INR) levels without increasing the risk of adverse events (14). Newer direct-acting oral anticoagulants (DOACs) have emerged as a potential substitute for anticoagulation among LVAD patients (15,16). Additionally, observations suggest that a lower dosage of aspirin (81 mg daily) achieves comparable antithrombotic effects compared to the standard dose (325 mg)(17).

Consequently, a range of worldwide antithrombotic protocols have been investigated, including those excluding aspirin (9,12,13,18), using reduced aspirin doses(17,19), adopting DOACs(15,16), and even utilizing phosphodiesterase type 5 inhibitors for their antithrombotic properties(20–22). Due to the absence of direct comparisons between numerous antithrombotic regimens, clinical equipoise exists concerning the most suitable antithrombotic therapy for LVAD patients. Meaningful advancements in antithrombotic treatment will likely emerge only by implementing well-designed randomized trials that directly measure the effects of different treatments. In the interim, an indirect comparison may offer additional insights into this crucial and current aspect of the lives of many LVAD patients worldwide. Therefore, we plan to conduct a living systematic review and network meta-analysis (NMA) of comparative cohort studies and randomised controlled trials to assess the incidence of thrombotic events and bleeding between various antithrombotic regimes in patients implanted with left ventricular assist devices.

METHODS

This protocol is reported following the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) Statement (*Appendix A*) (23,24) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The review will be conducted under the guidance of The Cochrane Handbook for Systematic Reviews of Interventions and will be reported following the PRISMA Extension Statement for NMA (23). Any protocol modifications will be described in the publication of the final report.

Types of studies

We will include randomized controlled trials and comparative cohort studies. The inclusion of non-randomized studies is justified by the predominance of observational studies over randomized trials in the literature, and the tendency of randomized trials to underreport rare or late-emerging adverse events.

Types of participants

Adult patients greater than 18 years old on continuous flow-LVAD support.

Types of interventions and comparators

Patients receiving vitamin K antagonist (INR goal between 2-3) with aspirin 325 milligrams will be the reference group (or comparator). As new interventions, we will include alternative antithrombotic regimens, such as:

- Vitamin K antagonists (at varying INR levels), either in combination with different aspirin doses or without.
- Direct thrombin inhibitors.
- Phosphodiesterase type 5 inhibitors.
- Factor Xa Inhibitors.
- The absence of antithrombotic medications.

We will include any of these interventions irrespective of dose and duration of administration.

Outcomes of interest

Stroke, thromboembolic events and pump thrombosis are our primary outcomes; bleeding and mortality are our secondary outcomes. We will define outcomes according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) study (25):

Ischemic stroke: "new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit";

Hemorrhagic stroke: "New acute neurologic deficit attributable to intracranial hemorrhage."

Pump thrombosis: "special case of major device malfunction and can be categorized as a suspected device thrombus or confirmed device thrombus."

Bleeding: "Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone)."

Studies with either primary and/or secondary outcomes will be included.

Search strategy and databases

The search strategy was developed with the assistance of an experienced librarian in systematic reviews and network meta-analyses. The search strategy is described in *Appendix B*, and we systematically search the following electronic sources: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE).

We will exclusively examine studies published in English from 2016 to the present. Studies conducted before 2016 will be omitted since our primary focus is evaluating continuous flow devices. It is noteworthy that studies before 2016 typically involved the assessment of pulsatile flow devices, which have since become obsolete.

We will conduct searches on clinicaltrials.gov and clinicaltrialregister.eu to locate ongoing trials. Furthermore, we will find additional references by manually reviewing the citations of the included articles. Our database searches will be refreshed every two months until publication.

Study selection

All records identified by the search strategy will be uploaded to Covidence 2.0 software (26), and duplicates will be removed. Two independent reviewers (SD vs OD or HS) will screen studies for eligibility based on titles, abstracts, and full texts using the eligibility criteria. Any discrepancies in the inclusion criteria will be resolved through discussion and consensus between the reviewers. If necessary, a third reviewer (DT) will be involved. We will use the discrepancies between the reviewers to calculate a kappa statistic and assess inter-reviewer reliability; a kappa statistic>0.6 will be considered acceptable.

We will document the reasons for excluding full texts and present this information using Covidence to create a PRISMA flowchart.

Data extraction

We will design a standardized data extraction form that will be piloted on 10% of included studies. Two reviewers will independently extract the data, and any inconsistencies will be resolved through discussion or with a third reviewer, if necessary. If we need further information or the data appears insufficient, we will contact the authors. If it is impossible to reach the authors, we will discuss this limitation in the final manuscript.

Using the data extraction form, we will capture the following information: title, authors, journal, publication date, study period, number of participants, country, type of implanted device, study population characteristics, antithrombotic regimens, and primary and secondary outcomes.

If necessary, our team will contact study authors to obtain additional information for our review.

Living systematic review

We will perform updates to our search every two months. A range of antiplatelet and anticoagulation strategies are being utilized, but there is a lack of studies directly comparing them. We are of the opinion that ongoing clinical trials focused on antithrombotic therapies have the potential to offer new perspectives that will enrich our network meta-analysis.

Network meta-analysis

Before proceeding with the network meta-analysis, we will assess if sufficient statistical data exists to evaluate their consistency and the assumption of transitivity.

According to this assumption, we can only examine these trials when we have closed loops, and it assumes that the distribution of the effect modifiers is comparable across treatments. For instance, if studies of warfarin and aspirin versus apixaban and aspirin, and warfarin-aspirin versus warfarin differ with respect to their effect modifiers, then it would not be appropriate to make an indirect comparison between apixaban-aspirin and warfarin-only regimen (**Figure 1**).

If network meta-analysis is conducted, we will adopt a Bayesian approach and a random effects model for binomial and continuous outcomes, assessing the effect estimate of each anticoagulation therapy.

Mean differences and odds ratios with 95% confidence intervals will be presented. Following unadjusted analysis, secondary analyses will be conducted to account for any imbalance in the distribution of effect modifiers, especially types of devices. Network meta-regression methods will be conducted to account for these differences.

Geometry of the network

The network diagram will visually represent the available evidence of each comparison between different antithrombotic regimens. **Figure 2** shows a draft of the possible network diagram for our future analysis.

Risk of bias in individual studies

To determine methodological validity, we will assess the risk of bias of the included studies at a study level using the Revised Cochrane Collaborations Risk-of-Bias (RoB 2) tool and ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions). Any discrepancies will be resolved through discussion until a consensus is reached.

Summary measures

Primary outcome

Incidence of stroke and thromboembolic events will be reported as dichotomous outcomes occurring at any time after implantation of the LVAD until three years of follow-up. Relative risks with 95% confidence intervals will be calculated to compare the incidence of stroke between different antithrombotic regimens.

Secondary outcomes

Bleeding will be reported as dichotomous data.

Pairwise meta-analysis

We will conduct a pairwise meta-analysis using random-effects model. Statistical heterogeneity within pairwise comparisons will be evaluated by visual inspection of forest plots and I^2 measure. If there is a high amount of heterogeneity (I^2> 75%), then sources of heterogeneity will be examined through subgroup and sensitivity analyses.

Subgroup and sensitivity analyses

If the studies have high heterogeneity, subgroup analysis will be performed based on age, type of device and recalled devices from 2021.

Sensitivity analysis will be used to verify the reliability of the results. According to the Cochrane Handbook, sensitivity analysis will be conducted in the three aspects of methodological quality, sample size, and statistical model. We will exclude studies with poor research quality, small sample size, and high risk of bias.

Assessment of inconsistency

Inconsistency in the data will be assessed by fitting inconsistency model scatterplots and using Cochran's *Q* test. A statistician with experience in systematic review and network meta-analysis will assist our team.

Ethics and dissemination

This study is SR protocol collecting data from published literature and, therefore does not require institutional review board approval. Results from this SR and NMA will be published in a peer-reviewed journal.

Patient and public involvement

No patients or members of the public will be directly assessed. Only data already reported in the literature will be used in this study.

DISCUSSION

This systematic review and network meta-analysis is conducted against a backdrop of evolving LVAD technology and antithrombotic therapy. With the HM3 emerging as the only available implantable pump in many regions and its notably low risk of thrombosis, the implications of antithrombotic management have never been more pivotal. The HM3's technological advancements have reduced the incidence of pump thrombosis, shifting the focus toward managing bleeding risks. The ARIES study's findings are particularly relevant here(9), as they underscore the safety and efficacy of excluding aspirin from the antithrombotic regimen, which could mark a paradigm shift in reducing bleeding events without increasing thromboembolic risks.

While we recognize the pivotal contributions of the ARIES study, particularly its insights into aspirin's role in the antithrombotic regimens for LVAD recipients, it's critical to underline that its findings predominantly pertain to those with the HeartMate 3 device. This focus leaves a gap in our understanding of therapy for individuals with other devices, such as the still-utilized HeartMate 2. Furthermore, our analysis seeks to broaden the scope of investigation by assessing the impact of various treatments—including direct oral anticoagulants (DOACs), phosphodiesterase type 5 inhibitors, and phenprocoumon—on both primary and secondary outcomes. This comprehensive approach is designed to offer a more nuanced understanding of antithrombotic therapy's efficacy and safety across the diverse spectrum of LVAD technologies and patient needs.

Authors' contributions

SD, OD, HS, DT, and GW contributed equally to this work. SD, DT, and GW conceived the idea and design for this systematic review. SD, OD, DT, and GW developed the methodology for the systematic review protocol. The contents of this manuscript were drafted by SD, OD, and GW with input from all members of the authorship team. The manuscript was reviewed by SD, OD, DT, HS and GW for important intellectual content. All authors read and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

None.

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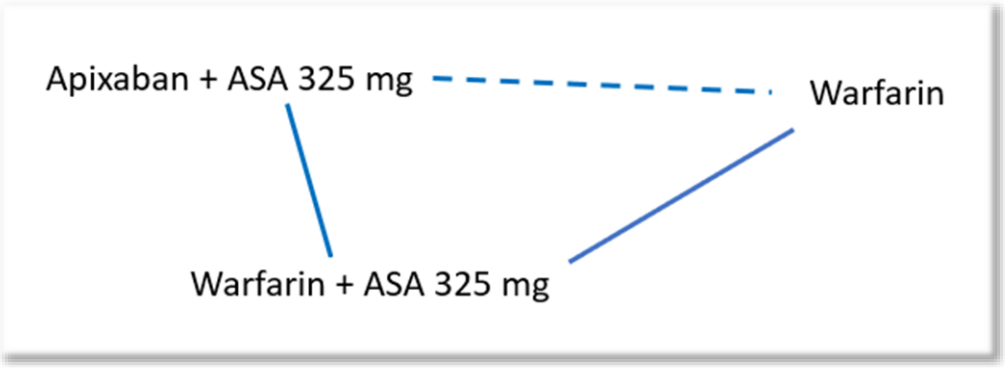
Figure 1. The dashed line indicates an indirect comparison.

Figure 2: The network diagram depicts multiple comparisons among different antithrombotic regimens used in LVAD patients. Although warfarin combined with 325 mg of aspirin was the standard treatment until recently, there has been a trend towards more conservative strategies in current practice. RCT: randomized controlled trial. ASA: aspirin.



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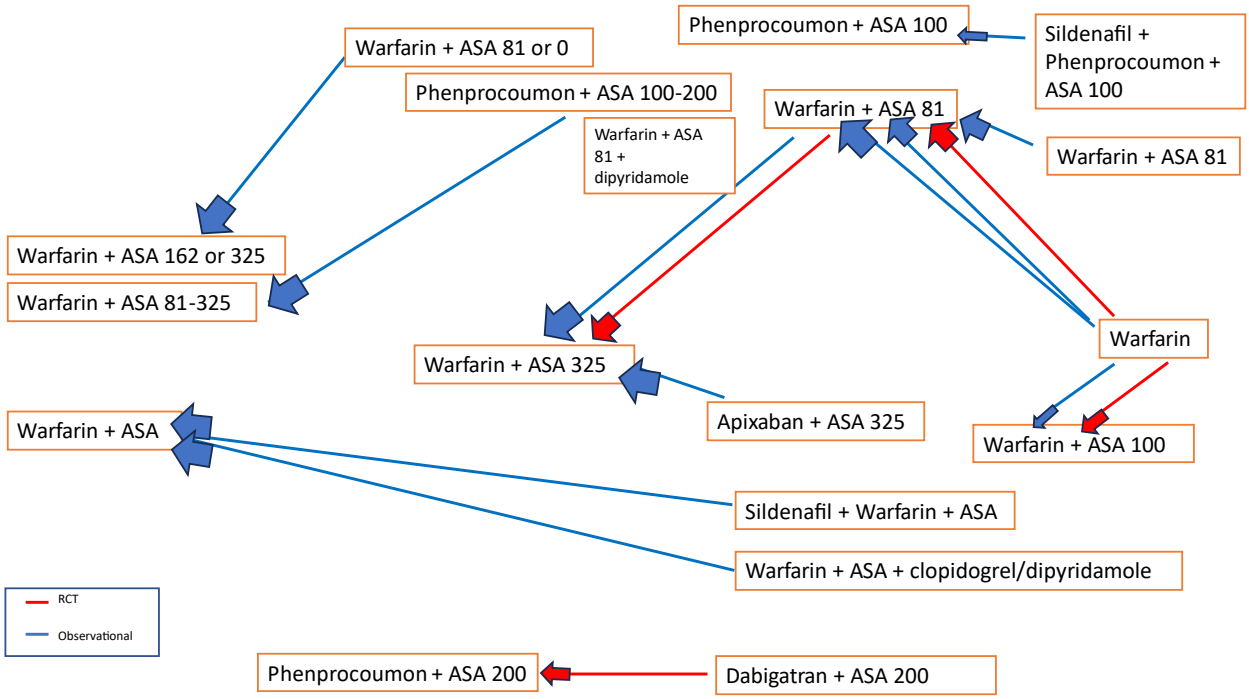

Figure 2: The network diagram depicts multiple comparisons among different antithrombotic regimens used in LVAD patients. Although warfarin combined with 325mg of aspirin was the standard treatment until recently, there has been a trend towards more conservative strategies in current practice.

SUPPLEMENTARY MATERIAL

APPENDIX A

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Performed
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Performed
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Performed
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Performed
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Performed
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Performed
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Performed
METHODS			

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Performed
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Performed
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Performed
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Performed
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Performed
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Performed
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Performed
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	

	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Performed
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Performed

Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647–g7647

APPENDIX B

Table 1 EMBASE search strategy

1. (left ventricular assist device or LVAD*).ti,ab,kf.
2. (Heartmate or Heartware or HVAD).ti,ab,kf.
3. exp left ventricular assist device/
4. 1 or 2 or 3
5. (stroke or cerebrovascular accident or cva or thrombo* or cerebral thrombosis or thrombosis).ti,ab,kf.
6. exp stroke/
7. limit 4 to yr="2016-2023"
8. 5 or 6
9. anticoagulant agent/ or fondaparinux/ or edoxaban/ or coumarin/ or dabigatran/ or rivaroxaban/ or low molecular weight heparin/ or hirudin/ or enoxaparin/ or heparin/ or phosphodiesterase type 5 inhibitors/ or viagra/ or sildenafil/ or tadalafil/ or warfarin/ or ximelagatran/ or acetylsalicylic acid/
10. exp anticoagulant agent/
11. exp coumarin/
12. (anticoagulation or anti-coagulation or anticoagulant* or antithrombotic or phytomenadione or doac or direct oral anticoagulants or fondaparinux or edoxaban or coumarin or dabigatran or apixaban or rivaroxaban or low molecular weight heparin or hirudin or enoxaparin or heparin or phosphodiesterase type 5 inhibitors or viagra or warfarin or ximelagatran or acetylsalicylic acid).ti,ab,tw,kf.
13. (vitamin adj3 antagonist*).mp.
14. 9 or 10 or 11 or 12 or 13
15. 7 and 8 and 14

Table 2 Medline search strategy

1. (left ventricular assist device or LVAD*).ti,ab,kf.
2. (Heartmate or Heartware or HVAD).ti,ab,kf.
3. Heart-Assist Devices/
4. 1 or 2 or 3
5. limit 4 to yr="2016-2023"
6. (stroke or cerebrovascular accident or cva or thrombo* or cerebral thrombosis or thrombosis).ti,ab,kf.
7. thrombosis/
8. thromboembolism/
9. exp stroke/
10. 6 or 7 or 8 or 9
11. coumarins/
12. exp anticoagulants/
13. exp heparin/
14. exp coumarins/
15. (anticoagulation or anti-coagulation or anticoagulant* or antithrombotic or phytomenadione or doac or direct oral anticoagulants or fondaparinux or edoxaban or coumarin or dabigatran or apixaban or rivaroxaban or low molecular weight heparin or hirudin or enoxaparin or heparin or phosphodiesterase type 5 inhibitors or viagra or warfarin or ximelagatran or acetylsalicylic acid).ti,ab,tw,kf.
16. aspirin/
17. (vitamin adj3 antagonist*).mp.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 5 and 10 and 18