Antithrombotic prophylaxis for thromboembolism in adult patients with a Left Ventricular Assist Device (LVAD): a systematic review update and meta-analysis

Antithrombotic prophylaxis for thromboembolism in adult patients with a Left Ventricular Assist Device (LVAD): a systematic review update and meta-analysis

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Health Research Methodology

McMaster University

Master of Health Research Methodology

Hamilton, Ontario (Health Research Methods, Evidence and Impact)

TITLE: Antithrombotic prophylaxis for thromboembolism in adult patients with a Left Ventricular Assist Device (LVAD): a systematic review update and meta-analysis

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PAGES: 69

Acknowledgments

I would like to express my gratitude to my supervisor and member of my committee, Dr. Mark Crowther. You have guided me to become a better researcher physician and have been an invaluable mentor. Thank you for your continued encouragement and patience. I would also like to thank the members of my committee, Drs. Lisa M. Baumann Kreuziger, Alfonso Iorio and Lehana Thabane, for their availability and invaluable input on my project.

I would like to thank the Department of Health Research Methods, Evidence, and Impact (HEI) staff for helping me along the way.

A special thanks to the team that contributed to this work and without whom this thesis would not be possible: Luca Ramelli, Sneha Sritharan, Brianna Bakow and Sooa Kim.

To my parents and sister, thank you for supporting me every step of the way and encouraging me to do my best.

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List of Abbreviations:

LVAD: Left ventricular assist device

RCT: Randomized controlled trial

NRS: Non-Randomized studies

AHA: American Heart Association

LVAD: Left ventricular assist devices

PF- LVAD: pulsatile flow Left ventricular assist devices

CF-LVAD: Continuous flow Left ventricular assist devices

INTERMACS: Interagency Registry for MechanicallCirculatoryCriculatory Support

UFH: unfractionated heparin

aPTT: activated partial thromboplastin times

VKA: vitamin K Antagonist

INR: International Normalized ratio

TSA: Trial sequential analysis

ICEMAN: Instrument to assess the credibility of effect modification analysis

DOAC: Direct oral anticoagulants

RR: relative risk

RoB: Risk of Bias

Declaration of Academic Achievement

The following is a declaration that Drs. Giovanna Muti Schuenemann created the systematic review search strategy, coordinated the systematic review, gathered reviewers, screened, collected, and analyzed data. Dr. Mark Crowther contributed to the study protocol for this thesis. Drs. Mark, Crowther, Alfonso Iorio, Lehana Thabane and Lisa M. Baumann Kreuziger reviewed the thesis manuscript. Systematic reviewers included Luca Ramelli, Sneha Sritharan and Sooa Kim.

Chapter 1: Background

Systematic reviews and meta-analyses provide clinicians with guidance on patient care. They are at the highest level of scientific evidence, able to provide conclusions from a rigorous process of data selection, analysis and synthesis.[1] This process prevents already over-worked clinicians from having to read several original research articles, which may also present discordant results. A very prominent issue currently impacting patient care is the inability of clinicians to critically analyze scientific literature due to a lack of knowledge of research methodology and therefore basing patient care decisions on poorly conducted trials and studies. While improvements are being made in instructing clinicians on the topic, it is essential to provide tools and enforce rigorous rules for the conduction of systematic reviews and meta-analyses. [2]

When assessing systematic reviews and meta-analyses, it is also essential to determine whether the information outlined is current or if new trials or new evidence has emerged pointing towards more efficient or less intolerant treatment options. Due to this, we must ensure that systematic reviews are updated and kept current.[3]

A significant issue encountered in clinical research is that of random error, simply implying that some positive or negative meta-analytic findings may not be due to an actual intervention effect but rather to the play of chance.[4] These types of errors, termed type I errors for false-positive events and type II errors for false-negative events, are often encountered in meta-analyses that include only a small number of trials and small population sizes. Random error is a commonly encountered phenomenon due to the lack of adequately conducted large RCTs in many fields of medicine. Additionally, the likelihood of encountering false positive or false negative results is due to the numerous statistical tests employed through the accumulation of additional data, as found in updates of systematic reviews and meta-analyses. [5–7]

In this systematic review update, we propose to perform a meta-analysis using the Copenhagen Trial unit trial sequential analysis (TSA) software to minimize the risk of committing type I or type II errors.[8] This approach suggests using a combination of modifications to the significance testing by quantifying the strength of the evidence and accounting for the number of significance tests done. This approach has been shown through empirical evidence to allow for reasonable control of type I errors in meta-analyses. [9,10]

In addition to this, we propose to use the ICEMAN tool for meta-analyses to determine the correct subgroup analyses we must conduct. This tool is based on effect modifiers and therefore aims to counter the overreliance on the p-value to explore the interaction between effectors and intervention when assessing an outcome.[11]

Chapter 2: Antithrombotic prophylaxis for thromboembolism in patients with a Left Ventricular assist device: a systematic review update and meta-analysis

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Abstract

Background: Left Ventricular Assist Device (LVAD) implantation is the treatment of choice in patients with end-stage systolic heart failure awaiting transplantation or ineligible for transplantation, significantly improving survival.[12] Recently, the demand for LVADs has been increasing, highlighting the risks of arterial and venous thromboembolism, bleeding and death.[13] Prevention of these complications is currently being studied to determine the best antithrombotic prophylactic regimen, particularly comparing mono antithrombotic to dual antithrombotic regimens.[14]

Methods: We conducted a systematic review and searched Medline, Embase, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1st, 2014 to March 13th, 2022. We identified all studies addressing antithrombotic prophylactic therapy in LVAD patients. The outcomes of interest included thromboembolic complications, mortality, and major bleeding. This systematic review is registered on PROSPERO, registration CRD42021244905.

Results: We screened 5,770 references and identified 529 studies on LVAD antithrombotic prophylaxis. A total of 45 studies met eligibility criteria and were extracted. We used the TSA approach to minimize random errors from repeated testing. However, results were inconclusive due to a lack of evidence and high risk of bias in the included studies.

Conclusion: To determine the best antithrombotic prophylaxis in LVAD patients, well-conducted non-randomized and randomized controlled trials are needed. Current evidence suggests superiority of dual antithrombotic prophylaxis in the prevention of thromboembolic events and mortality with no difference in bleeding.

2.1. Introduction

Heart failure is a current worldwide epidemic affecting over 23 million people.[15] The current life-saving treatment for heart failure consists of heart transplantation, presenting severe limitations in its application due to the lack of organ supply, cost and complexity. Data from the United Network for Organ Sharing reported that from 1987 to 2012, 40,253 people in the United States were waiting for heart transplantation, of which only 26,943 received transplantation.[16] While waiting for transplantation, patients are managed with left mechanical circulatory support devices. This group of machines includes total artificial hearts, pulsatile flow Left ventricular assist devices (PF- LVAD) and continuous flow LVADs (CF-LVADs) which are further divided into axial or centrifugal pumps. Thanks to improved pump mechanics, the current use of LVADs has expanded from a bridge to transplant to being considered destination therapy and bridge to recovery. However, despite advancements in the mechanics of LVADs, their basic design has stayed constant. Their functioning consists of an inlet cannula found in the apex of the left ventricle, which pumps blood through the ventricle and out via an outflow graft into the ascending or descending aorta.[17] The approved CF-LVADs include the axial flow Heartmate II (HM II, Thoratec Corporation, Pleasanton, CA) and the Jarvik 2000.[18.] The latter two devices were seen to have higher acceptance due to their smaller size, lower rate of infection of the external driveline, and more durable effect.[19] Currently, third-generation CF-LVADs have been developed, of which the most used are the HeartWare HVAD (HW, HeartWare International Inc., Framingham, MA) and HeartMate 3 (HM III, Thoratec Corporation, Pleasanton, CA). The critical difference from the previous generations is the use of contact versus non-contact bearings, which provides rotation without friction through magnetic levitation.[20] This design reduces the prothrombotic sites while maintaining a sufficient amount of efficiency and durability. In addition, these new-generation devices appeared to be more durable, lasting 5- to 10 years, and with lower risks of hemolysis and thrombosis.

Since the adoption of LVAD devices, heart failure complications have decreased while the indication and demand for LVADs have increased. Unfortunately, this increased use has also highlighted the risks associated with these devices.[13] The main complications associated with LVAD devices are due to the high nonphysiological shear stress transmitted to the blood while it moves through the machine. This is associated with increased bleeding events due to arteriovenous malformations in the gastrointestinal tract and the development of acquired von Willebrand syndrome. [21] In fact, bleeding is the most common adverse event after implantation

and over the course of therapy. The risk is exacerbated byb the need for long-term antithrombotic prophylaxis. Another significant complication in these patients is thrombosis, such as pump thrombosis and stroke. These, on the other hand, are mainly associated with a suboptimal antithrombotic regimen, atrial fibrillation and infection.[22]

Prevention of these complications is currently being studied to determine the best antithrombotic prophylactic regimen. It is essential to understand the differences in rates of thromboembolism and bleeding when patients are treated with an antithrombotic prophylaxis composed of a single anticoagulant or antiplatelet compared to a dual therapy consisting of a combination of an anticoagulant and antiplatelet.[14]

In 2015, Baumann-Kreuziger L.M. et al. published a systematic review addressing the question mentioned above of a prophylactic antithrombotic regimen post-implantation of an LVAD.[23] This systematic review included in the final manuscript 24 studies and outlined the most used strategy for the definitive antithrombotic prophylaxis. The antithrombotic prophylaxis assessed was either a dual anticoagulant and antiplatelet using a VKA and Aspirin or dipyridamole versus a single anticoagulant using a VKA. The comparison between these strategies was limited due to the variability in antithrombotic agents used and in outcome definitions such as major bleeding and thrombosis. The author highlighted the need for further studies comparing antithrombotic strategies in LVAD patients to answer the previous question. Our goal with this update would be to elucidate any evidence published on the topic since 2014. In our current systematic review, we look and try to reassess the existing body of evidence with the hope of providing further guidance on the topic. [23]

The goals of our study include:

1. Identify, update, and describe the recent existing literature on antithrombotic prophylaxis in patients with an LVAD device
2. Explore the role of using a TSA approach in the context of meta-analysis
3. Validate and use the ICEMAN tool for the identification of correct subgroup analysis to conduct in our systematic review and meta-analysis

2.2 Methods

This systematic review was performed in accordance with the recommendations of the PRISMA and MOOSE guidelines.[24,25] The protocol of this study was registered before commencement on PROSPERO (CRD42021244905).

2.2.1 Review Question

In adult patients with systolic heart failure who received a left ventricular assist device (LVAD), what are the effects of dual prophylactic antithrombotic therapy composed of an anticoagulant and an antiplatelet compared to single-agent antithrombotic prophylaxis with an anticoagulant or an antiplatelet, on venous and arterial thromboembolism, major bleeding and mortality.

2.2.2 Study design and searches

We performed a systemic literature search of MEDLINE, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). Registration of protocols on clinical trial databases were searched and considered for study inclusion. Both published and unpublished studies were sought after without applying any language restriction. Searches were run from January 1st, 2014 to March 13th, 2022 and will be repeated before submitting the article. We chose 2014 to capture studies published in the year of the previous systematic review by Baumann-Kreuziger L.M.[23] We collaborated with the author of this review. Exclusion criteria included review articles, single case reports and letters to the editor not containing any relevant primary data. Additionally, animal studies and basic science studies were excluded as well. Systematic and narrative reviews were excluded during the screening phase. These, however, were tagged for review of the references to assess for eligible missed studies. Forward and backward citation searches were conducted.

2.2.2 Inclusion and exclusion criteria

Inclusion criteria:

Participants/population

Our population included adult patients implanted with either axial CF-LVADs HeartMate II (Thoratec, Pleasanton, CA, USA) or Jarvik 2000 (Jarvik Heart, Manhattan, NY, USA) or Centrifugal CF-LVADs HeartWare HVAD (Heartware Inc., Framingham, MA, USA) or HeartMate3 (Abbott).

Interventions

Adult LVAD patients receiving dual antithrombotic prophylaxis composed of an antiplatelet and anticoagulant. Accepted antiplatelets included: clopidogrel**,** aspirin**,** dipyridamole with

aspirin, prasugrel and ticagrelor. Anticoagulants accepted were heparin family (unfractionated heparin or low molecular weight heparin), VKA, direct oral anticoagulants (dabigatran, rivaroxaban and apixaban) or fondaparinux.

Comparators

Adult LVAD patients receiving mono antithrombotic prophylaxis with an antiplatelet or anticoagulant. Accepted antiplatelets included: clopidogrel, aspirin, dipyridamole with aspirin, prasugrel and ticagrelor. Anticoagulants accepted were: heparin family (unfractionated heparin or low molecular weight heparin), VKA, direct oral anticoagulants (dabigatran, rivaroxaban and apixaban) or fondaparinux.

Main outcomes

The outcomes we evaluated were: thromboembolic complications, defined as pump thrombosis, fatal pulmonary embolism, pulmonary embolism, stroke, clinically overt DVT or other objectively confirmed arterial or venous thrombosis, major bleeding, defined according to the International Society on Thrombosis and Hemostasis (ISTH)[26] (described in table A1.5) and mortality.

Measures of effect

Studies had to report absolute and relative estimates of effect for the outcomes above, which we planned to display using forest plots and calculated using the random-effects model with their corresponding log odds ratio and their 95%CIs. We then synthesized them in a GRADE evidence profile and a summary of findings table.[27] We used study author definitions for the outcomes and to assess directness across study outcomes using GRADE guidance.[28]

Exclusion criteria:

We excluded studies in which LVAD patients were not being given antithrombotic prophylaxis or did not report the antithrombotic regimen. We also excluded studies including patients with thromboembolic events diagnosed by routine screening (asymptomatic DVT detection using duplex ultrasonography, D-dimer elevation in asymptomatic patients).

2.2.3. Study selection and data extraction

This systematic review and meta-analysis included RCTs of any size published in any language assessing antithrombotic prophylactic therapy in LVAD patients. We also included NRS to

retrieve long-term follow-up data, which is more likely to be measured in NRS. We did not expect the topic to have been addressed in a sufficient number of trials to allow a systematic and comprehensive investigation. We used comparative trials and NRSs to calculate the comparative estimates of interventions on the relative outcomes. In addition, we searched the literature for single-arm noncomparative NRS to estimate the pooled proportion of patients developing the outcomes of interest. For the same purpose, we considered as single-arm studies the individual study groups of RCTs or comparative NRS in which all patients received the same intervention of interest. Reviewers with relevant language skills reviewed non-English records and translated them as necessary. The studies were identified and screened for relevance and eligibility through a standardized two-step approach using COVIDENCE. [29] To assess comprehension, we performed a prior piloting exercise for both the "title and abstract" phase and the "full-text stage." We used a standardized data form to screen the identified studies' relevance. We performed the data extraction in a similar fashion. We performed all these steps in duplicate; a third researcher, GMS, resolved the disagreements if conflicts arose. The kappa statistics was used to determine concordance between screeners.

2.2.5 Quality assessment

We assessed the risk of bias of the identified studies independently and in duplicate using the ROBINS-I for NRS and ROB-2 for RCT.[30,31] We reached agreement on risk of bias judgments through either consensus or involvement of a senior methodologist. We used the GRADE methodology to assess the certainty of the body of evidence by outcome and produce an evidence profile and interactive Summary of Findings Table in GRADEpro. [27,32] We did not downgrade on the basis of the TSA analyses due to the incongruity we found between the two methods of imprecision assessment. While the GRADE approach uses a semi-quantitative approach with intrinsic subjectivity, the TSA analysis is a purely quantitative and objective approach. Therefore, this leads to a more stringent and severe judgement on certainty of the evidence.

2.2.6 Data Synthesis

Summary measures included absolute and relative effects for the outcomes outlined and displayed in a forest plot calculated using a random-effects model since we expected to find a high variation in intervention effects across studies.[33] We assessed heterogeneity using the I^2 statistic and the Chi-squared test (χ^2).

To determine publication bias, we visually assessed funnel plots and Harbord's modification of the Egger test. If necessary, the mean and standard deviation was calculated from medians, interquartile ranges or ranges by Wan's method.[34] We performed the data analysis using STATA 17.1. We performed all calculations by intention-to-treat (e.g., include all randomized patients to any treatment arm). This was verified by full-text review and/or contact with study authors. Using the log Odds ratio, we summarized dichotomous outcomes based on the DerSimonian-Laird random-effects model, with heterogeneity estimates provided via the Mantel-Haenszel model. Studies with no events in either the intervention or control group were corrected using the constant continuity correction method with a value of 1.[35.] Absolute effects are expressed as natural frequencies. All summary measures are reported with 95% CI.

Missing, unpublished or unclear data prompted us to contact study authors for clarification.
As anticipated, our meta-analysis contained sparse data; thus, we planned to analyze with a small number of trials or events. Considering the prior review did not include a meta-analysis, we did not believe repeated significance testing would be a concern; however, we proposed using a Trial Sequential Analysis (TSA) approach to minimize the risks of a type-1 error based on conclusions drawn in the prior review.[8,36] Using the TSA analysis, we synthesized the data using the reported effect size with its 95% confidence interval. We used the same random-effects meta-analytic technique applying the reported statistical heterogeneity. We added the included trials sequentially based on the year of publication forming the cumulative analyses. The alpha used for the calculation was 0.05 and beta of 0.20. The default threshold for the RRR remained 25%.

2.2.7 Analysis of subgroups or subsets

We consulted the instrument to assess the credibility of effect modification analysis (ICEMAN) in randomized controlled trials and meta-analyses to determine which subgroup analyses to perform. [11]
Planned subgroups include sex, age, comorbidities, previous thromboembolic event, type of LVAD device, INR levels and type of antithrombotic agent used.

2.2.8 Sensitivity analysis

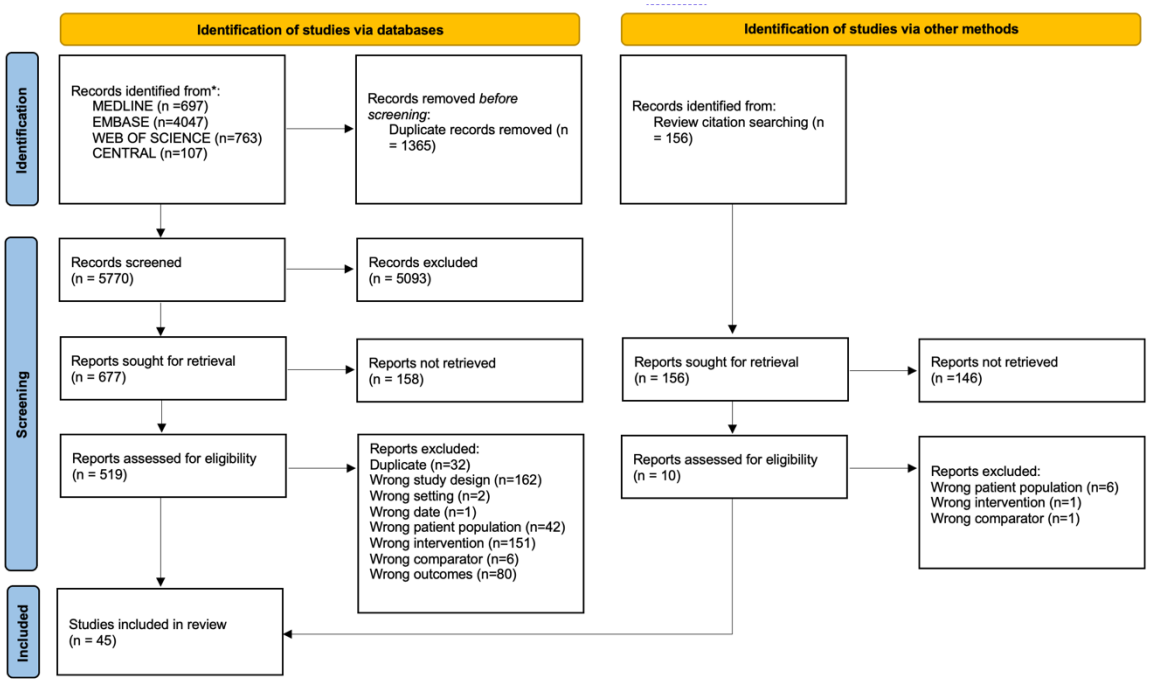
We controled for effect variation due to studies' risk of bias by running a sensitivity analysis (pooled estimate of all studies vs pooled estimates excluding high RoB).

2.3 Results

2.3.1 Description of the included studies

Database searches were run from January 1st[t] 2014 to March 13th[h] 2022 and identified 7,135 references. The title and abstract phase, done in duplicate by screeners G.M.S., S.K., S.S., LR, saw the exclusion of 6,399 studies. At the full-text stage, the number of studies assessed for eligibility was 529, of which we excluded 484. The entire process is illustrated in figure 1. The most common reasons for exclusion were: (162/484, 33%) wrong study design (151/484, 31%) wrong intervention, and (80/484, 17%) no outcome of interest with the inability to contact authors. The final number of studies extracted by the reviewers was 45. The included studies were composed of 43 NRS and 2 RCTs. The 43 NRS were composed of 83% retrospective cohort studies and 17% prospective cohort studies. Only 12 provided comparative data; the remaining 33 provided single-arm data on either the intervention or comparator. We judged the quality of the included studies to be at moderate to serious risk of bias, with a small proportion judged a low risk of bias. The complete list of included studies can be found in the appendix table A 2.1.

Figure 1: PRISMA flow chart



The studies provided outcome information for 5,798 patients, 4,733 in the intervention arm of dual antithrombotic prophylaxis and 1,052 in the control arm of mono antithrombotic prophylaxis, with a total of 5 patients lost to follow-up. Amongst LVAD devices, most patients included were implanted with the HeartMate II device (63.8%), followed by the HeartWare device (15.0%) and finally the HeartMate 3 device (11.6%), which was approved in 2017.

Most studies used an INR value of 2.0 - 3.0 as therapeutic range. However, some studies required a more stringent control maintaining the value of INR under 2.5. The mean age of patients in the included studies was 54.1 (SD 10.6), most patients were male (81.5%), and the most common comorbidities included: type 2 diabetes mellitus (30.6%), hypertension (51.4%) and dyslipidemia (63.0%). Although data on concomitant medication and comorbidities in patients was minimal, it was reported that 34.3% of patients had concomitant atrial fibrillation for which prophylactic treatment with Aspirin (81-325mg) was maintained.[37–44] Only three studies documented the use of prophylactic warfarin prior to implantation of the LVAD device, and no data was provided as to when it was suspended before the operation.[45–47] Even though relevant for determining the individual baseline risk of developing a thrombotic event, only five studies reported on prior thromboembolic events, with an average of 23% of patients experiencing such events before surgery.[40,41,44,48,49] The type of thromboembolic events was not specified, and in most cases, no information was given as to whether these patients were receiving antithrombotic treatment prior to the event.

The dosage of Aspirin ranged from 81-325 mg depending on both kidney function, using the GFR as a parameter and the estimated risk of patients. In 4 studies, DOAC were proposed using a dosage of 15mg of Rivaroxaban once daily, 5mg of Apixaban twice daily, and 110-150mg of dabigatran (75mg if renal impairment was found).[45,46,50,51]

In the remaining studies, the most used *chronic* anticoagulant was the VKA warfarin with phenprocoumon as an alternative in 1 study only.[52] The most common anticoagulation strategy used *as a bridge* from surgery to chronic therapy was a combination of an anticoagulant and an antiplatelet commenced within 24 hours of implantation and maintained for a duration of 2 to 3 day post-operatively. Patients were mainly administered a combination of anticoagulants such as heparin, unfractionated heparin, or low molecular weight heparin with low dose aspirin or clopidogrel as an antiplatelet. Patients were then switched to the definitive *chronic* antithrombotic regimen once the target INR was reached. The average aPTT target used post-operatively ranged from 40 to 60s.[53–55]

We considered thromboembolic complications a composite outcome comprising pump thrombosis, fatal pulmonary embolism, pulmonary embolism, myocardial infarction, stroke, clinically overt DVT and other objectively confirmed arterial or venous thromboembolism. We defined the outcome of major bleeding using the ISTH definition of major bleeding.[26]

2.3.2 Outcome of thromboembolic events

The number of thromboembolic complications was assessed in 37 NRS and 2 RCT with small sample sizes.[50,56] For comparative NRS, when evaluating the number of thromboembolic events in patients treated with a dual antithrombotic regimen versus a mono antithrombotic regimen, the odds ratio (OR) was 0.77 (95% CI of 0.45 to 1.34) and 38 fewer patients for every 1000 patients treated with a dual antithrombotic regimen (95% CI from 98 fewer to 51 more). While not large in its effect, this may suggest a benefit of using a dual prophylactic regimen to prevent thromboembolic complications (figure 2).[41,43–46,51,55,57–59] The results were then confirmed using the TSA method, which established the non-statistical significance of our results, excluding potential spurious treatment effects (figure 3).

Figure 2: Forest plot of comparative studies reporting on total thromboembolic events

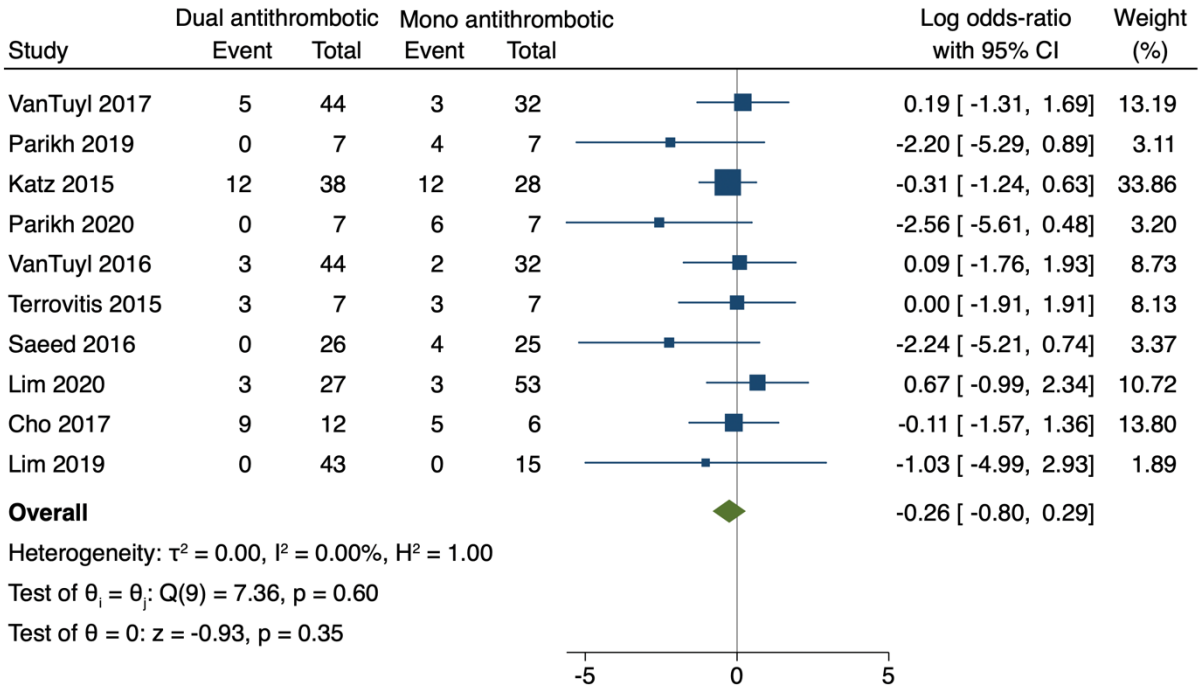
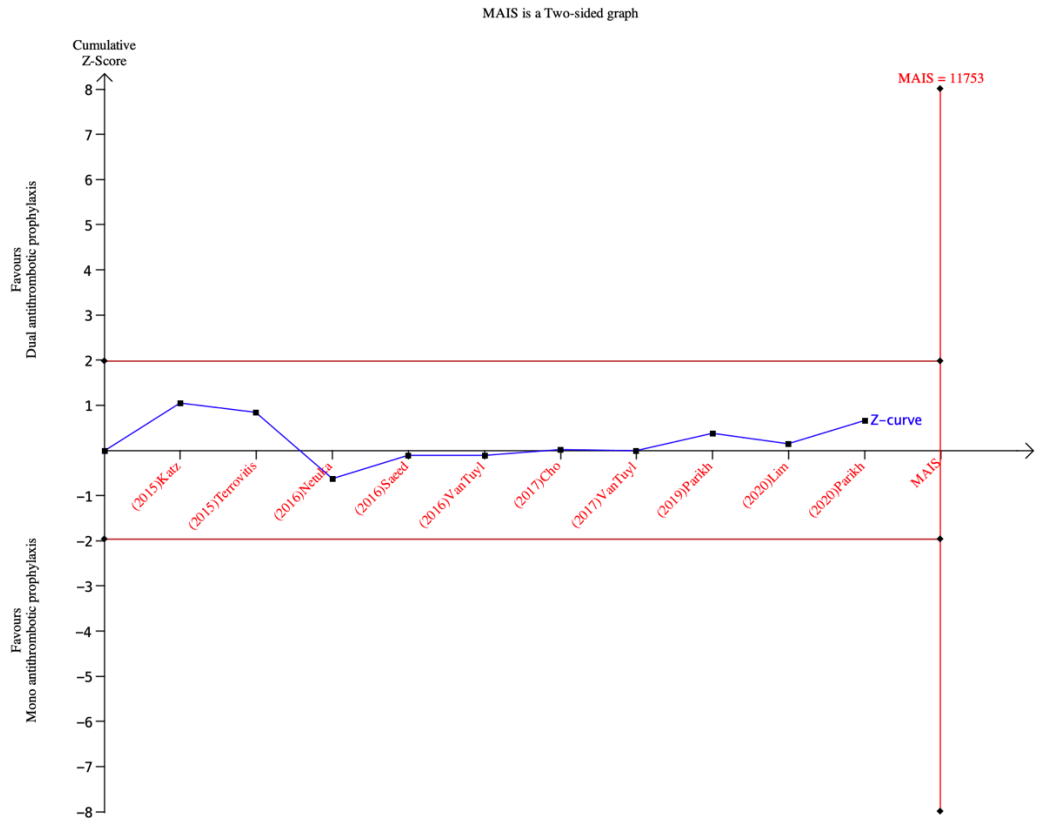


Figure 3: TSA analysis graph on studies reporting on total thromboembolic events



On the other hand, when assessing the 2 RCTs reporting on thromboembolism, the studies suggested an increased number of thrombotic events in LVAD patients receiving a dual antithrombotic regimen, as shown in Andreas et al., where 4 out of 8 patients developed a thrombotic event in the dual group and 1 out of 8 in the mono therapeutic group.[50] The study by Jorde et al. showed 12 thrombotic events in the 31 patients included in the dual antithrombotic group and 10 out of the 34 patients in the mono therapeutic group.[56] The study by Andreas et al. proposed the use of a DOAC in combination with aspirin while the study by Jorde et al. used a combination of VKA and aspirin. The 2 RCTs demonstrated a pooled OR of 1.54 (95% CI 0.63 to 3.78) and 91 more thromboembolic events per 1000 patients treated with a dual antithrombotic regimen (95% CI from 79 fewer to 311 more).[50,56] Figure 5 shows the result of the TSA method suggesting that while the number of patients accumulate, the ability to infer the actual effect of the intervention remains limited as the results do not appear statistically significant. The information size for this outcome could not be estimated due to limited number of studies included.

Figure 4: Forest plot of RCTs on total thromboembolic events

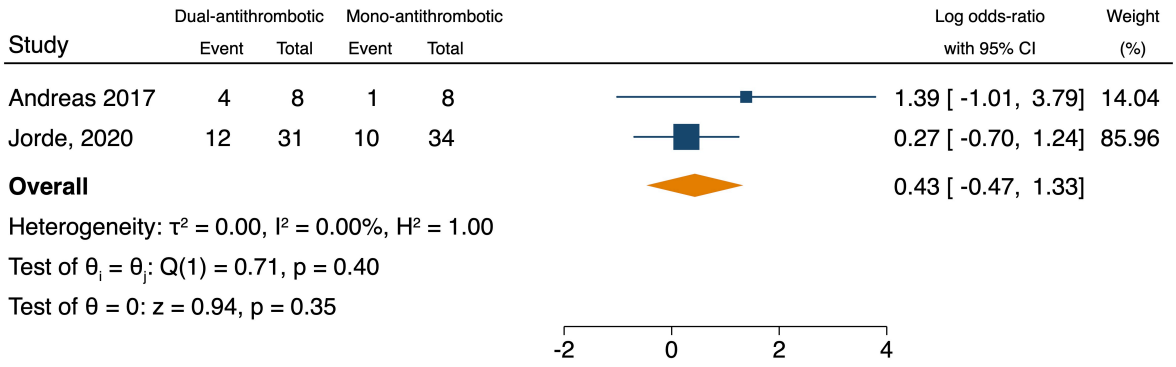
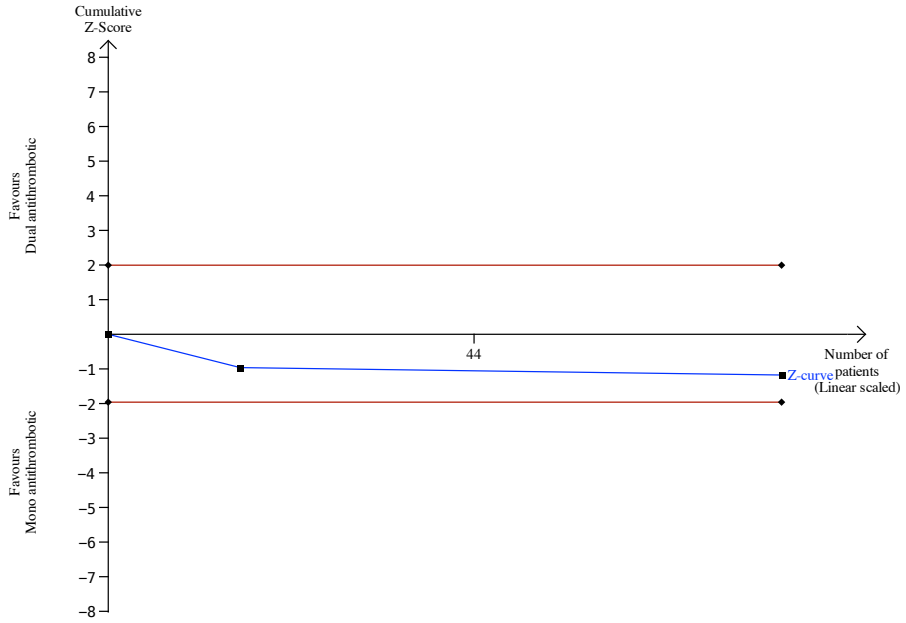


Figure 5: TSA analysis of RCT for total thromboembolic events



Single-arm data on thromboembolic complications were retrieved from 27 NRS, with most of them reportig a limited number of events. Specifically, when assessing the dual antithrombotic prophylaxis group, event rates ranged from 0% to 23%, as seen in the study by Willey et al., where 70 thrombotic events happened in 301 LVAD patients.[44,52,60] Most thromboembolic complications were pump thrombosis, experienced in 6% of patients receiving dual antithrombotic prophylaxis and in 4% of patients receiving the mono antithrombotic prophylaxis. To explore the differences between the two antithrombotic regimens, we further compared different types of thromboembolic events composing our composite outcome. Specifically, comparative studies on pump thrombosis revealed an overall OR of 0.66 (95% CI 0.27, 1.65), demonstrating a potential benefit of a dual antithrombotic regimen, as shown in the appendix figure A 3.1.[41,43–45,51,55,58,59] On the other hand, the number of strokes occurring in

patients were comparable between the two groups with 10% of patients experiencing a stroke in the intervention group and 10% of patients in the control group. This is demonstrated in the pooled analysis with an OR of 0.96 (95%CI 0.41, 2.20), as shown in the forest plot appendix A 3.2.[44–46,51,58,59] The remainder of thrombotic events which occurred in patients were seen in 8% of patients assessed in the dual antithrombotic group and 32% of patients evaluated in the mono antithrombotic group. These are demonstrated in the forest plot A 3.3, where we can see an OR of 0.72 (95% CI 0.34, 1.55) between the two regimens.[41,45,46,57] No outcome data was available for pulmonary emboli, myocardial infarction and symptomatic DVT. Three out of the 43 NRS assessed in this systematic review proposed using DOACs as an anticoagulant combined with an antiplatelet as a chronic prophylactic regimen.[45,46,51] These studies demonstrated a benefit in preventing thrombotic events in 2 studies by Parikh et al., and 1 showed comparable effects when compared to a mono VKA antithrombotic prophylaxis by Terrovitis et al.[45,46,51]

The results from these NRS suggest a potential improved effect of dual antithrombotic prophylaxis for the critical outcome of thromboembolic events. The data retrieved from the 2 RCT reported on patients treated with different antithrombotic regimens, one using dabigatran together with aspirin, while the other warfarin in combination with aspirin.[50,56]

2.3.3 Outcome of Major bleeding

When assessing the effect of dual antithrombotic regimen on major bleeding, the pooled OR seen for comparative NRS was 1.21 (95% CI of 0.61 to 2.41).[41,43–46,51,58,61] In absolute terms, this amounts to 38 more hemorrhagic complications for every 1000 patients treated with a dual antithrombotic regimen (95% CI from 83 fewer to 197 more), as shown in figure 6. While not demonstrating a large effect of dual antithrombotic therapy on the development of major bleeding, it may suggest that the two strategies are comparable in their ability to prevent this outcome. The TSA analysis is shown in Figure 7 and demonstrates the lack of statistically significant treatment effect, and the calculated information size is not met.

Figure 6: Forest plot of NRS reporting on major bleeding

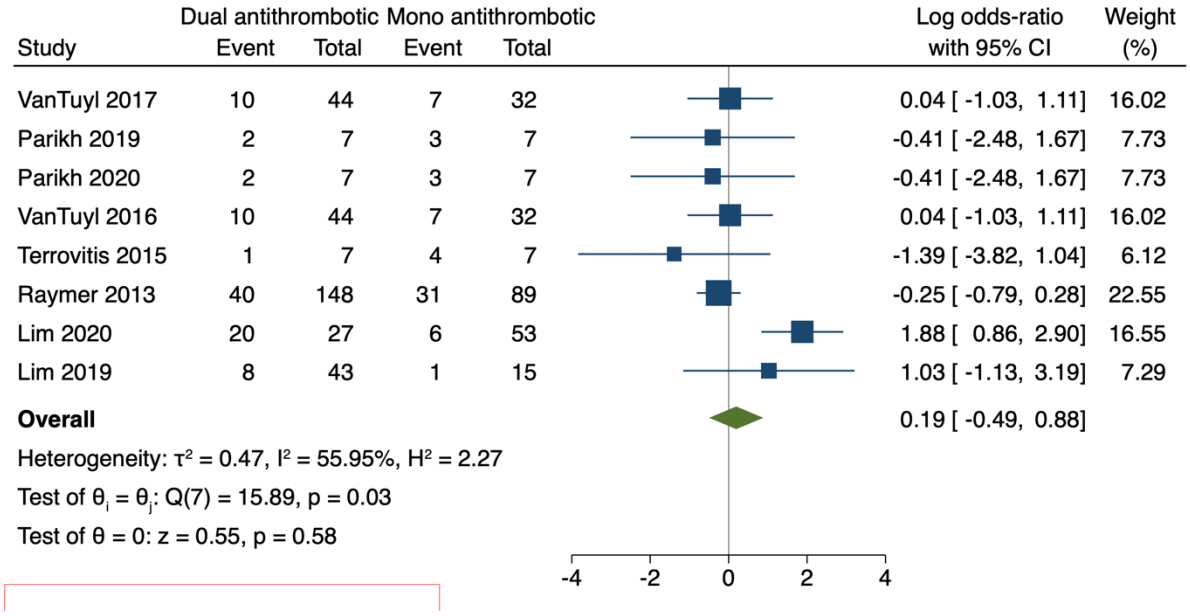
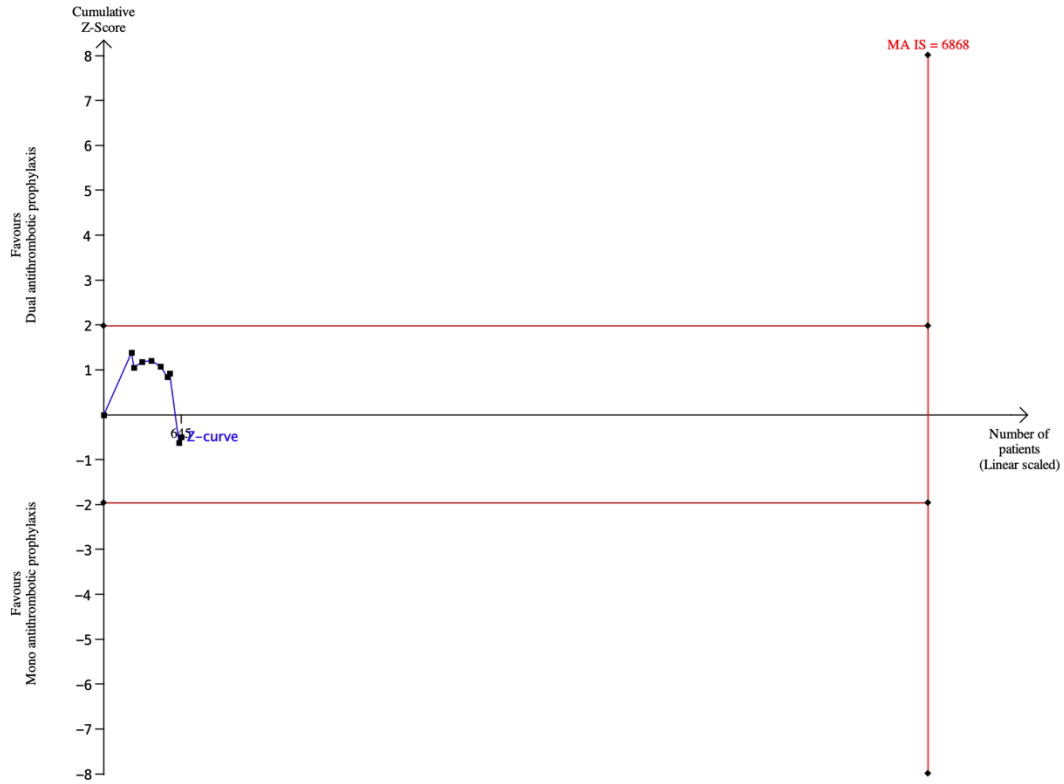


Figure 7: TSA analysis of NRS reporting on major bleeding



By assessing single-arm studies, the total number of bleeding events occurring was 448 out of 2,507 patients in the dual antithrombotic group and 245 out of the 959 in the mono antithrombotic group. The studies with the highest number of major bleeding events were two single-arm studies assessing dual antithrombotic prophylaxis, where Mueller et al. showed a bleeding event in every patient enrolled (27 out of 27 patients) and in the study by Bunte et al. where 58% patients experienced major bleeding (81 out of 139 patients).[62,63] Regarding monotherapy, the number of major bleeding events was comparable, as demonstrated in the study by Vantuyl et al.[41.] The studies mentioned above assessing the use of DOACs as an anticoagulant combined with an antiplatelet showed a benefit of DOACs compared to a single-agent anticoagulant.[45,46,51,56] Specifically, this was seen for Terrovitis et al., where the number of major bleedings experienced was in 1 out of 7 patients in the intervention group and 3 out of 7 patients in the control group.[51] Results were comparable in the studies by Parikh et al., where the number of major bleedings between the two groups was equal.[45,46] The single RCT assessing the outcome of major bleeding demonstrated that 39% (12 out of 31) dual antithrombic patients developed a major bleed compared to 65% patients (22 out of 34) in the mono antithrombotic group.[56]

2.3.4 Outcome of mortality

The effect of a dual antithrombotic regimen on mortality demonstrated an OR of 0.49 (95% CI 0.17 to 1.39) and 45 fewer deaths per every 1,000 patients treated with a dual antithrombotic regimen (95% CI from 75 fewer to 31 more), as seen in figure 8.[41,44,57,59] This difference was also noted in the single-arm NRS assessing mortality in LVAD patients where 146 patients out of 1,401 receiving dual antithrombotic prophylaxis died. In contrast, in the group of mono antithrombotic prophylaxis, 9 out of 98 patients died. Unfortunately, information on the cause of death was minimal and did not permit us to analyze the differences between the groups. We tested this outcome using the TSA analysis, which confirmed our previous results. The calculated information size is not met (figure 9).

Figure 8: Forest plot of NRS reporting on mortality

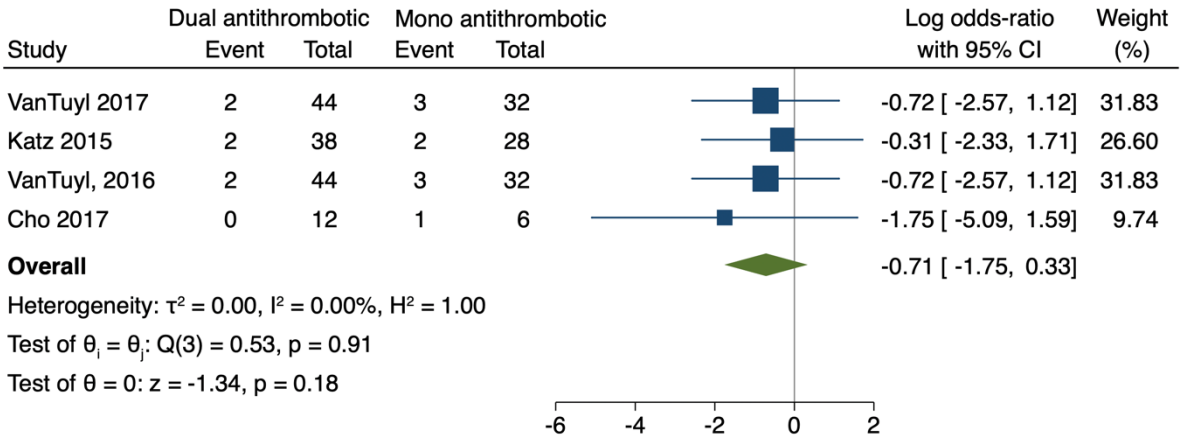
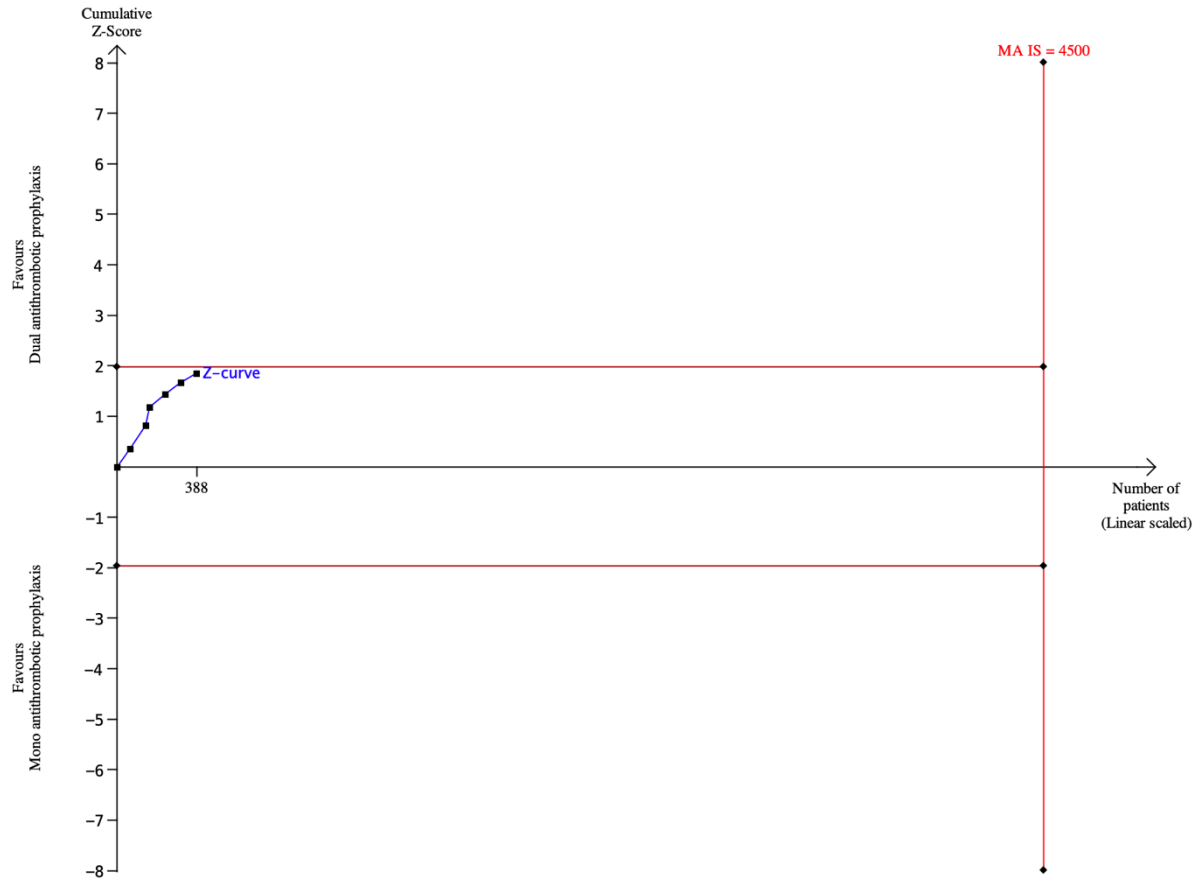


Figure 9: TSA analysis of NRS reporting on mortality



2.3.2 Subgroup and sensitivity analysis

To explore potential heterogeneity, we performed pre-specified subgroup analyses by stratifying the outcome by three variables: Age under 65 years of age and above 65 years of age, therapeutic range INR (2.0-3.0) vs. subtherapeutic INR, use of VKA with Aspirin vs. DOACs with Aspirin, and HeartMate LVAD device vs. HeartWare LVAD device. These figures can all be found in appendix A 4.

We used 65 years of age as a cut-off to differentiate adult from elderly patients and assessed these variables for all three outcomes. When evaluating the total thromboembolic events, the age cut-off did reveal a potential role of age. In fact, for patients below 65 years of age, the OR was 1.32 (95% CI 0.41, 1.40), while patients above 65 years of age showed an OR of 0.85 (95% CI 0.28, 2.53), as shown in figure A 4.1. [41,43–46,51,55,57–59] This would imply a potential benefit of a dual antithrombotic regimen in elderly patients. When considering the outcome of major bleeding, the OR in patients below 65 years of age was 2.08 (95% CI 0.66, 6.55), while in patients above 65 years of age an OR of 0.78 (0.49, 1.23) was seen, as shown in figure A 4.2. [41,43–46,51,58,61] This would indicate a benefit of a mono antithrombotic regimen

in younger patients, while a benefit of a dual antithrombotic regimen in elderly patients. Regarding the outcome of mortality, the data on elderly patients was too limited and did not permit us to perform a subgroup analysis.

While it would have been clinically relevant to test for INR levels and LVAD devices, we were unable to perform these due to the lack of comparative data for the outcomes above.

It was, however, possible to explore the effect of the combination of a VKA with Aspirin compared to DOACs with Aspirin, as shown in figure A 4.3. When looking at the outcome of total thromboembolic events, the OR of patients treated with a VKA in combination with Aspirin was 1.14 (95% CI 0.45, 2.286), while the OR, when treated with the DOACs and aspirin combination, was 0.30 (95%CI 0.05, 1.67). [41,43–46,51,55,57–59] On the other hand, when looking at the outcome of major bleeding, the OR in the VKA and aspirin subgroup was 1.80 (95%CI 0.59, 5.42), and in the DOACs and aspirin subgroup the OR was of 0.5 (95%CI 0.15, 1.8), as shown in figure A 4.4. [41,43–46,51,58,61]

We conducted a sensitivity analysis to test the hypothesis that there was no difference in effect when combining high risk of bias studies with low or moderate risk of bias studies. This was only relevant for the total thromboembolic outcome since the remaining outcomes were meta-analyzed with studies only at high risk of bias. The pooled OR of having a thromboembolic complication was 0.77 (95% CI 0.45, 1.34), while the OR when excluding studies at high risk of bias resulted in 0.48 (95% CI 0.10, 2.32), as demonstrated in figure A 4.5. [41,43–46,51,55,57–59]

We, unfortunately, could not use the ICEMAN tool for meta-analyses due to the lack of eligible RCTs for pooling and subgroup analysis.[11] We did not feel confident using it on the included NRS due to the complexity introduced by the variability of study designs and confounding effects which possibly would have yielded over-optimistic credibility judgements.

2.3.3 Quality assessment

The summary of findings table for the included outcomes is shown in table 10, and the evidence profile is in the appendix together with a link for the interactive summary of findings table (table 5.1). We judged the body of evidence for thromboembolic complications in the RCTs as low in the certainty in the evidence as per GRADE due to risk of bias and concerns about imprecision. The studies included small sample sizes and particularly expressed concerns regarding the deviation from the intended intervention and missing outcome data. The two studies contained essential differences in the intervention, with one containing a VKA with

Aspirin while the other a DOAC in combination with Aspirin. There were no concerns for inconsistency and indirectness. When rating the certainty in the evidence for the outcome of thromboembolic events in NRS, no concerns for inconsistency, indirectness, imprecision, or publication bias were suspected. Most included NRS were at high risk of bias using ROBINS-I, resulting in a low certainty of evidence. Our main concerns in the risk of bias assessment regarded the lack of reporting on potential confounders and definitions of outcomes and their measurement. The outcome of major bleeding in the NRS was rated low in its certainty in the evidence with major concerns in both risk of bias and inconsistency with variable definitions of the outcome and high heterogeneity in the point estimates of the studies. Regarding the single RCT reporting on major bleeding, we rated the certainty in the evidence once more as very low, with concerns in the risk of bias and imprecision. As per the mortality outcome, the included NRS were rated down for risk of bias and imprecision, resulting in low certainty in the evidence. Lack of reporting on the cause of death and missing patient data were reasons or major concerns. We did not suspect publication bias for any of the outcomes as demonstrated in the provided funnel plots and the non-significant results of Harbord's modification of the Eggers test (figure A.4.2).[64]

Table 10: GRADE summary of findings table

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with single agent antithrombotic prophylaxis	Risk difference with dual prophylactic antithrombotic therapy
Thromboembolic complications follow-up: range 183 days to 730 days	467 (10 observational studies)[41,43–46,51,55,57,58,65]	⊕⊕◯◯ Low[a,b,c,d,e,f]	**OR 0.77** (0.45 to 1.34)	198 per 1,000	**38 fewer per 1,000** (98 fewer to 51 more)
Major bleeding follow-up: range 30 days to 730 days	569 (8 observational studies)[41,43–46,51,58,61]	⊕⊕◯◯ Low[a,b,e,g]	**OR 1.21** (0.61 to 2.41)	256 per 1,000	**38 more per 1,000** (83 fewer to 197 more)
Mortality follow-up: range 48 days to 730 days	224 (4 observational studies)[41,44,57,65]	⊕⊕◯◯ Low[a,b,h]	**OR 0.49** (0.17 to 1.39)	92 per 1,000	**45 fewer per 1,000** (75 fewer to 31 more)
Thromboembolic complications follow-up: mean 12 months	81 (2 RCTs)[50,56]	⊕⊕◯◯ Low[b,c,i]	**OR 1.54** (0.63 to 3.78)	262 per 1,000	**91 more per 1,000** (79 fewer to 311 more)
Major bleeding follow-up: mean 12 months	68 (1 RCT)[56]	⊕◯◯◯ Very low[c,j,k]	**OR 1.00** (0.46 to 2.15)	647 per 1,000	**0 fewer per 1,000** (190 fewer to 151 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

Explanations

a. Patient follow-up time from the beginning of the intervention to the development of the outcome did not coincide for all patients, with some being followed over the course of years and some only months.
b. Major concerns in the risk of bias assessment due to the lack of patient demographic information such as comorbidities and concomitant medication. No further information was included regarding previous bleeding or thrombotic events.
c. Concerns were raised mainly due to the lack of a proper standardized definition of the outcome and how the outcome was assessed.
d. When assessing the sensitivity analysis for this outcome, differences were noted when removing studies at high risk of bias; due to this, we rate down for risk of bias
e. Even though evaluated with the ROBINS-I for non-randomized studies, major issues were found due to the lack of studies reporting on how the outcome was measured (i.e., pump thrombosis via clinical suspicion or imaging techniques), for repeated measurements, no explanation was given as to which results were reported.
f. Population size was too small to make an inference about the effect of the intervention.
g. The I^2 value of this outcome was 55%, with wide variation between point estimates of the studies.
h. The included studies had essential differences in the administered interventions, with some containing a DOAC with aspirin and others warfarin with Aspirin.
i. Sample size very limited to estimate the effect on the number of total thrombotic events
j. Concerns regarding missing data considering the lack of outcome information for each participant.
k. Only one study was included in this outcome.

2.4 Discussion

2.4.1 Summary of findings

LVAD devices have become the mainstay treatment for patients with congestive heart failure necessitating heart transplantation. Thanks to the improvement in pump mechanics and efficiency, the use of LVADs has now been proposed and used as destination therapy in patients not tolerating or not eligible for surgery.[66] Current literature has highlighted its use's long-term effects, such as the increased risk of thrombotic events due to impairment in the coagulation system.[21] The most common complications in the first 31 months post-LVAD implantation are bleeding and thrombosis, with multiorgan failure and sepsis comprising up to 70% of deaths.[66] Bleeding events have been seen to occur in approximately 30% to 60% of patients post-LVAD implantation, while thrombotic complications have happened with a rate of 0.014 to 0.05 events per patient-year.[67,68] Current evidence indicates that patients developing a thrombotic event, mainly pump thrombosis, lack medical options and are therefore considered for an emergent transplant.[67] The lack of organ supply makes this situation very difficult. The lack of routine availability of transplantation leads to the need for mechanical circulatory assist devices. The devices then necessitate antithrombotic regimens, permitting patients to minimize the risks of thrombosis and not excessively increase their risk of bleeding. The currently proposed regimens are a dual antithrombotic regimen composed of an anticoagulant and an antiplatelet or a single antithrombotic drug comprised of an antiplatelet or anticoagulant.[69] While these are reported to be efficient in decreasing the risks of thrombosis, they increase the number of hemorrhagic events requiring the discontinuation or substitution of therapy.[21] As demonstrated in the systematic review by Baumann-Kreuziger L.M. et al., the risk factors for bleeding include increased bilirubin values post-operatively, age >65 years, female sex and low postoperative hematocrit.[23] These factors are always essential to consider when deciding on the best chronic antithrombotic prophylaxis.

Currently, no consensus has been reached on the proper antithrombotic regimen. Even if very relevant to prolong the life and duration of the device, this is subject to interinstitutional variability depending especially on the treating physicians' experience. Based on the body of evidence we have gathered, the choice of which antithrombotic to administer was subject to high variability. Some studies reported using Aspirin as a monotherapy, with doses ranging from 81mg to 325mg, while others suggested using VKAs or DOACs with variable values of INR.[42,55,57,61,70] Additionally, the four studies reporting on the use of DOACs had minimal

population sizes with a high rate of failure either due to bleeding or thrombosis. [45,46,50,51] These studies reported on patients who had previously developed a thrombotic event under a warfarin based antithrombotic regimen. This would therefore alter their baseline risk of developing either a hemorrhagic or thrombotic event and hamper our ability to estimate their use in LVAD patients.

In line with our results, the current biggest issue remains to determine the proper balance between bleeding and thrombosis in a fragile set of patients such as these, many of which are not candidates for invasive surgery in case of device substitution. That is why the most crucial point of focus in LVAD research should not be the treatment of hemorrhagic or thrombotic complications but the prevention of such events through a proper pharmacologic regimen. This, of course, taken together with appropriate INR monitoring and adjustment of patients with subtherapeutic INR. As highlighted in many studies, it is suspected that the past two SARS-CoV-2 pandemic years have yielded a high number of adverse events in patients currently on antithrombotics due to the lack of INR monitoring and dose adjustment.[71,72] This was due to the lack of health care workers and the fear of patients accessing the hospitals with the risk of infection. Due to this, there have been reported changes in clinical decision making where treating physicians preferred to prescribe medication not requiring strict monitoring and therefore attempted to decrease the prescription of VKA agents.[71] There is still no clear evidence on how this affected decision making of LVAD patients and future studies on the topic may highlight essential effects.

Our current body of evidence, both in quality and quantity, does not permit us to confidently state that one regimen appears to be superior to the other in preventing thromboembolic events, major bleeding, or mortality. But it does set the ground for future studies and updates to investigate the best prophylactic regimen for LVAD patients. In this review, we highlight the current evidence status and urge further trials to explore this topic and provide physicians with the tools for proper evidence-based decision-making.[66]

2.4.2 Limitations

While done according to the Cochrane guidelines for systematic reviews of interventions, this systematic review presents limitations.[33] These can be seen in elements such as the inability to contact authors of potentially eligible studies, leading to the loss of relevant data.

Another critical limitation would be the inability to extract and verify all the studies included in duplicate. We extracted only 55% of studies in duplicate, with the remainder of studies extracted and verified by the author. This could influence the ability to interpret the risk of bias in these studies and may introduce errors not verified by a second reviewer.

Finally, we found a significant limitation in the body of evidence available. This limitation depends on two factors: the limited sample size found in the RCTs included and the second is the high risk of bias encountered in most NRS. This, therefore, does not permit us to have reliable results able to suggest or guide clinical decision-making. Additionally, for all outcomes, the number of studies reporting on the control arm was inferior compared to the intervention group and may underestimate the true event number in this population. Therefore, the latter would hamper our ability to determine the effect of a mono antithrombotic prophylaxis in LVAD patients.

2.4.3 Strengths

A strength of this systematic review was our stringent methodology. When doubts arose in any step of the project, we consulted the Cochrane handbook for systematic reviews of interventions.[33] We also made sure to use the best available risk of bias tool for the critical evaluation of our NRS, the ROBINS-I tool.[73,74] While time-consuming, this tool allows for a critical assessment of the several different study domains. We conducted a pilot exercise with all study members before commencing the project to ensure that all reviewers had fully understood the study domains and the steps of the study. Considering that the involved reviewers were not in the medical field, we ensured that the risk of bias tools were well understood regarding factors in which a medical background was required.

2.4.4. Implications for practice

Our results suggest that using a dual antithrombotic prophylaxis as a chronic therapy in LVAD patients could potentially be beneficial in preventing thromboembolic events and death while not increasing the number of hemorrhagic events. We do, however, consider the decision to be made on a balance of risks and benefits and therefore integrated with individual patient characteristics. This could be the first step in guiding physicians in the decision-making of which prophylactic regimen to administer. In addition, the prevention of these events through a proper and effective antithrombotic prophylaxis could prolong the duration and, therefore, the life of patients with LVAD devices.

2.4.5 Implications for research

A clear implication of our study is the need for further research to demonstrate a clear benefit of dual or mono antithrombotic prophylaxis. No well-conducted RCTs have assessed the true difference between dual and mono antithrombotic therapy. In addition, no high-quality NRS has been done investigating the long-term effects of a chronic dual antithrombotic prophylaxis in LVAD patients. Only four studies in our review examined the use of DOACs as prophylaxis in LVAD patients, with limited sample sizes and low quality. Therefore, further research re-proposing DOACs for LVAD patients would be needed. Another implication, once more evidence is gathered, would be the conduction of a network meta-analysis to explore the differences between the individual anticoagulants and antiplatelets.

An additional implication for research would be the need for studies assessing the quality of life of LVAD patients receiving antithrombotic prophylaxis. This would be important to determine the impact of this therapy on the everyday life of patients, also considering the frequent need for INR monitoring and hospital access.

The currently used TSA approach should be continued when updating our systematic review and meta-analysis to avoid the chances of committing false assumptions due to multiple statistical testing and further validate the use of this method.

2.5 Conclusion

Current practice still includes the use of a chronic dual antithrombotic prophylaxis composed of an anticoagulant and antiplatelet in patients implanted with an LVAD device.[69] In our systematic review and meta-analysis, we investigate and compare the current practice versus a single antithrombotic prophylaxis composed of an antiplatelet or anticoagulant. Our results suggest that patients prophylactically treated with a dual antithrombotic therapy show lower numbers of thromboembolic events and death with a comparable number of hemorrhagic complications. Our results are very limited in the certainty in the body of evidence given the elevated number of NRS with a high risk of bias, the limited sample size, and the lack of well-conducted RCTs. The impact of these two regimens on patients' quality of life remains to be explored and, together with additional data, may guide the decision-making of practitioners on the appropriate antithrombotic prophylaxis in LVAD patients. This review highlights the current evidence status and urges further trials to explore this topic.[66]

2.6 Contributors

G. E.U. Muti Schuenemann was responsible for the design, protocol, data collection, search, screening, abstraction, analysis, and manuscript writing. The components of data screening in the title and abstract phase, full text and data abstraction was aided by L. Ramelli, S. Sritharan and S. Kim. The final approval of the protocol and surveillance of the project was done together with M. Crowther. The protocol was approved by Dr. Lisa M. Baumann Kreuziger. Drs. Mark Crowther, Alfonso Iorio and Lehana Thabane reviewed and gave final approval of the manuscript.

Chapter 3: Conclusions

3.1 Main conclusions

In our systematic review and meta-analysis, we investigated the use of dual antithrombotic prophylaxis in LVAD patients. Due to the sparsity of our data, we considered using the TSA approach to avoid committing either type one or type two errors when making inferences on the treatment effect. While conducting our systematic review, we demonstrated that the results of our meta-analysis remained in line with the non-statistical significance seen in the TSA graphs.[10]

By using this new software, we explored the potentially important role of this testing and would like to suggest its use not only in first-time meta-analyses but also integrated into frequent updates.[8] Specifically, while many meta-analyses performed are judged on statistical significance and effect based on the p-value, this would provide researchers with the tools to combine the pooling of data with the quality of included studies.[10] This is portrayed by the fact that the "best available evidence" should not be synonymous with "strong or sufficient evidence." This approach uses different techniques to ensure that a sufficient number of events and patients are gathered in a term referred to as the *meta-analysis information size*.[6] A phenomenon extrapolated from what is currently used in clinical trials for sample size calculation where, based on the proportion of events in the control group and the expected RR of the intervention group, the correct amount of participants are enrolled to allow for reliable statistical inference. This in meta-analyses must be done with care since the heterogeneity in the trial population, definitions, methods, and interventions are very high, something often not considered by conducting researchers and demonstrated in our review.[75] In fact, many meta-analyses make inferences on intervention effects singularly based on the p-value even when the event rate and population size are small and unreliable. Furthermore, this is held by the fact that large positive effects in meta-analyses dissipate with the accumulation of further evidence.[76] On the other hand, the latter inflates the risk of type I errors as repeated significance testing is done. It is currently estimated that repeated significance testing in meta-analyses with p-values smaller than 0.05 have a chance of type I error of 10 to 30%. This would imply that 1-3 out of 10 inferences on treatment decisions that include a balancing of benefits and harms may be false.[9] Therefore, the accumulation of further data and multiple statistical testing may lead us to find spurious treatment effects which may be prevented by using the TSA approach. We plan to update this systematic review and meta-analysis, integrating future data in the current TSA graphs to avoid multiplicity due to repeated significance testing.[4] Specifically, by

penalizing the test statistic in relation to the strength of the evidence and on the number of tests performed for significance. The TSA software permits this and provides the appropriate tools for testing in updates of meta-analyses. The potential role of this method should be explored and further validated to be integrated into the current practice.

Appendix:

Table A1.1: Search strategy

Table A1.1: Search strategy on EMBASE run from January 1st 2014 to March 13th 2022

Database(s): **Embase** 1974 to March 13th 2022

Search Strategy:

#	Searches	Results
1	exp heart assist device/	39500
2	Heart-Assist Device*.mp.	8320
3	ventri* device*.mp.	335
4	Left ventricular assist device*.mp.	21094
5	exp left ventricular assist device/	16971
6	VAD.mp.	14998
7	LVAD.mp.	13381
8	1 or 2 or 3 or 4 or 5 or 6 or 7	53178
9	exp anticoagulant agent/	679520
10	Antithrombotic*.mp.	29016
11	Antiplatelet*.mp.	53089
12	exp antiplatelet activity/	736
13	antiplatelet.mp.	51127
14	prophylaxis.mp.	234816
15	exp heparin/	145695
16	exp warfarin/	94147
17	exp acetylsalicylic acid/	215957
18	anticoagulation.mp.	98271
19	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	928836
20	8 and 19	6900
21	limit 20 to yr="2014 -Current"	4047

Table A1.2: Search strategy on MEDLINE run from January 1st 2014 to March 13th 2022

Database(s): OVID Medline Epub Ahead of Print
Indexed Citations, Ovid MEDLINE(R) Daily and (
Present Search Strategy:

#	Searches	Results
1	Heart-Assist Devices/	14716
2	heart assist device*.mp.	14866
3	Ventric* Assist Device*.mp.	12764
4	LVAD.mp.	5094
5	VAD.mp.	9154
6	1 or 2 or 3 or 4 or 5	25532
7	exp Platelet Aggregation Inhibitors/	125789
8	exp Anticoagulants/	224983
9	Antithrombotic*.mp.	19095
10	prophylaxis.mp.	111789
11	Anticoagulant*.mp.	113198
12	Anticoagulation.mp.	43546
13	Antiplatelet*.mp.	29367
14	7 or 8 or 9 or 10 or 11 or 12 or 13	494307
15	6 and 14	1482
16	limit 15 to yr="2014 -Current"	697

Table A1.3: Search strategy on WEB of SCIENCE run from January 1st 2014 to March 13th 2022

(ALL=(Heart-Assist Devices or heart assist device*. or Ventric* Assist Device* or LVAD or VAD)) AND ALL=(Platelet Aggregation Inhibitors or Anticoagulants or Antithrombotic* or prophylaxis or Anticoagulant* or Anticoagulation or Antiplatelet*)	763

Table A1.4: Search strategy on CENTRAL run from January 1st 2014 to March 13th 2022

CENTRAL

Search Name: LVAD search
Date Run: 13/03/2022 14:59:25

	ID	Search Hits
1	Heart-Assist Devices or heart assist device*. or Ventric* Assist Device* or LVAD or VAD	**1354**
2	Platelet Aggregation Inhibitors or Anticoagulants or Antithrombotic* or prophylaxis or Anticoagulant* or Anticoagulation or Antiplatelet*	**50079**
3	#1 and #2	**107**

Table A1.5: Definition of major bleeding according to the ISTH criteria[26]

Major bleeding	• Fatal bleeding • Bleeding that is symptomatic and occurring in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon • Extra surgical site bleeding caused by a fall in hemoglobin level of 2g/dL or more or leading to transfusion of two or more units of whole blood or red cells with temporal association within 24-48 h to the bleeding • Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or deep wound infection. • Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 2g/dL, or transfusion indicated by the bleeding of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding. • The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations). The population is those who have received at least one dose of the study drug.

Figures A 2: Included studies

Figures A 2.1: Characteristics of included studies

Study name	Study year	Study design	Country	Type of LVAD device used	Intervention (Dual antithrombotic regimen)	Comparator (Mono antithrombotic regimen)	Outcome rep
Balcioglu[53]	**2018**	Retrospective cohort study	USA	84.4% HVAD 26.6% HM II	aspirin + warfarin		Mortality
Parikh[45]	**2019**	Retrospective cohort study	USA	86% HVAD 14% HM II	DOAC (Apixaban or Rivaroxaban) + aspirin	warfarin	Thromboembo Major bleedin
Mueller (2)[62]	**2020**	Retrospective cohort study	USA	63% HVAD 26% HM II 11% HM 3	aspirin + warfarin		Thromboembo Major bleedin
Tsiouris[54]	**2019**	Retrospective cohort study	USA	89% HM II 19% HVAD	aspirin + warfarin		Thromboembo
Cho[59]	**2019**	Retrospective review of prospectively collected data	USA	81% HMII 19% HVAD	aspirin + warfarin		Thromboembo
Borden[77]	**2015**	Retrospective cohort study	USA	61% HM 33% HVAD	aspirin + warfarin		Thromboembo
Katz[57]	**2015**	Retrospective cohort study	USA	100% HM II		aspirin or warfarin	Thromboembo Mortality Major bleedin
Willey[60]	**2016**	Retrospective cohort study	USA	88% HM II 12% HVAD	aspirin + warfarin		Thromboembo Major bleedin
Ertugay[78]	**2015**	Retrospective cohort study	USA	100% HM II	aspirin + warfarin		Thromboembo Mortality Major bleedin
Parikh[46]	**2020**	Retrospective cohort study	USA	86% HM II 14% HVAD	DOAC (Apixaban or Rivaroxaban) + aspirin	warfarin	Thromboembo Major bleedin
Carnicelli[37]	**2016**	Prospective cohort study	USA	100% HM II	aspirin + warfarin		Thromboembo

Netuka[70]	**2016**	Prospective cohort study	EU	100% HM II		antiplatelet or VKA	Thromboembo
Andreas[50]	**2017**	Randomized, open label balanced parallel group single center pilot clinical trial	Austria	100% HVAD	dabigatran + aspirin	phenprocoumon	Thromboembo
Veasey[38]	**2019**	Retrospective cohort study	USA	100% HM II	aspirin + warfarin		Thromboembo Mortality Major bleedin
Saeed[39]	**2020**	Retrospective chart review	USA	100% HM 3	aspirin + warfarin		Thromboembo Mortality Major bleedin
Bunte[63]	**2013**	Retrospective cohort study	USA	100% HM II	aspirin + warfarin		Mortality
VandenBergh[79]	**2014**	Retrospective cohort study	Netherlands	100% HM II	acenocoumarol + aspirin		Thromboembo Mortality
Szymanski[40]	**2020**	Retrospective cohort study	USA	61% HM II 33% HVAD 6% HM 3	aspirin + warfarin		Thromboembo
Akin[80]	**2016**	Retrospective cohort study	Netherlands	100% HM II	VKA + aspirin		Thromboembo
VanTuyl[41]	**2017**	Retrospective cohort study	USA	100% HM II	aspirin + warfarin	warfarin	Thromboembo Mortality Major bleedin
Jorde[56]	**2020**	Double blind randomized controlled trial	USA	100% HM II	aspirin + warfarin	warfarin plus placebo	Thromboembo Major bleedin
Mueller[81]	**2020**	Retrospective cohort study	Germany	50% HVAD 50% HM 3	VKA + aspirin		Thromboembo Mortality Major bleedin
Wilson[82]	**2013**	Retrospective cohort study	USA	100% HM	aspirin + warfarin		Mortality Major bleedin

Centofani[83]	**2017**	Retrospective cohort study	Italy	100% HVAD	aspirin + warfarin		Thromboembo Mortality Major bleedin
Netuka[84]	**2014**	Retrospective cohort study	Germany	100% HM II	warfarin		Thromboembo Major bleedin
Terrovitis[51]	**2015**	Retrospective cohort study	Greece	100% HM II	dabigatran + aspirin	acenocoumarol	Thromboembo Major bleedin
Raymer[61]	**2013**	Retrospective cohort study	USA	92.4% HM II 7.6% HVAD		aspirin	Major bleedin
Saeed[55]	**2016**	Retrospective cohort study	USA	100% HM II		aspirin or dipyridamole	Thromboembo Major bleedin
Lim[58]	**2020**	Retrospective cohort study	UK	100% HM 3	aspirin + warfarin	warfarin	Thromboembo Major bleedin
Levesque[85]	**2019**	Prospective cohort study	USA	58% HM II 8.6% HM 3 29% HVAD	aspirin + warfarin		Thromboembo Mortality Major bleedin
Netuka[48]	**2018**	Retrospective cohort study	Czech Republic	100% HM 3	aspirin + warfarin		Thromboembo Major bleedin
Faerber[86]	**2018**	Prospective cohort study	Germany	100% HM 3	phenprocoumon + aspirin		Thromboembo Mortality Major bleedin
Adcokc[87]	**2015**	Retrospective cohort study	USA	100% HM II	aspirin + warfarin		Major bleedin
Consolo[88]	**2020**	Retrospective cohort study	Italy	13% HM II 38% HM 3 49% HVAD	aspirin + warfarin	warfarin	Major bleedin
Gallo[42]	**2017**	Prospective cohort study	USA	58% HM II 28% HVAD		aspirin	Thromboembo Major bleedin
Cho[59]	**2017**	Retrospective cohort study	USA	81% HMII 19% HVAD	aspirin + warfarin	warfarin or aspirin alone	Thromboembo Mortality
Pappalardo[89]	**2012**	Prospective cohort study	Germany	80% HM II		Argratroban	Thromboembo Mortality Major bleedin

Hanke[52]	**2018**	Retrospective cohort study	Germany	100% HM 3	phenprocoumon + aspirin		Thromboembo Mortality Major bleedin
Kushnir[47]	**2012**	Prospective cohort study	USA	27% HM 73% HM II	aspirin + warfarin		Major bleedin
Kantorovich[90]	**2016**	Retrospective case series	USA	100% HM II			Thromboembo Major bleedin
Bansal[91]	**2020**	Retrospective cohort study	USA	50% HM II 50% HVAD	aspirin + warfarin	aspirin or dipyridamole	Thromboembo
VanTuyl[44]	**2016**	Retrospective cohort study	USA	100% HM	aspirin + warfarin	warfarin	Thromboembo Mortality Major bleedin
Bowman[49]	**2019**	Retrospective cohort study	USA	27% HVAD 63% HM II 10% HM 3		warfarin	Thromboembo
Cho[65]	**2019**	Retrospective cohort study	USA	81% HM II	aspirin + warfarin		Thromboembo Mortality
Lim[43]	**2019**	Retrospective cohort study	USA	100% HM 3	aspirin + warfarin	warfarin	Thromboembo Major bleedin

Figures A 2.2: Risk of bias assessment for NRS using ROBINS-I tool[30]

Figure A 2.2.1 Risk of bias assessment for NRS using ROBINS-I tool[30] for thromboembolic events

Total thromboembolic events									
Study		Pre-intervention		At intervention	Post-intervention				
Study first author	Sudy year	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall Risk of bias
Parikh	2019	Serious	Moderate	Low	Low	Low	Serious	Serious	Serious
Mueller (2)	2020	Serious	Moderate	Low	Low	Low	Moderate	Low	Moderate
Tsiouris	2019	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Cho	2019	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Borden	2015	Serious	Low	Low	Low	Low	Low	Low	Moderate
Katz	2015	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Willey	2016	Serious	Moderate	Moderate	Low	Low	Serious	Serious	Serious
Ertugay	2015	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Parikh	2020	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Netuka	2016	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Veasey	2019	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Saeed	2020	Serious	Low	Low	Low	Low	Serious	Moderate	Serious
vandenBergh	2014	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Szymanski	2020	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Akin	2016	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Mueller	2020	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Wilson	2013	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Centofani	2017	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Netuka	2014	Serious	Low	Low	Low	Moderate	Serious	Low	Serious
Terrovitis	2015	Serious	Moderate	Low	Low	Low	Serious	Low	Serious
VanDenBergh	2014	Low	Moderate	Low	Low	Low	Low	Low	Low
Saeed	2016	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Lim	2020	Serious	Moderate	Moderate	Low	Low	Serious	Low	Serious
Levesque	2019	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Netuka	2018	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Gallo	2017	Moderate	Moderate	Moderate	Low	Moderate	Serious	Low	Serious
Cho	2019	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Serious
Pappalardo	2012	Serious	Moderate	Moderate	Low	Low	Moderate	Serious	Serious
Hanke	2018	Serious	Low	Moderate	Low	Low	Low	Serious	Serious
Kantorovich	2016	Serious	Low	Moderate	Moderate	Serious	Serious	Serious	Serious
Bansal	2020	Serious	Moderate	Moderate	Low	Low	Moderate	Serious	Serious
Bouzas-Cruz	2020	Serious	Moderate	Low	Serious	Low	Moderate	Moderate	Serious
Lim	2019	Serious	Moderate	Moderate	Low	Low	Serious	Low	Serious

Figure A 2.2.2 Risk of bias assessment for NRS using ROBINS-I tool[30] for major bleeding

Major bleeding									
Study		Pre-intervention		At intervention		Post-intervention			
Study first author	Study year	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall Risk of bias
Balcioglu	2018	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Parikh	2019	Serious	Moderate	Moderate	Low	Low	Serious	Serious	Serious
Mueller (2)	2020	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Katz	2015	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Willey	2016	Serious	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Ertugay	2015	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Parikh	2020	Serious	Moderate	Moderate	Low	Low	Serious	Serious	Serious
Netuka	2016	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Veasey	2019	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Saeed	2020	Serious	Low	Low	Low	Low	Serious	Moderate	Serious
Bunte	2013	Serious	Low	Low	Low	Low	Low	Low	Moderate
VanTuyl	2017	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Wilson	2013	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Centofani	2017	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Terrovitis	2015	Serious	Moderate	Low	Low	Low	Serious	Low	Serious
Raymer	2013	Serious	Moderate	Moderate	Low	Low	Moderate	Low	Serious
Lim	2020	Serious	Moderate	Moderate	Low	Low	Serious	Low	Serious
Levesque	2019	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Netuka	2018	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Faerber	2018	Serious	Moderate	Serious	Low	Low	Moderate	Moderate	Serious
Adcokc	2015	Serious	Moderate	Low	Serious	Low	Moderate	Moderate	Serious
Consolo	2020	Serious	Moderate	Low	Serious	Low	Low	Low	Serious
Gallo	2017	Moderate	Moderate	Moderate	Low	Moderate	Serious	Low	Serious
Pappalardo	2012	Serious	Moderate	Moderate	Low	Low	Moderate	Serious	Serious
Hanke	2018	Serious	Low	Moderate	Low	Low	Low	Serious	Serious
Kushnir	2012	Serious	Low	Moderate	Moderate	Serious	Serious	Serious	Serious
Kantorovich	2016	Serious	Low	Moderate	Moderate	Serious	Serious	Serious	Serious
VanTuyl	2016	Low	Low	Moderate	Low	Low	Moderate	Serious	Serious
Lim	2019	Serious	Moderate	Moderate	Low	Low	Serious	Low	Serious

Figure A 2.2.1 Risk of bias assessment for NRS using ROBINS-I tool[30] for mortality

Mortality									
Study		Pre-intervention		At intervention	Post-intervention				
Study name	Study First author	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall Risk of bias
Katz	2015	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Ertugay	2015	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Veasey	2019	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Saeed	2020	Serious	Low	Low	Low	Low	Low	Moderate	Moderate
vandenBergh	2014	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Akin	2016	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
VanTuyl	2017	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Mueller	2020	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Wilson	2013	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Centofani	2017	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Levesque	2019	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Faerber	2018	Serious	Low	Moderate	Low	Serious	Serious	Low	Serious
Cho	2019	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Pappalardo	2012	Serious	Moderate	Moderate	Low	Low	Moderate	Serious	Serious
Hanke	2018	Serious	Low	Moderate	Low	Low	Low	Serious	Serious
VanTuyl	2016	Moderate	Low	Moderate	Low	Low	Moderate	Serious	Serious

Figures A 2.2.3: Risk of bias assessment for RCTs reporting on thromboembolic events using ROB.2 tool[74]

Thromboembolic events							
Study name	Study year	Bias arising from randomization process	Bias due to deviation from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in the selection of reported outcome	Overall risk of bias
Andreas	2017	Low	High	Low	Moderate	Low	High
Jorde	2020	Low	High	Moderate	Low	Low	High

Figures A 2.2.3: Risk of bias assessment for RCT reporting on major bleeding using ROB.2 tool[74]

Major bleeding							
Study name	Study year	Bias arising from randomization process	Bias due to deviation from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in the selection of reported outcome	Overall risk of bias
Jorde	2020	Low	High	Moderate	Low	Low	High

Figures A 3: Total thromboembolic complications per outcome

Figure A 3.1: Forest plot of NRS reporting on pump thrombosis

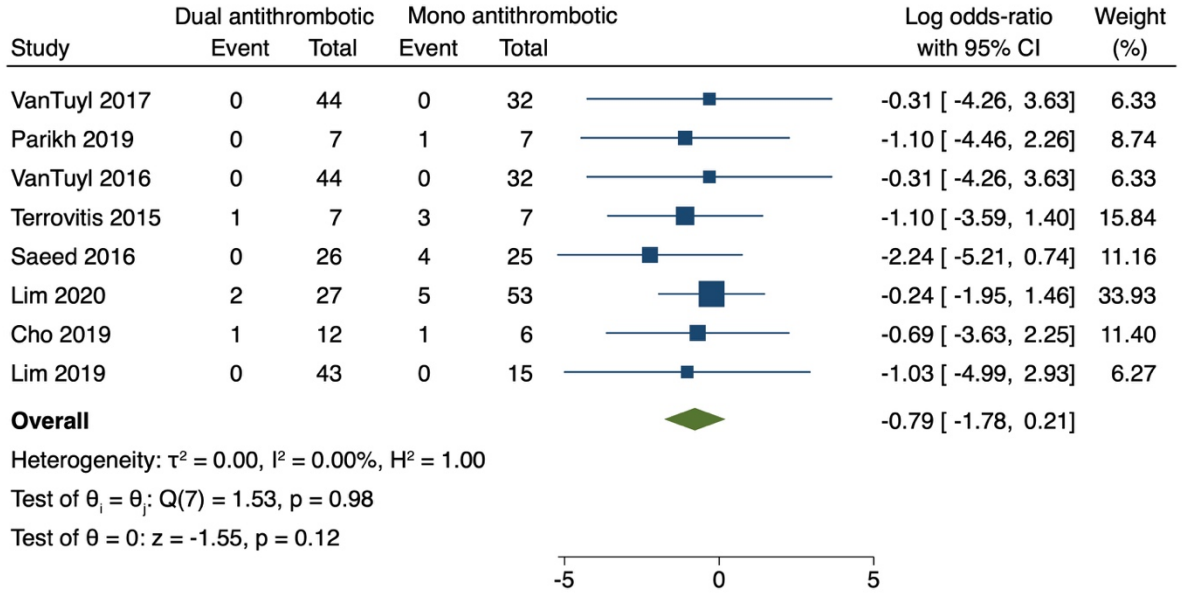


Figure A 3.2: Forest plot of NRS reporting on stroke

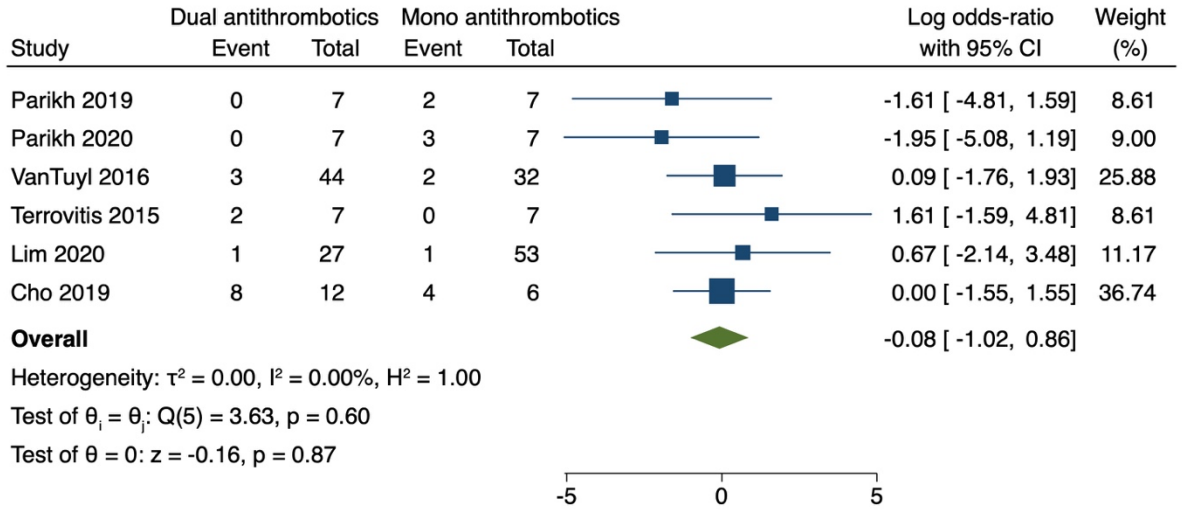
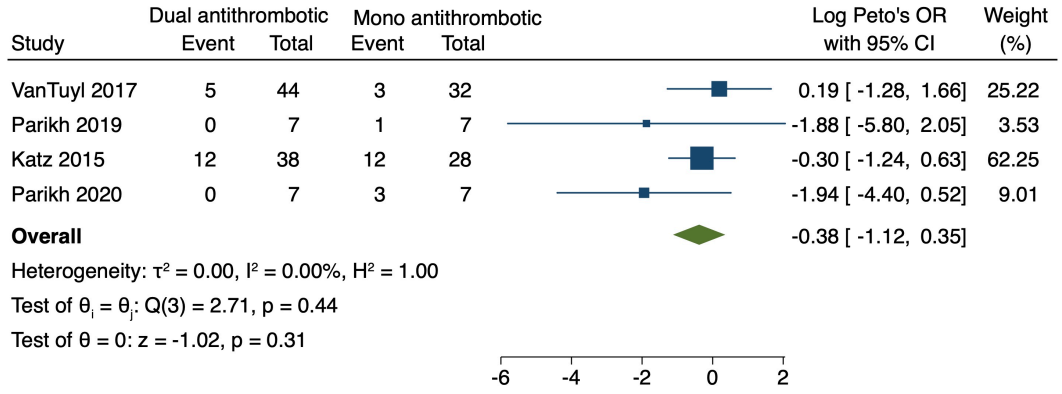


Figure A 3.3 Forest plot of NRS reporting on other objectively confirmed arterial or venous thrombosis



Figures A 4: subgroup and sensitivity analysis

Figure A 4.1 Subgroup of studies on patients <65 years of age and the total number of thromboembolic events

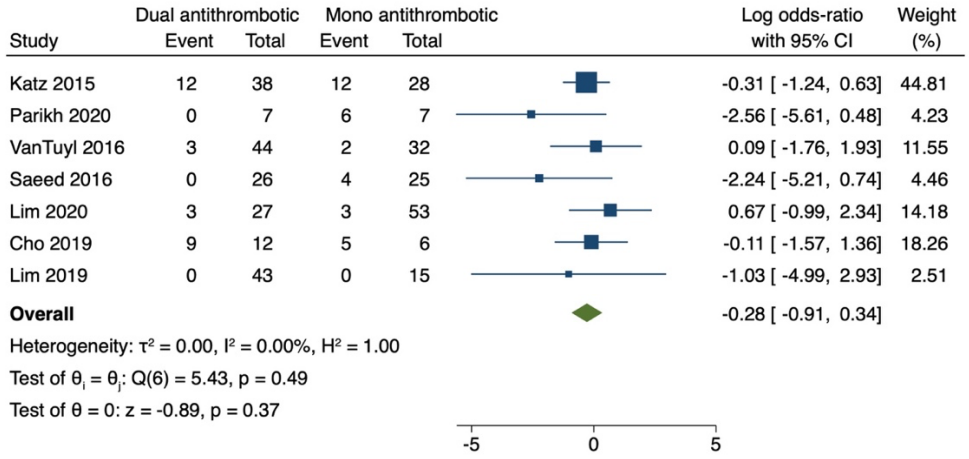


Figure A 4.2 Subgroup of studies on patients >65 years of age and the total number of thromboembolic events

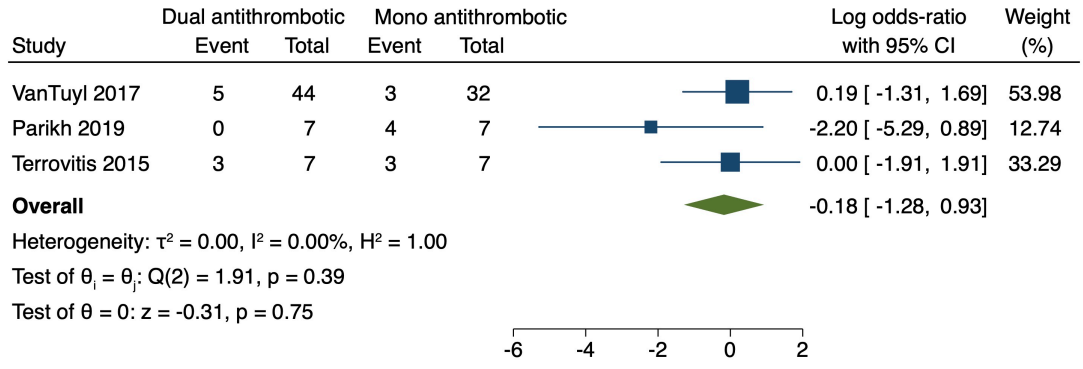


Figure A 4.3 Subgroup of studies on patients <65 years of age and major bleeding

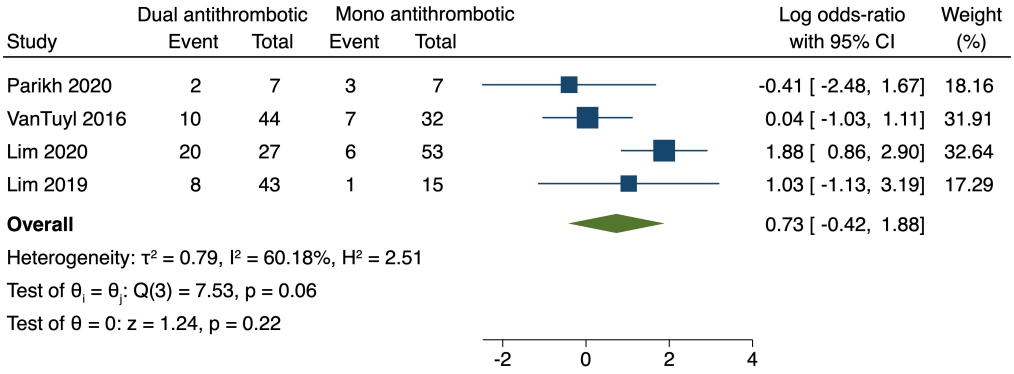


Figure A 4.4 Subgroup of studies on patients >65 years of age and major bleeding

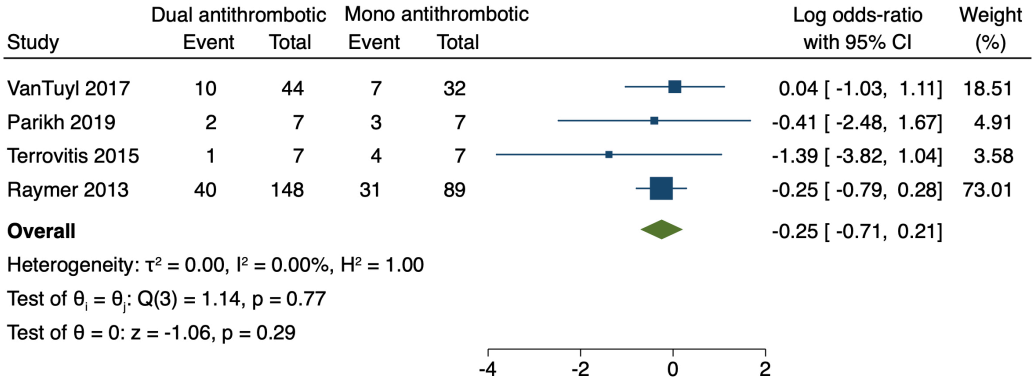


Figure A 4.5 Subgroup of studies using a VKA and Aspirin dual prophylaxis on total number of thromboembolic events

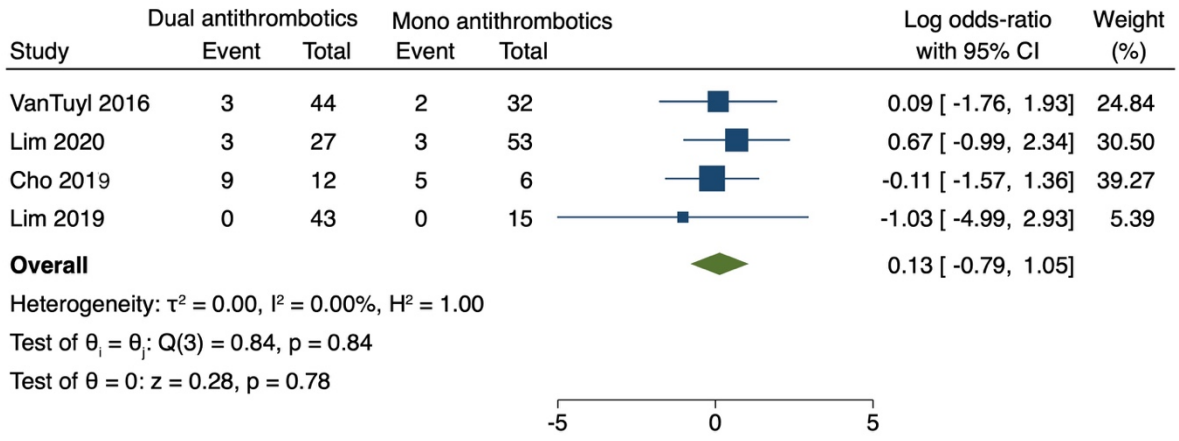


Figure A 4.6 Subgroup of studies using a DOAC and Aspirin dual prophylaxis on total number of thromboembolic events

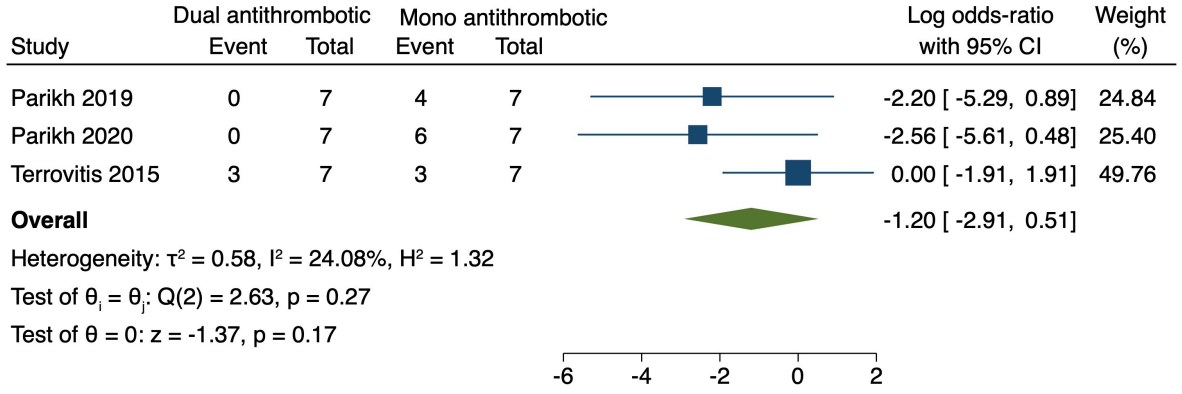


Figure A4.7 Subgroup of studies using a VKA and Aspirin dual prophylaxis on major bleeding events

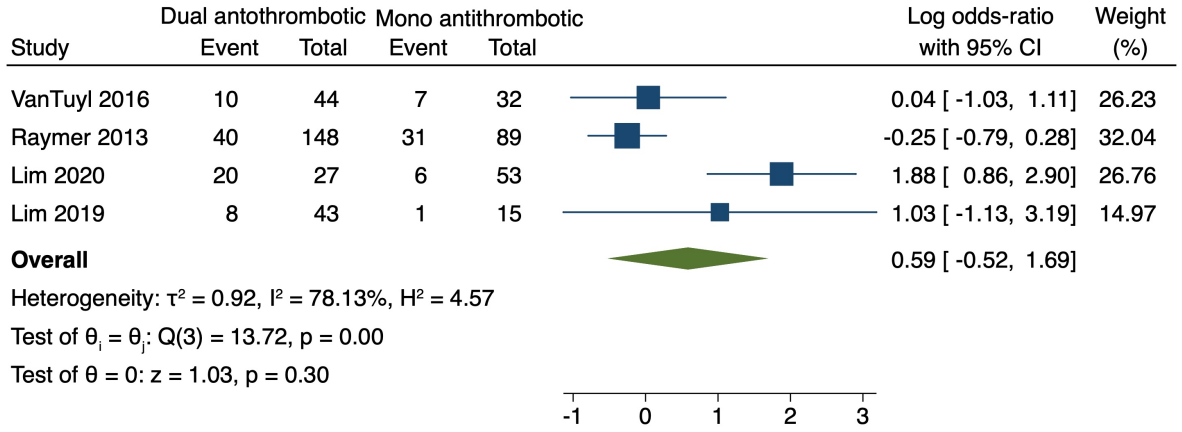


Figure A 4.8 Subgroup of studies using a DOAC and Aspirin dual prophylaxis on major bleeding events

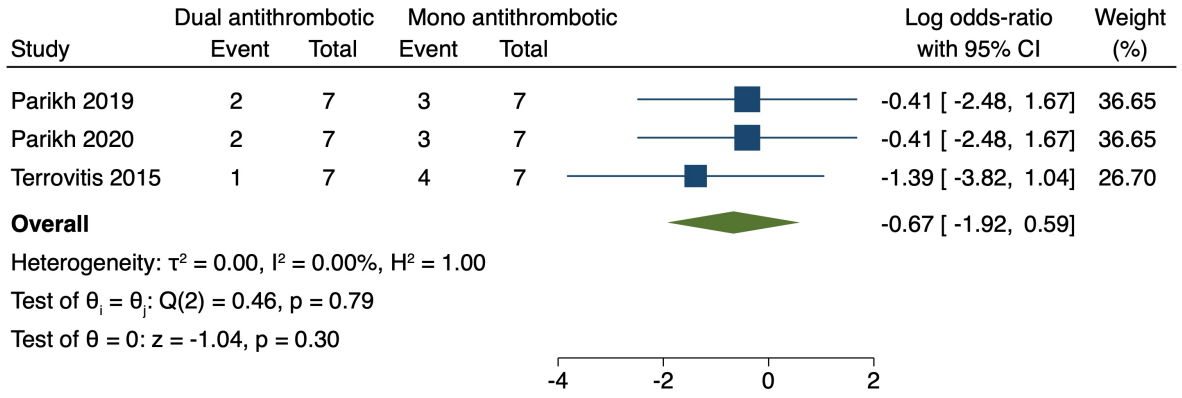
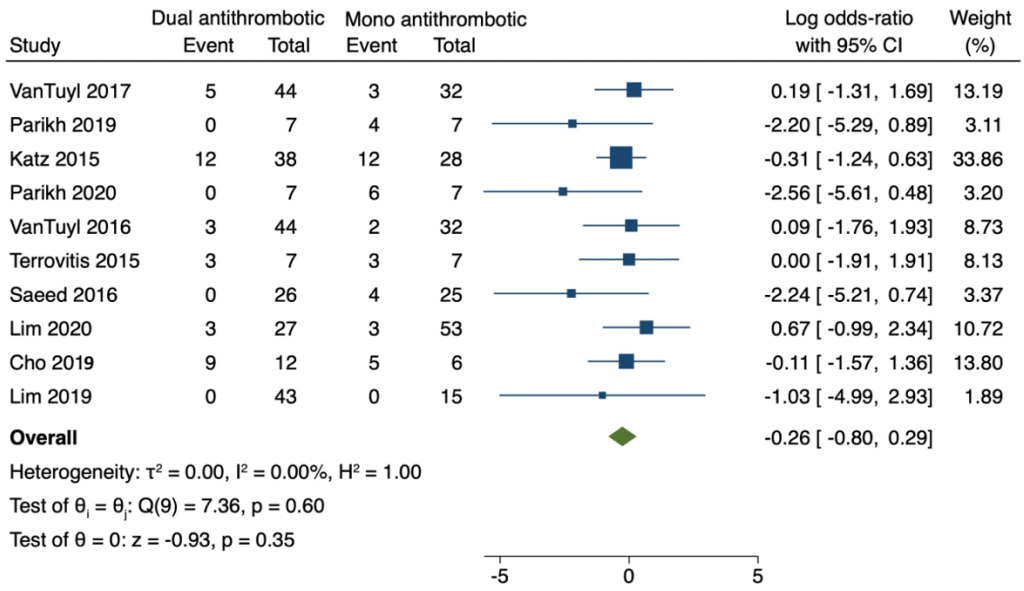


Figure A 4.9 Sensitivity analysis of total thromboembolic events with pooled data from all studies and those excluding high risk of bias



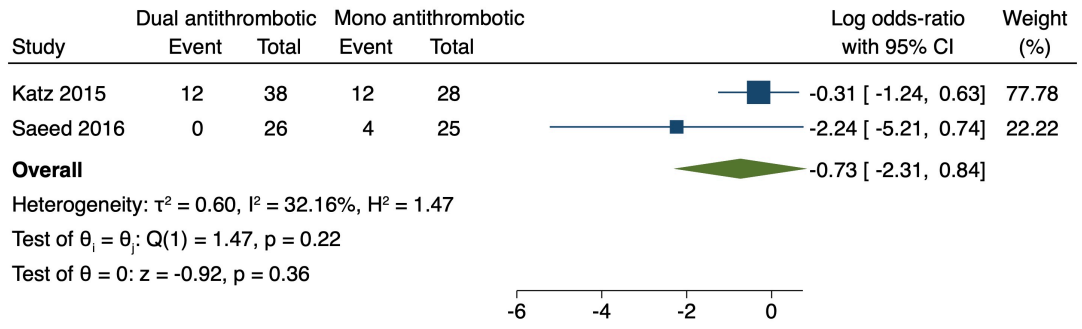


Table A 5: GRADE evidence profile table and publication bias funnel plots.

Table A 5.1 GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	dual prophylactic antithrombotic therapy	single agent antithrombotic prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Thromboembolic complications (follow-up: range 183 days to 730 days; assessed with: pump thrombosis, fatal pulmonary embolism, pulmonary embolism, myocardial infarction, stroke, clinically overt DVT and other objectively confirmed arterial or venous thrombosis)												
10[41,43–46,51,55,57,58,65]	observational studies	very serious[a,b,c,d,e]	not serious	not serious	serious[f]	all plausible residual confounding would suggest spurious effect, while no effect was observed	35/255 (13.7%)	42/212 (19.8%)	**OR 0.77** (0.45 to 1.34)	**38 fewer per 1,000** (from 98 fewer to 51 more)	⨁⨁◯◯ Low	CRITICAL
Major bleeding (follow-up: range 30 days to 730 days; assessed with: International Society on Thrombosis and Hemostasis criteria)												
8[41,43–46,51,58,61]	observational studies	very serious[a,b,e]	serious[g]	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	93/327 (28.4%)	62/242 (25.6%)	**OR 1.21** (0.61 to 2.41)	**38 more per 1,000** (from 83 fewer to 197 more)	⨁⨁◯◯ Low	CRITICAL
Mortality (follow-up: range 48 days to 730 days)												
4[41,44,57,65]	observational studies	very serious[a,b]	not serious	not serious	serious[h]	all plausible residual confounding would suggest spurious effect, while no effect was observed	6/126 (4.8%)	9/98 (9.2%)	**OR 0.49** (0.17 to 1.39)	**45 fewer per 1,000** (from 75 fewer to 31 more)	⨁⨁◯◯ Low	CRITICAL
Thromboembolic complications (follow-up: mean 12 months; assessed with: pump thrombosis, fatal pulmonary embolism, pulmonary embolism, myocardial infarction, stroke, clinically overt DVT and other objectively confirmed arterial or venous thrombosis)												
2[50,56]	randomised trials	serious[b,c,i]	not serious[i]	not serious	very serious[i]	all plausible residual confounding would suggest spurious effect, while no effect was observed	16/39 (41.0%)	11/42 (26.2%)	**OR 1.54** (0.63 to 3.78)	**91 more per 1,000** (from 79 fewer to 311 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	dual prophylactic antithrombotic therapy	single agent antithrombotic prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Major bleeding (assessed with: International Society on Thrombosis and Hemostasis criteria) (follow-up: mean 12 months)												
1[56]	randomised trials	serious[c,j,k]	not serious	not serious	very serious[k]	none	22/34 (64.7%)	22/34 (64.7%)	**OR 1.00** (0.46 to 2.15)	**0 fewer per 1,000** (from 190 fewer to 151 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

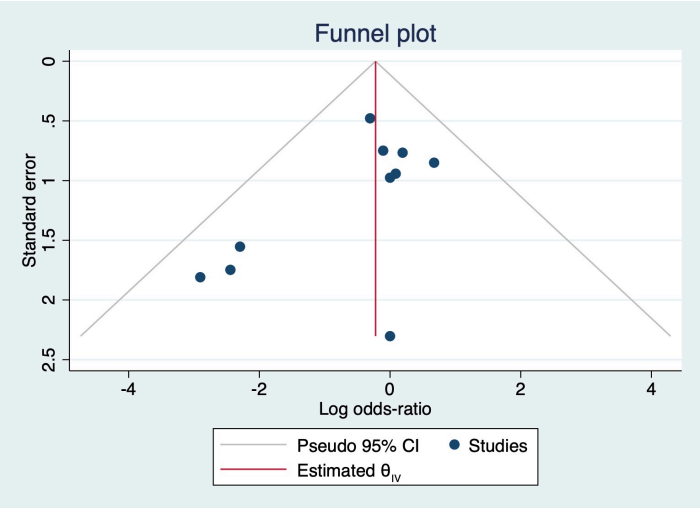
Explanations

a. Patient follow-up time from the beginning of the intervention to the development of the outcome did not coincide for all patients with some being followed over a course of years and some only months.
b. Major concerns in the risk of bias assessment due to the lack of patient demographic information such as comorbidities and concomitant medication. No further information was included regarding previous bleeding or thrombotic events.
c. Concerns were raised mainly due to the lack of proper standardized definition of the outcome and how the outcome was assessed.
d. When assessing the sensitivity analysis for this outcome, differences were noted when removing studies at high risk if bias, due to this we rate down for risk of bias
e. Even though evaluated with the ROBINS-I tool for non-randomized studies, major issues were found due to the lack of studies reporting on how the outcome was measured (i.e., pump thrombosis via clinical suspicion or imaging techniques) and for repeated measurements, no explanation was given as to which results were reported.
f. Population size was too small to make an inference about the effect of the intervention.
g. The I^2 value of this outcome was of 55% with wide variation between point estimates of the studies.
h. The included studies had important differences in the administered interventions with some containing a DOAC with aspirin and others warfarin with aspirin.
i. Sample size very limited to estimate effect on the number of total thrombotic events
j. Concerns regarding missing data considering the lack of outcome information for each participant.
k. Only one study was included in this outcome.

Link for interactive summary of findings table: https://gdt.gradepro.org/presentations/#/isof/isof_c2045b67-c5b8-4da2-bd01-5279a848d829-1650954311953

Figure A 5.3: Publication bias funnel plots

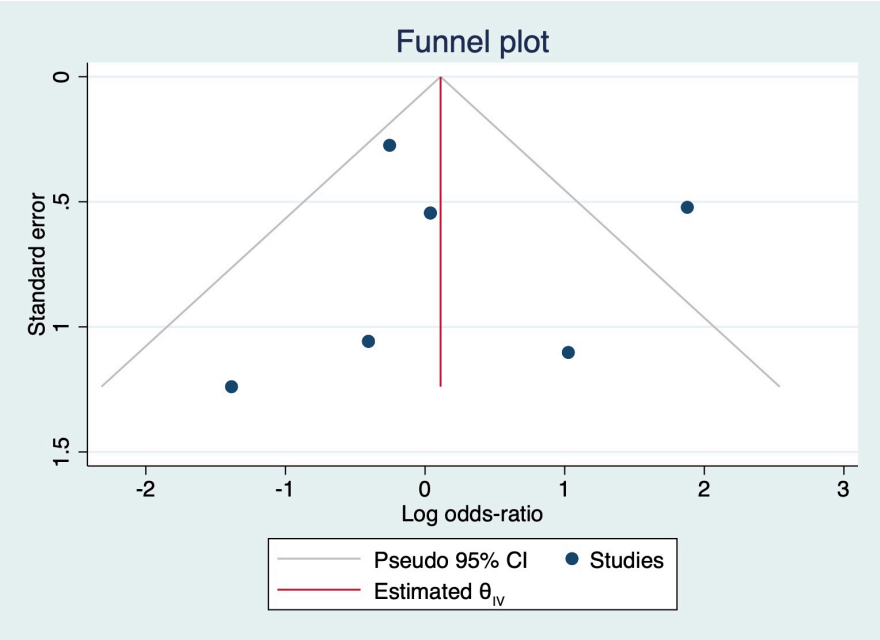
Figure A 5.3.1 Publication bias for NRS reporting on total thromboembolic events with the corresponding Forest plot and Harbord's modification of the Egger test




```
Regression-based Egger test for small-study effects
Random-effects model
Method: Empirical Bayes

H0: beta1 = 0; no small-study effects
            beta1 =     -0.69
      SE of beta1 =     0.645
                z =     -1.08
       Prob > |z| =    0.2813
```

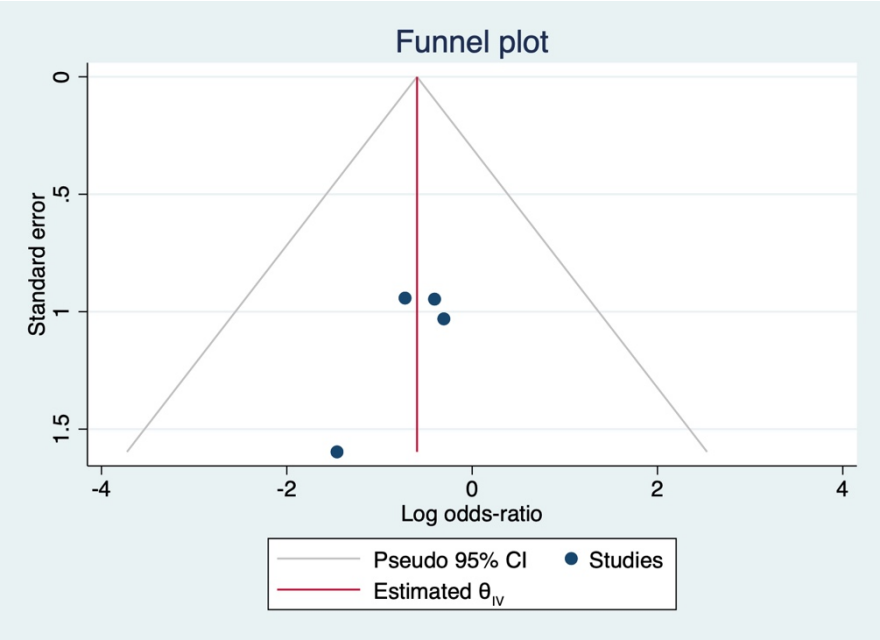
Figure A 5.3.2 Publication bias for NRS reporting on major bleeding with the corresponding Forest plot and Harbord's modification of the Egger test




```
Regression-based Egger test for small-study effects
Random-effects model
Method: REML

H0: beta1 = 0; no small-study effects
            beta1 =      0.01
      SE of beta1 =     0.900
                z =      0.01
       Prob > |z| =    0.9952
```

Figure A 5.3.3 Publication bias for NRS reporting on mortality with the corresponding Forest plot and Harbord's modification of the Egger test




```
Regression-based Egger test for small-study effects
Random-effects model
Method: REML

H0: beta1 = 0; no small-study effects
            beta1 =     -1.20
      SE of beta1 =     0.887
                z =     -1.36
       Prob > |z| =    0.1751
```

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