Does a Higher than Standard-Intensity INR Goal Benefit Patients with MAVR and Additional Thrombotic Risk Factors: A Protocol for Systematic Review and Meta-analysis

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Abstract

Background: Lifelong anticoagulation with vitamin K antagonists is required to prevent prosthetic valve thrombosis after mechanical aortic valve replacement (MAVR). Current guidelines recommend a standard international normalized ratio (INR) of 2.5 for MAVR patients without additional thromboembolic risk factors, while a higher INR of 3.0 is advised for those with conditions such as atrial fibrillation, prior thromboembolism, or left ventricular dysfunction. However, limited clinical data exist to validate the optimal anticoagulation intensity for this high-risk population, necessitating further investigation.

Objective: This systematic review and meta-analysis aim to assess the risks and potential benefits of higher-intensity anticoagulation goals (INR>3.0) in MAVR patients with additional thromboembolic risk factors.

Methods: A comprehensive literature search will be conducted, including case studies, randomized controlled trials (RCTs), and follow-up studies published before December 18, 2024. The study population includes MAVR patients on Warfarin therapy, with and without additional
thromboembolic risk factors. Studies involving bioprosthetic valves, non-bileaflet mechanical valves, and patients not on Warfarin will be excluded. Data will be extracted and analyzed following PRISMA guidelines, with statistical comparisons evaluating thromboembolic and
bleeding events.

Results: The study follows a structured timeline: protocol development was completed in December 2024, with the search strategy finalized in January 2025. Screening stages (title, abstract, and full-text) span February to May. Data extraction, synthesis, and risk of bias assessment occur in
May and June, followed by data analysis and manuscript drafting from July to August. Submission and peer review are scheduled for September 2025.

Conclusions: This systematic review will provide critical insights into anticoagulation management in MAVR patients with thromboembolic risk factors. Given the scarcity of targeted research, these findings may inform future guideline revisions,

balancing thrombotic prevention with bleeding risks.
Further prospective studies will be needed to validate these conclusions. Clinical Trial: CRD42025639037

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Abstract:

Background

Lifelong anticoagulation with vitamin K antagonists is required to prevent prosthetic valve thrombosis after mechanical aortic valve replacement (MAVR). Current guidelines recommend a standard international normalized ratio (INR) of 2.5 for MAVR patients without additional thromboembolic risk factors, while a higher INR of 3.0 is advised for those with conditions such as atrial fibrillation, prior thromboembolism, or left ventricular dysfunction. However, limited clinical data exist to validate the optimal anticoagulation intensity for this high-risk population, necessitating further investigation.

Objective

This systematic review and meta-analysis aim to assess the risks and potential benefits of higher-intensity anticoagulation goals (INR >3.0) in MAVR patients with additional thromboembolic risk factors.

Methods

A comprehensive literature search will be conducted, including case studies, randomized controlled trials (RCTs), and follow-up studies published before December 18, 2024. The study population includes MAVR patients on Warfarin therapy, with and without additional thromboembolic risk factors. Studies involving bioprosthetic valves, non-bileaflet mechanical valves, and patients not on Warfarin will be excluded. Data will be extracted and analyzed following PRISMA guidelines, with statistical comparisons evaluating thromboembolic and bleeding events.

Results

The study follows a structured timeline: protocol development was completed in December 2024, with the search strategy finalized in January 2025. Screening stages (title, abstract, and full-text) span February to May. Data extraction, synthesis, and risk of bias assessment occur in May and June, followed by data analysis and manuscript drafting from July to August. Submission and peer review are scheduled for September 2025.

Conclusions

This systematic review will provide critical insights into anticoagulation management in MAVR patients with thromboembolic risk factors. Given the scarcity of targeted research, these findings may inform future guideline revisions, balancing thrombotic prevention with bleeding risks. Further prospective studies will be needed to validate these conclusions.

Introduction:

Severe aortic valvular disease requiring surgical intervention necessitates either mechanical or prosthetic valve replacement, given its high mortality rate exceeding 90% [1-3]. Following mechanical aortic valve replacement (MAVR), long-term anticoagulation therapy with vitamin K antagonists is recommended to prevent prosthetic valve thrombosis. The 2020 ACC/AHA and 2012 ACCP guidelines suggest a target international normalized ratio (INR) of 2.5 for patients who undergo MAVR without additional thromboembolic risk factors. However, in the presence of risk factors such as atrial fibrillation, prior thromboembolism, hypercoagulable states, older-generation prostheses, or severe left ventricular dysfunction, the recommended target INR differs. The ACC/AHA guidelines advocate for a higher target INR of 3.0 with a Class I recommendation [1], whereas the ACCP guidelines continue to recommend the standard INR goal of 2.5 [4]. Since anticoagulation therapy is lifelong for patients with MAVR, it is essential to balance its benefits and risks to minimize the likelihood of bleeding or thrombotic complications.

Most patients with advanced aortic valvular disease already exhibit structural abnormalities, such as left ventricular hypertrophy or chamber dilation, due to compensatory mechanisms that accommodate the increased pressure and volume caused by the valvular disease [5,6]. These cardiac remodeling often lead to chronic conditions like atrial fibrillation or left ventricular systolic dysfunction [7]. As a result, the majority of patients who are ideal candidates for MAVR are already predisposed to thromboembolism due to these structural abnormalities. This underscores the need for further investigation into the optimal INR goal for this population with additional thromboembolic risk factors.

Currently, there is limited clinical data specifically addressing MAVR in patients with additional thromboembolic risk factors. To date, only one multicenter retrospective study has explored MAVR in this context [8]. This study found that standard-intensity anticoagulation resulted in fewer bleeding and thromboembolic events compared to high-intensity anticoagulation, challenging the validity of the ACC/AHA guidelines and raising concerns about the potential risks versus benefits. Given the scarcity of data, further research is required to substantiate the use of higher-dose anticoagulation therapy, as recommended by the ACC/AHA guidelines, for this group.

There is currently no systematic review or meta-analysis specifically focused on patients with MAVR and additional thromboembolic risk factors. Therefore, aggregating updated data is crucial to better understand the potential benefits of higher INR goals in this patient population. In contrast to patients with MAVR and additional thromboembolic risk factors—where only one study is available—several studies have examined anticoagulation therapy in MAVR patients without specifically addressing thromboembolic risk factors [9-13]. These studies, however, do include populations with characteristics that may predispose them to thromboembolic events. Thus, it is worth analyzing available data to identify the characteristics of patients with additional thromboembolic risk factors. This systematic review will compare the risks and benefits of higher-dose anticoagulation therapy for MAVR patients with additional thromboembolic risk factors.

Since our study will be the first to explicitly examine this population, it could potentially inform the development of new guidelines and guide future research in this area. This may help clarify the role of higher-dose anticoagulation therapy in this group, potentially reducing adverse events such as valve thrombosis, stroke, pulmonary embolism, right-sided heart failure, major bleeding, and even death.

Methods

Ethical Considerations and Protocol Registration

IRB approval was not required for this systematic review, as it did not involve patient interaction and was conducted using publicly available published data. To maintain project integrity, it was registered with PROSPERO (registration number CRD42025639037
, registered on 1/27/2025). PROSPERO is an international database where systematic reviews across various fields, including healthcare, can be registered to prevent duplication and minimize reporting bias by comparing the protocol with the final review.

Review Questions

Guided by the PECOS framework [14], this study was developed to answer the question: “Does a higher than standard-intensity INR goal benefit patients with MAVR and additional thrombotic risk factors?”

Inclusion and Exclusion Criteria

The systematic review will include case studies, randomized controlled trials (RCTs), and single-arm studies, while the meta-analysis primarily will consist of RCTs and follow-up studies. Only English-language articles published before December 18, 2024, will be included. Single patient Case reports, abstract-only articles, animal studies, commentaries, position papers, opinions, and editorials will be excluded, as were other meta-analyses and systematic reviews.

The study population comprised patients aged over 18 years with a prior mechanical aortic valve replacement who were on Warfarin therapy. A specific INR goal was not defined to expand the inclusion criteria, thereby maximizing the sample size and statistical power. Patients under 18 years of age or not on Warfarin therapy will be excluded. Additionally, patients with bioprosthetic aortic valve replacement (AVR) will be excluded, as they do not require Warfarin therapy. Non-bileaflet mechanical valves will also excluded due to the higher thromboembolic risks associated with single-leaflet AVRs compared to bileaflet prostheses [15,16]. Only studies with a patient population meeting the above criteria will be included in the systematic review. Among these, patients with and without additional thromboembolic risk factors—such as atrial fibrillation, previous venous thromboembolism (VTE), hypercoagulability, or severe left ventricular dysfunction—will be compared. Older-generation prostheses or non-bileaflet devices will be excluded due to practical concerns.

Table 1: Inclusion and Exclusion Criteria Guided by the PECOS Framework

Inclusion Criteria	Exclusion Criteria

Population	1)>18 years old 2)MAVR 3) With additional thromboembolic risk factors	1)<18 years old 2)not on Warfarin therapy 3)bioprosthetic AVR 4)non-bileaflet mechanical valves
Exposure	INR goals with Warfarin Therapy	
Control	Without additional thromboembolic risk factors	
Outcome	The primary end point (s): 1)Major or minor bleeding event 2)Major or minor thrombotic event The secondary endpoint: 1)all-cause mortality. 2)prosthetic endocarditis 3)preoperative aortic valve replacement or repair 4)hemolytic anemia	N/A
Study Design	All observational, experimental, English only articles	Case reports, conference abstracts, previous systematic meta-analysis, letters to editor, short commentary, documentary, non-English articles, studies without relevant data points

Informational Sources and Search Strategy

Bibliographic databases such as PubMed, Cochrane, and Embase were searched from the initial development through December 18, 2024. The search strategy was developed by an expert medical librarian and adheres to the guidelines outlined by the Peer-Reviewed Electronic Search Strategy (PRESS). Initially, the search strategy was designed for the PubMed database, utilizing search criteria specific to that platform. It was then adapted for use with other databases. The detailed search strategy is provided in Table 2.

Table 2. The search strategy

Database	Query used	Limit criteria	Results	Totals

PubMed				
#1	INR	Inception – 12/18/2024	20,246	
#2	International Normalized Ratio	Inception – 12/18/2024	13,833	
#3	Warfarin	Inception – 12/18/2024	35,162	
#4	Coumadin	Inception – 12/18/2024	35,662	
#5	Vitamin k antagonist	Inception – 12/18/2024	11,315	
#6	#1 OR #2 OR #3 OR #4 OR #5	Inception – 12/18/2024	56,899	
#7	Mechanical aortic valve replacement	Inception – 12/18/2024	4,375	
#8	MAVR	Inception – 12/18/2024	55	
#9	#7 OR #8	Inception – 12/18/2024	4,405	
#10	#6 AND #9	Inception – 12/18/2024	**341**	
Embase				
#1	INR	Inception – 12/18/2024	61,976	
#2	International Normalized Ratio	Inception – 12/18/2024	55,005	
#3	Warfarin	Inception – 12/18/2024	117,951	
#4	Coumadin	Inception – 12/18/2024	5,260	
#5	Vitamin k antagonist	Inception – 12/18/2024	9,682	
#6	#1 OR #2 OR #3 OR #4 OR #5	Inception – 12/18/2024	167,310	
#7	Mechanical aortic valve replacement	Inception – 12/18/2024	7,589	
#8	MAVR	Inception – 12/18/2024	82	
#9	#7 OR #8	Inception – 12/18/2024	7,626	
#10	#6 AND #9	Inception – 12/18/2024	**1,114**	
Cochrane Library				
#1	INR	All Text; Inception – 12/18/2024	4847	
#2	International Normalized Ratio	All Text; Inception – 12/18/2024	3434	
#3	Warfarin	All Text; Inception – 12/18/2024	5802	
#4	Coumadin	All Text; Inception – 12/18/2024	234	
#5	Vitamin k antagonist	All Text; Inception – 12/18/2024	909	
#6	#1 OR #2 OR #3 OR #4 OR #5	All Text; Inception – 12/18/2024	10974	
#7	Mechanical aortic valve replacement	All Text; Inception – 12/18/2024	261	
#8	MAVR	All Text; Inception – 12/18/2024	3	
#9	#7 OR #8	All Text; Inception – 12/18/2024	262	
#10	#6 AND #9	All Text; Inception – 12/18/2024	**61**	

			GRAND TOTAL	

Screening:

Each article identified through the search strategy described above will be reviewed by four independent researchers to ensure it met the inclusion criteria. This process will be carried out step-by-step, including the review of the title, abstract, and full text. A PRISMA flow diagram (Figure 1) will be included in the final review to further illustrate the screening process.

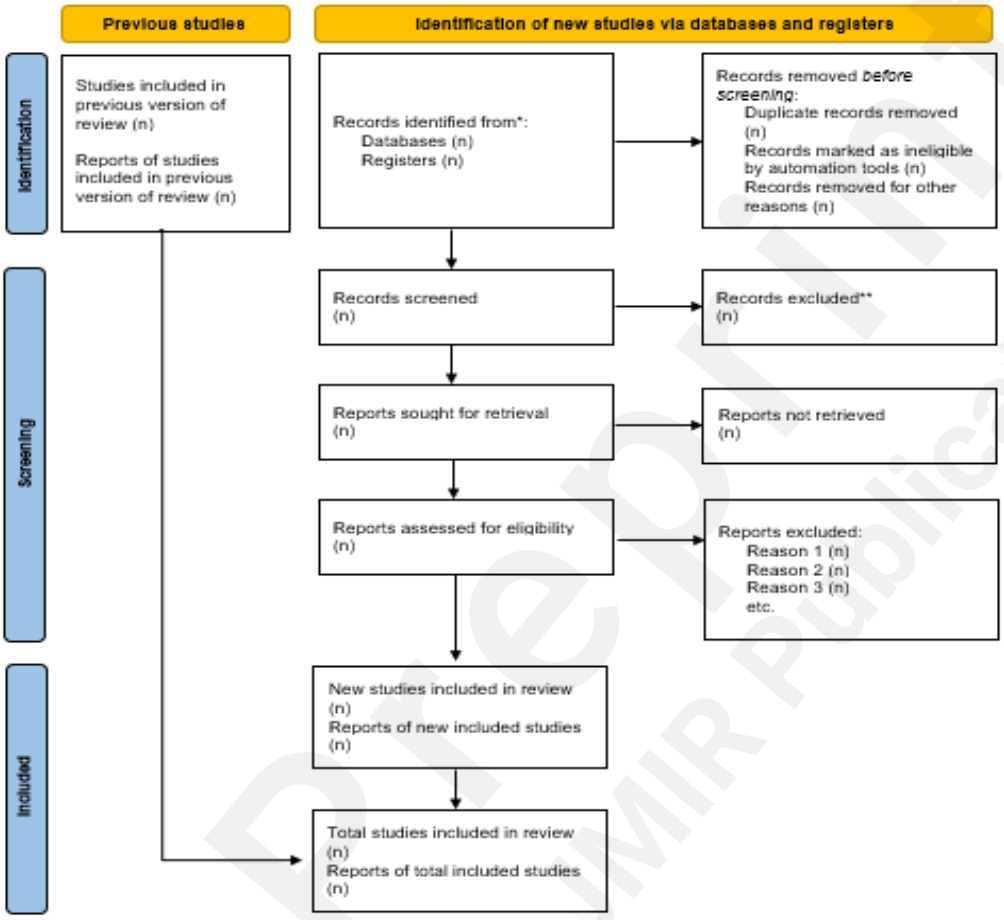

Figure 1. The PRISMA Flow Diagram to describe the study selection process (reproduced from Page MJ, et al. 2021[17]

Data Extraction and Main Data Elements:

Four research team members will independently extract data from the articles accepted through the screening process to ensure a thorough and accurate review. Any discrepancies in the findings after data extraction will be discussed among authors and another independent team member to determine their relevance to the systematic review. The outcomes of the meta-analysis/systematic review will include: 1) Occurrence of thromboembolic events during Warfarin therapy, 2) Occurrence of bleeding events during Warfarin therapy, 3) All-cause mortality, 4) Prosthetic endocarditis, 5) Preoperative aortic valve replacement or repair, and 6) Hemolytic anemia.

Quality or Risk of Bias Assessment:

All studies included in the final publication that met the original inclusion criteria will be assessed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool [18]. The evaluation will be conducted according to the NHLBI criteria outlined below (Figure 2). The scoring protocol followed the model previously developed by Elks W et al.

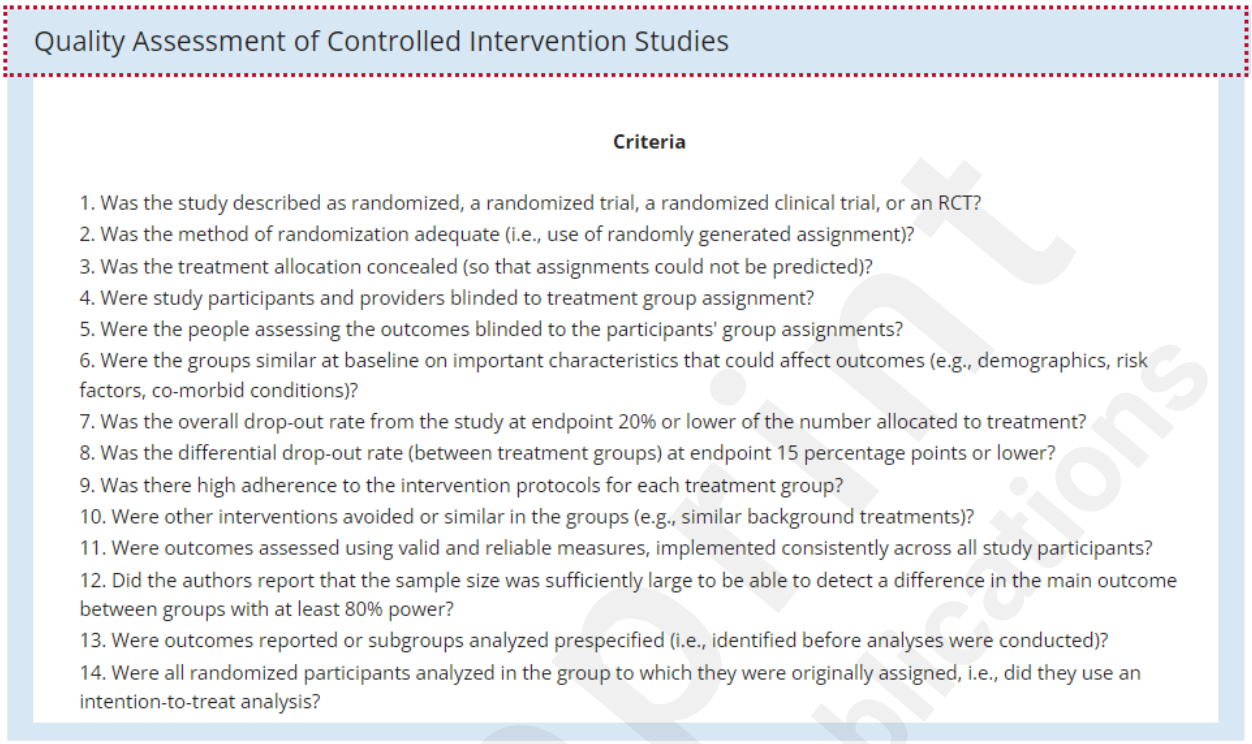

Figure 2. NHLBI Scoring Checklist

Strategy for Meta-Analysis:

The statistical analysis for this meta-analysis will involve several key steps to assess the practical benefits of higher-intensity Warfarin therapy for patients with MAVR and additional thromboembolic risk factors. First, data will be pooled using a random-effects model, as this approach accounts for potential variability between studies [19]. For continuous outcomes, such as INR level or left atrial dimension >50mm, mean differences (MD) or standardized mean differences (SMD) will be calculated. For dichotomous outcomes, such as bleeding or thromboembolic events, all-cause mortality, prosthetic endocarditis, preoperative aortic valve replacement or repair, and hemolytic anemia, risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CIs) will be computed. Subgroup analyses will explore potential differences based on factors such as additional thromboembolic risk factors (e.g., atrial fibrillation, prior thromboembolism, hypercoagulable states, or severe left ventricular dysfunction), spontaneous echocardiographic contrast in the left atrium, significant vascular disease, estrogen replacement therapy, as well as age, sex, and study design (randomized controlled trials vs. observational studies). Sensitivity analyses will be conducted by excluding studies with a high risk of bias or small sample sizes to evaluate the robustness of the results. The heterogeneity of the results will be assessed using the I^2 statistic, and if significant heterogeneity is detected, meta-regression and subgroup analyses will be performed to explore its sources. Publication bias will be assessed using funnel plots and Egger's test [20]. Statistical significance will be defined as a two-sided p-value of less than 0.05. The Comprehensive Meta-Analysis Package (CMA version 4.0, Englewood, NJ, USA) will be used for data analysis.

Data Analysis and Presentation:

Assuming sufficient data are extracted, it will be presented in a detailed table, accompanied by a final summary discussing the analysis performed. A data extraction form will be created and reviewed by all investigators before analysis. The articles included in the publication will be listed as horizontal rows in the table, and the variables agreed upon by the team will serve as columns. Quantitative analysis will be conducted on all variables extracted from the available data.

Results

A PRESS review of the search strategy with an academic librarian was conducted in December 2024. The development of the search strategy began in December, and the final strategy was completed by the team of investigators in January 2025. Database queries and title screenings will begin in February 2025, with abstract screenings scheduled for February and March 2025. Full-text retrieval will occur from March to May 2025. Data extraction, synthesis, and risk of bias assessment will be carried out in May and June 2025. Data analysis and manuscript drafting will take place during July and August 2025. The findings will be summarized, organized, and submitted to a peer-reviewed journal by September 2025. The primary goal of this effort is to assess the utility of higher INR goals in patients following MAVR with additional thromboembolic risk factors, balancing the benefits and risks of harm, and to inform the development of future guidelines for medical practice. A timeline is presented in Table 3 below.

Table 3: Project Milestones and Timelines

Tasks	December 2024	January 2025	February 2025	March 2025	April 2025	May 2025	June 2025	July 2025	August 2025	September 2025
1. Protocol Development	✓									
2. Design Search Strategy	✓	✓								
3. Title Screening			✓							
4. Abstract Screening			✓	✓						
5. Full-text Screening				✓	✓	✓				
6. Data Extraction						✓	✓			
7. Synthesis and Risk of Bias						✓	✓			

Assessment										
8. Data Analysis								✓	✓	
9. Manuscript Drafting								✓	✓	
10. Submission and Peer Review										✓

Discussion

Overview

Our systematic review will be a comprehensive analysis of the relevant literature to synthesize the need for higher-intensity anticoagulation therapy in patients with MAVR and additional thromboembolic risk factors. We anticipate that the results of our analysis will align with current guidelines, recommending higher INR goals (3.0-3.5) for this group, compared to the standard INR goals (2.5-3.0) for patients without additional risk factors. We will analyze each thromboembolic risk factor, such as atrial fibrillation, history of thromboembolism, hypercoagulable states, and left ventricular systolic dysfunction, to evaluate their individual contributions to thromboembolic events in this population. In addition to the thromboembolic risk factors highlighted in the 2020 ACC/AHA and 2012 ACCP guidelines, we will also explore other potential risk factors, including left atrial dimension >50mm, spontaneous echocardiographic contrast in the left atrium, significant vascular disease, and patients on estrogen replacement therapy. In addition to major and minor thromboembolic and bleeding events as primary endpoints, we will examine all-cause mortality, prosthetic endocarditis, preoperative aortic valve replacement or repair, and hemolytic anemia as secondary endpoints to assess both the positive and negative outcomes of higher-intensity anticoagulation therapy in this group.

Significance

Although studies have examined the optimal INR goals for patients with MAVR, no previous systematic review or meta-analysis has specifically addressed the group with additional thromboembolic risks. As our study will be the first to focus on thromboembolic risk factors in MAVR patients regarding anticoagulation therapy, it may help validate the current guidelines, establish new ones, and guide future research in this patient population. In addition to primary RCTs, our systematic review will include secondary or follow-up RCTs of the original studies. This broader inclusion will enhance subgroup analyses and provide a more comprehensive understanding of the safety profile of anticoagulation therapy in patients with additional thromboembolic risk factors. This study will balance the benefits of thromboembolic prevention against the harms of bleeding associated with higher-intensity Warfarin therapy in this group. Since the majority of MAVR candidates already have significant cardiac conditions, such as atrial fibrillation or left ventricular systolic dysfunction due to chronic severe aortic valvular disease, most MAVR patients are naturally at high thromboembolic risk. Given the lack of supporting data, many physicians and institutions continue to follow standard anticoagulation therapy guidelines, despite the presence of additional thromboembolic risk factors. We anticipate that our study will benefit the majority of MAVR patients, as most are at high thromboembolic risk for the reasons outlined above.

Limitations

Our study will have several limitations. First, the selected articles were conducted in different settings, with varying demographics, primary and secondary endpoints, time periods, follow-up periods for INR checks, and INR goals. This variability in methodologies will introduce inherent heterogeneity. Additionally, there is a potential for reviewer bias during article selection. To mitigate this, we will implement the following strategies: (1) an individualized filtering process with four independent reviewers, with the first author overseeing the entire screening process to resolve any disagreements; (2) full transparency of methods, with subject matter experts providing input at each step of the systematic review; and (3) a standardized risk of bias assessment for every article. There is also a risk of publication bias in the article selection process, as studies with small sample sizes or insignificant results are less likely to be published, potentially causing relevant literature to be overlooked. Finally, given the variable study methodologies, we may encounter diverse outcomes of interest. While we hope our study will provide valuable insights and future directions on this topic, there remains the possibility that the results may not reach statistical significance.

Dissemination Plan

Our systematic review will be submitted as a manuscript to a peer-reviewed journal by September 2025. Abstracts based on this study will be created, submitted, and presented at academic conferences.

Conclusions

This systematic review will provide a comprehensive evaluation of the safety of high-intensity anticoagulation therapy in patients with MAVR and additional thromboembolic risk factors, including atrial fibrillation, previous thromboembolism, a hypercoagulable state, or severe left ventricular dysfunction, as outlined in the 2020 ACC/AHA guidelines. We will also broaden the scope to include other thromboembolic risk factors, such as left atrial dimension >50mm, spontaneous echocardiographic contrast in the left atrium, significant vascular disease, and estrogen replacement therapy. The primary endpoints will include major or minor thromboembolic and bleeding events, while secondary endpoints will include all-cause mortality, prosthetic endocarditis, preoperative aortic valve replacement or repair, and hemolytic anemia. Our study will also generate a qualitative synthesis of evidence regarding the risks of thromboembolism and bleeding across different INR goals in this patient population. Ultimately, our findings may guide future research and either support or modify current guidelines.

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