ANTITHROMBOTIC THERAPY IN PATIENTS WITH SURGICAL BIOPROSTHETIC AORTIC VALVE REPLACEMENT

ANTITHROMBOTIC THERAPY IN PATIENTS WITH SURGICAL BIOPROSTHETIC AORTIC VALVE REPLACEMENT

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Lay Abstract

More than 10,000 Canadians require aortic valve replacement each year. Bioprosthetic valves (made out of cow or pig tissue) are often preferred over mechanical valves (made out of metal) because the risk of blood clots forming on the valve or causing a stroke is lower. The disadvantage of bioprosthetic valves is that they can wear out and require re-replacement. The reason why bioprosthetic valves wear out is uncertain, but it may be related to small blood clots on the valve that are only detectable on a CT scan. This doctoral thesis explores the use of blood thinners for patients with bioprosthetic aortic valve replacement. Ideally, blood thinners would be able to prevent blood clots and stroke, and to improve the durability of bioprosthetic valves, without causing too much bleeding. The thesis reviews the available evidence, identifies unanswered questions, and ends with a proposal for a study to generate new data.

Abstract

Aortic valve replacement (AVR) is the only life-saving treatment for patients with severe symptomatic aortic stenosis. Bioprosthetic valves are used in 90% of AVRs because they do not require lifelong anticoagulation. The major limitation of bioprosthetic valves is their limited durability compared to mechanical valves. In addition, bioprosthetic valves still carry a 2-3% risk of symptomatic valve thrombosis, stroke, and thromboembolism in the first 30 days after implantation, and a 1% annual risk thereafter. The risk of subclinical valve thrombosis is around 10% at 30 days and 25% at 1 year, and prevention of subclinical valve thrombosis is hypothesized to reduce the risk of clinical thrombotic events and perhaps even improve valve durability, although high-quality evidence is lacking.

This doctoral thesis comprises 7 chapters of varied methodology that summarize the evidence behind current recommendations for antithrombotic therapy after bioprosthetic AVR, identify evidence gaps, and present the design a randomized trial that aims to address some of these evidence gaps.

Chapter 1 introduces each included study with a brief summary.

Chapter 2 is a narrative review summarizing guideline recommendation for antithrombotic therapy after bioprosthetic AVR and the evidence upon which they are based.

Chapter 3 is an observational study describing antithrombotic prescribing practices in the VISION Cardiac Surgery cohort study.

Chapter 4 is a systematic review and network meta-analysis of randomized studies of antithrombotic therapy after transcatheter aortic valve replacement.

Chapter 5 is a systematic review and meta-analysis of randomized and observational studies of subclinical valve thrombosis.

Chapter 6 presents the design and rationale of a feasibility trial of direct oral anticoagulants versus vitamin K antagonists in patients with a new surgical bioprosthetic AVR and atrial fibrillation.

Chapter 7 discusses the implications, limitations, and future avenues of the research presented in this doctoral thesis.

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List of Abbreviations

ACCP	American College of Chest Physicians
ADAPT-TAVR	Anticoagulation Versus Dual Antiplatelet Therapy For Prevention Of Leaflet Thrombosis And Cerebral Embolization After Transcatheter Aortic Valve Replacement
AF	Atrial fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
ARISTOTLE	Apixaban for Reduction of Stroke and Other Thrombotic Events in Atrial Fibrillation
ASA	Acetylsalicylic acid
ATLANTIS	Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis
AVR	Aortic valve replacement
BAVR	Bioprosthetic aortic valve replacement
CI	Confidence interval
CrI	Credible interval
CT	Computed tomography
DANCE	Direct Oral Anticoagulant Versus Warfarin After Cardiac Surgery
DAPT	Dual antiplatelet therapy
DOAC	Direct oral anticoagulant
ENAVLE	Explore the Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement

ENGAGE	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation
ENVISAGE-TAVI AF	Edoxaban Versus Standard Of Care And Their Effects On Clinical Outcomes In Patients Having Undergoing Transcatheter Aortic Valve Implantation-Atrial Fibrillation
ESC	European Society of Cardiology
GALILEO	Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes
GRADE	Grading of Recommendations, Assessments, Development and Evaluation
HALT	Hypoattenuated leaflet thickening
HK	High molecular weight kininogen
INR	International normalized ratio
INVICTUS	Investigation Of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban Or Aspirin
IQR	Interquartile range
LOE	Level of evidence
MI	Myocardial infarction
OR	Odds ratio
PK	Plasma prekallikrein
POPular TAVI	Antiplatelet Therapy For Patients Undergoing Transcatheter Aortic Valve Implantation

PROACT	The Prospective Randomized On-X Valve Anticoagulation Clinical Trial
RCT	Randomized controlled trial
RE-ALIGN	Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement
RIVER	Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation
ROBINS-E	Cochrane Risk of Bias in Non-randomized Studies of Exposure
RR	Relative risk
SAVR	Surgical aortic valve replacement
SUNDANCE	Subclinical Valve Thrombosis in Patients with Surgical Bioprosthetic Aortic Valve Replacement: An imaging substudy of the DANCE trial
TAVR	Transcatheter aortic valve replacement
VISION	Vascular Events in Surgery Patients Cohort Evaluation
VKA	Vitamin K antagonist

Contributions

A full description of authors' contributions follows each chapter.

Chapter 1: Introduction

Valvular heart disease affects more than 100 million people worldwide.[1] In North America, more than 100,000 patients receive mechanical or bioprosthetic aortic valve replacements (AVRs) annually.[2] Mechanical valves are typically preferred in younger patients because they are more durable than bioprosthetic valves, but they require lifelong anticoagulation with a vitamin K antagonist (VKA). Bioprosthetic valves do not require lifelong anticoagulation and consequently are used for more than 90% of AVRs.[3] The biggest limitation of bioprosthetic valves is their propensity to undergo structural valve deterioration. However, bioprosthetic AVRs are increasingly used in younger patients because valve-in-valve transcatheter aortic valve replacement (TAVR) provides a low-risk alternative to redo sternotomy and bioprosthetic AVR when the initial valve deteriorates.[4]

Although bioprosthetic valves are thought not to require long-term antithrombotic therapy, they carry a risk of clinical valve thrombosis and thromboembolism of around 2-3% in the first 30 days after implantation,[5,6] and 1% per year thereafter.[7,8] The risk of thromboembolic events is believed to be higher in the first 3-6 months after valve implantation because the valve surfaces are not yet endothelialized and, recognized as foreign, trigger activation of coagulation.[9,10] Most patients who undergo surgical bioprosthetic AVR receive either oral anticoagulation or antiplatelet therapy for at least the first few months after valve implantation, but the optimal choice and duration of antithrombotic therapy remains unknown.

The focus of this thesis is the optimal antithrombotic therapy after bioprosthetic AVR. Using varied methodologies, chapters 2 through 5 identify gaps in the available evidence and highlight the need for rigorous randomized evaluation of different

antithrombotic approaches. Chapter 6 describes the design and rationale of such a trial, which will be enrolling patients by the time this thesis is published. The conclusion critically summarizes this body of work and outlines future avenues for investigation.

More literature is available regarding antithrombotic therapy after TAVR than surgical bioprosthetic AVR. The two types of valves are similar in that they treat similar diseases, are constructed of similar materials, and both have a propensity to activate coagulation. There are, however, major limitations to extrapolating from TAVR to surgical bioprosthetic AVR because the methods by which these two types of valves are implanted are vastly different, as are the patients who receive these valves. Nonetheless, the TAVR literature can provide important insights – both methodological and clinical – to those who wish to improve the literature regarding antithrombotic therapy after surgical bioprosthetic AVR. Several chapters of this dissertation involve a significant focus on the TAVR literature for precisely these reasons.

Key terms

Before introducing the contents of this dissertation, it is important to define some key terms. **Antithrombotic therapy** refers to medications that affect the function of any component of the coagulation system, reducing risk of thrombosis. Both **antiplatelet agents**, which inhibit platelet activation and aggregation (e.g., aspirin, clopidogrel), and **anticoagulants**, which act on components of the contact and tissue pathways of coagulation, are antithrombotic therapies. Two main types of oral anticoagulants are available for patients with bioprosthetic valves: **vitamin K antagonists** (VKAs), which inhibit factors II, VII, IX and X of the coagulation cascade; and **direct oral**

anticoagulants (DOACs), which inhibit either factor X (apixaban, edoxaban, and rivaroxaban are the most common) or thrombin (dabigatran).

One of the main reasons patients with bioprosthetic valves are treated with antithrombotic therapy is to prevent **clinical valve thrombosis.** Clinical valve thrombosis, also referred to as obstructive or symptomatic valve thrombosis, is thrombosis on valve leaflets that causes increased transvalvular gradients on echocardiography with signs and symptoms of aortic stenosis (dyspnea, syncope, or heart failure) and requires medical or surgical intervention.[3] In contrast**, subclinical valve thrombosis** is asymptomatic. It is diagnosed on computed tomography (CT) scan by hypoattenuated lesions on valve leaflets that cause leaflet thickening and may or may not cause reduced leaflet motion. Subclinical valve thrombosis is often undetectable on echocardiography.[3,11,12] The clinical implications of subclinical valve thrombosis are a major focus of this dissertation.

Guideline recommendations are inconsistent and based on low-quality evidence (Chapter 2)

Major society guidelines generally recommend more intense antithrombotic therapy in the first 3-6 months following surgical bioprosthetic AVR, followed by a transition to less intense or even no antithrombotic therapy.[13,14] **Chapter 2**[15] summarizes the evolution of these guidelines over the past 30 years and critically appraises the evidence cited by guideline committees to support their recommendations. The evidence is of low quality – sparse, mainly observational, and inconsistent – and different guidelines cite the same evidence to support incongruent recommendations.[13,14,16] A major challenge of studying antithrombotic therapy after

surgical bioprosthetic AVR is that randomized trials require large sample sizes because rates of clinical valve thrombosis and thromboembolism are low.

Antithrombotic therapy prescribing practices are variable in an international cohort (Chapter 3)

The inconsistent guideline recommendations are reflected in highly variable antithrombotic prescribing practices after surgical bioprosthetic AVR. The VISION Cardiac Surgery cohort study,[17] which investigated myocardial injury in 13,862 patients following cardiac surgery, enrolled around 2,511 patients undergoing surgical bioprosthetic AVR. **Chapter 3** is an observational study that describes antithrombotic therapy use in the first year after valve implantation and explores associations between antithrombotic therapy use and clinical outcomes. The majority of patients receive antiplatelet therapy only after bioprosthetic AVR, while those who are anticoagulated are much more likely to receive a VKA than a DOAC. Most thromboembolic and bleeding events occurred prior to hospital discharge, and the small numbers of events following discharge made it challenging to identify whether antithrombotic therapies differed in their efficacy and safety.

Randomized evidence in transcatheter aortic valve replacement (Chapter 4)

TAVR has transformed the management of aortic valve disease. More than 50% of patients with aortic stenosis now undergo TAVR rather than surgical AVR,[4] and young patients who historically received a surgical mechanical AVR are now receiving surgical bioprosthetic AVRs because of the possibility of valve-in-valve TAVR when the initial prosthesis fails.[18]

TAVR is also changing the standard of evidence for aortic valve interventions. Multiple large randomized controlled trials support choice of antithrombotic therapy following TAVR.[19-23] **Chapter 4** presents a systematic review and network meta-analysis of randomized controlled trials of different antithrombotic regimens after TAVR. The available data suggest that in TAVR patients without an indication for oral anticoagulation, DOAC therapy increases the risk of major bleeding and death compared to aspirin or dual antiplatelet therapy. In TAVR patients who have another indication for oral anticoagulation, DOAC and VKA appear to have similar efficacy and safety.

The TAVR literature provides insights into how to address similar questions in surgical AVR patients. For example, several key studies of antithrombotic therapy enrolled patients in two cohorts[20-22]: one comparing two anticoagulation strategies in patients after TAVR with another indication for anticoagulation, and the other comparing anticoagulation to antiplatelet therapy in patients after TAVR without another indication for oral anticoagulation.

Subclinical valve thrombosis is important, but understudied in surgical patients (Chapter 5)

A particularly important insight from TAVR trials is the importance of subclinical valve thrombosis as a marker of valve outcomes. Subclinical valve thrombosis was first identified in 2015[24] and since then has been a subject of great scrutiny in the TAVR literature. **Chapter 5** presents a systematic review and meta-analysis of randomized and observational studies of subclinical valve thrombosis in both TAVR and surgical AVR. Although subclinical valve thrombosis appears equally common in TAVR and

surgical AVR patients, the TAVR literature has 31 subclinical valve thrombosis studies compared to only 6 in the surgical AVR literature. This meta-analysis suggests that subclinical valve thrombosis is associated with an important increase in stroke, and that the risk is reduced with oral anticoagulation. These data suggest that randomized evaluation of different antithrombotic approaches in patients with surgical AVR should also measure the effects on subclinical valve thrombosis.

Protocol for a feasibility trial of DOAC versus VKA after surgical bioprosthetic aortic valve replacement (Chapter 6)

Chapter 6 describes the design and rationale of a feasibility trial of DOACs versus VKAs in patients with a new surgical bioprosthetic AVR and atrial fibrillation requiring anticoagulation. This 60-patient feasibility trial will, if successful, continue into a 910-patient randomized controlled trial of DOACs versus VKAs with respect to clinical outcomes and subclinical valve thrombosis. The full trial will be the largest study of subclinical valve thrombosis in surgical patients, and the first to randomly compared two anticoagulant strategies in this population.

Future steps

The final chapter of this thesis critically summarizes the work completed to date and suggests future approaches to further improve the quality of evidence for antithrombotic therapy in patients with surgical bioprosthetic AVR.

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How did we get here? Antithrombotic therapy after bioprosthetic aortic valve replacement: a review.

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Abstract

Importance: Aortic stenosis is the most common valvular disease, and more than 90% of patients who undergo aortic valve replacement receive a bioprosthetic valve. Yet optimal antithrombotic therapy after bioprosthetic aortic valve replacement remains uncertain, and guidelines provide contradictory recommendations.

Observations: Randomized studies of antithrombotic therapy after bioprosthetic aortic valve replacement are small and underpowered. Observational data present opposing, and likely confounded, results. Historically, changes to guidelines have not been informed by high-quality new data. Current guidelines from different professional bodies provide contradictory recommendations despite citing the same evidence.

Conclusions and relevance: Insufficient antithrombotic therapy after bioprosthetic aortic valve replacement has serious implications: ischemic stroke, systemic arterial thromboembolism, clinical and subclinical valve thrombosis. Unnecessarily intense antithrombotic therapy, however, increases risk of bleeding and associated morbidity and mortality. Professional bodies have used the current low-quality evidence and generated incongruent recommendations. Researchers should prioritize generating high quality, randomized evidence evaluating the risks and benefits of antiplatelet versus anticoagulant therapy after bioprosthetic aortic valve replacement.

Keywords: aortic valve replacement, bioprosthetic valve, valve thrombosis

Background

Valvular heart disease affects more than 100 million people worldwide. In North America, more than 100,000 patients receive mechanical or bioprosthetic aortic valve replacements (AVRs) annually.[1] Mechanical valves are typically preferred in younger patients because they are more durable than bioprosthetic valves, but they require lifelong anticoagulation with a vitamin K antagonist (VKA). Bioprosthetic valves do not require lifelong anticoagulation but are prone to structural valve deterioration. Nonetheless they are increasingly used in younger patients because valve-in-valve transcatheter aortic valve replacement (TAVR) provides a low-risk alternative to redo sternotomy and bioprosthetic AVR when the initial valve deteriorates.[2] More than 90% of AVRs are bioprosthetic.[3]

The optimal antithrombotic therapy after bioprosthetic AVR is uncertain. Guidelines cite low-quality observational studies and small randomized controlled trials (RCTs) and provide contradictory recommendations (Table 1).[4-6] We review the history of antithrombotic therapy after bioprosthetic AVR and critically appraise guideline recommendations and the evidence upon which they are based.

History of Bioprosthetic Aortic Valve Replacement

Mary and John Gibbons invented the heart-lung machine and Charles Hufnagel implanted the first prosthetic valve into human circulation in the early 1950s. The first surgical valve replacement was a Starr-Edwards caged-ball mechanical valve in 1960. Donald Ross[7] and Brian Barratt-Boyes[8] implanted the first biological cadaveric valves in 1962, and three years later Alain Carpentier implanted the first porcine valve.[9] The first bovine pericardial valve was implanted in 1971.[10] Tirone David implanted the first

stentless valve in 1988,[11] laying the foundation for sutureless valves in the 1990s and transcatheter valves in the 2000s. Today, the main categories of bioprosthetic AVR are 1) stented porcine or bovine pericardial valves mounted on a fabric-covered stent and sewing ring, 2) stentless valves, 3) rapid-deployment sutureless valves, and 4) transcatheter porcine or bovine pericardial valves mounted on a balloon-expandable or self-expanding metal frame (Figure 1).

While lifelong anticoagulation after mechanical valve replacement was standard as early as the mid-1960s,[12,13] experts did not initially believe that thrombus could form on bioprosthetic valves.[14] Case series published in the late 1960s and early 1970s reported thromboembolism rates after bioprosthetic AVR ranging from 0.5-2.8% (mean 1.4% +/- 0.2%) per year.[15] In a series of 627 consecutive patients from the Mayo Clinic, rates of thromboembolism were higher in the first 90 days after surgery (2.9 per 100 patient-years, versus 1.8 per 100 patient-years after 90 days)[16], prompting some physicians to prescribe anticoagulation for the first 8-12 weeks after bioprosthetic AVR.[15]

Due to bleeding concerns, other physicians treated patients with bioprosthetic AVR with high-dose aspirin instead of anticoagulation. An observational study of 768 patients with bioprosthetic valve replacements treated with high-dose aspirin (0.5-1 gram daily) rather than anticoagulation reported a 1.4% (11/768) incidence of thromboembolism, which was similar to anticoagulated patients.[17] Citing this study, the first American Heart Association/American College of Cardiology (AHA/ACC) guidelines on antithrombotic therapy after bioprosthetic AVR, published in 1968, recommended low-dose aspirin (80 mg daily), with three months of anticoagulation by life-long aspirin

as an alternative.[18] Since these guidelines, the question of aspirin versus oral anticoagulation in bioprosthetic AVR patients who do not have another indication for anticoagulation remains unresolved.

Mechanisms of Thrombosis

The mechanisms of thrombosis formation on bioprosthetic valves are complex and multifactorial.

Surface factors

Unlike native endothelium, which resists thrombosis, foreign surfaces placed in the bloodstream promote thrombosis by activating the contact pathway of coagulation through four interconnected mechanisms: 1) protein adsorption; 2) adhesion of platelets, leukocytes, and red blood cells; 3) contact pathway activation; and 4) complement activation (Figure 2).[19]

1. Protein adsorption: Large proteins such as fibrinogen, fibronectin, and von Willebrand factor adhere to the foreign surface in a flow-dependent manner. Fibrinogen activates components of the contact pathway (factor XII, factor XI, high molecular weight kininogen [HK], and plasma prekallikrein [PK]).
2. Platelet adhesion: Fibrinogen stimulates platelet and leukocyte adhesion to the foreign surface. Adhered platelets release thromboxane A2 and adenosine diphosphate which further amplify platelet adhesion and activation. Leukocytes release platelet activating factor, tumor necrosis factor, and interleukins which also promote platelet activation.
3. Contact pathway activation: The foreign surface triggers adhesion and activation of components of the contact pathway, starting with factors XI and XII, HK and

PK, and leading to thrombin release, the production of a fibrin clot, and further platelet activation. A platelet-fibrin coating forms on the foreign surface.

4. Complement activation: The foreign surface powerfully stimulates complement activation. This is true for cardiopulmonary bypass and extracorporeal membrane oxygenation circuits, intravascular catheters and grafts, and prosthetic heart valves. The complement system further amplifies the contact pathway.

The mechanisms that make mechanical valves more thrombogenic than bioprosthetic valves are incompletely understood. Mechanical valve leaflets appear to trigger more protein adsorption than bioprosthetic valve leaflets.[20] In bioprosthetic valves, the platelet-fibrin thrombus network only covers the sewing ring and sutures and does not extend to the valve leaflets.[21] After about three months, this platelet-fibrin network is replaced by neointima.[22] It was previously believed that this neointimal covering protects against valve thrombosis, but evidence suggests that risk of thrombosis after bioprosthetic AVR is highest between 13-24 months after surgery, while only 24% of bioprosthetic valve thromboses occurs in the first three months after surgery.[23,24] This finding reflects the complexity of bioprosthetic valve thrombosis and the limitations of current understanding, and calls into question guideline recommendations which treat the first 3 months after valve replacement as a period of elevated thrombotic risk.

Hemodynamic factors

Valve- and patient-specific hemodynamic factors influence the risk of thrombosis and explain why the same prosthetic valves carry different risks of thrombosis and thromboembolism depending on their location. Stasis and turbulence of blood flow

promote thrombosis. Right-sided heart valves are more prone to thrombosis because they are exposed to lower-pressure venous flow. On the left side of the heart, mitral valves are more prone to thrombosis than aortic valves because they are exposed to passive flow from the atrium. Valves with smaller effective orifice areas are more prone to thrombosis because they promote turbulent blood flow, whereas stentless valves, which achieve a larger effective orifice area than equivalently sized stented valves, may be less thrombogenic.[25] Patient-specific hemodynamic factors predisposing to valve thrombosis include ventricular dysfunction and atrial fibrillation.[21]

Procedure related factors

Factors related to surgery and cardiopulmonary bypass also predispose to early valve thrombosis. Surgery itself causes tissue damage and inflammation, which are stimuli for thrombosis. Cardiopulmonary bypass exposes blood to a foreign surface and causes inflammation. Systemic heparinization, on the other hand, reduces risk of thrombosis intraoperatively and may provide residual antithrombotic effect for freshly implanted valves in the early postoperative period.

Incidence and Clinical Sequalae of Bioprosthetic AVR Thrombosis

Incidence

The reported incidence of bioprosthetic AVR thrombosis ranges from 0.4-1.3%,[5,25-27] but the true incidence is likely much higher. Transthoracic echocardiography, which is the usual imaging modality for bioprosthetic valves, may not detect early valve thrombosis.[3,21] Pathological examination of 397 valves explanted due to valve dysfunction between 1997 and 2013 revealed thrombosis in 10.9% of bioprosthetic aortic valve explants, which translates to a 2% overall incidence of valve thrombosis.[28]

Computed tomography (CT) is more sensitive than echocardiography to bioprosthetic AVR thrombosis, as was first discovered in 2015 when a large RCT of TAVR versus bioprosthetic AVR conducted routine CT scans in a subset of participants.[29] The study identified a new phenomenon of hypoattenuated valve leaflet thickening on CT causing reduced leaflet motion without clinical symptoms.[29] The incidence of this phenomenon, called subclinical valve thrombosis, is 5-16.5% at 30 days[30-32] and 20-28.4% at one year in patients with bioprosthetic AVR.[30,32] Subclinical valve thrombosis is less common in patients receiving anticoagulation; in one study, its incidence was 10.8% in patients not taking warfarin and 1.8% in patients taking warfarin (relative risk (RR) 6.09, 95% confidence interval (CI) 1.86-19.84).[33] In a registry study of patients with TAVR and bioprosthetic AVR, 100% of anticoagulated patients had resolution of subclinical valve thrombosis while 91% of patients not taking anticoagulation had persistence of subclinical valve thrombosis upon repeat CT imaging.[31] However, most literature on subclinical valve thrombosis is in TAVR and cannot necessarily be applied to bioprosthetic AVR.

Clinical sequelae

Bioprosthetic AVR thrombosis causes valve dysfunction, defined as reduced or impaired valve leaflet motion, changes in valve effective orifice area (either increased, leading to regurgitation, or decreased, leading to stenosis and increased transvalvular gradients), with or without valve-related symptoms.[34] Valve dysfunction has four main etiologies: 1) thrombosis, 2) fibrous pannus ingrowth, 3) valve degeneration, and 4) endocarditis. Thrombosis is often present in fibrous pannus ingrowth and valve degeneration, suggesting that bioprosthetic valve thrombosis may in fact be a precursor

to the other three forms of valve dysfunction.[35] Thus, preventing and treating bioprosthetic valve thrombosis may reduce incidence of structural valve deterioration, which is the main factor which limits use of bioprosthetic valves.

Bioprosthesis thrombosis can also lead to thromboembolic complications such as stroke, transient ischemic attack, and systemic arterial embolism. Reported rates of thromboembolism after bioprosthetic AVR are higher than rates of clinical valve thrombosis. This may in part be due to underdiagnosis of clinical valve thrombosis but also reflects other etiologies for postoperative stroke including atrial fibrillation, which occurs in up to 50% of patients with bioprosthetic AVR, and periprocedural embolic stroke, which occurs in 1% of patients undergoing cardiac surgery.[36] In a recent meta-analysis of anticoagulation versus antiplatelet therapy after bioprosthetic AVR, which included 7 studies and 2,409 patients, stroke occurred in 4.1% of patients taking antiplatelet therapy and 4.5% taking anticoagulation (RR for randomized data 0.90, 95% CI 0.35-2.33; RR for observational data 0.57, 95% CI 0.31-1.03).[27] The largest observational study of clinical events after bioprosthetic AVR, including 25,656 patients from the Society of Thoracic Surgery database, reports only 0.9% incidence of stroke at 90 days, with no difference between patients who were and were not taking anticoagulation (RR 0.95, 95% CI 0.61-1.47).[37] After the first 90 days, stroke occurs at a rate of less than 1% per year in long-term cohort studies with no significant differences based on anticoagulant use.[16,38,39]

Subclinical valve thrombosis has uncertain clinical implications but may be a precursor to clinical valve thrombosis and thromboembolism. A recent meta-analysis of 3,456 patients with TAVR found a 3-fold increased rate of stroke in patients with

subclinical valve thrombosis compared to those without (7.0% versus 2.6%, odds ratio 3.0, 95% CI 0.63-1.57).[40] Subclinical valve thrombosis may also lead to fibrous pannus ingrowth and structural valve deterioration.[41] However, while anticoagulation may reduce the incidence of subclinical valve thrombosis compared to antiplatelet therapy alone in TAVR patients, it is associated with increased mortality due to excess bleeding.[42,43] The impact of anticoagulation versus antiplatelet therapy on subclinical valve thrombosis and long-term valve function has not been studied in bioprosthetic AVR patients.

Antithrombotic Therapy Options

Antiplatelet Therapy

Antiplatelet agents and oral anticoagulants are the two classes of antithrombotic therapies used to reduce risk of valve thrombosis and thromboembolic events in patients with bioprosthetic valves. Antiplatelet therapies (aspirin and P2Y12 inhibitors such as clopidogrel, ticagrelor and prasugrel) inhibit platelet activation and aggregation. Aspirin is used in most patients with bioprosthetic AVR, while P2Y12 inhibitors reserved for patients who have another indication (e.g., recent percutaneous coronary intervention). Meta-analysis of the four RCTs comparing dual antiplatelet therapy to aspirin alone after TAVR demonstrates increased risk of bleeding with dual antiplatelet therapy, without significant reduction in thrombosis.[44] There are no randomized data comparing dual to single antiplatelet therapy in patients with surgical bioprosthetic AVR.

Anticoagulation

Warfarin, which inhibits both the contact and the tissue factor pathways of coagulation, is the most commonly used oral anticoagulant in patients with prosthetic

valves. Warfarin has many drug-drug and drug-food interactions and requires routine monitoring and dose adjustments. It is particularly inconvenient in the immediate postoperative period when patients are convalescing at home and unable to drive to appointments. Direct oral anticoagulants (DOACs) have fewer drug-drug and drug-food interactions than warfarin and do not require monitoring. However, they inhibit only the contact pathway by targeting factor X (apixaban, rivaroxaban, and edoxaban) or thrombin (dabigatran). Unlike warfarin, DOACs have rapid onset of effect and their reversal agents are not yet widely available leading to concerns for bleeding, particularly in the perioperative period.

There are limited randomized data on DOACs in patients with surgical bioprosthetic valves, and there are no randomized data comparing DOACs to antiplatelet therapy. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial randomized patients with mechanical valve replacement to dabigatran or warfarin 3-7 days after surgery. Both major bleeding and stroke were increased in the dabigatran arm: there were 7 major bleeding events in patients taking dabigatran compared to 2 in patients taking warfarin, and all bleeding events were intrapericardial. There were 9 strokes in patients taking dabigatran compared to 0 strokes in patients taking warfarin. However, DOACs appear to be safe and effective in patients with bioprostheses. The Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation (RIVER) trial[45] randomized 1004 patients with atrial fibrillation to rivaroxaban or warfarin within 48 hours after bioprosthetic mitral valve replacement, demonstrating non-inferiority of rivaroxaban with respect to death, major cardiovascular events

(including valve thrombosis), or major bleeding at 12 months. The Explore the Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement (ENALVE) trial,[46] which randomized 218 patients with biological valve replacement or repair to three months of edoxaban or warfarin, found edoxaban noninferior to warfarin for a primary composite outcome of death, thromboembolic events, or intracardiac thrombus. Subgroup analyses of two large trials in atrial fibrillation, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE) trial,[47] which compared edoxaban to warfarin, and the Apixaban for Reduction of Stroke and Other Thrombotic Events in Atrial Fibrillation (ARISTOTLE) trial, which compared apixaban to warfarin, are consistent with these randomized data.

The lower thrombogenicity of bioprosthetic valves compared to mechanical valves may explain why DOACs appear effective in prevention of thrombosis and thromboembolism in bioprosthetic valves but not mechanical valves. When DOACs are initiated in the early postoperative period, concerns persist about risk of bleeding, particularly in light of the incidence of pericardial bleeding in the RE-ALIGN study. The ongoing Direct Oral Anticoagulant Versus Warfarin After Cardiac Surgery (DANCE) trial (NCT04284839), which randomizes patients within 14 days of cardiac surgery who have an indication for anticoagulation to DOACs versus warfarin, will provide further clarification on perioperative bleeding risk.[48] The Subclinical Valve Thrombosis substudy of DANCE (SUNDANCE) will examine the effect of DOACs versus warfarin on subclinical valve thrombosis and long-term valve function.

Evolution of Guidelines on Antithrombotic Therapy after Bioprosthetic AVR

Three professional societies publish guidelines for antithrombotic therapy in patients with bioprosthetic AVR who do not have another indication for oral anticoagulation: the American College of Chest Physicians (ACCP), the American Heart Association and American College of Cardiology (AHA/ACC), and the European Society of Cardiology (ESC). The guidelines provide discordant recommendations based upon low-quality evidence. The overall proportion of cardiology guideline recommendations based on high-quality, level A evidence is 8.5%, but only 2% when it comes to valvular heart disease.[49]

Table 2 presents a timeline of changes to guidelines on antithrombotic therapy following bioprosthetic AVR. The first ACCP guidelines, published in 1986, recommend aspirin (0.5 g/day) after bioprosthetic AVR based on observational studies suggesting increased risk of thromboembolism in the first three postoperative months.[15,16] In 1998, they added a grade 2C recommendation for three months of oral anticoagulation (INR target 2.5) after bioprosthetic AVR, followed by lifelong aspirin (162 mg/day, grade 1C). In support, the guidelines cite one observational study of thromboembolism in 57 patients not taking anticoagulation after bioprosthetic AVR.[50] In 2004, the ACCP amended its recommendation to either oral anticoagulation (INR 2.5) or aspirin (80-100 mg/day) for three months (grade 2C), followed by lifelong aspirin (grade 1C). They cite a trial of triflusal (a platelet aggregation inhibitor) or acenocoumarol (a VKA) in 200 patients with aortic or mitral bioprosthesis, finding no difference in thromboembolism, bleeding, or mortality.[51] They also cite three observational studies of 128,[52] 387,[53] and 275[54] patients, each showing no difference between antiplatelet or anticoagulant therapy. Since 2008, the ACCP has recommended aspirin alone (50-100 mg/day) after

BAVR, additionally citing a retrospective observational study of 1,151 patients which found no difference in thromboembolic events between antiplatelet and anticoagulant therapy.[55] In 2012, the ACCP downgraded their recommendation for aspirin alone from 1B to 2C.

The AHA/ACC's first guidelines on antithrombotic therapy after valve replacement, published in 1998, recommended warfarin (INR 2.5-3.5, class 1) and aspirin (80-100mg, class 2A) for three months after surgery, followed by lifelong aspirin monotherapy. In 2006, they modified their recommendation to either warfarin (INR 2-3, class 2A, level of evidence [LOE] C) or aspirin (75-100 mg, class 1, LOE C) for three months. This recommendation was based on two observational studies of thromboembolic events in the first three months after BAVR.[16,17] In 2014, they downgraded the class of recommendation for anticoagulation to class 2B and aspirin to class 2A. In support, the guidelines cite two RCTs of 157[56] and 75[57] patients which showed no difference between anticoagulation or antiplatelet therapy after bioprosthetic AVR. They also cite a retrospective study of 4,075 bioprosthetic AVR patients which showed increased risk of bleeding without a reduction in thromboembolic events in patients receiving anticoagulation versus antiplatelet therapy.[58] However, in 2017 and 2020 the AHA/ACC extended the recommended duration of anticoagulation to up to 6 months in patients at low bleeding risk (class 2A, LOE B-NR). They cite a retrospective study of 25,656 BAVR patients who had lower mortality and thromboembolism when treated with both warfarin and aspirin for the first three months after surgery.[37]

Since publishing its first guidelines on antithrombotic therapy after valve replacement in 2012 the ESC has recommended aspirin (75-100 mg, class 2A, LOE C)

or oral anticoagulation (class 2B, LOE C), but not both, for three months after surgery. The ESC does not recommend lifelong aspirin for patients with bioprosthetic valves in the absence of another indication. They cite two small RCTs[56,57] and two large database studies[37,58] also cited by the AHA guidelines and described in more detail below.

Best Available Evidence for Antithrombotic Therapy after Bioprosthetic AVR

The disagreement between major society guidelines regarding optimal antithrombotic therapy after BAVR reflects the low quality of available evidence. Available randomized data come from small, underpowered trials with low event rates. A systematic review and meta-analysis published in 2019[27] identified two RCTs (one pilot RCT of 75 patients by Colli et al.,[57] and the other of 370 patients by Rafiq et al.,[59]) and five observational studies of 2,409 patients which compared anticoagulant to antiplatelet therapy after bioprosthetic AVR.[27] Neither randomized nor observational data demonstrated a significant difference between anticoagulation and antiplatelet therapy with regard to stroke, thromboembolism, or mortality. Thromboembolism occurred in 4.1% of patients taking antiplatelet therapy and 4.5% taking anticoagulation (RR for randomized data 0.90, 95% CI 0.35-2.33; RR for observational data 0.57, 95% CI 0.31-1.03). Major bleeding was lower in patients receiving antiplatelet therapy alone compared with anticoagulation in observational studies (1.7% vs. 5.1%, RR 0.35, 95% CI 0.2-0.38, p<0.01); randomized data trended in the same direction but failed to reach statistical significance (2.0% vs. 6.0%, RR 0.34, 95% CI 0.11-1.04, p=0.06). The quality of evidence was low for RCTs and very low for observational studies.

The best available evidence, on which current guidelines are based, consists of two small RCTs and two large retrospective database studies. Aramendi et al.

randomized 200 patients after aortic or mitral bioprosthetic valve replacement to triflusal or acenocoumarol for the first three months after surgery.[56] They found no difference in thromboembolism, treatment-related bleeding, or valve-related mortality at three months (9.4% in the triflusal group vs. 11% in the acenocoumarol group, p=0.79). Colli et al. randomized 75 patients to warfarin or aspirin for three months after bioprosthetic AVR, finding no difference in stroke, bleeding, or mortality.[57] Event rates were low, however, with only one stroke in either group. Rafiq et al. randomized 370 patients to warfarin or aspirin for three months after bioprosthetic AVR, again finding no difference in thromboembolic events (6.6% in the warfarin group vs. 7.5% in the aspirin group, p=0.83) or bleeding (5.4% vs. 1.9%, p=0.14).[59] Given their small sample sizes and low event rates, these studies are underpowered to detect a difference between anticoagulation and antiplatelet therapy after bioprosthetic AVR.

The guidelines also cite two large database studies. The first is from the Society of Thoracic Surgeons' database, and reports on 25,656 patients after bioprosthetic AVR.[37] More than half of patients had concomitant coronary artery disease and underwent coronary artery bypass grafting, and 41% had atrial fibrillation. Patients taking warfarin preoperatively were excluded. In total, 49% were treated with aspirin alone, 23% with warfarin and aspirin, 12% with aspirin alone, and 6.5% did not receive antithrombotic therapy. At three months, risk-adjusted analyses demonstrated no difference between warfarin alone and aspirin alone, while the combination of warfarin and aspirin was associated with lower mortality (aspirin plus warfarin, 3.1%; warfarin only, 4.0%; RR 0.80, 95% CI 0.66-0.96) and thromboembolism (-0.4% absolute risk reduction, RR 0.52, 95% CI 0.35-076). However, this benefit came at an increase in

bleeding (2.8% vs 1.0%, RR 2.8, 95% CI 2.18 to 3.60). Although analyses were risk-adjusted, they are limited by their retrospective nature and the high risk for residual confounding.

The second registry study includes 4,075 Danish patients who received bioprosthetic AVR with or without coronary artery bypass grafting, followed for a median of 6.6 years.[58] Patients with preoperative or postoperative atrial fibrillation were excluded, as well as patients taking preoperative warfarin. Reflecting differences in European and North American prescription patterns, 56% of patients were treated with warfarin alone, 23% with warfarin and aspirin, 4% with aspirin alone, and 17% without any antithrombotic therapy. When taken alone or in combination with aspirin, discontinuation of warfarin within 180 days of surgery was associated with increased stroke, thromboembolism, and cardiovascular mortality in unadjusted analyses. However, the authors do not discuss differences in baseline characteristics between those who did and did not receive warfarin, nor do they explore reasons for warfarin discontinuation. The results are therefore likely to be confounded. The apparent benefit to anticoagulation in large observational trials is inconsistent with the results of small RCTs.

Future Directions

The generation of high-quality evidence regarding antithrombotic therapy after bioprosthetic AVR should be a priority. Ideally, this would consist of a trial which randomizes patients without another indication for oral anticoagulation to aspirin alone or anticoagulation. In addition to examining the effect of randomized therapy on thrombosis and bleeding, this trial should conduct routine CT scans on a subset of

patients to assess subclinical valve thrombosis and should include long-term follow-up to assess valve function. Similar studies have been successfully conducted in patients with TAVR. The Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) trial randomized 1644 patients to rivaroxaban plus aspirin or aspirin alone after TAVR,[42] while the Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial randomized 1500 patients to apixaban versus standard of care.[60]

Once high-quality data are available, risk prediction calculators for thrombosis and bleeding that are specific to the surgical bioprosthetic AVR population would further guide clinicians to balance risks and benefits and select the optimal antithrombotic therapy for individual patients. Risk prediction calculators already exist in the TAVR population, but the balance of risk and benefit is likely different in the surgical population, who are in general younger and healthier than TAVR patients and whose surgical valves likely have different prothrombotic profiles than TAVR valves.[61]

Finally, network meta-analysis would facilitate combining existing small RCTs with new data in order to generate more precise estimates of effect, and to compare multiple therapies (e.g., aspirin alone, VKAs, and DOACs).

Conclusion

As the prevalence of aortic valve disease requiring intervention increases, and as clinicians and patients increasingly choose bioprosthetic over mechanical valve replacement, high-quality evidence is needed to guide antithrombotic therapy after

bioprosthetic AVR. Insufficient antithrombotic therapy has serious implications: ischemic stroke, systemic arterial thromboembolism, and clinical and subclinical valve thrombosis. Unnecessarily intense antithrombotic therapy, however, increases the risk of bleeding and associated morbidity and mortality. Professional societies have used the current low-quality evidence and generated incongruent recommendations. It is their responsibility to issue nuanced recommendations that reflect the limitations of available evidence. Researchers should prioritize generating high quality, randomized evidence evaluating the risks and benefits of antiplatelet versus anticoagulant therapy after bioprosthetic AVR.

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Tables

Table 1: Current guideline recommendations for antithrombotic therapy after BAVR in the absence of other indications for anticoagulation

ACCP 2012	AHA/ACC 2020	ESC/EACTS 2021
Aspirin 50 to 100mg for 3 months is recommended over warfarin (Class 2c) Aspirin 50 to 100mg indefinitely is recommended over no aspirin (Class 2c) No recommendation for anticoagulation	Aspirin 75 to 100mg indefinitely (Class 2a, LOE B) OR anticoagulation with VKA (INR 2.5) for 3-6 months if low risk of bleeding, followed by aspirin 75 to 100mg indefinitely (Class 2a, LOE B-NR)	Aspirin 75 to 100mg OR oral anticoagulation should be considered for the first 3 months (Class 2a, LOE B) Aspirin plus VKA may be considered in patients with atherosclerosis and low risk of bleeding (Class 2b, LOE C) No recommendation for aspirin after 3 months

ACCP = American College of Chest Physicians, AHA = American Heart Association, ASA = aspirin, EACTS = European Association for Cardio-Thoracic Surgery, ESC = European Society of Cardiology, INR = international normalized ratio, LOE = level of evidence, OAC = oral anticoagulant, VKA = vitamin K antagonist

Table 2: Timeline of changes to guidelines

	2001	2004	2006	2008	2012	2014	2017	2020	2021
ACCP	VKA (INR 2.5) x3m (2c), then ASA indefinitely (2c)	ASA or VKA (INR 2.5) x3m (2c), then ASA indefinitely (1c)		ASA indefinitely (1b)	ASA preferred over VKA x3m (2c), then ASA preferred over no ASA indefinitely (2c)				
AHA			ASA (I, LOE C) or VKA (INR target 2-3) x3m (2a, LOE C)			ASA indefinitely (2a, LOE B) or VKA (INR target 2.5) x3m (2b, LOE B)	ASA indefinitely (2a, LOE B) or VKA (INR 2.5) x3-6m if low bleeding risk (2a, LOE B-NR)	No changes	
ESC					ASA (2a, LOE C) or OAC (2b, LOE C) x3m No recommendation after 3m				ASA or OAC x3m (2a, LOE B) ASA plus OAC x3m if concomitant atherosclerosis and low bleeding risk (2b, LOE C) No recommendation after 3m

ACCP = American College of Chest Physicians, AHA = American Heart Association, ASA = aspirin, ESC = European Society of Cardiology, INR = international normalized ratio, LOE = level of evidence, m = months, OAC = oral anticoagulant, VKA = vitamin K antagonist

Figures:

Figure 1: Examples of the four categories of bioprosthetic aortic valves

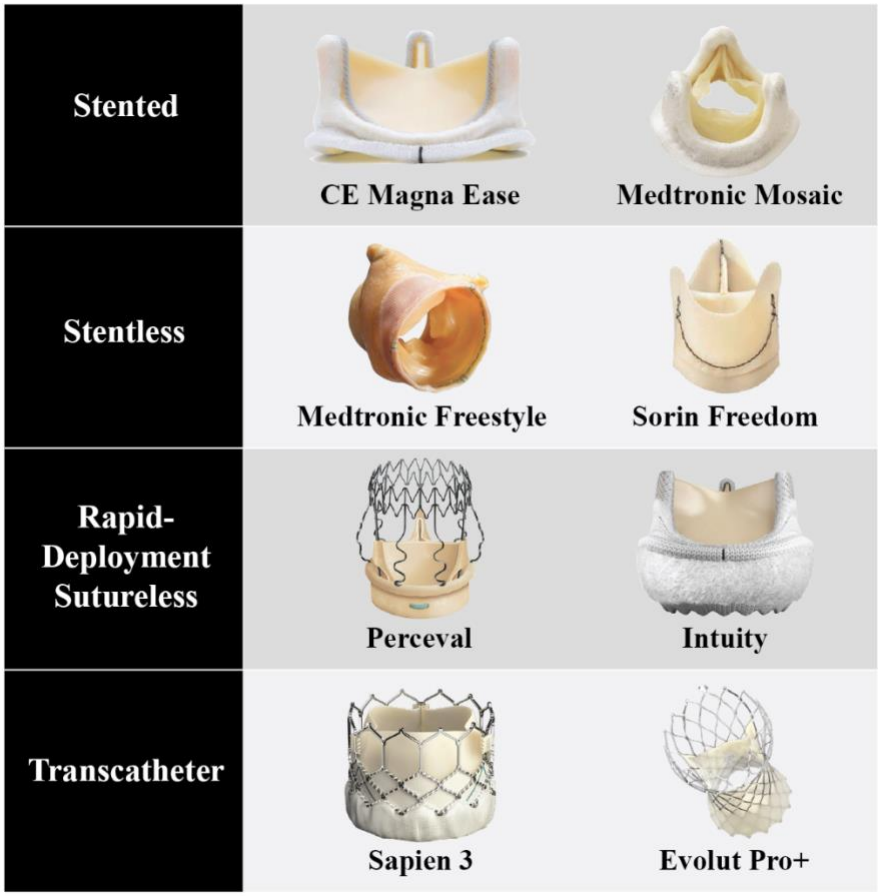
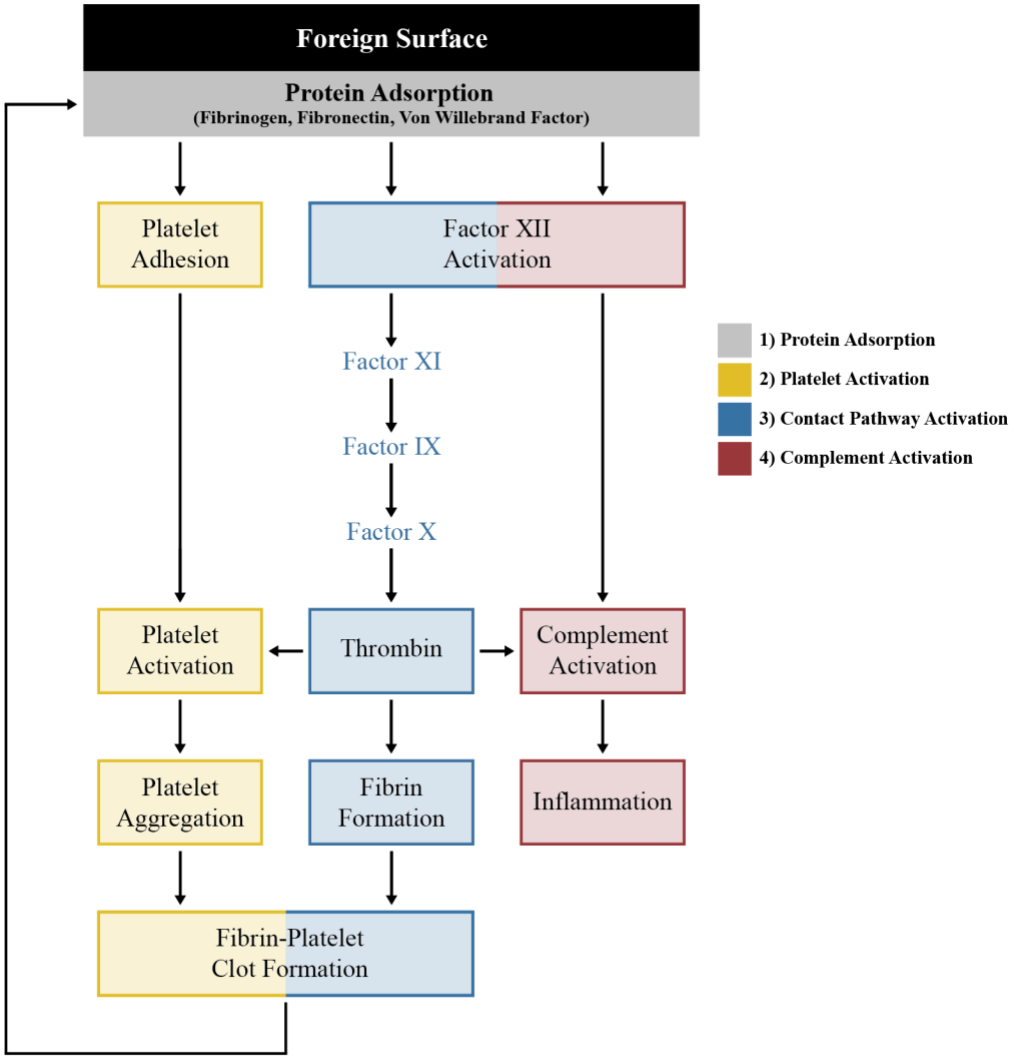


Figure 2: Mechanism of thrombosis formation on a foreign surface



Contributions

RE: Responsible for manuscript design, literature review, writing the first draft of the manuscript, and providing critical revisions to the manuscript.

PD: Created figures and tables and provided critical revisions to the manuscript.

RW, RL, DS, IJ, SS, and EBC: Contributed significantly to manuscript design and provided critical revisions to the manuscript.

Chapter 3: Antithrombotic therapy after surgical bioprosthetic aortic valve replacement: A secondary analysis of the VISION Cardiac Surgery cohort

Antithrombotic therapy after surgical bioprosthetic aortic valve replacement: A secondary analysis of the VISION Cardiac Surgery cohort

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Abstract

Background: Major society guidelines make conflicting recommendations on the use of antithrombotic therapy after surgical bioprosthetic AVR. We examined antithrombotic therapy use and association between antithrombotic therapy and outcomes in patients from the VISION Cardiac Surgery cohort who underwent surgical bioprosthetic AVR.

Objectives: 1) To describe antithrombotic therapy use at hospital discharge, 30 days, and 1 year; 2) To examine the association between antithrombotic therapy use at hospital discharge and thrombotic and bleeding events over 1 year.

Methods: 1) We described proportions of patients taking vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), antiplatelet only, or none at hospital discharge, 30 days, and 1 year. We separately described patients with preoperative or new clinically important postoperative atrial fibrillation (AF). 2) We performed Cox proportional hazards regression analysis to study the association between antithrombotic therapy and a composite thrombotic outcome (death, non-fatal cardiac arrest, myocardial infarction (MI), stroke, or repeat cardiac intervention) or a composite bleeding outcome (life-threatening or major bleeding).

Results: In the VISION Cardiac Surgery cohort of 13,862 patients, 2511 received a new surgical bioprosthetic AVR. 1) At hospital discharge, 37.9% received anticoagulation (31.3% VKA, 6.5% DOAC), 54.1% received antiplatelet only, and 8.0% received none. Anticoagulation use decreased to 22.4% at 1 year (15.1% VKA, 7.3% DOAC). At 1 year, 5.1% of patients experienced a composite thrombotic outcome; 70.9% of these events were deaths. Patients discharged on any antithrombotic trended towards lower incidence of thrombotic events compared to those discharged on none (reference

category), although estimates were imprecise (HR for VKA 0.73, 95% confidence interval [CI] 0.39-1.36; HR for DOAC 0.70, 95% CI 0.31-1.57; HR for antiplatelet only 0.56, 95% CI 0.31-1.02). Preoperative AF (HR 1.69, 95% CI 1.04-2.72) and CHA_2DS_2-VASc score (HR 1.17, 95% CI 1.05-1.31) were also associated with increased risk of thrombosis. Only 18 bleeding events (0.7%) occurred over follow-up, with no differences observed based on antithrombotic therapy.

Conclusions: Most patients are not anticoagulated after surgical bioprosthetic AVR, and among those that are, VKA therapy is preferred over DOAC, even at 1 year after valve implantation. The role of antithrombotic therapy in preventing valve-related thrombotic events remains uncertain.

Introduction

More than 100,000 surgical aortic valve replacements are performed each year in North America.[1] Mechanical prostheses are usually preferred over biological prostheses in younger patients because they are more durable but require lifelong anticoagulation. To avoid the need for life-long anticoagulation, more than 90% of aortic valve replacements are performed with biological prostheses.[2] However, optimal antithrombotic therapy after bioprosthetic aortic valve replacement (AVR) remains uncertain, particularly in the first three months following implantation when thrombotic risk is believed to be highest. Evidence informing the use of antithrombotic therapy during this time is low or very low quality,[3] and as a result major society guidelines provide weak and often conflicting recommendations.[4-6]

The Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study prospectively collected data on 13,862 patients undergoing cardiac surgery, including 2,511 patients who underwent bioprosthetic AVR.[7] Patients received antithrombotic therapy after bioprosthetic AVR at the discretion of their surgeon. To explore antithrombotic therapy after bioprosthetic AVR in contemporary practice and the association clinical outcomes, we performed a secondary analysis of these patients enrolled in the VISION Cardiac Surgery study.

Methods

VISION Cardiac Surgery is an observational study examining the relationship between high-sensitivity troponin I levels after cardiac surgery and 30-day mortality in a cohort of 13,862 patients in 29 countries. Our specific objectives were:

1. In VISION Cardiac Surgery participants with a new bioprosthetic AVR during their index procedure, to describe:
   A. Type of antithrombotic therapy (direct oral anticoagulant (DOAC) +/- antiplatelet; vitamin K antagonist (VKA) +/- antiplatelet; antiplatelet only; and none) at hospital discharge, overall and separately in patients with preoperative atrial fibrillation (AF), new clinically significant postoperative AF, and no AF;
   B. Type of antithrombotic therapy at 30 days and 1 year; and
   C. The proportion of patients prescribed DOAC or VKA at hospital discharge who discontinued or changed their oral anticoagulation at 30 days and 1 year.
2. To examine the association between type of antithrombotic therapy prescribed at hospital discharge and the following post-discharge events:
   A. Thrombotic events: the composite of death, non-fatal cardiac arrest, myocardial infarction (MI), stroke, or repeat cardiac intervention; and
   B. Bleeding events: the composite of life-threatening or major bleeding.

Outcomes

We used the same outcome definitions that were used by VISION Cardiac Surgery and present full outcomes definitions in Appendix Table 1. Of note, myocardial infarction is defined using the third universal definition of MI. Stroke is defined as new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours, and no distinction is made between ischemic and hemorrhagic stroke. Life-threatening bleeding is bleeding that is fatal or leads to significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage. Major bleeding is

defined as bleeding that is not specified under “life- threatening bleeding” and results in a postoperative hemoglobin ≤70 g/L and the patient receiving a transfusion of ≥2 units of red blood cells; results in a hemoglobin drop of ≥50 g/L and the patient receiving a transfusion of ≥2 units of red blood cells; results in the patient receiving a transfusion of ≥4 units of red blood cells within a 24 hour period; leads to one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); or is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

Statistical analysis

We conducted our analyses according to a prospectively developed statistical analysis plan. We summarized categorical data using counts and proportions and continuous data using means and standard deviations (or medians and interquartile ranges if non-normally distributed). We used Pearson chi-square tests for comparisons of categorical variables and student t-tests for continuous variables and reported p-values and 95% confidence intervals.

Objective 1A: Antithrombotic therapy at hospital discharge

We calculated the number and proportion of patients taking different types of antithrombotic therapy at discharge. We compared patient baseline characteristics according to type of antithrombotic therapy prescribed at hospital discharge, and separately according to use of anticoagulant versus antiplatelet therapy alone, and VKAs versus DOACs therapy. We examined type of antithrombotic therapy based on presence of AF (divided according to preoperative AF, new clinically important AF, or no AF).

Objective 1B: Antithrombotic therapy at 30 days and 1 year

We calculated the number and proportion of patients taking different types of antithrombotic therapy at 30 days and 1 year overall and separately according to preoperative AF or clinically important postoperative AF occurring prior to hospital discharge.

Objective 1C: Discontinuation or changing of oral anticoagulation at 30 days and 1 year

We compared proportions of patients who discontinued or changed oral anticoagulation (DOACs, VKAs) at 30 days and 1 year.

Objective 2A: Association between antithrombotic therapy at hospital discharge and a composite thrombotic outcome

We examined the association between antithrombotic therapy at hospital discharge and our composite thrombotic outcome using Cox proportional hazards regression analysis. We adjusted for pre-specified variables including CHA_2DS_2-VASc score, preoperative AF, and new clinically important postoperative AF, as well as for baseline characteristics that on univariate analysis were associated with outcome with a threshold $p<0.05$. We also examined type of antithrombotic therapy as a time-varying covariate.

We planned an exploratory analysis excluding death from our composite thrombotic outcome, but we did not perform this analysis because we were left with too few outcome events which would have resulted in an overfit model. We also performed a sensitivity analysis in which we excluded patients who received anticoagulation plus antiplatelet therapy or dual antiplatelet therapy at hospital discharge. In a separate sensitivity analysis, we excluded those who received oral anticoagulation at day 3 but not at hospital discharge.

We planned to separately examine the association between antithrombotic therapy at discharge and outcomes in patients with AF, but we decided not to report these analyses because we had too few events.

Objective 2B: Association between antithrombotic therapy at hospital discharge and a composite bleeding outcome

Because bleeding event rates were low, we described life-threatening and major bleeding events but did not perform adjusted analyses.

Results

From the VISION Cardiac Surgery cohort of 13,862 patients, we included 2511 patients who underwent bioprosthetic AVR. Table 1 describes baseline characteristics. Patients' mean age was 70.4 years and 33.8% (n=849) were female. More than half of patients had preoperative AF (n=507, 20.2%) or developed new clinically important AF prior to hospital discharge (n=795, 31.7%). A minority of patients (n=242, 9.7%) received anticoagulation preoperatively: 5.1% (n=128) took a VKA and 4.6% (n=114) took a DOAC.

1A. Antithrombotic therapy at hospital discharge

At hospital discharge, 37.9% of patients (n=951) were prescribed oral anticoagulation (31.3% VKA, 6.5% DOAC), 54.1% (n=1358) antiplatelet therapy alone, and 8.0% (n=202) no antithrombotic therapy.

Table 1 describes baseline characteristics according to type of antithrombotic therapy at discharge. Compared with patients discharged on antithrombotic therapy, those discharged on no antithrombotic therapy were younger (65.3 versus 70.9 years),

more likely to be female (41.1% versus 33.2%), and had fewer comorbidities (including hypertension, diabetes, previous MI, and AF).

Anticoagulated patients were of similar age to those prescribed antiplatelet only. Anticoagulated patients were more likely to have preoperative AF, previous stroke, or be anticoagulated at baseline compared to those prescribed antiplatelet only. The difference in CHA_2DS_2-VASc score between those treated with anticoagulation versus antiplatelet only was small (3.1 ± 1.6 versus 2.9 ± 1.5; Appendix Table 2)

Compared with patients taking a DOAC at discharge, those taking a VKA were younger (70.1 versus 73.1 years) and more likely to be female (35.7% versus 24.4%), had fewer comorbidities, and were less likely to be prescribed cardiovascular secondary prevention therapies at hospital discharge (aspirin, angiotensin-converting-enzyme inhibitors, and beta blockers; Appendix Table 3).

Relationship between AF and antithrombotic therapy at hospital discharge

Overall, 51.9% of patients (1302/2511) had preoperative AF or new clinically important AF prior to discharge. Patients with AF were more likely to be discharged on anticoagulation (n=706/1302, 54%) than antiplatelet only (n=522, 40.1%) or no antithrombotic therapy (n=77, 5.9%). The majority of patients with AF who were anticoagulated at hospital discharge received a VKA rather than a DOAC (567/706, 80.3% treated with VKA). Patients with preoperative AF were more likely to be anticoagulated than patients with new clinically important postoperative AF (375/507, 74.0% with preoperative versus 328/795, 45% with new clinically important postoperative AF).

In a post-hoc analysis, we explored antithrombotic prescribing practices by continent. VKA use was most prevalent in Asian sites and DOAC use was most prevalent in North American sites. In Europe, the most common discharge antithrombotic therapy was antiplatelet only (Appendix Table 4).

1B. Antithrombotic therapy at 30 days and 1 year

Figure 1 summarizes the proportion of patients on each type of antithrombotic therapy at hospital discharge, 30 days, and 1 year. At 30 days, 37.1% of patients were prescribed oral anticoagulation (30.7% VKA, 6.4% DOAC). At 1 year, only 22.4% of patients were still prescribed oral anticoagulation (15.1% VKA, 7.3% DOAC). The proportion of patients not receiving any antithrombotic therapy increased from 8% at discharge to 12.2% at 30 days and 22.8% at 1 year. The proportion of patients prescribed antiplatelet only remained relatively constant (54.1% at discharge, 50.7% at 30 days, 54.8% at 1 year).

Relationship between AF and antithrombotic therapy at 1 year

Patients with AF were more likely to be anticoagulated at 1 year (443/1295, 34.2%) than those without AF (119/1216, 9.82%). The majority of patients with AF who were anticoagulated at one year received a VKA rather than a DOAC (292/443, 65.9%). Patients with preoperative AF were more likely to be anticoagulated at 1 year than patients with new clinically important postoperative AF (303/507, 74.0% with preoperative versus 140/788, 17.8% with new clinically important postoperative AF).

1C. Discontinuation or changing of oral anticoagulation at 30 days and 1 year

At 30 days, 82.0% (645/787) of patients discharged on VKA therapy were still taking a VKA, while 64.6% (106/164) of patients discharged on a DOAC were still taking

a DOAC (Figure 2). More patients on DOAC at discharge switched to a VKA at 30 days (12/164, 7.3%) than patients on a VKA at discharge who switched to a DOAC at 30 days (22/787, 2.8%), although numbers were small.

At 1 year, 40.4% (318/787) of patients discharged on VKA therapy were still taking a VKA, while 48.8% (80/167) of patients discharged on a DOAC were still taking a DOAC (Figure 3). More patients (53/787, 6.7%) switched from VKA to a DOAC at one year than from a DOAC to a VKA (7/164, 4.3%).

2A. Association between antithrombotic therapy and composite thrombotic outcome

The composite thrombotic outcome occurred in 5.1% of patients overall (n=127). Death represented 70.9% of the composite outcome events, with an overall incidence of 3.6% at 1 year (n=90). Table 2 presents all outcome events by type of antithrombotic therapy at hospital discharge.

Outcome events based on AF status

Patients with preoperative AF had a higher incidence of the thrombotic composite outcome (41/507, 8.1%) than patients with new clinically important postoperative AF (42/795, 5.3%) or no AF (44/1209, 3.6%). Patients with preoperative AF also had a higher incidence of death (n=34, 6.7% versus n=29, 3.6% in patients with new clinically important postoperative AF and n=27, 2.2% in patients with no AF). Table 3 presents all outcomes events based on AF status at hospital discharge.

Adjusted analyses

Table 2 presents outcomes according to type of antithrombotic therapy at discharge. Appendix Table 5 presents univariate associations between baseline characteristics, discharge antithrombotics and outcome and Table 4 presents the results

of the adjusted Cox regression mode. After adjusting for CHA_2DS_2-VASc score, preoperative AF, new clinically important postoperative AF, end-stage renal disease, chronic obstructive pulmonary disease, and cancer, antithrombotic therapy at hospital discharge was not significantly associated with the composite thrombotic outcome. Compared to no antithrombotic therapy (reference category), the hazard ratio for the composite thrombotic outcome was lower for antiplatelet only (HR 0.56, 95% CI 0.31-1.02, p=0.06), VKA (HR 0.73, 95% CI 0.39-1.36, p=0.32), and DOAC (HR 0.70, 95% CI 0.31-1.57, p=0.38), although confidence intervals were wide and overlapping. Preoperative atrial fibrillation was associated with increased risk of the composite thrombotic outcome (HR 1.69, 95% CI 1.04-2.72, p=0.03). The results were unchanged with inclusion of antithrombotic therapy as a time dependent variable (results not presented).

Sensitivity analysis excluding patients taking oral anticoagulation plus antiplatelet therapy or dual antiplatelet therapy at discharge (n=601) yielded similar results to the original model (Appendix Table 6). Likewise, exclusion of patients who were prescribed oral anticoagulation on postoperative day 3 but not at hospital discharge (n=205) did not substantively change our results (Appendix Table 7).

2B. Association between antithrombotic therapy and bleeding

Only 18 life-threatening or major bleeding events (0.7%) occurred between hospital discharge and one year (Table 2), with no significant differences based on type of antithrombotic therapy.

In contrast, 10.8% of patients (n=271) experienced a life-threatening or major bleeding event prior to hospital discharge (Table 5). Most bleeding events during

hospitalization were intraoperative (n=79, 27.3%) or occurred within the first 24 hours after surgery (n=166, 57.4%).

Discussion

In this secondary analysis of VISION Cardiac Surgery participants with bioprosthetic AVR, we found that more than half of patients are prescribed antiplatelet only at hospital discharge, while around one third are prescribed a VKA and fewer than 10% are prescribed a DOAC. We found no significant association between antithrombotic therapy at discharge and thromboembolic or bleeding events at 1 year, but event numbers were low which made our estimates imprecise.

The pattern of antithrombotic therapy usage at hospital discharge in our cohort is consistent with major society guideline recommendations. The European Society of Cardiology (ESC) guidelines recommend VKA or aspirin therapy for the first 3 months after bioprosthetic AVR in patients without another indication for oral anticoagulation, and VKA therapy for the first 3 months in patients with an indication for oral anticoagulation.[8] The American College of Cardiology/American Heart Association (ACC/AHA) recommends either VKA or aspirin therapy for the first 3-6 months in patients without another indication for oral anticoagulation, but in patients with another indication for oral anticoagulation they do not comment on choice between DOAC and VKA.[6] While DOAC use at discharge appeared to be more common in North America (10%) than in Europe (5.8%), the overall infrequent use of DOACs suggests that clinicians remain hesitant to use them early after bioprosthetic AVR. This hesitance extended to patients with AF who were anticoagulated at discharge, most of whom received a VKA (80.3%). In the Left Atrial Appendage Occlusion Study III, which

examined left atrial appendage occlusion versus standard of care in patients with AF undergoing any type of cardiac surgery, anticoagulation prescribing practices were similar, with 77% of patients discharged on VKA versus 23% on DOAC.[9]

We were surprised to find that patients with AF who were anticoagulated at 1 year were still more likely to receive a VKA (292/443, 65.9%) than a DOAC (151/443, 34.1%). Large randomized trials in patients with AF have demonstrated that DOACs reduce risk of stroke or systemic embolism by 19% and risk of intracranial hemorrhage by 50% compared to VKAs.[10] In Canada, 84% of patients anticoagulated for AF receive a DOAC and only 16% receive a VKA.[11] A similar prescribing pattern is seen in European countries, including the Netherlands (88% DOAC versus 12% VKA).[12] The ESC guidelines recommend that patients with AF who are more than 3 months after bioprosthetic AVR should be prescribed a DOAC.[8] Possible explanations for persistent VKA use at 1 year include prescriber concerns about the safety of DOACs in patients with a bioprosthetic valve even after the first 3 months after valve implantation, or in European countries a lack of awareness of guideline recommendations to use DOACs after the first 3 months. It is also possible that prescribers were reluctant or simply forgot to switch from VKA to DOAC.

The association between antithrombotic therapy at discharge and outcomes remains uncertain both in our study and in other observational data. A study of 25,656 patients from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database found that warfarin plus aspirin, compared to aspirin alone, reduced risk of death and thromboembolism but increased risk of bleeding over the first 3 postoperative months.[13] In contrast, a study of 9060 patients from the Veteran Health Administration

System found no benefit to warfarin plus aspirin compared to aspirin alone with respect to death or thromboembolism over the first 3 postoperative months, but an increased risk of bleeding with warfarin plus aspirin.[14] Over a mean follow-up of 3.13 years, a Swedish database study of 9529 patients found that warfarin (with or without antiplatelet therapy) compared to antiplatelet therapy alone reduced risk of stroke and thromboembolism, increased risk of bleeding, and did not impact mortality.[15] So far two small randomized studies (combined n=397)[16,17] have examined this question but results were inconclusive. Only an adequately powered randomized trial can definitively resolve the uncertainties around optimal antithrombotic therapy after surgical bioprosthetic AVR.

Randomized studies in patients with transcatheter aortic valve replacement (TAVR) further emphasize the urgent need for high-quality data in surgical bioprosthetic AVR. Two randomized controlled trials in TAVR patients without another indication for oral anticoagulation found increased mortality in patients who were randomized to anticoagulation versus antiplatelet only. In the Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve replacement to Optimize Clinical Outcomes (GALILEO) trial, TAVR recipients without another indication for oral anticoagulation were randomized to rivaroxaban (plus aspirin for the first three months) or aspirin (plus clopidogrel for the first three months).[18] During a median follow up of 17 months, death occurred in 7.7% of patients in the rivaroxaban group compared to 4.6% of in the antiplatelet group (HR 1.69, 95% CI 1.13-2.53). In the Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation

for Aortic Stenosis (ATLANTIS) trial, TAVR recipients were randomized to apixaban or standard-of-care. In the subgroup of patients without another indication for oral indication, death occurred in 5.9% of patients taking apixaban compared to 3.4% of patients taking antiplatelet therapy (HR 1.86, 95% CI 1.04-3.34).

Bleeding event rates were low in our cohort, in part reflecting the stringent definition of life-threatening and major bleeding used by the VISION Cardiac Surgery study. Our data however suggest that even in patients undergoing bioprosthetic AVR who are prescribed anticoagulation at discharge, serious bleeding is uncommon after hospital discharge. In contrast, the high rates of serious bleeding prior to hospital discharge cautions against initiating antithrombotic therapy too early after surgery.

Limitations

Our study has several limitations. First, as with all observational studies, we are unable to exclude confounding despite careful adjustment for baseline differences. Second, follow-up data were only available at 3 timepoints (hospital discharge, 30 days, and 1 year) and we do not know what antithrombotic therapy patients were taking when thrombotic or bleeding events occurred. Third, the low number of events led to imprecise estimates of association.

Conclusion

In this secondary analysis of patients undergoing bioprosthetic AVR enrolled in the VISION Cardiac Surgery study, we found that 54.1% of patients are discharged on antiplatelet only and only 37.9% of patients receive anticoagulation, mostly (82.8%) VKA therapy. Although our data suggested a possible protective effect of antithrombotic therapy against subsequent thrombotic events, high-quality randomized data are

needed to reliably evaluate the efficacy and safety of anticoagulation versus antiplatelet therapy in patients with bioprosthetic AVR without an indication for oral anticoagulation, and of a VKA versus DOAC therapy in those with another indication for oral anticoagulation. The ongoing Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) trial (NCT04284839) is randomizing patients with recent cardiac surgery (including bioprosthetic AVR) and AF to DOAC or VKA for the first 3 months after surgery.

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Tables and Figures

Table 1: Baseline characteristics, overall and according to type of antithrombotic therapy at hospital discharge

*N (%) unless otherwise specified	**Overall (n=2511)**	**VKA +/- antiplatelet (n=787)**	**DOAC +/- antiplatelet (n=164)**	**Antiplatelet only (n=1358)**	**None (n=202)**
Age, mean (SD)	70.4 (10.4)	70.1 (11.5)	73.1 (7.5)	71.1 (9.1)	65.3 (13.6)
Female	849 (33.8)	281 (35.7)	40 (24.4)	445 (32.8)	83 (41.1)
BMI, mean (SD)	28.4 (5.6)	28.1 (5.8)	29.7 (5.7)	28.5 (5.5)	28.2 (5.4)
Medical history					
Congestive heart failure	446 (17.8)	181 (23.0)	28 (17.1)	193 (14.2)	44 (21.8)
NYHA score, mean (SD)	2.1 (1.0)	2.2 (1.0)	1.9 (1.1)	2.0 (1.0)	2.2 (1.1)
Hypertension	1662 (66.2)	515 (65.4)	121 (73.8)	905 (66.6)	121 (59.9)
Diabetes	640 (25.5)	202 (25.7)	46 (28.0)	357 (26.3)	35 (17.3)
Myocardial infarction	309 (12.3)	96 (12.2)	23 (14.0)	173 (12.7)	17 (8.4)
Any atrial fibrillation	1302 (51.9)	567 (72.0)	139 (84.8)	522 (38.4)	77 (38.1)
Preoperative	507 (20.2)	294 (37.4)	81 (49.4)	104 (7.7)	28 (13.9)
New clinically Important prior to discharge	795 (31.7)	270 (34.3)	58 (35.4)	418 (30.8)	49 (24.3)
Stroke	130 (5.2)	61 (7.8)	12 (7.3)	52 (3.8)	5 (2.5)
Pulmonary embolism	21 (0.8)	9 (1.1)	3 (1.8)	9 (0.7)	0 (0.0)
Deep vein thrombosis	39 (1.6)	16 (2.0)	4 (2.4)	18 (1.3)	1 (0.5)
Peripheral vascular disease	133 (5.3)	45 (5.7)	6 (3.7)	79 (5.8)	3 (1.5)
Peptic ulcer disease in previous year	27 (1.1)	7 (0.9)	3 (1.8)	15 (1.1)	2 (1.0)
End-stage renal disease	47 (1.9)	13 (1.7)	4 (2.4)	21 (1.5)	9 (4.5)
Chronic obstructive pulmonary disease	250 (10.0)	71 (9.0)	20 (12.2)	148 (10.9)	11 (5.4)
Cancer	85 (3.4)	19 (2.4)	8 (4.9)	51 (3.8)	7 (3.5)
Tobacco use	1296 (51.7)	350 (44.5)	92 (56.1)	765 (56.4)	89 (44.1)
CHA_2DS_2-VASc score, mean (SD)	2.9 (1.5)	3.0 (1.7)	3.2 (1.4)	2.9 (1.5)	2.4 (1.4)
Preoperative antithrombotic therapy					
ASA	941 (37.5)	255 (32.4)	51 (31.1)	579 (42.7)	56 (27.7)
Clopidogrel	108 (4.3)	31 (3.9)	4 (2.4)	62 (4.6)	11 (5.4)
Ticagrelor	14 (0.6)	0 (0.0)	2 (1.2)	12 (0.9)	0 (0.0)
Any anticoagulation	242 (9.7)	162 (20.7)	50 (30.5)	19 (1.4)	11 (5.5)
VKA	128 (5.1)	106 (13.5)	6 (3.7)	10 (0.7)	6 (3.0)
DOAC	114 (4.6)	56 (7.2)	44 (26.8)	9 (0.7)	5 (2.5)
Medications at discharge					
Aspirin	1771 (71.2)	346 (44.0)	107 (65.2)	1318 (97.1)	0 (0.0)
Clopidogrel	163 (6.5)	17 (2.2)	6 (3.7)	140 (10.3)	0 (0.0)
Ticagrelor	14 (0.6)	1 (0.1)	1 (0.6)	12 (0.9)	0 (0.0)
Prasugrel	2 (0.1)	0 (0.0)	1 (0.6)	1 (0.1)	0 (0.0)
Other Anti-platelet	9 (0.4)	0 (0.0)	1 (0.6)	8 (0.6)	0 (0.0)
ACE inhibitor	705 (28.3)	180 (22.9)	62 (37.8)	435 (32.0)	28 (15.5)
ARB	226 (9.1)	75 (9.5)	15 (9.1)	117 (8.6)	19 (10.5)
Beta blocker	1768 (71.0)	547 (69.5)	129 (78.7)	991 (73.0)	101 (55.8)

Calcium channel blocker	377 (15.1)	129 (16.4)	30 (18.3)	194 (14.3)	24 (13.3)
Digoxin	128 (5.1)	98 (12.5)	9 (5.5)	14 (1.0)	7 (3.9)
H2 antagonist	197 (7.9)	51 (6.5)	16 (9.8)	116 (8.5)	14 (7.7)
Proton pump inhibitor	1628 (65.4)	538 (68.4)	88 (53.7)	889 (65.5)	113 (62.4)
Cox inhibitor	15 (0.6)	3 (0.4)	1 (0.6)	10 (0.7)	1 (0.6)
NSAID	95 (3.8)	36 (4.6)	11 (6.7)	45 (3.3)	3 (1.7)

ARB: angiotensin receptor blocker; BMI: body mass index; DOAC: direct oral anticoagulant: H2: histamine 2 receptor; NSAID: non-steroidal anti-inflammatory drug; NYHA: New York Heart Association; SD: standard deviation: VKA: vitamin K antagonist

Table 2: Outcomes events between hospital discharge and one year, by type of antithrombotic therapy, unadjusted

N (%)	**Total events (n=2511)**	**VKA +/- antiplatelet (n=787)**	**DOAC +/- antiplatelet (n=164)**	**Antiplatelet only (n=1358)**	**None (n=202)**	**p-value**
Thrombotic composite outcome*	127 (5.1)	48 (6.1)	11 (6.7)	54 (4.0)	14 (6.9)	0.06
Bleeding composite outcome**	18 (0.7)	7 (0.9)	3 (1.8)	7 (0.5)	1 (0.5)	0.25
Death	90 (3.6)	33 (4.2)	7 (4.3)	39 (2.9)	11 (5.5)	0.17
Non-fatal cardiac arrest	2 (0.08)	1 (0.1)	1 (0.6)	0 (0.0)	0 (0.0)	0.06
MI	9 (0.3)	4 (0.5)	1 (0.6)	3 (0.2)	1 (0.5)	0.66
Stroke	26 (1.0)	12 (1.5)	2 (1.2)	10 (0.7)	2 (1.0)	0.38
Repeat cardiac intervention	12 (0.5)	6 (0.8)	0 (0.0)	5(0.4)	1 (0.5)	0.48

*Thrombotic composite outcome: death, non-fatal cardiac arrest, MI, ischemic stroke, repeat cardiac intervention
**Bleeding composite outcome: life-threatening or major bleeding
DOAC: direct oral anticoagulant; MI: myocardial infarction; VKA: vitamin K antagonist

Table 3: outcome events between hospital discharge and one year, by AF status at hospital discharge, unadjusted

	Overall (n=2511)	**Preoperative AF (N=507)**	**New clinically important AF (N=795)**	**No AF (N=1209)**
Thrombotic composite outcome*	127 (5.1)	41 (8.1)	42 (5.3)	44 (3.6)
Bleeding composite outcome**	18 (0.7)	3 (0.6)	10 (1.3)	5 (0.4)
Death	90 (3.6)	34 (6.7)	29 (3.6)	27 (2.2)
Non-fatal cardiac arrest	2 (0.08)	2 (0.4)	0 (0.0)	0 (0.0)
MI	9 (0.3)	1 (0.2)	3 (0.4)	5 (0.4)
Stroke	26 (1.0)	7 (1.4)	8 (1.0)	11 (0.9)
Repeat cardiac intervention	12 (0.5)	0 (0.0)	5 (0.6)	7 (0.6)

*Thrombotic composite outcome: death, non-fatal cardiac arrest, MI, ischemic stroke, repeat cardiac intervention
**Bleeding composite outcome: life-threatening or major bleeding
AF: atrial fibrillation, MI: myocardial infarction

Table 4: Cox regression model for thrombotic composite outcome

	HR (95% CI)	**p-value**
Antithrombotic therapy at hospital discharge		
VKA +/- antiplatelet	0.73 (0.39-1.36)	0.32
DOAC +/- antiplatelet	0.70 (0.31-1.57)	0.38
Antiplatelet only	0.56 (0.31-1.02)	0.06
None		
CHA2DS2-VASc score	1.17 (1.05-1.31)	0.01
Preoperative atrial fibrillation	1.69 (1.04-2.72)	0.03
New clinically important postoperative atrial fibrillation	1.25 (0.82-1.92)	0.30
End-stage renal disease	4.49 (2.23-8.66)	<.0001
Chronic obstructive pulmonary disease	1.68 (1.05-2.68	0.045
Cancer	2.60 (1.40-4.86)	0.01

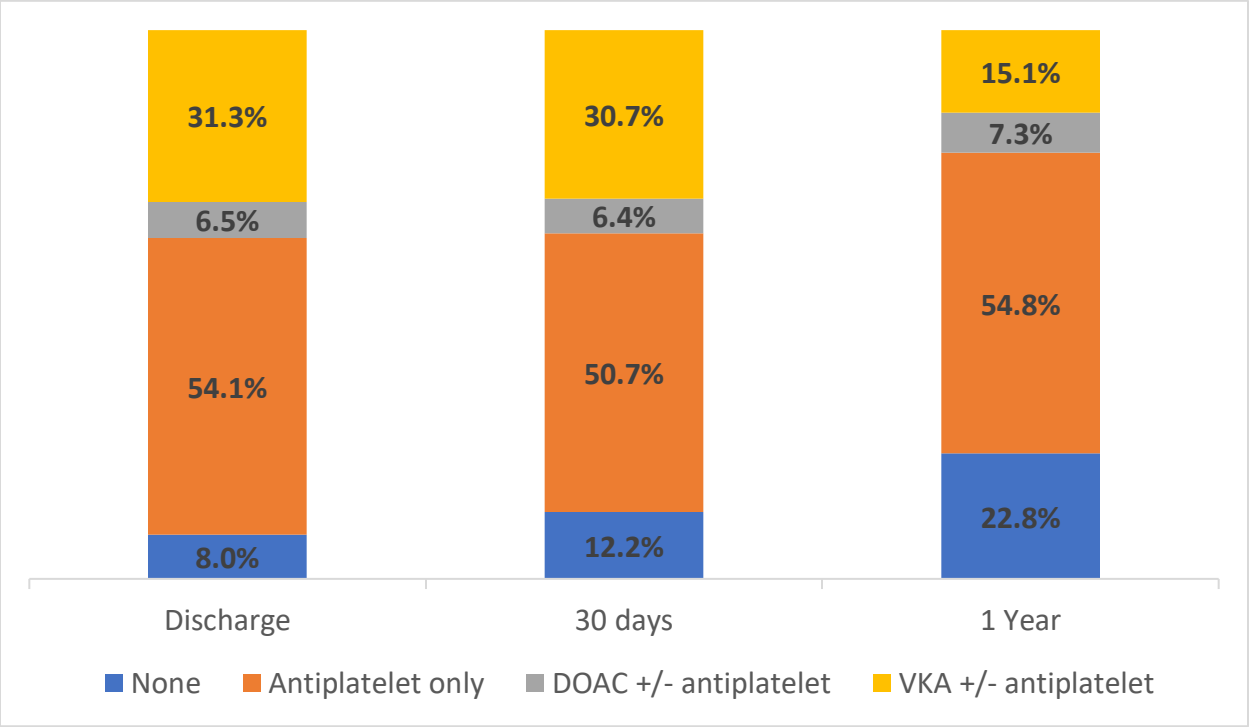
CI: confidence interval; DOAC: direct oral anticoagulant; HR: hazard ratio; VKA: vitamin K antagonist

Table 5: In-hospital bleeding, by type of antithrombotic therapy prescribed at discharge

N (%)	**Total events (n=2511)**	**VKA +/- antiplatelet (n=787)**	**DOAC +/- antiplatelet (n=164)**	**Antiplatelet only (n=1358)**	**None (n=202)**
Intraoperative	79 (27.3)	34 (32.4)	4 (16.7)	32 (24.4)	9 (31.0)
<24h surgery	166 (57.4)	58 (55.2)	16 (66.7)	79 (60.3)	13 (44.8)
24-72h surgery	15 (5.2)	3 (2.9)	1 (4.8)	10 (7.6)	1 (3.5)
>72h to hospital discharge	11 (3.8)	3 (2.9)	0 (0.0)	3 (2.3)	5 (17.2)
Total bleeding prior to hospital discharge	271 (10.8)	98 (12.5)	21 (12.8)	124 (9.1)	28 (13.9)

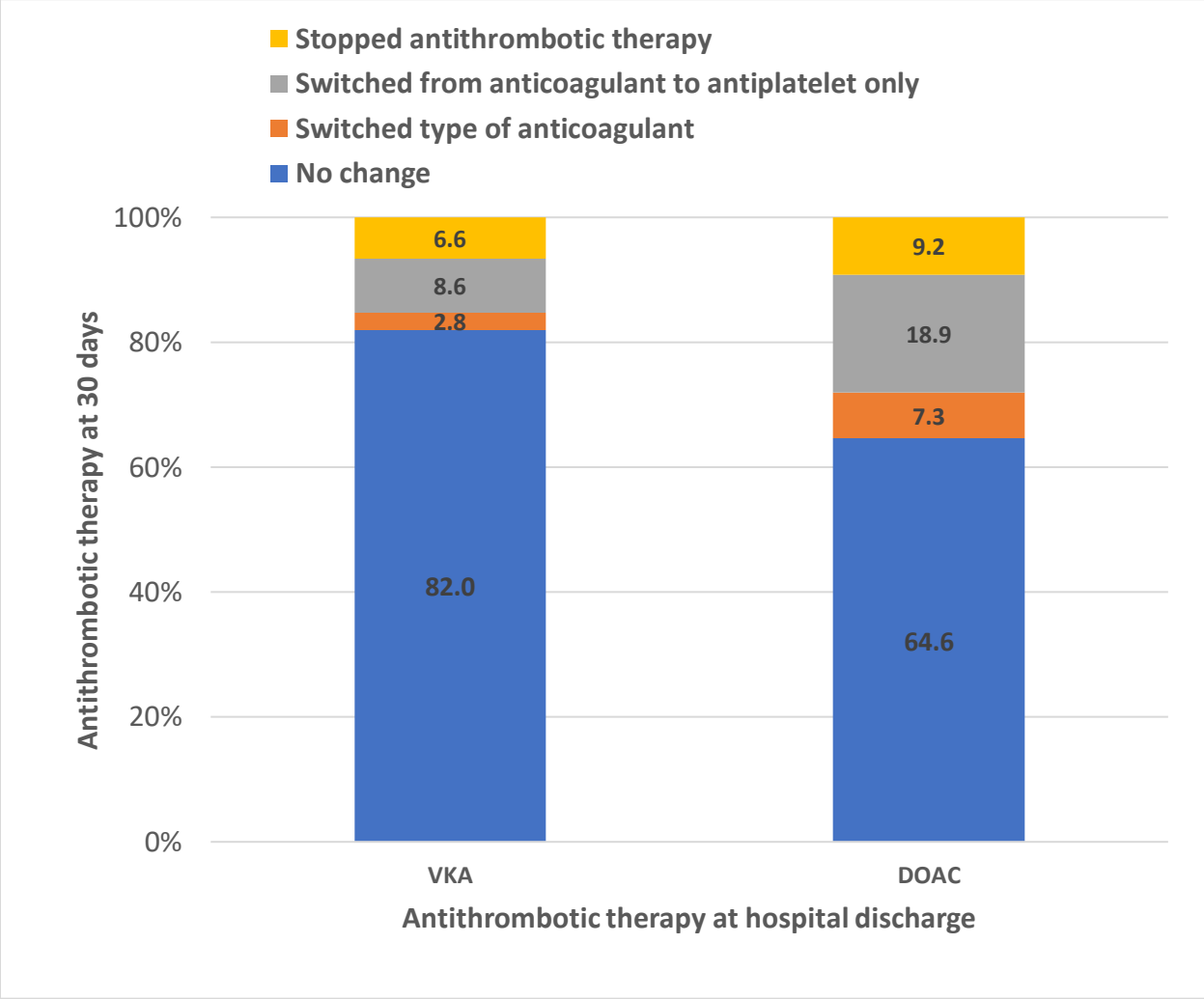
DOAC: direct oral anticoagulant; h: hours; VKA: vitamin K antagonist

Figure 1: Antithrombotic therapy at discharge, 30 days, and 1 year



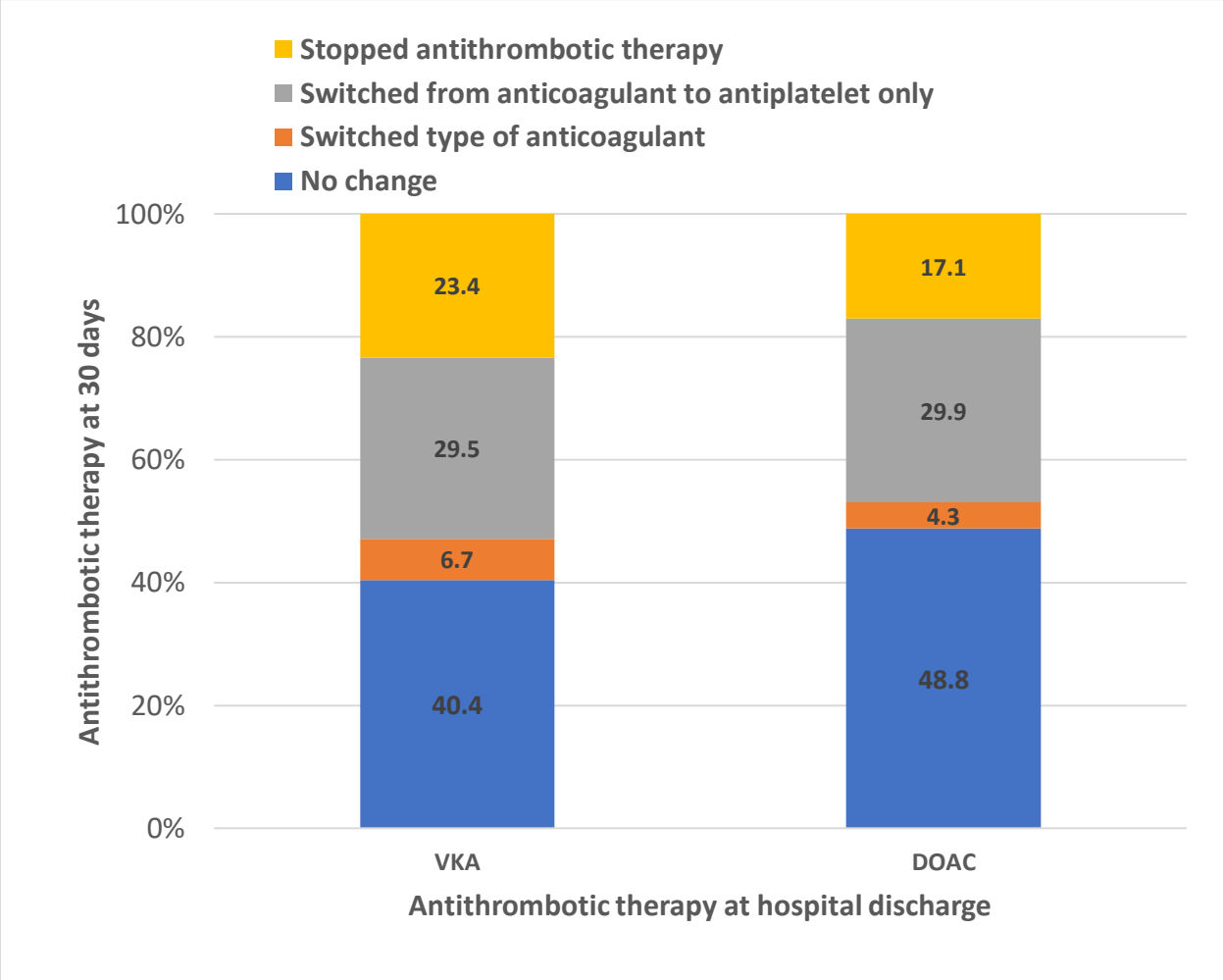
DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Figure 2: Antithrombotic therapy at 30 days, according to type of antithrombotic therapy prescribed at hospital discharge



DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Figure 3: Antithrombotic therapy at 1 year, according to type of antithrombotic therapy prescribed at hospital discharge



DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Appendix Table 1: Outcome definitions

Outcome	**Definition**
Death	Not subclassified.
Non-fatal cardiac arrest	Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring chest compressions, pharmacological therapy, or cardiac defibrillation occurring after cardiac surgery.
Myocardial infarction	According to the Third Universal Definition of Myocardial Infarction.
Stroke	New focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.
Repeat cardiac intervention	New CABG procedure, coronary angiography or PCI associated with documented ischemia by stress testing (ECG, echocardiography, or nuclear) and graft failure or new culprit lesion (≥ 70% luminal stenosis).
Life-threatening bleeding	Bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Bleeding that is not specified under “life- threatening bleeding” above, and results in a postoperative hemoglobin ≤70 g/L and the patient receiving a transfusion of ≥2 units of red blood cells; results in a hemoglobin drop of ≥50 g/L and the patient receiving a transfusion of ≥2 units of red blood cells; results in the patient receiving a transfusion of ≥4 units of red blood cells within a 24 hour period; leads to one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); OR is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging)
New clinically important atrial fibrillation	New atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

Appendix Table 2: Baseline characteristics of patients discharged on anticoagulant +/- antiplatelet therapy versus antiplatelet therapy alone

*N (%) unless otherwise specified	Anticoagulant +/- antiplatelet (n=951)	Antiplatelet therapy only (n=1358)
Age, mean (SD)	70.6 (10.9)	71.1 (9.1)
Female	321 (33.8)	445 (32.8)
BMI, mean (SD)	28.4 (5.8)	28.5 (5.5)
Medical history		
Congestive heart failure	209 (22.0)	193 (14.2)
NYHA score, mean (SD)	2.2 (1.1)	2.0 (1.0)
Hypertension	636 (66.9)	905 (66.6)
Diabetes	248 (26.1)	357 (26.3)
Myocardial infarction	119 (12.5)	173 (12.7)
Any AF	703 (73.9)	522 (38.4)
Preoperative AF	375 (39.4)	104 (7.7)
New clinically important AF	328 (34.5)	418 (30.8)
Stroke	73 (7.7)	52 (3.8)
Pulmonary embolism	12 (1.3)	9 (0.7)
Deep vein thrombosis	20 (2.1)	18 (1.3)
Peripheral vascular disease	51 (5.4)	79 (5.8)
Peptic ulcer disease in previous year	10 (1.1)	15 (1.1)
End-stage renal disease	17 (1.8)	21 (1.6)
Chronic obstructive pulmonary disease	91 (9.6)	148 (10.9)
Cancer	27 (2.8)	51 (3.8)
Tobacco use	442 (46.5)	765 (56.4)
CHA_2DS_2-VASc score, mean (SD)	3.07 (1.6)	2.87 (1.5)
Preoperative antithrombotic medications		
ASA	306 (32.2)	579 (42.7)
Clopidogrel	35 (3.7)	62 (4.6)
Ticagrelor	2 (0.2)	12 (0.9)
Prasugrel	0 (.)	0 (.)
Vitamin K antagonist	112 (11.8)	10 (0.7)
Direct oral anticoagulant	100 (10.6)	9 (0.7)
Medications at discharge		
Aspirin	453 (47.6)	1318 (97.1)
Clopidogrel	23 (2.4)	140 (10.3)
Ticagrelor	2 (0.2)	12 (0.9)
Prasugrel	1 (0.1)	1 (0.1)
ACE inhibitor	242 (25.5)	435 (32.0)
Angiotensin receptor blocker	90 (9.5)	117 (8.6)
Beta blocker	676 (71.1)	991 (73.0)
Calcium channel blocker	159 (16.7)	194 (14.3)
Digoxin	107 (11.3)	14 (1.0)
H2 antagonist	67 (7.1)	116 (8.5)
Proton pump inhibitor	626 (65.8)	889 (65.5)
Cox inhibitor	4 (0.4)	10 (0.7)
NSAID	47 (4.9)	45 (3.3)

*See Table 1 list of abbreviations

Appendix Table 3: Baseline characteristics of patients discharged on VKA +/- antiplatelet therapy versus DOAC +/- antiplatelet therapy

*N (%) unless otherwise specified	**VKA +/- antiplatelet (n=787)**	**DOAC +/- antiplatelet (n=164)**
Age, mean (SD)	70.1 (11.5)	73.05 (7.5)
Female	281 (35.7)	40 (24.4)
BMI, mean (SD)	28.08 (5.8)	29.68 (5.7)
Medical history		
Congestive heart failure	181 (23.0)	28 (17.1)
NYHA score, mean (SD)	2.22 (1.0)	1.88 (1.1)
Hypertension	515 (65.4)	121 (73.8)
Diabetes	202 (25.7)	46 (28.1)
Myocardial infarction	96 (12.2)	23 (14.0)
Any AF	664 (84.4)	139 (84.8)
Preoperative AF	294 (37.4)	81 (49.4)
New clinically important AF	270 (34.3)	58 (35.4)
Stroke	61 (7.8)	12 (7.3)
Pulmonary embolism	9 (1.14)	3 (1.8)
Deep vein thrombosis	16 (2.0)	4 (2.4)
Peripheral vascular disease	45 (5.7)	6 (3.7)
Peptic ulcer disease in previous year	7 (0.9)	3 (1.8)
End-stage renal disease	13 (1.7)	4 (2.4)
Chronic obstructive pulmonary disease	71 (9.02)	20 (12.2)
Cancer	19 (2.4)	8 (4.9)
Tobacco use	350 (44.5)	92 (56.1)
CHA_2DS_2-VASc score, mean (SD)	3.04 (1.7)	3.17 (1.4)
Preoperative antithrombotic medications		
ASA	255 (32.4)	51 (31.1)
Clopidogrel	31 (3.9)	4 (2.4)
Ticagrelor	0 (.)	2 (1.2)
Prasugrel	0 (.)	0 (.)
Vitamin K antagonist	106 (13.5)	6 (3.7)
Direct oral anticoagulant	56 (7.2)	44 (26.8)
Medications at discharge		
Aspirin	346 (44.0)	107 (65.2)
Clopidogrel	17 (2.2)	6 (3.7)
Ticagrelor	1 (0.1)	1 (0.6)
Prasugrel	0 (.)	1 (0.6)
ACE inhibitor	180 (22.9)	62 (37.8)
Angiotensin receptor blocker	75 (9.5)	15 (9.2)
Beta blocker	547 (69.5)	129 (78.7)
Calcium channel blocker	129 (16.4)	30 (18.4)
Digoxin	98 (12.5)	9 (5.5)
H2 antagonist	51 (6.5)	16 (9.8)
Proton pump inhibitor	538 (68.4)	88 (53.7)
Cox inhibitor	3 (0.4)	1 (0.6)
NSAID	36 (4.6)	11 (6.7)

*See Table 1 list of abbreviations

Appendix Table 4: Antithrombotic therapy use, by geographical region

	Asia	**Europe**	**North America**	**Other**	**Total**
VKA +/- antiplatelet	169 (71.9)	231 (24.5)	299 (29.3)	88 (28.2)	787
DOAC +/- antiplatelet	1 (0.4)	55 (5.8)	102 (10.0)	6 (1.9)	164
Antiplatelet only	48 (20.4)	614 (65.0)	542 (53.1)	154 (49.4)	1358
None	17 (7.2)	44 (4.7)	77 (7.5)	64 (20.5)	202
Total	235	944	1020	312	2511

DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Appendix Table 5: Univariate analysis

	Composite 1: death, non-fatal cardiac arrest, MI, stroke, or repeat cardiac intervention			Composite 2: Life-threatening or major bleeding		
	Estimate	HR (95% CI)	p-value	Estimate	HR (95% CI)	p-value
Age	0.03	1.03 (1.01,1.05)	0.003	0.03	1.03 (0.98,1.09)	0.29
Female	-0.26	0.77 (0.52,1.14)	0.19	-1.41	0.24 (0.06,1.06)	0.06
BMI	-0.02	0.98 (0.95,1.01)	0.25	0.00	1.00 (0.92,1.08)	0.93
Medical history						
CHF	0.45	1.56 (1.04,2.35)	0.03	-0.05	0.95 (0.27,3.28)	0.94
NYHA score	0.22	1.25 (1.05,1.49)	0.01	0.25	1.29 (0.80,2.07)	0.30
HTN	0.23	1.26 (0.86,1.85)	0.23	-0.21	0.81 (0.31,2.08)	0.66
DM	0.42	1.52 (1.05,2.20)	0.03	-0.17	0.84 (0.28,2.56)	0.76
MI	0.87	2.39 (1.59,3.58)	0.0000	0.39	1.47 (0.43,5.07)	0.54
Preoperative AF	0.67	1.95 (1.35,2.83)	0.0004	-0.22	0.81 (0.23,2.79)	0.73
New clinically important AF	0.05	1.06 (0.73,1.53)	0.77	0.99	2.69 (1.06,6.82)	0.037
Ischemic stroke	0.23	1.26 (0.61,2.57)	0.53	0.08	1.08 (0.14,8.15)	0.94
PE	0.75	2.12 (0.53,8.57)	0.29	-12.01	0.00 (0.00, .)	0.99
DVT	1.06	2.87 (1.18,7.03)	0.02	1.40	4.04 (0.54,30.3)	0.18
PVD	0.20	1.22 (0.60,2.50)	0.58	1.29	3.64 (1.05,12.6)	0.04
PUD in previous year	0.85	2.34 (0.74,7.34)	0.15	-12.02	0.00 (0.00, .)	0.99
ESRD	1.61	5.02 (2.63,9.57)	0.0000	1.21	3.36 (0.45,25.2)	0.24
COPD	0.66	1.94 (1.23,3.07)	0.005	0.97	2.62 (0.86,7.97)	0.09
Cancer	1.04	2.84 (1.53,5.27)	0.0009	0.54	1.71 (0.23,12.9)	0.60
Tobacco use	0.16	1.17 (0.89,1.55)	0.26	0.59	1.80 (1.37,2.35)	0.0000
CHADS-VASC	0.19	1.21 (1.09,1.35)	0.0006	-0.10	0.90 (0.67,1.23)	0.52
Medication at discharge						
ASA	-0.27	0.76 (0.53,1.11)	0.15	0.26	1.29 (0.42,3.97)	0.65
Clopidogrel	-0.15	0.86 (0.40,1.85)	0.71	-14.11	0.00 (0.00, .)	0.99
Ticagrelor	0.36	1.44 (0.20,10.3)	0.72	-12.01	0.00 (0.00, .)	0.99
Prasugrel	-10.00	0.00 (0.00, .)	0.98	-10.00	0.00 (0.00, .)	0.99
Other Anti-platelet	-11.01	0.00 (0.00,****)	0.98	-11.01	0.00 (0.00, .)	0.99
VKA	0.35	1.42 (0.99,2.04)	0.06	0.43	1.53 (0.58,4.02)	0.39
DOAC	0.35	1.42 (0.77,2.64)	0.27	1.11	3.04 (0.87,10.6)	0.08
Other AC	0.11	1.12 (0.46,2.73)	0.81	1.26	3.51 (0.80,15.4)	0.10
ACEi	-0.26	0.77 (0.51,1.17)	0.22	0.04	1.04 (0.37,2.96)	0.94
Angiotensin receptor blocker	0.19	1.20 (0.68,2.14)	0.53	-0.47	0.62 (0.08,4.69)	0.65
BB	-0.18	0.83 (0.57,1.22)	0.35	1.11	3.04 (0.69,13.3)	0.14
CCB	0.37	1.44 (0.93,2.24)	0.10	-0.29	0.75 (0.17,3.27)	0.70
Digoxin	0.40	1.49 (0.76,2.94)	0.25	0.16	1.17 (0.15,8.81)	0.88
H2 antagonist	0.13	1.14 (0.61,2.11)	0.68	-14.13	0.00 (0.00, .)	0.99
PPI	0.17	1.18 (0.80,1.73)	0.40	-0.04	0.96 (0.36,2.60)	0.94
Cox inhibitor	1.06	2.89 (0.71,11.7)	0.14	-12.01	0.00 (0.00, .)	0.99
NSAID	-1.57	0.21 (0.03,1.48)	0.12	-14.06	0.00 (0.00, .)	0.99

*See Table 1 list of abbreviations

Appendix Table 6: Cox proportional hazards regression model, excluding patients on anticoagulation plus antiplatelet therapy or dual antiplatelet therapy at hospital discharge

	Beta	**Standard error**	**p-value**	**HR**	**95% CI, lower**	**95% CI, upper**
Antithrombotic therapy at hospital discharge						
VKA +/- antiplatelet	-0.35	0.35	0.31	0.71	0.36	1.39
DOAC +/- antiplatelet	-0.42	0.58	0.47	0.66	0.21	2.06
Antiplatelet only	-0.56	0.31	0.07	0.57	0.31	1.05
None						
CHA2DS2-VASc score	0.15	0.07	0.03	1.16	1.01	1.33
Preoperative atrial fibrillation	0.65	0.29	0.02	1.93	1.09	3.41
New clinically important postoperative atrial fibrillation	0.41	0.25	0.10	1.51	0.93	2.45
End-stage renal disease	1.65	0.34	<.0001	5.22	2.66	10.27
Chronic obstructive pulmonary disease	0.34	0.30	0.25	1.41	0.78	2.53
Cancer	0.92	0.38	0.01	2.52	1.20	5.26

CI: confidence interval; DOAC: direct oral anticoagulant: HR: hazard ratio; VKA: vitamin K antagonist

Appendix Table 7: Cox proportional hazards regression model, excluding patients prescribed anticoagulation or antiplatelet therapy at day 3 but not at hospital discharge

	Beta	**Standard error**	**p-value**	**HR**	**95% CI, lower**	**95% CI, upper**
Antithrombotic therapy at hospital discharge						
VKA +/- antiplatelet	0.41	0.54	0.45	1.50	0.52	4.32
DOAC +/- antiplatelet	0.37	0.60	0.54	1.45	0.44	4.74
Antiplatelet only	0.18	0.53	0.73	1.20	0.43	3.38
None						
CHA2DS2-VASc score	0.19	0.06	0.00	1.20	1.07	1.36
Preoperative atrial fibrillation	0.42	0.26	0.11	1.52	0.91	2.52
New clinically important postoperative atrial fibrillation	0.14	0.23	0.53	1.16	0.73	1.82
End-stage renal disease	1.77	0.34	<.0001	5.87	3.04	11.32
Chronic obstructive pulmonary disease	0.49	0.25	0.05	1.63	1.00	2.65
Cancer	0.90	0.35	0.01	2.46	1.24	4.88

CI: confidence interval; DOAC: direct oral anticoagulant: HR: hazard ratio; VKA: vitamin K antagonist

Contributions:

RE: Responsible for manuscript design, writing statistical analysis plan, interpretation of results, writing the first draft of the manuscript, and providing critical revisions to the manuscript.

QY: Contributed significantly to manuscript design and statistical analysis plan; performed statistical analyses; and provided critical revisions to the manuscript.

PJD, AL, RL, DP, SS, DS, EBC, RW: Contributed significantly to manuscript design, statistical analysis plan, and provided critical revisions to the manuscript.

Chapter 4: Optimal antithrombotic therapy after transcatheter aortic valve replacement: A systematic review incorporating a network meta-analysis

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Optimal antithrombotic therapy after transcatheter aortic valve replacement: A systematic review incorporating a network meta-analysis

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Abstract

Objectives: We examined the relative effectiveness and safety of antithrombotic therapy (direct oral anticoagulation, vitamin K antagonist, dual antiplatelet therapy, aspirin alone) after transcatheter aortic valve replacement (TAVR) using network meta-analysis.

Background: TAVR is associated with a 2-3% risk of valve thrombosis, stroke, or systemic embolism in the first year after implantation in patients treated with aspirin (ASA) alone, and a 20-25% risk of subclinical valve thrombosis. More intense antithrombotic therapy may reduce thrombotic risk, but at the cost of increased bleeding risk. The optimal antithrombotic regimen remains uncertain.

Methods: We systematically searched EMBASE, MEDLINE and CENTRAL until December 24, 2022. Two reviewers independently screened titles, abstracts, and full texts, and then abstracted data in duplicate. We performed network meta-analysis with a Bayesian generalized linear model and random effects modelling. We assessed heterogeneity with the I^2 statistic and visual inspection of the forest plots. We appraised risk of bias using the Cochrane Risk of Bias tool and we evaluated the certainty of the evidence using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach.

Results: We included 8 studies of 4102 patients without another indication for oral anticoagulation. Over a median follow-up of 6 months, risk of thromboembolic events was similar among studied antithrombotic regimens (low to very low certainty). Major bleeding was increased with DAPT and DOAC compared to aspirin (low certainty). Death was increased with DOAC vs DAPT (very low certainty). Subclinical valve

thrombosis was less common in patients anticoagulated with either DOAC (high certainty) or VKA (low certainty) compared to antiplatelet therapy alone.

We included 3 studies of 2190 patients with another indication for oral anticoagulation (most commonly atrial fibrillation). Over a median follow-up of 12 months, risk of thromboembolic events, major bleeding, and death was similar between DOAC and VKA (moderate certainty). Risk of major bleeding was increased with oral anticoagulation plus clopidogrel compared to anticoagulation alone (moderate certainty).

Conclusions: In patients with TAVR and no other indication for oral anticoagulation, DOAC therapy increases risk of major bleeding and death compared to aspirin alone, but decreases risk of subclinical valve thrombosis, over a median follow-up of 6 months. In patients with TAVR and another indication for oral anticoagulation, we found no differences between DOAC and VKA therapy, over a median follow-up of 12 months. Future studies should be adequately powered to assess the impact of antithrombotic strategies on thromboembolic events and subclinical valve thrombosis, and should seek to explain why DOACs may be associated with increased mortality in patients with valvular disease or bioprosthetic valves.

Introduction

Aortic stenosis is the most common valvular disease, and aortic valve replacement is the only definitive, life-saving treatment. Around 130,000 aortic valve replacements are performed each year in North America and a growing majority of these are transcatheter.[1] Transcatheter aortic valve replacement (TAVR) is associated with a 2-3% risk of thromboembolic events in the first year after implantation in patients treated with aspirin alone.[2,3] More intense antithrombotic therapy with dual antiplatelet therapy (DAPT), vitamin K antagonists (VKAs), or direct oral anticoagulants (DOACs) may further reduce thrombotic risk, but at the cost of increased bleeding risk. To synthesize the body of randomized evidence and evaluate the relative effectiveness and safety of the available treatment options, including therapies that have not been directly compared in a randomized controlled trial,[4,5] we conducted a systematic review and network meta-analysis of randomized controlled trials evaluating antithrombotic therapy in patients after TAVR.

Methods

Objectives:

We aimed to systematically review randomized controlled trials comparing antithrombotic therapy strategies after TAVR, and to evaluate the relative effectiveness and safety of these strategies using network meta-analysis.

Search strategy and selection criteria:

We searched OVID MEDLINE, EMBASE, and CENTRAL from inception to December 24, 2022. We created a search strategy (Appendix 1) with the assistance of an academic librarian. We included randomized controlled trials (RCTs) evaluating any

two antithrombotic therapies in patients with transcatheter aortic valve replacement. We checked reference lists of relevant articles and reviewed the list of included studies with researchers with relevant expertise (RL, EBC, RW).

Four reviewers (RE, GE, YQ, AW) independently screened titles and abstracts using a standardized form. If a study's title or abstract suggested it might be relevant, then the same reviewers independently assessed the full text for eligibility, resolving disagreements by discussion.

The outcomes of interest were thromboembolic events (ischemic stroke, systemic arterial embolism, and clinical valve thrombosis), major bleeding (as defined by each individual study), death, aortic valve reintervention, subclinical valve thrombosis (defined as hypoattenuated leaflet thickening, with or without reduced leaflet motion, as diagnosed by computed tomography), and mean aortic transvalvular gradients on echocardiography.

We conducted our review in accordance with a pre-specified protocol (PROSPERO registration number CRD42022303459) and following the PRISMA extension guidelines for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions (Supplementary Table S1).[6]

Data abstraction and analysis:

Two authors (RE and GE) independently abstracted data about study design, sample size, baseline demographics, and outcomes into a standardized Microsoft Excel spreadsheet. We performed two separate meta-analyses: a network meta-analysis for studies including patients without another indication for anticoagulation, and a pairwise

meta-analysis for studies that included patients with an indication for anticoagulation other than TAVR (e.g., atrial fibrillation [AF]).

Network meta-analysis

For studies that included patients without another indication for anticoagulation, we used a Bayesian generalized linear model with a random-effects framework to perform network meta-analysis, reporting results as odds ratios (OR) with 95% credible intervals (CrI). We implemented the Hamiltonian Monte Carlo algorithm with the adaptive no-U-turn sampler to perform 4 chains for each analysis with each chain consisting of 1,000 warmup iterations and 2,000 draws from the posterior distribution.[7] We planned to assess coherence using node-splitting.[8] To evaluate heterogeneity, we used visual inspection of forest plots and the I^2 statistic.[9]

Pairwise meta-analysis

For studies that included patients with another indication for anticoagulation, we conducted standard pairwise meta-analyses comparing DOAC with VKA. We used a frequentist random effects meta-analysis model to generate pooled estimates of treatment effect for each pairwise comparison, reporting results as OR with 95% confidence intervals (CI). In cases of zero events in any arm, we imputed a value of 0.5 in the numerators and 1.0 in the denominators to allow for statistical analysis. We used visual inspection of forest plots and the I^2 statistic to evaluate heterogeneity.

We prespecified subgroup analyses according to TAVR valve type and baseline risk of bleeding. We used DataParty for all analyses (DataParty Inc., Hamilton, Ontario, Canada; available at https://dataparty.ca).

Risk of bias and certainty of evidence

Two authors (RE and YQ) independently assessed risk of bias for each study using the revised Cochrane Risk of Bias tool for randomized trials.[10] Two authors (RE and WA) evaluated the certainty of evidence using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach for each outcome.[11] We resolved disagreements by discussion and consensus.

Results

From 1352 citations, we found 10 eligible studies of 6292 patients (Figure 1). We summarize individual trials designs in Table 1. We found six studies to be at low risk of bias, while the remaining four studies had some concerns for bias (Figure 2).

Studies of patients without another indication for anticoagulation

We found 8 studies of 4102 patients without another indication for anticoagulation. Two studies[12,13] included patients both with and without another indication for anticoagulation but reported outcomes separately for these two groups; we included here only the subgroup of patients without another indication for anticoagulation. Most trials included patients undergoing TAVR without high risk of bleeding, recent myocardial infarction, or recent percutaneous coronary intervention. Duration of randomized therapy ranged from 30 days[14] to 12 months[12], with a median of 3 months (interquartile range [IQR], 3-5.25). Median follow-up was 6 months (IQR, 4.5-12).

Four studies compared DAPT to aspirin alone,[13,15-17] and four studies compared anticoagulation to antiplatelet therapy.[12,14,18,19] Only one study used a VKA, comparing warfarin plus aspirin to aspirin alone.[14] The three studies that compared DOACs to DAPT used slightly different DOAC regimens. The Antithrombotic Strategy To Lower All

Cardiovascular And Neurologic Ischemic And Hemorrhagic Events After Transaortic Valve Implantation For Aortic Stenosis (ATLANTIS) trial (stratum 2) compared either full-dose apixaban without aspirin or half-dose apixaban with aspirin to DAPT.[12] The Global Study Comparing A Rivaroxaban-Based Antithrombotic Strategy To An Antiplatelet-Based Strategy After Transcatheter Aortic Replacement To Optimize Clinical Outcomes (GALILEO) trial compared half-dose rivaroxaban plus aspirin to DAPT.[18] The Anticoagulation Versus Dual Antiplatelet Therapy For Prevention Of Leaflet Thrombosis And Cerebral Embolization After Transcatheter Aortic Valve Replacement (ADAPT-TAVR) trial compared full-dose edoxaban alone to DAPT.[19]

We classified antithrombotic therapy into four nodes: aspirin alone, dual antiplatelet therapy (DAPT; all included studies of DAPT used clopidogrel plus aspirin), direct oral anticoagulant (DOAC), and vitamin K antagonist (VKA). Our network geometry is presented in Figure 3. We had no complete loops of data, which meant that our network estimates were comprised exclusively of either direct data (for comparisons that have been directly compared in a study, e.g., DOAC vs DAPT) or indirect data (for comparisons that have not been directly compared, e.g., DOAC vs ASA). As a result, we were unable to evaluate consistency between direct and indirect estimates for network comparison. Because of the small number of studies and events, we decided not to perform our preplanned subgroup analyses. Supplementary Table S2 summarizes results of individual studies.

Thromboembolic events

The studied therapies did not significantly impact the risk of thrombosis over a median follow-up of 6 months (DAPT versus aspirin alone: OR 0.98, 95% CrI, 0.55 to

1.75, low certainty; DOAC versus aspirin alone OR 1.27, 95% CrI 0.30 to 6.5, very low certainty; DOAC versus DAPT OR 1.44, 95% CrI 0.77 to 1.68, very low certainty; VKA versus aspirin alone OR 0.22, 95% CrI 0.01 to 4.67, very low certainty). We could not calculate network estimates of the OR for thrombosis with VKA versus DAPT and VKA versus DOAC because no thrombotic events occurred in patients taking a VKA. Figure 4 summarizes the direct evidence and network meta-analysis, and Table 2 presents the GRADE assessments.

Major bleeding

Compared to aspirin alone, the risk of major bleeding was significantly higher with both DAPT (OR 2.12, 95% CrI 1.33 to 3.38; low certainty) and DOAC (OR 2.92, 95% CrI 1.14 to 7.33; low certainty) over a median follow-up of 6 months. We found no other significant differences in risk of major bleeding across other comparisons in our network. VKA did not increase risk of major bleeding compared to aspirin alone (OR 0.56, 95% CrI, 0.05 to 6.38, very low certainty). Neither DOAC (OR 1.30, 95% CrI 0.95 to 1.78; low certainty) nor VKA (OR 0.21, 95% CrI 0.01 to 3.72; very low certainty) increased the risk of major bleeding compared to DAPT. We found no difference in major bleeding between DOAC and VKA (OR 0.16, 95% CrI 0 to 3.02, very low certainty). Figure 5 summarizes the direct evidence and Table 2 presents the network estimates.

Death

Risk of death was significantly higher with DOAC compared to DAPT (OR 1.73, 95% CrI 1.24 to 2.42, very low certainty). None of the other antithrombotic regimens significantly impacted risk of death over a median follow-up of 6 months (DAPT vs

aspirin alone, OR 0.99, 95% CrI 0.60 to 1.63, low certainty; DOAC vs aspirin alone, OR 1.87, 95% CrI 0.69 to 6.30, very low certainty; VKA versus aspirin alone, OR 1.13, 95% CrI 0.02 to 58.40, very low certainty). Because there were no deaths in patients taking VKAs, we could not generate network estimates of the ORs for death with VKA versus DAPT and VKA versus DOAC. The direct evidence is summarized in Figure 6 and the network estimates are in Table 2.

Aortic valve reintervention

Two studies (n=199 patients) reported on aortic valve reintervention.[15,16] Both studies randomized patients to DOAC or aspirin alone. Over a median follow-up of 6 months, no aortic valve reintervention occurred in either study.

Subclinical valve thrombosis

Four studies (n=1316) reported subclinical valve thrombosis: one randomized patients to VKA or aspirin alone,[14] and three randomized patients to DOAC versus DAPT.[12,18,19] We performed simple pairwise meta-analysis of the three studies comparing DOAC to DAPT, but we could not perform network meta-analysis of the four studies because the nodes did not overlap.

At 30 days, subclinical valve thrombosis occurred in 5% (2/43) of patients taking VKA compared to 16% (8/49) of patients taking aspirin alone (OR 0.28, 95% CI 0.10 to 0.99; low certainty).

Over a median follow-up of 1 year, patients taking DOACs experienced 21 events of subclinical valve thrombosis (4%) and patients taking DAPT experienced 47 events (9%), resulting in an odds ratio of 0.45 (95% CI, 0.26 to 0.78, high certainty; Figure 7). In absolute terms, patients taking DOACs had 49 fewer events of subclinical valve

thrombosis per 1000 compared to patients taking DAPT (95% CI, from 67 fewer to 19 fewer).

Mean aortic valve gradients on echocardiography

Two studies (n=894) reported mean aortic valve transvalvular gradients on echocardiography.[13,19] Patients randomized to DAPT versus aspirin alone had similar mean gradients at 6-month follow-up (11 +/- 6 versus 11 +/- 6 mmHg), as did patients randomized to DOAC versus DAPT at 6-month follow-up (13 +/- 5 versus 14 +/- 6 mmHg).

Studies of patients with another indication for anticoagulation

We found three studies with 2190 patients who in addition to their recent TAVR had another indication for anticoagulation.[12,20,21] AF was the indication for anticoagulation in 96% of patients (2102/2190). Duration of randomized therapy was 3, 12, or 18 months, and follow-up was 12 or 18 months.

Two studies (n=1877) compared DOAC to VKA. In the ATLANTIS trial stratum 1, which randomized patients to apixaban or VKA, apixaban dosage was halved in patients who were also prescribed antiplatelet therapy.[12] In the Edoxaban Versus Standard Of Care And Their Effects On Clinical Outcomes In Patients Having Undergoing Transcatheter Aortic Valve Implantation-Atrial Fibrillation (ENVISAGE-TAVI AF) trial, patients received full-dose edoxaban irrespective of concomitant antiplatelet therapy.[21] The Antiplatelet Therapy For Patients Undergoing Transcatheter Aortic Valve Implantation (POPular TAVI) trial (cohort B) compared oral anticoagulation (DOAC or VKA) plus clopidogrel to oral anticoagulation alone.[20] Where possible, we performed

pairwise meta-analysis of ATLANTIS and ENVISAGE-TAVI AF and present a narrative summary of POPular TAVI. Table 1 summarizes further study characteristics.

Thromboembolic events

Patients taking DOACs experienced 38 thrombotic events (4%) and patients taking VKAs experienced 45 thrombotic events (5%) over a median follow-up of 12 months, resulting in an odds ratio of 0.84 (95% CI, 0.54 to 1.31; Figure 8; moderate certainty). In absolute terms, patients taking DOACs experienced 7 fewer thrombotic events per 1000 patients (from 21 fewer to 14 more) than patients taking VKAs. Patients taking oral anticoagulation plus clopidogrel experienced 9 thrombotic events (6%) and patients taking oral anticoagulation alone experienced 9 events (6%; OR 0.99, 95% CI 0.33 to 2.57; low certainty).

Major bleeding

Patients taking DOACs experienced 138 major bleeding events (15%) and patients taking VKAs experienced 113 major bleeding events (12%) over a median follow-up of 12 months, resulting in an OR of 1.2 (95% CI, 0.81 to 1.79; Figure 9; moderate certainty). In absolute terms, patients taking DOACs experienced 21 more major bleeding events per 1000 patients (from 21 fewer to 76 more) than patients taking VKAs. Patients taking oral anticoagulation plus clopidogrel experienced 26 major bleeding events (17%) and patients taking oral anticoagulation alone experienced 14 events (9%; OR 2.01, 95% CI 1.01 to 4.02; moderate certainty).

Death

We found 108 deaths (12%) in patients taking DOACs and 116 deaths (12%) in patients taking VKAs over a median follow-up of 12 months, resulting in an OR of 0.93

(95% CI, 0.7 to 1.32; Figure 10; moderate certainty evidence). In absolute terms, patients taking DOACs experienced 8 fewer deaths per 1000 patients (from 34 fewer to 24 more) than patients taking VKAs. Patients taking oral anticoagulation plus clopidogrel experienced 24 deaths (15%) and patients taking oral anticoagulation alone experienced 21 deaths (13%; OR 1.16, 95% CI 0.62 to 2.18; low certainty).

Aortic valve reintervention

No patients required aortic valve reintervention in any of the included studies.

Subclinical valve thrombosis

One study (n=451) reported subclinical valve thrombosis, with 4 cases in patients taking DOACs (2%) and 8 cases in patients taking VKAs (4%) over 12 months of follow-up (OR 0.51, 95% CI 0.30 to 0.86; low certainty).[22]

Mean aortic valve gradients on echocardiography

One study (n=313) reported aortic valve mean transvalvular gradients.[20] Mean transvalvular gradients were 9 +/- 6 mmHg in patients taking oral anticoagulation alone and 11 +/- 5 mmHg in patients taking oral anticoagulation plus clopidogrel over 12 months.

Discussion

In this systematic review and network meta-analysis, we first examined 10 randomized studies evaluating antithrombotic therapy in 4235 patients with TAVR who had no other indication for anticoagulation. We found similar rates of thrombotic events in patients treated with aspirin alone, DAPT, or anticoagulation. When compared to aspirin, we found low certainty evidence that DAPT and anticoagulation increase major bleeding risk without reducing thrombotic risk. We also found low certainty evidence that

DOAC may increase risk of death compared to DAPT. Subclinical valve thrombosis occurred less frequently in patients taking anticoagulation compared to those taking antiplatelet therapy only.

We also examined three randomized studies of antithrombotic therapy in 2189 patients with TAVR and another indication for anticoagulation (mostly AF). We found low certainty evidence of similar major bleeding and thrombotic risk with DOACs or VKAs, although adding clopidogrel to anticoagulation increased major bleeding risk compared to anticoagulation alone. We found little to no difference in risk of death between DOAC and VKA. Based on low certainty evidence, DOAC therapy was associated with a halving of the risk of subclinical valve thrombosis compared to VKA. However, thromboembolic events and subclinical valve thrombosis occurred infrequently, which emphasizes the need to balance risk of major bleeding against risk of thrombosis when making clinical decisions.

The increase in mortality with DOAC compared to DAPT for patients without another indication for anticoagulation, and the trend towards increased mortality with DOAC compared to aspirin (OR 1.87, 95% CrI 0.69 to 6.3, very low certainty), is difficult to explain. We found a signal for increased major bleeding with DOAC compared to DAPT (OR 1.3, 95% CI 0.95 to 1.78) and evidence of increased major bleeding with DOAC compared to aspirin (OR 2.92, 95% CrI 1.14 to 7.33; low certainty), but absolute major bleeding event rates were low (6% in the overall cohort) and unlikely to account for the finding of increased mortality. Little relevant randomized literature exists in other populations to help explain the finding of increased mortality with DOACs compared to DAPT.

We did not find an increase in mortality with DOACs compared to VKA. Direct comparisons in patients with AF indicate that DOACs reduce mortality compared with warfarin, primarily due to a reduction in intracranial bleeding.[23] However, the Investigation Of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban Or Aspirin (INVICTUS) trial demonstrated increased mortality with DOACs compared to VKAs in patients from low- and middle-income countries with severe rheumatic mitral valve disease and AF.[24] The population of INVICTUS was younger, from a different socioeconomic context, and had a different valvular disease process affecting a different valve compared to the patients included in this systematic review. Nonetheless, taken together with our finding that DOACs may increase mortality compared to DAPT and perhaps aspirin in patients with TAVR, the results of the INVICTUS trial underline the need for caution when expanding use of DOACs to new populations, especially those with valvular disease.

Studies of DOACs in patients with bioprosthetic valves should include assessment of subclinical valve thrombosis. Only three randomized trials have examined the impact of DOACs on subclinical valve thrombosis (compared either to antiplatelet therapy or VKA),[12,18,19] and provide very few events and low or very low certainty evidence. The ongoing Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) trial (NCT04284839) will randomize 6215 patients with recent cardiac surgery (<14 days) and AF requiring oral anticoagulation to DOACs versus VKAs for the first 90 days after cardiac surgery. In a subset of 900 patients with bioprosthetic aortic valve replacement, the SUNDANCE substudy will also conduct CT scans in order to assess the impact of DOAC vs. VKA on subclinical valve thrombosis

and correlate these findings with valve hemodynamics on echocardiography. Long-term follow-up to assess the impact of early DOAC vs. VKA therapy on valve durability is planned.

Strengths and limitations

This systematic review and network meta-analysis synthesizes all available randomized data on antithrombotic therapy after TAVR. It facilitates the comparison of therapies not directly compared in the literature, namely DOAC versus aspirin alone in patients without another indication for anticoagulation. However, as with all systematic reviews, the quality and precision of our results are limited by the available data. Many of our estimates were imprecise and are based on low certainty evidence. Our network is small with few connections which limits our ability to use indirect evidence to increase the precision of the effect estimates.

Conclusion

In patients with TAVR and no other indication for anticoagulation, both anticoagulation and dual antiplatelet therapy increase the risk of major bleeding compared to aspirin alone without evidence of reduced thromboembolic risk, although thromboembolic event numbers are small and follow-up is limited to less than 18 months. In patients with TAVR and another indication for anticoagulation, DOACs appear to have similar efficacy and safety compared to VKAs, while adding clopidogrel to anticoagulation leads to increased major bleeding. Future studies should be adequately powered to assess the impact of antithrombotic strategies on thromboembolic events and subclinical valve thrombosis, and should seek to explain

why DOACs may be associated with increased mortality in patients with valvular disease or bioprosthetic valves.

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Tables

Table 1: Characteristics of included studies

Study	Intervention	Comparison	Duration of randomized therapy	Follow-up	Sample size
Patients with another indication for anticoagulation					
Ussia et al. *Am J Cardiol 2011*	Clopidogrel + Aspirin	Aspirin	3m	6m	79
SAT-TAVI Stabile et al. *Int J Cardiol 2014*	Clopidogrel + Aspirin	Aspirin	6m	6m	120
ARTE Rodés-Cabau et al. *JACC Cardiovasc Interv 2017*	Clopidogrel + Aspirin	Aspirin	3m	12m	222
POPular TAVI cohort A Brouwer et al. *NEJM 2020*	Clopidogrel + Aspirin	Aspirin	3m	12m	665
GALILEO Dangas et al. *NEJM 2020*	Half-dose DOAC + Aspirin (x3m), then half-dose DOAC alone	Clopidogrel + Aspirin (x3m), then Aspirin alone	For duration of study	17m median	1644
ATLANTIS – stratum 2 Collet et al. *Eur Heart J 2022*	DOAC alone (74%); Half-dose DOAC + Clopidogrel or Aspirin (22%); Half-does DOAC + Clopidogrel + Aspirin (4%)	Clopidogrel + Aspirin (79%); Clopidogrel or Aspirin (21%)	12m	12m	1049
ADAPT-TAVR Park et al. *Circulation 2022*	DOAC alone	Clopidogrel + Aspirin	6m	6m	229
Rogers et al. *Circ Cardiovasc Interv 2021*	Warfarin + Aspirin	Aspirin	30d	30d	94
Patients without another indication for anticoagulation					
POPular TAVI cohort B Nijenhuis et al. *NEJM 2020*	Oral anticoagulation (DOAC or VKA) + clopidogrel	Oral anticoagulation (DOAC or VKA) alone	3m	12m	313
ENVISAGE-TAVI AF Van Mieghem et al. *NEJM 2021*	Direct oral anticoagulant (edoxaban) + antiplatelet therapy at discretion of treating physician	Vitamin K antagonist + antiplatelet therapy at discretion of treating physician	For duration of study	18m median	1426
ATLANTIS – stratum 1 Collet et al. *Eur Heart J 2022*	Direct oral anticoagulant (apixaban) alone (72%); half-dose DOAC + clopidogrel or aspirin (26%)	Vitamin K antagonist alone (68%); VKA + clopidogrel or aspirin (23%)	12m	12m	451

DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Table 2: Network meta-analysis results and GRADE

Comparison	Direct estimate OR (95% CI)	Direct estimate GRADE	Indirect estimate OR (95% CI)	Indirect estimate GRADE	Overall GRADE
Thrombosis					
DAPT vs ASA	0.98 (0.55 to 1.75)	Moderate	*Not estimable*	*N/a*	Low
DOAC vs ASA	*Not estimable*	*N/a*	**OR 1.27** (0.30 to 6.50)	Low	Very low
VKA vs ASA	0.22 (0.01 to 4.67)	Very low	*Not estimable*	*N/a*	Very low
DOAC vs DAPT	1.14 (0.77 to 1.68)	Low	*Not estimable*	*N/a*	Very low
Bleeding					
DAPT vs ASA	2.12 (1.33 to 3.38)	Moderate	*Not estimable*	*N/a*	Low
DOAC vs ASA	*Not estimable*	*N/a*	2.92 (1.14 to 7.33)	Low	Very low
VKA vs ASA	0.56 (0.05 to 6.37)	Very low	*Not estimable*	*N/a*	Very low
DOAC vs DAPT	1.30 (0.95 to 1.78)	Low	*Not estimable*	*N/a*	Very low
VKA vs DAPT	*Not estimable*	*N/a*	0.21 (0.01 to 3.72)	Moderate	Very low
DOAC vs VKA	*Not estimable*	*N/a*	0.16 (0.00 to 3.02)	Low	Very low
Death					
DAPT vs ASA	0.99 (0.60 to 1.63)	Moderate	*Not estimable*	*N/a*	Low
DOAC vs ASA	*Not estimable*	*N/a*	1.87 (0.69 to 6.3)	Low	Very low
VKA vs ASA	1.13 (0.02 to 58.4)	Very low	*Not estimable*	*N/a*	Very low
DOAC vs DAPT	1.73 (1.24 to 2.42)	Low	*Not estimable*	*N/a*	Very low

ASA: acetylsalicylic acid; CI: confidence interval; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; GRADE: Grading of Recommendations, Assessments, Development and Evaluation; OR: odds ratio; VKA: vitamin K antagonist

Figures

Figure 1: PRISMA diagram

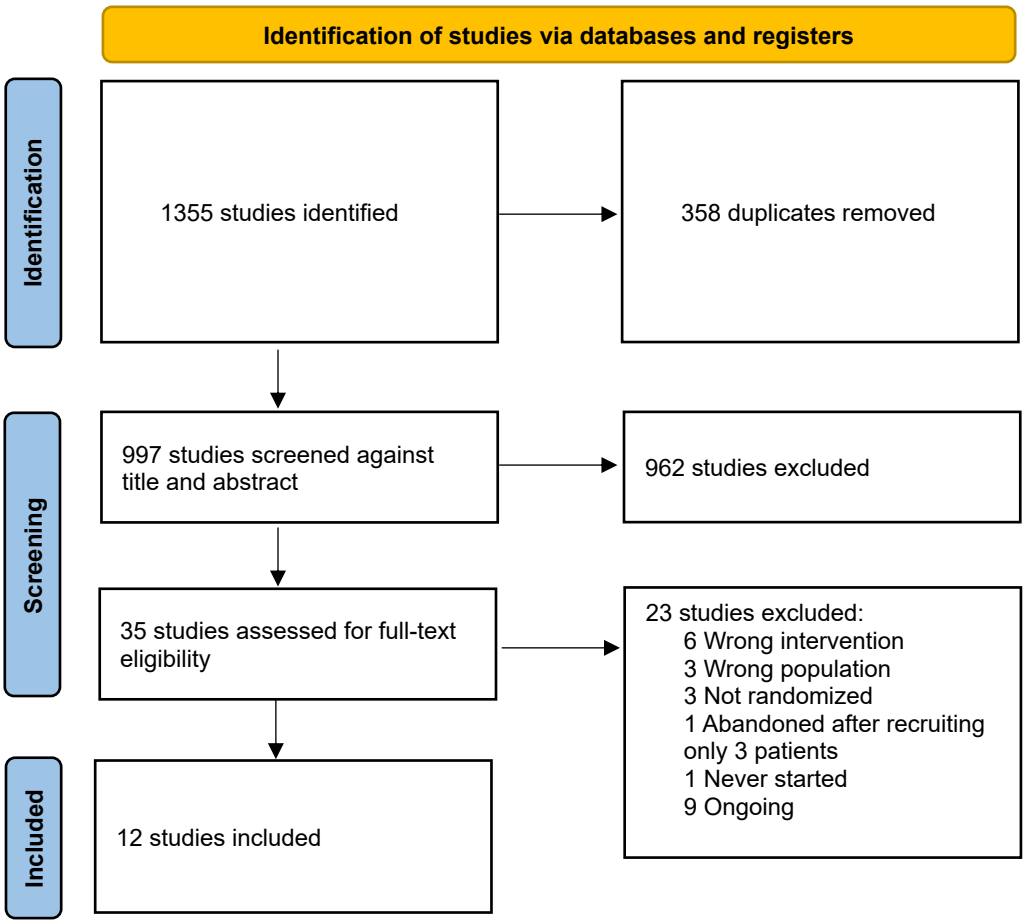


Figure 2: Risk of bias

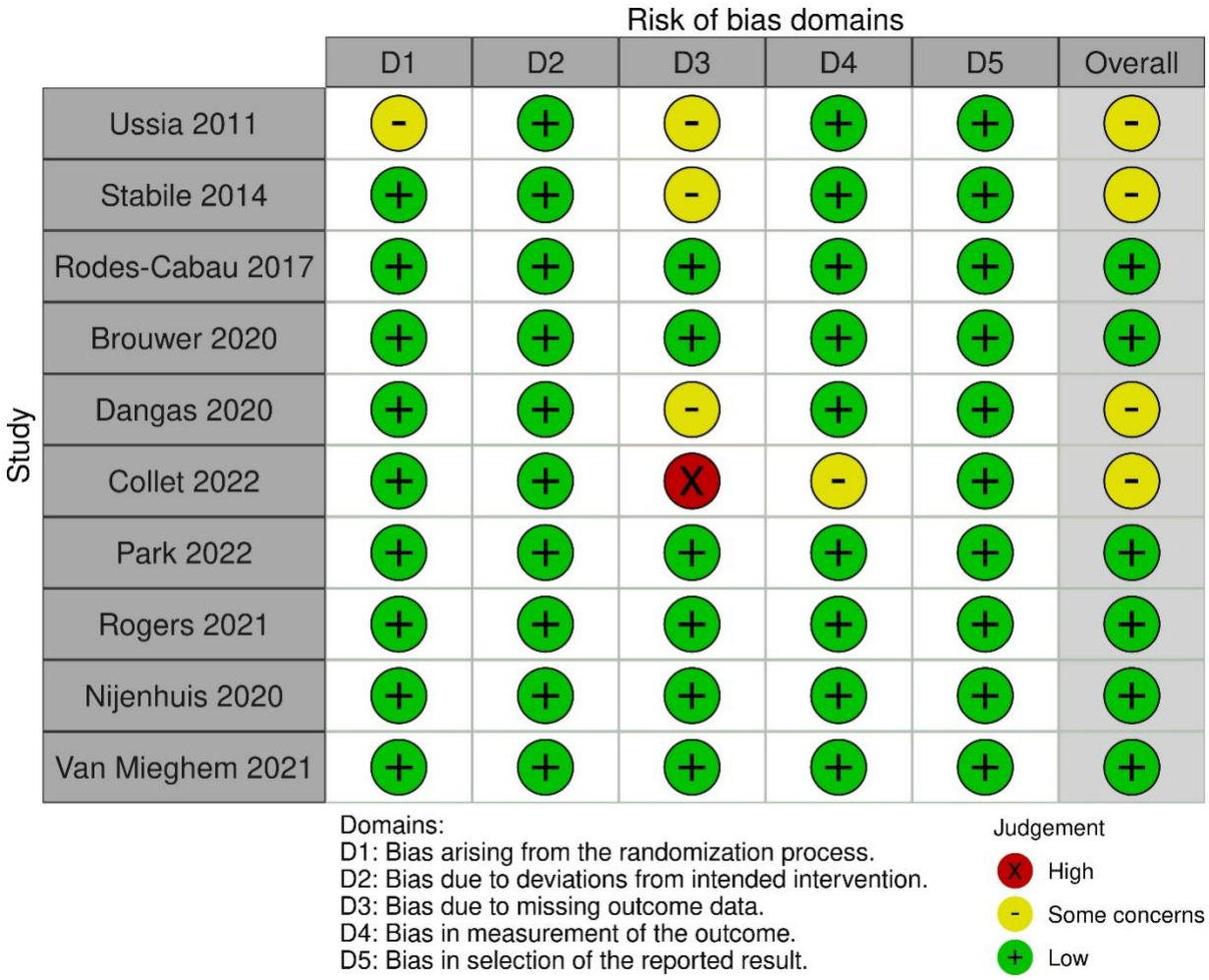
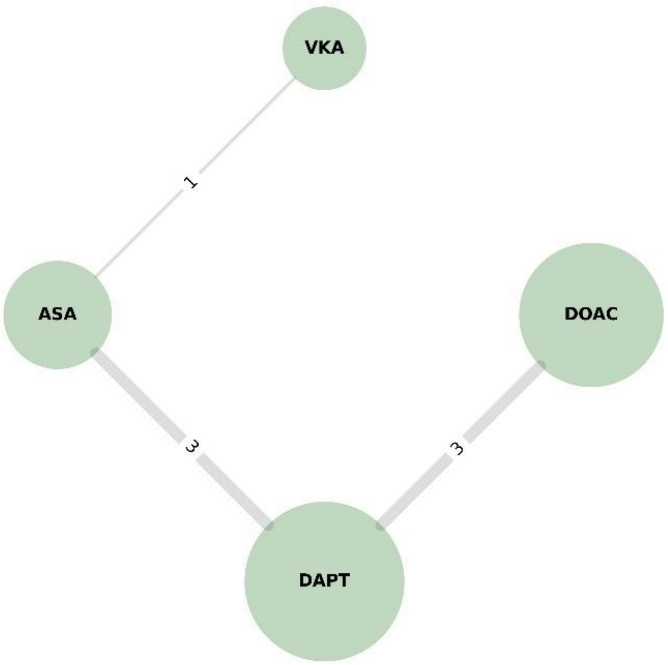


Figure 3: Network geometry



ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Figure 4: Thromboembolic events in patients without another indication for anticoagulation

Figure 4A: Thromboembolic events (DAPT vs aspirin)

Study	DAPT	(%)	Aspirin	(%)	Weight	OR [95% CI]
Ussia et al.	1/40	(2%)	2/39	(5%)	5.6%	0.47 [0.04, 5.45]
SAT-TAVI (Stabile et al.)	1/60	(2%)	2/60	(3%)	5.7%	0.49 [0.04, 5.57]
ARTE (Rodes-Cabau et al.)	3/111	(3%)	1/111	(1%)	6.5%	3.06 [0.31, 29.84]
POPular TAVI cohort A (Brouwer et al.)	20/334	(6%)	20/331	(6%)	82.2%	0.99 [0.52, 1.88]
Pooled Estimate	25/545	(5%)	25/541	(5%)	I^2: 0%	0.98 [0.55, 1.75]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.95, z=0.06 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

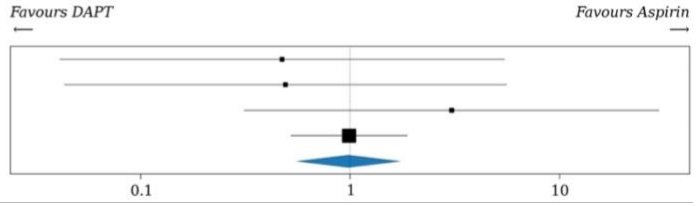


Figure 4B: Thromboembolic events (VKA vs aspirin)

Study	VKA	(%)	Aspirin	(%)	Weight	OR [95% CI]
Rogers et al.	0/44	(0%)	2/50	(4%)	100%	0.22 [0.01, 4.67]
Pooled Estimate	0/44	(0%)	2/50	(4%)	I^2: 0%	0.22 [0.01, 4.67]
Mantel-Haenszel Fixed Effects	*p=0.33, z=0.97*					*OR: Odds Ratio CI: Confidence Interval*

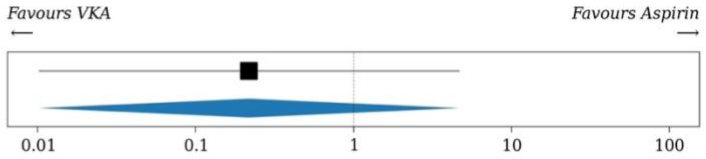


Figure 4C: Thromboembolic events (DOAC vs DAPT)

Study	DOAC	(%)	DAPT	(%)	Weight	OR [95% CI]
GALILEO (Dangas et al.)	34/826	(4%)	33/818	(4%)	63.0%	1.02 [0.63, 1.67]
ATLANTIS stratum 2 (Collet et al.)	19/526	(4%)	15/523	(3%)	31.8%	1.27 [0.64, 2.53]
ADAPT-TAVR (Park et al.)	4/111	(4%)	2/118	(2%)	5.1%	2.17 [0.39, 12.08]
Pooled Estimate	57/1,463	(4%)	50/1,459	(3%)	I^2: 0%	1.14 [0.77, 1.68]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.52, z=0.65 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

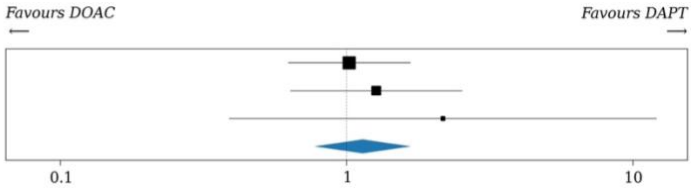


Figure 5: Major bleeding in patients without another indication for anticoagulation

Figure 5A: Major bleeding (DAPT vs aspirin)

Study	DAPT	(%)	Aspirin	(%)	Weight	OR [95% CI]
Ussia et al.	4/40	(10%)	3/39	(8%)	8.8%	1.33 [0.28, 6.39]
SAT-TAVI (Stabile et al.)	6/60	(10%)	5/60	(8%)	14.0%	1.22 [0.35, 4.24]
ARTE (Rodes-Cabau et al.)	12/111	(11%)	4/111	(4%)	16.0%	3.24 [1.01, 10.39]
Popular TAVI cohort A (Brouwer et al.)	37/334	(11%)	17/331	(5%)	61.1%	2.3 [1.27, 4.18]
Pooled Estimate	59/545	(11%)	29/541	(5%)	I^2: 0%	2.12 [1.33, 3.38]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.00, z=3.16 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

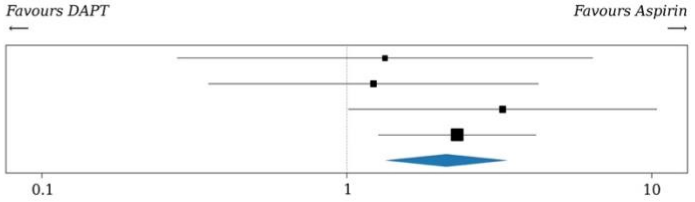


Figure 5B: Major bleeding (VKA vs aspirin)

Study	VKA	(%)	Aspirin	(%)	Weight	OR [95% CI]
Rogers et al.	1/44	(2%)	2/50	(4%)	100%	0.56 [0.05, 6.37]
Pooled Estimate	1/44	(2%)	2/50	(4%)	I^2: 0%	0.56 [0.05, 6.37]
Mantel-Haenszel Fixed Effects	*p=0.64, z=0.47*					*OR: Odds Ratio CI: Confidence Interval*

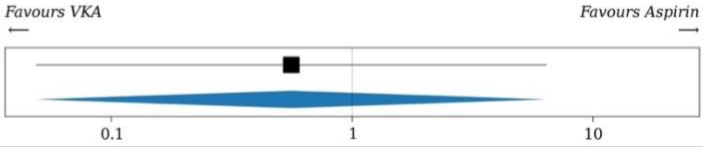


Figure 5C: Major bleeding (DOAC vs DAPT)

Study	DOAC	(%)	DAPT	(%)	Weight	OR [95% CI]
GALILEO (Dangas et al.)	48/826	(6%)	32/818	(4%)	47.1%	1.52 [0.96, 2.4]
ATLANTIS stratum 2 (Collet et al.)	41/526	(8%)	38/523	(7%)	47.0%	1.08 [0.68, 1.71]
ADAPT-TAVR (Park et al.)	6/111	(5%)	4/118	(3%)	5.9%	1.63 [0.45, 5.93]
Pooled Estimate	95/1,463	(6%)	74/1,459	(5%)	I^2: 0%	1.3 [0.95, 1.78]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.10, z=1.62 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

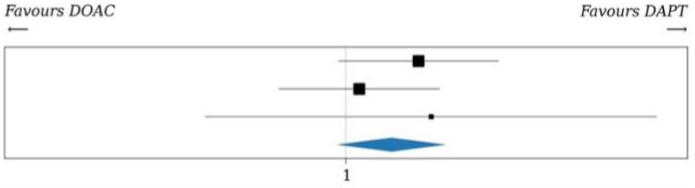


Figure 6: Death in patients without another indication for anticoagulation

Figure 6A: Death (DAPT vs aspirin)

Study	DAPT	(%)	Aspirin	(%)	Weight	OR [95% CI]
Ussia et al.	4/40	(10%)	5/39	(13%)	13.0%	0.76 [0.19, 3.05]
SAT-TAVI (Stabile et al.)	3/60	(5%)	3/60	(5%)	9.4%	1.0 [0.19, 5.17]
ARTE (Rodes-Cabau et al.)	7/111	(6%)	4/111	(4%)	16.0%	1.8 [0.51, 6.33]
POPular TAVI cohort A (Brouwer et al.)	19/334	(6%)	21/331	(6%)	61.7%	0.89 [0.47, 1.69]
Pooled Estimate	33/545	(6%)	33/541	(6%)	I^2: 0%	0.99 [0.6, 1.63]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.96, z=0.05 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

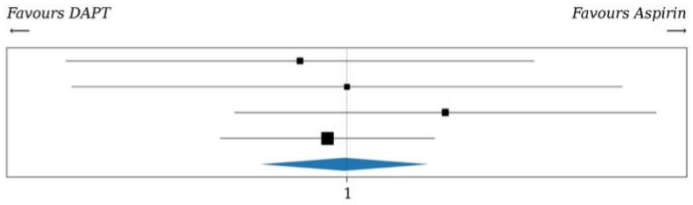


Figure 6B: Death (VKA vs aspirin)

Study	VKA	(%)	Aspirin	(%)	Weight	OR [95% CI]
Rogers et al.	0/44	(0%)	0/50	(0%)	100%	1.13 [0.02, 58.39]
Pooled Estimate	0/44	(0%)	0/50	(0%)	I^2: 0%	1.13 [0.02, 58.39]
Mantel-Haenszel Fixed Effects	*p=0.95, z=0.06*					*OR: Odds Ratio CI: Confidence Interval*

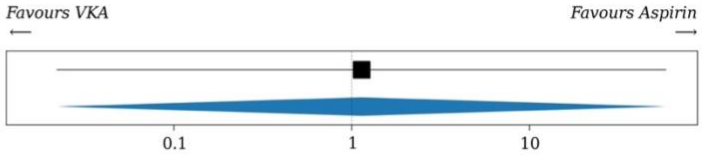


Figure 6C: Death (DOAC vs DAPT)

Study	DOAC	(%)	DAPT	(%)	Weight	OR [95% CI]
GALILEO (Dangas et al.)	64/826	(8%)	38/818	(5%)	65.0%	1.72 [1.14, 2.61]
ATLANTIS stratum 2 (Collet et al.)	31/526	(6%)	18/523	(3%)	31.6%	1.76 [0.97, 3.18]
ADAPT-TAVR (Park et al.)	3/111	(3%)	2/118	(2%)	3.4%	1.61 [0.26, 9.83]
Pooled Estimate	98/1,463	(7%)	58/1,459	(4%)	I^2: 0%	1.73 [1.24, 2.42]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.00, z=3.22 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

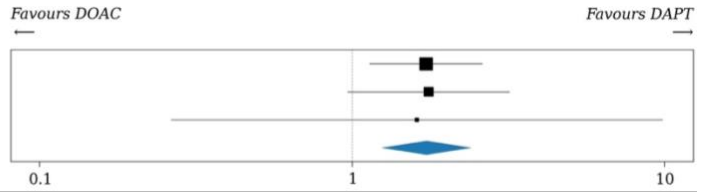


Figure 7: Subclinical valve thrombosis in patients without another indication for anticoagulation

Study	DOAC	(%)	DAPT	(%)	Weight	OR [95% CI]
GALILEO (Dangas et al.)	2/97	(2%)	11/101	(11%)	12.5%	0.17 [0.04, 0.8]
ATLANTIS stratum 2 (Collet et al.)	9/275	(3%)	16/283	(6%)	42.4%	0.56 [0.25, 1.3]
ADAPT-TAVR (Park et al.)	10/111	(9%)	20/118	(17%)	45.1%	0.49 [0.22, 1.09]
Pooled Estimate	21/483	(4%)	47/502	(9%)	I^2: 0%	0.45 [0.26, 0.78]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.00, z=2.85 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

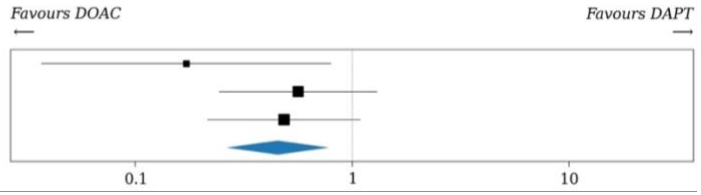


Figure 8: Thromboembolic events in patients with another indication for anticoagulation

Study	DOAC	(%)	VKA	(%)	Weight	OR [95% CI]
ENVISAGE TAVI-AF (Van Mieghem et al.)	31/713	(4%)	38/713	(5%)	82.7%	0.81 [0.5, 1.31]
ATLANTIS stratum 1 (Collet et al.)	7/223	(3%)	7/228	(3%)	17.3%	1.02 [0.35, 2.97]
Pooled Estimate	38/936	(4%)	45/941	(5%)	I^2: 0%	0.84 [0.54, 1.31]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.44, z=0.77 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*

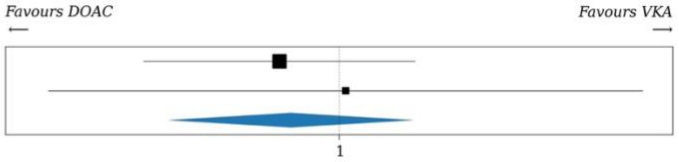


Figure 9: Major bleeding in patients with another indication for anticoagulation

Study	DOAC	(%)	VKA	(%)	Weight	OR [95% CI]
ENVISAGE TAVI-AF (Van Mieghem et al.)	115/713	(16%)	87/713	(12%)	67.9%	1.38 [1.02, 1.87]
ATLANTIS stratum 1 (Collet et al.)	23/223	(10%)	26/228	(11%)	32.1%	0.89 [0.49, 1.62]
Pooled Estimate	138/936	(15%)	113/941	(12%)	I^2: 40%	1.2 [0.81, 1.79]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.37, z=0.90 τ²=0.04*					*OR: Odds Ratio CI: Confidence Interval*

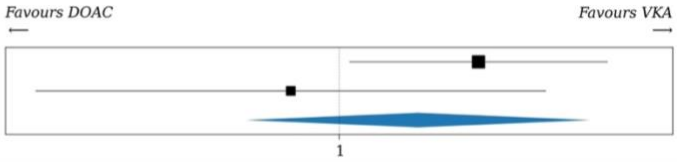
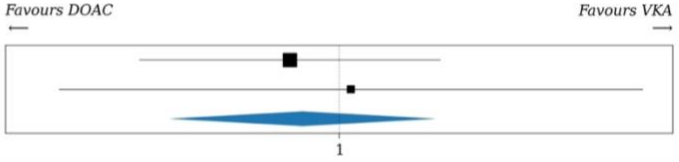


Figure 10: Death in patients with another indication for anticoagulation

Study	DOAC	(%)	VKA	(%)	Weight	OR [95% CI]
ENVISAGE TAVI-AF (Van Mieghem et al.)	85/713	(12%)	93/713	(13%)	79.0%	0.9 [0.66, 1.24]
ATLANTIS stratum 1 (Collet et al.)	23/223	(10%)	23/228	(10%)	21.0%	1.02 [0.56, 1.89]
Pooled Estimate	108/936	(12%)	116/941	(12%)	I^2: 0%	0.93 [0.7, 1.23]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.59, z=0.53 τ²=0.00*					*OR: Odds Ratio CI: Confidence Interval*



Appendices

Appendix 1: Search strategy

Ovid EMBASE

Population	Intervention	Study design
Emtree terms: Transcatheter aortic valve implantation Aortic valve Aortic valve stenosis Aortic valve replacement Aortic valve disease Heart valve prosthesis Transluminal valvuloplasty Keywords: TAVI TAVR Transcatheter aortic valve intervention Transcatheter aortic valve replacement Aortic valve	Emtree terms: Anticoagulant agent Antithrombocytic agent Antivitamin K Dual antiplatelet therapy Acetylsalicylic acid Clopidogrel Ticlodipine Prasugrel Ticagrelor Dipyridamole Warfarin Rivaroxaban Apixaban Dabigatran Dabigatran etexilate Edoxaban Ximelagatran Thrombin inhibitor Keywords: SAPT DAPT Antiplatelet P2Y12 inhibit* Aspirin NOAC DOAC VKA	Emtree terms: Random Double-blind Keywords: Placebo

OVID Medline

Population	Intervention	Study design
MeSH terms: Transcatheter aortic valve replacement Aortic valve Aortic valve stenosis Heart valve prosthesis Heart valve prosthesis implantation Balloon valvuloplasty Keywords: TAVI TAVR Transcatheter aortic valve intervention Transcatheter aortic valve replacement Aortic valve	MeSH terms: Anticoagulants Platelet aggregation inhibitors Ticlopidine Aspirin Clopidogrel Prasugrel hydrochloride Ticagrelor Dipyridamole Vitamin K Warfarin Factor Xa inhibitors Rivaroxaban Dabigatran Keywords: SAPT DAPT Antiplatelet P2Y12 inhibit* Aspirin ASA Anticoagula* NOAC DOAC Apixaban Edoxaban	MeSH terms: Randomized controlled trial Keywords: Randomized Placebo From HIRU website: find Hedges (filters for study designs) https://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx

Cochrane

Population	Intervention
Transcatheter aortic valve implantation Transcatheter aortic valve intervention Transcatheter aortic valve replacement TAVI TAVR Aortic valve Aortic valve stenosis Aortic valve replacement Aortic valve disease	Anticoagula* Antiplatelet DAPT SAPT P2Y12 inhibit* Acetylsalicylic acid Aspirin Clopidogrel Ticlopidine Prasugrel Ticagrelor Dipyridamole Vitamin K antagonist VKA Warfarin DOAC Direct oral anticoagula* Novel oral anticoagula* Factor Xa inhibitor NOAC Rivaroxaban Apixaban Dabigatran Edoxaban

Appendix Table 1: Results of individual studies

Study	Intervention											
	Thromboembolic events		Major bleeding		Death		Aortic valve reintervention		Subclinical valve thrombosis		Mean aortic valve gradients	
	Events, n	Patients, n	Events, n	Patients, n	Events, n	Patients, n	Events, n	Patients, n	Events, n	Patients, n	Mean (SD), mmHg	Patients, n
Patients with another indication for anticoagulation												
Ussia et al.[1] *Am J Cardiol 2011*	3	79	7	79	9	79	0	79	/	/	/	/
SAT-TAVI[2] Stabile et al. *Int J Cardiol 2014*	3	120	11	120	6	120	0	120	/	/	/	/
ARTE[3] Rodés-Cabau et al. *JACC Cardiovasc Interv 2017*	4	222	16	222	11	222	/	/	/	/	/	/
POPular TAVI cohort A[5] Brouwer et al. *NEJM 2020*	40	665	53	665	40	665	/	/	/	/	11 (6)	576
GALILEO[6] Dangas et al. *NEJM 2020*	67	1644	80	1644	102	1644	/	/	13	198	/	/
ATLANTIS[9] – stratum 2 Collet et al. *Eur Heart J 2022*	34	1049	79	1049	59	1049	/	/	25	558	/	/
ADAPT-TAVR[10] Park et al. *Circulation 2022*	6	229	10	229	5	229	/	/	30	229	13.5 (5)	229
Rogers et al.[7] *Circ Cardiovasc Interv 2021*	2	94	3	94	0	94	/	/	10	92	/	/

mmHg: millimeters of mercury; SD: standard deviation

Contributions:

RE: Responsible for study design, systematic review of the literature, data extraction, data analysis, writing the first draft of the manuscript, and providing critical revisions to the manuscript.

KU: Contributed significantly to study design and data analysis, and provided critical revisions to the manuscript.

KK, GW, YQ, and AW: Contributed significantly to systematic review of the literature, data extraction, and provided critical revisions to the manuscript.

WA, RL, SS, DS, and TS: Contributed significantly to study design and provided critical revisions to the manuscript.

EBC and RW: Contributed significantly to study design and data analysis, and provided critical revisions to the manuscript.

Chapter 5: Incidence, clinical implications, and prevention of subclinical valve thrombosis in transcatheter and surgical aortic valves: a systematic review and meta-analysis

Under review at:

Journal of the American Medical Association: Cardiology

Incidence, clinical implications, and prevention of subclinical valve thrombosis in transcatheter and surgical aortic valves: a systematic review and meta-analysis

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Abstract

Importance: Subclinical valve thrombosis is common after transcatheter aortic valve replacement (TAVR), but its clinical significance and the role of anticoagulation remain incompletely understood. Even less is known about subclinical valve thrombosis in surgical bioprosthetic aortic valve replacement (AVR).

Objective: To evaluate the incidence, clinical implications, and prevention of subclinical valve thrombosis in TAVR and surgical bioprosthetic AVR.

Data Sources: EMBASE, MEDLINE and CENTRAL until December 24, 2022.

Study Selection: Randomized or observational studies of subclinical valve thrombosis in patients with TAVR or surgical bioprosthetic AVR.

Data Extraction and Synthesis: Two independent reviewers extracted data and performed meta-analysis using random-effects modelling, reporting risk ratios (RR) and 95% confidence intervals (CIs).

Main Outcomes and Measures: 1) Incidence of subclinical valve thrombosis, 2) association between subclinical valve thrombosis and death, stroke, and thromboembolism, and 3) impact of oral anticoagulation on incidence, separately assessed for transcatheter and surgical valves.

Results: In 31 studies of 7434 TAVR patients and 6 studies of 786 SAVR patients, incidence of subclinical valve thrombosis was similar at 30-90 days (12%, 95% CI 9-16 versus 9%, 95% CI 3-20%) and 1 year (24%, 95% CI 20-29% versus 24%, 95% CI 18-31%). TAVR patients with subclinical valve thrombosis had higher risk of stroke compared to those without (RR 1.9, 95% CI 1.2-3.0), but similar risk of death (RR 1.1, 95% CI 0.8-1.6). Only 2 studies of 340 patients reported clinical outcomes in surgical

bioprosthetic AVR patients (5 deaths and 2 strokes). Anticoagulation was associated with lower risk of subclinical valve thrombosis in TAVR patients (RR 0.5, 95% CI 0.4-0.7 for randomized studies, RR 0.5, 95% CI 0.4-0.6 for observational studies). The impact of anticoagulation in surgical bioprosthetic AVR was similar, but the estimate was imprecise (RR 0.4, 95% CI 0.1-1.5).

Conclusions and Relevance: Subclinical valve thrombosis is equally common after TAVR and surgical bioprosthetic AVR. It is associated with increased risk of stroke after TAVR but has uncertainty clinical implications in surgical patients. Oral anticoagulation may reduce incidence of subclinical valve thrombosis, but further studies are required especially in surgical patients without another indication for anticoagulation.

Introduction

More than 100,000 aortic valve replacements (AVRs) are performed annually in North America.[1] More than 90% of AVRs are performed with either transcatheter or surgically implanted bioprosthetic valves, which are preferred to mechanical valves because they have a lower risk of valve thrombosis and thromboembolism and therefore do not require lifelong anticoagulation.[2,3] While clinical thrombosis occurs at a rate of less than 1% per year in bioprosthetic AVRs, however, subclinical valve thrombosis occurs in 5-15% at 30 days and 20-28% at 1 year.[4,5]

The clinical implications of subclinical valve thrombosis remain incompletely understood. Subclinical valve thrombosis may progress to clinical valve thrombosis, stroke, and thromboembolism,[6] and it is thought to be a precursor to structural valve deterioration.[2,7] Oral anticoagulation may reduce the incidence of subclinical valve thrombosis in patients with transcatheter aortic valve replacement,[8,9] but without evidence that it improves clinical outcomes in patients without an indication for oral anticoagulation.

We conducted a systematic review and meta-analysis of randomized and observational studies of subclinical valve thrombosis in patients with transcatheter or surgical bioprosthetic AVR. Our objectives were to quantify the incidence of subclinical valve thrombosis, examine its relationship to clinical and echocardiographic outcomes, and understand the impact of oral anticoagulation.

Methods

We conducted our review in accordance with a pre-specified protocol (PROSPERO registration number CRD42022308355).

Search strategy and selection criteria:

We searched EMBASE, MEDLINE and CENTRAL from January 1, 2015 until December 24, 2022. We created our search strategy (detailed in Appendix 1) with the assistance of an academic librarian. We restricted our search to publications from 2015 or later because subclinical valve thrombosis was first identified in 2015.[10] We checked references of relevant articles and reviewed the list of included studies with researchers with relevant expertise.

We included randomized and observational studies that performed computed tomography (CT) scans on patients with transcatheter or surgical bioprosthetic aortic valve replacement to look for subclinical valve thrombosis. We included studies that performed CT scans systematically on all participants as well as studies that reported series of patients who underwent clinically indicated CT scans. We excluded series with fewer than 5 patients.

Our outcomes of interest were incidence of subclinical valve thrombosis, association between subclinical valve thrombosis and clinical thromboembolic events, association between subclinical valve thrombosis and valve hemodynamics on echocardiography, and impact of oral anticoagulation on development of subclinical valve thrombosis.

Five reviewers (TA, AE, RE, AI, and PM) independently screened titles and abstracts of identified studies using a standardized form. If a study's title or abstract suggested it might be relevant, then the same reviewers independently assessed the full text for inclusion, resolving disagreements by discussion.

Data abstraction and analysis:

Four review authors (TA, RE, AM, and AS) independently abstracted data about study design, sample size, baseline demographics, and outcomes into a standardized Microsoft Excel spreadsheet.

We analyzed TAVR and SAVR patients separately. We used simple proportions to calculate the incidence of subclinical valve thrombosis at four timepoints: hospital discharge, 30-90 days, 6 months, and 1 year or longer after valve implantation. For incidence calculations, we only included prospective studies that enrolled patients at the time of valve implantation and systematically performed CT scans on all participants, excluding retrospective studies, case series, case control studies, or any study reporting clinically indicated CT scans.

We used the Mantel-Haenszel method and random effects modelling to generate estimates of the relationship between subclinical valve thrombosis and clinical events (death, stroke) or echocardiographic parameters (mean transvalvular gradient, effective orifice area). We were careful to ensure that we only counted events that occurred after patients had undergone their first CT scan to diagnose subclinical valve thrombosis. We did not include events that occurred before patients had undergone their CT scan because we did not know the patients' subclinical valve thrombosis status at the time of these events. We excluded studies that did not separately report clinical events that occurred after CT scan. For echocardiographic outcomes, we only included echocardiographic data that was generated simultaneously to or after the CT scan.

We used the Mantel-Haenszel method and random effects modelling to generate estimates of the effect of oral anticoagulation on incidence of subclinical valve thrombosis. We separately analysed randomized and observational studies.

We performed analyses in DataParty (DataParty Inc., Hamilton, Ontario, Canada; available at https://dataparty.ca). In cases of zero events, we imputed a value of 0.4 in the zero cell to allow for statistical analysis. To evaluate heterogeneity, we used visual inspection of forest plots and the I^2 statistic (0-40% = might not be important, 30-60% = moderate, 50-90% = substantial, 75-100% = considerable).

Risk of bias and certainty of evidence

Three review authors (RE, PM, and AI) assessed risk of bias of randomized trials using the revised Cochrane Risk of Bias tool for randomized trials,[11] and two authors (RM and BT) assessed risk of bias of observational trials using the Cochrane Risk of Bias in Non-randomized Studies of Exposure (ROBINS-E) tool.[12] We resolved disagreements by discussion. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[13] approach to summarize the certainty of evidence on an outcome-by-outcome basis as high, moderate, low, or very low. Two authors (RE and AI) determined certainty of evidence by discussion and consensus.

Results

From 1723 citations, we identified 27 studies of TAVR patients alone,[7-10,14-36] two studies of surgical aortic valve replacement (SAVR) patients alone,[37,38] and four studies of both TAVR and SAVR patients[4,5,39,40] that met inclusion criteria. Most studies were observational, and the four randomized studies included only TAVR patients. Table 1 presents a breakdown of the studies according to valve type and methodology.

Characteristics of included studies

Among the 31 studies that included 7434 TAVR patients, 4 studies (n=1316) randomized patients to antithrombotic therapies and examined the impact on subclinical

valve thrombosis,[8,9,14,15] 21 studies (n=4914) systematically performed CT scans to assess for subclinical valve thrombosis,[4,5,7,10,16-28,33-36] and 6 studies (n=1204) reported case series of patients who underwent clinically indicated CT scans.[29-32,39,40] Studies varied widely in terms of timing of CT scan (from discharge to 1 year), duration of follow-up (from 5 days to 23 years), type and duration of antithrombotic therapy after valve replacement, and management of subclinical valve thrombosis (no intervention, mandatory initiation of oral anticoagulation, or treatment at discretion of responsible physician). Table 2 summarizes characteristics of included studies in further detail.

The weighted mean age of TAVR patients was 81 years and 49% were female. Weighted mean left ventricular ejection fraction was 57%, 26% of patients had a history of atrial fibrillation, and 11% had a history of stroke.

Among the 6 studies that included 786 SAVR patients, 2 studies (n=303) systematically performed CT scans to assess for subclinical valve thrombosis[4,5] and 4 studies (n=483) reported case series of patients who underwent clinically indicated CT scans.[37-40] Timing of CT scan ranged from 30 days to 3.3 years, as did duration of follow-up. Most studies did not mandate type of antithrombotic therapy or management of subclinical valve thrombosis (Table 3).

The weighted mean age of SAVR patients was 72 years and 36% were female. Weighted mean left ventricular ejection fraction was 55%, 19% of patients had a history of atrial fibrillation, and 8% had a history of stroke.

<u>Risk of bias</u>

TAVR:

The 4 randomized studies were at low risk of bias (Figure 1). Among the 29 observational studies, 10 had some concerns for bias and 19 had high risk of bias. Risk of bias was caused by potential for confounding by anticoagulation therapy, co-interventions like changes in anticoagulation status after diagnosis of subclinical valve thrombosis, and missing data (Figure 2).

Incidence of subclinical valve thrombosis

TAVR:

We used all 4 randomized studies and 21 prospective studies in TAVR patients to estimate incidence of subclinical valve thrombosis incidence.[4,5,7-10,14-28,33-36] Subclinical valve thrombosis incidence increased over time: 12% (95% confidence interval [CI], 9-17%) at 5 days, 12% (95% CI, 9-16%) at 30-90 days, 16% (95% CI, 8-29%) at 6 months, and 24% (95% CI, 20-29%) at one year. The certainty of the evidence was very low, due to considerable inconsistency (I^2=34-89%) and some imprecision (Table 4; Figure 3-6).

SAVR:

Two prospective studies in SAVR patients provided estimates of incidence of subclinical valve thrombosis, with 9% (95% CI, 3-20%) of patients having subclinical valve thrombosis at 30 days and 24% (95%CI, 18-31%) at one year after valve implantation.[4,5] The certainty of the evidence was again very low, due to considerable inconsistency (I^2=29% and 79%) and some imprecision (Table 4; Figure 7-8).

Association between subclinical valve thrombosis and clinical outcomes

TAVR:

Fourteen studies provided observational data on the correlation between subclinical valve thrombosis, diagnosed on a CT scan performed 5 days to 3 months after valve implantation, and clinical outcomes of death and stroke over a median follow-up of 1 year.[4,5,8,10,20,22,24,26-28,31,36,39,40] Compared to 45 deaths (7%) in 635 patients with subclinical valve thrombosis, we found 298 deaths (8%) in 3509 patients without subclinical valve thrombosis, resulting in a relative risk of 1.1 (95% confidence interval [CI], 0.8 to 1.6; Figure 9). In absolute terms, patients with subclinical valve thrombosis experienced 7 fewer deaths per 1000 patients (95% CI, from 21 fewer to 47 more). Compared to 18 strokes (3%) in 661 patients with subclinical valve thrombosis, there were 65 strokes (2%) in 3770 patients without subclinical valve thrombosis, resulting in a relative risk of 1.9 (95% CI, 1.2 to 3.0; Figure 10). In absolute terms, patients with subclinical valve thrombosis experienced 16 more strokes per 1000 patients (95% CI, from 3 to 34 more).

Individual studies had consistent results, evidenced by visual inspection of the forest plots and statistical tests (I^2 = 10% for death and 15% for stroke). However, the certainty of the evidence was very low due to very serious risk of bias and serious imprecision. The confidence intervals associated with the estimates of effect included both harm and benefit for the outcome of death, and both important and unimportant differences for the outcome of stroke. Table 5 provides further details on the certainty of the evidence.

SAVR:

Two studies of 340 patients provided observational data on the correlation between subclinical valve thrombosis diagnosed one month after valve implantation and

clinical outcomes of death and stroke over a median follow-up of 1 year.[4,5] Compared to 2 deaths (7%) in 30 patients with subclinical valve thrombosis, we found 3 deaths (1%) in 310 patients without subclinical valve thrombosis, resulting in a relative risk of 8.8 (95% CI, 1.5 to 52.2; Figure 11). In absolute terms, patients with subclinical valve thrombosis experienced 76 more deaths per 1000 patients (95% CI, from 5 to 496 more). Similarly, the 30 patients with subclinical valve thrombosis experienced 1 stroke (3%) while the 310 patients without subclinical valve thrombosis experienced 1 stroke (0.3%), resulting in a relative risk of 8.8 (95% CI, 1.0 to 80.4; Figure 18). In absolute terms, patients with subclinical valve thrombosis experienced 25 more strokes per 1000 patients (95% CI, from 0 to 256 more).

The two studies present consistent results, evidenced by visual inspection of the forest plots and statistical tests (I^2 = 0%). However, the certainty of the evidence was very low due to serious risk of bias and very serious imprecision. With fewer than 5 events in either arm for either death or stroke, the confidence intervals included an implausibly large increase in clinical events with subclinical valve thrombosis. Table 6 provides further details on the certainty of the evidence.

<u>Association between subclinical valve thrombosis and echocardiographic parameters</u>

TAVR

Six studies patients provided observational data on the correlation between subclinical valve thrombosis diagnosed within 3 months of valve implantation and echocardiographic outcomes.[7,8,10,24,28,36] At 30-90 days, the mean difference in mean aortic transvalvular gradient was 0.8mmHg in 1822 patients (95% CI, from 0.1 to 1.5; Figure 13), while at one year it was 0.1mmHg in 1121 patients (95% CI, -1.3 to 1.5;

Figure 14). At one year, the mean difference in effective orifice area of the TAVR valve was 0cm^2 in 934 patients (95% CI, from -0.2 to 0.1cm^2; Figure 15).

Individual study results were heterogeneous, as is evident in the forest plots which show confidence intervals that fail to overlap as well as in statistical tests (I^2=1%, 66%, and 76%). When considered together with the very serious risk of bias of individual studies, the certainty of the evidence is very low. Table 5 provides further details on the certainty of the evidence.

SAVR

No studies of SAVR patients provided echocardiographic data.

Impact of oral anticoagulation versus no oral anticoagulation on subclinical valve thrombosis

TAVR

Four randomized studies of 1078 patients provided data on the impact of oral anticoagulation on the incidence of subclinical valve thrombosis.[8,9,14,15] Among 526 patients randomized to oral anticoagulation, there were 49 cases of subclinical valve thrombosis (9%), compared to 105 cases in 552 patients (19%) randomized to no oral anticoagulation (relative risk 0.5, 95% CI 0.4 to 0.7; Figure 16). In absolute terms, patients randomized to oral anticoagulation experienced 98 fewer cases of subclinical valve thrombosis per 1000 patients (95% CI, from 123 to 63 fewer). Results were similar between the three studies using direct oral anticoagulants (DOACs) and the one study using a vitamin K antagonist (VKA) (p for interaction 0.47). Individual studies had consistent results, evidenced by visual inspection of the forest plots and statistical tests (I^2 = 0%). The certainty of the evidence was deemed to be high (Table 7).

Seventeen observational studies of 3987 patients provided data on the impact of oral anticoagulation on the incidence of subclinical valve thrombosis.[7,10,16-18,20,22,24,26,27,29,31-36] Among 1324 patients who were prescribed oral anticoagulation, there were 112 cases of subclinical valve thrombosis (8%), compared to 417 cases in 2663 patients (15%) who were not prescribed oral anticoagulation (relative risk 0.5, 95% CI 0.3 to 0.7; Figure 17). In absolute terms, patients taking oral anticoagulation experienced 81 fewer cases of subclinical valve thrombosis per 1000 patients (95% CI, from 105 to 49 fewer). The observational data were inconsistent (I^2 = 54%) and at serious risk of bias. The certainty of the evidence was deemed to be very low (Table 7).

SAVR

One observational study of 139 patients provided data on the impact of oral anticoagulation on subclinical valve thrombosis in SAVR patients.[5] Compared to 2 cases in 19 patients who were prescribed oral anticoagulation (11%), there were 32 cases in 120 patients not taking oral anticoagulation (27%), resulting in a relative risk of 0.4 (95% CI, 0.1 to 1.5). In absolute terms, patients taking oral anticoagulation experienced 163 fewer cases of subclinical valve thrombosis per 1000 patients (95% CI, from 240 fewer to 136 more). Due to serious risk of bias and very serious impression, the certainty of the evidence was deemed to be very low (Table 7).

<u>Impact of direct oral anticoagulants versus vitamin K antagonists on subclinical valve thrombosis</u>

TAVR

Only one randomized study of 204 patients provided data on the impact of DOACs versus VKAs on the incidence of subclinical valve thrombosis.[9] Among 95

patients randomized to a DOAC, there were 8 cases of subclinical valve thrombosis (8%), compared to 7 cases in 109 patients (6%) randomized to VKAs (relative risk 1.3, 95% CI 0.5 to 3.5). In absolute terms, patients randomized to DOACs experienced 20 more cases of subclinical valve thrombosis per 1000 patients (95% CI, from 33 fewer to 159 more). The certainty of the evidence was deemed to be low due to very serious imprecision (Table 8).

Eight observational studies of 715 patients provided data on the impact of DOACs versus VKAs on the incidence of subclinical valve thrombosis.[7,10,17,22,27,29,31,36] Among 259 patients who were prescribed DOACs, there were 18 cases of subclinical valve thrombosis (7%), compared to 20 cases in 456 patients (4%) who were prescribed VKAs (relative risk 1.3, 95% CI 0.6 to 3.0; Figure 18). In absolute terms, patients taking DOACs experienced 3 more cases of subclinical valve thrombosis per 1000 patients (95% CI, from 26 fewer to 75 more). The data were generally consistent between studies (I^2 = 5%), but due to serious risk of bias and serious imprecision the certainty of the evidence was deemed to be very low (Table 8).

SAVR

No studies of SAVR patients reported incidence of subclinical valve thrombosis by type of oral anticoagulant.

Discussion

In this systematic review and meta-analysis of 33 studies and 8220 patients with transcatheter or surgical bioprosthetic aortic valves, we examined the incidence of subclinical valve thrombosis, its association with clinical and echocardiographic outcomes, and the impact of oral anticoagulation. Whereas subclinical valve thrombosis

has been a major focus of TAVR literature (reflected in the 29 TAVR studies included in this systematic review), it is less well studied in the SAVR literature (evaluated in only 6 studies), suggesting that the surgical literature is lagging behind. We found that the incidence of subclinical valve thrombosis at 30-90 days (12% after TAVR versus 9% after SAVR) and 1 year (24% after TAVR versus 24% after SAVR) is similar in TAVR and SAVR patients, suggesting it should merit similar attention for patients undergoing both types of procedures.

Subclinical valve thrombosis is thought to be a precursor to clinical valve thrombosis and thromboembolic events, and it may lead to structural valve deterioration.[41-44] We examined the association between subclinical valve thrombosis and clinical events (death, stroke) as well as echocardiographic indicators of structural valve deterioration (mean aortic transvalvular gradient, aortic valve effective orifice area). In TAVR patients, we found a similar incidence of death (RR 1.1, 95% CI 0.8 to 1.6) and increased incidence of stroke (RR 1.9, 95% CI 1.2 to 3.0) in patients with subclinical valve thrombosis compared to those without. It is biologically plausible that patients with thrombus on their valve leaflets are at higher risk of embolic stroke.[2] Another systematic review of subclinical valve thrombosis in TAVR patients also found that subclinical valve thrombosis was associated with increased risk of stroke, although the magnitude was lower in our study (2-fold compared to 3-fold).[6] The lower magnitude of risk found in our study may be explained by the exclusion of events that occurred prior to a patient's first CT scan. By excluding these events, we avoided including perioperative strokes, which usually result from atherosclerotic emboli or atrial fibrillation rather than thrombosis on valve leaflets.[45] We also reduced the likelihood of attributing a

stroke to subclinical valve thrombosis when it may have occurred before the patient developed subclinical valve thrombosis.

Given the nature of the data, we were unable to control for baseline differences in comorbidities or anticoagulation, or co-interventions such as initiating anticoagulation or scheduling follow-up appointments when patients were found to have subclinical valve thrombosis, all of which may confound the relationship between subclinical valve thrombosis and clinical events, leading to uncertainty. For example, a patient not taking anticoagulation will have a higher risk of both subclinical valve thrombosis and embolic stroke that may be mechanistically unrelated to the subclinical valve thrombosis (e.g., due to undiagnosed atrial fibrillation). In contrast, a patient diagnosed with subclinical valve thrombosis on CT scan might have been started on oral anticoagulation, which in addition to treating the subclinical valve thrombosis would reduce risk of other sources of embolic stroke.

We found no difference in mean aortic transvalvular gradient (mean difference at 30-90 days 0.8mmHg, 95% CI 0.1 to 1.5; mean difference at 1 year 0.1mmHg, 95% CI -1.3 to 1.5) or aortic valve effective orifice area (mean difference at 1 year: 0$cm^{2,}$ 95% CI, from -0.2 to 0.1cm^2) in TAVR patients with and without subclinical valve thrombosis. We were not able to separately examine hemodynamic parameters in patients who did and did not receive anticoagulation (whether to treat subclinical valve thrombosis or for other reasons). It is possible that untreated subclinical valve thrombosis results in worse echocardiographic outcomes, especially over a longer duration of follow-up. The connection between subclinical valve thrombosis, valve hemodynamic dysfunction, and structural valve deterioration requires examination over long-term (5+ years) follow-up.

In SAVR patients, our estimates of the relationship between subclinical valve thrombosis and clinical events were extremely imprecise due to low numbers of events (RR for death 1.5, 95% CI 1.5 to 52.2; RR for stroke 8.8, 95% CI 1.0 to 80.4), while no studies reported echocardiographic data. The SAVR population included in this systematic review is younger than the TAVR population (mean age 72 versus 81) and has fewer comorbidities (for example, 19% versus 25% with atrial fibrillation, 8% versus 11% with prior stroke), so we cannot combine them with the TAVR population or extrapolate from the TAVR results. In general, SAVR patients require more durability from their bioprosthetic valve than typical TAVR patients, who have a shorter life expectancy at valve implantation. If subclinical valve thrombosis is in fact a precursor to structural valve deterioration, then the scope of the problem in SAVR patients is potentially larger than in TAVR patients and requires scrutiny.

Finally, we found that anticoagulation is associated with lower incidence of subclinical valve thrombosis in both randomized (RR 0.5, 95% CI 0.4 to 0.7) and observational (RR 0.5, 95% CI 0.3 to 0.7) studies of TAVR patients, and in an observational study of SAVR patients (RR 0.4, 95% CI 0.1 to 0.5). While anticoagulation is an effective prophylactic measure, our findings regarding the clinical implications of subclinical valve thrombosis are not sufficiently compelling to outweigh the risks of recommending prophylactic anticoagulation for all bioprosthetic valve recipients. Large, randomized studies have demonstrated increased mortality in TAVR patients randomized to anticoagulation rather than antiplatelet therapy.[46-48] For patients undergoing bioprosthetic aortic valve replacement who do not have an indication for oral anticoagulation, the major question regarding subclinical valve thrombosis remains first

to clarify the clinical sequelae of this phenomenon. Only with this knowledge can the risks and benefits of anticoagulation be weighed appropriately.

We found minimal data on the relative efficacy of DOACs versus VKAs for prevention of subclinical valve thrombosis (one randomized study of 204 patients and six observational studies of 715 patients in TAVR, and no studies in SAVR). Studies of DOACs in patients with mechanical valves[49] and rheumatic valve disease[50] have demonstrated harms with DOACs compared to VKAs. While these studies included a different population than patients with bioprosthetic aortic valve replacement, they nonetheless provide a warning about assuming equivalent efficacy and safety of DOACs in new patient populations, particularly those with valvular disease or prosthetic valves. Patients with bioprosthetic aortic valves and another indication for oral anticoagulation will already be taking an anticoagulant. The key question regarding subclinical valve thrombosis is the relative efficacy and safety of DOACs versus VKAs. The Direct Oral Anticoagulation Versus Warfarin After Cardiac Surgery (DANCE) trial (NCT04284839) is randomizing patients with recent cardiac surgery and atrial fibrillation to DOACs or VKAs. The Subclinical Valve Thrombosis in Patients with Surgical Bioprosthetic Aortic Valve Replacement (SUNDANCE) substudy will examine the impact of randomized therapy on incidence of subclinical valve thrombosis at 60-90 days after SAVR and will provide the first evidence of the relative efficacy of DOACs versus VKAs in SAVR patients.

Conclusion

Subclinical valve thrombosis is common after both transcatheter and surgical bioprosthetic aortic valve replacement, but its clinical sequelae are imprecisely

described by existing literature, particularly in patients with surgical valves. Future high-quality work should focus on identifying the clinical implications of subclinical valve thrombosis and the potential role of anticoagulation in its prevention and treatment.

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Tables

Table 1: Overview of included studies

	Randomized studies	Prospective observational	Retrospective or case series	Total studies
TAVR	4 (n=1316)	21 (n=4914)	6 (n=1204)	27 (n=7434)
SAVR	0	2 (n=303)	4 (n=483)	6 (n=786)
				31 (n=8220) *4 studies reported both TAVR and SAVR patients

SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 2: Characteristics of included studies of TAVR patients

Table 2A: Randomized studies

Study	Inclusion criteria	Exclusion criteria	Intervention	Comparison	Duration of randomized therapy	Follow-up	Timing of CT scan	Timing of echo	Management of SCVT
De Backer 2019	TAVR and no indication for OAC	Contraindication to CT scan (dye allergy or CKD/dialysis)	Rivaroxaban 10 BID + aspirin	Aspirin + Plavix	3m	3m	3m	3m	No change to randomized therapy.
Montalescot 2022	TAVR	Contraindication to OAC	Apixaban 5mg BID	"Standard of care" - VKA if indication for OAC, APA if not	12m	12m	3m, 6m	3m, 6m	No change to randomized therapy.
Park 2022	TAVR and no indication for OAC	Indication for anticoagulation or DAPT, severe renal insufficiency prohibiting CT imaging	Edoxaban 10mg	Aspirin 100mg + clopidogrel 75mg	6m	6m	6m	Baseline, 1m, 6m	No change to randomized therapy.
Rogers 2021	TAVR and no indication for OAC	Indication for OAC	VKA + aspirin	Aspirin alone	30d	30d	30d	30d	No change to randomized therapy.

APA: antiplatelet agent; BID: twice daily; CKD: chronic kidney disease; CT: computed tomography; OAC: oral anticoagulation; SCVT: subclinical valve thrombosis; TAVR: transcatheter aortic valve replacement; VKA: vitamin K antagonist

Table 2B: Prospective observational studies

Study	Inclusion criteria	Exclusion criteria	Antithrombotic therapy	Follow-up	Timing of CT scan	Timing of echo	Management of SCVT
Apor 2022	TAVR	None	Various	3y	6m	6m	Not reported
Bak 2022	TAVR	Poor renal function, contraindication to CT scan	DAPT x12m, then aspirin only	3y	1y	Discharge, 6m, 1y	According to treating physician
Blanke 2020	Patients eligible for Evolut Low Risk trial: severe AS, low surgical risk (TAVR or SAVR). Originally excluded patients on OAC, but later allowed inclusion.	Severe renal insufficiency, unable to control HR <60bpm	TAVR: DAPT x1m then aspirin only; SAVR: not clear	1y	30d, 1y	30d, 1y	According to treating physician. Very few were started on OAC.
Garcia 2022	TAVR	Valve-in-valve TAVR, procedure failure, recipient of non-FDA approved TAVR device, GFR<30	No indication for OAC: DAPT x3-6m, then lifelong aspirin. Indication for OAC: OAC + aspirin x3-6m, then lifelong OAC	2y	30d	1m, 3m, 6m, 1y	Recommended VKA x3-6m
Hansson 2016	TAVR	Severely impaired renal function, frailty, patient refusal	No indication for OAC: DAPT x12m then aspirin. Indication for OAC: OAC +/- APA.	1y	1-3m	Discharge, follow-up visits 1 and 2	Recommended VKA +/- APA, but final decision at the discretion of the treating physician
Imaeda 2022	TAVR	Died within 1y of TAVR implantation, CKD, poor quality CT scan	No indication for OAC: DAPT x3m, then aspirin only. Indication for OAC: OAC + aspirin.	1y	Discharge, 6m, 1y	Discharge, 6m, 1y	No treatment
Jimenez 2019	TAVR	CKD	DAPT x3m	1y	Median 114d	Baseline, discharge, 1m, 1y	Not reported

Leetmaa 2015	TAVR	CKD or patient refusal	DAPT x3m	1-3m	1-3m	1-3m	OAC + APA (aspirin or clopidogrel)
Makkar 2015	Patients eligible for PORTICO IDE: severe symptomatic AS, high surgical risk	CT contraindication	Not reported	6m	30d	Baseline, discharge, 30d, 6m.	According to treating physician.
Makkar 2020	Patients eligible for PARTNER 3: severe AS, low surgical risk (TAVR or SAVR); no indication for OAC	CT contraindication	TAVR: DAPT x1m then aspirin only; SAVR: not clear	1y	30d, 1y	30d, 1y	Not reported
Nuhrenberg 2019	TAVR	On P2Y12 inhibitor, patient refusal	DAPT (duration unclear)	5d	5d	1-5d	Not reported
Rashid 2022	TAVR	GFR<45, too frail to do CT, unable to provide informed consent	No indication for OAC: DAPT x6m then aspirin. Indication for OAC: OAC +/-DAPT	2y	1-3m	Discharge, 1m, annually	Not reported
Ruile 2018	TAVR	CT contraindication	No indication for OAC: DAPT x6m then aspirin. Indication for OAC: OAC +/-DAPT	1y	5d	Discharge	2012 to 2015: VKA + clopidogrel x3m minimum, then DAPT x2m minimum. 2015 onward: no treatment
Szilveszter 2020	TAVR	CT contraindication	Not reported	Mean 1.7y	Mean 1.7y	Mean 1.7y	Not reported
Tang 2018	TAVR	CT contraindication	DAPT x3-6m	1y	30d	Discharge, 30d, 6m 1y	OAC for minimum 3m
Waksman 2020	Eligible for LRT 1: severe symptomatic AS, tricuspid aortic valve	CT contraindication	Not reported	30d	30d	Baseline, discharge, 30d	
Waksman 2021	Eligible for LRT 2: severe	CT contraindication	Not reported	2y	30d	Baseline, discharge,	Not reported

	symptomatic AS, bicuspid aortic valve					30 days, 1 year, 2 years	
Xiong 2020	TAVR	CT contraindication	DAPT x3-6m	5d	5d	Not done	Not reported
Yanagisawa 2016	TAVR	CT contraindication	DAPT x6m	1y	Discharge, 6 months, 1 year	Discharge, 6m, 1y	No treatment
Yanagisawa 2019	TAVR	CT contraindication	DAPT x3-6m	3y	3d, 6m, 1y, 2y, 3y	1y, 2y	No treatment
Zhu 2021	TAVR	CT contraindication	DAPT	1y	Discharge or 30d, 1y	Discharge, 30d, 1y	Not reported

APA: antiplatelet agent; AS: aortic stenosis; BID: twice daily; bpm: beats per minute; CKD: chronic kidney disease; CT: computed tomography; d: days; DAPT: dual antiplatelet therapy; FDA: Food and Drug administration; GFR: glomerular filtration rate; HR: heart rate; m: months; PARTNER 3: Placement of Aortic Transcatheter Valves 3; PORTICO IDE: Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial; OAC: oral anticoagulant; LRT: Low Risk TAVR; SCVT: subclinical valve thrombosis; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; VKA: vitamin K antagonist; y: years

Table 2C: Case series

Study	Inclusion Criteria	Exclusion criteria	Antithrombotic therapy	Follow-up	Timing of CT scan	Timing of echo	Management of SCVT
Basra 2018	All TAVR or SAVR patients with clinically indicated CT	None	DAPT x3-6m	TAVR patients: mean 393d (+/- 315). SAVR patients: not known	When clinically indicated	At time of CT scan	Treating physician decision
Chakravarty 2017	All TAVR or SAVR patients with clinically indicated CT	Impaired renal function	No protocol	Mean 540d	Median 83d (163d for SAVR and 58d for TAVR)	Discharge, at time of CT scan	Treating physician decision
Koo 2019	All TAVR patients with clinically indicated CT	None	No protocol	Median 364d	Median 18d (IQR 3-391)	Discharge, 1y	Not reported
Kuneman 2021	All TAVR patients with CT demonstrating SCVT	None	No indication for OAC: DAPT 3-12m; Indication for OAC: OAC +/- APA	1y	Median 37d (IQR 32-76)	Baseline, 1y	Treating physician decision
Marwan 2018	All TAVR patients with clinically indicated CT	Valve in valve	No indication for OAC: DAPT 3-6m; Indication for OAC: OAC +/- APA	1y	Median 4m	Baseline, at time of CT scan	Treating physician decision
Vollema 2017	All TAVR patients with clinically indicated CT	None	No indication for OAC: DAPT 1-3m; Indication for OAC: OAC +/- APA	3y	Median 3d, IQR 19-210 days	Discharge, 6m, annually	Not reported

APA: antiplatelet agent; CT: computed tomography; d: days; DAPT: dual antiplatelet therapy; m: months; IQR: interquartile range; OAC: oral anticoagulant; SCVT: subclinical valve thrombosis; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; VKA: vitamin K antagonist; y: years

Table 3: Characteristics of included studies of SAVR patients

Table 3A: Prospective observational studies

	Inclusion criteria	Exclusion criteria	Antithrombotic therapy	Follow-up	Timing of CT scan	Timing of echo	Management of SCVT
Blanke 2020	Patients eligible for Evolut Low Risk trial: severe AS, low surgical risk. Originally excluded patients on OAC, but later allowed inclusion.	Severe renal insufficiency, unable to control HR <60bpm	TAVR: DAPT x1m then aspirin only; SAVR: not clear	1y	30d, 1y	30d, 1y	According to treating physician. Very few were started on OAC.
Makkar 2020	Patients eligible for PARTNER 3: severe AS, low surgical risk; no indication for OAC	Contraindication to CT scan	TAVR: DAPT x1m then aspirin only; SAVR: not clear	1y	30d, 1y	30d, 1y	Not reported

AS: aortic stenosis; bpm: beats per minute; CT: computed tomography; d: days; DAPT: dual antiplatelet therapy; HR: heart rate; m: month; OAC: oral anticoagulant; SCVT: subclinical valve thrombosis; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 3B: Case series

	Inclusion Criteria	Exclusion criteria	Antithrombotic therapy	Follow-up	Timing of CT scan	Timing of echo	Management of SCVT
Basra 2018	All TAVR or SAVR patients with clinically indicated CT	None	DAPT x3-6m	TAVR patients: mean 393d (+/- 315). SAVR patients: not known	When clinically indicated	At time of CT scan	Treating physician decision
Chakravarty 2017	All TAVR or SAVR patients with clinically indicated CT	Impaired renal function	No protocol	Mean 540d	Median 83d (163d for SAVR and 58d for TAVR)	Discharge, at time of CT scan	Treating physician decision
Dagnegard 2021	Any patients with Perceval valve	Severely impaired renal function, not willing to undergo CT scan	No indication for OAC: aspirin alone; indication for OAC: OAC + aspirin	Median 491d (IQR, 287-933)	Median 491d (IQR, 287-933)	Not done	Treating physician decision
Themudo 2020	Anyone with full-root Freestyle valve	Freestyle explant	No protocol	Median 4.7y	Median 3.3y (IQR 2.1-5.7)	Median 3.3y (IQR 2.1-5.7)	Treating physician decision

CT: computed tomography; d: days; m: months; IQR: interquartile range; OAC: oral anticoagulant; SCVT: subclinical valve thrombosis; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 4: Incidence of subclinical valve thrombosis

	TAVR	SAVR
5 days	221/1688 = 12%	-
30-90 days	414/3709 = 12%	29/297 = 9%
6 months	79/502 = 16%	-
1 year	176/710 = 24%	54/228 = 24%

SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 5: Summary of Findings of the association between subclinical valve thrombosis and clinical and echocardiographic outcomes in TAVR patients

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Subclinical valve thrombosis**	**No subclinical valve thrombosis**	**Relative (95% CI)**	**Absolute (95% CI)**	
Death											
14	observational studies	very serious[a]	not serious	not serious	serious[b]	none	45/635 (7.1%)	298/3509 (8.5%)	**RR 1.08** (0.75 to 1.55)	**7 more per 1,000** (from 21 fewer to 47 more)	⊕◯◯◯ Very low
Stroke											
14	observational studies	very serious[a]	not serious	not serious	not serious[c]	none	18/661 (2.7%)	65/3770 (1.7%)	**RR 1.88** (1.16 to 3.04)	**15 more per 1,000** (from 3 to 35 more)	⊕◯◯◯ Very low
Mean aortic transvalvular gradient at 30-90 days											
6	observational studies	serious[d]	not serious	not serious	not serious	none	11.2mmHg	10.0mmHg	-	MD **0.8 mmHg higher** (0.1 to 1.5 higher)	⊕◯◯◯ Very low
Mean aortic transvalvular gradient at 1 year											
6	observational studies	very serious[e]	serious[f]	not serious	not serious	none	10.6mmHg	10.4mmHg	-	MD **0.1 mmHg lower** (1.3 lower to 1.5 higher)	⊕◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subclinical valve thrombosis	No subclinical valve thrombosis	Relative (95% CI)	Absolute (95% CI)	
Aortic valve effective orifice area at 1 year											
5	observational studies	very serious[e]	not serious	not serious	not serious	none	1.5	1.6	-	MD **0 cm2** (0.2 lower to 0.1 higher)	⊕◯◯◯ Very low

CI: confidence interval; MD: mean difference; RR: relative risk; TAVR: transcatheter aortic valve replacement

Explanations

a. Risk of bias is very serious because we are attempting to draw a relationship between two dependent variables (subclinical valve thrombosis and death/stroke).
b. 95% confidence interval includes both an important reduction in death and an important increase.
c. While the 95% confidence interval is wide, all possible values within the 95% confidence interval indicate an important increase in risk of stroke with subclinical valve thrombosis.
d. Risk of bias is serious because the studies are observational, with potential confounding due to use of oral anticoagulation and lack of blinding of outcome assessors. However, risk of bias for this outcome is less serious than for the other clinical outcomes of death and stroke because the echocardiogram (which determined transvalvular gradients) and the CT scan (which determined the diagnosis of subclinical valve thrombosis) occurred at the same time. Therefore there was no opportunity for post-exposure interventions to cause additional bias of the results.
e. Risk of bias is more serious than with transvalvular gradients at 30-90 days because, in addition to the bias concerns raised for that outcome, we must be wary that the echocardiographic outcomes at 1 year may be influenced by co-interventions such as changes to anticoagulation status made in response to the diagnosis of subclinical valve thrombosis.
f. I2 is 79%, which is high. Visual inspection of the forest plots reveals both increased and decreased transvalvular gradients associated with subclinical valve thrombosis.

Table 6: Summary of Findings of the association between subclinical valve thrombosis and clinical and echocardiographic outcomes in SAVR patients

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Subclinical valve thrombosis**	**No subclinical valve thrombosis**	**Relative (95% CI)**	**Absolute (95% CI)**	
Death											
2	observational studies	serious[a]	not serious	not serious	very serious[b]	strong association	2/30 (6.7%)	3/310 (1.0%)	**RR 8.83** (1.49 to 52.21)	**76 more per 1,000** (from 5 more to 496 more)	⊕◯◯◯ Very low
Stroke											
2	observational studies	serious[a]	not serious	not serious	very serious[c]	strong association	1/30 (3.3%)	1/310 (0.3%)	**RR 8.77** (0.96 to 80.36)	**25 more per 1,000** (from 0 fewer to 256 more)	⊕◯◯◯ Very low

CI: confidence interval; RR: relative risk; SAVR: surgical aortic valve replacement

Explanations

a. Risk of bias is very serious because we are attempting to draw a relationship between two dependent variables (subclinical valve thrombosis and death/stroke).

b. We have only 5 events. The 95% confidence interval only includes an important increase in death in patients who have subclinical valve thrombosis, but the confidence interval is very wide that we have little certainty about the true effect.

c. We have only 2 events. The 95% confidence interval includes no important difference or a huge increase in risk of stroke. The confidence interval is so wide that we cannot have much certainty about the true effect.

Table 7: Summary of Findings of the association between oral anticoagulation and incidence of subclinical valve thrombosis

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**OAC**	**No OAC**	**Relative (95% CI)**	**Absolute (95% CI)**	
TAVR: Incidence of subclinical valve thrombosis (randomized data)											
4	randomised trials	not serious	not serious	not serious	not serious	none	49/526 (9.3%)	106/552 (19.2%)	**RR 0.49** (0.36 to 0.67)	**98 fewer per 1,000** (from 123 fewer to 63 fewer)	⊕⊕⊕⊕ High
TAVR: Incidence of subclinical valve thrombosis (observational data)											
17	observational studies	serious[a]	serious[b]	not serious	not serious	none	112/1324 (8.5%)	417/2663 (15.7%)	**RR 0.48** (0.33 to 0.69)	**81 fewer per 1,000** (from 105 tp 49 fewer)	⊕◯◯◯ Very low
SAVR: Incidence of subclinical valve thrombosis (observational data)											
1	observational studies	serious[c]	not serious	not serious	very serious[d]	none	2/19 (10.5%)	32/120 (26.7%)	**RR 0.39** (0.10 to 1.51)	**163 fewer per 1,000** (from 240 fewer to 136 more)	⊕◯◯◯ Very low

CI: confidence interval; OAC: oral anticoagulation; RR: relative risk; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Explanations

a. Risk of bias is serious because most studies had significant amounts of missing data, outcome assessors were often unblinded to participant anticoagulation status, and in some cases patient selection was biased (patients were included only if they required a CT scan for clinical reasons). Anticoagulation status was measured at baseline but might have changed over the duration of follow-up, but we were unable to account for anticoagulation as a time-varying covariate because this information was not reported by included studies.

b. Inconsistency is high, reflected in an I2 value of 56%. Some studies estimate that oral anticoagulation reduces risk of subclinical valve thrombosis, and others estimate that it increases the risk.

c. Some risk of bias due to missing data.

d. 95% confidence interval includes both benefit and harm.

Table 8: Summary of Findings of the association between type of oral anticoagulation and incidence of subclinical valve thrombosis in TAVR patients

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**DOAC**	**VKA**	**Relative (95% CI)**	**Absolute (95% CI)**	
Incidence of subclinical valve thrombosis (randomized data)											
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	8/95 (8.4%)	7/109 (6.4%)	**RR 1.31** (0.49 to 3.48)	**20 more per 1,000** (from 33 fewer to 159 more)	⊕⊕◯◯ Low
Incidence of subclinical valve thrombosis (observational data)											
8	observational studies	serious[b]	not serious	not serious	serious[a]	none	18/259 (6.9%)	20/456 (4.4%)	**RR 1.32** (0.58 to 3.03)	**14 more per 1,000** (from 18 fewer to 89 more)	⊕◯◯◯ Very low

CI: confidence interval; DOAC: direct oral anticoagulant; RR: relative risk; TAVR: transcatheter aortic valve replacement; VKA: vitamin K antagonist

Explanations

a. Very few events. Wide 95% confidence interval which includes both harm and benefit.

b. Risk of bias is serious because most studies had significant amounts of missing data, outcome assessors were often unblinded to participant anticoagulation status, and in some cases patient selection was biased (patients were included only if they required a CT scan for clinical reasons). Finally, anticoagulation status was measured at baseline but might have changed over the duration of follow-up, but we were unable to account for anticoagulation as a time-varying covariate because this information was not reported by included studies.

Figures

Figure 1: Risk of bias for randomized studies

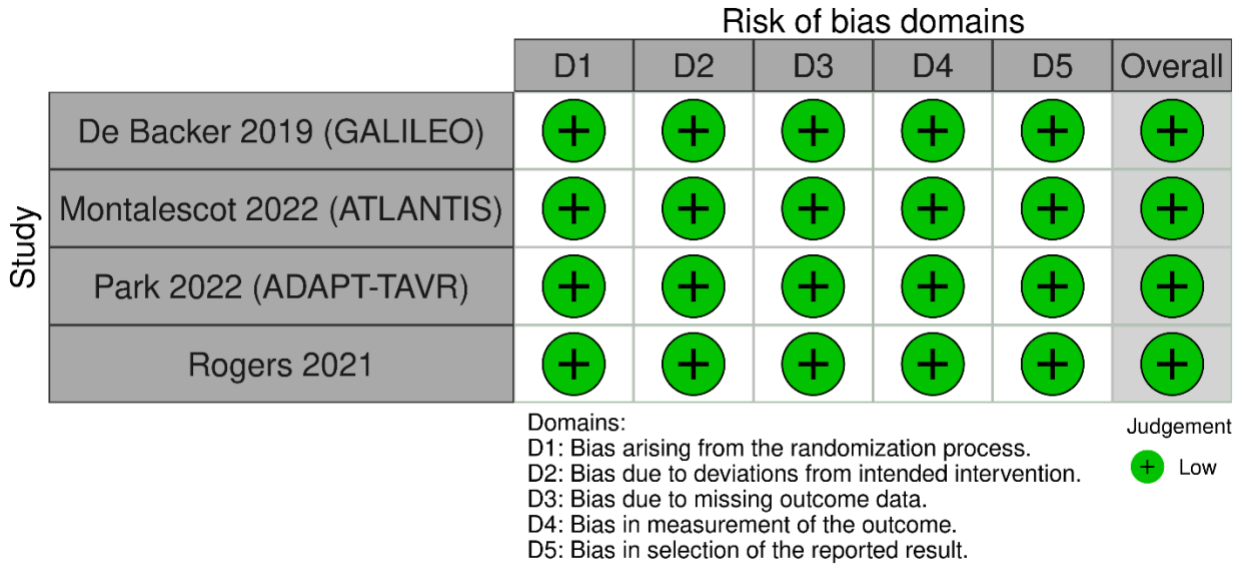


Figure 2: Risk of bias for observational studies

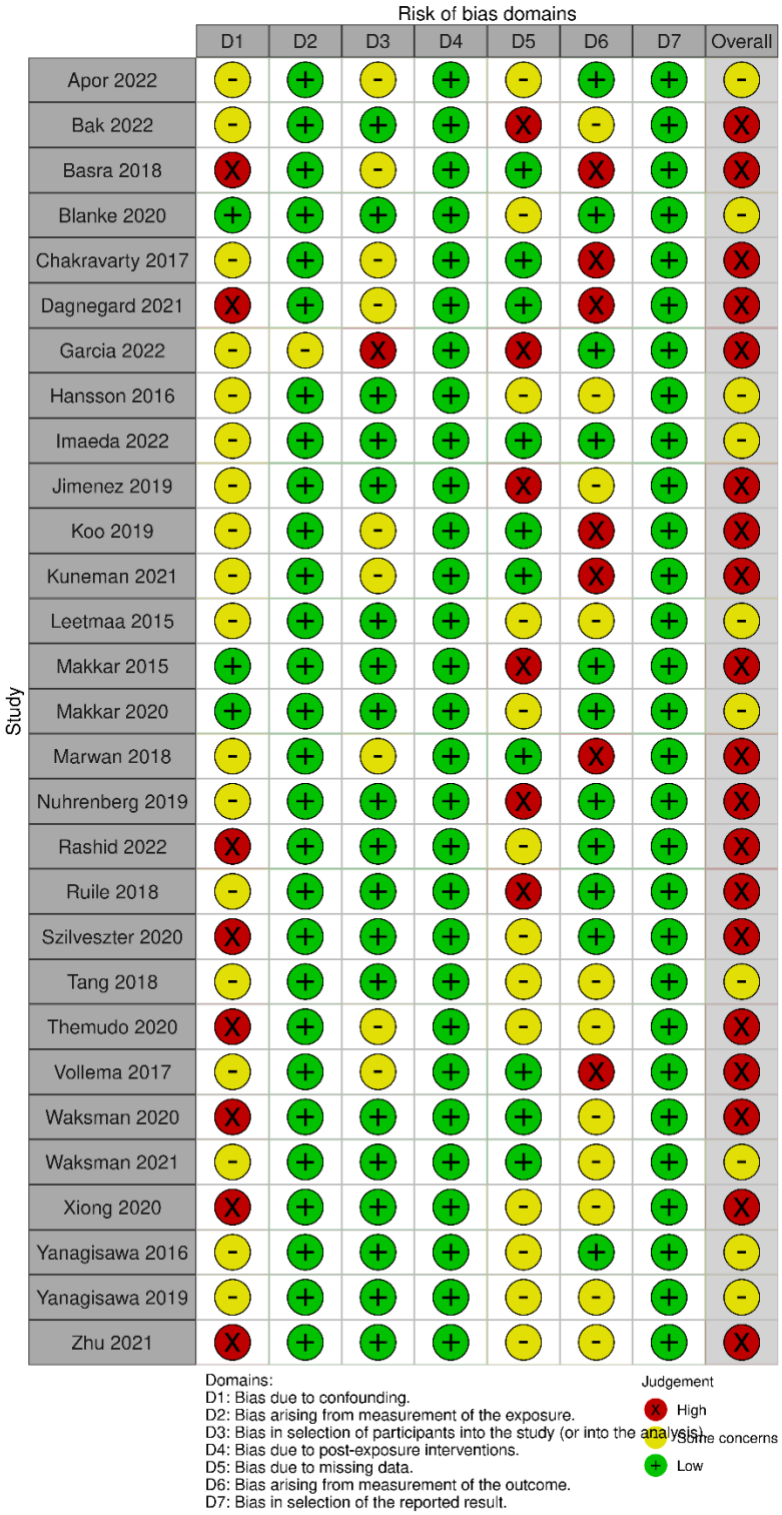


Figure 3: Incidence of subclinical valve thrombosis in TAVR, 5 days

Study	Incidence	Weight	SCVT [95% CI]
Nuhrenberg 2019	36/200	23.6%	0.18 [0.13, 0.24]
Ruile 2018	120/754	27.3%	0.16 [0.13, 0.19]
Xiong 2020	19/179	20.6%	0.11 [0.07, 0.16]
Yanagisawa 2016	1/70	3.6%	0.01 [0.0, 0.09]
Yanagisawa 2019	45/485	24.9%	0.09 [0.07, 0.12]
Pooled Estimate	221/1,688	I^2: 81%	0.12 [0.09, 0.17]

Inverse Variance, DerSimonian-Laird Random Effects

τ^2=0.14

CI: Confidence Interval

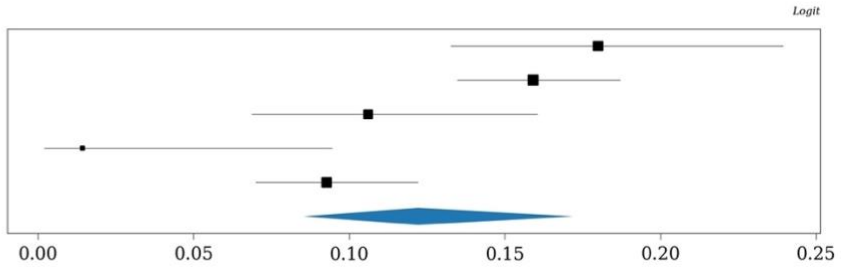


Figure 4: Incidence of subclinical valve thrombosis in TAVR, 30-90 days

Study	Incidence	Weight	SCVT [95% CI]
30 days			
Blanke 2020	31/179	7.5%	0.17 [0.12, 0.24]
Garcia 2022	79/638	8.1%	0.12 [0.1, 0.15]
Hansson 2016	28/405	7.6%	0.07 [0.05, 0.1]
Makkar 2015	22/55	6.9%	0.4 [0.28, 0.53]
Makkar 2020	22/165	7.3%	0.13 [0.09, 0.19]
Rashid 2022	33/186	7.6%	0.18 [0.13, 0.24]
Rogers 2021	10/92	6.3%	0.11 [0.06, 0.19]
Tang 2018	26/287	7.5%	0.09 [0.06, 0.13]
Waksman 2020	6/61	5.4%	0.1 [0.04, 0.2]
Waksman 2021	27/170	7.4%	0.16 [0.11, 0.22]
Zhu 2021	39/371	7.8%	0.11 [0.08, 0.14]
Subgroup Estimate	323/2,609	I^2: 82%	0.14 [0.1, 0.17]
90 days			
De Backer 2019	45/198	7.8%	0.23 [0.17, 0.29]
Leetma 2015	5/140	5.2%	0.04 [0.01, 0.08]
Montalescot 2022	41/762	7.8%	0.05 [0.04, 0.07]
Subgroup Estimate	91/1,100	I^2: 96%	0.08 [0.02, 0.25]
Pooled Estimate	414/3,709	I^2: 89%	0.12 [0.09, 0.16]

Inverse Variance, DerSimonian-Laird Random Effects Subgroup Effect

τ^2=0.33
χ^2=0.71, p=0.40, I^2=0.0%

CI: Confidence Interval

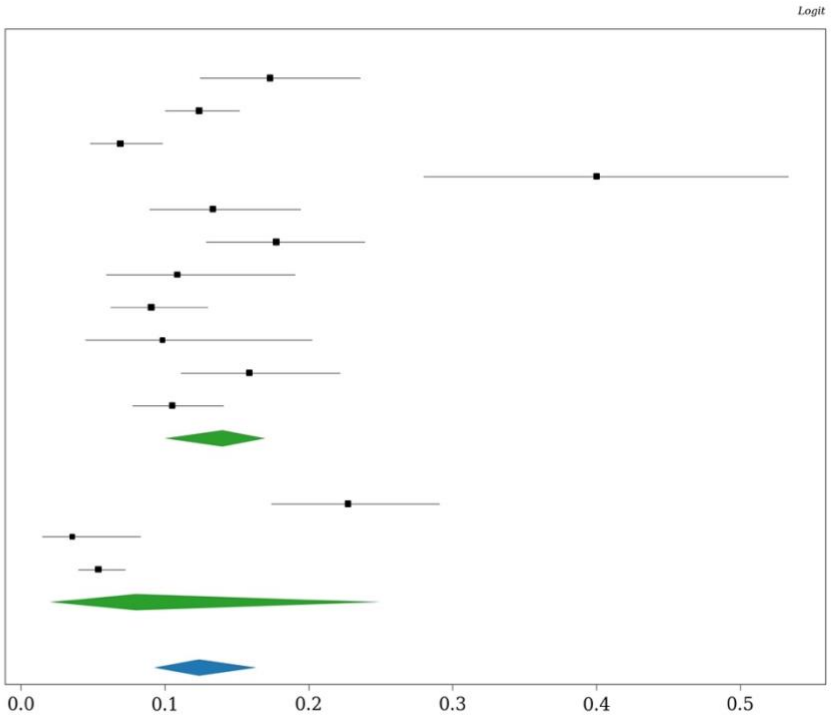


Figure 5: Incidence of subclinical valve thrombosis in TAVR, 6 months

Study	Incidence	Weight	SCVT [95% CI]
Apor 2022	12/117	24.6%	0.1 [0.06, 0.17]
Jiminez 2019	30/86	26.3%	0.35 [0.26, 0.45]
Park 2022	30/229	26.9%	0.13 [0.09, 0.18]
Yanagisawa 2016	7/70	22.3%	0.1 [0.05, 0.2]
Pooled Estimate	79/502	I^2: 89%	0.16 [0.08, 0.29]
Inverse Variance, DerSimonian-Laird Random Effects	τ^2=0.54		*CI: Confidence Interval*

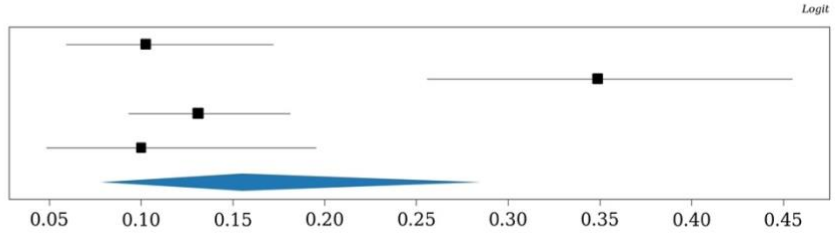


Figure 6: Incidence of subclinical valve thrombosis in TAVR, 1 year

Study	Incidence	Weight	SCVT [95% CI]
Bak 2022	20/94	14.3%	0.21 [0.14, 0.31]
Blanke 2020	47/152	21.2%	0.31 [0.24, 0.39]
Imaged 2022	27/124	17.0%	0.22 [0.15, 0.3]
Makkar 2020	42/153	20.6%	0.27 [0.21, 0.35]
Szilveszter 2020	30/117	17.6%	0.26 [0.19, 0.34]
Yanagisawa 2016	10/70	9.3%	0.14 [0.08, 0.25]
Pooled Estimate	176/710	I^2: 43%	0.24 [0.20, 0.29]
Inverse Variance, DerSimonian-Laird Random Effects	τ^2=0.04		*CI: Confidence Interval*

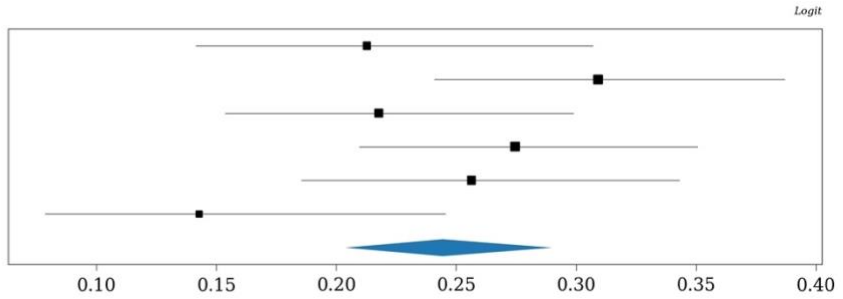


Figure 7: Incidence of subclinical valve thrombosis in SAVR, 30-90 days

Study	Incidence	Weight	SCVT [95% CI]
Blanke 2020	23/178	55.9%	0.13 [0.09, 0.19]
Makkar 2020	6/119	44.1%	0.05 [0.02, 0.11]
Pooled Estimate	29/297	I^2: 79%	0.09 [0.03, 0.20]

Inverse Variance, DerSimonian-Laird Random Effects τ^2=0.42

CI: Confidence Interval

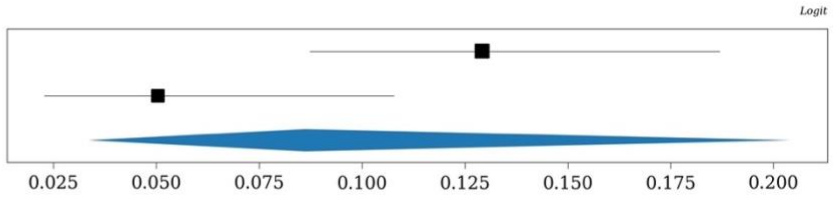


Figure 8: Incidence of subclinical valve thrombosis in SAVR, 1 year

Study	Incidence	Weight	SCVT [95% CI]
Blanke 2020	32/119	55.1%	0.27 [0.2, 0.36]
Makkar 2020	22/109	44.9%	0.2 [0.14, 0.29]
Pooled Estimate	54/228	I^2: 29%	0.24 [0.18, 0.31]

Inverse Variance, DerSimonian-Laird Random Effects τ^2=0.02

CI: Confidence Interval

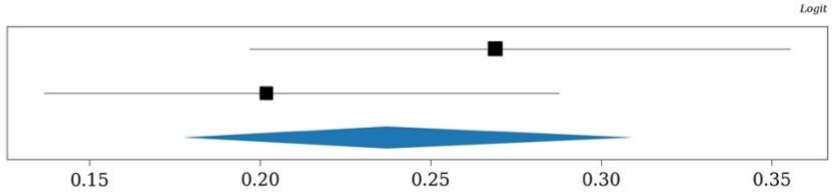


Figure 9: Association between subclinical valve thrombosis and death, TAVR

Study	SCVT	(%)	No SCVT	(%)	Weight	RR [95% CI]
Basra 2018	0/32	(0%)	4/69	(6%)	1.6%	0.24 [0.01, 4.25]
Blanke 2020	0/35	(0%)	0/162	(0%)	0.9%	4.53 [0.09, 224.43]
Chakravarty 2017	4/106	(4%)	34/784	(4%)	11.1%	0.87 [0.32, 2.4]
De Backer 2019	0/44	(0%)	6/151	(4%)	1.6%	0.26 [0.01, 4.52]
Garcia 2022	24/79	(30%)	112/558	(20%)	43.8%	1.51 [1.04, 2.2]
Makkar 2015	2/22	(9%)	1/33	(3%)	2.4%	3.0 [0.29, 31.12]
Makkar 2020	0/35	(0%)	0/311	(0%)	0.9%	8.67 [0.17, 430.21]
Marwan 2018	0/18	(0%)	0/60	(0%)	0.9%	3.21 [0.07, 156.41]
Ruile 2018	15/120	(12%)	109/634	(17%)	31.8%	0.73 [0.44, 1.2]
Waksman 2021	0/27	(0%)	1/143	(1%)	1.3%	1.71 [0.07, 41.02]
Yanagisawa 2016	0/10	(0%)	1/60	(2%)	1.3%	1.85 [0.08, 42.52]
Yanagisawa 2019	0/45	(0%)	30/440	(7%)	1.7%	0.16 [0.01, 2.53]
Zhu 2021	0/62	(0%)	0/104	(0%)	0.9%	1.67 [0.03, 82.96]
Pooled Estimate	45/635	(7%)	298/3,509	(8%)	I^2: 10%	1.08 [0.75, 1.55]

Mantel-Haenszel, DerSimonian-Laird Random Effects

p=0.68, z=0.41
τ^2=0.04

RR: Risk Ratio
CI: Confidence Interval

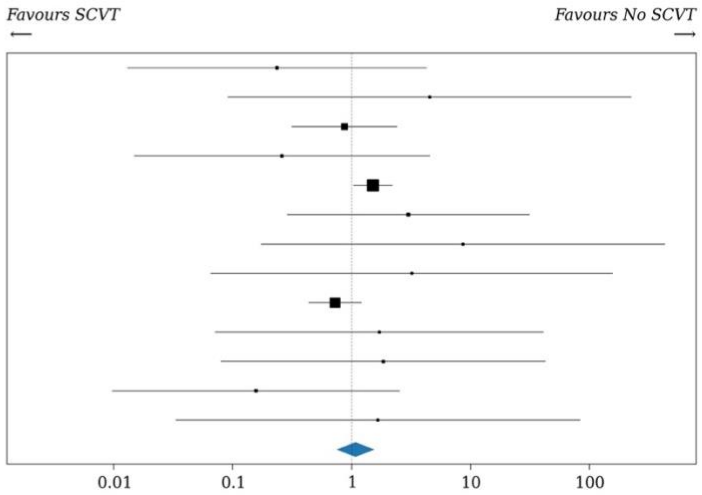


Figure 10: Association between subclinical valve thrombosis and stroke, TAVR

Study	SCVT	(%)	No SCVT	(%)	Weight	RR [95% CI]
Basra 2018	3/32	(9%)	3/69	(4%)	9.8%	2.16 [0.46, 10.1]
Blanke 2020	0/35	(0%)	1/162	(1%)	2.8%	1.51 [0.06, 36.3]
Chakravarty 2017	7/106	(7%)	2/784	(0%)	2.4%	25.89 [5.45, 122.99]
De Backer 2019	0/44	(0%)	1/151	(1%)	3.5%	1.13 [0.05, 27.17]
Garcia 2022	5/79	(6%)	25/558	(4%)	31.9%	1.41 [0.56, 3.58]
Makkar 2015	0/22	(0%)	0/33	(0%)	2.1%	1.48 [0.03, 71.88]
Makkar 2020	0/35	(0%)	1/311	(0%)	1.6%	2.89 [0.12, 69.61]
Marwan 2018	0/18	(0%)	0/60	(0%)	1.2%	3.21 [0.07, 156.41]
Ruile 2018	1/120	(1%)	13/634	(2%)	21.3%	0.41 [0.05, 3.08]
Tang 2018	1/26	(4%)	4/261	(2%)	3.7%	2.51 [0.29, 21.63]
Waksman 2021	1/27	(4%)	3/143	(2%)	4.9%	1.77 [0.19, 16.35]
Yanagisawa 2016	0/10	(0%)	0/60	(0%)	0.8%	5.55 [0.12, 265.08]
Yanagisawa 2019	0/45	(0%)	12/440	(3%)	12.1%	0.38 [0.02, 6.37]
Zhu 2021	0/62	(0%)	0/104	(0%)	1.9%	1.67 [0.03, 82.96]
Pooled Estimate	18/661	(3%)	65/3,770	(2%)	I^2: 15%	1.88 [1.16, 3.04]
Mantel-Haenszel Fixed Effects	*p=0.01, z=2.58*					*RR: Risk Ratio CI: Confidence Interval*

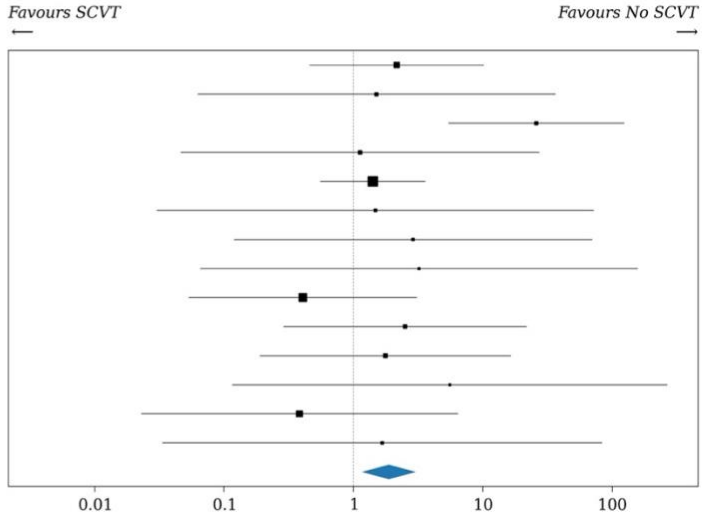


Figure 11: Association between subclinical valve thrombosis and death, SAVR

Study	SCVT	(%)	No SCVT	(%)	Weight	RR [95% CI]
Blanke 2020	2/23	(9%)	1/155	(1%)	51.4%	13.48 [1.27, 142.78]
Makkar 2020	0/7	(0%)	2/155	(1%)	48.6%	3.9 [0.2, 74.67]
Pooled Estimate	2/30	(7%)	3/310	(1%)	I^2: 0%	8.83 [1.49, 52.21]
Mantel-Haenszel Fixed Effects	*p=0.02, z=2.40*					*RR: Risk Ratio CI: Confidence Interval*

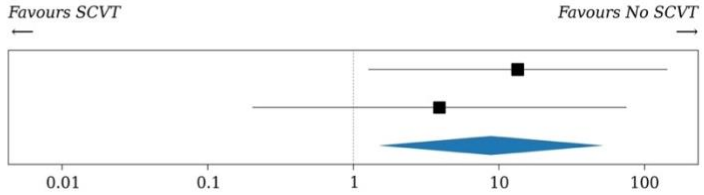


Figure 12: Association between subclinical valve thrombosis and stroke, SAVR

Study	SCVT	(%)	No SCVT	(%)	Weight	RR [95% CI]
Blanke 2020	1/23	(4%)	1/155	(1%)	84.1%	6.74 [0.44, 104.06]
Makkar 2020	0/7	(0%)	0/155	(0%)	15.9%	19.5 [0.41, 921.02]
Pooled Estimate	1/30	(3%)	1/310	(0%)	I^2: 0%	8.77 [0.96, 80.36]
Mantel-Haenszel Fixed Effects	*p=0.05, z=1.92*					*RR: Risk Ratio CI: Confidence Interval*

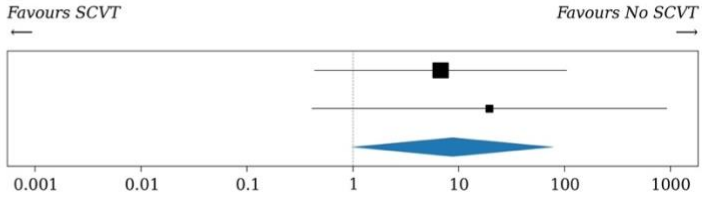


Figure 13: Association between subclinical valve thrombosis and mean transvalvular gradients, TAVR, 30-90 days

Study	SCVT	(N)	No SCVT	(N)	Weight	MD [95% CI]
De Backer 2019	11.0 ± 4.0	(44)	10.0 ± 5.0	(151)	23.6%	1.0 [-0.43, 2.43]
Garcia 2022	9.9 ± 4.8	(79)	9.3 ± 4.3	(558)	38.3%	0.6 [-0.52, 1.72]
Hansson 2016	10.0 ± 7.0	(28)	8.0 ± 3.0	(377)	7.1%	2.0 [-0.61, 4.61]
Makkar 2015	10.5 ± 4.3	(22)	9.0 ± 4.9	(33)	8.0%	1.5 [-0.95, 3.95]
Waksman 2021	15.1 ± 7.9	(27)	12.5 ± 4.5	(152)	5.2%	2.6 [-0.46, 5.66]
Zhu 2021	10.8 ± 4.8	(39)	11.3 ± 6.0	(312)	17.8%	-0.5 [-2.15, 1.15]
Pooled Estimate					I^2: 1%	0.77 [0.08, 1.47]

Inverse Variance, DerSimonian-Laird Random Effects — *p=0.03, z=2.18, τ²=0.01*

MD: Mean Difference CI: Confidence Interval

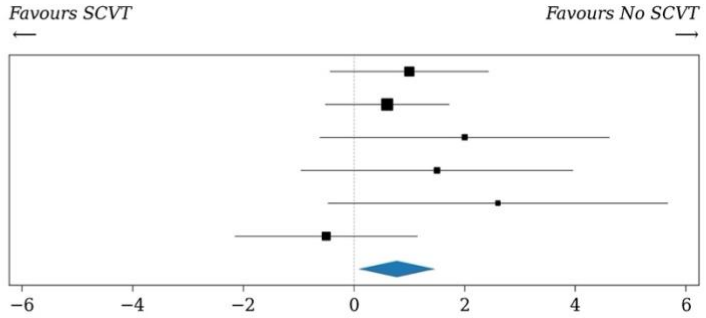


Figure 14: Association between subclinical valve thrombosis and mean transvalvular gradients, TAVR, 1 year

Study	SCVT	(N)	No SCVT	(N)	Weight	MD [95% CI]
Bak 2022	12.3 ± 5.8	(20)	9.6 ± 3.2	(74)	11.8%	2.7 [0.06, 5.34]
Hansson 2016	9.0 ± 4.0	(17)	8.0 ± 4.0	(229)	14.4%	1.0 [-0.97, 2.97]
Imaeda 2022	9.0 ± 3.7	(27)	10.0 ± 3.7	(90)	16.0%	-1.0 [-2.59, 0.59]
Jimenez 2019	10.8 ± 5.4	(24)	11.0 ± 5.8	(46)	11.4%	-0.2 [-2.93, 2.53]
Waksman 2021	13.4 ± 6.4	(26)	12.5 ± 5.0	(153)	12.0%	0.9 [-1.68, 3.48]
Yanagisawa 2016	8.3 ± 0.8	(10)	11.1 ± 4.9	(55)	16.8%	-2.8 [-4.19, -1.41]
Zhu 2021	11.5 ± 5.6	(149)	10.6 ± 5.1	(201)	17.7%	0.9 [-0.24, 2.04]
Pooled Estimate					I^2: 76%	0.08 [-1.34, 1.49]

Inverse Variance, DerSimonian-Laird Random Effects — *p=0.92, z=0.11, τ²=2.60*

MD: Mean Difference CI: Confidence Interval

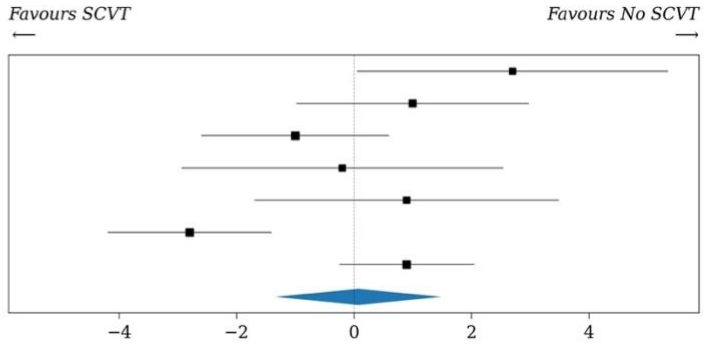


Figure 15: Association between subclinical valve thrombosis and valve effective orifice area, TAVR, 1 year

Study	SCVT	(N)	No SCVT	(N)	Weight	MD [95% CI]
Bak 2022	1.5 ± 0.4	(20)	1.8 ± 0.4	(74)	20.1%	-0.3 [-0.5, -0.1]
Hansson 2016	1.6 ± 0.6	(17)	1.6 ± 0.5	(229)	13.7%	0.0 [-0.29, 0.29]
Waksman 2021	1.7 ± 0.7	(26)	1.7 ± 0.5	(153)	14.4%	0.0 [-0.28, 0.28]
Yanagisawa 2016	1.18 ± 0.27	(10)	1.03 ± 0.25	(55)	21.5%	0.15 [-0.03, 0.33]
Zhu 2021	1.5 ± 0.3	(149)	1.6 ± 0.4	(201)	30.3%	-0.1 [-0.17, -0.03]
Pooled Estimate					I^2: 66%	-0.06 [-0.2, 0.08]

Inverse Variance, DerSimonian-Laird Random Effects — *p=0.42, z=0.81, τ²=0.02*

MD: Mean Difference CI: Confidence Interval

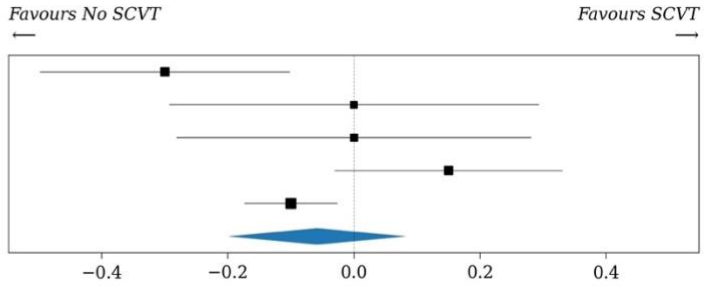


Figure 16: Association between oral anticoagulation and incidence of subclinical valve thrombosis, TAVR randomized data

Study	OAC	(%)	No OAC	(%)	Weight	RR [95% CI]
DOAC						
De Backer 2019 (GALILEO)	12/97	(12%)	33/102	(32%)	28.0%	0.38 [0.21, 0.7]
Montalescot 2022 (ATLANTIS)	25/275	(9%)	45/283	(16%)	47.6%	0.57 [0.36, 0.91]
Park 2022 (ADAPT-TAVR)	10/111	(9%)	20/118	(17%)	19.8%	0.53 [0.26, 1.08]
Subgroup Estimate	47/483	(10%)	98/503	(19%)	I^2: 0%	0.5 [0.36, 0.69]
VKA						
Rogers 2021 (Low Risk TAVR)	2/43	(5%)	8/49	(16%)	4.5%	0.28 [0.06, 1.27]
Subgroup Estimate	2/43	(5%)	8/49	(16%)	I^2: 0%	0.28 [0.06, 1.27]
Pooled Estimate					I^2: 0%	0.49 [0.36, 0.67]

Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect
p=0.00, z=4.43
τ^2=0.00
χ^2=0.52, p=0.47, I^2=0.0%
RR: Risk Ratio
CI: Confidence Interval

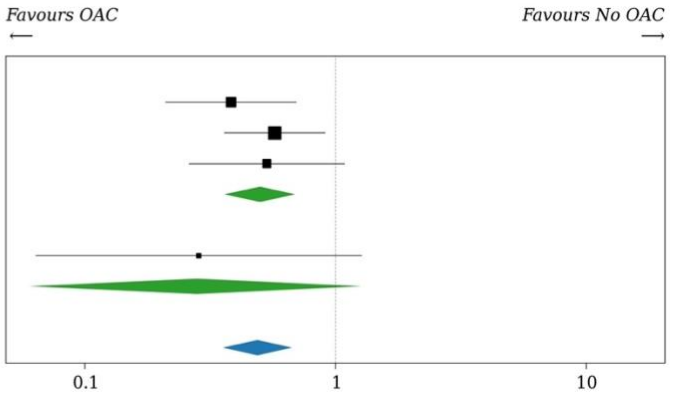


Figure 17: Association between oral anticoagulation and incidence of subclinical valve thrombosis, TAVR observational data

Study	OAC	(%)	No OAC	(%)	Weight	RR [95% CI]
Apor 2022	1/51	(2%)	11/66	(17%)	2.7%	0.12 [0.02, 0.88]
Bak 2022	0/15	(0%)	20/79	(25%)	1.6%	0.12 [0.01, 1.91]
Garcia 2022	12/190	(6%)	67/447	(15%)	10.2%	0.42 [0.23, 0.76]
Hansson 2016	3/176	(2%)	25/229	(11%)	5.7%	0.16 [0.05, 0.51]
Imaeda 2022	5/33	(15%)	22/91	(24%)	7.7%	0.63 [0.26, 1.52]
Jimenez 2019	1/33	(3%)	12/52	(23%)	2.7%	0.13 [0.02, 0.96]
Koo 2019	2/22	(9%)	23/116	(20%)	4.8%	0.46 [0.12, 1.81]
Leetmaa 2015	0/63	(0%)	5/77	(6%)	1.5%	0.11 [0.01, 1.97]
Marwan 2018	2/32	(6%)	16/46	(35%)	4.6%	0.18 [0.04, 0.73]
Makkar 2015	1/13	(8%)	21/41	(51%)	2.9%	0.15 [0.02, 1.01]
Nuhrenberg 2019	8/76	(11%)	28/124	(23%)	9.0%	0.47 [0.22, 0.97]
Ruile 2018	51/312	(16%)	69/442	(16%)	12.5%	1.05 [0.75, 1.46]
Tang 2018	9/104	(9%)	17/183	(9%)	8.6%	0.93 [0.43, 2.01]
Vollema 2017	3/38	(8%)	13/90	(14%)	5.6%	0.55 [0.17, 1.81]
Waksman 2021	3/39	(8%)	24/152	(16%)	5.9%	0.49 [0.15, 1.53]
Yanagisawa 2016	2/12	(17%)	8/58	(14%)	4.5%	1.21 [0.29, 5.0]
Yanagisawa 2019	9/115	(8%)	36/370	(10%)	9.3%	0.8 [0.4, 1.62]
Pooled Estimate	112/1,324	(8%)	417/2,663	(16%)	I^2: 54%	0.48 [0.33, 0.69]

Mantel-Haenszel, DerSimonian-Laird Random Effects
p=0.00, z=3.93
τ^2=0.25
RR: Risk Ratio
CI: Confidence Interval

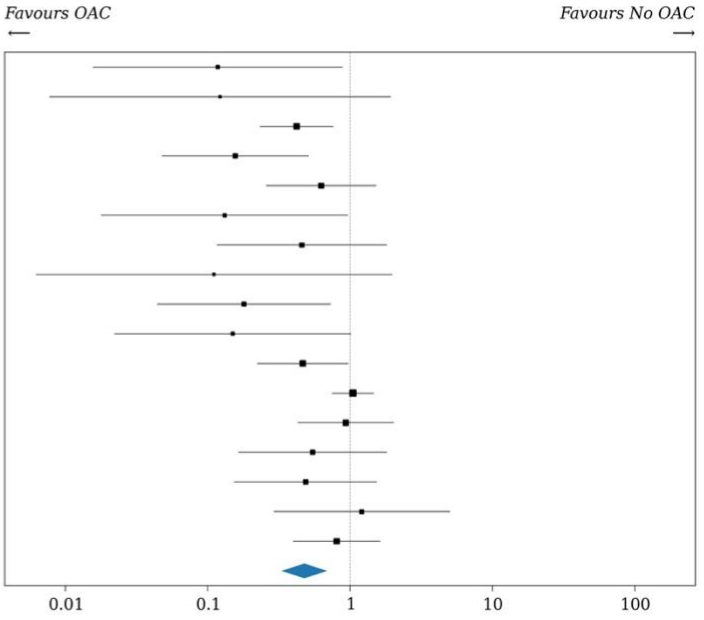
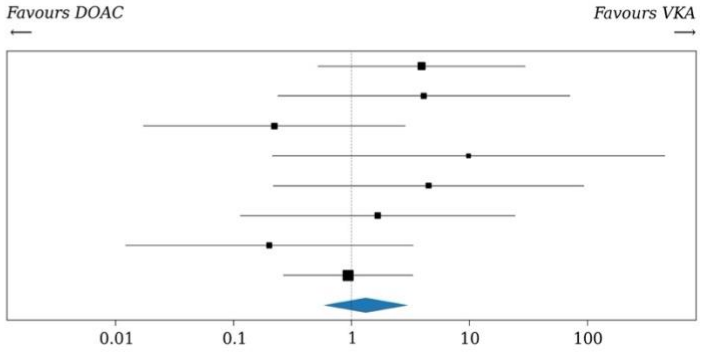


Figure 18: Association between DOAC versus VKA therapy and incidence of subclinical valve thrombosis, TAVR observational data

Study	DOAC	(%)	VKA	(%)	Weight	RR [95% CI]
Garcia 2022	11/140	(8%)	1/50	(2%)	15.7%	3.93 [0.52, 29.66]
Hansson 2016	0/5	(0%)	3/171	(2%)	8.2%	4.1 [0.24, 70.74]
Koo 2019	1/18	(6%)	1/4	(25%)	10.1%	0.22 [0.02, 2.85]
Leetmaa 2015	0/5	(0%)	0/58	(0%)	4.6%	9.83 [0.21, 452.48]
Makkar 2015	1/5	(20%)	0/8	(0%)	7.2%	4.5 [0.22, 93.08]
Marwan 2018	1/12	(8%)	1/20	(5%)	9.2%	1.67 [0.11, 24.26]
Tang 2018	0/21	(0%)	9/83	(11%)	8.4%	0.2 [0.01, 3.32]
Yanagisawa 2019	4/53	(8%)	5/62	(8%)	36.6%	0.94 [0.26, 3.31]
Pooled Estimate	18/259	(7%)	20/456	(4%)	I^2: 5%	1.32 [0.58, 3.03]

Mantel-Haenszel, DerSimonian-Laird Random Effects; *p=0.51, z=0.66, τ²=0.07*; *RR: Risk Ratio, CI: Confidence Interval*



Contributions

RE: Responsible for study design, systematic review of the literature, data extraction, data analysis, writing the first draft of the manuscript, and providing critical revisions to the manuscript.

TA, AE, AI, PM, AMI, RM, AS, and BT: Contributed significantly to systematic review of the literature, data extraction, and provided critical revisions to the manuscript.

RL, OS, SS, and TS: Contributed significantly to study design and provided critical revisions to the manuscript.

EBC and RW: Contributed significantly to study design and data analysis, and provided critical revisions to the manuscript.

Chapter 6: Subclinical Valve Thrombosis in Patients with Surgical Bioprosthetic Aortic Valve Replacement (SUNDANCE): the design and rationale of a feasibility trial

Subclinical Valve Thrombosis in Patients with Surgical Bioprosthetic Aortic Valve Replacement (SUNDANCE): the design and rationale of a feasibility trial

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Abstract

Background: Subclinical valve thrombosis is common after bioprosthetic aortic valve replacement, but its clinical implications and the role of anticoagulation in prevention and treatment remain uncertain.

Methods: The Subclinical Valve Thrombosis in Patients with Surgical Bioprosthetic Aortic Valve Replacement (SUNDANCE) vanguard is a 60-patient trial that examines the feasibility a full SUNDANCE randomized controlled trial of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) in patients with a recent bioprosthetic aortic valve replacement (AVR) and atrial fibrillation requiring anticoagulation. Feasibility objectives are: 1) ability to recruit ≥ 50% of 120 consecutive bioprosthetic AVR patients enrolled in the DANCE trial; 2) completion of 60-90-day cardiac gated computed tomography (CT) scans and echocardiograms in ≥ 90% of patients enrolled in the SUNDANCE vanguard; and 3) achievement of at least “good” quality in ≥ 90% of completed CT scans. Only CT scans of at least “good” quality can reliably diagnose subclinical valve thrombosis.

Discussion: If feasible, the SUNDANCE trial will provide urgently needed data on the incidence of subclinical valve thrombosis in patients with surgical bioprosthetic AVR, the clinical implications of subclinical valve thrombosis over the short term, and the impact of DOAC compared to VKA therapy.

Trial registration: The trial is registered at ClinicalTrials.gov (NCT04284839).

Keywords: subclinical valve thrombosis, bioprosthetic aortic valve replacement, anticoagulation, direct oral anticoagulants, vitamin K antagonist, feasibility trial, randomized controlled trial

Introduction

Aortic stenosis is the most common valvular disease, and aortic valve replacement is the only life-saving treatment for severe aortic stenosis. Among patients who undergo surgical aortic valve replacement, bioprosthetic valves are often preferred over mechanical valves because they do not require lifelong anticoagulation. However, bioprosthetic valves are prone to structural valve deterioration, and the choice between bioprosthetic and mechanical valves requires balancing valve durability against avoidance of anticoagulation.

In patients with bioprosthetic aortic valve replacement (AVR), clinical valve thrombosis is rare, but subclinical valve thrombosis occurs in 5-15% at 30 days and 20-28% at 1 year.[1-4] Untreated subclinical valve thrombosis can progress to clinical valve thrombosis and thromboembolism, including stroke.[5] Further, subclinical thrombosis formation on valve leaflets is hypothesized to trigger inflammation, leading to leaflet calcification and degradation, which may cause structural valve deterioration necessitating repeat valve replacement.[6,7] Clinical data are lacking regarding the relationship between subclinical valve thrombosis and structural valve deterioration.

Patients with a bioprosthetic AVR who are anticoagulated with either a direct oral anticoagulant (DOAC) or vitamin K antagonist (VKA) have a lower incidence of subclinical valve thrombosis than those not anticoagulated.[3,4,8,9] However, it remains unclear whether DOACs and VKAs are equally effective at preventing subclinical valve thrombosis. Given concerns about the effectiveness of DOACs in patients with mechanical valves,[10,11] transcatheter aortic valve replacement,[12,13] and rheumatic heart

disease,[14] DOACs warrant thorough investigation before they are used routinely in patients early after surgical bioprosthetic AVR.

The Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) trial is an ongoing multicentre randomized controlled trial comparing DOACs to VKAs after cardiac surgery in patients with atrial fibrillation (AF). The aim of the DANCE trial is to establish the non-inferiority of DOACs compared to VKAs with regard to major bleeding after cardiac surgery. One-third of patients in the DANCE trial undergo bioprosthetic AVR.

We designed the Subclinical Valve Thrombosis in Patients with Surgical Bioprosthetic Aortic Valve Replacement (SUNDANCE) trial as an imaging substudy of the DANCE trial. We will conduct cardiac gated computed tomography (CT) scans and transthoracic echocardiograms in consenting DANCE participants to examine the incidence and clinical implications of subclinical valve thrombosis in patients taking DOACs versus VKAs. In this paper, we describe the design and rationale for the SUNDANCE vanguard trial, which will examine the feasibility of a full SUNDANCE trial.

Methods and Analysis

Trial objectives

The SUNDANCE vanguard trial has three feasibility objectives:

1. Recruitment of ≥ 50% of 120 consecutive bioprosthetic AVR patients enrolled in the DANCE trial at centres participating in SUNDANCE;
2. Completion of 60-90-day CT scans and echocardiograms in ≥ 90% of patients enrolled in the SUNDANCE vanguard trial;
3. Achievement of at least “good” quality in ≥ 90% of completed CT scans.

We will consider the full SUNDANCE trial feasible if all three vanguard objectives are met. If an objective is not met, we will assess whether protocol modifications are likely to improve feasibility and implement these changes before proceeding with the full SUNDANCE trial.

Trial design

The SUNDANCE vanguard trial (ClinicalTrials.gov Identifier: NCT04284839) is a substudy of DANCE, which is a randomized, prospective, open-label, blinded endpoint multicentre clinical trial. DANCE will randomize 6,215 patients with open heart surgery within the last 10 days and AF requiring anticoagulation to DOAC or VKA for 90 days. The SUNDANCE vanguard trial will enrol 60 consenting DANCE participants with a new surgical bioprosthetic AVR over 2 years at 3 centres. We perform a cardiac gated CT scan and transthoracic echocardiogram at 60-90 days after randomization to assess for subclinical valve thrombosis. If the SUNDANCE vanguard trial meets its feasibility objectives, then we will proceed with the definitive SUNDANCE trial of 910 patients nested within the DANCE trial.

Trial population

We include patients ≥18 years of age who have undergone surgical bioprosthetic AVR in the last 10 days and have AF requiring anticoagulation. In addition to the DANCE exclusion criteria (listed in Table 1), we also exclude patients with a known contrast dye allergy or another condition that increases the risk of CT imaging, or who had a pulmonary autograft (Ross procedure) or Ozaki procedure.

Randomization

According to the DANCE trial protocol, patients are randomized in a 1:1 ratio to DOAC or VKA once they are deemed eligible for DANCE and SUNDANCE and provide informed consent. Randomization is stratified by centre, whether their indication for oral anticoagulation existed preoperatively (i.e., history of AF) or is new after surgery (i.e., post-operative AF), and SUNDANCE enrolment. Stratification by SUNDANCE enrolment ensures that baseline characteristics of SUNDANCE participants are balanced between the DOAC and VKA arms. Randomization occurs in randomly permuted blocks of various sizes via a 24-hour interactive web-based system maintained by the Population Health Research Institute, McMaster University, Hamilton, Canada.

Intervention

Patients in the intervention group receive a DOAC at doses recommended for AF. The choice of DOAC is at the discretion of the treating physician. Treatment in the DOAC group begins no earlier than postoperative day 5 or discharge, whichever occurs first. Patients in the control group receive a VKA titrated to achieve a guideline-recommended INR range.

Follow-up

SUNDANCE vanguard participants undergo follow-up according to the DANCE trial schedule of visits, which consist of follow-up at hospital discharge, as well as at 30 days, 90 days, and 6 months post-randomization by clinic visit or telephone (Figure 1). In addition, SUNDANCE vanguard participants undergo a CT scan and echocardiogram at 60-90 days post-randomization. The CT scan and echocardiogram ideally take place

on the same day for patient convenience, but they must occur within one week of each other to facilitate correlation of findings between the two imaging modalities.

Trial outcomes

The primary outcome of the SUNDANCE vanguard trial is feasibility according to the following criteria:

1. Proportion of the first 120 consecutive bioprosthetic AVR patients enrolled in the DANCE trial recruited at SUNDANCE participating centres, as justified below through our sample size calculations for the definitive SUNDANCE trial.
2. Proportion of SUNDANCE participants who undergo 60-90-day cardiac CT scan and transthoracic echocardiograms.
3. Proportion of completed CT scans that achieve at least “good” quality in ≥ 90% of completed CT scans. Only CT scans of at least “good” quality can reliably diagnose subclinical valve thrombosis.[15] Good quality CT scans demonstrate hypoattenuated leaflet thickening (HALT) on two-dimensional multiplanar reconstruction in any plane, or absence of HALT on a two-dimensional multiplanar reconstruction in diastole. They also demonstrate leaflet motion through all or most of systole. Appendix A comprehensively describes CT scan technical quality for the assessment of subclinical valve thrombosis, and Appendix B contains the SUNDANCE CT protocol.

We also collect the clinical outcomes of the planned definitive SUNDANCE trial. The primary outcome is subclinical valve thrombosis on CT scan performed at 60-90 days post randomization. Subclinical valve thrombosis is defined as any HALT, with or without reduced leaflet motion. The secondary outcomes of the SUNDANCE trial are:

1. Mean aortic valve gradient on echocardiography.
2. Clinically significant aortic valve thrombosis, stroke, or systemic embolism at 90 days.

Appendix C includes all outcome definitions.

Sample size

In its current design, the definitive SUNDANCE trial has a target sample size of 910, which will provide 80% power to demonstrate non-inferiority of DOACs compared to VKAs in the prevention of subclinical valve thrombosis, with a one-sided 97.5% confidence interval, a non-inferiority margin of 2%, and a control event rate of 6%. The estimated control rate is based on our systematic review of subclinical valve thrombosis. Unless the protocol changes meaningfully based on experience gained in the vanguard phase, SUNDANCE vanguard participants will be rolled in the main SUNDANCE trial.

The DANCE trial will enroll 6215 participants; we anticipate that about one third (or 1800 participants) will have had a bioprosthetic AVR. To reach its target sample size of 910, the SUNDANCE trial must recruit around 50% of DANCE participants with a bioprosthetic AVR. We estimate that each centre participating in the SUNDANCE vanguard trial will recruit around 120 DANCE patients per year, 40 of whom will be eligible for SUNDANCE. Therefore, we planned the SUNDANCE vanguard trial to recruit 50% of eligible SUNDANCE patients over 12 months (around 20 patients per site), at 3 sites, leading to a target sample size of convenience of 60 patients.

Statistical analysis

The SUNDANCE vanguard trial feasibility objectives will be analyzed using descriptive statistics and 95% confidence intervals. We will develop a detailed statistical

analysis plan for the definitive SUNDANCE trial, which will be written before the termination of the trial.

Trial organization

The Population Health Research Institute is the coordinating centre for the SUNDANCE vanguard and the DANCE trial. The institute is responsible for organizing the trials, developing the randomization scheme and study database, analysing the data, and coordinating the study centres. The trial steering committee consists of experts in research methods, perioperative medicine, cardiology, cardiac surgery, and thrombosis.

Funding and responsibilities

The SUNDANCE vanguard is funded by grants from Hamilton Health Sciences, the Physicians' Services Incorporated Foundation, and the Canadian Cardiovascular Society. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Discussion

Since first reported in 2015, subclinical valve thrombosis has been a major focus of TAVR literature but has received much less attention in patients with surgical bioprosthetic AVR. In our unpublished systematic review and meta-analysis of subclinical valve thrombosis, we identified 27 studies involving 6091 TAVR patients, compared to only 6 studies involving 786 surgical bioprosthetic AVR patients. The paucity of data in surgical patients highlights the urgent need for additional studies of subclinical valve thrombosis in this population.

In this systematic review, we found that the incidence of subclinical valve thrombosis is similar in surgical bioprosthetic AVR (9% at 30-90 days and 24% at one year) compared with TAVR (12% at 90 days and 26% at one year). These data suggest that among the 100,000 patients undergoing surgical bioprosthetic aortic valve replacement each year in North America,[15] about 10,000 patients have of subclinical valve thrombosis at 3 months and 24,000 at one year. Furthermore, the best available evidence suggests that subclinical valve thrombosis is not benign. A recent systematic review of 3456 TAVR patients reported 28 strokes in 370 patients with subclinical valve thrombosis (7.0%) and 84 strokes in 3052 patients without (2.7%),which translates into a three-fold increase in risk of stroke.[5] If the proportions are similar in patients with surgical bioprosthetic AVR, then subclinical valve thrombosis could lead to an excess of 400-600 strokes per year, assuming a conservative baseline risk of stroke at 30 days of 2-3%.[16,17]

The TAVR literature suggests that anticoagulation with a VKA both prevents and treats subclinical valve thrombosis. TAVR patients who are anticoagulated with a VKAs have a lower incidence of subclinical valve thrombosis than those not anticoagulated,[8,9,12,13] while subclinical valve thrombosis resolves with initiation of VKA therapy.[1,2] The relative effectiveness of VKAs versus DOACs in bioprosthetic aortic valves, however, remains uncertain with respect to both clinical outcomes and subclinical valve thrombosis.

In patients with mechanical valves, DOACs are less effective than warfarin with respect to thrombosis prevention. Both the RE-ALIGN trial[10] (which randomized patients with mechanical valves to dabigatran or warfarin) and the PROACT Xa trial (which

randomized patients with mechanical aortic valves to apixaban or warfarin)[11] were stopped early due to increased incidence of clinical valve thrombosis and stroke in patients taking DOACs. In TAVR patients who do not have an indication for oral anticoagulation, two randomized trials (GALILEO[13], which compared half-dose rivaroxaban to dual antiplatelet therapy, and ATLANTIS stratum 2[12], which compared apixaban to antiplatelet therapy) have demonstrated increased mortality in patients taking DOACs compared to antiplatelet therapy alone.

Only two randomized studies with a combined total of 407 patients compare DOACs to VKAs in patients with a surgical bioprosthetic AVR. Over a median follow-up of 12 months, thromboembolic events occurred in 2 of 203 patients taking DOACs (1%) compared to 5 events in 204 patients taking VKAs (2%; relative risk 0.46, 95% confidence interval 0.1 to 2.05). Similarly, bleeding occurred in 4 of 203 patients taking DOACs (2%) compared to 6 of 204 patient staking VKAs (3%, relative risk 0.76, 95% confidence interval, 0.05 to 10.72). Neither study evaluated subclinical valve thrombosis.[19] Trials are urgently needed in the surgical population to establish the relative efficacy and safety of DOACs versus VKAs, regarding both clinical events and subclinical valve thrombosis.

The strengths of the SUNDANCE trial are multiple. It is a pragmatic trial that uses the infrastructure of an existing randomized controlled trial to answer an important clinical question. With a planned sample size of 910, SUNDANCE will more than double the available randomized data on DOACs versus VKAs in patients with surgical bioprosthetic AVR, and it will provide the first randomized data on the effect of DOACs versus VKAs on subclinical valve thrombosis in that population.

SUNDANCE also has some limitations. Like DANCE, it is designed to study patients who have an indication for oral anticoagulation and will not address the question of whether anticoagulation should be used in patients with surgical bioprosthetic AVR who do not have another indication for anticoagulation. This important question would be best addressed in a separate trial comparing anticoagulation to antiplatelet therapy for prevention of subclinical valve thrombosis in patients after surgical AVR without an indication for anticoagulation. The data provided by the SUNDANCE vanguard trial and subsequent definitive trial on the incidence of subclinical valve thrombosis and its clinical implications in a surgical population will be instrumental in the design and rationale of such a trial.

Conclusion

The SUNDANCE vanguard trial will examine subclinical valve thrombosis and the impact of DOAC versus VKA therapy in a subset of 60 patients enrolled in the DANCE trial. The main SUNDANCE trial will provide urgently needed data on the incidence of subclinical valve thrombosis in patients with surgical bioprosthetic AVR, the clinical implications of subclinical valve thrombosis over the short term, and the impact of DOAC compared to VKA therapy.

Declarations:

Ethics approval and consent to participate: The SUNDANCE trial has obtained ethics approval from the Research Ethics Boards of Hamilton General Hospital, Hamilton, Ontario and St. Boniface Hospital, Winnipeg, Manitoba. All participants will provide informed consent.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

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Authors' contributions: All authors contributed to the design of the SUNDANCE trial and read and approved the final manuscript.

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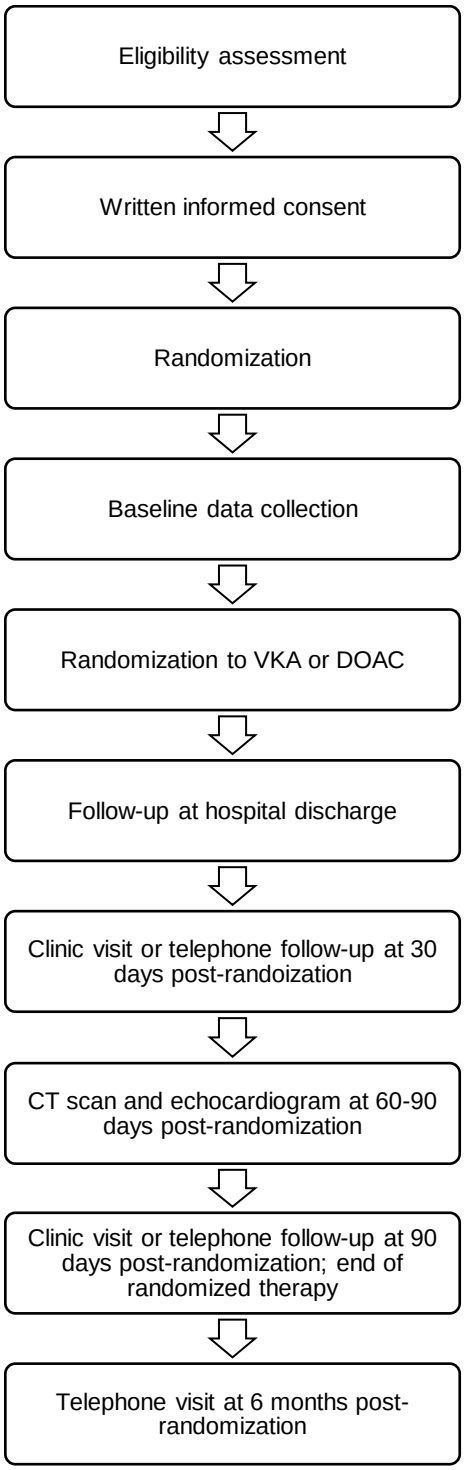
Tables

Table 1: SUNDANCE eligibility criteria

	Inclusion criteria	Exclusion criteria
DANCE	1. Age ≥18 years at the time of enrolment, 2. Open heart surgery in the last 10 days, 3. Atrial fibrillation requiring anticoagulation (including pre-existing or post-operative atrial fibrillation) 4. Informed consent from either the patient or a substitute decision-maker.	1. Mechanical valve replacement, 2. Antiphospholipid syndrome (triple positive), 3. Severe renal failure (Cockcroft-Gault equation; creatinine clearance <15 ml/min), 4. Known significant liver disease (Child-Pugh classification B and C), 5. Ongoing bleeding, hemorrhagic disorders, or bleeding diathesis, 6. Known contraindication for any direct oral anticoagulant or vitamin K antagonist, 7. Women who are pregnant, breastfeeding, or of childbearing potential, 8. Left ventricular thrombus, 9. Surgery including left ventricular assist device implantation or cardiac transplantation, 10. Uncorrected rheumatic moderate or severe valve disease, 11. Previously enrolled in this trial, 12. Follow-up not possible.
Additional criteria for SUNDANCE	1. Bioprosthetic aortic valve replacement during index procedure	1. Known contrast dye allergy, 2. Another condition that prohibits CT imaging, 3. Ross procedure, 4. Ozaki procedure.

Figures

Figure 1: SUNDANCE study overview



CT: computed tomography; DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

Appendices

Appendix A: CT Technical Quality in the Assessment of Subclinical Valve Thrombosis

Adapted from Jilaihawi et al, Systematic CT Methodology for the Evaluation of Subclinical Leaflet Thrombosis, *JACC Cardiovascular Imaging*, Apr 2017;10(4):461-470. doi:10.1016/j.jcmg.2017.02.005.

Quality	Evaluation for HALT	Evaluation for RLM
Extremely poor	HALT not clearly seen with considerable artifact (HALT inconclusive)	RLM inconclusive
Poor	HALT not clearly seen with no significant artifact, but leaflet coaptation cannot be seen on a 2D MPR diastolic phase, or considerable scan artifact precludes definitive assessment (HALT inconclusive)	RLM inconclusive
Borderline	HALT clearly seen on cross-sectional 2D MPR in any phase, OR no HALT and leaflet coaptation can be seen on a 2D MPR diastolic phase	Leaflet motion seen, but not clear through systolic phases (RLM inconclusive)
Good	As above	Leaflet motion seen, clear through all or most systolic phases but not clear through all phase
Very good	As above	Leaflet motion seen clearly through all phases
Excellent	As above	Leaflet motion seen very clearly through all phases

2D: two-dimensional; 4D: four-dimensional; CT: computed tomography; HALT: hypoattenuated leaflet thickening; MPR: multiplanar reconstruction; RLM: reduced leaflet motion

Appendix B: CT acquisition protocol

A. PRIOR TO THE CT

If the patient's HR is >70 bpm, they may be treated with a beta blocker (according to local practice, assuming there are no contraindications).

- Contraindications to beta-blockers include active asthma or obstructive pulmonary disease resulting in bronchospasm, and systolic blood pressure <100 mmHg.

B. CT ACQUISITION

1. Electrocardiographically synchronized
2. Heart rate <70 beats per minute with oral or intravenous beta-blockade if necessary
3. Retrospectively gated without dose modulation
4. Acquisition set to minimum slice thickness on scanner (0.5-0.625mm)
5. Contrast enhanced: minimum of 50mL, ideally 100mL
6. 120 kV
7. Coverage of heart only (do not require great vessels or peripheral vessels)
8. Reconstruction in increments of 10% or less

C. CT ANALYSIS

CT image analysis and interpretation will be conducted centrally at the PHRI. There will be no clinical report generated by the readers, but a copy of the case report form completed by the readers will be transmitted to each site investigator. Any serious abnormalities and findings that may be discovered incidentally by the readers at the PHRI will be reported to the SUNDANCE Project Office, who will then notify the site investigator who will be responsible for relaying the information to the appropriate parties.

Appendix C: Outcome definitions

Subclinical Valve Thrombosis

All hypoattenuated leaflet thickening (HALT), with or without restricted leaflet motion (RLM).

HALT: visually identified increase in leaflet thickness with typical meniscus appearance when viewed on long-axis.

- Quantify extent along the curvilinear leaflet: none, <25%, 25-50%, 50-75%, >75%

If HALT is present, then proceed to assess for RLM: incomplete leaflet opening in systole.

- Quantify severity: none, <25%, 25-50%, 50-75%, >75

HALT and RLM are assessed separately for each leaflet. Patient severity of subclinical valve thrombosis is equal to the severity of the most affected leaflet.[12]

Clinically Significant Aortic Valve Thrombosis (VARC-2 definition):

Any thrombus related to the valve that affects the function of the valve or partly occludes blood flow or require medical or surgical intervention.

Stroke

Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. Stroke will be sub- classified into hemorrhagic and non-hemorrhagic stroke. Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage.

1. Ischemic stroke: focal brain infarction caused by an arterial (or rarely venous) obstruction and as documented by CT/MRI that is normal or shows an infarct in the clinically expected area.
2. Secondary hemorrhagic transformation of ischemic stroke: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic.
    1. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.
    2. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation.
3. Undetermined stroke: definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence

whether the stroke was ischemic vs. hemorrhagic, even after review of CT/MRI images (e.g., primary 4. Hemorrhagic stroke: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage. A. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not.
Systemic Thromboembolism
Systemic thromboembolism is defined as abrupt vascular insufficiency associated with evidence of arterial occlusion in the absence of other likely mechanisms. Clinical signs and symptoms must be consistent with embolic arterial occlusion, there must be clear evidence of abrupt occlusion of a systemic artery, with at least one type of supporting evidence, such as surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy report.
Aortic Valve Reintervention
Any surgical or transcatheter intervention on the bioprosthetic aortic valve.
Death
All deaths will be classified as either cardiovascular or non-cardiovascular. Cardiovascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy). Any death within 30 days of index cardiac surgery are considered cardiovascular.

Contributions:

RE: Originated the idea for this study, responsible for study design, application for grants to fund the study, writing the first draft of the manuscript, and providing critical revisions to the manuscript.

JS: contributed significantly to the study design, responsible for trial running including ethics applications, and provided critical revisions to the manuscript.

RW, IJ, RL, OS, SS, TS, DS, and EBC: contributed significantly to the study design and provided critical revisions to the manuscript.

Chapter 7: Conclusion and Future Directions

Each year, more than 100,000 North Americans with severe symptomatic aortic stenosis must decide, along with their cardiologist and cardiac surgeon, whether to undergo mechanical or bioprosthetic aortic valve replacement (AVR), and if bioprosthetic, then by a surgical or transcatheter approach. Each type of aortic valve prosthesis has both benefits and drawbacks, and the balance between benefits and drawbacks may differ for individual patients depending on factors such as life expectancy, frailty, anatomy, need for concomitant procedures, and impact of oral anticoagulation. Mechanical valves have the advantage of durability, but they require lifelong oral anticoagulation to prevent valve thrombosis and thromboembolism. Bioprosthetic valves avoid the need for lifelong anticoagulation, but they have limited durability. Transcatheter valves are ideal for many patients who cannot tolerate surgical replacement or who do not require concomitant cardiac procedures, but the patient must have anatomy that allows for transcatheter implantation.

The ideal aortic valve replacement would be durable without requiring lifelong anticoagulation. For bioprosthetic aortic valves, the connection between valve durability and valve thrombosis may be stronger than previously recognized. The causes of bioprosthetic valve failure, while incompletely understood, have been described in four main categories: 1) thrombosis, 2) fibrous pannus ingrowth, 3) valve degeneration, and 4) endocarditis. Thrombosis is often present in fibrous pannus ingrowth and valve degeneration, and it is hypothesized to be a contributing factor to all forms of valve dysfunction.[1] Therefore, prevention of bioprosthetic valve thrombosis may improve bioprosthetic valve durability.[2] If bioprosthetic valve durability can be improved with antithrombotic therapy of shorter duration or lesser intensity than is required for patients

with mechanical valves, then bioprosthetic valves are one step closer to being an ideal valve prosthesis.

Summary of Findings

This doctoral thesis explored optimal antithrombotic therapy in patients with bioprosthetic AVR, with a particular focus on surgical valves. It began by examining the evolution of guideline recommendations for antithrombotic therapy after surgical bioprosthetic AVR, finding that the evidence upon which they are based is low quality and inconclusive (Chapter 2). As a result, guideline recommendations are inconsistent and prescribing practices vary greatly (Chapter 3). Next, this thesis systematically reviewed the randomized literature regarding antithrombotic therapy after transcatheter aortic valve replacement (TAVR; Chapter 4). Patients were separately analyzed according to presence of another indication for anticoagulation. In patients without another indication for anticoagulation, DOACs were associated with increased risk of death and bleeding compared to antiplatelet therapy. While DOACs reduced risk of subclinical valve thrombosis, they did not appear to reduce clinical valve thrombosis or thromboembolism. In patients with another indication for oral anticoagulation, DOACs and VKAs appeared similar with respect to death, bleeding, and thrombosis.

The thesis also systematically reviewed randomized and observational literature on subclinical valve thrombosis in transcatheter and surgical bioprosthetic AVR (Chapter 5). Subclinical valve thrombosis has been thought to affect transcatheter valves more than surgical valves,[3,4] but this systematic review demonstrates similar incidence at both 30 days and 1 year. Furthermore, in TAVR patients, subclinical valve thrombosis is associated with a two-fold increase in risk of stroke. Insufficient data are available to say

whether a similar association exists in patients with surgical bioprosthetic AVR. The thesis concludes with the design and rationale of a feasibility trial randomizing patients with a surgical bioprosthetic AVR and atrial fibrillation requiring anticoagulation to DOACs or VKAs, examining the impact on subclinical valve thrombosis and clinical outcomes (Chapter 6).

Studying antithrombotic therapy after bioprosthetic AVR: two populations

1. *Patients without another indication for oral anticoagulation*

To answer the question of optimal antithrombotic therapy after surgical bioprosthetic AVR, the first step must be to divide the population into two distinct categories: those who do not have an additional indication for anticoagulation, and those who do. For those without an additional indication for anticoagulation, the question is whether anticoagulation, compared to antiplatelet therapy only, can reduce clinical thrombotic and thromboembolic events as well as subclinical valve thrombosis, without an unacceptable increase in bleeding risk.

If performing an adequately powered randomized controlled trial of anticoagulation versus antiplatelet therapy after surgical bioprosthetic AVR were straightforward, undoubtedly one would already exist. One key challenge of conducting such a study is that the outcomes that antithrombotic therapy are intended to prevent – symptomatic valve obstruction, stroke, and systemic embolism – occur infrequently, so that a very large sample size would be required for such a trial to be adequately powered. Despite this challenge, however, randomized data are urgently required because thromboembolic valve complications are devastating when they do occur. Observational data have not provided a clear answer: instead, they present conflicting

results on the association between anticoagulation versus antiplatelet therapy and thrombotic and thromboembolic outcomes, likely due to residual confounding.[5-8]

The TAVR literature is instructive. Although TAVR has been available on the market for just over a decade, the randomized literature on antithrombotic therapy after TAVR already includes for three trials with over 1000 participants each (ATLANTIS, n=1500;[9] ENVISAGE-TAVI AF,[10] n=1426; and GALILEO, n=1644[11]), as well as multiple notable smaller trials.[12-14] One key finding from the TAVR literature is that DOACs are associated with increased risk of death compared to antiplatelet therapy.[9,11] This unexpected finding, which is not fully explained by the increased risk of bleeding with DOACs versus antiplatelet therapy, underlines the importance of randomized trials both to test hypotheses and to reveal unanticipated treatment effects. Only a randomized trial of anticoagulation versus antiplatelet therapy in surgical bioprosthetic AVR will clarify the optimal treatment for this population without another indication for oral anticoagulation.

2. *Patients with another indication for oral anticoagulation*

For patients with surgical bioprosthetic AVR who require anticoagulation for other reasons, the first important question is the relative efficacy and safety of DOACs compared to VKAs. DOACs have multiple potential advantages over VKAs, including reduced risk of bleeding (including intracranial bleeding) in patients with atrial fibrillation,[15] and improved convenience due to fewer drug-drug and drug-food interactions, and elimination of the need for monitoring bloodwork. However, the safety of DOACs compared to VKAs in patients with prosthetic valves or valvular disease is uncertain due to randomized data demonstrating increased mortality with DOACs in patients with rheumatic heart disease,[16] as well as increased bleeding and thrombosis

in patients with mechanical valves.[17] These findings cannot be extrapolated directly to patients with surgical bioprosthetic AVR, but the unexpected nature of these findings once again demonstrates the importance and need for high-quality randomized data.

The central importance of subclinical valve thrombosis

Another important lesson from this doctoral thesis pertains to subclinical valve thrombosis. In patients with TAVR, subclinical valve thrombosis appears to be associated with a two-fold increase in risk of stroke over 1 year according to the systematic review contained in this thesis. Data are lacking in patients with surgical bioprosthetic aortic valves, but surgical valves are composed of similar materials to TAVR valves, and if the relationship between subclinical valve thrombosis and stroke is similar in surgical valves, this would indicate a very large problem. Most large, randomized trials of antithrombotic therapy in TAVR have included a substudy examining the impact of randomized therapy on subclinical valve thrombosis;[12,18,19] trials in surgical bioprosthetic AVR should do the same.

Studying subclinical valve thrombosis is challenging. The presence of thrombus on valve leaflets causing restricted leaflet movement is of interest to clinicians, but one could argue that it is not a patient-important outcome because it is, at the time of diagnosis, without clinical implications. Surgical bioprosthetic AVR has been performed since the early 1960s,[20,21] but the first time that subclinical valve thrombosis was identified was more than 50 years later, in 2015, as an incidental finding on CT scan.[22] This is not to say, however, that subclinical valve thrombosis should be ignored. Quite the opposite: we urgently need for clearer evidence on whether subclinical valve thrombosis has direct clinical sequelae like symptomatic valve thrombosis, stroke,

thromboembolism, or accelerated valve failure in surgical bioprosthetic AVR. Establishing this evidence will be immensely challenging because, without the ability to randomize patients to presence or absence of subclinical valve thrombosis, we cannot establish balance of prognostic factors at baseline and the data will therefore be subject to confounding.

The SUNDANCE vanguard and, we hope, the full SUNDANCE trial will provide much needed information on the incidence of subclinical valve thrombosis in a surgical population, as well as the impact of randomized therapy on both subclinical valve thrombosis and clinical outcomes. While it may not provide definitive evidence regarding the relationship between subclinical valve thrombosis and clinical outcomes, it will significantly advance knowledge in this field and provide opportunities for thoughtful consideration and design of future studies.

Future Directions

The unanswered question of optimal antithrombotic therapy after surgical bioprosthetic AVR provides an opportunity to conduct high impact, clinically relevant research. I have described the design and rationale for a randomized trial comparing DOACs to VKAs in surgical bioprosthetic AVR who have another indication for oral anticoagulation, and I have outlined the need for a parallel trial comparing anticoagulation to antiplatelet therapy in patients without another indication for oral anticoagulation. Both trials should examine subclinical valve thrombosis carefully, thus laying a foundation for future work that clarifies its role in clinical thromboembolic events and valve durability over long-term follow-up.

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