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.

Conclusion   Insufficient antithrombotic therapy after bioprosthetic aortic valve replacement has serious implications: ischemic stroke, systemic arterial thromboembolism, and clinical and subclinical valve thromboses. 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 replacements
► bioprosthetic valves
► valve thrombosis

Introduction

Valvular heart disease affects more than 100 million people worldwide. In North America, more than 100,000 patients receive mechanical or bioprosthetic aortic valve replace-ments (AVRs) annually.[1] Mechanical valves are typically preferred in younger patients because they are more durable than bioprosthetic valves, but they require lifelong antico-agulation with a vitamin K antagonist (VKA). Bioprosthetic

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 50–100 mg for 3 months is recommended over warfarin (Class 2c) • Aspirin 50–100 mg indefinitely is recommended over no aspirin (Class 2c) • No recommendation for anticoagulation	• Aspirin 75–100 mg indefinitely (Class 2a, LOE B) OR anticoagulation with VKA (INR 2.5) for 3–6 months if low risk of bleeding, followed by aspirin 75–100 mg indefinitely (Class 2a, LOE B-NR)	• Aspirin 75–100 mg 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

Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; ASA, aspirin; BAVR, bioprosthetic aortic valve replacement; 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.

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 AVR (TAVR) provides a low-risk alternative to redo sternotomy and bioprosthetic AVR (BAVR) when the initial valve deteriorates.[2] More than 90% of AVRs are bioprosthetic.[3]

The optimal antithrombotic therapy after BAVR 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 BAVR 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 implanted 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 3 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 BAVR 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 (►Fig. 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 BAVR ranging from 0.5 to 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 to 12 weeks after BAVR.[15]

Due to bleeding concerns, other physicians treated patients with BAVR 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 g 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 BAVR, published in 1968, recommended low-dose aspirin (80 mg daily), with 3 months of anticoagulation followed by lifelong aspirin as an alternative.[18] Since the publication of these guidelines, the question of aspirin versus oral anticoagulation in BAVR 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 (►Fig. 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]).
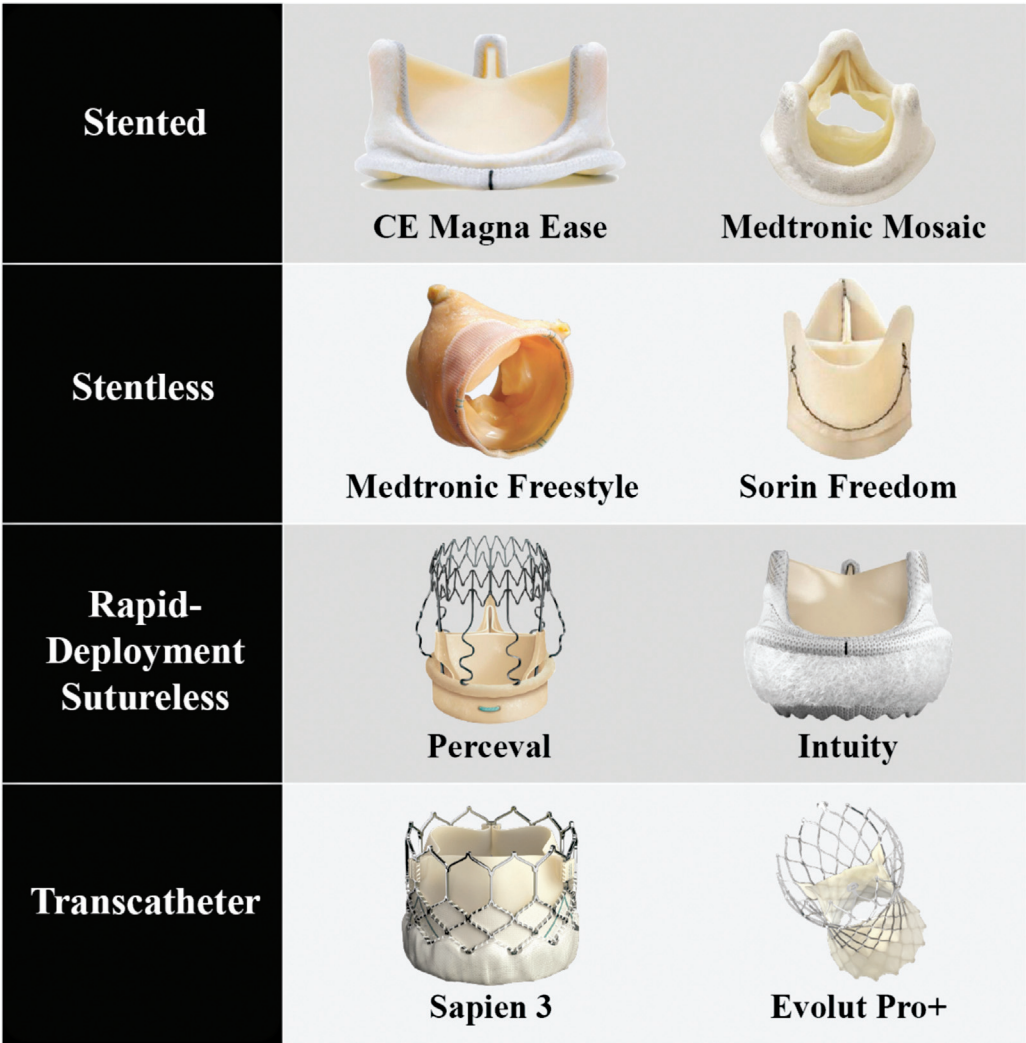
Fig. 1 Examples of the four categories of bioprosthetic aortic valves.

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 3 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 BAVR is highest between 13 and 24 months after surgery, while only 24% of bioprosthetic valve thromboses occur in the first 3 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
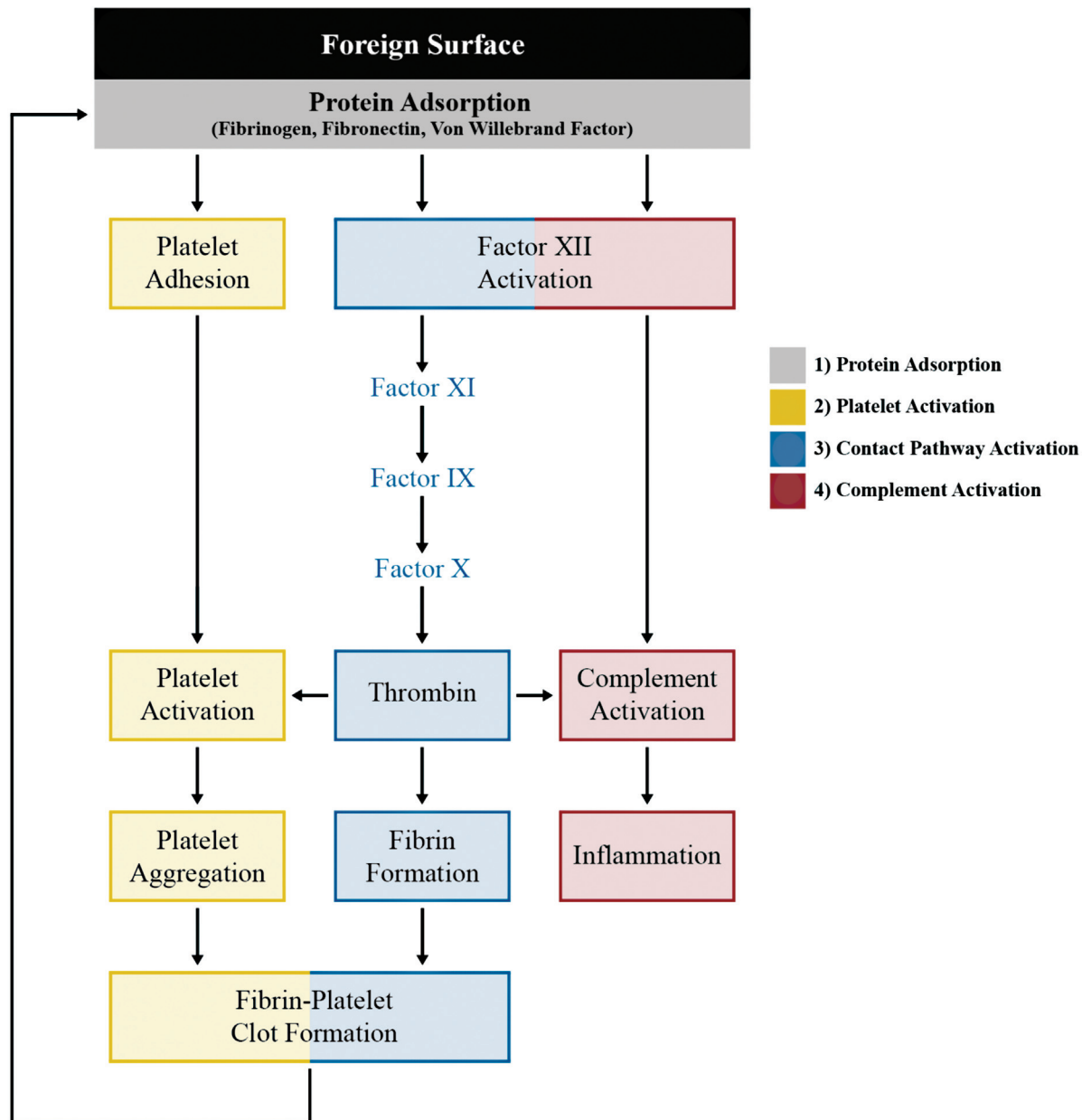
Fig. 2 Mechanism of thrombosis formation on a foreign surface.

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 a residual antithrombotic effect for freshly implanted valves in the early postoperative period.

Incidence and Clinical Sequelae of BAVR Thrombosis

Incidence
The reported incidence of BAVR thrombosis ranges from 0.4 to 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 BAVR thrombosis, as was first discovered in 2015 when a large RCT of TAVR versus BAVR 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 to 16.5% at 30 days[30–32] and 20 to 28.4% at 1 year in patients with BAVR.[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 BAVR, 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 BAVR.

Clinical Sequelae

BAVR 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 BAVR 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 BAVR, 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 BAVR, 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 BAVR,

including 25,656 patients from the Society of Thoracic Surgery database, reports only a 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 threefold increased rate of stroke in patients with subclinical valve thrombosis compared with those without (7.0 vs. 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 with 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 BAVR 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 BAVR, while P2Y12 inhibitors are 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 an 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 BAVR.

Anticoagulation

Warfarin, which inhibits both the contact and 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 to 7 days after surgery. Both major bleeding and stroke were increased in the dabigatran arm: there were seven major bleeding events in patients taking dabigatran compared with two in patients taking warfarin, and all bleeding events were intrapericardial. There were 9 strokes in patients taking dabigatran compared with 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 1,004 patients with atrial fibrillation and a bioprosthetic mitral valve to rivaroxaban or warfarin, demonstrating noninferiority 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 (ENAVLE) trial,[46] which randomized 218 patients with biological valve replacement or repair to 3 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 with 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 BAVR

Three professional societies publish guidelines for antithrombotic therapy in patients with BAVR who do not have another indication for oral anticoagulation: the American College of Chest Physicians (ACCP), 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 BAVR. The first ACCP guidelines, published in 1986, recommend aspirin (0.5 g/d) after BAVR based on observational studies suggesting increased risk of thromboembolism in the first 3 postoperative months.[15,16] In 1998, they added a grade 2C recommendation for 3 months of oral anticoagulation (international normalized ratio [INR] target 2.5) after BAVR, followed by lifelong aspirin (162 mg/d, grade 1C). In support, the guidelines cite one observational study of thromboembolism in 57 patients not taking anticoagulation after BAVR.[50] In 2004, the ACCP amended its recommendation to either oral anticoagulation (INR 2.5) or aspirin (80–100 mg/d) for 3 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/d) after BAVR, additionally citing a retrospective observational study of 1,151 patients which found no difference in thromboembolic events between antiplatelet and anticoagulant therapies.[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 (80–100 mg, class 2A) for 3 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 3 months. This recommendation was based on two observational studies of thromboembolic events in the first 3 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 BAVR. They also cite a retrospective study of 4,075 BAVR 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 3 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 3 months

Table 2 Timeline of changes to guidelines

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

Abbreviations: 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; mo, months; OAC, oral anticoagulant; VKA, vitamin K antagonist.

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] which are also cited by the AHA guidelines, which are described in more detail below.

Best Available Evidence for Antithrombotic Therapy after BAVR

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 BAVR.[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 3 months after surgery.[56] They found no difference in thromboembolism, treatment-related bleeding, or valve-related mortality at 3 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 3 months after BAVR, 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 3 months after BAVR, 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 therapies after BAVR.

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 BAVR.[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 3 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: 2.18–3.60). 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 BAVR 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 BAVR 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 trials 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 1,644 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 1,500 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 BAVR 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 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 BAVR. 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 BAVR.

Conflict of Interest
None declared.

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