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JACC GUIDELINE COMPARISON

ACC/AHA Versus ESC Guidelines on Prosthetic Heart Valve Management

JACC Guideline Comparison

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ABSTRACT

Prosthetic heart valve interventions continue to evolve with new innovations in surgical and transcatheter technologies. We compared the recommendations from the 2017 American College of Cardiology/American Heart Association guidelines for management of patients with prosthetic heart valves with the 2017 European Society of Cardiology guidelines. The 2 documents differed regarding recommendations for follow-up imaging, the choice of biological versus mechanical prosthesis, bridging therapies, role of aspirin, use of fibrinolytic therapy for prosthetic valve thrombosis, and management of paravalvular regurgitation. This review highlights the differences between the 2 guidelines, summarizes new evidence, and offers recommendations for the management of patients with prosthetic heart valves in these areas of controversy.
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Major society guidelines from the European Society of Cardiology (ESC) (1) and the American College of Cardiology/American Heart Association (ACC/AHA) regarding management of patients with valvular heart disease (2) were updated in 2017. There are notable differences in recommendations with regard to management of patients with prosthetic heart valves (PHV), as well as new evidence that has become available since the publication of the guidelines. The aim of this review is to compare the current ACC/AHA and ESC guideline recommendations with regard to management of patients with PHVs. This review focuses on the differences between the 2 guidelines and summarizes new data that address these areas of controversy.

EVIDENCE BASE AND STRENGTH OF RECOMMENDATIONS

Few recommendations for PHVs were based on Level of Evidence: "A" by both the guidelines: 6.7% for ACC/AHA and 3% for ESC (**Central Illustration**). ACC/AHA guidelines graded 57% of recommendations based on Level of Evidence: B; ESC guidelines graded 79% of recommendations based on Level of Evidence: C.

CONTROVERSIES REGARDING MANAGEMENT OF PATIENTS WITH PHVs

Differences between the 2 documents are summarized in **Table 1**.

ROUTINE FOLLOW-UP IMAGING. It is agreed that early post-operative imaging is recommended in all patients to establish a baseline for the prosthesis in a particular patient. ESC recommends follow up imaging at ~30 days, while ACC/AHA recommends 6 weeks to 3 months after valve implantation, although we generally perform it at the time of hospital dismissal. In the case of mechanical valves, guidelines do not recommend follow-up imaging for patients who are stable unless there is another

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

ASA = acetyl salicylic acid

ESC = European Society of Cardiology

INR = International Normalized Ratio

LMWH = low molecular weight heparin

PHV = prosthetic heart valve

TTE = transthoracic echocardiogram

UFH = unfractionated heparin

VKA = vitamin K antagonist

indication. Regarding follow-up imaging of bioprosthetic valves in asymptomatic patients, routine annual transthoracic echocardiography (TTE) is recommended by the ESC guidelines for both surgically and percutaneously implanted valves, whereas the ACC/AHA guidelines recommend annual TTE only after 10 years from the date of valve implant. Both guidelines recommend TTE for symptoms/signs of PHV dysfunction regardless of the date of implant and in certain patients who are at a higher risk for accelerated valve deterioration even in the absence of symptoms (**Figure 1**). The recommendation by ESC is based on a consensus statement document (3), which follows the Valve Academic Research Consortium-2 (4) recommendations. The recommendation by the ACC/AHA is based on observations that incidence of structural valve deterioration is low for bioprosthetic valves in the first 10 years after implant.

New evidence. Standardized definitions of structural valve deterioration are now available (5). Salaun et al. (6) showed that up to 13.1% of patients with bioprosthetic surgical aortic valve developed hemodynamic valve dysfunction between 2 consecutive echocardiographic assessments performed at a median time of 6.7 to 9.9 years after implant. In these patients, hemodynamic valve deterioration predicted a higher mortality or valve reintervention.

Another potential reason for bioprosthetic valve failure is thrombosis. A retrospective study showed that bioprosthetic valve thrombosis was responsible for majority of cases of early PHV dysfunction (median time of 26 months, interquartile range: 12 to 43 months) and was associated with an increase in transvalvular gradient, suggesting a possible role of TTE in recognizing valve dysfunction at an early stage (7). Most of these patients were asymptomatic at the time of initial diagnosis. It is likely that bioprosthetic valve deterioration and thrombosis have been underestimated in previous studies, as these did not include a uniform and standardized definition of valve deterioration and instead used reoperation or reintervention due to prosthetic failure as an endpoint (3,8).

Based on these observations, we recommend a routine annual surveillance echocardiography after bioprosthetic valve implantation, as this can detect valve dysfunction due to structural deterioration or thrombosis at a subclinical stage. Anticoagulation may be sufficient for treatment in appropriate cases.

HIGHLIGHTS

- Prosthetic heart valve replacement for native valve dysfunction is akin to trading one heart disease for another, warranting long-term follow-up and management.
- This review highlights the main areas of disagreement between 2 societal practice guidelines.
- The differences highlighted may help clinical decision-making with more cognizance of limitations of available evidence and catalyze future research.

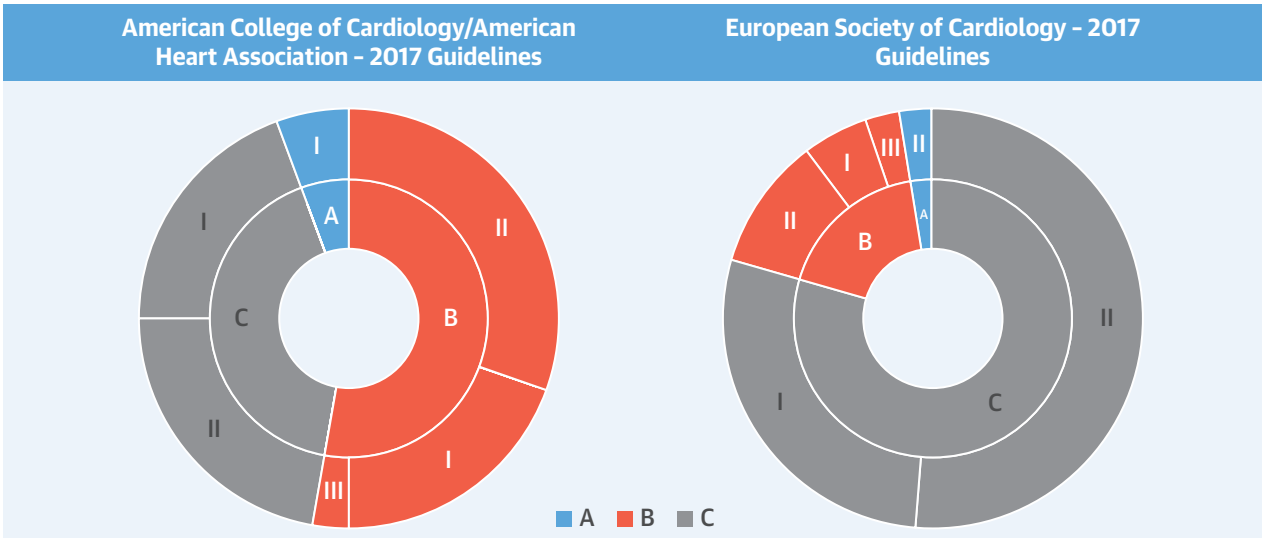
Early routine surveillance echocardiography is also important for certain types of prosthesis (Mitroflow), which are known to be associated with early structural deterioration (9).

CHOICE OF BIOPROSTHETIC VERSUS MECHANICAL VALVE. The ACC/AHA guidelines recommend a lower age cutoff (50 years) compared with the ESC guidelines (age <60 years for aortic, <65 years for mitral) for recommending mechanical rather than bioprosthetic valves (**Table 2**). Newer-generation bioprosthetic valves, with longer durability and increasing use of valve-in-valve procedure for degenerated bioprosthetic valves, were also considered by the ACC/AHA task force. Apart from age, both documents also clearly emphasize the importance of including patient preference (Class I) and a shared-decision making approach in choosing valve type.

Evidence cited by the guidelines regarding the type of valve and outcomes in patients age 50 to 70 years is conflicting. A retrospective study from the New York state database showed no significant difference in rates of stroke or mortality at 15 years in patients (age 50 to 69 years) who underwent mechanical versus bioprosthetic valve implant. Although there was a higher rate of reoperation in patients with bioprosthetic valves, the bleeding rates were lower (10). However, 2 other studies from Switzerland (11) and Sweden (12) also included patients younger than 60 years and showed a survival advantage with mechanical aortic prosthesis over biological prosthesis.

New evidence. A recent study (13) from the California state database compared >20,000 patients who underwent mechanical or bioprosthetic valve replacement. There was a survival advantage with mechanical prosthesis for mitral valve disease in patients up to 70 years of age. For patients with aortic valve disease, survival advantage with mechanical

CENTRAL ILLUSTRATION **Prosthetic Heart Valve Management: Comparison of Grade of Recommendation and Level of Evidence**



Singh, M. et al. J Am Coll Cardiol. 2019;73(13):1707–18.

A = Level of Evidence: A; B = Level of Evidence: B; C = Level of Evidence: C; I-III = grade of recommendation.

prosthesis was noted up to age 50 years. A study (14) including 41,227 patients showed higher odds of mortality with use of biological prosthesis. These studies suggest a survival advantage of mechanical valves over bioprosthetic valves for patients up to the age of 70 years.

Another factor that will likely play an important role in shared decision making about the choice of mechanical or bioprosthetic valve prior to surgery is the use of valve-in-valve procedure, which is feasible only in bioprosthetic valves. This is being increasingly used for patients with valve deterioration to avoid redo surgery. Current evidence regarding this procedure is still limited to small observational studies (15). More insights will be provided by the ongoing VIVID (Valve In Valve International Data) registry, a collaborative international effort (16).

BRIDGING WITH UNFRACTIONATED HEPARIN OR LOW-MOLECULAR-WEIGHT HEPARIN. ESC guidelines provide a Class I recommendation for the use of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in all patients when vitamin K antagonist (VKA) therapy must be interrupted. In contrast, the ACC/AHA guidelines use a risk-based approach and recommend no bridging (Class I) for low-risk patients (**Table 1**). ESC guidelines also recommend bridging for subtherapeutic International Normalized Ratio (INR) levels noted during routine monitoring. The ACC/AHA guidelines cite the American College of Chest Physicians: 2012 guidelines (17) and 2 other older studies (published in 1978 and 1997) (18,19). The ESC guidelines cite other guidelines (20,21).

Other evidence. Studies have consistently shown high bleeding events in patients who receive UFH or LMWH for periprocedural bridging (22,23). An observational study showed a 4-fold higher risk of bleeding in patients with mechanical valves who received periprocedural bridging versus those who did not (23). No thromboembolic events were noted in this study. Another observational study that evaluated bridging in the immediate post-operative period after mechanical aortic valve replacement showed higher rates of adverse events including bleeding, pericardial effusion, and reoperation in patients who were bridged with heparin (24). An observational study (25) showed a low incidence of thromboembolism in patients with mechanical heart valves with low risk of thromboembolism, in whom VKA therapy was temporarily interrupted perioperatively.

Even though most of these observational studies did not show a difference in rates of thromboembolism, they were underpowered due to low event rates. It is very likely that an adequately powered randomized trial will show a lower number needed to harm (bleeding) and probably a much higher number

TABLE 1 Differences Between the Guideline Recommendations for Prosthetic Valves

Recommendation	ESC 2017	Class	Level of Evidence	ACC/AHA 2014/2017	Class	Level of Evidence
TTE after valve implant*	Annually			Annually starting 10 yrs after implantation	IIa	C
Age cutoff for considering mechanical valve	<60 yrs—aortic <65 yrs—mitral	IIa	C	<50 yrs	IIa	B-NR
Age cutoff for considering bioprosthetic valve	>65 yrs—aortic >70 yrs—mitral	IIa	C	>70 yrs	IIa	B
Choice of prosthetic valve in young patients contemplating pregnancy	Bioprosthetic	IIa	C	Based on patient preferences		
Bridging during interruption of anticoagulation therapy for mechanical valve	Routinely recommended	I	C	1. Not recommended for bileaflet or newer generation tilting-disc mechanical valves in aortic position† 2. Recommended for others on individualized basis	I IIa	C C-LD
Subtherapeutic INR noted during routine monitoring	Bridging with UFH or LMWH recommended			No recommendations		
Supratherapeutic INR noted during routine monitoring in patients without bleeding.	No specific INR value recommended for use of vitamin K therapy. Rapid reversal suggested for INR ≥6 to lower the risk of subsequent bleeding			Reversal with vitamin K recommended for INR >10		
Use of aspirin in addition to VKA therapy for mechanical prosthetic valves	1. Routine use not recommended 2. After thromboembolic event despite adequate INR 3. With concomitant CAD	 IIa IIb	 C C	Routine indefinite use recommended	I	A
Use of aspirin for bioprosthetic valves	1. Not recommended indefinitely 2. Should consider for first 3 months after SAVR	 IIa	 C	Indefinite use of aspirin recommended for left-sided valves.	IIa	B
VKA therapy for bioprosthetic valves	1. Should consider for first 3 months after STVR or SMVR. 2. May consider for first 3 months after SAVR 3. No recommendations for TAVR	IIa IIb	C C	1. Should consider for up to first 6 months after SAVR and SMVR 2. May consider for first 3 months after TAVR	IIa IIb	B-NR B-NR
Post TAVR	DAPT × 3–6 months ASA indefinitely‡	IIa	C	Clopidogrel × 6 months ASA indefinitely	IIb	C
Lower INR target for On-X valve in aortic position§	Recommended INR target 2.5			May consider a lower INR range of 1.5–2.0	IIb	B-R
Transcatheter repair of paravalvular regurgitation in surgical high-risk patients	May be considered	IIb	C	Reasonable for patients with suitable anatomy, when performed in centers with expertise	IIa	B
Low-dose, slow-infusion fibrinolytic therapy for mechanical valve thrombosis	No recommendations. Standard-dose fibrinolytic therapy recommended when surgical risk is deemed high/not available or for right-sided valve thrombosis.			Recommended as an initial approach, comparable to surgery	I	B-NR

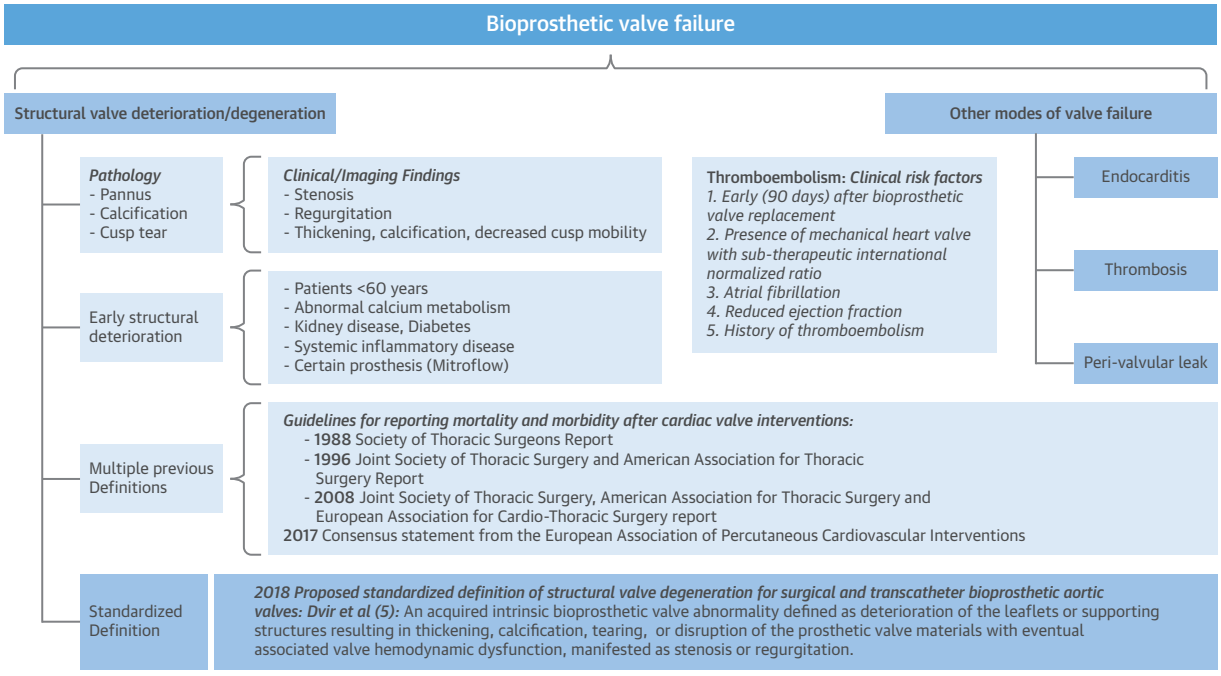
*In the absence of any symptoms or signs of valve deterioration. †With no additional risk factors for thromboembolism. ‡For patients who do not require anticoagulation for other reasons. §With no additional thromboembolic risk factors.

ACC = American College of Cardiology; AHA = American Heart Association; ASA = acetyl salicylic acid; DAPT = dual antiplatelet therapy; ESC = European Society of Cardiology; INR = International Normalized Ratio; LMWH = low-molecular-weight heparin; SAVR = surgical aortic valve replacement or repair; SMVR = surgical mitral valve replacement or repair; STVR = surgical tricuspid valve replacement; TAVR = transcatheter aortic valve replacement; TTE = transthoracic echocardiogram; UFH = unfractionated heparin; VKA = vitamin K antagonist.

needed to prevent a thromboembolic event. Based on this, we support the ACC/AHA recommendations for bridging anticoagulation only for the patients with moderate or high risk of thromboembolism and no bridging for low-risk patients. Bridging therapy can be a "double-edged sword" in low-risk patients and may be even counterproductive, as patients who experience a bleeding event while receiving bridging therapy are likely to have a longer interruption of anticoagulant therapy until the risk of rebleeding resolves. More insights will be provided by the PERIOP-2 (A Safety and Effectiveness of LMWH vs Placebo Bridging Therapy for Patients on Long Term Warfarin Requiring Temporary Interruption of Warfarin) trial, which compares safety and effectiveness of bridging versus no bridging for high-risk patients (26).

The ESC guidelines also recommend bridging for subtherapeutic INR noted during routine monitoring but cite no supporting evidence. The ACC/AHA guidelines do not provide any recommendations for this scenario. Bridging for a single subtherapeutic INR noted during routine monitoring is also not supported by the American College of Chest Physicians-2012 guidelines (17). Some atrial fibrillation studies have observed a median time >15% in the subtherapeutic range during routine monitoring (27). Assuming a similar prevalence of subtherapeutic INR in patients with prosthetic valves, the ESC recommendations would result in a significant number of patients requiring bridging therapy on a routine basis. We recommend an individualized, risk-based approach with careful consideration of risks and benefits.

FIGURE 1 Modes of Bioprosthetic Valve Failure



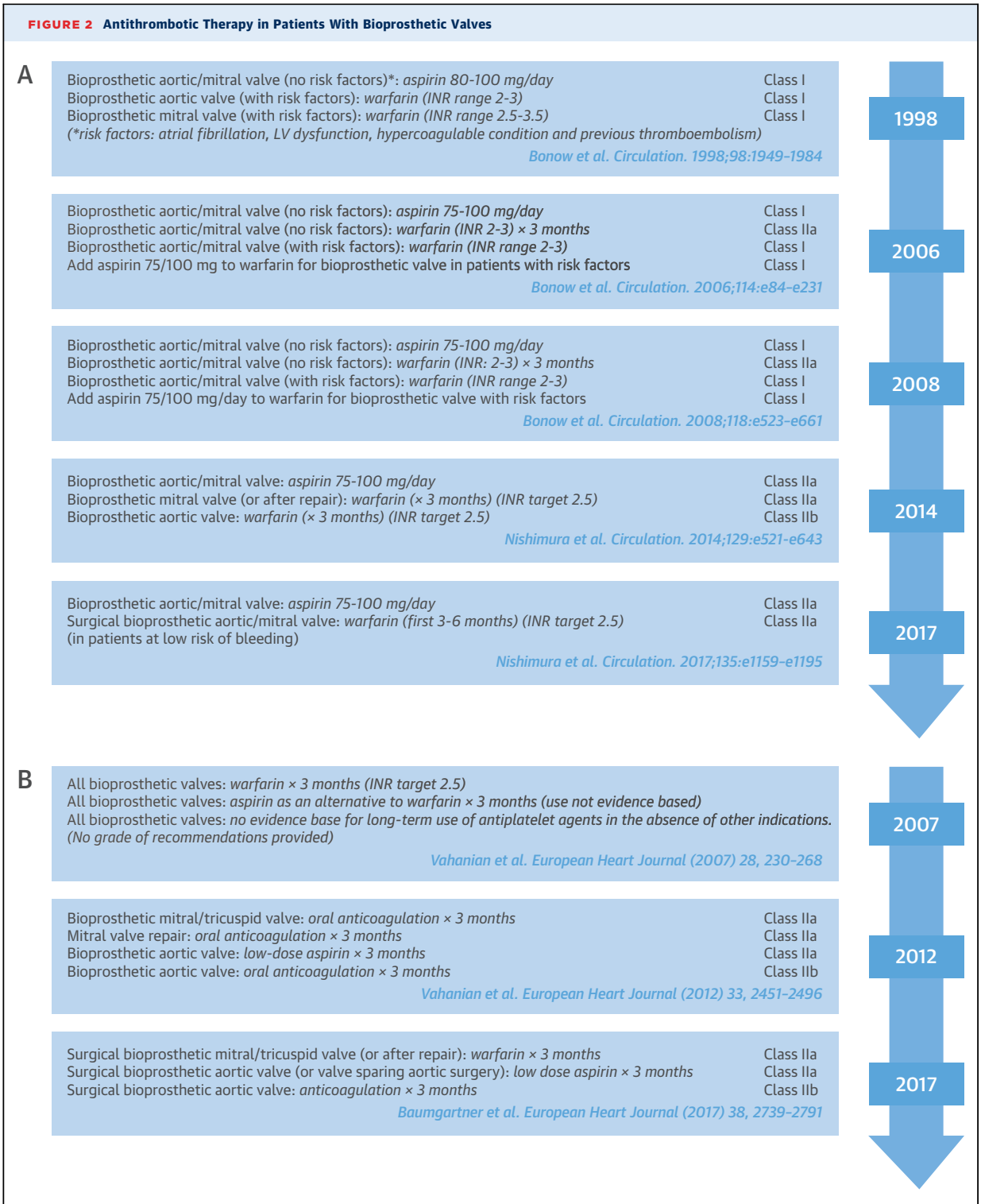
Various modes of bioprosthetic valve failure. Standardized definition of structural valve deterioration or degeneration. Definition used with permission from Dvir et al. (5).

TABLE 2 Summary of Selected Studies Comparing Mechanical and Bioprosthetic Valves

First Author (Ref. #) Year, N	Comparison	Population	Outcome	Comments/Limitations
Goldstone et al. (13) 2017, N = 25,445	BHV vs. MHV from 1993- 2013	• Patients from California administrative database • 50-69 yrs • MVR and AVR	1. BHV vs. MHV for MVR: ↑ mortality up to the age of 70 yrs 2 BHV vs. MHV for AVR: ↑ mortality up to the age of 50 yrs 3. ↑ reoperation in patients with BHV 4. ↑ bleeding and stroke in patients with MHV	1. Bias inherent to the use of administrative database (selection bias, missing clinical data) 2. Nonrandomized study
Dunning et al. (14) 2011, N = 41,227	Assessed trends and volumes of MHV use over 5 yrs from 2004-2009	• Patients from Great Britain and Ireland National database • AVR	1. ↑ in number of older, high risk patients undergoing AVR over study period 2. ↑ in number of BHV for AVR 3. Use of BHV was 1 of the multivariate predictors of mortality	1. Comparison of MHV with BHV was not the primary outcome/objective of this study. 2. Patients not stratified according to age or type of MVH/BHV. 3. Bias inherent to administrative databases. 4. Nonrandomized study
Chiang et al. (10) 2014, N = 4,253	BHV vs. MHV from 1997-2004	Retrospective cohort study from New York state administrative database • 50-69 yrs • AVR	1. Similar rates of stroke and survival in patients. 2. ↑ Reoperation, but lower bleeding with bioprosthetic valves	1. Study limited by biases inherent to administrative databases. 2. Results not generalizable to newer-generation valves that were not available during study period. 3. Nonrandomized study
Glaser et al. (12) 2016, N = 4,545	BHV vs. MHV from 1997-2013	Observational study from Sweden database • 50-69 yrs • AVR	1. ↑ long-term survival with mechanical versus bioprosthetic valve 2. Subgroup analysis showed mortality benefit in patients age 50-59 yrs, with similar survival in patients age 60-69 yrs	1. Does not provide any information about MHV vs. BHV for mitral valve replacement. 2. Selection bias. 3. Nonrandomized study

↑ = higher; AVR = aortic valve replacement; BHV = bioprosthetic heart valve; MHV = mechanical heart valve; MVR = mitral valve replacement.

FIGURE 2 Antithrombotic Therapy in Patients With Bioprosthetic Valves



Timelines showing changes in recommendations from the **(A)** American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and **(B)** European Society of Cardiology (ESC) guidelines over time. INR = International Normalized Ratio.

USE OF LOW-DOSE ASPIRIN OR ACETYL SALICYLIC ACID THERAPY IN ADDITION TO VKA THERAPY FOR MECHANICAL PHV. Probably the most debated difference between the 2 guidelines, the ACC/AHA guidelines provide a Class I recommendation for the use of low-dose acetyl salicylic acid (ASA) in all patients with mechanical valve in addition to warfarin. In contrast, the ESC recommends against routine use of ASA and recommends only selective use in patients with concomitant coronary artery disease (Class IIb) or in patients with thromboembolism despite an adequate INR (Class IIa). Supporting evidence cited by the ACC/AHA is based on 2 randomized studies that are now >20 years old. A study with enrollment from July 1988 to 1992 (28) randomized patients to aspirin 100 mg + INR target of 2.5 to 3.5 versus placebo + INR target of 3.5 to 4.5. The rate of thromboembolic events or hemorrhage was similar between the groups. This trial does not reflect current clinical practice, as a significant number of these patients had older-generation valves (26% Starr-Edwards), which are no longer used in contemporary clinical practice. The second trial, published in 1993 (29), randomized 370 patients to aspirin 100 mg or placebo in addition to warfarin with a target INR range of 3.0 to 4.5, and showed lower rates of mortality and major embolic events in patients who received combined therapy. Only 76% of patients in this trial had a mechanical PHV. Of all the patients, 45% also had atrial fibrillation. Another study (30) randomized patients to ASA versus placebo in addition to VKA therapy with an INR target of 1.8 to 2.5. There was a lower risk of thromboembolism in the ASA group while the risk of bleeding was similar in both groups. However, >50% of patients in this study had coronary artery disease and 40% of patients had atrial fibrillation.

The ESC guidelines argue that the use of ASA in patients with mechanical PHVs has not been studied in patients without vascular disease and support their recommendations based on a Cochrane database review (31), which showed a lower risk of thromboembolism with addition of ASA or dipyridamole but at the expense of increased bleeding events. Interestingly, the ACC/AHA 2014 guidelines cite a previous version (published in 2003) of the same review to support the recommendation of using ASA, whereas the ESC guidelines cite the updated version of the same paper to refute this recommendation.

Summary of evidence. From these studies, it is evident that: 1) high-class evidence regarding the use of ASA in addition to VKA therapy for patients with mechanical PHVs is lacking in current-generation mechanical PHVs, which have a lower thrombogenic potential; 2) most of the randomized trials are old and do not reflect current clinical practice; and 3) these studies are confounded by various other factors that increase thromboembolic risk, such as presence of atrial fibrillation or coronary artery disease. No trials have exclusively studied patients without vascular disease or atrial fibrillation. Studies that evaluated the use of combined ASA and anticoagulation therapy in patients with atrial fibrillation have shown higher bleeding events without any significant difference in thromboembolic events compared with anticoagulation alone (32). We recommend use of an individualized approach until more evidence becomes available.

USE OF LOW-DOSE ASA OR VKA THERAPY IN SURGICALLY IMPLANTED BIOLOGICAL PHV. Substantial changes in the guideline recommendations have occurred over time (**Figure 2**). Current ACC/AHA guidelines recommend routine, indefinite use of low-dose ASA therapy for all surgically implanted biological PHVs, whereas ESC guidelines do not recommend routine indefinite use. ESC guidelines consider the use of low-dose ASA therapy reasonable for the first 3 months after surgical implantation of aortic biological PHV or valve sparing aortic surgery (Class IIa). The ESC recommendation for use of VKA therapy after surgical implant of aortic valve is weaker (Class IIb) with shorter duration compared with the ACC/AHA guidelines (Class IIa) which recommend VKA therapy for the first 3 to 6 months.

Recommendations for use of anticoagulation by ACC/AHA are based on an older study (1995) that showed a high thrombotic risk for the first 3 months after bioprosthetic valve implantation (33). Evidence regarding use of antiplatelet therapy is largely based on studies that compared antiplatelet therapy with anticoagulation post-surgical valve implant and showed similar rates of thromboembolic events (34,35). Two studies, cited by both guidelines, are worth mentioning. An observational study (n = 25,656) compared outcomes between patients who received warfarin, aspirin, or a combination for the first 3 months after surgical aortic bioprosthesis implant (36). There was a lower risk of mortality and thromboembolic events at 3 months in the combination therapy group compared with aspirin alone, but a higher incidence of bleeding. In this study, 58% of patients in the combination therapy group had a history of atrial fibrillation and 15% had a prior history of thromboembolism. The ACC/AHA cites this study to support the use of warfarin for first 3 months and the ESC guidelines cite it to support only aspirin therapy for the first 3 months after implantation of a bioprosthetic aortic valve. Regarding duration of

TABLE 3 Summary of Selected Evidence/References Used in the Paper

First Author (Ref. #), Year, Design, N	Comparison	Population	Outcome	Comments/Limitations
Bridging with unfractionated heparin or low molecular weight heparin:				
Steinberg et al. (22), 2015, Obs, N = 2,200	Comparison of clinical outcomes in patients receiving bridging vs. no bridging during interruption in anticoagulation (AFib population).	Patients with AFib from ORBIT-AF registry	1. Patients who received bridging therapy were more likely to have prior CVA or MHVs. 2. ↑ bleeding in patients who received bridging. 3. ↑ rates of CVA, MI, systemic embolism, hospitalization, or death at 30 days in the bridging group.	1. This study evaluated bridging therapy in patients with AFib. Only a small proportion of patients had MHV. Thromboembolic risks associated with mechanical valves are higher and different compared with AFib. 2. Higher rates of embolic events in patients who were bridged, may suggest a possible selection bias.
Daniels et al. (25), 2009, Obs, N = 556	Thromboembolic events in patients who required interruption in anti-coagulation therapy.	Patients referred to Mayo clinic Thrombophilia Center from 1997–2003	1. Incidence of thromboembolic events over 3 months was 0.9%. 2. Incidence of major bleeding was 3.6%, and fatal in 0.2%.	1. Bridging protocol in this study resembles ACC/AHA guidelines recommendations and shows the risk-benefit ratio may not favor bridging due to high bleeding incidence. 2. Lack of a comparison group limits applicability of these findings.
Use of low-dose aspirin or acetyl salicylic acid therapy in addition to warfarin therapy for MHVs:				
Meschengieser et al. (28), 1997, RCT, N = 503	Assessment of bleeding and thromboembolic outcomes in: Arm A= aspirin 100 mg/day + low-intensity anticoagulation (INR: 2.5–3.5), n = 258 vs. Arm B: Placebo + INR target 3.5–4.5, n = 245.	All patients had MHVs: 1. Aortic: 66% 2. Mitral: 29% 3. Star Edwards: 26% 4. Tilting disc: 65% 5. St. Jude Medical: 4.6% 6. AFib: 18%	1. Embolic episodes: 1.32/100 patient-yrs (95% CI: 0.53 to 2.7) for arm A vs. 1.48/100 patient-yrs (95% CI: 0.59 to 3.03) for arm B. 2. Major hemorrhage: 1.13/100 patient-yrs (95% CI: 0.41 to 2.45) for arm A vs. 2.33/100 patient-yrs (95% CI: 1.17 to 4.14) for arm B.	1. Does not reflect contemporary clinical practice with use of older generation valves (26% had Starr-Edwards). Enrolled patients from 1988 to 1992. 2. INR was noted to be adequate only in 46%–49% of patients in arm A, and 32%–37% of patients in arm B. 3. Up to 45% of patients in arm B had subtherapeutic INR.
Turpie et al. (29), 1993, RCT, N = 370	Comparison of aspirin, (n = 184) vs. placebo (n = 186) in addition to warfarin with a target INR range: 3.0–4.5 in patients with prosthetic heart valves.	Patients with MHV (76%) or BHV (24%) with AFib or history of thromboembolism	1. Systemic embolism or death from vascular cause: 1.9%/yr vs. 8.5%/yr in aspirin vs. placebo ($p < 0.001$). 2. Bleeding: 35% vs. 22%, $p = 0.02$ in aspirin vs. placebo groups, respectively.	1. Only 76% of patients had MHV. 2. 45% of patients had AFib and 35% had IHD. 3. MHV type not specified. 4. Old study: does not reflect contemporary clinical practice. 5. Mortality benefit in aspirin group driven by a reduction in vascular deaths in aspirin group (1% vs. 7%).
Dong et al. (30), 2011, RCT, N = 1,496	Comparison of aspirin (75–100 mg) vs. placebo in addition to VKA (INR = 1.8–2.5) in patients with MHVs.	Patients with MHVs: 1. Unileaflet 64% 2. St. Jude Medical: 36% 3. Prior MI: 47% 4. Prior AFib: 40%	For aspirin vs. placebo respectively: 1. Thromboembolism: 2.1% vs. 3.6%; $p = 0.044$ 2. Bleeding: 3.5% vs. 3.8%; $p = 0.391$ 3. Mortality: 0.3% vs. 0.4%; $p > 0.05$	1. Significant number of patients had other thrombo-embolic risk factors such as CAD or AFib. 3. Lower INR range used in this study may not be protective for thromboembolic events in this group with other risk factors.
Lamberts et al. (32), 2014, N = 8,700	Comparison of VKA monotherapy vs. VKA + clopidogrel and/or aspirin.	Patients with AFib and stable CAD	1. Risk of thromboembolism was similar in all groups. 2. Risk of bleeding was ↑ with use of antiplatelet therapy in addition to VKA.	1. Results of this study cannot be generalized, as it did not include patients with prosthetic valves.
Use of low-dose aspirin or warfarin therapy in surgically implanted BHVs:				
Heras et al. (33), 1995, N = 816	This study evaluated the rates of thromboembolism and effect of anticoagulation or antiplatelet therapies after AVR or MVR with BHV.	All patients underwent surgical BHV implant: • AVR: 424 • MVR: 326 • AVR + MVR: 66	1. Risk of thromboembolism was high for the first 90 days after BHV implant. (10% for MVR and 3.6% for AVR). 2. Patients on VKA therapy after MVR had a lower rate of thromboembolism (2.5%/yr vs. 3.9%/yr without VKA; $p = 0.05$).	1. Patients who underwent MVR had other comorbidities that increase thromboembolic risk: • Pre-operative AFib: 55% • LA >55mm: 33% • Pre-op thromboembolism: 18% 2. Benefit of anticoagulation in these patients may be related to comorbidities.

Continued on the next page

TABLE 3 Continued

First Author (Ref. #), Year, Design, N	Comparison	Population	Outcome	Comments/Limitations
Colli et al. (34), 2007, Pilot Study, N = 75	VKA (INR: 2-3) for the first 3 months, followed by ASA vs. ASA alone.	Patients who are undergoing AVR with BHV	Both groups had similar rates of thromboembolism, major bleeding, and overall survival.	1. This study was a pilot study and underpowered to detect a statistically significant differences in outcomes.
Aramendi et al. (35), 2005, RCT, N = 193	Triflusal 600 mg vs. VKA (INR: 2-3) for 3 months after valve implant.	Patients undergoing BHV implant: 1. AVR: 93.8% 2. MVR: 5.2% 3. Double valve replacement: 1.0%	1. Similar rates of thromboembolic events noted in both groups. 2. Severe hemorrhage: higher event rates in VKA group (p = 0.048)	1. Triflusal not used in current clinical practice. 2. This study may be underpowered to detect a difference in rates of thromboembolic events.
Brennan et al. (36), 2012, Obs, N = 25,656	Comparison of 3 antithrombotic regimens at discharge: 1. ASA only (49% patients) 2. VKA only (12%) 3. ASA+VKA (23%)	Patients >65 yrs from the Society of Thoracic Surgery Database who underwent AVR with BHV • Median age was 77 yrs	Relative to Aspirin monotherapy: 1. VKA + ASA was associated with a ↓ adjusted risk of death and embolic events but with a ↑ risk of bleeding. 2. Warfarin monotherapy was associated with similar risk of death/embolic events and bleeding.	1. Selection and other biases associated with administrative databases.
Lower INR target range for On-X mechanical valves in aortic position:				
Puskas et al. (40), 2014, RCT, N = 375	A strategy of Low INR (1.5-2.0) vs. standard INR (2-3), 3 months after AVR	1. Patients undergoing isolated AVR with On-X valve	1. Major bleeding: 1.48% vs. 3.26%/patient-yr; (p = .047) for low INR group vs. standard INR group, respectively. 2. Thromboembolic events and all-cause mortality were similar between groups.	1. This study was likely underpowered to detect a difference in thromboembolic events. 2. Concerns regarding tight control of INR management with weekly home monitoring, which may not be feasible in routine practice.
Use of slow-infusion, low dose fibrinolytic therapy for mechanical valve thrombosis				
Özkan et al. (41), 2013	1. Use of low-dose, slow-infusion tissue plasminogen activator (25-100 mg over 6 h) under TEE guidance with repeat doses if needed 2. No comparison group	1. 24 pregnant women with 28 episodes of valve thrombosis 2. Included obstructive and nonobstructive* valve thrombosis	1. Complete resolution of thrombus was noted in all patients. 2. Improvement in valve area and transvalvular gradients in patients with obstructive thrombosis. 3. 1 placental hemorrhage resulting in preterm delivery 4. 5 miscarriages, that occurred 1-5 weeks after thrombolytic administration 5. No thromboembolism	1. Nonrandomized/observational study 2. Lack of comparison group
Özkan et al. (42), 2015, Obs	1. Use of low-dose ultra-slow infusion tissue plasminogen activator (25 mg over 25 h) with repeat doses if needed 2. No comparison group	1. 114 patients with 120 episodes of prosthetic valve thrombosis 2. Obstructive thrombosis 3. Nonobstructive thrombus (thrombus diameter of ≥10 mm)	1. Success rate: 90%. Higher NYHA functional class was the only multivariate predictor of unsuccessful result. 2. Complications: death = 1, nonfatal major complications = 4 (stroke, embolism, GI hemorrhage, intra-abdominal hematoma), minor complications = 3	1. Nonrandomized/observational study 2. No comparison group.
Karthikeyan et al. (43), Meta-analysis	This meta-analysis included 7 studies that compared thrombolysis with urgent surgery for prosthetic valve thrombosis	690 episodes of valve thrombosis in 598 patients (including 10 instances of bioprosthetic valve thrombosis) Surgery = 446 Thrombolysis = 244	1. Surgical treatment was associated with a higher odds of complete success compared to thrombolysis. 2. Higher trend toward mortality in surgical group (13.5% in surgical vs. 9% in thrombolytic group, pooled odds ratio: 1.67, 95% CI: 0.98-2.85; p = 0.060). 3. Other outcomes such major bleeding, thromboembolic events, recurrent valve thrombosis favored surgery.	1. Definitions of outcomes were not standardized in most of the studies. 2. All included studies were retrospective. 3. Heterogenous population, including 10 instances of bioprosthetic valve thrombosis and 15 instances of tricuspid valve thrombosis.

*For patients with nonobstructive valve thrombosis, this study included patients with recent thromboembolism if thrombus diameter >5 or >10 mm if no symptoms.

↑ = higher/increased; ↓ = lower; AFib = atrial fibrillation; AVR = aortic valve replacement; BHV = bioprosthetic heart valve; CAD = coronary artery disease; CI = confidence interval; CVA = cerebrovascular accident; GI = gastrointestinal; H/o = history of; IHD = ischemic heart disease; INR = international normalized ratio; MHV = mechanical heart valve; MI = myocardial infarction; MVR = mitral valve replacement; Obs. = observational; TEE = transesophageal echocardiogram.

anticoagulant therapy, a retrospective study of 4,075 patients from the Danish National Patient Registry compared patients who were treated with warfarin versus no warfarin after surgical implantation of bioprosthetic aortic valve. The risk of thromboembolic events and mortality was lower in those treated with warfarin therapy for 6 months after bioprosthetic aortic valve replacement (37). Again, this study is cited by both guidelines: by the ACC/AHA to support extended use of warfarin up to 6 months after implant of bioprosthetic aortic valve, and by the ESC to support use of aspirin alone. However, a major limitation in this study was infrequent use of aspirin in both the arms. In patients not on warfarin, <15% were on any antiplatelet agent (ASA, clopidogrel, dipyridamole, or combination). This may have resulted in a higher event rate in the "no-warfarin" group. Surprisingly, in patients who did not receive warfarin therapy, there was a trend toward higher bleeding episodes, which suggests selection bias and may have affected mortality in this group.

New evidence. Recent studies have provided insights about the thrombogenic potential of bioprosthetic valves. Case series have shown that bioprosthetic valve thrombosis is not as uncommon as previously thought (38) and is not limited just to the early period after valve implantation (7,38). These studies have further intensified the debate regarding ideal nature and duration of antithrombotic therapy after bioprosthetic aortic valve implantation. Based on this evidence, we support ACC/AHA recommendations for use of indefinite low-dose aspirin and VKA therapy for up to 6 months after valve implantation. The use of direct oral anticoagulants has been discouraging based on the GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes) trial (39), which was terminated early due to harm with rivaroxaban compared with antiplatelet therapy after transcatheter aortic valve replacement.

LOWER INR TARGET FOR CERTAIN MECHANICAL VALVES IN AORTIC POSITION. ACC/AHA guidelines recommend that a lower INR range (1.5 to 2.0) may be considered for patients with mechanical On-X valve in aortic position with no additional thromboembolic risk factors (Class IIb). However, ESC guidelines recommend standard INR target for these patients (INR target 2.5).

The ACC/AHA recommendations are based on a randomized study (40), which included 375 patients with increased risk for thromboembolism who underwent aortic valve replacement with On-X valve. There was a significantly lower incidence of bleeding in patients who were assigned to a lower INR range (1.5 to 2.0). There were higher thromboembolic events in the lower INR group that did not reach statistical significance, suggesting inadequate statistical power in this study. Other study design features, such as tight control of INR management with weekly home monitoring, may not be feasible in routine practice. Given these concerns, the ESC does not recommend using a lower INR target for On-X valve based on this study (**Table 3**).

We recommend that use of a lower INR target in patients with On-X valve in the aortic position may be an option in certain patients with high bleeding risk; however, this approach warrants a very close monitoring of INR.

USE OF SLOW-INFUSION, LOW-DOSE FIBRINOLYTIC THERAPY FOR MECHANICAL VALVE THROMBOSIS. ACC/AHA guidelines consider surgery or the use of slow-infusion, low-dose (25 mg of tissue-type plasminogen activator over 6 to 24 h without bolus) fibrinolytic therapy as a comparable initial approach (Class I). ESC guidelines, on the other hand, prefer surgery and recommend standard dose (recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 min with UFH) of fibrinolytic therapy (Class IIa) when surgical risk is deemed high/not available or for right-sided valve thrombosis.

ACC/AHA recommendations are based on few studies by Özkan et al. (41,42). The recommendation by the ESC is based on a meta-analysis of 7 trials (43) that favors surgery over thrombolysis. Most of the studies included in this meta-analysis used standard recommended doses of the thrombolytic agents.

We feel the choice of thrombolytic versus surgical approach should be individualized and based on a multidisciplinary team discussion after carefully weighing the risks and benefits of each approach.

TRANSCATHETER REPAIR OF PARAVALVULAR REGURGITATION. While both the guidelines recommend use of transcatheter closure for paravalvular leak in suitable patients who are at a higher risk for surgery, the grade of recommendation by ESC guidelines is weaker (Class IIb) compared with the ACC/AHA guidelines (Class IIa).

New evidence. A recent retrospective study (44) compared 195 patients who underwent percutaneous therapy with 186 patients who underwent surgical treatment. Higher technical success with surgery in this study was at a cost of higher in-hospital adverse events, although risk-adjusted

long-term survival was similar between the 2 groups. This study did not evaluate symptomatic improvement or freedom from heart failure or related readmissions. A second retrospective study (45), which included 231 patients, showed a lower composite endpoint of all-cause mortality and hospitalization for heart failure with a surgical approach compared with transcatheter approach, which was mainly driven by low incidence of hospitalization for heart failure, although there was a trend toward lower long-term mortality with the surgical approach.

Based on the results of these studies, surgery likely remains the preferred approach in low-risk patients due to lower long-term morbidity and freedom from heart failure, while transcatheter repair is an option in patients who have a suitable anatomy and higher perioperative risk of mortality.

ROSS PROCEDURE. The ACC/AHA guidelines consider replacement of the aortic valve by a pulmonary autograft (the Ross procedure) in young patients reasonable when performed by an experienced surgeon when anticoagulation is contraindicated or undesirable (Class IIb), while stressing that "experienced and focused surgeons" perform this procedure. No recommendations are provided by the ESC for Ross procedure.

New evidence. A recent retrospective study showed mortality benefits in patients (age 18 to 65 years) who underwent Ross procedure compared with patients who received an isolated mechanical aortic valve at 20 years follow-up despite a much higher bypass time and cross clamp time in these patients during Ross procedure (46). However, it is important to highlight that of the total 392 Ross procedures performed, the majority were performed by a single operator. Therefore, generalizability of this study and use of Ross procedure is likely to be limited. We support the ACC/AHA guidelines that this procedure should be preferred over a mechanical PHV implantation: 1) for relatively younger patients with few comorbidities; and 2) only when performed by a surgeon with extensive experience in this procedure.

CONCLUSIONS

We found multiple differences among 2 major society guidelines with regard to management recommendations of these patients. A small number of the guideline recommendations seem contradictory. We also found a small number of studies that are cited by both the guidelines, albeit to support opposing recommendations. It is evident from these differences that high-quality evidence is lacking with regard to management of patients with PHVs. Until more randomized trials are available for these patients, some of these recommendations will remain a subject of debate.

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