CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic and Thrombolytic Therapy for Valvular Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **Antithrombotic therapy in valvular disease is important to mitigate thromboembolism, but the hemorrhagic risk imposed must be considered.**
Methods: **The methods of this guideline follow those described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**
Results: **In rheumatic mitral disease, we recommend vitamin K antagonist (VKA) therapy when the left atrial diameter is > 55 mm (Grade 2C) or when complicated by left atrial thrombus (Grade 1A). In candidates for percutaneous mitral valvotomy with left atrial thrombus, we recommend VKA therapy until thrombus resolution, and we recommend abandoning valvotomy if the thrombus fails to resolve (Grade 1A). In patients with patent foramen ovale (PFO) and stroke or transient ischemic attack, we recommend initial aspirin therapy (Grade 1B) and suggest substitution of VKA if recurrence (Grade 2C). In patients with cryptogenic stroke and DVT and a PFO, we recommend VKA therapy for 3 months (Grade 1B) and consideration of PFO closure (Grade 2C). We recommend against the use of anticoagulant (Grade 1C) and antiplatelet therapy (Grade 1B) for native valve endocarditis. We suggest holding VKA therapy until the patient is stabilized without neurologic complications for infective endocarditis of a prosthetic valve (Grade 2C). In the first 3 months after bioprosthetic valve implantation, we recommend aspirin for aortic valves (Grade 2C), the addition of clopidogrel to aspirin if the aortic valve is transcatheter (Grade 2C), and VKA therapy with a target international normalized ratio (INR) of 2.5 for mitral valves (Grade 2C). After 3 months, we suggest aspirin therapy (Grade 2C). We recommend early bridging of mechanical valve patients to VKA therapy with unfractionated heparin (DVT dosing) or low-molecular-weight heparin (Grade 2C). We recommend long-term VKA therapy for all mechanical valves (Grade 1B): target INR 2.5 for aortic (Grade 1B) and 3.0 for mitral or double valve (Grade 2C). In patients with mechanical valves at low bleeding risk, we suggest the addition of low-dose aspirin (50-100 mg/d) (Grade 1B). In valve repair patients, we suggest aspirin therapy (Grade 2C). In patients with thrombosed prosthetic valve, we recommend fibrinolysis for right-sided valves and left-sided valves with thrombus area < 0.8 cm^2 (Grade 2C). For patients with left-sided prosthetic valve thrombosis and thrombus area ≥ 0.8 cm^2, we recommend early surgery (Grade 2C).**
Conclusions: **These antithrombotic guidelines provide recommendations based on the optimal balance of thrombotic and hemorrhagic risk.** ***CHEST 2012; 141(2)(Suppl):e576S–e600S***

Abbreviations: AF = atrial fibrillation; APA = antiplatelet agent; AVR = aortic valve replacement; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; ICH = intracerebral hemorrhage; IE = infective endocarditis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MAC = mitral annular calcification; MVP = mitral valve prolapse; NBTE = nonbacterial thrombotic endocarditis; NYHA = New York Heart Association; OAC = oral anticoagulation; PFO = patent foramen ovale; PICO = population, intervention, comparator, and outcome; PMBV = percutaneous mitral balloon valvotomy; PVE = prosthetic valve endocarditis; PVT = prosthetic valve thrombosis; RCT = randomized controlled trial; RR = relative risk; TEE = transesophageal echocardiography; TIA = transient ischemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.0.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm we suggest not using antiplatelet or vitamin K antagonist (VKA) therapy (Grade 2C)**.**

2.0.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm, we suggest VKA therapy (target international normalized ratio [INR], 2.5; range, 2.0-3.0) over no VKA therapy or antiplatelet (Grade 2C)**.**

2.0.3. For patients with rheumatic mitral valve disease complicated by the presence of left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A)**.**

2.0.4. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of atrial fibrillation or previous systemic embolism, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A)**.**

2.1.1. For patients being considered for percutaneous mitral balloon valvotomy (PMBV) with preprocedural transesophageal echocardiography (TEE) showing left atrial thrombus, we recommend postponement of PMBV and that VKA therapy (target INR, 3.0; range, 2.5-3.5) be administered until thrombus resolution is documented by repeat TEE over no VKA therapy (Grade 1A)**.**

2.1.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, if the left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1A)**.**

6.2.1. In patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C)**.**

6.2.2. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A)**.**

6.2.3. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C)**.**

6.2.4. In patients with cryptogenic stroke and PFO, with evidence of DVT, we recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0) (Grade 1B) **and consideration of device closure over no VKA therapy or aspirin therapy** (Grade 2C)**.**

7.1.1. In patients with infective endocarditis (IE), we recommend against routine anticoagulant therapy, unless a separate indication exists (Grade 1C)**.**

7.1.2. In patients with IE, we recommend against routine antiplatelet therapy, unless a separate indication exists (Grade 1B)**.**

7.2. In patients on VKA for a prosthetic valve who develop IE, we suggest VKA be discontinued at the time of initial presentation until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is

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deemed stable without contraindications or neurologic complications, we suggest reinstitution of VKA therapy (Grade 2C).

7.3. In patients with nonbacterial thrombotic endocarditis and systemic or pulmonary emboli, we suggest treatment with full-dose IV unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) over no anticoagulation (Grade 2C).

8.2.1. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we suggest aspirin (50-100 mg/d) over VKA therapy in the first 3 months (Grade 2C).

8.2.2. In patients with transcatheter aortic bioprosthetic valves, we suggest aspirin (50-100 mg/d) plus clopidogrel (75 mg/d) over VKA therapy and over no antiplatelet therapy in the first 3 months (Grade 2C).

8.2.3. In patients with a bioprosthetic valve in the mitral position, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy for the first 3 months after valve insertion (Grade 2C).

8.3. In patients with bioprosthetic valves in normal sinus rhythm, we suggest aspirin therapy over no aspirin therapy after 3 months postoperative (Grade 2C).

9.1. In patients with mechanical heart valves, we suggest bridging with unfractionated heparin (UFH, prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (Grade 2C).

9.2. In patients with mechanical heart valves, we recommend VKA therapy over no VKA therapy for long-term management (Grade 1B).

9.3.1 In patients with a mechanical aortic valve, we suggest VKA therapy with a target of 2.5 (range, 2.0-3.0) over lower targets (Grade 2C).

9.3.2. In patients with a mechanical aortic valve, we recommend VKA therapy with a target of 2.5 (range 2.0-3.0) over higher targets (Grade 1B).

9.4. In patients with a mechanical mitral valve, we suggest VKA therapy with a target of 3.0 (range, 2.5-3.5) over lower INR targets (Grade 2C).

9.5. In patients with mechanical heart valves in both the aortic and mitral position, we suggest target INR 3.0 (range 2.5-3.5) over target INR 2.5 (range 2.0-3.0) (Grade 2C).

9.6. In patients with a mechanical mitral or aortic valve at low risk of bleeding, we suggest adding over not adding an antiplatelet agent such as low-dose aspirin (50-100 mg/d) to the VKA therapy (Grade 1B).

Remarks: Caution should be used in patients at increased bleeding risk, such as history of GI bleeding.

9.7. For patients with mechanical aortic or mitral valves we recommend VKA over antiplatelet agents (Grade 1B).

10.1. In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, we suggest the use of antiplatelet therapy for the first 3 months over VKA therapy (Grade 2C).

10.2. In patients undergoing aortic valve repair, we suggest aspirin at 50 to 100 mg/d over VKA therapy (Grade 2C).

11.1. For patients with right-sided prosthetic valve thrombosis (PVT), in the absence of contraindications we suggest administration of fibrinolytic therapy over surgical intervention (Grade 2C).

11.2.1. For patients with left-sided PVT and large thrombus area ($\geq$0.8 cm^2), we suggest early surgery over fibrinolytic therapy (Grade 2C). **If contraindications to surgery exist, we suggest the use of fibrinolytic therapy** (Grade 2C).

11.2.2. For patients with left-sided PVT and small thrombus area ($<$0.8 cm^2), we suggest administration of fibrinolytic therapy over surgery. For very small, nonobstructive thrombus we suggest IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement over other alternatives (Grade 2C).

Thromboembolic complications of valvular heart disease are often devastating. Antithrombotic therapy can reduce the risk of thromboembolism, but at the cost of increased bleeding. This article seeks to provide recommendations based on the optimal balance of these competing factors.

Table 1 describes the population, intervention, comparator, and outcome (PICO) elements for the questions addressed in this article and the design of the studies used to address them. We define only

Table 1—*Structured Clinical Questions*

Section	PICO Question				Methodology
	Population	Interventions	Comparator	Outcome	
			2.0 Rheumatic mitral valve		
2.0.1	Normal sinus rhythm and left atrial diameter < 55 mm	Anticoagulation or antiplatelet	No anticoagulation or antiplatelet	Thromboembolism	Observational studies
2.0.2	Normal sinus rhythm and left atrial diameter > 55 mm	Anticoagulation	No anticoagulation	Thromboembolism	Observational studies
2.0.3	Presence of left atrial thrombus	Anticoagulation	No anticoagulation	Thromboembolism	Observational studies
2.0.4	Atrial fibrillation or previous systemic embolism	Anticoagulation	No anticoagulation	Total mortality, stroke, major bleeding event	RCT observational studies
2.1.1	Percutaneous mitral balloon valvotomy in presence of left atrial thrombus	Anticoagulation prior to procedure	No anticoagulation prior to procedure	Thromboembolism	Observational studies
2.1.2	Percutaneous mitral balloon valvotomy with nonresolving left atrial thrombus	PMBV	No PMBV	Thromboembolism	Expert consensus
			6.0 Aortic atheroma and PFO		
6.2.1	Asymptomatic PFO or atrial septum aneurysm	Anticoagulation or antiplatelet	No anticoagulation or antiplatelet	Stroke	Observational studies
6.2.2	Stroke in the presence of PFO	Antiplatelet	No antiplatelet	Recurrent stroke or death	RCT subgroup data
6.2.3	Recurrent stroke and PFO	Anticoagulation	Antiplatelet	Recurrent stroke	Observational studies
6.2.4	PFO in presence of DVT	Anticoagulation	No anticoagulation	Recurrent stoke, pulmonary embolism, mortality	RCT (indirect)
			7.0 Endocarditis		
7.1.1	Infective endocarditis	Anticoagulation	No anticoagulation	Thromboembolism, intracerebral bleed	Observational studies
7.1.2	Infective endocarditis	Antiplatelet	No antiplatelet	Thromboembolism, mortality, major bleed	RCT
7.2	Prosthetic valve endocarditis	Anticoagulation	No anticoagulation	Thromboembolism, bleeding	Observational studies
7.3	Nonbacterial thrombotic endocarditis with prior embolism	Anticoagulation	No anticoagulation	Recurrent embolism	Observational studies
			8.0 Bioprosthetic heart valves		
8.2.1	Aortic bioprosthesis with normal sinus rhythm	Anticoagulation for first 3 mo	Antiplatelet for first 3 mo	Thromboembolism, mortality, major bleeding event	RCT
8.2.2	Transcatheter aortic bioprosthesis with normal sinus rhythm	Anticoagulation in first 3 mo	Antiplatelet for first 3 mo	Thromboembolism, major bleeding event	Observational studies
8.2.3	Mitral bioprosthesis with normal sinus rhythm	Anticoagulation in first 3 mo	No anticoagulation for first 3 mo	Thromboembolism, major bleeding event	Observational studies

(Continued)

Table 1—*Continued*

Section	PICO Question: Population	Interventions	Comparator	Outcome	Methodology
			9.0 Mechanical heart valves		
9.1	Mechanical heart valves early postoperative (day 0-5)	UFH or LMWH (DVT dosing)	IV therapeutic UFH	Thromboembolism, bleeding	Observational studies
9.2	Mechanical heart valves	Long-term anticoagulation	No long-term anticoagulation	Thromboembolism, valve thrombosis	Meta-analysis of observational data
9.3.1	Mechanical aortic valve	Conventional INR target (2.0-3.0)	Lower INR targets	Thromboembolism, bleeding	RCT
9.3.2	Mechanical aortic valve	Conventional INR target (2.0-3.0)	Higher INR targets	Thromboembolism, major bleeding event, mortality	RCT
9.4	Mechanical mitral valve	Conventional INR target (2.5-3.5)	Lower INR targets	Thromboembolism, major bleeding event, mortality	RCT
9.5	Mechanical aortic and mitral valve	INR target 2.5-3.5	INR target 2.0 to 3.0	Mortality	RCT
9.6	Mechanical heart valves	Antiplatelet in addition to anticoagulation	Anticoagulation alone	Thromboembolism, mortality, valve thrombosis, major bleeding event	Meta-analysis of RCTs
			10.0 Heart valve repair		
10.1	Mitral valve repair with prosthetic band	Antiplatelet	Anticoagulation	Thromboembolism, valve thrombosis	Observational studies
10.2	Aortic valve repair	Antiplatelet	Anticoagulation	Thromboembolism, bleeding	Observational studies
			11.0 Prosthetic valve thrombosis		
11.1	Right-sided prosthetic valve thrombosis	Fibrinolytic therapy	Surgical intervention	Mortality, hemodynamic success, thromboembolism, bleeding, recurrence of obstruction	Observational studies
11.2.1	Left-sided prosthetic valve thrombosis with thrombus ≥ 0.8 cm^2	Fibrinolytic therapy	Surgical intervention	Mortality, hemodynamic success, thromboembolism, bleeding, recurrence of obstruction	Observational studies
11.2.2	Left-sided prosthetic valve thrombosis with thrombus < 0.8 cm^2	Fibrinolytic therapy	Surgical intervention	Mortality, hemodynamic success, thromboembolism, bleeding, recurrence of obstruction	Observational studies

INR = international normalized ratio; LMWH = low-molecular-weight heparin; PFO = patent foramen ovale; PICO = population, intervention, comparator, and outcome; PMBV = percutaneous mitral balloon valvotomy; RCT = randomized controlled trial; UFH = unfractionated heparin.

patient characteristics relevant to our questions. This article does not make recommendations specific to atrial fibrillation (AF); for this issue, we direct you to the article by You et al[1] on AF in this supplement. In areas of overlap with the AF article, where newer anticoagulants such as dabigatran may be considered for nonvalvular AF, caution must be used when extrapolating their use to the populations described in this article. This article continues to consider vitamin K antagonists (VKAs) as the first-line oral anticoagulant until evidence of efficacy and safety within the valve population is generated. For recommendations on the management of parenteral anticoagulation (dosing and monitoring), oral anticoagulation (dosing and monitoring), and bleeding complications, please refer to the article by Holbrook et al[2] about management of anticoagulation in this guideline. Finally, there

are very few data directly addressing the antithrombotic management of right-sided prosthetic valves. Indirect evidence from mitral and aortic valves provides the best evidence and the basis for recommendations regarding tricuspid and pulmonic prostheses.

1.0 Methods

The development of the current recommendations followed the general approach of Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[3] In brief, literature searches to update the existing database from the AT8 guidelines were performed (January 1, 2005 to October 2009). The literature was rated according to the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. The panel considered quality of information, balance of risk and harm, and patients' values and preferences to determine the strength of recommendation.

In making recommendations, we have taken a *primum non nocere* approach, placing the burden of proof with those who would claim a benefit of treatment. In other words, when there is uncertain benefit and an appreciable probability of important harm associated with treatment, we recommend against such treatments.

The value given to the harmful effect of an extracranial bleeding event (as compared with that of valve thrombosis, peripheral thromboembolism, or stroke) greatly impacts the balance of benefits and harms of a given therapy. There are limited data to guide us with respect to the relative value of these outcomes. For this article, we used the result of the preference-weighting exercise carried out by MacLean et al[4] as part of these guidelines, which attributes approximately three times the disutility (aversiveness, negative weight) to a stroke vs an extracranial bleeding event; a valve thrombosis carries slightly greater disutility than an extracranial bleeding event.

2.0 Rheumatic Mitral Valve Disease

Rheumatic mitral valve disease carries the greatest risk of systemic thromboembolism of any common form of acquired valvular disease. Wood[5] cited a prevalence of systemic emboli of 9% to 14% in several large early series of patients with mitral stenosis. In 1961, Ellis and Harken[6] reported that 27% of 1,500 patients undergoing surgical mitral valvotomy had a history of clinically detectable systemic emboli. Among 754 patients followed up for 5,833 patient-years, Szekely[7] observed an incidence of emboli of 1.5% per year, whereas the number was found to vary from 1.5% to 4.7% per year preoperatively in six reports of rheumatic mitral valve disease.[8] Although the risk may increase in the elderly and those with lower cardiac indices,[9-12] these findings have been inconsistent across studies.[5,13-21] Other characteristics that may increase the risk of systemic embolism include the presence of a left atrial thrombus and significant aortic regurgitation.[22]

The relationship between thromboembolism and left atrial size remains unclear. Early studies[5,13,14] of rheumatic mitral valve disease reported a weak correlation. However, several studies have now demonstrated an association between larger left atrial size and left atrial thrombus or spontaneous echocardiographic contrast.[15-17]

In those patients with rheumatic mitral valve disease who suffer a first embolus, recurrent emboli occur frequently (one-third to two-thirds of cases) and early (two-thirds within the first year).[5,23-25] A hypercoagulable state in mitral stenosis might contribute to the risk of thromboembolism.[26,27] No randomized trial has been completed in this population, but observational data suggest that the risk of recurrent emboli may be reduced by VKA therapy. Szekely[7] found a recurrence rate of 9.6%/y with no anticoagulation and 3.4%/y with warfarin (relative risk [RR], 0.36; 95% CI, 0.08-1.6). Similar estimates have been reported by others.[14,28] Among patients with mitral stenosis and left atrial thrombus on transesophageal echocardiography (TEE), VKA therapy results in a 62% thrombus disappearance over an average of 34 months.[29]

The onset of AF increases the risk of systemic embolization in patients with rheumatic mitral valve disease.[7,13] As in those with recurrent embolism, observational studies suggest a large decrease in risk with warfarin administration.[13,30] Indirect evidence from randomized trials in nonvalvular AF provide further support for the impact of warfarin in the prevention of thromboembolism in patients with rheumatic mitral valve with AF.

Recommendations

2.0.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm, we suggest not using antiplatelet or VKA therapy (Grade 2C)**.**

2.0.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy or antiplatelet (Grade 2C)**.**

2.0.3. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A)**.**

2.0.4. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of AF or previous systemic embolism, we recommend VKA therapy (target

INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A)**.**

2.1 Patients With Rheumatic Mitral Valve Disease Undergoing Percutaneous Mitral Balloon Valvotomy

During the percutaneous mitral balloon valvotomy (PMBV) procedure, when the catheter is pushed through the septum it often goes into the left atrial appendage, the usual site of thrombus. Thus, the presence of left atrial thrombus precludes PMBV. Accurate detection of thrombus requires a transesophageal echocardiogram (TEE). Silaruks et al[31] have demonstrated that 24.2% of left atrial thrombi will resolve within 6 months of anticoagulation. Further, Kang et al[32] have demonstrated that after thrombus resolution, PMBV can be safely performed. Predictors of thrombus resolution are New York Heart Association (NYHA) functional class II or better, left atrial appendage thrombus size ≤ 1.6 cm^2, less dense spontaneous echocardiographic contrast, and an INR ≥ 2.5. Patients with all of these predictors had a 94.4% chance of complete thrombus resolution at 6 months.[31]

In those patients without left atrial thrombus and no other indication for anticoagulation, Abraham et al[33] demonstrated PMBV can be performed in the absence of anticoagulation, with no patients in 629 procedures performed having an embolism within 3 months post procedure.

Recommendations

2.1.1. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, we recommend postponement of PMBV and that VKA therapy (target INR, 3.0; range, 2.5-3.5) be administered until thrombus resolution is documented by repeat TEE over no VKA therapy (Grade 1A)**.**

2.1.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, if the left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1A)**.**

3.0 Mitral Valve Prolapse and Mitral Valve Strands

Mitral valve prolapse (MVP) is a common congenital form of valve disease. Although early evidence from case series and control studies suggested an association with stroke,[34-40] Gilon et al[41] and the Framingham Heart Study[42] failed to replicate the results. More recently, Avierinos et al[43] found that people with MVP had an excess lifetime risk of stroke or transient ischemic attack (TIA) (RR, 2.2; $P < .001$). Thus, it is as yet unclear whether MVP truly increased the risk of thromboembolic process. Mitral valve strands, also known as Lambl's excrescences, have also been implicated as a potential embolic source, but they do not seem to increase the risk of stroke recurrence.[44] We therefore suggest that patients with MVP or strands who have not experienced systemic embolism, unexplained TIAs, or ischemic stroke, and do not have evident vascular disease should be managed as other patients considering primary prevention of vascular events. Given the risk of bleeding complications with anticoagulation and the lack of data to demonstrate a benefit in terms of reducing (recurrent) thromboembolic events, patients with MVP or strands and a history of ischemic stroke or TIA should be treated with antiplatelet agents following the recommendations by Landsberg et al[45] for patients with noncardioembolic stroke. In those patients with MVP or strands who have recurrent thromboembolic events despite antiplatelet agent (APA) therapy, the likelihood of a cardiac source increases.

4.0 Mitral Annular Calcification

Mitral annular calcification (MAC), like MVP, may be a source of cardioembolic stroke. The best estimate of the embolic potential of MAC comes from the Framingham Heart Study.[46] Among 1,159 individuals with no history of stroke at the index echocardiographic examination, the risk of stroke in those with MAC was 2.1 times greater than those without MAC (5.1% without MAC vs 13.8% with MAC, $P = .006$), independent of traditional risk factors for stroke. There was a continuous relationship between the risk of stroke and the severity of the MAC. A major issue in this condition is that emboli may represent thrombus or calcific spicules, the latter of which antithrombotic therapy will not prevent.[46-48] From the available literature, we suggest that patients with MAC who have not experienced systemic embolism, unexplained TIAs, or ischemic stroke, and do not have evident vascular disease should be managed as other patients considering primary prevention of vascular events. It would be reasonable to manage patients with MAC and evidence of thromboembolic process with no other identifiable source as patients with TIAs without MAC.[45] Failure of this antithrombotic therapy or evidence of multiple calcific emboli should prompt consideration of valve replacement.

5.0 Calcified Aortic Valve

Clinically significant systemic emboli in isolated aortic valve disease are uncommon. A lack of association between aortic valve calcification and clinical emboli has been supported by several studies.[49-51] Thus, in the absence of other indications, antithrombotic therapy does not have a role in calcified aortic valve disease.

6.0 Aortic Atheroma and Patent Foramen Ovale

6.1 Atherosclerotic Plaque of the Proximal Aorta

The presence of aortic plaque is associated with stroke risk.[52,53] In a TEE substudy of the Stroke Prevention in Atrial Fibrillation (SPAF) trial, the risk of stroke at 1 year in patients with AF with complex aortic plaque was 12% to 20% vs 1.2% if no plaque was observed.[54] Cohen et al[55] demonstrated that aortic plaques > 4 mm in thickness increased the risk of vascular events, and this risk was further increased by lack of plaque calcification (RR = 10.3; 95% CI, 4.2-25.2). There are no randomized trials assessing the effectiveness of anticoagulation therapy for the prevention of ischemic embolic events in patients with aortic plaque.

Ferrari et al[56] examined the effects of antithrombotic therapy in an observational study of 129 patients with aortic atheroma on TEE. They found that patients treated with APAs rather than VKAs had more combined vascular events and a higher mortality rate (RR = 5.9; 95% CI, 1.4-15). However, Tunick et al[57] reported that antithrombotic therapy did not significantly reduce recurrent events results in 519 patients with severe aortic plaque ($\geq$ 4 mm) identified during TEE evaluation for embolic events.

There is currently insufficient evidence to support the use of antithrombotic therapy for the prevention of ischemic events in patients with severe thoracic aortic atheroma.[58] We, therefore, suggest that patients with aortic atheroma who have not experienced systemic embolism, unexplained TIAs, or ischemic stroke, and do not have evident vascular disease should be managed as other patients considering primary prevention of vascular events.[45] Patients with atherosclerotic aorta and evidence of thromboembolic process with no other identifiable source should be managed as those with TIAs and no atheromatous disease.[45]

6.2 Patent Foramen Ovale and Atrial Septal Aneurysm

In patients with patent foramen ovale (PFO) and atrial septal aneurysm who suffer an ischemic stroke, the source is unclear in approximately 40%.[59] The interatrial septum has received considerable attention as a possible source of cryptogenic stroke. Paradoxical embolism through a PFO is well described, and atrial septal aneurysm with thrombus has been demonstrated.[60] However, PFO and septal aneurysm are weak risk factors for stroke.

Patient characteristics that have been associated with ischemic stroke in PFO include larger-sized PFO, hemodynamic states that result in right atrial pressure overload with right-to-left shunting, hypercoagulability, the presence of eustachian valve, Chiari network, and atrial septal aneuryms.[59,61] More recent studies[62,63] from Olmsted County, Minnesota and the Stroke Prevention: Assessment of Risk in a Community (SPARC) study have suggested that after adjusting for age and other comorbidities associated with stroke, PFO is not an independent risk factor for stroke. This may be a function of how PFOs are detected. TEE with saline contrast injection is the diagnostic technique of choice for demonstrating a PFO.[64] However, since the sensitivity of saline contrast TEE is greater than that of transthoracic echocardiography, whether smaller PFOs identified only by TEE are clinically relevant remains uncertain.

Mas et al[65] suggest that patients with both a PFO and atrial septal aneurysm who have had cryptogenic ischemic stroke are at particularly high risk for recurrence. At 4 years of follow-up, the risk of recurrent stroke in the presence of an isolated PFO was 2.3% (95% CI, 0.3%-4.3%), 15.2% (95% CI, 1.8%-28.6%) among the patients with both PFO and atrial septal aneurysm, and 4.2% (95% CI, 1.8%-6.6%) among the patients with neither of these abnormalities. All patients within this study received aspirin, with no comparator group. Therefore, conclusions on appropriate antithrombotic therapy vs no antithrombotic therapy are currently not possible. Patients with evidence of thromboembolic process and no other identifiable source should be managed as those with cryptogenic TIA or stroke.[45]

Homma et al[66] reported on the subgroup of 203 patients with PFO in the Warfarin-Aspirin Recurrent Stroke Study (Table 2, Table S1). (Tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement. See the "Acknowledgments" for more information.) For the outcome of stroke or death at 2 years, the results neither establish nor exclude a difference between aspirin therapy and VKA therapy (RR, 0.80; 95% CI, 0.41-1.55).

In patients with cryptogenic systemic thromboembolism, the demonstration of right-to-left shunting through a PFO warrants a search for DVT. Evidence for venous thrombosis (or pulmonary embolism) together with systemic embolism and a PFO

Table 2—*[Section 6.2.2] Summary of Findings: Aspirin vs Warfarin for the Prevention of Recurrent Stroke or Death in Patients With PFO*[61]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With VKA	Risk Difference With ASA (95% CI)
Recurrent stroke or death; clinical	203 (1 study) 2 y	Moderate[a] due to imprecision	RR, 0.8 (0.41-1.55)	165 per 1,000	33 Fewer per 1,000 (from 97 fewer to 91 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; RR = relative risk; VKA = vitamin K antagonist.

[a]Wide CIs for effect estimates.

provides a strong indication for anticoagulation, and when technically feasible, closure of the PFO. There are several ongoing trials of device closure which will better inform this area in the near future.

Recommendations

6.2.1. In patients with asymptomatic PFO or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C)**.**

6.2.2. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A)**.**

6.2.3. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C)**.**

6.2.4. In patients with cryptogenic stroke and PFO, with evidence of DVT, we recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0) (Grade 1B) **and consideration of device closure over no VKA therapy or aspirin therapy** (Grade 2C)**.**

7.0 Endocarditis

7.1 Native Valve Endocarditis: Role of Anticoagulants and Antiplatelet Agents

Native valve infective endocarditis (IE) is a serious infectious entity, the morbidity of which is primarily related to the consequences of systemic embolism from valve vegetations. The risk of embolization is proportional to the size of the vegetation and the type of organism (eg, *Staphylococcus aureus* increases risk).[67,68] The majority of clinically apparent emboli from left-sided lesions involve the CNS resulting in catastrophic stroke. The incidence of pulmonary emboli in right-sided endocarditis is also high, and this complication may contribute to significant respiratory complications, including lung abscess and pulmonary hypertension.[69]

Antibiotics are the most important medical therapy to decrease the incidence of emboli from native bacterial endocarditis. Whereas in the preantibiotic era, clinically detectable emboli occurred in 70% to 97% of patients, since that time the prevalence has ranged between 12% and 40%.[69-73] Further, the incidence of embolic complications, highest at the onset of disease, falls precipitously after 2 weeks of appropriate antibiotic therapy, from approximately 15 embolic events per 1,000 patient-days to fewer than two events per 1,000 patient-days.[69]

The use of anticoagulant therapy in IE was initially introduced as a mechanism to improve the penetration of antibiotics into infected vegetations.[75] When closely examined, the effect of anticoagulants on the incidence of embolism was not evident.[76] In a retrospective study of 61 patients with native valve endocarditis, Paschalis et al[77] reported that 18 patients suffered embolic neurologic complications. The incidence of embolism was the same with and without anticoagulation. Subsequent reports have demonstrated that patients treated with anticoagulant therapy were at significant risk of intracerebral hemorrhage (ICH). Thill et al[78] described 22 patients taking combined penicillin and dicumarol with a high incidence of fatal cerebral hemorrhage. Other groups have reported an alarming incidence of cerebral hemorrhage.[79-83]

A trial of 115 patients with IE who were randomized to aspirin treatment reported the effect of aspirin therapy on the risk of embolic events in IE (n = 60, 325 mg/d) or placebo (n = 55) for 4 weeks (Table 3, Table S2).[84] The addition of aspirin did not reduce the risk of embolic events, with 17 (28.3%) such events in the aspirin group vs 11 (20.0%) in the placebo group (OR, 1.62; 95% CI,

Table 3—*[Section 7.1.2] Summary of Findings: The Effect of Aspirin Therapy on Outcomes of Infective Endocarditis*[79]

Outcomes	No of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Control	Anticipated Absolute Effects: Risk Difference With Antiplatelet Agents (95% CI)
Mortality	114 (1 study)	Moderate[a] due to imprecision	OR, 0.58 (0.16-2.19)	109 per 1,000	43 fewer per 1,000 (from 90 fewer to 102 more)
Thromboembolism including stroke; clinical examination, CT scan	114 (1 study)	See comment	OR, 1.62 (0.62-3.86)	200 per 1,000	88 more per 1,000 (from 66 fewer to 291 more)
Major hemorrhage; well defined[b]	114 (1 study)	Moderate[a] due to imprecision	OR, 1.92 (0.76-4.86)	55 per 1,000	45 more per 1,000 (from 13 fewer to 164 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 legend for expansion of abbreviation.

[a]Wide confidence intervals for effect estimates

[b]Intracranial bleeding, overt bleeding resulting in a decrease in hemoglobin ≥ 20 g/L or requiring blood transfusion, and bleeding into a confined space, which can cause severe morbidity, such as pericardial hematoma or paraspinal hematoma.

0.68-3.86). These data provide moderate-quality evidence (wide CI includes benefit from aspirin) that there is no role for APA therapy in IE unless another indication exists.

In summary, there is no convincing evidence that prophylactic anticoagulant therapy reduces the incidence of emboli in this disorder. The evidence to date further suggests that anticoagulant therapy in this setting increases the rate of neurologic complications related to cerebral hemorrhage.

Recommendations

7.1.1. In patients with IE, we recommend against routine anticoagulant therapy, unless a separate indication exists (Grade 1C)**.**

7.1.2. In patients with IE, we recommend against routine antiplatelet therapy, unless a separate indication exists (Grade 1B)**.**

7.2 Role of Anticoagulants in Prosthetic Valve Endocarditis

The risk of thromboembolic events in prosthetic valve endocarditis (PVE) is higher than that in native valve endocarditis, with reports of rates between 50% and 88% of patients.[71,73,85,86] Antimicrobial therapy remains the mainstay of embolization prevention; delay in therapy is related to the frequency of embolic stroke within 3 days of diagnosis.[87]

Only one article has reported benefit of antithrombotic therapy in PVE. In an observational study, Wilson et al[86] described CNS complications in only three of 38 patients with PVE who received adequate anticoagulant therapy compared with 10 of 14 patients who received either inadequate or no anticoagulation. The majority of studies suggest the risk of continuing anticoagulation in this disorder outweighs the potential benefits. In another observational study, Yeh et al[88] reported that therapeutic anticoagulation not only failed to control emboli in PVE, but the risk of bleeding appeared to be greater among patients with infected prostheses. Others have published similar observational results.[73,89] Some authors continue to suggest that anticoagulant therapy should be continued in patients with PVE,[72,85,86] whereas others do not.[69,73]

In conclusion, the use of anticoagulants in PVE must steer a path between the potential for thromboembolism and the risk of serious bleeding, including ICH. Although one might expect that the incidence of thromboembolism will be reduced by anticoagulant therapy, there is no evidence that embolic vegetations are controlled by this therapy. Further, the consequences of ICH may be irreversible and not infrequently fatal. Embolic events in PVE may represent dislodged vegetations or, alternatively, true thromboembolism unrelated to the valve infection.

Recommendation

7.2. In patients on VKA for a prosthetic valve who develop IE, we suggest VKA be discontinued at the time of initial presentation until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is deemed stable without contraindications or neurologic complications, we suggest reinstitution of VKA therapy (Grade 2C)**.**

7.3 Nonbacterial Thrombotic Endocarditis

The clinical picture of nonbacterial thrombotic endocarditis (NBTE) has been well characterized by Lopez et al.[90] These lesions generally are rounded, sessile, > 3 mm, and heterogeneous in shape compared with excrescences, which are smaller (< 2 mm) and sometimes elongated. Excrescences are seen exclusively near leaflet closure lines.

Although most authors agree that key principle for dealing with NBTE is to control underlying disease, anticoagulants were recommended due to the general belief that Trousseau syndrome and NBTE represent a continuum and that disseminated intravascular coagulation is the basis for treating most patients with this disorder.[91] In support of anticoagulant therapy, recurrent thromboembolic complications have been reported after heparin therapy was discontinued, although little apparent benefit has been observed with VKA therapy.[90-92]

Recommendation

7.3. In patients with NBTE and systemic or pulmonary emboli, we suggest treatment with full-dose IV UFH or subcutaneous LMWH over no anticoagulation (Grade 2C)**.**

8.0 Bioprosthetic Heart Valves

8.1 Early Postoperative Bridging to Intermediate/ Long-term Therapy (Postoperative Day 0 to 5)

There are no studies examining early bridging therapy such as UFH or LMWH prior to antiplatelet therapy or VKA initiation in the bioprosthetic valve population. Therefore, we are currently unable to make recommendations on this topic.

8.2 Antithrombotic Therapy in the First 3 Months After Surgery

The first 3 months after valve implantation are a high-risk period for thromboembolic events, particularly in the mitral valve population.[93,94] Because the risk of a thromboembolic event varies by valve location, we have generated separate evidence profiles by this division.

8.2.1 Aortic Bioprosthesis: Evidence comparing VKA to no VKA is available from observational studies with a focus on stroke and major hemorrhage. The quality of the evidence is low due to study limitations and imprecision (Table 4, Table S3).[95,96] Moinuddeen et al[95] failed to demonstrate or exclude an effect of oral anticoagulation therapy on stroke (RR, 1.1; 95% CI, 0.38-3.28). Blair et al[96] demonstrated a trend toward increased risk of major hemorrhage but failed to establish or refute effect on thrombosis. Indirect supporting evidence that VKA therapy leads to an increased risk of hemorrhage compared with aspirin or no therapy also comes from studies in patients with AF.[1]

Two randomized trials have compared antiplatelet therapy with VKA for the initial antithrombotic management of patients with bioprosthetic heart valves (Table 5, Table S4).[97,98] Aramendi et al[97] randomized 191 patients to either antiplatelet therapy with triflusal 600mg/d (an antiplatelet agent similar to

Table 4—*[Section 8.2.1] Summary of Findings: Effect of VKA Therapy on Stroke and Major Bleeding in the First 3 mo After Bioprosthetic Aortic Valve Implantation*[90,91]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Control	Anticipated Absolute Effects: Risk Difference With Oral Anticoagulation for First 3 mo (95% CI)
Stroke; chart review, patient interview[a]	185 (1 study[b]) 3 mo[c]	Low[d,e] due to risk of bias, imprecision	RR, 1.1 (0.38-3.28)	66 per 1,000	7 more per 1,000 (from 41 fewer to 150 more)
Major hemorrhage; chart review and patient interview	239 (1 study[f]) 3 mo	Low[d,e] due to risk of bias, imprecision	RR, 5.12 (0.58-45.16)	7 per 1,000	30 more per 1,000 (from 3 fewer to 325 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 2 legends for expansion of abbreviations.

[a]Included new transient or permanent focal or global neurologic deficits.

[b]Moinuddeen et al.[95]

[c]Follow-up longer, mean not reported; 3 mo data used.

[d]Retrospective study: allocation by surgeon clinical choice, event ascertainment/adjudication not blinded to therapy received.

[e]CI includes values suggesting appreciable harm and values suggesting appreciable benefit.

[f]Blair et al.[96]

Table 5—*[Section 8.2.1] Summary of Findings: Antiplatelet vs VKA in the First 3 mo After Bioprosthetic Aortic Valve Replacement*[92]

Outcomes	No. of Participants (Studies) Follow up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With VKA	Anticipated Absolute Effects: Risk Difference With Antiplatelet Agent (95% CI)
Mortality; clinical follow-up	69 (1 study[a]) 3 mo	Low[b,c] due to risk of bias, imprecision	RR, 1.03 (0.15 to 6.9)	57 per 1,000	2 more per 1,000 (from 49 fewer to 337 more)
Major hemorrhage	260 (2 studies[a,d]) 3-6 mo	Low[b,c] due to risk of bias, imprecision	RR, 0.46 (0 to 1.6)[e]	69 per 1,000	37 fewer per 1,000 (from 69 fewer to 42 more)
Thromboembolism	191 (1 study[d]) 6 mo	Low[b,c,f] due to risk of bias, indirectness, imprecision	RR, 1.98 (0.51 to 7.68)	32 per 1,000	31 more per 1,000 (from 15 fewer to 211 more)
Stroke; clinical follow-up	260 (2 studies[a,d]) 3-6 mo	Low[b,c,f] due to risk of bias, indirectness, imprecision	RR, 1.52 (0.28 to 2.76)	31 per 1,000	16 more per 1,000 (from 22 fewer to 54 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 2 legends for expansion of abbreviations.

[a]Colli et al.[98]

[b]Patient and clinical care providers not blinded, allocation concealed, event adjudicators were the investigators who were blinded to treatment.

[c]CI includes values suggesting appreciable harm and values suggesting appreciable benefit.

[d]Aramendi et al.[97]

[e]Aramendi and Colli meta-analyzed, fixed effects model.

[f]Group mitral and aortic valves together (Aramendi).

aspirin that irreversibly inhibits cyclooxygenase) or acenocoumarol (target INR range, 2.0-3.0) using an open-label design. The study included patients with aortic (93.8%) and mitral (5.2%) bioprosthetic valves and is thus most applicable to patients with aortic valve prostheses. Study treatments were started within 48 h of surgery and were continued for 3 months with follow-up to 180 days. The primary outcome was the composite of thromboembolism, hemorrhage, and valve-related death. Results failed to demonstrate or exclude a beneficial effect or detrimental effect on the primary efficacy outcome (RR, 0.89; 95% CI, 0.38-2.09) or treatment-related bleeding (RR, 0.50; 95% CI, 0.13-1.92).

Colli et al[98] performed a pilot randomized trial of 75 aortic valve patients who received either warfarin (n = 34) or aspirin (n = 35) therapy. The warfarin group, starting on postoperative day 1, received VTE prophylaxis-dose LMWH, and warfarin was started on day 2. Warfarin was dosed to reach an INR of 2.0 to 3.0. This was continued for 3 months. The aspirin group also received VTE prophylaxis-dose LMWH starting on postoperative day 1 but were then given 100 mg daily of aspirin for 3 months. Given the size of the study, there are predictably no differences in the main outcomes of cerebral ischemic events, bleeding, and death. These studies were not blinded and reported few events. Therefore, the quality of this evidence is low.

Recommendation

8.2.1. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we suggest aspirin (50-100 mg/d) over VKA therapy in the first 3 months (Grade 2C)**.**

8.2.2 Transcatheter Aortic Valve Bioprosthesis: Transcatheter aortic bioprosthesis is a new technology that compresses a tissue valve onto an expandable balloon, permitting placement without the traditional open-chest approach. The first implant in a human was in 2002.[99] There are no studies that compare antithrombotic strategies for these valves. The approach that has been adopted is an extension of the therapy used in coronary stenting: clopidogrel and aspirin for 3 to 6 months, followed by long-term aspirin therapy.[100,101] Further studies addressing antithrombotic management are required.

Recommendation

8.2.2. In patients with transcatheter aortic bioprosthetic valves, we suggest aspirin (50-100 mg/d)

Table 6—*[Section 8.2.3] Summary of Findings: Effect of Anticoagulation on Thromboembolism and Major Bleeding in First 3 mo After Bioprosthetic Mitral Valve Implantation*[88,91]

Outcomes	No of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Control	Anticipated Absolute Effects: Risk Difference With Oral Anticoagulation for First 3 mo (95% CI)
Thromboembolism[a]; protocol definition[b]	326 (1 study) 3 mo[c]	Low[d,e] due to risk of bias, imprecision	RR, 0.31 (0.09-1)	87 per 1,000	60 fewer per 1,000 (from 79 fewer to 0 more)
Major hemorrhage; chart review and patient interview	239 (1 study[f]) 3 mo	Low[d,e] due to risk of bias, imprecision	RR, 5.12 (0.58-45.16)	7 per 1,000	30 more per 1,000 (from 3 fewer to 325 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 2 legends for expansion of abbreviations.

[a]Heras et al.[93]

[b]Included cerebral, retinal, peripheral, and coronary emboli.

[c]Study followed for mean 8.3 y; 3-mo data presented here.

[d]Confounding highly likely.

[e]Few events resulting in wide CIs.

[f]Blair et al.[96]

and clopidogrel (75 mg/d) over VKA therapy and over no antiplatelet therapy in the first 3 months (Grade 2C)**.**

8.2.3 Mitral Bioprosthesis: The risk of a stroke from a mitral bioprosthetic valve in the first postoperative month has been reported to be as high as 40 events per 100 patient-years.[93,94,102] The direct evidence on the effects of early anticoagulation on this risk is of low quality. Unlike the aortic bioprosthesis, randomized data comparing VKA to antiplatelet in the setting of mitral valve bioprosthesis is lacking. The best evidence comes from Heras et al[93] (Table 6, Table S5). Their observational study reports a trend toward reduced thromboembolic events in those receiving warfarin over no warfarin. However, the regimen of anticoagulation, target INR, and comparator are not clearly reported and the estimates are based on 11 events. Further, bleeding will increase relative to aspirin or no antithrombotic therapy.

Turpie et al[103] randomized patients with bioprosthetic valves to receive warfarin at a target INR range of 2.5 to 4.0 (n = 108) or 2.0 to 2.25 (n = 102) using an open-label design (Table 7, Table S6). This trial included patients with aortic, mitral, and tricuspid valves but was not large enough to present the results by subgroup of valve position. Patients started warfarin after surgery as soon as they were able to tolerate oral medications. Results failed to demonstrate or exclude a beneficial effect or detrimental effect of the

Table 7—*[Section 8.2.3] Summary of Findings: Comparison of Lower INR Target (2.0-2.25) to Higher Target (2.5-4.0) for Bioprosthetic Valves in the First 3 mo After Implantation*[98]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Low INR	Anticipated Absolute Effects: Risk Difference With High INR (95% CI)
Thromboembolism; protocol definition[a]	210 (1 study) 3 mo	Low[b,c] due to risk of bias, imprecision	RR, 0.94 (0.14-6.58)	20 per 1,000	1 fewer per 1,000 (from 17 fewer to 109 more)
Major hemorrhage	210 (1 study)	Low[b,c] due to risk of bias, imprecision	RR, 10 (1.27-10)	…	…

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. INR = international normalized ratio; MI = myocardial infarction. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Cerebrovascular accident lasting > 24 h, MI with normal coronaries, systemic embolism diagnosed with angiography or surgery.

[b]Sealed envelope randomization, not blinded, groups aortic valve with mitral valve and double valve replacements.

[c]Few events resulting in wide CI including values suggesting appreciable harm and values suggesting appreciable benefit.

different INR targets on thrombosis (1.9% vs 2.0% for major embolism and 10.2% vs 10.8% for minor embolism, *P* value not reported). There were significantly more bleeding events in patients treated with high- compared with low-intensity VKA therapy (13.9% vs 5.9%, $P = .04$). Different laboratory methods were used to monitor the intensity of VKA therapy in the two groups, and it is unclear whether this impacted results.

There is currently little evidence regarding the addition of APA to oral anticoagulation (OAC) in the early treatment of bioprosthetic valves. A Cochrane review provides indirect evidence in patients with mechanical valves that suggests a significant reduction in mortality and thromboembolic outcomes at the cost of increased risk of bleeding (section 9.6). However, the trials included were dominated by mechanical valves and we are not confident that the results are generalizable to the bioprosthetic valve population.

Recommendation

8.2.3. In patients with a bioprosthetic valve in the mitral position, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy for the first 3 months after valve insertion (Grade 2C)**.**

8.3 Long-term Antithrombotic Therapy for Bioprosthetic Valves

The long-term risk of thromboemboli with a bioprosthetic valve is in the range of 0.2% to 2.6%/y.[104] The risk is lower for patients with aortic valve position (0.2%/y) and sinus rhythm.[105] There is currently no evidence supporting the long-term use of oral anticoagulation in patients with bioprosthetic valves. Case series have reported very low event rates in patients receiving APA.[106-109] For aortic bioprosthesis, Goldsmith et al[108] report that 145 patients in normal sinus rhythm treated with aspirin 75 mg daily suffered no major thromboembolic events and no major bleeding events in 254 patient-years of follow-up. Nunez et al[109] report that aspirin therapy in 185 patients receiving a mitral porcine bioprosthesis and in normal sinus rhythm resulted in no thromboembolic events.

Thromboembolism in patients with bioprosthetic valves and AF presumably relates to both the bioprosthetic valve and to the AF.[1] The incidence of thromboembolism in these patients was reported to be as high as 16% at 31 to 36 months.[110,111] Other factors such as lower ejection fraction and large left atrium have also been suggested to increase thromboembolic risk in the setting of bioprostheses[105]; however, this evidence in not compelling and there is no evidence to support the use of oral anticoagulation in the presence of normal sinus rhythm.

Recommendation

8.3. In patients with bioprosthetic valves in normal sinus rhythm, we suggest aspirin therapy over no aspirin therapy after 3 months postoperative (Grade 2C)**.**

9.0 Mechanical Heart Valves

9.1 Early Postoperative Bridging to Intermediate/Long-term Therapy (Postoperative Day 0 to 5)

The options for antithrombotic therapy immediately after mechanical heart valve replacement include oral VKA therapy with or without initial bridging using UFH or LMWH. We identified no randomized trials comparing these strategies.

9.1.1 Oral VKA Therapy With Prophylactic Subcutaneous UFH: A systematic review addressing the different initial anticoagulation strategies identified 20 observational studies.[112] Among 3,056 patients who received VKA therapy immediately after surgery, there was an absolute rate of thromboembolism of 0.9% and a bleeding rate of 3.3% during the first 30 days.

9.1.2 Oral VKA Bridged With LMWH: A prospective observational study by Talwar and colleagues[113] compared initial therapeutic LMWH plus oral VKA therapy to VKA therapy alone in 538 patients. Group A (n = 245) consisted of consecutive patients undergoing mechanical valve replacement over a 2-year period who were started on VKAs on postoperative day 1. Group B (n = 293) consisted of consecutive patients undergoing mechanical valve replacement over a subsequent 2-year period who received enoxaparin 1 mg/kg started 6 hours after surgery, repeated every 12 h, in combination with VKA therapy (started day 1) and continued until the INR was therapeutic. The target INR was 2.5 to 3.5 for patients with a mitral valve replacement or multiple mechanical valves and 2.0 to 3.0 for patients with an aortic valve replacement (AVR). All patients received aspirin 150 mg daily and were followed for 6 months. The incidence of prosthetic valve thrombosis (PVT) was significantly lower in patients who received enoxaparin compared with those who did not receive enoxaparin (6.1% vs 2.0%, $P = .01$), and there was no significant difference in bleeding.

Three observational studies reviewed by Kulik and colleagues[112] involving a total of 168 patients who received oral anticoagulation in combination with LMWH found rates of thromboembolism and bleeding

during the first 30 days after surgery of 0.6% and 4.8%, respectively.

9.1.3 Oral VKA Therapy Bridged With Therapeutic UFH: Kulik et al[112] reviewed seven observational studies involving 2,535 patients who received oral anticoagulation and IV UFH postoperatively and reported rates of thromboembolism and bleeding during the first 30 days of 1.1% and 7.2%, respectively. Bleeding data were available from only two studies (n = 261) and were not well defined with respect to major and minor events.

9.1.4 Oral VKA Therapy Bridged With Therapeutic UFH vs Oral VKA Therapy Bridged With LMWH: Montalescot and colleagues[114] looked at 208 consecutive patients undergoing mechanical heart valve replacement. The first 106 patients were treated with IV UFH as soon as postoperative chest tube drainage had decreased to acceptable levels (approximately 2 days after surgery). They were then switched to subcutaneous UFH tid in conjunction with oral VKAs starting on postoperative day 6. The target activated partial thromboplastin time was 1.5 to 2.5 times control for both IV and subcutaneous heparin therapies. The next 102 patients were treated with LMWH (enoxaparin or nadroparin) immediately after surgery and were started on oral VKAs on postoperative day 6. LMWH doses were titrated according to anti-Xa levels (target 0.5 to 1.0 International Units/mL). In both groups, IV or subcutaneous anticoagulation was discontinued once the INR was therapeutic. One patient treated with UFH suffered a TIA, whereas there were no thromboembolic events in the LMWH group. There were two major bleeding events in each treatment group.

Fanikos and colleagues[115] compared 29 patients receiving postoperative LMWH to 34 retrospectively matched patients who had received UFH in a case-control study. In both groups, treatment was continued until the INR was therapeutic. One patient in the LMWH group and four patients in the UFH group died within 90 days of discharge. There were two (6%) thromboembolic events in the UFH group and none in the LMWH group. Three patients in each group experienced major bleeding.

Recommendation

9.1. In patients with mechanical heart valves, we suggest bridging with UFH (prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (Grade 2C)**.**

9.2 Long-term Antithrombotic Therapy for Mechanical Valves

The highest quality evidence regarding the need for anticoagulation for mechanical heart valves comes from a meta-analysis of studies of anticoagulation in patients with predominantly caged-ball or tilting disk in the aortic position.[116] We rated down the quality of the evidence because the meta-analysis included observational with randomized controlled trial (RCT) data and contained few events (Table 8, Table S7). However, the large effect size results in an overall rating of moderate quality of evidence. These data suggest that the relative risk of a thromboembolic event on warfarin compared with no antithrombotic therapy is 0.21 (95% CI, 0.16-0.27), and 0.11 (95% CI, 0.07-0.2) for valve thrombosis. Although one can

Table 8—*[Section 9.2] Summary of Findings: Effect of Long-term Anticoagulation on Thromboembolism and Valve Thrombosis in Mechanical Valve Prostheses*[111]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With Control	Risk Difference With Oral Anticoagulation (95% CI)
Thromboembolism	997 (46 studies) 48 mo	Moderate[a,b] due to risk of bias, large effect	RR, 0.21 (0.16 to 0.27)	Moderate	
				86 per 1,000	68 fewer per 1,000 (from 63 fewer to 72 fewer)
Valve thrombosis; operation or autopsy	2,000 (46 studies)	Moderate[a,b] due to risk of bias, large effect	RR, 0.11 (0.07 to 0.22)	Moderate	
				18 per 1,000	16 fewer per 1,000 (from 14 fewer to 17 fewer)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 2 legends for expansion of abbreviations.

[a]Grouping RCTs with observational data, few events within studies.

[b]Large magnitude of effect.

Table 9—*[Section 9.3.1] Summary of Findings: Comparison of Lower INR Target (1.5-2.5) to Conventional Target (2.0-3.0) for Low-Risk Mechanical Aortic Valves*[113]

Outcomes	No. of Participants (Studies) Follow up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Conventional INR	Anticipated Absolute Effects: Risk Difference With Low INR (95% CI)
Thromboembolism; clinical follow-up[a]	396 (1 study) 5.6 y	Moderate[b] due to imprecision	OR, 0.33 (0.006-4.2)	15 per 1,000	10 fewer per 1,000 (from 15 fewer to 45 more)
Hemorrhage; clinical follow-up	396 (1 study) 5.6 y	Moderate[b] due to imprecision	OR, 0.36 (0.11-0.99)	80 per 1,000	50 fewer per 1,000 (from 1 fewer to 71 fewer)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. TIA = transient ischemic attack. See Table 1 legend for expansion of other abbreviations.

[a]Valve thrombosis, ischemic stroke, TIA, coronary or peripheral embolism.

[b]Few events within study with corresponding wide CIs.

infer from indirect evidence that major hemorrhage risk is increased, this is greatly outweighed by the benefit.

Recommendation

9.2. In patients with mechanical heart valves, we recommend VKA therapy over no VKA therapy for long-term management (Grade 1B)**.**

For older valves, such as the caged-ball valve, which should no longer be implanted, we refer readers to the detailed information in the article by Stein et al[117] on antithrombotic therapy in prosthetic heart valves in the *Chest* supplement of 2001. These recommendations focus on INR targets and the addition of APA therapy to oral anticoagulation. The evidence we used, and subsequently the recommendations based on this evidence, relate mostly to bileaflet valves and newer generation tilting-disk.

9.3 Intensity of VKA Therapy for Mechanical Aortic Valve Prostheses

Several randomized trials compare different intensities of long-term VKA therapy in patients with mechanical valves. Most recently, Torella et al[118] reported the LOWERING-IT trial (Table 9, Table S8), which compared an INR target of 1.5 to 2.5 to the conventional 2.0 to 3.0 in low-risk mechanical aortic valve patients (single AVR, with valve prosthesis dimension ≥ 21 mm, normal ejection fraction, left

Table 10—*[Section 9.3.2] Summary of Findings: Comparison of Higher INR Targets (Range 3.0-9.0) vs Lower Targets (Range 2.0-3.5) in Patients With Mechanical Aortic Valve*[114-116,136]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk with High INR	Anticipated Absolute Effects: Risk Difference With Low INR (95% CI)
Thromboembolism	1,347 (1 study[a]) 30 mo	Moderate[b] due to imprecision	RR, 0.72 (0.29-1.79)	16 per 1,000	5 fewer per 1,000 (from 12 fewer to 13 more)
Major hemorrhage; varied, Hering used Karnofsky scale grade III	2,539 (4 studies) 33.5 mo	Low[b] due to risk of bias, imprecision	RR, 0.60 (0.16-1.03)	42 per 1,000	17 fewer per 1,000 (from 35 fewer to 1 more)
Mortality[c]	205 (1 study[c])	Low[b] due to imprecision	RR, 0.97 (0.2-4.7)	30 per 1,000	1 fewer per 1,000 (from 24 fewer to 110 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 2 legends for expansion of abbreviations.

[a]Hering et al.[119]

[b]Few events within study with corresponding wide CIs.

[c]Pengo et al.[121]

atrium diameter < 47 mm, and in normal sinus rhythm). After a total of 2,198 patient-years, the one-sided difference for the primary outcome (valve thrombosis, ischemic stroke, TIA) was 1.45%, which satisfied the trial's a priori definition for noninferiority. However, the quality of the evidence is low due to imprecision (only four thromboembolic events in the trial), and the authors rightfully conclude that larger studies are required.

The German Experience with Low Intensity Anticoagulation (GELIA) is the largest trial that adequately separated out important clinical outcomes by INR target for aortic valve vs mitral valve prostheses.[119] The events rates in GELIA are low, such that there is much imprecision in the estimates for thrombotic outcomes and death (Table 10, Table S9). Acar et al[120] compared a target INR of 2.0 to 3.0 vs target 3.0 to 4.5 in 380 patients who had predominantly mechanical aortic valve implants (n = 364). Their results failed to demonstrate or exclude a beneficial effect or detrimental effect of higher INR on thrombosis (RR, 1.14; 95% CI, 0.47-2.73) or hemorrhage (RR, 0.70; 95% CI, 0.36-1.37). A meta-analysis of the available studies demonstrates an increased risk of major hemorrhage for those targeted for a higher INR. However, the higher targets vary from 3.0 to 9.0. There exists no evidence that high INR for AVR mechanical results in fewer thrombotic events.

Recommendations

9.3.1. In patients with a mechanical aortic valve, we suggest VKA therapy with a target of 2.5 (range 2.0-3.0) over lower targets (Grade 2C)**.**

9.3.2. In patients with a mechanical aortic valve, we recommend VKA therapy with a target of 2.5 (range 2.0-3.0) over higher targets (Grade 1B)**.**

9.4 Intensity of VKA Therapy for Mechanical Mitral Valve Prostheses

Mechanical valves in the mitral position are generally more thrombogenic than in the aortic position secondary to the differing hemodynamic and flow characteristics across the valve. Only the GELIA study meaningfully reports important clinical outcomes by mitral valve position (Table 11, Table S10).[119,121] There are three strata within the GELIA trial: stratum A targeted an INR of 3.0 to 4.5, stratum B targeting an INR of 2.5 to 4.0, and stratum C targeting an INR 2.0 to 3.5. To avoid overlap and improve contrast, we present stratum C vs stratum A in the evidence profile. From their results, there is a trend toward fewer thromboembolic events with a higher INR based on 17 events (RR, 2.25; 95% CI, 0.84-6.53). INR measurements were in the target range less often for stratum A (44.5%) than stratum C (74.5%).

Pengo et al[121] compared an INR target of 3.0 to 4.0 in 205 patients undergoing AVR, mitral valve replacement, or both. Their results failed to demonstrate or exclude a beneficial effect or detrimental effect of higher INR on mortality (RR, 0.97; 95% CI, 0.20-4.70) or on thrombosis (RR, 0.98; 95% CI, 0.33-2.93) over 36 months of follow-up. However, the trial is underpowered for these outcomes. As previously presented, the bleeding risk is likely increased by targeting a higher INR.

Table 11—*[Section 9.4] Summary of Findings: Comparison of Higher INR Targets (Range 3.0-9.0) vs Lower Targets (Range 2.0-3.5) in Patients With Mechanical Mitral Valve*[114-116,136]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With High INR	Anticipated Absolute Effects: Risk Difference With Low INR (95% CI)
Major hemorrhage; definitions varied	2,539 (4 studies) 33.5 mo	Low[a,b] due to risk of bias, imprecision	RR, 0.60 (0.16-1.03)	42 per 1,000	17 fewer per 1,000 (from 35 fewer to 1 more)
Mortality[c]	205 (1 study[c])	Low[b] due to imprecision	RR, 0.97 (0.2-4.7)	30 per 1,000	1 fewer per 1,000 (from 24 fewer to 110 more)
Thromboembolism[d]	360 (1 study[d]) 30 mo	Moderate[b] due to imprecision	RR, 2.25 (0.84-6.53)	28 per 1,000	35 more per 1,000 (from 4 fewer to 155 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 2 legends for expansion of abbreviations.

[a]Wide variation in target ranges of INR among studies with likely differing effects on bleeding outcome.

[b]Few events within study with corresponding wide CIs.

[c]Pengo et al.[121]

[d]Hering et al.[119]

Cannegieter and associates[122] reported on 1,608 patients with mechanical heart valves. In this observational study there were 45 patients who had a thromboembolic event, yielding an incidence of thromboembolism of 0.5%/y with mechanical aortic valves, 0.9%/y with mechanical mitral valves, and 1.2%/y with double aortic and mitral mechanical valves.[122] Their groups examined the optimal intensity of anticoagulation, defining it as the INR level with the lowest incidence of both bleeding and thromboembolism. For all patients, this level appears to be in the range of 2.5 to 4.9. Further, when they looked at the subgroup of mitral valve, a target range of 3.0 to 3.9 appears better than a target of 2.0 to 2.9. Caution must be used when citing these data. First, the study is limited by its design, with high risk of confounding within the data. Second, the study is drastically underpowered when looking at the subgroup by valve position. Unfortunately, the 95% CI for the incidence of events within the mitral valve group by target INR is not provided, nor are any statistics to test for significant difference. Therefore, we would consider these data inconclusive and hypothesis generating only.

Recommendation

9.4. In patients with a mechanical mitral valve, we suggest VKA therapy with a target of 3.0 (range 2.5-3.5) over lower INR targets (Grade 2C)**.**

9.5 Intensity of VKA Therapy in Patients With Double Mechanical Valve or With Additional Risk Factors

The presence of double mechanical valve replacement increases the risk of thromboembolism to 1.2%/y from 0.5%/y for aortic, and 0.9%/y for mitral.[122] In

Table 12—*[Section 9.6] Summary of Findings: Effect of Addition of Antiplatelet Therapy to Anticoagulation in Patients With Mechanical Heart Valves*[137-145]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With OAC Alone	Anticipated Absolute Effects: Risk Difference With OAC Plus Antiplatelet Drug (95% CI)
Mortality; unclear	1,955 (8 studies) 19 mo	Moderate[a,b] due to risk of bias	RR, 0.58 (0.4-0.86)	69 per 1,000	29 fewer per 1,000 (from 10 fewer to 41 fewer)
Thromboembolism; not reported	1,686 (5 studies) 19 mo	Low[a,c,d] due to risk of bias	RR, 0.42 (0.21-0.81)	69 per 1,000	40 fewer per 1,000 (from 13 fewer to 55 fewer)
Mitral valve-arterial thromboembolism; unclear	163 (2 studies) 23 mo	Low[a,e,f] due to risk of bias, inconsistency, imprecision	RR, 1.18 (0.37-3.74)[g]	72 per 1,000	13 more per 1,000 (from 46 fewer to 199 more)
Aortic valve-arterial thromboembolism; unclear	423 (2 studies) 23 mo	Low[a,f] due to risk of bias, imprecision	RR, 0.29 (0.1-0.86)[g]	69 per 1,000	49 fewer per 1,000 (from 10 fewer to 62 fewer)
Valve thrombosis; unclear	1,203 (3 studies) 12-30 mo	Low[a,h] due to risk of bias, imprecision	RR, 0.40 (0.18-0.9)	44 per 1,000	26 fewer per 1,000 (from 4 fewer to 36 fewer)
Ischemic stroke; unclear	1,686 (6 studies) 12-30 mo	Low[a,i] due to risk of bias, imprecision	RR, 0.28 (0.15-0.52)	66 per 1,000	47 fewer per 1,000 (from 32 fewer to 56 fewer)
Major hemorrhage; not reported	1,854 (7 studies) 19 mo	Low[a,j] due to risk of bias	RR, 1.44 (1-2.08)	68 per 1,000	30 more per 1,000 (from 0 more to 73 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. ASA = acetylsalicylic acid; OAC = oral anticoagulants. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Mix of open-label and partially blinded studies, randomization and allocation concealment not described, outcome ascertainment not clearly described.

[b]One of nine studies finds OAC + ASA to have higher mortality (nonsignificant) than OAC alone; all others find mechanical valves protective, but only two are statistically significant before pooling.

[c]Types of thromboemboli reported varied and were not consistent across studies. Not clear how bleeding monitored.

[d]Statistical heterogeneity: Cochran Q = 9.763529 (df = 6) $P = .135$; $I^2 = 38.5\%$.

[e]Small numbers of events; point estimates differ.

[f]Fewer than 300 events, and CI includes > 25% relative increase/decrease in potential for benefit or harm.

[g]Fixed effects model; two studies.

[h]Fewer than 300 events (total = 41) and overall small sample sizes (total = 1,203). Resulting CI is wide.

[i]Fewer than 300 events (total = 74); total sample size = 1,686.

[j]Definition of major bleeding varied widely or was not provided. May include bleeding that could be considered minor.

the GELIA study,[123] less intensive anticoagulation (INR range, 2.0-3.5) was associated with a significantly ($P < .005$) lower survival than was more intensive anticoagulation (INR range, 2.5-4.5) among patients with double valve replacement.

Factors such as the presence of AF, low left ventricular ejection fraction, older age, and a history of prior thromboembolism have been suggested to increase risk of thromboembolic complications.[105] However, no evidence exists demonstrating that higher INR targets have additional benefit over harm in these patients.

Recommendation

9.5. In patients with mechanical heart valves in both the aortic and mitral position, we suggest target INR 3.0 (range 2.5-3.5) over target INR 2.5 (range 2.0-3.0) (Grade 2C)**.**

9.6 APA in Addition to VKA Therapy for Mechanical Aortic or Mitral Valve Prostheses

An updated meta-analysis (Table 12, Table S11) suggests a significant reduction in mortality (RR, 0.58; 95% CI, 0.4-0.86) and thromboembolic outcomes (RR, 0.42; 95% CI, 0.21-0.81) by the addition of APA with a relatively small increase in risk of major hemorrhage (RR 1.44; 95% CI, 1.00-2.08).

Recommendation

9.6. In patients with a mechanical mitral or aortic valve at low risk of bleeding, we suggest adding over not adding an antiplatelet agent such as low-dose aspirin (50-100 mg/d) to the VKA therapy (Grade 1B)**.**

Remarks: Caution should be used in patients at increased bleeding risk, such as history of GI bleeding.

9.7 APA Therapy Instead of VKA Therapy

There is currently no evidence to support the replacement of VKA therapy by APA for either mechanical aortic or mitral valve prostheses. Several studies in the pediatric population have demonstrated an unacceptable risk of thromboembolism when treating with APA alone.[124,125] Schlitt et al[126] undertook the CAPTA trial, which randomized patients with a mechanical aortic valve to Coumadin vs aspirin/clopidogrel. The trial was stopped after 22 patients due to one instance of valve thrombosis in the APA group.[126] Indirect evidence from trials in AF provides strong support for the effectiveness of VKA over APA in patients with mechanical valves.

Recommendation

9.7. For patients with mechanical aortic or mitral valves we recommend VKA over antiplatelet agents (Grade 1B)**.**

10.0 Heart Valve Repair

10.1 Antithrombotic Therapy After Mitral Valve Repair

Mitral valve repair commonly involves the removal of redundant or pathologic leaflet tissue, the placement of a synthetic ring or band to decrease annular

Table 13—*[Section 10.1] Summary of Findings: Comparison of Antiplatelet to Anticoagulation in the First 3 mo After Mitral Valve Repair*[101]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With VKA	Risk Difference With Antiplatelet Agent (95% CI)
Thromboembolism; guidelines from Edmunds et al[127]	162 (1 study[a]) 3.2 y	Low[b-d] due to risk of bias, indirectness, imprecision	RR, 0.16 (0.03-0.86)	100 per 1,000	84 fewer per 1,000 (from 14 fewer to 97 fewer)
Hemorrhage	162 (1 study[a]) 3.2 y	Low[b-d] due to risk of bias, indirectness, imprecision	RR, 0.98 (0.11-9.19)	25 per 1,000	0 fewer per 1,000 (from 22 fewer to 205 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. AF = atrial fibrillation; ITT = intention-to-treat. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Prospective observational.

[b]Imbalance in risk between groups. The Coumadin group carries greater risk with more AF and older patients. There is no adjustment for this. Study not analyzed as ITT.

[c]Major heterogeneity in types on patients included (ie, bioprosthetic mitral valve, bioprosthetic aortic valve, valve repair).

[d]Estimates based on few events with resultant wide CI.

size, and perhaps the resuspension of leaflets with new or transposed chordate. We have identified no randomized trial evaluating the use of antithrombotic therapy after mitral valve repair. Aramendi et al[106] published a prospective cohort study examining the outcomes of 235 mitral repair or replacement patients. The data suggest superiority of Ticlopidine over warfarin in preventing thromboembolism (RR, 0.16; 95% CI, 0.03-0.86) with no difference in bleeding. The quality of the evidence is low given the observational nature of the data and study limitations related to an imbalance between the groups in the prevalence of AF (Table 13, Table S12).

Recommendation

10.1. In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, we suggest the use of antiplatelet therapy for the first 3 months over VKA therapy (Grade 2C)**.**

10.2 Aortic Valve Repair

Aortic valve repair is less common than that of mitral valve. The operation usually involves reimplanting the aortic valve into a Dacron graft after having excised the aortic root. Further, pericardium (autologous or other) may be used to reconstruct the aortic leaflets. No trials exist that compare early approaches to antithrombotics after this procedure. Duran et al,[128,129] however, report in two publications on 173 patients that the use of aspirin 100 mg/d resulted in no valve thrombosis or thromboembolic events.

Recommendation

10.2. In patients undergoing aortic valve repair, we suggest aspirin at 50 to 100 mg/d over VKA therapy (Grade 2C)**.**

11.0 Prosthetic Valve Thrombosis

Prosthetic valve obstruction may be the result of thrombosis, pannus ingrowth, or both.[130] Clinical history and echocardiographic study are used to determine the cause. This is important, since thrombolysis will not be effective in pannus ingrowth.

Prosthetic valve thrombosis has an incidence ranging from 0.1% to 5.7% per patient-year. Although rare, this complication is potentially lethal. Treatment of this pathology consists of surgery, thrombolytic therapy, or anticoagulation. The choice of therapy is highly dependent on valve location, as a common complication of fibrinolytic therapy is thromboemboli, which is less serious when they are to the pulmonary circulation.

Table 14—*[Section 11.2.1] Summary of Findings: Comparison of Fibrinolysis to Surgical Intervention for Prosthetic Valve Thrombosis*[126]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With Surgery	Risk Difference With Fibrinolysis (95% CI)
Mortality; clinical follow-up	263 (1 study) 6 y	Low[a] due to risk of bias	RR, 1.14 (0.58-2.28)	103 per 1,000	14 more per 1,000 (from 43 fewer to 132 more)
Full hemodynamic success; hemodynamic normalization cinefluoroscopy, TTE, or TEE	263 (1 study) 6 y	Low[a] due to risk of bias	RR, 0.79 (0.7-0.9)	897 per 1,000	188 fewer per 1,000 (from 90 fewer to 269 fewer)
Thromboembolism; clinical follow-up	263 (1 study) 6 y	Low[a] due to risk of bias, large effect	RR, 20.35 (2.76-149.79)	7 per 1,000	142 more per 1,000 (from 13 more to 1,000 more)
Hemorrhage; not clearly defined	263 (1 study) 6 y	Low[a] due to risk of bias	RR, 6.4 (0.78-52.6)	7 per 1,000	40 more per 1,000 (from 2 fewer to 379 more)
Recurrence of obstruction	187 (1 study) 6 y	Low[a] due to risk of bias	RR, 2.13 (1.08-4.21)	114 per 1,000	128 more per 1,000 (from 9 more to 365 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. TEE = transesophageal echocardiography; TTE = transthoracic echocardiography. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Nonrandomized, nonblinded design, ascertainment bias likely.

11.1 Right-Sided Prosthetic Valve Thrombosis

The data on right-sided PVT are very limited. Authorities have suggested that PVT of right-sided valves can be treated safely and effectively with fibrinolytic therapy.[131,132]

Recommendation

11.1. For patients with right-sided PVT, in the absence of contraindications we suggest administration of fibrinolytic therapy over surgical intervention (Grade 2C)**.**

11.2 Left-Sided Prosthetic Valve Thrombosis

When treating left-sided PVT, the risks associated with reoperative surgery must be weighed against the risks of embolic complications and bleeding associated with the use of fibrinolytic therapy. Deviri et al[133] reported that perioperative mortality increases directly with NYHA class; 17.5% in NYHA IV and 4.7% in NYHA I to III. However, NYHA class is also a predictor of complication in fibrinolysis along with history of stroke, and thrombus area.[134] Tong et al[134] highlighted two predictors of complications with lysis: thrombus area (OR, 2.41 per 1-cm^2 increment; 95% CI, 1.12-5.19) and prior history of stroke (OR, 4.55; 95% CI, 1.35-15.38). Using receiver operating characteristic curve analysis, the best cutoff of thrombus size for predicting complications was 0.8 cm^2 (sensitivity 79%, specificity 68%).[134] This cutoff was applicable to both mitral and aortic valves as well as bileaflet or tilting disc valves.

In 2009, Roudaut et al[135] presented one of the first studies that directly compared fibrinolysis to surgery in a large single-center retrospective study (Table 14, Table S13). These data suggest no difference between the approaches with respect to mortality, a much higher rate of embolic episodes in the fibrinolysis group (RR, 20.35; 95% CI, 2.76-149.79), and less hemodynamic success (RR, 0.79; 95% CI, 0.70-0.90). Further, long-term freedom from recurrence was better in the surgical group (RR, 2.13; 95% CI, 1.08-4.21).

Recommendations

11.2.1. For patients with left-sided PVT and large thrombus area ($\leq$0.8 cm^2), we suggest early surgery over fibrinolytic therapy (Grade 2C)**. If contraindications to surgery exist, we suggest the use of fibrinolytic therapy** (Grade 2C)**.**

11.2.2. For patients with left-sided PVT and small thrombus area ($>$0.8 cm^2), we suggest administration of fibrinolytic therapy over surgery. For very small, nonobstructive thrombus we suggest IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement over other alternatives (Grade 2C)**.**

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Dr Whitlock: contributed as the Topic Editor.
Dr Sun: contributed as a panelist.
Dr Fremes: contributed as a panelist.
Dr Rubens: contributed as a panelist.
Dr Teoh: contributed as a panelist.

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