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Valvular and Structural Heart Disease* American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This chapter about antithrombotic therapy for valvular heart disease is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patient values might lead to different choices (for a full understanding of the grading see Guyatt et al, CHEST 2008; 133[suppl]:123S-131S). Among the key recommendations in this chapter are the following: for patients with rheumatic mitral valve disease complicated singly or in combination by the presence of atrial fibrillation (AF), previous systemic embolism, or left atrial thrombus, we recommend vitamin K antagonist (VKA) therapy (Grade 1A). For patients with rheumatic mitral valve disease and normal sinus rhythm, without left atrial enlargement, we do not suggest antithrombotic therapy unless a separate indication exists (Grade 2C). For patients with mitral valve prolapse (MVP), not complicated by AF, who have not had systemic embolism, unexplained transient ischemic attacks, or ischemic stroke, we recommend against antithrombotic therapy (Grade 1C). In patients with mitral annular calcification complicated by systemic embolism or ischemic stroke, we recommend antiplatelet agent (APA) therapy (Grade 1B). For patients with isolated calcific aortic valve disease, we suggest against antithrombotic therapy (Grade 2C). But, for those with aortic valve disease who have experienced ischemic stroke, we suggest APA therapy (Grade 2C). For patients with stroke associated with aortic atherosclerotic lesions, we recommend low-dose aspirin (ASA) therapy (Grade 1C). For patients with cryptogenic ischemic stroke and a patent foramen ovale (PFO), we recommend APA therapy (Grade 1A). For patients with mechanical heart valves, we recommend VKA therapy (Grade 1A). For patients with mechanical heart valves and history of vascular disease or who have additional risk factors for thromboembolism, we recommend the addition of low-dose aspirin ASA to VKA therapy (Grade 1B). We suggest ASA not be added to long-term VKA therapy in patients with mechanical heart valves who are at particularly high risk of bleeding (Grade 2C). For patients with bioprosthetic heart valves, we recommend ASA (Grade 1B). For patients with bioprosthetic heart valves and additional risk factors for thromboembolism, we recommend VKA therapy (Grade 1C). For patients with infective endocarditis, we recommend against antithrombotic therapy, unless a separate indication exists (Grade 1B).

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Key words: antithrombotic; aspirin; heart valve disease; heart valve prosthesis; heparin; oral anticoagulation; prosthetic heart valves; stroke; thromboembolism; valvular heart disease; vitamin k antagonists; warfarin

Abbreviations: AF = atrial fibrillation; APA = antiplatelet agent; ASA = aspirin; CI = confidence interval; GELIA = German Experience with Low Intensity Anticoagulation; ICH = intracranial hemorrhage; IE = infective endocarditis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MAC = mitral annular calcification; MR = aortic and mitral valve replacement; MVP = mitral valve prolapse; NBTE = nonbacterial thrombotic endocarditis; NYHA = New York Heart Association; OR = odds ratio; PFO = patent foramen ovale; PMBV = percutaneous mitral balloon valvotomy; PVE = prosthetic valve endocarditis; <math>PVT = prosthetic valve thrombosis; TEE = transeophageal echocardiography; TIA = transient ischemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist; WARSS = Warfarin-Aspirin Recurrent Stroke Study

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SUMMARY OF RECOMMENDATIONS

1.1.1. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of AF, previous systemic embolism, or left atrial thrombus, we recommend VKA therapy (target international normalized ratio [INR], 2.5; range, 2.0 to 3.0) [Grade 1A].

1.1.2. For patients with rheumatic mitral valve disease with AF who suffer systemic embolism or have left atrial thrombus while receiving VKAs at a therapeutic INR, we suggest the addition of low-dose ASA (50 to 100 mg/d) after consideration of the additional hemorrhagic risk (Grade 2C).

An alternative strategy might be the adjustment of VKA dosing to achieve a higher target INR (target INR, 3.0; range, 2.5 to 3.5) [Grade 2C].

1.2.1. 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 to 3.0) [Grade 2C].

Underlying values and preferences: This recommendation places a relatively high value on preventing systemic embolism and its consequences, and a relatively low value on avoiding the bleeding risk and inconvenience associated with VKA therapy.

1.2.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm, we do not suggest antithrombotic therapy, unless a separate indication exists (Grade 2C).

1.3.1. For patients being considered for percutaneous mitral balloon valvotomy (PMBV), we recommend preprocedural transesophageal echocardiography (TEE) to exclude left atrial thrombus (Grade 1C).

1.3.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, we recommend postponement of PMBV and administration of VKA therapy (target INR, 3.0; range, 2.5 to 3.5) until thrombus resolution is documented by repeat TEE (Grade

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1C). If left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1C).

2.0.1. In patients with mitral valve prolapse (MVP) who have not had systemic embolism, unexplained transient ischemic attacks (TIAs), or ischemic stroke, and do not have atrial fibrillation (AF), we recommend against any antithrombotic therapy (Grade 1C).

2.0.2. In patients with MVP who have documented but unexplained TIAs or ischemic stroke, we recommend ASA (50 to 100 mg/d) [Grade 1B].

2.0.3. In patients with MVP who have AF, documented systemic embolism, or recurrent TIAs despite ASA therapy, we suggest VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 2C].

3.0.1. In patients with mitral annular calcification (MAC) complicated by systemic embolism, ischemic stroke, or TIA, who do not have AF, we recommend ASA (50 to 100 mg/d) [Grade 1B].

For recurrent events despite ASA therapy, we suggest treatment with VKA therapy be considered (target INR, 2.5; range, 2.0 to 3.0) [Grade 2C]. In patients with MAC who have a single embolus documented to be calcific, the data are not sufficient to allow recommendation for or against antithrombotic therapy.

3.0.2. In patients with MAC and AF, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C].

4.1.1. In patients with isolated calcific aortic valve disease who have not had ischemic stroke or TIA, we suggest against antithrombotic ther**apy** (Grade 2C).

4.1.2. In patients with isolated calcific aortic valve disease who have experienced ischemic stroke or TIA not attributable to another source, we suggest ASA (50 to 100 mg/d) [Grade 2C].

4.2.1. In patients with ischemic stroke associated with aortic atherosclerotic lesions, we recommend low-dose ASA (50 to 100 mg/d) over no therapy. (Grade 1C) For patients with ischemic stroke associated with mobile aortic arch thrombi, we suggest therapy with either VKAs (target INR, 2.5; range, 2.0 to 3.0) or low-dose ASA (50 to 100 **mg/d**) [Grade 2C].

5.0.1. In patients with ischemic stroke and a PFO, we recommend APA therapy (Grade 1A) and suggest APA therapy over VKA therapy (Grade 2A).

5.0.2. In patients with cryptogenic ischemic stroke and PFO, with evidence of deep venous thrombosis or another indication for VKA therapy, such as AF or an underlying hypercoagulable state, we recommend VKA therapy (target INR, **2.5; range, 2.0 to 3.0**) [Grade 1C].

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6.0.1. In patients with mechanical heart valves, we recommend VKA therapy (Grade 1A). In patients immediately following mechanical valve replacement, and as dictated by clinical concerns regarding postoperative bleeding, we suggest administration of IV unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) until the INR is at a therapeutic level for 2 consecutive days (Grade 2C).

6.0.2. In patients with a bileaflet mechanical valve or a Medtronic Hall (Minneapolis, MN) tilting disk valve in the aortic position who are in sinus rhythm and without left atrial enlargement, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B].

6.0.3. In patients with a tilting-disk or bileaflet mechanical valve in the mitral position, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.4. In patients with a caged-ball or caged-disk valve, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.5. In patients with mechanical heart valves in either or both the aortic or mitral positions, and additional risk factors for thromboembolism, such as AF, anterior-apical ST-segment elevation myocarcial infarction, left atrial enlargement, hypercoagulable state, or low ejection fraction, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.6. In patients with mechanical heart valves who have additional risk factors for thromboembolism, such as AF, hypercoagulable state, or low ejection fraction, or who have a history of atherosclerotic vascular disease, we recommend the addition of low-dose ASA (50 to 100 mg/d) to long-term VKA therapy (Grade 1B). We suggest ASA not be added to VKA therapy in patients with mechanical heart valves who are at particularly high risk of bleeding, such as in patients with history of GI bleed, or in patients > 80 years of age (Grade 2C).

6.0.7. In patients with mechanical prosthetic heart valves who have systemic embolism despite a therapeutic INR, we suggest the addition of ASA (50 to 100 mg/d) if not previously provided and/or upward titration of VKA therapy to achieve a higher target INR. For a previous target INR of 2.5, we suggest the VKA dose be increased to achieve a target INR of 3.0 (range, 2.5 to 3.5). For a previous target INR of 3.0, we suggest the VKA dose be increased to achieve a target INR of 3.5 (range, 3.0 to 4.0) [Grade 2C].

7.0.1. In patients with a bioprosthetic valve in the mitral position, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for the first 3

months after valve insertion (Grade 1B). In the early postoperative period, in the absence of concerns for significant bleeding, we suggest administration of IV UFH or subcutaneous LMWH until the INR is at a therapeutic level for 2 consecutive days (Grade 2C). After the first 3 months, in patients who are in sinus rhythm and have no other indication for VKA therapy, we recommend ASA (50 to 100 mg/d) [Grade 1B].

7.0.2. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we recommend ASA (50 to 100 mg/d) [Grade 1B].

7.0.3. In patients with bioprosthetic valves who have a history of systemic embolism, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for at least 3 months after valve insertion, followed by clinical reassessment (Grade 1C).

7.0.4. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) until documented thrombus resolution (Grade 1C).

7.0.5. In patients with bioprosthetic valves who have additional risk factors for thromboembolism, including AF, hypercoagulable state, or low ejection fraction, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C]. We suggest the addition of low-dose aspirin (50 to 100 mg/d) be considered, particularly in patients with history of atherosclerotic vascular disease (Grade 2C). We suggest ASA not be added to long-term VKA therapy in patients with bioprosthetic heart valves who are at particularly high risk of bleeding, such as in patients with history of GI bleed or in patients > 80 years of age (Grade 2C).

8.0.1. For patients with right-sided prosthetic valve thrombosis (PVT), with large thrombus size or New York Heart Association (NYHA) functional class III to IV, we recommend administration of fibrinolytic therapy (Grade 1C).

8.0.2. For patients with left-sided PVT, NYHA functional class I to II, and small thrombus area $(< 0.8 \text{ cm}^2)$, we suggest administration of fibrinolytic therapy. Alternatively, administration of IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement, can be considered for very small, nonobstructive thrombus (Grade 2C).

8.0.3. For patients with left-sided PVT, NYHA functional class III to IV, and small thrombus area (< 0.8 cm²), we suggest fibrinolytic therapy (Grade 2C).

8.0.4. For patients with left-sided PVT and large thrombus area ($\geq 0.8 \text{ cm}^2$), we suggest emergency surgery be considered. If surgery is not

available or considered high risk, we suggest fibrinolytic therapy (Grade 2C).

8.0.5. For patients who have had successful resolution of PVT, we suggest initiation of IV UFH and VKA therapy. We suggest IV UFH be continued until a therapeutic INR is achieved. For a mechanical valve in the aortic position, we suggest maintaining a higher INR (target, 3.5; range 3.0 to 4.0) plus ASA (50 to 100 mg/d). For a mechanical valve in the mitral position, we suggest maintaining a higher INR (target, 4.0; range 3.5 to 4.5) plus ASA (50 to 100 mg/d) [Grade 2C].

9.1.1. In patients with infective endocarditis, we recommend against routine antithrombotic therapy, unless a separate indication exists (Grade 1B).

9.1.2. In the patient treated with VKA therapy who has infective endocarditis, we suggest VKA be discontinued at the time of initial presentation and UFH substituted, 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).

9.2.1. In patients with NBTE and systemic or pulmonary emboli, we recommend treatment with full-dose IV UFH or subcutaneous LMWH (Grade 1C).
9.2.2. In patients with disseminated cancer or debilitating disease with aseptic vegetations, we suggest administration of full-dose IV UFH or subcutaneous LMWH (Grade 2C).

F ew complications of valvular heart disease can be more devastating than systemic embolism. Antithrombotic therapy can reduce, though not eliminate, the likelihood of this catastrophe. If this therapy were risk free and of no cost, all at-risk patients with valvular heart disease should be treated. Unfortunately, antithrombotic therapy, particularly with heparin or coumarin derivatives, carries a substantial risk of bleeding. This bleeding risk varies with the drug used, the intensity of the anticoagulant effect, and the underlying clinical circumstances in individual patients. For example, risks of anticoagulant therapy are greater in patients with endocarditis, pregnancy, and bleeding diatheses. In addition, the incidence of bleeding increases substantially with advanced age.¹

This review will examine the risks of thromboembolism in various forms of native valvular heart disease, as well as mechanical and bioprosthetic heart valve replacements, and suggest strategies for using antithrombotic drugs in each condition. For the most part, these analyses and guidelines will concern the long-term use of antithrombotic therapy in ambulatory patients. Table 1 presents eligibility criteria for the questions addressed in this chapter.

Basic to these considerations is assessment of the risk of bleeding. While the rewards of anticoagulant therapy will be greatest in patients with a high risk of thromboembolism, these benefits may be offset by the potential for hemorrhagic complications. Generally, excluding large intracranial hemorrhage (ICH), the permanent consequences of a thromboembolic event are more serious than the potential bleeding complications associated with anticoagulant therapy. Most patients recognize this trade-off, and are ready to accept a substantial bleeding risk to prevent stroke.²

1.0 RHEUMATIC MITRAL VALVE DISEASE

Partly due to the introduction of antibiotics, rheumatic mitral valve disease has become rare in people raised in developed nations. Most of the cases in the United States and other developed nations are now found in patients who have emigrated from areas of the world where rheumatic heart disease remains endemic.³ The incidence of systemic embolism is greater in rheumatic mitral valve disease than in any other common form of acquired valvular heart disease. While the natural history of this disease has been altered during the past 40 years by surgery, percutaneous mitral balloon valvotomy (PMBV), and the frequent use of long-term oral vitamin K antagonist (VKA) therapy, Wood⁴ cited a prevalence of systemic emboli of 9 to 14% in several large early series of patients with mitral stenosis. In 1961, Ellis and Harken⁵ 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, Szekely⁶ observed an incidence of emboli of 1.5%/yr, while the number was found to vary from 1.5 to 4.7%/yr preoperatively in six reports of rheumatic mitral valve disease.⁷ As a generalization, it is perhaps reasonable to assume that a patient with rheumatic mitral valve disease has at least one chance in five of having a clinically detectable systemic embolus during the course of the disease.⁸

The risk of systemic emboli in rheumatic mitral disease is greater in older patients^{9–12} and those with lower cardiac indexes,⁹ but appears to correlate poorly with mitral calcification,¹³ mitral valve area,⁹ or clinical classification.^{4,9,13,14} Indeed, several investigators have pointed out that patients with mitral valve disease with emboli frequently are found to have minor valve disease, and Wood⁴ reported that in 12.4% of cases, systemic embolization was the initial manifestation of rheumatic mitral disease. The relationship between thromboembolism and left atrial size remains unclear. Early studies^{4,13,14} of rheumatic mitral valve disease reported a weak

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 Table 1—Antithrombotic Therapy in Valvular and Structural Heart Disease: Question Definition and Eligibility Criteria (Section: Introduction)

Section	Population	Intervention/Exposure	Outcomes	Methodology	Exclusion Criteria
1.1	Rheumatic mitral stenosis with AF or systemic embolism	VKA, ASA, ticlopidine, or clopidogrel	Arterial thromboemboli, bleeding, death	RCT and observational	None
1.2	Rheumatic mitral stenosis in sinus rhythm	VKA, ASA, ticlopidine, or clopidogrel	Aterial thromboemboli, bleeding, death	RCT and observational	None
1.3	Rheumatic mitral stenosis undergoing mitral valvuloplasty	VKA	Arterial thromboemboli, bleeding, death	RCT and observational	None
2.0	MVP	Time	Arterial thromboemboli	Observational	None
2.0	MVP	VKA, ASA, ticlopidine, or clopidogrel	Aterial thromboemboli	RCT and observational	None
3.0	MAC	Time	Arterial thromboemboli	Observational	None
3.0	MAC with AF or systemic embolism	VKA, ASA, ticlopidine, or clopidogrel	Arterial thromboemboli, bleeding	RCT and observational	None
4.1	Aortic valve calcification (with or without aortic stenosis)	Time	Arterial thromboemboli	Observational	None
4.1	Aortic valve calcification (with or without aortic stenosis)	VKA, ASA, ticlopidine, or clopidogrel	Arterial thromboemboli, bleeding	RCT and observational	None
4.2	Aortic arch plaque, atheroma and calcification	Time	Arterial thromboemboli	Observational	None
4.2	Aortic arch plaque, atheroma and calcification	VKA, ASA, ticlopidine, or clopidogrel	Arterial thromboemboli, bleeding	RCT and observational	None
5.0	PFO and atrial septal aneurysm	Time	Arterial thromboemboli	Observational	None
5.0	PFO and atrial septal aneurysm	VKA, ASA, ticlopidine, or clopidogrel	Arterial thromboemboli, bleeding	RCT and observational	None
6.0	Mechanical heart valves	VKA, UFH, LMWH, ASA, dipyridamole, clopidogrel, ticlopidine	Arterial thromboemboli, valve thrombosis, bleeding, death	RCT and observational	None
7.0	Bioprosthetic heart valves	VKA, UFH, LMWH, ASA, dipyridamole, clopidogrel, ticlopidine	Arterial thromboemboli, valve thrombosis, bleeding, death	RCT and observational	None
8.0	PVT	Surgery	Arterial thromboemboli, valve thrombosis, bleeding, death	Observational	None
8.0	PVT	Fibrinolytic therapy, UFH	Arterial thromboemboli, valve thrombosis, bleeding, death	Observational	None
9.1	IE	Time	Arterial thromboemboli	Observational	None
9.1	IE	VKA, UFH, LMWH, ASA, clopidogrel, ticlopidine	Arterial thromboemboli, bleeding	RCT and observational	None
9.2	NBTE	Time	Arterial thromboemboli	Observational	None
9.2	NBTE	VKA, UFH, LMWH, ASA, clopidogrel, ticlopidine	Arterial thromboemboli, bleeding	RCT and observational	None

correlation. However, several studies have now demonstrated an association between larger left atrial size and the presence of left atrial thrombus or spontaneous echocardiographic contrast.^{15–17} While some reports,^{18–20} primarily in patients with nonvalvular atrial fibrillation (AF), suggest that left atrial size is an independent risk factor for thromboembolism, one study²¹ describing 1,066 patients with AF found no such relationship.

In a prospective study of > 500 patients with mitral stenosis, Chiang et al²² identified risk factors for systemic embolism in patients with AF or sinus rhythm. Nine clinical and 10 echocardiographic variables were assessed for prediction of systemic embolism over a mean follow-up of 36.9 ± 22.5 months. Predictors of embolization for patients in sinus rhythm were age, the presence of a left atrial thrombus, and significant aortic regurgitation. In contrast to previous studies, mitral valve area was inversely related to an increased risk of embolization. A correlation between left atrial thrombus and systemic thromboembolism for patients in sinus rhythm was confirmed by this study, and supports the use of anticoagulation in this group. A previous embolic event was associated with subsequent embolism in patients with AF. In patients with mitral stenosis and

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Downloaded from chestjournal.chestpubs.org by guest on October 5, 2009 © 2008 American College of Chest Physicians AF, but no left atrial thrombus on transesophageal echocardiography (TEE), PMBV decreased the risk of systemic embolism. This observation suggests a potential benefit from the earlier use of this procedure in patients with mitral stenosis, though prospective studies of PMBV for this indication are lacking.

Among patients with rheumatic mitral valve disease who suffer a first embolus, recurrent emboli occur in 30 to 65% of cases,^{4,8,23,24} of which 60 to 65% are within the first year,^{23,24} most within the first 6 months. A hypercoagulable state in mitral stenosis might contribute to the risk of thromboembolism.^{3,25} Although indexes of hypercoagulability might be improved with PMBV,²⁵ the risk of thromboembolism is not eliminated,^{7,13} and anticoagulation will be necessary post-procedure for those patients in whom it was required prior to PMBV.

1.1 Rheumatic Mitral Valve Disease With AF or a History of Systemic Embolism

Although never evaluated in a prospective, randomized trial, there is little doubt that VKA therapy is effective in reducing the incidence of systemic emboli in patients with rheumatic mitral valve disease and AF or atrial thrombus. In an observational study,⁶ the incidence of recurrent embolism in patients with mitral valve disease who received warfarin was 3.4%/yr (relative risk, 0.35), while in the nonanticoagulation group it was 9.6%/yr. Adams et al²⁶ followed up 84 patients with mitral stenosis and cerebral emboli for up to 20 years, half of whom received no anticoagulant therapy (1949 to 1959), and half of whom received warfarin (1959 to 1969). Using life-table analyses, a significant reduction in embolic events was reported in the treated group. There were 13 deaths from embolic events in the untreated group vs 4 deaths in the treated group (relative risk, 0.31). Fleming¹⁴ found a 25% incidence of emboli among 500 untreated patients with mitral valve disease, while in 217 patients treated with warfarin, only five embolic episodes occurred, yielding an incidence of 0.8% per patient-year (relative risk, 0.32). VKA therapy in patients with mitral stenosis who are identified to have left atrial thrombus by TEE can result in thrombus resolution. In a study²⁷ of 108 patients with mitral stenosis and left atrial thrombus, there was a 62% disappearance rate of left atrial thrombus with warfarin therapy over an average period of 34 months. Smaller thrombus size and a lower New York Heart Association (NYHA) functional class were independent predictors of thrombus resolution.²⁷

The incidence of systemic emboli increases dramatically with the development of AF. Szekely⁶ reported that the risk of embolism was seven times greater in patients with rheumatic mitral valve disease and AF than in those with normal sinus rhythm. Among patients with mitral valve disease and AF, Hinton et al²⁸ found a 41% prevalence of systemic emboli at autopsy. Three fourths of the patients with mitral stenosis and cerebral emboli described by Harris and Levine²⁹ and by Wood⁴ had AF. Among 839 patients with mitral valve disease described by Coulshed et al,¹³ emboli occurred in 8% of mitral stenosis patients with normal sinus rhythm and 31.5% of those with AF (relative risk, 3.94). In a retrospective study of 254 patients with AF, of which 47% had mitral valve disease, an embolic rate of 5.46%/yr was reported for patients not receiving anticoagulation vs 0.7%/yr for those receiving longterm warfarin therapy (relative risk, 0.13).³⁰

Corroborative evidence supporting the utility of anticoagulation for the prevention of thromboembolism in patients with rheumatic mitral valve disease and AF comes from extrapolation of the results of four large randomized studies^{31–34} in patients with nonvalvular AF. Each of these studies demonstrated that warfarin was effective in reducing stroke incidence in patients with nonvalvular AF. An additional Canadian multicenter trial³⁵ was terminated prematurely when its results showed a trend consistent with the data reported in the four earlier trials. More recently, a metaanalysis that included six published, randomized trials with a total of 4,052 patients has provided further confirmation that warfarin is superior to aspirin (ASA) in decreasing the risk of stroke in patients with nonvalvular $AF.\overset{\mathbf{36}}{\mathbf{5}}$ Evidence is also mounting that supports the use of long-term anticoagulation for patients with AF who are treated with antiarrhythmic medications to maintain sinus rhythm.^{37,38} In the chapter of this supplement entitled "Antithrombotic Therapy in Atrial Fibrillation," Singer et al review in detail the evidence regarding anticoagulation in patients with nonvalvular AF.

In view of these data, as a general rule, all patients with rheumatic mitral valve disease complicated singly or in combination by AF (paroxysmal, persistent, or permanent), previous systemic embolism, and/or left atrial thrombus should be offered treatment with VKA therapy. Exceptions that require detailed trade-off analysis include the pregnant woman or the patient at high risk for serious bleeding, whether due to established concomitant disease, ongoing exposure to contact sports or trauma, bleeding diathesis, or inability to control the international normalized ratio (INR).

The risks and benefits of adding antiplatelet agents (APAs) to VKA in valvular AF remain under investigation. Until recently, the potential role for the addition of APA therapy was extrapolated from data in patients with prosthetic heart valves.^{39–44} There is

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evidence to suggest that dipyridamole or ASA added to VKA will reduce the incidence of thromboembolism in patients with prosthetic heart valves. In addition, the safety of combined therapy with VKA and ASA was assessed in a post-myocardial infarction trial.⁴⁵ The addition of low-dose ASA (75 mg/d) to warfarin (target INR, 2.0 to 2.5) did not increase the bleeding risk compared to therapy with warfarin alone (target INR, 2.8 to 4.2). However, in an analysis of the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation trials, the addition of ASA (in doses up to 100 mg/d) to warfarin (target INR, 2.0 to 3.0) was associated with a higher rate of major bleeding as compared to treatment with warfarin alone (3.9%/yr vs 2.3%/yr). The effectiveness and safety of combined therapy in patients with valvular and nonvalvular AF has also been directly examined in a randomized trial from Spain, the National Study for Prevention of Embolism in Atrial Fibrillation.⁴⁶ Eligible patients were classified into an intermediate-risk and a high-risk group, with the high-risk group composed of patients with mitral stenosis or nonvalvular AF with prior thromboembolism. In this trial, high-risk patients were randomized to full-intensity VKA with acenocoumarol (target INR, 2.0 to 3.0), or to 600 mg/d of the cyclooxygenase inhibitor triflusal combined with low-intensity acenocoumarol (target INR, 1.4 to 2.4). Triflusal is an APA that is structurally related to ASA, and at the time of this writing is approved for use in Europe but not in the United States. Clinical trials have shown that at a dose of 600 mg/d, it has similar efficacy to ASA 300 mg/d with fewer bleeding complications.^{47,48} The combined therapy group had a lower median INR vs acenocoumarol alone (2.17 vs 2.50). The primary outcome, a composite of vascular death and nonfatal stroke or systemic embolism, was lower in the combined therapy group than in acenocoumarol alone (hazard ratio, 0.51; p = 0.03). There was no difference in severe bleeding between the two groups with a higher rate of ICH in the acenocoumarol alone group and a higher rate of GI bleeding in the combined therapy arm. Patients with history of prior embolism had a significantly higher event rate than those without embolism at baseline, and this characteristic was a stronger predictor of the end point than was the presence of mitral stenosis.

Further randomized trials evaluating the safety and efficacy of combination therapy with APA and VKA in patients with rheumatic mitral valve disease and AF are still needed. In the United States, until further data become available, patients with rheumatic mitral valve disease with AF or those considered to be at substantial risk for thromboembolism should be administered VKAs (target INR, 2.0 to 3.0). If warfarin is contraindicated, APA therapy might be a reasonable, albeit uncertain, alternative. If there is a history of embolism or if therapeutic VKA therapy should fail, addition of low-dose ASA (50 to 100 mg/d) might be considered. Until there are further clinical studies supporting the use of dipyridamole in the setting of valvular heart disease, its role will remain unclear, though it is unlikely the drug is superior to ASA in this setting.⁴⁹

Recommendations

1.1.1. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of AF, previous systemic embolism, or left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1A].

1.1.2. For patients with rheumatic mitral valve disease with AF who have systemic embolism or have left atrial thrombus while receiving VKAs at a therapeutic INR, we suggest the addition of low-dose ASA (50 to 100 mg/d) after consideration of the additional hemorrhagic risks (Grade 2C). An alternative strategy might be the adjustment of VKA dosing to achieve a higher target INR (target INR, 3.0; range, 2.5 to 3.5) [Grade 2C].

1.2 Patients With Mitral Valve Disease in Sinus Rhythm

The rheumatic mitral valve disease patient in sinus rhythm might have a substantial risk of systemic embolism, possibly in relation to the severity of stenosis, and therefore might be a candidate for VKA therapy. This risk is particularly high if the patient has had prior AF or is being treated with antiarrhythmic medications to maintain sinus rhythm.^{37,38} It is not yet clear whether periodic echocardiography to detect atrial thrombus is indicated in older patients with mitral stenosis who remain in sinus rhythm and have not had AF. Other than age, there are no reliable clinical markers in such cases, and therefore the decision to treat is problematic. Because the risk of AF is high in the rheumatic mitral disease patient with a very large atrium, some authorities suggest that patients in normal sinus rhythm with a left atrial diameter > 55 mm, with or without spontaneous echocardiographic contrast, should receive VKA therapy.⁵⁰

Recommendation

1.2.1. 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 to 3.0) [Grade 2C].

Underlying values and preferences: This recommendation places a relatively high value on preventing systemic embolism and its consequences, and a relatively low value on avoiding the bleeding risk and inconvenience associated with VKA therapy.

1.2.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm, we do not suggest antithrombotic therapy, unless a separate indication exists (Grade 2C).

1.3 Patients Undergoing PMBV

Left atrial thrombus is a contraindication to PMBV, due to the risk of its dislodgement during catheter manipulation. Screening TEE is recommended to exclude left atrial thrombus prior to the procedure. Analogous to the situation for cardioversion of patients with paroxysmal or persistent AF, treatment with VKAs for 3 weeks before and 4 weeks after PMBV might be reasonable.^{51,52} However, Abraham et al⁵³ performed PMBV on 629 relatively young patients (mean age, 29.51 ± 9.9 years) with rheumatic mitral stenosis, normal sinus rhythm, no history of embolism, or echocardiographic evidence of thrombus, who did not receive anticoagulation prior to, during, or after the procedure. No patient had an embolism in the immediate postprocedure period or during a median follow-up of 3 months. Kang et al⁵⁴ reported on 49 patients with mitral stenosis with left atrial appendage thrombi who were otherwise candidates for PMBV.54 Twenty-five patients underwent PMBV after being treated with warfarin to achieve an INR of 2.0 to 3.0. PMBV was performed after resolution of left atrial appendage thrombi (mean resolution time was 5 ± 3 months). There were no procedure-related complications reported during or after PMBV. Silaruks et al⁵⁵ evaluated the resolution rate of left atrial thrombus as demonstrated by TEE in 219 PMBV candidates. At 6 months, the overall disappearance rate was 24.2%. Predictors of thrombus resolution included NYHA functional class II or better, left atrial appendage thrombus size ≤ 1.6 cm², 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.⁵⁵

Recommendations

1.3.1. For patients being considered for PMBV, we recommend preprocedural TEE to exclude left atrial thrombus (Grade 1C).

1.3.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, we recommend postponement of PMBV and administration of VKA therapy (target INR, 3.0; range, 2.5 to 3.5) until thrombus resolution is documented by repeat TEE (Grade 1C). If left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1C).

2.0 MITRAL VALVE PROLAPSE

Mitral valve prolapse (MVP) is the most common congenital form of valve disease in adults.⁵⁶ While generally innocuous, serious complications can occur. Cerebral ischemic events have been reported in several patients with MVP in whom no other source for emboli could be found. In 1974, Barnett⁵⁷ observed four patients with MVP who had cerebral ischemic events. Two years later, a total of 12 patients were described with recurrent transient ischemic attacks (TIAs) and partial nonprogressive strokes who had no evidence of atherosclerotic disease, hypertension, or coagulation disorders.⁵⁸ Similar observations have been made by other investigators,^{59–61} and as many as nine such patients have been reported from a single center.⁶¹

Earlier evidence linking MVP with stroke was provided by the case-control study of Barnett et al.⁶² Among 60 patients < 45 years old who had TIAs or partial stroke, MVP was detected in 40%. In 60 age-matched control subjects, the prevalence was 6.8% (p < 0.001). In 42 stroke patients > 45 years old, MVP was found in 5.7%, a prevalence comparable to that in the general population.⁶² The echocardiographic criteria for the diagnosis of MVP have changed resulting in a lower prevalence of the disease than previously reported. In fact, in the study by Gilon et al,⁶³ MVP was found to be less common than previously reported among young patients with stroke or TIA. In this case-control study of young stroke patients (age ≤ 45 years), 4 of 213 patients (1.9%) had MVP as compared with 7 of 263 control subjects (2.7%). Of the 213 patients with stroke, 71 were determined to be cryptogenic. Of this subgroup, two patients (2.8%) were found to have MVP. This prevalence was not significantly different than the control group. Evaluation of the Framingham Heart Study⁶⁴ offspring cohort has yielded similar results, with MVP in only 2.4% of this cohort. In the Framingham cohort,⁶⁴ no significant difference was found in the prevalence of stroke or TIA in individuals with MVP as compared to those without MVP. More recently, however, the association of MVP with stroke or TIA was assessed by Avierinos et al⁶⁵ in the Olmsted County, MN, database. Compared with expected events in the same community, subjects with MVP had an excess lifetime risk of stroke or TIA (relative risk, 2.2; p < 0.001).

Thus, although it appears that only a small number of patients with MVP are at risk for systemic throm-

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boembolism, consideration of denominators should temper our therapeutic approach to this problem. Assuming that 2.4% of the US population has MVP,⁶⁴ the incidence of thromboembolism in these approximately 7.5 million Americans must be extraordinarily low. Indeed, it has been estimated that the risk of stroke in young adults with MVP is only 1 in 6,000/yr.⁶⁶

The dilemma of cost-effective antithrombotic therapy in patients with MVP would best be solved by a reliable means of identifying the small subset of patients at relatively higher risk for thromboembolism. In a retrospective study of 26 patients with MVP, Steele et al⁶⁷ reported that platelet survival time was significantly shortened in all five patients with a history of thromboembolism, but this abnormality was also observed in one third of the patients without thromboembolism. Future studies of the clinical, genetic, and laboratory characteristics of MVP patients may succeed in identifying those at higher risk. Since myxomatous degeneration and denudation of the mitral endothelium are likely to be critical in the thrombogenic process, patients with "secondary" MVP,68 due solely to a reduction in left ventricular dimensions, would not be expected to be at increased embolic risk. It would also be important to learn whether the "click-only" or silent MVP patient is at risk for thromboembolism. However, observations have indicated they may be at risk because most MVP patients with cerebral ischemia are found to have normal results on physical examination.⁶⁹

In a prospective study of 237 patients with MVP, Nishimura et al⁷⁰ concluded that those with a redundant mitral valve on echocardiography constitute a subgroup of patients at high risk for aortic and mitral valve replacement (MR), infective endocarditis, sudden death, and cerebral ischemic events. Most of these observations were confirmed in a retrospective study by Marks et al,⁷¹ except that the risk of stroke was not correlated with valve thickening. Avierinos et al⁶⁵ indicated that independent determinants of events in subjects with MVP were older age (> 50 years), mitral valve thickening, AF, and the need for cardiac surgery, usually due to severe MR and left ventricular dysfunction.

These studies help to identify clinical and echocardiographic markers of risk for cerebral ischemic events in the MVP patient. However, to our knowledge, no studies of antithrombotic therapy in this disease have been reported. Therefore, guidelines for therapy are at best empiric and drawn from experience with other thromboembolic conditions. It seems reasonable that the MVP patient with convincing evidence of TIAs with no other source of emboli should receive antithrombotic therapy. Since repeated ischemic episodes are not uncommon,^{59,62,72,73} APA therapy is likely indicated as is the case for many patients with TIAs and no MVP.⁷⁴ As documented in the chapter of this supplement entitled "Antithrombotic and Thrombolytic Therapy for Ischemic Stroke," randomized trials have consistently shown that APAs reduce stroke risk in such patients. VKA therapy is appropriate for those patients with AF and for those with recurrent cerebral ischemic events despite ASA therapy.

Recommendations

2.0.1. In patients with MVP who have not had systemic embolism, unexplained TIAs or ischemic stroke, and do not have AF, we recommend against any antithrombotic therapy (Grade 1C).

2.0.2. In patients with MVP who have documented but unexplained TIAs or ischemic stroke, we recommend ASA (50 to 100 mg/d) [Grade 1B].

2.0.3. In patients with MVP who have AF, documented systemic embolism, or recurrent TIAs despite ASA therapy, we suggest VKA therapy (target INR, 2.5; range 2.0 to 3.0) [Grade 2C].

3.0 MITRAL ANNULAR CALCIFICATION

The clinical syndrome of mitral annular calcification (MAC), first clearly described in 1962,75 includes a strong female preponderance and might be associated with valvular stenosis (due to extension of the calcific process onto the leaflets) and/or regurgitation, calcific aortic stenosis, conduction disturbances, arrhythmias, embolic phenomena, and endocarditis. It must be emphasized that radiographic evidence of calcium in the mitral annulus does not in itself constitute the syndrome of MAC. While the true incidence of systemic emboli in this condition is not known, ischemic events appear conspicuously with or without associated AF.75-80 Four of the 14 original patients described by Korn et al⁷⁵ had cerebral infarction, and 5 of 80 patients described by Fulkerson et al⁷⁷ had systemic emboli, only 2 of whom had AF. In a report by Ching-Shen et al,⁸¹ 16 of 142 patients with MAC were found to have systemic calcareous emboli. In autopsy specimens, thrombi have been found on heavily calcified annular tissue,82 and echogenic densities have been described in the left ventricular outflow tract in this condition among patients with cerebral ischemic events.⁷⁸ Perhaps the best estimate of the embolic potential of MAC comes from the Framingham Heart Study.⁸⁰ Among 1,159 subjects with no history of stroke at the index echocardiographic examination, the relative risk of stroke in those with MAC

was 2.1 times greater than those without MAC (p = 0.006), independent of traditional risk factors for stroke. In addition, in the Strong Heart Study⁸³ the incidence of stroke was significantly increased in the presence of MAC (relative risk, 3.12; 95% CI, 1.77 to 5.25). After adjusting for a number of clinical variables (including age, diabetes, body mass index, serum creatinine, and total/high-sensity lipoprotein cholesterol ratio), and echocardiographic covariates (including left atrial enlargement and left ventricular hypertrophy), the increased risk for time to first stroke in this cohort was diminished, but still significant (hazard ratio, 1.89).

In addition to embolization of fibrin clot, calcified spicules might become dislodged from the ulcerated calcified annulus and present as systemic emboli.^{77,79,84} While the relative frequencies of calcific emboli and thromboembolism are unknown, it is likely that the incidence of the former problem has been underestimated since this diagnosis can be established only by pathologic examination of the embolus or by the rarely visualized calcified fragments in the retinal circulation.⁷⁷ Since there is little reason to believe that antithrombotic therapy would be effective in preventing calcific emboli, the rationale for using antithrombotic drugs in patients with MAC rests primarily on the frequency of true thromboembolism. In the Framingham Heart Study, the incidence of AF was 12 times greater in patients with MAC than in those without this lesion,85 and 29% of the patients with annular calcification described by Fulkerson et al⁷⁷ had AF. Endothelial abnormalities, including MAC, have been recognized as risk factors for thromboembolism in patients with AF.86 In addition, left atrial enlargement is not uncommon, even in those with normal sinus rhythm. MAC has also been associated with diffuse atherosclerotic disease, including aortic and carotid artery atheromas.^{87,88} Thus, the many factors contributing to the risk of thromboembolism in MAC include AF, the hemodynamic consequences of the mitral valve lesion itself (stenosis and/or regurgitation), fragmentation of calcific annular tissue, and diffuse vascular atherosclerosis.

In light of these observations, an argument can be made for VKA therapy in MAC patients with a history of an embolic event. However, since most of these patients are elderly (mean age, 73 to 75 years),^{70,77} the risks of VKA therapy with coumarin derivatives will be increased. Therefore, if the mitral lesion is mild or if an embolic event is clearly identified as calcific rather than thrombotic, the risks of VKA therapy might outweigh the benefits in patients without AF. For patients with repeated embolic events despite VKA therapy or in whom multiple calcific emboli are recognized, valve replacement should be considered.

Recommendations

3.0.1. In patients with MAC complicated by systemic embolism, ischemic stroke, or TIA, who do not have AF, we recommend ASA (50 to 100 mg/d) [Grade 1B]. For recurrent events despite ASA therapy, we suggest treatment with VKA therapy be considered (target INR, 2.5; range, 2.0 to 3.0) [Grade 2C]. In patients with MAC who have a single embolus documented to be calcific, the data are not sufficient to allow recommendation for or against antithrombotic therapy.

3.0.2. In patients with MAC and AF, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C].

4.0 AORTIC VALVE AND AORTIC ARCH DISORDERS

4.1 Calcific Aortic Value Disease

Clinically detectable systemic emboli in isolated aortic valve disease are distinctly uncommon. However, Stein et al⁸⁹ emphasized the thromboembolic potential of severe calcific aortic valve disease and demonstrated microthrombi in 10 of 19 calcified and stenotic aortic valves studied histologically. In only one, however, was a thrombus grossly visible on the excised valve, and clinical evidence of systemic embolism was not reported. Four cases of calcific emboli to the retinal artery in patients with calcific aortic stenosis were reported by Brockmeier et al,90 and four cases of cerebral emboli were observed in patients with bicuspid aortic valves in whom no other source of emboli could be found.⁹¹ In the latter group, all four patients were treated with ASA, and no recurrences were observed. Perhaps the most striking report of the incidence of calcific emboli in patients with calcific aortic stenosis is that of Holley et al.⁹² In this autopsy study of 165 patients, systemic emboli were found in 31 patients (19%)—the heart and kidneys were the most common sites of emboli-but again, clinically detectable events were notably rare.92

It appears, therefore, that calcific microemboli from heavily calcified, stenotic aortic valves are not rare, but because of their small size, they are not readily detected unless they can be visualized in the retinal artery. Indeed, the small but consistent frequency of systemic emboli reported in earlier studies of aortic valve disease might best be explained by unrecognized mitral valve disease, ischemic heart disease, or by coexisting AF. It is of interest in this regard that of 194 patients with rheumatic valve

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disease and systemic emboli described by Daley et al,¹¹ only 6 patients had isolated aortic valve disease, and in each AF was also present. The association of AF and aortic valve disease was further examined in a report by Myler and Sanders.⁹³ In 122 consecutive patients with proven isolated severe aortic valve disease, only 1 patient had AF; and in this case, advanced coronary heart disease with infarction was present as well.93 Boon et al94 prospectively compared the risk of stroke in 815 patients with aortic valve calcification with or without stenosis with 562 control subjects. These authors found no significant increase in stroke risk in patients with calcific aortic valve disorders (mean follow-up, 833 days) compared with a matched control group. Otto et al⁹⁵ evaluated 1,610 individuals with aortic sclerosis as well as 92 individuals with aortic stenosis enrolled in the Cardiovascular Health Study. No information on the presence or extent of aortic valve calcification was reported in this study. The authors found no significant increase in the incidence of stroke over a mean follow-up period of 5 years.95 More recently, Kizer et al reported no significant increase in the incidence of stroke in subjects with a rtic valve sclerosis enrolled in the Strong Heart Study.⁸³

Thus, in the absence of associated mitral valve disease or AF, clinically evident systemic embolism in patients with aortic valve disease is uncommon and long-term VKA therapy is not indicated. However, a significant number of patients with severe calcific aortic valve disease do have microscopic calcific emboli, although they are not often associated with clinical events or evidence of infarction. Since the value of anticoagulant therapy in preventing calcific microemboli has not been established and their clinical consequences are few, the risks of long-term VKA therapy in isolated aortic valve disease apparently outweigh its potential usefulness.

Recommendations

4.1.1. In patients with isolated calcific aortic valve disease who have not had ischemic stroke or TIA, we suggest against antithrombotic therapy (Grade 2C).

4.1.2. In patients with isolated calcific aortic valve disease who have had ischemic stroke or TIA not attributable to another source, we suggest ASA (50 to 100 mg/d) [Grade 2C].

4.2 Atherosclerotic Plaque of the Aortic Arch

The prevalence of severe aortic plaque in stroke patients (14 to 21%) is similar to that of carotid artery disease and AF.⁹⁶ TEE of the aortic arch and ascending aorta have identified atherosclerotic plaque size and morphology as risk factors for ischemic stroke.^{97,98} TEE was performed in 382 patients

enrolled in the Stroke Prevention in Atrial Fibrillation trial.99 In this cohort of AF patients, risk factors for thromboembolism included systolic hypertension, age > 75 years (women), previous thromboembolism, clinical heart failure, or impaired left ventricular systolic function. In 134 patients (35%) who had complex aortic plaque (ulcerated, pedunculated, mobile, and/or size > 4 mm), the risk of stroke at 1 year was 12 to 20%. The risk of stroke in patients with AF alone and no aortic plaque was 1.2%.99 In a prospective case-control study¹⁰⁰ of 250 patients with ischemic stroke, TEE revealed that 14.4% of patients with strokes had plaques > 4 mm in thickness. In contrast, the control subjects (no ischemic event) had only a 2% occurrence of plaques of this size. Similarly, in patients with prior ischemic events, Amarenco and colleagues¹⁰¹ found plaque size ≥ 4 mm to be a significant risk factor for recurrent ischemic events. These same researchers performed an analysis of 788 person-years of follow-up to determine the effect of plaque morphology on the risk of ischemic disease. They determined that the only plague characteristic that increased the risk of ischemic events was the absence of plaque calcification.¹⁰² Ulceration and hypoechoic plaques had no predictive value for vascular events. Overall, it was determined that a rtic plaques > 4 mm in thickness increased the risk of vascular events, and this risk was further increased by lack of plaque calcification (relative risk, 10.3; absence vs presence of calcification). These authors hypothesized that noncalcified plaques are probably lipid laden and are thus more unstable and prone to rupture, thrombosis, and embolization. While calcified aortic plaques might be the cause of atheroemboli with aortic manipulation-such as during cannulation at the time of cardiac surgery or catheter advancement-it is unlikely that antithrombotic therapy will be beneficial in this setting.¹⁰³

Large, prospective randomized trials assessing the effectiveness of anticoagulation therapy for the prevention of ischemic embolic events in patients with aortic plaque have yet to be published. Ferrari et al¹⁰⁴ examined the effects of antithrombotic therapy in an observational study of 129 patients identified as having aortic atheroma on TEE. They found that patients treated with APAs rather than VKAs had more combined vascular events and a higher mortality rate (relative risk, 7.1) and that the more severe the aortic atheroma, the more frequent the vascular event rate. A ninefold-higher mortality risk was demonstrated for patients with aortic debris treated with APAs as compared to patients treated with VKAs. Patients with a rtic plaques > 4 mm in thickness had almost a sixfold-higher risk for combined events when treated with APAs vs VKAs. In contrast to these data were an observational analysis

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by Tunick et al,¹⁰⁵ in which 519 patients with severe aortic plaque (≥ 4 mm) were identified during TEE evaluation for embolic events. In this study,¹⁰⁵ therapy with VKAs or APAs did not significantly reduce recurrent events. Interestingly, however, individuals receiving cholesterol-lowering therapy with HMG-CoA reductase inhibitors (statins) had significantly fewer embolic events than those not taking inhibitors (12% vs 29%). The authors concluded that this outcome might be a beneficial effect of statins on plaque stability. Aggressive statin therapy recently has been shown to be associated with regression in the size of aortic atherosclerotic plaques as assessed by MRI.^{106,107}

Mobile lesions attached to atheromas seen on TEE have proven most often to be thrombi.⁹⁶ Dressler et al¹⁰⁸ investigated the benefits of VKA therapy on recurrent stroke in 31 patients with systemic embolic events who were found to have mobile aortic atheroma on TEE. Those not receiving warfarin had a higher incidence of vascular events (27% had strokes), than those receiving warfarin (0% had strokes). They also determined that the dimensions of the mobile component of the atheroma should not be used to assess the need for anticoagulation therapy, since small (diameter <1 mm), medium (diameter >1 mm and area <10 mm²), and large (diameter >1 mm and area >10 mm²) mobile components had similar outcomes.¹⁰⁸

Thus, the effectiveness of VKA therapy for the prevention of ischemic events in patients with severe, thoracic aortic atheroma remains unclear, pending results of prospective randomized trials. Observational studies have suggested a beneficial effect. Patients with mobile lesions might be considered for antithrombotic therapy with VKAs. The predictive role of plaque size alone (ie, > 4 mm) is less clear.

Recommendation

4.2.1. In patients with ischemic stroke associated with aortic atherosclerotic lesions, we recommend low-dose ASA (50 to 100 mg/d) over no therapy (Grade 1C). For patients with ischemic stroke associated with mobile aortic arch thrombi, we suggest therapy with either VKAs (target INR, 2.5; range, 2.0 to 3.0) or low-dose ASA (50 to 100 mg/d) [Grade 2C].

5.0 PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM

The cause of ischemic stroke remains undiagnosed in approximately 40% of patients.¹⁰⁹ However, the incidence of paradoxical embolism as the mechanism of cryptogenic stroke remains unknown. In recent years, the role of developmental and acquired disease of the interatrial septum as a cause of cryptogenic stroke has received considerable attention. Paradoxical embolism through a patent foramen ovale (PFO) is well documented, and thrombus on the arterial side of an atrial septal aneurysm has been reported at autopsy, during surgery, and by TEE.¹¹⁰ Much of the uncertainty about the incidence of paradoxical embolism lies in the fact that 27 to 29% of normal hearts have demonstrable PFOs at autopsy,^{111,112} and thus the predictive value of this finding as a risk factor for paradoxical embolism is low. However, the demonstration by transthoracic echocardiography that 10 to 18% of normal people exhibit right-to-left shunting through a PFO during cough or Valsalva maneuver^{113,114} (by TEE the prevalence is higher and approaches the anatomic data (27 to 29%),¹¹⁵ and the observation that 57% of patients with PFOs and suspected paradoxical embolism were found to have venous thrombosis by venography,¹¹⁶ provide support for the hypothesis that paradoxical embolism might be more common than generally believed.

A number of studies^{114,117–120} have demonstrated a strong association between PFO and stroke. The evidence for this association is particularly apparent in younger patients for whom the likelihood of atherosclerotic embolic disease is less compelling. TEE with saline solution contrast injection is the diagnostic technique of choice for demonstrating a PFO.¹²¹ However, since the sensitivity of saline solution contrast TEE is greater than that of transthoracic echocardiography, the question might be asked whether smaller PFOs identified only by TEE are clinically relevant to the true incidence of paradoxical embolism. Two reports^{122,123} from Olmsted County, MN and the Stroke Prevention: Assessment of Risk in a Community study have suggested that after adjusting for age and other comorbidities associated with stroke, PFO is not an independent risk factor for future stroke in the general population.

Factors 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's network, and atrial septal aneuryms.^{109,124} Individuals with atrial septal aneurysm have a high incidence of PFO (approximately 60%), and the PFOs associated with atrial septal aneurysms tend to be larger.¹⁰⁹ A strong association between atrial septal aneurysm and stroke has been reported.^{110,125} Atrial septal aneurysm has been identified in 1% of autopsies and in 3 to 4% of nonstroke patients examined by TEE.^{110,125} Because of a high incidence of PFO in patients with

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atrial septal aneurysm and anecdotal reports of clot within the aneurysm, there are two potential sources of systemic embolism in this condition—paradoxical embolism and arterial thromboembolism arising from the left side of the atrial septal aneurysm. Paroxysmal atrial fibrillation might also contribute. The potential role of humoral substances that are shunted across the interatrial septum and bypass the pulmonary circulation has not been clarified.

In both isolated PFO and in atrial septal aneurysm, the indications for antithrombotic therapy remain uncertain. In the Warfarin-Aspirin Recurrent Stroke Study (WARSS),¹²⁶ there was no significant difference in the incidence of recurrent stroke or death in patients with cryptogenic stroke treated with ASA (325 mg/d) or warfarin (target INR, 1.4 to 2.8). Homma et al¹²⁷ identified PFO in 203 patients enrolled in WARSS. There was no significant difference in the time to recurrent stroke in patients with a PFO as compared to those without a PFO. There was also no effect of size of PFO or presence of atrial septal aneurysm and no significant difference on outcome between those treated with ASA vs those treated with warfarin. These results must be interpreted with caution, as this study was not designed to evaluate the efficacy of ASA vs warfarin in PFO. Hanna et al¹²⁸ reported on a relatively small series of patients who had what appeared to be PFO-related brain infarcts. These authors reported no recurrent infarcts during a mean follow-up period of 28 months and believed that ASA might be sufficient stroke prophylaxis while warfarin and surgical correction could be reserved for patients in whom ASA is not effective. Mas et al¹²⁹ examined 581 patients with ischemic stroke of unknown etiology who were treated with ASA (300 mg/d). Isolated PFO or atrial septal defect were not significant predictors of increased risk of recurrent stoke or TIA at 4 years. The 4-year risk of stroke or TIA for patients with an atrial septal aneurysm and PFO was significantly elevated (19.2%). The authors concluded that ASA might be insufficient protection against recurrent stroke or TIA in patients with both a PFO and atrial septal aneurysm.

In patients with unexplained cerebral ischemia, stroke, or systemic embolism, the demonstration of right-to-left shunting through a PFO warrants a search for deep vein thrombosis. Evidence for venous thrombosis (or pulmonary embolism) together with systemic embolism and a PFO provides a strong indication for long-term anticoagulation, venous interruption, or in some cases, closure of the PFO or atrial septal defect. In the absence of evidence for venous thromboembolism, the threshold for these interventions is higher and must be made on a case-by-case basis. Certainly, long-term anticoagulation would not be recommended for asymptomatic PFOs or atrial septal aneurysms, although low-dose ASA would not seem unreasonable to reduce the likelihood of thrombosis on the arterial side of an atrial septal aneurysm. Subsequent studies of the role of PFO in patients with cryptogenic stroke may broaden the indications for long-term warfarin therapy or elective catheter-based closure. The low specificity of right-to-left shunting through a PFO as a risk factor for stroke and the known risks of long-term anticoagulation, mandate that we apply caution in recommending life-long anticoagulation for patients suspected of paradoxical embolism, unless the diagnostic evidence is quite convincing or alternative causes are identified that would justify this therapy. The role of antithrombotic therapy with VKAs or APAs is also likely to evolve as technological advancements are made in PFO closure devices and their benefit is more clearly defined by ongoing trials. Reports of transcatheter closure of PFOs have demonstrated both low complication rates as well as low rates of recurrent thromboembolic events.^{130,131} Retrospective analysis suggests percutaneous closure might be at least as effective as medical treatment for prevention of recurrent cerebrovascular events in patients with PFO and cryptogenic stroke. Randomized controlled trials designed to evaluate the role of medical vs interventional strategies in these patients are ongoing.¹⁰⁹ PFO closure might be considered for patients with recurrent cryptogenic ischemic strokes, despite antithrombotic therapy.

Recommendations

5.0.1. In patients with ischemic stroke and a PFO, we recommend APA therapy (Grade 1A), and suggest APA therapy over VKA therapy (Grade 2A).

5.0.2. In patients with cryptogenic ischemic stroke and PFO, with evidence of deep venous thrombosis or another indication for VKA therapy, such as AF or an underlying hypercoagulable state, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C].

6.0 Prosthetic Heart Valves–Mechanical Prosthetic Heart Valves

It is well established that patients with mechanical valves require antithrombotic prophylaxis. Lack of prophylaxis in patients with St. Jude Medical bileaflet valves is associated with an unacceptable rate of major complications (embolism or valve thrombosis in 12%/yr with aortic valves and 22%/yr with mitral valves).¹³² In one study of patients with the Bjork Shiley spherical-disk valves who received no prophy-

laxis or prophylaxis with APAs alone, thromboemboli occurred in 23%/yr.¹³³ In the present guidelines, we continue to examine the literature that may permit a more refined assessment of the optimal level of anticoagulation for patients with current generation mechanical prosthetic heart valves. We address whether low doses of ASA or other APA drugs, in combination with VKAs, may be beneficial and safe. Investigations of the use of warfarin targeted to lower INRs are also assessed, particularly with newer valves. Investigations included in the present guideline are generally limited to those studies that have reported anticoagulant prophylaxis in terms of the INR. Much detailed information, particularly for older-generation mechanical valves, is provided in the chapter on antithrombotic therapy in prosthetic heart valves in the CHEST supplement of 2001, and will not be repeated.¹³⁴

Most reports of antithrombotic prophylaxis are from nonrandomized case series without controls. The safety and efficacy of a given range of INR are usually reported on the basis of an intention-to-treat analysis rather than on the basis of the intensity of anticoagulant effect actually achieved. In some important investigations, less than half of the INRs were in the target range.^{42,135} Intention-to-treat analysis might yield misleading results about the safety and efficacy of a target INR, especially when failure to tightly regulate the INR range in any study is coupled with the lack of reporting of the actual INRs at which events occurred. These limitations weaken the strength with which therapeutic recommendations can be made. They also indicate the need for further research in this area. Ideally, more prospective studies, which address risk factors among patients with each type and location of prosthetic valve, the level of anticoagulation actually achieved, and the level of anticoagulation at which complications occurred, are needed before controversy regarding prophylaxis can be resolved.

St. Jude Medical Bileaflet Mechanical Value: Experience with St. Jude Medical bileaflet mechanical valves is shown in Table 2.^{136–138} Horstkotte et al¹³⁹ showed that relatively less intense anticoagulation for patients with aortic St. Jude medical valves, (at an estimated INR of 1.8 to 2.8 vs an estimated INR of 2.5 to 3.5) resulted in an increase in the rate of thromboemboli from 2.8 to 3.9%/yr, but a reduced rate of major bleeding from 1.25 to 0.4%/yr. These results formed the hypothesis for the randomized multicenter GELIA study (German Experience with Low Intensity Anticoagulation),¹⁴⁰ which enrolled 2,848 patients and provided 8,061 patient years of follow-up.¹⁴⁰ The GELIA data demonstrated no significant influence of the intensity of anticoagula-

tion on the incidence of thromboemboli among patients randomized to three different target INR ranges (3.0 to 4.5, 2.5 to 4.0, and 2.0 to 3.5).¹⁴¹ However, the target range INRs overlapped in this trial and measured INRs were frequently out of range.^{141,142} Notably, instability of VKA therapy was a strong predictor of major adverse events. In addition, loss of atrial contraction, as with AF, was associated with a marked increase in thromboembolic event rates.¹⁴³

Among patients in the AREVA trial, of whom 82% had St. Jude Medical valves, (96% in the aortic position), thromboembolic events were not more frequent at an INR of 2.0 to 3.0 than at an INR of 3.0 to 4.5, provided patients were in sinus rhythm and had a normal-sized left atrium.¹⁴⁴ In patients with bileaflet valves in the aortic, mitral, or both positions, Cannegieter et al¹⁴⁵ showed fewer adverse events (bleeding or thromboemboli) at an INR of 2.0 to 2.9 than at higher INRs. Arom et al,¹⁴⁶ in a retrospective case series of patients \geq 70 years old with St. Jude Medical aortic valves, showed a frequency of thromboemboli of 0.7%/yr at an INR of 1.8 to 2.5. The INR was measured only during the later years of the investigation. The prevalence of AF was not reported.

¹ Baudet et al¹³⁶ reported a combined incidence of thromboemboli or valve thrombosis of 1.06%/yr among patients with a St. Jude Medical valve in the aortic position, treated to an INR of 2.4 to 2.8. Emery et al¹³⁷ reported an incidence of thromboemboli of 0.69 to 0.80%/yr among patients with a St. Jude Medical valve in the aortic position treated to an estimated INR of 1.8 to 2.0. The higher value (0.80%/yr) was reported for patients who had also required concomitant coronary artery bypass grafting.

Rates of thromboembolic complications are somewhat higher among patients with St. Jude Medical valves in the mitral vs the aortic position. Baudet et al¹³⁶ reported a 2.2%/yr incidence of thromboemboli or valve thrombosis with St. Jude Medical mitral valve prostheses vs 1.1%/yr for aortic prostheses among patients treated to an estimated INR of 2.4 to 2.8.

In the GELIA study,¹⁴² linearized rates for bleeding were greatest in the group treated to the highest INR range (INR 3.0 to 4.5 vs 2.5 to 4.0, or 2.0 to 3.5). However, differences in bleeding rates were due to minor bleeding, whereas the incidence of moderate to severe bleeding was not significantly different among the three groups. If minor thromboembolic events (TIAs) and minor bleeding events (small hematomas, mild epistaxis or gingival bleeding) usually not documented in studies with a less restrictive follow-up protocol than that of GELIA—were excluded, the rates of thromboembolic events and

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			(S	ection 6.0)*				
Study/yr	Interventions	Target INR	Patients Analyzed, No./Total	Mean Length of Follow-up	Valve Thrombosis, No. (%pty)	Arterial Thromboemboli, No. (%/pty)	Late Mortality,† No. (%/pty)	Major Hemorrhage, No. (%/pty)
Randomized trials Aortic valve Acar J/1996 AREVA	Heparin and acenocoumarol after 48 h; two	2.0-3.0 3.0-4.5	INR 2.0–3.0: 179/188 INR 3.0–4.5: 185/192	2.2 yr	INR 2.0–3.0:0 INR 3.0–4.5:0	INR 2.0–3.0: 10 (1.9) INR 3.0–4.5:	INR 2.0–3.0: NR INR 3.0–4.5:	INR 2.0-3.0: 13 (4.0) INR 3.0-4.5:
Hering D/2005 GELIA	mtensities OAC; three intensities	Stratum A: 3.0-4.5 Stratum B: 2.5-4.0 Stratum C: 2.0-3.5	Stratum A: 672 Stratum B: 677 Stratum C: 675	2.5 yr	NR	9 (1.7) Stratum A: 11 (0.7) Stratum B: 8 (0.5) Stratum C: 8(0.5)	N K N N	19 (5.6) Stratum A: 13 (0.8) Stratum B: 8 (0.5) Stratum C: 5 (0.3)
Mitral valve Hering D/2005 GELIA	OAC; three intensities	Stratum A: 3.0-4.5 Stratum B: 2.5-4.0 Stratum C: 2.0-3.5	Stratum A: 178 Stratum B: 193 Stratum C: 182	2.3 yr	NR	Stratum A: 11 (0.7) Stratum B: 8 (0.5) Stratum C: 8 (0.5)	NR	Stratum A: 1 (0.2) Stratum B: 2 (0.5) Stratum C: 0 0 0)
Laffort P/2000	OAC plus ASA: 200 mg/d OAC alone	2. 77-73. 2. 77 7. 72	OAC plus ASA: 109/109 OAC alone: 120/120	l yr	OAC plus ASA: 4 (4.6) OAC alone: 8 (8.1)	OAC plus ASA: 10 (9.1) OAC alone: 30 (25.0)	OAC plus ASA: 4 (3.9) OAC alone: 3 (2.6)	OAC plus aspirin: 21 (19.3) OAC alone: 10 (8.3)
Cohort and case se Aortic valves Baudet E/1985 Vogt S*/1990 Emery R/ 1996 Emery R/ 1996 Horstkotte D/1994 Horstkotte D/1993	sries studies OAC No OAC OAC Isolated AVR AVR plus CABG St. Jude Medical bileaflet prosthesis implantation	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	OAC: 471 No OAC: 65 47 Isolated AVR: 904/904 AVR plus CABG: 527/ 527 298/298	2.6 yr 4.3 yr Isolated AVR: 6.1 yr; AVR plus CABC: 5.5 yr 9.7 yr	OAC: 0 (0) No OAC: 4 (6.2) 0 (0) Isolated AVR: 1 (2) AVR plus CABG: 0 (0) 0 (0)	OAC: 4 (0.3) No OAC: 4 (6.2) 6 (3.0) Isolated AVR: 38 (0.7) AVR plus CABG: 23 (0.8) 4.0-6.0; 5 (1.4) 3.0-4.5; 17 (1.9) 3.0-4.5; 23 (2.8) 1.75-2.75; 33 (3.9)	OAC: 3 (0.3) No OAC: 1 (1.6) 9 (2.2) across all valve types Isolated AVR: 187 (3.4) AVR plus CABG: 179 (6.2) 39 (1.4)	0 7 (1.7) across all valve types NR 4.0-6.0: 3 (0.9) 3.0-4.5: 6 (0.7) 2.5-3.5: 4 (0.5) 1.75-2.75: 0
	followed by OAC					All: 78 (2.8)		All: 13 (0.5)

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Study/yr	Interventions	Target INR	Patients Analyzed, No./Total	Mean Length of Follow-up	Valve Thrombosis, No. (%/pty)	Arterial Thromboemboli, No. (%/pty)	Late Mortality,† No. (%/pty)	Major Hemorrhage, No. (%/pty)
Talwar S/2004	Group A: OAC alone Group B: enoxaparin plus OAC		Group A: 67/67; Group B: 87/87	6 mo	Group A: 3 (8.9) Group B: 0 (0)	NR	NR	NR
Mitral valve								
Baudet E/1985	OAC	2.4-2.8	OAC: 95	2.4 yr	OAC: 0 (0)	OAC: 1 (0.5)	OAC: 2 (0.9)	OAC: 0 (0)
	No OAC		No OAC: 10		No OAC: 1 (5.6)	No OAC: 3 (16.7)	No OAC: 0 (0)	No OAC: 0 (0)
Horstkotte	St. Jude Medical	4.0-6.0	MVR: 215/215	$8.6 \mathrm{ yr}$	(0) (0)	4.0-6.0: 6 (2.5)	30(1.71)	4.0-6.0: 4 (1.1)
D/1994	bileatlet	3.0-4.5 2.7.9.7				3.0-4.5: 16 (2.9)		3.0-4.5:5(0.9)
Horstkotte D/1993	prostnesss implantation	2.5–3.5 1.75–2.75				2.5-3.5: 24 (4.7) 1.75-2.75: 36 (6.5)		2.5-3.5: 3 (0.6) 1.75-2.75: 0
Voort C+/1000	Tollowed by UAC	0813	65	3.4	0/30	All: 52 (4.4) 8 (9 0) across all	[[6 330406 (6 6) 0	All: 12 (0.7) 7 (1 7) across all
0021 7 tr 1300		0.1-0.7	40	14 ±.0	70/0	valve types	valve types	valve types
Fiore $A_{4}^{\dagger}/1998$	OAC	2.5–3.5	80/80	4.9 yr	2(0.5)	26 (3.4) entire population	22(7.4)	9(2.3)
Talwar S/2004	Group A: OAC		Group A: 245/245	6 mo	Group A: 8 (16.8)	NR	NR	NR
	alone Group B:		Group B: 293/293		Group B: 2 (3.2)			
	enoxaparin plus OAC							
Double or multi	ple heart valves							
Baudet E/1985	0AC No 0AC	2.4-2.8	AC: 64 No. AC: 3	2.1 yr	OAC: 0 (0) No OAC: 1 (91)	OAC: 0 (0) No OAC: 0 (0)	OAC: 3 (0.7) No OAC: 0 (0)	0/66
Horstkotte	Treatment with	1.8 - 6.0	87/87	8.5 yr	0 (0)	39 (5.3)	19 (2.6)	19(2.6)
D/1994	OAC							
Horstkotte D/ 1993								
Talwar S/2004	Group A: OAC alone		Group A: 83/83 Group B: 82/82	6 mo	Group A: 4 (9.6) Group B: 4 (9.8)	NR	NR	NR
	Group B:							
	enoxaparm puus OAC							
1.20*	· · · · · · · ·						-	

Table 2—Continued

 $\frac{*\%}{\text{pty}}$ = percent per patient-year (if this value was not presented in a study, it was calculated: outcomes/[No. of patients × mean length of follow-up]); AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; NR = not reported. The methodologic quality description portion of this Table can be found in the online version of this article as a data #Major hemorrhage defined as requiring transfusion or hospitalization or resulting in death or grade III Karnofsky. tLate mortality is defined as death occurring after discharge from hospital. supplement.

Single arm of an RCT.

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Downloaded from chestjournal.chestpubs.org by guest on October 5, 2009 © 2008 American College of Chest Physicians bleeding events for the entire study population were 0.43%/yr and 2.62%/yr respectively.¹⁴² Other studies have shown comparable rates with lower target INRs of 1.4,¹⁴⁷ or 1.5,¹⁴⁸ but the actual INR range achieved was wide or not reported.^{147,148}

Other Bileaflet Mechanical Valves: Based on an analysis of published data, David et al¹⁴⁹ concluded that there was no clinically important difference in the rate of systemic embolism among patients with the St. Jude Medical bileaflet valve and the Carbo-Medics (Austin, TX) bileaflet valve. Abe et al¹⁵⁰ reported a 1.1%/yr rate of thromboemboli or valve thrombosis in patients with a CarboMedics bileaflet valve in the aortic position, the mitral position or both positions, when treated to an INR of 2.0 to 3.5. Wang et al¹⁴⁸ used a target INR of 1.5 in patients with a CarboMedics valve in either the aortic or mitral position, and observed thromboemboli in 2.7%/yr. Other investigators have used wider ranges of target INRs in patients with the CarboMedics valve¹⁵¹ or the Duromedic (Baxter Healthcare, Edwards Division; Santa Ana, CA) valve,¹⁵² but a safe lower INR value has not been assessed.

The Sorin bicarbon bileaflet aortic valve (Sorin Biomedica Cardio; Saluggia, Italy), is associated with a risk of thromboemboli of 1.2%/yr with treatment to an INR of 2.0 to $3.0.^{153}$ Thromboembolic event rates are 0.7%/yr for patients with Sorin mitral valves treated to an INR of 3.0 to 4.0.

Monoleaflet or Tilting-Disk Valves: A 0.7%/yr thromboembolic event rate has been reported among patients with an Omnicarbon monoleaflet valve (MedicalCV; Minneapolis, MN) in the aortic position treated to an INR of 2.5 to $3.5^{.154}$ This rate appears to be the same for patients treated to a lower target INR (2.0 to 3.0).¹⁵⁵ For patients with an Omnicarbon mitral valve treated to an INR of 2.5 to 3.5^{155} or 3.0 to 4.0,¹⁵⁴ the rate of thromboembolic complications is 0.9 to 1.1%/yr.

Thromboembolic events are more frequent with mitral vs aortic Sorin Monostrut valve prostheses (Sorin Biomedica Cardio).¹⁵⁶ The range of INR used in this particular case series (2.5 to 4.0) was too broad to assess whether a lower target INR would be effective.

Previous investigations of the Bjork-Shiley spherical-disk valve^{157,158} and the Bjork Shiley Convexo Concave valve¹⁵⁸ used relatively high INR target ranges and it is not known whether lower ranges (either 2.0 to 3.0 or 2.5 to 3.5) might be safe and effective (Table 3). However, in one case series that included 1,354 patients with tilting-disk valves, the incidence of adverse events (both bleeding and thromboembolic) was similar for patients treated to an INR range of 3.0 to 3.9 vs those treated to an INR range of 4.0 to 4.9.¹⁴⁵ Patients with tilting-disk valves treated to an INR range of 2.0 to 2.9 had a greater incidence of adverse events in this study.

The effectiveness of anticoagulant therapy in patients with Medtronic-Hall valves (Medtronic; Minneapolis, MN) has been reported.^{159–161} Anticoagulant therapy to a target INR range of 2.0 to 3.0 for aortic prostheses is associated with low event rates (Table 3).¹⁵⁹ An INR range of 2.5 to 3.5 is associated with a trend toward a higher frequency of embolic events than an INR range of 3.0 to 4.5 in patients with Medtronic-Hall valves in the mitral position.^{159,161,162}

Other Valves: Saour et al,¹⁶³ in a randomized trial among patients with various types of mechanical valves, reported similar thromboembolic event rates (3.7 vs 4%/yr) in patients treated with VKAs to an average INR of 9.0 vs an average INR of 2.7 respectively. More frequent major bleeding, however, was shown in the group assigned to the higher target INR. These conclusions, however, are based on intention-to-treat analysis. Although the levels of anticoagulation reported in the two groups appeared equally effective in preventing major thromboembolic events, all thromboembolic events occurred at an estimated INR below the high-intensity range of 7.4 to 10.8. Similarly, all major bleeding events occurred with an INR outside the target range of 7.4 to 10.8.

Pengo et al¹⁶⁴ reported a thromboembolic event rate of 1.8%/yr among patients with a variety of mechanical prostheses (60% tilting-disk, 1% cagedball valves) in the aortic, mitral, or both positions treated to an INR range of 2.5 to 3.5 and a comparable rate of 2.1%/yr with treatment targeted to an INR range of 3.5 to 4.5. In a case series that included 53 patients with caged-ball and caged-disk valves, Cannegieter et al¹⁴⁵ found that an INR of 4.0 to 4.9 (when compared to lower INR ranges) was associated with the lowest overall event rates.

First-Generation Valves Compared With Current-Generation Valves: The frequency of thromboembolic events is lower with current-generation mechanical valves than with first-generation valves.¹⁴⁵ In one study, the frequency of thromboembolic events was 0.5%/yr with bileaflet valves, 0.7%/yr with tilting- disk valves, and 2.5%/yr with caged-ball and caged-disk valves in patients treated to an INR of 2.0 to 2.9.¹⁴⁵ There were trends toward fewer adverse events for patients with bileaflet valves treated to an INR of 2.0 to 2.9, for patients with tilting-disk valves treated to an INR of 3.0 to 3.9, and for patients with either caged-ball or caged-disk valves treated to an INR

		Dotton Andred		Jo diamo I ano M	Vol. Thursday	Lodano danadr	T ato Mondality +	Major
Study/yr	Valve Type	rauents Analyzea, No/Total	INR	Follow-up, yr	varve 1 monibosis, No. (%/pty)	Infomboemboll, No. (%/pty)	Late Mortality, No. (%/pty)	nemormage, § No. (%/pty)
Aortic valves Sethia B/1986	Björk-Shiley tilting-disc	184/184	3.0-4.0	5.3	2 (0.2)	4(0.4)	13 (1.4)	2 (0.2)
Sethia B/1986	valve Bjork-Shiley Convexo-	125/125	3.0-4.0	1.9	(0) (0)	1 (0.5)	5 (2.6)	(0) (0)
Vallejo J/1990	Concave valves Medtronic-Hall	117/117	3.0-4.5	4.3	0 (0)	4 (0.72)	43 (2.8) total	6(0.39) total
Bloomfield P/1991	Björk-Shiley 60°	109/109	2.0 - 4.5	12	$0\ (0)$	NR	population 38 (2.9)	population NR
Akins C/1996	spherical tilting-disc valve Medtronic-Hall	176/177	2.0-3.5	4.3	(0) (0)	10~(1.3)	19(2.5)	13(1.7)
Mitral valves Sethia B/1986	Björk-Shiley tilting-disc	323/323	3.0-4.0	5.3	15(1.1)	21(1.2)	53(3.9)	2(0.1)
Sethia B/1986	valve Bjork-Shiley Convexo-	228/228	3.0 - 4.0	1.9	4(0.9)	9(2.1)	18(4.2)	1(0.2)
Vallejo J/1990	Concave valves Medtronic-Hall	143/143	3.0-4.5	4.3	1 (0.1)	9(1.5)	43 (2.8) total	6 (0.39) total
Bloomfield P/1991	Björk-Shiley 60°	129/129	2.0 - 4.5	12	(0) (0)	NR	population 62 (4.0)	population NR
Akins C/1996	spherical tilting-disc valve Medtronic-Hall	104/106	2.0-3.5	4.6	1(0.2)	10~(2.1)	21 (4.4)	9 (1.9)
Fattents with valves in bi Sethia B/1986	oth aortic and mitral positions Björk-Shiley tilting-disc	222/222	3.0 - 4.0	5.3	3(0.3)	11 (1.0)	31 (2.9)	4(0.4)
Sethia B/1986	valve Bjork-Shiley convexo-	89/89	3.0-4.0	1.9	(0) (0)	3(2.3)	7 (5.4)	1(0.8)
Vallejo J/1990	concave valves Medtronic-Hall	16/16	3.0-4.5	4.3	NA	11(2.9)	43 (2.8) total	6 (0.39) total
Bloomfield P/1991†	Björk-Shiley 60° spherical tilting-disc valve	29/29	2.0-4.5	12	0 (0)	NR	population 9 (2.6)	population NR

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement. See Table 2 for expansion of abbreviations. †Bloomfield results presented from one arm of a randomized trial: patients randomized by type of prostheses implanted. ‡Late mortality defined as death occurring after discharge from hospital. §Major hemorrhage defined as requiring transfusion, hospitalization or resulting in death.

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Downloaded from chestjournal.chestpubs.org by guest on October 5, 2009 © 2008 American College of Chest Physicians of 4.0 to 4.9.¹⁴⁵ It has been suggested that this higher range of INR (4.0 to 4.9) might be recommended for patients with caged-ball or caged-disk valves or for patients with two or more mechanical valves. Randomized trials are required to clarify this issue.¹⁴⁵

Value Position, Number of Values, and Value Size: The incidence of thromboembolic events is higher with tilting disk prosthetic valves in the mitral position than in the aortic position (Table 3). There is likely a higher incidence with bileaflet mechanical mitral vs aortic valves as well, but data derived from careful assessment of achieved INR ranges are sparse (Table 2). Cannegieter et al¹⁴⁵ reported an incidence of thromboembolism of 0.5%/yr with mechanical aortic valves, 0.9%/yr with mechanical mitral valves, and 1.2%/yr with double aortic and mitral mechanical valves. For mechanical valves in the aortic position, an INR of 2.0 to 2.9 was as effective as an INR of 3.0 to 3.9.145 Valve size has not been identified as an independent predictor of thromboembolic complications after valve replacement.¹⁶⁵ In the GELIA study,¹⁶⁶ less intensive anticoagulation (INR range, 2.0 to 3.5) was associated with a significantly (p < 0.005) lower survival than was more intensive anticoagulation (INR range, 2.5 to 4.5) among patients with double valve replacement.

In summary, life-long therapy with VKAs offers the most consistent protection against thromboembolism in patients with mechanical heart valves. Doses of VKAs sufficient to prolong the INR to 2.0 to 3.0 appear satisfactory for patients with St. Jude Medical bileaflet and Medtronic-Hall tilting disk valves in the aortic position, provided they are in sinus rhythm and the left atrium is not enlarged.^{139,144,159} This level of anticoagulation is likely adequate for management of patients with an aortic CarboMedics bileaflet valve.¹⁴⁹ Mechanical valves in the mitral position are generally more thrombogenic than those in the aortic position due to differing hemodynamic and flow characteristics, as well as an increased incidence of AF with mitral valve disease. Doses of VKAs that prolong the INR to 2.5 to 3.5 are satisfactory for tilting-disk valves or for bileaflet prosthetic valves in the mitral position.139,145,159 There are relatively few data available for caged-ball valves.^{145,163} These prostheses are rarely used in current practice and the number of patients surviving with them has continued to decrease. It has been suggested that the most effective level of the INR in patients with caged-ball or caged-disk valves may be as high as 4.0 to 4.9.145

Elderly Patients, Patients With AF, Coronary Artery Disease, Left Ventricular Dysfunction, or Other Risk Factors: Higher rates of thromboembolic complications with prosthetic mitral valves might be attributed to an increased incidence of AF, left atrial enlargement, and perhaps endocardial damage from rheumatic mitral valve disease.¹⁴³ Low left ventricular ejection fraction, older age, and a history of thromboembolism also are associated with an increased risk of thromboembolic complications.¹⁶⁷ The risks and benefits of VKAs in combination with ASA have been studied extensively in patients with AF and MI who did not have prosthetic heart valves. In the Stroke Prevention in Atrial Fibrillation III (SPAF III) trial, the addition of ASA at 325 mg/d to VKAs (target INR, 1.2 to 1.5) resulted in significantly more strokes than treatment with VKAs alone (target INR, 2.0 to 3.0).¹⁶⁸ Consequently, in patients with prosthetic heart valves who have AF, care should be taken to maintain the INR > 2.0 even in patients receiving concomitant ASA therapy. Both the Warfarin Aspirin Reinfarction Study (WARIS)-II and Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-2 trial showed that among patients with acute coronary syndromes, ASA 81 mg/d combined with VKAs (target INR, 2.0 to 3.0) or VKAs alone (target INR, 3.0 to 4.0), resulted in similar reductions in stroke, recurrent MI, and death when compared to ASA monotherapy.45,169 The addition of low-dose ASA to VKA therapy (target INR, 2.0 to 3.0) is reasonable following presentation with acute coronary syndromes in patients with mechanical prosthetic heart valves. Alternatively, VKA therapy alone, targeted to an INR of 3.0 to 4.0 may be considered in this setting.

Cannegieter et al¹⁴⁵ showed that the risks of thromboembolism and of bleeding were highest among patients \geq 70 years old. However, a retrospective case series among elderly patients (> 70 years old)¹⁴⁶ suggested that the use of VKAs targeted to a slightly lower INR range was adequately safe and effective with St. Jude Medical valves in the aortic position. Many of these patients were treated before the INR was used to titrate therapy, but in the later years of this trial, an INR of 1.8 to 2.5 appeared to be effective.

ASA in Combination With VKAs: The addition of APA therapy to oral anticoagulation in patients with prosthetic heart valves was examined in several early studies.¹⁷⁰ APA agents added to oral anticoagulation were effective in further reducing the risk of thromboembolism. However, the observed decrease in thromboembolic risk was at the expense of a substantial increase in the rate of bleeding. The doses of APA agents used in those studies generally were high (up to 1,000 mg/d of ASA). More contemporary trials have addressed the addition of low-dose ASA (100 mg/d) to full-dose oral anticoagulation. In a prospec-

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tive, randomized, double-blind, placebo-controlled trial of patients with mechanical heart valves (n = 281) or tissue values with AF or a history of thromboembolism (n = 89), Turpie et al⁴² showed that ASA 100 mg/d in combination with warfarin to a target INR of 3.0 to 4.5 was associated with a lower incidence of major systemic thromboembolic events than warfarin plus placebo (1.6%/yr vs 4.6%/yr, p = 0.039). In addition, total mortality was reduced in the ASA group (2.8%/yr vs 7.4%/yr, p = 0.01). The rate of major bleeding was higher in the ASA group (8.5%/yr vs 6.6%/yr); however, this difference was not statistically significant (p = 0.43). Of note, the mean INR values in the ASA and placebo groups were 3.0 and 3.1, respectively, and were within the target range only 40% of the time. However, 77% of the time, the INR was between 2.0 and 4.5.

In a randomized, open-label trial that excluded patients with hemorrhagic diatheses or prior GI bleeding, Meschengieser et al¹³⁵ showed that ASA 100 mg/d in combination with warfarin targeted to an INR of 2.5 to 3.5 was as effective as warfarin targeted to an INR of 3.5 to 4.5. The incidence of thromboembolic events or valve thrombosis was 1.32%/yr for patients allocated to low-dose ASA plus warfarin, vs 1.48%/yr for patients assigned to warfarin alone. Rates of major bleeding were similar, 1.13%/yr for low-dose ASA plus warfarin (target INR, 2.5 to 3.5) vs 2.33%/yr for patients given warfarin alone (target INR, 3.5 to 4.5). INRs were in the target range only 47% of the time for patients in the warfarinplus-ASA group and 36% of the time in the warfarinalone group. The warfarin-alone group was below target range more often than the group allocated warfarin plus ASA (40% vs 28%). As a result, the levels of anticoagulation achieved for the two groups were closer than prespecified by the study protocol.

Thus, the addition of ASA may increase the effectiveness of VKA therapy, albeit at the expense of a higher risk of bleeding (Table 4). However, the risk of major hemorrhage might be substantially reduced with the use of low-dose (100 mg/d), rather than high-dose, ASA.¹⁷⁰⁻¹⁷² After careful consideration of the hemorrhagic risk, the addition of low-dose ASA (50 to 100 mg/d) to VKA therapy for patients with mechanical heart valves should be reserved for patients who would be expected to derive the greatest benefit, such as patients with concomitant coronary or peripheral arterial disease, and those with multiple risk factors for atherosclerotic disease. Addition of low-dose ASA might also be considered in patients with mechanical heart valves who haver systemic embolism despite a therapeutic INR and in those with additional risk factors for thromboembolism, including AF, hypercoagulable state, or low ejection fraction. Similar benefit may extend to patients with tissue valves and AF or a history of thromboembolism, although the supporting data are less robust. The risks of combination therapy might outweigh the benefits in patients at particularly high risk of bleeding, such as in those with history of GI bleeding and in the elderly.

Dipyridamole in Combination With VKAs: Two case series^{173,174} reported the use of dipyridamole, 300 mg/d, in combination with warfarin (INR, 2.0 to 2.5) for patients with St. Jude Medical aortic, mitral, or double valves. Thromboembolic event rates ranged from 0.6 to 1.5%/yr, and the incidence of major hemorrhage ranged from 1.3 to 1.6%/yr.^{173,174} Data are insufficient to recommend dipyridamole in combination with VKAs. Whether dipyridamole plus ASA is more effective than ASA alone when used with VKAs is also undetermined.

Fixed-Dose Warfarin Plus APAs: Katircioglu et al¹⁷⁵ used a fixed dose of warfarin (2.5 mg/d) in combination with ASA (100 mg/d) and dipyridamole (225 mg/d) and reported a 1.4%/yr thromboembolic event rate (with no prosthetic valve thrombosis) for patients with aortic St. Jude Medical valves. Using the same treatment regimen in patients with St. Jude Medical aortic, mitral, or double valve replacements, Yamak et al¹⁷⁶ reported a thromboembolic event rate of 0.7%/yr, prosthetic valve thrombosis rate of 0.8%/ yr, and major bleeding rate of 1.2%/yr.

APAs Alone: For patients with St. Jude Medical aortic valves, the use of combination APA therapy with dipyridamole and ASA resulted in a rate of valve thrombosis or arterial thromboembolic events of 2.1 to 3.2%/yr.^{177,178} A rate of 0.9%/yr has been reported with a Smeloff-Cutler aortic valve.¹⁷⁹ Thromboembolic event rates as low as 0.41 to 0.80%/yr have been reported for a few patients with older-generation valves treated with ASA alone.¹⁸⁰ An investigation by Schlitt et al¹⁸¹ compared treatment with clopidogrel plus ASA vs treatment with VKAs alone in patients with aortic mechanical heart valves. The trial was stopped prematurely after 50 days due to nonfatal aortic valve thrombosis in 1 of 11 patients in the antiplatelet arm. High rates of valve thrombosis and thromboemboli have been observed in children and adolescents with St. Jude Medical valves treated with APAs alone: 31 to 68%/yr with aortic valves and 19 to 22%/yr with mitral valves.182,183

Aortic Value Reconstruction: No value thrombosis or thromboembolic events were reported in patients who received ASA 100 mg/d following aortic value reconstruction.^{184,185}

Low-Molecular-Weight Heparin: The literature provides little data on the use of unfractionated

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Table 4—Studies of Alternative Anticoagulant Regimens (Oral Anticoagulation Plus Aspirin and/or Dipyridamole) in Patients With Aortic, Mitral, or Multiple Mechanical Valves: Clinical Description and Results (Section 6.0)*

Study/yr	Valve Type	Target INR	Interventions	Patients Analyzed, No./Total (%)	Mean Length of Follow-up, mo	Valve Thrombosis, No. (%/pty)	Arterial Thromboemboli, No. (%/pty)	Late Mortality, No. (%/pty)	Major Hemorrhage, No. (%/pty)
Randomized trials Altman R, 1991	Bicer Bjork-Shiley	Group A: 2.0–2.99 Group B: 3.0–4.5	All patients received OAC + ASA 660 mg/d and dipyridamole 150mg/d	Group A: 51/59 (86) Group B: 48/58 (83)	Group A: 12.2 Group B: 10.1	Group A: 0 Group B: 0	Group A: 1 (1.9) Group B: 2 (4.9)	Group A: 0 Group B: 0	Group A: 2 (3.8) Group B: 10 (24.7)
Turpie A, 1993	Various	3.0-4.5	OAC plus ASA 100 mg/d OAC + placebo	OAC + ASA: 186/186 OAC + placebo: 184/ 184	30	NR	$\begin{array}{l} \text{OAC} + \text{ASA: 5} \ (1.6) \\ \text{OAC} + \text{placebo: 13} \ (4.6) \end{array}$	OAC + ASA: 9 (2.8) OAC + placebo: 22 (7.4)	OAC + ASA: 24 (8.5) OAC + placebo: 19 (6.6)
Altman R, 1996	Bicer Bjork-Shiley	2.0-3.0	OAC + ASA 100 mg/d ASA 650 mg/d +/- dipyridamole	OAC + ASA: 207/207 ASA: 202/202	OAC + ASA: 24.1 ASA: 21.7	OAC + ASA: 0 ASA:0	OAC + ASA: 2 (0.5) ASA: 4 (1.1)	OAC + ASA: 19 (4.6) ASA: 9 (2.5)	OAC + ASA: 15 (3.6) ASA: 19 (5.1)
Meschengieser S, 1997	Various	OAC + ASA: 2.5-3.5 OAC: 3.5-4.5	OAC + ASA 100 mg /d OAC	OAC + ASA: 258/258 OAC: 245/245	OAC + ASA: 24.6 [†] OAC: 27.9 [†]		$\begin{array}{l} \mathrm{OAC} + \mathrm{ASA:} \ 7 \ (1.32) \\ \mathrm{OAC:} \ 7 \ (1.4) \end{array}$	OAC + ASA: 9 (1.7) [†] OAC: 21 (3.7) [†]	OAC + ASA: 6 (1.1) OAC: 11 (2.3)
Laffort P, 2000	St. Jude Medical	2.5-3.5	OAC + ASA 200 mg/d OAC	OAC + ASA: 109/109 OAC: 120/120	All patients followed up for 12	NR	$ \begin{array}{l} \mbox{Major events:} \\ \mbox{OAC} + ASA: 1 (0.9); \\ \mbox{OAC} : 5 (4.2) \\ \mbox{Minor events:} \\ \mbox{OAC} + ASA 9 (8.3) \\ \mbox{OAC} + 25 (20.1) \\ \mbox{OAC} : 25 (20.1) \\ \end{array} $	OAC + ASA: 4 (3.7)† OAC: 3 (2.5)†	OAC + ASA: 21 (19.3)† OAC: 10 (8.3)†
Cohort studies Albertal J, 1993	Various	2.5-3.5	OAC + ASA 325 mg/d OAC + ASA 100 mg/d	OAC + ASA 325 mg/d: 105/105 OAC + ASA 100 mg/d: 91/91	35.5	NR	OAC + ASA 325 mg/d: 6 (2.0) OAC + ASA 100 mg/d: 5 (2.8)	5 (0.9)§	OAC + ASA 325 mg/d: 10 (3.4) OAC + ASA 100 mg/d: 9 (5.1)
Kontozis L, 1998 Skudicky D, 1994	St. Jude Medical	2.0-2.5	OAC + dipyridamole 300 mg/d	200/200	52	NR	11 (1.5)	33 (3.8)	11 (1.3)
*The methodolog †Estimated.	ic quality desc	ription portion of th	nis Table can be found i	n the online version of	of this article as a	data suppleme	nt. See Table 2 for exp	ansion of abbreviations.	

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heparin (UFH) or low-molecular-weight heparin (LMWH) immediately after prosthetic valve insertion. However, it is common practice in some centers to administer UFH or LMWH as soon as it is considered safe, and to continue such therapy until VKAs have been initiated and the INR is within therapeutic range. In a nonrandomized case series of 208 patients followed for 2 weeks after insertion of a prosthetic heart valve, Montalescot et al¹⁸⁶ found that therapeutic anticoagulation was more rapidly and more predictably achieved with LMWH than with UFH. Major bleeding was the same in both groups. There was one stroke in the UFH group (106 patients) and none in the LMWH group (102 patients). In patients who had recently undergone mechanical heart valve replacement, Meurin et al¹⁸⁷ showed that LMWH as a bridge between postoperative UFH and achievement of therapeutic INR with VKA therapy was feasible in preventing thromboembolic events. However, this was a single-arm study without a control group receiving IV UFH. In a case-control study performed by Fanikos et al,188 bridging to VKA therapy after mechanical valve replacement was as safe and effective with LMWH as was bridging with UFH. The patients who received LMWH had a shorter length of stay that resulted in lower postoperative costs (average \$5,894 per patient). However, this was a relatively small study and due to its nonrandomized design, may have been subject to significant bias.

The use of LMWH in patients with mechanical prosthetic heart valves was reviewed in 2002.¹⁸⁹ Short-term perioperative use for noncardiac surgical procedures in 114 patients was not associated with an increased risk of thromboembolic events.¹⁸⁹ In 16 patients with intolerance to VKAs, the long-term use of LMWH was not associated with any thromboembolism.¹⁸⁹ However, thromboembolic complications occurred in 2 of 10 pregnant women with mechanical heart valves treated with LMWH. There were no thromboembolic events reported in another small series of 13 women managed with LMWH.¹⁸⁹ At the time of this writing, the package insert for enoxaparin¹⁹⁰ specifically cautions that the use of enoxaparin for patients with prosthetic heart valves (including in pregnant patients) has not been adequately studied. It should be recognized, however, that this caution is not a contraindication. Further, the available data suggest that similar limitations exist with the use of UFH.^{191,192} Recently, the use of fixed-dose subcutaneous weight-adjusted UFH was proven to be as safe and effective as LMWH for the treatment of venous thrombosis.¹⁹³ Whether this therapy will be as effective in preventing thromboembolic events in patients with mechanical heart valves remains to be determined.

Available data suggest that neither adjusted-dose

UFH nor fixed-dose LMWH provide adequate protection to pregnant patients with mechanical heart valves.^{190–192} However, because there is evidence to show that the pharmacokinetics of LMWH change over the course of pregnancy,194-197 it has been suggested that LMWH might provide superior protection against thromboembolism if the dose is adjusted throughout pregnancy, based either on anti-Xa levels, ^{194,195,197} the patient's changing body weight, 194, 195 or against elevations of indicators of clotting activation, such as thrombin-antithrombin complex and d-dimer levels.¹⁹⁶ It is possible that LMWH might provide adequate protection to pregnant patients with mechanical heart valves provided the dose is adjusted to accommodate for the changes in the pharmacokinetics of LMWH that occur during the course of pregnancy. The use of these agents, as well as VKAs, in pregnancy is highly controversial and is discussed in more detail in the chapter of this supplement entitled, "Venous Thromboembolism, Thrombophilia, Antithrombotic Therapy and Pregnancy."

Periprocedural interruption of anticoagulant therapy, management of patients including home monitoring of INR, management of major bleeding, reversal of anticoagulation with vitamin K_1 , and management of anticoagulation in pregnancy and in children. Detailed discussion on these topics can be found elsewhere in this supplement, in the chapter on "The perioperative Management of Antithrombotic Therapy," in the chapter on "The Pharmacology and Management of the Vitamin K Antagonists," in the chapter on "Venous Thromboembolism, Thrombophilia, Antithrombotic Therapy and Pregnancy," and in the chapter on "Antithrombotic Therapy in Neonates and Children."

Recommendations

6.0.1. In patients with mechanical heart valves, we recommend VKA therapy (Grade 1A). In patients immediately following mechanical valve replacement, and as dictated by clinical concerns regarding postoperative bleeding, we suggest administration of IV UFH or subcutaneous LMWH until the INR is > 2.0 for 2 consecutive days (Grade 2C).

6.0.2. In patients with a bileaflet mechanical valve or a Medtronic Hall tilting-disk valve in the aortic position who are in sinus rhythm and without left atrial enlargement, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B].

6.0.3. In patients with a tilting-disk or bileaflet mechanical valve in the mitral position, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.4. In patients with a caged-ball or caged-

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disk valve, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.5. In patients with mechanical heart valves in either or both the aortic or mitral positions, and additional risk factors for thromboembolism, such as AF, anterior-apical ST-segment elevation myocardial infarction, left atrial enlargement, hypercoagulable state, or low ejection fraction, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.6. In patients with mechanical heart valves who have additional risk factors for thromboembolism, such as AF, hypercoagulable state, or low ejection fraction, or who have a history of atherosclerotic vascular disease, we recommend the addition of low-dose ASA (50 to 100 mg/d) to long-term VKA therapy [Grade 1B]. We suggest ASA not be added to VKA therapy in patients with mechanical heart valves who are at particularly high risk of bleeding; such as in patients with history of GI bleed or in patients > 80 years of age (Grade 2C).

6.0.7. In patients with mechanical prosthetic heart valves who have systemic embolism despite a therapeutic INR, we suggest the addition of ASA (50 to 100 mg/d) if not previously provided and/or upward titration of VKA therapy to achieve a higher target INR. For a previous target INR of 2.5, we suggest the VKA dose be increased to achieve a target INR of 3.0 (range, 2.5 to 3.5). For a previous target INR of 3.0, we suggest the VKA dose be increased to achieve a target INR of 3.5 (range, 3.0 to 4.0) [Grade 2C].

7.0 Prosthetic Heart Valves – Bioprosthetic Valves

First 3 Months After Value Insertion

The frequency of thromboemboli has been reported to be high in the first 3 months after bioprosthetic valve insertion among patients not receiving antithrombotic therapy, particularly among patients with bioprosthetic valves in the mitral position (Table 5).^{198,199} Among patients with bioprosthetic valves in the mitral position, Ionescu et al¹⁹⁹ reported thromboemboli during the first 3 months after operation in 4 of 68 patients (5.9%) who did not receive anticoagulants and in 0 of 182 patients (0%)who received anticoagulants. Among patients with bioprosthetic valves in the mitral position, Orszulak et al²⁰⁰ reported a stroke rate during the first postoperative month of 40 events per 100 patient-years. The regimen for prophylaxis was variable. Heras et al¹⁹⁸ showed that VKAs (INR range, 3.0 to 4.5) in patients with bioprosthetic valves in the mitral position decreased the frequency of thromboemboli. However, the frequency remained high during the first 10 postoperative days¹⁹⁸ and may have been due to a delay in achieving therapeutic levels of anticoagulation. It was suggested that the early administration of UFH might explain why some groups observed lower rates of thromboemboli in patients who received short-term VKAs.¹⁹⁸ Among patients with bioprosthetic valves in the mitral position, thromboemboli during the first 3 months occurred in 2 of 40 patients (5.0%) with an estimated INR of 2.5 to 4.5 and in 2 of 39 patients (5.1%) with an estimated INR of 2.0 to 2.3.201 These patients also received subcutaneous UFH 5,000 U q12h. All of the patients with thromboembolic events also had AF.²⁰¹ Thromboemboli during the first 3 months after operation may occur in spite of adequate anticoagulation in patients with AF, a history of thromboembolism or left atrial thrombi.²⁰²

Among patients with bioprosthetic valves in the aortic position who received subcutaneous UFH 22,500 IU/d and ASA 100 mg/d for the first 14 to 22 days after operation, but who did not receive VKAs, the incidence of thromboemboli during the first 6 months was 1 in 57 (1.8%).²⁰³ Among patients who received VKAs and heparin 5,000 U subcutaneously q12h, 0 of 109 patients with bioprosthetic valves in the aortic position had thromboemboli during the first 3 months.²⁰¹ However, Moinuddeen et al²⁰⁴ showed no advantage of early anticoagulation among patients with bioprosthetic valves in the aortic position. With no anticoagulation, 5 of 76 patients (6.6%)had cerebral ischemic events during the first 3 months after valve insertion, vs 8 of 109 patients (7.3%) who received postoperative UFH followed by warfarin.²⁰⁴ In a retrospective analysis, Sundt et al²⁰⁵ also did not find a protective effect of VKAs after bioprosthetic aortic valve insertion. Recently, Gherli et al²⁰⁶ prospectively examined the efficacy of postoperative warfarin compared with ASA for the prevention of valve thrombosis and arterial thromboembolism after bioprosthetic aortic valve replacement. Among the exclusion criteria in this study were AF, history of thromboembolism, coagulopathy, carotid atherosclerotic disease, and peripheral vascular disease. Outcomes in patients receiving ASA (100 mg/d) started on postoperative day 2 were compared with those receiving LMWH started on postoperative day 1 followed by warfarin (target INR, 2.0 to 3.0). During the first 3 months after insertion, the frequency of thromboembolic events was comparable between the ASA and LMWH/warfarin groups: 3 of 141 (2.1%) vs 4 of 108 (3.7%), respectively.²⁰⁶ Aramendi et al²⁰⁷ showed similar results in patients randomized to triflusal (600 mg/d) or acenocoumarol (target INR, 2.0 to 3.0) for 3 months after bioprosthetic valve replacement (94% of which were in the aortic position). There was no difference in the rate of thromboembolism between the two groups, with patients administered triflusal showing a significantly lower incidence of bleeding. Among the exclusion criteria in this trial were use of APA or VKA for any reason other than valve disease and left atrial diameter > 60 mm.

Long-term Treatment

Patients with bioprosthetic valves, whether porcine or pericardial, have a long-term risk of thromboemboli of 0.2 to 2.6%/yr (Table 6).²⁰⁸ The risk of thromboembolic stroke in patients with bioprosthetic valves in the aortic position is 0.2%/yr if they are in sinus rhythm.¹⁶⁷ A low ejection fraction or large left atrium may be considered as potential contributing factors to late thromboemboli in patients with bioprosthetic valves.¹⁶⁷ A permanent pacemaker also appears to increase the risk of thromboemboli in patients with bioprosthetic valves.²⁰⁹

APAs appear to reduce the rate of late thromboemboli.^{210–213} ASA,^{210,211,213} ASA plus dipyridamole,²¹³ or ticlopidine²¹¹ therapy in patients with bioprosthetic valves in the aortic or mitral position are associated with a thromboembolic event rate \leq 0.8%/yr. ASA was not effective in reducing the rate of thromboemboli in at least one study.²¹⁴

Thromboembolism in patients with bioprosthetic valves and AF presumably relates to both the bioprosthetic valve and to the AF (see the chapter in this supplement on "Antithrombotic Therapy in Atrial Fibrillation"). The incidence of thromboemboli in these patients was reported to be as high as 16% at 31 to 36 months.^{215,216}

Recommendations

7.0.1. In patients with a bioprosthetic valve in the mitral position, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for the first 3 months after valve insertion (Grade 1B). In the early postoperative period, in the absence of concerns for significant bleeding, we suggest administration of IV UFH or subcutaneous LMWH until the INR is at therapeutic levels for 2 consecutive days (Grade 2C). After the first 3 months, in patients who are in sinus rhythm and have no other indication for VKA therapy, we recommend ASA (50 to 100 mg/d) [Grade 1B].

7.0.2. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we recommend ASA (50 to 100 mg/d) [Grade 1B].

7.0.3. In patients with bioprosthetic valves who

have a history of systemic embolism, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for at least 3 months after valve insertion, followed by clinical reassessment (Grade 1C).

7.0.4. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) until documented thrombus resolution (Grade 1C).

7.0.5. In patients with bioprosthetic valves who have additional risk factors for thromboembolism, including AF, hypercoagulable state, or low ejection fraction, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C]. We suggest the addition of low-dose aspirin (50 to 100 mg/d) be considered, particularly in patients with history of atherosclerotic vascular disease (Grade 2C).

We suggest ASA not be added to long-term VKA therapy in patients with bioprosthetic heart valves who are at particularly high risk of bleeding, such as in patients with history of GI bleed, or in patients > 80 years of age (Grade 2C).

8.0 Prosthetic Heart Valves – Valve Thrombosis

Prosthetic valve thrombosis (PVT) is a rare but potentially lethal complication. Incidence has ranged from 0.1 to 5.7% per patient-year.²¹⁷ Higher rates are observed in patients with mitral valve prostheses and in those who have mechanical valves and are inadequately anticoagulated. Rates are similar for patients with bioprosthetic heart valves and those with mechanical heart valves who receive adequate anticoagulation.²¹⁷ Patients suspected of valve obstruction should undergo immediate echocardiographic study to determine the cause. Causes of valve obstruction can include pannus ingrowth, valve thrombosis, or both.²¹⁸ TEE should be undertaken if adequate visualization is not achieved with a transthoracic study. Fluoroscopy may supplement the findings of Doppler echocardiography in patients with mechanical valves.

Although data are limited, it has been suggested that PVT of right-sided valves can be treated safely and effectively with fibrinolytic therapy.²¹⁹ For very small, left-sided, nonobstructive thrombus, treatment with IV UFH can be considered.²¹⁹ For larger, left-sided, obstructive thrombus, a decision between fibrinolytic therapy and surgery must be made. The risks associated with reoperative surgery must be weighed against the risks of embolic complications

Studylyr	Intervention	Target INR	Valve Type and Location (%)	Patients, No.	Valve Thrombosis < 3 mo	$\begin{array}{l} \mbox{Arterial} \\ \mbox{Thromboenboli} < 3 \\ \mbox{mo, No/Total} (\%) \end{array}$	Death $< 3 \text{ mo, No./}$ Total (%)	Major Bleeding † < 3 mo, No/Total (%)
RCTs Turpie AGG/1988	OAC, two intensities Group A. less intensive therapy Group B: standard therapy	Group A: 2.0–2.25 Group B: 2.5–4.0	Tissue heart valve replacement: Mitral (37.6) Double (6.2)	Group A: 102/102 Group B: 108/108	NR	Group A: 13/102 (12.7) Group B: 13/108 (12.0) RR: L06 (0.52, 2.17)	NR	Group A: 0/102 (0%) Croup B: 5/108 (4.6%) RR: 0.10 (95% CI 0.0172)
Aramendi JI/2005	Triffusal 600 mg/d for 3 mo OAC for 3 mo	OAC: 2.0–3.0	Assorted Carpentier- Edwards Perimount (52) Aortic (95) Mitral (5)	Triflusal: 96/96 OAC: 95/95	NR	Triflusal: 6/96 (6.3) OAC: 3/95 (3.2) RR: 1.98 (95% CI 0.51-7.68)	Triflusal: 8/96 (8.3) OAC: 3/95 (3.2) RR: 2.64 (CI 0.72–9.65)	Triflusal: 3/96 (3.1) OAC: 6/95 (6.3) RR: 0.3 (95% CI 0.08–1.05)
Case series and cohort stu Porcine aortic	udies							
Moinuddeen K/1998	Group A: postoperative anticoagulation with heparin followed by OAC Group B: no postoperative OAC	PT: Group A: 20–25 s Group B: NA	Carpentier-Edwards	Group A: 109/109 Group B: 76/76	NR	NR	Group A: 5/109 (4.5) Group B: 4/76 (5.2) RR: 0.87 (95% CI 0.24–3.14)	Group A: 7/109 (6,4) Group B: 7/76 (9.2) RR: 0.7 (95% CI 0.25–1.91)
Gherli T/2004	Group A: OAC Group B: aspirin 100 mg/d	2.0–3.0	Carpentier-Edwards (53)	OAC: 108/108 ASA: 141/141	NR	OAC: 8/108 (7.4) ASA: 4/141 (2.8) RR: 2.61 (95% CI 0.81–8.44)	OAC: 2/108 (1.9) ASA: 1/141 (0.7) RR: 2.61 (95% CI 0.24-28.42)	OAC: 4/108 (3.7) ASA: 3/141 (2.1) RR: 1.74 (95% CI 0.4–7.62)
Pericardial aortic Babin-Ebell J/1995	Subcutaneous heparin 22,500 U + ASA 100 mg/d	NA	Hancock, Mitroflow, and Edwards stentless	57/57	0/57 (0)	1/57(1.8)	2/57 (3.5)	1/57 (1.8)
Sundt TM/2005	OAC No OAC	NR	Pericardial aortic	OAC: 624/624 No OAC: 527/527	NR	NR	OAC: 6/624 (1.0) No OAC: 41/527 (7.8) RR: 0.12 (95% CI 0.05-0.29	OAC: 7/624 (1.1) No OAC: 4/527 (0.8) RR. 1.48 (95% CI 0.44–5.02)
Porcine mitral Orszulak TA/1995	Ranges from no anticoagulation to IV heparin alone or combined with OAC + antiplatelet agents	NR	Carpentier-Edwards	MVR: 199/199 MVR + CABG: 86/86	NR	NR	MVR: 23/199 (11.5) MVR + CABG: 22/ 86 (25.5)	MVR: 0/199 (0) MVR + CABG: 0/86 (0)
Pericardial mitral Ionescu MI/1982	OAC for 5 to 6 wk	NR	Shiley pericardial	All MVR: 250/250	All MVR:	All MVR: 4/250 (1.6)	All MVR:	NR
Poroine and hovine vari	sici		xenograft	MR: 116/116	0/250(0) MR: $0/116(0)$	MR: 1/116 (0.9)	17/250 (6.8) MR: 11/116 (9.5)	
Heras M/1995	IV heparin 25,000 U/24 h or OAC	3.0-4.5	Hancock (48) Carpentier- Edwards (18) Ionescu-Shiley (34) Atrial (31.9) Mirtal (39.9) Double (8.1)	AVR: 424/424 MVR: 326/326 MR: 66/66	AVR: 0/424 (0) MVR: 0/326 (0) MR: 0/66 (0)	AVR: 8/424 (1.9) MVR: 11/326 (3.4) MR: 0/66 (0)	AVR: 9/424 (2.1) MVR: 11/326 (3.4) MR: 4/66 (6.1)	NR
*The methodologic qu	ality description portion of t	his table can be fou	and in the online ver	sion of this article a	s a data suppleme	nt. RR = relative risk.	See Table 2 for exp	ansion of abbreviations.

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Study/yr	Valve Type and Intervention	Patients, No./Total	Mean Length of Follow-up, yr	Valve Thrombosis, No. (%/pty)	Arterial Thromboemboli, No. (%/pty)	Late Mortality,‡ No. (%/pty)	Major Bleeding§, No. (%/pty)
Porcine aortic	H moody 11 kierweekhoeie	702/702	ר ע	0/702	κ1 /1 0)‡	158 /4 1)4	0 /0 0)4
Clourer et al /1998	LIARCOCK II DIOPLOSHESIS CarmanHer-Feluvards mrothesis	531/531	0.1 6.3†	NB	50 (1 5))	NB	13(0.4)
Khan et al/1998	Hancock porcine valve	243/243	1000	NR	80 (4.7)	99 (6.4)	27(1.6)
Moinuddeen et $al^{204}/1998$	Carpentier-Edward porcine biological valves Group A: postoperative anticoagulation with heparin followed	Group A: 109/109	Group A: 3.9	NR	NR	Group A: 2 (0.5) [†]	Group A: 10 (2.4) [†]
	by UAC Group B: no anticoagulation	Group B: 76/76	Group B: 4.9			Group B: $4(1.2)$ [†]	Group B: 7 (1.9) [†]
Pericardial aortic							
Banbury et al/1998	Carpentier-Edwards pericardial valves (model 2700) OAC for 3 mo	310/310	8.8	NR	45(1.8)	150(5.8)†	25(1.0)
Borowiec et al/1998 Neville et al/1998	Pericarbon pericardial bioprosthesis OAC (no doses provided) Carpentier-Edwards pericardial bioprosthesis Hepathi for 2 d Cafrinn henarin for 1 no or OAC	204/204 787/787	2.0	0/204 NR	7 (1.7) 39 (1.1)	24 (5.9) 191 (4.1) total population	4 (0.9) 10 (0.3)
Porcine mitral							
Orzulak et al/1995	Carpentier-Edwards Ranges from no anticoagulation to IV heparin alone or combined with OAC and antiplatelet agents	285/285	3.9	NR	NR	97 (8.7) †	NR
David et al ¹⁴⁹ /1998	Hancock II bioprosthesis OAC for 3 mo	328/328	5.7	$1 (0.1)^{\frac{1}{7}}$	18(1.2)	92(5.4)	2(0.1)
Glower et al/1998	Carpentier-Edwards Not described	492/492	6.4†	NR	54(1.7)	NR	22 (0.7)
Khan et al/1998	Hancock porcine valve Not described	248/248	7	NR	47 (7.3)†	96 (5.6)†	14(0.8)
Pericardial mitral							
Ionescu et al ¹⁹⁹ /1982	Shiley pericardial xenograft OAC for 5 to 6 wk PT between 18 to 24 s	All MVR: 250/250 MR: 116/116	All MVR: 4 MR: 2.5	0; 0	All MVR: 2 (0.2)† MR: 0	$\begin{array}{c} \text{All MVR:} \\ 25 (2.7) \\ \text{MR:} 17 (6.5) \end{array}$	NR
Neville et al/1998	Carpentier-Edwards pericardial bioprosthesis Heparin for 2 d Calcium heparin for 1 mo or OAC	182/182	0 0	NR	6(0.6)	191 (4.1)† total population	11 (1.1)†
Porcine aortic, mitral or >	1 *						
Jamieson et al/1998	Carpentier-Edwards standard porcine bioprosthesis Not described	1,198/1,198	8.8	NR	177(1.7)	591 (5.7)	48~(0.5)
Jamieson et al/1998	Carpentier-Edwards Supraannular porcine bioprosthesis Not described	3,024/3,024	5.9	NR	415(2.4)	901(5.2)	98 (0.6)
Jamieson et al/1998	Medtronic intact porcine bioprosthesis Not described	1,286/1,286	4.2	NR	112 (2.07)†	227 (4.2)†	$58\ (1.08)$
Pericardial aortic, mitral or	·> I						
Heras et al/1995	Hancock (48) Carpentier-Edwards (18) Ionescu-Sinley (34) IV heparin 32,000 U/24 h or OAC Target INR 3.0-4.5	AVR: 424/424 MVR: 326/326 MR: 66/66	AVR: 8.3 MVR: 9.5 MR: 8.1	NR	AVR: 49 (1.9) MVR: 50 (2.4)	AVR: 173 (5.0) MVR: 154 (5.8) MR: 32 (6.4)	All bleeds, all valves: 111 (2.3)
Poirier et al/1998	Carrentier-Edwards pericardial bioprosthesis OAC and antiplatelef therapy	812/812	4.8	2(0.1)	51(1.7)	120 (3.3)†	9 (0.3)
*The methodologic quality d †Estimated. ‡Late mortality is defined as	lescription portion of this table can be found in the online versior the death occurring after discharge from hospital.	n of this article as a c	ata supplement. I	T = prothron	nbin time. See Tab	les 2, 5 for expansic	n of abbreviations.

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Downloaded from chestjournal.chestpubs.org by guest on October 5, 2009 © 2008 American College of Chest Physicians and bleeding associated with the use of fibrinolytic therapy. Thrombus size as assessed by TEE has been shown to be an independent predictor of outcome. In an observational study of 107 patients who were administered fibrinolytic therapy for PVT, Tong et al²²⁰ showed that thrombus area by TEE (odds ratio [OR], 2.41 per 1 cm² increment; 95% confidence interval [CI], 1.12 to 5.19) was an independent predictor of complications from fibrinolysis. A thrombus area $< 0.8 \text{ cm}^2$ identified patients at lower risk for complications with fibrinolysis. History of stroke was also an independent predictor of poor outcome with fibrinolytic therapy in this study (OR, 4.55; 95% CI, 1.35 to 15.38). Gupta et al²²¹ showed a high success rate of fibrinolytic therapy (complete hemodynamic resolution in 82% of cases); however, this intervention was associated with a substantial rate of systemic embolism. Patients with AF were at especially high risk of embolic complications (OR, 2.3; 95% CI, 1.3 to 3.9). AF was also a significant predictor of PVT recurrence. Roudaut et al²²² analyzed the results of fibrinolytic therapy in a large single center observational study of 110 patients with PVT. Complete dissolution of PVT was observed in 71% of patients, partial dissolution in 17%, and failure of dissolution in 12%. Severe hemorrhagic complications were documented in 5% of patients and embolic events in 15%. These results were consistent with the rate of embolism in other series of fibrinolysis for PVT (14 to 19%).^{219–221} Patients at risk for adverse outcomes with fibrinolytic therapy include those with active internal bleeding, a history of hemorrhagic stroke, recent cranial trauma, cerebral tumor, large and mobile thrombi, substantial hypertension, cardiogenic shock, and poor NYHA functional class (III-IV).²¹⁹ Reoperative valve replacement is an effective strategy in the management of PVT, but outcomes are also largely dependent on NYHA functional class. In a series by Deviri et al,²²³ perioperative mortality was 17.5% in patients presenting with NYHA functional class IV and 4.7% in those with functional class I to III.

Administration of IV UFH and VKAs should follow successful resolution of PVT for both bioprosthetic and mechanical valves. UFH should be continued until a therapeutic INR is achieved. Target INRs should be increased for mechanical heart valves.

Recommendations

8.0.1. For patients with right-sided PVT, with large thrombus size or NYHA functional class III to IV, we recommend administration of fibrinolytic therapy (Grade 1C).

8.0.2. For patients with left-sided PVT, NYHA

functional class I to II, and small thrombus area (< 0.8 cm²), we suggest administration of fibrinolytic therapy. Alternatively, administration of IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement, can be considered for very small, nonobstructive thrombus (Grade 2C).

8.0.3. For patients with left-sided PVT, NYHA functional class III to IV, and small thrombus area (< 0.8 cm²), we suggest fibrinolytic therapy (Grade 2C).

8.0.4. For patients with left-sided PVT and large thrombus area ($\geq 0.8 \text{ cm}^2$), we suggest emergency surgery be considered. If surgery is not available or considered high risk, we suggest fibrinolytic therapy (Grade 2C).

8.0.5. For patients who have had successful resolution of PVT, we suggest initiation of IV UFH and VKA therapy. We suggest IV UFH be continued until a therapeutic INR is achieved. For a mechanical valve in the aortic position, we suggest maintaining a higher INR (target, 3.5; range, 3.0 to 4.0) plus ASA (50 to 100 mg/d). For a mechanical valve in the mitral position, we suggest maintaining a higher INR (target, 4.0; range, 3.5 to 4.5) plus ASA (50 to 100 mg/d) [Grade 2C].

9.0 INFECTIVE ENDOCARDITIS AND Nonbacterial Thrombotic Endocarditis

9.1 Infective Endocarditis

With the advent of effective antimicrobial therapy, the incidence of systemic emboli in infective endocarditis (IE) has decreased. In the preantibiotic era, clinically detectable emboli occurred in 70 to 97% of patients with IE.²²⁴ Since that time, the prevalence has been reported to be 12 to 40%.^{225–229} Emboli may occur more frequently in patients with acute endocarditis than in those with subacute disease,²³⁰ though at present the clinical designation of endocarditis as acute or chronic is less frequently cited. The incidence of pulmonary emboli in right-sided endocarditis is particularly high.^{227,231} The majority of clinically apparent emboli involve the CNS and impact negatively on outcome. Systemic embolic events may be more common among patients with mitral valve endocarditis, particularly with anterior leaflet involvement and with Staphylococcus aureus infection. This observation is not explained by the occurrence of AF.²²⁶ The incidence of embolic complications, which is 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 < 2 events per 1,000 patient-days.²³² A first embolus does not predict a second.

The use of anticoagulant therapy in IE was initially introduced in the sulfonamide era, not as a means of preventing thromboembolism, but as a mechanism to improve the penetration of antibiotics into infected vegetations.²³³ While complications of this therapy were not always encountered,^{234,235} many investigators reported an alarming incidence of cerebral hemorrhage,^{236–238} and it was suggested that the routine use of anticoagulant therapy in patients with endocarditis be abandoned.^{236,239,240} However, the issue remained controversial. While reference to the early adverse experience of anticoagulant therapy in endocarditis frequently has been made, Lerner and Weinstein²²⁷ concluded that anticoagulants were "probably not contraindicated" in IE.

Several echocardiographic findings related to vegetation size, mobility, consistency, and location have been proposed to stratify risk of embolization in patients with IE.^{231,241-243} However, in a review of this subject, O'Brien and Geiser²⁴⁴ report that 80% of patients with IE have vegetations detected by echocardiography while only one third have systemic emboli. TEE is now routinely performed in the majority of patients with suspected IE. Its predictive value is so high that Popp²⁴⁵ concluded that "the current state of the art in TEE imaging makes the likelihood of endocarditis low in patients without demonstrated vegetations." TEE may also be helpful in determining the likelihood of systemic embolism. In a study of 178 patients with endocarditis, Di Salvo et al²⁴⁶ determined that both the size and the mobility of the vegetation when evaluated by TEE were strong independent predictors of embolic events. In this study²⁴⁶ there was a 60% incidence of embolic events in those patients with a vegetation > 10 mm; the incidence was as high as 83% in patients with vegetations > 15 mm. Further evidence of the utility of the TEE in predicting embolic events comes from the evaluation of 217 patients with left-sided endocarditis after institution of antibiotic therapy. In this study, Vilacosta et al²⁴⁷ found that the risk for embolic events was higher with an increase in vegetation size during the course of antibiotic therapy. In addition, this risk was higher for vegetation size > 10 mm, infection with *S* aureus, or mitral valve involvement. Similar results were seen in a recent study by Thuny et al,²⁴⁸ in which 384 patients with IE underwent TEE and were prospectively evaluated. In this study, vegetation length > 10 mm and severe vegetation mobility were strong predictors of new embolic events. The organisms, S aureus and Streptococcus bovis, were also independently associated with total embolic events. Thus,

patients with large vegetations (> 10 mm) should be regarded as high risk for embolization. A more aggressive strategy (including early surgery) should be considered in such patients, especially when other relative indications for surgery exist (eg, severe mitral regurgitation) and there is a high likelihood of successful valve repair by an experienced surgeon in a high volume center. In the Thuny et al²⁴⁸ study, vegetation length > 15 mm was an independent predictor of 1-year mortality. Prospective studies evaluating clinical outcomes with prophylactic surgery to prevent embolization are needed.

There is no convincing evidence that prophylactic anticoagulant therapy reduces the incidence of emboli in native valve endocarditis, and it is generally believed that the routine use of anticoagulant drugs is not justified in this circumstance. In a study²⁴⁹ of the rate of cerebral embolic events in relation to antibiotic and anticoagulant therapy in patients with IE, a prompt reduction in emboli was observed soon after antibiotic therapy was started, while the incidence of emboli was the same among those who did or did not receive anticoagulant therapy. However, in a patient with another indication (eg, the patient with mitral valve disease and recent onset of AF) appropriate anticoagulant therapy should not be withheld if there are no signs of CNS involvement. The effect of ASA therapy on the risk of embolic events in IE was evaluated in a study by Chan et al.²⁵⁰ In this trial, 115 patients with IE were randomized to ASA treatment (325 mg/d) or placebo for 4 weeks. The addition of ASA did not reduce the risk of embolic events, with 17 such events (28.3%) in the ASA group vs 11 events (20.0%) in the placebo group (OR, 1.62, p = 0.29). There was also a trend toward a higher incidence of bleeding in the ASA group.

The patient with prosthetic valve endocarditis (PVE) deserves special comment. In contrast to patients with bioprostheses in normal sinus rhythm, patients with mechanical valves are at constant risk of thromboembolism, and there are important reasons not to interrupt anticoagulant therapy. The risk of thromboembolic events in PVE is higher than that in native valve endocarditis; emboli have been reported in 50 to 88% of patients with PVE.^{225,226,228,251,252} However, opinion is divided on the effectiveness of anticoagulation in reducing the number of embolic events associated with PVE. Wilson et al²⁵² reported CNS complications in only 3 of 38 patients with PVE who received adequate anticoagulant therapy, while events were observed in 10 of 14 patients who received either inadequate or no anticoagulation. However, Yeh et al²⁵³ found that adequate anticoagulation failed to control emboli in PVE, and the risk of bleeding appeared to be greater among patients with infected

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prostheses.²²⁸ Pruitt et al²²⁶ found that 23% of hemorrhagic events in IE occurred in the 3% of patients receiving anticoagulants and a 50% incidence of hemorrhage was observed by Johnson²⁵⁴ in patients with PVE treated with anticoagulants. Other investigators, have reported a high incidence of ICH in patients with PVE who received anticoagulant therapy.^{228,255}

Thus, the use of anticoagulants in PVE must steer a path between the potential for thromboembolism and the risk of serious bleeding, including ICH. There seems little doubt that the risk of the former is substantial without the protection of continued anticoagulation, yet the consequences of ICH may be irreversible and not infrequently fatal. It should be appreciated that embolic events in PVE may represent dislodged vegetations or, alternatively, true thromboembolism unrelated to the valve infection. While it might be expected that the incidence of the latter can be reduced by anticoagulant therapy, there is no evidence that embolic vegetations are controlled by this therapy. Nevertheless, most investigators suggest that anticoagulant therapy should be continued in patients with PVE,^{226,251,252,254} while others express some doubt about its value.^{226,227} Since the most serious and potentially lethal complications of cerebral embolism are due to intracranial bleeding, due either to a rupture mycotic aneurysm or hemorrhagic transformation of a bland infarct, CT/CTA or MRI/MRA may provide a means of identifying the patient at high risk for such complications.²⁵⁶ In patients with IE and CNS events, it is imperative to search for a mycotic aneurysm when parenchymal hemorrhage is present. A ruptured mycotic aneurysm will necessitate neurosurgical or interventional neuroradiologic treatment. Since the risk of thromboembolism in patients not receiving anticoagulant therapy with bioprostheses who are in normal sinus rhythm is low,²⁰⁸ anticoagulation therapy is not indicated. A study of 61 patients with PVE found no protective effect of warfarin anticoagulation and confirmed the observation that antibiotic therapy was more important than anticoagulation in preventing neurologic complications.²⁵⁷ Although Pruitt et al²²⁶ suggested a possible role for APAs in PVE, the utility of this form of therapy has not been established.

Recommendations

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

9.1.2. If the patient treated with VKA therapy has IE, we suggest VKA be discontinued at the time of initial presentation and UFH substituted, 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).

9.2 Nonbacterial Thrombotic Endocarditis

The evolution of the syndrome of nonbacterial thrombotic endocarditis (NBTE) has been clearly detailed in a comprehensive review of this disease by Lopez et al.²⁵⁸ Originally described by Ziegler in 1888, the lesions were considered to be fibrin thrombi deposited on normal or superficially degenerated cardiac valves. In 1936, Gross and Friedberg introduced the term nonbacterial thrombotic endocarditis; and in 1954, Angrist and Marquiss²⁵⁹ first called attention to the frequent association of systemic emboli with this disease. Numerous reports have identified the relationship between NBTE and a variety of malignancies and other chronic debilitating diseases, but also have emphasized its occurrence in patients with acute fulminant diseases such as septicemia or burns, and particularly as part of the syndrome of disseminated intravascular coagulation.

While NBTE has been reported in every age group, it most commonly affects patients between the fourth and eighth decades. The reported incidence of systemic emboli varies widely (14 to 91%; average 42%).²⁵⁸ While NBTE most commonly affects the aortic and mitral valves, any cardiac valve may be affected; vegetations on the atrioventricular valves are present on the atrial surface, while those involving the semilunar valves are found on the ventricular surface of the valve.²⁵⁸ Although the pathogenesis of NBTE is not fully understood, the most important predisposing factors appear to be an underlying coagulopathy (usually disseminated intravascular coagulation), microscopic edema, degeneration of valvular collagen, and perhaps a local valvular effect of mucin-producing carcinomas.²⁵⁸

The diagnosis of NBTE is not easily made and is considerably more elusive than that of IE. Not only is the marker of bloodstream infection lacking, but the small friable vegetations frequently embolize leaving only small remnants to be identified on the valve. Indeed, cardiac murmurs, a hallmark of infective endocarditis, are frequently absent and there is some evidence that echocardiography is less sensitive for the detection of NBTE than it is for IEs.^{258,260}

NBTE lesions need to be differentiated from valve excrescences. In contrast to thrombotic vegetations that are generally rounded, sessile, measure > 3 mm in diameter, have heterogeneous echoreflectance and no independent mobility, valve excrescences are thin (≤ 2 mm), elongated (≥ 3 mm) structures that are seen near leaflet close lines. Roldan et al²⁶¹ used

TEE to compare 90 healthy volunteers, 88 patients without suspected cardioembolism, and 49 patients referred for suspected cardioembolism. They found valve excrescences in 38% of normal subjects, 47% of patients without suspected cardioembolism, and 41% of those with suspected cardioembolism. These authors concluded that valve excrescences were common findings on left-sided heart valves of both normal subjects and patients regardless of gender or age, that they persist over time, and that they do not seem to be a primary source of cardiac embolism. In an accompanying editorial, Armstrong²⁶² concluded that the above-mentioned carefully controlled TEE study should serve as a model for studying other possible lesions associated with cardioembolism such as atrial septal defect, patent foramen ovale, and isolated MVP without vegetation. Dutta et al²⁶³ examined the frequency of NBTE and other cardiac sources of embolism in cancer patients referred for TEE evaluation due to recent stroke. They noted a high frequency of definite cardiac source of embolism (47%), with the source of embolism attributed to NBTE lesions in 18% of these patients.

Treatment of NBTE is directed toward control of the underlying disease, in most instances neoplasm and/or sepsis, and toward treatment of thromboembolism, with or without associated disseminated intravascular coagulation. The case for anticoagulant therapy in NBTE is strengthened by the general belief that Trousseau syndrome and NBTE represent a continuum²⁶⁴ and that disseminated intravascular coagulation represents the substrate for treating most patients with NBTE. The most effective agent appears to be heparin, and recurrent thromboembolic complications have been reported after heparin therapy was discontinued.^{258,264} Rogers et al²⁶⁵ suggest that anticoagulant therapy should be withheld from patients with disseminated cancer when there is no hope of tumor regression, but in most instances, a diagnosis of NBTE or a strong suspicion of this diagnosis warrants treatment with IV UFH. Although the utility of subcutaneous heparin therapy for outpatient use has not been established, its use has been suggested to improve the quality of life of patients with NBTE and persistent neoplasm or chronic debilitating disease. Little benefit has been observed with VKA therapy.^{258,264,265}

Recommendations

9.2.1. In patients with NBTE and systemic or pulmonary emboli, we recommend treatment with full-dose IV UFH or subcutaneous LMWH (Grade 1C).

9.2.2. In patients with disseminated cancer or debilitating disease with aseptic vegetations, we

suggest administration of full-dose IV UFH or subcutaneous LMWH (Grade 2C).

CONCLUSION

The decision to initiate anticoagulant therapy in a patient with valvular heart disease is frequently difficult because of the many variables that influence the risks of thromboembolism and of bleeding in a given individual. The patient's age, the specific valve lesion, the heart rhythm, the duration of the valve disease, a history of thromboembolism, patient attitude and lifestyle, associated diseases, and medications all must be considered. In addition, for patients with a prosthetic heart valve, the valve type and location need also be considered. Because the state of such variables might change with time, a proper decision at one point in a patient's life might be inappropriate at another time. In some instances, the literature on a given subject is sparse or contains conflicting data that further confound the issue. Since the database for these guidelines is constantly being modified, particularly as a consequence of new randomized clinical trials, the clinician would do well to review his or her decisions regarding antithrombotic therapy at regular intervals.

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