Antithrombotic Therapy in Valvular Heart Disease—Native and Prosthetic

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This chapter about antithrombotic therapy in native and prosthetic valvular heart disease is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients’ values may lead to different choices (for a full understanding of the grading see Guyatt et al, CHEST 2004; 126:1798–1875). Among the key recommendations in this chapter are the following: For patients with rheumatic mitral valve disease and atrial fibrillation (AF), or a history of previous systemic embolism, we recommend long-term oral anticoagulant (OAC) therapy (target international normalized ratio [INR], 2.5; range, 2.0 to 3.0) [Grade 1A]. For patients with rheumatic mitral valve disease with AF or a history of systemic embolism who suffer systemic embolism while receiving OACs at a therapeutic INR, we recommend adding aspirin, 75 to 100 mg/d (Grade 1C). For those patients unable to take aspirin, we recommend adding dipyridamole, 400 mg/d, or clopidogrel (Grade 1C). In people with mitral valve prolapse (MVP) without history of systemic embolism, unexplained transient ischemic attacks (TIAs), or AF, we recommended against any antithrombotic therapy (Grade 1C). In patients with MVP and documented but unexplained TIAs, we recommend long-term aspirin therapy, 50 to 162 mg/d (Grade 1A). For all patients with mechanical prosthetic heart valves, we recommend vitamin K antagonists (Grade 1C+). For patients with a St. Jude Medical (St. Paul, MN) bileaflet valve in the aortic position, we recommend a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1A]. For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, we recommend a target INR of 3.0 (range, 2.5 to 3.5) [Grade 1C+]. For patients with caged ball or caged disk valves, we suggest a target INR of 3.0 (range, 2.5 to 3.5) in combination with aspirin, 75 to 100 mg/d (Grade 2A). For patients with bioprosthetic valves, we recommend vitamin K antagonists with a target INR of 2.5 (range, 2.0 to 3.0) for the first 3 months after valve insertion in the mitral position (Grade 1C+) and in the aortic position (Grade 2C). For patients with bioprosthetic valves who are in sinus rhythm and do not have AF, we recommend long-term (>3 months) therapy with aspirin, 75 to 100 mg/d (Grade 1C+).

Key words: antithrombotic; aspirin; heart disease; heart valves; prophylaxis

Abbreviations: AF = atrial fibrillation; APA = antiplatelet agent; GELIA = German experience with low intensity anticoagulation; INR = international normalized ratio; LMWH = low molecular weight heparin; MAC = mitral annular calcification; MVP = mitral valve prolapse; NBTE = nonbacterial thrombotic endocarditis; OAC = oral anticoagulant; PMV = percutaneous mitral valvuloplasty; RCT = randomized controlled trial; TEE = transesophageal echocardiography; TIA = transient ischemic attack

Few complications of valvular heart disease can be more devastating than systemic embolism. Antithrombotic therapy can reduce, although not eliminate, the likelihood of this catastrophe. If this therapy were risk free, and if no cost, all patients with significant valvular heart disease should be treated. Unfortunately, antithrombotic therapy, particularly with coumarin derivatives or heparin, carries a substantial risk of bleeding: that risk varies with the drug used, the intensity of the anticoagulant effect, and the clinical circumstances in individual patients. For example, risks of anticoagulant therapy are greater in patients with endocarditis, pregnancy, and bleeding diatheses. 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 disease. 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 assessing the risk of bleeding. While the rewards of anticoagulant therapy will be greater in patients with a high risk of thromboembolism than in those at low risk for this event, the benefits of anticoagulation may be offset by the hemorrhagic complications of antithrombotic therapy. At the same time, the permanent consequences of a thromboembolic event are generally more serious than the ultimate outcome of hemorrhagic complications of anticoagulant therapy. Most patients recognize this, and are ready to accept a substantial bleeding risk to prevent strokes.

1.0 Rheumatic Mitral Valve Disease

The incidence of systemic embolism is greater in rheumatic mitral valve disease than in any other common
<table>
<thead>
<tr>
<th>Section</th>
<th>Population</th>
<th>Intervention/Exposure</th>
<th>Outcomes</th>
<th>Methodology</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Rheumatic mitral stenosis with AF or systemic embolism</td>
<td>Warfarin, aspirin, ticlopidine, or clopidogrel</td>
<td>Thromboembolic events (thromboemboli), mortality, bleeding</td>
<td>RCT and observational</td>
<td>None</td>
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<tr>
<td>1.2</td>
<td>Rheumatic mitral stenosis in sinus rhythm</td>
<td>Warfarin, aspirin, ticlopidine, or clopidogrel</td>
<td>Thromboembolic events (thromboemboli),* mortality, bleeding</td>
<td>RCT and observational</td>
<td>None</td>
</tr>
<tr>
<td>1.3</td>
<td>Rheumatic mitral stenosis undergoing mitral valvuloplasty</td>
<td>Warfarin</td>
<td>Thromboemboli,* mortality, bleeding</td>
<td>RCT and observational</td>
<td>None</td>
</tr>
<tr>
<td>2.1</td>
<td>MVP</td>
<td>Time</td>
<td>Thromboemboli</td>
<td>Observational</td>
<td>None</td>
</tr>
<tr>
<td>2.1</td>
<td>MVP</td>
<td>Warfarin or aspirin, ticlopidine or clopidogrel</td>
<td>Thromboemboli</td>
<td>RCT and observational</td>
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<td>3.1</td>
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<td>Time</td>
<td>Thromboemboli</td>
<td>Observational</td>
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<tr>
<td>3.1</td>
<td>MAC or mitral regurgitation with AF or systemic embolism</td>
<td>Warfarin or aspirin, ticlopidine or clopidogrel</td>
<td>Thromboemboli, bleeding</td>
<td>RCT and observational</td>
<td>None</td>
</tr>
<tr>
<td>4.1</td>
<td>Aortic valve calcification (with or without aortic stenosis)</td>
<td>Time</td>
<td>Thromboemboli</td>
<td>Observational</td>
<td>None</td>
</tr>
<tr>
<td>4.2</td>
<td>Aortic valve calcification (with or without aortic stenosis)</td>
<td>Warfarin or aspirin, ticlopidine or clopidogrel</td>
<td>Thromboemboli</td>
<td>RCT and observational</td>
<td>None</td>
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<tr>
<td>4.3</td>
<td>Aortic arch plaque and calcification</td>
<td>Time</td>
<td>Thromboemboli</td>
<td>Observational</td>
<td>None</td>
</tr>
<tr>
<td>4.4</td>
<td>Aortic arch plaque, atheroma, and calcification</td>
<td>Warfarin or aspirin, ticlopidine or clopidogrel</td>
<td>Thromboemboli</td>
<td>RCT and observational</td>
<td>None</td>
</tr>
<tr>
<td>5.0</td>
<td>Mechanical heart valves</td>
<td>Warfarin, direct thrombin inhibitors (lepirudin, argatroban, bivalirudin), unfractionated heparin, LMWH, aspirin, dipyridamole, clopidogrel, ticlopidine</td>
<td>Valve thrombosis, arterial thromboemboli, death</td>
<td>RCTs and observational studies</td>
<td>None</td>
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<tr>
<td>6.0</td>
<td>Bioprosthetic heart valves</td>
<td>Warfarin, direct thrombin inhibitors (lepirudin, argatroban, bivalirudin), heparin, aspirin, dipyridamole, clopidogrel, ticlopidine</td>
<td>Valve thrombosis, arterial thromboembolism, death</td>
<td>RCTs and observational studies</td>
<td>None</td>
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<tr>
<td>7.0</td>
<td>Infective endocarditis</td>
<td>Time</td>
<td>Thromboemboli</td>
<td>Observational</td>
<td>None</td>
</tr>
<tr>
<td>7.0</td>
<td>Infective endocarditis</td>
<td>Warfarin, aspirin, ticlopidine or clopidogrel or heparin (include LMWH)</td>
<td>Thromboemboli</td>
<td>RCT and observational</td>
<td>None</td>
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<tr>
<td>7.0</td>
<td>NBTE</td>
<td>Time</td>
<td>TE</td>
<td>Observational</td>
<td>None</td>
</tr>
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<td>NBTE</td>
<td>Warfarin, aspirin, ticlopidine, or clopidogrel or heparin (include LMWH)</td>
<td>TE</td>
<td>RCT and observational</td>
<td>None</td>
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<tr>
<td>8.0</td>
<td>Patients with valvular heart disease receiving antithrombotic therapy who undergo surgical procedures</td>
<td>Time antithrombotic therapy is stopped</td>
<td>TE</td>
<td>RCT and observational</td>
<td>None</td>
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</table>

*Thromboembolic events including stroke and TIAs.
form of valvular heart disease. While surgery and the frequent use of long-term anticoagulant therapy have altered the natural history of this disease during the past 40 years, Wood\(^2\) cited a prevalence of systemic emboli of 9 to 14% in several large early series of mitral stenosis; in 1961, Ellis and Harken\(^3\) reported that 27% of 1,500 patients undergoing mitral valvuloplasty had a history of clinically detectable systemic emboli. Among 754 patients followed up for 5,533 patient-years, Szekely\(^4\) 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.\(^5\) 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.\(^6\)

The incidence of systemic emboli increases dramatically with the development of atrial fibrillation (AF). Szekely\(^4\) 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 with AF, Hinton et al\(^2\) found a 41% prevalence of systemic emboli at autopsy. Three fourths of the patients with mitral stenosis and cerebral emboli described by Harris and Levine\(^8\) and by Wood\(^2\) had AF. Among 539 patients with mitral valve disease described by Coulshed and associates,\(^9\) emboli occurred in 8% of mitral stenosis patients with normal sinus rhythm, 31.5% of those with AF, 7.7% of those with dominant mitral regurgitation and normal sinus rhythm, and 22% of those with mitral regurgitation and AF. Wood\(^2\) confirmed that emboli occur 1.5 times as frequently in mitral stenosis as in rheumatic mitral regurgitation.

The risk of systemic emboli in rheumatic mitral disease is greater in older patients\(^10–13\) and those with lower cardiac indexes,\(^10\) but appears to correlate poorly with mitral calcification,\(^9\) mitral valve area,\(^10\) or clinical classification.\(^2,9^{,}10,14\) Indeed, several investigators have pointed out that patients with mitral valve disease with emboli frequently are found to have minor valve disease, and Wood\(^2\) 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\(^2,9^{,}14\) of rheumatic mitral valve disease reported a weak correlation. While some reports,\(^15–17\) primarily in patients without AF, suggest that left atrial size is an independent risk factor for thromboembolism, another study\(^18\) describing 1,066 patients with AF found no such relationship.

In a prospective study of > 500 patients with mitral stenosis, Chiang et al\(^19\) 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 (± SD). 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 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. Previous embolism was associated with subsequent embolism in patients in AF. Percutaneous balloon mitral commissurotomy decreased the risk of systemic embolism in patients with mitral stenosis who were in AF. This suggests benefits from early use of this procedure.

Among patients with valvular disease who suffer a first embolus, recurrent emboli occur in 30 to 65% of cases,\(^2,6,20,21\) of which 60 to 65% are within the first year,\(^20,21\) and most occur within 6 months. Mitral valvuloplasty does not appear to eliminate the risk of thromboembolism.\(^5,9\)

Thus, a successful mitral valvuloplasty does not eliminate the need for anticoagulation in patients who required long-term anticoagulation prior to the procedure, and patients will continue to require this therapy postoperatively.

There is good reason to believe that the frequency of systemic emboli due to rheumatic valve disease is decreasing, while the number due to ischemic heart disease is on the rise. This reduction in the number of systemic emboli due to rheumatic heart disease is due both to a decrease in the absolute number of rheumatic heart disease patients and to the widespread use of long-term anticoagulant therapy in these patients.

### 1.1 Rheumatic mitral valve disease with AF or a history of systemic embolism

Although never evaluated by randomized trial, there is little doubt that long-term anticoagulant therapy is effective in reducing the incidence of systemic emboli in patients with rheumatic mitral valve disease. In an observational study,\(^4\) the incidence of recurrent embolism in patients with mitral valve disease who received warfarin was 3.4%/yr, while in the nonanticoagulation group it was 9.6%/yr. Adams et al\(^22\) 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 emboli was reported in the treated group, with 13 deaths from emboli in the untreated group and 4 deaths in the treated group. Fleming\(^14\) 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 with an incidence of thromboembolism of 0.8% per patient-year. In a retrospective study of 254 patients with AF, an embolic rate of 5.46%/yr was reported for patients not receiving anticoagulation, vs 0.7%/yr for those receiving long-term warfarin therapy.\(^23\) Long-term anticoagulant therapy in patients with mitral stenosis who were found to have left atrial thrombus by transesophageal echocardiography (TEE) can result in the disappearance of left atrial thrombus. In a study\(^23\) 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 size of the thrombus and a lower New York Heart Association functional class were independent predictors of thrombus disappearance.\(^24\)
Perhaps the strongest evidence supporting the utility of anticoagulation for the prevention of thromboembolism in mitral valve disease comes from extrapolation of the results of four, large, randomized studies35–38 in patients with nonvalvular AF. Each of these studies demonstrated that warfarin was effective in reducing stroke in patients with nonvalvular AF. An additional Canadian multicenter trial39 was terminated prematurely when its results developed a trend consistent with the data reported in the four earlier trials. More recently, a meta-analysis that included six published, randomized trials with a total of 4,052 patients has provided further confirmation that warfarin was superior to aspirin in decreasing the risk of stroke in patients with nonvalvular AF.30 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.31,32 Singer et al, in this Supplement, 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 and AF (paroxysmal or chronic), or who have demonstrated their high risk by previous systemic embolism, should be offered treatment with long-term oral anticoagulant (OAC) therapy. Exceptions that require detailed tradeoff analysis include the pregnant woman or the patient at high risk for serious bleeding, whether due to established concomitant disease, exposure to contact sports or trauma, or inability to control the international normalized ratio (INR).

In a randomized study33 of patients with prosthetic heart valves, the addition of dipyridamole to warfarin therapy proved effective in reducing the incidence of systemic emboli. Similar findings were reported in a study by Cheseboro et al.34 Dale and associates35 performed a randomized trial of aspirin (1.0 g/d) plus warfarin vs warfarin alone in 148 patients with prosthetic heart valves, and noted a significant reduction of emboli in the aspirin-treated group. Intracranial bleeding occurred with equal frequency in both groups, while GI complications, including bleeding, were encountered more often in the patients receiving aspirin. At the completion of the study, all patients were treated with aspirin alone and had unsatisfactory control of embolic events. Turpie et al36 reported that the addition of aspirin (100 mg/d) to warfarin (INR 3.0 to 4.5) reduced mortality and major thromboembolism in patients with mechanical heart valves and in high-risk patients with bioprosthetic heart valves with no significant increase in major bleeding. The safety and effectiveness of combined warfarin and antiplatelet therapy have since been confirmed in a nonrandomized prospective study of patients with St. Jude Medical (St. Paul, MN) valve prostheses.37

Thus, there is evidence that dipyridamole will normalize shortened platelet survival and reduce the incidence of emboli in some patients with valvular heart disease, and that dipyridamole and/or aspirin added to vitamin K antagonists therapy will reduce the incidence of thromboembolism in patients with prosthetic valves. However, until these findings are confirmed and the effectiveness of platelet-active drugs compared with that of OACs in randomized trials, patients with rheumatic mitral valve disease considered to be at risk for thromboembolism should be administered OACs unless the risk of bleeding is unusually high. If this therapy should fail, a platelet-active agent should be added; or, if OACs are contraindicated, antiplatelet therapy might be a reasonable, albeit uncertain, alternative. Until there are further clinical studies supporting the use of dipyridamole in the setting of valvular heart disease, the role of dipyridamole will remain unclear. There is some evidence that the drug offers little beyond the effect of aspirin administered concomitantly.38

Recommendations

For patients with rheumatic mitral valve disease and AF, or a history of previous systemic embolism:

1.1.1. We recommend long-term OAC therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C+].

For patients with rheumatic mitral valve disease and AF, or a history of previous systemic embolism:

1.1.2. We suggest clinicians not use concomitant therapy with an OAC and an antiplatelet agent (APA) [Grade 2C].

Underlying values and preferences: This recommendation places a relatively high value on avoiding the additional bleeding risk associated with concomitant OAC and antiplatelet therapy.

1.1.3. For patients with rheumatic mitral valve disease with AF or a history of systemic embolism who suffer systemic embolism while receiving OACs at a therapeutic INR, we recommend adding aspirin, 75 to 100 mg/d (Grade 1C). For those patients unable to take aspirin, we recommend adding dipyridamole, 400 mg/d, or clopidogrel (Grade 1C).

1.2 Patients with mitral valve disease in sinus rhythm

Despite the powerful thromboembolic potential of AF, the rheumatic mitral valve disease patient in sinus rhythm still has a substantial risk of systemic embolism and is, therefore, a possible candidate for long-term OAC therapy. This is particularly true if the patient has had prior AF or is being treated with antiarrhythmic medications to maintain sinus rhythm.31,32 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. Other than age, there are no reliable clinical markers in such cases, so 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 should receive anticoagulant therapy.39
Recommendations

1.2.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 5.5 cm, we suggest long-term OAC 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 avoiding systemic embolism and its consequences, and a relatively low value on avoiding the bleeding risk and inconvenience associated with OAC therapy.

1.2.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 5.5 cm, we suggest clinicians not use antithrombotic therapy (Grade 2C).

1.3 Patients undergoing mitral valvuloplasty

With the advent of percutaneous balloon mitral valvuloplasty, clinicians face a small chance that the catheter will dislodge the left atrial clot during the procedure. Accordingly, some centers have made it a practice to treat all such patients with OACs for a minimum of 3 weeks before the balloon valvuloplasty, regardless of the presence or absence of AF. An alternate strategy might be to perform TEE just prior to balloon mitral valvuloplasty and withhold anticoagulation prior to valvuloplasty if the examination does not reveal a left atrial clot.

Recently, Abraham et al reported on performing percutaneous transvenous mitral valvuloplasty on 629 relatively young patients (mean age, 29.5 ± 9.9 years [±SD]) with rheumatic mitral stenosis, normal sinus rhythm, no history of embolism, or echocardiographic evidence of clot without anticoagulation prior, during, or after the procedure. No patient had an embolism in the immediate postprocedure period or during a median follow-up of 3 months. However, until this study is reproduced, based on experience with patients undergoing cardioversion of AF, the absence of atrial clot by TEE at the time of the procedure does not preclude the need for prompt anticoagulation after cardioversion to prevent thromboembolism. Indeed, one can make a good case for anticoagulation therapy in most patients after balloon mitral valvuloplasty for at least 4 weeks. Kang et al reported on 49 patients with mitral stenosis with left atrial appendage thrombi who were otherwise candidates for percutaneous mitral valvuloplasty (PMV). Twenty-five patients underwent PMV after being treated with warfarin to achieve an INR of 2.0 to 3.0. PMV was performed after the resolution of left atrial appendage thrombi (mean resolution time, 5 ± 3 months [±SD]). There were no procedure-related complications reported during or after PMV.

Recommendation

1.3.1. For patients undergoing mitral valvuloplasty, we suggest anticoagulation with vitamin K antagonists with a target INR of 2.5 (range, 2.0 to 3.0) for 3 weeks prior to the procedure and for 4 weeks after the procedure (Grade 2C).

2.0 Mitral Valve Prolapse

Mitral valve prolapse (MVP) is the most common form of valve disease in adults. While generally innocuous, it is sometimes annoying, and serious complications can occur. During the past 20 years, embolic phenomena have been reported in several patients with MVP in whom no other source for emboli could be found. In 1974, Barnett observed four patients with MVP who suffered 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.

Similar observations have been made by other investigators and as many as nine such patients have been reported from a single center.

Earlier evidence linking MVP to stroke was provided by the case-control study of Barnett and associates. Among 60 patients < 45 years old who had TIAs or partial stroke, MVP was detected in 40%; in 60 age-matched control subjects, the incidence was 6.8% (p < 0.001); and in 42 stroke patients > 45 years old, MVP was found in 5.7%, an incidence comparable to that in the general population.

More recently, with the use of two-dimensional echocardiography, the criteria for the diagnosis of MVP have changed resulting in a lower prevalence than previously believed. In fact, in a study by Gilon et al, 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%). Seventy-one of 213 patients had unexplained stroke: no identifiable or recognized cause of stroke or TIA. Of this subgroup, two patients (2.8%) had prolapse. This rate was not significantly different than the control group. Evaluation of the Framingham Heart Study offspring cohort has yielded similar results, with MVP in only 2.4% of this cohort. In the Framingham cohort, no significant difference was found in the prevalence of stroke or TIA in individuals with MVP as compared to those without MVP.

Thus, although it appears that a small number of patients with MVP are at risk for systemic thromboembolism, consideration of denominators should temper our therapeutic approach to this problem. Assuming that 6% of the female and 4% of the male population have MVP, the incidence of thromboembolism in these > 12 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. As suggested by Cheitlin, informing the patients with MVP of this risk is not indicated, “nor is it reasonable to recommend prophylactic platelet-active drugs” to all patients with MVP. However, 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, long-term aspirin therapy appears indicated as in many patients with TIAs and no MVP. No studies of antithrombotic therapy in
results of physical examination. Patients with cerebral ischemia are found to have normal ventricular dimensions, would not be expected to be at increased risk of thromboembolism. However, past observations indicate otherwise, as most MVP 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 and laboratory characteristics of MVP patients may succeed in reducing the fraction at risk. Since myxomatous degeneration and demudation of the mitral endothelium are likely to be critical in the thrombogenic process, patients with "secondary" MVP, due solely to a reduction in left ventricular dimensions, would not be expected to be at risk. It would also be important to learn whether the "click-only" or silent MVP patients represent a subpopulation without increased risk of thromboembolism. However, past observations indicate otherwise, as most MVP patients with cerebral ischemia are found to have normal results of physical examination.

In a prospective study of 237 patients with MVP, Nishimura et al concluded that those with a redundant mitral valve on echocardiography constituted a subgroup of patients at high risk for MR, infectious endocarditis, sudden death, and cerebral embolic events. Most of these observations were confirmed in a retrospective study by Marks et al, except that the risk of stroke was not correlated with valve thickening. Thus, at this time, there appears to be no clinical or echocardiographic marker that clearly identifies the MVP patient at risk for cerebral ischemic events.

Clinicians can consider patients with documented but unexplained TIAs in the same way they would other patients with unexplained TIAs. As documented in the guideline chapter on prevention of stroke (see the article by Albers et al in this Supplement), randomized trials have consistently shown that aspirin reduces stroke risk in such patients.

**Recommendations**

2.0.1. In people with MVP who have not experienced systemic embolism, unexplained TIAs, or AF, we recommended against any antithrombotic therapy (Grade 1C).

2.0.2. In patients with MVP who have documented but unexplained TIAs, we recommend long-term aspirin therapy, 50 to 162 mg/d (Grade 1A).

2.0.3. In patients with MVP who have documented systemic embolism or recurrent TIAs despite aspirin therapy, we suggest long-term vitamin K antagonist 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, includes a strong female preponderance and may be associated with mitral stenosis and 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 embolism in this condition is not known, embolic events appear conspicuous with or without associated AF. Four of the 14 original patients described by Korn et al had cerebral emboli, and 5 of 80 patients described by Fulkerson et al had systemic emboli, only 2 of whom had AF. More recently, 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, and echogenic densities have been described in the left ventricular outflow tract in this condition among patients with cerebral ischemic events.

Perhaps the best estimate of the thromboembolic potential of MAC comes from the Framingham Heart Study. Among 1,159 subjects with no history of stroke at the index echocardiographic examination, the relative risk of stroke in those with MAC was 2.10 times that without MAC (p = 0.006), independent of traditional risk factors for stroke. Even in those subjects without prevalent AF, the risk of stroke in subjects with MAC was twice that of those without MAC.

In addition to embolization of fibrin clot, calcified spicules may become dislodged from the ulcerated calcified annulus and present as systemic emboli. While the relative frequency of calcific emboli and thromboembolism is 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. Since there is little reason to believe that anticoagulant 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 study, the incidence of AF was 12 times greater in patients with MAC than in those without this lesion, and 29% of the patients with annular calcification described by Fulkerson et al had AF. 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. 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 regurgitation), fragmentation of calcific annular tissue, and diffuse vascular atherosclerosis. In light of these observations, a good argument can be made for prophylactic anticoagulant therapy in patients with AF or a history of an embolic event. However, since most of these patients are elderly (mean age, 73 to 75 years), the risks of...
anticoagulation with vitamin K antagonists 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 from anticoagulation may outweigh the benefit of OAC therapy in patients without AF. Certainly the clinician should be discouraged from initiating anticoagulant therapy merely on the basis of radiographic evidence of MAC. Antiplatelet drugs might represent an uncertain compromise for those with advanced lesions, although to our knowledge no studies indicate that this therapy is effective in preventing thromboembolism in MAC. For patients with repeated embolic events despite OAC therapy or in whom multiple calcific emboli are recognized, valve replacement should be considered.

**Recommendation**

3.0.1. In patients with MAC complicated by systemic embolism, not documented to be calcific embolism, we suggest treatment with long-term OAC therapy with a target INR of 2.5 (INR range, 2.0 to 3.0) [Grade 2C].

**4.0 Aortic Valve and Aortic Arch Disorders**

Clinically detectable systemic emboli in isolated aortic valve disease are distinctly uncommon. However, Stein et al[76] 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.,[72] and four cases of cerebral emboli were observed in patients with bicuspid aortic valves in whom no other source of emboli could be found. In the latter group, all four patients were treated with aspirin, and no recurrences were observed. Perhaps the most startling report of calcific emboli in a patient with calcific aortic stenosis is that of Holley et al.[78] In this autopsy study[78] 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.

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 valvular disease may best be explained by unrecognized mitral valvular or ischemic heart disease or by coexisting AF. It is of interest in this regard that of 194 patients with rheumatic valvular disease and systemic emboli described by Daley et al.,[78] only 6 patients had isolated aortic valve disease, and in each AF was also present. More recently, the association of AF and aortic valve disease was examined by Myler and Sanders.[80] In 122 consecutive patients with proved isolated severe aortic valve disease, only 1 had AF, and in that instance, advanced coronary heart disease with infarction was present as well.[80] Boon et al[81] 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 strokes in patients with calcific aortic valve disorders compared with a matched control group. Otto et al[82] 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 collected in this study. The authors found no significant increase in the incidence of stroke over a mean follow-up period of 5 years.[82]

Thus, in the absence of associated mitral valve disease or AF, systemic embolism in patients with aortic valve disease is uncommon, and long-term anticoagulation 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 anticoagulant therapy in isolated aortic valve disease apparently outweigh the potential usefulness.

TEE of the aortic arch and ascending aorta have been used to identify plaque size and morphology as risk factors for ischemic stroke.[83,84] An evaluation of 382 patients enrolled in the Stroke Prevention in Atrial Fibrillation trial who underwent TEE found that 134 patients (35%) had complex aortic plaque > 4 mm; in these patients, 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%. In a prospective case-control study[86] of 250 patients with ischemic stroke, TEE revealed that 14.4% of patients with strokes had plaques ≥ 4 mm in thickness; this is in contrast to the control subjects (no ischemic event) who had a 2% occurrence of plaques of this size. Similarly, in patients with prior ischemic events, Amarenco and colleagues[87] found plaques ≥ 4 mm to be significant risk factors for recurrent ischemic events. These same researchers performed an analysis of 788 person-year follow-up to determine the affect of plaque morphology on the risk of ischemic disease. They determined that the only plaque morphology that increased the risk of ischemic events was the absence of plaque calcification.[88] Ulceration and hypoechogenic plaques had no predictive value in evaluating vascular events. Overall, it was determined that aortic plaques ≥ 4 mm in thickness increased the risk of vascular events, and this risk is further increased by a lack of plaque calcification (RR = 10.3, lack vs presence of calcification). These authors hypothesized that the non-calciﬁed plaques are probably lipid laden, and are thus unstable and prone to rupture and thrombosis. While calcified aortic plaques may be the cause of atheroemboli, particularly with aortic manipulation such as during bypass or catheter advancement, it is unlikely that antithrombotic therapy will be beneficial in this condition.[89]
To study the effect of OACs on patients with atherosclerosis of the aorta, Ferrari et al. used TEE in a prospective cohort to compare treated vs nontreated patients. They found that patients treated with antiplatelet agent (APA) rather than OAC had more combined vascular events and a higher mortality rate (RR = 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 APA as compared to patients treated with OACs. Patients with aortic plaques > 4 mm in thickness had almost a sixfold-higher risk for combined events when treated with APA vs OACs. This study did not provide information regarding patients who were receiving neither APA nor OAC therapy. Dressler et al. found similar results in that patients with mobile aortic atheroma not receiving warfarin had a higher incidence of vascular events (27% had strokes) than those with warfarin treatment (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, medium, and large atheromas had similar outcomes. This is in contrast to current practice patterns, since studies reveal that 79% of patients with large or medium atheromas (medium diameter > 1 mm and area < 10 mm²) were prescribed warfarin, as opposed to 53% of patients with small plaques (defined as diameter < 1 mm). More recently, in a retrospective analysis by Tunick et al., a group of 519 patients with severe aortic plaque were evaluated for embolic events. In this study, individuals receiving statins for cholesterol lowering had significantly less embolic events than those not receiving statins (12% vs 29%). OAC and APA therapy did not significantly reduce the risk of embolic events. The authors concluded that this may be a beneficial effect of statins on plaque stability. Thus, patients with mobile atheroma should be considered for anticoagulation with OACs, while the role of the dimension of the plaque (ie, > 4 mm) in determining therapy is still not totally clear.

**Recommendations**

4.0.1. In patients with aortic valve disease, we suggest that clinicians not use long-term vitamin K antagonist therapy unless they have another indication for anticoagulation (Grade 2C).

4.0.2. We suggest OAC therapy in patients with mobile aortic atheromas and aortic plaques > 4 mm as measured by TEE (Grade 2C).

**5.0 Prosthetic Heart Valves—Mechanical Prosthetic Heart Valves**

It is well established that patients with all types of mechanical valves require antithrombotic prophylaxis. Lack of prophylaxis in patients with St. Jude Medical bileaflet valves gave unacceptable results (embolism or valve thrombosis in 12%/yr with aortic valves and 22%/yr with mitral valves). Among patients with the Bjork Shiley spherical disk valves who received no prophylaxis or prophylaxis with APAs alone, thromboemboli occurred in 23%/yr. In the present consensus report, we continue to address literature that may permit a more refined assessment of the optimal level of INR for patients with modern mechanical prosthetic heart valves. We address whether low doses of aspirin or other antithrombotic drugs in combination with OACs may be beneficial. Investigations of low levels of warfarin are also assessed, particularly in newer valves. Investigations included in the present report are generally limited to those that report antithrombotic prophylaxis in terms of the INR. Much detailed information, particularly on the older valves, is given in the chapter on Antithrombotic Therapy in Prosthetic Heart Valves in the *CHEST* Supplement of 2001, and this will not be repeated.

Most results 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 anticoagulation actually achieved. In some important investigations, less than half of the INRs were in the target range. If failure to maintain tight control of the INR coupled with the failure to report the INRs at which events occurred, intention-to-treat analysis may yield misleading results about the safety or effectiveness of a given INR range. These limitations weaken the basis on which therapeutic recommendations can be made. They also indicate a need for further research in this area. Prospective studies that 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.

The literature provide little data on the administration of heparin or low molecular weight heparin (LMWH) immediately after valve insertion. However, it is common practice to administer unfractionated heparin or LMWH as soon as it is safe to do so, and to continue such therapy until the INR is within the therapeutic range for 2 consecutive days. In a case series of 208 patients followed 2 weeks after insertion of a prosthetic heart valve, Montalescot and associates found that therapeutic levels were more rapidly and more predictably achieved with LMWH than with unfractionated heparin. Major bleeding was the same in both groups. There was one stroke in the unfractionated heparin group and none in the LMWH group.

**St. Jude medical bileaflet mechanical valve**

Experience with St. Jude Medical bileaflet mechanical valves is shown in Table 2. Horstkotte and associates, among patients with St. Jude Medical valves in the aortic position, showed that less-intense anticoagulation, at an estimated INR of 1.8 to 2.8, in comparison to an estimated INR of 2.5 to 3.5, resulted in an increase in the rate of thromboembolism from 2.8 to 3.9%/yr, and a reduction in the rate of major bleeding from 1.25 to 0.4%/yr.
These results formed the hypothesis for the randomized multicenter GELIA (German experience with low intensity anticoagulation) study,\textsuperscript{102} which enrolled 2,848 patients accounting for 8,061 follow-up years.\textsuperscript{103} The GELIA data demonstrated no significant influence of the intensity of OAC (among patients randomized to target INR ranges of 3.0 to 4.5, 2.5 to 4.0, and 2.0 to 3.5) on the incidence of thromboemboli as well as bleeding.\textsuperscript{104} However, all of the target range INRs overlapped, and frequently the INRs were out of target range.\textsuperscript{104} Instability of OAC therapy was increasing the target range without an increase in thromboembolic rates.\textsuperscript{105} Among patients, 82% of whom had St. Jude Medical valve in the aortic position, thromboemboli were not more frequent at an INR of 1.8 to 2.0 than at an INR of 3.0 to 4.5, providing the higher value was among patients who underwent a coronary artery bypass graft as well.

Among patients with St. Jude Medical valves in the mitral position, rates of thromboemboli were somewhat higher than in the aortic position. With an estimated INR of 2.4 to 2.8, Baudet and associates\textsuperscript{98} showed thromboemboli or valve thrombosis with the mitral valve at a rate of 2.2%/yr and a rate of 1.1%/yr thromboemboli or valve thrombosis in the aortic position. In the GELIA study,\textsuperscript{104} linearized rates for bleeding (grade II, bleeding treated as an outpatient) were not statistically different with the treatment groups (INR 3.0 to 4.5, 2.5 to 4.0, or 2.0 to 3.5. However, the frequency of severe bleeding complications (grade III, requiring hospitalization) decreased with decreasing the target range without an increase in thromboembolic events.\textsuperscript{104} 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 for thromboembolic events were 0.78%/yr and bleeding events were 2.50%/yr.\textsuperscript{109} Some studies showed comparable results with lower target ranges of INR of only 1.4,\textsuperscript{110} or 1.5,\textsuperscript{111} but the actual range used was wide\textsuperscript{110} or not stated.\textsuperscript{110,111}

### Other bileaflet mechanical valves

Based on an analysis of published data, David and associates\textsuperscript{112} 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 CarboMedics (Austin, TX) bileaflet valve. Abe and associates,\textsuperscript{113} in patients with a CarboMedics bileaflet valve in the aortic position, mitral position, or both, showed ap-

![Table 2—Thromboemboli With St. Jude Medical Bileaflet Mechanical Valves in Patients Who Received Prophylaxis With Coumarin Derivatives](https://www.chestjournal.org/CHEST/126/3/SEPTEMBER,2004.SUPPLEMENT/465S)

<table>
<thead>
<tr>
<th>Valve</th>
<th>Patients, No.</th>
<th>INR</th>
<th>Valve Thrombosis, %/yr</th>
<th>Thromboemboli, %/yr</th>
<th>Source</th>
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<tr>
<td>Aortic</td>
<td>1,431*</td>
<td>1.8–2.0</td>
<td>0.7–0.8</td>
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<tr>
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<td>Horstkotte et al\textsuperscript{101}</td>
<td></td>
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<td>Aortic</td>
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<td>2.5–3.5†</td>
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<tr>
<td>Aortic</td>
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<td>0</td>
<td>Vogt et al\textsuperscript{124}</td>
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<tr>
<td>Aortic</td>
<td>192</td>
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<tr>
<td>Aortic</td>
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<td>3.0–4.5†</td>
<td></td>
<td>Horstkotte et al\textsuperscript{101}</td>
<td></td>
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<tr>
<td>Aortic</td>
<td></td>
<td>4.0–6.0</td>
<td>1.9</td>
<td>Horstkotte et al\textsuperscript{101}</td>
<td></td>
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<tr>
<td>Mitral</td>
<td></td>
<td>1.5–2.8†</td>
<td>6.5</td>
<td>Horstkotte et al\textsuperscript{101}</td>
<td></td>
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<tr>
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<td>207</td>
<td>2.4–2.8†</td>
<td>0.4</td>
<td>Baudet et al\textsuperscript{105}</td>
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<tr>
<td>Mitral</td>
<td>120</td>
<td>2.5–3.5</td>
<td>0.8</td>
<td>Laffort et al\textsuperscript{100}</td>
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<tr>
<td>Mitral</td>
<td>80</td>
<td>2.5–3.0</td>
<td>0.6</td>
<td>Fiore et al\textsuperscript{125}</td>
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<td>2.5</td>
<td>Horstkotte et al\textsuperscript{101}</td>
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</tbody>
</table>

* Aortic, n = 904; aortic plus mitral, n = 527.
† Estimated.
‡ Aortic valves, 96%; St. Jude Medical valves, 82%.
proximately 1.1%/yr thromboemboli or thrombosis with an INR of 2.0 to 3.5. Wang and associates 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. Others with the CarboMedics valve or the Duromedic (Baxter Healthcare, Edwards Division; Santa Ana, CA) valve used wider ranges of the target INR, so a safe lower value could not be assessed.

The Sorin bicarbon bileaflet valve (Sorin Biomedica Cardio; Saluggia, Italy), in patients with the valve in the aortic position, using an INR of 2.0 to 3.0, showed thromboemboli in 1.2%/yr. In the mitral position, using an INR of 3.0 to 4.0, the rate of thromboemboli was 0.7%/yr.

Monoleaflet or tilting disk valves

Among patients with an Omnicarbon monoleaflet valve (MedicalCV; Minneapolis, MN) in the aortic position, using an INR of 2.5 to 3.5, a rate of thromboemboli of 0.7%/yr was shown. Others, using a lower INR of 2.0 to 3.0 found the rate of thromboemboli to be no higher. In the mitral position, with an INR of 2.5 to 3.5 or 3.0 to 4.0, the rate of thromboemboli of was 0.9 to 1.1%/yr.

The Sorin Monostrot valve (Sorin Biomedica Cardio) showed more thromboemboli when in the mitral position than in the aortic position. The range of INR used in this case series (2.5 to 4.0) was too broad to assess whether a low INR would be effective.

Regarding the Bjork Shiley spherical disc valve, and the Bjork Shiley Convexo Concave valve, there are no investigations that use an INR of 2.0 to 3.0 or 2.5 to 3.5. Therefore, whether such levels of the INR can be used safely with these valves is undetermined (Table 3). However, in one case series that included 1,354 tilting disc valves, patients with tilting disc valves had the lowest rate of complications with an INR of 3.0 to 3.9, although an INR of 4.0 to 4.9 gave comparable results.

Anticoagulant prophylaxis in patients with Medtronic Hall valves (Medtronic; Minneapolis, MN) has been described. A low level of the INR (2.0 to 3.0) gave good results in a case series of patients with Medtronic Hall valves in the aortic position Table 3. An INR of 2.5 to 3.5 showed a trend toward a higher frequency of thromboemboli than an INR of 3.0 to 4.5 in patients with Medtronic Hall valves in the mitral position. However, in one case series that included 1,354 tilting disc valves, patients with tilting disc valves had the lowest rate of complications with an INR of 3.0 to 3.9, although an INR of 4.0 to 4.9 gave comparable results.

Table 3—Thromboemboli in Patients With Tilting Disc Valves Treated With Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Variables</th>
<th>Aortic Position</th>
<th>Mitral Position</th>
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<tbody>
<tr>
<td></td>
<td>Valve</td>
<td>Patients, No.</td>
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<tr>
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<td>Thromboemboli, %/yr</td>
<td>INR</td>
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<td>Medtronic Hall</td>
<td>2.0 – 3.5†</td>
<td>176</td>
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<tr>
<td>Medtronic Hall</td>
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<tr>
<td>Bjork Shiley</td>
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<td>109</td>
</tr>
<tr>
<td>Spherical Disc</td>
<td>3.0 – 4.0</td>
<td>162</td>
</tr>
<tr>
<td>Bjork Shiley</td>
<td>3.0 – 4.0</td>
<td>120</td>
</tr>
<tr>
<td>Converge Concave</td>
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<td></td>
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<table>
<thead>
<tr>
<th>Source</th>
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<td>Akins</td>
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<tr>
<td>Vallejo et al.</td>
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<tr>
<td>Sethia et al.</td>
<td>114</td>
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</tbody>
</table>

*Table includes only investigations of ≥ 100 patients with valves in aortic position and valves in mitral position.
†Aortic valves INR, 2.0–3.0; mitral valves INR, 2.5–3.5.
‡Estimated.

Other valves

Saour and associates, in a randomized trial among patients with various types of mechanical valves, showed similar thromboembolic event rates (3.7%/yr vs 4%/yr) in patients treated with vitamin K antagonists at an average INR of 9.0 and at an average INR of 2.7 respectively. More frequent major bleeding, however, was shown in the group assigned to the higher INR. These conclusions, however, are based on intention-to-treat analysis. Although either level of anticoagulation 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 of the target range of 7.4 to 10.8.

Pengo and associates, in patients with various valves (60% tilting disc valves, 1% ball valves) in the aortic, mitral, or both positions, reported a rate of thromboembolic of 1.8%/yr when an INR of 2.5 to 3.5, and a comparable rate of 2.1%/yr with an of INR 3.5 to 4.5. In a case series that included 53 patients with caged ball and caged disk valves, Cannegieter and associates found 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 modern valves

The frequency of thromboemboli is lower with modern valves than with first-generation valves. At an INR of 2.0
to 2.9, the frequency of thromboemboli 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.107 Trends also suggested that patients with bileaflet valves showed fewest adverse effects at an INR of 2.0 to 2.9, whereas patients with tilting disk valves had fewest adverse effects at an INR of 3.0 to 3.9.107 Trends in patients with caged ball or caged disk valves showed the lowest frequency of adverse effects at an INR of 4.0 to 4.9.107 It has been suggested that such levels of the INR might be recommended in patients with caged ball or caged disk valves or two mechanical valves, but randomized trials are required to clarify this issue.107

Valve position, number of valves, and valve size

The prevalence of thromboemboli is higher with tilting disk prosthetic valves in the mitral position than in the aortic position (Table 3). This is probably true with bileaflet mechanical valves as well, but data that used strict criteria for the measurement of the INR are sparse (Table 2). Cannegieter and associates,107 in a case series, showed an incidence of thromboembolism of 0.5%/yr with prosthetic aortic valves, 0.9%/yr with prosthetic mitral valves, and 1.2%/yr with both aortic and mitral valves. In the GELIA study,109 less intensive anticoagulation (INR, 2.0 to 3.5) was associated with a significantly (p < 0.005) lower survival than with more intensive anticoagulation (INR, 2.5 to 4.5) only after double (mitral plus aortic) valve replacement. Irrespective of the type of mechanical valve, if the valve was in the aortic position, an INR of 2.0 to 2.9 gave results comparable to an INR of 3.0 to 3.9.107 Valve size was not identified as an independent predictor of thromboembolic complications after valve replacement.128

In summary, permanent therapy with vitamin K antagonists offers the most consistent protection in patients with mechanical heart valves. Levels of vitamin K antagonists that prolong the INR to 2.0 to 3.0 appear satisfactory for patients with St. Jude Medical bileaflet and Medtronic Hall tilting disk mechanical valves in the aortic position, provided they are in sinus rhythm and the left atrium is not enlarged.101,106,122 Presumably, this is also true for the CarboMedics bileaflet valve, based on the observation of no clinically important difference in the rate of systemic embolism with this valve and the St. Jude Medical bileaflet valve.112 Levels of vitamin K antagonists that prolong the INR to 2.5 to 3.5 are satisfactory for tilting disk valves and bileaflet prosthetic valves in the mitral position.101,107,122 Experience in patients with caged ball valves who had anticoagulant levels reported in terms of the INR is sparse, because few such valves have been inserted in recent years.107,128 The number of surviving patients with caged ball valves continues to decrease. It has been suggested that the most advantageous level of the INR in patients with caged ball or caged disk valves should be as high as 4.0 to 4.9.107 However, others106 have shown a high rate of major hemorrhage with an INR that is even somewhat lower, 3.0 to 4.5. The problem is self limited, however, because few such valves are being inserted.

Elderly patients, patients with AF or myocardial infarction, or other risk factors

Higher rates of thromboembolic complications with valves in the mitral position may be attributed to a higher incidence of AF, left atrial enlargement, and perhaps endocardial damage from rheumatic mitral valve disease.105 A low left ventricular ejection fraction, old age, and history of prior thromboembolism also are associated with thromboembolic complications.129 In the absence of data on how to manage patients with prosthetic heart valves who also have AF or who have experienced a myocardial infarction, one must rely on studies of patients who had these conditions but did not have prosthetic heart valves. The risk and benefit of vitamin K antagonists in combination with aspirin has been studied extensively in patients with AF and myocardial infarction who did not have prosthetic heart valves. In Stroke Prevention in Atrial Fibrillation III, the addition of aspirin at 325 mg to vitamin K antagonists (INR range, 1.2 to 1.5) resulted in significantly more strokes than with an INR of 2.0 to 3.0.110 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 aspirin therapy. Both the Warfarin, Aspirin, Reinfarction Study (WARIS)-II and Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-2 trials, in patients with acute coronary syndromes, showed that aspirin, 81 mg/d, combined with an INR of approximately 2.0 to 3.0 or a vitamin K antagonist alone at an INR of approximately 3.0 to 4.0, when compared to aspirin alone, gave comparable reductions of stroke, recurrent myocardial infarction, and death.131,132 Therefore, it is reasonable to expect that patients with prosthetic heart valves who have experienced a recent acute coronary event would benefit from the addition of aspirin, 81 mg/d, in combination with an INR of 2.0 to 3.0. Alternatively, INR of 3 to 4 without aspirin may give comparable results.

Cannegieter and associates107 showed that the risk of thromboembolism and of bleeding was highest among patients ≥ 70 years old. However, among elderly patients (≥ 70 years old), a retrospective case series108 suggested that a low level of vitamin K antagonists was satisfactory with St. Jude Medical valves in the aortic position. Many of these patients were treated before the INR was in use, but in recent years an INR of 1.8 to 2.5 was satisfactory.

Children

Antithrombotic therapy in children with prosthetic heart valves is discussed in the chapter on Antithrombotic Therapy in Children, by Michelson and associates, in this Supplement.

Aspirin in combination with vitamin K antagonists

Meta-analysis supports the concept that the rate of thromboemboli is diminished with aspirin in combination
with vitamin K antagonists. Among the investigations reviewed in this meta-analysis, however, major bleeding was increased.

In individual investigations, Turpie and associates, in a randomized trial of patients with various types of prosthetic valves, showed that aspirin, 100 mg/d, in combination with vitamin K antagonists at a target INR of 3.0 to 4.5, was associated with fewer major systemic thromboemboli than vitamin K antagonists alone: 1.6%/yr vs 4.6%/yr (p = 0.039). The rate of major bleeding, 8.5%/yr with aspirin plus vitamin K antagonists vs 6.6%/yr with vitamin K antagonists alone, was not statistically significantly different. However, the combined event rates of major bleeding plus major thromboembolism with aspirin plus vitamin K antagonists, 10.1% compared to vitamin K antagonists alone, 11.2% were comparable. The fact that the INRs were within the target range 40% of the time and below the target range 49% of the time weakens any conclusions about the added benefit of aspirin compared to well-controlled anticoagulation alone.

Meschengieser and associates, in a randomized, open-label trial that excluded those with hemorrhagic tendencies or prior GI bleeding, showed that aspirin, 100 mg/d, in combination with vitamin K antagonists at an INR of 2.5 to 3.5 was as effective as vitamin K antagonists at an INR of 3.5 to 4.5 in patients, most of whom had a caged ball or tilting disk valve. The frequency of thromboemboli or valve thrombosis was 1.3%/yr with aspirin in combination with the lower-intensity anticoagulation, and 1.5%/yr with the more intense anticoagulation without aspirin. Major bleeding was comparable, 1.1%/yr, with aspirin in combination with the lower-intensity anticoagulation, and 2.3%/yr with the more intense anticoagulation alone. However, here again the degree of control of the INR was an issue because the INRs in patients in the warfarin-plus-aspirin group were in the target range 47% of the time, whereas the warfarin-alone group was within the target range only 36% of the time. The warfarin-alone group was below target range more often (40% vs 28%), resulting in the levels of anticoagulation achieved for the two groups to be closer than the protocol indicated. By contrast, in the large case series reported by Cannegieter and associates, the thromboembolic rate was only 0.7%/yr in patients whose INRs were within the target range of 3.6 to 4.8 for 61% of the time.

Aspirin in combination with warfarin appears to increase the risk of major bleeding in comparison to warfarin alone especially if the INR is high (Table 4). Aspirin in low doses (100 mg/d) in patients whose INR was 2.0 to 3.5 was associated with major bleeding ranging from 1.1 to 5.1%/yr. If the INR was higher, 3.0 to 4.5, major bleeding with aspirin 100 mg/d occurred in 8.5%/yr. With somewhat higher doses of aspirin (200 to 325 mg/d) at the same INR, an unacceptable rate of major bleeding (19.2%/yr) was observed by some, but not by others (3.4%/yr). With high doses of aspirin, 650 to 660 mg/d, major bleeding with an INR of 2.0 to 3.0 occurred in 3.8 to 5.1%/yr. At an INR of 3.0 to 4.5, the rate of major bleeding with this dose of aspirin was unacceptable (24.7%/yr).

In a randomized trial that compared anticoagulation at an INR of 2.5 to 3.5 with or without aspirin, 200 mg/d, major bleeding occurred in 8.3%/yr of patients who were treated with vitamin K antagonist alone. The high rate of major bleeding among patients treated with vitamin K antagonist plus aspirin (19.2%/yr) may reflect the unusually high rate of major bleeding in all patients, including those treated with vitamin K antagonist alone. While it appears that aspirin combined with warfarin may reduce thromboembolic complications, it also appears that the risk of bleeding is increased. Because of relatively poor INR control in several of these trials, it is difficult to resolve the question of how well-controlled anticoagulation compares with anticoagulation plus aspirin. The combination of vitamin K antagonists and aspirin may be particularly useful in patients with prosthetic valves who have coronary artery disease or stroke.

<table>
<thead>
<tr>
<th>INR</th>
<th>Aspirin, mg/d</th>
<th>Dipyridamole, mg/d</th>
<th>Valve</th>
<th>Thrombosis, %/yr</th>
<th>Thromboemboli, %/yr</th>
<th>Major Hemorrhage, %/yr</th>
<th>Source</th>
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<tr>
<td>2.0–2.5</td>
<td>200</td>
<td>300</td>
<td>St. Jude Medical</td>
<td>0</td>
<td>1.5</td>
<td>1.3</td>
<td>Kontozis et al</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>200</td>
<td>300</td>
<td>St. Jude Medical</td>
<td>0</td>
<td>0.6</td>
<td>1.6</td>
<td>Skudlicky et al</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>100</td>
<td>Various</td>
<td>Various</td>
<td>0</td>
<td>0.5</td>
<td>3.6</td>
<td>Altman et al</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>650</td>
<td>Various</td>
<td>Various</td>
<td>0</td>
<td>1.1</td>
<td>5.1</td>
<td>Altman et al</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>660</td>
<td>150</td>
<td>Bicer, Bjork Shiley</td>
<td>0</td>
<td>1.9</td>
<td>3.8</td>
<td>Altman et al</td>
</tr>
<tr>
<td>2.5–3.5</td>
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<td>St. Jude Medical</td>
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<td>0.9</td>
<td>19.2</td>
<td>Laffort et al</td>
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<td>2.8</td>
<td>5.1</td>
<td>Albertal et al</td>
<td></td>
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<tr>
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<td>1.3</td>
<td>1.1</td>
<td>Meschengiesen et al</td>
<td></td>
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<tr>
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<td>2.0</td>
<td>3.4</td>
<td>Albertal et al</td>
<td></td>
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<tr>
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<td>5.5</td>
<td>Turpie et al</td>
<td></td>
<td></td>
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<tr>
<td>3.0–4.5</td>
<td>660</td>
<td>150</td>
<td>St. Jude Medical, Bjork Shiley</td>
<td>0</td>
<td>4.9</td>
<td>24.7</td>
<td>Altman et al</td>
</tr>
</tbody>
</table>
Dipyridamole in combination with vitamin K antagonists

Two case series\textsuperscript{137,138} reported the use of dipyridamole, 300 mg/d, in combination with warfarin (INR, 2.0 to 2.5) among patients with St. Jude Medical aortic, mitral, and double valves. The frequency of thromboemboli was 0.6%/yr and 1.5%/yr; major hemorrhage occurred in 1.3%/yr and 1.6%/yr.\textsuperscript{137,138} Data are insufficient to recommend dipyridamole over low doses of aspirin in combination with warfarin. Whether dipyridamole plus aspirin is more effective than aspirin alone when used with warfarin is undetermined.

Fixed-dose warfarin plus APAs

Katircioglu and associates\textsuperscript{139} used a fixed dose of warfarin (2.5 mg/d) in combination with aspirin (100 mg/d) and dipyridamole (225 mg/d). In patients with St. Jude Medical aortic valves, they showed thromboemboli at a rate of 1.4%/yr with no valve thrombosis. Using the same regimen, also in patients with St. Jude Medical aortic, mitral, and double-valve replacements, Yamak and associates\textsuperscript{139} showed thromboemboli in 0.7%/yr, valve thrombosis in 0.8%/yr, and major bleeding in 1.2%/yr.

APAs alone

In patients with St. Jude Medical aortic valves, dipyridamole plus aspirin, but no warfarin, resulted in valve thrombosis or arterial thromboemboli in 2.1 to 3.2%/yr.\textsuperscript{141,142} Others, with the Smeloff-Cutter ball valve showed valve thrombosis or thromboemboli at a rate of 0.9%/yr with valves in the aortic position.\textsuperscript{143} With aspirin alone, a few patients with older model valves had thromboemboli at a rate of only 0.41 to 0.80%/yr.\textsuperscript{144} An investigation by Schlitt et al\textsuperscript{145} compared clopidogrel plus aspirin with vitamin K antagonist alone in patients with aortic mechanical heart valves. The trial was stopped prematurely after 50 days of therapy due to a nonfatal aortic valve thrombosis in one of 11 patients in the platelet arm. High rates of thrombosis and thromboemboli were observed in children and adolescents, however. Rates of thrombosis or thromboemboli in children or adolescents with St. Jude Medical prosthetic valves reached 31 to 68%/yr with aortic valves and 19 to 22%/yr with mitral valves when treated only with APAs.\textsuperscript{146,147}

Interruption of anticoagulant therapy for major surgery, management of patients including home monitoring of INR, management of major bleeding, reversal of anticoagulation with vitamin K<sub>1</sub>, and management of pregnancy

These subjects are discussed in the chapter by Ansell and associates on Vitamin K Antagonists, Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range in this Supplement, and also in the chapter on Use of Antithrombotic Agents During Pregnancy by Ginsberg and Hirsh. Also, see the following discussion on LMWH.

Aortic valve reconstruction

No valve thrombosis or thromboemboli were reported in patients who received aspirin, 100 mg/d, following aortic valve reconstruction.\textsuperscript{148,149}

LMWH

The use of LMWH in patients with mechanical prosthetic heart valves was reviewed in 2002.\textsuperscript{150} Short-term perioperative use for noncardiac procedures in 114 patients was not associated with thromboemboli.\textsuperscript{150} In 16 patients with intolerance to vitamin K antagonists, long-term use of LMWH was not associated with any thromboembolism.\textsuperscript{150} In 10 patients during pregnancy, however, use of LMWH resulted in thromboemboli in 20%, although in another study of 13 patients during pregnancy, there were no thromboemboli.\textsuperscript{150} This issue has drawn considerable attention since the package insert of enoxaparin specifically cautions that it is not indicated for prosthetic heart valve patients, pregnant patients, or pregnant patients with heart valves. It should be recognized, however, that this caution is not a “contraindication” or even a “black box” warning. Further, the available data regarding the use of unfractionated heparin in these patients suggest that similar limitations exist for unfractionated heparin.\textsuperscript{151,152}

Available data suggest that neither adjusted-dose unfractionated heparin nor fixed-dose LMWH provide adequate protection in pregnant patients with mechanical heart valves.\textsuperscript{151–153} However, because there is evidence to show that the pharmacokinetics of LMWH change over the course of pregnancy,\textsuperscript{154–157} it has been suggested that LMWH may provide superior protection against thromboembolism if the dose is adjusted throughout pregnancy based either on anti-Xa levels,\textsuperscript{154,155,157} the patient’s changing body weight,\textsuperscript{154,155} or against elevations in such indicators of clotting activation as the thrombin-antithrombin complex and D-dimer levels.\textsuperscript{156} It may be, therefore, that LMWH gives adequate protection in nonpregnant patients with prosthetic heart valves and in pregnant patients, provided that the dose of LMWH is adjusted to accommodate for the changes in the pharmacokinetics of LMWH that occur throughout pregnancy. The use of these agents in pregnancy is discussed in more detail in the chapter on Use of Antithrombotic Agents During Pregnancy in this Supplement.

Home monitoring

Home monitoring and self-management will be discussed elsewhere.

Recommendations

5.1. For all patients with mechanical prosthetic heart valves, we recommend vitamin K antagonists (Grade IC+). We suggest administration of unfractionated heparin or LMWH until the INR is stable and at a therapeutic level for 2 consecutive days (Grade 2C).
5.2 For patients with a St. Jude Medical bileaflet valve in the aortic position, we recommend a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1A].

5.3 For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, we recommend a target INR of 3.0 (range, 2.5 to 3.5) [Grade 1C+].

5.4 For patients with CarboMedics bileaflet valves or Medtronic Hall tilting disk mechanical valves in the aortic position, with normal left atrium size and in sinus rhythm, we recommend a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1C+].

5.5 In patients who have mechanical valves and additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction, we recommend a target INR of 3.0 (range, 2.5 to 3.5), combined with low doses of aspirin, 75 to 100 mg/d (Grade 1C+).

5.6.1 For patients with caged ball or caged disk valves, we suggest a target INR of 3.0 (range, 2.5 to 3.5) in combination with aspirin, 75 to 100 mg/d (Grade 2A).

5.6.2 For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, we recommend aspirin, 75 to 100 mg/d, in addition to vitamin K antagonists, and maintenance of the INR at target of 3.0 (range, 2.5 to 3.5) [Grade 1C+].

5.7 In patients with prosthetic heart valves in whom vitamin K antagonist must be discontinued, we recommend LMWH (Grade 1C).

6.0 Prosthetic Heart Valves—Bioprosthetic Valves

6.1 First 3 months after valve 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.158,159 Among patients with bioprosthetic valves in the mitral position, Ionescu and associates159 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 al160 reported strokes during the first postoperative month at a rate of 40%/yr. The regimen for prophylaxis was variable. Heras and associates158 showed that vitamin K antagonists (estimated INR, 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 days.158 This may have been due to delay in achieving therapeutic levels of the INR. It was suggested that the early administration of heparin might explain why some groups observed lower rates of thromboemboli in patients who received short-term vitamin K antagonists.158 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 4.0, and in 2 of 39 patients (5.1%) with an estimated INR of 2.0 to 2.3.161 These patients also received heparin, 5,000 U q12h. All of the patients with thromboemboli had AF.161 Thromboemboli during the first 3 months after operation may occur in spite of adequate anticoagulation in patients with AF, a history of prior thromboembolism, or thrombi in the left atrium.162

Among patients with bioprosthetic valves in the aortic position who received subcutaneous heparin (22,500 IU/d) and aspirin (100 mg/d) for the first 14 to 22 days after operation, but did not receive vitamin K antagonists, the frequency of thromboemboli during the first 6 months was 1 of 57 cases (1.8%).163 Among patients who received vitamin K antagonists 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.163 However, some showed no advantage of early anticoagulation among patients with bioprosthetic valves in the aortic position.164 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%) among those who received postoperative heparin followed by warfarin.164 Among patients with aortic bioprosthetic valve insertion, aspirin 100 mg/day starting on postoperative day 2 was compared with LMWH starting on postoperative day 1 followed by warfarin (INR 2.0-3.0) (164.1). During the first 3 months after insertion, comparing aspirin to warfarin, the frequency of cerebral ischemic events was comparable, 3 of 141, (2.1%) vs 5 of 108 (4.6%), and the frequency of major bleeding was also comparable, 3 of 141 (2.1%) vs 4 of 108 (3.7%).164

In summary, patients with bioprosthetic valves in the mitral position, as well as patients with bioprosthetic valves in the aortic position, may be at risk of thromboemboli during the first 3 months after operation.158 In a randomized trial161 among patients with bioprosthetic valves in the mitral position, administration of vitamin K antagonists at an INR of 2.0 to 2.3 was as effective as an INR of 2.5 to 4.0, and was associated with fewer bleeding complications during the first 3 months after operation. In patients with bioprosthetic valves in the aortic position, aspirin was as effective as LMWH followed by warfarin.164

**Recommendations**

6.1.1 For patients with bioprosthetic valves in the mitral position, we recommend vitamin K antagonists with a target INR of 2.5 (range, 2.0 to 3.0) for the first 3 months after valve insertion (Grade 1C+).

6.1.2 For patients with bioprosthetic valves in the aortic position, we suggest vitamin K antagonists with a target INR of 2.5 (range, 2.0 to 3.0) for the first 3 months after valve insertion or aspirin 80 to 100 mg/day (Grade 1C).

6.1.3 In patients who have undergone valve replacement, we suggest heparin (low molecular weight or un-
fractionated) until the INR is stable at therapeutic levels for 2 consecutive days (Grade 2C).

6.1.4. For patients with bioprosthetic valves who have a history of systemic embolism, we recommend vitamin K antagonists for 3 to 12 months (Grade 1C).

6.1.5. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, we recommend vitamin K antagonists with a dose sufficient to prolong the INR to a target of 2.5 (range, 2.0 to 3.0) [Grade 1C].

Values and preferences: This recommendation places a relatively high value on preventing thromboembolic events and a relatively lower value on bleeding complications.

6.2 Long-term treatment

Patients with bioprosthetic valves, whether porcine or pericardial, have a long-term risk for thromboemboli of 0.2 to 3.3%/yr (Table 5).165–175 The risk of thromboembolic stroke in patients with bioprosthetic valves in the aortic position is 0.2%/yr if they are in sinus rhythm.176 A low ejection fraction or large left atrium may be considered as potential contributing causes to late-occurring thromboemboli in patients with bioprosthetic valves.129 A permanent pacemaker also appears to increase the risk of thromboemboli in patients with bioprosthetic valves.177

Patients treated with APAs appear to have a lower rate of late thromboemboli,178–181 Aspirin,178,179,181 aspirin plus dipyridamole,180 or ticlopidine179 in patients with bioprosthetic valves in the aortic or mitral position were complicated by thromboemboli at a rate of ≤ 0.8%/yr. Some, however, showed that aspirin was not effective in reducing the rate of thromboemboli.182

Thromboembolism in patients with bioprosthetic valves who are in AF presumably relates to both the bioprosthetic valve and to the AF (see the chapter on Antithrombotic Therapy in Atrial Fibrillation in this Supplement by Laupacis and associates.) The occurrence of thromboemboli in these patients was reported to be as high as 16% at 31 to 36 months.183,184 Randomized trials in patients with AF who did not have prosthetic valves showed that long-term vitamin K antagonists are effective, and they are more effective than aspirin.

Recommendations

6.2.1. In patients with bioprosthetic valves who have AF, we recommend long-term treatment with vitamin K antagonists with a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1C+].

6.2.2. For patients with bioprosthetic valves who are in sinus rhythm and do not have AF, we recommend long-term therapy with aspirin, 75 to 100 mg/d (Grade 1C+).

7.0 Infective Endocarditis and Nonbacterial Thrombotic Endocarditis

With the advent of effective antimicrobial therapy, the incidence of systemic emboli in infective endocarditis has decreased. In the preantibiotic era, clinically detectable emboli occurred in 70 to 97% of patients with infective endocarditis,185 while, since that time, the prevalence has

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Table 5—Thromboemboli With Bioprosthetic Valves After the First 3 Months

<table>
<thead>
<tr>
<th>Valves/Patient-Years</th>
<th>Valve Thrombosis, %/yr</th>
<th>Thromboemboli, %/yr</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine aortic</td>
<td>3.361</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>4.049*</td>
<td>0</td>
<td>1.2*</td>
<td>Khan et al170</td>
</tr>
<tr>
<td>1.673</td>
<td>0</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Pericardial aortic</td>
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<td>1.8</td>
</tr>
<tr>
<td>3.81</td>
<td>0</td>
<td>1.0</td>
<td>Nakajima et al165</td>
</tr>
<tr>
<td>3.624</td>
<td>0</td>
<td>1.0</td>
<td>Neville et al171</td>
</tr>
<tr>
<td>408</td>
<td>0</td>
<td>0.2</td>
<td>Borowiec et al174</td>
</tr>
<tr>
<td>Porcine mitral</td>
<td>3.128</td>
<td>0</td>
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</tr>
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<td>1.0*</td>
<td>David et al175</td>
</tr>
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<td>1.781</td>
<td>0</td>
<td>2.6</td>
<td>Khan et al170</td>
</tr>
<tr>
<td>Pericardial mitral</td>
<td>969</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Porcine aortic, mitral, or &gt; 1</td>
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<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>17.471</td>
<td>0</td>
<td>2.4</td>
<td>Jamieson et al165</td>
</tr>
<tr>
<td>5.464</td>
<td>0</td>
<td>2.1</td>
<td>Jamieson et al172</td>
</tr>
<tr>
<td>Pericardial aortic, mitral, or &gt; 1</td>
<td>3,000</td>
<td>0.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*Estimated.
been reported to be 12 to 40%. Emboli occur more frequently in patients with acute endocarditis than in those with subacute disease, and the incidence of pulmonary emboli in right-sided endocarditis is particularly high. Cerebral emboli are considerably more common in mitral valve endocarditis than in infection of the aortic valve; interestingly, this observation is not explained by the occurrence of AF. While embolic rate (in terms of events per patient-week) has not been reported in endocarditis (to our knowledge), considering the relatively short course of the disease, an unusually high event per unit time may be inferred.

The use of anticoagulant therapy in infective endocarditis was initially introduced in the sulfonamide era, not as a means of preventing thromboembolism but to improve the penetration of antibiotic into the infected vegetations. While complications of this therapy were not always encountered, most workers reported an alarming incidence of cerebral hemorrhage, and it was suggested that the routine use of anticoagulant therapy in patients with endocarditis should be abandoned. However, the issue remained controversial. While reference to the early adverse experience of anticoagulant therapy in endocarditis frequently has been made, Lerner and Weinstein concluded that anticoagulants were "probably not contraindicated" in infective endocarditis.

With the advent of echocardiography, means of identifying the patient at risk for embolization have been proposed, and a high correlation between echocardiographically demonstrable vegetations and embolism has been reported. However, in a review of this subject, O'Brien and Geiser report that 80% of patients with infective endocarditis have vegetations detected by echocardiography, while only one third have systemic emboli. TEE has added a further dimension to the diagnostic accuracy of endocarditis. Indeed, Popp concluded that "the current state of the art in transesophageal echocardiographic 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 al determined that both the size and the mobility of the vegetation when evaluated by TEE were potent independent predictors of embolic events. In this study, there was a 60% incidence of embolic events in those patients with a vegetation > 10 mm; this 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 al 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 related to the size of the vegetation > 10 mm when the microorganism was Staphylococcus or the vegetation was located on the mitral valve. 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 study of the rate of cerebral embolic events in relation to antibiotic and anticoagulant therapy in patients with infective endocarditis, 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 the patient with a special indication, e.g., the patient with mitral valve disease and the recent onset of AF, appropriate anticoagulant therapy should not be withheld.

The patient with prosthetic valve endocarditis deserves special comment. With the exception of those patients with bioprostheses in normal sinus rhythm, patients with prosthetic valves are at constant risk of thromboembolism and there are important reasons not to interrupt anticoagulant therapy in this circumstance. The risks of thromboembolic events in prosthetic valve endocarditis are higher than that in native valve endocarditis; emboli have been reported in 50 to 88% of patients with prosthetic valve endocarditis. However, opinion is divided on the effectiveness of anticoagulation in reducing the number of embolic events associated with prosthetic valve endocarditis. Wilson et al reported CNS complications in only 3 of 38 patients with prosthetic valve endocarditis who received adequate anticoagulant therapy, while events were observed in 10 of 14 patients who received either inadequate or no anticoagulation. However, Yeh et al found that adequate anticoagulation failed to control emboli during prosthetic valve endocarditis, and the risk of bleeding appears to be greater among patients with infected prostheses. Pruitt and associates found that 23% of the hemorrhagic events occurred in the 3% of patients receiving anticoagulants, and a 50% incidence of hemorrhage was observed by Johnson in patients with prosthetic valve endocarditis treated with anticoagulants. Other workers as well have reported a high incidence of intracranial hemorrhage in patients who received anticoagulation therapy with prosthetic valve endocarditis.

Thus, the use of anticoagulants in prosthetic valve endocarditis must steer a path between the Scylla of thromboembolism and the Charybdis of serious bleeding. There seems little doubt that the risk of the former is substantial without the protection of continued anticoagulation, yet the consequence of intracranial hemorrhage may be irreversible and not infrequently fatal. It should be appreciated that embolic events in prosthetic valve endocarditis may represent dislodged vegetations or, alternatively, true thromboembolism unrelated to the valve infection. While the incidence of the latter can be expected to be reduced by anticoagulation therapy, there is no evidence that embolic vegetations are controlled by this therapy. Nevertheless, most workers suggest that long-term anticoagulant therapy should be continued in patients with prosthetic valve endocarditis, while others express some doubt about its value. Since the most serious and potentially lethal complications of cerebral embolic events are due to intracranial bleeding, CT scanning may provide the means of identifying the patient at high risk for such complications. Based on experience in patients without endocarditis, the Cerebral Embolism
Study Group recommends that in nonhypertensive patients with cardiogenic cerebral emboli, if there is no evidence of hemorrhage on CT scan 24 to 48 h after stroke, immediate anticoagulation should be undertaken, although a delay of 7 days might be more prudent in those patients with large cerebral infarctions. Since the risk of thromboembolism in patients not receiving anticoagulation therapy with bioprostheses who are in normal sinus rhythm is low, anticoagulation therapy is not indicated. A study of 61 patients with prosthetic valve endocarditis found no protective effect of warfarin anticoagulation, and confirmed the observation that antibiotic therapy was more important than anticoagulation in preventing neurologic complications. While Pruitt et al suggest a possible role for antiplatelet drugs in prosthetic valve endocarditis, the utility of this form of therapy has not been established.

The evolution of the syndrome of nonbacterial thrombotic endocarditis (NBTE) has been clearly detailed in a comprehensive review of this disease by Lopez and associates. 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; in 1954, Angrist and Marquis 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%). 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. 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.

Treatment of NBTE is directed toward control of the underlying disease, in most instances neoplasia and/or sepsis, and toward treatment of thromboembolism with or without associated disseminated intravascular coagulation. The most effective agent appears to be heparin, and renewed thromboembolic complications have been reported after heparin therapy was discontinued. Little benefit has been observed with vitamin K antagonist therapy.

The diagnosis of NBTE is not easily made and is considerably more elusive than that of bacterial endocarditis. 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 bacterial endocarditis, are frequently absent, and there is some evidence that echocardiography is less sensitive for the detection of NBTE than it is for bacterial endocarditis.

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

The case for anticoagulant therapy in NBTE is strengthened by the general belief that Trousseau syndrome and NBTE represent a continuum, and that disseminated intravascular coagulation represents the substrate for treating most patients with NBTE. Rogers et al suggest that anticoagulation therapy should be withheld from patients with disseminated cancer when there is no hope of tumor regression; in most instances, a diagnosis of NBTE or a strong suspicion of this diagnosis warrants treatment with IV heparin. 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 neoplasia or chronic debilitating disease.

**Recommendations**

7.0.1. In patients with a mechanical prosthetic valve and endocarditis who have no contraindications, we suggest continuation of long-term vitamin K antagonists (Grade 2C).

7.0.2. For patients with NBTE and systemic or pulmonary emboli, we recommend treatment with full-dose unfractionated IV or subcutaneous heparin (Grade 1C).

7.0.3. For patients with disseminated cancer or debilitating disease with aseptic vegetations, we suggest administration of full-dose unfractionated heparin (Grade 2C).
8.0 Withdrawal of Anticoagulation Therapy Prior to Surgery

Patients with valvular heart disease receiving OAC therapy who require surgical procedures present special problems related to withholding and restarting anticoagulation therapy. The risks of bleeding vs thromboembolism as well as the costs must be carefully balanced. Eckman et al assessed the risks of anticoagulation before and after elective surgery. Reviewing the literature, they concluded that it takes approximately 4 days after stopping vitamin K antagonist therapy for the INR to reach 1.5, and approximately 3 days after restarting therapy for the INR to reach 2. Thus, if vitamin K antagonist therapy is withheld for 4 days preoperatively and restarted as soon as possible after surgery, a patient would be expected to be exposed to the equivalent of 1 day of no anticoagulation the day prior, the day of, and the day after surgery, for a total of 3 days. There is very little information on perioperative thromboembolism in patients with valvular heart disease; thus, we must rely on estimates of embolization based on data regarding mechanical heart valves or AF. In reviewing the currently available data, Kearon and Hirsh assessed the risks of anticoagulation before and after elective surgery. Reviewing the literature, they concluded that it takes approximately 4 days after stopping vitamin K antagonist therapy for the INR to reach 1.5, and approximately 3 days after restarting therapy for the INR to reach 2. Thus, if vitamin K antagonist therapy is withheld for 4 days preoperatively and restarted as soon as possible after surgery, a patient would be expected to be exposed to the equivalent of 1 day of no anticoagulation the day prior, the day of, and the day after surgery, for a total of 3 days.

There is very little information on perioperative thromboembolism in patients with valvular heart disease; thus, we must rely on estimates of embolization based on data regarding mechanical heart valves or AF. In reviewing the currently available data, Kearon and Hirsh concluded the following: (1) in the first month after an acute episode of arterial embolism, preoperative heparin therapy is indicated; however, risk of bleeding complications from heparin postoperatively mitigate against postoperative heparin therapy except for patients undergoing minor surgery where the risk of bleeding is low; (2) in conditions with a lower risk of arterial thromboembolism, their analysis suggests that the postoperative IV heparin therapy increases serious morbidity; and (3) preoperative or postoperative prophylaxis against thromboembolism should be considered for the period during which the INR is < 2.0. This review was followed by several letters to the editor stating that perioperative bleeding complications of heparin administration were less serious than embolic complication of a decreased INR. Use of LMWHs as a “bridging therapy” to surgery after discontinuation of vitamin K antagonist has been proposed. Other approaches include the potential use of newly developed oral direct thrombin inhibitors with a shorter half-life than vitamin K antagonists (such as ximelagatran) may potentially decrease the amount of time that patients are without therapeutic anticoagulation. However, there are little data with regard to these therapeutic approaches. Thus, until clinical trials that specifically target the perioperative management of patients with valvular heart disease requiring vitamin K antagonist anticoagulation prior to surgical procedures are performed, treatment of such patients will remain controversial and we are not making a recommendation.

Summary

The decision to initiate long-term 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 to these factors, for patients who have a prosthetic heart valve, the location as well as the type of valve need to be considered. Because the state of such variables may change with time, a proper decision at one time in a patient’s life may 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 (RCTs), the clinician would do well to review his or her decision at frequent intervals.

Summary of Recommendations

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

For patients with rheumatic mitral valve disease and AF, or a history of previous systemic embolism:

1.1.1. We recommend long-term oral anticoagulant therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C+].

For patients with rheumatic mitral valve disease and AF, or a history of previous systemic embolism:

1.1.2. We suggest clinicians not use concomitant therapy with OAC and APA (Grade 2C).

Underlying values and preferences: This recommendation places a relatively high value on avoiding the additional bleeding risk associated with concomitant OAC and antiplatelet therapy.

For patients with rheumatic mitral valve disease with AF or a history of systemic embolism who suffer systemic embolism while receiving OACs at a therapeutic INR:

1.1.3. We recommend adding aspirin, 75 to 100 mg/d (Grade 1C). For those patients unable to take aspirin, we recommend adding dipyrindamole, 400 mg/d, or clopidogrel (Grade 1C).

1.2 Patients With Mitral Valve Disease in Sinus Rhythm

1.2.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 5.5 cm, we suggest long-term vitamin K antagonist 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 avoiding systemic embolism and its consequences, and a relatively low value on avoiding the bleeding risk and inconvenience associated with OAC therapy.

1.2.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 5.5 cm, we suggest clinicians not use antithrombotic therapy (Grade 2C).

1.3 Patients Undergoing Mitral Valvuloplasty

1.3.1. For patients undergoing mitral valvuloplasty, we suggest anticoagulation with vitamin K antagonists with a target INR of 2.5 (range, 2.0 and 3.0) for 3 weeks prior to the procedure and for 4 weeks after the procedure (Grade 2C).

2.0 MVP

2.0.1. In people with MVP who have not experienced systemic embolism, unexplained TIA, or AF, we recommend against any antithrombotic therapy (Grade 1C).

2.0.2. In patients with MVP who have documented but unexplained TIA, we recommend long-term aspirin therapy, 50 to 162 mg/d (Grade 1A).

2.0.3. In patients with MVP who have documented systemic embolism or recurrent TIAs despite aspirin therapy, we suggest long-term vitamin K antagonist therapy (target INR, 2.5; range, 2.0 to 3.0) (Grade 2C).

3.0 MAC

3.0.1. In patients with MAC complicated by systemic embolism, not documented to be calcific embolism, we suggest treatment with long-term OAC therapy (target INR, 2.5; INR range, 2.0 to 3.0) (Grade 2C).

4.0 Aortic Valve and Aortic Arch Disorders

4.0.1. In patients with aortic valve disease, we suggest that clinicians not use long-term vitamin K antagonist therapy unless they have another indication for anticoagulation (Grade 2C).

4.0.2. We suggest OAC therapy in patients with mobile aortic atheromas and aortic plaques ≥ 4 mm as measured by TEE (Grade 2C).

5.0 Prosthetic Heart Valves—Mechanical Prosthetic Heart Valves

5.1. For all patients with mechanical prosthetic heart valves, we recommend vitamin K antagonists (Grade 1C+). We suggest administration of unfractionated heparin or LMWH until the INR is stable and at a therapeutic level for 2 consecutive days (Grade 2C).

5.2. For patients with a St. Jude Medical bileaflet valve in the aortic position, we recommend a target INR of 2.5 (range 2.0 to 3.0) [Grade 1A].

5.3. For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, we recommend a target INR of 3.0 (range 2.5 to 3.5) [Grade 1C+].

5.4. For patients with CarboMedics bileaflet valve or Medtronic Hall tilting disk mechanical valves in the aortic position, normal left atrium size, and sinus rhythm, we recommend a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1C+].

5.5. In patients who have mechanical valves and additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction, we recommend a target INR of 3.0 (range 2.5 to 3.5), combined with low doses of aspirin, 75 to 100 mg/d (Grade 1C+).

5.6.1. For patients with caged ball or caged disk valves, we suggest a target INR of 3.0 (range, 2.5 to 3.5) in combination with aspirin, 75 to 100 mg/d (Grade 2A).

5.6.2. For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, we recommend aspirin, 75 to 100 mg/d, in addition to vitamin K antagonists, and maintenance of the INR at target of 3.0 (range 2.5 to 3.5) [Grade 1C+].

5.7. In patients with prosthetic heart valves in whom vitamin K antagonist must be discontinued, we recommend LMWH (Grade 1C) or aspirin 80–100 mg/day (Grade 1C).

6.0 Prosthetic Heart Valves—Bioprosthetic Valves

6.1 First 3 months after valve insertion

6.1.1. For patients with bioprosthetic valves in the mitral position, we recommend vitamin K antagonists with a target INR of 2.5 (range 2.0 to 3.0) for the first 3 months after valve insertion (Grade 1C+).

6.1.2. For patients with bioprosthetic valves in the aortic position, we suggest vitamin K antagonists with a target INR of 2.5 (range 2.0 to 3.0) for the first 3 months after valve insertion (Grade 2C) or aspirin 80–100 mg/day (Grade 1C).

6.1.3. In patients who have undergone valve replacement, we suggest heparin (low molecular weight or unfractionated) until the INR is stable at therapeutic levels for 2 consecutive days (Grade 2C).

6.1.4. For patients with bioprosthetic valves who have a history of systemic embolism, we recommend vitamin K antagonists for 3 to 12 months (Grade 1C).
6.1.6. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, we recommend vitamin K antagonists with a dose sufficient to prolong the INR to a target of 2.5 (range 2.0 to 3.0) [Grade 1C].

Values and preferences: This recommendation places a relatively high value on preventing thromboembolic events and a relatively lower value on bleeding complications.

6.2 Long-term Treatment

6.2.1. In patients with bioprosthetic valves who have AF, we recommend long-term treatment with vitamin K antagonists with a target INR of 2.5 (range 2.0 to 3.0) [Grade 1C+].

6.2.2. For patients with bioprosthetic valves who are in sinus rhythm and do not have AF, we recommend long-term therapy with aspirin, 75 to 100 mg/d (Grade 1C+).

7.0 Infective Endocarditis and Nonbacterial Thrombotic Endocarditis

7.0.1. In patients with a mechanical prosthetic valve and endocarditis who have no contraindications, we suggest continuation of long-term vitamin K antagonists (Grade 2C).

7.0.2. For patients with NBTE and systemic or pulmonary emboli, we recommend treatment with full-dose unfractionated IV or subcutaneous heparin (Grade 1C).

7.0.3. For patients with disseminated cancer or debilitating disease with aseptic vegetations, we suggest administration of full-dose unfractionated heparin (Grade 2C).

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