Antithrombotic Therapy in Valvular Heart Disease

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Abbreviations: AF = atrial fibrillation; APA = antiplatelet agent; INR = international normalized ratio; MAC = mitral annular calcification; MR = mitral regurgitation; MVP = mitral valve prolapse; NBTE = nonbacterial thrombotic endocarditis; OAC = oral anticoagulant therapy; PFO = patent foramen ovale; PMV = percutaneous mitral valvuloplasty; RR = relative risk; TEE = transesophageal echocardiography; TIA = transient ischemic attack

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Few complications of valvular heart disease can be more devastating than systemic embolism. It is well recognized that antithrombotic therapy can reduce, although not eliminate, the likelihood of this catastrophe. If this therapy were risk free, all patients with valvular heart disease should be treated. Unfortunately, antithrombotic therapy, particularly with coumarin derivatives or heparin, carries a substantial risk of bleeding; this 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 valvular heart disease and attempt to establish 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.

Basic to these considerations is assessment of the risk of bleeding. For example, it is appreciated that 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, but the benefits of anticoagulation may be offset by the hemorrhagic complications of antithrombotic therapy. It is also important to emphasize that the permanent consequences of a thromboembolic event are generally more serious than the ultimate outcome of many hemorrhagic complications of anticoagulant therapy, and thus the rate of embolic phenomenon is not necessarily counterbalanced by an equal event rate of bleeding.

1. Rheumatic Mitral Valve Disease (Mitral Stenosis and/or Mitral Regurgitation)

The incidence of systemic embolism is greater in rheumatic mitral valve disease than in any other common form of valvular heart disease. While the natural history of this disease has been altered during the past 40 years by surgery and the frequent use of long-term anticoagulant therapy, Wood\(^1\) cited a prevalence of systemic emboli of 9 to 14\% in several large early series of mitral stenosis; in 1961, Ellis and Harken\(^2\) reported that 27\% of 1,500 patients undergoing mitral valvuloplasty had a history of clinically detectable systemic emboli. Among 754 patients followed up for 5,833 patient-years, Szekely\(^3\) observed an incidence of embolism of 1.5%/yr, while the figure was found to vary from 1.5\% to 4.7%/yr preoperatively in six reports of rheumatic mitral valve disease.\(^4\) 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.\(^5\)

The incidence of systemic emboli increases dramatically with the development of atrial fibrillation (AF). Szekely\(^3\) 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\(^6\) 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\(^7\) and by Wood\(^8\) had AF. Among 839 patients with mitral valve disease described by Coulshed and associates,\(^8\) 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 (MR) and normal sinus rhythm, and 22\% of those with MR and AF. Wood\(^9\) confirmed that emboli occur 1.5 times as frequently in mitral stenosis as in rheumatic MR.

The risk of systemic emboli in rheumatic mitral disease is greater in older patients\(^8\)–\(^12\) and those with lower cardiac indexes,\(^9\) but appears to correlate poorly with mitral calcification,\(^9\) mitral valve area,\(^9\) or clinical classification.\(^1,8,9,13\) Indeed, several investigators have pointed out that patients with mitral valve disease with emboli frequently are found to have minor valve disease, and Wood\(^1\) 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. In early studies of rheumatic mitral valve disease, a poor correlation was observed.\(^1,8,13\) While some reports, primarily in patients with nonvalvular AF, suggest that left atrial size is an independent risk factor for thromboembolism,\(^14,15\) a 1998 study\(^17\) describing 1,066 patients with AF found no such relationship.

In a prospective study of > 500 patients with mitral stenosis, Chiang et al\(^16\) 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 period of 36.9 ± 22.5 months. Predictors of embolization for patients in sinus rhythm were age, the presence of a left atrial thrombus, and significant aortic regurgitation. In contrast to previous studies, mitral valve area was 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 was a negative predictor 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,\(^1,5,19,20\) of which 60 to 65% are within the first year\(^19,20\) and most occur within 6 months. Mitral valvuloplasty does not appear to eliminate the risk of thromboembolism.\(^4,6\) 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.

Although never evaluated by randomized trial (to our knowledge), 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, 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.\(^2\) Adams et al\(^21\) 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 only 4 deaths in the treated group. Fleming and Bailey\(^13\) 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%/patient-year. In a retrospective study of 254 patients with AF, an embolic rate of 5.46%/yr was reported for nonanticoagulated patients vs 0.7%/yr for those receiving long-term warfarin therapy.\(^22\)

Perhaps the strongest evidence to date supporting the utility of anticoagulation for the prevention of thromboembolism in mitral valve disease comes from extrapolation of the results of four, large, randomized studies in patients with nonvalvular AF.\(^23-26\) Each of these studies demonstrated that warfarin was effective in reducing stroke in patients with nonvalvular AF. An additional Canadian multicenter trial\(^27\) was terminated prematurely when its results revealed a trend consistent with the data reported in the four earlier trials.

In view of these data, as a general rule, all patients with rheumatic mitral valve disease and AF (paroxysmal or chronic) should be treated with long-term warfarin 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).

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 warfarin therapy. 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, it has been suggested that such patients in normal sinus rhythm with a left atrial diameter > 55 mm should receive anticoagulant therapy.\(^28\)

With the advent of percutaneous balloon mitral valvuloplasty, clinicians are faced with 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 warfarin 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 transesophageal echocardiography (TEE) just prior to balloon mitral valvuloplasty, and if the examination does not reveal a left atrial clot, anticoagulation prior to the valvuloplasty can be avoided.\(^29-30\)

Recently, Abraham et al\(^31\) reported on performing percutaneous transvenous mitral valvuloplasty on 629 relatively young patients (mean age, 29.51 ± 9.9 years) with rheumatic mitral stenosis, normal sinus rhythm, no history of embolism, or echocardiographic evidence of clot without anticoagulation prior, during, or after the procedure. There was no incidence reported of embolism in the immediate postprocedure period or during a median follow-up period of 3 months. However, until this study is reproduced, based on experience with patients undergoing cardioversion of AF, it is suggested that the absence of atrial clot by TEE at the time of the procedure does not preclude the need for prompt anticoagulation after valvuloplasty to prevent thromboembolism. Indeed, one can make a good case for giving anticoagulation therapy to most patients after balloon mitral valvuloplasty for at least 4 weeks.\(^30\) Interestingly, Kang et al\(^32\) reported on 49 patients with mitral stenosis with left atrial appendage thrombi who were otherwise candidates for percutaneous mitral valvuloplasty (PMV).\(^32\) 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). There were no procedure-related complications reported during or after PMV.

In an effort to study the mechanism of decreased embolization in patients with mitral stenosis receiving warfarin therapy, Peverill et al\(^33\) studied peripheral venous and left atrial coagulation activity in mitral stenosis patients receiving warfarin therapy that was withheld prior to valvuloplasty. Their results suggested that warfarin not only reduced systemic coagulation activity but was associated with a greater reduction in left atrial coagulation activity. Recently, Tse et al\(^34\) reported that measures of platelet activation, platelet factor 4, and β-thromboglobulin were significantly elevated in patients with rheumatic
MR when compared with control subjects. Several studies have suggested that systemic embolism in patients with valvular heart disease occurs more frequently in those with shortened platelet survival times.\textsuperscript{35–38} Steele and Rainwater\textsuperscript{46} reported that shortened platelet survival was a sensitive index of past thromboembolism in rheumatic valve disease, but the specificity of this finding was low, since 78% of patients without thromboembolism also had shortened platelet survival. Although sulfinpyrazone appeared to decrease the incidence of thromboembolism in these patients with mitral stenosis, two thirds were also receiving warfarin, and efficacy of sulfinpyrazone as monotherapy for the prevention of thromboembolism remains unproved.\textsuperscript{41}

It has also been shown that shortened platelet survival in patients with prosthetic heart valves can be normalized by sulfinpyrazone\textsuperscript{35} and by dipyridamole.\textsuperscript{36} Similar observations have been made in patients with mitral stenosis treated with sulfinpyrazone\textsuperscript{30,40} and in patients with arterial grafts treated with dipyridamole.\textsuperscript{42} Furthermore, in a randomized study of patients with prosthetic heart valves, the addition of dipyridamole to warfarin therapy proved effective in reducing the incidence of systemic emboli.\textsuperscript{43} Similar findings were reported in a study by Cheseboro et al.\textsuperscript{44} and the combination of dipyridamole, 450 mg/d, and aspirin, 3.0 g/d, was also observed to reduce the incidence of thromboembolism in patients with prosthetic heart valves.\textsuperscript{38} Dale and associates\textsuperscript{45} performed a randomized study 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 al\textsuperscript{46} have 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 Valve prostheses.\textsuperscript{47}

Thus, there is evidence that dipyridamole and sulfinpyrazone 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 warfarin 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 warfarin in randomized trials, patients with rheumatic mitral valve disease considered to be at risk for thromboembolism should be administered warfarin unless the risk of bleeding is unusually high. If this therapy should fail, a platelet-active agent should be added; or, if warfarin is 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 is to be regarded as unclear. There is some evidence that the drug offers little beyond the effect of aspirin administered concomitantly.\textsuperscript{48}

The decision to treat will remain difficult in many cases. For example, should antithrombotic therapy be given to the 35-year-old, physically active man with trivial mitral stenosis and normal sinus rhythm or to the asymptomatic patient with mitral valve disease with AF and history of recurrent GI bleeding? In some instances, decision analysis will help to clarify whether to use antithrombotic therapy.\textsuperscript{49} In others, where the merits of anticoagulant therapy are questionable, the finding of a shortened platelet survival may lead the clinician to recommend the use of platelet-active drugs. In these settings, the patient’s preference may also be important. In all cases, the risks of treatment will be influenced by the choice and dose of the agent to be used.

### 2. Mitral Valve Prolapse

Mitral valve prolapse (MVP) is the most common form of valve disease in adults.\textsuperscript{50} 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\textsuperscript{51} 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.\textsuperscript{52} Similar observations have been made by other investigators,\textsuperscript{53–55} and as many as nine such patients have been reported from a single center.\textsuperscript{55}

Earlier evidence linking MVP to stroke was provided by the case-control study of Barnett and associates.\textsuperscript{56} 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.\textsuperscript{56} However, in a recent study by Gilon at al,\textsuperscript{57} 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.

A pathologic basis for thromboembolism in MVP has been suggested by several investigators. Pomerance\textsuperscript{58} examined the hearts of 35 patients with a ballooning deformity of the mitral valve and found that 10 exhibited a “fibrous endocarditis” of the mitral valve. Guthrie and Edwards\textsuperscript{50} observed endothelial demudation of the mitral valve in patients with myxomatous degeneration with deposits of fibrin on the denuded surface of the valve, and
Mural thrombus has been reported at the junction of a prolapsed mitral leaflet and the atrial wall by Kostuk et al. Tse et al studied patients with MVP with and without MR and found that only the MVP patients with MR had significant platelet activation. They postulated that the mechanism of platelet activation may be due to the turbulent flow in the left atrium caused by the regurgitant jet in the presence of an abnormal valvular surface, and that the activated platelet may then adhere and aggregate on the abnormal mitral valvular surface leading to possible thromboembolism. While clinicopathologic correlations have been lacking in most studies, fibrin thrombi on a prolapsed valve with myxomatous degeneration were demonstrated in a patient who suffered multiple emboli, to brain, heart, and kidneys. It also seems likely that the phenomenon of transmural myocardial infarction in MVP patients with angiographic normal coronary arteries may best be explained on the basis of coronary embolism.

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 1/6,000/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. No studies of antithrombotic therapy in this disease have been reported (to our knowledge), so guidelines for therapy are at best empirical and drawn from experience with other thromboembolic conditions. Long-term warfarin therapy is appropriate for those patients with AF and for those who continue to have cerebral ischemic events despite aspirin therapy.

The dilemma of cost-effective antithrombotic therapy in patients with MVP would best be solved by a reliable means of identifying the small cohort of patients at high risk for thromboembolism. In a retrospective study of 26 patients with MVP, Steele et al reported that platelet survival time was significantly shortened in all 5 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 of patients at risk. Since myxomatous degeneration and denudation 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 patient with “click-only” or silent MVP can be excluded from the 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.

3. Mitral Annular Calcification and Nonrheumatic MR

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, conduc-

tion disturbances, arrhythmias, embolic phenomena, and endocarditis. It must be emphasized that radiographic evidence of calcium in the mitral annulus does not in itself constitute the syndrome of MAC. While the true incidence of systemic emboli in this condition is not known, 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. 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 (RR) 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 embolic. 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 enlarge-
ment is not uncommon, even in those with normal sinus rhythm. 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), and fragmentation of calcific annular tissue. 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 warfarin 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 warfarin 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 warfarin therapy or in whom multiple calcific emboli are recognized, valve replacement should be considered.

4. AORTIC VALVE AND AORTIC ARCH DISORDERS

Clinically detectable systemic emboli in isolated aortic valve disease are distinctly uncommon. However, Stein et al\textsuperscript{84} 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,\textsuperscript{79} and four cases of cerebral emboli were observed in patients with bioprosthetic aortic valves in whom no other source of emboli could be found.\textsuperscript{82} 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.\textsuperscript{83} In this autopsy study of 165 patients, systemic emboli were found in 31 patients (19%); the heart and kidneys were the most common sites of emboli, but again, clinically detectable events were notably rare.

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,\textsuperscript{84} only 6 patients had isolated aortic valve disease; in each, AF was also present. More recently, the association of AF and aortic valve disease was examined by Myler and Sanders.\textsuperscript{85} In 122 consecutive patients with proved isolated severe aortic valve disease, only 1 patient had AF; in that instance, advanced coronary heart disease with infarction was present as well. Boon et al\textsuperscript{86} 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.

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 has been used to identify plaque size and morphology as risk factors for ischemic stroke. In a prospective case-control study 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.\textsuperscript{87} These same researchers performed an analysis of 789 person-year follow-up to determine the effect 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.\textsuperscript{88} Ulceration and hypoechoic plaques had no predictive value in evaluating vascular events. Overall, it was determined that aortic plaques that were ≥ 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 noncalcified plaques are probably lipid laden and are thus unstable and prone to rupture and thrombosis.

To study the effect of oral anticoagulants on patients with atherosclerosis of the aorta, Ferrari et al\textsuperscript{89} used TEE in a prospective cohort to compare treated vs nontreated patients. They found that patients treated with antiplatelet agents (APAs) rather than oral anticoagulant therapy (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 OAC. 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 not receiving APAs or OAC. Similar results were found by Dressler et al,\textsuperscript{90} who found that patients with mobile aortic atheroma and not receiving warfarin had a higher incidence of vascular events (27% had strokes), than those receiving 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 (median diameter > 1 mm and area < 10 mm²) were prescribed warfarin, as opposed to 53% of patients with small plaques (defined as diameter < 1 mm). Thus, patients with mobile atheroma should be considered for anticoagulation with warfarin, while the role of the dimension of the plaque (ie, > 4 mm) in determining therapy is still not totally clear.

5. Patent Foramen Ovale and Atrial Septal Aneurysm

The incidence of paradoxical embolism is unknown. In recent years, however, the role of developmental and acquired disease of the interatrial septum as a cause of cryptogenic stroke has received considerable attention. Paradoxical embolism through a patent foramen ovale (PFO) is well documented and thrombus on the arterial side of an atrial septal aneurysm has been reported at autopsy, during surgery, and by TEE. Much of the uncertainty about the incidence of paradoxical embolism lies in the fact that 27 to 29% of normal hearts have demonstrable PFOs at autopsy,92,93 and thus the specificity of this finding as a marker of paradoxical embolism is low. However, the demonstration by transthoracic echocardiography that 10 to 15% of normal people exhibit right-to-left shunting through a PFO during cough or Valsalva maneuver94,95 (by TEE, the incidence approaches the left shunting through a PFO during cough or Valsalva),96,97 provides support for the thesis that paradoxical embolism may be more common than generally believed. However, in the study citing a 57% incidence of venous thrombosis, only 17 of 42 patients had venous studies within 1 week before or after an embolic event. Recently, Lethen et al98 reported performing lower-limb venous studies independent of clinical signs of thrombosis at the time of presentation on 53 patients presenting with PFO and unexplained cerebral ischemia and found a 9.5% incidence of deep venous thrombosis. The PFOs associated with stroke in this report were all medium or large.

A number of studies99–101 have demonstrated a strong association between PFO and stroke. The evidence for this association is particularly apparent in younger patients, in whom the likelihood of atherosclerotic embolic disease is less compelling. Nevertheless, in a thoughtful review of this subject, Movsowitz et al96 conclude that the role of “paradoxical embolism through a PFO remains controversial.” Archer et al102 reported on 55 patients who had completed the Department of Veterans Affairs Cooperative Study of Stroke Prevention in Nonrheumatic Atrial Fibrillation trial without an embolic event. PFO was found in 54% and atrial septal aneurysm was found in 7.3%, suggesting a higher incidence of these abnormalities in patients with AF. It is generally agreed that contrast TEE is the diagnostic technique of choice for demonstrating a PFO. However, since the sensitivity of contrast TEE is greater than that of noncontrast transthoracic echocardiography, the question may be asked whether the smaller PFOs identified only by TEE are likely to be clinically relevant to the true incidence of paradoxical embolism.

The finding of a PFO in patients with pulmonary embolism may have significant clinical implications. Konstantinides et al103 studied 139 consecutive patients with major pulmonary embolism. PFO was present in 35% of the patients, which is higher than the incidence reported in the normal population. The death rate was 33% in this group as opposed to 14% in patients with a normal echocardiographic contrast examination (p = 0.015). Patients with a PFO also had a significantly higher incidence of ischemic stroke (13% vs 2.2%; p = 0.02) and peripheral arterial embolism (15 vs 0%; p < 0.001). Information regarding the effect of treatment of patients with pulmonary embolism and PFO is lacking.

A strong association between atrial septal aneurysm and stroke has also been reported.91,104 The former condition has been identified in 1% of autopsies and in 3 to 4% of nonstroke patients examined by TEE.91,104 Because of a high incidence of PFO in patients with atrial septal aneurysm (70 to 83%) and anecdotal reports of clot within the aneurysm, there are two potential sources of systemic embolism in this condition: paradoxical embolism and arterial thromboembolism from the left side of the atrial septal aneurysm. Atrial septal aneurysm has also been associated with MVP.105 Surgical repair of atrial septal aneurysm has been suggested when embolic phenomena have been demonstrated, but the evidence for this remains unclear.106

In both isolated PFO and in atrial septal aneurysm, the indications for antithrombotic therapy remain problematic. Atrial septal aneurysm and right-to-left shunting demonstrated by echocardiography may be predictive of a PFO that predisposes to stroke.105 In patients with unexplained cerebral ischemia or stroke, the demonstration of right-to-left shunting through a PFO warrants a search for deep vein thrombosis. In this circumstance, evidence for venous thrombosis (or pulmonary embolism) together with systemic embolism and a PFO provides a strong indication for long-term anticoagulation. The threshold for these interventions is higher and must be made on a case-by-case basis. Certainly, long-term anticoagulation would not be recommended for asymptomatic patients with PFOs or atrial septal aneurysms, although low-dose aspirin would seem prudent therapy to reduce the likelihood of thrombosis on the arterial side of an atrial septal aneurysm. Hanna et al106 reported on a relatively small series (n = 15) of patients who had what appeared to be PFO-related brain infarcts. These authors reported no recurrent infarcts during a mean follow-up period of 28 months and believed that aspirin may be sufficient stroke prophylaxis while warfarin and surgical correction could be reserved for patients in whom aspirin is not effective. While subsequent studies of the role of PFO in patients with cryptogenic stroke may broaden the indications for long-term warfarin therapy, the low specificity of PFO shunting as a risk factor for
stroke and the known risks of long-term anticoagulation mandate that we apply caution in recommending lifelong anticoagulation for patients suspected of having paradoxical embolism, unless the diagnostic evidence is quite convincing or alternate causes for stroke in themselves would justify this therapy. Decision analysis may be helpful in guiding therapy in the more difficult cases.

6. Infective 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, while, since that time, the prevalence has 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. 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 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, Poppi concludes that “the current state of the art in transesophageal echocardiographic imaging makes the likelihood of endocarditis low in patients without demonstrated vegetations.”

However, the ability of these techniques to identify the patient at risk for embolism is low. Further, 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, eg, 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 those in native valve endocarditis; emboli have been reported in 50 to 88% of patients with prosthetic valve endocarditis. However, the 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 emboli 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, too, 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 pa-
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 previous 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.

7. Nonbacterial Thrombotic Endocarditis

The evolution of the syndrome of nonbacterial thrombotic endocarditis (NBTE) has been clearly detailed in a comprehensive review of this disease by Lopez 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 and in 1954, Angrist and Marquiss 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 fulminating diseases, such as sepsis, and toward treatment of thromboembolism with or without associated disseminated intravascular coagulation. The case for anticoagulant therapy in NBTE is strengthened by the general belief that Trousseau syndrome and NBTE represent a 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, but 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.

8. Withdrawal of Anticoagulation Therapy Prior to Surgery

Patients with valvular heart disease receiving warfarin 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 used decision analysis to examine the cost-effectiveness of varying strategies for treating patients with prosthetic heart valves undergoing noncardiac surgery. These authors concluded the marginal cost of prolonging hospitalization to administer heparin was prohibitively high, except when the patient has “the most thrombogenic of valves.” Kearon and Hirsh assessed the risks of anticoagulation before and after elective surgery. Reviewing the...
literature, they concluded that it takes about 4 days after stopping warfarin therapy for the INR to reach 1.5 and about 3 days after restarting therapy for the INR to reach 2. Thus, if warfarin 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.148 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 Hirsh148 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 mitigates against postoperative heparin therapy, except for patients undergoing minor surgery in whom 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. Thus, until clinical trials that specifically target the perioperative management of patients with valvular heart disease requiring warfarin anticoagulation prior to surgical procedures are performed, treatment of such patients will remain controversial.

**Conclusion**

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. 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, the clinician would do well to review his or her decision at frequent intervals.

**Recommendations**

1. **Rheumatic Mitral Valve Disease (Mitral Stenosis and/or MR)**

2.1. We recommend the use of long-term warfarin therapy at a target INR of 2.5 (range, 2.0 to 3.0) in patients with rheumatic mitral valve disease who have either a history of systemic embolism or who have paroxysmal or chronic AF (grade 1C+).

2.2. In patients with MVP who have documented but unexplained TIAs, we recommend long-term, low-dose aspirin therapy (grade 2C). The dose currently recommended is 160 to 325 mg/d (see chapter on cerebrovascular disease).

3. **MAC and Nonrheumatic MR**

3.1. In patients with MAC complicated by systemic embolism, not documented to be calcific embolism, we recommend long-term warfarin therapy (target INR, 2.5; range, 2.0 to 3.0; grade 2C).

3.2. Patients with MAC and associated AF should also be treated with long-term warfarin therapy (target INR 2.5; range, 2.0 to 3.0; grade 1C+). Note: This latter recommendation is based on the high incidence of systemic embolism in older AF patients and the demonstrated efficacy of anticoagulant therapy in patients with AF without rheumatic valve disease.

3.3. We recommend that clinicians use long-term anticoagulation therapy for patients with MR who have AF or a history of systemic embolism (grade 1C+).
4. Aortic Valve and Aortic Arch Disorders

4.1. We do not recommend that clinicians use long-term warfarin therapy for patients with aortic valve disease unless they have another indication for anticoagulation (grade 2C).

4.2. In patients with mobile aortic atheromas and aortic plaques > 4 mm as measured by TEE, we recommend that clinicians use warfarin therapy (grade 2C).

5. PFO and Atrial Septal Aneurysm

5.1. For patients with unexplained systemic embolism or TIAs and demonstrable venous thrombosis or pulmonary embolism and either PFO or atrial septal aneurysm, we recommend that clinicians treat with long-term warfarin therapy, unless venous interruption or closure of the PFO is considered preferable therapy (grade 1C). Note: In the case of atrial septal aneurysm, the possibility of both paradoxical embolism and systemic embolism from the arterial side of the aneurysm should be considered in choosing therapy.

6. Infective Endocarditis

6.1. We recommend that long-term warfarin therapy be continued when endocarditis occurs in patients with a mechanical prosthetic valve unless there are specific contraindications (grade 2C). Note: It is to be noted that the risk of intracranial hemorrhage is substantial in patients with infective endocarditis. The indications for anticoagulant therapy when systemic embolism occurs during the course of infective endocarditis involving a native or bioprosthetic heart valve are uncertain. The therapeutic decision should consider comorbid factors, including AF, evidence of left atrial thrombus, evidence and size of the left atrium, and particularly the success of antibiotic therapy in controlling the infective endocarditis.

7. NBTE

7.1. For patients with NBTE and systemic or pulmonary emboli, we recommend treating with heparin (grade 1C).

7.2. We recommend the use of heparin therapy for patients with disseminated cancer or debilitating disease who are found to have aseptic vegetations on echocardiographic study (grade 2C).

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