Antithrombotic Therapy in Valvular Heart Disease

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Few complications of valvular heart disease can be more devastating than systemic embolism. With little regard for the severity of the underlying valve lesion, a cerebral or mesenteric embolus can, in a moment’s time, cripple or kill a previously asymptomatic patient. 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 warfarin 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 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 a hemorrhagic complication of anticoagulant therapy, and thus the rate of embolic phenomenon is not necessarily counterbalanced by an equal event rate of bleeding.

Rahimtoola reported that the risk of major bleeding in patients with prosthetic heart valves who received warfarin was 1 to 2% per year, and in a careful analysis of ten reports of anticoagulant therapy in patients with prosthetic valves covering 215.5 patient centuries of follow-up, Edmunds found the weighted mean rate of serious bleeding complications to be 2.19% per year, with fatalities due to bleeding in 0.17% per year. Interestingly, the same rate of serious bleeding (2.11% per year) was reported in patients with atrial fibrillation during 284 patient-years of warfarin therapy. In a recent review of 46 studies of patients with mechanical heart valve prostheses who had undergone anticoagulation with warfarin derivatives (53,647 patient-years of follow-up), the incidence of major bleeding was 1.4% per year.

Another consideration that will influence greatly our assessment of the risk-benefit ratio of anticoagulant therapy relates to the intensity of anticoagulation, particularly as reported in recent studies of less-intensive regimens of warfarin therapy. It has been reported that prothrombin times (PTs) performed with the commonly used commercial North American thromboplastin, maintained in the range of 1.3 to 1.5 times normal control (international normalized ratio [INR], 2.0 to 3.0), retained effectiveness against recurrent venous thromboembolism with a greatly reduced frequency of bleeding complications. Of greater relevance to patients with valvular heart disease is the report by Turpje et al. which suggests that a less-intensive regimen of warfarin therapy is “no less effective, and is safer than standard anticoagulant therapy in patients with tissue heart valve replacement.” Similar findings have been reported in patients with mechanical heart valves. Among 258 patients randomized to regimens of moderate-intensity warfarin therapy (PT ratio, 1.5; INR, 2.65) vs high-intensity therapy (PT ratio, 2.5; INR, 9.0), thromboembolism occurred with similar frequency in the two groups, while the risk of bleeding was significantly lower in the moderate-intensity group.

The utility and safety of a lower intensity of warfarin effect has also been shown in patients with mechanical heart valves treated with concomitant antiplatelet therapy. Altman et al. found that among patients given aspirin (330 mg/d) and dipyridamole (75 mg twice daily), those randomized to modest-intensity warfarin therapy (INR, 2.0 to 3.0) had less bleeding than those given higher-intensity warfarin (INR, 3.0 to 4.5), while the incidence of thromboembolism was similar in the two groups.

Further evidence to support the use of lower-intensity warfarin anticoagulation comes from five large, multicenter, randomized studies of patients with nonvalvular atrial fibrillation. In these studies, all of which showed a substantial benefit of warfarin, the utility of the anticoagulant therapy was independent of the target range of INR, which varied from 1.4 to 2.8 to 2.5 to 4.2 to 4.5, suggesting a better risk-benefit ratio with the lower-dose range. It should be emphasized, however, that the utility of lower-intensity anticoagulation in patients with nonvalvular atrial fibrillation should not necessarily be extrapolated to patients with mitral valve disease.

Rheumatic Mitral Valve Disease

The incidence of systemic embolism is greater in rheumatic mitral valve disease than in any other common form of 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 cited a prevalence of systemic emboli of 9 to 14% in several large early series of mitral stenosis, and in 1961, Ellis and Harken 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 observed an incidence of emboli of 1.5% per year, while the figure was found to vary from 1.5 to 4.7% per year preoperatively in six reports of rheumatic mitral valve disease. 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.

The incidence of systemic emboli increases dramatically
with the development of atrial fibrillation (AF). Szekely,\textsuperscript{16} 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, and among mitral patients with AF, Hinton et al\textsuperscript{19} found a 41% prevalence of systemic emboli at autopsy. Three quarters of the patients with mitral stenosis and cerebral emboli described by Harris and Levine\textsuperscript{20} and by Wood\textsuperscript{14} had AF. Among 839 patients with mitral valve disease described by Coulshed and associates,\textsuperscript{21} 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\textsuperscript{14} confirmed that emboli occur 1.6 times as frequently in patients with mitral stenosis as in patients with rheumatic mitral regurgitation.

The risk of systemic emboli in patients with rheumatic mitral disease is greater in older patients\textsuperscript{22-25} and those with lower cardiac indices\textsuperscript{26} but appears to correlate poorly with mitral calcification,\textsuperscript{21} mitral valve area,\textsuperscript{22} or clinical classification.\textsuperscript{14,21,22,26} Indeed, several investigators have pointed out that mitral patients with emboli frequently are found to have minor valve disease, and Wood\textsuperscript{14} 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 earlier studies of rheumatic mitral valve disease, a poor correlation was observed,\textsuperscript{14,21,26} but more recent reports, primarily in patients with nonvalvular atrial fibrillation, suggest that left atrial size is an independent risk factor for thromboembolism.\textsuperscript{27-29}

Among patients with valvular disease who suffer a first embolus, recurrent emboli occur in 30 to 65% of cases,\textsuperscript{14,15,30,31} of which 60 to 65% are within the first year,\textsuperscript{30,31} and the majority occur within 6 months. Mitral valvuloplasty does not appear to decrease the risk of thromboembolism.\textsuperscript{17,21} Thus a successful mitral valvuloplasty does not eliminate the need for anticoagulation, 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, 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 a level IV study, the incidence of recurrent embolism in mitral valve patients who received warfarin was 3.4%/yr, while in the nonanticoagulation group it was 9.6%/yr.\textsuperscript{16} Adams et al\textsuperscript{32} 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) (level IV study). 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,\textsuperscript{36} in a level IV study, 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-yr. In a retrospective study of 254 patients with AF (level IV study), an embolic rate of 5.46%/yr was reported for patients who did not receive anticoagulation vs 0.7%/yr for those receiving long-term warfarin therapy.\textsuperscript{3}

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, recent, large, randomized studies in patients with nonvalvular atrial fibrillation.\textsuperscript{9-11,13} Each of these level I studies demonstrated that warfarin was effective in reducing stroke in patients with nonvalvular AF. An additional Canadian multicenter trial\textsuperscript{12} was terminated prematurely when its results developed a trend consistent with the data reported in the four earlier trials. In one of these trials,\textsuperscript{10} aspirin was also found to decrease the rate of thromboembolism in patients younger than 75 years of age.

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 PT.

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 candidate for long-term warfarin therapy. 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 rheumatic mitral disease patients with a very large atrium, it has been suggested that such patients in normal sinus rhythm with a left atrial diameter greater than 55 mm should receive anticoagulant therapy.\textsuperscript{33}

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, regardless of the presence or absence of AF, for a minimum of 3 weeks before the balloon valvuloplasty. An alternate strategy might be to perform transesophageal echocardiography (TEE) just prior to balloon mitral valvuloplasty and if the examination reveals no left atrial clot, anticoagulation prior to the valvuloplasty can be avoided.\textsuperscript{34,35} However, experience with patients undergoing cardioversion of atrial fibrillation suggests that 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.\textsuperscript{39} Therefore, one can make a good case for providing anticoagulation therapy for most patients after balloon mitral valvuloplasty for at least 4 weeks.

Several studies have suggested that systemic embolism in patients with valvular heart disease occurs more frequently in those with shortened platelet survival times.\textsuperscript{36-40} Steele and Rainwater\textsuperscript{41} reported that shortened platelet survival was a sensitive index of past thromboembolism in patients
with 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 taking warfarin, and efficacy of sulfinpyrazone as monotherapy for the prevention of thromboembolism remains unproved.42

It has also been shown that shortened platelet survival in patients with prosthetic heart valves can be normalized by sulfinpyrazone36 and by dipyridamole.87 Similar observations have been made in patients with mitral stenosis treated with sulfinpyrazone40,41 and in patients with arterial grafts treated with dipyridamole.43 Furthermore, in a level I randomized study of patients with prosthetic heart valves, the addition of dipyridamole to warfarin therapy proved effective in reducing the incidence of systemic emboli.44 Similar findings were reported in a level III study,45 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 (level IV study).39 Dale and associates46 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 taking aspirin. At the completion of the study, all patients were treated with aspirin alone and had unsatisfactory control of embolic events. More recently, Turpie et al47 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.48

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 given 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. The recommendation concerning the use of dipyridamole is to be regarded as tentative as there is increasing evidence that the drug offers little beyond the effect of aspirin administered concomitantly.49

The relative utility of warfarin vs aspirin as antithrombotic monotherapy in patients with nonvalvular atrial fibrillation has recently been addressed.50 Seven hundred fifteen patients aged 75 years or younger and 385 patients older than 75 years were separately randomized to warfarin (INR, 2.0 to 4.5) or aspirin (325 mg/d) therapy; mean follow-up was 3.1 and 2.0 years in the two age groups, respectively. The primary event rate (ischemic stroke and systemic embolism) was 1.3%/yr with warfarin and 1.9% with aspirin (p=0.24) in the younger group, and 3.6% with warfarin vs 4.9% with aspirin (p=0.39) in the older group. While it was concluded that warfarin may be more effective than aspirin for prevention of ischemic stroke, the absolute reduction in stroke rate by warfarin was small and not statistically significant. Furthermore, in the older age group, the rate of all stroke with residual deficit (ischemic and hemorrhagic) was 4.6%/yr with warfarin and 4.3% with aspirin, and again this difference was not statistically significant.

While these findings suggest that risk stratification of individual patients with nonvalvular atrial fibrillation is recommended when choosing warfarin or aspirin therapy to prevent stroke and systemic emboli, extrapolation of these results to patients with rheumatic mitral valve disease or to those with significant nonrheumatic mitral disease is problematic. Furthermore, an analysis of pooled data from five randomized, controlled studies of antithrombotic therapy in nonvalvular AF, the European Atrial Fibrillation Trial, and the SPAF II study concludes that, "Patients with risk factors are optimally protected from stroke with warfarin if they are good candidates for anticoagulation. Unreliable individuals or those with other contraindications to anticoagulation should be considered for aspirin therapy.51

Since to our knowledge randomized studies of the relative utility of warfarin vs aspirin have not been carried out in patients with mitral valve disease, guidelines for antithrombotic therapy in this circumstance have been borrowed from studies of patients with nonvalvular AF. Since rheumatic mitral valve disease has long been associated with a high incidence of thromboembolism, extrapolation of the lessons learned from patients with nonvalvular AF to patients with mitral valve disease seems appropriate.

The decision to treat will remain difficult in many cases. For example, should antithrombotic therapy be given to the 35-year-old, physically active male with trivial mitral stenosis and normal sinus rhythm or to the asymptomatic mitral valve patient with AF and history of recurrent GI bleeding? In some instances, decision analysis will help to clarify whether to use antithrombotic therapy.52 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.

MitrAL Valve Prolapse

Mitr al valve prolapse (MVP) is the most common form of valve disease in adults.53 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, Barnett54 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 described from a single center.

Perhaps the most convincing evidence linking MVP to stroke is provided by the case-control study of Barnett and associates. Among 60 patients younger than 45 years who had TIAs or partial stroke, MVP was detected in 40%. While in 60 age-matched controls, the incidence was 6.8% (p<0.001), and in 42 stroke patients older than 45 years, MVP was found in 5.7%, an incidence comparable to that in the general population. However, in a recent preliminary report of 244 patients younger than 45 years with stroke or TIAs who were referred for transthoracic echocardiography (TTE) in search of a source of embolus, only 1.2% had MVP. The authors suggest that these results reflect the recently validated two-dimensional echocardiographic criteria for MVP.

A pathologic basis for thromboembolism in MVP has been suggested by several investigators. Pomerance examined the hearts of 35 patients with a ballooning deformity of the mitral valve and found that 10 exhibited a "fibrinous endocarditis" of the mitral valve. Guthrie and Edwards observed endothelial denudation 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. 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 tranmurual 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 5% of the female and 4% of the male population have MVP, the incidence of thromboembolism in these more than 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. Because repeated ischemic episodes are not uncommon, long-term aspirin therapy appears indicated.

To our knowledge, no studies of antithrombotic therapy in this disease have been reported, so guidelines for therapy are at best empiric 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 at risk. Because 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 "click-only" or silent MVP patient can be excluded from the risk of thromboembolism. However, past observations indicate otherwise as most MVP patients with cerebral ischemia are found to have a normal 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 mitral regurgitation, 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.

**Mitrail 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 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 Fulker son et al had systemic emboli, only 2 of whom had AF. In autopsy specimens, thrombi have been found on heavily calcified annular tissue, and echocographic 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=.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 un-
known, it is likely that the incidence of the former problem has been underestimated, because this diagnosis can be established only by pathologic examination of the embolus or by the rarely visualized calcified fragments in the retinal circulation.\textsuperscript{76,82} 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 mitral annular calcification 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,\textsuperscript{83} and 29\% of the patients with annular calcification described by Fullkerson et al\textsuperscript{76} had AF. In addition, left atrial enlargement 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, because most of these patients are elderly (mean age, 73 to 75 years,\textsuperscript{72,75}) 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. 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 patients with MAC. For patients with repeated embolic events despite warfarin therapy or in whom multiple calcific emboli are recognized, valve replacement should be considered.

**Aortic Valve Disease**

Clinically detectable systemic emboli in patients with 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{82} and four cases of cerebral emboli were observed in patients with bicuspid aortic valves in whom no other source of emboli could be found.\textsuperscript{85} 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{86} 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{57} only 6 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.\textsuperscript{88} 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.

Thus, in the absence of associated mitral valve disease, 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. Because 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 patients with isolated aortic valve disease apparently outweigh the potential usefulness, unless there is a history consistent with prior thromboembolism.

**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.\textsuperscript{90} 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,\textsuperscript{90,91} and thus the specificity of this finding as a marker of paradoxical embolism is low. However, the demonstration by TTE that 10 to 18\% of normal people exhibit right-to-left shunting through a PFO during cough or Valsalva’s maneuver,\textsuperscript{92,93} (by TEE the incidence approaches the anatomic data\textsuperscript{87}), and the observation that 57\% of patients with PFOs and suspected paradoxical embolism were found to have venous thrombosis by venography,\textsuperscript{94} provides support for the thesis that paradoxical embolism may be more common than generally believed.

A number of studies have demonstrated a strong association between PFO and stroke.\textsuperscript{93,95-97} The evidence for this association is particularly apparent in younger patients where the likelihood of atherosclerotic embolic disease is less compelling. Nevertheless, in a thoughtful review of this subject, Movsowitz et al\textsuperscript{98} conclude that the role of “paradoxical embolism through a PFO remains controversial.” It is generally agreed that contrast TEE is the diagnostic technique of choice for demonstrating a PFO. However, because the sensitivity of contrast TEE is greater than that of contrast TTE, 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.
A strong association between atrial septal aneurysm and stroke has also been reported. The former condition has been identified in 1% of autopsies and in 3 to 4% of nonstroke patients examined by TEE. 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: namely paradoxical embolism and arterial thromboembolism from the left side of the atrial septal aneurysm.

In both isolated PFO and in atrial septal aneurysm, the indications for antithrombotic therapy remain problematic. 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, venous interruption, or in some cases closure of the PFO. In the absence of evidence for venous thromboembolism, the threshold for these interventions is higher and must be made on a case-by-case basis. Certainly, long-term anticoagulation would not be recommended for asymptomatic PFOs or atrial septal aneurysms, although low-dose aspirin therapy would seem prudent therapy to reduce the likelihood of thrombosis on the arterial side of an atrial septal aneurysm. 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 therapy mandate that we apply caution in recommending life-long anticoagulation for patients suspected of 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.

**INFECTIVE ENDOCARDITIS**

With the advent of effective antimicrobial therapy, the incidence of systemic emboli in patients with 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 patients with mitral valve endocarditis than in those with 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, considering the relatively short course of the disease, an unusually high event per unit time may be inferred.

The use of anticoagulant therapy in patients with 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 be abandoned. However, the issue remained controversial. While reference to the early adverse experience of anticoagulant therapy in patients with endocarditis frequently has been made, Lerner and Weinstein concluded that anticoagulants were "probably not contraindicated" in patients with infective endocarditis.

With the advent of echocardiography, means of identifying the patient at risk for embolism 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 50% 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 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 patients with 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 patients with prosthetic valve endocarditis are higher than in those with 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 to 14 patients who received either inadequate or no anticoagulation (level IV). 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 (level IV). 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 prothopathic valve endocarditis.105,127

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,104,123,124,126 while others express some doubt about its value.103,104 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 the complication.128 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.129,130 Since the risk of thromboembolism in patients who have not undergone anticoagulation therapy with bioprostheses who are in normal sinus rhythm is low,104 anticoagulation therapy is not indicated. A recent 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.132 While Pruitt et al104 suggest a possible role for antiplatelet drugs in prosthetic valve endocarditis, the utility of this form of therapy has not been established.

**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.133 Originally described by Ziegler in 1888,133 the lesions were considered to be fibrin thrombi deposited on normal or superficially degenerated cardiac valves. In 1936, Gross and Friedberg133 introduced the term nonbacterial thrombotic endocarditis and in 1954, Angrist and Marquiss134 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%); it averages 42%.133 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.133

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 and degeneration of valvular collagen, and perhaps a local valvular effect of mucin-producing carcinomas.133

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,133,135,136 and renewed thromboembolic complications have been reported after heparin therapy was discontinued.135,136 Little benefit has been observed with warfarin therapy.133,135,136

The diagnosis of NBTE is not easy 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.133,137

The case for anticoagulant therapy in NBTE is strengthened by the general belief that Trousseau’s syndrome and NBTE represent a continuum and that disseminated intravascular coagulation represents the substrate for treating most patients with NBTE. Rogers et al136 suggest that anticoagulation 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 outpatients 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.136

**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. Because 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 decision at frequent intervals.
RECOMMENDATIONS

Rheumatic Mitral Valve Disease

1. It is strongly recommended that long-term warfarin therapy sufficient to prolong the INR to 2.0 to 3.0 be used in patients with rheumatic mitral valve disease who have either a history of systemic embolism or who have paroxysmal or chronic atrial fibrillation. This recommendation is based on three level IV studies\textsuperscript{16,26,32} demonstrating efficacy in patients with mitral valve disease and five level I studies showing efficacy in subjects with nonvalvular atrial fibrillation.\textsuperscript{9,13}

2. It is recommended that long-term warfarin therapy (INR, 2.0 to 3.0) be considered in patients with rheumatic mitral valve disease and normal sinus rhythm, if the left atrial diameter is in excess of 5.5 cm. This recommendation is based on the belief that the likelihood of developing AF in such cases will be high. Furthermore, since it is recognized that the risk of thromboembolism may be substantial in some patients with rheumatic mitral valve disease and normal sinus rhythm, it is recommended that the decision to use warfarin be adjudicated on the basis of comorbid risk factors, particularly left atrial size, age, and the hemodynamic severity of the lesion. These grade C recommendations are not based on published studies.

3. It is recommended that if recurrent systemic embolism occurs despite adequate warfarin therapy, that the addition of aspirin (80 to 100 mg/d) be considered.\textsuperscript{47} For those patients unable to take aspirin, alternative strategies would be to increase the warfarin dose sufficient to prolong the PT to an INR of 2.5 to 3.5, add dipyridamole, 400 mg/d, or add ticlopidine, 250 mg twice daily.

Aortic Valve Disease

1. It is strongly recommended that long-term antithrombotic therapy not be given to patients with aortic valve disease unless they also have concomitant mitral valve disease, AF, or a history of systemic embolism. This grade C recommendation is made because of the low incidence of clinically detectable systemic thromboembolism in these patients.

Mitral Valve Prolapse

1. It is strongly recommended that long-term antithrombotic therapy not be given to patients with MVP who have not experienced systemic embolism, unexplained TIA, or AF. This grade C recommendation is based on the low incidence of systemic embolism in patients with this common disorder.\textsuperscript{53,66}

2. It is recommended that patients with MVP who have documented but unexplained TIs be treated with long-term low-dose aspirin therapy. The dose currently recommended is 160 to 325 mg/d (see article on cerebrovascular disease by Sherman et al, pp 4445-4565 in this supplement).

3. It is recommended that patients with MVP who have (1) documented systemic embolism, (2) chronic or paroxysmal AF, or (3) recurrent TIA despite aspirin therapy be treated with long-term warfarin therapy (INR, 2.0 to 3.0).

Mitral Annular Calcification

1. It is recommended that long-term antithrombotic therapy not be given to patients with MAC who lack a history of thromboembolism or AF. This grade C recommendation is based on the relatively low incidence of thromboembolism in patients with this common disorder.\textsuperscript{76,79}

2. It is recommended that patients with MAC complicated by (1) systemic embolism not documented to be calcific embolism or (2) associated AF be treated with long-term warfarin therapy (INR, 2.0 to 3.0). This grade A recommendation is based on the high incidence of systemic embolism in older AF patients and the demonstrated efficacy of anticoagulant therapy in patients with nonvalvular atrial fibrillation.\textsuperscript{9-13}

Patient Foramen Ovale and Atrial Septal Aneurysm

1. It is strongly recommended that anticoagulant therapy not be given to patients with asymptomatic PFOs or atrial septal aneurysms. This grade C recommendation is made because of the high incidence of demonstrable PFOs in the population at large.

2. It is strongly recommended that patients with unexplained systemic embolism or TIAs and demonstrable venous thrombosis or pulmonary embolism and either PFO or atrial septal aneurysm be treated with long-term warfarin therapy, unless venous interruption or closure of the PFO is considered preferable therapy. 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.

Infective Endocarditis

1. It is strongly recommended that anticoagulant therapy not be given to patients in normal sinus rhythm with uncomplicated infective endocarditis involving a native valve or a bioprosthetic valve. This grade C recommendation is based on the increased incidence of hemorrhage in these patients\textsuperscript{112-114} and the lack of demonstrated efficacy of anticoagulant therapy in this setting.\textsuperscript{122,132}

2. It is recommended that long-term warfarin therapy be continued when endocarditis occurs in patients with a mechanical prosthetic valve unless there are specific contraindications. This grade C recommendation is based on the high frequency of systemic thromboembolism in these patients.\textsuperscript{104-106,123,125} However, it is to be noted that the risk of intracranial hemorrhage is substantial.\textsuperscript{104,105,127}

3. 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 co-morbid factors, including AF, evidence of left atrial thrombus, evidence and size of valvular vegetations, and particularly the success of antibiotic therapy in controlling the infective endocarditis.

Nonbacterial Thrombotic Endocarditis

1. It is recommended that patients with NBTE and systemic or pulmonary emboli be treated with heparin. This grade C recommendation is based on a strong association between NBTE and disseminated intravascular coagulation and uncontrolled studies demonstrating efficacy in hospitalized patients.\textsuperscript{133,135,136}

2. It is recommended that heparin therapy be considered for patients with disseminated cancer or debilitating disease
who are found to have aseptic vegetations on echocardiographic study. This grade C recommendation is based on a high incidence of systemic emboli in patients with NBTE.133,135,136

REFERENCES
4 Camneveger SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1984; 89:635-41
18 Levine HJ. Which atrial fibrillation patients should be on chronic anticoagulation? J Cardiovasc Med 1981; 6:485-87
24 Hay WE, Levine SA. Age and atrial fibrillation as independent factors in auricular mural thrombus formation. Am Heart J 1942; 24:1-4
45 Chesebro HJ, Fuster V, McGoon DC, et al. Trial of combined warfarin plus diprydamole or aspirin therapy in prostatic heart valve replacement: danger of aspirin compared to diprydamole. Am J Cardiol 1983; 51:1537-41

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Albers GW. Atrial fibrillation and stroke: three new studies, three remaining questions. Arch Intern Med 1994; 154:1443-48


Hirsowitz GS, Saffer D. Hemiplegia and the billowing mitral leaflet syndrome. J Neurol Neurosurg Psychiatry 1978; 41:381-53

Saffro R, Talano JV. Transient ischemic attack associated with mitral systolic clicks. Arch Intern Med 1979; 139:639-94


Pomerance A. Balloon deformaity (mucoid degeneration) of atrioventricular valves. Br Heart J 1969; 31:343-51


Cheitlin MD. Thromboembolic studies in the patient with the prolapsed mitral valve: has Salome dropped another veil? [editorial]. Circulation 1979; 60:46-7


Levine HJ, Isner JM, Salem DN. Primary vs secondary mitral valve prolapse: clinical features and implications. Clin Cardiol 1982; 5:371-75

Jackson AC, Boughner DR, Barnett HJM. Mitral valve prolapse and cerebral ischemic events in young people. Neurology 1984; 34:784-87


Ridolfi RL, Hutchins GM. Spontaneous calcific emboli from calcific mitral annulus fibrosus. Arch Pathol Lab Med 1976; 100:117-20


Thompson T, Evans W. Parasadoxical embolism, Q J Med 1930; 23:135-50


ovale in young stroke patients. Lancet 1988; 2:11-12
101 Cates JE, Christie RV. Subacute bacterial endocarditis: a review of 442 patients treated in 14 centers appointed by the penicillin trials committee of the MRC. Q J Med 1951; 20:93
102 Brunson JC. Coronary embolism in bacterial endocarditis. Am J Pathol 1953; 26:689
113 Katz LN, Elek SR. Combined heparin and chemotherapy in subacute bacterial endocarditis. JAMA 1944; 124:149-52
115 Finland M. Current status of therapy in bacterial endocarditis. JAMA 1959; 166:364-73
129 Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: a randomized trial. Stroke 1983; 14:669-76