Antithrombotic Therapy in Valvular Heart Disease

Deob N. Salem, MD, FCCP, Chair; Herbert J. Levine, MD; Stephen G. Pauker, MD, Mark H. Eckman, MD; and Denise Hartnett Daudelin, RN, MPH

(CHEST 1998; 114:5905-6018)

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; 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.

Rheumatic Mitral Valve Disease

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, Wood1 cited a prevalence of systemic emboli of 9 to 14% in several large early series of mitral stenosis, and in 1961, Ellis and Harken2 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, Szekely3 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.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). Szekely6 reported that the risk of embolism was seven times greater in patients with rheumatic mitral valve disease and AF than in those with normal sinus rhythm, and among patients with mitral valve disease with AF, Hinton et al7 found a 41% prevalence of systemic emboli at autopsy. Three quarters of the patients with mitral stenosis and cerebral emboli described by Harris and Levine8 and by Wood9 had AF. Among 839 patients with mitral valve disease described by Coulsed and associates,10 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. Wood1 confirmed that emboli occur 1½ times as frequently in mitral stenosis as in rheumatic mitral regurgitation.

The risk of systemic emboli in rheumatic mitral disease is greater in older patients10-12 and those with lower cardiac indexes13 but appears to correlate poorly with mitral calcification,14 mitral valve area,15 or clinical classification.1,16,17,18 Indeed, several investigators have pointed out that patients with mitral valve disease with emboli frequently are found to have minor valve disease, and Wood1 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,1,15,16 but more recent reports, primarily in patients with nonvalvular AF, suggest that left atrial size is an independent risk factor for thromboembolism.14-16

Among patients with valvular disease who suffer a first embolus, recurrent emboli occur in 30 to 65% of cases,1,5,17,18 of which 60 to 65% are within the first year1,17,18 and most occur within 6 months. Mitral valvuloplasty does not appear to decrease the risk of thromboembolism.14,16 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 patients with mitral valve disease who received warfarin was 3.4% per year, while in the nonanticoagulation group it was 9.6% per year.3 Adams et al19 followed up 84 patients with mitral stenosis and cerebral emboli for up to 20 years, half of whom received no anticoagulant therapy (1949 to

Correspondence to: Deob N. Salem, MD, FCCP, New England Medical Center, Box 79, 750 Washington St, Boston, MA 02111-1326

590S Fifth ACCP Consensus Conference on Antithrombotic Therapy
immediate
relatively
prior
dure.
Accordingly,
with
catheter
loplasty,
diameter
risk of
the
therefore,
to
disease,
exclude
exposure
to
AF.20
Perhaps
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.21-24 Each of these level I studies demonstrated that warfarin was effective in reducing stroke in patients with nonvalvular AF. An additional Canadian multicenter trial25 was terminated prematurely when its results developed 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 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 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.26

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 does not reveal a left atrial clot, anticoagulation prior to the valvuloplasty can be avoided.27,28

Recently, Abraham et al29 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 of 3 months. However, until this study is reproduced, based on experience with patients undergoing cardioversion of AF 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. Indeed, one can make a good case for giving anticoagulation therapy to most patients after balloon mitral valvuloplasty for at least 4 weeks.29 Interestingly, Kang et al30 recently reported on 49 patients with mitral stenosis with left atrial appendage thrombi who were otherwise candidates for percutaneous mitral valvuloplasty (PMV).30 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 was 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 al31 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 al32 reported that measures of platelet activation, platelet factor 4 and β-thromboglobulin, were significantly elevated in patients with rheumatic mitral regurgitation 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.33-37 Steele and Rainwater38 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 taking warfarin, and efficacy of sulfinpyrazone as monotherapy for the prevention of thromboembolism remains unproved.39

It has also been shown that shortened platelet survival in patients with prosthetic heart valves can be normalized by sulfinpyrazone33 and by dipyridamole.34 Similar observations have been made in patients with mitral stenosis treated with sulfinpyrazone37,38 and in patients with arterial grafts treated with dipyridamole.40 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.41 Similar findings were reported in a level III study,42 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).43 Dale and associates44 performed a randomized study of aspirin (1.0 g/d) plus warfarin vs warfarin alone in 145 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 complica-
tions, 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. Turpie et al. 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.

Thus, there is evidence that dipyridamole and sulfipyrazone 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.

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 G1 bleeding? In some instances, decision analysis will help to clarify whether to use antithrombotic therapy. 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

Mitral valve prolapse (MVP) is the most common form of valve disease in adults. While generally innocuous, it is sometimes annoying, and serious complications can occur. During the past 20 years, embolic phenomena have been reported in several patients with MVP in whom no other source for emboli could be found. In 1974, Barnett observed four patients with MVP who suffered cerebral ischemic events. Two years later, a total of 12 patients were described with recurrent transient ischemic attacks (TIAs) and partial nonprogressive strokes who had no evidence of atherosclerotic disease, hypertension, or coagulation disorders. Similar observations have been made by other investigators, and as many as nine such patients have been reported from a single center.

Perhaps the most convincing evidence linking MVP to stroke is provided by the case-control study of Barnett and associates. Among 60 patients <45 years who had TIAs or partial stroke, MVP was detected in 40%, while in 60 age-matched control subjects, the incidence was 6.8% (P < 0.001), and in 42 stroke patients >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 <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. 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 endocardial debridement 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 mitral regurgitation (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 valvar surface leading to possible thromboembolism. While clinicopathologic correlations have been lacking in most studies, fibrin thrombi on a prolapsed valve with myxomatous degeneration was 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 knowl-

5925

Fifth ACCP Consensus Conference on Antithrombotic Therapy

Downloaded From: http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21888/ on 06/16/2017
edge), 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. 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 "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 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.

**Mitral Annular Calcification**

The clinical syndrome of mitral annular calcification (MAC), first clearly described in 1962, includes a strong female preponderance and may be associated with mitral stenosis and regurgitation, calcific aortic stenosis, conduction disturbances, arrhythmias, embolic phenomena, and endocarditis. It must be emphasized that radiographic evidence of calcium in the mitral annulus does not in itself constitute the syndrome of MAC. While the true incidence of systemic 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 Fullkerson 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 of stroke in those with MAC was 2.10 times that without MAC (p = 0.006), independent of traditional risk factors for stroke. Even in those subjects without prevalent AF, the risk of stroke in subjects with MAC was twice that of those without MAC.

In addition to embolization of fibrin clot, calcified spicules may become dislodged from the ulcerated calcified annulus and present as systemic emboli. While the relative frequency of calcific emboli and thromboembolism is unknown, it is likely that the incidence of the former problem has been underestimated, since this diagnosis can be established only by pathologic examination of the embolus or by the rarely visualized calcified fragments in the retinal circulation. Since there is little reason to believe that anticoagulant therapy would be effective in preventing calcific emboli, the rationale for using antithrombotic drugs in patients with MAC rests primarily on the frequency of true thromboembolism. In the Framingham study, the incidence of AF was 12 times greater in patients with MAC than in those without this lesion, and 29% of the patients with annular calcification described by Fullkerson et al. 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, 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. 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.

**Aortic Valve Disease**

Clinically detectable systemic emboli in isolated aortic valve disease are distinctly uncommon. However, Stein et al. 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. and four cases of cerebral emboli were observed in patients with bicuspid aortic valves in whom no other source of emboli could be found. In the latter group, all
four patients were treated with aspirin, and no recurrences were observed. Perhaps the most startling report of calcific emboli in a patient with calcific aortic stenosis is that of Holley et al.58 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.62 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.83 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. Boon et al.84 prospectively compared the risk of stroke in 815 patients with aortic valve calcification with or without stenosis with 562 control subjects.84 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, 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.85 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,85,86 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 maneuver86,89 (by TEE the incidence approaches the anatomic data49), and the observation that 57% of patients with PFOs and suspected paradoxical embolism were found to have venous thrombosis by venography,53 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 al.85 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 studies have demonstrated a strong association between PFO and stroke.89,93-95 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, Moshowitz et al.90 conclude that the role of “paradoxical embolism through a PFO remains controversial.” Archer et al.91 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 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.85,97 The former condition has been identified in 1% of autopsies and in 3 to 4% of nonstroke patients examined by TEE.85,97 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. Atrial septal aneurysm has also been associated with MVP.88 Surgical repair of atrial septal aneurysm has been suggested when embolic phenomenon have been demonstrated, but the evidence for this remains unclear.99

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.98 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 would seem prudent therapy to reduce the likelihood of thrombosis on the arterial side of an atrial septal aneurysm. Hanna et al.\textsuperscript{109} reported on a relatively small series (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 screening as a risk factor for stroke and the known risks of long-term anticoagulation mandate that we apply caution in recommending life-long anticoagulation for patients suspected of paradoxical embolism, unless the diagnostic evidence is quite convincing or that 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 infective endocarditis has decreased. In the preantibiotic era, clinically detectable emboli occurred in 70 to 97% of patients with infective endocarditis,\textsuperscript{100} while, since that time, the prevalence has been reported to be 12 to 40%.\textsuperscript{101–106} Emboli occur more frequently in patients with acute endocarditis than in those with subacute disease,\textsuperscript{107} and the incidence of pulmonary emboli in right-sided endocarditis is particularly high,\textsuperscript{103,108} 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.\textsuperscript{104} 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.\textsuperscript{109} While complications of this therapy were not always encountered,\textsuperscript{100,111} most workers reported an alarming incidence of cerebral hemorrhage,\textsuperscript{112–114} and it was suggested that the routine use of anticoagulant therapy in patients with endocarditis be abandoned.\textsuperscript{113,115,116} However, the issue remained controversial. While reference to the early adverse experience of anticoagulant therapy in endocarditis frequently has been made, Lerner and Weinstein\textsuperscript{103} 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.\textsuperscript{108,117–119} However, in a review of this subject, O'Brien and Geiser\textsuperscript{120} report that 80% of patients with infective endocarditis have vegetations detected by echocardiography while only one third have systemic emboli. TEE has added a further dimension to the diagnostic accuracy of endocarditis. Indeed, Popp\textsuperscript{121} 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.\textsuperscript{122} 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 that in native valve endocarditis; emboli have been reported in 50 to 85% of patients with prosthetic valve endocarditis.\textsuperscript{104,106,123,124} However, opinion is divided on the effectiveness of anticoagulation in reducing the number of embolic events associated with prosthetic valve endocarditis. Wilson et al.\textsuperscript{124} reported CNS complications in only 3 of 38 patients with prosthetic valve endocarditis who received adequate anticoagulant therapy, while events were observed in 10 of 14 patients who received either inadequate or no anticoagulation (level IV). However, Yeh et al.\textsuperscript{125} 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).\textsuperscript{105} Pruitt and associates\textsuperscript{104} 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\textsuperscript{126} 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.\textsuperscript{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,\textsuperscript{104,123,124,126} while others express some doubt about its value.\textsuperscript{105,106} 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.\textsuperscript{120} 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.\textsuperscript{120,130} Since the risk of thromboembolism in patients not receiving anticoagulation therapy with bioprostheses who are in normal sinus rhythm is low,\textsuperscript{131} 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.\textsuperscript{132} While Pruitt et al\textsuperscript{104} 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.\textsuperscript{133} 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\textsuperscript{134} 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%.\textsuperscript{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.\textsuperscript{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, degeneration of valvular collagen, and perhaps a local valvular effect of mucin-producing carcinomas.\textsuperscript{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,\textsuperscript{133,135,136} and renewed thromboembolic complications have been reported after heparin therapy was discontinued.\textsuperscript{135,136} Little benefit has been observed with warfarin therapy.\textsuperscript{133,135,136}

The diagnosis of NBTE is not easily made and is considerably more elusive than that of bacterial endocarditis. Not only is the marker of bloodstream infection lacking, but the small friable vegetations frequently embolize leaving only small remnants to be identified on the valve. Indeed, cardiac murmurs, a hallmark of bacterial endocarditis, are frequently absent and there is some evidence that echocardiography is less sensitive for the detection of NBTE than it is for bacterial endocarditis.\textsuperscript{132,137}

NBTE lesions need to be differentiated from valve excrescences. In contrast to thrombotic vegetations that are generally rounded, sessile, measure $>3$ mm in diameter, have heterogeneous echoreflectance and no independent mobility, valve excrescences are thin ($\leq 2$ mm), elongated ($\geq 3$ mm) structures that are seen near leaflet close lines.\textsuperscript{138} Roldan et al\textsuperscript{138} used TEE to compare 90 healthy volunteers, 88 patients without suspected cardioembolism, and 49 patients referred for suspected cardioembolism. They found valve excrescences in 38% of normal subjects, 47% of patients without suspected cardioembolism, and 41% of those with suspected cardioembolism. These authors concluded that valve excrescences were common findings on left-sided heart valves of both normal subjects and patients regardless of gender or age, that they persist over time, and that they do not seem to be a primary source of cardiac embolisms. In an accompanying editorial, Armstrong\textsuperscript{139} concluded that the above-mentioned carefully controlled TEE study should serve as a model for studying other possible lesions associated with cardioembolism such as atrial septal defect, PFO, and isolated MVP without vegetation.

The case for anticoagulant therapy in NBTE is strengthened by the general belief that Trousseau syndrome and NBTE represent a continuum\textsuperscript{135} and that disseminated intravascular coagulation represents the substrate for treating most patients with NBTE. Rogers et al\textsuperscript{136} 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.\textsuperscript{136}
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.140 used decision-making 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.” Recently Kearon and Hirsh141 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.141 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 Hirsh141 concluded the following: (1) in the first month after an acute episode of arterial embolism, preoperative heparin therapy is indicated; however, risk of bleeding complications from heparin postoperatively mitigate against postoperative heparin therapy except for patients undergoing minor surgery where the risk of bleeding is low; (2) in conditions with a lower risk of arterial thromboembolism, their analysis suggests that the postoperative IV heparin therapy increases serious morbidity; and (3) preoperative or postoperative prophylaxis against thromboembolism should be considered for the period during which the INR is < 2.0. This review was followed by several letters to the editor stating that perioperative bleeding complications of heparin administration were less serious than embolic complication of a decreased INR.142 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

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 (target INR 2.5) be used in patients with rheumatic mitral valve disease who have either a history of systemic embolism or who have paroxysmal or chronic AF. This is a level C1 recommendation.

2. It is recommended that long-term warfarin therapy target INR 2.5 (range, 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 in 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 are grade C1 recommendations.

3. It is recommended that if recurrent systemic embolism occurs despite adequate warfarin therapy, the addition of aspirin (80 to 100 mg/d) be considered.44 For those patients unable to take aspirin, alternative strategies would be to add dipyridamole, 400 mg/d, or add ticlopidine, 250 mg po bid or add clopidogrel (C2 recommendations).

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 is a grade C1 recommendation.

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 C1 recommendation is based on the low incidence of systemic embolism in this common disorder.49,63

2. It is recommended that patients with MVP who have documented but unexplained TIAS be treated with long-term low-dose aspirin therapy. The dose currently recommended is 160 to 325 mg/d (see chapter on cerebrovascular disease). This is a C1 recommendation.

3. It is recommended that patients with MVP who
have (1) documented systemic embolism, (2) chronic or paroxysmal AF, or (3) recurrent TIAs despite aspirin therapy be treated with long-term warfarin therapy (target INR 2.5 [range 2.0 to 3.0]). This is a C1 recommendation.

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 C1 recommendation is based on the relatively low incidence of thromboembolism in this common disorder.71,74

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 (target INR 2.5 [range 2.0 to 3.0]). This grade C1 recommendation is based on the high incidence of systemic embolism in older AF patients and the demonstrated efficacy of anticoagulant therapy in non-valvular AF.21-25

PFO 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 C1 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. This is a C1 recommendation.

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 C1 recommendation is based on the increased incidence of hemorrhage in these patients112-114 and the lack of demonstrated efficacy of anticoagulant therapy in this setting.112,112

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 C1 recommendation is based on the high frequency of systemic thromboembolism in these patients.104-106,123,125 However, it is to be noted that the risk of intracranial hemorrhage is substantial.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 comorbid 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 C1 recommendation is based on a strong association between NBTE and disseminated intravascular coagulation and uncontrolled studies demonstrating efficacy in hospitalized patients.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 C2 recommendation is based on a high incidence of systemic emboli in NBTE.133,135,136

REFERENCES


5 Levine HJ. Which atrial fibrillation patients should be on chronic anticoagulation? J Cardiovasc Med 1981; 6:483-487


7 Harris AW, Levine SA. Cerebral emboli in mitral stenosis. Ann Intern Med 1941; 51:637-643


11 Hay WE, Levine SA. Age and atrial fibrillation as independent factors in auricular mural thrombus formation. Am Heart J 1942; 24:1-4


16 Moulinier-Vehier B, Leys D, Rondepierre P, et al. Silent infarcts in patients with ischemic stroke are related to age and size of the left atrium. Stroke 1993; 24:1347-1351
Weily Harker 34
33
Weily 31
29
28
27
Black Pumphry Connolly 23
20
20
Friedberg 18 Carter 19
17
17
16
16
51 Hirstowitz GS, Saifer D. Hemiplegia and the billing mitral leaflet syndrome. J Neurol Neurosurg Psychiatry 1978; 41:381–383
52 Saffro R, Talano JV. Transient ischemic attack associated with mitral systolic clicks. Arch Intern Med 1979; 139:693–694
55 Gilon D, Buonanno FS, Kistler JP, et al. Mitral valve prolapse: is it associated with acute ischemic neurologic events [abstract]? J Am Coll Cardiol 1995; 33A
56 Pomerance A. Balloon deformity (mycoid degeneration) of atrioventricular valves. Br Heart J 1969; 31:343–351
59 Geyer SJ, Franzini DA. Myxomatous degeneration of the mitral valve complicated by nonbacterial thrombotic endo-
62 Cheitlin MD. Thromboembolic studies in the patient with the prolapsed mitral valve: has Salome dropped another veil [editorial]? Circulation 1979; 60:46–47
66 Jackson AC, Boughner DR, Barnett HJM. Mitral valve prolapse and cerebral ischemic events in young people. Neurology 1984; 34:784–787
70 Guthrie JJ, Fairgrieve JJ. Aortic embolism due to a myxoid tumor associated with myocardial calcification. Br Heart J 1963; 25:137–140
76 Ridolfi RL, Hutchins GM. Spontaneous calcific emboli from calcific mitral annulus fibrosus. Arch Pathol Lab Med 1976; 100:117–120
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
103 Lerner PI, Weinstein L. Infective endocarditis in the anti-