Antithrombotic Therapy in Cardiac Disease
An Emerging Approach Based on Pathogenesis and Risk

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For more than 50 years, thrombosis within the circulatory system has been recognized as the principal mechanism responsible for cardiovascular morbidity and mortality, and throughout this period various antithrombotic drugs have been used for purposes of both prevention and therapy. The vast existing literature is so rapidly supplemented by new data that confusion may arise among clinicians who confront decisions involving patient management. Although periodically a consensus is reached regarding specific therapeutic approaches, sound integration of emerging information requires a conceptual framework consisting of an understanding of pathogenetic mechanisms and an appreciation of relative risks. This review combines a perspective on pathogenesis with stratification of thrombotic and embolic risk to derive a rational approach to the application of antithrombotic therapy. The discussion is limited to cardiac syndromes, although many of the principles apply to peripheral circulatory and cerebrovascular diseases as well.

Pathogenesis of Thrombosis and Embolism
Coronary Arteries

Vascular injury—Activation of platelets and the coagulation system. The entire intimal layer of the cardiovascular system is lined with endothelial cells, which provide a surface highly resistant to thrombus formation. This property is lost with even superficial vascular injury, as occurs in experimental hyperlipidemic animal models, and results in adhesion of a monolayer of platelets to the damaged endothelium or to exposed subendothelium. When arterial wall injury is more severe, as in cases of rupture of an atherosclerotic plaque or immediately after angioplasty, components of the medial layer—particularly type I collagen—become exposed to the circulating blood. Marked platelet activation typically occurs under these circumstances, with release from intracytoplasmic granules of substances such as adenosine diphosphate, thromboxane A2, and serotonin, all of which potentiate further platelet aggregation and thrombus formation. Vascular damage of this magnitude also stimulates thrombin formation through both the intrinsic (surface-activated) and extrinsic (tissue factor-dependent) coagulation pathways, in which the platelet membrane facilitates interactions between clotting factors (Figure 1). Thrombin promotes the formation and polymerization of fibrin, which is responsible for stabilization of the expanding thrombotic mass, allowing it to resist dislodgement by the forces of arterial blood flow. Like collagen, thrombin is also a powerful activator of platelet aggregation. Platelets and the coagulation system are therefore clearly interrelated in the genesis of arterial thrombosis.

Labile versus fixed thrombus. Delivery and activation of platelets at the site of injury are dependent on both shear rate, which is a measure of the difference in blood velocity between the center and the periphery of the vessel, and the degree of vessel wall injury. In areas of luminal stenosis, high shear rate promotes contact between blood elements and the vessel wall and favors platelet activation. More importantly, the influence of the severity of vascular injury on thrombus formation has been demonstrated in perfusion chamber experiments in which different tissue substrates were exposed to blood at various shear rates. With superficial vessel injury, platelet deposition and thrombus formation occurred, but the phenomenon was transient; with deep vessel injury, however, platelet deposition was considerably enhanced, leading to fixation of platelet thrombus and persistent vascular occlusion.

Thrombus composition and extension. Histologically, thrombus in an area of stenotic, disrupted atherosclerotic plaque, where shear rate is relatively high, is composed predominantly of platelets and sonofibrin; thrombus, which extends distally in the lumen of the vessel, where shear rate is low, contains a higher proportion of fibrin and erythrocytes. These concepts are important in the pathogenesis of acute coronary syndromes. In up to two thirds of
patients with unstable angina, plaque fissuring leading to transient vessel occlusion by thrombus is associated with ischemia without detectable myocardial necrosis. Myocardial infarction, on the other hand, is associated with more severe plaque disruption and more persistent thrombotic coronary occlusion in the face of inadequate collateral flow. In addition, spontaneous or pharmacologic lysis of thrombus occurs in some patients with infarction, placing them at high risk of reocclusion. The presence of residual stenosis after lysis of thrombus produces high local shear rate, which facilitates the deposition and activation of platelets on the vessel wall and predisposes to recurrent thrombosis. In addition, the residual thrombus commonly found after thrombolysis constitutes a powerful stimulus to platelet aggregation and fibrin formation, which may result in acute thrombotic vessel reocclusion.

Cardiac Chambers

Intracavitary mural thrombi develop frequently in patients with acute myocardial infarction, chronic left ventricular aneurysm, dilated cardiomyopathy, and atrial fibrillation. The pathogenesis of thrombosis may be outlined along the lines established more than a century ago by pathologist Rudolf Virchow, who defined a triad of precipitating factors: endothelial injury, a zone of circulatory stasis, and a hypercoagulable state. In addition to these factors, the clinical significance derives from the potential for systemic embolism, which also depends on dynamic forces of the circulation.

Endocardial injury. In the first few days after acute myocardial infarction, leukocytic infiltration separates endothelial cells from their basal lamina. The resulting exposure of subendothelial tissue to intracavitary blood serves as the nidus for thrombus development. Specific endocardial abnormalities have also been identified histologically in surgical and postmortem specimens from patients with left ventricular aneurysms and at necropsy in patients with idiopathic dilated cardiomyopathy.

Blood stasis. Both experimental and clinical studies have emphasized the importance of wall motion abnormalities in the development of left ventricular mural thrombi, and it seems clear that stasis of blood in regions of akinesia or dyskinesis is the essential factor. Similarly, stasis is important in the development of atrial thrombi, when effective mechanical atrial activity is impaired, as occurs in atrial fibrillation, atrial enlargement, mitral stenosis, and cardiac failure. Stasis is tantamount to conditions of low shear rate, in which activation of the coagulation system rather than of platelets leads to fibrin formation and constitutes the predominant pathogenetic mechanism in the development of intracavitary thrombi.

Hypercoagulable state. One study of patients with acute myocardial infarction found a significantly greater incidence of thromboembolism in cases of elevated serum fibrinogen levels, suggesting a hypercoagulable tendency in this condition. Although this limb of Virchow’s triad is controversial, it is conceivable that a systemic procoagulant tendency arises during the acute stage of myocardial—
TABLE 1. Thromboembolism in Cardiac Disease Based on Pathogenesis and Risk

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>High (&gt;6% per yr)</th>
<th>Medium (2–6% per yr)</th>
<th>Low (&lt;2% per yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial system</td>
<td>Unstable angina</td>
<td>Chronic stable angina</td>
<td>Primary prevention of cardiovascular disease</td>
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<td>Platelets + fibrin</td>
<td>Acute MI</td>
<td>Chronic phase after MI</td>
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<td>After thrombolysis</td>
<td>PTCA—early phase</td>
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<tr>
<td>Cardiac chambers</td>
<td>A-fib—prior embolism</td>
<td>A-fib—other forms of organic heart disease</td>
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<td>Fibrin</td>
<td>A-fib—mitral stenosis</td>
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<td>Prosthetic valves</td>
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<td>Fibrin + platelets</td>
<td>Mechanical prostheses—prior embolism</td>
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<td>Bioprostheses—normal sinus rhythm</td>
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<tr>
<td>Bioprostheses—A-fib</td>
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MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SVBG, saphenous vein bypass graft; A-fib, atrial fibrillation; LV, left ventricular.

dial infarction and predisposes to thromboembolic events. More relevant is experimental evidence that suggests that the surface of a fresh thrombus is itself highly thrombogenic, producing, at least, a local if not a systemic hypercoagulable state.2

**Dynamic forces of the circulation.** The problems of thromboembolism originating from the cardiac chambers prompt consideration of the balance between the effects of regional injury, stasis, and procoagulant factors, which favor thrombus formation, and dynamic forces of the circulation, which are responsible for the migration of thrombotic material into the systemic circulation. Even though stasis favors thrombus formation within the sac of a left ventricular aneurysm, isolation from dynamic circulatory forces protects against embolic migration.18,19 In diffusely dilated cardiomyopathy, on the other hand, mural thrombus is not isolated from the circulation, and the embolic risk is higher. Thus, factors leading to thrombus formation are not the same as those that produce systemic embolism, and this paradox must not be neglected in the selection of therapeutic options.

**Prosthetic Valves**

**Mechanical prostheses.** Once circulation is restored after implantation of a prosthetic cardiac valve, platelet deposition begins almost immediately both on the prosthetic surface itself—particularly on the endocardium-suture-prosthesis interfaces—and on damaged perivalvular tissues.20 The prosthetic surface area exposed to the circulation is the major factor leading not only to platelet deposition but, more important, to activation of Factor XII, initiating the coagulation cascade.21 Flow stasis and abnormal hemodynamic characteristics of the prosthetic devices promote mainly fibrin generation and, less important, platelet activation.

**Biological prostheses.** Bioprosthetic valves are considerably less thrombogenic, mainly because of the natural properties of the material used in their construction and also because of characteristics of axial flow profile, leaflet pliability, and cyclic sinusoidal washout.22

In summary, the pathogenesis of arterial thrombosis involves damage to the vessel wall and exposure of a thrombogenic substrate, leading to platelet activation and fibrin formation. Intracavitary thrombosis mainly occurs in situations of blood stasis, which favor the activation of the coagulation system and the generation of fibrin. Endocardial injury and the presence of a hypercoagulable stimulus may additionally contribute to thrombus formation. Finally, mechanical prostheses mainly promote the activation of the coagulation system, but platelet aggregation plays an additional role in thromboembolism. Biological prostheses are significantly less thrombogenic.

**Risk Stratification: Implications for Antithrombotic Therapy**

With the foundation established in the foregoing section, which relates pathogenesis to the site of thrombosis in the cardiovascular system, it is germane to classify the various clinical heart disease syndromes according to absolute and relative risk of developing thromboembolic events. We shall discuss three general risk categories: the highest involving more than six episodes per 100 patients per year, a medium risk range of 2% to 6% annually, and a lower risk rate of less than two events per 100 patients per year (Tables 1 and 2). Individuals without overt evidence of heart disease have a comparable annual event rate well below 1%. In general, for patients at high risk, aggressive antithrombotic management is recommended. In contrast, in patients at low risk, antithrombotic therapy may not even be necessary. For the medium risk group, an intermediate approach is suggested (Table 2).

**Coronary Arteries**

During the early phase of the acute coronary syndromes of unstable angina and acute myocardial infarction, the risk of developing thrombotic occlu-
sion (or reocclusion after vessel reperfusion) is substantial, varying between 5% and 20%.25 Patients with stable angina and survivors of myocardial infarction have a medium risk of coronary thrombosis. According to the Framingham Heart Study,24 patients with stable angina followed for 10 years develop a myocardial infarction or suspected cardiac death at an averaged annualized (not actuarial) rate of 5% for men and 2.5% for women. Furthermore, in survivors of myocardial infarction, the annualized rate of recurrent coronary events is just over 5% in both men and women. In addition, patients in the stable phase after coronary angioplasty and saphenous vein bypass surgery can be included in this group because of their intermediate but continuous risk of developing a thrombotic coronary event. Finally, individuals without clinical evidence of coronary disease have a risk of thrombotic arterial events below 1% per year.25

Unstable angina. Disruption of atherosclerotic plaque, both with and without superimposed thrombus, has been clearly demonstrated in patients with unstable angina by angiographic,26,27 angioscopic,28 and histologic29 studies. Plaque rupture exposes underlying vessel media, collagen, and lipid components to the circulating blood, which provokes platelet aggregation and initiation of thrombosis. The resulting thrombus may be evanescent,2 however, and not lead to appreciable myocardial necrosis. Although other factors such as vasospasm and changes in myocardial oxygen balance are certainly important in many cases, the high risk of subsequent myocardial infarction caused by thrombotic coronary occlusion makes antithrombotic therapy advisable for most patients with unstable angina.

The results of two randomized trials support administration of aspirin as a platelet inhibitor to patients with unstable angina. A Veterans Administration cooperative study30 found a 51% collective reduction in mortality and nonfatal myocardial infarction with a daily aspirin dose of 324 mg during a period of 12 weeks, and benefit was still detected after a full year. A Canadian multicenter trial31 corroborated these findings using higher aspirin dosage (1,300 mg daily) for a mean of 18 months. An identical 51% reduction in myocardial infarction and death was found; sulfipyrazone conferred no added benefit. Preliminary evidence from an Italian multicenter trial32 of ticlopidine in patients with unstable angina revealed that this potent platelet inhibitor significantly reduced the combined incidence of cardiac death and myocardial infarction by 53%. Recently, the effects of aspirin, heparin, or both were compared in a short-term (6-day) randomized trial conducted in two Montreal hospitals.33 Aspirin (325 mg twice daily) reduced the combined rate of fatal and nonfatal myocardial infarction by 72% compared to placebo.

For anticoagulant therapy in unstable angina, an earlier study suggested that intravenous heparin reduced the incidence of myocardial infarction by as much as 80%, but deficiencies in patient recruitment left the conclusions of this trial less credible.34 In the Montreal study mentioned above,33 the 240 patients treated with heparin, with or without aspirin, had a striking 89% reduction in the rate of infarction compared to placebo. There was a trend favoring heparin over aspirin, although the sample size was insufficient to permit meaningful statistical comparisons among the three treatment arms.

There is already strong evidence supporting the use of either intravenous heparin or aspirin in the management of patients with unstable angina beginning as soon as possible after onset. Because a substantial proportion of these patients develop myocardial infarction despite treatment with one agent or the other, there is a pressing need to test combinations of low-dose aspirin and heparin in larger clinical trials. There is emerging evidence35 that suggests that this combination is better than either agent alone for prevention of infarction.
Beyond the acute phase, we presently recommend aspirin in a dose of 325 mg daily.

**Acute myocardial infarction.** As in unstable angina, rupture of an atherosclerotic plaque and superimposed thrombotic occlusion play major roles in the development of acute myocardial infarction. In some patients, particularly those with non-Q wave infarction, spontaneous early vessel reperfusion occurs as a result of thrombus lysis or resolution of vasospasm, limiting myocardial necrosis but setting the stage for subsequent ischemic events. The more extensive necrosis, which occurs in Q wave infarction, probably results from persistent thrombotic coronary occlusion in the face of inadequate collateral flow. Because spontaneous vessel recanalization seems to occur in both non-Q and Q wave infarction, an aggressive antithrombotic approach to these patients is beginning to emerge for prevention of thrombotic reoclusion.

In the large Second International Study of Infarct Survival (ISIS-2), patients with suspected myocardial infarction treated within 24 hours of onset with aspirin had a 23% reduction in 5-week vascular mortality compared with those given placebo. This dramatic benefit was possibly related to prevention of reinfarction in patients with spontaneous vessel recanalization. Indeed, aspirin reduced the rate of nonfatal reinfarction by almost half.

The issue of short-term anticoagulation in acute myocardial infarction, aimed at reducing the incidence of death, infarct extension, or reinfarction, is still not settled. Despite a large number of studies published during the past 40 years, only three randomized controlled trials were of sufficient size to establish a significant reduction in mortality with anticoagulants. Of these, only one found a statistically significant decrease in mortality; the other two showed a beneficial trend. In addition, all three revealed a trend toward lower reinfarction rate. When the results of the only six published randomized trials were pooled, a significant 21% reduction in mortality in treated patients emerged. Despite the limitation inherent in retrospective meta-analysis of heterogeneous trials, short-term anticoagulation in acute myocardial infarction appears to provide, at least a modest reduction in early mortality. Because of the high risk of reinfarction and death in the first weeks following acute infarction, however, the combination of aspirin and an anticoagulant may prove beneficial and deserves clinical testing.

Patients with acute myocardial infarction treated with thrombolytic agents are at high risk of early coronary reoclusion, which approaches 5% to 20%. The importance of concomitant platelet inhibitor therapy in patients undergoing thrombolysis was emphasized by the results of the ISIS-2 trial, in which streptokinase alone decreased early cardiovascular mortality by 25%, while the combination of aspirin and streptokinase decreased the death rate by 42% compared with placebo. The benefits of these agents appeared independent of one another, and the addition of aspirin to streptokinase reduced the clinical reinfarction rate by 50%. The use of heparin was neither randomized nor controlled; thus its role cannot be assessed based on this trial. We advocate aspirin (160–325 mg daily) as early as possible in the treatment of acute myocardial infarction, whether or not thrombolytic agents are given. Given the marked thrombogenicity of the residual thrombus following vessel recanalization, and while awaiting the results from two large randomized trials, heparin therapy is sensible for a period of 3–7 days after thrombolysis. The lower incidence of reoclusion in some recent thrombolytic trials may be related to the use of combined therapy with aspirin plus heparin. Daily aspirin should then be continued on discharge.

**Chronic phase after myocardial infarction.** Survivors of acute myocardial infarction are at a medium risk of recurrent infarction or cardiac death (Table 1). Because cardiac morbidity and mortality during this period (within 2 years of infarction) may be related to a number of factors including left ventricular dysfunction, ventricular arrhythmias, and recurrent myocardial infarction, proving that antithrombotic therapy is beneficial in these patients has been difficult and has generated controversy for several decades. Since 1974, there have been no fewer than 10 randomized trials involving platelet inhibitors in patients with prior myocardial infarction, and an extensive meta-analysis of these studies has recently been published. Despite the inherent problems of pooled data, this overview concluded that among survivors of myocardial infarction, platelet inhibitors reduced vascular mortality by 13%, nonfatal reinfarction by 31%, nonfatal stroke by 42%, and all important vascular events by 25%. Aspirin alone was at least as effective as the combination of aspirin and dipyridamole and more effective than sulfinpyrazone. Available data do not justify the additional cost and frequency of administration of drugs other than aspirin in this group of patients.

Despite numerous trials of long-term anticoagulation conducted since 1950, only three have been adequately designed to demonstrate a salutary effect in postinfarction patients. Only one study showed a trend toward lower case fatality rate; all suggested a reduction in reinfarction of 25% to 50%, but this was statistically significant in only one trial. A pooled analysis of nine trials of anticoagulation in postinfarction patients showed that this therapy decreased overall mortality by about 20%. However, because not all trials were properly controlled, the conclusions of this collective analysis must be interpreted with caution. Emerging evidence from a Norwegian trial supports the use of warfarin after myocardial infarction, for the prevention of reinfarction and mortality.

Considering the above data, the evidence supporting the use of aspirin in the secondary prevention...
of cardiovascular morbidity and mortality beyond the acute phase of myocardial infarction is at least as strong as that supporting anticoagulation. At a daily dose of 325 mg, aspirin offers several advantages over long-term anticoagulants in cost, ease of administration, and side effects. Thus, to survivors of myocardial infarction, daily aspirin is recommended.

**Chronic stable coronary artery disease.** Patients with a remote history of myocardial infarction (beyond 2 years) and those with chronic stable angina are at medium risk of coronary ischemic events, which varies between 2.5% and 5% per year. In patients with remote myocardial infarction, recurrent coronary thrombotic events are probably the main cause of mortality. Most studies of platelet inhibitors in survivors of myocardial infarction have shown a beneficial trend toward lower mortality and reinfarction, which became significant only when the data derived from all available trials were pooled.47

For anticoagulant therapy, in the Sixty Plus Reinfarction study,51 patients older than 60 and treated for a median of 6 years with warfarin after myocardial infarction were randomly assigned to continue anticoagulant or substitute placebo. The design was double-blind, and anticoagulant dosage was tightly controlled for a period of 2 more years, at which point anticoagulated patients had 26% lower mortality (p=0.071) and 55% lower incidence of reinfarction (p=0.0005) when compared with placebo. It appears, therefore, that both aspirin and anticoagulants are effective in prevention of reinfarction and reduction in mortality in asymptomatic patients after remote myocardial infarction, but the former is associated with lower cost and risk.

Although no randomized trial of antithrombotic therapy in chronic stable angina has been published, the sustained beneficial effects of aspirin after initial therapy of patients with unstable angina30,31 suggest a role for aspirin in stable coronary disease. A dose of 325 mg daily is associated with minimal gastrointestinal toxicity and should be considered in these patients. Preliminary evidence52 from an angiographic study in patients with stable coronary disease, suggests that platelet inhibitors reduce the incidence of myocardial infarction and new lesion formation, but do not prevent progression of disease in those with preexisting lesions.

**Primary prevention of coronary events.** Although platelet inhibitor therapy has been shown to decrease the incidence of vascular events by 25% when used for secondary prevention in patients with evidence of cardiovascular or cerebrovascular disease,47 the same benefit is not as apparent when aspirin is given for primary prevention in apparently healthy individuals.25,53 In the final report from the US Physicians’ Health Study,25 which included 22,071 male physicians followed for 4.8 years, aspirin (325 mg every other day) significantly reduced the incidence of myocardial infarction by 44%, from about 0.4% to 0.2% per year. The incidence of cardiovascular death was identical in the aspirin and placebo groups, but aspirin was associated with a slight increase in the number of severe hemorrhagic strokes (13 vs. 6). In a British primary prevention trial of 5,139 male physicians, two thirds were randomly assigned to take aspirin (500 mg daily), and one third was instructed to avoid it (no placebo was used). After 6 years, no difference in the incidence of myocardial infarction or cardiovascular mortality was detected. Although the number of enrolled subjects was smaller than in the American trial, cardiovascular event rates were five to 10 times higher. When both studies are considered together, there appears to be reduction in coronary events with aspirin but at the price of an increased risk of hemorrhagic stroke. Before recommending aspirin to every adult, the risks of therapy must be carefully weighted against its potential benefits. Aspirin appears to exert a greater beneficial impact in patients with risk factors for coronary disease and those with cerebral or peripheral artery disease.25

**Coronary Intervention**

**Coronary angioplasty.** Coronary angioplasty is associated with endothelial denudation and exposure of thrombogenic elements of the disrupted atherosclerotic plaque and vessel wall, which may lead to mural thrombosis and acute occlusion. Experimentally,54 when angioplasty results in mild arterial injury, only minimal deposition of platelets occurs. On the other hand, severe damage or dissection of the arterial wall leads to exposure of collagen, smooth muscle cells, and other components of the atherosclerotic lesion and to the release of tissue thromboplastin. Contact with these substances results in activation of platelet and coagulation processes, predisposing to acute thrombotic occlusion.55 Thrombus formation at the site of angioplasty is not only important in acute occlusion but may also contribute to later restenosis.

Several studies55–57 have clearly shown that pretreatment of patients with aspirin alone, aspirin plus dipyridamole, or ticlopidine, significantly reduces the rate of acute thrombotic complications after angioplasty. The role of heparin in prevention of acute vessel occlusion during angioplasty has not been properly tested clinically, but there is experimental evidence that suggests an inverse relation between the dose of heparin and both platelet deposition and mural thrombosis.58 In addition, uncontrolled preliminary studies in patients with unstable angina have demonstrated that pretreatment with heparin for 1 to 8 days reduces the incidence of acute thrombotic complications during and after angioplasty.59–61 Therefore, high-dose heparin is widely used during this intervention. Given the substantial risk of acute thrombotic complications associated with angioplasty, pretreatment with aspirin combined with adequate heparinization throughout the procedure is strongly recom-
Antithrombotic Therapy

Atrial fibrillation. Systemic embolism is a common and potentially devastating complication of atrial fibrillation associated with both mitral valve disease and certain other forms of organic heart disease. Blood stasis appears to play a predominant pathogenetic role in thrombus formation in patients with atrial fibrillation. Patients at highest risk are those with a history of systemic embolism in the previous 2 years; in this group, the embolic risk approaches 10% to 20% in the first 1 or 2 years. Although no prospective randomized trials of anticoagulants are available, the current recommendation is for long-term anticoagulant therapy aimed at prolonging prothrombin time (PT) to 1.5–2.0×control (standard international normalized ratio of prothrombin suppression [INR] 3.0–4.5) in these patients. Patients at somewhat lower but nevertheless substantial risk of embolism (which approaches 6% per year) are those with atrial fibrillation associated with mitral stenosis. Data from numerous nonrandomized and controlled trials have suggested that anticoagulation reduces the rates of embolism and death in patients with rheumatic valvular disease by 25%. Based on known embolic risk and on results of clinical trials, chronic anticoagulation to prolong PT to 1.3–1.5×control (INR, 2.0–3.0) is recommended for these patients. In addition, patients with uncontrolled hyperthyroidism and heart failure appear to be at increased risk of embolism. Although anticoagulation for these patients has not been evaluated by prospective randomized trials, this therapy is recommended until the patient becomes euthyroid and reversion to sinus rhythm has been achieved.

At the lower end of the spectrum of embolic risk in patients with atrial fibrillation are those without evidence of associated organic heart disease. The natural history of lone atrial fibrillation was
addressed by the Framingham investigators,\textsuperscript{74} who followed 30 of these patients for more than 10 years and found a fourfold increase in the incidence of stroke as compared with matched controls. Aside from the small sample size, other limitations of the analysis were the relatively advanced age of the subjects (mean, 70 years) and the inclusion of patients with hypertension. In another study,\textsuperscript{75} 97 normotensive patients younger than 60 years with lone fibrillation were followed for a mean of 17 years at the Mayo Clinic. Anticoagulants were used in just a few patients. Only eight embolic events were identified, an overall incidence well below 1% per year. These data suggest that for patients younger than 60 years with atrial fibrillation but no evidence of organic heart disease, the hazards of chronic anticoagulation outweigh its potential benefits.

Between these two poles exists a large group of patients with an intermediate but incompletely defined risk of embolism: those with nonvalvular atrial fibrillation associated with various forms of cardiovascular disease.\textsuperscript{69,76} The embolic risk in these patients lies between 4% and 6% per year\textsuperscript{77,78} and accounts for almost one half of cardioembolic strokes. Given the severe functional deficits that often follow embolic stroke and the fact that these events are usually unheralded by warning signs, preventive therapy is the only rational approach. In a retrospective study at the Montreal Heart Institute,\textsuperscript{78} nonanticoagulated patients had an incidence of systemic embolism of 5.5% per year, whereas anticoagulated patients had a significantly lower embolic rate of 0.7% per year.

In a recently completed Danish trial,\textsuperscript{76} patients with nonvalvular atrial fibrillation were randomized to receive warfarin, aspirin, or placebo. The total incidence of stroke and transient ischemic attacks was reduced nearly 75% with warfarin adjusted to maintain the INR at 2.8–4.2 (approximate PT, 1.4–1.9×control). The incidence of severe and fatal stroke, however, was similar in both treatment groups. This study suggests that chronic anticoagulation with warfarin may be beneficial for prevention of embolic stroke in patients with constant, nonvalvular atrial fibrillation, although a high proportion of anticoagulated patients were withdrawn from active treatment. The warfarin dose used in this trial was higher than the one recommended by a consensus of investigators,\textsuperscript{70} who proposed that prolonging the PT to 1.3–1.5×control (INR, 2.0–3.0) is sufficient for patients without prior history of embolism. In the Danish trial,\textsuperscript{76} no advantage of aspirin over placebo for embolism prevention was identified. Although the results of this study support the use of warfarin, the differentiation of subgroups in the broad category of nonvalvular atrial fibrillation that stand to gain most from anticoagulation remains to be accomplished.

**Acute myocardial infarction.** Approximately one third of patients with acute anterior myocardial infarction and less than 5% of those with inferior infarction develop left ventricular mural thrombi.\textsuperscript{79} These thrombi tend to occur in the first week and particularly in the first 2 days. Thrombi are more likely to form in cases of large infarcts (peak serum creatine kinase, >2,000 units/l). Systemic embolism, which occurs in about 10% of cases in which left ventricular thrombi are echocardiographically apparent, is the most important complication, affecting 2% to 5% of victims of myocardial infarction.\textsuperscript{23,79} Echocardiographically, thrombi that protrude into the left ventricular cavity and have increased mobility are more likely to embolize than those without these characteristics.\textsuperscript{80}

Because the incidence of embolism is highest in the first 1–3 months after infarction and short-term anticoagulation has been shown to reduce the embolic rate by 25% to 75%,\textsuperscript{40–42} the following approach is recommended: Patients with increased embolic risk, namely, those with large anterior infarcts, congestive heart failure, or atrial fibrillation, should receive heparin on admission (aimed at prolonging the activated partial thromboplastin time to 1.5–2.0×control). A recent study by Turpie et al\textsuperscript{81} showed that high-dose subcutaneous heparin (12,500 units every 12 hours) significantly reduced the incidence of mural thrombosis in patients with anterior infarcts as compared with low-dose heparin (5,000 units twice daily). Heparin therapy may be followed by warfarin to prolong the PT to 1.2–1.5×control (INR, 2.0–3.0) in patients with echocardiographic evidence of mural thrombi or large akinetic regions. Warfarin may be stopped after 1–3 months unless the risk of thromboembolism remains elevated as a result of heart failure, impaired left ventricular function, or persistent echocardiographic evidence of mural thrombi.\textsuperscript{82} The optimum duration of anticoagulant therapy in this group has not been determined.

**Chronic left ventricular aneurysm.** In contrast to the prevalence of thromboembolism in acute myocardial infarction, the incidence of embolism in chronic left ventricular aneurysm is significantly lower (0.35% per year).\textsuperscript{83} The reason for this difference is probably twofold. First, thrombi formed after acute infarction are usually mobile, friable, and protrude into the ventricular cavity, whereas thrombi in chronic aneurysms are laminated and more adherent to the endocardium.\textsuperscript{11,79} Second, thrombi located within an aneurysmal sac, which is devoid of contractile fibers, are less prone to propulsion into the ventricular outflow tract.\textsuperscript{19} Although some investigators\textsuperscript{82} have found a persistent risk of embolism in postinfarction patients, it was not the presence of an aneurysm but rather the mobility and protrusion of thrombus that predicted embolic events. Given available data, patients with remote infarction and chronic left ventricular aneurysm are at low risk of embolism and need not receive anticoagulants. Whether these drugs should be given to patients with echocardiographic evidence of mobile or protruding thrombi, however, remains to be determined.
Dilated cardiomyopathy. Postmortem studies have found a high prevalence of right and left ventricular mural thrombi in patients with idiopathic dilated cardiomyopathy. Blood stasis and low shear rate present in a dilated, hypocontractile ventricle lead to activation of coagulation processes. Because the mural thrombus is not mechanically isolated, as occurs in a ventricular aneurysm, embolism of thrombotic material may occur. In a retrospective study, patients treated with anticoagulants had no evidence of systemic embolism, whereas those not anticoagulated had an embolic rate of 3.5% per year. Lacking any prospective trial of antithrombotic therapy in these patients at medium risk for embolism, this evidence supports chronic warfarin administration, particularly in those with overt heart failure or atrial fibrillation.

In summary, since thrombosis within the cardiac chambers is related to activation of the coagulation system, anticoagulation (of variable intensity) is recommended to patients at high and medium risk for thromboembolism. In contrast, patients at low risk, in general, do not require this therapy.

Prosthetic Valves

Mechanical prostheses. Prosthetic surfaces are thrombogenic by virtue of their ability to activate both the intrinsic coagulation system and platelets. Increased shear rate, blood stasis (particularly in high-profile prosthetic devices), and associated disturbances of the cardiac chambers predispose to thromboembolism. Patients with history of embolism and valve manufacture before the mid-1970s are at highest risk, which exceeds six events per 100 patients per year. Atrial fibrillation and left atrial thrombus contribute additional risk.

Warfarin, at a dose sufficient to prolong the PT to 1.5–2.0×control (INR, 3.0–4.5), is the most important agent for prevention of thromboembolism (Table 2). Studies in patients with mechanical prostheses have consistently shown that anticoagulation significantly reduces the incidence of valvular thrombosis and embolism. Platelet inhibitors in themselves cannot be expected to have much impact in reducing the incidence of embolic events in this high-risk group. However, the addition of a platelet inhibitor such as dipyridamole (300–400 mg daily) to warfarin may reduce the thromboembolic risk below that of warfarin alone. Indeed, the antithrombotic effects of dipyridamole are more evident on prosthetic materials such as artificial heart valves than on biologic surfaces. In patients with mechanical prostheses, the combination of warfarin and aspirin was also found effective in some studies, although the risk of gastrointestinal bleeding was increased when aspirin was given in daily doses of 500 mg or more. We suggest supplementing warfarin with dipyridamole (300–400 mg daily) in patients with mechanical prostheses and prior embolism and in those with older prosthetic devices.

Patients with newer mechanical prostheses have a risk of thromboembolism that ranges between 1% and 5% per year despite anticoagulants; the risk is higher for those with prosthetic valves in the mitral position, multiple prostheses, and Starr-Edwards models. Inadequate anticoagulation increases the thromboembolic risk twofold to sixfold, whereas excessive anticoagulation (PT, more than 2.5×control) increases the risk of bleeding complications fourfold to eightfold. Platelet inhibitors alone have not been found to confer protection against embolism in patients with mechanical prostheses. Indeed, studies of aspirin plus dipyridamole in these patients have shown an incidence of thromboembolism as high as 10% per year. Patients with mechanical prostheses treated with warfarin had significantly fewer thromboembolic events compared to those treated with aspirin combined with either dipyridamole or pentoxifylline. It seems clear, therefore, that patients with mechanical prostheses should receive anticoagulant therapy indefinitely, aimed at PT of 1.5–2.0×control (INR, 3.0–4.5).

Biological prostheses. Although bioprosthetic valves are less thrombogenic than mechanical devices, thromboembolism may occur in two to three per 100 patients per year, particularly in the first 3 months after surgery, and more often in those patients with mitral than aortic prostheses and in those with atrial fibrillation or prior embolism. Patients with mitral bioprostheses should receive warfarin postoperatively, aimed at PT of 1.3–1.5×control (INR, 2.0–3.0) for 1–3 months, unless atrial fibrillation persists, in which case warfarin should be used indefinitely. Although aortic bioprostheses are associated with a lower incidence of embolism, the concomitant presence of atrial fibrillation may warrant the use of chronic warfarin therapy in these patients as well.

Patients who maintain normal sinus rhythm postoperatively without left ventricular dysfunction or prior embolism are at lower risk. In these patients there may be no need for sustained anticoagulant therapy. This is particularly true for patients with aortic bioprostheses, in whom even platelet inhibitors may be unnecessary. No randomized, controlled studies of platelet inhibitors in patients with bioprostheses have been reported. In an uncontrolled trial, long-term aspirin was associated with a low incidence of embolism in these patients.

In summary, activation of the coagulation system, and secondarily, of platelets occur in patients with prosthetic valves. For those at high risk, the combination of anticoagulant and a platelet inhibitor is suggested. Medium-risk patients can be managed with an anticoagulant alone, and those at low risk may not require antithrombotic therapy.

Conclusion

Rooted in ideas about thrombosis and embolism planted more than a century ago, an approach to antithrombotic therapy in various cardiovascular
disease states has emerged based on current knowledge of pathophysiology and an appreciation of differential clinical features determining morbid risk. The essential parameters of this approach, as it takes shape in 1989, form the framework of Tables 1 and 2. In Table 1, the numerical values corresponding to the relatively high-, medium-, and low-risk clinical situations, defined at the top of the columns, should be taken as approximate and even flexible, as distinguishing variables in individual patients avoid rigidly defined categories. In Table 2, a rational therapeutic approach is formulated along the lines of anatomic location represented by the horizontal rows, and the relative risk is depicted in the columns.

In the arterial circulation, vessel wall injury leads to both platelet activation and production of thrombin and fibrin, suggesting a combined therapeutic approach with a platelet inhibitor and an anticoagulant. The propensity to thrombosis determines the intensity of antithrombotic therapy. High-risk patients with unstable angina or evolving acute myocardial infarction may be treated aggressively, perhaps with a combination of a platelet inhibitor and an anticoagulant, although final recommendations await the results from ongoing clinical trials. Patients undergoing coronary angioplasty or saphenous vein bypass surgery should receive platelet inhibitors and adequate anticoagulation during the procedure. Coronary disease patients at moderate risk in the chronic phase of stable angina, past myocardial infarction, angioplasty, or bypass surgery are best managed with a platelet inhibitor rather than an anticoagulant for reasons of convenience, safety, and economy. In low-risk patients in whom prevention of complications of atherosclerosis is desired, aspirin may sensibly be prescribed to those with certain risk factors such as diabetes, family history, tobacco exposure, and hypercholesterolemia. However, a hint that long-term aspirin administration may be associated with an escalated chance of intracerebral hemorrhage mitigates against its indiscriminate use.

Within the cardiac chambers, stasis of blood flow causes coagulation to predominate over platelet activation as the principal mechanism of thrombus formation, and anticoagulant therapy alone seems most appropriate in management of these patients. At highest risk are patients with atrial fibrillation and prior embolism; at somewhat lower but yet substantial risk are those with mitral stenosis and uncontrolled hyperthyroidism. Patients at medium risk are those immediately after large anterior myocardial infarction and uncompensated dilated cardiomyopathy. For these groups, there is sufficient evidence to indicate chronic anticoagulation. Some patients with nonvalvulopathic atrial fibrillation also with other forms of cardiac disease benefit from warfarin therapy, but subgroups in this population have not yet been sufficiently defined. At lowest risk are patients with lone atrial fibrillation without overt heart disease and those with chronic left ventricular aneurysm, who do not require anticoagulants.

The thrombogenicity of prosthetic heart valves involves both fibrin formation and, to a lesser degree, platelet activation, and is considerably greater for mechanical than biological devices. Patients at highest risk—those with older mechanical prostheses or prior embolism—should be treated with a combination of an anticoagulant and a platelet inhibitor; while either dipyridamole or aspirin has proved beneficial, dipyridamole has the advantage of not potentiating bleeding. At medium risk are patients with modern mechanical valvular prostheses and those with bioprostheses in the presence of atrial fibrillation, who can be successfully managed with an anticoagulant alone. When bioprostheses are in place along with normal sinus rhythm, the embolic risk is low enough that antithrombotic therapy is not needed.

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