Heart attack (acute myocardial infarction or sudden cardiac death related to disease of the large arteries supplying the heart) and ischemic stroke (focal neurological deficit secondary to cerebrovascular disease of the large and small arteries supplying the brain or emboli from the heart or aorta) are among the foremost serious health problems in the Western hemisphere. Because coronary artery disease is so prevalent, medical treatment and coronary revascularization, through coronary artery bypass grafting and/or percutaneous coronary angioplasty, are important components of health care costs in the United States.

The purpose of this report, which is based on a concise review of the current knowledge about the role of aspirin in cardiovascular disease, is to provide a position statement for physicians to serve as a guideline for the use of aspirin in the primary and secondary prevention of cardiovascular disease.

Role of Platelets and Thrombosis in Cardiovascular Disease

Platelets, platelet products, and thrombosis play a critical role in cardiovascular disease, particularly in the development and progression of coronary artery disease leading to acute coronary syndromes (i.e., heart attack), transient cerebral ischemic attack, acute cerebral infarction or ischemic stroke, and in the early occlusion rates associated with coronary artery bypass grafting and percutaneous coronary angioplasty. They are also likely to be important factors in the fibroproliferative lesions that result from mechanical or immunological injury to the endothelium.

Coronary Artery Disease Progression and Acute Coronary Syndromes

Each year in the United States about 1.5 million people suffer heart attacks, most related to coronary thrombosis. Nearly 300,000 die before admission to the hospital, and another 200,000 die within the first month, with most of these deaths occurring during the first 24 hours as a result of the initial attack or of subsequent reinfarction. Thus, the cumulative mortality during the first month is about 33%. By 1 year, another 10% have died. After patients have survived a year, reinfarction and death rates, stabilized at 3–5% per year, are similar to those of patients with symptomatic coronary artery disease (i.e., angina pectoris) but significantly greater than those of the general population.

Coronary mural thrombosis and its fibrotic organization contributing to the atherosclerotic process was suggested by von Rokitansky in the mid-19th century and later by Duguid in the 1940s. Indeed, more recent technology—angiographic, angioscopic, pathological, and experimental—has documented that disruption of small platelet- and fibrin-rich atherosclerotic plaques, with subsequent mural thrombosis and fibrotic organization of the thrombus, may contribute to the progression of coronary atherosclerosis. However, it is not known how prevalent this process of intermittent plaque progression is compared with the more chronically progressive proliferative process secondary to chronic endothelial irritation postulated by Ross. Nevertheless, it would be of potential clinical significance if mural thrombosis could be decreased by platelet inhibitor or anticoagulant therapy.

Disruption of an atherosclerotic plaque with resultant intraluminal thrombosis also plays a fundamental role in the pathogenesis of unstable angina, acute myocardial infarction, and sudden death. Thus, although coronary thrombotic occlusion as a cause of acute myocardial infarction was suspected by Herrick at the turn of the century, only over the last few years have clinical and pathological observations and experimental investigation led to a better understanding of how a thrombus forms and how it is involved in acute ischemic coronary events. DeWood et al., Buja and Willerson, Rentrop et al., Falk, Richardson (Davies) et al., and Davies et al. have clearly shown that formation of platelet- and fibrin-rich thrombi (also containing leukocytes), usually secondary to atherosclerotic plaque disruption, plays a fundamental role in development of the acute coronary syndromes.

In addition, accumulating evidence indicates that the resulting intraluminal thrombotic process is dynamic and repetitive. In some patients with unstable angina, plaque disruption may lead to intermittent or transient vessel occlusion and ischemia by a labile
thrombus. In others, more severe vascular damage in the form of a large ulcer may lead to formation of a fixed thrombus and a more chronic occlusion, resulting in acute myocardial infarction. However, even these thrombotic occlusions may resolve, not only with thrombolytic therapy but often spontaneously, and within hours or days they can recur, both pathologically and clinically.

Finally, sudden coronary death frequently involves a rapidly progressing coronary lesion in which plaque disruption and resultant thrombosis abruptly lead to ischemia and fatal ventricular arrhythmia. Absence of collateral flow to the myocardium distal to the occlusion or formation of platelet-rich microemboli may also contribute to sudden ischemic death.

**Transient Ischemic Attacks and Ischemic Strokes**

Clinical manifestations of atherosclerotic disease in the brain circulation (intracranial and extracranial) result in a spectrum of acute ischemic syndromes ranging from transient ischemic attack to full-blown brain infarction. In the United States about 500,000 new and recurrent strokes and 145,000 deaths due to stroke occur each year. A high percentage of those who survive have various degrees of neurological sequelae, and the annual estimated direct cost is $13–14 billion. Furthermore, after a first stroke, even a minor stroke or transient ischemic attack, the risk of a subsequent stroke is estimated at about 5% per year for the first 3 years (with the highest incidence within the first month) and 3% annually thereafter.

Thrombosis overlying an atherosclerotic plaque may play a key pathogenic role in patients suffering from these vascular diseases. However, in contrast to the well-documented role of thrombosis in the acute coronary syndromes, the frequency of a clinically relevant thrombotic component in brain ischemic syndromes is not as well defined. Atherosclerotic plaques with overlying thrombi are not necessarily ulcerated, and other pathogenic mechanisms also play a role in a proportion of these patients. For example, nearly 20% of ischemic strokes are secondary to cardiogenic emboli; these are associated with greater functional impairment and higher early mortality (11–21%) than are those due to cerebrovascular mechanisms. The proportion of emboli due to atherothrombosis of the aorta should be better defined in the near future through the use of transesophageal echocardiography.

Although transient ischemic attacks only represent a transient focal neurological deficit, they are often a presenting manifestation or a marker of a stroke that will occur within days to years. Furthermore, transient ischemic attacks can be a marker for atherosclerosis in other circulations and may indicate increased risk of myocardial infarction. In general transient ischemic attacks evolve from two causes: focal low flow and embolism. The mechanism of focal low flow in transient ischemic attacks is not well defined, but probably a critically stenotic or occluded artery reduces flow to a focal area of normal brain. Poor collateral circulation to the ischemic area may play a prominent role, but viscosity, vessel wall compliance, and other unknown factors explain why the reduction is transient. Evidence from recent pathological and imaging studies indicates that transient ischemic attacks can result from progressive luminal narrowing that leads to precarious hemodynamic insufficiency. Platelet- and fibrin-rich mural thrombi at the subocclusive stage can either contribute to the obstruction or give rise to embolism. However, the exact proportion of patients with transient ischemic attacks of intra-arterial embolic origin is unknown. Another pathogenic mechanism can be fibrin-rich cardiogenic emboli. Clinical data indicate that at least 20–25% of all cerebral ischemic events and more than 50% of cerebral ischemic events in the elderly are associated with atrial fibrillation, and clearly some of these are due to emboli originating in the heart, aorta, or carotid arteries.

Because of the morbidity, mortality, rate of recurrence, and health costs associated with brain infarction, a better understanding of its mechanisms, as well as the development of secondary and primary prevention strategies, should be a priority for the medical community. The clinical hallmark of stroke is the abrupt development of a focal neurological deficit attributable to ischemia or bleeding in a particular territory. Intra-cerebral or subarachnoid hemorrhage accounts for 15–20% of strokes. However, the vast majority of strokes (80–85%) are ischemic in origin, and a substantial proportion result from atherosclerotic disease of the large and small cerebral arteries. Clinical studies suggest that about 15% (range, 6–23%) of all ischemic strokes are the result of fibrin-rich cardiogenic emboli.

In a large, multicenter stroke data bank project, 19% of strokes were cardioembolic, based on carefully defined clinical criteria. The prevalence of presumed cardioembolic causes varied between 13% and 34% at the four centers in this study, suggesting either patient population differences or intercenter variability in the application of diagnostic criteria. In addition to the lack of validated, reliable, clinical diagnostic criteria for differentiating between cardioembolic and nonembolic ischemic stroke, a significant proportion of patients are at risk for both mechanisms of stroke. Thus, in recent reports, about 30% of patients with ischemic stroke had a potential cardiac source of embolism, but about one third of these patients also had concomitant cerebrovascular atherosclerosis that could be responsible for brain ischemia.

**Coronary Revascularization: Coronary Artery Bypass Grafting and Percutaneous Coronary Angioplasty**

Coronary artery bypass grafting and percutaneous coronary angioplasty are common in the practice of cardiovascular medicine. Recent data indicate that in the United States 392,000–500,000 coronary revascularization procedures are performed annually at an estimated direct cost of nearly $10 billion. Atherothrombosis is not only the basis of coronary disease leading to revascularization procedures but is also an important factor in the early complication rates of such interventions.

Saphenous vein graft disease accounts for substantial morbidity after coronary artery bypass grafting. The graft occlusions are mainly platelet-thrombotic in origin and seem related to endothelial disruption caused by surgical manipulation, exposure of the graft to high intra-arterial pressure, and vessel damage at the distal anastomotic site; because in internal mammary artery grafts these processes do not occur to the same extent,
their occlusion rate is quite low. The risk of early saphenous graft occlusion within the first postoperative month is about 5–15% per distal anastomosis; at 1 year the risk of occlusion is 15–20%, and at 10 years up to 50% of vein grafts will be occluded. Antithrombotic agents have demonstrated a clear benefit in preventing early thrombotic occlusion of saphenous vein grafts. However, because late vein graft disease in the first postoperative year involves an accelerated hyperplastic response (e.g., as a result of vein graft damage secondary to chronic high pressure and pulsatile flow, causing graft atherothrombosis), antithrombotic agents are less effective in its prevention.

Percutaneous coronary angioplasty has become a successful and widely used treatment for patients with coronary artery disease since its first clinical application by Gruntzig et al in 1979. The primary success rate has improved despite the increase in complexity of procedures and cases. However, acute occlusion, which occurs in about 7–15% of patients, and late restenosis, which occurs in about 25–40%, are the most important problems after successful angioplasty. A multifactorial pathophysiological process accounts for acute occlusion; it involves formation of platelet-and fibrin-rich thrombi, intimal dissection, medial and subintimal hemorrhage (especially with thrombolytic therapy), vascular recoil, and vasoconstriction. In contrast, chronic restenosis involves the development of fibrocellular intimal hyperplasia in a milieu created by vascular injury, platelet activation, thrombin generation, and the release of mitogens. Accordingly, current pharmacological approaches involving antithrombotic therapy have been effective in lowering the rate of acute occlusion but not in preventing chronic restenosis. That is, the aforementioned prothrombotic entities—vascular injury, platelet activation, thrombin generation, and mitogenic activity—cannot be completely prevented by currently available therapies.

Aspirin—Mechanisms of Action, Dose–Response Relations, and Side Effects

Because of its antipyretic and analgesic effects, relatively good tolerance, low cost, and easy accessibility, aspirin is the most consumed drug today. In the United States alone, between 20 and 30 billion tablets are ingested each year. Nevertheless, unsupervised aspirin therapy is hazardous because it easily induces a hemorhagic diathesis. Surprisingly, although aspirin is an old and often-used drug, new therapeutic uses for it are still being discovered. Aspirin’s antithrombotic role in one of our most significant health problems, atherothrombotic cardiovascular disease, is still evolving.

Historical and Pharmacological Background

The salutary effects of willow bark have been known to several cultures for centuries. Salicin, its active ingredient, is a bitter glycoside from which sodium salicylate was isolated in 1829 by Leroux, who demonstrated its antipyretic effects. The pharmaceutical chemist Hoffman, while employed by the Bayer Company, prepared acetylsalicylic acid, which was shown to have anti-inflammatory and analgesic effects. Acetylsalicylic acid was introduced into clinical medicine at the turn of the century under the name “aspirin.”

The inhibitory effect of this compound on the action of blood platelets was not discovered until the late 1960s, and it has been little more than a decade since this property was linked to the irreversible inhibition of the cyclooxygenase enzyme responsible for the synthesis of eicosanoids. In platelets aspirin prevents the formation of thromboxane A2, a substance that induces platelet aggregation; because platelets are unable to generate new cyclooxygenase, inhibition of the en 

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suggested that the higher the dose of aspirin the greater the chance of inhibiting platelet involvement, given that the strength of the local vascular agonist (e.g., collagen) is unknown and may be high.\textsuperscript{65} However, differences in efficacy with different aspirin dosages cannot be excluded, particularly in patients with cerebrovascular disease. Accordingly, except for patients with cerebrovascular disease, low aspirin doses (75–325 mg/day) are currently recommended.\textsuperscript{54} However, if the lowest dose (75 mg/day) is considered, the evidence suggests that for a prompt antplatelet effect patients should receive an initial loading dose of 160–325 mg aspirin.\textsuperscript{66,67} For those with cerebrovascular disease, the effects of lower doses are less clear. Although a dose as low as 75 mg/day has shown benefit, until the optimal dose has been established through properly controlled, well-designed studies comparing low and high doses, no strong recommendations can be made.

**Dose of Aspirin and Side Effects**

Most trials of aspirin in a dose of 900 mg/day or more have reported an increased incidence of stomach pain, heartburn, nausea, constipation, and occult gastrointestinal blood loss.\textsuperscript{54} However, the most serious complications are gross gastrointestinal hemorrhage and hemorrhagic stroke.

**Gastrointestinal hemorrhage.** An association between aspirin ingestion and gastrointestinal bleeding was originally documented in a case-control study.\textsuperscript{68} More recent longitudinal studies in volunteers and patients have demonstrated that both acute and chronic aspirin use produce dose-related increases in acute gastric bleeding.\textsuperscript{69} A small but significant increase in gastric bleeding was observed with a dose of 75 mg/day; this effect was approximately doubled with a dose of 300 mg/day and increased fivefold with a dose of 1.8–2.4 g/day.\textsuperscript{70} A number of antithrombotic trials using aspirin at various dosages have confirmed that the gastrointestinal side effects of the drug are dose related.\textsuperscript{54,72,73} If patients have a very mild or undetected hemorrhagic diathesis, the effect may be amplified by even low doses of aspirin, and bleeding may occur.

Although early studies in animals suggested that aspirin administered by intravenous injection produces an increase in gastrointestinal blood loss, recent studies in humans have failed to confirm these findings and indicate instead that the gastric effects of aspirin are due to local effects induced by oral administration.\textsuperscript{74,75} The exact cause of aspirin-induced gastric injury has not been elucidated. Inhibition of eicosanoid synthesis in the gastric mucosa by aspirin\textsuperscript{76} has been proposed as an important mechanism. Another possibility is that aspirin has no effect on hydroxy acid synthesis, and that leukocytes may therefore produce leukotrienes in excess after aspirin administration; aspirin could also damage gastric and intestinal mucosa. There is evidence that the gastric side effects of aspirin can be reduced by oral administration of diluted solutions of aspirin,\textsuperscript{77} treatment with cimetidine,\textsuperscript{78} by antacids,\textsuperscript{77,79} and by the use of enteric-coated or highly buffered aspirin.\textsuperscript{80,81}

**Hemorrhagic stroke.** A trend toward an increase in the incidence of stroke in healthy men treated with aspirin was reported by both the American Steering Committee of the Physicians’ Health Study Research Group (325 mg aspirin every other day)\textsuperscript{82,83} and the British Physicians’ Primary Prevention Studies (500 mg/day).\textsuperscript{84} However, this trend was not statistically significant, hemorrhagic stroke was not a primary end point, and, most important, its occurrence was very low (less than 0.3%). Otherwise, with some exceptions,\textsuperscript{85} aspirin has been shown to significantly reduce the incidence of stroke in randomized trials of patients with diverse manifestations of atherosclerosis.\textsuperscript{84,86–88} It is possible that, because of its antihemostatic effect, aspirin produces a slight increase in the risk of primary cerebral hemorrhage or of embolic–hemorrhagic conversion, but this is less evident in patients with atherosclerosis because their increased risk for thromboembolic stroke is reduced by aspirin.\textsuperscript{84,86–88}

**Aspirin Plus Anticoagulants and/or Thrombolytic Agents: Risk of Bleeding Versus Antithrombotic Potential**

Aspirin does not cause a generalized bleeding abnormality except in patients with an underlying hemostatic defect, such as hemophilia, uremia, or that induced by anticoagulant therapy or thrombolytic therapy.\textsuperscript{54} Indeed, aspirin may reveal a mild hemorrhagic disorder or vascular defect by inducing bleeding when used therapeutically. The generalized hemostatic defect can, in part, contribute to the risk of focal hemorrhage, mainly gastrointestinal hemorrhage and hemorrhagic stroke.\textsuperscript{89,90}

**Gastrointestinal hemorrhage.** The chronic use of the combination of aspirin plus warfarin increases the risk of gastrointestinal bleeding.\textsuperscript{91–94} Particularly if the dose of aspirin is high (500–1,000 mg) and the dose of warfarin is also high (INR [International Normalized Ratio], 3–4.5).\textsuperscript{92} The combination of low-dose aspirin (100 mg/day) and high-dose warfarin (INR, 3.0–4.5) was compared in a recent study of patients with mechanical heart valves. Investigators reported that the antithrombotic efficacy of this combination was markedly better than that of warfarin plus placebo and did not cause an increase in major gastrointestinal bleeding.\textsuperscript{95} A similar study with a slightly higher dose of aspirin (330 mg/day) in combination with high-dose warfarin (INR, 3.0–4.5) confirmed the low incidence of gross gastrointestinal bleeding but noted an incidence of minor bleeding in other regions (e.g., minor gastrointestinal bleeding might have been missed).\textsuperscript{91} Studies are under way to determine if the combination of anticoagulants and aspirin is safe, in terms of gastrointestinal and other hemorrhagic risks, by using low doses of both, because antithrombotic efficacy is enhanced by the combination compared with single-dose therapy. Preliminary results of a study involving prosthetic heart valves,\textsuperscript{91} one of patients with unstable angina,\textsuperscript{96} and one of primary prevention\textsuperscript{97} suggest that the combination of a low dose of aspirin (75–330 mg/day) with a low dose of warfarin (INR, 1.5–3) is safe. However, even though this regimen may be safer than a higher-dose regimen, it should not be undertaken unless coagulation and platelet function tests can be monitored by a high-quality laboratory.

**Hemorrhagic stroke.** In all the reports mentioned above in which aspirin and long-term oral anticoagulants were combined, the incidence of hemorrhagic stroke did not appear to be higher than that of single-drug therapy, except in one study.\textsuperscript{94} However, the short-term combination of aspirin, heparin, and throm-
bolytic agents in patients with acute myocardial infarction has raised concerns about excess bleeding and particularly about hemorrhagic stroke.

First, ISIS-2 investigators demonstrated significant benefit with both the combination of aspirin (160 mg/day) and streptokinase and with aspirin alone (160 mg/day), compared with placebo. There was no significant difference in the frequency of major bleeds among the three groups; there was only a small absolute excess of minor bleeding in the two groups taking aspirin, and there were no hemorrhagic strokes.66

After ISIS-2 documented the efficacy and safety of aspirin added to thrombolytic therapy, the relatively small European Cooperative Study Group trial demonstrated that patients receiving the combination of intravenous tissue plasminogen activator, aspirin (250–300 mg bolus followed by 75–125 mg every other day), and intravenous heparin had a patency rate higher than, but mortality rate similar to, those receiving only tissue plasminogen activator and aspirin. Bleeding complications (mostly minor) were similar in both groups, and there were no hemorrhagic strokes.66

The results of GISSI-2 (plus its international extension), a large mortality trial, suggested that the addition of heparin (12,000 IU subcutaneously hay twice daily, starting 12 hours after randomization) to thrombolytic therapy (tissue plasminogen activator or streptokinase) plus aspirin (325 mg daily) confers no significant additional benefit on survival, slightly increases the risk of major bleeding (requiring transfusion) from 0.6% to 1%, and minimally increases “presumed” hemorrhagic stroke from 0.3% to 0.4%.99 This finding is consistent with results from ISIS-2,66 which also indicated that, for those receiving streptokinase with aspirin (160 mg daily), the frequency of major bleeding (requiring transfusion) was 0.3% among those getting no heparin and 1.1% among those getting intravenous heparin; however, this subgroup analysis was not a randomized comparison and must be interpreted cautiously.99

ISIS-3 is the largest and most recent mortality trial to provide information on the combined use of thrombolytic agents (tissue plasminogen activator, streptokinase, or anisoylated plasminogen streptokinase activator complex [APSAC]), aspirin (160 mg/day), and heparin (12,500 IU subcutaneously twice daily starting 4 hours after randomization). Data analysis showed no significant differences in mortality; consistent with the GISSI-2 findings, the addition of heparin was associated with a slight increase in major bleeding from 0.8% to 1.0% and a minimal increase in probable hemorrhagic stroke from 0.4% to 0.56%.100

Overall, both ISIS-3 alone and ISIS-3 combined with GISSI-2 showed a 0.5% benefit of heparin on mortality at the expense of a 0.2% increase in hemorrhagic stroke.100 It is hoped that the ongoing GUSTO trial will provide further information about the risks and benefits of heparin and its route of administration when combined with aspirin and thrombolytic therapy in patients with acute myocardial infarction.

**Aspirin Plus Dipyridamole: No More Efficacious Than Aspirin Alone**

Dipyridamole increases platelet cAMP (cyclic adenosine monophosphate) and consequently may slightly inhibit platelet reactivity by three possible mechanisms: 1) blocking its breakdown by inhibiting phosphodiesterase, 2) activating adenylyl cyclase by a prostacyclin-mediated effect on the platelet membrane, and 3) increasing levels of plasma adenosine by inhibiting its uptake by vascular endothelium and erythrocytes. There is as yet no convincing evidence that the combination of aspirin and dipyridamole is more effective than aspirin alone.101 Reports by Chesbro and associates showed that dipyridamole (225 mg/day) plus aspirin (975 mg/day) improved the patency of coronary bypass grafts at both early and late follow-up,102,103 However, aspirin alone was as effective as the combination of aspirin and dipyridamole in recent antithrombotic trials of myocardial infarction, saphenous vein graft disease, and stroke.104–110 The combination of aspirin and dipyridamole has been reported to be slightly more effective than aspirin alone in reducing the rate of progression of peripheral atherosclerotic disease111 and in the prevention of aortocoronary bypass graft occlusion112; however, this finding must be confirmed by other studies before it can be accepted.

**Aspirin in the Prevention of Cardiovascular Events**

In the late 1960s, almost as soon as aspirin’s properties as an inhibitor of platelet aggregation had been discovered, its potential role in the prevention of coronary thrombosis was anticipated. During the 1970s, however, hope dissipated because the role of thrombosis as the cause of acute myocardial infarction came into question and because a number of major clinical trials of platelet inhibitors for the prevention of recurrent coronary events showed only a slightly beneficial effect. Only recently, with the revived appreciation of the importance of platelets and thrombosis in arterial disease and with better-designed clinical trials involving patients with overt atherosclerotic disease, has the effectiveness of antithrombotic therapy with aspirin been convincingly demonstrated; studies have included patients with coronary artery disease, those with ischemic stroke or transient ischemic attacks, those undergoing coronary artery bypass grafting and percutaneous coronary angioplasty, and those with miscellaneous conditions (certain subsets of patients with nonvalvular atrial fibrillation, peripheral vascular disease, prosthetic heart valves, arteriovenous cannulas for hemodialysis, preeclampsia, and venous thrombosis).

**Coronary Artery Disease**

**Unstable angina.** Most frequently, unstable angina results from atherosclerotic plaque disruption, which leads to an acute change in plaque configuration and a reduction in coronary blood flow, causing sudden onset or progression of exertional angina. Episodes of thrombotic occlusion and vasoconstriction at the site of plaque disruption may occur, resulting in angina at rest, myocardial infarction, or sudden death.3

To investigate this thrombotic component, there have been four large, randomized placebo-controlled, double-blind studies of aspirin administration in unstable angina. In the Veterans Administration Cooperative Study, 1,266 men with unstable angina were randomized to receive buffered aspirin (325 mg/day) or placebo for 12 weeks. During the treatment period, the incidence of death and acute myocardial infarction was reduced from 10.1% to 5% in the aspirin-treated group (a risk
reduction of 51%) and the overall benefits of aspirin were maintained during the 1-year follow-up period. In the Canadian Multicenter Trial, 555 patients (73% male) with unstable angina were randomly selected to receive aspirin (1,300 mg/day), sulfipyrazone (800 mg/day), the combination of both, or placebo. After 18 months the incidence of death and myocardial infarction was reduced in the aspirin-treated groups from 17% to 8.6%, a risk reduction of 49%; sulfipyrazone conferred no benefit.

In the Montreal Heart Institute Study, 479 patients (71% of whom were men) with unstable angina were randomly selected to receive aspirin (325 mg twice daily), intravenous heparin, the combination of both, or placebo. After a mean of 6 days, final therapeutic decisions for individual patients were made on the basis of the results of cardiac catheterization. Aspirin significantly reduced the rate of myocardial infarction by 72% compared with placebo, and heparin reduced the rate by 89%. Although there were no statistically significant differences among patients treated with aspirin, heparin, or the combination, there was a trend favoring the efficacy of heparin over that of aspirin. In the European RISC study group, 794 men with unstable angina or non-Q wave infarction were randomly selected to receive aspirin (75 mg/day) for 3 months, intravenous heparin for 5 days, both, or neither. At 3 months the risk of myocardial infarction or death was significantly reduced by aspirin and even more by the combination of aspirin and heparin. Further support for the use of antiplatelet agents in unstable angina comes from the recently published Italian Study of Ticlopidine in Unstable Angina. At a dose of 250 mg twice daily for 6 months, ticlopidine reduced the incidence of death and myocardial infarction by 46%.

In summary, there is already strong evidence supporting the use of either aspirin or intravenous heparin in the early treatment of patients with unstable angina. Because a substantial proportion of these patients develop myocardial infarction despite such treatment, there is a pressing need to test combinations of low-dose aspirin and heparin in larger clinical trials. For patients beyond the acute phase (after 3–5 days), aspirin is recommended.

Acute myocardial infarction. Most frequently, myocardial infarction results from atherosclerotic plaque disruption that leads to fixed and persistent occlusive thrombus formation. Patients with acute infarction receiving thrombolytic therapy, or those not receiving thrombolytic therapy but having spontaneous vessel recanalization, have a high incidence (5–15%) of early reocclusion. Therefore, for these patients aspirin may help reduce early reinfarction and mortality.

Treatment without thrombolytic therapy. The most convincing evidence of the efficacy of aspirin alone, without thrombolytic therapy, in acute evolving myocardial infarction comes from the recently reported large-scale ISIS-2 trial. In this trial, 17,187 patients presenting within 24 hours of symptoms were randomly selected for treatment with intravenous streptokinase, 160 mg of oral aspirin daily for 30 days, both, or neither. In the group taking aspirin alone there was a highly significant 23% reduction in mortality compared with the group taking neither streptokinase nor aspirin; the risk reduction for nonfatal reinfarction was 49% and that for nonfatal stroke was 46%.

In comparisons of risk reductions by aspirin and anticoagulant therapy without thrombolytic therapy in acute myocardial infarction, the beneficial effects on mortality appear similar: a 23% reduction in overall mortality in ISIS-2 compared with a 16–22% reduction in studies using heparin, oral anticoagulants, or both. Contributions of risk reduction to administration of aspirin, however, are more certain because they are based on a single large randomized trial, while those to administration of anticoagulants are based on an overview of numerous smaller trials, most of which were conducted more than 30 years ago when clinical trial methodology was far less rigorous.

Treatment with thrombolytic therapy. The major data on the additional benefit of aspirin for acute myocardial infarction treated with thrombolytic therapy also come from ISIS-2. The beneficial effects of streptokinase and aspirin (160 mg/day) appear to be largely independent of each other and their combined benefits appear additive. Patients given both agents had a 42% reduction in mortality compared with those given placebo. Aspirin alone, as previously noted, was associated with a 23% reduction in mortality and streptokinase with a 25% reduction. There was an even more striking 53% reduction in mortality, compared with placebo, when treatment with streptokinase and aspirin was initiated within 6 hours of onset of symptoms. The combination of streptokinase and aspirin was associated with significantly fewer reinfarctions than streptokinase alone or no active treatment (1.8% in the combined treatment group, 2.9% in the placebo group, and 3.8% in those given streptokinase alone). The combination of streptokinase and aspirin, like aspirin alone, was associated with a reduction in strokes (0.6% in the combined treatment group, 0.6% in the aspirin group, and 1.1% in the placebo group).

How does the addition of heparin to thrombolytic therapy compare with the above-mentioned addition of aspirin? In the recent SCATI trial, 711 patients were randomly assigned to receive, within 24 hours of the onset of myocardial infarction, intravenous heparin (2,000 IU bolus) and subcutaneous heparin (12,500 IU twice daily) or no anticoagulation. (No patient received aspirin.) In addition, 433 of these patients, admitted within 6 hours of onset of chest pain, received intravenous streptokinase. For the patients who received streptokinase, mortality was 8.8% in control (no heparin) patients and 4.5% in the heparin group. No significant differences in the rates of recurrent ischemia or nonfatal reinfarction were observed. Thus, it appears that both aspirin and heparin are beneficial for patients treated with streptokinase during the acute phase of infarction.

If patients with acute infarction and thrombolytic therapy are treated with aspirin, is heparin necessary? Although the ISIS-2 trial was not designed to answer this question and heparin therapy was not randomized, it is important to note that in patients treated with streptokinase and aspirin, the addition of subcutaneous or intravenous heparin is associated with a significant reduction in 5-week mortality. Although in the large-scale GISSI-2—International TPA/Streptokinase Mortality trials and ISIS-3 trial researchers attempted to
answer this question, the relatively low\textsuperscript{99} and late\textsuperscript{100}
dose of heparin (12,000 IU subcutaneously started at 12 hours and 12,500 IU started at 4 hours following thrombolytic therapy, respectively, given twice daily) probably resulted in subtherapeutic anticoagulation for 1–2 days after infarction; thus, the slight but significant decrease in mortality\textsuperscript{99,100} and reinfarction\textsuperscript{100} during heparin therapy is of interest. Therefore, the question of the benefit of adjunct heparin therapy can only be answered by designing a trial in which a thrombolytic agent plus aspirin and in which heparin or placebo is received intravenously within the first 1–2 days of infarction (after 1–2 days, heparin may be given subcutaneously). The ongoing GUSTO trial fulfills part of this approach.

In summary, available data clearly support the use of aspirin in acute myocardial infarction, regardless of whether the patient is a candidate for thrombolysis. If a thrombolytic agent is given, aspirin’s effect on reduced mortality and reinfarction is additive. Evidence supporting the use of heparin for preventing death and reinfarction is not as strong as that supporting the use of aspirin, but it is suggestive. Given the high risk of reocclusion and reinfarction, particularly when a thrombolytic agent is administered, the combination of low-dose aspirin and high-dose intravenous heparin in the acute stage of infarction is appealing if the risk of bleeding is low (as early as possible and throughout therapy, it should be established that the platelet count is within normal range). Final recommendations await the results of randomized clinical trials.

Survivors of myocardial infarction. Within the first year after acute myocardial infarction, cardiac morbidity and mortality are determined by a number of factors, including reinfarction, left ventricular dysfunction, and ventricular arrhythmias; therefore, proving that antithrombotic drugs are beneficial in this group of patients has been difficult. This has generated considerable controversy during the last few decades.

Six randomized, placebo-controlled, double-blind tri¬als in patients surviving myocardial infarction have been conducted with aspirin alone (at doses of 300–1,500 mg/day).\textsuperscript{104,122–126} Among these trials, the time between infarction and study entry varied from 1 week to 7 years (with the majority being within 1 year) and study duration varied from 1 to 4 years. No clear evidence of benefit from therapy was shown in any single study because of the statistically insufficient number of patients involved. However, the reduction in the cardiac mortality rate varied from 5% to 42% and the reduction in the nonfatal reinfarction rate varied from 12% to 57%. Furthermore, meta-analysis or pooled analysis of trials of antiplatelet therapy in secondary prevention after myocardial infarction (trials that, aside from the six regimens of aspirin alone, also included two regimens of sulfipyrazone and two combining aspirin and dipyridamole) suggested that platelet inhibitors significantly reduced the vascular mortality rate by 13%, the nonfatal reinfarction rate by 31%, and the nonfatal stroke rate by 42%; no statistically significant differences among the various antiplatelet regimens used were found.\textsuperscript{84,87} Although a criticism has been that in the meta-analysis methodology the patients' treatment, duration of treatment, quality of follow-up, and endpoint definition may vary among trials, such statistical methodology is becoming increasingly valuable in assessing therapeutic agents, as is the case for aspirin in studies of survivors of myocardial infarction.

The evidence supporting the use of antithrombotic agents in survivors of infarction derives from the recently published Warfarin Re-Infarction Study (WARIS). In this large study 1,214 patients were randomly selected to receive warfarin or placebo, with a follow-up period of about 3 years. Warfarin was shown to reduce the mortality rate by 24%, reinfarction by 34%, and stroke by 55%. Major bleeding episodes occurred in only 2% of treated patients.\textsuperscript{127} Meta-analyses\textsuperscript{128} of the strictly randomized studies on anticoagulant agents versus placebo\textsuperscript{127,129–131} revealed similar benefit by anticoagulant therapy that may be slightly superior to that observed for aspirin.\textsuperscript{84} Nevertheless, two studies in which aspirin and oral anticoagulants were compared directly did not support the superiority of either approach, with slightly increased frequency of bleeding in the anticoagulant group and an increased frequency of gastrointestinal side effects in the aspirin group.\textsuperscript{132,134}

In summary, when the results of trials of aspirin and anticoagulant therapy for secondary prevention in sur¬vivors of myocardial infarction are analyzed together, both treatments appear to convey protection against death and reinfarction. Thus, for most patients, the advantage of aspirin over anticoagulant agents is not higher effectiveness but lower cost, ease of administration, and less need for monitoring. For patients intolerant of aspirin, at risk of embolism from the left ventricle (i.e., those with mural thrombi or severe myocardial dysfunction) or left atrium (i.e., those with atrial fibrillation), or with prior embolism, oral anticoagulant treatment is preferred.\textsuperscript{133,134}

Stable coronary disease. Disruption of atherosclerotic plaques with variable mural thrombosis and its fibrotic organization, with or without clinical symptoms, appears to be a major mechanism of progression of coronary atherosclerosis.\textsuperscript{42} Preliminary evidence from a 5-year trial of aspirin (975 mg/day) plus dipyridamole (225 mg/day) for prevention of progression of coronary disease in patients with stable angina revealed that these platelet inhibitors reduced new lesion formation as detected angiographically (with no effect on the progression of existing lesions) and reduced the incidence of myocardial infarction from 12% to 4% (a 67% reduction).\textsuperscript{135} In a study of 333 men with chronic stable angina, aspirin alone (325 mg every other day) reduced the incidence of myocardial infarction by 87% compared with placebo. There was only a slight trend toward decreased mortality, but the risk of stroke, presumed to be hemorrhagic, increased.\textsuperscript{85} Angiographic assessment of progression was not performed.

To study anticoagulation for patients with stable coronary disease, the Sixty Plus Reinfarction Study involved patients over 60 years of age who had been taking anticoagulant agents for a median time of 6 years after infarction. Patients were randomly assigned to continue anticoagulant therapy or placebo substitute for 2 more years. By intention-to-treat analysis, patients receiving anticoagulant therapy had a 26% lower death rate (15.7% compared with 11.6%) and an impressive 51% lower rate of reinfarction (8.4% compared with 4.1%) than patients taking placebo. A trend toward reduced frequency of cerebrovascular events was observed in the group receiving anticoagulant therapy.\textsuperscript{129}
When results of the trials of aspirin and anticoagulant agents in patients with stable coronary disease are analyzed together, both treatments appear to convey protection against death and reinfarction, and again aspirin's main advantages are its lower cost, ease of administration, and less need for monitoring.

**Primary prevention.** Because aspirin has a significant protective effect in secondary prevention of vascular disease, the possible benefit of aspirin in primary prevention has also been tested. Two randomized trials, the United States Physicians' Health Study\(^{42,136}\) and the British Doctors' Trial\(^{84}\) have addressed this question.

Results from the American trial of more than 22,000 male physicians, aged 40–84 years, assigned to receive aspirin (325 mg every other day) or placebo for 5 years revealed a 44% reduction in the incidence of myocardial infarction, from approximately 0.4% to 0.2% per year. This effect was limited to those older than 50 years. Over the 5-year period the incidence of cardiovascular death was similar in the aspirin and placebo groups; in the aspirin-treated group there was a slight increase in hemorrhagic stroke that was not statistically significant (0.2% in the aspirin group compared with 0.1% in the placebo group), but a significant increase in gastrointestinal hemorrhage requiring transfusion (0.5% in the aspirin group compared with 0.3% in the placebo group).\(^{82,136}\)

In the British primary prevention trial of more than 5,000 male physicians, aged 50–78 years, two thirds were randomly assigned to take aspirin (500 mg/day) and one third were instructed to avoid it (no placebo used). After 6 years, no difference in the rate of myocardial infarction or cardiovascular death was detected; however, there was a slight increase in disabling strokes and a decrease in transient ischemic attacks among those assigned to aspirin.\(^{83,84,87}\)

Any decision to use aspirin in the primary prevention of cardiovascular disease should be based on an individual clinical judgment by a physician or other health care provider in which the cardiovascular risk profile of the patient is considered. The United States Preventive Services Task Force has recommended that "low-dose aspirin therapy be considered for men aged 40 and over who are at significantly increased risk of myocardial infarction and who lack contraindications to the drug."\(^{113,137}\) Observational epidemiological studies have suggested a possible benefit in women;\(^{138}\) however, definitive recommendations for women will have to await the results of the Women's Health Study.\(^{139}\) A large randomized trial of low-dose aspirin use among more than 40,000 female nurses 45 years old and older. It is also important that aspirin be considered an adjunct, not an alternative, to coronary heart disease risk factor management. Although it has been suggested that aspirin may reduce risk of colon cancer,\(^{140-142}\) these data are from observational studies and require confirmation in randomized clinical trials. In an ongoing thrombosis prevention trial among men at high risk of coronary heart disease,\(^{97,143}\) the effects of low-dose aspirin (75 mg/day), low-dose warfarin, and the combination of both agents is being evaluated. The results of this trial will further define the role of antithrombotic agents in primary prevention.

**Ischemic Stroke and Transient Ischemic Attacks**

**Ischemic stroke.** The results of the original studies of the effectiveness of platelet inhibitor drugs in the secondary prevention of stroke recurrence were controversial. The French AICLA study of patients with an ischemic event (84% with minor stroke, 16% with transient ischemic attacks) showed that aspirin had a significant beneficial effect,\(^{108}\) but the Swedish Cooperative Study Group found that, in patients with minor or major stroke, aspirin failed to reduce stroke recurrence or death.\(^{144}\) These two studies involved 500–600 patients. However, in a more recent, large study involving 1,360 patients it was reported that a dose of 75 mg/day was superior to placebo.\(^{65}\) In the large European Stroke Prevention Study, 2,500 patients with a recent ischemic neurological event (60% with minor stroke, 33% with transient ischemic attack, and 6% with reversible ischemic neurological deficit) were randomly selected to receive aspirin (325 mg) plus dipyridamole (75 mg) three times daily; after 2 years the treated group had a striking 33% reduction in the combined rate of stroke and death.\(^{145}\) In the recent Dutch TIA trial, 3,131 patients with a recent ischemic neurological event (68% with minor stroke and 32% with transient ischemic attack) were randomly assigned to receive either 30 or 283 mg of aspirin a day. After 2.5 years of follow-up there was no difference in vascular events, but those receiving the lower dose had fewer adverse side effects.\(^{72}\) The event rate was low, suggesting that the population might have been at low risk and raising the issue of comparability of this study population to the populations of other studies. Meta-analysis of eight trials of aspirin after stroke found a 26% reduction in stroke recurrence.\(^{64}\) No single study has compared a high dose (about 1,300 mg/day) with a low dose (325 mg/day or less)\(^{146}\) to determine the ideal aspirin dose for patients with ischemic stroke.

The role of aspirin in the prevention of ischemic stroke associated with nonvalvular atrial fibrillation is controversial. Left atrial thrombus is related more to fibrin formation than to platelet deposition and therefore is more amenable to anticoagulant therapy than to treatment with aspirin. The reason aspirin has been successful in some trials may depend on the presence of associated arterial conditions, like hypertension and vascular disease, that may be associated with a stroke that is more dependent on arterial platelet deposition than on embolism from the left atrium. Thus, while atrial fibrillation may be a marker for stroke, it is not necessarily the cause of stroke.\(^{147}\)

In a large Canadian-American study of 1,072 patients with recent ischemic stroke, the novel antplatelet agent ticlopidine was found to decrease the combined rate of recurrent stroke, myocardial infarction, and vascular death by 23% at the end of 3 years. Adverse side effects associated with ticlopidine included reversible neutropenia (severe in 1%), skin rash (severe in 2%), and diarrhea (severe in 2%).\(^{148}\)

Several trials have shown that anticoagulant therapy in stroke is potentially hazardous because of the increased risk of bleeding or that it is without benefit, and it is not recommended.\(^{22,23}\) However, no randomized trial of anticoagulation in prevention of thrombotic stroke has been conducted recently. When these data
become available, it will be necessary to balance the risk of bleeding against the benefit of stroke prevention, as has been done with aspirin. Furthermore, the striking benefit of anticoagulation in the prevention of stroke in patients with atrial fibrillation does not rule out the possibility that some of the benefit was due to prevention of noncardiogenic emboli.

In summary, long-term antiplatelet treatment with aspirin or ticlopidine for secondary prevention is recommended for survivors of noncardiogenic stroke. In contrast, long-term anticoagulant therapy in patients with cardiogenic embolism is mandatory. In ischemic stroke, identification of risk factors and specific etiology is essential for appropriate treatment.

Transient ischemic attacks. Aspirin has been compared with placebo or other antithrombotic therapy in numerous studies of patients with transient ischemic attacks, but such studies also included some patients with minor completed stroke (according to the 24-hour rule for clinical event duration). While the smaller trials (50–200 patients) showed no advantage of aspirin over placebo in reducing stroke incidence or mortality, the small number of patients limits the significance of these results. More important, all four larger trials (600–2,500 patients) demonstrated that aspirin (75–1,300 mg/day) significantly reduced the rate of stroke and death. Results from the largest study, the United Kingdom Transient Ischemic Attack (UK-TIA) aspirin trial, revealed a significant 18% reduction in the combined rate of nonfatal stroke, nonfatal myocardial infarction, and death in patients treated with aspirin. In this study, the effects of 300 mg/day and 1,200 mg/day of aspirin were not significantly different, but the lower dose caused substantially less gastric toxicity. In judging the benefit of aspirin observed in this trial, it is important to note that because neither aspirin dose was significantly better than placebo alone, both doses were considered together as a single treatment in the analysis. Overall, meta-analysis of 10 trials of aspirin after transient ischemic attack indicated a 21% reduction of primary stroke.

In the TASS trial more than 3,000 patients with recent transient or mild persistent focal cerebral ischemia were randomly allocated to receive ticlopidine (500 mg/day) or aspirin (1,300 mg/day). At the end of 3 years death or nonfatal stroke had occurred in 17% of patients in the ticlopidine-treated group and in 19% in the aspirin-treated group. The incidence of fatal or nonfatal stroke was 21% lower in the ticlopidine-treated patients (10% compared with 13%). However, adverse reactions were more common in the ticlopidine-treated group and included diarrhea (20%), skin rash (12%), and severe but reversible neutropenia (<1%). Unlike major bleeding, minor bleeding was more prevalent in the ticlopidine-treated patients (ticlopidine prolongs bleeding time). The use of anticoagulant therapy in patients with transient ischemic attacks is still controversial because both beneficial and harmful trends have been observed.

In summary, in patients with transient ischemic attacks, evidence supports the use of aspirin (without diprydamole) or ticlopidine over other platelet inhibitors or anticoagulant agents, in part because the risks of cerebral hemorrhage are lower. Identification of risk factors and specific etiology is essential for appropriate treatment of these patients (e.g., carotid endarterectomy for severe carotid artery stenosis).

Primary stroke prevention. As previously discussed, the US and British physicians' studies of aspirin in the prevention of cardiovascular disease have raised questions about the use of aspirin by those without cardiac and cerebrovascular disease. The results of these two large studies led to the conclusion that the routine use of aspirin by healthy men may not be universally recommended when the risks of gastrointestinal hemorrhage and, to a much lesser degree, possible hemorrhagic stroke are compared with the reduction in risk of nonfatal myocardial infarction. However, the use of aspirin may be justified when patients have atherosclerotic disease or risk factors for stroke because the high risk of embolic stroke reduced by aspirin overshadows the risk of gastrointestinal hemorrhage or the minimal risk of hemorrhagic stroke caused by the drug. Nevertheless, it is important that aspirin be used as adjunctive therapy rather than as an alternative to vigorous risk management. Long-term aspirin use should not be initiated except by prescription by physicians. Meta-analysis of 10 trials on platelet inhibitors, mainly aspirin, involving about 18,000 patients with a history of myocardial infarction and of the ISIS-2 trial on aspirin (with or without streptokinase) involving about 8,500 patients with acute myocardial infarction revealed a reduction in nonfatal stroke of 42% and 46%, respectively, and a reduction in vascular mortality of 13% and 21%, respectively. Conversely, meta-analysis of 13 trials on platelet inhibitors, again mainly aspirin, involving 9,000 patients with a history of either stroke or transient ischemic attack, revealed a reduction in nonfatal myocardial infarction of 35% and a reduction in vascular mortality of 15% in the treatment groups.

Aspirin after carotid endarterectomy. In a retrospective study, Kretschmer et al observed a marked reduction in death in patients receiving 1,500 mg/day of aspirin after carotid endarterectomy. Based on this observation, they did a prospective study using 1,000 mg/day of aspirin, and with only 68 patients again demonstrated a statistical difference in death rates. Preliminary data of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) indicate that for patients who had endarterectomy, ipsilateral stroke occurred in 11% of those who received 325 mg/day of aspirin, 10% of those on 650 mg/day, and only 4% of those who received 1,300 mg/day. These data must be interpreted with caution because the study was not designed to test the effect of aspirin, and endarterectomy and ipsilateral stroke were not primary or secondary endpoints of the study. Nevertheless, it indicates that aspirin may be of benefit in cerebrovascular disease and after carotid endarterectomy, although the dose issue is not yet settled.

Coronary Revascularization Procedures

Atherothrombosis is not only the basis of coronary disease leading to the need for coronary artery bypass grafting and percutaneous coronary angioplasty but is also an important factor in the early complication rate of such interventions.

Saphenous vein bypass graft disease. Vein graft disease can be divided into three phases: an early postoperative
phase, within 1 month, of thrombotic occlusion; an intermediate phase, within the first postoperative year, characterized by intimal hyperplasia, resulting in a form of accelerated atherosclerosis that may have a superimposed thrombotic tendency; and a late phase, after the first postoperative year, composed of graft atherosclerosis similar to that affecting the native coronary arteries.57

The importance of platelets in the pathogenesis of thrombosis in this setting suggests that antiplatelet agents should inhibit early thrombotic graft occlusion and decrease the frequency of late occlusive events related to thrombosis that is superimposed on intimal hyperplasia or late vein-graft atherosclerosis; because these processes do not apply to the same extent to internal mammary artery graft, the occlusion rate of this type of graft is quite low. Accordingly, in the original Mayo Clinic trial on saphenous vein bypass grafting, patients received dipyridamole (100 mg four times daily) for 2 days before surgery, followed by aspirin (325 mg) and dipyridamole (75 mg) three times daily, starting 7 hours after surgery and continuing for 1 year. There was no increased incidence of bleeding complications in the treatment group. At vein graft angiography 1 month after surgery, there was a significant reduction in graft occlusion in the treated group, from 10% to 2% per distal graft anastomosis and from 22% to 6% per patient.102,103 The ongoing study and reviews of all reported studies to date have convincingly demonstrated the importance of initiating platelet inhibitor therapy in the perioperative period, preferably before but not later than 48 hours after surgery.39-41 Indeed, when therapy was started more than 48 hours after surgery, no reduction in the vein graft occlusion rate was observed.

In the Veterans Administration Cooperative Study, 555 patients receiving saphenous vein grafts were randomly assigned into five groups, taking 325 mg aspirin per day, 325 mg aspirin three times daily, 325 mg aspirin plus 75 mg dipyridamole three times daily, 267 mg sulfipyrazone three times daily, or placebo. Except for aspirin, which was started 12 hours preoperatively, therapy was initiated 48 hours before surgery. Early graft patency at a median of 9 days was significantly higher in the aspirin-treated groups (92%) than in those given placebo (85%).105 At 1 year benefit was seen only in patients at high risk of graft occlusion (those with vein grafts placed to vessels ≤1.5 mm in diameter) taking aspirin.157 It is important to note that one daily dose of aspirin was as effective as aspirin given three times daily. Dipyridamole conferred no additional benefit over aspirin alone. There was a non–statistically significant trend toward an improved patency rate with sulfipyrazone.

In another Veterans Administration cooperative study, preoperative aspirin use was associated with increased bleeding complications and no additional benefit in early vein graft patency compared with aspirin started 6 hours after surgery.38 Because preoperative aspirin use is associated with increased intraoperative bleeding, dipyridamole, which prevents activation of platelets by the extracorporeal pump and does not increase bleeding, appears to be a safer agent; however, whether it offers additional benefit over postoperative aspirin alone is unknown.

Other trials on antithrombotic therapy within the first year of saphenous vein bypass grafting have provided information of some interest. First, of all the trials comparing aspirin with aspirin plus dipyridamole,158 the only suggestion of an additional effect of dipyridamole derives from preliminary results of the GESIC study.112 Second, aspirin alone, at the low dose of 100 mg/day, was found by Lorenz and colleagues159 to be effective in reducing vein graft closure; however, this study was characterized by a high rate of graft occlusion in the placebo group (32% at 4 months), compared with a rate of 10–20% for most centers. Third, in one study ticlopidine (250 mg twice daily), started on the second postoperative day, significantly reduced the incidence of vein-graft occlusion by approximately 40%, as assessed angiographically at 10, 180, and 360 days after surgery160; although not reported in this study, other studies of ticlopidine in cerebrovascular disease have revealed an incidence of various side effects with this drug.148,152 Finally, heparin and oral anticoagulants have been shown to be of some benefit for the prevention of graft occlusion in various trials156; however, the perioperative use of anticoagulants may be undesirable because of the risk of surgical bleeding.161

In summary, platelet inhibitor therapy appears mandatory for prevention of early thrombotic occlusion of saphenous vein bypass grafts. Aspirin should be started immediately after surgery and continued for at least 1 year162 and probably indefinitely. No currently available agent prevents graft atherosclerosis, although control of risk factors such as hyperlipidemia and cigarette smoking may be beneficial;163 in one study aggressive treatment of hyperlipidemia resulted in reduction of progression and even regression of atherosclerosis in a selected group of patients after bypass surgery.164 In a new trial sponsored by the National Institutes of Health for prevention of vein graft atherosclerosis, the use of aspirin and lipid-lowering therapy, either alone or in combination, is being tested.

Oclusion following coronary angioplasty. Among the multifactorial pathophysiological processes accounting for early occlusion after percutaneous transluminal coronary angioplasty (which occurs in about 7–20% of patients49), thrombosis plays a major role.44 Three prospective165–167 and two retrospective168,169 angiographic studies have indicated that pretreatment with aspirin alone,166,168,169 aspirin plus dipyridamole,165,167,168 or ticlopidine alone165 significantly reduces the incidence of acute thrombotic occlusion and periprocedural Q wave infarction in patients undergoing coronary angioplasty. A prospective study indicated that aspirin alone was as effective as the combination of aspirin and dipyridamole in reducing acute complications of percutaneous coronary angioplasty.170

Given the substantial risk of acute thrombotic complications associated with plaque disruption during angioplasty, pretreatment with aspirin combined with adequate heparinization throughout the procedure, as in most of the above studies, is strongly recommended. Unfortunately, the results of clinical trials of the use of different antiplatelet drugs and anticoagulant agents aimed at reducing the restenosis rate have been disappointing.

Miscellaneous Conditions

Certain subsets of patients with nonvalvular atrial fibrillation, peripheral vascular disease, prosthetic heart
valves, arteriovenous cannulas for hemodialysis, pre-eclampsia, and venous thrombosis have shown a good antiplatelet response to aspirin.

**Nonvalvular atrial fibrillation.** Patients with atrial fibrillation and mitral stenosis or previous embolism are at high risk of thromboembolism and should be treated with long-term anticoagulant therapy.\(^{22,23}\) Patients at low risk for embolism (those less than 60 years old with no associated heart disease [none fibrillators]) usually do not require anticoagulant therapy.\(^{171}\) Between these two groups is a large group of patients with an intermediate but incompletely defined risk of embolism, namely, those with nonvalvular atrial fibrillation associated with various forms of cardiovascular disease. In the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK), 1,007 patients were randomly allocated to receive warfarin, aspirin (75 mg/day), or placebo. At the end of 2 years, the incidence of stroke, transient ischemic attack, and systemic embolism was significantly lower in the warfarin group (1.5%) than in the aspirin and placebo groups (6% each).\(^{172}\) In the Stroke Prevention in Atrial Fibrillation (SPAF) Study, 588 patients with nonvalvular atrial fibrillation were randomly selected to receive warfarin, aspirin (325 mg/day), or placebo. In addition, 656 patients not eligible for treatment with warfarin received aspirin or placebo in a double-blind fashion. At the end of 1 year, the placebo arm of the study was terminated because active treatment (either warfarin or aspirin) reduced the risk of stroke and systemic embolism by an impressive 81%. The study also revealed that aspirin reduced the risk of stroke and embolism by 50% but was not effective in patients more than 75 years old.\(^{173}\) In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF),\(^ {174}\) the Canadian Atrial Fibrillation Anticoagulation Study (CAFAS),\(^ {175}\) and the most recent Stroke Prevention in Nonrheumatic Atrial Fibrillation Study (SPINAF),\(^ {176}\) low-dose warfarin therapy (INR, 1.5–2.7, 2.0–3.0, and 1.4–2.8 respectively) significantly reduced the incidence of strokes in patients with nonvalvular atrial fibrillation.

In summary, these prospective, randomized studies indicated that warfarin reduces the stroke rate in patients with nonvalvular atrial fibrillation. In addition, the SPAF study revealed the beneficial effects of aspirin in patients less than 75 years old.\(^ {173}\) Various mechanisms of stroke may explain the lack of effectiveness of aspirin in the AFASAK study compared with that in the SPAF study. This difference may be related to a higher prevalence of left atrial or ventricular stasis-related thrombi, which are anticoagulant sensitive, in the older patients in the AFASAK study, as indicated by the threefold to fourfold higher incidence of heart failure and the twofold higher incidence of previous myocardial infarction in patients in that study. Thus, aspirin may have some stroke prevention benefit in patients with nonvalvular atrial fibrillation who tend to develop platelet-rich in situ thrombi or emboli: for example, patients with associated hypertension or associated cerebrovascular or ascending aortic atherosclerotic disease. In these patients atrial fibrillation is probably only a marker of vascular disease rather than a cause of left atrial thromboembolism.\(^ {134}\) Future challenges include the direct comparison of warfarin and aspirin therapy in certain subgroups of patients with nonvalvular atrial fibrillation (this comparison is being made in the ongoing SPAF II study).

**Peripheral vascular disease.** The combination of aspirin and dipyridamole reduced the progression of peripheral atherosclerosis in a 2-year study of patients with peripheral vascular disease.\(^ {111}\) Studies with aspirin alone are needed. Other studies suggest a beneficial effect of ticlopidine in patients with chronic arterial insufficiency.\(^ {177}\) Despite encouraging results from some studies,\(^ {178}\) there are no convincing data from properly designed, large trials showing that anticoagulation therapy delays the progression of peripheral vascular disease.

**Prosthetic heart valves.** Studies in patients with mechanical valves have consistently shown that appropriate anticoagulation significantly reduces the incidence of thromboembolism;\(^ {179–184}\) without long-term anticoagulation, the incidence of thromboembolism is two times higher or more. Platelet inhibitors alone have not been found to confer protection against embolism in patients with a mechanical prosthesis; thus, several studies of aspirin plus dipyridamole without anticoagulation in these patients have shown an incidence of thromboembolism as high as 10% per year.\(^ {181}\) On the other hand, in patients at high risk of thromboembolism, the addition of dipyridamole to an oral anticoagulant agent has been shown to decrease the incidence of thromboembolism in five trials,\(^ {182–186}\) and the combination of aspirin and an oral anticoagulant agent was beneficial in two other trials\(^ {63,95}\) but not in a third,\(^ {92}\) in which an increased incidence of gastrointestinal bleeding was also found.

**Arteriovenous cannulas.** Thrombosis of arteriovenous cannulas results in significant morbidity in patients with chronic renal failure on hemodialysis. Anticoagulant agents may decrease the incidence of thrombosis, but their use is hazardous in patients with uremia. In a study using aspirin (160 mg/day)\(^ {187}\) and another using sulfinpyrazone\(^ {188}\) there was a reduction in the incidence of thrombosis of arteriovenous shunts in patients with renal failure. However, because these patients may be predisposed to hemorrhage, platelet inhibition must be used with caution.

**Placental insufficiency and pre-eclampsia.** Aspirin reduces the risk of severe low birth weight among newborns\(^ {189}\) and the rate of cesarian section in women with pregnancy-induced hypertension.\(^ {190}\) Pregnancy-induced hypertension can be manifested clinically as pre-eclampsia, eclampsia, isolated hypertension, and fetal growth retardation. The pathogenesis is related to reduced placental blood flow, which is believed to be caused by constriction or thrombosis of small placental arteries.\(^ {190}\) The effectiveness of low-dose aspirin (60–150 mg/day) in preventing these manifestations of placental insufficiency might indicate that the reduction in placental flow is mediated by thromboxane A2. Use of aspirin during pregnancy appears to be safe; it has not been associated with fetal or maternal complications.\(^ {190}\)

**Prophylaxis of venous thromboembolism.** All acceptable studies indicate that aspirin is ineffective in reducing the incidence of venous thrombosis in general surgical patients. However, in one study it was effective in reducing the incidence of venous thrombosis by 35% after hip surgery, a reduction due entirely to a reduction in proximal vein thrombosis.\(^ {191}\) This finding is biologically plausible and consistent with the hypothesis that after hip surgery aspirin is effective in reducing isolated
femoral vein thrombosis, which is thought to be induced by direct injury to the femoral vein but is ineffective in reducing the risk of calf vein thrombosis, which is induced by increased blood coagulability.

Summary and Recommendations

Platelets and thrombosis play a critical role in cardiovascular disease, particularly in the development and progression of coronary artery disease leading to acute coronary syndromes (i.e., heart attack); of transient cerebral ischemic attacks, acute cerebral infarction, or ischemic stroke; and the early occlusion rates associated with coronary artery bypass grafting and percutaneous coronary angioplasty. Aspirin is an inhibitor of platelet function and has been effective in prevention of some of these clinical–pathological syndromes.

The following is a summary of the recommendations contained in this report.

Dose-Response Relations, Effectiveness, and Side Effects of Aspirin

A number of antithrombotic trials using aspirin at various dosages have confirmed that its gastrointestinal side effects are dose related. A small but significant increase in bleeding is observed with a dose of 75 mg/day; this effect on gastric bleeding was approximately doubled with a dose of 300 mg/day and increased fivefold with a dose of 1.8-2.4 mg/day. The combination of chronic use of aspirin plus warfarin increases the risk of gastrointestinal bleeding, particularly if the aspirin dose is high (500–1,000 mg) and the warfarin dose is also high (INR, 3–4.5). There is evidence that the gastric side effects of aspirin can be reduced by oral administration of diluted solutions of aspirin, treatment with cimetidine, antacids, and the use of enteric-coated or highly buffered aspirin.

A trend toward an increase in the incidence of stroke in healthy men treated with aspirin was reported in both the US Physicians’ Health Study (325 mg every other day) and the British Doctors’ Trial (500 mg/day). However, with some exceptions, aspirin significantly reduces the incidence of stroke in randomized trials in patients with diverse manifestations of atherosclerosis. Because of its antithrombotic effect, aspirin may produce a slight increase in risk of primary cerebral hemorrhage or embolic–hemorrhagic conversion, but these risks appear to be extremely low.

The short-term combination of aspirin, heparin, and thrombolytic agents in patients with acute myocardial infarction appears to produce a slight increase in incidence of hemorrhagic stroke. No long-term risk has been reported.

Recommendation. Except for patients with cerebrovascular disease, low doses of aspirin (75–325 mg/ day) are currently recommended. However, if the lowest dose (75 mg/day) is considered, evidence suggests that, for a prompt antplatelet effect, patients should receive an initial loading dose of 160–325 mg.

Recommendation. For patients with transient ischemic attack and nondisabling ischemic stroke, the effective dose in all studies except one (75 mg/day in SALT) was 975–1,500 mg/day. After the recent Dutch study comparing two low dosages of aspirin (30 mg/day and 283 mg/day), it is important that further studies comparing high- and low-dose aspirin be performed to determine the most beneficial dosage for patients with cerebrovascular disease.

Aspirin in Coronary Artery Disease

Recommendation. There is strong evidence supporting the use of either aspirin or intravenous heparin in the early treatment of patients with unstable angina. Because a substantial proportion of these patients develop myocardial infarction despite such treatment, there is a need to test combinations of low-dose aspirin and heparin in larger clinical trials. Otherwise, after the acute phase of unstable angina (after 3–5 days), aspirin alone is recommended.

Recommendation. Available data clearly support the use of aspirin in patients with acute myocardial infarction, regardless of whether the patient is a candidate for thrombolysis. Given the high risk of reocclusion and reinfarction, particularly when a thrombolytic agent is administered, the combination of low-dose aspirin and high-dose intravenous heparin in the acute stage of infarction is appealing if the risk of bleeding is low; final recommendations await the results of randomized clinical trials.

When the results of trials of aspirin and anticoagulant therapy for stable coronary angiina and for secondary prevention in survivors of myocardial infarction are analyzed together, both treatments appear to convey protection against death and reinfarction. The same is true when trials of aspirin and anticoagulant agents for stable coronary angiina are analyzed together. Thus, for most patients, the advantage of aspirin over anticoagulant agents is not higher effectiveness but lower cost, ease of administration, and less need for monitoring.

Recommendation. For patients intolerant of aspirin, those at risk of embolism from the left ventricle (those with mural thrombi or severe myocardial dysfunction) or left atrium (those with atrial fibrillation), and those with prior embolism, oral anticoagulant treatment is preferred.

Given the available data, the clinical decision to use aspirin in primary prevention should be made on an individual basis by a physician or other health care provider. The use of aspirin seems prudent for middle-aged and older men whose risks of a first myocardial infarction are sufficiently high (i.e., risk factor for coronary heart disease, cerebrovascular disease, or peripheral vascular disease) to warrant the possible adverse effects of long-term use of the drug. No randomized trial data are yet available for women. Aspirin should always be an adjunct, not an alternative, to coronary risk factor management.

Aspirin in Ischemic Stroke and Transient Ischemic Attacks

Identification of risk factors and specific etiology is essential for appropriate treatment of ischemic stroke and transient ischemic attack (e.g., carotid endarterectomy for severe carotid artery stenosis).

Recommendation. Long-term antplatelet treatment by inhibiting platelet function with aspirin is recommended for secondary prevention in survivors of noncardiogenic stroke. Ticlopidine is effective and should be considered for selected patients, particularly those in whom aspirin has been ineffective. The use of long-term
anticoagulant therapy in patients with cardiogenic embolism is appropriate.

**Recommendation.** In patients with transient ischemic attacks, evidence supports the use of aspirin (without dipyridamole) or ticlopidine rather than other platelet inhibitors or anticoagulant agents, in part because the risks of cerebral hemorrhage are lower. Again, ticlopidine has been effective and should be considered for selected patients, particularly those in whom aspirin is ineffective.

**Aspirin in Coronary Revascularization Procedures**

**Recommendation.** Platelet inhibitor therapy appears mandatory for prevention of early thrombotic occlusion of saphenous vein bypass grafts. Aspirin should be started within 6–12 hours after surgery and continued for at least 1 year and probably indefinitely. No currently available agent prevents graft atherosclerosis, although control of risk factors, such as hyperlipidemia and cigarette smoking, may be beneficial.

**Recommendation.** Given the substantial risk of acute thrombotic complications associated with plaque disruption during angioplasty, pretreatment with aspirin combined with adequate heparinization throughout the procedure, as in most of the studies mentioned in “Occlusion following coronary angioplasty,” is strongly recommended.

**Aspirin in Other Cardiovascular Conditions**

Some patients with nonvalvular atrial fibrillation, peripher al vascular disease, prosthetic heart valves, arteriovenous cannulas for hemodialysis, placental insufficiency or preeclampsia, and venous thrombosis (after hip surgery) have shown a good antiplatelet response to aspirin (or, in high-risk patients with prosthetic heart valves, low-dose aspirin combined with coumadin). 

**Recommendation.** Until more information is available, the recommendation for aspirin use should be based on an individual clinical judgment.

**References**


Aspirin as a Therapeutic Agent in CVD


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