Antithrombotic Therapy for Cerebrovascular Disorders
An Update

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Ischemic stroke is a syndrome, and the optimal use of antithrombotic therapies in patients at risk for ischemic stroke is guided by the specific pathogenesis (Figs 1 and 2). Patients with increased risk for ischemic stroke can be identified (Table 1). Atherosclerosis of arteries, large and small, supplying the brain is the most common cause of ischemic stroke in North America and Europe. Atherosclerosis of the proximal aorta is another source of atherogenic emboli recently detectable by transesophageal echocardiography. Microatheroma and other occlusive disease of the small penetrating brain arteries are the most frequent causes of small, subcortical “lacunar” infarcts. About 20% of ischemic strokes are due to cardiogenic embolism. A variety of other arterial occlusive disorders may be the primary cause or variably contribute to stroke pathogenesis. Overall, about 30% of ischemic strokes remain “cryptogenic” despite a reasonably thorough evaluation. Cerebral angiography done within a few hours of cryptogenic stroke often reveals occlusions of intracranial arteries. Most of these occlusions resolve within a few days, suggesting embolic obstruction. Thus, the specific pathogenesis of stroke in an individual patient is sometimes difficult to elucidate, and the optimal choice of antithrombotic therapy to prevent stroke worsening or recurrence is often challenging. This report summarizes new information available since the previous Antithrombotic Consensus Conferences, focusing on therapeutic implications of antithrombotic agents in stroke.

AntiplATELET Therapy

In 1994, the Antiplatelet Trialists’ Collaboration published the updated results of a worldwide meta-analysis of trials of antiplatelet therapy.1,2 These analyses conclude that antiplatelet therapy reduces vascular mortality by 17% (p<0.00001) and nonfatal vascular events, such as myocardial infarction (MI) and stroke, by about 25%. In trials involving patients with transient ischemic attacks (TIAs) or minor stroke given any type of antiplatelet drugs, treatment reduced nonfatal stroke by 22% (p=0.00001). These analyses lumped all agents whose primary mode of action on the vascular system was thought to be through inhibition of platelet aggregation, adhesion, or both. Patients with prior MI, acute MI, prior stroke, or TIA, were combined with other high-risk groups and patients from primary prevention studies. It remains to be determined how the overall estimates from such heterogenous patient groups are specifically applicable to patients with stroke and TIAs. Whether all beneficial effects of antiplatelet agents are due to the effect on platelet aggregation and whether all are similar in effectiveness are unclear. Although meta-analysis enables the pooling of data from a large number of similar studies to increase statistical power, individual randomized clinical trials of adequate sample size remain the gold standard for estimating the therapeutic effectiveness in specific patient situations.3–11

For aspirin, two recent prospective, double-blind, placebo-controlled studies have addressed stroke prevention:

Table 1—Stroke Rates in High-risk Patients

<table>
<thead>
<tr>
<th>Ischemic Stroke Rates, %/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population, age 70 yr</td>
</tr>
<tr>
<td>Asymptomatic bruit</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Asymptomatic carotid stenosis</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
</tr>
<tr>
<td>TIA</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
</tr>
</tbody>
</table>

Figure 1. The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke.

Figure 2. A classification of stroke by mechanism with estimates of the frequency of various categories of abnormalities. About 30% of ischemic strokes are cryptogenic.
Table 2—Aspirin Dose and Stroke Prevention: Individual Clinical Trials*

<table>
<thead>
<tr>
<th>Dose, mg/d</th>
<th>Level I Studies</th>
<th>Level I Studies</th>
<th>Level II Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>—</td>
<td>—</td>
<td>SALT</td>
</tr>
<tr>
<td>1,000</td>
<td>AICLA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1,300</td>
<td>—</td>
<td>Canadian</td>
<td>ESPS</td>
</tr>
</tbody>
</table>

*Considering ischemic and hemorrhagic stroke as the end point.

1 Level I studies combined aspirin in the doses indicated with dipyridamole or sulfinpyrazone, but no effect of the second agent was shown in these same studies, suggesting that the benefit was due to aspirin.

The Swedish Aspirin Low-Dose Trial (SALT)\(^2\) comparing 75 mg of aspirin a day to placebo and a Danish postendarterectomy study,\(^3\) comparing aspirin titrated to a platelet antiaggregant effect (doses ranging from 50 to 100 mg/d). The SALT demonstrated a significant effect of low-dose aspirin therapy, but the Danish study did not. In aggregate, all published studies overwhelmingly establish the beneficial effect of aspirin for reducing stroke and death in patients presenting with TIAs or stroke. However, varying dosage regimens that are not tested using randomization within individual studies cannot be compared directly. For example, because one dose of aspirin is effective in one study and another dose is similarly effective in a second study, it cannot be concluded with confidence that they are equally efficacious. The populations from which the patients are drawn may differ in important ways that influence the efficacy of aspirin.

**Differential Effects of Antplatelet Therapy by Gender**

The Canadian aspirin study\(^4\) reported a 31% reduction in stroke with aspirin, with benefit limited to men. The United Kingdom TIA study,\(^5\)\(^6\) also showed less effect in women. Other evidence suggests this may be an artifact of study design.\(^7\) Women with TIA consistently have lower rates of subsequent stroke and death than men. The lack of apparent effect of aspirin in women could be β-error in these studies, due to low event rates and inclusion of relatively small numbers of women.

The European Stroke Prevention Study,\(^5\) (ESPS) compared 926 patients who received aspirin (975 mg/d) and dipyridamole (225 mg/d) with 935 patients receiving placebo. Women were well represented (44%), and about 60% of those had a stroke at entry. Stroke and death decreased by 36.5% overall, and the same magnitude of significant differences was found for women and men. In the French AICLA study,\(^8\)\(^9\) the same beneficial effect was seen for women and men. In short, aspirin appears to be equally effective for stroke prevention in women; but because women have lower event rates, studies with larger numbers and longer periods of follow-up are needed to detect the effect. The Antiplatelet Trialists' meta-analysis supports the lack of gender difference in aspirin effect.\(^1\)

**Comparability of Different Agents**

To date and to our knowledge, the only antiplatelet agents that have been established as efficacious in properly designed studies for secondary prevention of stroke are aspirin and ticlopidine. Dipyridamole,\(^10\)\(^11\) sulfinpyrazone,\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) and sulcotidic\(^17\)\(^18\) have also been studied and have not been shown to be individually effective. Three studies have compared aspirin alone with aspirin plus dipyridamole; the French Toulouse study,\(^19\) the French AICLA study,\(^9\)\(^10\)\(^16\) and the Canadian-American study.\(^20\) None demonstrated any benefit of adding dipyridamole to aspirin. A fourth study assessing dipyridamole for stroke prevention is underway (ESPS II).

The antiplatelet effect of ticlopidine is not completely understood, but it appears to function primarily as an inhibitor of the adenosine diphosphate pathway. Ticlopidine inhibits most of the known stimuli to platelet aggregation, but in contrast to aspirin, it does not affect thromboxane in platelets or prostacyclin in the endothelium. Randomized clinical trials comparing ticlopidine with placebo have established it as an effective antithrombotic agent. The key clinical issue is how ticlopidine compares with aspirin. The Ticlopidine Aspirin Stroke Study (TASS)\(^21\) with 3,009 patients demonstrated a statistically significant difference in favor of ticlopidine over aspirin for stroke prevention. This was a double-blinded trial comparing ticlopidine (500 mg/d) and aspirin (1,300 mg/d). The ticlopidine group had a 21% decrease in all types of stroke at 3 years and a 47% relative risk reduction in stroke at 1 year compared with the aspirin-treated group. The effect appeared to be present in both men and women. The effect on the event constellation of ischemic stroke, MI, or death was less impressive.

The most serious side effect of ticlopidine is neutropenia, which occurs in about 2% of patients. In clinical practice, this requires biweekly blood counts during the first 3 months of ticlopidine therapy. In the clinical trials, when ticlopidine therapy was stopped, the neutropenia reversed.

In summary, ticlopidine is an effective antiplatelet agent for secondary stroke prevention. In patients with TIA, it is superior to aspirin for those who can tolerate it. The absolute risk reduction in stroke by ticlopidine over aspirin is small (about 1%/yr) in unselected TIA patients. In subgroup analysis of TASS, patients with TIA during aspirin therapy prior to enrollment had a particular high stroke risk if aspirin therapy was continued and greater benefit of ticlopidine compared with aspirin. It is essential that patients be monitored for neutropenia if ticlopidine is used, and its greater expense may also influence patient compliance. A related antiplatelet agent, clopidogrel, is being compared with aspirin in a large international clinical trial, with results expected in 1996.

**Low-Dose vs High-Dose Aspirin**

Most clinical trials showing a beneficial effect of aspirin for patients with cerebrovascular disease used doses of 975 to 1,300 mg/d (Table 2).\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^29\)\(^30\) Only two studies using doses in this range did not.\(^32\)\(^33\) It is controversial whether lower doses are as effective as higher doses, yet lower doses are in wide clinical use to prevent stroke. This policy is based on (1) in vitro studies of platelet inhibition, (2) extrapolation from a meta-analysis of antiplatelet therapy in a broad spectrum of patients, and (3) the results of the SALT.\(^12\)

Evidence is mounting that the brain and systemic circu-
Table 3—Common Sources of Cardiogenic Embolism

<table>
<thead>
<tr>
<th>Major Risk Sources</th>
<th>Minor Risk Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>Mitral valve prolapse±</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>myxomatous changes</td>
</tr>
<tr>
<td>Mechanical cardiac valves</td>
<td>Severe mitral annular</td>
</tr>
<tr>
<td>Recent MI</td>
<td>calcification</td>
</tr>
<tr>
<td>Left ventricular thrombus (especially if mobile or protruding)</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Atrial myxoma</td>
<td>Atrial septal aneurysm or calcific aortic stenosis</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>wall motion abnormalities</td>
</tr>
<tr>
<td>Dilated cardiomyopathies</td>
<td>(prior MI)</td>
</tr>
<tr>
<td>Marantic endocarditis</td>
<td>Aortic arch or atheromatous plaques</td>
</tr>
</tbody>
</table>

*These are associated with substantial absolute risk of stroke, firmly linked to an embolic mechanism.
†These are associated with low absolute risk of initial or recurrent stroke or are incompletely established as a direct embolic source based on current knowledge.

lations may not be identical, and the effects of aspirin may extend beyond its platelet antiaggregative effect. Many effects are different at higher doses than lower doses. These include variable strength of the agonist collagen, variable aspirin hydrolysis, hyperreactivity to shear stress in patients with vascular disease, disaggregation response, variability of response to aspirin, decreased platelet membrane fluidity, generation of thrombin, inhibition of smooth muscle cell growth, inhibition of megakaryocyte cyclooxygenase, altered platelet activity, and response to aspirin in disease states, among others. For all of these reasons, many clinical scientists consider the optimal dose of aspirin for stroke to be controversial. It is possible that the optimal dose may vary depending on the pathogenesis of threatened stroke (Fig 1).

Studies in animals of the effect of different doses of aspirin on thrombus formation after arterial injury have reported that the inhibition of thrombus formation, the number of emboli formed, and the duration of embolization are all dose dependent.

The SALT reported that 75 mg of aspirin a day resulted in an 18% decrease in stroke and death, significantly better than placebo. This suggests that low-dose aspirin therapy is effective, but it gives no information concerning whether it is more or less effective than higher doses (the effect on stroke alone was not statistically significant).

A Dutch study compared low-dose (283 mg/d) and very-low-dose aspirin (30 mg/d) therapy. In this well-designed and well-executed study, there were no significant differences in the primary end points of vascular death, stroke, or MI. From this study, one cannot conclude that low-dose aspirin therapy is as effective as high-dose therapy, but that 30 mg is equivalent to 283 mg for prevention of this event constellation.

The Physicians' Health Study reported the effect of low-dose aspirin therapy on events in the cardiac and the cerebral circulation. In this study, 22,071 male physicians received 325 mg of aspirin every other day or placebo for 5 years. Because of a highly significant (p<0.0002) decrease in MI in the aspirin-assigned group, this study was stopped sooner than planned. A total of 217 strokes occurred, 119 in those given aspirin and 98 in those assigned placebo. This lack of effect of aspirin on stroke is statistically inconsistent with aspirin's effect on MI in these patients. Therefore, the optimal dose of aspirin for myocardial ischemia may not be identical to the optimal dose for stroke prevention.

Clinical studies have shown dose-related differences in progression of carotid plaque size, restenosis after balloon injury, and recurrence of stroke. Ranke et al reported a substudy of patients recruited for a prospective, double-blind, study of the effect of 900 mg vs 50 mg of acetylsalicylic acid (ASA) per day on restenosis of arteries after lower limb angioplasty. In 104 plaques in 27 patients, the average carotid plaque size remained unchanged during treatment with 900 mg of aspirin daily but increased with 50 mg of aspirin (p=0.01), and significantly more lesions in the 50-mg group showed progression than in the 900-mg group (p=0.02). While higher-dose aspirin therapy had a significant effect on carotid artery plaques, no significant differences were noted for the restenosis of the arteries after lower limb angioplasty.

In summary, no definitive data exist establishing that low-to-intermediate-dose aspirin therapy (ie, ≤325 mg/d) is better than or even comparable to 975 mg or more for patients with cerebrovascular disease. Until this is done, the weight of evidence supports treating those patients with TIA and stroke who do not have contraindications to aspirin with 325 to 1,300 mg/d, if it is tolerated (Table 2). Although GI hemorrhage is slightly increased with higher doses of aspirin, stroke is a more serious outcome. If higher-dose aspirin therapy is more effective, a risk-benefit analysis would likely favor the use of the higher dose.

Table 4—Stroke and Oral Anticoagulants Following MI

<table>
<thead>
<tr>
<th>Study</th>
<th>WARIS111</th>
<th>Sixty-Plus112</th>
<th>ASPECT113</th>
<th>Aggregate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo, %/yr</td>
<td>2.3</td>
<td>1.3</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Anticoagulants, %/yr</td>
<td>0.7</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo, %/yr</td>
<td>0</td>
<td>0.1</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Anticoagulants, %/yr</td>
<td>0.3</td>
<td>0.9</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Unspecified strokes in Sixty-Plus Study and ASPECT are included with ischemic strokes.
†Patients in the Sixty-Plus study had been treated with anticoagulants for a mean of 6 years between the qualifying MI and study entry.
ORAL ANTICOAGULANTS FOR PRIMARY CEREBROVASCULAR DISEASES

Between the late 1950s and 1970s, results of several case series and nonrandomized comparisons generally favored oral anticoagulants (OAs) for patients with TIA and stroke.58-75 Four very small randomized trials compared OAs with control in patients with TIA.76-79 The total number of patients treated with OAs was only 93, follow-up was generally short and incomplete, and OA administration and the cause of TIA were poorly characterized. Aggregate results suggested a benefit of OAs for stroke prevention (9%/yr control, 3%/yr OA; p=0.05), but these results are at best inconclusive and at worst uninterpretable.80-81 In short, no convincing data exist to assess the value of OAs vs antithrombotic therapy for secondary prevention of brain ischemia in patients with primary cerebrovascular diseases. Anecdotal observations from that era consistently suggest that OAs reduce stroke and were relatively safe.

Following the recognition of the value of antiplatelet agents for ischemic stroke, three small randomized trials in Sweden compared OAs (approximate international normalized ratio [INR] range, 1.5 to 3.6) with platelet antagonists in patients with TIA and minor stroke.82-84 No clear benefit of anticoagulation was demonstrated (relative risk reduction, 18%; 95% confidence interval, 63 to +83%), but the small number of strokes made type II error (missing a true benefit) a concern, and aggregate results are inconclusive (also see Eriksson85 1985 for an additional nonrandomized comparison). Secondary analyses of a clinical trial involving patients with atrial fibrillation showed similar rates of presumed noncardioembolic stroke in patients receiving aspirin vs OAs, but confidence intervals were wide.86

Neurologists more often prescribe OAs for vertebrobasilar ischemia than for carotid territory ischemia.87 This is largely the result of an influential, nonrandomized, observational study from the Mayo Clinic88 reporting fewer strokes in patients with vertebrobasilar TIA given heparin and warfarin. Of note, the early stroke rate was very high in patients not treated with anticoagulants (20% at 3 months) and perhaps this study is more suggestive than heparin favorably alters the early course. Another nonrandomized comparison was not supportive.88 As a group, patients with vertebrobasilar TIs appear to have a better prognosis than those with carotid territory TIs.89-92 Thus, available data do not settle the value of OAs for vertebrobasilar ischemia, in our view.

In summary, whether OAs are of net benefit in patients with threatened stroke due to primary cerebrovascular disease is unsettled. In 1991, about one third of American neurologists routinely prescribed OAs for patients with TIA; the frequency of OA use was related to physician age and had decreased since 1988.93 At present, OAs cannot be recommended as initial therapy for unselected patients with threatened stroke due to primary cerebrovascular diseases, as insufficient data exist to settle whether they are superior to the safer and proven effective antiplatelet agents.93-95 Some physicians empirically use OAs in patients who have TIA or stroke while taking aspirin. Ticlopidine is a better validated alternative in this situation.96,97 Others occasionally recommend OAs for patients with severe symptomatic, inoperable carotid or vertebrobasilar stenosis.98,99 The inherent risk of stroke is highest during the 3 to 6 months following TIA or minor stroke, but whether short-term anticoagulation is more advantageous than long-term use has not been tested adequately. Lacking definitive data, most physicians who employ OAs in primary cerebrovascular disease do so for 3 to 6 months and confine OA use to patients who have ischemic events during antiplatelet therapy.77

Large clinical trials are underway in Europe and North America comparing OAs with aspirin in patients with cerebrovascular disease. The Dutch Stroke Prevention in Reversible Ischemia Trial (SPRIT) is an open-label comparison of very-low-dose aspirin with warfarin (INR, 3.0 to 4.5) therapy. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) is a double-blind comparison of 325 mg of aspirin against warfarin at lower target INR (1.4 to 2.8).

ORAL ANTICOAGULANTS FOR CARDIOEMBOLIC STROKE

Emboli originating from the cardiac chambers and valves account for about 20% of ischemic strokes in recent series (Fig 1). The value of OAs for prevention of cardioembolic stroke is firmly established for several major cardiac disorders predisposing to embolism.100-102 Emboli from the heart and proximal aorta can consist of thrombi of varying proportions of platelets and fibrin, calcific or cholesterol fragments, tumor particles, or bacterial clusters. The natural history and response to antithrombotic therapies of each are unique, and hence cardioembolic sources must be considered individually. It is conceptually useful to separate potential cardioembolic sources into “major risk” and “minor risk” (Table 3). Major risk sources are associated with a substantial absolute rate of stroke, often warranting prophylactic antithrombotic therapies. Minor risk sources have a low or uncertain risk of initial embolism, and antithrombotic therapies are usually reserved for secondary prevention.

Atrial fibrillation (AF) is the most frequent substrate for cardiogenic embolism.100 Previously unrecognized AF discovered in a patient with acute stroke might be a consequence of brain infarction mediated by other processes.103 Recent studies indicate that the risk of early recurrent stroke (within 2 weeks) is lower in AF patients than thought a decade ago.104,105 Initiating treatment with oral anticoagulation within a few days after submassive infarcts is a reasonable practice; delaying warfarin therapy for 1 week or more in AF patients with large infarcts may also be prudent to avoid accentuating secondary brain hemorrhage. Prophylaxis against deep venous thrombosis (DVT) with low-dose, subcutaneous heparin therapy in those with lower limb paresis is safe.104

ANTITHROMBOTIC THERAPY FOR SURVIVORS OF MYOCARDIAL INFARCTION

The long-term rate of ischemic stroke following MI is 1 to 2%/yr. While many of these strokes result from cardiogenic embolism of left ventricular thrombi, a substantial fraction are due to concomitant primary cerebrovascular diseases,106,107 as risk factors for coronary artery atherosclerosis and primary cerebrovascular diseases overlap. The initial 3 months following MI are particularly high risk.108-110 OAs reduce the long-term rate of ischemic stroke by about

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Table 5—Predictors of Anticoagulant-Related ICH

<table>
<thead>
<tr>
<th>Firmly Linked</th>
<th>Occasionally Reported</th>
<th>Potential Precipitating Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Atrial fibrillation</td>
<td>Minor head trauma</td>
</tr>
<tr>
<td>Intensity of</td>
<td>Diabetes mellitus</td>
<td>Acute alcohol</td>
</tr>
<tr>
<td>anticoagulation</td>
<td></td>
<td>intoxication</td>
</tr>
<tr>
<td>Prior ischemic</td>
<td>Proximity to</td>
<td>Acutely elevated</td>
</tr>
<tr>
<td>cerebrovascular</td>
<td>initiation of</td>
<td>BP (extreme</td>
</tr>
<tr>
<td>disease</td>
<td>anticoagulation therapy</td>
<td>cold exposure,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dental work)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Concomitant use of</td>
<td>Severe migraine attack</td>
</tr>
<tr>
<td>(especially</td>
<td>antiplatelet agents</td>
<td></td>
</tr>
<tr>
<td>systolic)</td>
<td></td>
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</tbody>
</table>

75% in patients with prior MI, but the absolute rate reduction is only about 1%/yr among unselected survivors of MI. In these patients, OAs (INR, 2.5 to 4.8) increased the rate of intracranial bleeding tenfold, to about 0.4%/yr (Table 4).111-114 While OAs effectively lower the rate of ischemic stroke by about 1%/yr, they increase the rate of more severe hemorrhagic stroke by about 0.4%/yr, so that the net benefit to the brain is minimal for unselected survivors of MI who have received anticoagulation to these intensities. The value of OAs for the prevention of vascular death and recurrent MI is discussed elsewhere in this supplement (see page 380S) and is clearly key to overall risk-benefit assessment.

Antiplatelet agents (particularly aspirin) are known to reduce ischemic stroke by about 30% in patients with prior MI, but this absolute rate reduction is also small (<0.5%/yr).115-120

Specific subsets of patients with prior MI have a higher risk for ischemic stroke and may benefit from OAs. Patients surviving anterior wall infarcts probably carry a higher risk for stroke than patients with MIs in other locations, although recent studies are conflicting.106,108,109 Following hospital discharge for acute MI, the risk for embolism in patients with left ventricular thrombi detected by echocardiography is 5 to 10% during the subsequent 6 to 12 months, although this risk varies substantially in existing clinical reports, perhaps due to small numbers of patients and variable use of antiplatelet agents.101,121-123 OAs appear to reduce embolism by about two thirds,101 and low-intensity anticoagulation (INR, 2 to 3) seems reasonable for patients with left ventricular thrombi detected within 3 to 6 months of MI. Whether left ventricular thrombi that appear later after MI have similar embolic potential is uncertain.107,122 There is a general consensus that “chronic” ventricular thrombi following MI have low embolic potential, and that anticoagulation may not be warranted unless thrombus morphologic features are mobile or protruding.124 Echocardiography at hospital discharge to detect left ventricular thrombi, and selective anticoagulation if thrombi are present, may be sensible in patients with heart failure following MI.125

In summary, OA use (INR, 2.5 to 4.8) does not substantially lower the stroke risk for unselected patients following hospital discharge for acute MI. The value of lower-intensity anticoagulation (INR, 2.0 to 3.0) and comparison of OAs to antiplatelet agents for stroke prevention in this situation await results of ongoing trials. Obviously, the risk of recurrent coronary ischemia and vascular death must also be considered. Survivors of MI with AF or with left ventricular thrombi detected within a few months are high-risk subgroups; OAs (INR, 2.0 to 3.0) are recommended to prevent stroke in suitable candidates for anticoagulation.

The role of complex atheromatous plaques of the aortic arch in the cause of stroke has received considerable recent attention,126,127 prompted in large part by the recent ability to visualize these lesions using transesophageal echocardiography.128-131 The natural history and optimal antithrombotic therapy of these lesions are as yet unknown.

Ischemic stroke caused by congenital and acquired deficiencies of coagulation inhibitors is relatively uncommon, but OAs are usually recommended for secondary prevention.131,132 Antiplatelet agents have not been evaluated, but theoretically should be less effective than OAs. Optimal antithrombotic therapy of secondary prevention of ischemic stroke related to the antiphospholipid antibody syndrome is unclear; OAs have been generally advocated.133,134

Patient foramen ovale has been associated with stroke and TIA in young adults, presumably by serving as a conduit for paradoxical embolism.135,136 However, patent foramen ovale can be demonstrated by contrast echocardiography in 20% of people without thromboembolism and is associated with mitral valve prolapse and atrial septal aneurysms.137 When patent foramen ovale is discovered in a patient with ischemic stroke but in the absence of venous thrombosis or sustained elevation of right atrial pressure, the diagnosis of paradoxical embolism remains uncertain. In this setting, some recommend antplatelet therapy,138 while others favor OAs for most strokes believed to be related to their patient foramen ovale.139

Short-term use of OAs has been advocated for dissections of the cervical carotid and vertebral arteries with distal embolism, but optimal antithrombotic therapy is unclear.140 OAs have been used in patients with radiation-induced vascular injury of the brain.141

NERVOUS SYSTEM COMPLICATIONS OF ANTITHROMBOTIC THERAPY

Intracerebral hemorrhage (ICH) is the most common, most lethal, and least treatable neurologic complication of OAs.142,143 Conventional intensities of anticoagulation (INR, 2.5 to 4.5) increase the risk of ICH by five to ten times.60,144-146 The mortality of OA-associated ICH is about 60% (range, 40 to 65%), making these strokes far more lethal than brain infarction. ICHs are immediately visible on CT scans; in patients who have received anticoagulation, an almost unique fluid-blood interface can be seen within the first 12 h due to uncongealed blood.149-151 Simultaneous ICHs at multiple sites occur especially often in patients who have received excessive anticoagulation.

In patients taking OAs, about 40% of all strokes are ICHs.142,146,148,152-153 Importantly, in OA-associated ICH, the bleeding evolves slowly, for 24 h or more, in about half of patients.142,154-156 This is in contrast to spontaneous ICH in patients who have not received anticoagulation, in whom the duration of bleeding is usually brief (about 10 h, showing progressive enlargement in the first 24 h).157-163 In OA-associated ICH, it is likely that emergent reversal of the coagulopathy improves outcome. Infusion of prothrombin com-
plex concentrate appears to reverse the coagulopathy more rapidly than fresh frozen plasma and was associated with improved outcome in one small study.155

Patient factors associated with increased risk of OA-related ICH have been identified (Table 5). CT or MRI findings of diffuse white matter abnormalities ("leukoaraiosis") may be a predictor of OA-associated ICH, as these lesions are related to degenerative subcortical vasculopathy in many patients.164

The relative and absolute risks of OA-associated ICH are proportional to the intensity of anticoagulation. There is no absolutely "safe" INR; many patients given OAs have experienced ICH well within the conventionally therapeutic INR range,142,145,153

Both patient factors and anticoagulation intensity are crucial determinants of the absolute rate of ICH. While conventional intensities of anticoagulation increase the risk of ICH by fivefold to tenfold, the quantitative relationship between intensity and ICH risk has not been fully defined precisely.165 The absolute rate of OA-related ICH for specific patient groups is difficult to predict accurately, representing a complex interaction of several patient factors with anticoagulation intensity.

Because conventional intensities of anticoagulation increase the risk of ICH as much as ten times, elderly patients must have a substantial risk for ischemic stroke to benefit from OAs when all-important absolute rates are considered. Ideal candidates for OAs may be patients with a high rate of thromboembolism, reduced 50 to 75% by OAs, who have a low inherent risk of ICH. Unfortunately, risk factors for ischemic stroke and ICH overlap in many patients (eg, advanced age, hypertension, prior stroke). Patients who are elderly (>70 years old) with hypertension have a substantial inherent risk for ICH that is multiplied by OAs to an absolute rate approaching 1%/yr. To justify anticoagulation in these patients, a larger absolute reduction in disabling ischemic strokes must result from OA therapy. Lowering the target intensity (INR, 1.5 to 2.5) may be sensible for patients at high risk for ICH, although the efficacy is not well established for stroke prevention and characterization of patients at high-risk for ICH is incomplete. Aspirin probably doubles the risk for ICH, regardless of the dose,166 and aspirin is less effective than OAs for prevention of thromboembolism in most situations. How lower intensities of anticoagulation (INR <2.5), with or without aspirin, will shift the risk/benefit equation for stroke prevention is not presently clear.

CERVICAL BRUITS AND ASYMPTOMATIC CAROTID STENOSIS

An asymptomatic carotid bruit is a physical finding that may be indicative of underlying atherosclerosis. An asymptomatic cervical bruit can be heard in about 5% of people older than 50 years. Only about one half of those with cervical bruises have a carotid artery stenosis, and most patients with severe carotid stenosis will not have an associated bruit. A carotid bruit is a marker of generalized atherosclerosis and thus identifies a patient with an increased risk of stroke, M1, and vascular death. The recommendations for treatment of patients with an asymptomatic cervical bruit include control or elimination of vascular risk factors such as hypertension, smoking, and hyperlipidemia, and education about the symptoms of TIA and stroke. In addition, patients with an asymptomatic bruit should be given aspirin if tolerated (proved to reduce MI in patients with asymptomatic stenosis).

The investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) recently reported that for patients with asymptomatic stenosis of greater than 60%, after endarterectomy had a statistically significant absolute reduction of 5.8% in the risk of the primary end point of stroke over 5 years (about 1.1%/yr) and a relative risk reduction of 55% as compared with those who did not undergo surgery.167 The investigators stressed that these results applied only to carefully selected patients who continued to have aggressive modifiable risk factor management and limited to surgeons with documented combined peroperative morbidity and mortality for asymptomatic endarterectomy of less than 3%. Reliable identification of "high-risk" patients with asymptomatic carotid artery stenosis is eagerly awaited.

ANTIPLATELET AGENTS AND HEPARIN IN ACUTE STROKE

The rationale for the use of antithrombotic medication at the time of acute stroke is based first on its efficacy in the prevention of DVT and pulmonary embolism.168 DVT complicates stroke in up to 75% of patients and 5% of early deaths are due to pulmonary embolism. Both aspirin and heparin reduce these risks by about 60% in other contexts, for example, after major surgery, and its seems reasonable to expect a comparable degree of protection after stroke, though few stroke patients have been randomized in prophylactic trials. The second argument concerns the assumed role of thromboembolism in the deterioration after onset in acute stroke deficit. Some 30% of patients show neurologic deterioration after hospital admission. Although this may be due to systemic factors and the evolution of edema, there is sometimes evidence of thromboembolism distal to the initial site of occlusion.169 This theoretically might be reduced by antithrombotic treatment, and the tendency to spontaneous recanalization might similarly be facilitated.170

Once a progressive or fluctuating course in acute ischemic stroke has been identified, further deterioration occurs in at least one third of patients.171,172 Because some percentage of unstable strokes may be caused by a progressive thrombotic process, urgent heparin administration has often been recommended for these patients in the hope of preventing further clinical deterioration. Early clinical studies suggested that heparin therapy was beneficial in patients with unstable ischemic stroke, reducing the likelihood of further worsening by about 50%.173-175 In these studies, however, criteria for both inclusion and progression were poorly defined, most control groups were not randomized, and outcomes were assessed by nonblinded observers over differing periods.176 More recent studies of consecutive patients with unstable stroke who received IV heparin therapy have shown high rates (27 to 50%) of further progression despite treatment.177-179

Despite the absence of supporting data from clinical trials, progressing or fluctuating ischemic stroke remains an accepted indication for urgent anticoagulation therapy. Such
treatment is typically reserved for patients who show progressive deterioration within 48 h of stroke onset, no other cause for the deterioration, and no contraindications (especially uncontrolled and severe hypertension) to heparin therapy. The clinical features of unstable ischemic stroke are similar to those seen in ICH, subdural hematoma, or tumors: thus, a brain imaging study should be done before the initiation of heparin therapy in this setting. The value of antiplatelet therapy for unstable stroke has not been assessed (to our knowledge).

The risks associated with antithrombotic treatment have always been assumed to be greatest in those with fresh cerebral infarcts, especially those of cardiac embolus origin. There is little direct evidence, however, and in one study of cerebral hemorrhage, heparin given to prevent DVT caused no clear-cut excess of adverse events.

An overview in 1993 found ten trials of heparin in 1,047 patients with acute ischemic stroke. There was a 50% reduction in DVT detected by fibrinogen scanning or venography (2p=0.00001) and a 58% reduction in pulmonary embolism when it was separately defined. Mortality was insignificantly reduced by 18%. Only a few patients had repeated scans on which the risks of hemorrhagic transformation could be assessed and these few scans showed no increase.

The safety and efficacy of aspirin and heparin are being investigated in the International Stroke Trial (IST). This study will recruit 20,000 acute stroke patients within 48 h of onset comparing the effects of heparin (in one of two doses), aspirin, neither, or both, with vascular death at 2 weeks as the principal end point. Subcutaneous heparin was chosen as being more effective than IV in prevention of DVT, and is perhaps safer, more patient friendly, and cheaper. A sister trial, also with a target of 20,000 patients seen within 48 h, has started in China comparing aspirin with placebo.

Low molecular weight heparinoids have a profile of equivalent anticoagulation but a theoretically lesser hemorrhagic risk and thrombocytopenia. Turpie et al reported that a heparinoid was more successful in preventing DVT in stroke victims than unfractionated heparin (9% vs 31%). The major systemic bleeding risk was the same (2%). Hemorrhagic transformation of the cerebral infarct was seen in 9.3% receiving the heparinoid, and 5.6% of those receiving heparin (nonsignificant). The same agent, IV Org10172, is now under study in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Study.

Until the IST and Chinese study results are available, patients with weakness of the leg or other reason to prevent mobility after ischemic stroke should be considered for prophylaxis against DVT and pulmonary embolism. Low-dose heparin or heparinoid therapy would be appropriate. If there are contraindications to the use of anticoagulants, aspirin should be considered. Delay in onset of antithrombotic treatment is currently advised if there is evidence of hemorrhagic infarction, but the necessity for this caution may be revised when the trial results are available.

Thrombolysis in the Treatment of Acute Ischemic Stroke

Pathologic and radiologic data demonstrate that some 80% of ischemic strokes are due to arterial occlusion, whether embolic or thrombotic. Angiography delayed for a few days after stroke rarely shows such occlusions, implying that spontaneous revascularization is common. The rationale for earlier therapeutic disobliteration of occluded vessels is based on the experimental evidence that neuronal death depends on both the depth and duration of ischemia. Restoring flow in an occluded carotid artery is surgically possible and can be carried out with low morbidity, but its efficacy is unknown, with only anecdotal data available. The possibility of pharmacologic clot lysis, which would be appropriate for both cervical and intracranial occlusions, has been an attractive one for more than 30 years. Experimental data show that autologous clot emboli in the animal cerebral circulation can be lysed without high risks of hemorrhage.

The early human trials met with unacceptable hemorrhagic risks, due to the difficulty in pre-CT days of avoiding treating some patients with cerebral hemorrhage, delays in onset of treatment, and from the lack of experience with the agents used. With the advent of newer thrombolytic agents and the ability to exclude hemorrhage within a few hours of stroke, there is renewed interest in this possible therapy. The striking success of thrombolysis in acute M1 has been a further spur. Theoretically, thrombolysis within hours, combined with neuroprotection of ischemic tissue, holds out the best hope for the limitation of the volume of infarction, which in turn is directly linked to mortality and functional outcome.

Safety trials have been carried out in stroke patients. Of 33 patients treated by Von Kummer et al with tissue plasminogen activator and heparin, 3 developed a cerebral hematoma and 7 developed hemorrhagic transformation. Wolpert et al reported 11% hematoma formation and 20% hemorrhagic transformation in an open study of recombinant tissue plasminogen activator (rtPA) in 104 stroke patients in the first 24 h of observation. Hemorrhagic transformation appears to be more common with delayed treatment beyond 6 h, larger doses, and elevated blood pressure.

Efficacy has also been looked at in two ways. The actual success of restoring patency of the obstructed artery has been sought by repeated angiography and or transcranial Doppler at the end of the therapeutic infusion. Most studies reveal that the success rate with IV therapy depends greatly on the site of occlusion. Recanalization is unlikely with combined occlusions of the carotid and middle cerebral artery, rare with carotid occlusion in the neck, but is to be expected in 30 to 40% of occlusions of the carotid and middle cerebral artery, and most distal branch occlusions. Mori et al reported on a small trial of rtPA in 30 patients. Recanalization was achieved in 9 of 19 treated subjects compared with 2 of 12 controls. The Japanese tPA randomized trial reported recanalization (defined as at least a 50% patency of the vessel) after thrombolysis in 25.6%, compared with a rate of spontaneous recanalization in the placebo-treated patients of only 4.3%, among 98 patients.

Clearly the more important criterion is that of mortality and morbidity. In animal models, infarct volume and mortality are reduced. The Japanese tPA study, despite the success of recanalization, showed no convincing clinical bene-
fit at 24 h or 7 or 28 days, though there were only 98 patients involved. ECASS is a randomized double-blind trial of alteplase within 6 h of hemispheric stroke: 1.1 mg/kg of the rtPA is infused over 60 min. Patients were recruited to a protocol requiring a CT scan that was normal or had early hypodensity of less than one third the middle cerebral artery territory within the time window of 6 h. The intention was to exclude patients with hemorrhagic infarction or hematomas and those with large infarcts (visible on early scans) or with marked swelling. Central review of the 620 patients randomized revealed that 109 had violated the protocol. The majority of the violations were for CT scan abnormalities indicative of large early infarction. An intention to treat analysis with Rankin and Barthel indexes as end points revealed no significant difference. When the patients with protocol violations were excluded, a significantly improved functional outcome followed the use of rtPA. When the exclusions are looked at, they contain an excess mortality due to TPA. The implication is that patients at high risk of hemorrhage or the complications of a large infarct on treatment can be identified by careful attention to the results of early imaging. Patients with nonhemorrhagic milder infarcts may well benefit functionally from early thrombolysis.

MAST-E, a multicenter acute stroke trial, is a randomized double-blind comparison of streptokinase (SK) and placebo within 6 h of ischemic stroke in middle cerebral artery territory. Early mortality has proved greater with SK (48% of 137) than with placebo (24% of 133, p<0.001). MAST-I, the Italian portion of the study, is comparing 1,500,000 U of SK, aspirin (300 mg/d for 10 days), and their combination, on death and disability at 6 months. There is evidence of an increase in early adverse events (<10 days) with SK that appears to be balanced out later as death and disability are matched at 90 days. The detailed results are to be published shortly. An Australian study is scheduled to recruit 600 patients within 4 h of stroke to receive the same dose of SK or placebo infused over 60 min within 3 to 4 h. SK was associated with a higher 90-day mortality (46/106 of 27/122) but patients recruited in less than 3 h showed a better safety profile. The NINDS rtPA trial is comparing the 3-month Barthel, Rankin, Glasgow outcome, and NIH stroke scale after randomization within 90 min, or between 90 to 180 min according to treatment with 0.9 mg/kg rtPA or placebo. Results should be available in late 1995.

The theoretical potential of thrombolysis is thus being tested in randomized controlled trials, with important results expected by late 1995. In the meanwhile, there is no mandate for its widespread use and substantial concern about its safety. It seems likely that the therapeutic window of current thrombolytic regimens will be narrow for acute stroke, limited by safety to the first few hours after stroke onset.

**Recommendations**

**Transient Ischemic Attacks and Minor Ischemic Strokes**

It is strongly recommended (grade A) that men and women with TIA be treated initially with aspirin (Table 6). Aspirin has been established as effective in doses ranging from 75 to 1,300 mg/d. While many experts recommend 75 to 325 mg of aspirin daily, other authorities believe that the higher dose, ie, 975 to 1,300 mg, may confer greater benefit. Ticlopidine is more effective than aspirin (in one level I study), but it also is more toxic. If close hematologic monitoring is not feasible, ticlopidine should not be used. At this time, ticlopidine is recommended for patients who are intolerant of aspirin or for patients with recurrent ischemic events during aspirin therapy. It is recommended that prolonged anticoagulation therapy not be routinely carried out in patients with TIA or minor stroke due to cerebrovascular disease, pending results of ongoing trials.

**Cervical Bruits and Asymptomatic Carotid Artery Stenosis**

A carotid bruit is a marker of generalized atherosclerosis and thus identifies patients with an increased risk of stroke, MI, and vascular death. The recommendations for treatment of a patient with an asymptomatic cervical bruit include management of vascular risk factors such as hypertension, smoking and hyperlipidemia, along with education about the symptoms of TIA and stroke. In addition, patients with an asymptomatic bruit should be given aspirin if tolerated. Carotid endarterectomy reduces the risk of stroke, but the absolute risk reduction appears to be small (about 1%/yr) for unsellected patients with asymptomatic carotid stenosis.

**Symptomatic Carotid Artery Stenosis**

Three randomized clinical trials have demonstrated that

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**Table 6—Antithrombotic Therapy for Stroke Prevention**

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommended Therapy</th>
<th>Acceptable Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA or stroke†</td>
<td>Aspirin 75-1,300 mg/d</td>
<td>Aspirin 75-1,300 mg/d, Ticlopidine 250 mg bid</td>
</tr>
<tr>
<td>TIA or stroke‡</td>
<td>Ticlopidine 250 mg bid</td>
<td>Warfarin INR 2-3</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>Warfarin INR 2.3‡</td>
<td>Warfarin INR 1.5-3, Aspirin 325 mg/d</td>
</tr>
</tbody>
</table>
| Asymptomatic carotid stenosis | Aspirin 325 mg/d‡ | Aspirin 75-1,300 mg, Ticlopidine 250 mg/d (
| Asymptomatic people ≥60 years old | No Rx | Aspirin 75-325 mg/d if vascular risk factors |

*Carotid artery endarterectomy for TIA or minor stroke associated with 70 to 99% ipsilateral stenosis (see text).

†Experts disagree about whether ≥975 mg of ASA offers more benefits than lower doses. Role of warfarin is unsettled.

‡Identification of “low-risk” patients who may not require anticoagulation is controversial; the optimal range of INR in elderly patients (>75 years old) may be lower (1.5 to 2.5). See also page 352S in this issue.

§Selection of patients for carotid endarterectomy is controversial (see text).

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carotid endarterectomy performed by experienced surgeons is superior to current medical therapy alone in the prevention of stroke following TIA or non-disabling stroke in appropriately selected patients. Patients with a greater than 70% carotid stenosis without major operative risk factors operated on by selected surgeons had a relative reduction of about 60% and absolute risk reduction of 5 to 10%/yr within the subsequent 2 years. Thus, symptomatic patients found to have a cervical carotid artery stenosis of this magnitude should be considered as candidates for carotid endarterectomy. The role of carotid endarterectomy in TIA patients with carotid stenosis in the range of 30 to 69% is still under investigation in randomized trials.

Progressing Ischemic Strokes

Heparin anticoagulation for 3 to 5 days is reasonable in the setting of a progressing ischemic stroke, especially those involving the vertebrobasilar circulation. A CT scan should be performed prior to anticoagulation to exclude brain hemorrhage. This grade B recommendation is based on two level II studies, each with a trend favoring anticoagulation. Some experts do not administer anticoagulants to such patients because of a paucity of convincing clinical data, and they recommend aspirin.

Completed Thrombotic Strokes

Level II evidence is inadequate to determine if long-term anticoagulation is of value to patients with completed strokes. Level I trials of aspirin support its use in patients with minor stroke. Patients with completed stroke have a higher risk for recurrent stroke compared with patients with TIA (Table 1). Thus, the absolute risk reduction by ticlopidine compared with aspirin may be greater and may favor its use. We recommend the use of aspirin or ticlopidine.

Acute Cardioembolic Stroke

It is recommended that heparin followed by warfarin therapy, at a dose that prolongs the prothrombin time and INR of 2.0 to 3.0, be instituted in nonhypertensive patients with small to moderate-sized embolic strokes in whom a CT scan done 48 h or more after stroke onset documents the absence of spontaneous hemorrhagic transformation. Anticoagulant therapy should be postponed 5 to 14 days in patients with large embolic strokes or uncontrolled hypertension because of the predisposition of these patients to hemorrhagic transformation.

In patients with AF as the presumed embolic source, initiation of warfarin therapy (following CT at ≥48 h) without initial heparin therapy seems reasonable in view of the relatively low risk of early recurrent embolism.

References

10. Shapiro S. Is there is or is there ain’t no baby. Dr. Shapiro replies to Drs. Petitti and Greenland. Am J of Epidemiol 1994; 140:789-91
12. The SALT Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. Lancet 1991; 336:1345-49
23. Robertson JT, Duggdale M, Sally N, et al. The effect of a platelet inhibiting drug (sulfinpyrazone) in the therapy of patients with transient ischemic attacks (TIAs) and minor strokes. Thromb Diathesis Haemorrhagiae 1975; 34:598
50 Lacoste L, Lami JYT, Letchacovski G. Comparative antithrombotic efficacy of aspirin: 80 mg vs 325 daily [abstract 2971]. Circulation 1994; 90(suppl)1:552


Cerebral Embolism Task Force. Cardiogenic brain embolism: a clinical review. (To be published).


Sixty Plus Reinfarction Study Research Group. Risks of long-term oral anticoagulant therapy in elderly patients after myo-


134 Bahkian VL, Levine SR. Therapeutic considerations for stroke patients with antiphospholipid antibodies. Stroke 1992; 23(suppl 1):33-7


143 Landeufeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989; 87:144-52


178 Britton M, Roden A. Progression of stroke after arrival at hospital. Stroke 1985; 16:629-33

179 Haley EC Jr, Kasell NF, Torner JC. Failure of heparin to prevent progression in progressing ischemic infarction. Stroke 1988; 19:10-4


190 ISIS-3 Collaborative Group. A randomized comparison of streptokinase vs tissue plasminogen activator vs antistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected myocardial infarction. Lancet 1992; 338:753-70


199 Major ongoing stroke trials. Stroke 1995; 26:1140-42


201 European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or mild (0-29%) carotid stenosis. Lancet 1991; 337:1235-43
