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Oral Anticoagulant Therapy for the Prevention of Stroke

THIS year in the United States, 450,000 people will have a first ischemic stroke.[1-3] For these patients (including those receiving thrombolytic therapy), the primary therapeutic goals will be rehabilitation and the prevention of another stroke. The optimal preventive therapy should be determined on the basis of the results of randomized, controlled trials. Trials have demonstrated that selected patients with an ischemic stroke in the territory of a stenotic carotid artery have a lower risk of recurrence if they are treated with carotid endarterectomy, rather than with antiplatelet therapy.[4] Patients with atrial fibrillation have a lower risk of recurrence with oral anticoagulant therapy than with aspirin.[5] Oral anticoagulant therapy is often recommended for a variety of other cardioembolic sources of stroke on the basis of varying levels of evidence.[6]

More than two thirds of patients with a first ischemic stroke (approximately 300,000 patients per year) have no identified cardiac source of stroke and are not candidates for carotid endarterectomy.[2,7] Antiplatelet therapy reduces the rate of recurrence of stroke in these patients by 30 percent.[6] Unfortunately, even when such therapy is combined with vigorous interventions designed to reduce other risk factors under the best conditions in clinical trials, the cumulative rate of recurrence of noncardioembolic stroke is still 3 to 7 percent per year. Recurrent stroke accounts for one third of all strokes.[1] We need to do better.

For more than 50 years, physicians have prescribed warfarin and other coumarin drugs for patients with noncardioembolic stroke in the hope that subsequent strokes could be prevented. Treatment recommendations have been based on a mixture of clinical experience, observational studies, and inferences about the pathophysiology of the first stroke. Until now, there has been no conclusive evidence from clinical trials demonstrating or refuting the benefit of this therapeutic approach in general or in specifically defined subgroups. The Warfarin–Aspirin Recurrent Stroke Study (WARSS), reported in this issue of the *Journal*,[8] provides evidence from a well-designed, well-conducted clinical trial to address this matter. WARSS was a double-blind, randomized, multicenter trial comparing aspirin (325 mg daily) with warfarin (target international normalized ratio [INR], 1.4 to 2.8) for the prevention of recurrent ischemic stroke or death within 2 years in 2206 patients who had had an ischemic stroke within the previous 30 days. Those who were scheduled for carotid endarterectomy or who had a presumed cardioembolic source of stroke (most commonly atrial fibrillation) were ineligible.

Important aspects of this study that attest to its high-quality design and execution include double-blinding by means of fabricated INR values in the aspirin group, low rates of hemorrhage in both the aspirin group (1.5 percent per year) and the warfarin group (1.9 percent per year), follow-up that was 98.5 percent complete, and narrow confidence intervals for the primary end point. Warfarin showed no significant superiority over aspirin for the prevention of recurrent ischemic stroke or death. The confidence intervals for the hazard ratio indicate that there is a 95 percent chance that warfarin is no more than 8 percent more effective than aspirin.

These results complement those of the Stroke Prevention in Reversible Ischemia Trial (SPIRIT).[9] This prospective, randomized, unblinded trial, involving 1316 patients with transient ischemic attack or minor stroke, compared aspirin (30 mg daily) with oral anticoagulant therapy, but it used a much higher target INR of 3.0 to 4.5. As in WARSS, patients who were scheduled for carotid endarterectomy or who had a presumed cardioembolic source of stroke were ineligible. SPIRIT was stopped after the first scheduled interim analysis because the primary end point (death from cardiovascular causes, nonfatal stroke, myocardial infarction, or major bleeding) had occurred more than twice as often in the anticoagulant-therapy group. This excess was entirely attributable to an increase in the incidence of major bleeding. There was no significant difference between the groups in the incidence of the nonhemorrhagic end points (hazard ratio, 1.03; 95 percent confidence interval, 0.6 to 1.75).

Thus, warfarin at a dose adjusted to achieve an INR of 1.4 to 2.8 has no benefit over aspirin, whereas warfarin at an INR of 3.0 to 4.5 is dangerous. Is it possible that oral anticoagulant therapy at some target INR level intermediate between these two levels will be superior to aspirin for the prevention of recurrent noncardioembolic stroke? This seems unlikely,

given the lack of benefit demonstrated in WARSS and SPIRIT, although the confidence intervals in SPIRIT are too wide to exclude such a benefit. Nevertheless, this hypothesis is currently being tested in the European–Australian Stroke Prevention in Reversible Ischemia Trial, which is comparing oral anticoagulant therapy (with a target INR of 2.0 to 3.0) with two different antiplatelet regimens.[10] At this time, the evidence does not support the use of oral anticoagulant therapy at any INR as a general strategy for preventing recurrent noncardioembolic stroke. It provides no therapeutic benefit over aspirin. It is more expensive and more difficult to manage, and it is unlikely that the low incidence of hemorrhage achieved in WARSS can be matched in routine clinical practice.[11]

The failure to demonstrate a benefit of warfarin over aspirin in the entire WARSS cohort, however, does not exclude the possibility that there are subgroups of patients for whom warfarin would be superior. The classification of patients with ischemic stroke according to the pathophysiologic mechanism of their stroke may prove useful in identifying subgroups of patients who respond differently to treatment and thereby lead to appropriate individualization of therapy. Unfortunately, precise causative mechanisms can almost never be determined; we can only describe associations with other factors — for example, stroke may occur with atrial fibrillation but not necessarily be caused by atrial fibrillation. Whether or not these associated factors lead to different responses to therapy can be determined only by a clinical trial.

The WARSS investigators provide data on five subgroups defined according to the clinically inferred mechanism of stroke. In none of these subgroups was a benefit of warfarin evident, although the smaller samples result in such wide confidence intervals that a benefit cannot definitively be ruled out. However, such negative subgroup analyses provide valuable information, because they are based on blinded data from randomized samples and are not subject to the selection bias involved in nonrandomized, observational studies. Several nonrandomized, unblinded, observational studies have suggested that there are associated factors that may define subgroups of patients with noncardioembolic stroke among whom oral anticoagulant therapy prevents recurrence more effectively than antiplatelet therapy; these associated factors include the presence of antiphospholipid antibodies, intracranial large-artery stenosis, and aortic-arch atheroma (Table 1).[16,20-22] Patients with these factors were not excluded from WARSS. Given the failure of this rigorous clinical trial to demonstrate the superiority of oral anticoagulant therapy in general or in any of the five subgroups that were examined, the associated factors described by the observational studies should not be considered as definitive indications for anticoagulation, although these studies suggest that further clinical trials involving the subgroups with these factors are needed.

Fortunately, such trials are already in progress. The Antiphospholipid Antibody Stroke Study is analyzing the type and titer of antiphospholipid antibodies

TABLE 1. EVIDENCE DEFINING THE ROLE OF ORAL ANTICOAGULANT THERAPY FOR SECONDARY PREVENTION AFTER NONCARDIOEMBOLIC TRANSIENT ISCHEMIC ATTACK OR STROKE.

CHARACTERISTICS OF PATIENTS STUDIED	LEVEL OF EVIDENCE*	FINDINGS REGARDING ORAL ANTICOAGULANT THERAPY	STUDIES
General	I and II	Not different from antiplatelet therapy	Mohr et al.,[8] SPIRIT Study Group†,[9] Liu et al.[13]
Progressing stroke	II	Not different from control	Carter,[14] Baker et al.[15]
Lacunar stroke	II	Not different from antiplatelet therapy	Mohr et al.[8]
Large-artery disease	II and III	Conflicting evidence regarding difference from antiplatelet therapy	Mohr et al.,[8] Chimowitz et al.[16]
Vertebrobasilar disease	III	Conflicting evidence regarding difference from control	WASID Study Group‡,[17] Whisnant[18]
Carotid-artery dissection	III	Not different from antiplatelet therapy	Lyrer and Engelter[19]
Antiphospholipid antibodies	III	Superior (at INR ≥3.0) to no antithrombotic treatment	Rosove and Brewer,[20] Khamashta et al.[21]
Aortic-arch atheroma	III	Superior to antiplatelet therapy	Ferrari et al.[22]

*The levels of evidence[12] were defined as follows: level I denotes evidence from randomized trials with low false positive and low false negative error rates; level II denotes evidence from randomized trials with high false positive or high false negative error rates; and level III denotes evidence from nonrandomized, concurrent cohort studies (i.e., those with nonhistorical controls).

†SPIRIT denotes the Stroke Prevention in Reversible Ischemia Trial.

‡WASID denotes Warfarin–Aspirin Symptomatic Intracranial Disease.

in a subgroup of the WARSS patients.[23] Results of this study should be available soon. Patients are currently being enrolled in the Warfarin–Aspirin Symptomatic Intracranial Disease Study for Stroke, which is comparing warfarin (target INR, 2.0 to 3.0) with aspirin (1300 mg daily) for the prevention of stroke and death from cardiovascular causes in patients with symptomatic stenosis of a major intracranial artery. Physicians should refer eligible patients to participating centers for enrollment (http://www.sph.emory.edu/WASID/). The Aortic Arch Related Cerebral Hazard Trial comparing warfarin with aspirin plus clopidogrel in patients with aortic-arch atheroma is funded by the Australian National Health and Medical Research Council and the French Medical Research Council and will begin soon (Donnan G: personal communication).

The prevention of recurrent stroke in patients with noncardioembolic stroke remains a frustrating problem of major importance. At this time, there is no evidence from clinical trials to support the use of oral anticoagulant therapy. Much more work needs to be done. Ongoing trials will determine whether there are associated factors that define subgroups of patients who will benefit from oral anticoagulant therapy. Additional studies with new antiplatelet drugs or combination therapy with antiplatelet drugs, angiotensin-converting–enzyme inhibitors, statins, and other agents will define the role of these agents. These efforts should be supported vigorously by physicians, patients, insurance companies, and government agencies.

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THERAPY FOR ACUTE HEPATITIS C

INFECTION with the hepatitis C virus (HCV) is now the most frequent cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the United States and most Western nations.[1-3] Population-based surveys show that 1 to 2 percent of adults in the United States are chronically infected with HCV.[2] Although hepatitis C has been described as an epidemic and a national emergency, the epidemic reflects the identification of chronic cases rather than a large outbreak of new cases.

Acute hepatitis C is no longer very common in the United States. The incidence has decreased from a peak level of 250,000 to 500,000 cases per year in the 1980s to fewer than 40,000 per year today.[4] The reasons include the near-elimination of post-transfusion hepatitis as a result of the screening of blood for HCV, increased use of aseptic techniques and universal precautions, and most important, a decrease in injection-drug use and in the number of cases of hepatitis C among injection-drug users.

Acute hepatitis C is uncommon enough that it is difficult to study. There have been many randomized, controlled trials of therapy in patients with chronic hepatitis C, but none of adequate size or rigor in pa-