Why Is WASID an Important Clinical Trial?

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Fifty years ago, coumarins (i.e. warfarin and other oral vitamin K antagonists) were first given for secondary prevention of ischemic stroke and were widely prescribed for this purpose during the subsequent decades despite the paucity of good evidence supporting their benefit, not unusual for neurological therapeutics of the era. More recently, it has been established that antiplatelet agents reduce subsequent stroke and other major vascular events by about 20% for patients with cerebral ischemia, a benefit that is not offset for most patients by a modestly increased risk of major bleeding [1]. When, if ever, should warfarin anticoagulation be given instead of antiplatelet therapy to patients with noncardioembolic brain ischemia?

To date, six randomized clinical trials involving 4,090 participants have compared aspirin in dosages of 30–1,300 mg/day with oral anticoagulants in such patients [2, 3]. Individually and in aggregate, these trials demonstrated no advantage of oral anticoagulation over aspirin. The recent Warfarin-Aspirin Recurrent Stroke Study (WARSS) is the largest (2,206 participants) and most methodologically rigorous; it showed that warfarin, mean achieved INR = 1.9, is not better and could be worse than aspirin 325 mg/day for unselected patients with noncardioembolic brain ischemia [3, 4]. In another of these trials, a mean achieved INR of about 3 resulted in an intolerable rate of brain hemorrhage that caused early termination [5]. In short, for unselected elderly patients with

noncardioembolic brain ischemia, an INR of 3 is too much and an INR of 2 is too little. At present, warfarin in any intensity should not be routinely used instead of antiplatelet therapy for secondary prevention of noncardioembolic brain ischemia, as there is no clear evidence favoring its use over the safer, more easily administered alternative.

In this issue, the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial investigators report their trial design and initial experience [6]. Patients with TIA or minor ischemic stroke associated with arteriographically proven intracranial stenosis are randomly assigned to warfarin (target INR range 2–3) vs. aspirin 650 mg twice daily in a double-blind design and followed for development of stroke or vascular death, the primary outcome. In all, 806 participants will be included. With recruitment over halfway completed, a discouragingly high false-positive rate for prediction of intracranial stenosis by noninvasive tests has been found. The relatively young mean age (63.5 years) probably reflects screening biases rather than the population prevalence of the disorder.

Will WASID add importantly to stroke prevention? Yes, without question. Several features make WASID unique among trials comparing warfarin with aspirin in noncardioembolic brain ischemia. The target INR of 2.5 in a double-blind design will test the most relevant intensity of anticoagulation in a scientifically rigorous manner.

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The dwindling few who believe that high-dose aspirin offers additional protection for stroke prevention will be pleased with the dosage tested in WASID. Most importantly, WASID offers the only randomized comparison of warfarin with aspirin in high-risk patients with arteriographically proven occlusive cerebrovascular atherosclerosis. Consequently, the implications of WASID potentially extend beyond secondary prevention of the 10% of cerebral ischemia attributed to intracranial atherosclerosis. Subsets at particularly high risk of stroke will likely be identified by arteriographic data.

The importance of testing antithrombotic agents in well-defined etiological subgroups of ischemic stroke patients is dramatically illustrated by the very large reduction in stroke by warfarin over aspirin in atrial fibrillation patients [7] compared with trends favoring aspirin over warfarin for unselected patients with noncardioembolic brain ischemia. This disparity is seen in the substantially higher rates of anticoagulation-associated intracerebral

hemorrhage in those with noncardioembolic ischemia [8]. Compared with patients with atrial fibrillation, warfarin in patients with intrinsic cerebrovascular disease is less efficacious and more dangerous. Ischemic stroke etiological subtypes *do* matter, for antithrombotic prophylaxis and probably for other interventions as well. The prevalence of leukoaraiosis detected by neuroimaging among WASID participants and its relationship to brain hemorrhage will be of great interest [9]. Intracerebral hemorrhage is exquisitely sensitive to blood pressure [10], and careful monitoring, control and reporting of blood pressure will be integral to understanding the results of WASID.

WASID promises to be a landmark clinical trial. It is an especially challenging trial to execute, requiring invasive arteriography and double-blind administration of anticoagulation during a prolonged follow-up. The WASID investigators and study participants will make important, unique contributions to the fight against stroke.

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