Ever Decreasing Circles: Advances in Antiplatelet Therapy and Anticoagulation

J. Kennedy, MB, MSc, MRCP; A.M. Buchan, MD, FRCP

Aspirin and anticoagulation with warfarin have been the mainstays of secondary stroke prevention. However, questions remain as to whether antiplatelet therapy or anticoagulation is superior and whether the two are synergistic in stroke prevention. This review highlights new advances in stroke prevention in 2002 using these agents. We conclude by exploring possible areas for future inquiry.

Expanding and Contracting the Role of Anticoagulation

Aspirin has only a modest but significant benefit in preventing recurrent stroke. Anticoagulation has been viewed as a more potent agent than aspirin, particularly given the success of warfarin in stroke prevention in patients with nonrheumatic atrial fibrillation.1-2 The Warfarin-Aspirin Recurrent Stroke Study (WARSS) examined this potential superiority of warfarin compared with aspirin.3

WARSS involved the randomization of 2206 patients to active-aspirin (325 mg) and warfarin-placebo or active-warfarin and aspirin-placebo with follow-up for 2 years. Randomization occurred within 30 days of an ischemic stroke, in cases in which no cardiac source was suspected and no surgery for a high-grade carotid stenosis was planned. The trial was double-blinded, and the trial organizers are to be commended their efforts to maintain blinding, with plausible false international normalized ratio (INR) values generated for those randomized to warfarin-placebo. The dose of warfarin was adjusted to achieve and maintain a range of INR from 1.4 to 2.8.

The trial failed to show a benefit of warfarin compared with aspirin. Warfarin was associated with a nonsignificant additional risk of stroke or death compared with aspirin (17.8% receiving warfarin versus 16.0% receiving aspirin). Safety, in terms of major hemorrhage, was comparable between the groups (3.4% receiving warfarin versus 2.7% receiving aspirin). However, questions remain. Although it cannot be argued that all patients should receive warfarin, it also cannot be unequivocally stated that the two therapies are of equal value, because the trial was not powered to show this.

Was the INR level achieved in the trial high enough? The range chosen reflects current practice in proven cardioembolic events, given the increasing hazard of treatment with a target therapeutic range in excess of 3.0.4 The Stroke Prevention in Reversible Ischemia Trial (SPIRIT), with a similar trial design but with a higher target INR range (3.0 to 4.5, mean 3.5), was stopped after the first interim analysis because of the unacceptable complication rate of major bleeding in the warfarin group.5 This trial has emerged in a new form, the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT),6 randomizing patients to warfarin (target INR 2.0 to 3.0, unblinded), aspirin (30 to 325 mg), or aspirin (30 to 325 mg) and dipyridamole (400 mg daily). Once published, the full range of INR from 1.4 to 4.5 will have been explored to establish warfarin’s superiority compared with aspirin, and this question can be put to rest.

Are there subgroups of patients who would benefit from anticoagulation? Further evidence of the trial’s exceptional design is the number of independently funded a priori hypothesis–driven substudies that were contained within the broad WARSS umbrella. There were four other trials: the Antiphospholipid Antibodies and Stroke Study (APASS), the Patent Foramen Ovale in Cryptogenic Stroke Study (PICCS), the Hemostasis System Activation Study (HAS), and the Genes in Stroke Study (GENESIS). The data as presented at the 27th American Heart Association Stroke Conference in San Antonio, Texas, 2002, indicated that there seemed to be no subgroup that benefited from warfarin compared with aspirin. However, only the data from PICSS have appeared thus far in peer-reviewed form, and we await the publishing of the other studies before drawing any firm conclusions.7

PICSS enrolled 630 patients, balanced in their allocation to warfarin and aspirin. In 203 of these patients, a patent foramen ovale (PFO) was found with transesophageal echocardiography. Two hundred sixty-five of these patients had a cryptogenic stroke and 365 had a known stroke subtype. Warfarin was not shown to be superior to aspirin in the overall cohort (16.5% receiving warfarin versus 13.2% receiving aspirin). The presence or absence of a PFO or stroke mechanism did not influence these results. This study also showed that the presence or absence of an atrial septal aneurysm did not influence the event rate, in contrast to previous studies.8,9 This trial does completely resolve the role of anticoagulation in this specific group of patients given that the risk of stroke related to PFO may vary across age groups and in those who have paradoxical embolism as a clearly...
documented stroke mechanism. Therefore it would seem that there are no subgroups of patients in whom warfarin is a superior treatment to aspirin, with the caveat as mentioned above.

The aspirin and coumadin after acute coronary syndromes (the ASPECT-2) study was also published. It involved the open randomization of patients with previous acute coronary syndrome within 8 weeks to aspirin (80 mg), anticoagulation (INR target 3.0 to 4.0), or aspirin (80 mg) and anticoagulation (INR target 2.0 to 2.5), with a median follow-up of 12 months. Both anticoagulation and combination aspirin and anticoagulation were more effective than aspirin alone in preventing the composite endpoint of myocardial infarction, stroke, or death. Bias may exist because of the unblinded nature of the trial. The rate of death from all causes, the most robust endpoint, was unaffected by the treatment allocation, and the numbers of strokes were too small to draw any meaningful conclusion.

The role of warfarin versus aspirin in patients with reduced left ventricular ejection fraction (WARCEF) or symptomatic intracranial artery disease (AVASIS, WASID) and the role of warfarin versus combination aspirin and clopidogrel in patients with AF (ACTIVE) or the aortic arch as a source of embolism (ARCH) are the subjects of ongoing or forthcoming trials.

Antiplatelet Agents: Alone or in Combination

The Antithrombotic Trialists meta-analysis was updated, clearly showing the benefit of aspirin in stroke prevention. After an initial loading dose of at least 150 mg, any dose greater than 75 mg seems to be equivalent in preventing recurrent vascular events. Clopidogrel was shown to have a marginal improvement compared with aspirin in preventing the combined outcome of myocardial infarction, stroke, and vascular death in those with symptomatic atherosclerotic disease. These findings were qualified by the lack of benefit to those enrolled with stroke as the entry event.

The addition of other antiplatelet agents to aspirin with putative synergistic mechanisms of action is currently the subject of many trials. The meta-analysis downplayed the merits of the addition of dipyridamole to aspirin, in contrast to the results of the European stroke prevention study II (ESPS-II), which showed a significant reduction in recurrent stroke and vascular events. ESPRIT will further clarify this issue.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial showed a reduction of vascular events when the combination of aspirin and clopidogrel versus aspirin alone was commenced in patients with acute coronary syndromes. There are forthcoming trials that will provide information on the superiority of the combination of aspirin and clopidogrel versus aspirin alone in patients with symptomatic atherosclerotic disease (CHARISMA) and with subcortical stroke (SPS3). There is an ongoing trial that randomized patients with transient ischemic attack or previous ischemic stroke on clopidogrel to aspirin or placebo. This trial will provide information specific to those with cerebrovascular disease (MATCH).

New Directions?
The trials that have been listed above advance the old paradigm of treatments initiated in the short to medium term after an event. The field of cerebrovascular disease has been transformed by the demonstration of efficacy of thrombolysis with the changes in the organization of care that have taken place to maximize the number of patients that may receive treatment. However, there are many patients who lie outside of the current treatment protocols, who are at high immediate risk of stroke. The treatment paradigm of acute stroke prevention, treatments started in the immediate aftermath of transient ischemic attack or stroke, therefore needs to be explored given the paucity of current evidence beyond the use of aspirin.

The second new direction comes from the increasing appreciation that atherosclerosis is an inflammatory disease, C-reactive protein (CRP), a reflection of inflammation, is an independent predictor of recurrent stroke. Characterizing aspirin and clopidogrel as antiplatelet agents alone does not do justice to their pharmacology. Both have been shown to suppress CRP. Exploiting the anti-inflammatory properties of these drugs in patients with raised CRP, particularly in a primary prevention population, may lead to more focused treatment of those at risk of stroke and vascular events. It may even lead to reopening old debates, such as the optimal dose of aspirin in selected patients, and may in part explain the results of WARSS.

Conclusion
We conclude that aspirin is the current treatment of choice compared with anticoagulation for patients with noncardioembolic stroke in view of ease of treatment and its proven role in prevention throughout the vascular bed. The role of combination antiplatelet strategies versus either aspirin or warfarin is yet to be defined.

The real truth is that these patients remain at high risk of recurrent events no matter which therapy is chosen, and the arguments about antiplatelet treatment or anticoagulation should be seen in the context of other medical (eg, blood pressure control with angiotensin-converting enzyme inhibitors, statin therapy) and interventional (eg, carotid endarterectomy) strategies of proven benefit.

References
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