Antiplatelet therapy for acute stroke: Aspirin and beyond

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Recent recommendations from a joint scientific statement of the American Heart Association (AHA) and the American Academy of Neurology (AAN)[1] address a number of key issues in the use of antiplatelet therapy for acute stroke. This review spotlights a number of these key recommendations and surveys the current evidence underlying them.

ACUTE ASPIRIN ENDORSED FOR MOST PATIENTS

The AHA/AAN joint statement recommends the following:

> "Aspirin should be given within 24 to 48 hours of stroke onset in most patients (grade A recommendation)."[1]

Few trials of antiplatelet therapy have focused on stroke in the acute setting, but two of them[2,3] had a similar trial design and together randomized more than 40,000 patients.

The **International Stroke Trial**[2] (IST) involved 19,435 patients with acute stroke who were randomized within 48 hours of symptom onset to aspirin 300 mg/day, heparin, both, or neither for 14 days of therapy. Randomization was by a factorial design in which patients fell into 6 treatment groups: aspirin alone, aspirin and low-dose heparin (5,000 IU twice daily), aspirin and high-dose heparin (12,500 IU twice daily), low-dose heparin, high-dose heparin, or no study medication. The primary end points were death within 14 days and death or dependency at 6 months. Secondary end points included early (within 14 days) hemorrhagic stroke, recurrent ischemic stroke, major hemorrhage, and pulmonary embolism.

Compared with patients who did not receive aspirin, those who received aspirin had modestly but significantly lower rates of recurrent ischemic stroke (2.8% vs 3.9%) and of nonfatal stroke or death (11.3% vs 12.4%). At 6 months, the rate of death or dependency was also significantly lower for the aspirin-treated patients (61.2% vs 63.5%). Although patients who received heparin had significantly lower rates of recurrent ischemic stroke (2.9% vs 3.8%) and pulmonary embolism (0.5% vs 0.8%) compared with their counterparts who did not receive heparin, these benefits were offset by equally significant increases in the risk of hemorrhagic stroke (1.2% vs 0.4%) and major bleeding (1.3% vs 0.4%). As a result, the rate of death or dependency at 6 months was identical—62.9%—in both the patients who received heparin and those who did not. The subgroup that received aspirin and low-dose heparin looked like it might have fared better than the aspirin-only subgroup in the short term, with less early mortality (8% vs 9.3%) and less early recurrent stroke and intracranial hemorrhage (2.8% vs 3.7%), but the analysis of 6,000 patients was not large enough to be conclusive.[2]

The **Chinese Acute Stroke Trial** (CAST)[3] randomized 21,106 patients with acute stroke within 48 hours of symptom onset to aspirin 160 mg/day or placebo for up to 28 days of therapy. Compared with placebo, aspirin reduced mortality (3.3% vs 3.9%) and the rate of nonfatal stroke or death (5.3% vs 5.9%). The rate of recurrent ischemic stroke was reduced by about 15% with aspirin use, although there was a small increase in the risk of hemorrhagic stroke.

Although the patients enrolled in IST and CAST differed, these studies taken together[4] demonstrate a modest effect of early aspirin use in a wide range of patients with acute stroke. Although entry was per-

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mitted within 48 hours of symptom onset, 14% of patients (5,600) were randomized within the first 6 hours, with treatment initiated immediately after randomization. The risk of early recurrent stroke was low (2% risk of ischemic stroke, 1% risk of hemorrhagic stroke, and 1% risk of stroke of unknown type), and recurrent strokes occurred primarily within the first week. Early aspirin administration reduced the risk of early recurrent ischemic stroke to 1.6% compared with 2.3% with control therapy, which corresponds to an absolute risk reduction of 7 per 1,000 and a relative risk reduction of 30%. At the same time, early aspirin use carried a slightly increased risk of hemorrhagic transformation or hemorrhagic stroke (1.0% vs 0.8%, for an absolute risk increase of 2 per 1,000). The effect of aspirin on reducing death or dependency at 6 months was somewhat better (45.6% vs 46.9%, for an absolute risk reduction of 12 per 1,000). Aspirin was associated with a definite excess in other major hemorrhages, particularly when heparin was used (0.7% for aspirin vs 0.5% for control, for an excess of 2 per 1,000; and 1.8% for aspirin plus heparin vs 0.9% for heparin alone, for an excess of 9 per 1,000).

In a meta-analysis, these results were not substantially affected by age, gender, level of consciousness, blood pressure, stroke subtype, CT findings, atrial fibrillation, or concomitant heparin use. In addition, for the 9,000 patients (22%) randomized without a prior CT scan and the 773 (2%) inadvertently randomized after a hemorrhagic stroke, there was no excess of adverse outcomes (hemorrhagic stroke or further stroke or death).[4]

NO ADJUNCTIVE OR SUBSTITUTE ROLE FOR ACUTE ASPIRIN

The AHA/AAN joint statement advises the following:

> "The administration of aspirin as an adjunctive therapy, within 24 hours of the use of thrombolytic agents, is not recommended (grade A)."[1]

The Multicenter Acute Stroke Trial–Italy[5] (MAST-I) was terminated prematurely after interim results showed, among other findings, an excess of intracranial hemorrhage and death in patients who received combination therapy with aspirin and streptokinase. The NINDS IV t-PA protocol permitted the treatment of patients taking aspirin so long as other exclusion criteria were met, but it prohibited the use of adjunctive antiplatelet or antithrombotic therapy within 24 hours of therapy. Indirect data from the cardiology literature indicate that the risk of systemic and intracranial bleeding is increased with the aggressiveness of combination therapies, particularly in the elderly.

The AHA/AAN joint statement also states:

> "Aspirin should not be used as a substitute for other acute interventions, especially intravenous administration of rt-PA, for the treatment of acute ischemic stroke (grade A)."[1]

Aspirin therapy is simple and readily available, but because its effect is modest, more effective therapies should take precedence.

JURY STILL OUT ON ACUTE USE OF OTHER ANTIPLATELETS

On the acute use of other antiplatelet agents, the AHA/AAN joint statement advises as follows:

> "No recommendation can be made about the urgent administration of other antiplatelet aggregating agents (grade C)."[1]

Most of the clinical trials assessing antiplatelet agents in stroke have focused on the long-term prevention of recurrent stroke in patients at risk for stroke. Although aspirin is the standard preventive therapy, the optimum dosage for the prevention of vascular events remains controversial despite 20 years of study. As an inhibitor of thromboxane A_2 generation, aspirin has a modest effect. In patients with prior transient ischemic attack (TIA) or stroke, its major effect is the 23% reduction of recurrent nonfatal stroke. Thus, establishing superior preventive efficacy has been the goal for other antiplatelet agents targeting platelet surface glycoproteins, ADP receptors, or platelet-dependent thrombin generation, alone or in combination with aspirin.

Although hemorrhagic transformation of acute ischemic stroke can occur in the absence of any therapy, the risk is enhanced with the aggressiveness of such therapies, setting the risk-to-benefit ratio on a razor's edge. Although data on other antiplatelet therapies are extensive in the treatment of acute cardiovascular conditions, data on these therapies in the setting of acute stroke are limited.

For unstable angina or acute non–Q-wave myocardial infarction, the combination of clopidogrel 75 mg/day and aspirin 75 to 325 mg/day was superior to aspirin alone without an increase in stroke risk (1.2% vs 1.4%).[6] A study with a similar design is now under way to compare clopidogrel 75

mg/day plus aspirin 75 mg/day with clopidogrel 75 mg/day alone in 7,600 high-risk patients with recent TIA or ischemic stroke. Results of this trial, known as MATCH (Management of Atherothrombosis with Clopidogrel in High-risk Patients), are expected by May 2004. Although it is not designed as an acute stroke trial, roughly one quarter of the initial 3,800 patients were entered within the first week of symptom onset, so some information on the safety of early combination antiplatelet therapy in acute ischemic stroke might be available.

GPIIb/IIIa receptor antagonists

There are currently some data exploring the safety of glycoprotein IIb/IIIa receptor antagonists in the setting of acute ischemic stroke, with small case series of tirofiban therapy in progressive stroke[7] and of eptifibatide combined with intra-arterial t-PA in acute ischemic stroke.[8] A small pilot dose-escalation study of abciximab was performed to assess its safety in acute ischemic stroke of less than 24 hours' duration,[9] paving the way for a larger safety trial using the standard dose used in cardiac interventions.

The Abciximab in Emergent Stroke Treatment Trial (AbESTT)[10] assessed the safety of abciximab (0.25-mg/kg bolus followed by 0.125-μg/kg/min infusion for 12 hours) in a randomized, double-blind, placebo-controlled trial involving 394 patients with acute ischemic stroke randomized within 6 hours of symptom onset. The primary safety end point, symptomatic intracranial hemorrhage through discharge or day 5, occurred more often with abciximab than with placebo (3.6% vs 1%), but asymptomatic intracranial hemorrhage on surveillance neuroimaging was more common in placebo recipients (16.6%, vs 12.3% in abciximab recipients). Although the trial was not powered for efficacy, analysis of functional outcomes at 3 months showed that significantly more abciximab recipients than placebo recipients achieved a modified Rankin score of 0 or 1 (53.9% vs 34.6%; $P = .013$).

On the basis of these data, the pivotal trial, AbESTT 2, will enroll patients with acute ischemic stroke of less than 5 hours' duration.

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