# Secondary Stroke Prevention: Plavix versus Aggrenox

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**Lay Abstract**

Stroke is the third leading cause of death and a leading cause of disability in the United States (See Sacco, 2000). Patients who experience a TIA (transient ischemic attack) are at high risk for subsequent stroke; some say the risk may be as high as 40% within 5 years. Antiplatelet agents have been shown to reduce the risk of subsequent stroke. Options for antiplatelet therapy include aspirin, ticlopidine (Ticlid) and clopidogrel (Plavix), and Aggrenox (extended release dipyridamole plus aspirin). Aspirin was the first antiplatelet agent to be studied, and it has been shown to reduce the risk of recurrent stroke in many different trials. Ticlopidine was then shown to be superior to aspirin, but it has fallen out of favor because of its side effect profile. Clopidogrel, a close relative of ticlopidine, was compared to aspirin in the CAPRIE trial (CAPRIE, 1996). With fewer side effects, clopidogrel was marginally superior to aspirin in preventing a combined endpoint of stroke, MI, and vascular death. Aggrenox is a combination of extended-release dipyridamole and aspirin; it was superior to aspirin alone in the second European Stroke Prevention Study (Diener et al, 1996). Multiple randomized clinical trials have examined antiplatelet agents in prevention of vascular events, but no study has compared clopidogrel to dipyridamole plus aspirin.

The present study compares the efficacy of Plavix and Aggrenox for the prevention of recurrent stroke in adults who have had a minor ischemic stroke or TIA. This multicenter international prospective randomized double-blind clinical trial seeks to enroll a total of 4600 patients who will be followed for 3 years. Following a qualifying event (minor ischemic stroke or TIA), patients will be randomized to Plavix or Aggrenox. The primary endpoint will be recurrent stroke.

**IRB Protocol**

**A. Purpose**

This study compares Plavix and Aggrenox, two previously studied antiplatelet agents, for the prevention of recurrent stroke in patients who have experienced a minor ischemic stroke or TIA.

**B. Study Design**

A total of 4600 patients will be enrolled in this prospective randomized double-blind clinical trial. One-half (2300) will receive Plavix and one-half will receive Aggrenox. They will be randomly assigned a number, corresponding to a treatment package. Patients will not be crossed over. The sample size of 2300 per group is based on a power analysis using an alpha of 0.05 and a power of 0.80. The predicted event rates in each group were calculated from two prior studies: the ESPS-2 trial and the CAPRIE trial. In the ESPS-2 trial, the rate of recurrent stroke at 2 years was 12.49% for aspirin, 9.51% for Aggrenox, and 15.16% for placebo. Extrapolating these percentages to 3 years of follow up predicts an event rate of 14.27% for Aggrenox and 18.74% for aspirin. In the subgroup of stroke patients CAPRIE trial, Plavix was 7.3% better than aspirin, which predicts an event rate for Plavix of 17.36% at 3 years. Thus, the power calculation assumes an event rate of 17.36% for Plavix versus 14.27% for Aggrenox. Approximately 50 patients with minor stroke (Sacco, personal communication) will be enrolled at CPMC per year along with 25 patients with TIA (total = 75/yr). Patients will be enrolled over a 2 year period at 32 centers.

**C. Study Procedure**

After beginning the trial, patients will be seen for follow-up visits at one month and then every 3 months for 3 years. Compliance will be assessed with pill counting. Outcome events, concomitant medications, and adverse effects will be recorded at the follow-up visits. Patients will be instructed not to use NSAIDs including aspirin and will be encouraged to use Tylenol for analgesia. Patients will be instructed not to drink more than 3 alcoholic drinks per day. Physicians will be blinded to the treatment assignment. The primary outcome will be recurrent stroke. Secondary endpoints will be incidence of major bleeding events (defined as requiring transfusion or hospitalization), myocardial infarction, TIA, and death.

**D. Study Drugs**

1. Plavix (clopidogrel) 75mg tablets (standard dose) will be administered in the morning and an identical placebo tablet will be given at night. Plavix is approved for the reduction of atherosclerotic events. Adverse reactions are similar to side effects of aspirin and include bleeding (2%), neutropenia (0.8%), gastrointestinal complaints (27.1%), and rash (15.8%). TTP (thrombotic thrombocytopenic Purpura) has rarely been reported (11 cases out of 3 million patients).

2. Aggrenox (extended release dipyridamole 200mg plus aspirin 25mg) will be administered twice a day (standard dose). Aggrenox is approved for ischemic stroke prophylaxis. Adverse reactions include headache (39.2%), dyspepsia (18.4%), dizziness (5%), and bleeding. Most side effects tend to disappear with continued use.

**E. Study Subjects**

1. Inclusion Criteria: Patients age 40 or older seen by a neurologist at the participating centers will be eligible for the trial if they have had a transient ischemic attack (symptoms for less than 24 hours) or a minor ischemic stroke (lasting more than 24 hours) in the preceding 3 months. Patients with minor ischemic stroke must have an imaging study of the brain (CT or MRI) to rule out hemorrhagic stroke. Patients with minor stroke must, by 3 weeks after the event, be discharged home, walking without assistance, and relatively independent in their activities of daily living (SALT trial, 1991).
2. Exclusion Criteria: Patients with symptoms thought to be cardioembolic in origin (atrial fibrillation, valve disease, recent MI) will be excluded. Patients 1) who require warfarin (i.e. for a hypercoagulable state or atrial fibrillation) or aspirin; or 2) with severe coronary artery disease (recent MI or unstable angina); or 3) with severe renal or hepatic disease; 4) who have childbearing potential and are not using contraception; 5) who are pregnant or breast feeding; 6) with previous or planned carotid surgery; 7) with a life-threatening condition; and 8) with uncontrolled hypertension will be excluded. Patients with an absolute contraindication to aspirin, dipyridamole, or clopidogrel will be excluded. These contraindications include hypersensitivity or allergy, active bleeding (such as peptic ulcer or intracranial hemorrhage), bleeding disorders, and severe liver disease.
3. Recruitment: Potential subjects will be identified through the emergency room, the medicine and neurology clinics, and private neurologist offices at 32 medical centers and their surrounding communities.

**F. Ethics**

Including a placebo arm in this trial would be unethical given that antiplatelet therapy has been shown to be superior to placebo. Patients will likely benefit from the trial in that their risk of stroke will be reduced; both medications have been shown to be superior to aspirin. They will be provided either Aggrenox or Plavix for three years (estimated cost $2940 and $3281, respectively, according to www.drugstore.com).

**G. References**

CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-1339.

Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2: Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13.

The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30mg vs 283mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med. 1991;325:1261-1266.

The SALT Collaborative Group. Swedish Aspirin Low-dose Trial (SALT) of 75mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991;338:1345-1349.
Sacco RL, Elkind MS. Update on antiplatelet therapy for stroke prevention. Arch Intern Med 2000;160: 1579-1582.