

What is better antiplatelet agent to prevent recurrent stroke?

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Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) Study Group.

Why is this study of clinical importance?

Stroke is the second leading cause of death in the world. However, nonfatal stroke is approximately 3 times as common as fatal stroke; therefore, secondary prevention to prevent stroke is a critical treatment priority. Clinical trials have proved the efficacy of antiplatelet agents for the prevention of recurrent stroke after non-cardioembolic stroke. Antiplatelet options for the prevention of recurrent stroke includes aspirin (50 mg to 325 mg per day), the combination of low dose aspirin and extended-release dipyridamole, and clopidogrel alone. Aspirin has shown to reduce the stroke recurrence risk by about 23% as compared with placebo. Clopidogrel has shown 8% relative risk reduction of stroke recurrence, as compared with aspirin, among stroke patients. Studies of aspirin plus extended-release dipyridamole have suggested relative risk reductions of 20 to 23% as compared with aspirin alone. Combination of two antiplatelet agents with different mechanisms of action maybe more effective in preventing recurrent stroke than either is alone, increased bleeding may result.

There is no guideline for using one of these therapies over the other. Thus, this trial was aimed to compare the relative efficacy and safety of aspirin plus extended-release dipyridamole with that of clopidogrel among patients who had a recent ischaemic stroke.

Who were the participants?

A total of 20,333 patients were enrolled from 695 centers in 35 countries including Asian contributions. The inclusion criteria were a recent ischaemic stroke (within <90 days before randomization), defined by symptoms persisting for more than 24 hours or symptoms of a shorter duration but with evidence of a recent brain infarction on a computed tomographic scan or magnetic resonance imaging; clinical and neurologic stability before randomization; and an age of 55 years or older. Patients were excluded if they had contraindications to one of the antiplatelet agents or were otherwise unsuitable for

randomization. There was protocol amendment to include younger patients (50 to 54 years of age) or those with less recent strokes (within 90 to 120 days before randomization) if they also had at least two additional vascular risk factors.

What was the intervention?

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial was a 2-by-2 factorial, double-blind, active and placebo-controlled study. Eligible and consenting patients were randomly assigned, through a central telephone randomization system, to receive either aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily or clopidogrel (75 mg daily) and telmisartan (80 mg daily) or placebo. Patients were evaluated in the hospital at the time of discharge or at 1 week after discharge and then at 1, 3, and 6 months and every 6 months thereafter. The mean duration of follow-up was 2.5 years (range, 1.5 to 4.4); 1495 patients (7.4%) died during the study and 125 patients (0.6% in each treatment group) were lost to follow-up.

What was the outcome?

The primary outcome was recurrent stroke of any type. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11).

Premature discontinuation of the study drug was significantly more frequent among patients receiving aspirin plus extended-release dipyridamole (2961 [29.1%] patients) than among those receiving clopidogrel (2290 [22.6%], $P < 0.001$).

What were the conclusions?

This trial concluded that similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.

How does this impact us?

The large number and international representation

of patients, who were from 35 countries enhances the generalizability of this trial. In patients with a non-cardioembolic ischaemic stroke the risks of recurrent stroke are similar with aspirin plus extended release dipyridamole and with clopidogrel. It appears that for a patient with stroke requiring secondary prevention Clopidogrel alone, or Aspirin combined with slow release Dipyridamole are all acceptable options with no clear superiority of one to another. In a developing nation like Pakistan these decisions must be based by keeping in view finance (these are life long drugs), compliance issues, individual susceptibilities and reaction to any component of drug combination.

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Recommended Reading

1. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al; PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; 359: 1238-51.