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Evidence Based Medicine

What is the best antiplatelet agent for prevention of recurrent stroke in Pakistani Patients? Do combinations offer significant advantages in the South Asian Context?

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European Stroke Prevention Study ESPS 2, Clopidogrel vs Aspirin for Prevention of Recurrent Ischemic Events-CAPRIE AND Management of ATherothrombosis with Clopidogrel in High-risk patients-MATCH.

Why are these studies of clinical importance?

Before these trials it was already known that antiplatelets like aspirin and ticlopidine reduce the incidence of a composite outcome of ischaemic stroke, MI or vascular death. However, both these drugs have serious potential side effects, like GI bleeding, bone marrow suppression, rash and diarrhoea.

ESPS 1 came out in 1987. In this trial dipyridamole 75 mg tid was given with ASA 330 mg tid for two years in people with previous ischaemic stroke or TIA. The combination showed a striking 38% reduction in secondary stroke over the group treated with placebo. Prior to this two other studies had failed to show superiority of this combination. ESPS 2 was then undertaken in 1996 to answer clearly the efficacy of ASA and Dipyridamole alone in secondary prevention of ischaemic strokes and to see whether the combination had any real advantage.

Clopidogrel was a new agent which had shown benefit in animal studies. It inhibits platelet aggregation by inhibiting binding of ADP to its receptor (GpIIb-IIIa) on platelets and thereby blocking platelet activation.

CAPRIE was a randomized clinical trial with a head to head comparison of aspirin and clopidogrel in patients with history of ischaemic stroke, myocardial infarction or peripheral vascular disease. The outcome was a composite of ischaemic stroke, MI or vascular death.

MATCH on the other hand was a study undertaken once the results of CAPRIE were out and had shown some advantage of clopidogrel over aspirin. The purpose of this study was to evaluate whether aspirin added to clopidogrel would reduce the risk of recurrent ischaemic vascular events in high risk patients with TIA or stroke.

Who were the participants?

In ESPS 2, 6602 patients were recruited from 13 European countries. Patients were eligible if they were more than 18 years old and had experienced a TIA or a completed

ischaemic stroke within the preceding three months. Randomization was done centrally by a computerized system.

In CAPRIE 19,185 patients from 384 clinical centers in sixteen countries were randomized. Most of these were again European countries, and no Asian contribution was there. All participants had to have either a history of acute ischaemic stroke (1 week to 6 months before randomization), or history of MI (<35 days before randomization) or atherosclerotic peripheral arterial disease. Computer generated randomization was done by the Independent Statistical Center and the treatment allocation was double blinded.

MATCH included 7599 patients from 507 centers in 28 countries. Again most were European nations, except some contribution from Singapore, Taiwan and Hong Kong. People with ischaemic stroke or TIA in the previous 3 months plus one or more of the following; previous ischaemic stroke, previous MI, angina pectoris, DM, or symptomatic PAD in the past 3 years were included. Treatment allocation was done centrally by a computer generated list.

What was the intervention?

In ESPS 2, four treatment groups were assigned randomly- ASA 25 mg bid, modified release dipyridamole 200mg bid, ASA 25 mg bid plus dipyridamole 200 mg bid and matched placebo. Each patient was followed up for two years regardless of compliance with study medication or occurrence of a non fatal end point. Follow-up was done at one month after randomization, and then at three month intervals throughout.

In CAPRIE patients received blister packs containing either 75 mg tablets of clopidogrel plus aspirin placebo or 325 mg tablets of aspirin plus clopidogrel placebo. Patients were asked to take one of each tablet daily with their morning meal. Follow-up visits took place monthly for the first 4 months and every 4 months thereafter. At these visits, information was collected on adverse events and use of study drug and concomitant medications, and blood was taken for hematological and biochemical assessments by one of three central laboratories.

In MATCH patients were randomly allocated either aspirin 75 mg once daily or matching placebo tablet; furthermore, all patients received clopidogrel 75 mg once daily.

Study treatment was started on the day of randomization and continued for 18 months. After the randomization visit, follow-up visits were scheduled at 1, 3, 6, 12, and 18 months. These visits were supplemented by monthly follow-up telephone calls to the patient.

What was the outcome?

ESPS2: There was a significant difference for ASA and for Dipyridamole for reducing the risk of recurrent stroke ($p < 0.001$ for both) and stroke or death ($p = 0.003$ and $p = 0.002$). Stroke risk was significantly reduced by 18.1% with ASA alone, by 16.3% with DP alone and by 37% by the combination. With the combination therapy there was a significant 23.1% risk reduction in stroke risk over ASA alone and a significant 24.7% over DP alone.

CAPRIE: For a composite outcome of ischaemic stroke, MI or vascular death, there were 939 events in the clopidogrel arm and 1021 events in the aspirin arm. This translated to a relative risk reduction of 8.7% and reached a statistical significance at $p = 0.043$. For patients with stroke and MI, the relative risk reduction in composite outcome was 7.3% and 3.7% respectively, although both these were not significant. For peripheral arterial disease patients however, the relative risk reduction was 23.8% in favour of clopidogrel ($p = 0.0028$). The frequency of severe rash and diarrhoea was higher with clopidogrel. More frequent with aspirin were severe upper GI discomfort, ICH, and GI haemorrhage.

MATCH: The primary endpoint was the first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular or rehospitalisation for an acute ischaemic event. The relative risk reduction in favour of clopidogrel in the intention-to-treat population was 6.4% and was in the range that was reported in the CAPRIE trial (8.7%). Even though there were fewer events in the aspirin plus clopidogrel arm, compared to clopidogrel alone, the combination resulted in a significantly higher bleeding rate that offset any beneficial effect. However, no significant increase in fatal bleeding was recorded and mortality was the same in both groups.

What were the conclusions?

ESPS 2 concluded that DP modified release formulation, 200 mg bid is effective in the secondary prevention of stroke and TIA when compared to placebo and that the combination of ASA and DP provides a truly additive benefit with an odds reduction of 43.7%. DP was associated with headache and GI disorders, particularly diarrhoea, generally early in the trial. ASA containing regimens had significantly more bleeding complications even at low dose but

the combination was no worse than ASA alone.

CAPRIE concluded that clopidogrel provides an additional 8.7% relative risk reduction over and above the 25% reduction expected to be provided by aspirin. However, it was not powered to detect the risk reduction of particular events like ischaemic stroke or MI. The benefits of clopidogrel were truly much more in patients with peripheral arterial disease.

MATCH concluded that because of a significantly large number of bleeding events, and no significant reduction in the recurrent events, there was no additional clinical value of adding aspirin to clopidogrel in high risk patients with ischemic stroke or TIA.

How does this impact us?

It appears that for a patient with stroke requiring secondary prevention Aspirin alone, Clopidogrel alone, or Aspirin combined with slow release Dipyridamole are all acceptable first options. However, these decisions must be made with careful considerations to finance (these are lifelong drugs), individual susceptibilities and reaction to any component of drug combination.

Dipyridamole combined with Aspirin is somewhat advantageous over either drug alone for secondary prevention of non fatal stroke and TIA. However it does not have any evidence of impact on composite vascular outcomes including vascular death. There is no evidence that dipyridamole alone is more efficacious than aspirin. It must also be assured that the combination does not pose risk to patient - e.g. exacerbation of tachycardia or coronary ischaemia by Dipyridamole. The combination however, does not carry additional risk of haemorrhage as for Clopidogrel and ASA.

Clopidogrel is a relatively expensive medication for a poor nation like ours. The evidence for benefit in patients with one particular disease group like ischaemic stroke or MI is not robust, and therefore it is probably advisable to stick to good old aspirin unless a composite risk has to be addressed. The combination of aspirin and clopidogrel is not advisable as its benefit is not proven and the risk of bleeding is quite significant.

Recommended Reading

1. 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
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