

Secondary stroke prevention set to benefit from PROFESS trial

Extended-release dipyridamole plus aspirin (Asasantin Retard) and clopidogrel share very similar benefit–risk ratio in vascular prevention

The first head-to-head study of two antiplatelet regimens recommended for the secondary prevention of ischaemic stroke, conducted in the PROFESS study, demonstrate that the risks of recurrent stroke or the composite risk of stroke, myocardial infarction or vascular death are very similar with either extended-release dipyridamole (ER-DP) plus aspirin or clopidogrel in patients with non-cardioembolic ischaemic stroke.

The combination of dipyridamole plus aspirin had earlier shown superiority over aspirin monotherapy in two independent trials, ESPS2¹ and ESPRIT,² leading to the comparison of this regimen to clopidogrel in the PROFESS (Prevention Regimen for Effectively avoiding Second Strokes) study.

Reporting on the outcomes of the antiplatelet aspects of the PROFESS study, Prof Ralph Sacco, Department of Neurology, University of Miami, Florida pointed out that 40% of patients were selected within 10 days of their CT scan-confirmed stroke or transient ischaemic attack (TIA). They were randomised to either extended-release dipyridamole, (200 mg) plus aspirin (25 mg) given twice daily, or to clopidogrel (75 mg) once daily.

At the start of the trial, patients were randomised to clopidogrel plus aspirin, but after eight months and the announcement of the MATCH results showing increased bleeding on this combination,³ the protocol was altered and aspirin was removed from the clopidogrel arm.

PROFESS was conducted in 35 countries, including South Africa, and the 20 332 patients were followed up for a median of 2.4 years; a minimum of 1.5 and a maximum of four years. Background risk factors were similar in the two groups and the presence of atherosclerotic disease other than stroke was almost 20% in both groups at baseline.

There were some differences in medication actually taken, compared to intention to treat, with overall, almost 70% of patients in the ER-DP arm being on their

medication, compared to slightly higher levels (76.8%) in the clopidogrel arm.

Results were presented on an intention-to-treat basis, although it was noted that per-protocol evaluation did not significantly alter the results.

The primary outcome of the study was first recurrent stroke, with a pre-specified non-inferiority margin. Across an average observation time of 2.5 years, the rates of first recurrent stroke were similar for the two treatments. The recurrent stroke risk reduction was 9% for the ER-DP-plus-aspirin arm and 8.8% for the clopidogrel arm [hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.92–1.11].

Among those with recurrent strokes, there were 25 fewer patients with recurrent ischaemic strokes with ER-DP plus aspirin, compared to clopidogrel (7.7 vs 7.9%), but 38 more patients with haemorrhagic strokes with ER-DP plus aspirin compared to clopidogrel (0.8 vs 0.4%).

Overall, there were 17 more strokes in the dipyridamole-plus-aspirin arm compared to the clopidogrel arm but this did not reach statistical significance. There was no difference between these treatment groups with regard to the functional outcome and cognitive function of patients experiencing recurrent stroke.

Rates for the main secondary outcome of stroke, myocardial infarction or vascular death were identical (13.1% ER-DP plus aspirin, 13.1% clopidogrel; HR 0.99, 95% CI 0.92–1.07, $p = 0.83$). Although the event rates for both the primary and secondary outcomes were nearly identical with the two antiplatelet regimens, the trial failed to meet the non-inferiority criteria.

In the patients treated with the combination therapy, there were fewer cases of new heart failure and less progression of chronic heart failure than in the clopidogrel group. This difference was statistically significant.

These results were consistent across all subgroups.

Safety was evaluated by assessing the risk of major haemorrhagic events. These

events were classified as (1) those associated with significant disability: intracranial haemorrhage, intraocular bleeding resulting in loss of vision, and symptomatic intracranial haemorrhage requiring two or more transfused units; and (2) life-threatening haemorrhagic events, which were either fatal or required inotropic agents to maintain blood pressure, or required surgery using four or more transfused units.

Major haemorrhagic events and intracranial bleeds were observed more frequently in the ER-DP-plus-aspirin group compared with the clopidogrel group (major haemorrhagic events: 4.1 vs 3.6%; HR 1.15, 95% CI 1.00–1.32, $p = 0.06$). The benefit–risk ratio expressed as the combination of recurrent stroke and major haemorrhage was not significantly different between ER-DP plus aspirin and clopidogrel (11.7% ER-DP plus aspirin, 11.4% clopidogrel; HR 1.03, 95% CI 0.95–1.11, $p = 0.50$).

Also, the distribution of the functional outcome measured by modified Rankin scale three months post-stroke was similar. Drop outs due to headache (6%) were more frequent with ER-DP plus aspirin than with clopidogrel, but much less frequent than in earlier trials (ESPS2, ESPRIT).

‘Given the high prevalence of stroke and recurrent stroke in our societies, physicians need a range of treatment options so they can offer patients a regimen tailored to their individual needs. Landmark trials like PROFESS[®] help clinicians make evidence-based treatment choices and ensure that patients receive optimal therapy for their condition’, concluded one of the three principal investigators of the study, Professor Hans-Christoph Diener, MD, University of Essen, Germany.

1. Diener H-C, *et al.* *J Neurol Sci* 1996; **143**: 1–13.
2. ESPRIT study group. *Lancet* 2006; **367**: 1665–1673.
3. Diener H-C, *et al.* *Cerebrovasc Dis* 2004; **17**: 253–261.

Early initiation of blood pressure lowering with telmisartan after a stroke

PROFESS results of the addition of telmisartan 80 mg compared to placebo in ischaemic stroke

Initiation of blood pressure lowering with telmisartan early after a stroke (at an average of 15 days), with a relatively short duration of therapy of 2.5 years, showed a non-statistically similar rate of stroke or other major vascular events compared to the placebo arm, according to the results of the PROFESS trial, presented at the 17th European Stroke conference in Nice, France.

Following the 2.5-year follow up, in the period beyond six months, the rate of recurrent stroke in the telmisartan arm was non-statistically lower at 5.3% (533) versus 6% (608) in the placebo group.

Similarly, with regard to the rate of major vascular events, the number of events for telmisartan was non-statistically lower at 8.8% compared to the placebo group of 10.1%.

The mean follow-up period was only 2.5 years, which might be the main reason for this non-statistical result, since a posi-

tive trend in preventing recurrent strokes, cardiovascular events and new-onset diabetes was seen in the telmisartan arm at study end.

PROFESS confirmed that telmisartan is safe and well tolerated in stroke patients.

Commenting on this aspect of the trial, Dr Philip Bath, Division of Stroke Medicine, University of Nottingham, UK noted that the study would strengthen the European Stroke Organisation (ESO) guidelines of regular blood pressure checking after a stroke, with consideration now to be given to earlier antihypertensive drug therapy sooner after the acute phase of the stroke.

South African experts attending Eurostroke comment

Prof Allan Bryer, UCT and head of Groote Schuur Hospital Stroke Unit, Cape Town

‘I suspect, from the figures I have seen in the presentations, that we are observing a lower rate of recurrent strokes in both arms of this trial. This is likely to be due to an improvement in the overall management of strokes, better blood pressure lowering and statin use, and more careful attention to risk-factor modification, including the appropriate use of antiplatelet agents.’

Dr Peter Haug, neurologist, private practice, Milnerton, Cape Town

‘It is clear that antiplatelet therapy is an integral part of preventing recurrent strokes and one will have to make decisions about the appropriate choice of antiplatelet agent, according to the individual patient’s profile. Further analyses of the study results may identify subgroups more likely to benefit from either extended-release dipyridamole plus aspirin or clopidogrel.’