PRoFESS – Expected Implications for Oral Antiplatelet Therapy in Secondary Stroke Prevention Therapy

a report by

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Patients who have suffered an ischaemic stroke are at an increased risk of a recurrent cerebrovascular episode. Standard secondary prevention for such patients includes the use of antiplatelet treatment, namely acetylsalicylic acid (ASA). Recent clinical studies have shown that other antiplatelet drugs such as clopidogrel are similarly beneficial in preventing secondary stroke, although a combination of ASA and dipyridamole may be even more effective. Furthermore, blocking the renin–angiotensin system may also have an additive effect in preventing recurrent stroke. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial is a multicentre clinical trial designed to examine whether Aggrenox®/Asasantin® (ASA + extended-release dipyridamole (ER-DP)) reduces the risk of recurrent stroke compared with clopidogrel. The study will also evaluate whether angiotensin receptor blockers such as telmisartan provide any additional protection. The study involves 20,333 patients randomised to one of four treatment groups according to a 2x2 factorial design, with the primary end-point being recurrence of stroke. The PRoFESS study, being the largest secondary stroke prevention trial, aims to determine the most effective treatment for secondary stroke prevention.

Current Prevention of Secondary Stroke

Ischaemic stroke is a major cause of morbidity and mortality in modern life, ranking as the third most common cause of death after cardiovascular disease and cancer,[1] and its prevalence is expected to rise in line with extended life expectancy.[2] Eight to 12% of ischaemic strokes result in death within 30 days,[3] while surviving patients are at an increased risk of subsequent vascular events, the most common being a second stroke.[4,5] The risk of a recurrent stroke or transient ischaemic attack (TIA) is between 5 and 15% per year and is highest immediately after the primary episode.[6,7] This accounts for approximately three-quarters of all secondary vascular events following stroke.[4] Secondary prevention strategies focus on reducing cardiovascular risk factors such as cigarette smoking, diabetes mellitus (DM), obesity, high blood pressure and increased cholesterol levels.[8] In addition, pharmacological antiplatelet therapy is indicated in such patients. ASA is the the most widely used treatment. Clinical trials have shown that treating stroke patients with ASA significantly reduces the risk of a recurrent episode compared with placebo.[9–11] However, the absolute risk reduction is low. The protective effect was found not to be dose-dependent, leading to the use of lower doses with a more favourable side effect profile.

To explore other treatment possibilities, later studies compared the efficacy and safety of alternativee antiplatelet drugs with ASA in secondary stroke prevention. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial examined the efficacy of clopidogrel compared with ASA in preventing recurrent vascular events among patients suffering from stroke, myocardial infarction (MI) or peripheral arterial disease.[12] Although clopidogrel was found to be more effective among the general study population, this was not significant in the stroke subgroup, and clopidogrel was deemed to be only as good as an ASA in preventing stroke.

The next step towards improving antiplatelet therapy was examining combination treatments. In the Clopidogerl in Unstable Angina to Prevent Recurrent Events (CURE) trial, the combination of clopidogrel and ASA was compared with ASA alone in the prevention of vascular ischaemic events. No significant differences were found in stroke prevention between the treatment groups. Furthermore, patients receiving the combination therapy were at a significantly greater risk of major bleeding.[13,14] The later Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial also looked at the benefit of adding clopidogrel to ASA compared with ASA monotherapy in secondary vascular prevention among a high-risk population. Here, too, no significant differences were found in the rate of cardiovascular disease, but an increase in the risk of major bleeding was evident.

However, subgroup analysis indicated a possible benefit, specifically in recurrent stroke prevention, warranting further investigation. The Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent TIA or Ischaemic stroke (MATCH) study compared the combination of clopidogrel and ASA with clopidogrel monotherapy in high-risk patients who had suffered a recent TIA or ischaemic stroke. Once again, it was found that combination therapy failed to produce any significant difference in risk reduction,[15,16] but it did increase the risk of major bleeding compared with monotherapy. These studies revealed that, while both antiplatelet drugs were equally effective in preventing recurrent vascular events, no real benefit was acquired from their combined use. Moreover, the combination increased the risk of serious side effects, namely major bleeding.

Recent clinical studies have explored combining ASA with other antiplatelet drugs in an attempt to achieve further reduction in the rate of recurrent stroke. The European Stroke Prevention Study 2 (ESPS II) and

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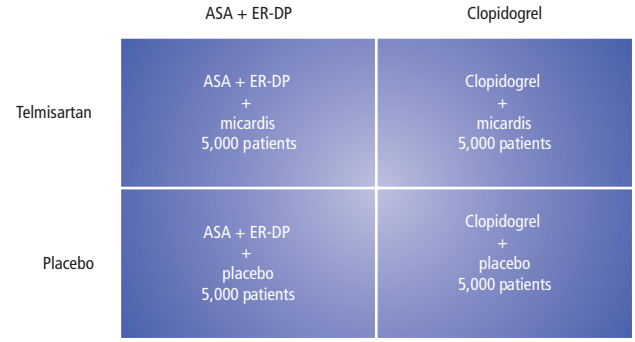
Figure 1: PRoFESS Trial Design



the later European–Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) both explored the efficacy of combining ASA and dipyridamole in secondary stroke prevention. It was found that the combination therapy was more effective in preventing stroke than either treatment alone, and that the combined effect did not increase the risk of severe or fatal bleeding compared with ASA alone.[10,17]

Thus far, clinical trials have examined the role of ASA as well as the comparative efficacy of other drugs and combinations with regard to secondary stroke prevention. While ASA and others have been shown to reduce the risk of a recurrent episode, it still remains unclear which is the preferable regime in the general patient population or any specific subpopulation.

In addition to antiplatelet treatment, stroke patients may also benefit from reductions in other significant risk factors, most notably in blood pressure. The use of drugs blocking the renin–angiotensin system has resulted in a significant reduction in vascular ischaemic events. In the Heart Outcome Prevention Evaluation (HOPE) study, treatment with an angiotensin-converting enzyme (ACE) inhibitor resulted in a significant decline in ischaemic events among patients with previous vascular disease or diabetes.[18] The results indicated that blocking the renin–angiotensin pathway achieved its beneficial effect through mechanisms other than blood-pressure reduction. Recent studies have also suggested that angiotensin II receptor blockers (ARBs) may have a similar effect in reducing the risk of recurring vascular events.[19,20] However, these drugs are currently not used for routine treatment of patients after stroke. Thus, to date, the issues regarding optimal antiplatelet treatment, as well as the role of ARBs, remain unresolved.

Study Goals

The PRoFESS trial was set up to answer two main questions: 'Is combination therapy of ASA and ER-DP more effective than clopidogrel alone at secondary stroke prevention?' and 'What is the added benefit of an ARB (telmisartan) to secondary stroke prevention?'

Drug Information

Aggrenox/Asasantin

Aggrenox/Asasantin is an oral combination antiplatelet agent containing ER-DP 200mg and ASA 25mg. Aggrenox/Asasantin inhibits platelet aggregation through multiple mechanisms of action. ASA functions by irreversible inhibition of platelet cyclo-oxygenase and inhibits generation of thromboxane A_2, a potent platelet aggregator. Dipyridamole acts by impeding adenosine uptake by platelets, erythrocytes and endothelial cells, resulting in increased extracellular adenosine levels. This leads to A_2-receptor activation and inhibition of platelet aggregation in response to various stimuli such as platelet-activating factor, collagen and adenosine diphosphate. It has also been shown to induce vasodilatation through unrelated mechanisms.[21] This combination therapy results in enhanced antiplatelet activity as well as improved vessel wall protection. Aggrenox/Asasantin is recommended by the American College of Chest Physicians (ACCP), the European Stroke Initiative (EUSI) and the National Institute for Clinical Excellence (NICE) as a first-line treatment in secondary stroke prevention.

Telmisartan

Telmisartan (Micardis®) is an orally active non-peptide type I ARB. It has a profound antihypertensive effect by selectively blocking the binding of angiotensin II to the AT1 receptor. Thus, telmisartan impedes the vasoconstrictor effects of angiotensin II, independent of its rate of synthesis. Telmisartan is approved for hypertension treatment by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA).

The Prevention Regimen for Effectively Avoiding Second Stroke Trial Design

The PRoFESS trial is the largest clinical study to date aimed at examining secondary stroke prevention therapy. It is an ongoing, randomised, parallel-group, multinational, double-blind, double-dummy, active and placebo-controlled study. The trial includes 20,333 patients with stroke, enrolled at 695 sites in 35 countries worldwide. Patients are randomised to one of four study arms according to a 2x2 factorial design (see *Figure 1*). The four groups were set up to compare ASA and ER-DP given twice daily with clopidogrel given once daily, and telmisartan given once daily with placebo. Patients are assigned to a study group following two simultaneous randomisations, with randomisation to telmisartan stratified based on current treatment with ACE inhibitors.[22]

The main inclusion criteria with regard to the two main groups of patients are as follows. In the first group are patients aged ≥55 years who have suffered an ischemic stroke within a 90-day period prior to enrolment, and in the second group are patients aged 50–54 years with an ischaemic stroke within a 90–120-day period prior to study entry and at least two of the following risk factors: DM, hypertension, current smoker, obesity (body mass index >30), previous vascular disease (stroke, MI or peripheral arterial disease), end organ damage (retinopathy, left ventricular hypertrophy or microalbuminuria) and hyperlipidaemia. The main exclusion criteria include: haemorrhagic stroke, recent coronary artery disease, recent major surgery, severe hepatic or renal insufficiency and uncontrolled hyper/hypotension.

The primary end-point for the study is time to recurrent stroke of any type. The secondary end-points are a composite of vascular events (stroke, MI or vascular death), a composite of vascular events with new or worsened congestive heart failure and new onset of diabetes. Follow-up evaluation is performed at one week, one month, three months, and six months, then at six-month intervals for the duration of the trial.

Four substudies have also been approved for the PRoFESS trial:

- a cognitive substudy for determining whether the study medication can reduce the rate of cognitive decline;

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- Recommended by ASA, ACCP and EUSI as first-line treatment in secondary stroke prevention
- Possesses beneficial antithrombotic and vessel wall properties that may explain superior protective effects
- A low risk of bleeding, comparable to low-dose ASA

Asasantin®

Aggrenox®

Extended-release dipyridamole + ASA

Asasantin Retard (dipyridamole and aspirin). Capsules containing dipyridamole 200 mg (modified release) and aspirin 25 mg (standard release). **Indication:** Secondary prevention of ischaemic stroke and transient ischaemic attacks. **Dose:** *Adults only:* 1 capsule twice daily, with meals. **Contraindications:** Hypersensitivity to any component or salicylates; active gastric or duodenal ulcers or bleeding disorders. **Precautions:** Severe coronary artery disease, subvalvular aortic stenosis, haemodynamic instability; coagulation disorders; asthma, allergic rhinitis, nasal polyps, chronic or recurring gastric or duodenal complaints, impaired renal or hepatic function or G6PD deficiency; hypersensitivity to NSAIDs; patients should not receive additional intravenous dipyridamole. Do not give to children aged under 16 years unless specifically indicated (e.g. Kawasaki disease). **Interactions:** Adenosine, hypotensive agents, cholinesterase inhibitors, anticoagulants, NSAIDs particularly ibuprofen, corticosteroids, hypoglycaemic agents, methotrexate, spironolactone, uricosuric agents. **Pregnancy and lactation:** Avoid in 3rd trimester, caution at other times. **Side effects:** Vomiting, diarrhoea, dizziness, nausea, dyspepsia, headache, myalgia; hypotension, hot flushes, tachycardia, and rarely, worsening of the symptoms of coronary heart disease; prolonged bleeding time and, rarely, increased bleeding during or after surgery; epigastric distress, gastro or duodenal ulcers and erosive gastritis which may lead to serious GI bleeding; occult GI bleeding may result in iron deficiency anaemia; occasional hypersensitivity such as rash, angioedema, bronchoconstriction; very rarely, thrombocytopenia; dizziness and tinnitus suggest aspirin overdosage. Prescribers should consult the Summary of Product Characteristics in relation to other side-effects. **Pack size and NHS price:** 60 capsules £ 8.20. PL 00015/0224 POM. **Product licence holder:** Boehringer Ingelheim Ltd, Ellesfield Avenue, Bracknell RG12 8YS. For full prescribing information please see Summary of Product Characteristics. Date of Preparation: February 2007.

Adverse events should be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). Information about adverse event reporting can be found at www.yellowcard.gov.uk

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- a haemodynamic substudy that will investigate the haemodynamic effects of the study drugs, including any effects on central compliance, central blood pressure, myocardial perfusion and other 24-hour ambulatory blood pressure measures;
- a magnetic resonance imaging (MRI) substudy that will evaluate whether patients with silent infarcts have a higher risk of recurrent stroke and whether patients with white-matter lesions at study entry are developing vascular dementia more quickly; and
- a biomarker and genetic analysis substudy that will perform these analyses on blood samples collected at baseline and after two years.

Baseline Data

During the recruitment period between September 2003 and June 2006, a total of 20,333 stroke patients were enrolled into the PRoFESS trial.[22] The average patient age at enrolment was 66.1±8.6 years, with women representing 36% of patients. The study included patients from diverse ethnic and racial backgrounds from across the globe. Patients were categorised according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria as follows: 52.1% had small-artery occlusion; 28.5% had large artery atherosclerosis; and 15.5% were of undetermined etiology. 73.9% of patients suffered from hypertension, 46.1% from hyperlipidaemia, 28.1% from DM and 29.8% from various cardiac diseases (including previous MI, congestive heart failure, atrial fibrillation and valvular disease); 18.3% of patients had a previous stroke and 8.6% a previous TIA. Upon enrolment, blood pressure was well-controlled in participating patients, with an average value of 144/84mmHg. Mean body mass index was 26.8, and the mini mental state examination score was 28. Patients were categorised as mild impairment according to the modified Rankin Scale, with 67.3% scoring 0–2. Median time to randomisation was 15 days, with over 8,000 patients (39.4%) randomised within 10 days.

> The PRoFESS trial is the largest clinical study to date dedicated to examining secondary stroke prevention regimes.

The Prevention Regimen for Effectively Avoiding Second Stroke Trial and Future Stroke Prevention

The PRoFESS trial is the largest clinical study to date dedicated to examining secondary stroke prevention regimes. Previous studies have already shown that alternative drugs are as effective as or even superior to ASA in secondary stroke prevention. Clopidogrel was found to be an effective alternative to ASA, and the combination of ASA and ER-DP showed an increased benefit compared with ASA monotherapy in secondary stroke prevention. However, it remains unclear which of these two alternative regimes is the most effective treatment. The working hypothesis of the antiplatelet arm of the trial is that the combination of ASA and ER-DP will be more effective than clopidogrel alone in secondary stroke prevention. PRoFESS is intended to be able to answer questions regarding these issues among a general patient population. The size of the cohort, together with its diversity of populations, will also allow for specific identification of different subgroups that might benefit from one of the antiplatelet treatment regimes or the addition of ARBs.

The cohort of patients enrolled in the trial represents a high-risk population; one-third are diabetic, two-thirds are hypertensive and approximately one-third have a concomitant cardiovascular disease. PRoFESS is targeted to address therapy options for this subpopulation of patients with an increased risk of a secondary event. Furthermore, with over two-thirds of the patients recruited during the early phase after a stroke and with over 8,000 patients randomised within 10 days, PRoFESS will also be able to provide, for the first time, important information regarding the efficacy of starting antiplatelet treatment early after stroke. It should be noted that during the trial not only will the benefit of each treatment arm be recorded, but also possible adverse effects, in particular those related to bleeding complications. A difference in the bleeding risk may very well be a decisive factor in the recommendation of a first-line choice of treatment.

ARBs have been proposed to exhibit neuroprotective properties in addition to their antihypertensive effect.[23] They may also play a role in the prevention of DM and renal function deterioration.[24] The addition of study arms to examine ARBs in secondary prevention of stroke and other vascular events will also allow for a detailed inspection of its part in decreasing the other secondary end-points, as well as its influence on vascular dementia and mental deterioration. The substudies of the trial will explore any effect on mental deterioration in stroke patients, as well as the possible impact on silent infarcts and white-matter lesions. Biomarker analysis will identify any potential role these may have in predicting secondary stroke occurrence.

The results of the PRoFESS trial will contribute to determining the choice of first-line prevention regimes among the general patient population, as well as in specific subpopulations. This will help physicians to better identify and manage the different types of patients at risk of recurrent stroke. Trial results are expected to be presented at the European Stroke Conference (ESC) in May 2008. ■

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