

## Expected Implications for Oral Antiplatelet Therapy in Secondary Stroke Prevention Therapy

a report by

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Patients who have suffered a non-cardioembolic ischemic 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, aspirin). Recent clinical studies have shown that other antiplatelet drugs, such as clopidogrel, are similarly beneficial in preventing secondary stroke, although a combination of ASA with dipyridamole may be even more effective than such monotherapy treatment. Furthermore, blocking the renin-angiotensin system may have an added effect in preventing recurrent stroke. The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial is a multicenter clinical trial designed to examine whether ASA + extended-release dipyridamole (ER-DP, Aggrenox®) reduces the risk of recurrent stroke compared with clopidogrel. The study will also evaluate whether angiotensin receptor blockers provide any additional protection. The study involves 20,333 patients randomized 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

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

To explore other treatment possibilities, later studies compared the efficacy and safety of alternate 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 a history of peripheral arterial disease.<sup>12</sup> 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 as good as an ASA only in preventing stroke.

The next step towards improving antiplatelet therapy was examining combination treatments. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial the combination of clopidogrel + ASA was compared with ASA alone in the prevention of vascular ischemic events. No significant differences were found in stroke prevention between the treatment groups, although the primary outcomes of this trial were not targeted specifically at stroke. Furthermore, patients receiving the combination therapy were at a significantly greater risk of major bleeding.<sup>13,14</sup> 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 ischemic stroke (MATCH) study compared the combination of clopidogrel + ASA with clopidogrel monotherapy in high-risk patients with recent TIA or ischemic stroke. Once again, it was found that combination therapy failed to produce any significant difference in risk reduction,<sup>15,16</sup> but 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 grave side effects, namely the incidence of major bleeding.



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**Figure 1: The Prevention Regimen for Effectively Avoiding Second Stroke Trial Design**

	Aggrenox®/Asasantin®	Clopidogrel
Micardis®	<p>Aggrenox/Asasantin + Micardis 5,000 patients</p>	<p>Clopidogrel + Micardis 5,000 patients</p>
Placebo	<p>Aggrenox/Asasantin + placebo 5,000 patients</p>	<p>Clopidogrel + placebo 5,000 patients</p>

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 the later European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) both explored the efficacy of combining ASA and dipyridamole in secondary stroke prevention. It was found that 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.<sup>10,17</sup>

Thus far, clinical trials have examined the role of ASA as well as comparative efficacy of other drugs and combinations in 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, as well as in specific subpopulations.

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 ischemic events. In the Heart Outcome Prevention Evaluation (HOPE) study, treatment with an angiotensin-converting enzyme (ACE) inhibitor resulted in a significant decline in ischemic events among patients with previous vascular disease or diabetes.<sup>18</sup> The results indicated that blocking the renin–angiotensin pathway may have 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.<sup>19,20</sup> However, these drugs are currently not routinely used for treatment of the majority 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 + 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

#### Acetylsalicylic Acid + Extended-release Dipyridamole (Aggrenox)

Aggrenox is an oral combination antiplatelet agent containing 200mg ER-DP and 25mg ASA. Aggrenox inhibits platelet aggregation through multiple mechanisms of action. ASA functions by irreversible inhibition of platelet cyclo-oxygenase and inhibits generation of thromboxane A<sub>2</sub>, 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<sub>2</sub>-receptor activation and inhibition of platelet aggregation in response to various stimuli such as platelet-activating factor, collagen, and adenosine diphosphate. The magnitude of adenosine-induced vasodilation has been shown to correlate with plasma dipyridamole concentrations.<sup>21</sup> The combination of aspirin and dipyridamole results in enhanced antiplatelet activity as well as improved vessel wall protection. Aggrenox is recommended by the American Academy of Chest Physicians (AACP), the American Heart Association (AHA), the European Stroke Initiative (EUSI), and other important guidelines as a first-line treatment in secondary stroke prevention. The National Stroke Association also cites Aggrenox as a suitable first-choice therapy for TIA patients.

#### Telmisartan (Micardis®)

Telmisartan is an oral active non-peptide type I ARB. It has a profound antihypertensive effect by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor. Thus, telmisartan impedes the vasoconstrictor effects of angiotensin II, independent of its rate of synthesis. It has been proposed that ARBs may exhibit neuroprotective properties in addition to their antihypertensive effect.<sup>23</sup> They may also play a role in the prevention of DM and renal function deterioration.<sup>24</sup> Telmisartan is approved for hypertension treatment by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

### PROfESS Trial Design

The PROfESS trial is the largest clinical study to date aimed at examining secondary stroke prevention therapy. It is an ongoing, randomized, 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 across the globe. Patients are randomized to one of four study arms according to a 2x2 factorial design (see Figure 1). The four groups were set up to compare ASA + 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 randomizations, with randomization to telmisartan stratified based on current treatment with ACE inhibitors.<sup>22</sup> The main inclusion criteria regard two main groups of patients: in the first are patients aged ≥55 years who have suffered an ischemic stroke within 90 days prior to enrollment; in the second are patients aged ≥55 years who have suffered an ischemic stroke between 90 and 120 days prior to enrollment plus patients aged 50–54 years with an ischemic stroke within 120 days of study entry. These patients must have 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 hyperlipidemia. The main exclusion criteria include: hemorrhagic 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 sub-studies have also been approved for the PROfESS trial:

- a cognitive sub-study for determining whether the study medication can reduce the rate of cognitive decline;
- a hemodynamic sub-study that will investigate the hemodynamic 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) sub-study 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 sub-study that will perform these analyses on blood samples collected at baseline and after two years.

### Baseline Data

During the recruitment period from September 2003 to June 2006, a total of 20,333 stroke patients were enrolled into the PROfESS trial.<sup>22</sup> The average patient age at enrollment was 66.1±8.6 years, with 36% of the patients being women. The study included patients from diverse ethnic and racial backgrounds from across the globe. Patients were categorized 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% remained of undetermined etiology; 73.9% of patients suffered from hypertension, 46.1% from hyperlipidemia, 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 enrollment 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 categorized with mild impairment according to the modified Rankin Scale, with 67.3% scoring 0–2. Median time to randomization was 15 days, with over 8,000 patients (39.4%) randomized within 10 days.

### PROfESS and Future Stroke Prevention

The PROfESS trial is the largest clinical study to date dedicated to examining secondary stroke prevention regimens. 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 + ER-DP showed an increased benefit compared with ASA monotherapy in secondary stroke prevention. However, it remains unclear which of these two alternative regimens is the most effective treatment. The working hypothesis of the antiplatelet arm of the trial is that the combination of ASA + 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 regimens or the addition of ARBs. The cohort of patients enrolled in the trial represents a high-risk population; one-third have diabetes, two-thirds have hypertension, and approximately one-third have a concomitant cardiovascular disease.

PROfESS is targeted to address therapy options for patients with an increased risk of a secondary event. Furthermore, with more than two-thirds of the patients recruited during the early phase after a stroke and with more than 8,000 patients randomized within 10 days, PROfESS will also be able to provide, for the first time, important information regarding the efficacy of starting antiplatelet and ARB treatment early after stroke. It should be noted that during the trial not only the benefit of each treatment arm will 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.

The sub-studies 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 analyses may identify any potential role these might 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 manage stroke patients and prevent recurrent events. Trial results are expected to be presented at the European Stroke Conference in May 2008. ■

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