Targeting the Renin–Angiotensin System in Secondary Stroke Prevention

a report by
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Stroke is the leading cause of disability and the third leading cause of death in the US.[1] Although prognosis following a stroke can vary greatly, it has been estimated that 21% of men and 24% of women aged ≥40 years die within a year of their initial stroke. The mortality rate increases among people aged 65 years and older. Furthermore, 13% of men and 22% of women aged 40–69 years who have a first stroke experience a recurrent stroke within five years.[1] Thus, the consequences of stroke are associated with a considerable social and economic burden.[1,2] Furthermore, this burden is predicted to increase as the relative incidence of stroke increases in line with the aging population.[3] Accordingly, the prevention of initial stroke and recurrent stroke is still a major healthcare priority.

Addressing Modifiable Risk Factors in Stroke Prevention

Greater scrutiny over stroke care has led to major improvements in the quality of care of acute stroke patients and better recurrent stroke prevention. Medical treatment of modifiable risk factors—such as high blood pressure (BP), diabetes, and hyperlipidemia—has been shown to reduce the frequency of stroke, and remains an important mainstay of preventive treatment for initial stroke.[1,4] In patients who have already had a first stroke, preventive measures include the use of antithrombotic agents, notably antiplatelet or anticoagulant therapy. The continued control of modifiable primary risk factors is also particularly important in these patients.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that high-dose lipid-lowering therapy in addition to antiplatelet therapy could reduce fatal or non-fatal stroke in patients with recent stroke or transient ischemic attack (TIA) and without known coronary heart disease, with an approximately 16% relative risk reduction over a five-year period.[5] Importantly, the benefit associated with lipid-lowering therapy was even greater for reduction of coronary events (35–42%).

In patients who have suffered a stroke there is a steep and direct relationship between usual systolic BP (SBP) and diastolic BP (DBP) and the subsequent risk of stroke. Indeed, stroke has been labeled the most important 'hypertension-related' complication.[6] It has been estimated that a reduction of approximately 12mmHg in usual SBP and 5mmHg in usual DBP would be expected to reduce the risk of secondary stroke by about 30%.[7] Primary prevention trials have shown that small differences in BP can lead to significant differences in vascular events.[8,9] Although the specific target BP to achieve maximal benefits among survivors of stroke and TIA is not precisely known, the JNC7 guidelines suggest that, if at all possible, BP should be lower than 140/90mmHg for all persons with uncomplicated hypertension and lower than 130/80mmHg for those who have diabetes or proteinuria. However, these recommendations are not limited to secondary stroke prevention.[10]

Several randomized controlled clinical trials have attempted to determine the optimal antihypertensive regimen for the prevention of recurrent stroke.[11–13] These trials and additional meta-analyses demonstrated that antihypertensive agents that target the renin–angiotensin system (RAS) reduce the frequency of recurrent stroke, and that this effect may be independent of blood pressure lowering. Direct comparisons between the beneficial effects of RAS inhibition in addition to antithrombotic therapy are not currently available. An ongoing large secondary stroke prevention trial (Prevention Regimen for Effectively Avoiding Second Strokes, PRoFESS) is investigating the possible benefit of this therapeutic regimen.

The Rationale for Renin–Angiotensin System Inhibitors in Stroke Prevention

Hypertension induces target-organ damage, leading to an increased risk of stroke, cardiovascular disease and renal failure. Angiotensin II (Ang II) is the major RAS effector and activates AT_1 receptors on blood vessels, leading to generalized vasoconstriction and increased BP.[14] Ang II also increases the release of noradrenaline from sympathetic nerve terminals, which in turn reinforces vasoconstriction.[14] In chronic hypertension, there is increasing evidence that locally produced Ang II is involved in the development of organ damage via oxidative, proliferative, inflammatory, and fibrotic pathways.[15,16] Thus, there is a strong rationale, based on both pharmacological research and clinical trials, that treatments that target the RAS may provide additional benefits beyond BP control in preventing initial or recurrent stroke.

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Evidence from Primary Prevention Trials

The undeniable beneficial effects of BP lowering have made it ethically unacceptable to perform placebo-controlled trials. The Study on Cognition and Prognosis in the Elderly (SCOPE) study aimed to provide outcome data on cardiovascular end-points and cognitive function in 4,500 elderly hypertensive patients (aged >70 years) and was originally designed to compare the angiotensin receptor blocker (ARB) candesartan versus placebo. The protocol was later changed to compare candesartan, frequently administered on top of a diuretic, against placebo plus other concomitant antihypertensives. The candesartan group showed a modest reduction in BP versus placebo (difference 3.2mmHg versus 1.6mmHg). Although the primary end-point of combined cardiovascular mortality, non-fatal myocardial infarction (MI), and non-fatal stroke was not significantly reduced by active treatment plus diuretic (relative risk reduction 11%; p=0.19), there was a significant 27.8% reduction in non-fatal stroke and a 23.6% reduction of all stroke with candesartan-based therapy.[17]

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study compared the benefits of the ARB losartan and the beta-blocker atenolol in more than 9,000 hypertensive patients with electrocardiographic left ventricular hypertrophy (LVH). While mean BP was reduced to the same extent in both treatment groups, analysis of the five-year follow-up data revealed that losartan-treated patients showed a significant 25% difference in the incidence of initial stroke.[9,18]

In comparison, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial the ARB valsartan was compared with the calcium antagonist amlodipine in more than 15,000 high-risk hypertensive patients. Over the five-year follow-up period the incidence of cardiac events and death (the primary outcome) was not significantly different between the two treatment groups.[8]

Evidence from Secondary Prevention Trials

Data from primary prevention trials such as SCOPE and LIFE suggest that inhibition of the RAS provides protective properties beyond BP control; this hypothesis has been tested in the recurrent stroke setting.

The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial was designed to assess the safety of a modest BP reduction with candesartan in the early treatment of stroke. In the study, patients were randomized to candesartan or placebo in the six- to 36-hour period following admission for acute ischemic stroke. BP entry criteria were the mean of at least two measurements of ≥200mmHg SBP and/or ≥110mmHg DBP six to 24 hours after admission, or ≥180mmHg SBP and/or ≥105mmHg DBP 24–26 hours after admission. Other antihypertensives were allowed in both treatment groups after the first seven days of candesartan or placebo therapy to achieve a target BP below 140/90mmHg. The review board ended the ACCESS trial early after 342 patients had been randomized due to the significant difference (47.5% reduction) in cumulative 12-month mortality and the number of vascular events between the candesartan and placebo treatment groups in the absence of BP lowering. This favorable effect was not seen in the placebo group that started candesartan treatment seven days after the acute stroke, which suggests that the difference was due to treatment with candesartan during the first week following an acute stroke.[11]

> Data from primary prevention trials suggest that inhibition of the renin–angiotensin system provides protective properties beyond blood pressure control.

> The PRoFESS trial will be a landmark study because it will be the largest recurrent stroke prevention study to date.

The Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) was the first published large-scale prospective BP study in secondary prevention after stroke. This landmark study provided clear evidence that antihypertensive therapy with the angiotensin-converting enzyme (ACE) inhibitor perindopril in combination with the diuretic indapamide prevented recurrent strokes. A BP reduction of 9/4mmHg or as much as 12/5mmHg decreased the risk of secondary stroke by 28% compared with placebo.[13] Prior to PROGRESS, many clinicians were cautious of lowering BP in the long term in patients who had ischemic stroke because of concerns that a reduction in profusion pressure to the brain might be deleterious. PROGRESS also reported benefits in both hypertensive and normotensive patients.

In the Morbidity and Mortality After Stroke—Eprosartan Compared with Nitrendipine in Secondary Prevention (MOSES) trial, 1,405 hypertensive patients with a previous cerebrovascular event (a TIA, prolonged reversible neurological deficit, or intracerebral hemorrhage in the 24 months before enrollment) were randomized to either the ARB eprosartan or the calcium antagonist nitrendipine. The primary end-point of the trial was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events. During a mean follow-up of 2.5 years, a similar BP reduction was seen in both treatment groups. First cardiovascular events and the total number of cerebrovascular events were significantly lower in eprosartan-treated patients compared with the nitrendipine group, although there was no significant difference in the secondary end-point of first cerebrovascular events.[12]

A Complementary Role for Renin–Angiotensin System Inhibition and Oral Antiplatelet Therapy?

The PRoFESS trial will be a landmark study because it will be the largest recurrent stroke prevention study to date, including over 20,000 people worldwide. The trial is a randomized, parallel-group, multinational, double-blind, double-dummy, active and placebo-controlled study. Patients in

PRoFESS have been randomized to one of four study arms according to a 2x2 factorial design:

- aspirin (ASA) plus extended-release dipyridamole (ER-DP) plus the ARB telmisartan;
- ASA plus ER-DP plus placebo;
- clopidogrel plus telmisartan; or
- clopidogrel plus placebo.

Randomization to telmisartan is stratified based on current treatment with ACE inhibitors. 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 days and 120 days prior to enrollment and also 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 primary end-point for PRoFESS is time to recurrent stroke of any type.

> PRoFESS will hopefully resolve the issue of angiotensin receptor blocker therapy and its ability to reduce recurrent strokes.

The comparison of ASA plus ER-DP versus clopidogrel, in itself, will be a major result because PRoFESS will hopefully provide answers to the question 'Which is the most effective antiplatelet treatment for secondary stroke prevention?' Additionally, the study will hopefully resolve the issue of ARB therapy and its ability to reduce recurrent strokes. The factorial design will allow us to look at the combination of an antiplatelet therapy and an ARB versus antiplatelet therapy alone, which will provide evidence about the potential value of antiplatelet therapy and RAS inhibition as a possible synergistic therapeutic regimen. The study will provide useful data on the benefits of ARB therapy on top of usual antiplatelet therapy in secondary stroke prevention, and will hopefully add to the evidence regarding the hypothesis that ARBs provide protective benefits beyond BP control.

It should be noted that the PRoFESS study is not a BP lowering trial *per se*; thus, the study will not answer questions regarding BP lowering goals in secondary stroke prevention. This is because all patients in the trial should have their BP controlled with other antihypertensives in the placebo arm, while in the telmisartan arm additional antihypertensives may be added to achieve BP goals.

Conclusion

Treating high risk factors such as elevated BP has clear benefits in terms of reducing the incidence of first strokes and TIAs, and there is mounting evidence that addressing BP control helps to reduce the frequency of recurrent strokes. This is particularly important since patients who have suffered a stroke/TIA are at an increased risk of a recurrent episode. Moreover, evidence from clinical trials increasingly supports the view that targeting the RAS may provide protection from recurrent strokes and that this protective effect is independent of BP control. The results of PRoFESS, the largest secondary stroke prevention trial to date, are expected in the first half of 2008 and are highly anticipated. Not only will the study provide valuable data on the comparative benefits of ASA plus ER-DP versus clopidogrel in secondary prevention, but will also provide information on the potential benefits of including ARB therapy. These data will help to further develop and build on systems of care to ensure recurrent stroke prevention at a population level. ■

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