Angiotensin-converting enzyme (ACE) inhibitors undoubtedly represent one of the major advances in cardiovascular therapeutics over the past 20 years. Having been originally derived from the venom of the Brazilian arboreal viper Bothrops jararaca, captopril and subsequent ACE inhibitors are currently well-established agents for the treatment of patients with hypertension, heart failure, and left ventricular dysfunction. They have also been shown to reduce the risk of major vascular events and progression of renal disease in patients with diabetes and proteinuria, while the Heart Outcomes Protection Evaluation (HOPE) study demonstrated benefits of ramipril in patients with coronary artery disease and preserved left ventricular function. Most recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that an ACE inhibitor (perindopril)–based therapy reduced the risks of both ischemic and hemorrhagic stroke in patients with established cerebrovascular disease. Moreover, the benefits of treatment were consistent across different patient subgroups, such as those with and without a history of hypertension (or high blood pressure [BP] at entry), ischemic subtypes and intracerebral hemorrhage, and ethnicity (Asian versus non-Asian), and occurred on a background of other therapies. The evidence is, therefore, strong for ACE inhibitors being pivotal to the primary and secondary prevention of cardiovascular disease across a broad range of “high-risk” individuals. The therapy is particularly relevant to patients with stroke, given that the absolute risks of recurrent stroke and other vascular events are very high, and the treatment is now proven to be safe, well tolerated, applicable across all major stroke subtypes, and it is relatively inexpensive.

Reduction in the synthesis of the potent vasoconstricting and salt-retaining peptide angiotensin II, while simultaneously decreasing degradation of bradykinin within the renin-angiotensin system, is considered the principal mechanism of action of ACE inhibitors. Because the BP reduction as a consequence of vasodilation and salt depletion is similar to that achieved with other antihypertensive agents, the benefits of ACE inhibitors on cardiovascular morbidity and mortality could be readily explained by a BP-lowering action. Certainly, no definitive evidence that ACE inhibitors are superior to other antihypertensive agents was found in a recent large meta-analysis, although the authors acknowledged that the number of endpoints included was inadequate to show modest but important differences between agents. In addition, PROGRESS confirms pooled prospective cohort and clinical trials data of an approximate one third reduction in the incidence of stroke being conferred by decreases of 10 to 12 mm Hg in systolic and 5 to 6 mm Hg in diastolic BP, with additional benefits of combination therapy (perindopril and indapamide) being consistent with a greater BP reduction.

There is evidence, though, of additional benefits of ACE inhibitors mediated by unique vascular protective effects leading to regression or prevention of atherosclerosis. Local tissue synthesis of ACE is induced by hypertension, ischemia, endothelial dysfunction, and pressure overload, which may cause permanent structural changes, such as myocardial and vascular remodeling. Furthermore, animal and human studies demonstrate that ACE inhibitors reduce cardiac hypertrophy and favorably influence ventricular remodeling after myocardial infarction. Additionally, ACE inhibitors have been shown to restore or improve endothelial function, antagonize angiotensin II–mediated vascular smooth muscle cell growth and proliferation, decrease macrophage migration and function, have antioxidant properties, and decrease thrombotic activity.

Although demonstration of an anti-atherosclerotic effect of ACE inhibitors in humans is controversial, with studies both for and against this hypothesis, the substantially larger-than-expected benefits resulting from modest BP reductions (for example, 3 mm Hg systolic and 1 mm Hg diastolic BP in HOPE) in cardiac trials support beneficial mechanisms over and above BP lowering. It is possible that the cardioprotective effects from angiotensin II inhibition may be more important in patients with coronary artery disease and left ventricular dysfunction, as suggested in the Losartan Intervention For Endpoint reduction (LIFE) trial. LIFE showed that the angiotensin II receptor antagonist, losartan, compared with atenolol, in 9193 individuals aged 55 to 80 years with severe hypertension and left ventricular hypertrophy, reduced the primary composite vascular endpoint by a significant 13%, despite both agents providing substantial and comparable BP reductions. In addition, losartan had a more pronounced effect on the prevention of stroke, with a 25% risk reduction.

Clearly, the benefits of ACE inhibitors have extended from their original use for the treatment of hypertension. Of course, the relative benefits of any particular BP-lowering agent over another, and the merits of different therapeutic combinations, will only be resolved by more randomized data. In the meantime, though, the evidence is...
The questions that need to be addressed in this debate are 3-fold. First, do antihypertensive agents, including angiotensin-converting enzyme (ACE) inhibitors, prevent recurrent stroke and other vascular events? Second, is this effect dependent on their blood pressure (BP)–lowering properties? And last, are potentially beneficial non-BP effects limited to ACE inhibitors? The answers are straightforward: antihypertensive drugs do prevent further vascular events; the effect is dependent on the degree to which BP is lowered; and most antihypertensive drug classes, not just ACE inhibitors, exhibit multimodal vascular activity beyond their effects on BP, although whether these are important remains to be established. The rest of the article fleshes out these assertions.

Seven randomized controlled trials have assessed whether antihypertensive drugs prevent recurrence in patients with previous stroke or transient ischemic attack (TIA).1 Two trials (2193 patients) used a β-receptor antagonist (β-RA, atenolol) reported a small fall in BP (5/3 mm Hg), and were neutral, ie, there was no protective effect.3,4 Three trials (6216 patients) studied a diuretic4–6; the largest of these, PATS (5665 patients), reported that indapamide reduced BP by 6/3 mm Hg and stroke recurrence by 29%.6 Finally, 2 trials used an ACE inhibitor. The HOPE study recruited a total of 9541 subjects with vascular disease, of whom 1013 had a prior stroke or TIA.7 Ramipril reduced subsequent stroke by 32% across the whole trial and had a small reported effect (3/1 mm Hg) on BP; however, this reduction is probably an underestimate for 2 reasons: (1) ramipril was mostly taken in the evening while BP was measured the next day, ie, some 12 to 18 hours or 2 to 3 half-lives later; and (2) a substudy of HOPE reported a 10/4 mm Hg fall in 24-hour ambulatory BP.8 The latest trial, PROGRESS (6105 patients), reported that perindopril-based therapy reduced stroke recurrence.9 These 7 trials varied not just in the intervention but in other significant design aspects; notably, both HOPE and PROGRESS studies corrected for the regression dilution bias.10

The opinions expressed in this editorial are not necessarily those of the editors or of the American Stroke Association.

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**Blood Pressure–Lowering for Secondary Prevention of Stroke: ACE Inhibition Is Not the Key**

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The potential benefits to be derived now in vascular disease, and the direct evidence for using ACE inhibitor–based therapy to maximize BP reduction in patients with vascular disease, and the direct evidence is in favor of the combination of perindopril and indapamide in patients with stroke. The potential benefits to be derived now in terms of the secondary prevention of stroke, globally, represents a Holy Grail that has now been realized with the completion of PROGRESS, thus completing an amazing journey for ACE inhibitors from poison to panacea.

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**Key Words**: angiotensin-converting enzyme inhibitors ■ blood pressure ■ stroke prevention
Trials involving patients with any type of vascular disease \(^1\); it also occurred in PROGRESS, in which dual antihypertensive therapy (perindopril and indapamide) was superior to monotherapy (perindopril) in reducing both BP (12.3/5.0 mm Hg versus 4.9/2.8 mm Hg) and stroke recurrence (relative risk reduction 43\% versus 5\%). \(^9\)

This is not to say that differences do not exist between drug classes in the prevention of various vascular events following stroke or TIA—diuretics reduced stroke but not myocardial infarction, ACE inhibitors reduced myocardial infarction but not stroke, and \(\beta\)-RA did not appear to moderate any outcome. \(^1\)

Although some of these findings might reflect the limited data size (\(<16\,000\) subjects across all drug classes), similar differential effects have been found in the primary prevention of vascular disease whereby CCB prevent stroke more than myocardial infarction and ACE inhibitors do the opposite.

A current vogue in vascular prevention is to ascribe beneficial drug effects to their multiple modes of action, eg, statins not only lower lipids but have modifying effects on the vessel wall and circulating blood cells. Several antihypertensive classes of drugs (including ACE inhibitors, ARA, \(\beta\)-RA, and CCB) are also multimodal in their action, having anti-inflammatory, antiplatelet, antiproliferative, and neuroprotective activity. Whether these effects are vital over and above BP lowering remains unanswered, but it is nevertheless unreasonable to suggest that the non-BP effects of ACE inhibitors are special or limited to that class because they are present in other antihypertensive drugs.

The key to the secondary prevention of stroke through lowering blood pressure is by using agents that have been shown to be effective in randomized controlled trials, ie, the practice of evidence-based medicine. The current data unequivocally support the use of diuretics (in particular, indapamide), ACE inhibitors (perindopril, ramipril), and especially their combination. \(\beta\)-RA appear to be ineffective, at least when used alone, and other drug classes have no data for this indication and may, therefore, also be ineffective until shown otherwise. Nevertheless, many patients with a raised BP need multiple drug treatment, in addition to nonpharmacological measures, and other agents should be added to a diuretic and ACE inhibitor to further lower BP after stroke or TIA. Finally, treatment should be started irrespective of baseline levels of BP once the patient’s medical state has stabilized poststroke, typically after 1 to 2 weeks.

References


Key Words: angiotensin-converting enzyme inhibitors ■ blood pressure ■ randomized controlled trials ■ stroke prevention

Blood Pressure Reduction and ACE Inhibition in Secondary Stroke Prevention: Mechanism Uncertain

Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP

Of all the controversies presented to date, the issue of a specific benefit of blockade of the renin-angiotensin system at a number of levels, over and above blood pressure (BP) lowering in stroke prevention, is the most difficult to tease out. This is despite the large body of accumulated evidence. It is not a minor issue given that BP remains the most important and modifiable risk factor for stroke. As outlined by our protagonists, the history of BP reduction in stroke prevention has been an evolving saga over a number of decades.

By 1990, the evidence supporting BP lowering for primary stroke prevention was conclusive, using the older antihypertensive agents, mainly diuretics and beta blockers. \(^1\) With the introduction of the newer agents, particularly those affecting the angiotensin system, possible class effects became a real issue. For example, the HOPE trial suggested ACE-specific benefits using ramipril in a largely primary prevention study. There have been arguments about how much of this benefit...
reflected BP reduction and how much was due to the putative effects of the ACE inhibitor on various cardiac, endothelial, and intravascular mechanisms. Similarly, another ACE-based BP-lowering strategy was proven effective in the PROGRESS trial, the first pivotal study in secondary stroke prevention, again independent of the initial blood pressure. However, the benefits also appeared to be consistent with the degree of blood pressure lowering expected from epidemiological data. Anderson has nicely highlighted the evidence and biological appeal of angiotensin blockade, with wider vascular effects than solely BP reduction. There may even be additional advantages in more specific blockade of the angiotensin receptor, compared with ACE inhibitors, being tested in secondary stroke prevention in the ONTARGET trial. Supporting the argument favoring this class effect, the LIFE study indicated the superiority of angiotensin receptor blockade over a beta blocker strategy in the presence of similar BP-lowering effects. At this stage of the saga, we agreed that these trials seemed to be conveying a consistent message, namely that non–BP-lowering effects of angiotensin inhibition were important.

In contrast, Bath argues that these other vascular benefits are not necessarily confined to blockade of the angiotensin system. Indeed, since receiving the submissions from our protagonists, the ALLHAT trial, although a primary prevention study, suggested the potential superiority of diuretics over ACE inhibition in stroke prevention, particularly in black patients.

Where does this leave us in secondary stroke prevention? Despite real uncertainties about class effects generally, there is still only one pivotal trial, namely PROGRESS, that showed unequivocal benefits of BP lowering using a combination of perindopril and indapamide. In our view, the issue of an ACE-specific effect is unresolved. While we await further data, the common denominator of these primary and secondary trials appears to be BP reduction. In practical terms, the evidence lies with perindopril plus indapamide for secondary prevention. Despite their differences of opinion concerning mechanism, both our contributors endorse this view.

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