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

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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), recorded a small fall in BP (5/3 mm Hg), and were neutral, ie, there was no protective vascular effect.2,3 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 BP by 6/3 mm Hg and stroke recurrence by 29%.9 Finally, this effect dependent on their blood pressure (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.

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 moderating effects on the vessel wall and circulating blood cells. Several antihypertensive classes of drugs (including ACE inhibitors, ARA, β-RA, and CCB) are also multimodal in their action, having anti-inflammatory, antiplatelet, antiproliferative, and neuro-protective 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. β-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

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