Angiotensin-Converting Enzyme Inhibitors for Stroke Prevention
Is There HOPE for PROGRESS After LIFE?
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In the 1990s, it was established that increasing blood pressure (BP) is a causal risk factor for stroke and that lowering BP by any major class of antihypertensive medication reduces the risk of first-ever stroke. In 2000 and 2001, it was established from the Heart Outcomes Prevention Evaluation (HOPE) trial and particularly the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial that lowering BP in the long term, months to years after stroke, by means of angiotensin-converting enzyme (ACE) inhibitors (perindopril or ramipril) and diuretics (indapamide) reduces the risk of recurrent stroke (and cognitive impairment). The relative risk (RR) reduction was similar, irrespective of the patient’s baseline BP, age, sex, race, pathological subtype of stroke, and time since stroke onset. The absolute risk reduction was greater among patients at greater baseline risk and with more intensive reductions in BP.

In 2001 and 2002, evidence emerged from 3 clinical trials to support the hypothesis, raised 30 years ago, that angiotensin II might exert detrimental effects beyond the mechanical damage of high BP and be a risk factor for ischemic stroke independent of its effect on BP.

Evidence for Angiotensin II as a Risk Factor for Stroke, Independent of BP
The first trial was the HOPE study, in which a 32% (95% CI, 1.6 to 4.4) reduction in RR of stroke and 20% (95% CI, 1.1 to 3.0) reduction in RR of myocardial infarction (MI) among patients allocated ramipril, compared with placebo, was associated with a reduction in daytime office BP of only 3.3 mm Hg systolic and 1.4 mm Hg diastolic. Because previous epidemiological studies and randomized trials had shown that prolonged reductions in BP of 3.3 mm Hg systolic and 1.4 mm Hg diastolic were associated with only a 13% reduction in stroke and a 5% reduction in MI, it was hypothesized that most (about two thirds) of the effect of ramipril on serious vascular events in HOPE was attributable to effects of ramipril that were independent of its BP-lowering effect.

An alternative interpretation of the HOPE data were that the daytime office measurements of BP underestimated the BP-lowering effect of ramipril over 24 hours, after it had been administered as a nighttime dose. A very small substudy of HOPE, in which 38 patients with peripheral arterial disease, randomized to ramipril (20 patients) or placebo (18 patients) taken at night and followed up with 24-hour ambulatory BP monitoring after 1 year, revealed that the 20 patients allocated ramipril had a reduction in daytime BP of 6 mm Hg systolic and 2 mm Hg diastolic, a reduction in office BP of 8 mm Hg systolic and 2 mm Hg diastolic, and a reduction in 24-hour BP of 17 mm Hg systolic and 8 mm Hg diastolic compared with the 18 patients allocated placebo. However the study sample size was very small.

The second trial was the Losartan Intervention For Endpoint reduction in hypertension study (LIFE). Among 9193 patients with essential hypertension who were randomized to once-daily atenolol or losartan (a selective angiotensin II type 1 receptor blocker [ARB]), there was no significant difference in mean BP recordings among patients in each treatment group during the mean follow-up period of 4.8 years. However, there was a significant 25% (95% CI, 11 to 37, \(P=0.001\)) reduction in the RR of stroke among patients allocated losartan compared with atenolol, as well as a 13% (2% to 23%) reduction in the RR of stroke, MI, or death (the primary outcome event) and a 25% reduction in the incidence of new-onset diabetes mellitus. These data suggested that losartan conferred benefits beyond reduction in BP.

The third trial, which offered weaker support, was the Study on Cognition and Prognosis in the Elderly (SCOPE), which randomized 4937 elderly patients with mild hypertension (mean BP 166/90), who are often an untreated group, to once-daily candesartan cilexetil (an ARB) 8 mg or placebo. Allocation to candesartan was associated with an 11% (95% CI, 1.6 to 20.7, \(P=0.031\)) reduction in the risk of nonfatal stroke, nonfatal MI, or cardiovascular death (the primary outcome event), a 28% (\(P=0.041\)) reduction in the risk of nonfatal stroke, and a 20% (\(P=0.083\)) reduction in onset of new diabetes (secondary outcome events).

The results of the HOPE and LIFE trials, and to a lesser extent SCOPE, indicate that inhibiting the formation or action of angiotensin II prevents stroke and other vascular events (and perhaps new-onset diabetes) and suggest that a substantial proportion of the effect may be independent of BP lowering. The possible mechanisms by which angiotensin II may be an independent risk factor for stroke are illustrated in...
However, this hypothesis remains to be established in clinical trials designed to test the hypothesis a priori. A systematic review of earlier trials that directly compared the effects of ACE inhibitor–based therapy with diuretic, \( \beta \)-blocker, and calcium antagonist–based therapies on stroke and major cardiovascular events did not show a statistically significant benefit of any regimen. More data are awaited from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, which compares an ARB (valsartan 80 mg) with a calcium-channel blocker (amlodipine 5 mg) in 15,314 high-risk hypertensive patients and is expected to report its results in 2004.

**Recommendations for Clinical Practice**

Patients who have had a previous stroke or TIA who are clinically stable and have no contraindication to antihypertensive therapy should aim to gradually lower their BP by means of lifestyle modification and antihypertensive drug therapy, irrespective of their BP at the time. However, not all patients benefit from antihypertensive therapy, such as those with “misery perfusion” of the brain attributable to severe occlusive cerebrovascular disease, a short life expectancy, and adverse effects of the medication.

**How Far to Lower Blood Pressure?**

Epidemiological studies and clinical trials suggest that the lower the BP, the lower the risk of stroke because of the log-linear association between decreasing BP and decreasing stroke risk. Because a lower level of BP, below which the risk of stroke does not decline, has not been identified, it could be construed rather flippantly that it is unhealthy to have any BP. However, the realistic options in practice are to “treat to target” and aim for a BP of \( \leq 130/85 \) (and 120/80 in diabetics) or as low as the patient can tolerate or to “fire and forget,” prescribing optimal antihypertensive treatment for the patient and concentrating on maintaining compliance rather than a particular BP level. The former may be more effective for the individual, but the latter may be more cost-effective for the population.

**Which Antihypertensive Drug?**

For secondary stroke prevention, a diuretic (indapamide) and ACE inhibitor (perindopril or ramipril) are effective and complementary to other antiatherogenic and antithrombogenic therapies, including aspirin. For primary stroke prevention, all major classes of antihypertensive drugs are effective. Systematic drug rotation studies and renin profiling suggest that although the response to different antihypertensive drug classes varies substantially among individual patients, there are two broad patterns, named after the initials of the major drug classes. The AB pattern is seen in type 1 (high-renin) hypertensive patients who are younger and white and who respond best to drugs that suppress the renin system, ACE-inhibitors and ARBs and \( \beta \)-blockers. The CD pattern is seen in type 2 (low-renin) patients who are Afro-Caribbean and older and white and who respond best to calcium-channel blockers and diuretics. Aldosterone-sensitive hypertension, responsive to spironolactone, is recognized in 5% to 10% of patients with uncontrolled BP and low renin despite triple therapy with an ACE inhibitor, calcium channel blocker, and diuretic.

**Are All ACE Inhibitors the Same?**

The more specific the therapeutic target (eg, the ACE), the more difficult it is to differentiate one agent from another, except in terms of pharmacokinetics and potency. Indirect comparisons of the effects of different ACE inhibitors compared with placebo suggest that they are reasonably consistent and that it may be reasonable to extrapolate the findings obtained with perindopril in PROGRESS and ramipril in HOPE to other ACE inhibitors. However, indirect comparisons are prone to biases, and the only reliable way to assess whether one ACE inhibitor has a similar treatment effect to perindopril or ramipril is by a direct head-to-head comparison in a randomized trial.

**Adverse Effects of ACE Inhibitors**

About 1 in 7 patients is unable to tolerate an ACE inhibitor because of cough, postural hypotension (which may result in falls, fractures, and other injuries), hyponatremia, renal impairment, and, rarely, angioedema. These adverse effects are most likely to occur soon after initiating therapy, with the introduction of other medication (particularly nonsteroidal anti-inflammatory drugs), and during episodes of illness or dehydration that lower intravascular volume and renal perfusion.
If Patients Cannot Tolerate an ACE Inhibitor, Should They Try an ARB?

The evidence to date, from indirect placebo-controlled comparisons in nonstroke populations, suggests (but does not prove) that the beneficial effects of ACE inhibitors can be duplicated with ARBs and without the adverse effects.8,9,17–19 More data are awaited, such as those from the Ongoing Telmisartan Alone and in combination with Ramipril Global End-point Trial (ONTARGET). ONTARGET aims to randomize 23,400 patients with symptomatic atherothrombosis of the heart, brain, and limbs or diabetes mellitus to an ACE inhibitor (ramipril 10 mg daily), an ARB (telmisartan 80 mg daily), or the combination of ramipril 10 mg and telmisartan 80 mg daily and follow-up patients over a mean of 5.5 years for the occurrence of nonfatal stroke, nonfatal MI, death attributable to vascular causes, or hospitalization for heart failure. Up to 5000 such patients who are unable to tolerate the ACE inhibitor will be randomized to placebo or telmisartan 80 mg daily in the Telmisartan Randomization Assessment of Multinational Study in ACE Intolerant patients with cardiovascular disease (TRANSCEND).

References


Key Words: angiotensin II ■ angiotensin converting enzyme inhibitors ■ risk factors ■ stroke prevention
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*Stroke.* 2003;34:354-356
doi: 10.1161/01.STR.0000054261.97525.4B

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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