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.

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, 16 to 44) reduction in RR of stroke and 20% (95% CI, 10 to 30) 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

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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, H-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 ≤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 H-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. 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 Study in aCE iNtolerant patients with cardiovascular disease (TRANSCEND).

References


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