ACEI, ARB AND STROKE

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Stroke is one of the the leading cause of death and disability worldwide. Preventive measures to reduce risk factors, such as hypertension can help to improve stroke morbidity and mortality. Agents that block the activity of the renin-angiotensin system (RAS) can play an important role in achieving risk reduction. Although both ARBs and ACE inhibitors have protective effects against cerebral damage, the two types of drugs have differential effects on the RAS. Both the ACEi and the ARB have properties that would be expected to reduce vascular events, but the clinical trials are contradictory.

Data from the HOPE and LIFE studies provided clinical evidence for the effect of ACE inhibitors and ARBs on the incidence of stroke. HOPE study showed that ramipril reduced the relative risk for any stroke by 32% (95% CI 0.56–0.84; P = .0002) and the risk for fatal stroke by 61% (95% CI 0.61–0.94). However, the average reduction in blood pressure was modest (3.8 mm Hg systolic and 2.8 mm Hg diastolic), indicating that ACE inhibitors may protect against stroke by mechanisms that are additional to blood pressure reduction.

The LIFE study in patients with hypertension and left ventricular hypertrophy showed that losartan reduced the incidence of stroke compared with atenolol (adjusted hazard ratio 0.75, P = .001) There was a much more drastic reduction in blood pressure with both atenolol and losartan (29 and 30 mm Hg systolic, respectively; 16.8 and 16.6 mm Hg diastolic, respectively).

Although there were no significant differences in the levels of mean arterial blood pressure or diastolic blood pressure between the groups at the end of the study, the small treatment difference for systolic blood pressure was significant (1 mm Hg P = .017).

In the VALUE trial valsartan was not as effective as amlodipine. Acute vascular events were less frequent in the amlodipine-treated patients and a 15% (p = 0.08) increase in stroke could be detected throughout the course of the trial.

The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) recently assessed the blood pressure-dependent and -independent effects of ACE inhibitors and ARBs on major cardiovascular events in patients with hypertension, diabetes, a history of coronary disease, or stroke. A meta-analysis of 26 trials involving either drug class found that the magnitude of the risk reduction for stroke was positively associated with the blood pressure reduction. Treatment with ACE inhibitor-based regimens was associated with a reduction in the risk for stroke by 19% , for each 5-mm Hg reduction in blood pressure; corresponding data for ARBs was 26%. There were no significant differences between ARB- and ACE inhibitor-based regimens for blood pressure-dependent effects on stroke. Neither ARBs or ACE inhibitors were associated with a significant additional relative risk reduction for stroke beyond that explained by observed blood pressure differences.

The meta-analysis of BPLTTC found a mean 0.7-mm Hg lower follow-up systolic blood pressure with ARB-based regimens compared with ACE inhibitor-based ones. However, there were no significant differences in the effects of ARBs or ACE inhibitors on stroke.

Recent pre-clinical studies have suggested that telmisartan might have properties associated with vascular protection.

Secondary stroke prevention with telmisartan has been currently investigated in the large PRevention regimen For Effectively avoiding Second Strokes (PRoFESS) study, involving 20,300 patients. The PRoFESS study compared the efficacy and safety in the prevention of recurrent stroke of telmisartan and placebo in addition to usual care, including standard antiplatelet therapy comprising extended-release dipyridamole plus aspirin or clopidogrel, and antihypertensive treatment as required. The PROFESS trial also examined the effect of early blood pressure lowering after a stroke using telmisartan vs placebo in the same patients and found there was no benefit with the addition of the angiotensin receptor blocker in prevention of stroke recurrence, at least during the 2.5 years of follow-up in this trial. The PROFESS showed no neuroprotective effect of either dipyridamole or telmisartan that were on board when recurrent strokes did occur in this trial, despite suggestive results from previous preclinical studies.

A combination of an ARB and an ACE inhibitor may be more effective than either agent alone. A meta-analysis of the combination of ACE inhibitors and ARBs vs ACE inhibitors alone found that combination reduced ambulatory blood pressure by 4.7/3.0 mm Hg overall compared with 3.8/2.9 mm Hg for ACE inhibitor monotherapy.

In order to achieve the optimal blood pressure targets, however, and to effectively protect against stroke morbidity and mortality, the majority of patients at risk will require several drug classes. Therefore, we urgently need comprehensive data on the long-term safety of the combination approach in clinical practice, in which patients may be taking complex drug combinations. The complementary mechanisms of action of these 2 drug classes create a strong rationale for combination therapy in high-risk patients. Thus, combination therapy with ARBs and ACE inhibitors may be necessary to achieve more complete RAS blockade than can be achieved with either agent alone. This approach has the potential advantage that angiotensin II produced by non-ACE pathways would be available to bind to the AT2 receptor, producing potentially beneficial effects, such as vasodilation and decreased cell proliferation. Unfortunately, the clinical trials do not confirm always this plausible theory.

The ONTARGET compared the ACE inhibitor ramipril, the ARB telmisartan and the combination of the two drugs in patients with vascular disease or high-risk diabetes. ONTARGET involved more than 25,500 patients from 40 countries worldwide. The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes. Unfortunately, the combination of the two drugs was associated with more adverse events without an increase in benefit.

While ACE inhibitors have been convincingly shown to reduce rates of death, myocardial infarction, stroke the role of ARB and the combination therapy (ACEi+ARB) need further clinical investigations.