Angiotensin Receptor Blockers Should Be Regarded as First-Line Drugs for Stroke Prevention in Both Primary and Secondary Prevention Settings

No

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“It is a wise man’s part, rather to avoid sickness, than to wish for medicines.”
—Thomas More (1475 to 1535), Utopia

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ngiotensin II receptor blockers (ARBs) are hypothesized to have superior stroke protection as compared with other antihypertensives based on their moderating effects of the renin–angiotensin–aldosterone system. Activation of the renin–angiotensin–aldosterone system plays an important role in both the pathophysiology of hypertension and atherosclerotic vascular disease. ARB attenuate renin–angiotensin–aldosterone system activation by competitively inhibiting the binding of angiotensin II (Ang II) to AT$_{1}$ receptors while allowing for unopposed stimulation of the AT$_{2}$ receptors.$^{1}$ AT$_{1}$ blockade interrupts a negative feedback loop leading to a 3- to 5-fold increase in Ang II levels from baseline with hyperstimulation of AT$_{2}$ receptors. AT$_{2}$ activation is hypothesized to protect against stroke by recruiting cerebral collateral vessels and enhancing neuronal resistance to anoxia$^{2}$ and by attenuating prothrombosis, inflammation, and endothelial dysfunction that mediate atherosclerosis.$^{3}$

Analyses of multiple large clinical trials do not, however, support any unique blood pressure-“independent” effects of ARB on stroke prevention. In a meta-analysis of ARB versus any active comparator or placebo by these authors (n=53 318, 11 trials), ARB did not reduce stroke (OR, 0.92; 95% CI, 0.79 to 1.08).$^{1}$ Furthermore, 2 large metaregression analyses (n=45 212, 9 trials; n=39 487, 8 trials$^{4}$), one of which was from the Blood Pressure Lowering Treatment Trials Collaboration,$^{3}$ found no blood pressure-“independent” effects of ARB on stroke after blood pressure differences within the trials were adjusted for.

The trials with the most positive stroke data in favor of ARB include JIKEI, Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES),$^{5}$ and Losartan Intervention For Endpoint reduction in hypertension study (LIFE).$^{6}$ but these trials have important design limitations. In JIKEI (n=3081), a study of high-risk Japanese patients, the addition of valsartan to conventional cardiovascular treatment did reduce neurologic events, but the end point was for transient ischemic attacks plus stroke and not stroke alone. MOSES$^{5}$ (n=1405) compared the ARB eprosartan with the calcium channel blocker nitrendipine in hypertensive patients with stroke. Eprosartan did reduce “total events,” but this was driven by transient ischemic attacks rather than by stroke and by individual patients with multiple events. There was no difference in the “time to first occurrence” of a cerebral vascular event, cognitive or physical disability, or reduction in mortality, which are the true measures of eprosartan’s efficacy or perhaps lack thereof. In LIFE$^{6}$ (n=9193), the ARB losartan was compared with the β-blocker atenolol in patients with hypertension and left ventricular hypertrophy. Losartan did reduce stroke by 25% as compared with atenolol ($P=0.001$); however, atenolol is known not to reduce stroke despite favorable effects on blood pressure.$^{2}$ The losartan arm had the advantage of a 1.7-mm Hg lower mean pulse pressure as well as by having fewer patients with isolated systolic hypertension, atrial fibrillation, and tobacco use, all powerful predictors of stroke.

In 2 major trials this year, ARB compared with placebo had absolutely no impact on stroke. Telmisartan compared with placebo in both Telmisartan Randomized AssessmeNt Study iNtolerant subjects with cardiovascular Disease (TRANSCEND),$^{7}$ a trial of high-risk patients (n=5926), and in Prevention Regi-

ments for Effectively Avoiding Second Strokes Study (PRO-

FESS),$^{8}$ a trial in early stroke patients (n=20 332), failed to reduce stroke (OR, 0.82; 95% CI, 0.64 to 1.06; $P=0.136$ and OR, 0.95; 95% CI, 0.86 to 1.04; $P=0.23$; respectively) despite favorable reductions in blood pressure (4.0/2.2 and 3.8/2.2 mm Hg, respectively). Telmisartan compared with the active comparator ramipril in ONTARGET$^{9}$ (n=17 118) had a slightly lower mean blood pressure (0.9/0.6 mm Hg) but no reduction in stroke either (OR, 0.91; 95% CI, 0.79 to 1.05).

It has been suggested that antihypertensive agents that increase Ang II levels (eg, ARB, dihydropyridine calcium...
channel blocker, diuretics) are more effective at preventing stroke than those that reduce Ang II levels (eg, angiotensin-converting enzyme inhibitor and β-blockers). This hypothesis is supported by the superior stroke benefits of calcium channel blockers as well as the complete absence of any stroke benefit with β-blockers. However, ARBs and angiotensin-converting enzyme inhibitors both inhibit the renin–angiotensin–aldosterone system, have a similar blood pressure-dependent impact on stroke, yet have opposite effects on Ang II levels, making any correlation of an antihypertensives’ impact on Ang II levels with stroke untenable.

Patients at risk of stroke are also at significant risk of myocardial infarction and cardiovascular death. Metaregression analyses confirm ARBs have no blood pressure-independent benefits on myocardial infarction or cardiovascular death either. Angiotensin-converting enzyme inhibitors in marked contrast to ARBs have a relative risk reduction in myocardial infarction and cardiovascular death of 9% (3% to 14%) to 12% (OR, 1.12; 95% CI, 1.01 to 1.23; \( P = 0.028 \)) above that of blood pressure-lowering alone. The divergent cardiovascular effects of ARBs and angiotensin-converting enzyme inhibitors are apparent in a meta-analysis of 48 clinical trials that includes more than 200 000 patients. For every 200 “high-risk” patients randomized to an ARB rather than any comparator, there was an excess of one myocardial infarction despite no differences in stroke.

Extensive clinical trials confirm ARBs have no unique role in the prevention of stroke. If one considers the unique cardiovascular protective benefits of angiotensin-converting enzyme inhibitors, however, the choice of first-line therapy for prevention of stroke is perhaps not a choice at all!

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References


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