

Comparing the cerebroprotective properties of antihypertensive drugs in terms of their effects on angiotensin

Original article Boutitie F *et al.* (2007) Does a change in angiotensin II formation caused by antihypertensive drugs affect the risk of stroke? A meta-analysis of trials according to treatment with potentially different effects on angiotensin II. *J Hypertens* 25: 1543–1553

SYNOPSIS

KEYWORDS angiotensin, antihypertensive, cerebroprotection, stroke

BACKGROUND

The capacity of antihypertensive therapy to prevent stroke could be mediated by angiotensin II.

OBJECTIVE

To evaluate the effects of antihypertensive drugs on the risk of stroke, in terms of their effects on angiotensin II production.

DESIGN AND INTERVENTION

This meta-analysis included randomized controlled trials of antihypertensive agents for primary and secondary stroke prevention in patients without congestive heart failure. Trials were selected if a difference in angiotensin II levels was expected between the treatment arms because of a difference in the pharmacodynamic effects of the drugs on angiotensin II production (as estimated by their effect on renin secretion). Studies that evaluated tighter than normal blood pressure control or involved fewer than 20 strokes were excluded. For analysis, antihypertensives were divided into three groups: drugs that potentially increase angiotensin II production (thiazide diuretics, dihydropyridine calcium-channel blockers [CCBs] and angiotensin receptor blockers [ARBs]), drugs that potentially reduce angiotensin II production (sympatholytics, long-acting non-dihydropyridine CCBs, β -blockers and angiotensin-converting-enzyme inhibitors), and drugs or drug combinations that potentially neither increase nor decrease angiotensin II production ('angiotensin-neutral' drugs; placebo, α_1 -blockers, diuretics plus sympatholytics, and β -blockers plus diuretics).

Relative stroke risks determined by intention to treat analyses were combined and compared for angiotensin-II-decreasing drugs and angiotensin-II-increasing drugs.

OUTCOME MEASURE

The end point was the weighted average log stroke risk estimate (relative to the randomized comparator) for each group of antihypertensive agents.

RESULTS

The meta-analysis included 26 trials ($n=206,632$; 7,505 strokes), which provided data for 36 head-to-head drug comparisons. The pooled estimate of stroke risk relative to placebo was significantly lower for angiotensin-increasing drugs than for angiotensin-decreasing drugs (0.67 [95% CI 0.60–0.74] vs 0.87 [95% CI 0.80–0.95]; $P=0.00001$). The pooled estimate of stroke risk relative to an angiotensin-neutral comparator was also lower for angiotensin-increasing drugs than for angiotensin-decreasing drugs (0.84 [95% CI 0.77–0.92] vs 1.04 [95% CI 0.94–1.15]; $P=0.002$). When trials that directly compared an angiotensin-increasing drug with an angiotensin-decreasing drug were analyzed, the risk of stroke was again greater for angiotensin-decreasing drugs (1.17 [95% CI 1.06–1.30]; $P=0.003$). Angiotensin-increasing agents were associated with significantly greater decreases in blood pressure than were angiotensin-decreasing agents in some, but not all, comparisons. Meta-regression analysis indicated that angiotensin-increasing drugs are associated with a lower risk of stroke than angiotensin-decreasing drugs, independent of systolic blood pressure.

CONCLUSION

Antihypertensive drugs that increase production of angiotensin II might offer better protection against stroke than those that reduce angiotensin II production.

COMMENTARY

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A steep linear relationship exists between blood pressure and risk of stroke, and antihypertensive treatment is the most effective means of preventing ischemic and hemorrhagic cerebral events. Maintaining a 5–6 mmHg reduction in elevated blood pressure lowers the incidence of stroke by up to 40%, which reflects one of the most beneficial therapeutic interventions in general practice. Is it this blood-pressure-lowering effect that accounts for the cerebroprotective action of currently available antihypertensives, or do some of these drugs have additional properties that prevent or even ameliorate the outcome of an ischemic or hemorrhagic insult? This question is reminiscent of similar debates fuelled by recent clinical trials in hypertensive diabetic nephropathy (including IRMA 2, IDNT and RENAAL), which reported that, at similar levels of blood pressure reduction, ARBs were superior to 'conventional' antihypertensives in preventing renal damage.

Boutitie and colleagues have taken an original, provocative approach to determine whether there are blood-pressure-independent differences between antihypertensives with respect to stroke prevention. Rather than analyzing drug classes, these researchers introduced a new classification criterion: the perceived effect on angiotensin II production. They found that agents that decrease angiotensin II were associated with a higher risk of stroke than were angiotensin-II-increasing or angiotensin-II-neutral agents. In some—but not all—comparisons, blood pressure was significantly higher in the patients who received angiotensin-II-decreasing drugs than in those who received angiotensin-II-increasing or angiotensin-II-neutral drugs; however, according to the authors, these differences were not large enough to explain the excess stroke risk.

At first glance, these results undoubtedly have an appeal, particularly as they might have been expected in view of the findings of previous clinical trials and meta-analyses. In the Blood Pressure Lowering Treatment Trialists' report,¹ ARBs (which are angiotensin-II-increasing) performed particularly well, compared with angiotensin-converting-enzyme inhibitors (which are angiotensin-II-reducing), in reducing

stroke risk relative to conventional anti-hypertensive comparators. Similarly, greater stroke protection has consistently been observed with diuretics (angiotensin-II-increasing) than with β -blockers (angiotensin-II-reducing), and dihydropyridine CCBs have always been thought to offer stroke protection beyond their mere antihypertensive effects.² On second thought, however, a host of methodological and conceptual questions arise from the Boutitie *et al.* study, many of which are rightly addressed by the authors themselves. To my mind, one of the most pressing problems is—assuming that angiotensin II levels are really increased by drugs such as ARBs, dihydropyridine CCBs and thiazides—where does angiotensin II act? If it acts on the AT₂ receptor, which clearly possesses cerebroprotective properties in experimental settings,^{3,4} where does this interaction occur, given that angiotensin II does not cross the blood–brain barrier? In addition, how can we tell whether the reduction of stroke incidence occurs by a predominantly vascular mechanism, or via a brain-tissue-related effect (e.g. prevention of secondary strokes)? Finally, Boutitie *et al.* categorized many of the drug classes and their combinations according to conjecture based on their mechanisms of action, rather than by their actual effects on angiotensin II levels.

Nevertheless, prescribing a high-dose ARB and a low-dose thiazide for hypertension, and adding a long-acting dihydropyridine CCB if blood pressure remains uncontrolled, will probably reduce stroke risk more than would be expected from blood pressure reduction alone, and will also slow the progression of hypertensive and/or diabetic nephropathy.

References

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Competing interests

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PRACTICE POINT

When stroke prevention is a key goal of antihypertensive therapy, patients should be given an angiotensin receptor blocker rather than an angiotensin-converting-enzyme inhibitor