Letters to the Editor

Response to Letter by Castilla-Guerra et al

Response:

It is six years since I, and others, suggested that blocking the formation and action of angiotensin II may have protective effects for stroke that are independent of blood pressure reduction, such as antiatherosclerotic properties mediated by anti-inflammatory, antiproliferative, and oxidative stress-lowering properties.

Subsequent support for the hypothesis came from a meta-regression analysis of the direct relationship between the net reduction in systolic blood pressure (SBP) and relative risk (RR) of stroke observed in each of seven meta-analyses of randomized controlled trials comparing the effects of different antihypertensive drug regimens. This analysis showed a dose–response relationship between reduction in SBP and reduction in RR of stroke; the slope of the weighted linear regression line suggested that a 10-mm Hg reduction in SBP would be associated with a reduction in RR of stroke by about 31% (ie, a 1-mm Hg reduction in SBP would be associated with a reduction in RR of stroke by about 3.1%). In the meta-analysis of the six trials that had compared the effects of an angiotensin-converting enzyme (ACE) inhibitor with placebo or no treatment, SBP was reduced by 5 mm Hg among patients assigned an ACE inhibitor compared to placebo. It would have been expected, from the meta-regression analysis, that the RR of stroke would be reduced by about 15.5% (5 mm Hg × 3.1%) with ACE inhibitors compared to placebo, but it was observed that the RR of stroke was reduced by 28% (95% CI: 17% to 32%), suggesting additional benefits of ACE inhibitors beyond blood pressure reduction.

Although the above hypothesis continues to be promoted, Castilla-Guerra et al question its validity.

I agree with Castilla-Guerra et al that the totality of evidence now does not support the hypothesis that the effect of ACE inhibitors and angiotensin II receptor blockers (ARB) in stroke prevention are significantly greater than would be expected from the observed SBP reduction.

The reasons are that a more recent meta-regression analysis, in which treatment-specific RRs for stroke were regressed against follow-up SBP differences using data from 26 large trials comparing an ACE inhibitor or ARB with placebo or another drug class in a total of 146,838 individuals with high BP or an elevated risk of cardiovascular disease, showed comparable BP-dependent reductions in stroke risk with ACE inhibitors and ARB, but no evidence of any BP-independent effects of either ACE inhibitors or ARB on stroke risk. Further, the recently published PROFESSION trial also showed that, among 20,332 patients with recent ischemic stroke, the observed effect of a 3.8-mm Hg reduction in SBP among patients randomly assigned telmisartan compared with placebo on the RR of stroke (RRR = 5%, 95% CI: −4% to 14%) was consistent with expected effect of a 3.8-mm Hg reduction in SBP on the RR of stroke (RRR = 11.8% [3.8 mm Hg × 3.1%]) derived from the meta-regression analysis.

It would appear that the size of the blood pressure reduction achieved with ACE inhibitors and ARBs is directly associated with the size of the reductions in the risk of stroke. It probably does not matter how blood pressure is lowered, as long as it is lowered safely, affordably, and appropriately—in the context of the patients other comorbidities.

Disclosures

None.

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