Does the MOSES Trial Establish Superiority of AT1-Receptor Blockers Over Dihydropripyridine/Calcium Antagonists in Secondary Stroke Prevention?

To the Editor:

The MOSES study\(^1\) has unequivocally shown that in patients with a history of cerebrovascular events, a blood pressure (BP)–lowering treatment based on eprosartan is more protective against both cerebrovascular event recurrence and cardiac complications than a treatment based on nitrendipine. Of paramount importance is the fact that this superiority was documented with similar BP decrease in both treatment arms and no difference in baseline BP. Furthermore, BP was monitored not only by office BP but also by 24-hour ambulatory BP at baseline and after 12, 24 and 48 months of follow-up. The office BP-lowering effect of eprosartan was even slightly smaller (1.5 and 0.6 mm Hg for the systolic and diastolic BP, respectively), which formally excludes any BP bias. Can we therefore postulate that a specific BP-independent stroke preventive effect of eprosartan is the only possible explanation for this better cardiovascular protection compared with nitrendipine?

To answer this question, it is important to carefully look at the add-on therapy. Interestingly as pointed out by the authors, the add-on therapy was comparable with the exception of the use of angiotensin-converting enzyme inhibitors (ACEI) and dihydropyridine calcium channel blockers (CCBs). In the eprosartan arm, ACEIs were less frequently used (11.3% versus 21%), whereas CCBs were used twice as often (14.4% versus 7.5%) when compared with the nitrendipine arm. Could this difference in add-on therapy have influenced the outcomes, considering that monotherapy with randomized drugs was used only in 34% and 33% of both arms? To elucidate this issue the last BP-lowering treatment (BPLT) trialist collaboration meta-analysis\(^2\) should be recalled: it showed that myocardial infarction was equally prevented by ACEI and dihydropyridine (DHP) CCBs but that prevention of stroke was better with CCBs, whereas that of heart failure was better with ACEIs (relative risk=0.89 and 0.82, respectively). This suggests that the differences in use of ACEI and DHP between the 2 groups would increase the heart failure risk but decrease the cerebrovascular risk in the eprosartan group. Conceivably, therefore, the superiority of eprosartan in cardiovascular prevention may have been attenuated with this add-on therapy, whereas superiority of eprosartan in cerebrovascular protection was likely to be enhanced.

However, it is unlikely that the 25% greater stroke risk reduction by eprosartan could entirely be explained by the difference in DHP/ACEI use prevalence because the greater reduction of stroke with DHP compared with ACEI in the BPLT trialist collaboration meta-analysis was only 11%. Furthermore, the ACEI/CCB prescription differences between the 2 arms affected only 7% of the patients not on monotherapy (ie, about 5% of the whole population).

Therefore, we quite agree with the editorial by Strandberg\(^3\) that the greater BP-independent cerebroprotection with eprosartan is real and might be explained by greater stimulation of AT2-receptor than with nitrendipine. Indeed, renin secretion and therefore angiotensin II formation might be increased by both dihydropyridines\(^4\) and by AT1-blockers,\(^5\) but stimulation of renin secretion may be greater with AT1-blockers because of blunting the strong AT1-mediated angiotensin II negative feedback on renin secretion. Indeed, long acting dihydropyridines may stimulate renin only by activation of the sympathetic nervous system, and this latter is heterogenous with the various DHP-CCB as documented in the recent comparison of lercanidipine with nifedipine-gastrointestinal therapeutic system.\(^6\)\(^\#\)

AT2-mediated protection against cerebral ischemia has now been formally evidenced in experimental models. The group of Unger et al\(^7\) showed that intracerebroventricular preadministration of irbesartan decreased the neurological deficit induced in the rat by transient occlusion of the midcerebral artery and that this protection was cancelled by coadministration of an AT2-receptor-blocker which impeded the blockade of anoxia-induced neuronal apoptosis. This AT2-mediated cerebroprotection has also been confirmed by the comparison of AT2-receptor gene–deleted mice with wild mice because for the same middle cerebral artery occlusion, the ischemic area was larger and the neurological deficit more severe in the AT2 gene–deleted mice. Furthermore, 10 day pretreatment with valsartan significantly reduced mortality, neurological deficit and ischemic area, and this protective effect was significantly weaker in the AT2-KO mice than in wild-type mice, evidencing the involvement of AT2-receptor in the protective effect of valsartan.\(^8\)

In spite of this well established AT2-mediated cerebroprotective mechanism, it may be premature to promote eprosartan as the first choice treatment for secondary stroke prevention, all the more because its comparator nitrendipine was validated in primary\(^9,10\) but not in secondary stroke prevention. To prevent stroke recurrence in patients with or without hypertension, only indapamide alone in PATS trial\(^11\) and indapamide–perindopril in PROGRESS trial\(^12\) have been validated. Because the latter combination therapy decreased stroke recurrence risk by 43%, whereas indamide alone decreased it only by 29%, the combination therapy “indapamide–perindopril” should now be considered as the gold standard of secondary stroke prevention. Therefore, to establish which bitherapy is the most efficient in secondary stroke prevention, we propose that in association with indapamide (or another thiazide), eprosartan (or another sartan) be compared with perindopril (or ramipril which decreased stroke risk by 32% in HOPE trial,\(^13\) whereas perindopril alone in PROGRESS nonsignificantly decreased stroke recurrence only by 5%).

Given that about two thirds of hypertensive patients need >1 drug to control BP, the identification of the most stroke-protective bitherapy is of primary public health importance.

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The reality of greater stimulation of systemic angiotensin II with a sartan when compared with a DHP has been documented by a double blind cross over study in 18 hypertensive patients since angiotensin II levels were 2.02±0.3 ng/ml with amlopidine and 2.96±0.33 with valsartans (\(P<0.05\)) (Jan Struck et al. J Hypertension. 2002;20:1143–1149).


12. PROGRESS collaborative group: Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033–1041.

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Stroke. published online January 5, 2006;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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