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Differences Between Primary vs Secondary Prevention Trials Regarding the Stroke Protective Effect of Antihypertensive Drugs

In the very interesting case-control study by Klungel et al,[1] we noted 2 intriguing observations about which we would like to comment: (1) among patients without cardiovascular complication treated with monotherapy, the risk ratio (RR) for ischemic stroke was much higher in those treated with calcium antagonist alone (RR, 2.30; 95% confidence interval [CI], 1.16-4.56) compared with those treated with thiazide alone; (2) among patients treated with 1 or 2 drugs, the risk of ischemic stroke associated with no thiazide treatment compared with thiazide treatment was remarkably higher in those with clinically recognized cardiovascular disease than in those without this complication (RR, 1.85 vs 1.25; 95% CI, 1.26-2.71 vs 0.87-1.80).

Regarding the first observation, we are puzzled by the fact that the greater stroke protective effect of thiazide over calcium antagonists suggested by this case-control study is not confirmed by the results of more reliable randomized controlled trials. Thus, in the INSIGHT trial,[2] the long-acting drug nifedipine was directly compared with a combination of thiazide and amiloride, and the RR for fatal and nonfatal stroke for nifedipine was 0.90 (67/74; $P > .50$), even though that for fatal and nonfatal myocardial infarction was 1.26 (77/61; $P = .045$).

The second observation, showing that the better stroke protective effect of thiazide over other antihypertensive drugs is higher only in hypertensive patients who have no cardiovascular complication but not in those who already have such complications, is reminiscent of the contrast between the higher stroke risk observed with captopril compared with conventional treatment in the CAPPP trial[3] and with the significant decrease of stroke with ramipril compared with placebo in the HOPE trial.[4] Indeed, cardiovascular complications were present in 90% of the subjects in the HOPE trial population but in only 4% of those in the CAPPP trial. In the HOPE trial, a 32% decrease in stroke risk was observed with ramipril compared with placebo, while the decrease in blood pressure (BP) (of 3 and 1 mm Hg for the systolic and diastolic BP, respectively) accounted for only a 13% decrease, so the BP-independent decrease could be evaluated at 19%. In the CAPPP trial, the stroke risk increase with captopril was 25% in the intention-to-treat analysis and 43% in the on-treatment analysis, while the difference in BP between the group treated with thiazide and/or β-blocker was the same as that between the 2 groups in the HOPE trial.[5] Application of the same BP-dependent stroke risk difference found in the HOPE trial to the CAPPP trial leads to the estimation of the BP-independent risk increase with captopril at 12% and 30%, respectively, according to the type of analysis used.

Rather than dismiss the stroke increase that was observed in the CAPPP trial as being the result of less than optimal randomization, we think that it is more interesting to give the following pathophysiological explanation. The SHEP trial[6] has shown that the effect of thiazide therapy was quite different according to the pathophysiological types of stroke, the decrease being only 1% and 43% for strokes linked to atherosclerotic plaques and emboli, respectively, whereas it was 64% to 47% for the other types of ischemic strokes and for the hemorrhagic ones that are more closely related to hypertension. The prevalence of strokes due to atherosclerotic plaques and cardiac emboli, however, was only 9.5 and 10% in the SHEP trial population, which, like the CAPPP trial population, had only a low prevalence of previous cardiovascular complications (6%). In contrast, in the HOPE trial population, the incidence of stroke due to either cardiac emboli or atherosclerotic plaque destabilization as a result of overexpression of the tissular angiotensin-converting enzyme gene[7] may be presumed to be much higher than in the population of the SHEP and CAPPP trials, as the prevalence of symptomatic atherosclerotic complications was 90%. Therefore, the BP-independent protective effect of angiotensin I–converting enzyme and β-blockers (both of which decrease angiotensin II formation) against stroke will be potentially greater in patients with cardiovascular complications than in those without.

This greater potential protective stroke effect of angiotensin I–converting enzyme inhibitors in patients with cardiovascular complications explains the protective effect of ramipril against stroke compared with placebo in the HOPE trial but not the paradoxical higher BP-independent protective effect of thiazides over angiotensin I–converting enzyme inhibitors in the CAPPP trial and over β-blockers that was reported by Klungel et al.[1] We suggest that this paradoxical protective effect can be explained by the hypothesis proposed by Brown and Brown[8] after the publication of the MRC trial in mild hypertension to account for the twice-higher protective effect of high-dose thiazides against stroke compared with propanolol: "angiotensin II may be stroke protective." This provocative hypothesis has received a great deal of experimental support during the last 14 years, thanks to the discovery of the duality of angiotensin II receptors. Besides the angiotensin AT1 receptors, which mediate BP increase, cardiovascular remodeling, and atherosclerotic intimal modification, there are the angiotensin AT2 receptors, which mediate protective mechanisms such as collateral circulation recruitment[9] and decrease in neuronal apoptosis factor expression[10] after overexpression of their gene due to ischemic insults.[11]

Because calcium antagonists (whether short- and long-acting dihydropyridine or short-acting nondihydropyridine) produce long-term sympathetic counterregulation,[12] they stimulate renin secretion[13] like diuretics and therefore angiotensin II formation. This stimulation of angiotensin II could account for their well-established protective effect against stroke, as recently illustrated by the comparison of the short-acting diltiazem mainly with β-blockers in the NORDIL trial.[14,15] Only long-term treatment with long-acting nondihydropyridines has been associated with decreased levels of norepinephrine.[12] A high

prevalence of this variety of calcium antagonists in the study of Klungel et al[1] could explain the paradoxical higher stroke risk of calcium antagonists compared with thiazides.

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In reply

In our case-control study of the association between antihypertensive drug therapies and the risk of ischemic stroke, we found that antihypertensive drug regimens that did not include a thiazide diuretic were associated with an increased risk of ischemic stroke. Fournier and colleagues are puzzled by the fact that among patients without cardiovascular complications, calcium antagonists were associated with an increased risk of ischemic stroke; whereas in the INSIGHT trial, long-acting nifedipine was not associated with an increased risk of stroke compared with the combination of hydrochlorothiazide and amiloride.[1] In our study, the nondihydropyridines represented about 84% (176/209) of all calcium antagonist use as monotherapy. There were too few subjects receiving dihydropyridines to estimate the RR of ischemic stroke for these users. Therefore, our results are difficult to compare with those from the INSIGHT trial. Fournier and coworkers offer some interesting hypotheses regarding the potential role of angiotensin II and the difference in the stroke-protective effect of thiazide diuretics between subjects with and without cardiovascular complications. Indeed, non-BP–mediated effects of antihypertensive drugs are important to consider and emphasize the importance of evaluating antihypertensive drugs with regard to their effects on clinically important end points such as myocardial infarction and stroke.

Lankipalli and Khan ask about the potential confounding influence of race, left ventricular function, left atrial size, and treatment with anticoagulation, aspirin, and statins. As can be derived from Table 1 of our article, most subjects in our study were white (90%), and we adjusted for aspirin and use of statins in our analyses. Data on left ventricular function and atrial size were not available for most subjects. For most subjects, physicians could not adjust therapy according to measures of left ventricular function or atrial size because few subjects underwent echocardiography. However, subjects with clinical congestive heart failure were excluded from all analyses and could not have confounded the results. The beneficial effects of thiazide diuretics on the risk of stroke and coronary heart disease have been firmly established in several randomized placebo-controlled trials.[2] Additional evidence about the efficacy of thiazide diuretics compared with alternatives will come from meta-analyses of completed trials[3] and results of ongoing trials, such as ALLHAT.[4]

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Clinical and Ethical Concerns About Switching Patient Treatment to "Therapeutically Interchangeable" Medications

The worsening of symptoms in 52% of previously stabilized patients with heartburn or gastroesophageal reflux disease when their treatment is switched from omeprazole to lansoprazole therapy as described by