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COMMENTS AND OPINIONS

Designing Appropriate Clinical Trials to Assess ACEI Use and Cognitive Decline in Older Adults With Hypertension

Sink et al¹ report that exposure to angiotensin-converting enzyme inhibitors (ACEIs) is not associated with dementia risk or cognitive decline in older hypertensive adults compared with other antihypertensive drugs. Centrally active ACEIs, ie, those that cross the blood-brain barrier (BBB) (animal data), reduced cognitive decline, whereas noncentrally acting ACEIs (BBB impermeable) were associated with greater risk of incident dementia and disability in instrumental activities of daily living.¹ These effects were independent of blood pressure regulation and prompted a call for a randomized clinical trial of centrally active ACEIs in the prevention of cognitive decline and dementia.¹

Controversies remain. Angiotensin-converting enzyme inhibitors modulate progression of amnesic mild cognitive impairment.² With the analysis limited to dihydropyridines or diuretics, significant benefits on dementia are suggested.³ The only study in older hypertensive patients to show a significant effect was nitrendipine based.³ A recent study found that any antihypertensive medication, but particularly potassium-sparing diuretics, was associated with lower risks for Alzheimer disease (AD).³ The most recent study findings in very elderly people, involving perindopril and indapamide, were negative.⁴

In their discussion, Sink et al¹ fail to make the point that the intervention in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was perindopril based, ie, treatment was perindopril plus indapamide (received by 58% of subjects). Therefore, an effect could not be concluded to be on the basis of perindopril use alone.³ The design of hypertension studies was not powered primarily on the outcome of cognition or dementia. The following unresolved issues remain: Does treatment of hypertension in middle age reduce cognitive decline and/or dementia in late-life? Does treatment of hypertension in older adults reduce cognitive decline and the risk of dementia? Are any benefits associated with a specific regimen? Future studies must have cognition and dementia as a primary outcome. Given that the study population is relatively cognitively normal, the optimal study design should include specific tests of attention, episodic memory, and other measures of executive function.⁵ It may be possible to examine the effects of individual agents within those designs but the numbers required are likely

to be very large. The important issue of equivalent blood pressure control in comparative groups compared with the treatment regimen is problematic but achievable. With the current focus on management of overall cardiovascular risk, studies must factor in the use of antiplatelet, lipid-lowering, and other interventions. Perhaps the priority area for study, given the increasing awareness of the interface between AD and cardiovascular risk factors, is the role of modulation of cardiovascular risk on disease progress in patients with established AD.

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Centrally Active ACEIs and Cognitive Decline

We read with interest the article by Sink and colleagues¹ describing an association between the use of centrally active ACEIs that can cross the BBB and a reduction in cognitive decline in a large, well-characterized cohort of treated older adults with hypertension. Using computerized information on patients in our university hospital, we also found that the long-term use of centrally active ACEIs (captopril or perindopril) is associated with a lower risk of incident dementia compared with other antihypertension drugs in elderly hypertensive patients.² Furthermore, we found that the centrally active ACEIs significantly reduce the