Hypertension is the leading cause of stroke,\(^1\) a major catastrophe from a human, financial, and societal point of view. Blood pressure (BP) levels are also associated with cognitive impairment in older adults with vascular dementia and may contribute to the progression of Alzheimer disease.\(^2\)\(^-\)\(^5\) Indeed, hypertension induces a 2.3-fold increase in the risk of Alzheimer-type dementia.\(^6\) Control of BP may thus not only contribute to the prevention of stroke\(^6\) but also to slowing down the progression of cognitive impairment in hypertensive individuals.\(^5\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^12\) Interventional studies such as Systolic Hypertension in Europe (Syst-Eur) showed that control of high BP was followed by a significantly reduced incidence of stroke and by a decrease in the development of dementia of almost 50%.\(^7\) Using an angiotensin-converting enzyme (ACE) inhibitor in association with a diuretic in most patients, the PeRindopril prOtection Against Recurrent Stroke Study (PROGRESS) showed conclusively that BP lowering allows secondary prevention of stroke.\(^9\) Furthermore, during the mean follow-up period of 3.9 years, cognitive decline occurred in 9.1% of the 3051 randomized participants in the actively treated group and 11.0% of the 3054 randomized participants in the placebo group, a risk reduction of 19% \((P=0.01)\).\(^10\) Risk of the composite outcomes of dementia with recurrent stroke and cognitive decline with recurrent stroke were reduced by 34% \((P=0.03)\) and 45% \((P<0.001)\), respectively, and interestingly, with no effect on dementia or cognitive decline in the absence of recurrent stroke. This has been confirmed to some degree by the Study on Cognition and Prognosis in the Elderly (SCOPE) with an angiotensin receptor blocker, although the study was weakened by switching the placebo group to usual care after the acute phase of the study.\(^11\) In that study, which had a mean follow-up period of 3.7 years, patients were assigned randomly to receive the angiotensin receptor blocker candesartan or placebo, with open-label active antihypertensive therapy added as needed. As a consequence, active antihypertensive therapy was extensively used in the control group. There were no significant differences in myocardial infarction and cardiovascular mortality, but there was a significant reduction in nonfatal stroke. There were no significant differences in cognitive impairment or development of dementia between the 2 treatment groups.

**See p 1644**

The anatomic substratum of brain target-organ damage in hypertension, be it stroke or cognitive impairment, is well understood: stroke resulting from ischemia of thrombotic or embolic origin, hemorrhagic stroke, or small artery disease characterized by tortuosity and irregularity of small arteries and arterioles, sclerosis and hyalinosis associated with lacunes, gliosis, Virchow-Robin space dilation, and cystic formations.\(^12\)\(^,\)\(^13\) All ultimately lead to different degrees of atrophy of the brain.\(^14\) In some studies, atrophy of the brain in hypertension has been localized, typically affecting the thalamus and hippocampus.\(^15\)\(^,\)\(^16\) On a CT scan, microvascular lesions associated with aging but more particularly with hypertension will manifest as leukoaraiosis. On MRI, ischemic lesions associated with aging and with hypertension will appear as white matter hyperintensities (WMH).\(^18\)\(^,\)\(^19\)\(^,\)\(^16\)\(^,\)\(^17\)\(^,\)\(^18\) There is a correlation of WMH with BP and between WMH and risk of stroke as well as cognitive deterioration.\(^18\) White matter findings were significantly associated with age, silent stroke, and hypertension and were accompanied by cognitive impairment. White matter lesions have been shown to progress on repeat MRI scans in older adult individuals, they correlate with cognitive decline, and they have complex relationships with cardiovascular risk factors.\(^20\)

Control of BP may be associated with reduced progression of WMH.\(^21\) Although systolic hypertension is the predominant form of elevated BP in older people, diastolic hypertension has been correlated with progression of WMH in some studies.\(^19\) This may relate to the role that small arteries in the brain play in diffuse ischemia associated with vascular-type dementia and may also contribute to degenerative dementia in older adults. In the present issue of *Circulation*, Dufouil et al\(^22\) add to our knowledge about our ability to modify the progression of target-organ damage in the brain by BP control. In a substudy of PROGRESS, patients were randomized as in the main study to placebo or to an “ACE inhibitor (perindopril)–based” antihypertensive regimen as a strategy for secondary prevention of stroke. When the treating physician considered it appropriate, the diuretic indapamide was added, which could be withdrawn if clinically indicated. Most patients in the active group received both agents. The active treatment group was associated with significantly less new WMH than was the placebo group. In the

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main PROGRESS study, BP lowering was 5/2 mm Hg with perindopril alone and there was no statistically significant beneficial effect on secondary prevention of stroke. Perindopril plus indapamide reduced BP by 12.5 mm Hg, and results were statistically highly significant in favor of the active treatment.\(^8\) In the study by Dufouil et al.,\(^2\) BP was reduced in the active treatment group by 12/8 mm Hg, suggesting that most, if not all, patients were receiving the ACE inhibitor and the diuretic; however, the authors do not provide us any of these important details. Extension of WMH that were present at baseline was not evaluated because this was a secondary prevention study and the object of the investigators was to prevent the appearance of new lesions. Given the anatomic basis of WMH, extension of preexisting WMH may represent new microvascular lesions and ischemia. Hippocampal atrophy has also been correlated with BP elevation and associated with cognitive impairment.\(^15\) Should hippocampal atrophy therefore have been evaluated? Another limitation of the study is the small number of subjects investigated, who may not be representative of the whole cohort. We cannot know whether the findings in the whole cohort with regard to stroke and dementia or impairment of cognition\(^16\) were reproduced in this small group of selected patients. Thus, most importantly, we are not provided with a clinical evaluation correlated with the neuroradiological imaging results. Was there a correlation between new WMH or, as mentioned above, increased volume of preexisting ones, and neurological deterioration or cognitive impairment? This would certainly make control of the progression of WMH with antihypertensive treatment matter very much to patients, practitioners, and health authorities.

A final question relates to the specificity of the effect of the agents used. Was it the lowering of BP, the use of an ACE inhibitor (any ACE inhibitor or specifically the one in the study), or the diuretic (or the use of both in combination) that resulted in these presumably favorable results?

The study of Dufouil et al.\(^2\) points the way to new studies that should examine in larger groups, to have adequate power, the results of treating patients with these or other antihypertensive agents on both imaging signs and cognitive and neurological variables: results from the systolic hypertension in elderly people. Arch Intern Med. 1994;154:2154–2160.


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Blood Pressure Lowering in PROGRESS (Perindopril Protection Against Recurrent Stroke Study) and White Matter Hyperintensities: Should This Progress Matter to Patients?

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