

Blood Pressure, Cognitive Functions, and Prevention of Dementias in Older Patients With Hypertension

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The prevalence and incidence of degenerative and vascular dementias increase exponentially with age, from 70 years onward. In view of the increasing longevity of humans, both varieties are bound to evolve into a major problem worldwide. According to several longitudinal studies, hypertension appears to predispose individuals to the development of cognitive impairment and ensuing dementia, after a period varying from a few years to several decades. Antihypertensive drug treatment, according to preliminary evidence, may serve to reduce the rates of such events. Such findings await to be confirmed by formal therapeutic trials against a backdrop of “historical” observational sources. *Arch Intern Med.* 2001;161:152-156

Dementia is characterized by the development of a range of intellectual and other mental defects, such as a progressive loss of memory, disorientation in space and time, loss of autonomy, and emotional depersonalization. The most dominant types of dementia are Alzheimer disease and vascular dementia, in proportions of roughly 2:1. The prevalence and incidence of both disorders increase exponentially with age, from 70 years onward. Both varieties are evolving into a major health problem worldwide, as a natural consequence of increasing longevity.

Among various factors supposedly predisposing to the incidence and prevalence of cognitive impairment and the development of different forms of dementia, a history of hypertension has become increasingly discernable in observational studies.

COGNITIVE PERFORMANCE AND DEMENTIA IN RELATION TO BLOOD PRESSURE

Hypertension, through its well-recognized contribution to the development of macro-

scopic cerebrovascular lesions, might equally well be expected to predispose to the development of more subtle cerebral processes, based on arteriolar narrowing, allied microvascular pathological features, or both, in due time leading to cognitive impairment and finally overt dementia.

The results from cross-sectional observational studies on the relation between hypertension and cognitive function seem to support such a notion, although the evidence is far from uniform, according to an overview by Seux and Forette.¹ These researchers collected data from a dozen studies including older patients with normotension and hypertension and came up with the following findings. In 4 studies,²⁻⁵ no correlation between cognitive function and blood pressure was observed. By contrast, other studies revealed a negative correlation between cognition and systolic blood pressure (SBP),⁶ diastolic blood pressure (DBP),⁷⁻⁹ or SBP and DBP.^{10,11} One series¹² exhibited a positive correlation between SBP or DBP and cognitive function. Such variability is likely to depend, at least in part, on the selection of populations investigated and differences between neuropsychological detection methods.¹ Perhaps more important, a concurrent examination of blood pressure and cognition starts from a possibly misleading concept of synchronicity in the development of both features.

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A more realistic approach by longitudinal long-term investigations has allowed the possibility of discerning more distant associations between high blood pressure and cognitive dysfunction chronologically.

In this regard, Elias et al¹³ have broken ground by reviewing cognitive function and memory performance in the Framingham cohort, 12 to 14 years after recruitment, in relation to initial blood pressure measurement. Most hypertensive subjects (88%) had received no treatment in the interim. After correction for demographic variables and cardiovascular risk factors other than high blood pressure, cognitive performance was found to be negatively correlated with the initial SBP and DBP readings.

A similar pattern, focused on SBP and subsequent cognitive function, has been observed during the Honolulu-Asia Aging Study¹⁴: a significant relation was established between SBP at enrollment and the risk of cognitive impairment 25 years later.

Skoog et al¹⁵ conducted a 15-year follow-up study of blood pressure and dementia in Gothenburg, Sweden. They analyzed the relation between blood pressure and dementia starting with patients without dementia at the age of 70 years, and observing them up to the age intervals of 70 to 75, 75 to 79, and 79 to 85 years. Participants who developed dementia at age 79 to 85 years had a higher SBP and DBP at the age of 70 years, compared with those who did not. An additional remarkable finding in this study was that blood pressure in the years just preceding the onset of dementia paradoxically tended to become lower than in individuals without dementia. This applied in particular to those developing Alzheimer disease and in those with white matter lesions on computed tomography.

Another follow-up study,¹⁶ of 40 months' duration in very elderly patients (aged 75-101 years), likewise demonstrated that the lower the SBP, the worse the cognitive performance.

Tentative explanations for these paradoxical findings may be as follows. First, the decline in blood pressure shortly preceding dementia may

be due to loss of physical activity. In addition, a failure of maintaining blood pressure at this stage may be an expression of brain lesions accompanying Alzheimer disease in prefrontal autonomic centers, resulting in central dysregulation of blood pressure.¹⁷ Conversely, the decrement in blood pressure, presumably exaggerated during orthostasis, through periods of cerebral ischemia, to a certain extent may have furthered the pathogenesis of Alzheimer disease.

A recently finished investigation¹⁸ dealt with a study population of 999 men, aged 50 years at enrollment and followed up for 20 years. At the age of 70 years, cognitive function was highest in those with an initial DBP lower than 70 mm Hg and lowest in subjects with a DBP higher than 105 mm Hg. The end point age herein was identical with the starting age in Gothenburg,¹⁵ so that this study agewise may have fallen short of the possibility of detecting a biphasic phenomenon, as previously referred to.

Another recently published report¹⁹ dealt with 2068 inhabitants of the East Boston, Mass, area. These subjects had participated in 2 successive studies, the Hypertension Detection and Follow-up Program, organized from 1973 to 1974, and the Established Populations for the Epidemiologic Study of the Elderly, organized from 1982 to 1983. In the latter part of this serially combined evaluation, subjects were aged 65 to 102 years at baseline. Blood pressure, mental status, and memory were assessed at baseline and 3 and 6 years later. In analyses adjusted for age, sex, and educational level, there was no strong linear association between blood pressure and cognition. The only suggestive finding was that an SBP of 160 mm Hg or higher 9 years before (ie, at randomization for the Hypertension Detection and Follow-up Program trial) was associated with a (statistically significant) 14% higher rate of test errors in the Established Populations for the Epidemiologic Study of the Elderly phase, compared with a reference group with an SBP of 130 to 139 mm Hg. The weakness of this association could be caused by interference of secondary factors in the high-

est age range, as indicated earlier. Moreover, the analysis of the combined Hypertension Detection and Follow-up Program—Established Populations for the Epidemiologic Study of the Elderly data is fraught with the lack of a proper discrimination between antihypertensive treatment and nontreatment.

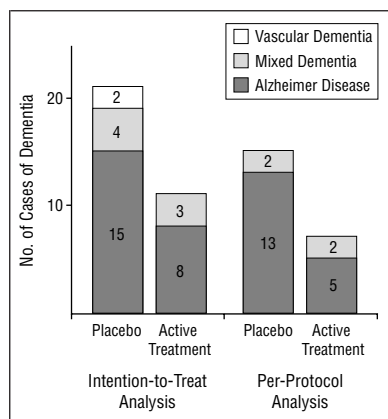
In summary, longitudinal cohort studies appear to support the notion that hypertension predisposes to cognitive decline and development of dementia, although with a considerable time lag that may amount to several decades. In the late interval shortly preceding dementia, the original negative relation between blood pressure and cognitive function may become unrecognizable due to a terminal decline in blood pressure. This phenomenon would seem to require extremely careful vigilance in the practical management of the very elderly patient with hypertension, including monitoring of blood pressure and cognition.

EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON COGNITIVE FUNCTION AND PREVENTION OF DEMENTIA

Guided by the successful effects of antihypertensive medication in containing stroke rates in elderly patients, particularly those with systolic hypertension,²⁰⁻²⁴ one could reasonably hope to see rather similar effects for the prevention of dementia given the latter's association with hypertension.

In several observational studies relating hypertension with cognitive function, the influence of concurrent antihypertensive medication use has been taken into consideration as well.

In the Kungsholmen (Sweden) Project,²³ 1301 subjects aged 75 years and older were followed up for an average of 3 years. Cognitive functions were assessed using the Mini-Mental State Examination and other psychometric tests, and *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*,²⁵ criteria when needed for establishing dementia (more information about these methods is available from the



Number of incident cases of dementia by cause in the Vascular Dementia Project of the Systolic Hypertension in Europe trial.²² The median observation period in the placebo-treated and actively treated (the dihydropyridine calcium channel blocker nitrendipine being the primary drug) groups covered 2 years, after which the trial had to be stopped due to the attainment of a predeclared statistically significant difference between stroke rates in both groups. Except for one case in the placebo group (intention-to-treat analysis), patients exhibiting dementia had remained free from stroke. The dominance of Alzheimer disease in association with systolic hypertension was still unprevalent when the Vascular Dementia Project was conceived (1989).

authors). At the end of the follow-up period, 987 subjects were still alive. In the subpopulation with an SBP higher than 160 mm Hg, a DBP higher than 95 mm Hg, or both (n=458), 122 received diuretic therapy. Compared with untreated patients, the subjects thus treated showed an adjusted relative risk for dementia of 0.6 (95% confidence interval, 0.3-1.2). This trend was tentatively interpreted by the authors as a potential benefit from diuretic treatment. But they fully recognized the limitations of the results, in that information of drug use was only available at baseline, the duration of treatment being unknown. Moreover, the group using antihypertensive medication in this cohort differed inherently from the untreated group due to the presence of heart disease and stroke in the latter, another example of confounding by indication. Therefore, these authors, like the previous ones, admitted the need for clinical trials.

The recently finished Epidemiology of Vascular Aging Study²⁴ recruited 1389 subjects aged 59 to 74 years, including 167 hypertensive subjects who were reexamined 2 and 4 years later. After 4 years, 81 hy-

pertensive individuals had received antihypertensive treatment with various drugs (β -blockers, calcium channel blockers [CCBs], angiotensin-converting enzyme inhibitors, and diuretics). In untreated hypertensive participants, a correlation was observed between the level of blood pressure and a subsequent decline in cognitive function (a decrement of >4 points on the 30-point Mini-Mental State Examination scale). The relative risk amounted to 4.3 (95% confidence interval, 2.3-8.0) compared with normotensive enrollees. In the treated group, the relative risk appeared to be reduced to 1.3 (95% confidence interval, 0.3-3.9).

The results described seem to carry a promise for routine antihypertensive treatment in reducing the incidence of cognitive impairment. Nevertheless, such achievements would need to be confirmed by formally administered prospective therapeutic trials.

Three major randomized placebo-controlled hypertension trials have encompassed substudies focusing on the course of cognitive function and the incidence of dementia: the Systolic Hypertension in the Elderly Program,²⁰ the Medical Research Council trial,²¹ and the Systolic Hypertension in Europe (Syst-Eur) trial.²²

The Systolic Hypertension in the Elderly Program²⁰ involved a group of 2034 subjects aged 60 years and older recruited because of isolated systolic hypertension (SBP, ≥ 160 mm Hg; and DBP, <90 mm Hg) for active and placebo treatment with the diuretic chlorthalidone as the primary drug. These patients underwent an elaborate battery of psychometric tests at baseline, repeated at intervals of 6 months up to an average observation period of 5 years. The outcome was that neither the evolution of cognitive function nor the incidence of dementia was significantly different between the active treatment and placebo groups. The incidence of dementia was 1.6% and 1.9%, respectively.

In a subset of 2584 participants in the Medical Research Council trial²¹ of treatment in older patients with hypertension randomized to a diuretic, β -blocker, or placebo,

psychometric tests were performed covering a period of 54 months. Again, no significant difference in test scores was detected between the active treatment and placebo groups.

The Syst-Eur trial,²² dealing with older (≥ 60 years) patients with isolated systolic hypertension (SBP, ≥ 160 mm Hg; and DBP, <95 mm Hg) included a side project investigating 2418 subjects in whom cognitive function and incidence of vascular and degenerative dementias were assessed comparing outcome while taking active treatment (with nitrendipine as the primary drug) vs a matching placebo.²² Methods used were the Mini-Mental State Examination, followed by more specific approaches in case of scores less than 23 (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition*; Hachinski scoring; and imaging techniques). The median follow-up period lasted only 2 years because of the necessity of termination of the trial, due to the statistical attainment of preset stroke rate differences between the active and placebo treatment groups as the predeclared primary end point. According to the intention-to-treat analysis, 21 cases of dementia were seen in the placebo group vs 11 in the actively treated group. A breakdown according to the type of dementia is presented in the **Figure**. Active treatment reduced the rate of dementia by 50%, from 7.7 to 3.8 per 1000 patient-observation years ($P=.05$).

Thus, when over-viewing the results of these 3 randomized placebo-controlled trials, the dihydropyridine CCB nitrendipine so far has emerged as the only first-line antihypertensive drug exhibiting a statistically valid potential of preventing dementia, reducing its incidence by half.

Such a preventive action of a (lipid-soluble) dihydropyridine CCB could be reconciled with views on the pathogenesis of dementia,^{22,26,27} in which intracellular neuronal surfeit of calcium with aging is considered to be a prime mover in elaborating a veritable cascade of neurotoxic precursors of degenerative and vascular dementias.

But, while the theoretical basis for such a pattern of pathogenesis is being developed, its therapeutic cor-

ollary in terms of calcium channel blockade should be examined in more detail, for various reasons. First, the Syst-Eur substudy, although statistically significant, is based on relatively few patients. Second, some studies^{28,29} have indicated that CCBs might be far from ideal when compared with the incidence of cognitive impairment during other antihypertensive drug regimens. However, the latter studies lacked a well-founded trial plan and had the bias of confounding by indication, a particular feature in the use of CCBs because they are a treatment of choice in patients with exaggerated cardiovascular risk.³⁰

We believe there is a compelling reason for initiating a new randomized therapeutic hypertension trial focusing on cognitive function and the occurrence of dementia and comparing the specific efficacies of the various main drug classes in this regard. Such a trial is being prepared under the acronym DEPHY (Dementia Prevention in Hypertension) by the European Working Party on High Blood Pressure in the Elderly.

CONCLUSIONS

The attempt to analyze a possible association between hypertension and dementia has led into a maze and toward a challenge. A challenge, because a causal relation might offer a unique opportunity to influence the catastrophic process of dementia in elderly patients with hypertension, representing one third of the population aged 70 years and older. And a maze, in view of the confusing experience regarding the complicated nature of an entanglement, if any, between the 2 disease entities. We had to help ourselves with historical data, for the simple reason that on principle no hypertensive patient should henceforth be left untreated, except through his or her own volition.

Fortunately, we have been able to sample plenty of relevant historical data based on longitudinal observational studies, most of them reported in recent years. Despite some inconsistencies between these studies, a common picture seems to emerge, in that hypertension becoming manifest at a relatively early age tends to presage the occurrence of

cognitive impairment later. The interval between the 2 developments appears to be extremely variable, extending from a mere few years to a lag phase of some 2 decades or more. Such variations apparently do not only depend on natural history but are also influenced by the design of such follow-up studies, particularly for planned repeated-visit intervals. Such arbitrary periods, taken together with different age cutoffs, have thwarted our attempts to integrate the temporal relations among these studies. The issue has been complicated further by a paradoxical decline in blood pressure shortly preceding the onset of overt Alzheimer disease in very elderly patients with hypertension. Nevertheless, our assessment still seems to indicate a role for hypertension in a more or less distant elaboration of impaired cognition and dementia, whether of vascular or degenerative origin.

This takes us to the question of whether antihypertensive treatment may ameliorate the prospects of cognitive function in hypertensive patients in the future. This could admittedly be a mere theoretical issue because of the established need to treat hypertension anyway, with a view on the containment of "organic" cardiovascular sequelae. We nevertheless believe that a positive effect on dementia prevention would be a major step forward in the interest of public health by creating a general awareness of the sheer possibility of obviating dementia through antihypertensive drug treatment.

The evidence obtained so far must be judged as still being ambiguous. Two longitudinal observational studies^{23,24} encompassing a subgroup of routinely treated patients with hypertension by non-specified regimens have shown a reduced relative risk of 0.6 compared with nontreated patients with hypertension in an aging population. This is a promising result, but one that should be corroborated by properly conducted studies in which antihypertensive medications have been properly apportioned in a randomized fashion vs placebo-based "treatment." Unfortunately, a mere 3 properly administered prospective therapeutic trials in hypertensive populations have paid atten-

tion to cognitive function: the Systolic Hypertension in the Elderly Program, the Medical Research Council trial, and the Syst-Eur trial. The first 2, using diuretics or β -blockers as the first-line drug, failed to demonstrate any substantial effect of treatment on cognition. By contrast, the third trial (Syst-Eur) actually achieved a reduction of the number of patients exhibiting dementia by half. The primary drug in that trial happened to be a dihydropyridine CCB, nitrendipine. A particular protecting mechanism for prevention of mental deterioration could possibly be tied in with prevalent concepts about the genesis of degenerative dementia. Nevertheless, these findings may constitute a rather slim basis for advocating a universal preventive policy.

The resulting ambiguity is simply intolerable from the viewpoint of public health worldwide and should not be allowed to continue. Hence our call for a broadly based comparative antihypertensive trial (the Dementia Prevention in Hypertension trial) encompassing a focus on assessment of cognitive function on top of registering somatic cardiovascular events.

In the meantime, general hypertension care physicians should be encouraged to incorporate the Mini-Mental State Examination method into their diagnostic arsenal.

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