



# Searching for a link between calcium-channel blockers and cognitive function

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Until recently, physicians tended not to treat hypertension in older people. Opinion held that high blood pressure was a useful adaptation to maintain flow in rigid arteriosclerotic arteries and that treatment with antihypertensive drugs would cause postural hypotension and confusion.<sup>1</sup> Well-controlled trials have now demonstrated that treating hypertension in elderly patients reduces the risk of cardiovascular disease and death from this cause.<sup>2-4</sup> In fact, the largest reduction is among those at least 75 years of age.<sup>5</sup>

Treatment of hypertension is the most important method available to reduce the incidence of stroke.<sup>3,6</sup> It has been estimated that a reduction in diastolic blood pressure of as little as 2 mm Hg would result in a 15% reduction in the risk of stroke and transient ischemic attacks.<sup>7</sup> Treatment of isolated systolic hypertension produces equally significant reductions in the incidence of stroke.<sup>4</sup> The reduction of death from cardiovascular disease in the past 20 years is due largely to better treatment<sup>8</sup> and may be improved further with attention to subgroups, such as those with hyperlipidemia.<sup>9</sup> But in spite of increasing public awareness and an expanding array of antihypertensive medications, hypertension remains a leading cause of cardiovascular disease and death. Studies relating to any aspect of this important health problem deserve close scrutiny.

In this issue (page 501) Colleen J. Maxwell and colleagues<sup>10</sup> examine the effects that one class of drugs for the treatment of hypertension, the calcium-channel blockers (CCBs), might have on cognitive function in elderly patients. They were prompted to analyse data from the Canadian Study of Health and Aging (CSHA) by a report that patients using CCBs had worse cognitive function and greater leukoaraiosis than those using  $\beta$ -blockers.<sup>11</sup>

The Canadian Study of Health and Aging is a population-based prospective study of 10 623 people 65 years of age and older, who were initially interviewed between February 1991 and May 1992. Most lived in the community, and 1225 resided in institutions. All subjects underwent a standardized interview including a Modified Mini-Mental State (3MS) examination (scale 0 to 100). The subjects were classified as cognitively normal, cognitively impaired but not demented or demented (according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*). The subjects were reassessed in 1996/97.

Maxwell and colleagues analysed data for the 509 subjects identified at baseline as not having dementia, who were using one or more antihypertensive medications, and who had a history of hypertension. Of that group, 276 had died or were otherwise unavailable for follow-up or one of their 3MS scores was missing. The subjects were classified according to the classes of drugs they were receiving: CCBs,  $\beta$ -blockers, angiotensin-converting-enzyme (ACE) inhibitors, or thiazide diuretics or other antihypertensive agents. The 28 subjects who were using loop diuretics were excluded on the assumption that they were more seriously ill. This left a total of 205 subjects for analysis, of whom 68 were taking CCBs, either as monotherapy ( $n = 39$ ) or in combination with other antihypertensive drugs ( $n = 29$ ). The mean duration of therapy for these subjects was 34.6 months. A decline of 10 points or more on the 3MS scale was considered clinically significant. After adjustment for selected covariates, the subjects using CCBs were considered to have a significantly greater risk for cognitive decline than those using other antihypertensive drugs. An inverse relation was found for a small subgroup using nitrates.

The duration of treatment was short, the number of subjects was small, the variables were numerous and the confidence limits were wide. The definition of significant cognitive change was an arbitrary quantity on an infrequently used scale. Imaging studies that might have documented otherwise undetected focal brain lesions had not been performed as part of the Canadian Study of Health and Aging. The authors are therefore cautious in their conclusions, stating that their findings are consistent with those of previous reports.<sup>11</sup> They suggest further trials to examine associations between treatment of hypertension, changes in blood pressure and cognitive function in elderly patients. What might those associations be?

There are conflicting reports about a possible association between blood pressure and cognition. The Framingham study found a modest inverse relation.<sup>12</sup> A report from Britain concluded that treatment of moderate hypertension with diuretics or  $\beta$ -blockers was unlikely to influence, for better or for worse, subsequent cognitive function.<sup>13</sup> A European study reported a lower incidence of dementia in elderly patients with systolic hypertension treated with antihypertensive drugs, including CCBs.<sup>14</sup>

Investigators should be cautious interpreting imaging



changes in cerebral white matter (leukoaraiosis) as a marker for cerebrovascular disease and cognitive decline. Leukoaraiosis refers to bilateral patchy or diffuse areas of hypoattenuation (on CT) or hyperintensity (on  $T_2$ -weighted MRI) in the cerebral white matter. The most common risk factor for this condition is aging. However, the pathogenesis of leukoaraiosis and its clinical significance in individual patients remains unclear.<sup>15</sup>

The effects of calcium antagonists on cognitive function and dementia remain speculative. Future work may shed light on the matter. In the meantime, practitioners faced with the need to treat hypertension in elderly patients can be advised that ACE inhibitors are the agents of choice in patients with type I and probably type II diabetes.<sup>16</sup> For most other hypertensive patients, current guidelines recommending diuretics and  $\beta$ -blockers as first-line therapy should be supported. Other classes of medications should be reserved for patients whose condition is refractory and those with severe hypertension.<sup>17</sup>

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## References

- McWhinney IR. *A textbook of family medicine*. New York: Oxford University Press; 1989.
- Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2. Short term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet* 1990;335:827-38.
- Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;304:405-12.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-64.
- National Center for Health Statistics. *Health, United States, 1990*. Hyattsville (MD): US Public Health Service; 1991. p. 85. Department of Health and Social Services publ no. (PHS) 91-1232.
- Kannel WB, Dawber TR, Sorlie P, Wolfe PA. Components of blood pressure and risk of atherothrombotic brain infarction: the Framingham study. *Stroke* 1976;4:327-31.
- Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med* 1995;155:701-9.
- Mosterd A, D'Agostino RB, Silbershatz H, Sytowski PA, Kannel WB, Grobbee DE, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. *N Engl J Med* 1999;340:1221-7.
- Perreault S, Dorais M, Coupal L, Paradis G, Joffres MR, Grover SA. Impact of treating hyperlipidemia or hypertension to reduce the risk of death from coronary artery disease. *CMAJ* 1999;160:1449-55.
- Maxwell CJ, Hogan DB, Ebly EM. Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging. *CMAJ* 1999;161(5):501-6.
- Heckbert SP, Longstreth WT, Psaty BM, Murros KE, Smith NL, Newman AB, et al. The association of antihypertensive agents with MRI white matter findings and with modified mini-mental state examination in older adults. *J Am Geriatr Soc* 1997;45:1423-33.
- Farmer ME, Kittner SJ, Abbott RD, Wolz MM, White LR. Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: the Framingham Study. *J Clin Epidemiol* 1990;43:475-80.
- Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. *BMJ* 1996;312:800-5.
- Forette F, Seux ML, Staessen JA, Lutgarde T, Birkenhäger WH, Babarskiene MR, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352:1347-51.
- Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis. A review. *Stroke* 1997;28:652-9.
- Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff MS, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. *N Engl J Med* 1998;338:645-52.
- Captopril Prevention Project (CAPPP) Study Group. Effect of angiotensin-converting-enzyme inhibitor compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-6.

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