Hypertension

The Effects on Dementia of Long-Term Treatment of Hypertension

Reviewed by Michael A. Weber, MD

SUNY Health Science Center at Brooklyn, Brooklyn, NY

[*Rev Cardiovasc Med.* 2003;4(3):197–198]

An interesting outcome of the original Systolic Hypertension in Europe (Syst-Eur) study was a 50% reduction in incident cases of dementia.[1] This observation, though, was based on a total of only 32 events, largely because this large-scale, double-blind trial was stopped early when it was observed that actively treated hypertensive patients had a sharply lower incidence of stroke and other major cardiovascular outcomes than patients in the untreated control group. After terminating the trial, the investigators decided to offer the same antihypertensive regimen used in the study to all patients, including those previously receiving placebo, and to continue the follow-up for at least an additional 2 years.

The Prevention of Dementia with Antihypertensive Treatment: New Evidence from the Systolic Hypertension in Europe (Syst-Eur) Study

Forette F, Seux ML, Staessen JA, et al.

Arch Intern Med. 2002;162:2046–2052.

The original cohort in this trial had isolated systolic hypertension (systolic blood pressure [BP] ≥ 160 mm Hg and diastolic BP < 95 mm Hg). The treatment regimen in the study, continued into the extended follow-up, was based on the calcium channel blocker, nitrendipine (which could be titrated from 5 mg to 40 mg daily as required to reduce systolic BP to < 160 mm Hg). If needed, enalapril (5–20 mg) or hydrochlorothiazide (12.5–25 mg) or both could be added. There were 1485 patients in the original active treatment group and 1417 patients in the original placebo group. The duration of treatment was increased from an average of 2.0 years to 3.9 years in this follow-up protocol.

Despite full access to treatment, the former control patients never achieved the same blood pressure reduction as the original treated group; at the end of the main study, the BP difference was 7.0/3.2 mm Hg; by the end of the follow-up, there was still a difference of 4.2/2.9 mm Hg. This difference probably reflected the fact that a higher proportion of the original active treatment group remained on drug therapy than the patients who were allocated to drugs at the start of the extension period. The diagnosis of dementia in this study was based simply on a reduction in the score of the Mini-Mental State Examination (MMSE)[2] to 23 or below.

Compared with the 32 total events that occurred by the end of the original double-blind phase, the extended period now increased the total to 64, of whom 41 had Alzheimer's disease. The results remained as dramatic as in the previous observation, with 43 diagnoses of dementia in the original control group and only 21 in the original treatment group ($P < .001$). This translated to a difference in incidence between these two groups of 7.4 vs 3.3 events per 1000 patient-years. The original antihypertensive agent, nitrendipine, was associated with a hazard ratio of 0.38 (95% confidence interval [CI]: 0.23-0.64, $P < .001$). The investigators estimated that, based on these results, treatment of a thousand older patients with systolic hypertension for 5 years would prevent 20 new cases of dementia.

The results of this study have broad implications that go well beyond hypertension, particularly as dementia is emerging as one of the major clinical, social, and economic issues in our aging population.

These results have broad implications that go well beyond hypertension, particularly as dementia is emerging as one of the major clinical, social, and economic issues in our aging population.[3] This study is by no means the first to demonstrate that antihypertensive therapy can effect changes in cognitive function and prevent progression to frank dementia. Drugs that block the renin–angiotensin system, including the angiotensin receptor blockers, as well as calcium channel blockers, have been shown to provide beneficial effects. Hypertensive patients are more likely than people with normal blood pressure to develop dementia. But it seems likely that the benefit of antihypertensive therapy may involve mechanisms beyond reduction of blood pressure alone, for there have been differences between drugs in their ability to protect cognitive function. Nor is hypertension the only cardiovascular risk factor that is associated with adverse central effects. High cholesterol levels also appear to be associated

with poor outcomes, and effective treatment of lipid disorders has been shown to retard progression of cognitive decline. Interestingly, anti-inflammatory agents also can produce benefits, suggesting that any type of intervention that can affect the atherosclerotic process has the potential for providing benefits in the central nervous system.

It is slightly unexpected that the antihypertensive therapy in the Sys-Eur trial was at least as effective in preventing Alzheimer's disease as in preventing vascular dementia. Of course, accurate diagnostic discrimination between these two types of dementia is not always possible, and it seems likely that they may to some extent have common pathophysiologic mechanisms. Clinical trialists have already noted the potential importance of cardiovascular therapy in preserving intellectual function, and a number of ongoing trials, in such areas as hypertension or the protection of high-risk cardiovascular patients, are already including dementia as an important clinical endpoint. Because the Mini-Mental State Examination is relatively easy to apply, even by inexperienced observers, one of the lessons from this research is that clinicians should be encouraged to use this instrument for evaluating their aging patients on a regular basis. Clearly, any signs that patients have early reductions in their MMSE scores should be regarded as a strong incentive to start or upgrade management of cardiovascular risk factors. ■

References

1. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet*. 1998;352:1347–1351.
2. Gagnon M, Letanneur L, Darigues JF, et al. The validity of the Mini-Mental State Examination as a screening instrument for cognitive impairment and dementia in French elderly community residents. *Neuroepidemiology*. 1990;3:143–150.
3. Fratigliani L, De Ronchi D, Aphero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging*. 1999;15:365–375.