EDITORIAL

Antihypertensive treatment and dementia

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Dementia is a syndrome of global cognitive decline which intervenes with social and occupational functioning. The two most common dementias are Alzheimer's disease (AD), caused by neurodegeneration, and vascular dementia, caused by cerebrovascular disease. These two causes often co-occur (often referred to as "mixed dementia"), especially after the age of 80. Dementia is common in the elderly and constitutes one of the largest burdens for individuals and society. Its prevalence increases from around 3% at the age of 70 to 30% at the age of 85. It can be expected that the number of demented in the world will increase from less than 40 million in 2005 to more than 130 million in 2050, mainly due to an increasing number of elderly individuals, especially those aged >80 years. It is therefore important to find ways of preventing dementia.

Since the mid 1990s, a large number of observational studies have reported an association between previous high blood pressure and later development of dementia, including Alzheimer's disease.[1,2,3] High mid-life blood pressure has also been related to the presence of senile plaques and neurofibrillary tangles, the hallmarks of AD in the brain, in late life.[4] At the same time, observational population studies suggest that the use of antihypertensive drugs may reduce the incidence of AD and dementia.[2,5,6] Furthermore, it is reported that previous high blood pressure is only related to late-life dementia in those not on antihypertensive treatment.[3]

Five antihypertensive trials with dementia as secondary end-points have been conducted.[7-12] All these trials observed significant reductions in the primary cardiovascular outcomes, but only the Syst-Eur (Systolic Hypertension in Europe) trial[8] reported a reduction in the incidence of dementia in the treatment group. However, only 32 persons developed dementia in this trial. In the SCOPE trial, a secondary analysis showed that the treatment group had less cognitive decline than the placebo group among those with mild cognitive impairment at baseline.[9] The first trials were mainly conducted among individuals aged <80 years, where risk for dementia is low.[12] Last year, results from HYVET (The Hypertension in the Very Elderly Trial) were published. This was a double-blind placebo controlled study conducted on patients aged ≥80 who had systolic hypertension.[13] In this age group, dementia incidence is very high. The HYVET trial had to terminate early when interim analyses showed reduction in both stroke and total mortality in actively treated patients. However, the cognitive function substudy[7], found no statistical differences between treatment and placebo groups regarding dementia incidence or cognitive decline. Thus, the results of the HYVET trial suggest that treatment of systolic hypertension is indicated also in very elderly individuals to decrease the risk of stroke and total mortality, while short-term treatment shows no effect on the incidence of dementia.

Several methodological factors might explain the lack of beneficial effects on dementia incidence in antihypertensive trials.[12] First, all trials were on short-term treatment, with follow-ups between 2 and 5 years, while observational studies report that blood pressure is increased 5–15 years before dementia onset, and then decreases approximately 5 years before dementia onset.[1,2,3] Cross-sectional studies and studies with short follow-ups (i.e. <5 years) report associations between low blood pressure and prevalent or incident dementia. This low blood pressure is probably secondary to the brain changes occurring in dementia disorders, which may affect blood pressure regulating areas.[2] Thus, lengths of follow-up conducted in trials might have been too short to detect an effect on the incidence of dementia. Therefore, no conclusions can be made about the effects of long-term antihypertensive treatment on dementia incidence. For ethical reasons, it may not be possible to conduct long-term placebo-controlled studies in the future, due to the benefit of treatment on cardiovascular outcomes. Other methodological factors that might explain the lack of treatment effect on dementia incidence includes that antihypertensive trials have

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Received: August 12, 2009.
Accepted: August 12, 2009.
Conflict of interest: Ingmar Skoog received consultant fee from AstraZeneca during the SCOPE trial. Ingmar Skoog has been on Speaker's Bureau for Shire, AstraZeneca, JansenCilag, Pfizer, Novartis, Esai, Hoechst Marrion Rousell and GE.
Pol Arch Med Wewn. 2009; 119 (9): 524-525

mainly included mentally very healthy participants at baseline. This group is expected to have a low short-term incidence of dementia and a ceiling effect may occur when change in test score is measured. Other methodological issues include practice or learning effects, selective drop-out in relation to dementia, and difficulties to diagnose dementia reliably in large trials.[12]

No antihypertensive trial has been conducted in hypertensives with Alzheimer's disease. Although individuals with Alzheimer's disease as a group have lower blood pressure than nondemented controls, a large proportion may still have hypertension. Two observational studies report that cognitive decline was faster in Alzheimer patients with hypertension at baseline[14,15], and in one of these studies those on antihypertensive drugs had a slower decline[15]. Observational studies also report that Alzheimer patients treated for hypertension have better cognitive function than those without.[16,17] This indicates that antihypertensive treatment may be beneficial on cognition in demented individuals, but the results need to be taken cautiously until confirmed in randomized controlled trials. However, it could be discussed whether randomized controlled trials with antihypertensives are ethical in demented individuals with hypertension, due to the beneficial effect of antihypertensives on cardiovascular outcomes shown in large trials.

There are some important clinical implications of these findings. First, antihypertensive trials in the elderly, including those aged >80 years, show that short-term antihypertensive treatment is beneficial in relation to stroke and total mortality. It is thus important to detect and treat hypertension in the elderly irrespective of whether it prevents dementia or not, as it might prevent cardiovascular disease. Second, antihypertensive treatment seems to be safe in relation to brain function in the elderly. There is a common belief among many doctors that treatment of hypertension in the very elderly might have negative effects on brain function by reducing cerebral blood flow. In fact, this common concept has no empirical support. No trial so far has found that treatment of hypertension increased risk of dementia or cognitive decline. Furthermore, observational population studies suggest that the use of antihypertensive drugs may reduce the incidence of AD and dementia[2,5,6], and no study reports that antihypertensive treatment increases risk. Finally, most individuals with hypertension or dementia are not detected by the health care system. Hypertension is important to detect due to its effect on cardiovascular health. Cognitive impairment and dementia is important to detect in elderly hypertensives due to its potential impact on the patient's compliance with treatment. It also needs to be emphasized that when detected, hypertension needs to be treated also in demented individuals.

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