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Treatment of isolated systolic hypertension and dementia prevention in older patients

Results of the Systolic Hypertension in Europe Trial (SYST-EUR) vascular dementia project

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Aims The purpose of the vascular dementia project, set up in the framework of the double-blind placebo-controlled Systolic Hypertension in Europe (SYST-EUR) trial, was to investigate whether antihypertensive drug treatment could reduce the incidence of dementia.

Methods and Results The study was run on non-demented patients, at least 60 years old, with isolated systolic hypertension. Treatment was initiated with nitrendipine (10–40 mg . day^{-1}) possibly associated with enalapril (5–20 mg . day^{-1}) and/or hydrochlorothiazide (12·5–25 mg . day^{-1}). Cognitive function was assessed by the Mini Mental State Examination (MMSE). The diagnosis of dementia was based on the DSM-III-R criteria. The aetiology of dementia was established using either the Modified Ischaemic Score with brain imaging or the Hachinski score. The median time of follow-up was 2·0 years. By intention-to-treat, the incidence of dementia was reduced by 50% from 7·7 per 1000 patients-years in the placebo group (number of patients 1180) to 3·7 cases per 1000 patient-years in the active treatment one (n=1238) (21 vs 11 patients, P=0·05). At the last available evaluation, systolic and diastolic blood pressure were 8·3 mmHg and 3·8 mmHg lower (P<0·001) in the active-treatment group, but on average the MMSE scores remained stable in both groups.

Conclusion In older people with isolated systolic hypertension, antihypertensive treatment started with nitrendipine reduced the incidence of dementia.
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Key Words: Dementia, systolic hypertension, antihypertensive treatment, calcium channel blocker.

Introduction

Dementia is an important cause of disability in older people. Alzheimer's disease and vascular dementia are the leading causes, which represent 50–70% and 8–20% of all cases, respectively[1]. Hypertension is a powerful risk factor for vascular dementia, although not necessarily by causing stroke[2]. Moreover, in the Rotterdam study, hypertension and other indicators of atherosclerosis were also associated with Alzheimer's disease[3]. Nevertheless, antihypertensive treatment initiated with chlortalidone did not prevent dementia in the

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placebo-controlled Systolic Hypertension in the Elderly Program (SHEP)[4].

The Vascular Dementia Project was set up in the framework of the double-blind placebo-controlled Systolic Hypertension in Europe (SYST-EUR) Trial[5,6]. Its principal goal was to investigate whether antihypertensive treatment starting with the calcium-channel blocker nitrendipine could reduce the incidence of dementia in older patients with isolated systolic hypertension.

Methods

The protocol of the SYST-EUR trial, described elsewhere, was approved by the Ethics Committees of all participating centres[5]. Eligible patients had to be non-demented and comply with the following criteria: (1) age, 60 years or over, (2) sitting systolic blood pressure, 160–219 mmHg with diastolic blood pressure below 95 mmHg, (3) standing systolic blood pressure, 140 mmHg or more, (4) informed consent, (5) availability for long-term follow-up. The blood pressure criteria for entry were based on the average of six sitting and six standing readings, i.e. two in each position at three baseline visits 1 month apart on single-placebo treatment. After stratification by centre, sex and previous vascular complications, patients were randomized to double-blind treatment with active medication or placebo by means of a computerized random function. Active treatment was initiated with nitrendipine (10–40 mg . day^{-1}) with the possible addition of or replacement by enalapril (5–20 mg . day^{-1}), hydrochlorothiazide or both drugs. Patients in the control group received matching placebo tablets. The study medications were stepwise titrated and combined to reduce the sitting systolic blood pressure by 20 mmHg or more to less than 150 mmHg. Patients withdrawing from double-blind treatment remained in open supervised follow-up. The SYST-EUR trial stopped on 14 February 1997 because at the second of four planned interim analyses, according to predefined stopping rules, a significant benefit for stroke, the primary end-point of the main trial, had been reached. Active treatment reduced the incidence of strokes by 42% (P=0·003) from 13·7 to 7·9 events per 1000 patient-years[7].

SYST-EUR investigators could opt to enroll their patients in the Vascular Dementia Substudy[6]. To avoid bias in recruitment and follow-up, participating centres had to evaluate all their patients at baseline and at annual examinations during follow-up using the Mini-Mental State Examination (MMSE)[8]. This widely used test for cognitive impairment assesses orientation in time and space, instantaneous recall and short-term memory, attention and calculation, constructional capacities and language. The original MMSE was translated into 11 languages (Bulgarian, Dutch, Finnish, French, Greek, Hebrew, Italian, Polish, Portuguese, Russian and Spanish) and validated by translation back into English. The 30 items were each scored by one point if successfully completed; missing items received a score of zero. Patients who were unable to complete the 30 items because of physical or visual handicap received a proportional score with the total number of items answered as the denominator. As specified a priori in the protocol, incapacitated patients who completed less than 25 items were excluded from analysis. In keeping with the generally accepted convention, a score of 23 points or less indicated cognitive impairment and led to further diagnostic evaluation to ascertain the presence and type of dementia[9]. These diagnostic tests were also performed if, at any follow-up visit, symptoms reported by the patient or his family and clinical signs observed by the investigator suggested incipient cognitive impairment. The final diagnosis of dementia was then based on the criteria of the Diagnostic and Statistical Manual of Mental Disorder (DSMIII-R)[10]. The aetiology of dementia relied on the Modified Ischaemic Score which includes a computerized tomographic (CT) brain scan[11]. If a CT scan could not be performed, the Hachinski Score replaced the Modified Ischaemic Score to differentiate vascular from degenerative disease[12]. Investigators were trained to administer these tests and adhered to strictly standardized diagnostic criteria. Two independent neuroradiologists checked the CT scans. Finally, all demented cases were validated by a blinded review board. Other clinical measures used in the analysis were the level of education expressed as the age at which full-time school education stopped, smoking and drinking habits and the activities of daily living (ADL) scored by the Katz Index[13]. Cardiovascular complications, i.e. angina or myocardial infarction, left ventricular hypertrophy or congestive failure, retinopathy, renal insufficiency and stroke or transient ischaemic attack and previous antihypertensive treatment were also determined according to medical reports or by interview.

Statistical analysis

On the basis of epidemiological studies, the original calculations for the sample size assumed a rate of dementia in the placebo group of 16 cases per 1000 patient-years[14]. A total of 3000 patients with an average follow-up of 5 years was required to test the two-sided hypothesis of a 40% change in the incidence of dementia with 1% significance and 90% power.

Database management and statistical analysis were performed using appropriate SAS software, version 6·12 (SAS Institute Inc.). Only after the trial had stopped was the null hypothesis tested by an intention-to-treat and by a per-protocol analysis. The latter included only the data collected while the patients were still on double-blind medication. Means were compared by the standard normal-z test and the proportions by the χ^2 statistic. Correlations between the changes in the MMSE scores and blood pressure were calculated using the differences from baseline to the last available follow-up measurement. The incidence of dementia was analysed using

Table 1 Baseline characteristics

Characteristic	Treatment group	
	Placebo (n=1180)	Active treatment (n=1238)
Mean (± SD)		
Age (years)	69·9 (± 6·2)	69·9 (± 6·5)
Body-mass index (kg . m^{-2})	27·0 (± 4·0)	27·0 (± 4·2)
Sitting blood pressure (mmHg*)		
Systolic	173·4 (± 10·1)	173·5 (± 10·1)
Diastolic	86·0 (± 5·7)	86·1 (± 5·6)
Age when leaving school	16·2 (± 4·4)	16·4 (± 4·7)
Median MMSE† score (range)	29 (15–30)	29 (18–30)
Number (%) of patients with characteristics at randomization		
Women	767 (65·0%)	822 (66·4%)
Previous antihypertensive medication	476 (40·3%)	467 (37·7%)
Cardiovascular complications	337 (28·6%)	340 (27·5%)
Atrial fibrillation	44 (3·7%)	46 (3·7%)
MMSE† score equal to 30	350 (29·7%)	360 (30·4%)
MMSE† score of 23 or less	23 (1·9%)	24 (1·9%)

*Average of six sitting measurements, i.e. two at three baseline visits 1 month apart.
†MiniMental State Examination.

Kaplan–Meier survival function estimates and the log-rank test.

Results

A total of 3162 patients was enrolled in the Vascular Dementia Substudy at 106 centres from 19 European countries. Of these, 744 were excluded because they had accumulated less than 1 year of follow-up and had a cognitive evaluation only at baseline (n=692), because a baseline evaluation was not available (N=20), because a DSM-IIIR evaluation had not been performed in patients with a MMSE score at baseline of less than 23 (n=16), because patients with dementia before enrollment were diagnosed only after randomization (n=9) or because more than five MMSE items remained unanswered (n=7). Thus, for the present analysis, the number of patients totalled 2418 (1589 women, 829 men). At randomization, the patients of the placebo group (n=1180) and of the active-treatment group (n=1238) had similar characteristics (Table 1). The median time of follow-up in the intention-to-treat analysis was 2·0 years. The number of patient-years was 2737 and 2885 in the placebo and active treatment groups, respectively.

At the last available measurement, the sitting systolic blood pressure had fallen by a mean (± SD) of 13·4 (± 16) mmHg and 21·7 (± 16·2) mmHg in the placebo and active groups, respectively (Table 2); the corresponding values for the sitting diastolic blood pressure were 2·6 (± 7·8) mmHg and 6·4 (± 8·3) mmHg.

To assess the impact of antihypertensive treatment on cognitive functions, the MMSE scores of the patients treated with the active drugs and with placebo were compared at the first, second, third, fourth and last available visit of follow-up. Because the results were the same for all analyses, only those for the last available visit will be reported. A follow-up examination took place in 1062 (90%) patients of the placebo group and 1108 (89·5%) of the active-treatment group (Table 2). Compared with baseline, the MMSE scores decreased slightly, but the between-group difference remained non-significant (Table 3). The last median MMSE score was 29 (P_5–P_{95} interval 24–30) in both groups. In the placebo group, the MMSE changes were correlated with those in systolic (P=0·001) and diastolic (P=0·04) blood pressure (Table 4). Active treatment suppressed the significant correlation with the changes in systolic blood pressure (P=0·53) and inverted the correlation with diastolic blood pressure (P=0·01). These associations were adjusted for age, sex, level of education, previous cardiovascular complications, antihypertensive treatment before randomization and smoking and drinking habits at entry.

By intention-to-treat, there were 21 cases of dementia (15 Alzheimer's disease, two vascular dementia and four

Table 2 Follow-up status

Status	Treatment group	
	Placebo (n=1180)	Active treatment (n=1238)
Patients with MMSE	1060	1104
MMSE during double-blind follow-up	861	1000
MMSE during open follow-up	199	104
Patients without MMSE	120	134
Cognitive evaluation not performed	77	84
Only DSM III-R performed	2	4
Deaths	13	8
Non-supervised open follow-up	20	20
Lost to follow-up*	8	18

*Patients without follow-up data for more than one year.

Table 3 Mean (± SD) changes in blood pressure and MMSE scores at the last available visit

Measurement	Placebo (n=1060)	Active treatment (n=1104)	Difference (placebo minus active) (95% CI)*	*P*-value
Changes in blood pressure (mmHg)				
Systolic	−14·8 ± 16·9	−24·0 ± 15·3	−9·3(−10·6; −7·9)	<0·001
Diastolic	−2·9 ± 8·1	−7·1 ± 8·5	−4·2(−4·9; −3·5)	<0·001
Changes in MMSE scores (points)	0·01 ± 2·27	0·009 ± 1·87	+0·008(−0·10;0·25)	0·59

*95% Confidence interval.

Table 4 Correlations† between changes in MMSE scores and changes in systolic and diastolic blood pressure (BP) at last available visit

	Placebo (n=1060)		Active treatment (n=1104)		*P*-value for between-groups difference in slope	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
Correlation coefficient	0·98**	0·060*	0·023	−0·073*		
Slope ± SE‡	−0·199 ± 0·062	−0·048 ± 0·025	−0·066 ± 0·088	0·114 ± 0·047	0·045	0·002

Significance of correlations: $*P \leq 0{\cdot}05$; $** \leq 0{\cdot}01$.
†Adjusted for sex, age, level of education and cardiovascular complications, antihypertensive treatment and alcohol intake at randomization.
‡Slopes ± SE are expressed as the changes in the MMSE score that would be associated with the mean change in systolic and diastolic blood pressure.

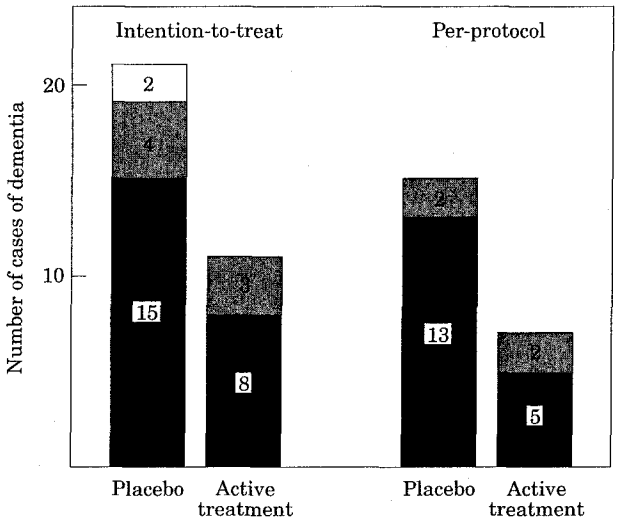

Figure 1 **Aetiology of dementia. □=vascular dementia; ▨=mixed dementia; ■=Alzheimer's dementia.**

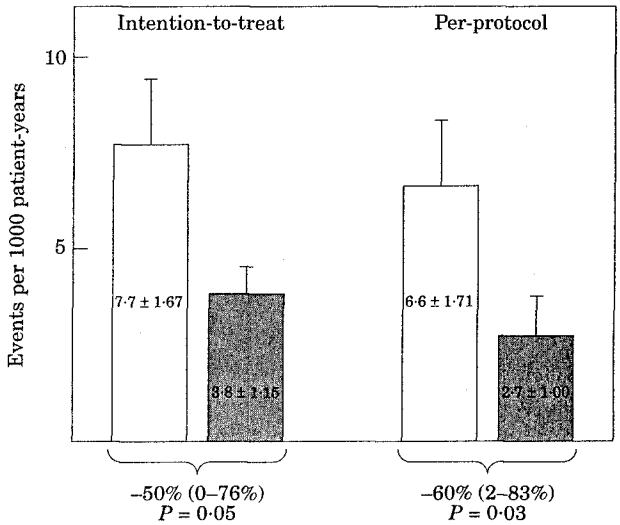

Figure 2 **Incidence of dementia. □=placebo; ▨=active treatment.**

mixed dementia) in the placebo group and 11 cases of dementia (eight Alzheimer's disease and three mixed dementia) in the active-treatment group (Fig. 1). Thus active treatment reduced the rate of dementia by 50% (95% CI 0–76%) from 7·7 to 3·8 per 1000 patient-years ($P=0{\cdot}05$) (Fig. 2).

At the last visit, 602 (60%) of the patients who stayed on double-blind medication in the active-treatment group (n=1000) and 347 (40%) in the placebo group (n=861) received only nitrendipine or its placebo as antihypertensive treatment. In the active-treatment and the placebo groups 315 (32%) and 462 (54%) received enalapril or its placebo, respectively, and 150 (15%) and 272 (32%) received hydrochlorothiazide. In the active-treatment group, the mean daily doses ± SD of nitrendipine, enalapril and hydrochlorothiazide at the last visit were 28 ± 12 mg, 13 ± 6 mg and 22 ± 5 mg, respectively.

A total of 989 patients in the placebo group and 1072 in the active-treatment group were included in the per-protocol analysis. The incidence of dementia was

reduced by 60% (95% CI 2–83%) in the active-treatment group from 6·6 to 2·7 cases per 1000 patient-years ($P=0·03$).

Discussion

Hypertension is a major risk factor for dementia. In their longitudinal survey of the Göteborg cohort, Skoog *et al.* reported that blood pressure at 70 years predicted the incidence of dementia among the 85-year-old subjects[15]. However, at the end of their follow-up, the blood pressure difference between demented and non-demented people had disappeared. Along similar lines, in a cross-sectional study Guo *et al.* found lower blood pressures in demented than in non-demented patients[16]. Physical inactivity and debilitation could explain the lower blood pressure in demented patients.

A deleterious effect of antihypertensive drugs on cognitive function has also been implicated in the relationship between hypertension and dementia. Two randomized placebo-controlled trials in the hypertensive elderly did not support this hypothesis. The Medical Research Council's trial of hypertension in older adults did not show any association between antihypertensive treatment with a diuretic or a beta-blocker and cognitive outcome (memory and attention) during a 54-month follow-up period[17]. The placebo-controlled SHEP failed to show a positive effect of diuretic treatment on cognitive function[4]. In this trial the incidence of dementia in the control group was 44 cases in 2371 patients (19%).

The randomized placebo-controlled SYST-EUR trial using the dihydropyridine nitrendipine as first line drug in older patients with isolated hypertension reported that this treatment reduced the incidence of dementia by 50% from 7·7 to 3·8 cases per 1000 patient-years. Our study did not support the findings of Heckbert *et al.* who suggested that treatment of elderly hypertensive patients with calcium channel blockers would be associated with a worsening of cognitive function[18]. However, the mode of selection of the patients and confounding by indication could explain the findings in the Heckbert study.

The mechanism of dementia prevention in our study remains speculative. The primary hypothesis was that a reduction of blood pressure would protect against vascular dementia[6]. The protective effect of antihypertensive treatment against Alzheimer's disease was unexpected. According to the results of the SHEP trial, which failed to establish a reduction of the incidence of dementia in the active treatment group (12–25 mg of chlorthalidone with the possible addition of 25–50 mg of atenolol or 0·05–0·1 mg of reserpine), lowering blood pressure per se does not necessarily protect against the development of dementia[4]. Specific neuroprotection conferred by calcium channel blockage is a hypothetical mechanism, which could explain, at least in part, the reduction of dementia, particularly of Alzheimer's disease, in the SYST-EUR trial. The latter hypothesis is supported by the abnormalities of intraneuronal calcium regulation in the brain of patients with Alzheimer's disease and in the ageing brain[19,20]. The results of therapeutic trials with nimodipine in Alzheimer's disease and vascular dementia corroborate this hypothesis[21].

In our study, the incidence of dementia in the placebo group (7·7 per 1000 patient-years) was low compared with the EURODEM study (10 per 1000 patient-years)[22]. Age dependency of the occurrence of dementia may explain the lower incidence rate in our population (≥ 60 years), which was younger than the population in the EURODEM study (≥ 65 years)[23,24]. Selection of patients who were expected to comply with the study protocol for several years is another factor explaining the low incidence of dementia in the SYST-EUR trial. The median MMSE score observed at entry in our study was high (29). Such a median score is usually found in healthy volunteers[25] and in community-dwellers without neurological or psychiatric disorder[26] but not in population-based studies[27]. Abnormalities in psychometric tests such as the MMSE are strongly related to the risk of dementia[28]. A low score is a predictor of dementia even after adjustment for age and educational level. Given the high median MMSE score at entry, our population was at low risk of dementia even if hypertension increased the risk. At the level of risk of dementia observed in the placebo group, antihypertensive treatment would prevent 19 cases of dementia in older hypertensive patients. This benefit is likely to be larger in an unselected group of people with a higher risk of dementia.

The long-term effect of antihypertensive treatment in our cohort of older patients with isolated systolic hypertension will be measured by the evaluation of cognitive function for 5 years after the end of the trial. The correlation between the incidence of cognitive impairment and dementia and the patient-years of exposure to nitrendipine will be analysed.

The SYST-EUR vascular dementia project was a concerted action of the European Union's Biomed Research Programme and was conducted under the auspices of the Fondation Nationale de Gérontologie (France). The SYST-EUR trial was carried out in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension and the World Hypertension League. The SYST-EUR trial was supported by Bayer AG (Wuppertal, Germany). The study medication was donated by Bayer AG and Merck Sharpe and Dohme Inc. (West Point PA, U.S.A.). Additional grants in support of the vascular dementia project were provided by the Belgian National Research Fund (Brussels, Belgium), Specia SA (Paris, France) and INSERM (Paris, France).

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Appendix

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