

Study on COgnition and Prognosis in the Elderly (SCOPE): Baseline Characteristics

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The Study on COgnition and Prognosis in the Elderly (SCOPE) is a multi-centre, prospective, randomized, double-blind, parallel-group study. The primary objective of SCOPE is to assess the effect of the angiotensin II type 1 (AT₁) receptor blocker, candesartan cilexetil 8–16 mg once daily, on major cardiovascular events in elderly patients (70–89 years of age) with mild hypertension (DBP 90–99 and/or SBP 160–179 mmHg). The secondary objectives of the study are to test the hypothesis that antihypertensive therapy can prevent cognitive decline (as measured by the Mini Mental State Examination, MMSE) and dementia, and to assess the effect of therapy on total mortality, myocardial infarction (MI), stroke, renal function, and hospitalization. A total of 4964 patients from 15 participating countries were recruited during the randomization phase of SCOPE, exceeding the target population of 4000. The mean age of the patients at enrolment was 76 years, the ratio of male to female patients was approximately 1:2, and 52% of patients were already being treated with an antihypertensive agent at enrolment. The majority of patients (88%) were educated to at least primary school level. At randomization, mean sitting blood pressure values were SBP 166 mmHg and DBP 90 mmHg, and the mean MMSE score was 28. Previous cardiovascular disease in the study population included myocardial infarction (4%), stroke (4%) and atrial fibrillation (4%).

Men, more often than women, had a history of previous MI, stroke and atrial fibrillation. A greater percentage of men were smokers (13% vs 6% in women) and had attended university (11% vs 3% of women). Of the randomized patients, 21% were 80 years of age. In this age group smoking was less common (4% vs 10% for 70–79-year-olds) and fewer had attended university (4% vs 7% for 70–79-year-olds). The incidence of MI was similar in both age groups. However, stroke and atrial fibrillation had occurred approximately twice as frequently in the older patients.

The patients' mean age at baseline was similar in the participating countries, and most countries showed the approximate 1:2 ratio for male to female patients. There was also little inter-country variation in terms of mean SBP, DBP or MMSE score. However, there was considerable regional variation in the percentage of patients on therapy prior to enrolment. *Key words: candesartan cilexetil, cognitive function, elderly, mild hypertension.*

INTRODUCTION

Data from two large studies carried out recently, one in the USA (NHANES III) [1] and the other in Europe (STEPHY) [2], have confirmed Framingham study evidence that the prevalence of hypertension and

associated cardiovascular risk increase with age in both men and women [3]. The risk of cardiovascular events has also been shown to be higher in elderly hypertensive patients than in younger patients with the same level of blood pressure [4]. Although both systolic (SBP) and diastolic blood pressure (DBP) increase progressively up

Table I. Comparison of events expected and prevented by antihypertensive treatment in elderly hypertensive patients and in middle-aged patients with mild hypertension [11]. The values shown are the number of events/1000 patients/5 years

Events	Middle-aged patients with mild hypertension		Elderly patients with hypertension	
	Expected	Prevented	Expected	Prevented
Cardiovascular deaths	15	4–5	120	40
Strokes	15	10	123	49
Coronary events	30	2–3	97	14

to approximately 60 years of age, DBP tends to decline thereafter [3]. As a result, isolated systolic hypertension (ISH; i.e. SBP > 140 mmHg/DBP < 90 mmHg) is the most prevalent form of hypertension in older patients, and SBP is a better predictor of cardiovascular events than DBP in the elderly [5].

It is only quite recently that the benefits of treating hypertension in the elderly have become apparent. Meta-analysis of nine randomized, controlled trials published over the period January 1980 to February 1992 involving 15 559 patients older than 59 years of age revealed a 36% reduction in stroke, a 25% decrease in coronary heart disease and a 12% reduction in all-cause mortality [6]. Several studies (STOP, SHEP, SYST-EUR and MRC elderly) have documented the benefits of antihypertensive therapy specifically among elderly patients with ISH, and showed a reduction in major cardiovascular events ranging from 17 to 40% [7–10].

Because the elderly hypertensive population may be expected to experience more cardiovascular events compared to a middle-aged hypertensive population, in absolute terms—that is, in terms of the number of events saved—antihypertensive treatment is 5–10 times more successful in elderly patients than in middle-aged patients with mild hypertension (Table I) [11]. Nevertheless, there remain a number of unanswered questions concerning the treatment of elderly patients with hypertension:

- (i) The term 'elderly' is generally used to indicate patients over the age of 60–65 years, but what are the benefits of antihypertensive therapy in patients over 80 years of age?
- (ii) Is the treatment of mild hypertension of benefit in the elderly?
- (iii) Since it has been shown that high blood pressure may be associated with subsequent development of dementia and cognitive decline in the elderly [12], can antihypertensive therapy reduce cognitive decline and the incidence of dementia?
- (iv) Is angiotensin II type 1 (AT₁)-receptor blockade an effective therapeutic strategy for improving outcomes in an elderly population with mild hypertension?

The Study on COgnition and Prognosis in the Elderly (SCOPE) has been initiated to address these questions. The study protocol has been described fully in a previous issue of this journal [13]. Briefly, SCOPE is a multicentre, prospective, randomized, double-blind, parallel-group study designed to compare the effects of the angiotensin II type 1 (AT₁) receptor blocker, candesartan cilexetil 8–16 mg once daily, versus placebo in elderly patients (70–89 years of age) with mild hypertension (defined as sitting SBP 160–179 mmHg and/or DBP 90–99 mmHg), and a Mini-Mental State Examination (MMSE) score of 24, or higher. Patients who remain at SBP 160 mmHg and DBP 90 mmHg are recommended open-label additional antihypertensive medication, starting with HCTZ 12.5 mg.

The primary objective of SCOPE is to assess the effect of candesartan cilexetil on major cardiovascular events. The secondary objectives of the study are to test the hypothesis that antihypertensive therapy can prevent cognitive decline (as measured by the MMSE) and dementia, and to assess the effect of therapy on total mortality, myocardial infarction, stroke, renal function and hospitalization. In addition, at least 1000 patients will be assessed for quality of life and health economics data. The study will also allow us to evaluate the possible influence on major cardiovascular events and cognitive function of a number of variables, including age, gender, antihypertensive treatment, previous myocardial infarction (MI) or stroke, diabetes mellitus, smoking, body mass index, hyperlipidaemia or treatment with lipid-lowering drugs, and level of education.

PATIENT CHARACTERISTICS

Overall

Patients were considered eligible for enrolment in SCOPE if they fulfilled the inclusion and exclusion criteria, as described previously [13]. A total of 4964 patients from 15 participating countries were recruited during the randomization phase, from 24 March 1997 to 20 January 1999, exceeding the original target population of 4000 (Table II). The mean age of the patients at enrolment was 76 years (Table III), reflecting the predominance of patients in the younger, 70–79-year, age group (Fig. 1).

Table II. Number of patients recruited to SCOPE per country (total n = 4964)

Country	Number
Belgium	436
Canada	68
Finland	84
France	434
Germany	617
Hungary	326
Israel	147
The Netherlands	617
Norway	418
Poland	173
Portugal	53
Spain	324
Sweden	283
UK	883
USA	101

Nevertheless, approximately one in five of the patients in the study ($n=1053$) was aged 80 years and over at randomization. The ratio of male to female patients was approximately 1:2 ($n=1787$ and $n=3177$, respectively). At randomization, mean sitting blood pressure values were SBP 166 mmHg and DBP 90 mmHg, and the mean MMSE score was 28 (maximum score 30). The distribution of SBP, DBP and MMSE at randomization is shown in Figs 2 and 3.

Just over half (52%) of all patients were receiving antihypertensive therapy at enrolment and nearly a quarter (22%) of the patient population was taking either a non-steroidal anti-inflammatory drug (NSAID) or ASA. A relatively small percentage of patients (9%) were being treated with lipid-lowering drugs, and a similar number were receiving psychopharmacological drugs (8%). The occurrence of previous cardiovascular

Table III. Baseline patient characteristics (n = 4964)

Age, years (mean)	76
Male/female (%)	36/64
Smoker (%)	9
Mean sitting BP: SBP/DBP mmHg	166/90
Mean MMSE score	28
Treated at enrolment with:	52
Antihypertensive agents (%)	
NSAID/ASA (%)	22
Lipid-lowering drugs (%)	9
Psychopharmacological drugs (%)	8
Previous MI (%)	4
Previous stroke (%)	4
Atrial fibrillation (%)	4

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction.

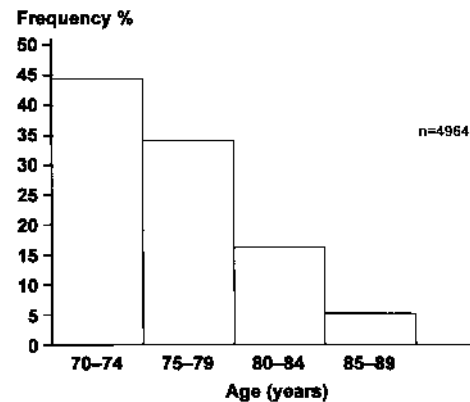


Fig. 1. Age distribution at baseline.

disease in the study population was found to be relatively low, including myocardial infarction (4%), stroke (4%) and atrial fibrillation (4%; Table 3). The vast majority of patients had been educated to at least primary school level (Table 4).

Gender-based differences in baseline characteristics. There were a number of notable differences in the baseline characteristics between the men and women randomized to the study. The men had a higher occurrence of previous MI (7.8% compared with 2.7% of women), atrial fibrillation (4.9% compared with 2.9% of women) and stroke (4.8% compared with 3.3% of women). A greater percentage of the men were smokers (13.2%) compared with the women (6.1%). Differences in the level of education between men and women were most notable at university level, with a considerably greater percentage of men who had attended university (11.1%) compared with women (3.1%). The proportion of men and women treated at enrolment was similar for most classes of medication with the exception of psychopharmacological drugs, which were being taken by 11.4% of women compared with 5.6% of men.

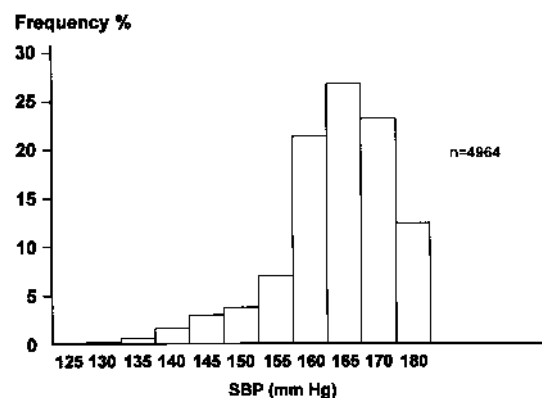


Fig. 2. Distribution of systolic blood pressure (SBP) at baseline.

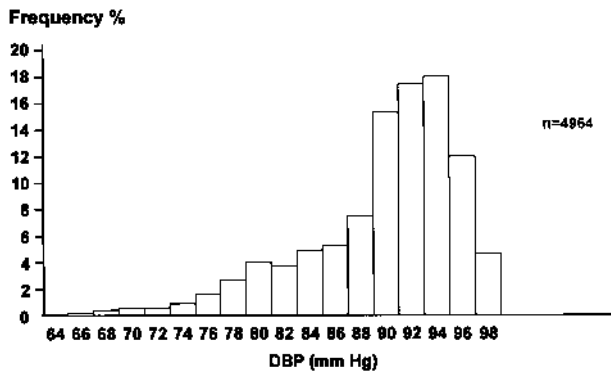


Fig. 3. Distribution of diastolic blood pressure (DBP) at baseline.

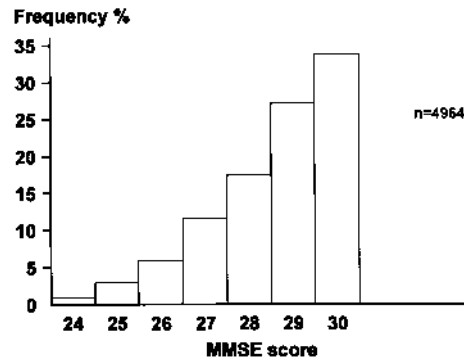


Fig. 4. Distribution of Mini Mental State Examination (MMSE) score at baseline.

Age-based differences in baseline characteristics. The SCOPE study includes a large cohort of patients of 80 years of age and older, allowing a comparison of baseline characteristics with patients in the decade below them (those in the 70–79-year-old age group). There were slightly more than twice as many smokers amongst the 70–79-year-olds (9.8%), as amongst patients 80 years of age and older (4.3%). Also, more of the younger age cohort had attended university (6.5%), compared with the older group (3.8%). The incidence of MI was similar in both groups (4.4% in the 70–79-year-olds and 4.9% in patients of 80 years of age and older). However, stroke and atrial fibrillation had occurred more frequently in the older patients (5.9% compared with 3.3% for stroke and 5.9% compared with 3.0% for atrial fibrillation).

Treatment with antihypertensive medication was similar between the age groups (52.8% for the 70–79-year-olds and 52.6% for those of 80 years of age and older). The use of NSAIDs or ASA was also similar between the two groups (23.2% in the 70–79-year-olds and 23.9% in the older group). However, more patients in the younger group used lipid-lowering agents (10.1% compared with 6.2%), while more patients in the older group were taking psychopharmacological drugs compared with patients in younger group (12.4% compared with 8.5%).

Regional variations

The mean age at baseline was similar within populations

Table IV. Education level (n = 4964)

Less than primary school (%)	12
Primary school (%)	43
Higher than primary school (%)	39
University (%)	6

from each participating country (range 74–77 years). Most countries also showed the approximate 1:2 ratio for male to female patients. There was little inter-country variation in terms of mean SBP (range 160–167 mmHg), DBP (range 86–92 mmHg) or MMSE score (range 28–29). However, considerable regional variations were seen for the percentage of patients on therapy prior to enrolment, including antihypertensive therapy (29–83%), NSAID/ASA (11–49%), lipid-lowering therapy (2–24%) and psychopharmacological therapy (1–26%).

SAMPLE SIZE AND RISK PROFILE

The original target study population was 4000, based on the incidence of clinical events in the STOP-Hypertension study [7]. This represents the calculated number of patients required in order to detect a 23% reduction in the yearly incidence of major cardiovascular events over a 2.5-year period, assuming a starting DBP of 95 mmHg. Although the actual mean baseline DBP in SCOPE is lower (90 mmHg), the study population is larger than expected (4964) and has been randomized over a longer period, thereby maintaining the power of the study.

In the baseline data, information regarding the following risk factors (according to WHO/ISH guidelines) is available: BP, age and gender, smoking habit, s-cholesterol, diabetes mellitus, obesity, s-creatinine and previous cardiovascular diseases. Thus, all patients in the study have at least one risk factor (age >65 years), and Grade 1 or Grade 2 hypertension.

EVALUATION OF COGNITIVE FUNCTION

The potential impact of antihypertensive therapy on cognitive function in SCOPE patients will be assessed using the MMSE, which has been demonstrated to be a sensitive, specific and predictive tool in measuring cognitive function and screening for dementia. The MMSE score is based on 20 clearly defined questions and tasks (which are documented in a manual developed

for this study), giving a maximum potential score of 30. Based on a comparison of the MMSE and clinical diagnosis of dementia in 85–88 year old patients [15] and information from the literature [16], a decline of four points in MMSE score has been selected to indicate dementia. Suspected cases of dementia will be further evaluated by dementia specialists in the study endpoint committee.

Patients who achieve the maximum MMSE score of 30 may have cognitive function well above the upper limit of the test, allowing them to suffer a decline in cognitive function of equivalent to the four MMSE points defined here, and yet remain above the maximum score level. However, more than 60% of the patients in the SCOPE study have an MMSE score of between 24 and 29. Hence, any decline in cognitive function in these patients will be within the detection range of the MMSE, suggesting that it will be possible in this study to evaluate the potential of antihypertensive therapy to prevent cognitive decline.

THERAPEUTIC REGIMEN

The SCOPE therapeutic regimen has been described previously and is summarized briefly here [13]. The study begins with an open, run-in period lasting 1–3 months, during which patients are assessed for eligibility and those who are already on antihypertensive therapy at enrolment are switched to hydrochlorothiazide (HCTZ) 12.5 mg once daily (o.d.). Subsequently, patients are randomized to receive either candesartan cilexetil 8 mg o.d. or matching placebo o.d. At subsequent study visits, if SBP remains >160 mmHg, or has decreased by <10 mmHg since the randomization visit, or DBP is >85 mmHg, study treatment is doubled to candesartan cilexetil 16 mg o.d. (two 8-mg tablets), or two placebo tablets. If SBP remains 160 mmHg, or DBP is 90 mmHg, despite treatment with two tablets, then the study protocol recommends the initiation of additional antihypertensive therapy, starting with HCTZ 12.5 mg.

DISCUSSION

Although the advantages of antihypertensive therapy in elderly patients with hypertension have been clearly demonstrated [6–11], there have been no specific studies to date to assess the benefits of treating those with only mildly elevated blood pressure (SBP 160–179 mmHg and/or DBP 90–99 mmHg), in terms of preventing cardiovascular events, stroke and the development of cognitive dysfunction. Currently, many such patients may go untreated, possibly resulting in earlier death, disability or hospitalization, with the associated personal, social and economic costs. The results of SCOPE will provide the necessary data to determine the value of antihypertensive therapy in this setting also in the very old patients.

The theory that elevated blood pressure may predispose patients to the development of dementia has been investigated in Sweden by Skoog *et al.* in a 15-year longitudinal study following up subjects who were non-demented at 70 years of age [13]. They found that patients who developed dementia after the age of 79 had significantly higher mean SBP and DBP at 70 years of age than those who did not develop dementia (178/101 mmHg vs 164/92 mmHg, respectively). The theory is supported by sub-study results from the SYST-EUR trial showing that antihypertensive therapy with nitrendipine (with or without enalapril and/or hydrochlorothiazide) in non-demented patients with isolated systolic hypertension over the age of 60 years reduced the incidence of dementia by 50% versus placebo over the 2-year follow-up period (7.7 versus 3.8 cases per 1000 patient years, $p=0.05$) [17]. However, there were only 32 cases of dementia in this study.

If it can be demonstrated that treatment of even mild hypertension in the elderly can reduce the incidence of dementia, this may have major consequences in terms of the socio-economic costs of the disease. Dementia undoubtedly takes a major toll on both the patients and their carers, who are frequently family and friends. Moreover, a significant positive correlation has been demonstrated between the evolution of dementia and healthcare costs, even in out-patients [18]. As the population of the western world continues to age, the prevalence of dementia and other diseases associated with old age will almost certainly increase [19]. Although studies analysing the economics of treating patients with Alzheimer's disease have considered the costs of antidementia treatments rather than antihypertensive therapies, it has been suggested that large savings in the costs of caring for home-dwelling patients with Alzheimer's disease may be achievable even with interventions that have only minor effects on patients' cognitive status [20].

The AT₁-receptor blocker, candesartan cilexetil, is a rational choice of antihypertensive agent for the treatment of mild hypertension in the elderly, having a well-established profile of dose-dependent efficacy [21] with placebo-like tolerability [22] and long-lasting antihypertensive effect from a once-daily dose [23]. Studies have already demonstrated that candesartan cilexetil 8–16 mg is effective and very well tolerated in elderly hypertensive patients [24]. Importantly, AT₁-receptor blockers may help to maintain, or even improve cognitive function through specific mechanisms other than BP reduction, since angiotensin II has been shown to impair performance in learning and memory paradigms [25]. The potential benefits of AT₁-receptor blockers in this setting have already been demonstrated in animal studies [26, 27].

CONCLUSIONS

The baseline characteristics of the 4964 patients enrolled in SCOPE indicate that the target population of elderly patients with mild hypertension and with no current dementia has been achieved. The results will provide important data on the impact of antihypertensive therapy with candesartan cilexetil in this population, both in terms of cardiovascular events and cognitive function.

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