BLOOD PRESSURE 1999; 8: 177–183

Study on COgnition and Prognosis in the Elderly (SCOPE)

L. HANSSON[1], H. LITHELL[1], I. SKOOG[2], F. BARO[3], C. M. BÁNKI[4], M. BRETELER[5], P. U. CARBONIN[6], A. CASTAIGNE[7], M. CORREIA[8], J.-P. DEGAUTE[9], D. ELMFELDT[10], K. ENGEDAL[11], C. FARSANG[12], J. FERRO[8], V. HACHINSKI[13], A. HOFMAN[5], O. F. W. JAMES[14], E. KRISIN[10], M. LEEMAN[9], P. W. DE LEEUW[15], D. LEYS[16], A. LOBO[17], G. NORDBY[11], B. OLOFSSON[10], G. OPOLSKI[18], M. PRINCE[19], F. M. REISCHIES[20], J. B. ROSENFELD[21], L. RUILOPE[22], J. SALERNO[23], R. TILVIS[24], P. TRENKWALDER[25] AND A. ZANCHETTI[26]

From [1]Uppsala, [2]Göteborg, Sweden, [3]Bierbeek, Belgium, [4]Nagykálló, Hungary, [5]Rotterdam, The Netherlands, [6]Roma, Italy, [7]Créteil, France, [8]Lisboa, Portugal, [9]Bruxelles, Belgium, [10]Mölndal, Sweden, [11]Oslo, Norway, [12]Budapest, Hungary, [13]London, Ontario, Canada, [14]Newcastle upon Tyne, UK, [15]Maastricht, The Netherlands, [16]Lille, France, [17]Zaragoza, Spain, [18]Warsaw, Poland, [19]London, UK, [20]Berlin, Germany, [21]Tel-Aviv, Israel, [22]Madrid, Spain, [23]Washington DC, USA, [24]Helsinki, Finland, [25]Starnberg, Germany, [26]Milan, Italy

Hansson L, Lithell H, Skoog I, Baro F, Bánki CM, Breteler M, Carbonin PU, Castaigne A, Correia M, Degaute J-P, Elmfeldt D, Engedal K, Farsang C, Ferro J, Hachinski V, Hofman A, James OFW, Krisin E, Leeman M, De Leeuw PW, Leys D, Lobo A, Nordby G, Olofsson B, Opolski G, Prince M, Reischies FM, Rosenfeld JB, Ruilope L, Salerno J, Tilvis R, Trenkwalder P, Zanchetti A. *Study on cognition and prognosis in the elderly (SCOPE).* Blood Pressure 1999; 8: 177–183.

The Study on COgnition and Prognosis in the Elderly (SCOPE) is a multicentre, prospective, randomized, double-blind, parallel-group study designed to compare the effects of candesartan cilexetil and placebo in elderly patients with mild hypertension. The primary objective of the study is to assess the effect of candesartan cilexetil on major cardiovascular events. The secondary objectives of the study are to assess the effect of candesartan cilexetil on cognitive function and on total mortality, cardiovascular mortality, myocardial infarction, stroke, renal function, hospitalization, quality of life and health economics. Male and female patients aged between 70 and 89 years, with a sitting systolic blood pressure (SBP) of 160–179 mmHg and/or diastolic blood pressure (DBP) of 90–99 mmHg, and a Mini-Mental State Examination (MMSE) score of 24 or above, are eligible for the study. The overall target study population is 4000 patients, at least 1000 of whom are also to be assessed for quality of life and health economics data. After 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 12.5 mg o.d., patients are randomized to receive either candesartan cilexetil 8 mg once daily (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. or two placebo tablets o.d. Recruitment was completed in January 1999. At that time 4964 patients had been randomized. All randomized patients will be followed for an additional 2 years. If the event rate is lower than anticipated, the follow-up will be prolonged. *Key words: mild hypertension, elderly, candesartan cilexetil, cardiovascular events, cognitive function.*

INTRODUCTION

The proportion of the elderly people in the general population, and particularly of very elderly people, is increasing in most industrialized countries [1]. This trend is expected to continue well beyond the year 2000, leading to a greater prevalence of cardiovascular and cerebrovascular disease, which increase considerably with age. Recent data from a worldwide study show that cardiovascular and cerebrovascular disease are already the leading causes of death and disability in the industrialized world [2].

Hypertension is one of the major risk factors for both coronary heart disease and stroke, which have been shown to increase by around five-fold and ten-fold, respectively, with increasing diastolic blood pressure (DBP) from 76 mmHg to 105 mmHg [3]. Cerebrovascular disease, as manifested by stroke and ischaemic white matter changes, results in varying degrees of brain dysfunction, including dementia, and represents a chronic health problem with important personal, social and economic implications. A history of atherosclerosis alone, excluding the effects of age and education, has also been shown to be associated with decreased cognitive performance [4].

 ISSN 0803-7051

Prevention of cardiovascular and cerebrovascular complications

The beneficial effects of treating hypertension have been documented in a number of studies. In a meta-analysis of several, prospective randomized intervention trials involving nearly 48 000 patients, a DBP reduction of 5–6 mmHg was found to decrease the risk of stroke by 38% and heart disease by 16% [5]. Four major studies have also shown that stroke morbidity and mortality in the elderly can be significantly reduced with antihypertensive therapy: the Systolic Hypertension in the Elderly Program (SHEP) [6] in the USA, the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) [7], the British Medical Research Council (MRC) study in older adults [8] and the Systolic Hypertension in Europe (Syst-Eur) study [9]. In all of these studies, the entry systolic blood pressure (SBP) was relatively high. However, the value of antihypertensive treatment in elderly patients with DBP in the range 90–99 mmHg remains an open issue, since DBP at entry in both the STOP and MRC trials was above these values, and the SHEP and Syst-Eur studies specifically recruited patients with isolated systolic hypertension.

The impact of hypertension on cognitive function and dementia

Hypertension is generally recognized to be a major risk factor for the development of ischaemic white matter lesions [10, 11], as well as stroke [12]. Old age, and especially very old age, is associated with an increased risk of dementia [13]. More than 60 diseases are associated with the syndrome of dementia, the most common being Alzheimer's disease (AD) and vascular dementia (VAD) [14]. In a recent study, VAD was found to be more common than previously assumed [15]. Although all the risk factors for VAD have yet to be identified, it is obvious that arterial hypertension plays an important role [10]. In a longitudinal study of nearly 1000 elderly Swedish men, there was an inverse relationship between DBP at 50 years of age and cognitive function at 70 years of age [16], as determined by psychometric testing and use of the Mini-Mental State Examination (MMSE) [17, 18]. In a further Swedish study, a significant link was found between the presence of high SBP and DBP at age 70 years and the development of dementia 10–15 years later [19].

The risk of developing dementia increases at least ninefold after a stroke [20, 21]. Furthermore, ischaemic white matter lesions have also been linked to AD and to VAD [10]. Other cardiovascular disorders, such as myocardial infarction [22, 23] and generalized atherosclerosis [24], may also increase the risk of developing dementia.

Rationale for proposed study

At the time of planning SCOPE, an analysis of nine prospective observational studies suggested that there was no apparent threshold DBP below which the risk of stroke was not continuously reduced [25]. The results of the recently completed Hypertension Optimal Treatment (HOT) Study indicated that the lowest risk of stroke (fatal and non-fatal) was achieved at a DBP of <85 mmHg [26]. However, HOT was not a study in the elderly, since in this cohort the mean age was 62 years and, furthermore, patients had a mean DBP of 105 mmHg (± 3.4) at randomization.

An as yet unanswered question, is whether antihypertensive treatment provides protection against stroke in patients with an initial DBP of 90–99 mmHg. In addition, although the term "preventable senility" has been used [27], there is no definitive evidence to show that lowering of elevated blood pressure can reduce the incidence of dementia. However, a subgroup analysis from the Syst-Eur Study [28] showed that treatment of isolated systolic hypertension with the long-acting calcium antagonist nitrendipine reduced the incidence of dementia and AD by 50%. These results further emphasize that treatment of hypertension may be a potential way to prevent development of dementia and cognitive decline in the elderly. A clinical study to assess the effects of antihypertensive drug treatment on major cardiovascular events and cognitive function in elderly patients with mild hypertension is therefore warranted.

There may be a considerable benefit of antihypertensive therapy in this group of patients, since there is a continuum between dementia and cognitive impairment in the elderly population [29]. Hence, even if treatment of vascular risk factors results in only a small improvement in the whole distribution of cognitive ability, it may lead to a substantial reduction in the prevalence of overt dementia [4, 29]. Furthermore, since hypertension and other cardiovascular disorders are common in the elderly, they may make a much greater contribution to the number of cases of dementia than more infrequent disorders associated with a higher risk [4, 29].

Rationale for using candesartan cilexetil

Angiotensin II type 1 (AT_1) receptor blockers represent a new class of antihypertensive agents. Unlike ACE-inhibitors, AT_1-receptor blockers do not inhibit the breakdown of bradykinin or other kinins, and this novel class of drugs is not associated with a dry cough [30]. The excellent tolerability and relative lack of contraindications of these agents make them highly suitable for the treatment of hypertension in the elderly. Moreover, AT_1-receptor blockers may help to maintain or even improve cognitive function through mechanisms other than blood pressure

(BP) reduction. In experimental models of cognitive function, angiotensin II has been shown to impair performance in learning and memory paradigms, which appears to be the result of angiotensin II-induced inhibition of acetylcholine release [31]. Animal studies have also shown that treatment with the AT_1-receptor blocker losartan can improve cognitive performance [32]. Therefore, it seems plausible that selective antagonists for the AT_1 subtype of the angiotensin II receptor may represent a novel approach for the treatment of cognitive disorders.

Candesartan cilexetil is an AT_1-receptor blocker that provides a dose-related antihypertensive effect in doses of up to 16 mg [33]. Given once daily it results in a smooth blood pressure reduction over the 24-h dosing interval. It has also proven effective and well tolerated in elderly and very old patients [34].

THE SCOPE STUDY

The Study on COgnition and Prognosis in the Elderly (SCOPE) is a multicentre, prospective, randomized, double-blind, parallel-group study designed to compare the effects of candesartan cilexetil and placebo on cardiovascular events and cognitive function in elderly patients with mild hypertension. Based on data from the STOP-Hypertension study [7], the overall target study population is 4000 patients. This represents the calculated number of patients required to detect a 23% difference (with a power of 0.80 and a significance level of 0.05), between the groups, in reduction in incidence of major cardiovascular events over the study period, assuming a starting DBP of 95 mmHg. Randomization was performed centrally at the Coordinating Center at Sahlgrenska University Hospital/Östra, Göteborg, Sweden.

Objectives

The primary objective of the study is to assess the effect of candesartan cilexetil on major cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) in elderly patients with mild hypertension.

The secondary objectives of the study are to assess the effect of candesartan cilexetil on cognitive function, as measured by the MMSE, and also on total mortality, cardiovascular mortality, myocardial infarction, stroke, renal function, hospitalization, quality of life and health economics.

The influence of a number of variables on major cardiovascular events and cognitive function will also be investigated, as outlined in the listed objectives of SCOPE, below.

1. Primary objective
   a. to assess the effect of candesartan cilexetil on major cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) in elderly patients with mild hypertension.
2. Secondary objectives
   a. to assess the effect of candesartan cilexetil on:
      i) cognitive function as measured by the Mini Mental State Examination (MMSE)
      ii) total mortality
      iii) cardiovascular mortality
      iv) fatal and non-fatal myocardial infarction
      v) fatal and non-fatal stroke
      vi) impaired renal function (a doubling of S-creatinine values compared with baseline)
      vii) hospitalization
      viii) quality of life
      ix) health economics
3. Variables to be investigated for possible influence on major cardiovascular events and cognitive function
   a. age
   b. gender
   c. antihypertensive treatment at entry
   d. previous myocardial infarction
   e. previous stroke
   f. diabetes mellitus (treated with diet or drugs) at entry
   g. smoking at entry
   h. body mass index at entry
   i. ECG signs of left ventricular hypertrophy at entry
   j. hyperlipidaemia or treatment with lipid-lowering drugs at entry
   k. cognitive function (MMSE score) at entry
   l. level of education.

Patients

The patients were recruited from participating centres in 15 different countries. Both treated and untreated hypertensive patients could be enrolled. Male and female patients aged between 70 and 89 years, with a sitting SBP 160–179 mmHg and/or DBP 90–99 mmHg, and an MMSE score of 24 or above, were eligible for the study. The inclusion and exclusion criteria are summarized in the list below. When further inclusion of patients was stopped in January 1999, 4964 patients had been randomized.

1. Inclusion criteria
   a. male or female, aged 70–89 years, with or without antihypertensive treatment. If treated, both the investigator and the patient should accept that the antihypertensive medication is standardized to HCTZ 12.5 mg o.d.
   b. BP: systolic 160–179 mmHg or diastolic 90–99 mmHg or both (mean of two measurements)

after 5–10 min of rest in the sitting position, on two consecutive occasions, separated by at least 14 days

c. MMSE score 24 or above on two consecutive occasions, separated by at least 14 days
d. signed informed consent

2. Exclusion criteria
   a. General:
      i) need of antihypertensive treatment other than HCTZ
      ii) standing SBP < 140 mmHg after 2 min or a history of symptomatic orthostatic hypotension
      iii) sitting SBP ≥ 180 mmHg or DBP ≥ 100 mmHg
      iv) secondary hypertension
      v) stroke or myocardial infarction within 6 months prior to randomization
      vi) decompensated congestive heart failure
      vii) other serious concomitant diseases considered by the investigator to affect survival during the next 3–4 years
      viii) alcoholism, drug abuse or any other problems which may compromise compliance
      ix) known hypersensitivity to the study drug
      x) current participation in another clinical study
      xi) known contraindications to HCTZ
      xii) clinically significant impaired renal function (serum creatinine $\geq$180 μmol/l for males and $\geq$140 μmol/l for females)
      xiii) serum ASAT or ALAT more than three times the upper limit of normal
   b. Cognitive function:
      i) obvious dementia, even if MMSE score remains above 23
      ii) current treatment with antidementia drugs
      iii) conditions which preclude MMSE (e.g. illiteracy, poor eye sight, hearing impairment, paralysis, aphasia or other speech disorders)
      iv) vitamin B_{12} deficiency, untreated or treated less than 12 months
      v) hypothyroidism, untreated or treated less than 12 months
      vi) neurosyphilis or AIDS
      vii) severe brain disorder that may interfere with cognitive function
      viii) severe depression within the last 12 months or psychotic disorder
      ix) psychopharmacological treatment (instituted within the last 6 months)

Overall study design

After an open run-in period (1–3 months) which included the initial (enrolment) and qualifying visits, patients were randomized in a double-blind fashion to receive either candesartan cilexetil 8 mg once daily (o.d.) or a matching placebo tablet (o.d.). After all patients had been randomized, follow-up will continue for 2 further years (Fig. 1). The follow-up may be prolonged if the event rate is lower than anticipated.

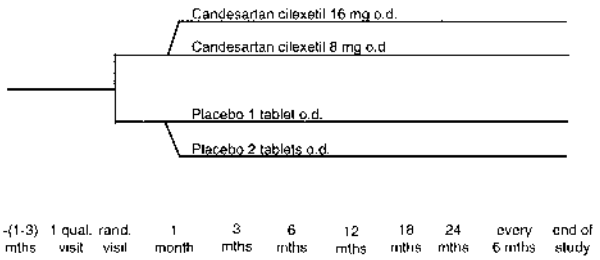

Fig. 1. Overall study design.

Enrolment visit. At this initial visit, the patients' eligibility was checked together with the absence of exclusion criteria. All patients on current antihypertensive therapy had their medication standardized to hydrochlorothiazide (HCTZ) 12.5 mg o.d. after an appropriate reduction of prior treatment.

First qualifying visit. All patients considered eligible for the study at the enrolment visit were asked to return after at least 14 days, when repeat BP, heart rate (HR) and MMSE assessments were carried out. For patients who fulfilled the BP and MMSE inclusion criteria, this visit was regarded as the first qualifying visit. All patients (whether or not fulfilling the inclusion criteria) were asked to return for a second visit 14 days later and thereafter at 14-day intervals until both BP and MMSE inclusion criteria were met on two consecutive visits.

Second qualifying/randomization visit. If inclusion criteria were fulfilled at the second consecutive visit, a medical history was recorded and patients underwent a physical examination, ECG, laboratory analysis, and any adverse events were recorded. Patient data were sent by fax to the Coordinating Center, where patients fulfilling all of the inclusion criteria and none of the exclusion criteria were randomized to receive either candesartan cilexetil 8 mg o.d. or placebo o.d. The investigators were informed about treatment allocation in the form of patient number by return fax. The following variables were taken into account when randomizing patients: age, gender, previous myocardial infarction, atrial fibrillation, previous stroke, treatment with non-steroid anti-inflammatory drug or acetylsalicylic acid, MMSE score, level of education, body mass index, chronic treatment with lipid-lowering drugs, chronic treatment with psychopharmacological therapy, previously treated with antihypertensive drugs, smoking and language area.

Study visits. Patients were asked to return for the first study visit 1 month after the randomization visit and

then for a second visit 3 months after the randomization visit. Thereafter, the patients are scheduled to be followed regularly on a 6-month basis until the close of the study. Extra visits may be performed according to medical need.

Treatment schedule

After initial randomization to candesartan cilexetil 8 mg o.d. or corresponding placebo o.d., patients whose SBP remains >160 mmHg or has decreased by <10 mmHg since the randomization visit, or whose DBP is >85 mmHg will have their treatment doubled to two tablets (candesartan cilexetil 16 mg o.d. or two matching placebo tablets o.d.). If, at subsequent visits, a patient's SBP remains ≥160 mmHg or the DBP ≥ 90 mmHg, it is recommended that additional antihypertensive medication is given. Recommended add on treatment is HCTZ 12.5 mg. The addition of other AT_1-receptor blockers or ACE-inhibitors is not allowed as antihypertensive treatment. This and any other treatment that is considered necessary for the patient's welfare may be given at the discretion of the investigator.

Efficacy variables

Cardiovascular. At all visits, SBP, DBP and HR are measured in the sitting position after 5–10 min of rest. Three recordings of BP are made, at least 1 min apart. The mean SBP/DBP is calculated from the last two measurements. A 12-lead resting ECG was recorded at the randomization visit and after 1 month.

Cognition. Cognitive function is evaluated by using the MMSE, which is an instrument that has been widely used to screen for cognitive function in different populations. After recording of BP and HR, an MMSE is performed at each visit, except after 1 and 3 months. As far as possible, the test is performed by the same person throughout the study. As the application of the MMSE differs widely, a standardized protocol for the use of the MMSE in this study was developed after discussions among members of the Steering Committee.

Quality of life. Two standard quality of life questionnaires (the Psychological General Well-Being Index and the Subjective Symptom Assessment Profile) and one utility index are used to assess quality of life at the preselected participating centres. These assessments are made at the randomization visit (baseline questionnaire) and after 6, 12 and 24 months of treatment. The questionnaires are administered according to a standardized procedure and completed by the patients themselves during the visit to the clinic.

Health economics. Healthcare resource utilization data are collected in participating centres at each visit. Some clinical data will also be used for the economic analyses.

Definition of events

Clinical events. Clinical events are divided into three categories:

1. cardiovascular (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke);
2. non-cardiovascular deaths;
3. significant cognitive decline (a reduction in MMSE score of 4 points compared with the randomization visit score).

The occurrence of a suspected clinical event is recorded on the Serious Adverse Event/Clinical Event form. This information together with additional documentation (such as hospital records, ECG tracings, CT scan reports, etc.) will form the basis on which the Independent Clinical Event Committee will validate the reported events.

Adverse events. Any adverse events, including serious adverse events, are recorded in connection with study visits.

Time schedule

Recruitment to SCOPE began in March 1997 and was completed in January 1999. As noted above, all randomized patients are scheduled for a follow-up period of at least 2 years. If the event rate is lower than anticipated (approximately 40 major cardiovascular events per 1000 patient years), the follow-up may be prolonged. Alternatively, the study may be terminated if recommended by the Independent Safety Committee.

Ethics

Informed consent, in accordance with the Declaration of Helsinki, was obtained from all patients prior to entering the study. Good clinical practice is observed and the study protocol was approved by the Ethics Committee concerned before enrolment of patients into the study.

Organization

An Executive Committee is responsible for the planning and conduct of the study and reports to the Steering Committee. In addition to the Chairmen, Secretary and Statistician, the Executive Committee[1] consists of three representatives from different countries as well as non-voting representatives from the sponsoring pharmaceutical company.

[1] Executive Committee members: L. Hansson, H. Lithell, I. Skoog, D. Elmfeldt, B. Olofsson (Sweden), P. Trenkwalder (Germany), A. Hofman (The Netherlands), A. Zanchetti (Italy).

The Steering Committee[2] comprises the members of the Executive Committee, together with one or two representatives from each participating country. The chairpersons, secretary and statistician are the same in both committees. The Steering Committee is in charge of approval of the protocol and amendments, organization, data handling and general conduct of the study.

An Independent Safety Committee[3], comprising three members who are independent of other parts of the study organization, is supervising the evolution of the study, especially with respect to the occurrence of clinical events. It is also empowered to advise the Steering Committee on study termination.

An Independent Clinical Event Committee[4], consisting of three members who are independent of other parts of the study organization, evaluates and classifies all reported clinical events, without knowledge of the study group to which the patient belongs.

Study monitors have been appointed in each of the participating countries to have regular contact with the investigational sites in order to confirm acceptability of facilities, adherence to the study protocol, accurate recording of data and to provide information and support to the investigators.

The SCOPE[5] trial is sponsored by AstraZeneca.

REFERENCES

1. Caird FI, Cargill D. Viewpoint. Chronic brain failure: the silent epidemic. N Z Med J 1987; 100: 13–6.
2. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349: 1269–76.
3. MacMahon S, Peto R, Cutler J, *et al*. Blood pressure, stroke and coronary heart disease, part I: Effects of prolonged differences in blood pressure – evidence from nine prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765–74.
4. Breteler MMB, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam study. Br Med J 1994; 308: 1604–8.
5. MacMahon S, Rodgers A. The effects of antihypertensive treatment on vascular disease: reappraisal of the evidence in 1994. J Vasc Med Biol 1993; 4: 265–71.
6. 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. JAMA 1991; 265: 3255–64.
7. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester P-O. Mortality and morbidity in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991; 338: 1281–5.
8. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: Principal results. Br Med J 1992; 304: 405–12.
9. Staessen JA, Fagard R, Thijs L, *et al*. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350: 757–63.
10. Skoog I. Guest editorial. Status of risk factors for vascular dementia. Neuroepidemiology 1998; 17: 2–9.
11. Skoog I. A reveiw on blood pressure and ischaemic white matter lesions. Dement Geriatr Cogn Disord 1998; 9 (Suppl 1): 13–19.
12. Strandgaard S, Paulson OB. Cerebrovascular consequences of hypertension. Lancet 1994; 344: 519–21.
13. Jorm AF. The epidemiology of Alzheimer's disease and related disorders. London: Chapman & Hall, 1990.
14. Katzman R. Alzheimer's disease. N Engl J Med 1986; 314: 964–73.
15. Skoog I, Nilsson L, Palmertz B, Andreasson L-A, Svanborg A. A population-based study of dementia in 85-year-olds. N Engl J Med 1993; 328: 153–8.
16. Kilander L, Nyman H, Andrén B, *et al*. Hypertension and associated metabolic disturbances are related to cognitive impairment. A 20-year follow-up of 999 men. Hypertension 1998; 31: 780–6.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
18. Tombaugh TN, McIntyre NJ. The mini-mental state examination: A comprehensive review. J Am Geriatr Soc 1992; 40: 922–35.
19. Skoog I, Lernfelt B, Landahl S, *et al*. 15-year longitudinal study of blood pressure and dementia. Lancet 1996; 347: 1141–5.
20. Tatemichi TK, Foulkes MA, Mohr JP, *et al*. Dementia in stroke survivors in the Stroke Data Bank cohort: prevalence, incidence, risk factors, and computed tomographic findings. Stroke 1990; 21: 858–66.
21. Tatemichi TK, Desmond DW, Mayeux R, *et al*. Dementia after stroke: Baseline frequency, risks, and clinical features in a hospitalized cohort. Neurology 1992; 42: 1185–93.
22. Aronson MK, Ooi WL, Morgenstern H, *et al*. Women, myocardial infarction, and dementia in the very old. Neurology 1990; 40: 1102–6.
23. Sparks DL, Hunsaker JC, Scheff SW, *et al*. Cortical senile plaques in coronary artery disease, aging and Alzheimer's disease. Neurobiol Aging 1990; 11: 601–7.
24. Hofman A, Ott A, Breteler MMB, *et al*. Atherosclerosis,

[2] Steering Committee members: C. M. Bánki (Hungary), F. Baro (Belgium), M. Breteler (The Netherlands), P. U. Carbonin (Italy), A. Castaigne (France), M. Correia (Portugal), J.-P. Degaute (Belgium), D. Elmfeldt (Sweden), K. Engedal (Norway), C. Farsang (Hungary), J. Ferro (Portugal), L. Hansson (Sweden), V. Hachinski (Canada), A. Hofman (The Netherlands), O. F. W. James (UK), M. Leeman (Belgium), P. W. de Leeuw (The Netherlands), D. Leys (France), H. Lithell (Sweden), A. Lobo (Spain), G. Nordby (Norway), G. Opolski (Poland), B. Olofsson (Sweden), M. Prince (UK), F. M. Reischies (Germany), J. B. Rosenfeld (Israel), L. Ruilope (Spain), J. Salerno (USA), I. Skoog (Sweden), R. Tilvis (Finland), P. Trenkwalder (Germany), A. Zanchetti (Italy).

[3] Independent Safety Committee members: T. Erkinjuntti (Finland), J. Swales (UK), H. Wedel (Sweden).

[4] Independent Clinical Event Committee Members: B. Carlberg (Sweden), H. Holzgreve (Germany), K. H. Rahn (Germany).

[5] SCOPE Study Co-ordinating Group: E. Krisin, M. Althoff, S. Borg, L. Curiac, I. Eliasson, S. Lilja, S. Mjörnstedt, N. Persson, C. Urbath, Å. Westin, AstraZeneca R&D Mölndal (Sweden).

apolipoprotein E, and the prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997; 349: 151–4.
25. MacMahon S. Blood pressure and the risks of cardiovascular diseases. In: Swales JD, ed. Textbook of hypertension. Oxford: Blackwell, 1994: 46–57.
26. Hansson L, Zanchetti A, Carruthers SG, *et al*. For the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351: 1755–62.
27. Hachinski V. Preventable senility: a call for action against the vascular dementias. Lancet 1992; 340: 645–8.
28. Forette F, Seux M-L, Staessen JA, *et al*. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352: 1347–51.
29. Prince M. Vascular risk factors and atherosclerosis as risk factors for cognitive decline and dementia. J Psychosomat Res 1995; 39: 525–30.
30. Messerli FH, Weber MA, Brunner HR. Angiotensin II receptor inhibition. A new therapeutic principle. Arch Intern Med 1996; 156: 1957–65.
31. Barnes JM, Barnes NM, Costall B, Horovitz ZP, Naylor RJ. Angiotensin II inhibits the release of [^{3}H]acetylcholine from rat entorhinal cortex in vitro. Brain Res 1989; 492: 136–43.
32. Barnes NM, Champaneria S, Costall B, Kelly ME, Murphy DA, Naylor RJ. Cognitive enhancing actions of DUP 753 detected in a mouse habituation paradigm. Neuroreport 1990; 1: 239–42.
33. Elmfeldt D, George M, Hübner R, *et al*. Candesartan cilexetil, a new generation angiotensin II antagonist, provides dose dependent antihypertensive effect. J Hum Hypertens 1997; 11 (Suppl 2): S49–53.
34. McInnes GT, O'Kane KP, Jonker J, Roth J. The efficacy and tolerability of candesartan cilexetil in an elderly hypertensive population. J Hum Hypertens 1997; 11 (Suppl 2): S75–80.

Submitted April 12, 1999; accepted May 4, 1999

Address for correspondence:

Professor Lennart Hansson
University of Uppsala
Department of Public Health
Section of Geriatrics
Clinical Hypertension Research
PO Box 609
SE-751 25 Uppsala
Sweden
Tel: + 46 18 10 13 84
Fax: + 46 18 17 79 73