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CLINICAL RESEARCH **Clinical Trials**

Stroke Prevention With the Angiotensin II Type 1-Receptor Blocker Candesartan in Elderly Patients With Isolated Systolic Hypertension

The Study on Cognition and Prognosis in the Elderly (SCOPE)

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OBJECTIVES The aim of this study was to test the hypothesis that the angiotensin II type 1 receptor blocker (ARB) candesartan can reduce the risk of stroke in elderly patients with isolated systolic hypertension (ISH).

BACKGROUND Isolated systolic hypertension is the predominant form of hypertension in the elderly, and stroke is the most common cardiovascular (CV) complication.

METHODS In the Study on Cognition and Prognosis in the Elderly (SCOPE), 4,964 patients age 70 to 89 years were randomly assigned to double-blind candesartan or placebo with open-label antihypertensive therapy (mostly thiazide diuretics) added as needed to control blood pressure. Of the 4,964 patients, 1,518 had ISH (systolic blood pressure >160 mm Hg and diastolic blood pressure <90 mm Hg). The present study is a predefined subgroup analysis of outcome results in the ISH patients.

RESULTS Of the ISH patients, 754 were randomized to the candesartan group and 764 to the control group. Over the study period, blood pressure was reduced by 22/6 mm Hg in the candesartan group and by 20/5 mm Hg in the control group (difference between treatments 2/1 mm Hg; $p = 0.101$ and 0.064). A total of 20 fatal/non-fatal strokes occurred in the candesartan group (7.2/1,000 patient-years) and 35 in the control group (12.5/1,000 patient-years); relative risk (RR) was 0.58 (95% confidence interval 0.33 to 1.00), that is, a RR reduction of 42% ($p = 0.050$ unadjusted, $p = 0.049$ adjusted for baseline risk). There were no marked or statistically significant differences between the treatment groups in other CV end points or all-cause mortality.

CONCLUSIONS In elderly patients with ISH, antihypertensive treatment based on the ARB candesartan resulted in a significant 42% RR reduction in stroke in comparison with other antihypertensive treatment, despite little difference in blood pressure reduction. (J Am Coll Cardiol 2004;44:1175–80) © 2004 by the American College of Cardiology Foundation

Isolated systolic hypertension (ISH) is the most common form of hypertension in the elderly and a major risk factor for cardiovascular (CV) disease (1,2). Large-scale, placebo-controlled clinical trials have demonstrated the value of treating older patients with ISH. In the Systolic Hypertension in the Elderly Program (SHEP), antihypertensive treatment lowered the risk of stroke by 36% (3), and in the Systolic Hypertension in Europe (Syst-Eur) study, active treatment decreased the occurrence of stroke by 42% (4). Stroke prevention is exceedingly important because it is now the primary hypertensive complication of untreated hypertension in the elderly. A recent meta-analysis suggested that in studies carried out since the early 1990s, the incidence of stroke exceeds that of myocardial infarction (5).

Although the benefit of treating ISH in older hypertensive populations has been clearly established (3,4), it is not clear whether specific drug therapies confer additional benefit beyond blood pressure control. The only publication, so far, is based on an analysis of patients with ISH and electrocardiographic evidence of left ventricular hypertrophy, participating in the Losartan Intervention For Endpoint reduction (LIFE) study (6). This LIFE substudy demonstrated substantial reduction in CV mortality, stroke, and new-onset diabetes mellitus with the angiotensin II

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Abbreviations and Acronyms

ARB = angiotensin II type 1 receptor blocker
AT_1 = angiotensin II type 1
CI = confidence interval
CV = cardiovascular
DBP = diastolic blood pressure
HCTZ = hydrochlorothiazide
ISH = isolated systolic hypertension
LIFE = Losartan Intervention For Endpoint reduction study
MMSE = Mini Mental State Examination
RR = relative risk
SBP = systolic blood pressure
SCOPE = Study on Cognition and Prognosis in the Elderly

type 1 (AT_1) receptor blocker (ARB) losartan-based treatment as compared with the beta receptor blocker atenolol-based treatment in patients with ISH, despite similar blood pressure reduction.

The Study on Cognition and Prognosis in the Elderly (SCOPE) was designed as the first large-scale clinical trial to determine the effects of an ARB on CV and cognitive outcomes in elderly patients with mild to moderate hypertension (7). The SCOPE was initially conceived as a comparison of candesartan with placebo. However, treatment guidelines changed during the recruitment phase of the study, and the protocol was amended, for ethical reasons, to recommend the addition of open-label antihypertensive therapy in patients whose blood pressure remained too high. As a result, a large proportion of patients, especially in the "placebo" group, received additional antihypertensive medication, and the trial became a comparison of a candesartan-based regimen with a regimen not containing candesartan. Indeed, 84% of the patients in the control group received active antihypertensive medication. The primary results from the SCOPE have been published (8). The mean blood pressure reduction was pronounced in both the candesartan group (21.7/10.8 mm Hg) and the control group (18.5/9.2 mm Hg, mean difference between treatments: 3.2/1.6 mm Hg). Non-fatal stroke was 27.8% lower in patients treated with candesartan compared with those in the control group ($p = 0.04$), and all stroke was reduced by 23.6% ($p = 0.06$). Other CV events were not significantly different between groups.

The present study is a predefined subgroup analysis of outcome results in the SCOPE patients with ISH, defined as systolic blood pressure (SBP) ≥160 mm Hg and diastolic blood pressure (DBP) <90 mm Hg.

PATIENTS AND METHODS

Details on study methods have been previously published (7,8). In brief, hypertensive patients between 70 and 89 years of age, with treated or untreated SBP of 160 to 179 mm Hg, or DBP of 90 to 99 mm Hg, or both, and a Mini Mental State Examination (MMSE) score of 24 or higher on two consecutive occasions, were eligible for enrollment in the SCOPE study. Antihypertensive medications at study entry were standardized to hydrochlorothiazide (HCTZ) 12.5 mg daily at study enrollment and were continued throughout the study.

The study consisted of an open run-in period (one to three months) followed by a double-blind treatment period of three to five years. Patients were randomized (1:1) by a central, computer-generated randomization schedule to receive either candesartan 8 mg or a matching placebo tablet once daily in the morning. Study medication was doubled to two tablets once daily if, at any consecutive visits, the patient met any of the following criteria: SBP >160 mm Hg, decrease in SBP of <10 mm Hg compared with the randomization visit, or DBP above 85 mm Hg. Patients with SBP ≥160 mm Hg or DBP ≥90 mm Hg after receiving two tablets of study medication could receive additional antihypertensive medication. In accordance with the protocol, HCTZ 12.5 mg daily was the preferred medication to be added to study treatment. Subsequently, any other antihypertensive medication could be added, excluding ARBs or angiotensin-converting enzyme inhibitors.

The primary end point of the SCOPE was a first major CV event (CV death, non-fatal myocardial infarction, or non-fatal stroke). A number of secondary end points were also prespecified. These included cognitive function as measured by the MMSE, dementia, total mortality, CV mortality, fatal and non-fatal myocardial infarction (separate and combined), fatal and non-fatal stroke (separate and combined), new-onset diabetes mellitus, and discontinuation of study drug as a result of adverse events.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol and patient consent forms were approved by the appropriate ethics committee at each institution that participated in the study. Patients were recruited into the study between March 1997 and January 1999, and the follow-up phase ended in March 2002. A total of 527 centers in 15 countries, mainly in Europe, participated in the study.

Statistical methods. The analysis was conducted according to the intention to treat and last value carried forward principles. Differences between the treatment groups in "time to event" were analyzed with a log-rank test and in a Cox regression model. The p values for the interaction treatment by subgroups (ISH/non-ISH) were calculated in a Cox regression analysis. Adjustment for baseline CV risk according to the criteria given in the 1999 World Health Organization-International Society of Hypertension guidelines (9) was done in a Cox regression model to account for possible differences in risk at baseline. Differences in proportions of patients with an event were analyzed using the chi-square test. The continuous variables, such as change in blood pressure or MMSE score from baseline, were symmetrically distributed and tested in an analysis of covariance model, with prespecified factors adjusting for country and

Table 1. Baseline Characteristics of Patients With ISH*

Characteristics	Candesartan (n = 754)	Control (n = 764)
Age (yrs, mean)	77.3	76.9
Age ≥80 yrs (%)	28.2	25.1
Women (%)	63.3	65.3
MMSE (score, mean)	28.6	28.6
Blood pressure (mm Hg, mean)	168.7/82.3	169.3/82.5
Previously treated hypertension (%)	47.7	45.2
Previous MI (%)	4.2	4.5
Previous stroke (%)	4.4	3.9
Atrial fibrillation (%)	2.4	2.9
Abnormal ECG (%)	27.6	28.8
Diabetes (%)	13.5	11.0
Smokers (%)	10.1	8.9
Heart rate (beats/min, mean)	74.2	73.7
BMI (kg/m^2, mean)	26.7	26.3
Serum cholesterol (mmol/l, mean)	6.2	6.2
Serum creatinine (μmol/l, mean)	91.3	90.9
Treated with		
Lipid-lowering drug (%)	10.3	9.4
ASA/NSAID (%)	28.5	24.9
Psychopharmacologic drug (%)	11.3	10.3
Education		
Less than primary school (%)	7.0	7.7
Primary school (%)	39.7	39.5
More than primary school (%)	48.3	48.2
University (%)	5.0	4.6
Cardiovascular risk		
High or very high (%)	38.9	32.5
Medium (%)	61.1	67.5

*ISH = SBP ≥160 mm Hg and DBP <90 mm Hg.

ASA = aspirin; BMI = body mass index; DBP = diastolic blood pressure; ECG = electrocardiogram; ISH = isolated systolic hypertension; MI = myocardial infarction; MMSE = Mini Mental State Examination; NSAID = nonsteroidal anti-inflammatory drug; SBP = systolic blood pressure.

baseline value. Two-sided p values and 95% confidence intervals (CI) are used in this report. Data are shown as mean values with standard deviation where appropriate.

RESULTS

Of the 4,964 randomized patients, 1,518 met the criteria for ISH. The average duration of follow-up in ISH patients was 3.6 years corresponding to 5,506 patient-years. Of the ISH patients, 754 were randomized to the candesartan arm and 764 were randomized to the control arm. One patient only (in the candesartan arm) was lost to follow-up, that is, no data were available after randomization. The baseline characteristics were generally similar in the two treatment groups (Table 1). However, the distribution of CV risk indicated a slightly higher risk in the candesartan group than in the control group. Compared with non-ISH patients, patients with ISH were older, had lower DBP, and were less likely to have received previous antihypertensive medication (data not shown). The average age for all ISH patients was 77.1 years, and more than 26% of them were over the age of 80 years. Approximately 64% of them were women, and about 46% of all patients were previously treated for hypertension. A small percentage of patients equally distributed among the two groups had a history of previous myocardial infarction, stroke, or diabetes, and approximately 10% of them were current smokers. About 2.7% of the patients had a history of atrial fibrillation, and approximately 28% had abnormal electrocardiograms according to the investigator. Mean baseline blood pressure was similar in the two groups.

Table 2. Use of Different Antihypertensive Medication During the Study (% Patients)

Antihypertensive Treatment	Candesartan (n = 754)	Control (n = 764)
Study drug only	26	18
Study drug + HCTZ 12.5 mg from baseline	21	15
Add-on treatment	53	68
Diuretic*	36	46
Beta-blocker	19	27
Calcium channel blocker	21	30
ACE inhibitor	8	12
ARB	3	3

*A dose increase from HCTZ 12.5 mg baseline treatment or HCTZ started after randomization.

ACE = angiotensin-converting enzyme; ARB = angiotensin II type 1 receptor blocker; HCTZ = hydrochlorothiazide; ISH = isolated systolic hypertension.

As a consequence of the treatment schedule specified in the study protocol, only 18% of the patients in the control group received placebo alone, and the vast majority (82%) received active antihypertensive medication (Table 2). Fifteen percent remained on the low-dose HCTZ (12.5 mg) already given at baseline, and 67% received open-label add-on therapy. In the candesartan group 26% of the patients received candesartan alone, 21% remained on the low-dose HCTZ given at baseline, and 53% received open-label add-on therapy.

Blood pressure response. During the follow-up period, blood pressure was reduced significantly in both the candesartan and the control groups (Fig. 1). At the end of the study, the average decline in blood pressure compared with baseline was 22.2/6.0 mm Hg in the candesartan group and 20.2/4.8 mm Hg in the control group. In both groups, the SBP and DBP reductions were significant ($p < 0.001$). The

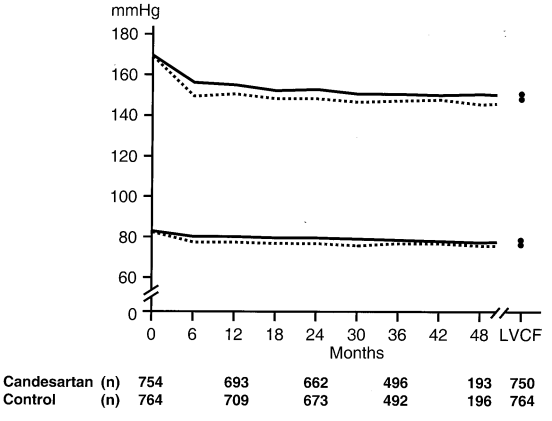

Figure 1. Systolic and diastolic blood pressure during the study. **Solid lines** = control group; **dashed lines** = candesartan group. LVCF = last value carried forward.

Table 3. Clinical Outcomes in Patients with ISH

	Rate, n (%)		Events/ 1,000 Follow-Up Years			
	Candesartan (n = 751–754)	Control (n = 761–764)	Candesartan	Control	RR (95% CI)*	p Value*
Major CV event	75 (9.9)	85 (11.0)	27.3	30.8	0.890 (0.652–1.214)	0.461
CV death	47 (6.2)	48 (6.3)	16.8	16.9	1.00 (0.669–1.495)	1.00
Fatal/non-fatal MI	23 (3.1)	25 (3.3)	8.3	8.9	0.932 (0.529–1.642)	0.807
Fatal/non-fatal stroke	20 (2.7)	35 (4.6)	7.2	12.5	0.577 (0.333–1.000)	0.050
Fatal MI	6 (0.8)	7 (0.9)	2.1	2.5	0.871 (0.293–2.593)	0.804
Non-fatal MI	18 (2.4)	20 (2.6)	6.5	7.1	0.911 (0.482–1.723)	0.775
Fatal stroke	3 (0.4)	7 (0.9)	1.1	2.5	0.443 (0.115–1.714)	0.238
Non-fatal stroke	17 (2.3)	28 (3.7)	6.1	10.0	0.611 (0.334–1.116)	0.109
Total mortality	82 (10.9)	90 (11.0)	29.3	31.7	0.928 (0.688–1.251)	0.623

*RR and p values correspond to events/1,000 follow-up years, calculated from a Cox regression.
CV = cardiovascular; ISH = isolated systolic hypertension; MI = myocardial infarction; RR = relative risk.

average difference in blood pressure decline between the two groups was 2.0 mm Hg (95% CI −0.4 to 4.4, p = 0.064) for SBP and 1.2 mm Hg (95% CI −0.1 to 2.4, p = 0.064) for DBP in favor of the candesartan group.

CV events and other end points. In patients with ISH, a first major CV event (CV death, non-fatal myocardial infarction, or non-fatal stroke) occurred in 75 patients in the candesartan group (27.3 events/1,000 patient-years) and in 85 patients in the control group (30.8 events/1,000 patient-years), corresponding to a relative risk (RR) of 0.89 (95% CI 0.65 to 1.21, p > 0.20) (Table 3). A first stroke, fatal or non-fatal, occurred in 20 of the patients receiving candesartan-based therapy (7.2 events/1,000 patient-years) and in 35 of the patients in the control group (12.5 events/1,000 patient-years), giving a RR of 0.58 (95% CI 0.33 to 1.00, p = 0.05) (Table 3 and Fig. 2). When adjusted for the slightly higher CV risk at baseline in the candesartan group, the RR and its 95% CI changed marginally toward lower values and the advantage of candesartan-based therapy was statistically significant (p = 0.049). In the candesartan group, 2.7% of the patients suffered a stroke compared with 4.6% in the control group. Thus, the absolute risk reduction was 1.9 per 100 patients treated, that is, 53 patients needed to be treated with candesartan-based therapy, rather than control therapy, to prevent one stroke. Fatal stroke occurred in three patients in the candesartan group and seven in the control group (RR = 0.44, p > 0.20). Non-fatal stroke occurred in 17 candesartan patients and 28 control patients (RR = 0.61, p = 0.109 unadjusted, p = 0.110 adjusted). There was little difference between the treatment groups in the occurrence of fatal or non-fatal myocardial infarctions, CV deaths, or deaths from all causes (Table 3).

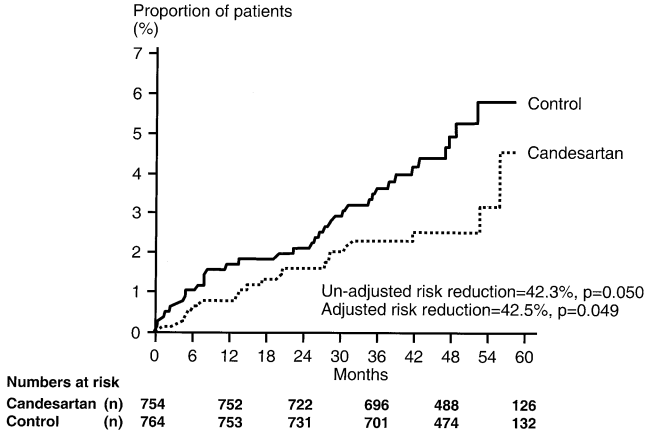

Figure 2. Kaplan-Meier curves for all stroke (fatal or non-fatal).

At baseline, in patients with ISH, the mean MMSE score was 28.6 in both the candesartan and control groups. There was no significant difference in change in MMSE score between the treatment groups during the study (candesartan −0.58, control −0.64, p > 0.20). Dementia occurred in 2.1% of the patients in the candesartan group and in 2.7% of the patients in the control group (p > 0.20). There was a trend toward fewer patients developing new diabetes in the candesartan group than in the control group (3.4% vs. 4.7%, p > 0.20).

Treatment was generally well tolerated in both groups. A similar proportion of patients in the candesartan group and the control group discontinued treatment because of adverse events (candesartan 17.3%, control 17.6%), whether considered related to the study drug or not. The most common adverse events reported were dizziness/vertigo, accident/injury, back pain, and bronchitis, and they occurred in similar proportions of patients in both treatment groups.

DISCUSSION

The present study demonstrated a substantial, 42% RR reduction in all stroke (fatal + non-fatal) in elderly patients with ISH treated with a candesartan-based regimen compared with a comparator regimen, mostly diuretic-based. This risk reduction achieved statistical significance after adjustment for the slightly higher CV risk at baseline in the candesartan group, despite the overall small number of events. The favorable effect of candesartan-based therapy was observed despite a very small blood pressure difference between the candesartan and control groups. It may there-

fore be suggested that at least part of the beneficial effect observed is due to specific vascular protective effects of AT_1-receptor blockade.

No statistically significant differences between the treatment groups were noted in any other individual health outcome measure, although trends toward benefit with candesartan-based treatment were noted for several end points, for example, major CV events, all myocardial infarction (fatal + non-fatal), all-cause death, and new-onset diabetes mellitus. The observed risk reduction in stroke with candesartan-based therapy is important not only because stroke is a disabling and much feared complication of hypertension, it is also the predominant complication in elderly patients with hypertension. As noted in recent trials (5) and also observed in the SCOPE, strokes have surpassed coronary events in treated older patients with hypertension.

The estimated mean RR reduction in all stroke with candesartan was greater in patients with ISH (42%) than in the entire SCOPE population (24%), or in the non-ISH population (16%). However, this does not preclude similar benefit in ISH and non-ISH patients, because the 95% CI were wide (because of relatively few events) and overlapping, and the interaction test (treatment by ISH/non-ISH) was non-significant ($p > 0.20$).

There was no significant difference between the treatment groups with respect to cognitive function as measured by MMSE or dementia in patients with ISH. This was similar to the overall study results (8). There was a marked reduction, 28%, in new-onset diabetes in the candesartan group compared with the control group in this subset of patients, although not statistically significant. These observations are consistent with the results of the main analysis, including the entire SCOPE study population, and possible explanations have been discussed (8).

The stroke results in patients with ISH in the SCOPE are in line with the results reported by the LIFE investigators in a similar analysis of patients with ISH (6). Patients in LIFE with ISH, treated with losartan experienced 40% fewer strokes, 46% lower CV mortality, and 38% lower new-onset diabetes as compared with those treated with atenolol. Although the two studies have similarities, they also differ in several important aspects: Patients in the LIFE trial were selected to be hypertensive with left ventricular hypertrophy, whereas patients in the SCOPE were of high age, both known strong independent markers of increased risk for CV events. However, the rate of stroke per 1,000 patient-years was 10.6 for losartan and 18.9 for atenolol in the LIFE trial and 6.1 for candesartan and 10.0 for control in the SCOPE. The comparator in the LIFE trial was a beta-blocker, whereas in the SCOPE it was mostly a diuretic.

There were fewer events in the SCOPE than originally expected, probably at least partly because of extensive antihypertensive treatment in the control group. This reduces the power of the statistical analyses and is a limitation of the trial, especially when subgroups of patients are considered. For example, there were only a total of 55 strokes in the ISH patients.

It is important to note that the SCOPE was conducted in elderly patients, a population in which ISH is the dominant subtype of hypertension. The median age of the ISH participants in the SCOPE was 77.3 years, and nearly 30% of the patients were 80 years old or above. In comparison, the study populations in the SHEP and the Syst-Eur trials were younger (mean age, 70 to 72 years) (3,4).

Blood pressure reduction was slightly better (2.0/1.2 mm Hg) with the candesartan-based regimen compared with the control regimen, but the difference was not statistically significant. It is possible that these relatively small differences in blood pressure could account for part of the observed clinical benefit on stroke. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), use of the diuretic chlorthalidone lowered SBP by only 2 mm Hg more than the angiotensin-converting enzyme inhibitor lisinopril, yet resulted in a 15% lower risk of stroke ($p = 0.02$) (10). Other studies have likewise demonstrated the impact of incremental reductions in blood pressure on stroke. Reducing DBP by 2 mm Hg in previously untreated hypertensive patients has been estimated to prevent 15% of strokes (11), and similar results have been estimated for small reductions in SBP (12). A recent meta-analysis (13) of data from close to one million adults from 61 prospective, observational studies showed the impact of small changes in SBP or DBP. The risk of stroke was incremental and continuous from SBP of 115 mm Hg and above. These observations indicate that the small difference in blood pressure between the treatment groups in the SCOPE could account for a difference in stroke of approximately 15%.

Thus, it is possible that the favorable effect on stroke in the ARB-treated groups in both the SCOPE and LIFE trials is related to AT_1-receptor blockade (and/or AT_2-receptor activation) and not just to blood pressure lowering. The hypothesis of cerebroprotection by AT_2-receptor activation has recently been emphasized (14). It is supported by several animal studies (15–21) that indicate neuroprotective effects of specific AT_1-receptor blockade at concentrations not affecting blood pressure. Similarly, results from clinical trials indicate that specific AT_1-receptor blockade may have value in the secondary prevention of stroke, which cannot be fully explained by blood pressure reduction (22).

CONCLUSIONS

In elderly patients with ISH, antihypertensive treatment based on the ARB candesartan resulted in a significant 42% RR reduction in stroke in comparison with other antihypertensive treatment, despite little difference in blood pressure reduction. This finding is particularly important given the high stroke risk in this elderly hypertensive population.

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