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A large scale study of angiotensin II inhibition therapy in an elderly population: the CHANCE study

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Abstract: This 8-week, multicenter study evaluated the efficacy and safety of candesartan cilexetil (CC, 8–16 mg) in elderly (>65 years) hypertensive patients. Patients (n=3013) received CC 8 mg during 8 weeks which eventually doubled to CC 16 mg at week 4 if blood pressure remained uncontrolled ($\geq 140/90$ mmHg). At week 8, 65.5% of patients were normalized (BP <140/90 mmHg). Mean changes at week 8 were –25.8, –13.2, and –12.7 mmHg for systolic, diastolic, and pulse pressure, respectively. Age, sex, and diabetic status did not influence the antihypertensive effect of CC. 68% of the patients treated with, but uncontrolled or intolerant of, prior antihypertensive treatment were normalized by CC 8–16 mg. In summary, CC 8–16 mg once daily was effective and well tolerated in the management of arterial hypertension in elderly subjects.

Keywords: candesartan cilexetil, angiotensin II receptor antagonist, hypertension, elderly subject, CHANCE study

Introduction

Hypertension is the most prevalent epidemic disease with a major impact on morbidity and mortality in the current world. Its prevalence is increasing in the adult population, and is estimated to be 30% in developed countries (Asmar et al 2001; ESH 2003).

With increasing longevity, there is a shift from diastolic to systolic high blood pressure (BP). Diastolic BP (DPB) increases until about the age of 60, whereas systolic BP (SBP) continues to rise with age (Vasan et al 2002). Isolated systolic hypertension affects 10%–20% of the elderly and becomes the predominant type of hypertension (nearly 60%) in both treated and untreated elderly subjects (Chobanian et al 2003; Thijs et al 2004). In older patients with isolated systolic hypertension there is an increased risk of developing cardiovascular disease. Clinical trials have demonstrated that control of isolated systolic hypertension reduces global mortality, cardiovascular mortality, stroke, and heart failure events (Chobanian et al 2003). Randomized studies have demonstrated that treating hypertensive older persons is useful in decreasing mortality and morbidity (Mulrow et al 1994). There is strong evidence from clinical trials to support the treatment of systolic hypertension in older person with SBP of at least 160 mmHg (Chaudhry et al 2004).

Despite this knowledge, there is an important gap between the number of hypertensive patients and the percentage of normalized patients (Chaudhry et al 2004). Two principal reasons could explain this gap: on the one hand, there is a poor patient adherence to treatment, and on the other hand, physicians are not aggressive enough in the management of hypertension (Berlowitz et al 1998). Therapeutic approaches include increased doses of antihypertensive agents, the use of combination therapy, or introduction of an alternative class of therapeutic agent.

Initial therapeutic approaches include beta-blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin II receptor antagonists, and low dose combinations (Reif et al 1998; HAS 2005).

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The development of angiotensin II receptor antagonists represented an important advance in the treatment of hypertension. Candesartan cilexetil (CC) is an angiotensin II type 1 (AT1) receptor antagonist. In controlled clinical trials, candesartan has proven to be effective in lowering BP; its efficacy increases up to a dose of 32 mg po once daily (Reif et al 1998; Meredith 2000; Neldam and Forsen 2001). The antihypertensive effect of CC in doses up to 16 mg/day has been confirmed (Elmfeldt et al 1997) with acceptable tolerability in numerous patient groups, including women, diabetics, and patients with severe hypertension (Oparil et al 1999; Trenkwalder 2000).

Materials and methods

Patients

This study included outpatients, over 65 years old, with a diagnosis of essential hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg). Hypertension was untreated, treated with poor tolerability, or treated but not normalized. Patients were enrolled by general practitioners in France.

The exclusion criteria were as follows: age <65 years; orthostatic hypotension; poor tolerance to angiotensin II inhibitors; secondary arterial hypertension; cardiac arrhythmia; congestive cardiac failure; valvular stenosis; ischemic cardiomyopathy or stenosis of a clinically important cerebral artery; surgery or gastrointestinal pathology potentially affecting the absorption or elimination of the treatment study; severe renal or hepatic insufficiency.

Methodology

This 8-week, multicenter study evaluated the efficacy and tolerability of CC in treating elderly hypertensive patients. During the study, the investigator examined the patient at three visits: at inclusion, and after 4 and 8 weeks of treatment. At inclusion, all patients were given CC at a dose of 8 mg once daily. If BP remained uncontrolled (SBP ≥ 140 and/or DBP ≥ 90 mmHg) at week 4, CC was increased to 16 mg once a day. If BP was controlled at week 4, patients remained on CC 8 mg for an additional 4 weeks.

The study was conducted according to the Declaration of Helsinki for biomedical research. The protocol was approved by the French Independent Ethics Committee (IE). Written informed consent was obtained from each patient.

Efficacy and safety criteria

The primary efficacy endpoint was the proportion of patients normalized (BP <140/90 mmHg) by CC at the end of week

8. The secondary efficacy criteria were the proportions of patients normalized at week 4, and the mean BP changes from baseline to week 4 and week 8.

Sitting BP was measured according to guidelines (O'Brien et al 2003) from the dominant arm (arm with the higher SBP) 3 times at 2-minute intervals after the patient had been sitting for at least 5 minutes.

Cardiovascular risk was calculated following ESH guidelines (ESH 2003). Safety was assessed by monitoring the incidence of adverse events during the treatment period, whether reported as related or unrelated to the use of CC. In addition, orthostatic hypotension was surveyed.

Statistical analysis

Efficacy was determined for an intent-to-treat (ITT) population which included all patients who took at least one dose of treatment and for whom the baseline BP value was available. Per-protocol (PP) population consisted of all patients from the ITT population not presenting major protocol deviations. Qualitative variables were compared using the Chi-square test. Groups were compared by analysis of variance (ANOVA). A p value ≤ 0.05 was considered statistically significant.

Results

Patient

A total of 3077 patients were included in the study. Among them, 64 patients were excluded from the analysis (no treatment intake and/or missing BP values at baseline). During follow-up, 2884 patients (95.7%) completed the study, and 129 patients (4.3%) withdrew prematurely (adverse events, $n=28$; protocol deviation, $n=27$; consent withdrawal, $n=13$; lost to follow-up, $n=13$; not determined, $n=17$; inefficacy, $n=4$; other reasons, $n=27$).

ITT population consisted of 3013 patients. At the end of the study (week 8), 58% of patients had received CC 8/8 mg (CC 8 mg the first 4 weeks followed by 8 mg the last 4 weeks), and 42% of patients received CC 8/16 mg (CC 8 mg the first 4 weeks followed by 16 mg the last 4 weeks).

Demographics and baseline characteristics

Baseline clinical characteristics of the patients are presented in Table 1. The arterial hypertension was principally systolic (99.8%). The mean \pm SD hypertension duration was 4.7 ± 6.5 years, with 43.5% of patients diagnosed during the last year and 16.2% of patients diagnosed more than 10 years ago.

Patients with grade I (SBP 140–159 mmHg or DBP 90–99 mmHg), grade II (SBP 160–179 mmHg or DBP 100–109 mmHg), and grade III (SBP \geq 180 mmHg or DBP \geq 110 mmHg) hypertension at entry was 27.7%, 61.2%, and 8.9%, respectively. Hypertension was previously treated in 59% of patients; previous antihypertensive therapy was diuretics (28.6%), calcium inhibitors (23.6%), ACE inhibitors (18.6%), and beta-blockers (8.5%). 85% of patients switched to CC 8 mg because of poor therapeutic response to previous therapy. 99.4% of patients had at least one cardiovascular risk factor.

Antihypertensive effect of candesartan cilexetil

BP normalization

The target of SBP <140 mmHg and DBP <90 mmHg was achieved at week 4 by 1267 patients (42.9%) and at week 8 by 1865 patients (65.5%) (Figure 1). The dose adjustment at week 4 from CC 8 mg to CC 16 mg increased the proportion of responders for both SBP/DBP <140/90 mmHg

Table 1 Baseline characteristics of patients

Characteristics	Total
Age (years) ^a	73 \pm 7
Sex (female) ^b	1696 (56.4)
BMI (kg/m ²) ^a	26.6 \pm 4.2
Isolated systolic HTA ^b	3006 (99.8)
Treated by an anti-hypertensive treatment	1769 (59.0)
Duration of hypertension (years) ^a	4.7 \pm 6.5
Systolic BP (mmHg)	163 \pm 11
Diastolic BP (mmHg)	92 \pm 8
Heart rate (bpm)	75 \pm 8
Pulsed pressure (mmHg)	71 \pm 11
Major cardiovascular risk factors ^b	
Hypercholesterolemia ^c	1019 (33.8)
Current smokers	377 (12.5)
Organ damage	372 (12.3)
Diabetes ^d	278 (9.2)
Abdominal obesity ^e	940 (31.2)
Familial history of cardiovascular disease	678 (22.5)
Risk factors numbers/patient ^a	2.9 \pm 1.2
Level of cardiovascular risk ^b	
Mild	7 (0.2)
Moderate	1056 (35.8)
High	1619 (54.9)
Very high	267 (9.1)
Not available	64 (2.1)

^a Mean \pm SD

^b N(%): absolute number (percentage)

^c Hypercholesterolemia (HDL-cholesterol <0.35 g/L (0.9 mmol/L); LDL-cholesterol >1.90 g/L (4.9 mmol/L))

^d Diabetes was defined by the presence of anti-diabetic treatment

^e Abdominal obesity was assessed by a yes/no question

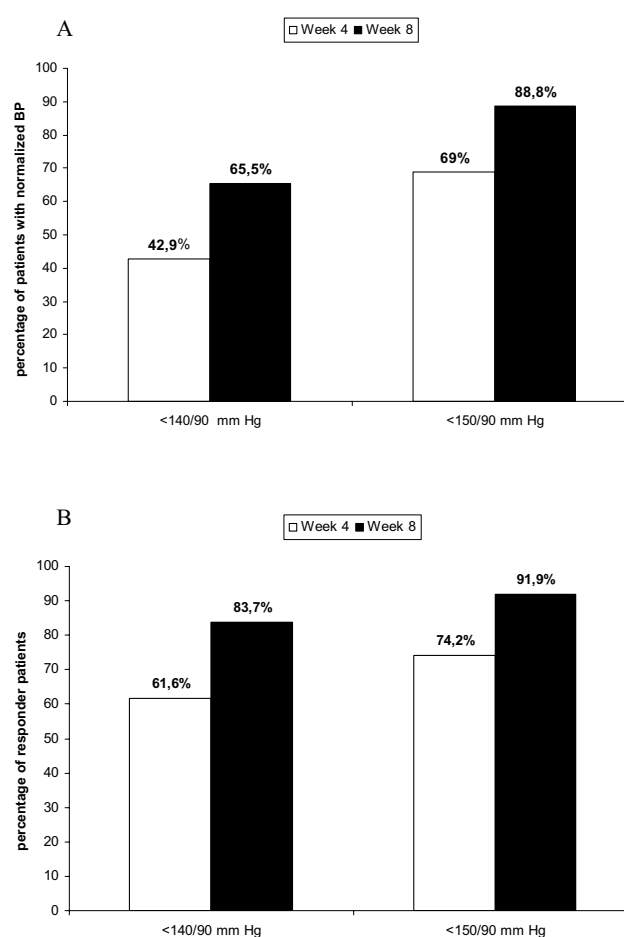


Figure 1 Patients with normalized blood pressure (BP) (A) and responders (B) to candesartan cilexetil (CC) (8–16 mg) at week 4 and week 8. Patients were considered as normalized according to two systolic (S) and diastolic (D) BP targets: SBP/DBP <140/90 mmHg, and SBP/DBP <150/90 mmHg. Patients were considered as responders if they achieved SBP <140 mmHg or a reduction of 20 mmHg on the SBP compared with the baseline value and DBP <90 mmHg or a reduction of 10 mmHg on the DBP compared with the baseline value. Two BP targets were evaluated: SBP/DBP <140/90 mmHg, and SBP/DBP <150/90 mmHg. Week 4, n=2951 and week 8, n=2847. At week 8, 1659 patients received CC 8/8 mg and 1187 patients received CC 8/16 mg.

by 22.6%. Among the patients not responding to CC 8 mg at week 4, 47.9% of patients responded when treated by CC 16 mg. With reference to a target of SBP/DBP <150/90 mmHg, 69% and 88.8% of patients were normalized at week 4 and week 8 respectively (Figure 1A). Similar results with higher proportions of normalized patients were observed in the PP population analysis: the target of SBP/DBP <140/90 mmHg was achieved by 53.4% and 70.5% at week 4 and week 8, respectively.

BP responders

At the end of the study, 83.7% patients showed a clinically significant response (SBP <140 mmHg or reduction of 20 mmHg compared with the baseline value and DBP

Table 2 Mean blood pressure (BP) values (mean \pm SD) at baseline, and after 4 weeks and 8 weeks of candesartan cilexetil (CC)

	Baseline	Week 4	Week 8		
		CC 8mg	Total	CC 8mg	CC 16mg
Systolic BP (mmHg)	163 \pm 11	142 \pm 11	137 \pm 9	134 \pm 7	141 \pm 10
Diastolic BP (mmHg)	92 \pm 8	82 \pm 8	79 \pm 7	78 \pm 6	81 \pm 7
Pulse pressure (mmHg)	71 \pm 11	60 \pm 10	58 \pm 8	56 \pm 7	60 \pm 9
Heart rate (bpm)	75 \pm 8	73 \pm 7	73 \pm 7	72 \pm 7	73 \pm 7

<90 mmHg or reduction of 10 mmHg compared with the baseline value) (Figure 1B). Comparable results were observed in the PP population: the target was achieved by 63.8% and 85.6% at week 4 and week 8, respectively.

BP reduction

BP values showed a significant decrease at week 4 following CC 8 mg treatment. The changes over time in SBP, DBP, and PP values are shown in Table 2. The most important change occurred between baseline and week 4 (SBP/DBP: $-21/-10$ mmHg); BP values continued to decrease up to week 8 (SBP/DBP: $-26/-13$ mmHg). Patients not normalized at week 4 by CC 8 mg, and in whom the dose of CC was increased to 16 mg, showed a decrease in their SBP/DBP values of $-11/-6$ mmHg at week 8.

BP control was inversely related to the degree of hypertension at baseline. Hypertensive patients of grade I, grade II, and grade III were normalized at week 4 in 57.5%, 37.1%, and 27.9% of cases, respectively, and at week 8 in 75.5%, 62.6%, and 47.4% of the cases, respectively.

Previous antihypertensive therapy at baseline did not influence the percentage of normalized patients (68% and 64.1% for treated and untreated, respectively) at the end of the study. Despite different SBP baseline values between previously treated vs untreated patients (161 ± 11 and 164 ± 11 mmHg, $p<0.001$) no differences were found after treatment (136 ± 9 and 137 ± 9 mmHg, treated vs untreated patients).

Antihypertensive effect of CC according to previous treatment, age, sex, and diabetes

After 8 weeks of treatment with CC, significant decreases of SBP were observed for all patients, a mean of 136 mmHg with 95% confidence interval ranging from 135 to 138 mmHg, irrespective of previous treatment (Figure 2).

Variation of SBP and DBP were similar for men and women. Neither age (≤ 80 or >80 years of age) nor diabetes were related to the antihypertensive effect of CC 8–16 mg (Table 3).

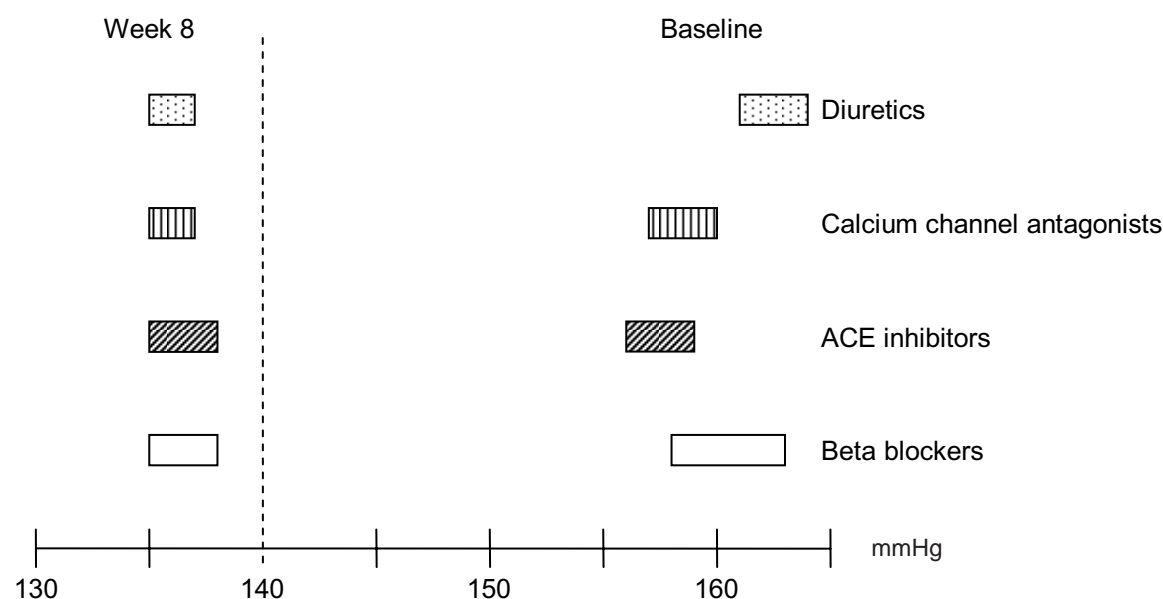


Figure 2 Effect of candesartan cilexetil on systolic blood pressure according to previous antihypertensive treatment. Values are presented as confidence interval 95%. **Abbreviations:** ACE, angiotensin converting enzyme.

Table 3 Influence of age, sex, and diabetes on the systolic and diastolic blood pressure (SBP, DBP) changes (mean \pm SD) of patients treated with candesartan cilexetil (CC)

	Patients N (%)	Baseline		Week 4		Week 8	
		SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Age (years)							
<80	2535 (84)	162 \pm 11	92 \pm 8	142 \pm 11	82 \pm 8	137 \pm 9	79 \pm 7
\geq 80	470 (16)	164 \pm 11	91 \pm 8	143 \pm 12	81 \pm 8	137 \pm 10	78 \pm 6
Sex							
Female	1696 (56)	163 \pm 11	92 \pm 8	142 \pm 11	82 \pm 8	137 \pm 9	78 \pm 7
Male	1313 (44)	162 \pm 11	93 \pm 8	142 \pm 11	82 \pm 8	137 \pm 9	79 \pm 7
Diabetes							
Present	278 (9)	162 \pm 12	92 \pm 8	143 \pm 12	82 \pm 8	137 \pm 10	80 \pm 6
Absent	2735 (91)	163 \pm 11	92 \pm 8	142 \pm 11	82 \pm 8	137 \pm 9	79 \pm 7

Safety results

A total of 219 adverse events (AEs) were reported by 174 patients (5.8%). 51 AEs experienced by 49 patients (1.6%) were considered. 36 AEs resulted in discontinuation in 28 patients (0.9%); 2 of these were severe AEs (breast cancer and severe arterial hypotension). The most common AEs resulting in study discontinuation were vertigo (n=5), rash (n=4), headache (n=3), and nausea (n=2).

Orthostatic hypotension was reported in 4 patients (0.1%) at week 4 and 3 patients (0.1%) at week 8.

Discussion

Treatment of hypertensive patients may be considered to be the achievement of SBP/DBP <140/90 mmHg (Reif et al 1998; HAS 2005). This study demonstrated that CC is an effective treatment for BP control in elderly patients (aged >65 years). Administration of CC 8 mg for 4 weeks and doubling CC dose if the patients did not achieve BP normalization resulted in 65.5% of patients being normalized after 8 weeks of treatment.

At baseline, 59% of patients were already treated by one antihypertensive treatment (28.6% diuretics, 23.6% calcium channel blockers, 18.6% ACE inhibitors, and 8.5% beta-blockers). The results observed in these elderly hypertensive patients corroborate those observed with similar studies performed in middle-aged populations. A European multicenter study showed that switching to angiotensin II receptor blocker (ARB) treatment (candesartan 8–16 mg once daily) was associated with a significant decrease of BP with a higher percentage of responders (Asmar et al 2004). An analysis of the patient subgroup aged >65 years of age in the Switch study (n=236) showed that BP benefit was observed irrespective of age or to previous treatment (Asmar et al 2004).

In patients aged over 60 years, systolic hypertension is a more important cardiovascular disease risk factor than diastolic hypertension. Consequently the control of SBP should be the focus of treatment in this population (Chobanian et al 2003; HAS 2005).

In the present study population, hypertension was principally systolic (99.8% of the patients).

SBP values decreased by an average of 25.8 mmHg. Studies have shown that a small decrease in mean SBP has benefit in terms of cardiovascular morbidity and mortality (Turnbull 2003). Antihypertensive treatment has demonstrated efficacy in primary prevention of cardiac events and stroke in high-risk patients >60 years of age, particularly by lowering SBP (Dahlof et al 1991; SHEP 1991; Staessen et al 1997; Andrawes et al 2005). A recent study conducted by the Study on Cognition and Prognosis in the Elderly Group (Trenkwalder et al 2005) indicated a reduction in major cardiovascular events and stroke in elderly people (70–89 years) treated with candesartan.

One objective of treating elderly subjects (more than 80 years old) is to achieve SBP <150 mmHg in the absence of orthostatic hypotension (HAS 2005). Thomas et al (2006) highlighted the benefit of ARBs in elderly patients with hypertension. In this study, 88.2% of patients were normalized <150 mmHg after being treated for 8 weeks with candesartan 8–16 mg. Orthostatic hypotension was rarely observed (0.1%).

During the last decade, the role of high pulse pressure as an independent marker of cardiovascular morbidity and mortality has been largely described in both treated and untreated hypertensive patients aged over 50 years. Anti-hypertensive agents have varying effects. ARBs decrease high pulse pressure in hypertensive patients. These results demonstrated a significant reduction of 13 mmHg for PP,

which confirm previous studies in hypertensive patients (Vaccarino et al 2001).

Hypertension is often associated other risk factors (sex, age, diabetes). In the present study, the SBP values at baseline demonstrated a significant difference according to age (<80 vs ≥80 years, $p=0.004$) and with the existence of a previous antihypertensive treatment (treated vs untreated, $p<0.001$). After 8 weeks of treatment with CC, no subgroup differences were found for the final BP values (sex, age, diabetes). The results are interesting to compare with the ALLHAT study, where predictive factors for antihypertensive treatment inefficacy included female sex and diabetes (Cushman et al 2002). In the LIFE study, diabetic patients needed more medication than non diabetics for hypertension (Kjeldsen et al 2000). In this study the key factor to predict normalization of both SBP and DBP was the severity of hypertension.

Elderly subjects have an increased susceptibility to adverse reactions from pharmacological treatment. All subjects participating in the present study were more than 65 years old, 470 subjects (16%) were over 80 years old. In this study 1.6% of patients developed an AE related to the treatment and 0.9% discontinued the study. The most common AEs resulting in study discontinuation were vertigo, rash, headache, and nausea. These results suggest that CC is generally tolerated in elderly patients with an acceptable safety profile (Trenkwalder 2000; Neldam and Forsen 2001; Skoog et al 2005). A limitation of the present study is that it was not a controlled study, and it was conducted in general practice.

In conclusion, this large-scale study in elderly hypertensive patients in France, demonstrated that candesartan (8–16 mg once daily) is suitable therapy for effective control of blood pressure and enhanced patient compliance.

Disclosure

Dr Asmar has no conflict of interest. Dr Nisse-Durgeat is an employee of Laboratoire Takeda.

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