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SWITCH FROM ABCD PRETREATMENT TO A-II-A TREATMENT: A MULTINATIONAL, OPEN, CENTRALLY RANDOMIZED, PROSPECTIVE PARALLEL GROUP COMPARISON

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Summary: *The aim of this trial was to evaluate the efficacy and safety of switching antihypertensive monotherapy from a non-angiotensin II receptor blocker treatment,* i.e.*, angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, calcium (Ca^{2+}) channel blocker or diuretic, to monotherapy with candesartan cilexetil 8 or 16 mg once daily. Patients (age 18-74 years) with mild to moderate essential hypertension were enrolled in this multinational, open-label, centrally randomized, prospective parallel group study. Previous antihypertensive treatment, with either an ACE inhibitor, a beta-blocker, a Ca^{2+} channel blocker or a diuretic, was maintained for a run-in period of 4 weeks and was then substituted at the baseline visit where patients were randomized into two groups to receive either candesartan cilexetil 8 mg (*n = 985*) or 16 mg (*n = 982*) once daily for an 8-week treatment period. Blood pressure (BP) reduction was the primary endpoint after 4 weeks of therapy and the secondary endpoint after 8 weeks of therapy. Results of the first 4 weeks of therapy are presented here. A total of 1,967 patients were included: 985 received candesartan cilexetil 8 mg and 982 candesartan cilexetil 16 mg once daily; 1,879 patients were included in the intention-to-treat analysis. The percentages of patients receiving an ACE inhibitor, a beta-blocker, a Ca^{2+} channel blocker or a diuretic as previous antihypertensive treatment were 44.7, 18.8, 30.6 and 5.9%, respectively. After 4 weeks of treatment with candesartan cilexetil 8 and 16 mg, sitting diastolic and systolic BP were reduced (mean ± SD): -7 ± 10 and -14 ± 17 mmHg, and -8 ± 10 and -16 ± 16 mmHg, respectively. The percentage of patients who were still borderline hypertensive or hypertensive after 4 weeks of substitute treatment was lower in the candesartan cilexetil 16 mg group than in the 8 mg group: 7.1 and 5.3%, respectively, versus 9 and 7.4%, respectively. Reported adverse events were mild or moderate in intensity and in accordance with those reported in the literature. Candesartan cilexetil can be considered an effective and safe alternative to other common antihypertensive monotherapies in a large spectrum of patients with mild and moderate hypertension.*

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Introduction

Hypertension is a very common disease associated with increased cardiovascular morbidity and mortality. Cardiovascular risk increases with increasing blood pressure (BP) level. The aim of practitioners, therefore, is to obtain effective BP reduction using one or more antihypertensive drugs (1). Nevertheless, only about one quarter of hypertensive patients show controlled BP < 140/90 mmHg. Different explanations for this high percentage of uncontrolled hypertension have been suggested, ranging from choice and type of antihypertensive drugs, severity of hypertension and its progression, patient understanding of their disease, treatment compliance, cost of the health care procedure, *etc*. (2). Older antihypertensive agents, such as diuretics and beta-blockers, have the advantages of being well accepted, effective and inexpensive. Angiotensin-converting enzyme (ACE) inhibitors are widely used in hypertension because of their additional end organ protection related to their specific action on the renin-angiotensin system (RAS). Calcium (Ca^{2+}) antagonists are efficient with a low level of adverse events and are one of the therapies of choice in the elderly hypertensive patient. According to the international guidelines on hypertension management, switching to an alternative antihypertensive class in case of inadequate BP response or in the presence of problems related to tolerability and/or compliance is recommended (3).

The purpose of this study was to evaluate the efficacy and tolerability of an angiotensin II receptor blocker (ARB), candesartan cilexetil, as an alternative first-line therapy in hypertensive patients.

The RAS plays an important role in the pathophysiology of hypertension. ARBs provide specific blockade of the RAS by blocking the action of angiotensin II directly at the angiotensin type 1 (AT_1) receptor. Candesartan cilexetil is a highly selective, insurmountable angiotensin II AT_1 subtype receptor antagonist devoid of agonist activity. Controlled studies have demonstrated a sustained dose-effect throughout the 24-h dosing interval with a high trough to peak ratio, and most effective BP reduction with doses of 8 and 16 mg once daily. Candesartan cilexetil has the added advantage that its use is not associated with some of the adverse events common with other antihypertensive drug classes (4-6).

The present clinical trial was designed to investigate whether candesartan cilexetil 8 or 16 mg once a day provided an acceptable alternative antihypertensive treatment for patients who could be switched from non-ARB antihypertensive treatment. The study was carried out in three European countries: France, Germany and Italy.

Patients and methods

Subjects. The study was carried out in men and women aged 18-74 years with mild to moderate essential hypertension diagnosed at least 3 months prior to inclusion. All patients had antihypertensive monotherapy with either an ACE inhibitor, a beta-blocker, a Ca^{2+} antagonist or a diuretic, in the 4 weeks prior to the start of the study, and all had a sitting diastolic BP of ≤ 95 mmHg and systolic BP of ≤ 180 mmHg. Exclusion criteria included secondary, severe or malignant hypertension; chronic diseases, including cancer and wasting disease; hepatic disease [serum glutamic oxaloacetic transaminase (SGOT) ≥ 108 IU/ml or gamma-GT ≥ 224 U/l]; impairment of renal function [serum creatinine > 200 μmol/l, 2.2 mg/100 ml if ≥ 65 years; > 250 μmol/l, 2.8 mg/100 ml (females), > 300 μmol/l, 3.3 mg/100 ml (males) if ≤ 65 years]; and known hypersensitivity to ACE inhibitors or ARBs. Patients receiving antihypertensive combination therapy or beta-blocker therapy for treatment of coronary heart disease (CHD)/angina pectoris were not included in the study. Pregnant or breast-feeding women were also excluded.

Written informed consent was obtained from all patients prior to their inclusion in the study. The study was approved by the local and/or national ethics committees of the investigation centres and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study design. General practitioners and specialists in internal medicine were selected as investigators to obtain a broad sample of physicians able to switch antihypertensive therapies. The study was designed as a multicenter, multinational, open-label, prospective parallel group study to assess the efficacy and tolerability of candesartan cilexetil 8 and 16 mg. Patients satisfying selection criteria after a 4-week run-in period, during which previous antihypertensive treatment was continued, were randomized, in a 1:1 ratio, to treatment with candesartan cilexetil 8 or 16 mg once daily. Patients treated with a beta-blocker treatment during the run-in period had to reduce the treatment dose progressively (down-titration) during the week prior to the start of candesartan cilexetil intake, in order to avoid abrupt withdrawal. At the end of the first 4-week treatment period, if sitting BP was not lowered to ≤ 140/90 mmHg, then the dose had to be doubled in patients randomized to candesartan cilexetil 8 mg and treatment had to be continued for an additional 4 weeks. In Germany, all patients on the candesartan cilexetil 8 mg dose had the dose increased to 16 mg. In the group randomized to candesartan cilexetil 16 mg, non-responders could be withdrawn, or alternatively continue treatment until the end of the study, at the discretion of the investigator. The patients were seen at day 14, which was optional and for safety reasons, and at days 28 and 56 after randomization. Patients whose diastolic BP exceeded 120 mmHg or whose systolic BP was above 220 mmHg were withdrawn.

Drug treatment. The study medication consisted of candesartan cilexetil 8 or 16 mg in tablet form. All doses were taken once daily between 06:00 am and 09:00 am. Patients were urged to return their unused study drugs at each visit. Returned/unused tablets were counted to assess compliance. Patients showing compliance of less than 75% or more than 125% were withdrawn from the study. Concomitant use of other antihypertensive or antianginal treatments, vasoactive drugs, antiarrhythmics, systemic glucocorticoids or mineral corticoids, immunosuppressive or cytotoxic agents, and drugs likely to affect the gastrointestinal absorption of study medication were not permitted during the study. The use of oral contraceptives and hormone replacement therapy was permitted.

Measurements. BP, heart rate and adverse events were recorded at each visit. A 12-lead electrocardiogram (ECG), a physical examination, and blood samples for biochemistry and hematology were performed at the screening visit and at the end of the 8-week treatment period.

BP was measured clinically using a standard sphygmomanometer according to the World Health Organization (WHO) recommendations. At the first visit, BP was measured in both arms, and the arm with the highest BP was used for all subsequent measurements. The sitting diastolic and systolic BP were assessed in triplicate with an interval of at least 2 min between measurements, and after a period of rest of at least 5 min. The arithmetic mean of the last two measurements was used as the clinical BP reference value.

Adverse events were recorded in response to the question: “Have you been uncomfortable since the last visit?”. Objectively observed adverse events were also noted. An adverse event was defined as any untoward medical occurrence in a patient taking an investigational drug or a marketed drug, whether or not

considered drug-related. At each visit, the type, intensity and duration of the adverse events were recorded and the causal relationship with the study medication was assessed according to standard criteria.

Statistical analysis. Assuming a standard deviation (SD) of 8.5 mmHg and a dropout rate of approximately 20% for the primary efficacy variable, 250 patients per pretreatment group would provide a power of 90% to detect a mean difference in diastolic BP of ≥ 2 mmHg with a two-sided *p*-value of <0.05. Efficacy analysis was performed on all randomized patients who received at least one dose of the treatment drug and who provided at least one post-baseline BP recording in the intention-to-treat population. The primary efficacy parameter of the study was BP response to candesartan cilexetil after 4 weeks of treatment. Secondary efficacy parameters were changes in mean sitting BP after 8 weeks of treatment. The percentage of normotensive (diastolic BP ≤ 90 mmHg), borderline hypertensive (diastolic BP 90-95 mmHg) and hypertensive (diastolic BP $>$ 95 mmHg) patients was calculated at baseline and after 4 weeks of treatment. Comparison of the percentages between baseline and after 4 weeks of treatment was performed using Bowker's test of symmetry. The results were presented in a three-by-three frequency table (row: baseline data, column: treatment data).

Changes from baseline were expressed as a mean value with standard deviation and a 95% confidence interval. A paired Student's *t*-test was used to assess the statistical significance of changes in mean values.

Subgroup analyses were performed with regard to the different pretreatment medications (ACE inhibitor, beta-blocker, Ca^{2+} antagonist or diuretic) and with regard to the different baseline demographic characteristics, *e.g.,* gender, age and body mass index (BMI). Efficacy data at 8 weeks are not presented because there were variations in the protocol dose titration recommendations in the various participating countries.

Safety analysis was performed on all randomized patients who received at least one dose of the treatment drug. The frequency, severity, outcome and relationship to study drug were tabulated for all adverse events.

Data are shown as mean ± SD, unless otherwise indicated. All statistical tests were performed at a significance level of 0.05.

Results

Demographic and clinical data. A total of 1,967 patients were included in the study, with 427 in France, 574 in Germany, and 966 in Italy. Of these patients, 985 received candesartan cilexetil 8 mg once daily, while 982 received candesartan cilexetil 16 mg once daily. A total of 1,879 patients were included in the intention-to-treat analysis: 939 patients in the 8-mg group and 940 patients in the 16-mg group. Their clinical characteristics are shown in Table I. Half of the patient population was either overweight or obese; 1,449 patients (74%) were under the age of 65 years. A total of 163 patients discontinued the study due to adverse events ($n = 41$); major protocol deviations ($n = 32$); lack of efficacy of trial medication ($n = 8$); patients lost to follow-up ($n = 7$); and other reasons ($n = 75$).

Previous antihypertensive treatments included ACE inhibitors (47%), beta-blockers (18.8%), Ca^{2+} antagonist (30.6%), or diuretics (5.9%). The most commonly used ACE inhibitor was enalapril, which made up 26.6% of the total ACE inhibitor use, while atenolol was the most commonly used beta-blocker (27.4%). Amlodipine was the most commonly used Ca^{2+} antagonist (34.6%), and spironolactone plus altizide (aldactizine) was the most commonly used diuretic (32.7%). At baseline, the percentage of normotensive,

Table I *Baseline clinical characteristics of the population (mean ± SD)*

	Candesartan cilexetil 8 mg (n = 985)	Candesartan cilexetil 16 mg (n = 982)
Age (years)	56 ± 11	56 ± 11
Sex		
Male (%)	44	46
Female (%)	56	54
Height (cm)	167 ± 9	167 ± 9
Weight (kg)	76 ± 14	78 ± 15
BMI (kg/m^2)	27 ± 4	28 ± 5
Alcohol intake		
Yes (%)	15	15
No (%)	56	56
Smokers		
Yes (%)	18	15
No (%)	81	85

BMI: body mass index.

borderline hypertensive, and hypertensive patients was 40, 34.7 and 25.3%, respectively; there was similar distribution in both treatment groups.

Gender, BMI and type of previous antihypertensive therapy did not significantly influence the BP response to candesartan cilexetil.

Blood pressure and heart rate. Four weeks after switching to candesartan cilexetil, BP of the entire population was significantly reduced ($p < 0.001$) (Table II). In the candesartan cilexetil 8 mg group, the mean decrease from baseline was -7 ± 10 mmHg and -14 ± 17 mmHg for sitting diastolic and systolic BP, respectively. In the candesartan cilexetil 16 mg group, sitting diastolic and systolic BP were reduced by -8 ± 10 mmHg and -16 ± 16 mmHg, respectively. Analyses per pre-treatment group showed that BP was significantly reduced by candesartan cilexetil 8 mg or 16 mg, irrespective of the previous type of antihypertensive drug used (Table III).

Reduction in BP was also reflected in the percentage distribution of patients classified normotensive, borderline hypertensive, or hypertensive at baseline and after 4 weeks of treatment. The percentage of patients classified normotensive after 4 weeks of candesartan cilexetil treatment was 77.7 and 85.5% in the 8 mg and 16 mg groups, respectively (Fig. 1). The percentage of patients classified borderline hypertensive or hypertensive after 4 weeks of treatment was lower in the candesartan cilexetil 16 mg group (8.1 and 6.4%, respectively) *versus* candesartan cilexetil 8 mg group (12 and 10.2%, respectively). Bowker's test of symmetry revealed these differences from baseline to be statistically significant ($p < 0.0001$).

Subpopulation analysis according to the previous antihypertensive treatment and age was performed.

Results of BP reduction after 4 weeks of candesartan cilexetil treatment are shown separately, according to previous type of treatment, and for patients < 65 and > 65 years of age (Table III). BP was reduced by candesartan cilexetil 8 mg or 16 mg, irrespective of the previous type of antihypertensive drug. The mean reduction in diastolic BP and the corresponding lower and upper bounds of the confidence interval were greater than 2 mmHg, irrespec-

Table II *Mean values of sitting diastolic blood pressure (DBP), systolic BP (SBP) and heart rate in total population and subgroups by age (mean ± SD)*

	Candesartan cilexetil 8 mg		Candesartan cilexetil 16 mg	
	Baseline	At 4 weeks	Baseline	At 4 weeks
Total population	$n = 939$		$n = 940$	
DBP (mmHg)	92 ± 8	86 ± 8	92 ± 8	84 ± 8
SBP (mmHg)	157 ± 16	143 ± 14	157 ± 17	142 ± 14
Heart rate (bpm)	75 ± 10	74 ± 9	74 ± 10	74 ± 9
Patients < 65 years	$n = 703$		$n = 686$	
DBP (mmHg)	92 ± 8	86 ± 8	92 ± 8	84 ± 8
SBP (mmHg)	155 ± 16	142 ± 14	155 ± 17	140 ± 14
Patients 65 years	$n = 236$		$n = 253$	
DBP (mmHg)	93 ± 8	86 ± 8	92 ± 9	85 ± 8
SBP (mmHg)	163 ± 15	147 ± 13	163 ± 16	146 ± 14

tive of the previous type of antihypertensive therapy. Results of BP reduction by age *versus* the whole population are shown (Table II).

Heart rate remained unchanged during the study in both the candesartan cilexetil 8 and 16 mg groups (Table II).

Table III *Changes in blood pressure values (mmHg) and heart rate (bpm) in total population and subgroups at 4 weeks from baseline (*± SD)

	Candesartan cilexetil 8 mg			Candesartan cilexetil 16 mg		
	DBP (mmHg)	SBP (mmHg)	Heart rate (mmHg)	DBP (mmHg)	SBP (mmHg)	Heart rate (bpm)
Total population ($n = 939$)	-7 ± 10	-14 ± 17	-1 ± 10	-8 ± 10	-16 ± 16	0 ± 9
Pretreatment						
ACE inhibitors ($n = 400$)	-5 ± 10	-13 ± 16	0 ± 9	-8 ± 10	-15 ± 15	0 ± 9
Beta-blockers ($n = 164$)	-8 ± 9	-18 ± 16	2 ± 11	-9 ± 10	-17 ± 18	4 ± 10
Ca^{2+} antagonists ($n = 278$)	-6 ± 9	-12 ± 17	-2 ± 9	-7 ± 10	-14 ± 16	-1 ± 8
Diuretics (n = 53)	-13 ± 9	-21 ± 13	-3 ± 8	-12 ± 8	-24 ± 14	-5 ± 8
Patients < 65 years ($n = 703$)	-6 ± 9	-13 ± 17	0 ± 10	-8 ± 9	-16 ± 16	0 ± 9
Patients 65 years ($n = 236$)	-7 ± 10	-16 ± 17	-1 ± 9	-8 ± 10	-16 ± 16	0 ± 8

DBP: diastolic blood pressure; SBP: systolic blood pressure.

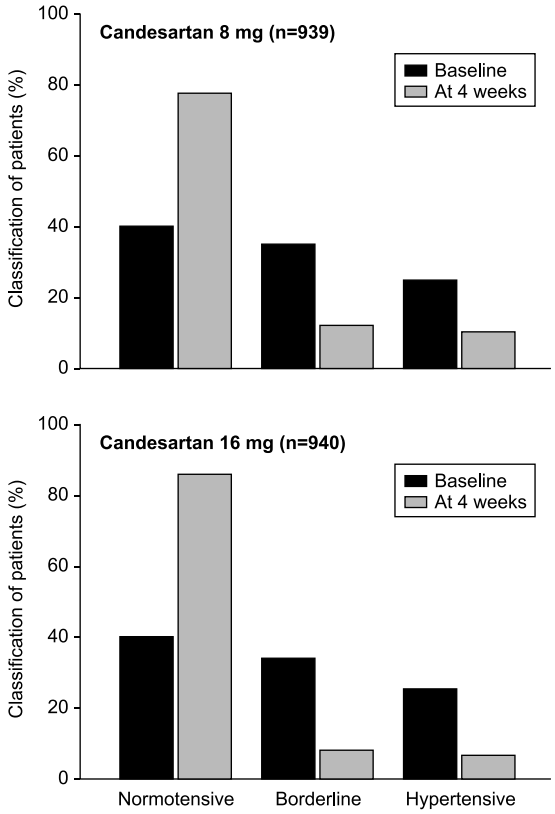

Fig. 1 Patient classification at baseline and at 4 weeks for candesartan 8 mg and 16 mg groups.

Adverse events. The proportion of patients experiencing any adverse event was similar in the two treatment groups: 128/985 (13.0%) patients in the candesartan cilexetil 8 mg group, and 124/982 (12.6%) patients in the 16 mg group. The most commonly experienced adverse event, reported in > 1% of the patients in one of the treatment groups, was headache. The majority of adverse events were mild to moderate in intensity. The safety and tolerability of candesartan cilexetil was also assessed in the subpopulation of elderly patients 65 and older (n = 517). Overall, there were no major adverse events that occurred more frequently in these subgroups than in the entire population.

Discussion

This large-scale, 8-week, open-label, clinical trial evaluated the efficacy and tolerability of candesartan cilexetil 8 and 16 mg once daily as substitute therapy in patients with mild to moderate essential hypertension previously treated with either an ACE inhibitor, Ca^{2+} antagonist, beta-blocker or diuretic.

The study was conducted in three European countries—France, Germany and Italy—in a large population of patients. Use of different antihypertensives was recorded, giving a sense of the drugs of choice in the participating countries.

The antihypertensives of choice at baseline were by far the ACE inhibitors (44.7%), of which enalapril was the most frequently used. Ca^{2+} antagonists were the second therapy of choice (30.6%), of which amlodipine was most commonly used. Contrary to what is generally perceived, beta-blockers and diuretics were not prescribed as frequently as recommended by guidelines. This finding may reflect that the additional properties or benefits of ACE inhibitors and Ca^{2+} antagonists are well accepted by practitioners. Efficacy and tolerability of both 8 and 16 mg candesartan cilexetil once daily on sitting diastolic and systolic BP showed that switching to this treatment may be considered in treated hypertensive patients with uncontrolled BP. With BP levels at baseline similar in both treatment groups, a tendency towards more adequate BP reduction was observed with candesartan cilexetil 16 mg after 4 weeks of treatment.

The study also indicated that patients benefited from switching to candesartan cilexetil: after 4 weeks of candesartan cilexetil therapy, more patients had

their diastolic BP normalized (< 90 mmHg) than those recorded at baseline, 81.6 *versus* 40%, respectively. The percentage of patients under adequate control by treatment at baseline matched data available in the literature, *i.e.,* 30% (7, 8). The dose that achieved the best normalization values was candesartan cilexetil 16 mg, thus reflecting the currently accepted view that there is a dose-response effect (9-11).

The subpopulation analysis of the improved response, according to previous type of antihypertensive treatment received, showed no major differences in BP reduction compared with the overall population. Patients pretreated with an ACE inhibitor were shown to benefit from additional BP reductions with both candesartan 8 mg and 16 mg (Table III). This is an interesting finding: it is often believed that nonresponders to ACE inhibitors will also be nonresponders to an ARB. It has been hypothesized that patients may have additional benefits from direct angiotensin I receptor blockade. In patients previously treated with beta-blockers or diuretics, there was a tendency towards a greater BP reduction. This may be due to a lower compliance rate in these patients due to adverse events, or because their BP may have rebounded after withdrawal of the pre-treatment drug in the case of beta-blockers (12-14). The subpopulation analysis by age showed no major differences in BP reduction compared to the overall population.

Heart rate remained almost unchanged during the study in both treatment groups. In general, side effects recorded were minor and similar to those reported for candesartan cilexetil in the literature and on the product information leaflet (15, 16). The most commonly experienced adverse event was headache. Adverse events were generally not dose-related and were of mild to moderate severity. Of the related adverse events, headache and dizziness, known possible side effects of antihypertensive treatment, were most frequently reported (13). In the subpopulations analyzed, the incidence of side effects was no higher than that of the overall population. The finding that candesartan cilexetil was equally well tolerated in elderly and younger patients, as well as in men and women, has already been discussed in previous studies (15-17). Furthermore, while this study did not include a direct comparison of the tolerability of candesartan cilexetil with that of other antihypertensive agents, it is worth noting that the drug was not associated with many of the adverse events common to other antihypertensive drug classes, *e.g.,* it was not associated with cough, a common side effect with ACE inhibitors, nor with ankle edema, a possible side effect of Ca^{2+} channel blockers treatment (13, 18, 19). The overall tolerability of the treatment at both doses of candesartan cilexetil was assessed as very good or good in more than 95% of the patients for the entire study population as well as for all the subgroups analyzed.

These results concurred with similar efficacy and tendency towards better tolerability of candesartan observed in other comparative studies (20, 21). The combination of good efficacy, excellent tolerability and once daily dosing regimen of candesartan cilexetil might have a positive impact on patient compliance and strengthen the position of candesartan cilexetil as a first-line therapy. This may be especially true for elderly patients who are more prone to adverse effects.

Conclusion

The present study shows that switching from monotherapy with an ACE inhibitor, a beta-blocker, a Ca^{2+} antagonist or a diuretic, to candesartan cilexetil 8 or 16 mg in patients with mild to moderate essential hypertension reduces BP in patients after a treatment period of 4 weeks. Both candesartan cilexetil 8 and 16 mg once daily were well tolerated. In general, after 4 weeks of treatment candesartan cilexetil 16

mg gave a more pronounced BP reduction than the 8 mg dose. Efficacy and tolerability appear to be unrelated to the previous type of antihypertensive treatment or age. Candesartan cilexetil, at doses of 8 and 16 mg, can be considered as an effective and safe alternative to classical antihypertensive drugs: ACE inhibitors, beta-blockers, Ca^{2+} antagonists and diuretics.

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