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ORIGINAL ARTICLE

A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM Study II

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An 8-week, multicentre (72 sites in the US), double-blind, randomised, parallel group, forced titration study compared the antihypertensive efficacy of candesartan cilexetil and losartan. A total of 611 patients with essential hypertension (diastolic blood pressure 95 to 114 mm Hg) were randomised initially to candesartan cilexetil 16 mg once daily or losartan 50 mg once daily. After 2 weeks of randomised treatment, the doses of candesartan cilexetil and losartan were doubled to 32 mg and 100 mg once daily and continued respectively for 6 weeks. At week 8, candesartan cilexetil lowered the blood pressure (BP) at 24 h (trough), 6 h (peak) and 48 h post dose to a significantly greater extent ($P < 0.05$) than losartan: candesartan cilexetil lowered trough BP by 13.4/10.5 mm Hg, peak BP by 15.5/12.9 mm Hg and 48-h BP by 10.5/9.9 mm Hg compared to a reduction of trough BP by 10.1/9.1 mm Hg, peak BP by 12.0/9.5 mm Hg, and 48-h BP by 5.9/7.0 mm Hg by losartan. The responder and control rates were numerically higher in the candesartan cilexetil group, but the differences did not reach statistical significance; the responder rates were 58.8% for the candesartan cilexetil group and 52.1% for the losartan group and control rates were 49.0% for the candesartan cilexetil group and 44.6% for the losartan group. Overall, both treatment regimens were well tolerated. A total of 15 of the 611 (2.5%) patients withdrew from the study due to an adverse event, including nine (2.9%) in the candesartan cilexetil group and six (2.0%) in the losartan group. In conclusion, this forced titration study confirms that candesartan cilexetil is more effective in lowering BP than losartan when compared at once daily maximum doses.
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Introduction

The two angiotensin II type 1 receptor blockers (ARBs), candesartan and losartan, exhibit different binding characteristics to the AT_1 subtype of the angiotensin II receptor. Morsing *et al*[1] demonstrated that candesartan acted as an insurmountable antagonist with a marked and long-lasting blockade of the vascular contractile effects of angiotensin II whereas losartan and its active metabolite, EXP 3174, behaved like surmountable or partially surmountable antagonists with a relatively short duration of action. Vanderheyden *et al*[2] found that the dissociation half-life from the AT_1 receptor was 152 min for candesartan, 5 min for losartan and 31 min for EXP3174.

Three previous randomised, controlled trials have demonstrated greater antihypertensive effects of candesartan cilexetil over losartan. These studies either evaluated the starting doses of both drugs or used a response titration design for comparison of their maximum doses.[3–5] A fourth study by Bakris *et al*[6] (CLAIM Study I) and the present study (CLAIM Study II), are two identically designed, concurrently conducted, double-blind, randomised forced titration studies to provide direct comparison of the blood pressure (BP) lowering effects at once daily maximum doses. CLAIM Study I showed that

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[6]See Appendix
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candesartan cilexetil lowered all the primary and secondary BP parameters by a significantly greater amount ($P < 0.05$) than losartan in 654 hypertensive patients.[6] The present report summarises the findings of CLAIM Study II on 611 patients with systemic hypertension.

Patients and methods

Patients

A total of 611 men or women (without child bearing potential) between 18 and 80 years of age, with essential hypertension (diastolic BP (DBP) 95–114 mm Hg) were enrolled into the study. Major exclusion criteria included systolic BP ⩾180 mm Hg or diastolic BP ⩾115 mm Hg, known hypersensitivity reaction to ARBs, secondary hypertension, severely impaired liver function, significant renal impairment, haemodynamically significant valvular heart disease, angina pectoris requiring more than short-acting nitrates, recent history of myocardial infarction, coronary revascularisation procedures, stroke or transient ischaemic attack. Current use of an antihypertensive agent was cause for exclusion unless it could be discontinued safely by the first week of the placebo-run-in period.

Study design

This was an 8-week, multicentre (72 sites in US), double-blind, randomised, parallel group, forced titration study. After a 4- or 5-week single-blind, placebo run-in period, enrolled patients were randomised centrally with a computer generated randomisation list in a 1:1 ratio to candesartan cilexetil 16 mg tablet once daily or losartan 50 mg once daily. After 2 weeks of randomised treatment, the doses of candesartan cilexetil and losartan were doubled and continued for 6 weeks. The patients were asked to take the study medication in the morning with no specific instruction regarding food. In general, food does not affect the absorption of candesartan and has only minor effects on the AUC of losartan and its metabolite.[7] Visits were scheduled at weeks 1, 2, 4 and 8 of the 8-week double-blind treatment period. Patients were also seen 48 h following their last dose of study medication and 2 weeks after they discontinued therapy with the study medication for follow-up visits. Post-study treatment for hypertension was not instituted until after the 48-h assessment was completed.

For each patient, visits were scheduled at the same time in the morning. Patients were instructed to refrain from taking the study medication on the morning of clinic visits until after BP was measured. All BP determinations were performed in the sitting position using a mercury sphygmomanometer from the right arm after the patient had sat quietly for at least 5 min. BP was measured 3 times at 2-min intervals and the mean value computed. The differences in the diastolic BP readings were required to be no more than 5 mm Hg with additional readings performed if necessary until such consistency was obtained.

At each visit, trough sitting diastolic (D) and systolic (S) BP (24 ± 3 h after dose), heart rate, concomitant medications and adverse events were recorded. An adverse event is defined as any unfavourable changes in symptoms, signs or laboratory data temporally associated with the use of study medication whether or not considered related to the use of study medication. In addition, peak BP (6 ± 2.5 h after dose) was measured at week 3 or 4 of the placebo run-in period and also at week 8 of the double-blind period. The definition of a peak effect at 6 h after dose was chosen as previous studies indicated that the peak effect of losartan occurred approximately 6 h and that of candesartan cilexetil occurred after 4 to 8 h.[8,9] The trough-to-peak ratio was determined from dividing the trough DBP effect by the peak DBP effect. Laboratory tests including blood counts, renal and liver function tests were performed by a central laboratory (SmithKline Beecham Clinical Laboratories) at week 3 of the placebo run-in period and also at week 8 of the double-blind period. Any abnormal laboratory values from week 8 were re-evaluated at the 2-week follow-up visit.

Statistical methods

The primary efficacy parameter was mean change from baseline to week 8 in trough DBP. Based on this sample size and the 1:1 randomisation scheme, the study had at least 90% power to detect a true difference in mean change from baseline in trough sitting diastolic BP of 2.0 mm Hg between the two treatment groups. This estimate assumes a standard deviation of 7.5 mm Hg and is based on a two-tailed test with $\alpha = 0.05$. Secondary efficacy variables included change from baseline to week 8 in trough SBP and peak SBP/DBP, proportion of responders (patients with either a DBP of <90 mm Hg or a decrease from baseline in DBP of ⩾10 mm Hg at week 8) and controlled patients (DBP of <90 mm Hg at week 8), and the change from baseline BP at 48 h post last dose of study medication. An analysis of covariance for a randomised block design was used to assess the primary and secondary variables, with baseline as the covariate and the study site as the block. All data analyses are presented using the least-squares means (LSM) and 95% confidence intervals (CI). Efficacy analyses for trough sitting DBP, SBP were performed using an intent-to-treat approach with the last observation carried forward. Efficacy analyses with peak sitting and 48 h post last dose BP were performed with actual values as these readings were taken at baseline and once again at their respective and points—either at week 8 or 48 h after the week 8 visits. The statistical difference in the responder and control rates between the treatment groups at week 8 were determined using Fish-

Table 1 Patient characteristics at baseline

	Candesartan cilexetil (n = 307)	*Losartan (n = 304)*	*Overall (n = 611)*
Age (yrs)[a]	55.5 (9.9)	55.1 (11.0)	55.3 (10.5)
Weight (lbs)[a]	204.7 (44.5)	200.6 (41.3)	202.6 (43.0)
Duration of hypertension (yrs)[a]	10.5 (9.4)	10.3 (9.8)	10.4 (9.6)
Sex[b]			
Male	179 (58.3)	179 (58.9)	358 (58.6)
Female	128 (41.7)	125 (41.1)	253 (41.4)
Race[b]			
Non-black	245 (79.8)	245 (80.6)	490 (80.2)
Black	62 (20.2)	59 (19.4)	121 (19.8)
Baseline trough sitting DBP (mm Hg)[a]	100.4 (4.3)	100.2 (4.3)	100.3 (4.3)
Baseline trough sitting SBP (mm Hg)[a]	153.6 (11.7)	152.2 (12.3)	152.9 (12.0)
Baseline peak sitting DBP (mm Hg)[a]	97.8 (6.1)	97.3 (6.1)	97.5 (6.1)
Baseline peak sitting SBP (mm Hg)[a]	151.5 (11.7)	150.3 (12.6)	150.9 (12.2)

[a]Expressed as mean (s.d.).
[b]Expressed as number (%).

Table 2 Least squares mean changes from baseline to week 8 in blood pressure

BP measure (mm Hg)	*Candesartan cilexetil LSM*	*Losartan LSM*	*Mean difference*	*P-value*
Trough sitting DBP[a]	−10.5	−9.1	1.5	0.0411
Trough sitting SBP[a]	−13.4	−10.1	3.4	0.0050
Peak sitting DBP[b]	−12.9	−9.5	3.4	0.0001
Peak sitting SBP[b]	−15.5	−12.0	3.5	0.0032
48-h, post-dosing trough sitting DBP[b]	−9.9	−7.0	2.8	0.0002
48-h, post-dosing trough sitting SBP[b]	−10.5	−5.9	4.6	0.0003

LSM, least squares mean.
[a]Intent-to-treat, last-observation-carried forward population (candesartan cilexetil: $n = 306$; losartan: $n = 303$).
[b]Patients with data available: peak sitting BP (candesartan cilexetil: $n = 274$; losartan: $n = 266$); 48-h, post-dosing BP (candesartan cilexetil: $n = 246$; losartan: $n = 247$).

er's exact test. Both descriptive and inferential statistics between treatment groups were calculated for the primary and secondary BP parameters. Patient characteristics at baseline, trough-to-peak ratios, adverse events and laboratory data were compared descriptively between the two treatment groups. Laboratory data were evaluated according to predefined limits of change and mean change from baseline.

Results

Of the 611 patients, 307 patients were randomised to candesartan cilexetil and 304 patients to losartan. A total of 535 patients (88%) completed the study: 87% for candesartan cilexetil and 88% for losartan. The study population was 58.6% male, 19.8% black with a mean age of 55 years and a baseline BP of 152.9/100.3 mm Hg. Patient characteristics at baseline were similar in the two treatment groups (Table 1).

Table 2 lists the comparison between the candesartan cilexetil and losartan treatment groups in lowering the trough, peak and 48-h post last dose diastolic and systolic BP, all being statistically significant. Figure 1 shows the mean trough BP at week 8 in each group with candesartan cilexetil lowering trough SBP/DBP by 13.4/10.5 mm Hg compared to 10.1/9.1 mm Hg by losartan ($P < 0.05$).

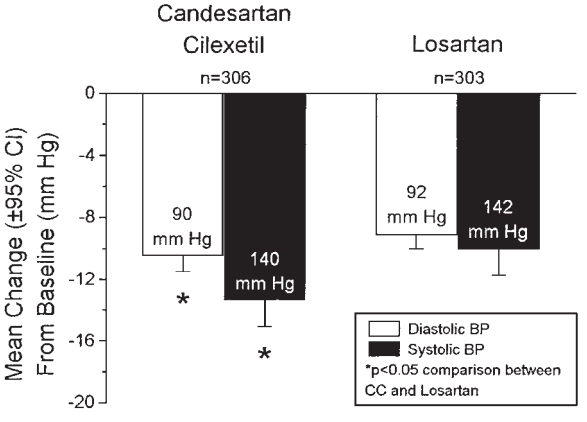

Figure 1 Effects of candesartan cilexetil and losartan on trough blood pressure (BP). Labels within bars are means of intent-to-treat, last value carried forward, readings of the trough sitting BP readings (24 ± 3 h after dosing) at week 8. CI, confidence intervals; CC, candesartan cilexetil.

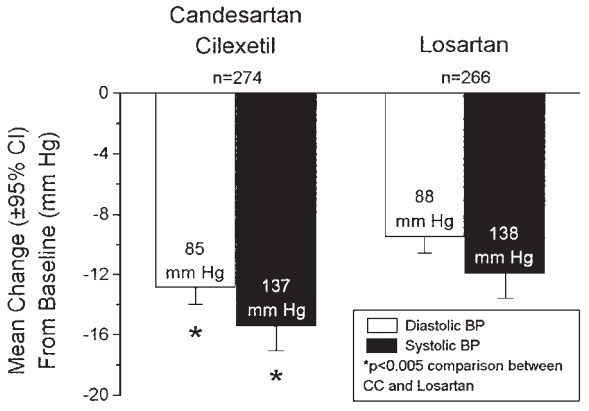

Figure 2 Effects of candesartan cilexetil and losartan on peak blood pressure (BP). Labels within bars are means of the peak sitting BP readings (6 ± 2.5 h after dosing) at week 8. CI, confidence intervals; CC, candesartan cilexetil.

Figure 2 shows the mean peak BP at week 8 in each group with candesartan cilexetil reducing peak SBP/DBP by 15.5/12.9 mm Hg compared to 12.0/9.5 mm Hg by losartan ($P < 0.005$). Figure 3 shows the mean 48-h BP at week 8 in each group with candesartan cilexetil lowering the 48-h post last dose SBP/DBP by 10.5/9.9 mm Hg *vs* 5.9/7.0 mm Hg by losartan ($P < 0.0005$). At the week 8 visit, the trough-to-peak ratios were 0.86 for candesartan cilexetil and 0.92 for losartan. Candesartan cilexetil also produced a numerically higher responder rate (58.8% for candesartan cilexetil and 52.1% for losartan) and control rate (49.0 for candesartan cilexetil and 44.6% for losartan) but the differences did not reach statistical significance.

Overall, the incidence and intensity of adverse events were similar in the two treatment groups. A total of 276 of 611 (45.2%) patients reported adverse event: 45.6% in the candesartan cilexetil group and 44.7% in the losartan group. Most adverse events were mild in intensity and resolved with continued treatment including dose escalation. The three most common adverse events for the candesartan cilexetil group were headache (7.2%), respiratory infection (3.9%), and sinusitis (3.9%), whereas those for the losartan group were respiratory infection (7.9%), headache (5.9%), and rhinitis (3.6%). A total of 15 of the 611 (2.5%) patients withdrew from the study due to an adverse event, including nine (2.9%) in the candesartan cilexetil group and six (2.0%) in the losartan group. Only four of the 611 (0.7%) patients reported adverse events that were considered serious due to hospitalisation during the double-blind treatment period; two were in the candesartan cilexetil group and two were in the losartan group. There were no deaths during this trial. Minor changes from baseline in laboratory values were observed in isolated individuals. There were no clinically meaningful changes in mean laboratory values in either treatment group and no laboratory evidence of deterioration in renal, hepatic, or metabolic function.

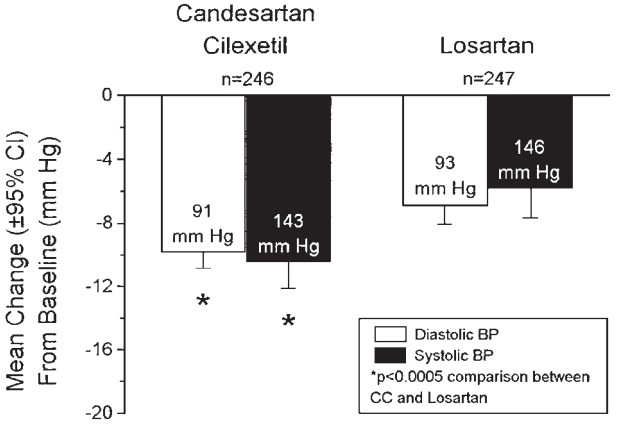

Figure 3 Effects of candesartan cilexetil and losartan on blood pressure (BP) 48 h after the last dose of study medications. Labels within bars are means of the 48 h BP readings at week 8. CI, confidence intervals; CC, candesartan cilexetil.

Discussion

The present study was designed to provide an effective comparison of the BP lowering effects of these two ARBs. Candesartan is a once-daily drug although losartan is occasionally used twice daily as its package insert states that peak effects are uniformly but moderately larger than trough effects. Thus, the study measured not only trough SBP/DBP but also peak and 48 h post dose BP. Although the trough-to-peak ratio did not give any details of the actual BP effects during the 24-h period, a high trough/peak ratio confirms a substantial persistence of the peak BP lowering effects of the drug before the next dosing. With the value exceeding 80% for each drug, both drugs were effective as once daily antihypertensive agents. The 48-h post dose BP was measured to evaluated whether the insurmountable AT_1 receptor binding characteristics of candesartan translated clinically into more sustained BP lowering effects. Although only about 80% of patients showed up for the 48-h post dose BP measurement, the drop outs were comparable from each group and the reading was available in a fairly large number of patients (a total of 493 patients). The findings of the impressive extended therapeutic BP lowering effects of candesartan cilexetil compared to losartan suggest that the different receptor binding properties of the two ARBs resulted in tangible clinical benefits in case of a missed dose. Candesartan had an AT_1 binding affinity in rabbit aorta 80 times greater than that of losartan and 10 times greater than that of EXP 3174.[10] In summary, the superior blockade of candesartan on the AT_1 receptor of angiotensin II than losartan probably accounted for the greater antihypertensive efficacy of the drug with the results of the study showing candesartan cilexetil lowering trough, peak and 48 h post dose BP to a greater extent than losartan ($P < 0.05$).

The findings of this study are similar to those of

CLAIM Study I, the other identically-designed, comparative study of candesartan cilexetil ($n = 332$) and losartan ($n = 322$).[6] CLAIM Study I showed that at week 8, candesartan cilexetil 32 mg once daily was more effective in lowering all the measured BP parameters than losartan 100 mg once daily ($P < 0.05$): candesartan cilexetil lowered trough BP by 13.3/10.9 mm Hg, peak BP by 15.2/11.6 mm Hg and 48-h post dose BP by 11.2/10.2 mm Hg compared to a reduction of trough BP by 9.8/8.7 mm Hg, peak BP by 12.6/10.1 mm Hg, and 48-h post dose BP by 5.3/6.0 mm Hg by losartan. In addition, CLAIM Study I showed that candesartan cilexetil produced higher responder and control rates (62% and 56%) than losartan (54% and 47%); the differences being statistically significant ($P < 0.05$). With two independent studies showing the greater efficacy of candesartan cilexetil, the probability of this occurring by chance is minimal as the one-sided *P*-value associated with two such trials is $0.025 \times 0.025 = 0.000625$, and the corresponding two-sided *P* value is 0.00125.[11] Overall, including the present study, there have been five sizable, double-blind, randomised, controlled studies providing direct comparison between candesartan cilexetil and losartan.[3–6] The Andersson and Neldam study[3] showed that candesartan cilexetil 16 mg once daily lowered SBP/DBP more effectively than losartan 50 mg once daily by 4.6/3.7 mm Hg with the difference in DBP statistically significant. In the CANDLE (Candesartan Versus Losartan Efficacy Comparison Study), candesartan cilexetil 16 mg dose-titrated if needed to 32 mg once daily reduced SBP/DBP more than losartan 50 mg dose titrated if needed to 100 mg once daily by 1.9/2.1 mm Hg, with the difference in DBP statistically significant.[4] In a forced titration study, candesartan cilexetil 16 mg once daily lowered 24-h ambulatory SBP/DBP more than losartan 100 mg by 4.1/1.8 mm Hg, with the difference in SBP statistically significant.[5] These three studies, however, did not test the recommended once daily maximum doses of the two drugs by a forced titration design. Thus, with the strikingly consistent demonstration of greater peak, trough and 48-h post dose BP lowering of candesartan cilexetil, these two CLAIM studies establish convincingly the greater antihypertensive efficacy of candesartan cilexetil over losartan when compared at once daily maximum dosage.

These head-to-head comparisons are important to differentiate the antihypertensive efficacy of ARBs. A recent meta-analysis of 43 published, randomised, controlled trials concluded comparable antihypertensive efficacy of losartan, valsartan, irbesartan and candesartan cilexetil and a near flat dose response of these ARBs.[12] The meta-analysis consists essentially of data on the two earlier ARBs, losartan and valsartan (81% of the ARB monotherapy starting dose data and 72% of the ARB monotherapy titration data). It is also noteworthy that only 8–16 mg candesartan cilexetil doses were evaluated in the meta-analysis. Thus, the conclusions of this meta-analysis are probably applicable to the earlier ARBs but not to candesartan cilexetil.

Conclusion

This randomised, controlled, forced titration study demonstrated consistently that candesartan cilexetil 32 mg once daily, lowered trough, peak and 48 h post dose BP more effectively than losartan 100 mg once daily in a diverse population with systemic hypertension in the US. Both drugs were well tolerated.

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Appendix

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