A new approach to assessing antihypertensive therapy: effect of treatment on pulse pressure

Roland Asmar[a] and Yves Lacourcière[b], on behalf of the Candesartan cilexetil in Hypertension Ambulatory Measurement of Blood Pressure (CHAMP) Study Investigators

Background **A high pulse pressure is an independent cardiovascular risk factor. It has therefore been suggested that antihypertensive treatment should not only reduce systolic blood pressure (SBP) and diastolic blood pressure (DBP), but should also decrease pulse pressure (SBP minus DBP). In a previous analysis, we showed that two angiotensin II type 1 (AT_1)-receptor blockers, candesartan cilexetil and losartan, differed in their effects in reducing SBP and DBP.**

Objective **To compare the efficacy of candesartan cilexetil and losartan according to a new approach – their effect on pulse pressure – and to describe the dose–effect relationship for SBP, DBP and pulse pressure, in a placebo-controlled study.**

Methods **After a 4-week placebo run-in period, 268 patients with mild-to-moderate hypertension were allocated randomly to groups to receive placebo, candesartan cilexetil (8 mg once daily) or losartan (50 mg once daily), for 4 weeks. The doses were then doubled to 16 and 100 mg, respectively, for the final 4 weeks of the study. Clinic blood pressure was measured 24 and 48 h after each dose of drug or placebo, and ambulatory blood pressure was monitored from 0 to 36 h after each dose, at baseline and after 4 and 8 weeks of treatment.**

Results **Candesartan cilexetil decreased ambulatory pulse pressure significantly ($P < 0.05$) more than did losartan during both daytime and night-time, and over the 24 h period after the previous dose. A different dose–effect relationship on SBP, DBP and pulse pressure was observed. The duration of action of candesartan cilexetil was greater than that of losartan. After a missed dose (i.e. approximately 24–36 h after the previous dose), mean ambulatory pulse pressure values after 4 and 8 weeks of treatment with candesartan cilexetil were lower than those observed with losartan ($P < 0.005$). Clinic pulse pressure measurements were consistent with these ambulatory measurements.**

Conclusions **AT_1-receptor blockers differ both in their ability to reduce pulse pressure and in their duration of effect, candesartan cilexetil having a greater and more sustained effect than losartan. Different dose–effect relationships on SBP, DBP or pulse pressure were observed. Further prospective studies based on pulse pressure are needed to analyse the mechanism of reduction of pulse pressure and to determine its prognostic value.** ***J Hypertens*** **18:1683–1690 © 2000 Lippincott Williams & Wilkins.**

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[a]L'Institut CardioVasculaire, Paris, France and [b]Hypertension Research Unit, Centre Hospitalier de Laval, Québec, Canada.

Correspondence and requests for reprints to Professor Roland Asmar, L'Institut CardioVasculaire, 21 Boulevard Delessert, 75016 Paris, France.
Tel: +331 55 74 66 66; fax: +331 55 74 66 65; e-mail: icv@icv.org

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Introduction

Treatment of arterial hypertension is essential for the prevention of cardiovascular disease [1,2]. High pulse pressure, which is the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), has recently been shown to be related to increased artery stiffness [3–8]. Several trials have also suggested that it may have predictive value in terms of cardiovascular complications such as atherosclerosis [9], myocardial infarction [10–12], increased left ventricular mass [13,14], and coronary disease [4,8,15]. Thus evidence is accumulating that pulse pressure may be a predictor of total and cardiovascular mortality, independently of other cardiovascular risk factors [1,4,11,12,16–18]. In assessing the efficacy of antihypertensive treatment, it may therefore be important to determine changes in pulse pressure in addition to reductions in SBP and DBP. Most previous studies have been based on clinic pulse pressure measurements, although it has been suggested that ambulatory pulse pressure correlates more closely with organ damage than does clinic pulse pressure [3,5,7,18–20].

Angiotensin II type 1 (AT_1)-receptor blockers are a

new class of drugs used for the treatment of arterial hypertension. They have been shown to be at least as effective at decreasing blood pressure as other classes of antihypertensive agents, with a good tolerability [21–27]. The present double-blind, placebo-controlled study was conducted to compare the duration of effect of candesartan cilexetil (8–16 mg) with that of losartan (50–100 mg), using 36 h ambulatory blood pressure monitoring (ABPM) in patients with mild-to-moderate hypertension. Results for SBP and DBP have been published in detail elsewhere [28]. This article presents an analysis of the effects of these AT_1-receptor blockers according to a new approach – their efficacy on pulse pressure – as evaluated by clinic measurements and ABPM during the normal dosing interval of 24 h and between 24 and 36 h after the previous dose. It also describes the different dose–effect relationships observed for SBP, DBP and pulse pressure.

Patients and methods

Patient selection

Men and women, aged 20–80 years, with treated or untreated mild-to-moderate hypertension, were eligible for enrolment in the study. The inclusion criteria were a mean sitting DBP between 95 and 110 mmHg, a mean sitting SBP of less than 200 mmHg and a mean ambulatory DBP of at least 85 mmHg during the period between drug intake and 2200 h (i.e. when the patient was awake). Exclusion criteria comprised concomitant diseases that would present safety hazards, concomitant medications that directly or indirectly act on blood pressure, and night-shift working. The study was approved by the Investigational Review Board of each institution participating in the study and written informed consent was obtained from all patients before their enrolment.

Study design

This was a multicentre, double-blind, placebo-controlled, three-arm, parallel-group study, with a forced dose titration. Each patient was allocated to one of the three parallel groups of the study according to an unbalanced randomization schedule (3 : 3 : 1 with candesartan cilexetil, losartan and placebo, respectively). After a 4-week-placebo run-in period, patients received candesartan cilexetil (8 mg once daily), losartan (50 mg once daily) or placebo, for 4 weeks. During the subsequent 4 weeks, the doses were increased to 16 mg for candesartan cilexetil and 100 mg for losartan.

Procedures

To compare the efficacy and safety of the two AT_1-receptor blockers, clinic blood pressure and heart rate measurements were taken at each visit. The patients were also screened for adverse events at these visits. Laboratory tests were undertaken at the beginning and end of the trial.

Clinic measurements of blood pressure and heart rate were performed using a validated automated device (Omron HEM-705 CP) at all study visits. At each visit, clinic blood pressure measurements were obtained at trough-dose time, that is 24 ± 2 h after the previous dose. In addition, in all Canadian centres, clinic blood pressure assessments were performed at 48 ± 2 h after drug or placebo was administered. Sitting blood pressure was measured three times, at least 1 min apart, after the patient had rested for at least 5 min. The mean of the three measures was used for data analysis.

To evaluate the duration of the treatment effect on blood pressure, ABPM was performed at baseline and after 4 weeks (lower doses) and 8 weeks (higher doses) of double-blind treatment. ABPM was performed using portable monitoring devices (Spacelabs 90207) for the 36 h after the study drug intake, on regular working days. The devices were programmed to record blood pressure every 15 min during the daytime period (0600–2200 h) and every 30 min during the night-time period (2200–0600 h). Each ABPM report had to meet the following criteria: a minimum of 24 or 36 h of data after the dose; at least 75% of the readings valid; a maximum of two consecutive hours of missing data on only one occasion. If these criteria were not met, ABPM was repeated within 7 days.

Statistical analysis

The statistical evaluation of the reduction in pulse pressure from baseline in response to treatment was based on an analysis of covariance (ANCOVA). The linear model in the ANCOVA included treatment, centre, and a centre-by-treatment interaction as factors, and the baseline value as a covariate. Adjusted means, confidence intervals and P values were obtained from the ANCOVA fittings; a value less than 0.05 was considered significant.

Results

Baseline characteristics of the study population

The intention-to-treat population consisted of 267 patients (165 men, 92 women): 115 (72 men, 43 women) in both the candesartan cilexetil and losartan groups, and 37 (21 men, 16 women) in the placebo group; mean age was 55.1 ± 9.4 years. At baseline, all groups were similar regarding age, sex, race (96% white, 2% black, 2% oriental), height, body mass index (29 kg/m^2 $\leqslant$ for men and 28 kg/m^2 $\leqslant$ for women), medical history, duration of hypertension, blood pressure and heart rate. The clinic SBP/DBP and heart rate at baseline were $162.1 \pm 15.1/101.3 \pm 4.8$ mmHg and 76.0 ± 11.8 beats/min for the candesartan cilexetil group, $160.6 \pm 16.4/100.1 \pm 4.8$ mmHg and 76.6 ± 11.8 beats/min for the losartan group, and $161.6 \pm 15.7/100.6 \pm 4.9$ mmHg and 76.1 ± 11.9 beats/min for the placebo group.

Reductions in clinic and ambulatory systolic and diastolic blood pressures

The reductions in SBP and DBP have been published elsewhere [28] and are summarized in Figure 1, for clinic and 24 h ambulatory blood pressure.

Clinic blood pressure

In brief, compared with placebo treatment, both candesartan and losartan significantly reduced clinic sitting blood pressure 24 h after administration after 4 and 8 weeks of treatment, with a trend for a greater reduction ($P = 0.057$) in SBP with candesartan at week 8. When the doses (week 4 to week 8) were increased from 8 to 16 mg for candesartan and from 50 to 100 mg for losartan, the adjusted mean changes in clinic blood pressure with candesartan were significant for both SBP and DBP 24 h after the dose, but with losartan were significant only for DBP (Fig. 1).

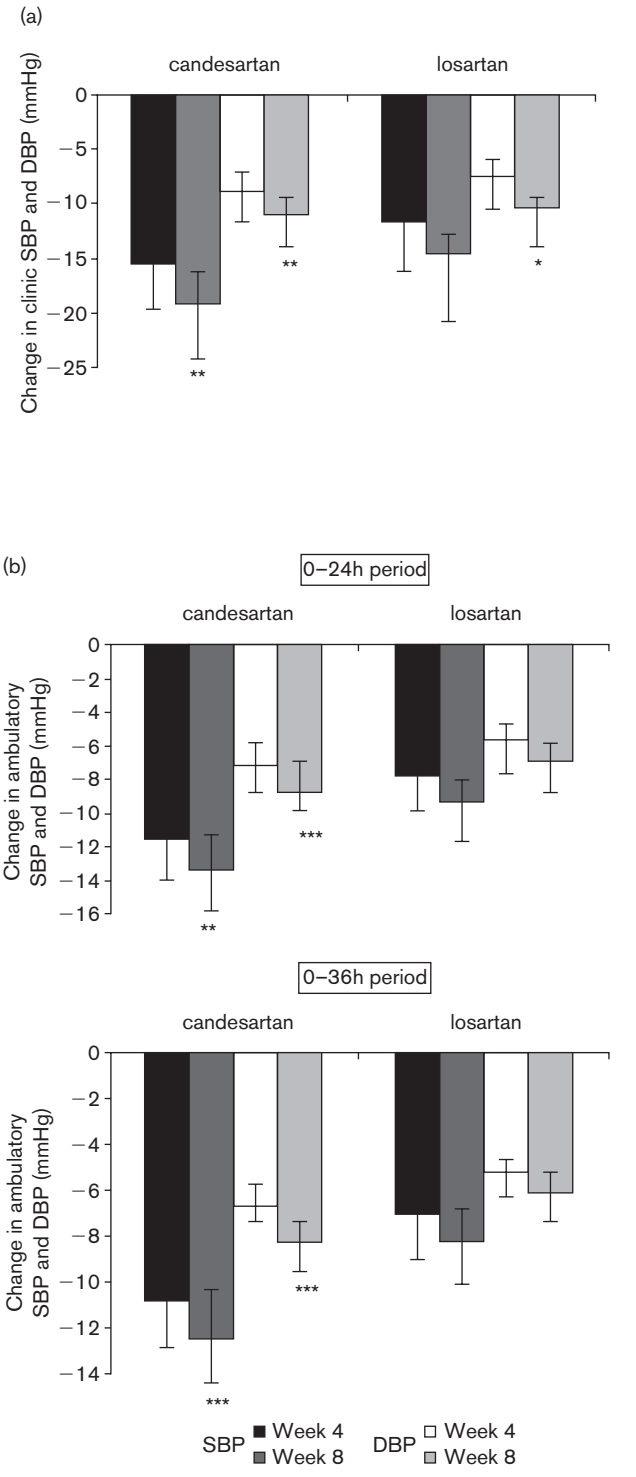
Ambulatory blood pressure

Both candesartan and losartan significantly reduced ambulatory blood pressure at week 4 and week 8. Compared with patients receiving losartan, the group treated with candesartan cilexetil had a significantly ($P < 0.01$) greater reduction in ambulatory SBP. At week 4, mean SBP reductions during the daytime and night-time periods with candesartan cilexetil (8 mg) were 12.3 and 10.7 mmHg, respectively, with corresponding reductions of 8.4 and 6.9 mmHg with losartan (50 mg). At week 8, mean SBP reductions during the daytime and night-time periods with candesartan cilexetil (8 mg) were 14.5 and 12.4 mmHg, respectively, with corresponding reductions of 10.3 and 8.2 mmHg with losartan (100 mg). At week 4, mean reductions in daytime ambulatory DBP were 7.6 and 6.0 mmHg, and mean changes in night-time ambulatory DBP were 6.5 and 4.8 mmHg for candesartan and losartan, respectively. At week 8, mean daytime DBP reductions were 9.4 and 7.7 mmHg, and mean changes in night-time DBP were 8.2 and 5.8 mmHg for candesartan and losartan, respectively.

The additional reductions in ambulatory SBP and DBP that were obtained when the dose of losartan was increased from 50 to 100 mg did not reach statistical difference. In contrast, ambulatory blood pressure reductions with candesartan cilexetil (16 mg) were significantly greater than those seen with candesartan cilexetil (8 mg) during every period of the ambulatory blood pressure recording, supporting a dose–response relationship (Fig. 1).

After 8 weeks of treatment, the reduction in mean ambulatory SBP and DBP on the day after a missed dose (0600–1800 h – that is, 24–36 h after the previous dose) was significantly better maintained ($P \leqslant 0.001$) with candesartan cilexetil (reductions of 11.9/

Fig. 1



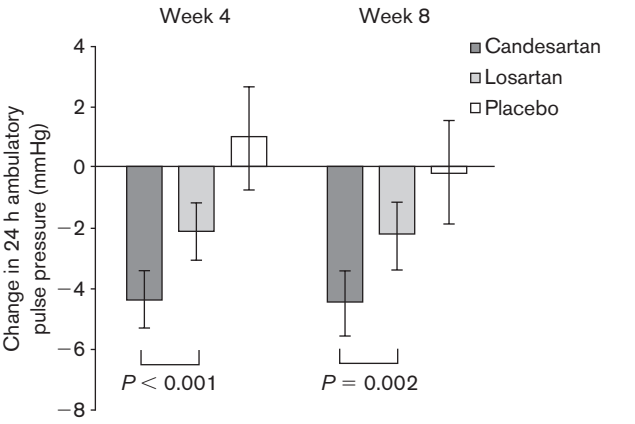
Mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline values in hypertensive patients, 24 h after a once-daily treatment with candesartan cilexetil (8 mg, week 4; 16 mg, week 8), or losartan (50 mg, week 4; 100 mg, week 8). (a) clinic values. (b) 24 h ambulatory values; mean blood pressure values for the 0–24 h and 0–36 h periods after drug administration are shown. ** $P < 0.01$, *** $P < 0.001$ compared with candesartan (8 mg); * $P < 0.05$ compared with losartan (50 mg).

8.0 mmHg) than with losartan (reductions of 6.1/4.5 mmHg). It was therefore concluded that candesartan cilexetil has a greater antihypertensive effect than losartan, not only over the normal 24 h dosing interval, but also after a missed dose [28].

Clinic pulse pressure

Clinic pulse pressure at 24 h after administration of drug was reduced from baseline with both AT_1-receptor blockers after 4 and 8 weeks of treatment, whereas clinic pulse pressure at 48 h after dosing was reduced only with candesartan cilexetil, after 8 weeks of treatment. After 4 weeks, the difference between candesartan cilexetil (8 mg), and losartan (50 mg) was not significant, both 24 h and 48 h after the administration. In contrast, at week 8, candesartan cilexetil (16 mg) decreased pulse pressure significantly ($P < 0.05$) more than losartan (100 mg), both 24 h and 48 h after the administration. The adjusted mean changes in pulse pressure from baseline to week 8 were −8.2 and −3.2 mmHg with candesartan cilexetil, and −4.2 and +1.1 mmHg with losartan, at 24 and 48 h after dosing, respectively.

Fig. 2



Change from baseline in 24 h ambulatory pulse pressure in patients with mild-to-moderate hypertension who were given once-daily treatment with candesartan cilexetil (8 mg in weeks 1–4 of treatment and 16 mg in weeks 4–8 of treatment), losartan (50 mg in weeks 1–4 of treatment and 100 mg in weeks 4–8 of treatment), or placebo, after 4 and 8 weeks of treatment. Values are adjusted means with 95% confidence intervals.

Ambulatory pulse pressure

After both 4 and 8 weeks of treatment, ambulatory pulse pressure was reduced from baseline during the daytime and night-time periods and over the 24 h period after drug administration (Table 1) in patients treated with either candesartan cilexetil or losartan. Reductions in pulse pressure from baseline after 8 weeks were similar to those after 4 weeks for both treatments. However, candesartan cilexetil was significantly more effective than losartan at reducing pulse pressure after both treatment periods.

Figure 2 shows the changes in mean 24 h ambulatory pulse pressure after 4 and 8 weeks of treatment. After 4 weeks of treatment with candesartan cilexetil (8 mg), pulse pressure was reduced by 4.3 mmHg from baseline, compared with a reduction of 2.1 mmHg with losartan (50 mg). The adjusted mean difference of 2.3 mmHg between the treatments was statistically significant ($P < 0.001$). Similarly, after 8 weeks of treatment there was a significant ($P = 0.002$) difference (2.2 mmHg) between the 4.5 mmHg reduction in pulse pressure obtained with candesartan cilexetil (16 mg) and the 2.3 mmHg reduction obtained with losartan (100 mg). For the 0–36 h period after drug administration, results similar to those observed for the 0–24 h period were obtained. The adjusted mean values were respectively 47.7, 50.0, and 52.8 mmHg for candesartan,

Table 1. Effects of once-daily treatment with candesartan cilexetil (8 mg in weeks 1–4 of treatment, and 16 mg in weeks 4–8 of treatment) or losartan (50 mg in weeks 1–4 of treatment, and 100 mg in weeks 4–8 of treatment) on daytime (0600–2200 h), night-time (2200–0600 h) and 24 h ambulatory pulse pressure (APP) in patients with mild-to-moderate hypertension

	Placebo	Candesartan cilexetil	Losartan
Daytime APP (mmHg)			
Baseline	55.1 ± 11.9 (36)	53.3 ± 11.9 (114)	52.4 ± 11.5 (111)
Week 4	55.1 ± 11.4 (33)	48.7 ± 11.0 (110)**	50.5 ± 11.5 (109)
Week 8	54.2 ± 12.6 (33)	48.3 ± 10.1 (106)**	50.9 ± 11.8 (104)
Night-time APP (mmHg)			
Baseline	51.6 ± 12.2 (36)	49.8 ± 11.7 (114)	50.0 ± 10.0 (111)
Week 4	52.8 ± 13.4 (33)	45.9 ± 10.1 (110)*	47.9 ± 10.9 (109)
Week 8	50.4 ± 12.1 (33)	45.6 ± 10.1 (106)*	48.3 ± 10.5 (104)
24 h APP (mmHg)			
Baseline	53.7 ± 12.0 (36)	51.6 ± 11.4 (114)	51.2 ± 10.7 (111)
Week 4	53.9 ± 12.0 (33)	47.4 ± 10.1 (110)***	49.3 ± 11.0 (109)
Week 8	52.6 ± 12.1 (33)	47.2 ± 9.8 (106)**	49.7 ± 10.9 (104)

Values are mean ± SD for the number of patients given in parentheses. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with losartan.

losartan, and placebo, with a mean difference of –2.3 mmHg between candesartan and losartan [95% confidence interval (CI) −3.5 to −1.1 mmHg; $P < 0.001$]. At week 8, adjusted mean values were 47.7, 50.3, and 52.3 mmHg respectively for candesartan, losartan, and placebo, with a mean difference of –2.5 mmHg between candesartan and losartan (95% CI −3.8 to −1.3; $P < 0.001$). Figure 3 shows the mean hourly changes in ambulatory pulse pressure from baseline to 24 h after drug administration after 4 and 8 weeks of treatment with candesartan cilexetil, losartan, or placebo. Candesartan cilexetil was more effective than losartan at reducing pulse pressure throughout the dosing interval.

Ambulatory pulse pressure after a missed dose

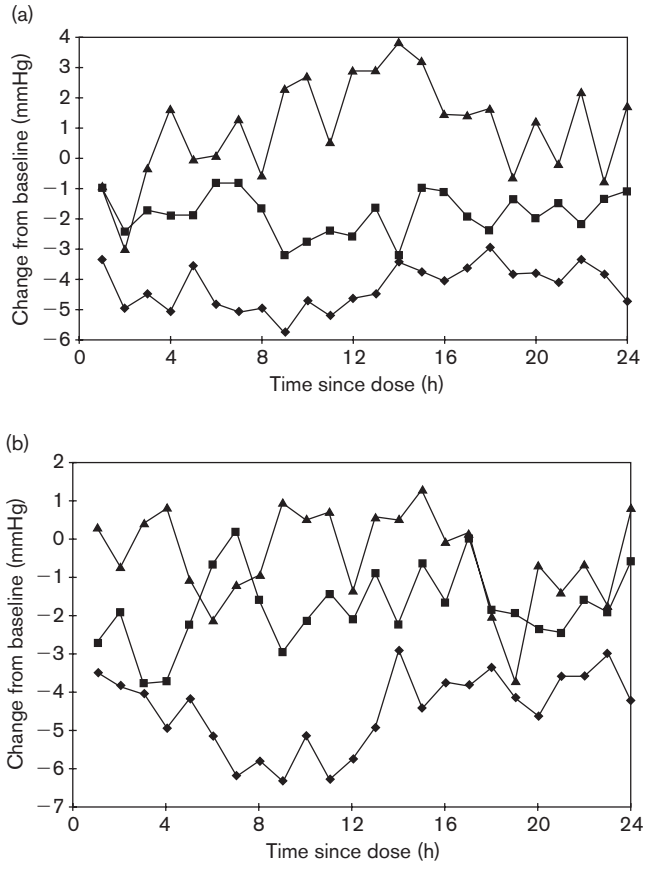
To determine the effect of missing a dose, ambulatory pulse pressure was measured 24–36 h (between 0600 and 1800 h), after the previous dose of candesartan cilexetil or losartan. With candesartan cilexetil (8 mg), ambulatory pulse pressure during this period was decreased from 51.6 ± 11.5 mmHg at baseline to 47.9 ± 10.2 mmHg after 4 weeks of treatment. The corresponding value after a further 4 weeks of treatment at the higher dose of 16 mg was 47.7 ± 9.7 mmHg. With losartan, ambulatory pulse pressure was reduced from a baseline value of 50.8 ± 12.0 mmHg to 49.7 ± 11.9 mmHg and 49.7 ± 11.3 mmHg, respectively at weeks 4 (50 mg dose) and 8 (100 mg dose). Reductions from baseline in adjusted mean ambulatory pulse pressure 24–36 h after drug administration were 3.5 and 3.8 mmHg, respectively, after 4 and 8 weeks of treatment with candesartan cilexetil, and 1.4 and 1.5 mmHg, respectively, after 4 and 8 weeks of treatment with losartan (Fig. 4). The mean differences in pulse pressure of 2.1 and 2.3 mmHg at 4 and 8 weeks, respectively, in favour of candesartan cilexetil over losartan were statistically significant ($P < 0.005$).

Discussion

The main aims of this study were to assess the efficacy and duration of action of antihypertensive treatments using a new approach – pulse pressure analysis – and to investigate whether there may be a different dose–effect relationship of efficacy of antihypertensive therapy on SBP, DBP or pulse pressure.

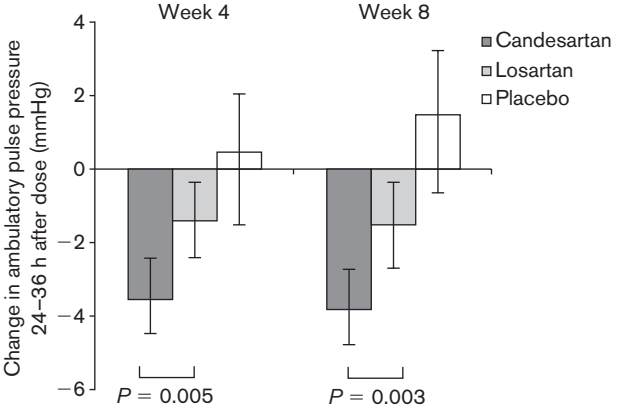
To our knowledge, this is the first study to show an effect of AT_1-receptor blockade on pulse pressure. This is an important finding, as evidence is accumulating that pulse pressure may be a predictor of total and cardiovascular mortality, independently of other cardio-

Fig. 3



Mean changes from baseline in hourly ambulatory pulse pressure in the interval 0–24 h after drug administration in patients with mild-to-moderate hypertension given once-daily treatment with candesartan cilexetil (◆), losartan (■) or placebo (▲). (a) After 4 weeks of treatment with candesartan cilexetil (8 mg), losartan (50 mg), or placebo. (b) After 8 weeks of treatment with candesartan cilexetil (16 mg), losartan (100 mg), or placebo.

Fig. 4



Changes from baseline in ambulatory pulse pressure between 24 and 36 h after drug administration in patients with mild-to-moderate hypertension given once-daily treatment with candesartan cilexetil (8 mg in weeks 1–4 of treatment and 16 mg in weeks 4–8 of treatment), losartan (50 mg in weeks 1–4 of treatment and 100 mg in weeks 4–8 of treatment), or placebo, after 4 and 8 weeks of treatment. Values are adjusted means with 95% confidence intervals.

vascular risk factors [1,4,11,12,16–18]. Both clinic and ambulatory measurements showed that pulse pressure was reduced by antihypertensive treatment with the AT_1-receptor blockers, candesartan cilexetil and losartan, although the effect was greater for candesartan cilexetil. These results cannot be attributed to a 'regression to the mean' phenomenon, as all the results were compared with those of the placebo group, in which high reproducibility and no significant changes over time were observed on pulse pressure, whether by clinic or by ambulatory assessments of blood pressure. Candesartan cilexetil was significantly more effective than losartan at reducing pulse pressure throughout the normal dosing interval after both 4 and 8 weeks of treatment. The greater antihypertensive efficacy and longer-lasting effect of candesartan cilexetil compared with losartan was confirmed by the results obtained 24–36 h after the previous dose. During this period, the antihypertensive efficacy of candesartan cilexetil persisted to a significantly greater extent than that of losartan.

The capacity of an antihypertensive agent to extend its action beyond 24 h is likely to be important, as many patients inadvertently miss at least one dose of medication each week [2]. The long duration of action of candesartan cilexetil appears to be explained by its receptor-binding kinetics, particularly its slow dissociation from the receptor [29]. The duration of effect is not directly related to plasma kinetics, as the elimination half-life of candesartan from plasma is about 9 h and plasma concentrations are low 24 h after its administration [30].

Although candesartan cilexetil (16 mg) reduced clinic pulse pressure significantly more than did losartan (100 mg), no significant difference in clinic pulse pressure was observed between the two AT_1-receptor blockers with the lower doses. This contrasts with the significantly greater reduction in pulse pressure observed by ABPM for both doses of candesartan cilexetil compared with losartan, and is probably related to the well-known greater sensitivity of ABPM than of clinic measurements in evaluating antihypertensive efficacy.

Similar conclusions were reached by Kassler-Taub *et al.* [31], from a comparative efficacy study of two AT_1-receptor blockers in patients with mild-to-moderate hypertension. They found that the maximally effective once-daily doses of irbesartan and losartan resulted in clinically significant differences in blood pressure reductions, highlighting the potential importance of the pharmacokinetic and pharmacodynamic differences between drugs in the same therapeutic class. Published data suggest that losartan administered in a dose of 50 mg twice daily may provide somewhat better 24 h mean ambulatory blood pressure control than a dose of 100 mg once daily. Although this apparent difference between losartan and candesartan may suggest that a twice-daily regimen comparison would tend to favour losartan relative to candesartan, a comparison using a regimen other than once-daily should be based upon the doses of each drug that represent the maximally effective dose when given using the regimen intended for comparison [24,31].

The design of this study – double-blind, randomized, placebo-controlled, and forced dose titration – also offers the possibility of assessing the dose–effect relationship of antihypertensive drugs on the different arterial pressures: SBP, DBP and pulse pressure. The dose–effect relationship analysis of losartan showed no significant differences between losartan 50 and 100 mg on SBP, DBP and pulse pressure, thus indicating a plateau effect reached at 50 mg. With candesartan, the data showed a dose–response relationship in both clinic and ambulatory SBP and DBP, but not in pulse pressure.

Taken together, these data suggest that the dose–effect relationship may vary for SBP, DBP or pulse pressure. These differences may be explained, at least partly, by unequal effects of the drug on the haemodynamic determinants (cardiac parameters, vascular resistance, arterial compliance, wave reflections, reflection sites) of each of the arterial pressures. Further specific pharmacological studies are needed to confirm this interesting observation.

Analysis of pulse pressure provides additional useful information on the efficacy of antihypertensive therapies, as it is now established that pulse pressure is a predictor of cardiovascular risk.

Many studies have shown that a high pulse pressure is closely associated with artery stiffness and end-organ damage [4,11,12,16–19,32]. In a long-term study of cardiovascular mortality in men, Benetos *et al.* [4] showed that a high pulse pressure was due to both an increase in SBP and a decrease in DBP, indicating that increased pulse pressure is a marker of arterial stiffness and thus has consequences for cardiovascular mortality. They observed that, even in a population at relatively low cardiovascular risk, with mean arterial blood pressure values within the normal range (less than 107 mmHg), a high pulse pressure is a significant independent predictor of all-cause, cardiovascular and, particularly, coronary mortality.

In a prospective study, Madhavan *et al.* [11] assessed the value of pretreatment pulse pressure as a predictor of myocardial infarction. They found that a high pretreatment pulse pressure (at least 63 mmHg) was associated with subsequent cardiovascular complica-

tions. Patients with the greatest pretreatment pulse pressure and either large or small decreases in DBP during treatment had the greatest risk of myocardial infarction. The power of a high pulse pressure to predict myocardial infarction was also reported by Fang *et a*l. [10] in a study on treated and untreated hypertensive patients.

Ambulatory pulse pressure has several advantages over clinic pulse pressure as a predictor of cardiovascular risk. First, pulse pressure may be affected by the clinic visit [18]; second, values obtained by ABPM are more reproducible than clinic measurements [3,19,20]; finally, a number of studies have suggested that ambulatory pulse pressure correlates with end-organ damage more closely than does clinic pulse pressure [5,18,33].

Moreover, Verdecchia *et al*. [18] proposed threshold values for predicting cardiovascular morbidity and mortality of 53 mmHg for 24 h ambulatory pulse pressure and 65 mmHg for clinic blood pressure, Madhavan *et al*. [11] noted an association between subsequent cardiovascular complications and a pretreatment clinic pulse pressure greater than 63 mHg. Whether the pulse pressure reduction may improve the cardiovascular prognosis of hypertensive patients needs to be analysed in specific large clinical trials. Nevertheless, the results of this study show that antihypertensive treatment with angiotensin II antagonists may significantly reduce pulse pressure. Even though this reduction appears to be of small amplitude, its significance in terms of prognosis should not be disregarded. In fact, according to Fang *et al*. [10], the difference in pulse pressure between two population controls and patients with myocardial infarction was of small amplitude (about 5 mmHg). Moreover, analysis of our data according to the tertile classification of Verdecchia *et al*. [18] shows that the proportions of patients whose pulse pressure (calculated from the mean over 24 h) was greater than 53 mmHg (higher tertile) at baseline and had been reduced to no more than 53 mmHg after 8 weeks of treatment were 48.9, 29.3 and 20.0% in the candesartan, losartan and placebo groups, respectively. Taken together, all these data suggest that pulse pressure reduction, even when of small magnitude, may improve the cardiovascular prognosis of the patients. Further specific studies are needed to assess this hypothesis and its possible extrapolation to individuals.

Antihypertensive agents having a vasodilatory action, such as the angiotensin converting enzyme inhibitors, have been shown to improve arterial compliance [8,33] and may thus decrease the higher pulse pressure observed in hypertensive patients. As pulse pressure is partly related to the arterial stiffness and compliance, the favourable effect on pulse pressure observed in this study may be related to an improvement in arterial compliance with AT_1-receptor blockers; this has to be confirmed by specific studies. The decrease in pulse pressure may help to reduce end-systolic wall stress and therefore help to reverse ventricular hypertrophy [8,14].

The exact relationship between decreases in pulse pressure and reduction of cardiovascular risk during antihypertensive treatment remains to be established.

Conclusion

The present study has shown that pulse pressure may be reduced by antihypertensive therapy with AT_1-receptor blockers. Of the two such blockers studied, candesartan cilexetil showed significantly greater efficacy than losartan in reducing pulse pressure throughout the normal 24 h dosing interval. Furthermore, the effect of candesartan cilexetil was longer lasting than that of losartan, with a significant difference between the two treatments 24–36 h after the previous dose.

The results of this study also suggest a differential dose–effect relationship on systolic, diastolic, or pulse pressure, which needs to be confirmed by specific pharmacological studies.

These observations may have major implications in terms of the treatment of hypertension, as a high pulse pressure has been shown to be an independent risk factor for cardiovascular morbidity and mortality. The prevention or improvement of end-organ damage by antihypertensive agents is related to their effects on SBP and DBP. The measurement of pulse pressure, which is partly related to arterial structure and function, could be used to further evaluate the potential of antihypertensive therapies to provide end-organ protection.

Appropriate clinical, prospective, and epidemiological studies, designed to define and validate threshold values for clinic and ambulatory pulse pressure, would be of great interest in terms of identifying and treating those hypertensive patients at high risk of cardiovascular disease.

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