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A similar 24-h blood pressure control is obtained by zofenopril and candesartan in primary hypertensive patients

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Abstract

Objective. To compare the antihypertensive effect of treatment with zofenopril vs candesartan by office and ambulatory blood pressure (BP). *Design and methods*. Following a 2-week wash-out from previous treatment, 236 grade I–II primary hypertensive patients were randomized double-blind to 12 weeks treatment with zofenopril 30 mg or candesartan 8 mg od. After 4 weeks, treatment was doubled in responder non-normalized (office systolic BP$\geqslant$140 mmHg and office diastolic BP reduction $\geqslant$10 mmHg) or non-responder patients (office systolic BP$\geqslant$140 mmHg and office diastolic BP reduction $<$10 mmHg). Following a further 4 weeks, non-responder or non-normalized patients were withdrawn. *Results*. In the intention-to-treat population, office systolic BP and diastolic BP reductions after 12 weeks of treatment were similar between the two groups (zofenopril: $21 \pm 11/15 \pm 8$ mmHg, n=114 vs C: $20 \pm 11/15 \pm 7$ mmHg, n=122; p=NS). In the 163 patients of the per-protocol population, office BP dropped by $22 \pm 11/15 \pm 8$ mmHg (zofenopril) and $20 \pm 10/15 \pm 7$ mmHg (candesartan; p=NS). Also 24-h ambulatory BPs were equally reduced by zofenopril and candesartan ($7 \pm 13/5 \pm 8$ mmHg vs $7 \pm 12/5 \pm 8$ mmHg; p=NS). The trough-to-peak ratio and smoothness index were not significantly different between zofenopril and candesartan. Tolerability of both drugs was good. *Conclusions*. Monotherapy with zofenopril and candesartan similarly reduced office and 24-h BPs. Since almost 90% of patients were normalized by either zofenopril or candesartan, this result supports the importance of considering low- or high-dose monotherapies as initial treatment for most hypertensive patients of mild degree.

Key Words: *Ambulatory blood pressure monitoring, candesartan, primary hypertension, smoothness index, trough-to-peak ratio, zofenopril*

Introduction

Angiotensin-converting enzyme (ACE) inhibitors are widely used as first-choice drugs in the treatment of hypertension (1–3). Zofenopril calcium, a prodrug of the active compound zofenoprilat, is an ACE inhibitor that has been successfully and safely employed in the treatment of acute myocardial infarction (4–6), heart failure (7,8) and primary hypertension (9–11). The early administration of zofenopril in patients with acute myocardial infarction attenuates the progression of the clinical symptoms of heart failure and its clinical consequences (4), even in case of patients with other associated clinical conditions like hypertension or diabetes (5,6). In patients with primary hypertension, zofenopril has been shown to be as effective as atenolol (9), hydrochlorothiazide (10) and lisinopril (11). However, there are no comparative data with angiotensin II antagonists, i.e. other first-class antihypertensive drugs acting on the renin–angiotensin system with a mechanism different from that of ACE inhibitors.

The present study has been set up in order to compare the antihypertensive effect on office and 24-h blood pressure (BP) of zofenopril vs that of an angiotensin II antagonist, candesartan (12).

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Patients and methods

Study population

The study included 236 outpatients of either gender, with grade I–II primary hypertension. The main inclusion criteria were an age between 18 and 65 years and a clinic sitting diastolic BP (DBP) between 90 and 109 mmHg with a clinic systolic BP (SBP) between 140 and 179 mmHg, after 2 weeks of wash-out from previous antihypertensive treatment. Patients were excluded if they had: (i) secondary hypertension; (ii) clinic sitting office DBP$\geqslant$110 mmHg or SBP$\geqslant$180 mmHg; (iii) clinically significant heart disease (cardiac valvular disease, major arrhythmias, heart failure, unstable angina, myocardial infarction in the previous 6 months); (iv) cerebrovascular accidents in the previous 6 months; (v) renal insufficiency (serum creatinine >2 mg/dl); (vi) bilateral renal artery stenosis; (vii) hypokalemia (serum potassium <3.5 mEq/l) or hyperkalemia (serum potassium >5.0 mEq/l); (viii) serious concomitant diseases (neoplasia, AIDS, hepatic disorders, psychiatric disease, etc.); (ix) history of alcohol or drug abuse; (x) obesity (body mass index >30 kg/m^2); (xi) known hypersensitivity to ACE inhibitors or angiotensin II antagonists. Pregnant women and breast-feeding mothers or women with childbearing potential but not practicing an effective method of birth control were excluded as well.

Written informed consent was obtained from all patients prior to their inclusion into the study. The study was approved by the Ethics Committees of the centers involved.

Study design

This was an Italian, multicenter (29 centers), randomized, double-blind, parallel-group study, consisting of a 2-week wash-out period, during which previous antihypertensive treatment had to be withdrawn, followed by 12 weeks of treatment with zofenopril 30 mg or candesartan 8 mg given once daily. After the initial 4 weeks of treatment, zofenopril or candesartan dose was doubled in responder non-normalized (office SBP$\geqslant$140 mmHg and office DBP reduction $\geqslant$10 mmHg) or non-responder patients (office SBP$\geqslant$140 mmHg and office DBP reduction <10 mmHg); 8 weeks after randomization patients were dropped out from the study if still responder non-normalized or non-responder. The drugs were administered once daily between 09.00 and 11.00 h.

At screening visit, medical history was collected, and a physical examination, a 12-lead ECG and informed consent were obtained. Physical examination was repeated at each visit, while ECG was assessed again at randomization, and after 4 and 12 weeks of treatment. Hematology, biochemistry and urinalysis were performed at randomization and at the final visit. Patients were seen 2, 4, 8 and 12 weeks after randomization. During these visits BP, heart rate, adverse events and compliance to treatment were assessed. BP and heart rate were also taken at screening and randomization visit.

At the end of the wash-out and follow-up period, BP was also measured by ambulatory monitoring.

BP and heart rate measurement

BP was measured in the clinic by a standard sphygmomanometer 24 h after last drug intake. Three measurements, taken at 2-min intervals, after 5 min of rest in the sitting position were averaged and used as the office BP reference value. SBP and DBP were taken at the reading of the first and fifth Korotkoff sounds, respectively. Heart rate was measured by the palpation of the radial artery pulse. Three BP and heart rate values were also taken after 2 min of standing.

Ambulatory BP monitoring was performed non-invasively over the 24 h by an oscillometric or microphonic validated device (13). The device cuff was wrapped around the non-dominant arm and the patient was asked to keep her/his arm still during the occurrence of an automatic BP measurement. Each recording started in the morning, immediately after office BP assessment and administration of active treatment, when foreseen. The device was programmed to measure BP every 15 min during the day (from 06.00 to 22.00 h) and every 30 min during the night (from 22.00 to 06.00 h).

Data analysis

The study aimed at assessing the equivalence of zofenopril and candesartan in terms of sitting office DBP reduction at the end of treatment as compared to baseline.

The calculation of the sample size assumed a maximal between treatment difference in DBP changes from baseline of 5 mmHg with a standard deviation of 11 mmHg. Using a two-tailed test with a power=90% (beta=0.10) and an alpha=0.05, at least 103 patients for each of the two groups of randomization had to be enrolled. The total number of subjects (206) was increased up to 250 in order to take into account a 10% drop-out rate and 10% of patients with possible protocol deviations.

Analysis was separately performed on patients valid for intention-to-treat (all randomized patients who received at least one dose of active treatment drug and who had at least one visit after baseline) and on patients valid according to the protocol (all randomized patients who completed the 12-week study period without major protocol violations, i.e. per-protocol population).

The primary efficacy end-point of the study was the comparison of the office DBP changes (final visit−baseline, average of three consecutive measurements taken in sitting position) with zofenopril vs candesartan. Efficacy was also assessed on secondary end-points, which included between-treatments comparison of: (i) sitting SBP changes; (ii) standing SBP and DBP changes; (iii) the percentage of normalized (DBP values <90 mmHg and SBP values <140 mmHg) at the final visit; (iv) changes in 24-h, daytime (06.00 to 22.00 h) and night-time (22.00 to 06.00 h) average DBP, SBP and pulse pressure (computed as SBP minus DBP) after 12 weeks of treatment; (v) hourly averages of BP before and during treatment; (vi) trough-to-peak ratio of DBP and SBP at the end of treatment; (vii) smoothness index of DBP and SBP after 12 weeks of treatment; (viii) changes in office and ambulatory heart rate with treatment.

The analysis of 24-h BP recordings was preceded by removal of artifacts according to previously described editing criteria (14). Recordings were considered valid when no more than 3 non-consecutive hours were missing over the 24 h and when at least 70% of expected measurements were available.

The trough-to-peak ratio was computed after selection of peak and trough changes has been done for each individual subject (15). Peak changes were calculated by selecting the hour with the maximal reduction in BP after treatment between the second and the eighth hour after drug administration, and by averaging this change with the immediately adjacent hour in which the reduction was most evident. Trough BP changes were calculated by averaging the last 2 h of the recording (15). Group trough-to-peak ratios have been expressed as median and 10th and 90th percentile of the distribution. This was done because individual trough-to-peak ratios did not show a normal distribution (15).

The smoothness index was computed by dividing the average of the 24-hourly BP changes after treatment by the corresponding standard deviation (16–18). This has been shown to reflect in a more appropriate fashion than the trough-to-peak ratio (17–19) whether treatment smoothly reduces BP throughout the 24 h.

Safety analysis was applied to all randomized patients, by calculating the incidence of adverse events and changes in laboratory data or ECG during the study.

Assessment of treatment effect at each study visit as compared to baseline was done by analysis of covariance. Between-treatments difference in baseline-adjusted mean sitting office and ambulatory DBP changes at week 12 (and 95% confidence interval) were also computed. Comparison of trough-to-peak ratio was done by the Mann–Whitney U Test. Analysis of variance was used to assess differences in smoothness indices. Comparison of normalized, responder non-normalized and non-responder patients between the two treatment groups was performed by the chi-square test or logistic regression. The level of statistical significance was kept at 0.05 throughout the whole study. Data are shown as mean $\pm$ standard deviation.

Results

Demographic and clinical data

A total of 240 patients were screened, but four were lost during the run-in period. Thus the number of patients randomized to one of the two treatment arms was 236. Before randomization all groups were similar for age, gender distribution, weight, smoking habit, use of alcohol and hemodynamic data (Table I).

Of the 236 patients randomized to treatment, 196 patients completed the 12-week randomized phase. A total of 40 patients discontinued the study because of adverse events ($n=2$), responder non-normalized or non-responder to treatment at week 8 ($n=21$), lack of compliance to study procedures ($n=4$), consent withdrawn ($n=11$) or investigator's decision ($n=2$).

The patients valid for the intention-to-treat analysis were all the 236 randomized patients (114 in the zofenopril and 122 in the candesartan treatment group). In this population, 234 patients were available after 2 weeks, 232 after 4 weeks, 227 after 8 weeks and 204 after 12 weeks of treatment. Patients valid for per protocol analysis were 163 (72 in the zofenopril and 91 in the candesartan treatment group); 106 of 196 patients with evaluable ambulatory BP recordings were valid for analysis (47 randomized to zofenopril and 59 to candesartan).

Office BP and heart rate

Rate of responder non-normalized and non-responder patients at week 4 was 14.9% and 20.2% under

Table I. Demographic and clinical data of the patients at the time of randomization (n=236).

	Zofenopril 30–60 mg (n=114)	Candesartan 8–16 mg (n=122)
Age (years)	51±8	51±9
Males (%)	63	65
Weight (kg)	76±10	76±11
Smokers (%)	23	21
Alcohol (%)	25	19
Sitting DBP (mmHg)	96±5	96±5
Sitting SBP (mmHg)	150±10	149±10
Sitting HR (beats/min)	72±9	74±9
Standing DBP (mmHg)	97±5	97±6
Standing SBP (mmHg)	152±9	150±10
Standing HR (beats/min)	73±9	75±9

Data are separately shown for the two groups of randomization and reported as mean±standard deviation or frequency (%). DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate.

zofenopril and 14.2% and 18.3% under candesartan (p=0.912) in the intention-to-treat population; the corresponding figure for the per-protocol population was 18.1% and 12.5% (zofenopril), 11.0% and 17.6% (candesartan; p=0.346). In these patients, drug dose was doubled according to protocol. At week 8, the percentage of responder non-normalized patients was 6.4% under zofenopril and 2.6% under candesartan, while that of non-responders was 9.1% and 3.4% (p=0.068, intention-to-treat population only).

In both the intention-to-treat and per-protocol population, baseline office sitting BP data were comparable between the two treatment groups and were significantly (p<0.01) and similarly reduced by any of the two drugs (Figure 1). At week 12, the between-treatments difference in baseline-adjusted mean sitting office DBP changes was −0.4 (−2.0/1.3) mmHg for the intention-to-treat (p=0.685) and −0.2 (−2.1/1.8) mmHg for the per-protocol population (p=0.863).

In the patients continuing the study after week 8, the rate of normalized subjects at the end of treatment (week 12) was high in both treatment groups (90.4% vs 90.9% zofenopril vs candesartan for the intention-to-treat, p=0.906, and 93.1% vs 91.2% for the per-protocol population, p=0.888).

The antihypertensive effect of zofenopril and candesartan on office BP was the same in spite of the dosage employed (30 and 60 mg for zofenopril or 8 and 16 mg for candesartan). Rate of normalized patients at the end of treatment was 71.3% and 67.3% with the lowest, and 19.1% and 23.6% with the highest dose of zofenopril and candesartan (intention-to-treat population, p=0.902).

Neither drug induced any increase in sitting office heart rate, which was indeed slightly reduced at the end of the study (1.0±7.8 beats/min with zofenopril and 2.9±7.9 beats/min with candesartan, p=0.355, intention-to-treat; 1.0±7.4 and 2.6±8.2 beats/min, p=0.538, per-protocol). Analysis of BP and heart rate values taken in the upright position gave results similar to those observed for sitting parameters (data not shown).

Ambulatory BP and heart rate

In the population of 106 patients with valid ambulatory recordings, the rate of patients treated with zofenopril 60 mg was 23.4%, whereas that of patients treated with candesartan 16 mg was 30.5% (p=0.551). Baseline 24-h DBP and SBP values were much lower than office ones and were significantly (p<0.01) reduced by treatment (Table II). Also daytime and night-time BP values were significantly (p<0.01) lower during treatment than at baseline (Table II), although the BP reduction during daytime was greater than during the night-time. No statistically significant between-treatment differences were observed over the 24 h [difference in baseline adjusted average DBP changes and 95% confidence interval: −0.2 (−2.8/2.5) mmHg, p=0.887], during the daytime [0.3 (−2.5/3.2) mmHg, p=0.814] or the night-time [−2.1 (−5.0/0.7) mmHg, p=0.143]. The antihypertensive effect of both drugs was similarly extended also to pulse pressure values (Table II).

Both zofenopril and candesartan reduced BP during every hour of the 24 h, with non-statistically significant different effects in the last 2 h of the recording (trough DBP: 4.6±10.7 vs 5.3±9.1 mmHg, p=0.737; trough SBP: 6.4±14.6 vs 7.6±16.7 mmHg, p=0.709, zofenopril vs candesartan respectively; Figure 2).

The trough-to-peak ratio (Figure 3, left panel) computed under zofenopril was not significantly different from that obtained with candesartan (p=0.987 for DBP and SBP).

Assessment of the homogeneity of the BP control by the smoothness index showed similar between-treatments values (p=0.983 for DBP and p=0.840 for SBP; Figure 3, right panel).

Twenty-four-hour average DBP and SBPs reductions tended to be greater under the lowest (zofenopril 30 mg and candesartan 8 mg: 5.2±8.3/7.0±12.1 mmHg, n=77) than under the highest drug doses (zofenopril 60 mg and candesartan 16 mg: 4.7±6.6/5.9±12.1 mmHg, n=29; p=NS). This was particularly evident for DBP and for the trough-to-peak ratio [0.63 (−0.50/2.48) for

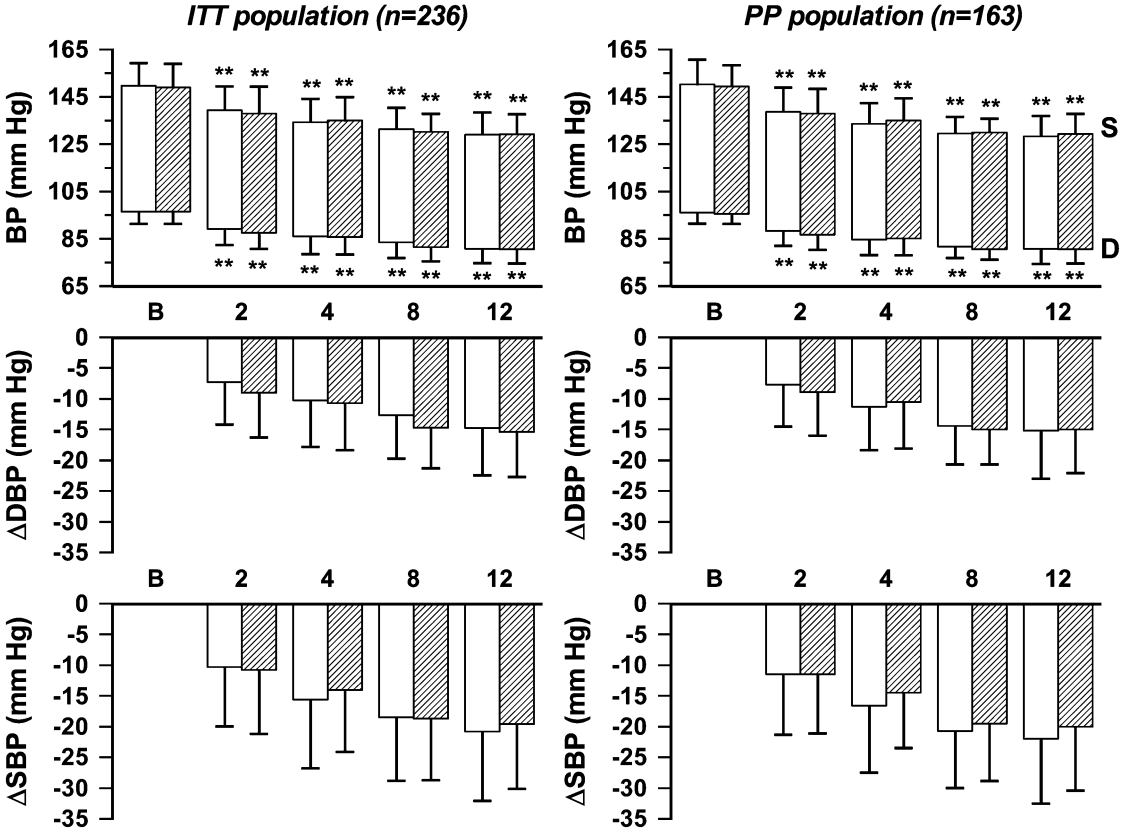

Figure 1. Office sitting diastolic (D) and systolic (S) blood pressure (BP) means values at baseline and after 2, 4, 8 and 12 weeks of treatment, and corresponding reductions (Δ) in the zofenopril 30–60 mg (open bars) and candesartan 8–16 mg (striped bars) groups. Data are shown as means ± standard deviation, separately for the intention-to-treat (ITT) and per-protocol (PP) population. Asterisks refer to the statistical difference vs baseline (**$p < 0.01$).

Table II. Ambulatory diastolic (DBP), systolic blood pressure (SBP) and pulse pressure (PP) at randomization and treatment-baseline changes (means ± standard deviation).

	DBP		SBP		PP	
	Zofenopril, 30–60 mg (n=47)	Candesartan, 8–16 mg (n=59)	Zofenopril, 30–60 mg (n=47)	Candesartan, 8–16 mg (n=59)	Zofenopril, 30–60 mg (n=47)	Candesartan, 8–16 mg (n=59)
24-h						
Baseline	84.4 ± 8.6	84.1 ± 8.2	134.7 ± 10.6	132.9 ± 11.2	50.2 ± 8.5	48.8 ± 8.1
Treatment-baseline	5.1 ± 8.2	5.1 ± 7.6	6.6 ± 12.7	6.8 ± 11.7	1.5 ± 8.3	1.7 ± 6.8
p	0.887		0.601		0.569	
Daytime						
Baseline	87.7 ± 9.6	87.4 ± 8.6	138.4 ± 11.4	137.1 ± 11.8	50.7 ± 8.8	49.8 ± 8.6
Treatment-baseline	5.8 ± 8.5	5.3 ± 8.5	7.6 ± 13.4	7.4 ± 12.8	1.7 ± 9.0	2.0 ± 7.5
p	0.814		0.843		0.631	
Night-time						
Baseline	75.3 ± 8.1	73.8 ± 8.8	123.9 ± 11.3	119.6 ± 12.0	48.6 ± 8.7	45.7 ± 8.2
Treatment-baseline	3.2 ± 9.0	4.6 ± 7.9	3.8 ± 12.9	5.4 ± 11.4	−0.6 ± 7.5	−0.8 ± 6.7
p	0.143		0.109		0.435	

The value of p refers to between-treatments difference.

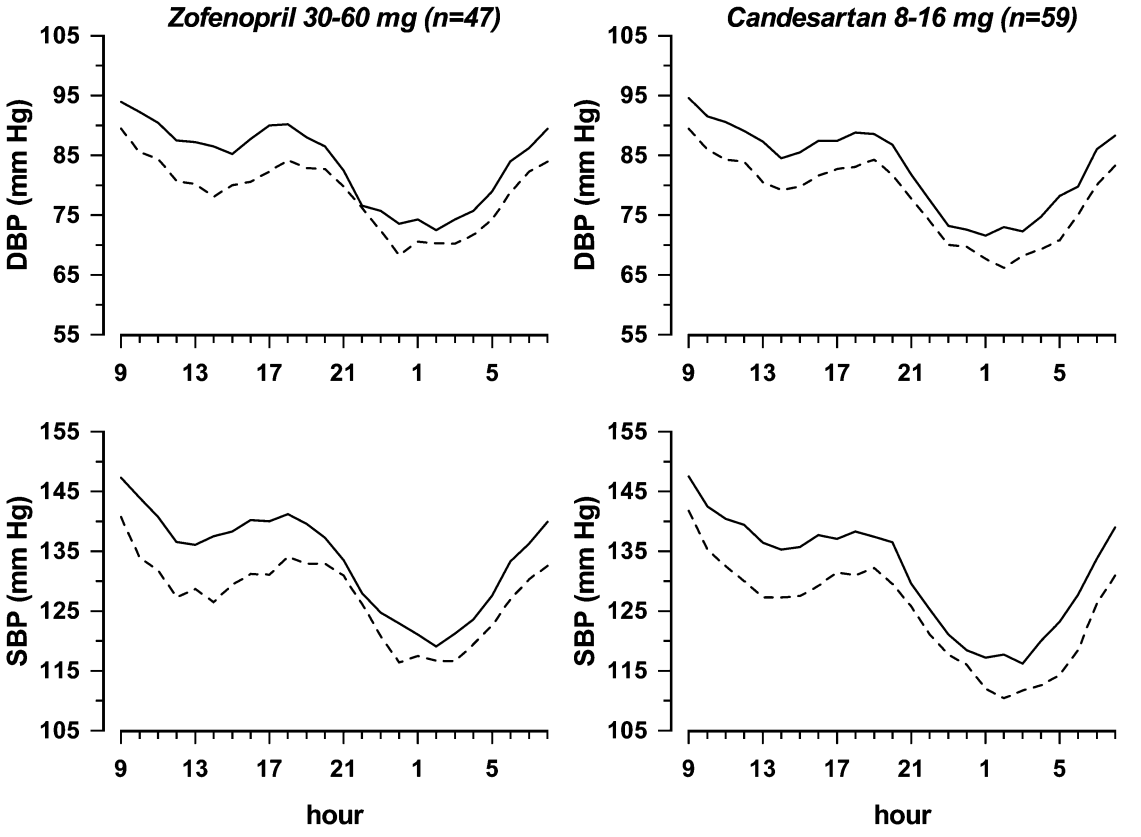

Figure 2. Average hourly diastolic (DBP) and systolic blood pressure (SBP) values at baseline (continuous line) and at the end of treatment (dashed line) with zofenopril or candesartan.

zofenopril 30 mg and 0.61 (−0.50/3.40) for candesartan 8 mg; $p=0.030$ vs lowest doses] and the smoothness index [0.64 ± 1.03 for zofenopril 30 mg and 0.55 ± 0.92 for candesartan 8 mg; $p=0.362$ vs lowest doses].

Twenty-four-hour, daytime and night-time average heart rate values did not significantly change with treatment in any of the two treatment groups.

Safety and tolerability

Laboratory and safety analysis was carried out in all randomized patients ($n=236$).

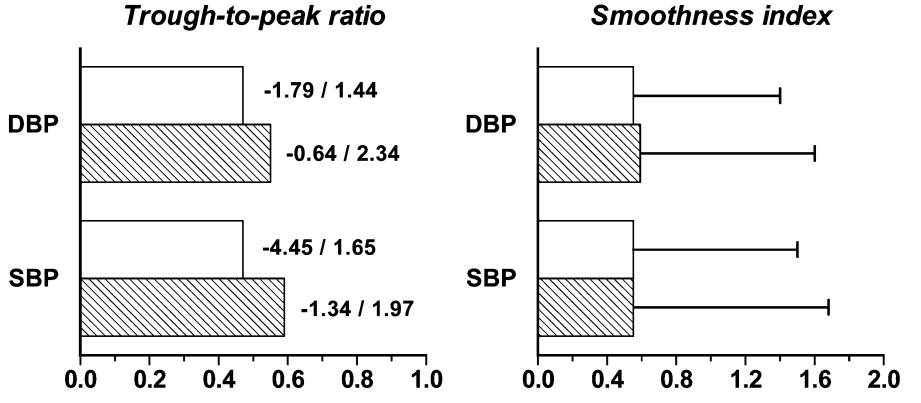

Figure 3. Median and 10th and 90th percentile of trough-to-peak (T/P) ratios and average ($\pm$standard deviation) smoothness index (SI) of diastolic (DBP) and systolic blood pressure (SBP) in the zofenopril 30–60 mg (open bars) and candesartan 8–16 mg (striped bars) treatment group.

A total number of 18 (7.6%) patients reported adverse events (10 in the zofenopril and eight in the candesartan treatment group) for an overall number of 27 adverse events (16 under zofenopril and 11 under candesartan). Most of the events (88.5%) were of a mild intensity; four (1.7%) patients were withdrawn from the study for adverse events, two in each treatment group.

Events attributed to study treatment were 16 (61.5% of total events) and occurred in 12 patients (66.7% of patients with adverse events). Rate of patients with and distribution of drug-related adverse events was not significantly different between the two treatment groups (Table III).

Treatment was accompanied by no change or by small and not significant increases or reductions in the various blood chemistry values considered in the study. Significant (but non-specific) ECG changes were observed in one case only.

Discussion

In the present study, zofenopril and candesartan given alone once daily were equally effective in reducing sitting DBP in patients with grade I–II primary hypertension over a 12-week treatment period. This equivalence was found also for SBP. Most of the patients were treated with the lowest dose of both drugs and only a small fraction of the study population had to be withdrawn from the study because they were non-responsive to treatment, even at the highest dose. In addition, both drugs induced a comparable BP reduction over the 24 h, as assessed by ambulatory BP monitoring.

There are some important findings of this study that deserve to be discussed. First, since the study design foresaw removal from the study of non-responder or non-normalized patients after 8 weeks of treatment and since the number of these subjects was small, this study supports the hypothesis that monotherapy with ACE inhibitors or angiotensin II antagonists may be effective in a number of patients with grade I–II primary hypertension, which is larger than expected (1–3). This is also demonstrated by the fact that in more than 90% of patients continuing the study under (low or high dose), monotherapy BP normalization (<140/90 mmHg) was achieved.

Table III. Number and frequency (%) of patients with at least one drug-related adverse event (AE).

	Zofenopril 30–60 mg (n=114)	Candesartan 8–16 mg (n=122)
Ankle edema	1 (0.9)	–
Asthenia	1 (0.9)	1 (0.8)
Cough	2 (1.8)	–
Diarrhea	1 (0.9)	–
Epigastric pain	1 (0.9)	–
Gastrointestinal disorder	–	1 (0.8)
Headache	2 (1.8)	–
Hypertension	–	1 (0.8)
Other	2 (1.8)	1 (0.8)
Total number of AEs	11	5
Total number of patients with AEs	8 (7.0)	4 (3.3)

Second, in the present study, the antihypertensive effect on office and ambulatory BP of zofenopril and candesartan was similar or even better than that observed in previous studies, thus strengthening the relevance of our results (9–11, 20–22). In the only available study evaluating the effect of zofenopril on a full 24-h monitoring period, performed in a relatively small sample of elderly hypertensive patients (16 patients under zofenopril vs 47 of our study), 24-h DBP and SBP were reduced by 3% and 4% vs 6% and 6% of our study (11).

Third, the BP control over the 24 h, quantified by the trough-to-peak ratio and by the more powerful smoothness index (15–18), was comparable between the two treatment groups. However, the values found for these parameters were not as high as those expected with other antihypertensive drugs (21, 23–25), and in particular, the values observed at the lowest doses were higher than those at the highest doses. As far as the trough-to-peak ratio is concerned, this can partly but not entirely be ascribed to its large scattering of individual data, poor reproducibility and limited prognostic value, which makes it often unreliable when obtained from ambulatory BP recordings (15,18,26).

Fourth, the antihypertensive effect over the 24 h was better under the lowest than the highest dose. This supports the hypothesis that monotherapy with an antihypertensive drug in responder patients has a greater chance to be more effective in controlling the whole 24 h when given at the lowest than at the highest dose, and that a combination treatment should probably be preferred when patients are not responding at highest doses of monotherapy (1–3).

Fifth, in the present study, zofenopril and candesartan significantly reduced not only 24-h SBP and DBP, but also 24-h pulse pressure, though the reduction was quantitatively small. This is an important finding because recent studies have shown that even a limited pulse pressure reduction may be clinically and prognostically beneficial for the hypertensive patient (21,27,28). Also the fact that heart rate, a well-known cardiovascular risk factor, was not increased by the drugs employed in this study may be regarded as a positive study drug feature (29).

The tolerability profile of the two drugs was good, since a limited fraction of patients (7%) reported adverse events related to study treatments and these were compatible with those observed under ACE inhibitors or angiotensin II antagonists.

Finally, the results of this study deserve a note of caution. The sample size of patients with valid ambulatory BP recordings was much smaller than that included in the analysis of office BP. This occurred because many recordings were missing or qualitatively inadequate. This might have made the study underpowered to demonstrate the equivalence in ambulatory BPs. However, it is well known that when drug efficacy is tested on 24-h BP, fewer patients are needed, because it is devoid of the white-coat and placebo effect (30,31), and is much more reproducible than office BP (32).

In conclusion, zofenopril at a dose of 30 or 60 mg represents an effective and safe antihypertensive drug treatment for patients with grade I–II primary hypertension, its efficacy being comparable to that of a widely employed angiotensin II antagonist, candesartan.

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Appendix – List of study sites

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