Advances in Therapy® | *Volume 23 No. 5*
September/October 2006

Hydrochlorothiazide Added to Valsartan Is More Effective Than When Added to Olmesartan in Reducing Blood Pressure in Moderately Hypertensive Patients Inadequately Controlled by Monotherapy

R. Fogari, MD
A. Zoppi, MD
A. Mugellini, MD
P. Preti, MD
M. Destro, MD
A. Rinaldi, MD
G. Derosa, MD
Department of Internal Medicine
Clinica Medica II
IRCCS Policlinico San Matteo
University of Pavia
Pavia, Italy

ABSTRACT

This study was undertaken to evaluate the effects on blood pressure of hydrochlorothiazide (HCTZ) 12.5 mg added to valsartan 160 mg or to olmesartan 20 mg in hypertensive patients. After a 2-wk placebo period, 130 patients, aged 35 to 75 y, with diastolic blood pressure (DBP) ≥99 and <110 mm Hg were randomly assigned to olmesartan 20 mg once daily or to valsartan 160 mg once daily according to a prospective, parallel-arm study design. After 4 wk of monotherapy, patients whose BP was not controlled (DBP ≥90 mm Hg) were given combination treatment with HCTZ 12.5 mg for an additional 4 wk. At the end of the placebo period and at the end of each treatment period, clinical and ambulatory BP measurements were recorded. At the end of the combination therapy period, venous blood samples were drawn 2, 4, and 24 h after

0986

Address reprint requests to
Roberto Fogari, MD
Clinica Medica II
Piazzale Golgi 19
27100 Pavia Italy

drug intake for evaluation of HCTZ plasma concentrations. Both combinations induced a greater ambulatory BP reduction than monotherapy. However, mean reduction from baseline in the valsartan/HCTZ-treated patients (–21.5/–14.6 mm Hg for 24 h, –21.8/–14.9 mm Hg for daytime, and –20.4/–13.7 mm Hg for nighttime systolic blood pressure [SBP]/DBP) was greater than in the olmesartan/HCTZ-treated patients (–18.8/–12.3 mm Hg for 24 h, –19.3/–12.8 mm Hg for daytime, and –17.4/–10.6 mm Hg for nighttime SBP/DBP). The difference between the effects of the 2 treatments was significant ($P<.01$). In particular, compared with monotherapy, the add-on effect of HCTZ 12.5 mg was significantly greater in the valsartan group than in those treated with olmesartan; the difference was more evident for nighttime BP values. Plasma concentrations of HCTZ were significantly greater with valsartan than with olmesartan at each determination time ($P<.05$). These findings suggest that the addition of HCTZ 12.5 mg to valsartan 160 mg monotherapy produces a greater BP reduction than the addition of the same dose of HCTZ to olmesartan 20 mg monotherapy.

Keywords: hydrochlorothiazide; valsartan; olmesartan; hypertension

INTRODUCTION

Current hypertension management guidelines advocate a goal of <140/90 mm Hg in the general population with uncomplicated hypertension.[1,2] Lower blood pressure (BP) goals are recommended for high-risk patients, such as those with concomitant diabetes mellitus, renal disease, or evidence of other target organ damage. These recommendations are supported by evidence accumulated from long-term trials suggesting that lower BP values are associated with better outcomes in a broad range of patients.[3,4] Major studies have shown that most patients with hypertension need 2 or more antihypertensive drugs to achieve their BP goals, regardless of the medication chosen as initial therapy.[5-8] Advantages of combination therapy include the following: (1) greater BP reduction and higher response rates than with monotherapy, probably caused by the simultaneous attack on several regulatory systems involved in abnormal BP elevation; (2) favorable alterations in pharmacokinetics; (3) fewer adverse effects with consequent better tolerability and improved compliance with treatment; and (4) possibly lower costs of treatment.[9,10]

Given the vast array of available antihypertensive agents, the number of potential combinations is large; however, rational choice must be based on the characteristics of each agent and their complementary mechanisms of action.[9,10] Thus, a logical combination consists of a thiazide diuretic, like hydrochlorothiazide (HCTZ), and an angiotensin receptor blocker (ARB).[11-13] Salt depletion induced by the diuretic triggers the release of renin from juxtaglomerular cells. This reactive hyperreninemia renders BP maintenance dependent on angiotensin II, thereby blunting the antihypertensive efficacy of the diuretic. The addition of an ARB makes it possible to counteract the activation of the renin-angiotensin system elicited by the diuretic and, in this way, enhances the BP-lowering effects of salt depletion.[11-13] Even minimally natriuretic doses of HCTZ (12.5 mg/d) can boost the BP-reducing effects of an ARB.[14] Furthermore, such a combination of drugs provides advantages in enhancing tolerability, in that ARBs prevent or attenuate metabolic adverse effects of HCTZ, such as hypokalemia, hyperglycemia, and hyperuricemia.[12,13,15]

Given the general validity of these pharmacodynamic considerations, the efficacy of the HCTZ/ARB combination must be assessed in a clinical setting, specifically for the single ARB, especially when low doses of diuretic are used, as is often the case. In fact, the different pharmacokinetic properties of the various ARBs might produce different interactions with HCTZ, with a consequent possible influence on clinical efficacy.

The purpose of this study was to evaluate the antihypertensive effect, evaluated by ambulatory BP monitoring, of HCTZ 12.5 mg added to valsartan 160 mg monotherapy, as compared with the addition of the same dose of diuretic to olmesartan 20 mg monotherapy, in moderately hypertensive patients with at least 1 additional cardiovascular risk factor. For detection of different pharmacokinetic interference, plasma HCTZ concentrations were evaluated at the end of each combination treatment.

PATIENTS AND METHODS

This was a prospective, randomized, open-label, blind (masked) end point evaluation, parallel-arm study.[16] Consecutive outpatients of both sexes, aged 35 to 75 y, were eligible for enrollment if they had a sitting diastolic BP (DBP) of ≥99 mm Hg and <110 mm Hg at the end of an initial 2-wk washout period. An additional inclusion criterion was the presence of at least 1 of the following cardiovascular risk factors: familial history of ischemic heart disease, a history of smoking, total cholesterol >200 mg/dL or treatment with hypocholesterolemic drugs, electrocardiographic evidence of left ventricular hypertrophy (LVH), or known microalbuminuria (urinary albumin excretion >30 mg/dL). Subjects with sitting DBP >110 mm Hg or sitting systolic BP (SBP) >200 mm Hg at the end of the washout period were excluded from the study, as were those with secondary or malignant hypertension, type 1 or type 2 diabetes mellitus, myocardial infarction or cerebrovascular accident within the preceding 6 mo, heart failure, clinically significant valvular heart disease or arrhythmia, renal or hepatic insufficiency, pregnancy, or known hypersensitivity to the drugs used in the study.

The study protocol was approved by the local ethical committee, and written informed consent was obtained from all patients before they were included in the study.

According to the study design, after a 2-wk washout period, during which any previous antihypertensive therapy was discontinued, eligible patients were randomized to olmesartan 20 mg once daily or to valsartan 160 mg once daily. After 4 wk of monotherapy, patients whose BP was not adequately controlled (DBP ≥90 mm Hg) were treated with the combination of olmesartan 20 mg and HCTZ 12.5 mg, or valsartan 160 mg and HCTZ 12.5 mg, both of which were given once daily in the morning for 4 wk. At the end of each study period (placebo, monotherapy, combination), BP was measured in the clinic environment and through noninvasive ambulatory BP monitoring. Clinic BP was obtained with a standard mercury sphygmomanometer with the patient in the sitting position, 24 h after drug intake. Three measurements, taken at 2-min intervals after 10 min of sitting, were averaged, and these averages were used as clinic BP reference values. Heart rate (HR) was measured after each BP measurement through the palpatory method at the radial artery level.

Ambulatory BP monitoring was performed over 24 h with the use of a clinically validated device (Spacelabs 90207, Spacelabs Inc., Redmond, Wash)[17] that was pro-

grammed to measure BP every 15 min during the entire course of the recording. Each recording was started in the morning, immediately after clinic BP assessment and drug administration. Patients were instructed to remain motionless each time a reading was taken. Analysis of 24-h BP recordings was preceded by removal of artifacts, according to previously described editing criteria.[18] Recordings were considered valid when no more than 2 nonconsecutive hours were missing over 24 h. For each patient, the following data related to SBP, DBP, and HR were obtained through analysis of the recordings: 24-h mean values, as well as daytime (7 AM–11 PM), nighttime (11 PM–7 AM), and hourly mean values. The trough-to-peak (T/P) ratio, computed after peak and trough changes were selected, was calculated for each individual subject.[19] To calculate peak changes, the clinician selected the hour in which maximal reduction in BP was noted after treatment—between the second and eighth hours after drug administration—and averaged this change with data from the immediately adjacent hour in which reduction was most evident. Trough BP changes were calculated by averaging the last 2 h of the recordings.[19] Data were averaged (mean) for all patients.

The smoothness index (SI) was computed by dividing the average of the 24-h BP changes after treatment by the corresponding standard deviation.[20,21] This has been shown to reflect more accurately than the T/P ratio whether treatment smoothly reduced BP during the 24-h period.[20,21]

On the last day of combination therapy, venous blood samples were drawn from each patient 2, 4, and 24 h after drug intake so that HCTZ plasma concentrations could be evaluated. Plasma HCTZ was assayed by high-performance liquid chromatography with ultraviolet detection at 229 nm, according to the method of Sabanathan et al.[22] Intra-assay variability (coefficient of variation) for plasma HCTZ was 7.5%, 4.0%, and 3.6% at 15, 100, and 250 g/mL, respectively.

At each visit, adverse events spontaneously reported or elicited by indirect questioning were recorded.

Statistical Analysis

All analyses were conducted with the SAS system, version 6.12 (SAS Institute, Inc., Cary, NC). Analysis of variance was used for BP results. Differences in T/P ratios between treatments were evaluated with nonparametric tests (univariate signed rank test), whereas the paired Student's *t* test was used to assess differences in SI. The level of statistical significance was kept at .05. Data are shown as mean± standard deviation (SD).

RESULTS

One hundred and thirty patients were recruited for this study and, after the initial washout placebo period, they were randomized to receive olmesartan 20 mg once daily (n=65) or valsartan 160 mg once daily (n=65). At the end of monotherapy, BP was inadequately controlled by treatment in 57 patients in the olmesartan treatment group and 56 in the valsartan treatment group, so HCTZ 12.5 mg was added. Results of this study pertain to these 113 patients whose main demographic and clinical characteristics are shown in Table 1. No statistically significant differences were noted between groups in any baseline characteristics.

Table 1. Demographic and Clinical Characteristics of the Study Population

	Olmesartan + HCTZ	Valsartan + HCTZ
Total randomized, n	57	56
Women/men, n	25/32	26/30
Age, y ± SD	59.3±11.3	59.9±11.5
SBP, mm Hg	168.9±12.3	169.7±11.9
DBP, mm Hg	103.3±5.8	103.7±6.4
HR, beats/min	75.1±6.8	74.9±6.9
Smoking habit, n (%)	12 (21.1%)	13 (23.0%)
Hypercholesterolemia, n (%)	19 (33.3%)	20 (35.1%)
ECG-LVH, n (%)	6 (10.5%)	5 (8.7%)
Microalbuminuria, n (%)	3 (5.3%)	4 (7.0%)
Familial history of IHD, n (%)	20 (35.1%)	19 (33.3%)

ECG-LVH=electrocardiographic left ventricular hypertrophy; IHD=ischemic heart disease.

Average 24-h, daytime, and nighttime ambulatory SBP and DBP values are shown in Table 2. Monotherapy with olmesartan and with valsartan significantly reduced ambulatory BP values as compared with baseline, with no significant difference observed between the 2 treatments: mean decreases in 24-h, daytime, and nighttime SBP/DBP were –15.0±8.8/–11.0±4.8 mm Hg, –15.2±8.7/–11.5±4.8 mm Hg, and –14.4±9.6/–9.4±5.6 mm Hg, respectively, with olmesartan (all $P<.001$ vs baseline); with valsartan, values were –16.4±9.1/–12.1±4.8 mm Hg, –16.6±9.4/–12.6±4.8 mm Hg, and –15.9±8.7/–11.2±5.4 mm Hg, respectively (all $P<.001$ vs baseline). In the group of patients whose BP was not adequately controlled by monotherapy, a further decrease in ambulatory BP was observed at the end of 4 wk of combination therapy (Table 2). However, in the valsartan/HCTZ-treated patients, a mean reduction from baseline (–21.5±10.1/–14.6±5.2 mm Hg for 24 h, –21.8±10.2/–14.9±5.2 mm Hg for daytime, and –20.4±10.3/–13.7±5.9 mm Hg for nighttime SBP/DBP) was greater than in the olmesartan/HCTZ-treated patients (–18.8±9.8/–12.3±4.9 mm Hg for 24-h, –19.3±9.8/–12.8±4.9 mm Hg for daytime, and –17.4±10.2/–10.6±5.5 mm Hg for nighttime SBP/DBP); the difference between the 2 treatments was statistically significant (Fig 1). Furthermore, when the difference in ambulatory BP between the end of monotherapy and the end of combination treatment was considered, the mean decrease in 24-h, daytime, and nighttime SBP and DBP values obtained with the addition of HCTZ 12.5 mg to valsartan monotherapy was significantly greater than that attained with the addition of HCTZ 12.5 mg to olmesartan monotherapy (Fig 2). The difference was particularly evident for nighttime SBP and DBP values.

Table 2. Mean±SD 24-H, Daytime, and Nighttime SBP, DBP, and HR on Ambulatory BP Monitoring at Baseline and After Olmesartan or Valsartan Monotherapy (4 Wk) and Their Combination With HCTZ 12.5 mg (8 Wk)

	24-H			Daytime			Nighttime		
	Baseline	4 Wk (mono-therapy)	8 Wk (+ HCTZ)	Baseline	4 Wk (mono-therapy)	8 Wk (+ HCTZ)	Baseline	4 Wk (mono-therapy)	8 Wk (+ HCTZ)
SBP, mm Hg									
Olmesartan	152.5±9.8	137.5±5.9	133.7±6.1	156.8±9.6	141.6±6.3	137.5±6.5	139.6±11.8	125.1±7.4	122.2±7.3
Valsartan	152.6±10.4	136.2±6.2	131.1±6.6	156.9±10.2	140.3±6.2	135.1±6.5	139.7±12.1	123.8±8.6	119.4±8.2
P (ANOVA–between treatment)		.145	.012		.145	.016		.242	.021
P (ANOVA–vs baseline)		<.001	<.001		<.001	<.001		<.001	<.001
DBP, mm Hg									
Olmesartan	90.0±4.5	79.1±5.0	77.8±5.2	93.4±4.8	82.0±5.1	80.6±5.3	79.8±5.9	70.4±6.1	69.2±6.2
Valsartan	90.2±3.9	78.0±5.9	75.6±5.8	93.5±3.9	80.9±5.4	78.6±6.5	80.3±6.1	69.2±7.5	66.7±7.9
P (ANOVA–between treatment)		.162	.015		.218	.027		.104	.006
P (ANOVA–vs baseline)		<.001	<.001		<.001	<.001		<.001	<.001
HR, beats/min									
Olmesartan	69.9±6.4	70.4±6.1	70.4±5.9	72.4±7.4	73.0±6.9	72.8±6.8	62.7±4.8	62.8±5.4	62.9±4.7
Valsartan	70.3±7.3	71.0±8.7	71.1±8.8	72.5±7.9	72.9±7.4	72.8±7.3	63.5±6.3	65.2±16.5	65.5±17.3
P (ANOVA–between treatment)		.638	.538		.208	.373		.413	.380

Fig 1. Mean ambulatory SBP and DBP reduction from baseline at the end of combination therapy.

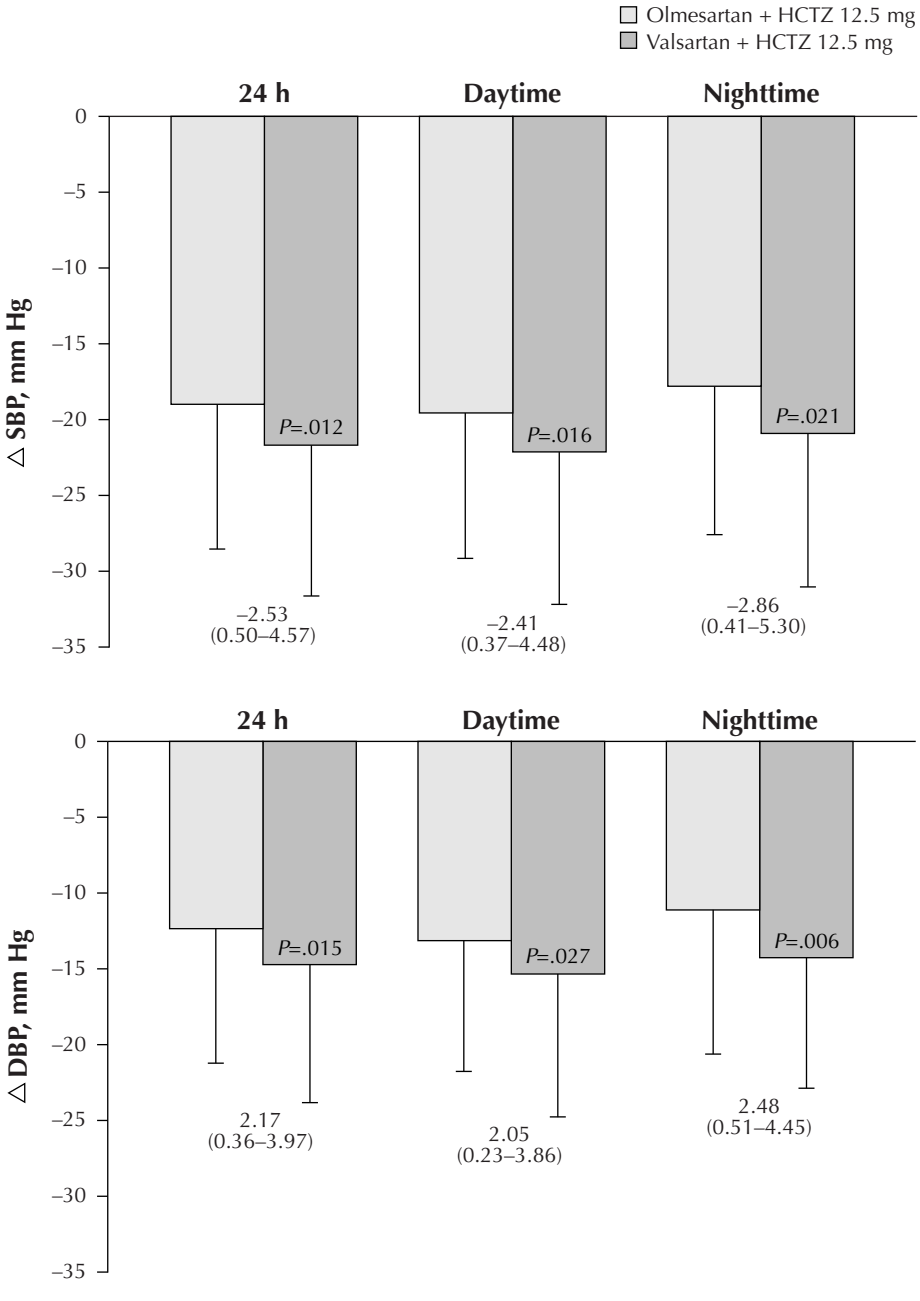
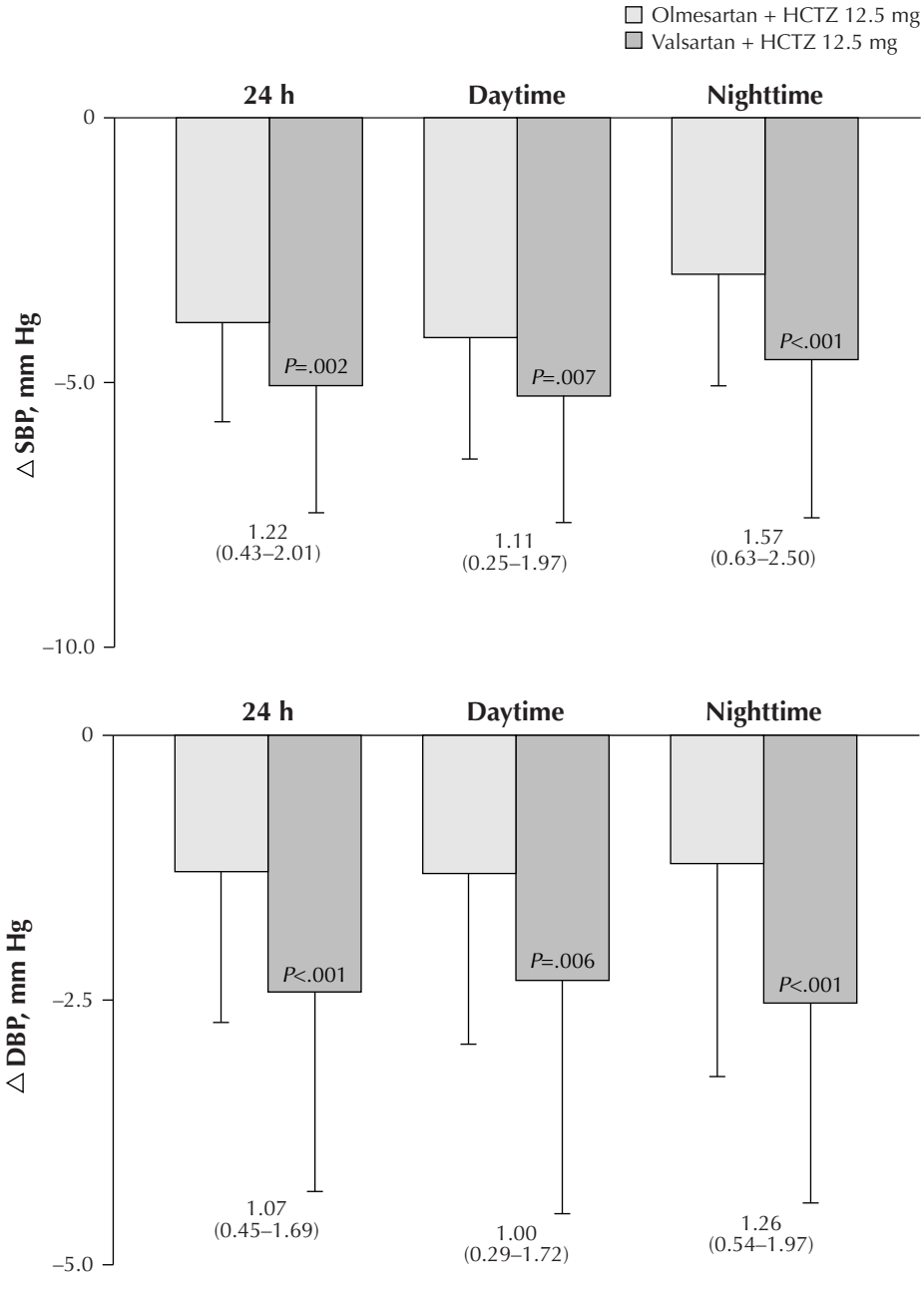


Fig 2. Mean ambulatory SBP and DBP reduction induced by addition of HCTZ 12.5 mg to olmesartan or valsartan monotherapy.



Calculation of hourly average SBP and DBP (Figs 3 and 4) showed that the BP reduction attained with both combinations was more consistent than that observed with respective monotherapy, with no negative influence on the circadian BP profile. Analysis of hourly profiles also confirmed that BP reduction attained with the addition of HCTZ to valsartan monotherapy was greater than that attained with the addition of HCTZ to olmesartan, particularly at nighttime (Fig 5).

The T/P ratio, computed at the end of combination treatment, was below the threshold of 0.5, which is universally regarded as clinically acceptable, and showed no significant difference between the 2 regimens (Table 3). As with the T/P ratio, the average SI for SBP and DBP was similar in the 2 combination treatment groups (Table 3).

Plasma concentrations of HCTZ were significantly greater at each determination time in patients treated with valsartan than in those treated with olmesartan ($P<.05$); the difference was more marked at 24 h (Table 4).

Clinic BP data (Table 5) showed a significant reduction in SBP/DBP levels with olmesartan and valsartan monotherapy as compared with baseline; this reduction was much greater after 4 wk of treatment with olmesartan/HCTZ and valsartan/HCTZ combinations. Again, compared with monotherapy, the changes in SBP and DBP values were significantly greater when HCTZ 12.5 mg was added to valsartan than when HCTZ 12.5 mg was added to olmesartan.

Table 3. Mean Values of T/P Ratio and SI After 4 Wk of Treatment With Olmesartan 20 mg/HCTZ 12.5 mg and Valsartan 160 mg/HCTZ 12.5 mg

	Trough/Peak Ratio	SI
SBP		
Olmesartan/HCTZ	0.58±0.32	2.60±1.71
Valsartan/HCTZ	0.58±0.37	2.94±1.74
DBP		
Olmesartan/HCTZ	0.53±0.24	2.06±1.04
Valsartan /HCTZ	0.60±0.31	2.47±1.02

Table 4. Plasma Concentrations of HCTZ (Mean±SD) 2, 4, and 24 H After HCTZ 12.5 mg Administration in Olmesartan- and Valsartan-Treated Groups

	HCTZ, ng/mL		
	Olmesartan	Valsartan	*P*
2 h	73.9±16.6	82.7±18.3	<.05
4 h	78.6±17.1	89.9±18.9	<.05
24 h	22.2±6.3	33.7±7.9	<.05

Fig 3. Twenty-four-hour SBP and DBP after treatment with olmesartan monotherapy (4 wk) and olmesartan/HCTZ combination (8 wk).

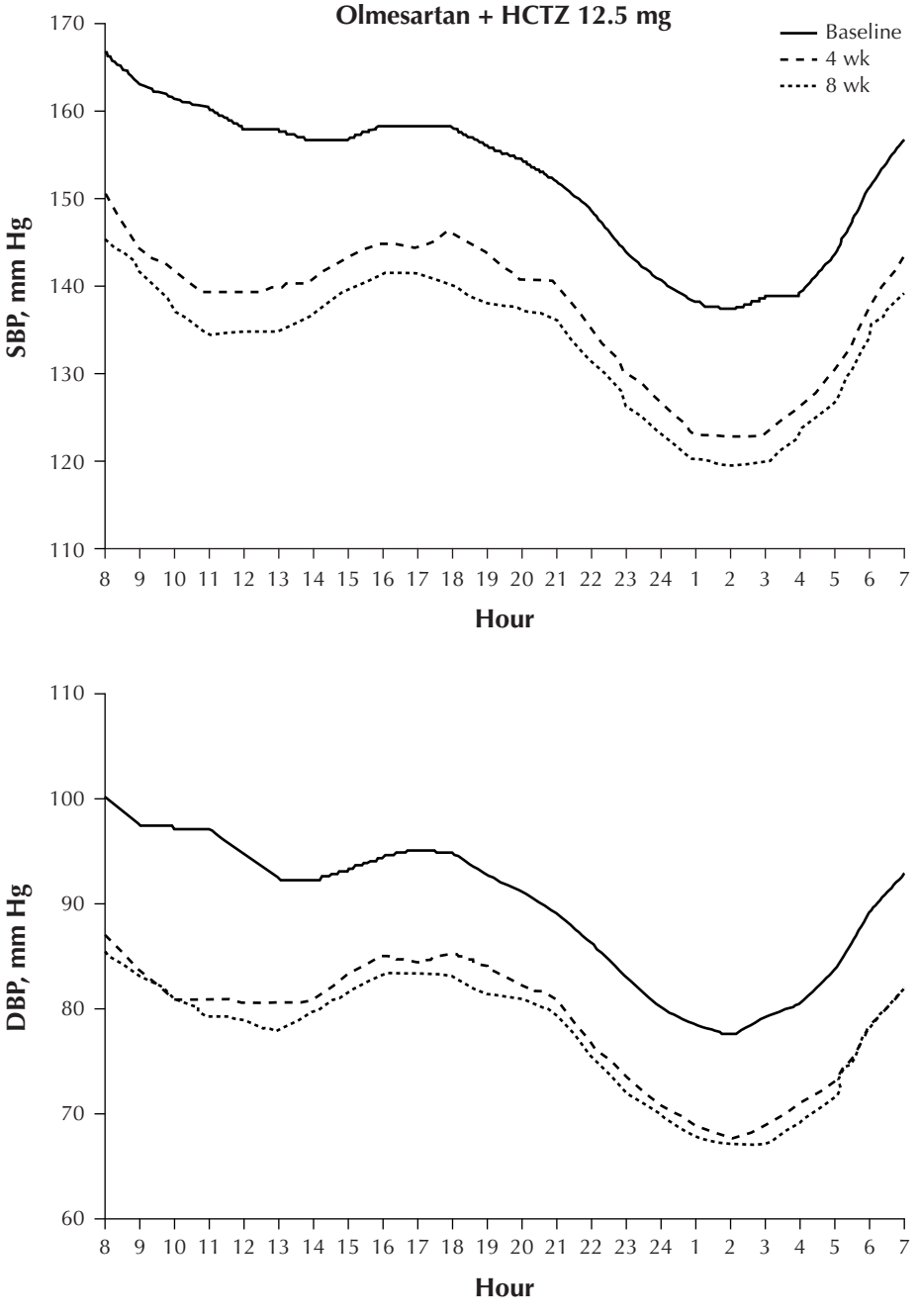


Fig 4. Twenty-four-hour SBP and DBP after treatment with valsartan monotherapy (4 wk) and valsartan/HCTZ combination (8 wk).

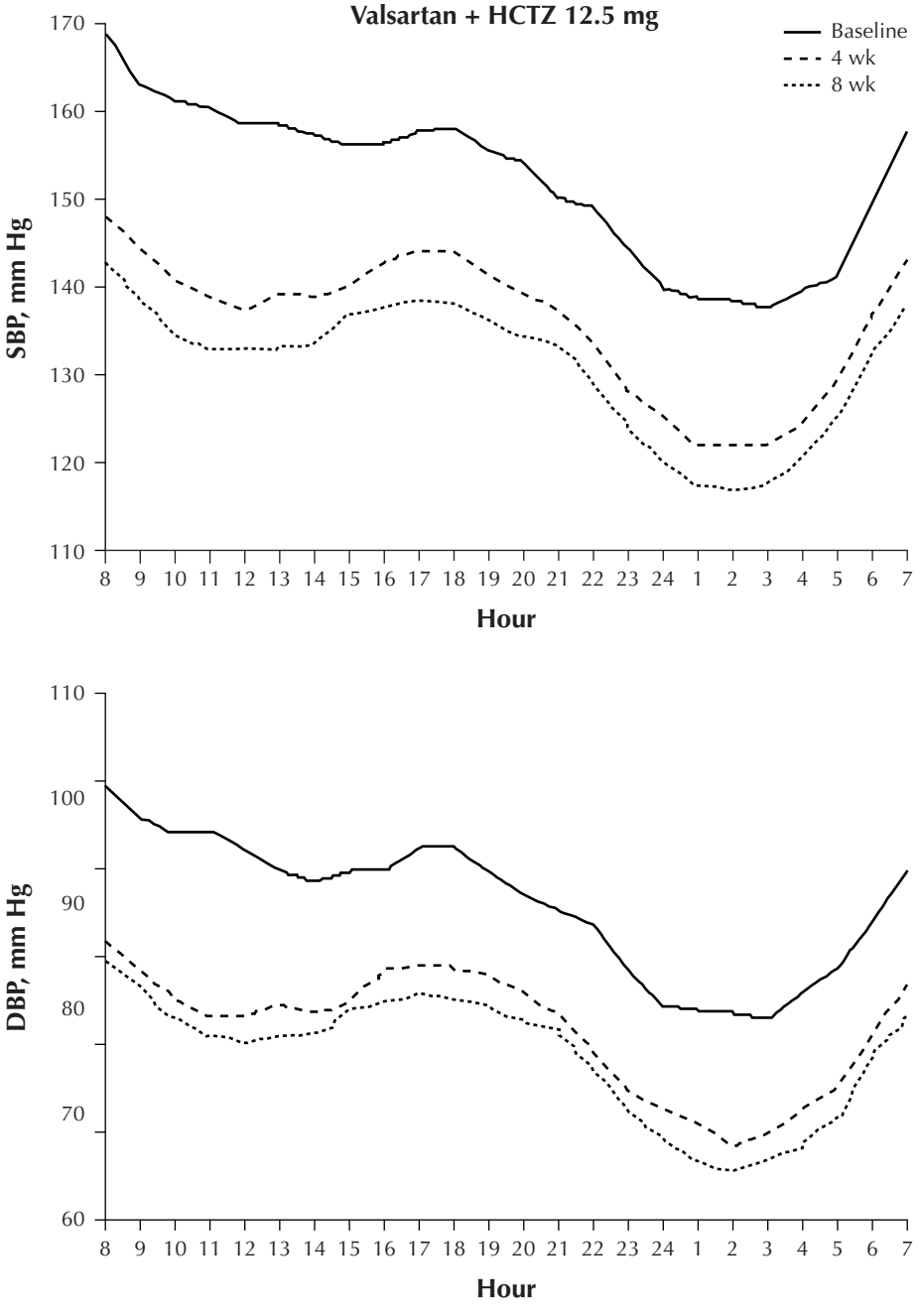
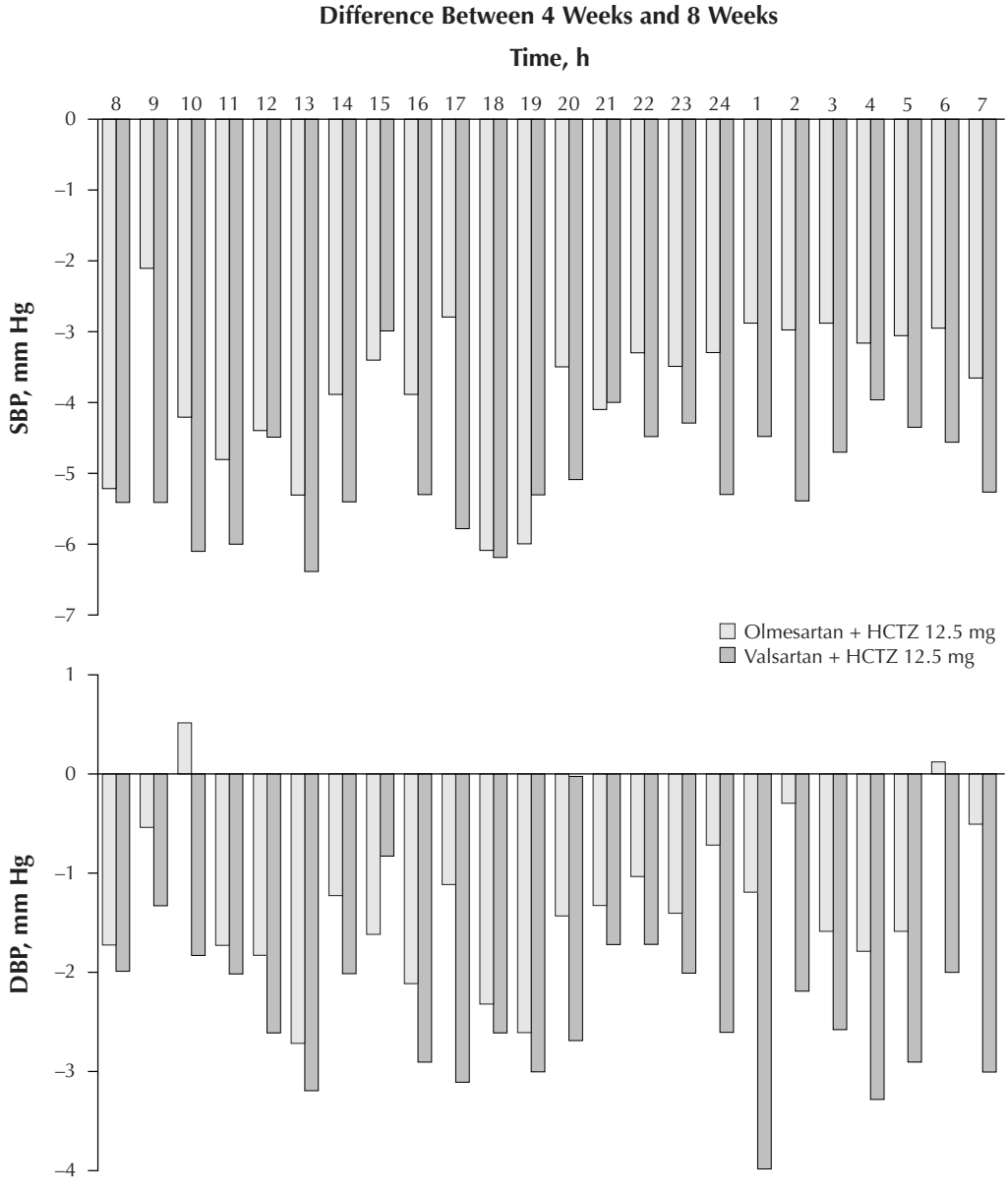


Fig 5. Mean differences from monotherapy in hourly SBP and DBP values after 4 wk of HCTZ added to olmesartan or valsartan.



The rate of adverse events (7% with olmesartan/HCTZ and 5% with valsartan/HCTZ) was not significantly different between the 2 combinations and was similar to the rate observed with correspondent monotherapy.

Table 5. Mean±SD Clinical BP Monitoring and HR at Baseline and After Olmesartan or Valsartan Monotherapy (4 Wk) and Their Combination With HCTZ 12.5 mg (8 Wk)

	Baseline	4 Wk, Monotherapy	8 Wk, + HCTZ 12.5 mg
SBP, mm Hg			
Olmesartan	169.9±12.3	152.2±6.2	146.1±6.1
Valsartan	169.7±11.9	149.1±6.4	141.8±6.2±6.4*
DBP, mm Hg			
Olmesartan	103.7±7.6	93.8±5.1	88.9±4.9
Valsartan	103.9±7.4	93.1±4.9	86.2±4.8*
HR, beats/min			
Olmesartan	75.1±7.8	75.8±7.1	75.7±6.9
Valsartan	75.6±7.9	75.9±7.6	75.8±7.4

*$P<.05$ vs olmesartan.

DISCUSSION

The results of the present study indicate that, in moderately hypertensive patients with at least 1 additional cardiovascular risk factor, combination therapy with olmesartan 20 mg/HCTZ 12.5 mg and valsartan 160 mg/HCTZ 12.5 mg provides a clinically meaningful antihypertensive effect that is better than that attained with monotherapy. This is consistent with findings from previous studies, which showed that the addition of HCTZ enhances the efficacy of valsartan[23-25] and olmesartan.[26-28] However, the BP decrease resulting from the addition of HCTZ to valsartan monotherapy was significantly greater than that observed when HCTZ was added to olmesartan monotherapy. This was true for SBP and DBP 24-h mean values, as well as for daytime and nighttime mean values. Such a difference in efficacy could be due to the different pharmacologic power of the 2 ARBs, but it could also reflect the different pharmacokinetic profiles of valsartan and olmesartan,[29,30] which might result in different pharmacokinetic interactions with HCTZ. In the present study, plasma concentrations of HCTZ evaluated after 4 wk of combination therapy were always significantly greater in patients treated with valsartan than in those treated with olmesartan at each determination time, but particularly 24 h after drug intake. This suggests that concomitant administration of olmesartan and HCTZ might in some way decrease the bioavailability of HCTZ, at least at a dose of 12.5 mg.

Clinic BP results confirmed that (1) the antihypertensive effect of the valsartan/HCTZ combination was superior to that of olmesartan/HCTZ at the end of the dosing interval after 4 wk of combination treatment; and (2) the add-on effect of HCTZ

12.5 mg as compared with monotherapy was significantly greater in patients treated with valsartan than in those treated with olmesartan.

Because a continuous and graded relationship exists between BP values and cardiovascular risk, lower BP values are associated with better outcomes in a broad range of patients.[31,32] Therefore, from a clinical point of view, even a moderate decrease in BP has the potential to significantly reduce hypertension-related morbidity and mortality, particularly in high-risk patients.

When the duration of hypotensive action was evaluated over 24 h, the T/P ratios for SBP and DBP obtained with olmesartan/HCTZ and valsartan/HCTZ combinations given once daily fulfilled US Food and Drug Administration guidelines (T/P ratio >50%), and no significant difference was noted between the 2 regimens. Observed T/P ratios indicate that the antihypertensive effects of both combinations were sustained during the entire 24-h period, a fact that renders them suitable for once-daily administration. The SI, which provides information about the homogeneity of the antihypertensive effect,[20,21] was not statistically different between the 2 treatment groups, although slightly higher values for SBP and DBP were observed in the valsartan/HCTZ group. Greater T/P ratios and SI values reflect less variability in BP, which has been demonstrated to have an independent effect on organ damage and disease prognosis.[33]

The olmesartan/HCTZ and valsartan/HCTZ combinations were well tolerated. The incidences of adverse events were comparable between the 2 treatment groups and were similar to the rates observed with monotherapy. Most adverse events were of mild or moderate intensity and were transient in duration. This is consistent with the proven tolerability profiles of ARBs when administered alone or in combination with HCTZ.[12-15]

CONCLUSIONS

In spite of study limitations due to the open design and the relatively short duration of treatment, findings of the present study indicate that the addition of HCTZ 12.5 mg to valsartan 160 mg monotherapy produces greater ambulatory and clinic BP reductions than result from the addition of the same dose of HCTZ to olmesartan 20 mg; this probably reflects different pharmacokinetic interactions between the 2 ARBs and HCTZ. This suggests that, at least when this low dose of HCTZ is used, the combination with valsartan might offer some advantage in terms of better BP response—a fact that is of clinical relevance in high-risk hypertensive patients.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA.* 2003;289:2560-2572.
2. Guidelines Committee. 2003 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens.* 2003;21:1011-1053.
3. Turnbull F. Effects of different blood-pressure lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet.* 2003;362:1527-1535.

4. Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until March 1, 2003. *J Hypertens.* 2003;21:1055-1076.
5. Hansson L, Zanchetti A, Carruthers SG, et al, for the HOT study group. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. *Lancet.* 1998;351:1755-1762.
6. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317:703-713.
7. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med.* 2000;342:145-153.
8. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002;288:2981-2997.
9. Moser M, Black HR. The role of combination therapy in the treatment of hypertension. *Am J Hypertens.* 1998;11:73S-78S.
10. Sica DA. Rationale for fixed dose combinations in the treatment of hypertension: the cycle repeats. *Drugs.* 2002;62:443-462.
11. Waeber B. Combination therapy with ACE-inhibitors/angiotensin II receptor antagonists and diuretics in hypertension. *Expert Rev Cardiovasc Ther.* 2003;1:43-50.
12. Palatini P. Combination therapy in the management of hypertension: focus on angiotensin receptor blockers combined with diuretics. *J Clin Hypertens.* 2005;7:96-101.
13. Kjeldsen SE, Os I, Hoieggen A, Beckey K, Gleim GW, Oparil S. Fixed-dose combinations in the management of hypertension: defining the place of angiotensin receptor antagonists and hydrochlorothiazide. *Am J Cardiovasc Drugs.* 2005;5:17-22.
14. Sica DA. Pharmacotherapy review: angiotensin receptor antagonists. *J Clin Hypertens.* 2005;7: 681-684.
15. Meredith PA. Angiotensin II receptor antagonists alone and in combination with hydrochlorothiazide: potential benefits beyond the antihypertensive effect. *Am J Cardiovasc Drugs.* 2005;5: 171-183.
16. Hansson L, Hedner T, Dahlof B. Prospective, randomized, open, blinded end-point (PROBE) study: a novel design for intervention trials. *Blood Press.* 1992;1:113-114.
17. Groppelli A, Omboni S, Ravogli A, et al. Validation of the Spacelabs 90202 and 90207 devices for ambulatory blood pressure monitoring by comparison with intra-arterial resting and ambulatory measurements. *J Hypertens.* 1991;9(suppl 3):S334-S335.
18. Parati G, Bosi S, Castellano M, et al. Guidelines for 24-hour non-invasive ambulatory blood pressure monitoring: report from a working group of the Italian Society of Hypertension. *High Blood Press.* 1995;4:168-174.
19. Omboni S, Parati G, Zanchetti A, Mancia G. Calculation of trough:peak ratio of antihypertensive treatment from ambulatory blood pressure: methodological aspects. *J Hypertens.* 1995;13:1105-1112.
20. Rizzoni D, Castellano M, Muiesan ML, Porteri E, Agabiti-Rosei E. Beyond trough:peak ratio. A new index of the smoothness of the antihypertensive effect of a drug. *High Blood Press.* 1997; 6:110-115.
21. Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. *J Hypertens.* 1998;16:1685-1691.
22. Sabanathan K, Castelden CM, Adam HK, Ryan J, Fitzimmons TJ. A comparative study of the pharmacokinetics and pharmacodynamics of atenolol, hydrochlorothiazide and amiloride in normal young and elderly subjects and elderly hypertensive patients. *Eur J Clin Pharmacol.* 1987;32:53-60.

23. Wellington K, Faulds DM. Valsartan/hydrochlorothiazide: a review of its pharmacology, therapeutic efficacy and place in the management of hypertension. *Drugs.* 2002;62:1983-2005.

24. Mallion JM, Caretta R, Trenkwalder P, et al. Valsartan/hydrochlorothiazide is effective in hypertensive patients inadequately controlled by valsartan monotherapy. *Blood Press.* 2003; 12(suppl 1):36-43.

25. Palatini P, Mugellini A, Spagnuolo V, et al. Comparison of the effects on 24-hour ambulatory blood pressure of valsartan and amlodipine, alone or in combination with a low-dose diuretic, in elderly patients with isolated systolic hypertension (Val-syst Study). *Blood Press Monit.* 2004; 9:91-97.

26. Chrysant SG, Chrysant GS. Antihypertensive efficacy of olmesartan medoximil alone and in combination with hydrochlorothiazide. *Expert Opin Pharmacother.* 2004;5:657-667.

27. Sellin L, Stegbauer J, Laeis P, Rump LC. Adding hydrochlorothiazide to olmesartan dose dependently improves 24-hour blood pressure and response rates in mild-to-moderate hypertension. *J Hypertens.* 2005;23:2083-2092.

28. Rump LC, Ambrosioni E, Burnier M, Horl W, Rabelink AJ. Initial combination therapy with olmesartan/hydrochlorothiazide in moderate to severe hypertension. *J Hum Hypertens.* 2006;20:299-301.

29. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs.* 1997;54:299-311.

30. Nussberger J, Koike H. Antagonizing the angiotensin II subtype I receptor: focus on olmesartan medoximil. *Clin Ther.* 2004;26(suppl A):A21-A27.

31. Stamler R. Implications of the INTERSALT Study. *Hypertension.* 1991;17(suppl 1):I16-I20.

32. Lewington S, Clarke R, Qizilbash N, et al, for the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903-1913.

33. Palatini P, Penzo M, Racioppa A, et al. Clinical relevance of night-time blood pressure and daytime blood pressure variability. *Arch Intern Med.* 1992;152:1855-1860.