Journal of Human Hypertension (1998) 12, 861–866

http://www.stockton-press.co.uk/jhh

ORIGINAL ARTICLE

Valsartan and hydrochlorothiazide in patients with essential hypertension. A multiple dose, double-blind, placebo controlled trial comparing combination therapy with monotherapy

JR Benz[1], HR Black[2], A Graff[3], A Reed[4], S Fitzsimmons[5] and Y Shi[5]
[1]*Clinical Research, Cedar Rapids, IA;* [2]*Rush-Presbyterian-St Lukes Medical Center, Chicago, IL;* [3]*University of Miami School of Medicine, Miami, FL;* [4]*Smith and Reed Clinic, Lincoln, NB;* [5]*Novartis, NJ, USA*

Objective: **This study compares the antihypertensive efficacy and tolerability of valsartan, a novel angiotensin II antagonist, given with hydrochlorothiazide (HCTZ) *vs* placebo or *vs* valsartan or HCTZ alone.**
Design: **871 adult out-patients with essential hypertension participated in this double-blind study. Patients were randomised in equal number to receive either combination therapy of valsartan (80 mg or 160 mg) and HCTZ (12.5 mg or 25 mg), or valsartan (80 mg or 160 mg) or HCTZ (12.5 mg or 25 mg) alone, or placebo. Patients were treated once daily for 8 weeks and assessed at 2, 4 and 8 weeks after randomisation.**
Main outcome measures: **The primary efficacy variable was change from baseline in mean sitting diastolic blood pressure (MSDBP) at end-point. The secondary variable was change in mean sitting systolic blood pressure (MSSBP) from baseline to end-point.**
Results: **All active treatments produced a statistically significant difference in MSDBP ($P < 0.001$) from baseline to end-point compared with placebo. Similar results were obtained for MSSBP. All combination regimens produced a statistically significantly greater reduction in MSDPB and MSSBP than the corresponding monotherapies. Dizziness and headache were the most common treatment-related adverse experiences reported. Hypokalaemia, associated with the use of thiazide diuretics, was more commonly reported in the higher dose HCTZ 25 mg groups.**
Conclusions: **Valsartan 80 mg and 160 mg act additively with HCTZ 12.5 mg or 25 mg to lower MSDBP and MSSBP in patients with essential hypertension. The addition of HCTZ to valsartan 80 mg or 160 mg was well tolerated.**

Keywords: valsartan; angiotensin II antagonist; angiotensin receptor blocker (ARB); AT_1 blocker; essential hypertension; hydrochlorothiazide

Introduction

Pharmacological approaches to the treatment of hypertension have focused on the use of drug therapies such as diuretics, beta-blockers, calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors. More recently, a new class of orally active antihypertensive drugs has been discovered that specifically blocks type I angiotensin II (AT_1) receptors.[1] Valsartan is a new, potent, highly selective angiotensin II AT_1 receptor antagonist belonging to this class,[2] which has been shown to produce clinically relevant and statistically significant decreases in blood pressure (BP) and to be well tolerated at once-daily doses of 80 mg and 160 mg compared to placebo.[3] In studies comparing valsartan and other antihypertensive drugs, valsartan has been shown to be at least as effective as amlodipine,[4] enalapril,[5] lisinopril[6] and hydrochlorothiazide[7] in the treatment of mild to moderate hypertension. These studies have also shown valsartan to be very well tolerated with a good risk:benefit ratio, and without the side effects characteristic of the dihydropyridine calcium antagonists, ACE inhibitors or thiazide diuretics.

Although a single antihypertensive agent is considered to be the ideal in terms of convenience and compliance, many patients with essential hypertension require a combination drug regimen.[8,9] Hydrochlorothiazide (HCTZ) is a thiazide diuretic which is commonly used for the treatment of essential hypertension, at recommended doses of 12.5 mg or 25 mg.[10] In published clinical studies, HCTZ has been shown to act additively in combination with several classes of antihypertensive medication.[11–14]

Correspondence: Dr Joan Ryder Benz, Clinical Research, 788 8th Ave SE, Cedar Rapids, IA 52401, USA
Sponsorship: This study was sponsored by Novartis
Received 21 May 1998; revised and accepted 20 August 1998

In addition to its diuretic effect HCTZ is known to activate the renin-angiotensin system. There are therefore theoretical reasons why a combination of HCTZ and an angiotensin II antagonist may offer a highly effective and well-tolerated combination regimen.

The current study was therefore designed to investigate whether the combined use of valsartan and HCTZ would offer a regimen that has greater efficacy than these agents as monotherapy, and to determine the tolerability of this combined regimen.

Materials and methods

Patients

Male and female out-patients aged over 18, with uncomplicated essential hypertension, were eligible for randomisation into the study. Patients were required to have a mean sitting diastolic blood pressure (MSDBP) of 95–115 mm Hg and a difference in MSDBP between enrolment and randomisation not greater than 10 mm Hg. Patients with a history of heart failure in the preceding 6 months, second or third degree heart block, concomitant angina pectoris, clinically relevant arrhythmia, clinically significant valvular heart disease, hypertensive retinopathy grade III or IV, a history of hypertensive encephalopathy or cerebrovascular accident, confirmed hepatic disease or renal impairment, insulin dependent diabetes mellitus, proven or suspected sodium depletion, gastrointestinal disease in the preceding 3 months, or a history of gastrointestinal surgery or disease that could interfere with drug absorption, were all excluded from participation in the study. Female patients were also required to be either post-menopausal for 1 year or surgically sterile, with fertile women required to use effective contraception and show negative serum pregnancy tests at the start and throughout the study.

All patients gave written consent to participate in the study, which was approved by a local Institutional Review Board. The study was performed according to Good Clinical Practice Requirements.

Study design

The study was performed in several major centres in the United States as a randomised, double-blind, multiple dose, placebo controlled, multifactorial, parallel trial. After an initial antihypertensive washout period of a minimum of 2 weeks, patients were given single-blind placebo treatment for 2 to 4 weeks. During this period, placebo responders were identified and excluded from study participation, and patients were acclimatised to the daily therapeutic regimen. Eligible patients were randomised into one of nine double-blind treatment groups, and received a once-daily oral dose of either placebo, valsartan 80 mg or 160 mg, HCTZ 12.5 mg or 25 mg, or a combination of valsartan (80 or 160 mg) with HCTZ (12.5 mg or 25 mg) for 8 weeks. Study drugs were packaged in double-dummy fashion to maintain blinding, with each patient taking two capsules per day at 8 am. Valsartan 80 mg and 160 mg were supplied as capsules of identical appearance. HCTZ 12.5 mg and 25 mg were also supplied as identical capsules, but different in appearance from the valsartan capsules. Placebo capsules matched the valsartan and HCTZ capsules in appearance. Patients were assessed once during the placebo treatment period, again at randomisation, and then at 2, 4 and 8 weeks of active double-blind treatment. Scheduled visits were made in the morning, after a 12-h fast and before the study medication for that day was taken, to provide trough BP measurements.

At each visit, systolic and diastolic BP, pulse and weight were recorded. Blood pressures were measured by the same clinician in the same arm using the same sphygmomanometer each time. All BP measurements were made using WHO criteria,[15] to the nearest 2 mm Hg. For diastolic pressure, phase V (disappearance of Korotkoff sounds) was used. Three measurements were taken at 1 to 2-min intervals after the patient had been sitting for 5 min. Then the patient was asked to stand for 2 min, and one standing measurement was taken. The pulse rate was also measured for 30 sec immediately prior to BP measurements, once in the sitting and once in the standing position.

The primary hypotheses were that the combination therapy was equal to each of the component monotherapies *vs* that they were not equal. The primary efficacy variable was the change from baseline in trough MSDBP. The secondary efficacy variable was the change in trough mean sitting systolic blood pressure (MSSBP). Other efficacy variables included responder rates (percentage of patients with trough MSDBP or $<$90 mm Hg, or a $\geqslant$10 mm Hg decrease from baseline), change in standing systolic and diastolic BP, change in sitting or standing pulse rate, and change in body weight from baseline.

Safety and tolerability were evaluated at each visit by physical examination and direct questioning. Standard laboratory analyses of complete blood chemistry, haematology and urinalysis were performed at week –4, baseline and at the final visit after 8 weeks of double-blind treatment. A 12-lead ECG was performed at baseline.

Statistical analysis

It was calculated that a sample size of 765 patients (85 completed patients per treatment group) would be needed to detect a 4 mm Hg difference in MSDBP between treatments at the 0.05 level (two-sided) with 90% power, assuming a standard deviation for MSDBP of 8 mm Hg.[16]

The primary efficacy analysis was an intent-to-treat analysis conducted on the dataset of all randomised patients who had both a baseline and post-treatment measurement of the variable of interest.

The treatment groups were compared for baseline comparability by sex, race, medical history and previous antihypertensive medication using the Cocran–Mantel—Haenszel chi-square test, with the F-test used for age, height, weight and duration of hypertension. Baseline comparability for the pri-

mary, secondary and other efficacy variables was also performed using the F-test.

The primary and secondary variables were analysed using a two-way covariance model with treatment and centres as factors, and baseline measurement as a covariate. Both treatment-by-centre and treatment-by-baseline interactions were included. The two-sided *t*-test was performed for each of the between-treatment comparisons at the 0.05 significance level.

Responder rates were compared by means of a one-way logistic model. All randomised patients were included in the descriptive safety and tolerability analysis.

Results

Patients

A total of 871 patients were randomised into nine treatment groups. Demographic characteristics and medical history were similar in all nine treatment groups, as were baseline measurements (Table 1). No statistically significant differences between treatment groups at baseline were found. The majority of study participants were white (75%), with 14% black and 11% of other race; 58% were male, 42% female, and the patients' age ranged from 22 to 86 (mean age: 52 ± 11.0 years). The mean duration of exposure to study drug among the nine treatment groups was comparable, with a range from 50 to 57 days.

A total of 792 patients completed the trial. Seventy-nine patients discontinued study drug medication prematurely. Of these, 41 patients discontinued because of adverse experiences, nine for unsatisfactory therapeutic effect, seven because they did not meet protocol criteria, two for non-compliance, 15 because they withdrew consent, and five because they were lost to follow-up. The number of patients included in the primary efficacy analysis at end-point was 865 (six prematurely-discontinued patients had no post-randomisation measurements).

Efficacy

The intent-to-treat results are presented here. All the combination treatments and all the active monotherapies showed clinically and statistically significantly greater reductions from baseline in MSDBP at end-point compared with placebo. Similar results were obtained for MSSBP, the secondary variable (Table 2).

All the combination treatments produced a clinically and statistically significantly greater reduction in MSDBP than the corresponding monotherapies (Table 3). The placebo-subtracted changes in MSDBP for each of the four combination treatment groups were greater (0.2 to 1.5 mm Hg) than the sum of the changes from baseline for the respective monotherapies. No statistically significant interaction was observed for treatment-by-centre, or treatment-by-baseline. Standing systolic and diastolic BP also decreased statistically significantly in all active treatment groups compared with baseline. The decreases were consistent with the results for sitting systolic and diastolic BP.

The percentage of responders in each treatment group is shown in Figure 1. All active treatment groups showed a statiatically significantly ($P < 0.001$) higher response rate than placebo (29%). The response rate for the combination treatments ranged from 64 to 81.

There were no observable statistically or clinically significant differences between treatment groups in sitting or standing pulse rate, or in body weight when compared with baseline values.

Safety and tolerability

Study medications were generally well tolerated in all treatment groups. Of the 871 patients random-

Table 1 Comparability of treatment groups: demographic and baseline data

	Treatment group								
	P	*V80*	*V160*	*H12.5*	*H25*	*V80/H12.5*	*V160/H12.5*	*V80/H25*	*V160/H25*
No. of patients randomised	94	99	99	100	100	96	97	92	94
Sex: Male (%)	58	63	61	58	55	58	58	47	51
Female (%)	36	36	38	42	45	38	39	45	43
Race: White (%)	70	75	75	66	77	69	78	72	68
Black (%)	14	15	13	22	11	12	11	9	15
Other (%)	10	9	11	12	12	15	8	11	11
*Age (yrs)	52 (±10.4)	52 (±10.2)	52 (±10.5)	52 (±11.4)	52 (±11.0)	52 (±11.9)	53 (±11.3)	51 (±11.2)	53 (±11.2)
*Duration of hypertension (yrs)	8.0 (±8.0)	8.6 (±9.0)	7.9 (±8.7)	7.2 (±5.8)	8.7 (±8.3)	9.1 (±9.3)	8.4 (±7.9)	7.5 (±9.0)	8.4 (±8.4)
Previous antihypertensive treatment (%)	78	74	74	75	72	73	74	76	74
Baseline blood pressure (mm Hg)									
*SDBP	101.4 (±5.0)	101.5 (± 4.9)	101.5 (±4.8)	101.2 (±4.5)	100.8 (±4.6)	101.0 (±4.9)	101.0 (±4.5)	100.4 (±4.6)	101.4 (±4.8)
*SSSP	152.7 (±17.1)	153.7 (±14.4)	153.5 (±15.1)	153.6 (±16.4)	152.0 (±15.5)	153.0 (±14.4)	154.5 (±15.4)	152.0 (±14.2)	155.9 (±14.8)

*Mean ± s.d.; *P* = placebo; V80 = valsartan 80 mg; V160 = valsartan 160 mg; H12.5 = HCTZ 12.5 mg; H25 = HCTZ 25 mg.

Table 2 Comparison of all combination treatments and active monotherapies *vs* placebo: change from baseline in mean sitting diastolic blood pressure and mean sitting systolic blood pressure at end-point of therapy[a]

Treatment group	*Diastolic blood pressure*			*Systolic blood pressure*		
	Difference (mm Hg)	*CI (95%)*	*P*	*Difference (mm Hg)*	*CI (95%)*	*P*
Val 160/H 25 *vs* placebo	–11.19	(–13.62, –8.76)	<0.001*	–20.53	(–24.63, –16.44)	<0.001*
Val 160/H 12.5 *vs* placebo	–9.39	(–11.81, –6.97)	<0.001*	–15.84	(–19.82, –11.86)	<0.001*
Val 80/H 25 *vs* placebo	–11.16	(–13.63, –8.70)	<0.001*	–19.23	(–23.27, –15.18)	<0.001*
Val 80/H 12.5 *vs* placebo	–7.71	(–10.14, –5.27)	<0.001*	–14.59	(–18.61, –10.58)	<0.001*
Val 160 *vs* placebo	–5.30	(–7.71, –2.89)	<0.001*	–10.19	(–14.16, –6.23)	<0.001*
Val 80 *vs* placebo	–4.51	(–6.93, –2.09)	<0.001*	–6.89	(–10.86, –2.92)	<0.001*
H 25 *vs* placebo	–5.16	(–7.56, –2.76)	<0.001*	–10.81	(–14.78, –6.83)	<0.001*
H 12.5 *vs* placebo	–3.04	(–5.44, –0.63)	0.0133*	–5.39	(–9.36, –1.42)	0.0078*

[a]Summary of comparison of least-squares treatment means, intent-to-treat data set; CI = confidence interval; *indicates a statistical significance at the level of 0.05 ($P < 0.05$); Val 160 = valsartan 160 mg; Val 80 = valsartan 80 mg; H 25 = HCTZ 25 mg; H 12.5 = 12.5 mg.

Table 3 Comparison of all combination treatments to individual monotherapies: change from baseline in mean sitting diastolic blood pressure and mean sitting systolic blood pressure at end-point of therapy[a]

Treatment group	*Diastolic blood pressure*			*Systolic blood pressure*		
	Difference (mm Hg)	*CI (95%)*	*P*	*Difference (mm Hg)*	*CI (95%)*	*P*
V 160/H 25 *vs* V 160	–5.89	(–8.30, –3.47)	<0.001*	–10.34	(–14.41, –6.27)	<0.001*
V 160/H 25 *vs* H 25	–6.03	(–8.43, –3.62)	<0.001*	–9.73	(–13.81, –5.65)	<0.001*
V 160/H 12.5 *vs* V160	–4.09	(–6.49, –1.69)	<0.001*	–5.64	(–9.60, –1.69)	0.0053*
V 160/H 12.5 *vs* H 12.5	–6.35	(–8.75, –3.96)	<0.001*	–10.45	(–14.40, –6.49)	<0.001*
V 80/H 25 *vs* V 80	–6.65	(–9.11, –4.19)	<0.001*	–12.34	(–16.37, –8.31)	<0.001*
V 80/H 25 *vs* H 25	–6.00	(–8.44, –3.56)	<0.001*	–8.42	(–12.45, –4.39)	<0.001*
V 80/H 12.5 *vs* V 80	–3.19	(–5.62, –0.77)	0.0099*	–7.71	(–11.70, –3.71)	<0.001*
V 80/H 12.5 *vs* H 12.5	–4.67	(–7.08, –2.26)	<0.001*	–9.20	(–13.19, –5.21)	<0.001*

[a]Summary of comparison of least-squares treatment means, intent-to-treat data set; CI = confidence interval; *indicates a statistical significance at the level of 0.05 ($P < 0.05$); V 160 = valsartan 160 mg; V 80 = valsartan 80 mg; H 25 = HCTZ 25 mg; H 12.5 = HCTZ 12.5 mg. Least-square treatment mean change from baseline in mean sitting/diastolic blood pressure was –1.93/–4.12 mm Hg in the placebo group.

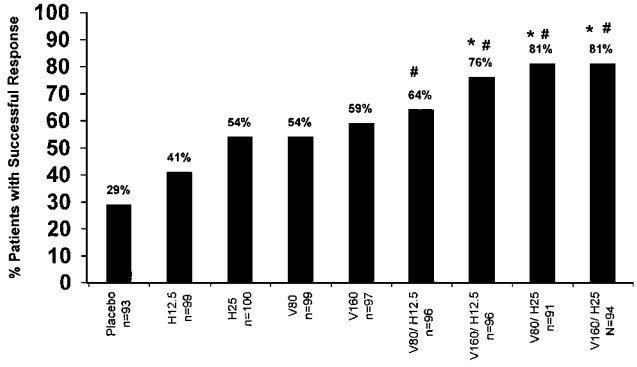

Figure 1 Proportion of patients achieving a successful response in the control of mean sitting diastolic blood pressure (MSDBP) at end-point for placebo, valsartan (80, 160 mg) and HCTZ (12.5, 25 mg) monotherapy and valsartan (80, 160 mg) in combination with HCTZ (12.5, 25 mg), intent-to-treat data set. Successful response was defined as MSDBP < 90 mm Hg or a ⩾10 mm Hg decrease compared to baseline. (V 160 = valsartan 160 mg, V 80 = valsartan 80 mg, H 12.5 = HCTZ 12.5 mg, H 25 = HCTZ 25 mg). Between-treatment comparison of combination therapies with monotherapies at end-point: *(*vs* valsartan monotherapy), # (*vs* HCTZ monotherapy) indicates $P < 0.05$.

ised, 867 patients were included in the safety analysis. Four patients were lost to follow-up and had no post-baseline adverse experience (AE) data. A total of 464 patients (53.5%) of the 867 included in the safety analysis reported AEs (irrespective of relationship to trial medication) during the trial. The group receiving valsartan 160 mg showed the lowest incidence (43%), while the other groups had proportions (53–57%) similar to that for placebo (52%).

A total of 189 patients (21.8%) reported AEs that were considered by the investigator to be at least possibly related to the study drug. The percentage reporting drug-related AEs ranged from 30.9% (combination valsartan 160 mg + HCTZ 25 mg) to 14.4% (valsartan 160 mg group); see Table 4. The commonest drug-related AEs reported were dizziness, headache and fatigue. The highest incidence of dizziness was reported for the valsartan 160 mg/HCTZ 25 mg (10.6%) treatment group compared with 5.4% for placebo, and the lowest incidence (1%) was reported for valsartan 160 mg monotherapy. Headache occurred most frequently in the placebo and HCTZ 12.5 mg group (10%) compared with the other treatment groups (2–6%). There were no statistically significant differences in the inci-

Table 4 Drug-related adverse experiences (AEs) with an incidence >3% in all combination groups combined

	P (*n* = 93)	*V 80* (*n* = 99)	*V 160* (*n* = 97)	*H 12.5* (*n* = 100)	*H 25* (*n* = 100)	*Val 80/H12.5* (*n* = 96)	*Val 160/H12.5* (*n* = 96)	*Val 80/H25* (*n* = 92)	*Val 160/H25* (*n* = 94)
Total No. patients with drug-related AEs	17 (18.3%)	21 (21.2%)	14 (14.4%)	23 (23%)	18 (18%)	22 (22.9%)	23 (24%)	22 (23.9)	29 (30.9%)
Dizziness	5 (5.4%)	2 (2%)	1 (1%)	6 (6%)	4 (4%)	5 (5.2%)	10 (10.4%)	7 (7.6%)	10 (10.6%)
Headache	9 (9.7%)	6 (6.1%)	3 (3.1%)	10 (10%)	2 (2%)	5 (5.2%)	3 (3.1%)	4 (4.3%)	4 (4.3%)
Fatigue	1 (1.1%)	1 (1%)	3 (3.1%)	5 (5%)	3 (3%)	4 (4.2%)	3 (3.1%)	3 (3.3%)	4 (4.3%)

AEs considered possibly, probably or highly probably related to study medication by investigator.
P = placebo; V80 = valsartan 80 mg; V160 = valsartan 160 mg; H 12.5 = HCTZ 12.5 mg; H 25 = HCTZ 25 mg.

dence of dizziness, headache or fatigue between any valsartan or combination treatment group and placebo. The drug-related incidence of cough was similarly low across all treatment groups. There were nine serious adverse events reported, regardless of relationship to trial medication: two reports in each of the HCTZ 25 mg, valsartan 160 mg/12.5 mg, and valsartan 160 mg/25 mg treatment groups and one report in each of the valsartan 160 mg, HCTZ 12.5 mg, and placebo treatment groups. However, all but one of these (a woman on valsartan 160 mg/HCTZ 25 mg, with orthostatic hypotension and dehydration) were considered unrelated to the study drug treatment.

Overall, the number of patients with changes in laboratory parameters was small, and the majority of these changes were clinically insignificant and not considered by the investigator to be study drug-related (Table 5). A slightly higher percentage of patients demonstrated an increase in serum potassium of >20% in the valsartan 80 mg group (10.2%) compared to the other treatment groups (1–6%).

Discussion

Although other forms of dual therapy (eg, beta-blockers and diuretics) are known to be helpful in controlling BP, this is the first report showing the efficacy and tolerability of combined therapy with valsartan/HCTZ in the treatment of essential hypertension. The results reported in this study are in line with those reported for HCTZ given concomitantly with some other antihypertensives, including losartan.[12,17]

A combination of valsartan and HCTZ in the doses used (valsartan 80 mg/HCTZ 12.5 mg, valsartan 160/HCTZ 12.5 mg, valsartan 80 mg/HCTZ 25 mg, valsartan 160 mg/HCTZ 25 mg) was more effective than each of the corresponding monotherapies (valsartan 80 mg, valsartan 160 mg, HCTZ 12.5 mg, HCTZ 25 mg) at reducing mean systolic and diastolic BP in patients with essential hypertension. The difference between combination treatments and corresponding monotherapies was clinically and statistically ($P < 0.05$) significant.

The addition of HCTZ 12.5 mg and 25 mg to valsartan 80 mg or 160 mg was generally well tolerated. The higher doses of the combination produced a slightly greater incidence of dizziness compared to valsartan monotherapy. As expected, hypokalaemia associated with the use of thiazide diuretics was more commonly reported in the higher dose HCTZ 25 mg groups, as were increases in (blood urea nephropathy) (BUN). The combination treatment groups had a smaller incidence of decreased serum potassium compared to HCTZ 25 mg monotherapy. It appears that the different effects on serum potassium of valsartan and HCTZ may balance each other in many patients. In other patients, one or the other effect may be dominant. In addition, greater diastolic BP reduction was observed with valsartan 80 mg/HCTZ 12.5 mg and valsartan 160 mg/HCTZ 12.5 mg compared to HCTZ 25 mg. Therefore, patients whose BPs are adequately controlled with HCTZ 25 mg daily but experience hypokalaemia may achieve similar BP control without electrolyte disturbance if they switch to valsartan/HCTZ 80/12.5 mg or 160/12.5 mg. Combination therapy with HCTZ therefore extends the clinical utility of valsartan, providing a way to tailor therapy more closely to the individual patient's requirements.

Table 5 Number of patients with specific percent change from baseline for selected laboratory parameters

	Placebo	*V80*	*V160*	*H12.5*	*H25*	*V80/12.5*	*V160/12.5*	*V80/25*	*V160/25*
Serum potassium									
>20% ↑	4 (4.4)	10 (10.2)	6 (6.3)	1 (1.0)	3 (3.0)	3 (3.1)	6 (6.4)	5 (5.6)	3 (3.3)
>20% ↓	3 (3.3)	1 (1.10)	0	6 (6.2)	11 (11.1)	1 (1.0)	2 (2.1)	8 (8.9)	4 (4.4)
Creatinine >50%↑	1 (1.1)	2 (2.2)	1 (1.1)	0	0	1 (1.1)	1 (1.1)	0	2 (2.2)
BUN >50% ↑	2 (2.3)	4 (4.4)	2 (2.2)	5 (5.6)	8 (8.5)	8 (8.5)	3 (3.3)	13 (14.6)	14 (15.4)
Urate >50%↑	2 (2.3)	4 (4.4)	0	0	2 (2.1)	2 (2.1)	2 (2.2)	3 (3.4)	3 (3.3)

Acknowledgements

We would like to acknowledge the collaboration and commitment of all the local investigators and their staff and study coordinators without whom the present study would not have been possible. Principal investigators: A Aarons, LK Alwine, HE Bays, R Berger, B Berry, AA Carr, SG Chrysant, GV Collins, GS DeCherney, TC Fagan, WT Garland, DC Henry, RW Hilty, SD Hsi, L Kirkegaard, TD Klein, JW Lacey, EW Lee, J Levine, B Levy, AJ Lewin, JE Lewis, T Littlejohn III, AJ Lonigro, D Lynch, CV Manion, T Marbury, M McCartney, CR Mershon, DJ Miller, JL Newman, S Oparil, TS Parker, JH Portner, D Ruff, WM Ryan, M Sack, J Schoenberger, D Schumacher, D Shute, C Singleton, D Smith, WB Smith, JM Stafford, WW Stoever, RR Stoltz, C Stringer, D Sugimoto, HM Surath, RD Thorsen, and AU Waks.

References

1 Kang PM, Landau AJ, Eberhardt RT, Frishman WH. Angiotensin II receptor antagonists: a new approach to blockade of the renin-angiotensin system. *Am Heart J* 1994; **127**: 1388–1401.
2 Criscione EL *et al*. Pharmacological profile of valsartan: a potent, orally active, nonpeptide antagonist of the angiotensin II AT1 receptor subtype. *Br J Pharmacol* 1993; **110**: 761–771.
3 Oparil S *et al*. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996; **18**: 797–810.
4 Corea L *et al*. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: A comparative study of the efficacy and safety against amlodipine. *Clin Pharm Ther* 1996; **60**: 341–346.
5 Holwerda NJ *et al*. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J Hypertens* 1996; **14**: 1147–1151.
6 Benz J *et al*. Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. *J Clin Pharmacol* 1997; **37**: 101–107.
7 Hegner G *et al*. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with hydrochlorothiazide. *Eur J Clin Pharmacol* 1997; **52**: 173–177.
8 Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on detection, evaluation and treatment of high blood pressure (JNCV). *Arch Intern Med* 1993; **153**: 154–183.
9 Epstein M, Bakris G. Newer approaches to antihypertensive therapy. Use of fixed dose combination therapy. *Arch Intern Med* 1996; **156**: 1969–1978.
10 Schrijver G, Weinberger MH. Hydrochlorothiazide and spironolactone in hypertension. *Clin Pharmacol Ther* 1979; **25**: 33–39.
11 Frishman WH, Goldberger J, Sherman D. Enalapril, hydrochlorothiazide, and combination therapy in patients with moderate hypertension. *J Clin Hypertens* 1987; **3**: 520–527.
12 MacKay JH *et al*. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. A double-blind, placebo-controlled trial of concomitant administration compared with individual components. *Arch Intern Med* 1996; **156**: 278–285.
13 Townsend RR, Holland OB. Combination of converting enzyme inhibitor with diuretic for the treatment of hypertension. *Arch Intern Med* 1990; **150**: 1175–1183.
14 Gavros HP, Salerno CM. The angiotensin II type I receptor blocker losartan in clinical practice: a review. *Clin Ther* 1996; **18**: 1058–1067.
15 Subcommittee of WHO/ISH Mild Hypertension Liaison Committee. Summary of 1993 World Health Organisation-International Society of Hypertension guidelines for the management of mild hypertension. *BMJ* 1993; **307**: 1541–1546.
16 McHugh RB, Le CT. Confidence estimation and size of a clinical trial. *Controlled Clin Trials* 1984; **5**: 157–163.
17 Soffer BA *et al*. Effects of losartan on a background of hydrochlorothiazide in patients with hypertension. *Hypertension* 1995; **26**: 112–117.