

Valsartan/Hydrochlorothiazide is Effective in Hypertensive Patients Inadequately Controlled by Valsartan Monotherapy

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Mallion J-M, Carretta R, Trenkwald P, Martinez J-F, Tykarski A, Teitelbaum I, Oddou P, Fagan T. Valsartan/hydrochlorothiazide is effective in hypertensive patients inadequately controlled by valsartan monotherapy. Blood Pressure 2003; 12 (Suppl 1): 36–43.

Objective: This double-blind parallel-group randomized trial compared the efficacy and safety of fixed combination valsartan 160 mg/hydrochlorothiazide 12.5 mg (Val 160/HCTZ 12.5) once daily (o.d.) and Val 160/hydrochlorothiazide 25 mg (Val 160/HCTZ 25) o.d. vs Val 160 o.d. monotherapy in patients with mild-to-moderate essential hypertension not adequately controlled with valsartan monotherapy. **Method:** A total of 2002 patients whose BP was inadequately controlled with 4 weeks of Val 160 mg o.d. monotherapy were randomized to treatment for 8 weeks with Val 160 ($n = 666$), Val 160/HCTZ 12.5 ($n = 670$) or Val 160/HCTZ 25 ($n = 666$). **Results:** Active treatment significantly reduced BP in all groups over the 12 weeks of the study ($p < 0.001$). The greatest reductions were achieved with Val 160/HCTZ 25. Reductions were 10.8, 12.8 and 14.2 mmHg (sitting diastolic blood pressure) and 15.7, 19.4 and 21.8 mmHg (sitting systolic blood pressure), for the Val 160, Val 160/HCTZ 12.5 and Val 160/HCTZ 25 groups, respectively. Responder rates were high in all groups (49%, 62% and 68%). In elderly patients (≥ 65 years) responder rates of 70% were achieved with Val 160/HCTZ 25. All treatments were well tolerated, in all patient groups. **Conclusions:** The combination of Val 160 plus HCTZ 12.5 or HCTZ 25 provides effective and well-tolerated treatment in patients inadequately controlled after 4 weeks of monotherapy. In elderly patients a responder rate of 70% was achieved with Val 160/HCTZ 25. **Key words:** combination therapy, diastolic blood pressure, elderly, responder rates.

INTRODUCTION

The lowering of blood pressure (BP) with pharmacotherapy has been characterized as one of the major medical successes of the last 50 years [1]. Today, both the World Health Organization – International Society of Hypertension (WHO-ISH) [2] and the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) [3] define optimal BP as $< 120/80$ mmHg and normal BP as $< 130/85$ mmHg. In the elderly, the target should be high normal BP ($< 140/90$ mmHg) [4].

In practice, however, these targets are very seldom met. Less than 30% of hypertensive Americans are treated successfully and other Western nations report similar low rates [5–7]. Reasons are the asymptomatic nature of hypertension, side-effects of antihypertensive treatments as well as inadequate efficacy. Initial antihypertensive monotherapy normalizes BP in less than 50% of treated individuals [8]. This is recognized in the guidelines,

which recommend the use of combinations of BP-lowering agents to achieve and maintain the target BP with minimal adverse experience 2, 3.

Well-designed combination therapy exploits the fact that essential hypertension is multifactorial and disrupts more than one mechanism of BP control. For example, the combination of an angiotensin-receptor blocker (ARB) with a diuretic combines reduction of the angiotensin II-mediated sodium retention and vasoconstriction with the volume-reducing benefits of the diuretic.

Valsartan is an orally active ARB, which is registered in most countries worldwide for the treatment of hypertension. The high efficacy, excellent safety and tolerability profile of valsartan are well documented [4, 9, 10]. In recent years, the mean doses of ARBs used in therapy have tended to increase, which reflects an increasing awareness of the tolerability and of the still low risk associated with higher doses. In addition, benefits from treatment beyond BP reduction have been seen with ARBs at higher doses [11–13].

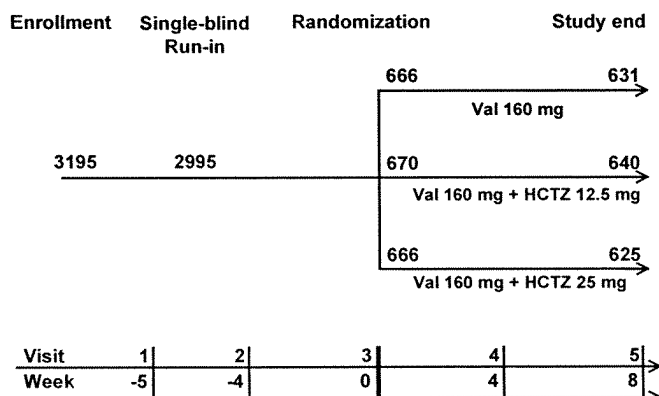


Fig. 1. Study design and patient disposition

The current study is an assessment of whether the fixed combination of valsartan 160 mg (Val 160) plus hydrochlorothiazide (HCTZ) 12.5 or 25 mg provides better antihypertensive control in patients with mild to moderate hypertension inadequately controlled after 4 weeks of Val 160 once daily (o.d.).

MATERIALS AND METHODS

Study population

Patients were recruited at 183 centers in 20 countries in Europe, North America and South America. Patients included in the screening phase of the study had to be at least 18 years old, with mild to moderate essential hypertension WHO/ISH grades 1 and 2 [2], defined as mean sitting diastolic BP (SDBP) of <110 mmHg and ≥ 95 mmHg in unmedicated patients.

Patients with severe or secondary hypertension, hypertensive retinopathy, significant cardiac, renal or hepatic disease, type I/II diabetes, or malignancy, were excluded, as were pregnant or lactating women and women of child-bearing potential not practicing reliable birth control. Use of any antihypertensive medication other than study medication was prohibited throughout the study.

The study was conducted in accordance with the Declaration of Helsinki, concerning medical research in humans ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients", Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996), and in accordance with Good Clinical Practice. The study protocol and written subject information were reviewed and approved by the Ethics Review Committees for each site. All patients gave written informed consent prior to entering the study.

Study design

This was a double-blind, double-dummy, active-controlled, parallel-group, randomized trial in patients with mild to moderate essential hypertension. The study design

is shown in Fig. 1. During the 2-week washout period, all antihypertensive medication was withdrawn. After the washout phase, patients with SDBP ≥ 95 and <110 mmHg received Val 160 mg o.d. monotherapy during a 4-week single-blind period. Patients with mean SDBP ≥ 95 and ≤ 110 mmHg were considered inadequately controlled and were subsequently randomized to one of three treatment groups to receive either Val 160, Val 160/HCTZ 12.5 o.d. or Val 160/HCTZ 25 o.d. for 8 weeks. A total of 2002 patients were randomized to study treatment. Efficacy and safety assessments were performed every 4 weeks during the double-blind randomized treatment phase.

Efficacy and safety evaluations

BP measurement. At enrollment, sitting BP was measured in both arms, and the arm with the highest mean sitting SDBP was used for subsequent measurements. BP determinations were made according to the 1988 AHA Committee Report on BP determination [3, 14]. All BP measurements were performed at trough (i.e. at least 24 h after the last dose of study medication). At each study visit, three BP measurements were taken at 1–2-min intervals, after the patient had been rested in a sitting position for 5 min; the mean of these measurements was used for analysis. Measurement of standing BP was performed once at each visit after standing for 2 min, immediately after the sitting measurements.

Pulse rate. At each visit, heart rate was measured for 30 s just prior to BP measurements, once standing and once sitting.

Other assessments. Adverse events (AEs) and serious AEs (SAEs) were monitored and recorded during physical examination and by questioning the patient. Initial hematology and blood chemistry tests and urinalysis were performed, and blood urea nitrogen (BUN), serum creatinine and potassium levels were monitored during the clinical visits throughout the study. All laboratory analyses were performed centrally in one certified laboratory.

Treatment compliance was evaluated by counting dispensed and retrieved study medication tablets (fixed combinations valsartan/HCTZ or placebo combination) and capsules (valsartan or valsartan placebo) at each study visit.

Outcome measures

Primary efficacy variable was the change in mean sitting diastolic BP (trough mean SDBP) during the active-treatment phase. The secondary efficacy variables were the change in mean sitting systolic BP (trough mean SSBP) during the active-treatment phase, and the

Table I. Baseline characteristics

Treatment	Val	Val 160/HCTZ 12.5	Val 160/HCTZ 25	All	p-value
Total randomized	666	670	666	2002	
Women (%)	320 (48.0%)	325 (48.5%)	313 (47.0%)	958 (47.9%)	0.852
Men (%)	346 (52.0%)	345 (51.5%)	353 (53.0%)	1044 (52.1%)	
Race, n (%)					0.307
Caucasian	600 (90.1%)	611 (91.2%)	599 (89.9%)	1810 (90.4%)	
Black	14 (2.1%)	11 (1.6%)	14 (2.1%)	39 (1.9%)	
Oriental	1 (0.2%)	2 (0.3%)	7 (1.1%)	10 (0.5%)	
Other	51 (7.7%)	46 (6.9%)	46 (6.9%)	143 (7.1%)	
Age (years, mean \pm SD)	55.3 \pm 11.2	56.0 \pm 11.1	55.7 \pm 11.2	55.6 \pm 11.2	0.527
Height (cm) at visit 1 (mean \pm SD) ^a	168.0 \pm 9.8	167.6 \pm 9.9	168.1 \pm 9.7	167.9 \pm 9.8	
Weight (kg) at visit 1 (mean \pm SD) ^b	82.7 \pm 16.7	82.5 \pm 17.6	82.7 \pm 15.2	82.6 \pm 16.5	0.981
Heart rate	73.0 \pm 9.59	73.4 \pm 8.97	73.4 \pm 9.29		
BUN (mmol/l)	5.6 \pm 1.6 (n = 656)	5.8 \pm 1.6 (n = 660)	5.7 \pm 1.5 (n = 657)		

^a Data missing for one Val + three Val 160/HCTZ 25 patients.

^b Data missing for one Val + four Val 160/HCTZ 25 patients.
SD, standard deviation; BUN, blood urea nitrogen.

responder rate, defined as patients with a mean sitting DBP <90 mmHg and/or decrease in mean sitting DBP >10 mmHg at the end of treatment.

Statistical analyses

Covariance analysis was used for the primary efficacy variable with treatment and center as fixed factors, and the baseline measurement as covariate. Dunnett's test was used for the comparisons of Val 160 with Val 160/HCTZ 12.5 and Val 160/HCTZ 25 in order to maintain a global significance level of 5%. The same statistical method was used to analyze changes in mean SSBP. The responder rate was analyzed by logistic regression with treatment as factor and baseline as covariate.

Primary and secondary efficacy analyses included all randomized patients who received trial medication and from whom at least one BP measurement (either systolic or diastolic) was obtained after randomization (i.e. intention-to-treat population). The safety population

included all randomized patients who received at least one dose of the study drug during the double-blind treatment phase.

A subpopulation analysis was conducted on elderly patients, defined as ≥ 65 years of age at screening. All statistical tests were two-sided at the 5% level of significance.

RESULTS

Patients

Patient disposition is shown in Fig. 1. After 4 weeks of monotherapy, 2002 patients were randomized to study treatment: Val 160 monotherapy (n = 666); Val 160/HCTZ 12.5 (n = 670) and Val 160/HCTZ 25 (n = 666). All randomized patients received study medication. Baseline characteristics at study enrollment after 2 weeks' placebo washout period (at visit 2) are given in Table I. Baseline BP data are shown in Table II.

The treatment groups were comparable at baseline for

Table II. Blood-pressure data (at start of monotherapy) for overall populations and elderly (≥ 65 years) and non-elderly subpopulations

	Val 160	Val 160/HCTZ 12.5	Val 160/HCTZ 25
Overall population	663	665	666
SDBP (mean \pm SD)	101.3 \pm 4.06	101.4 \pm 4.11	101.5 \pm 3.99
SSBP (mean \pm SD)	160.2 \pm 12.40	160.5 \pm 12.68	160.4 \pm 12.22
≥ 65 years			
n	132	153	140
SDBP (mean \pm SD)	100.2 \pm 3.81	100.5 \pm 3.98	100.4 \pm 3.77
SSBP (mean \pm SD)	163.8 \pm 12.24	165.0 \pm 12.59	165.2 \pm 11.88
<65 years			
n	531	512	516
SDBP (mean \pm SD)	101.6 \pm 4.08	101.7 \pm 4.12	101.8 \pm 4.00
SSBP (mean \pm SD)	159.4 \pm 12.29	159.2 \pm 12.42	159.1 \pm 12.00

SDBP, sitting diastolic blood pressure; SSBP, sitting systolic blood pressure; SD, standard deviation.

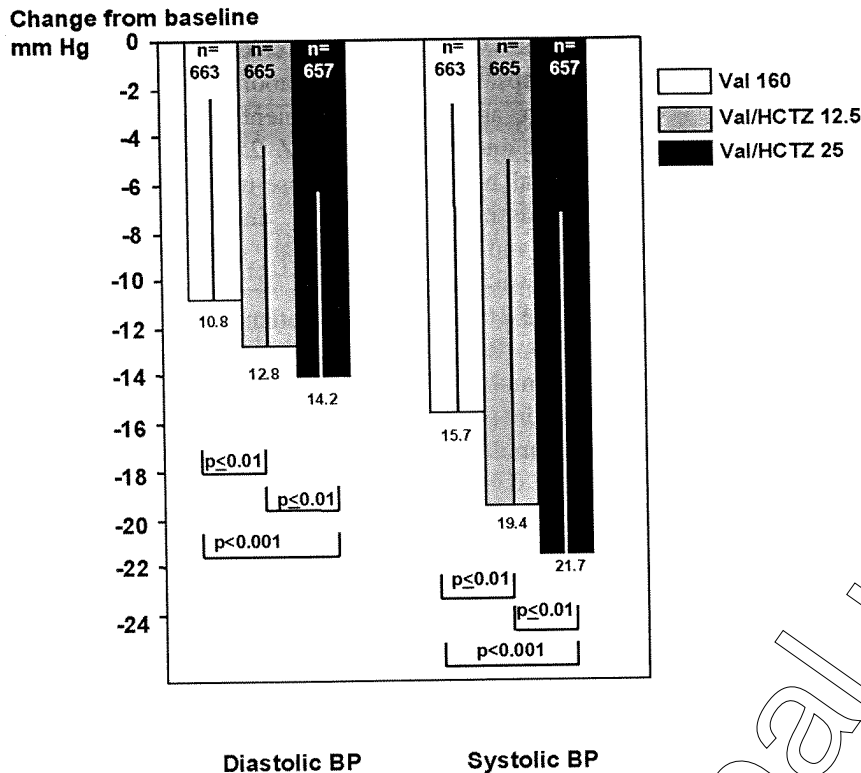


Fig. 2. Mean change in sitting diastolic and systolic blood pressure (BP) in the three treatment groups during the active-treatment phase. Bars indicate standard deviation.

the parameters assessed, with no statistically significant differences between groups (Table I). The majority of subjects were Caucasian and the proportions of men and women were close to equal in all three groups. Mean SSBP and SDBP at baseline was not statistically different in the three groups.

Discontinuation rates were similar in all three groups, with a total of 5.3% for the entire trial population. Main reasons were AEs (1.9%) and protocol violations (1.5%). Thirteen patients (0.6%) discontinued due to unsatisfactory therapy and the same number were considered lost to follow-up.

Efficacy

Both SDBP and SSBP were reduced during monotherapy and during the double blind treatment phase in all treatment groups. Reductions were greater in the groups receiving combination therapy. Monotherapy reduced SDBP by an average of 6.6 ± 7.9 mmHg and SSBP by an average of 11.0 ± 13.1 mmHg. Overall reductions during the active treatment phases are shown in Fig. 2. The greatest reductions were achieved with Val 160/HCTZ 25. SDBP reductions were 10.8, 12.8 and 14.2 mmHg in the Val 160, Val 160/HCTZ 12.5 and Val 160/HCTZ 25 groups, respectively. SSBP reductions were 15.7, 19.4 and 21.8 mmHg in the respective groups. The greater efficacy of the combination treatments vs monotherapy and of Val 160/HCTZ 25 vs Val 160/HCTZ 12.5 were statistically significant ($p \leq 0.01$ for all comparisons; Fig. 2).

The efficacy differences between treatments were further reflected in responder rates (Fig. 3). In this population, which was inadequately controlled after 4 weeks of monotherapy, higher responder rates were seen with combination treatment (49% responder rates in Val 160; 61.7% in Val 160/HCTZ 12.5; 68% in Val 160/HCTZ 25).

Subgroup analyses

A pre-defined subgroup analysis of efficacy in elderly patients (≥ 65 years) was undertaken. Baseline BP data for these two subpopulations are given in Table II. The treatment groups were well balanced in terms of BP, with the elderly patient groups having slightly elevated values compared with the non-elderly population.

Treatment-related reductions in trough SDBP and SSBP were significant in both the elderly and non-elderly populations (Fig. 4; Table III). Treatment efficacy was highly similar in the elderly and non-elderly patient groups (Fig. 4). In terms of responder rates, treatment tended to be more effective in the elderly patients than in the non-elderly groups. This was particularly the case for Val 160/HCTZ 25, where responder rates reached 70.7% (Table IV).

There were no significant changes in heart rate during the study in all treatment groups, and the effects on standing BP (SBP and DBP) were similar to those in the sitting position.

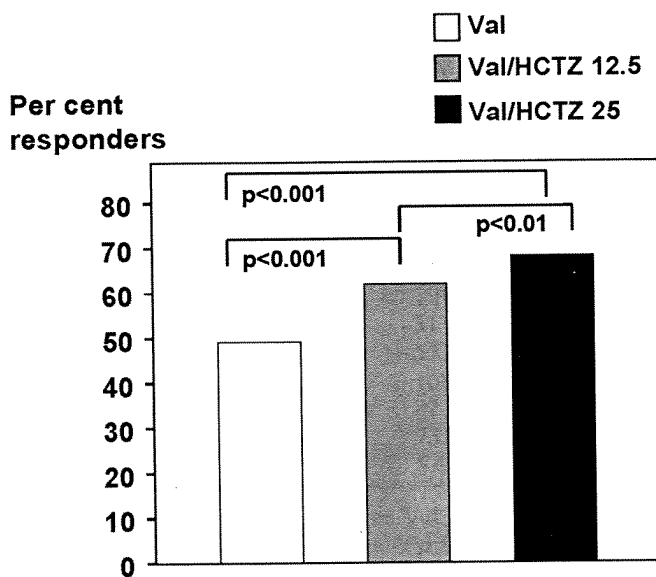


Fig. 3. Percentage of responders (patients with sitting diastolic blood pressure <90 or decrease by >10 mmHg at study end).

Safety data

All treatments were generally well tolerated and the frequency of AEs was very low and similar in all treatment groups (Table V). The most common treatment-related AEs were headache and dizziness. There were no significant differences in withdrawal rates between groups: 38 patients (1.9%) withdrew from the study because of AEs; 10 (1.5%) in the Val 160 group, 12 (1.8%) in the Val 160/HCTZ 12.5 group and 16 (2.4%) in the Val 160/HCTZ 25 group.

Of relevance to the subgroup analysis, treatment was tolerated very well both in the elderly and non-elderly patient groups. No significant laboratory changes were observed in any of the treatment groups. Val 160/HCTZ 12.5 and Val 160/HCTZ 25 produced predictable minimal non-significant dose-related reductions in serum potassium and slight increases in serum creatinine and BUN. A 50% increase in serum creatinine was seen in 0.8% of Val 160 patients, 1.6% of Val 160/HCTZ 12.5 patients and 1.4% of Val 160/HCTZ 25 patients. BUN increased by 0.1 ± 1.3 mmol/l in the Val 160 group, by 0.4 ± 1.5 mmol/l in the Val 160/HCTZ 12.5 patients and by 0.6 ± 1.4 mmol/l in the Val 160/HCTZ 25 patients.

DISCUSSION

This study compared the efficacy and tolerability of the fixed-combinations Val 160/HCTZ 12.5 and Val 160/HCTZ 25 mg o.d. with Val 160 o.d. monotherapy in a population of patients inadequately controlled after 4 weeks of valsartan monotherapy. Although all treatments were effective at reducing BP over the 12 weeks of the study, both combination therapies were more effective than monotherapy, with a dose-related increase in efficacy between Val 160/HCTZ 12.5 and Val 160/HCTZ 25. Treatments were effective at reducing both SDBP and SSBP. Similar differences between treatment groups favoring combination therapies were seen in responder rates.

The importance of combination therapies as antihypertensive treatments has become apparent in recent

Change from baseline

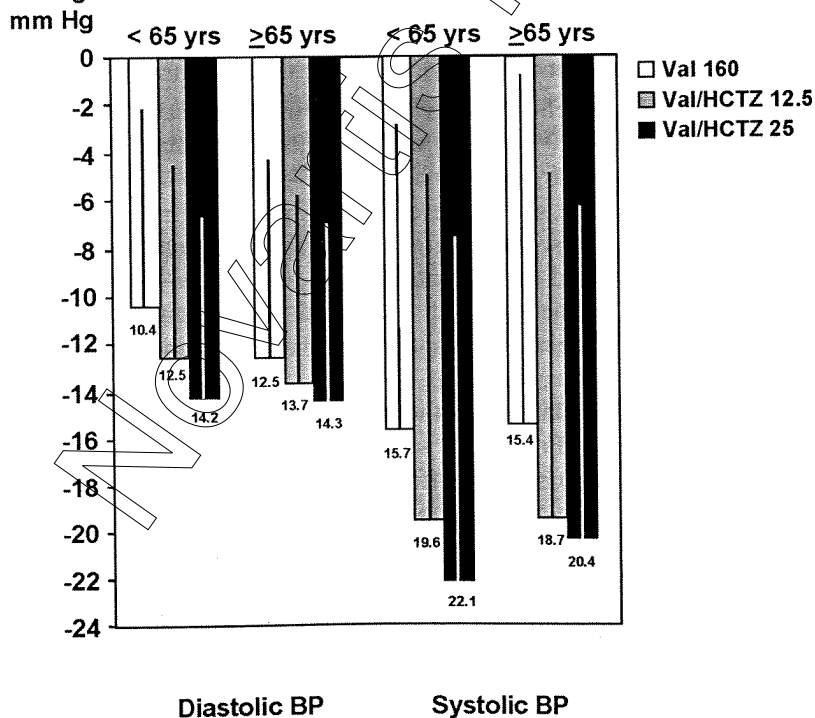


Fig. 4. Efficacy in elderly (≥ 65 years) and non-elderly (< 65 years) patients in terms of blood pressure reduction during the active treatment phase. Bars indicate standard deviation. $p < 0.001$ for all overall changes during the active-treatment phase. For numbers of patients in respective treatment groups, see Table IV.

Table III. Mean change (\pm SD) to endpoint in BP for the overall population and the elderly (≥ 65) treatment subgroup

	Val 160	Val 160/HCTZ 12.5	Val 160/HCTZ 25
Overall population	(n = 663)	(n = 665)	(n = 656)
SDBP (mmHg)	-10.8 ± 8.43^a	-12.8 ± 8.22^a	-14.2 ± 7.77^a
SSBP (mmHg)	-15.7 ± 13.32^a	-19.4 ± 14.56^a	-21.8 ± 13.91^a
Elderly (≥ 65 years)	(n = 132)	(n = 153)	(n = 140)
SDBP (mmHg), mean (SD)	-12.5 ± 8.51^a	-13.7 ± 7.97^a	-14.3 ± 7.73^a
SSBP (mmHg), mean (SD)	-15.4 ± 14.48^a	-18.7 ± 13.72^a	-20.4 ± 14.41^a

^a $p < 0.001$ for reductions in BP compared with start of therapy.

SDBP, sitting diastolic blood pressure; SSBP, sitting systolic blood pressure; SD, standard deviation.

Table IV. Responder rates in elderly (≥ 65 years) and non-elderly patient groups

	Val 160 (n = 663)	Val 160/HCTZ 12.5 (n = 665)	Val 160/HCTZ 25 (n = 657)
Patients < 65 years			
Responders	247	308	348
%	46.5%	60.2%	67.3%
Patients ≥ 65 years			
Responders	78	102	99
%	59.1%	66.7%	70.7%

$p < 0.001$ for comparison Val 160 vs Val 160/HCTZ 12.5 and vs Val 160/HCTZ 25; $p < 0.01$ for comparison Val 160/HCTZ

Table V. Incidence rates of most common overall adverse events (AEs, $\geq 1.0\%$) by treatment group (safety population)

AE, n (%)	Val 160 (n = 666)	Val 160/HCTZ 12.5 (n = 670)	Val 160/HCTZ 25 (n = 666)
Headache NOS	25 (3.8)	10 (1.5)	16 (2.4)
Dizziness (exc. vertigo)	10 (1.5)	6 (0.9)	10 (1.5)
Back pain	12 (1.8)	1 (0.1)	10 (1.5)
Nasopharyngitis	7 (1.1)	10 (1.5)	6 (0.9)
Cough	9 (1.4)	6 (0.9)	2 (0.3)
Vertigo NEC	2 (0.3)	2 (0.3)	9 (1.4)

NOS, not otherwise specified; NEC, not elsewhere classified.

years, as evidence has accumulated of the benefits of controlling BP in the population. A number of studies have shown that even minor decreases in DBP and SBP are associated with a remarkable reduction in cardiovascular morbidity [15, 16]. Particularly in elderly patients, studies such as SHEP [16] and STOP-hypertension [17] have reported major reductions in rates of stroke, myocardial infarction and other hard endpoints, associated with reductions in BP. The HOT Study reported the optimum target BP to be a mean DBP of 82.6 mmHg. This was based on an association with the lowest incidence of major cardiovascular events (acute myocardial infarction, stroke, all cardiovascular mortality). In HOT, if DBP was lowered from the baseline level at randomization (105 mmHg) to this point this would prevent approximately four major cardiovascular events per 1000 patients per year, which would represent a 30% reduction in the risk of a major cardiovascular event [15]. The optimum SBP was 139 mmHg.

However, as was clear from HOT, BP targets are frequently difficult to achieve in practice with monotherapy. In HOT, a striking 74% of patients that achieved the target BP (140/81 mmHg) needed combination therapy. This need is reflected in the current treatment guidelines: based on the results of epidemiological studies and clinical trials, both WHO-ISH [2] and JNC-VI [3] guidelines recommend combination treatments to reach BP targets.

In non-selected patients, the combinations of Val 160 mg plus HCTZ 12.5 or HCTZ 25 have been shown to provide additional benefits compared to Val 160 mg [18]. The current study shows valsartan/HCTZ to be an effective treatment option in selected populations of patients inadequately controlled after 4 weeks of monotherapy.

Of particular interest are the results indicating that elderly and non-elderly patients respond highly similarly to therapy. Rates of hypertension increase with age [19],

which is reflected in the higher baseline values for the elderly treatment groups compared with the non-elderly, although the differences in the present study may be somewhat affected by the use of SDBP as selection criterion. It is known that the absolute benefits of BP reduction in the elderly are greater than in younger individuals [20]. This, combined with the slightly higher responder rates in the ≥ 65 -year-olds in our study, indicate that Val 160/HCTZ combinations might be particularly beneficial in the elderly.

Moreover, the simple dosing regimens of fixed-dose combination therapies would be expected to be a particularly relevant factor in the elderly. Compliance is a major problem with antihypertensive medications and the complexity of regimens is thought to influence compliance [21]. As the elderly frequently need medication for indications other than hypertension, well-tolerated fixed-combinations like Val 160/HCTZ should have a minimal impact on daily medication schedules.

This study confirms the good tolerability of valsartan that has been well documented both as monotherapy and in combination with HCTZ [18, 22]. Less than 1.5% patients reported 50% increase in creatinine levels and the increases in BUN with combination treatment were similar to those normally found with similar doses of HCTZ.

Both Neutel *et al.* [23] and Bremner *et al.* [24] have reported good tolerability of valsartan monotherapy in elderly hypertensive patients (≥ 65 years), with or without HCTZ, and the current study found similar results. The elderly age group also tolerated the combination regimens very well, with similar rates of SAEs as in the monotherapy group. In fact, the good tolerability in all groups is evident from the extremely low overall incidence rates of treatment-related AEs.

CONCLUSION

Combinations of Val 160 with HCTZ are an effective BP-lowering therapy in patients whose BP is inadequately controlled with monotherapy. Both combinations are effective and well tolerated, in non-elderly and in elderly hypertensive patient populations, with achieved responder rates above 70%.

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