Treating Systolic Hypertension in the Very Elderly With Valsartan-Hydrochlorothiazide vs Either Monotherapy: ValVET Primary Results

Joseph L. Izzo Jr, MD;[1] Howard S. Weintraub, MD, FACC;[2] Daniel A. Duprez, MD;[3] Das Purkayastha, PhD;[4] Dion Zappe, PhD;[4] Rita Samuel, MD;[4] William C. Cushman, MD[5]

From the State University of New York at Buffalo, Buffalo, NY;[1] the New York University School of Medicine, New York, NY;[2] the University of Minnesota, Minneapolis, MN;[3] Novartis Pharmaceuticals Corporation, East Hanover, NJ;[4] and the University of Tennessee, Memphis, TN[5]

This 16-week trial investigated the efficacy and safety of single-pill valsartan/hydrochlorothiazide (HCTZ) vs the individual components in patients 70 years and older with systolic hypertension. Patients were randomized to valsartan/HCTZ 160/12.5 mg (n=128), HCTZ 12.5 mg (n=128), or valsartan 160 mg (n=128) for 4 weeks. Patients whose blood pressure (BP) was ≥140/90 mm Hg at weeks 4, 8, or 12 were uptitrated to a maximum of valsartan/HCTZ 320/25 mg. Week 4 systolic BP reduction (primary efficacy outcome) was greater with valsartan/HCTZ than valsartan (−17.3 mm Hg vs −8.6 mm Hg, $P < .0001$) but only marginally greater than HCTZ (−13.6 mm Hg, $P = .096$). Median time to BP control was shorter with valsartan/HCTZ (4 weeks) vs HCTZ (8 weeks, $P < .05$) or valsartan (12 weeks, $P < .0001$). Thiazide monotherapy was more effective than angiotensin receptor blocker monotherapy (by about 5 mm Hg), but greater antihypertensive efficacy was achieved by initiating treatment with combination valsartan/HCTZ in the elderly. *J Clin Hypertens (Greenwich).* 2011;13:722–730. ©2011 Wiley Periodicals, Inc.

The prevalence of hypertension increases with advancing age, from about 7% in individuals aged 18 to 39 years to 66% in those 60 years or older, largely as a result of the steady increase in systolic blood pressure (SBP) with age.[1,2] Blood pressure (BP) control rates in older individuals remain low, in part because of the difficulty in controlling SBP: only one third of individuals with hypertension older than 60 years have BP values <140/90 mm Hg (or <130/80 mm Hg in diabetics).[2] The value of antihypertensive therapy in older individuals is clearly established. The Systolic Hypertension in the Elderly Program (SHEP)[3] and the Medical Research Council studies[4] proved that diuretic-based therapy reduces rates of stroke and myocardial infarction in older hypertensive patients. More recently, the Hypertension in the Very Elderly Trial (HYVET) proved that mortality and cardiovascular disease rates could be reduced in persons 80 years or older.[5]

In general, ≥2 antihypertensive agents are needed to achieve BP goals,[6,7] but there is a general reluctance by clinicians to initiate combination therapy in older patients, often because of perceived safety concerns such as orthostatic hypotension.[8] Reasons to choose different drug classes may differ with age. For example, older people with hypertension usually have lower plasma renin activity (PRA) compared with younger people with hypertension.[9] Although largely unproven by clinical trial data, recent European and British Hypertension Society guidelines suggest that blockers of the renin-angiotensin system (RAS), including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are less effective in individuals older than 55 years.[6,10] An ARB/diuretic combination was somewhat better than ARB monotherapy in a secondary analysis of individuals younger than 65 years,[11,12] but no study to date has directly compared a RAS blocker with a diuretic in an elderly cohort.

The Valsartan Very Elderly Trial (ValVET) is the first prospective trial in individuals 70 years or older that compares: (1) efficacy and safety of initial combination therapy with valsartan and hydrochlorothiazide (HCTZ) with either component as monotherapy; and, (2) HCTZ with ARB monotherapy.

METHODS

Patients

Study participants were men and women (70 years or older) with systolic hypertension (mean sitting SBP [MSSBP] 150–200 mm Hg). Excluded were patients with recent use of investigational drugs, history of hypersensitivity to drugs in similar chemical classes, inability to discontinue prior antihypertensive medications, MSSBP ≥160 mm Hg despite ≥3 antihypertensive drugs at screening, mean sitting diastolic BP (MSDBP) ≥120 mm Hg at any time during the screening or washout phases, known secondary hypertension, clinically significant cardiac arrhythmias or cardiac valvular disease, history or symptoms of

Address for correspondence: Joseph L. Izzo Jr, MD, Department of Medicine, Erie County Medical Center, 462 Grider Street, Buffalo, NY 14215
E-mail: jizzo@buffalo.edu

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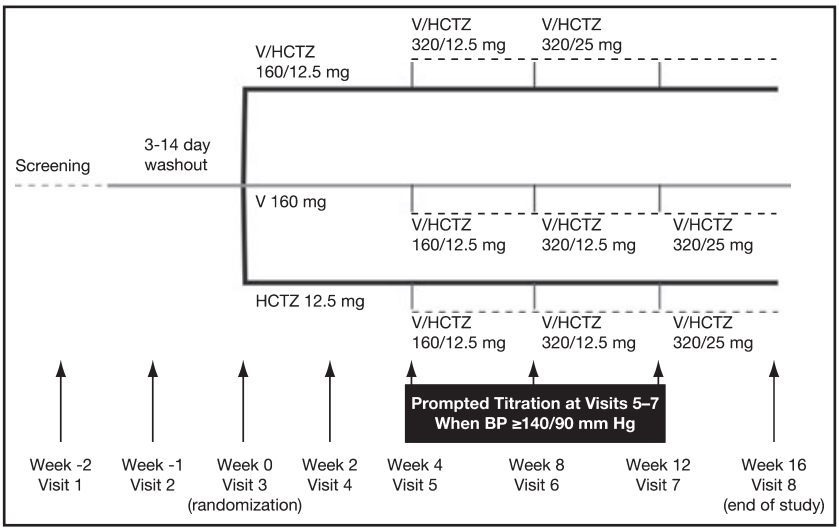


FIGURE 1. Study design. BP indicates blood pressure; HCTZ, hydrochlorothiazide; V, valsartan.

chronic heart failure, orthostatic hypotension, uncontrolled diabetes, malignancies, significant autoimmune disorders, acute gout within the previous year, or renal, pancreatic, or hepatic impairment. Patients with a recent history (<6 months of screening) of stroke, transient ischemic attack, myocardial infarction, significant coronary artery disease, or atherosclerotic vascular disease were also excluded.

The protocol was approved and monitored by the institutional review board of each study center in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before inclusion.

Study Design

This 16-week randomized, double-blind, prompted-titration trial was conducted at 80 centers in the United States and Canada. The study design (Figure 1) included a 3- to 14-day washout period, after which patients were randomized 1:1:1 to 1 of 3 treatment groups: valsartan/HCTZ 160/12.5 mg combination therapy (valsartan/HCTZ), HCTZ 12.5 mg monotherapy (HCTZ), or valsartan 160 mg monotherapy (valsartan). At weeks 4, 8, and 12, patients not at the BP goal of <140/90 mm Hg had their study medication up-titrated as described below. Up-titration was prompted via an Interactive Voice Response System (IVRS). Patients in the initial combination therapy arm were up-titrated to valsartan/HCTZ 320/12.5 mg at 4 weeks and then to valsartan/HCTZ 320/25 mg at 8 or 12 weeks, if needed. Patients in the initial monotherapy arms who were not at goal at 4 weeks were up-titrated to valsartan/HCTZ 160/12.5 mg and then, if needed, to valsartan/HCTZ 320/12.5 mg at 8 weeks and to valsartan/HCTZ 320/25 mg at 12 weeks. All treatments were administered once daily.

Concomitant medications likely to interfere with evaluation of the study medication, including any nonstudy antihypertensive agent, were prohibited throughout the trial. Sildenafil and vardenafil were disallowed within 24 hours and tadalafil within 48 hours prior to any scheduled visit. Hematology, blood chemistry, and urinalysis were performed at a central laboratory.

BP Determination

Sitting BP measurements were performed at each office visit using an Omron automated BP monitor (model #HEM-705 CP; Omron, Kyoto, Japan). Patients rested for 5 minutes before any measurements were taken. Means of 3 MSSBP and MSDBP assessments taken at 1- to 2-minute intervals in the seated position were used for each visit.

Adverse Events

Safety was assessed in all randomized patients who received ≥1 dose of the double-blind study drug. All adverse events (AEs) and serious AEs were recorded along with severity and perceived relationship to study drug.

Statistical Analysis

Demographic and baseline characteristics were compared across the 3 treatment groups using a 1-way analysis of variance (continuous variables) or a chi-square test (categorical variables). The primary efficacy outcome was the change in MSSBP from baseline to Week 4. Secondary efficacy outcomes included the change in MSSBP from baseline to weeks 2, 8, 12, and 16; the change in MSDBP from baseline to all time points; the proportion of patients achieving MSSBP/MSDBP <140/90 mm Hg and MSSBP <140 mm Hg; and the time to first achievement of MSSBP/MSDBP <140/90 mm Hg. A sample size of approximately 375 patients (125 per group) was required to ensure that the study had 83% power to detect superiority of

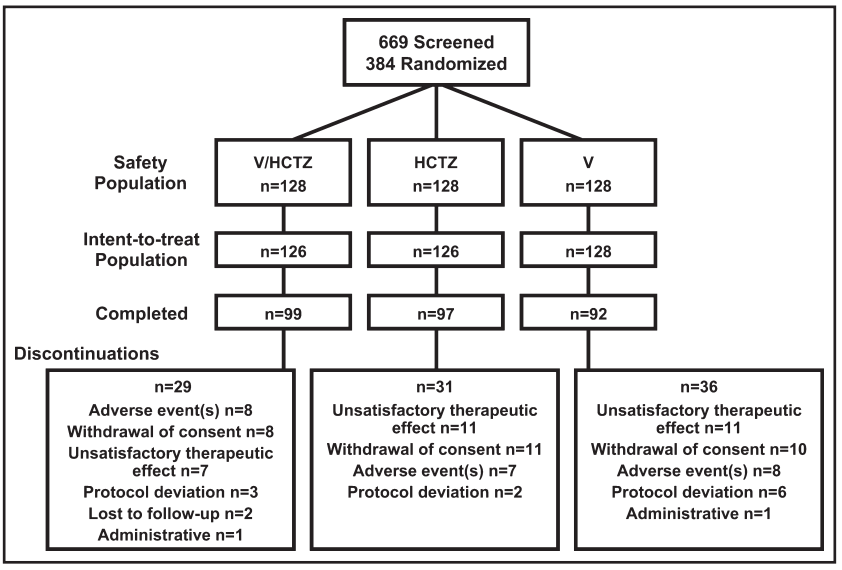


FIGURE 2. Patient disposition. HCTZ indicates hydrochlorothiazide; V, valsartan.

valsartan/HCTZ combination therapy over valsartan monotherapy in the primary efficacy outcome (change in MSSBP from baseline to week 4). Additional analyses were contingent on the primary comparison between valsartan/HCTZ and valsartan. If statistical significance was achieved, the MSSBP differences at week 4 between the valsartan/HCTZ and HCTZ groups could be analyzed. A post hoc comparison was made between the HCTZ and valsartan groups.

All randomized patients who received ≥1 dose of study drug and who had ≥1 postbaseline assessment of the primary efficacy outcome were included in the analyses, which used a last-observation-carried-forward (LOCF) and observed cases (OC) approach. Least-squared means (LSM) for each treatment arm were also computed. Within-treatment changes from baseline in MSSBP and MSDBP were analyzed using a paired *t* test. Between-treatment differences were assessed by an analysis of covariance (ANCOVA) model that used the baseline measurement as the covariate, with treatment and pooled center as factors. Based on this fitted model, a 2-sided 95% confidence interval (CI) and the associated *P* values were obtained for the mean treatment difference between valsartan/HCTZ and each monotherapy and a 2-sided test was performed at the 5% significance level. For testing of differences in the proportion of patients achieving MSSBP/MSDBP <140/90 mm Hg and MSSBP <140 mm Hg, *P* values were used from the Cochran-Mantel-Haenszel chi-square test, adjusting for pooled center. The primary analysis was based on the OC approach, but a supplemental analysis was also performed using an LOCF approach in which patients who discontinued (due to any reason) were also included in the assessment of BP goal. Patients who achieved BP goal <140/90 mm Hg any time prior to each visit measure before their discontinuation were included in the calculations. The Kaplan-Meier approach was used to estimate the time to first achievement of MSSBP/MSDBP <140/90 mm Hg, and the Wilcoxon test was used for between-treatment comparisons.

RESULTS

Patients

Of the 669 patients screened, 284 failed to meet diagnostic or severity criteria and one was not eligible due to a randomization error, yielding 384 randomized patients (n=128 in each of the 3 treatment groups). A total of 288 patients completed the study. The most common reasons for discontinuation were unsatisfactory therapeutic effect (n=29) and withdrawal of consent (n=29). Disposition for randomized patients is summarized in Figure 2.

Baseline demographic and clinical characteristics were well matched across the 3 treatment groups, with no statistically significant differences observed. As shown in Table I, the mean age of the study population at baseline was 77.5 years (32.8% were aged 70–75 years, 47.1% were 76–80 years, and 20.1% were older than 80 years), 55.7% were women, and 83.1% were Caucasian. Patients were predominantly overweight, with a mean body mass index of 28.7 kg/m^2. Mean office sitting BP was 165.1/85.1 mm Hg. Approximately 20.6% of patients were diabetic.

Dosing and Titration

By week 8, 48.4% of patients in the HCTZ group and 57.0% in the valsartan group had been switched to combination therapy (Table II), while 32.8% of patients in the valsartan/HCTZ group had been

TABLE I. Baseline Demographic and Clinical Characteristics in the Valsartan/HCTZ, HCTZ, and Valsartan Groups (Safety Population)

Parameter	Valsartan/HCTZ (n=128)	HCTZ (n=128)	Valsartan (n=128)	Total (N=384)
Age, y	77.2±4.0	77.7±4.8	77.7±4.2	77.5±4.3
70–75, No. (%)	44 (34.4)	41 (32.0)	41 (32.0)	126 (32.8)
76–80, No. (%)	65 (50.8)	56 (43.8)	60 (46.9)	181 (47.1)
>80, No. (%)	19 (14.8)	31 (24.2)	27 (21.1)	77 (20.1)
Sex, No. (%)				
Male	57 (44.5)	66 (51.6)	47 (36.7)	170 (44.3)
Female	71 (55.5)	62 (48.4)	81 (63.3)	214 (55.7)
Race, No. (%)				
Caucasian	105 (82.0)	109 (85.2)	105 (82.0)	319 (83.1)
Black	12 (9.4)	6 (4.7)	8 (6.3)	26 (6.8)
Asian	2 (1.6)	7 (5.5)	4 (3.1)	13 (3.4)
Other	9 (7.0)	6 (4.7)	11 (8.6)	26 (6.8)
Height, cm	166.4±10.0	166.5±10.1	164.8±11.2	165.9±10.5
Weight, kg	79.4±15.8	79.6±16.6	78.8±17.8	79.3±16.7
BMI, kg/m^2	28.6±4.3	28.6±4.9	28.9±5.5	28.7±4.9
Diabetic, No. (%)	28 (21.9)	29 (22.7)	22 (17.2)	79 (20.6)
Antihypertensive therapy in past 3 days, No. (%)	109 (85.2)	106 (82.8)	107 (83.6)	322 (83.9)
Serum creatinine, mg/dL	0.96±0.2	0.96±0.2	0.93±0.2	0.95±0.2
eGFR, mL/min/1.73 m^2	70.0±17.5	70.3±17.5	69.3±14.9	69.9±16.6
Serum potassium, mEq/L	4.3±0.4	4.3±0.4	4.3±0.4	4.3±0.4
Office sitting SBP, mm Hg	164.4±11.8	164.6±12.0	166.2±11.1	165.1±11.6
Office sitting DBP, mm Hg	84.9±9.4	85.6±9.1	84.9±9.8	85.1±9.4
Office sitting pulse, bpm	69.6±10.7	71.2±11.3	71.4±9.6	70.7±10.6

Abbreviations: BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure. Values are expressed as means±standard deviation unless otherwise indicated.

TABLE II. Number (%) of Patients by Actual Dose and Week (Safety Population)

Valsartan/HCTZ		HCTZ		Valsartan	
Dose, mg	n=128	Dose, mg	n=128	Dose, mg	n=128
By Week 8		By Week 8		By Week 8	
Valsartan/HCTZ 160/12.5	65 (50.8)	HCTZ 12.5	47 (36.7)	Valsartan 160	31 (24.2)
Valsartan/HCTZ 320/12.5	42 (32.8)	Valsartan/HCTZ 160/12.5	62 (48.4)	Valsartan/HCTZ 160/12.5	73 (57.0)
By Week 12		By Week 12		By Week 12	
Valsartan/HCTZ 160/12.5	51 (39.8)	HCTZ 12.5	31 (24.2)	Valsartan 160	21 (16.4)
Valsartan/HCTZ 320/12.5	28 (21.9)	Valsartan/HCTZ 160/12.5	48 (37.5)	Valsartan/HCTZ 160/12.5	39 (30.5)
Valsartan/HCTZ 320/25	24 (18.8)	Valsartan/HCTZ 320/12.5	24 (18.8)	Valsartan/HCTZ 320/12.5	36 (28.1)
				Valsartan/HCTZ 320/25	1 (0.8)
By Week 16		By Week 16		By Week 16	
Valsartan/HCTZ 160/12.5	45 (35.2)	HCTZ 12.5	26 (20.3)	Valsartan 160	17 (13.3)
Valsartan/HCTZ 320/12.5	23 (18.0)	Valsartan/HCTZ 160/12.5	36 (28.1)	Valsartan/HCTZ 160/12.5	37 (28.9)
Valsartan/HCTZ 320/25	32 (25.0)	Valsartan/HCTZ 320/12.5	24 (18.8)	Valsartan/HCTZ 320/12.5	14 (10.9)
		Valsartan/HCTZ 320/25	14 (10.9)	Valsartan/HCTZ 320/25	26 (20.3)

Abbreviation: HCTZ, hydrochlorothiazide.

titrated to the next highest dose (320/12.5 mg). The number of patients in the HCTZ or valsartan groups who were switched to combination therapy increased during the course of the study so that by week 16, 57.8% and 60.2%, respectively, had been switched to combination therapy; 43.0% of patients in the valsartan/HCTZ group had been titrated to higher dose levels. By week 16, only 20.3% and 13.3% of patients, respectively, in the HCTZ and valsartan groups remained on initial monotherapy, while 35.2%

of those in the valsartan/HCTZ group remained on initial low-dose combination therapy (Table II).

Changes in MSSBP and MSDBP From Baseline

All treatments produced significant reductions in MSSBP/MSDBP from baseline at all time points (all $P<.0001$) (Figure 3). At week 4, mean reductions in MSSBP from baseline (primary efficacy outcome) were greater for valsartan/HCTZ compared with valsartan treatment (−17.3 mm Hg vs −8.6 mm Hg; LSM difference, 9.3; 95% CI, 5.0–13.6 mm Hg; $P<.0001$) and trended higher compared with HCTZ treatment (−13.6 mm Hg; LSM difference, 3.7; 95% CI, −0.7 to 8.0 mm Hg; $P=.096$). Reductions in MSSBP and MSDBP from baseline in favor of combination therapy were observed as early as week 2 ($P<.01$ vs either monotherapy group). From week 8 onward, reductions in MSSBP and MSDBP numerically favored valsartan/HCTZ over valsartan or HCTZ, but not all comparisons differed. By week 16, no differences were observed among the 3 treatment groups, although the magnitude of BP reduction in the valsartan/HCTZ group generally persisted. In the post hoc analysis, the only difference between the HCTZ and valsartan groups was the greater reduction in MSSBP from baseline to week 4 found with HCTZ ($P=.011$).

BP Goal

In the OC analysis, a greater proportion of patients in the valsartan/HCTZ group achieved MSSBP/MSDBP goal (<140/90 mm Hg) than those in the valsartan group at week 4 (primary time point; $P<.0001$) (Figure 4), and goal attainment rates were greater with valsartan/HCTZ than HCTZ treatment at week 8 and valsartan/HCTZ vs valsartan treatment at weeks 8 and 16 ($P<.05$). A similar pattern was observed for the proportion of patients achieving the MSSBP goal (<140 mm Hg, data not shown). The median time to MSSBP/MSDBP goal was also shorter in the valsartan/HCTZ group (4 weeks) than in the HCTZ group (8 weeks; $P<.05$) or valsartan group (12 weeks; $P<.0001$).

Results of the supplemental analysis using LOCF are shown in Table III. From a statistical perspective, the results were no different from those of the OC analysis.

Subgroup Analyses

Subgroup analyses by age were performed for the primary efficacy variable (change in MSSBP from baseline). During the course of the study, patients in the valsartan/HCTZ group generally had the largest reductions in MSSBP from baseline, regardless of age. In both the 70- to 75-year-old and 76- to 80-year-old subgroups, a greater reduction in MSSBP was observed at week 2 with valsartan/HCTZ compared with valsartan treatment ($P<.05$). In patients older than 80 years, the valsartan/HCTZ group exhibited a greater decline in MSSBP than the HCTZ group at week 4 and the valsartan group at all study weeks ($P<.05$).

Subgroup analyses by sex and race were also performed. In either sex, valsartan/HCTZ treatment resulted in greater reductions in MSSBP than valsartan at week 4 ($P<.01$). At the same time point, Caucasian patients (the majority of patients enrolled in this trial) treated with valsartan/HCTZ had greater reductions in MSSBP than Caucasian patients treated with HCTZ or valsartan alone ($P<.05$).

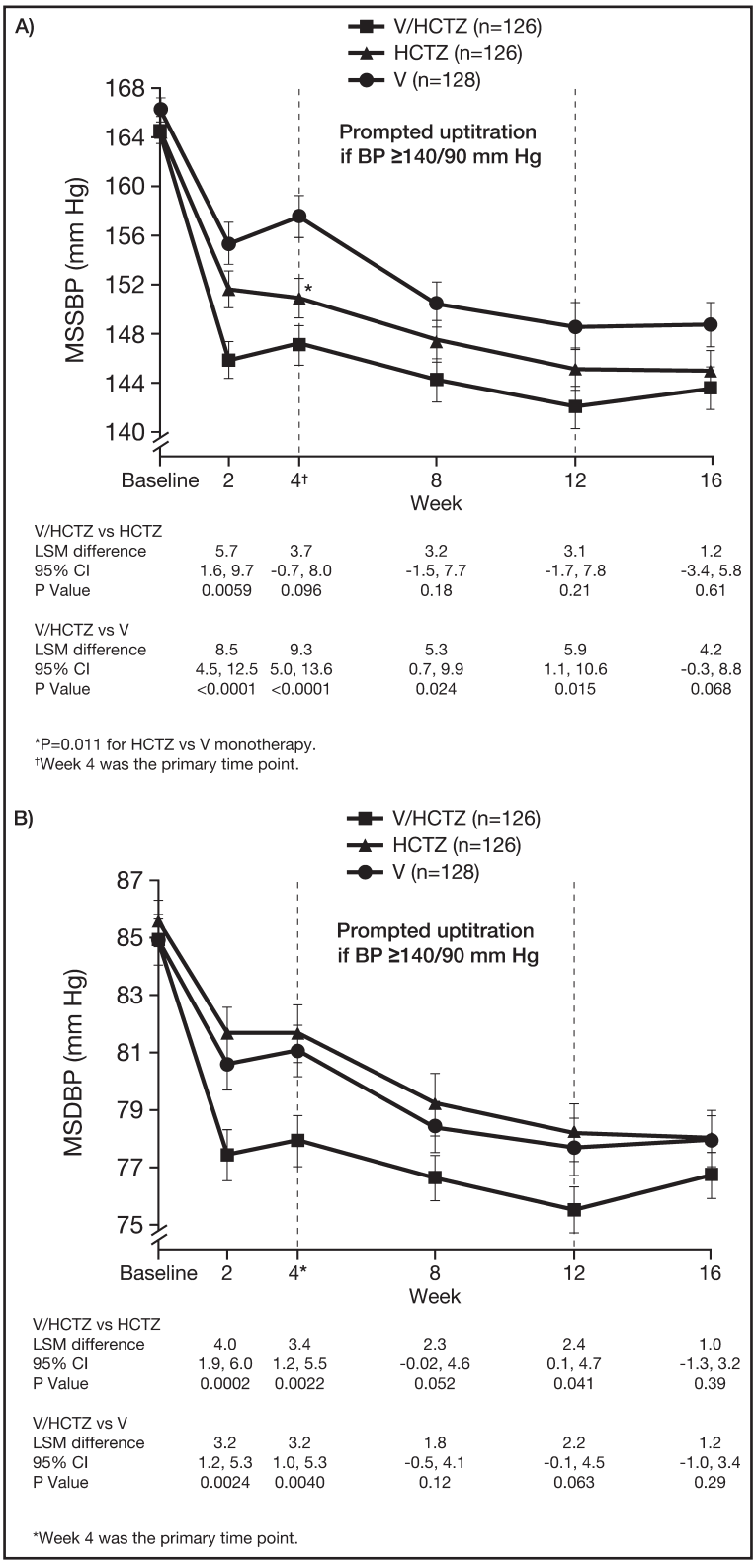
AEs and Discontinuations

AEs were experienced by 214 patients (55.7%) overall: 65 (50.8%) in the valsartan/HCTZ group, 77 (60.2%) in the HCTZ group, and 72 (56.3%) in the valsartan group (Table IV). During the course of the 16-week study, the most frequent AEs were dizziness (3.9%, 6.3%, and 7.0%, respectively), fatigue (3.9%, 7.8%, and 3.9%), and headache (4.7%, 7.0%, and 2.3%). At week 4 (prior to prompted up-titration), the occurrence of AEs related to hypotension was similar in the 3 treatment groups: dizziness (1 [0.8%] patient in the valsartan/HCTZ group, 4 [3.1%] in the HCTZ group, and 4 [3.1%] in the valsartan group), reported hypotension (1 [0.8%], 0, and 1 [0.8%]), orthostatic hypotension (1 [0.8%], 1 [0.8%], and 0), and vertigo (2 [1.6%], 0, and 0). By week 16, dizziness was reported in 5 (3.9%), 8 (6.3%), and 9 (7.0%) patients in the valsartan/HCTZ, HCTZ, and valsartan groups, respectively; hypotension in 2 (1.6%), 1 (0.8%), and 3 (2.3%); orthostatic hypotension in 1 (0.8%), 2 (1.6%), and 0; and vertigo in 2 (1.6%), 1 (0.8%), and 1 (0.8%).

A total of 96 patients (25.0%) discontinued the study prematurely: 29 in the valsartan/HCTZ group, 31 in the HCTZ group, and 36 in the valsartan group. Most (75.0%) of the discontinuations occurred during the first 4 weeks, prior to prompted up-titration. Throughout the study, discontinuation rates due to AEs were similar across the treatment groups: 8 (6.3%) patients in the valsartan/HCTZ group, 7 (5.5%) in the HCTZ group, and 8 (6.3%) in the valsartan group (Table IV).

DISCUSSION

In elderly individuals with systolic hypertension, initial low-dose combination therapy with valsartan/HCTZ lowered BP more effectively and allowed patients to reach BP goal in a shorter time than either valsartan or HCTZ monotherapy. Other advantages of this approach included improved tolerability and fewer titration steps. After 4 weeks of treatment, goal BP (<140/90 mm Hg) was reached in 42% of those taking valsartan/HCTZ 160/12.5 mg compared with 29% with HCTZ 12.5 mg and 14% with valsartan 160 mg daily. After 16 weeks, patients started on either monotherapy did not achieve the level of BP control seen with valsartan/HCTZ, even though the same maximum dose (valsartan/HCTZ 320/25 mg)



V/HCTZ vs HCTZ					
LSM difference	5.7	3.7	3.2	3.1	1.2
95% CI	1.6, 9.7	-0.7, 8.0	-1.5, 7.7	-1.7, 7.8	-3.4, 5.8
P Value	0.0059	0.096	0.18	0.21	0.61
V/HCTZ vs V					
LSM difference	8.5	9.3	5.3	5.9	4.2
95% CI	4.5, 12.5	5.0, 13.6	0.7, 9.9	1.1, 10.6	-0.3, 8.8
P Value	<0.0001	<0.0001	0.024	0.015	0.068

*P=0.011 for HCTZ vs V monotherapy.
†Week 4 was the primary time point.

V/HCTZ vs HCTZ					
LSM difference	4.0	3.4	2.3	2.4	1.0
95% CI	1.9, 6.0	1.2, 5.5	-0.02, 4.6	0.1, 4.7	-1.3, 3.2
P Value	0.0002	0.0022	0.052	0.041	0.39
V/HCTZ vs V					
LSM difference	3.2	3.2	1.8	2.2	1.2
95% CI	1.2, 5.3	1.0, 5.3	-0.5, 4.1	-0.1, 4.5	-1.0, 3.4
P Value	0.0024	0.0040	0.12	0.063	0.29

*Week 4 was the primary time point.

FIGURE 3. Mean sitting systolic blood pressure (MSSBP) (A) and mean sitting diastolic blood pressure (MSDBP) (B). BP indicates blood pressure; HCTZ, hydrochlorothiazide; LSM, least-squared mean; V, valsartan. Error bars represent 95% confidence interval (CI).

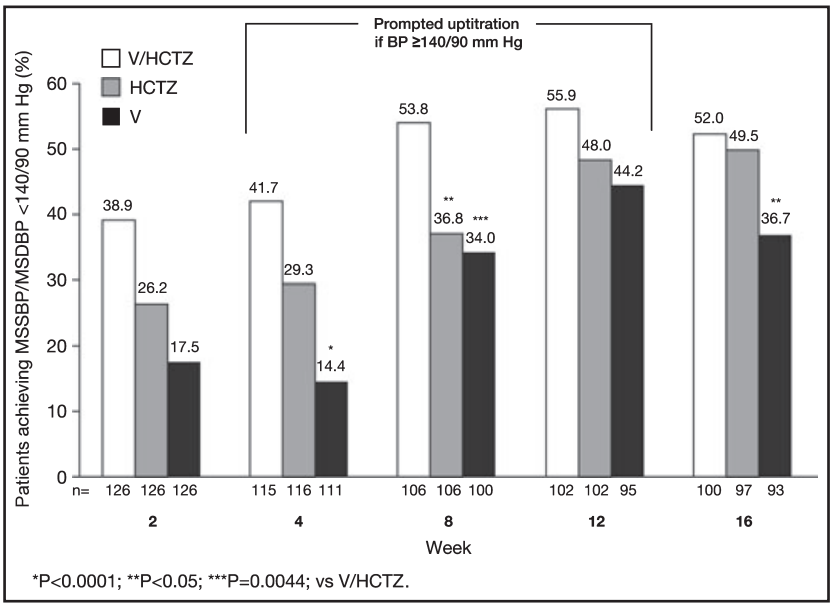


FIGURE 4. Proportion of patients achieving mean sitting systolic blood pressure/mean sitting diastolic blood pressure (MSSBP/MSDBP) <140/90 mm Hg. HCTZ indicates hydrochlorothiazide; V, valsartan.

TABLE III. Analysis of BP Goal (<140/90 mm Hg) Using OC and LOCF Methods of Analysis

Treatment Group and Week	OC Analysis of BP Goal, n/N (%)	Dropouts During Active Therapy, No.	Dropouts Achieving BP Goal (LOCF), No.	LOCF analysis of BP goal, n/N (%)
Valsartan/HCTZ (n=126)				
Week 2	49/126 (38.9)			
Week 4	48/115 (41.7)	11	0	48/126 (38.1)
Week 8	57/106 (53.8)	20	3	60/126 (47.6)
Week 12	57/102 (55.9)	24	4	61/126 (48.4)
Week 16	52/100 (52.0)	26	6	58/126 (46.0)
HCTZ (n=126)				
Week 2	33/126 (26.2)			
Week 4	34/116 (29.3)	10	3	37/126 (29.4)
Week 8	39/106 (36.8)[a]	20	5	44/126 (34.9)[a]
Week 12	49/102 (48.0)	24	5	54/126 (42.9)
Week 16	48/97 (49.5)	29	7	55/126 (43.7)
Valsartan (n=128)				
Week 2	22/126 (17.5)			
Week 4	16/111 (14.4)[b]	17	3	19/128 (14.8)[b]
Week 8	34/100 (34.0)[c]	28	3	37/128 (28.9)[c]
Week 12	42/95 (44.2)	33	6	48/128 (37.5)
Week 16	34/93 (36.6)[a]	35	6	40/128 (31.3)[a]

Abbreviations: BP, blood pressure; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward; OC, observed cases. [a]$P<.05$, [b]$P<.0001$, [c]$P<.01$; vs valsartan/HCTZ at the same time point.

was available for all. From week 8 onward, the study design permitted combination therapy in the groups initially assigned to monotherapy but the duration of maximal dose combination therapy (ie, dose-duration product) tended to be somewhat lower in the monotherapy groups. This may account for a part of the between-treatment comparisons and lower efficacy of monotherapy. To provide additional information, statistical analysis was carried out two ways: LOCF and per-protocol BP goal values in those who completed the study. No matter which way the data were analyzed, the noted trends persisted, albeit with slightly lower BP control rates using the LOCF approach. AE rates were low, including those related to hypotension.

TABLE IV. AEs Experienced by >2% of Patients in any Treatment Group (Safety Population)

Parameter	Valsartan/HCTZ (n=128), No. (%)	HCTZ (n=128), No. (%)	Valsartan (n=128), No. (%)	Overall (N=384), No. (%)
Patients with any AE	65 (50.8)	77 (60.2)	72 (56.3)	214 (55.7)
Dizziness	5 (3.9)	8 (6.3)	9 (7.0)	22 (5.7)
Fatigue	5 (3.9)	10 (7.8)	5 (3.9)	20 (5.2)
Headache	6 (4.7)	9 (7.0)	3 (2.3)	18 (4.7)
Upper respiratory tract infection	1 (0.8)	4 (3.1)	8 (6.3)	13 (3.4)
Urinary tract infection	3 (2.3)	5 (3.9)	5 (3.9)	13 (3.4)
Nausea	5 (3.9)	4 (3.1)	3 (2.3)	12 (3.1)
Nasopharyngitis	5 (3.9)	2 (1.6)	3 (2.3)	10 (2.6)
Sinusitis	3 (2.3)	3 (2.3)	2 (1.6)	8 (2.1)
Back pain	2 (1.6)	1 (0.8)	4 (3.1)	7 (1.8)
Muscle spasms	2 (1.6)	3 (2.3)	2 (1.6)	7 (1.8)
Diarrhea	1 (0.8)	3 (2.3)	2 (1.6)	6 (1.6)
Peripheral edema	1 (0.8)	1 (0.8)	4 (3.1)	6 (1.6)
Cough	3 (2.3)	2 (1.6)	1 (0.8)	6 (1.6)
Epistaxis	1 (0.8)	4 (3.1)	1 (0.8)	6 (1.6)
Hypotension	2 (1.6)	1 (0.8)	3 (2.3)	6 (1.6)
Constipation	0 (0.0)	4 (3.1)	1 (0.8)	5 (1.3)
Musculoskeletal chest pain	0 (0.0)	3 (2.3)	1 (0.8)	4 (1.0)
Osteoarthritis	3 (2.3)	1 (0.8)	0 (0.0)	4 (1.0)
Hypoesthesia	0 (0.0)	1 (0.8)	3 (2.3)	4 (1.0)
Discontinuations due to AEs	8 (6.3)	7 (5.5)	8 (6.3)	23 (6.0)

Abbreviations: AEs, adverse events; HCTZ, hydrochlorothiazide.

The present results are consistent with a Canadian study in a younger population (mean age, 61 years) that also demonstrated superiority of initial combination therapy (with either ARB/HCTZ or ACE inhibitor/HCTZ) over monotherapy.[13] The present results are also consistent with other studies of systolic hypertension in elderly populations treated with ARBs, with or without HCTZ.[14–21] In the Valsartan in Isolated Systolic Hypertension (Val-Syst) trial in patients aged 60 to 80 years, valsartan with or without HCTZ was as effective as amlodipine with or without HCTZ in lowering SBP with greater tolerability compared with either monotherapy.[19]

An important secondary hypothesis was that HCTZ would be superior to ARB in an elderly population. The scientific background for this hypothesis is the notion that the cardiovascular impact of the RAS wanes with age, generated largely by the inverse relationship between age and PRA.[9] Previous studies comparing a RAS blocker with a non–RAS blocker have not focused exclusively in the elderly and present findings in the elderly that were derived from secondary analyses. Nevertheless, ValVET is the first head-to-head trial to date conducted in the elderly that compares a RAS blocker with a drug with a "non-RAS" mechanism of action. Although both monotherapies lowered SBP, HCTZ (12.5 mg daily) was about 5 mm Hg more effective than valsartan (160 mg daily). Moreover, since full doses of neither agent were used, titration of HCTZ in individuals with systolic hypertension would be expected to add another 5 mm Hg to the effect of HCTZ,[16,22] whereas the titration of valsartan would add only 1 to 2 mm Hg.[23] Thus, it is most likely that a direct comparison of HCTZ 25 mg monotherapy with valsartan 320 mg would heighten, not reduce, the magnitude of the BP differences between valsartan and HCTZ. The overall trend may be consistent with British and European recommendations but only applies to individuals in the 8th decade of life and beyond. Current British and European guidelines, which suggest that a diuretic or calcium channel blocker is preferred over a RAS blocker as initial therapy in individuals older than 55 years, were generated without formal evidence.[6,10] ValVET results among individuals older than 70 years cannot shed light on the age cutoff, but it is possible that the 55 years of age recommended in the European guidelines is too low. ValVET results also suggest that there is no obvious reason to avoid ARB therapy in the elderly, particularly in combination with thiazide-type diuretics.

LIMITATIONS

We acknowledge certain limitations of the study design. First, as already mentioned, the primary comparison was based on submaximal doses of HCTZ (12.5 mg) and valsartan (160 mg), and titration involved adding the alternative agent before increasing doses. Another limitation is that the dropout rate was about 25%, but this attrition rate was similar among all treatment groups. Third, the study was not powered to detect treatment differences in some of the secondary subgroups (eg, age tertiles). Also, about 90% of all randomized patients were previously

treated with antihypertensive therapy, so the short washout period (3–14 days) may not have been enough to allow for full washout of prior therapy effects. However, any carryover effects of prior therapy would tend to mitigate against finding a significant difference between treatment arms and should have had similar effects in each randomized group. Finally, the time-to-BP-control data are clearly influenced by the protocol design and doses chosen.

CONCLUSIONS

Initial combination therapy with valsartan/HCTZ is effective in reducing BP and well tolerated in an elderly population with systolic hypertension. ValVET results are consistent with guidelines suggesting that thiazide monotherapy is somewhat more effective than ARB monotherapy in the elderly, but the overall greater antihypertensive efficacy of initial valsartan/HCTZ combination therapy supports considering an initial combination therapy approach for treating systolic hypertension in the elderly.

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