Office and Ambulatory Blood Pressure–Lowering Effects of Combination Valsartan/Hydrochlorothiazide vs Hydrochlorothiazide-Based Therapy in Obese, Hypertensive Patients

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The authors evaluated the blood pressure (BP)–lowering effects of combination valsartan/hydrochlorothiazide (HCTZ) vs amlodipine/HCTZ in a 16-week, double-blind, randomized, forced-titration study and ambulatory BP monitoring (ABPM) substudy involving centrally obese hypertensive patients 40 years and older. Patients were started on valsartan/HCTZ 160/12.5 mg or HCTZ 12.5 mg monotherapy, force-titrated at week 4 to valsartan/HCTZ 320/25 mg and HCTZ 25 mg, respectively. The HCTZ group initiated amlodipine 5 mg at week 8 and 10 mg at week 12. A subset of patients had 24-hour ABPM at baseline and weeks 8 and 16. At week 16 in the intent-to-treat population (n=401), valsartan/HCTZ and amlodipine/HCTZ lowered office systolic BP (–30.6 vs –28.3 mm Hg; *P*=.14). In the ABPM subgroup (n=111), valsartan/HCTZ was more effective than amlodipine/HCTZ in reducing 24-hour systolic BP (–20.6 vs –14.5 mm Hg; *P*=.011). In obese hypertensive patients, valsartan/HCTZ reduced office BP similar to amlodipine/HCTZ but lowered 24-hour systolic BP more. *J Clin Hypertens (Greenwich).* 2011;13:731–738.

The coexistence of abdominal obesity and a combination of blood pressure (BP), glucose, and lipid abnormalities, termed the cardiometabolic syndrome, has become an increasingly prevalent clinical problem.[1] Of all the various elements comprising the cardiometabolic syndrome, hypertension has been identified as the key contributor to the significant cardiovascular (CV) morbidity and mortality rates among overweight or obese individuals.[2] Overall, considering the high propensity for patients with the cardiometabolic syndrome to develop target-organ damage not only from hypertension but also other contributing causes, aggressive BP lowering to target BP <130/80mm Hg has been recommended.[3]

Obese patients are prone to develop salt-sensitive hypertension, which may be the clinical consequence of the sodium-retentive effects of hyperinsulinemia (resulting from insulin resistance) and/or hyperaldosteronism known to be associated with increased abdominal adiposity.[4,5] The renin-angiotensin-aldosterone system (RAAS) is believed to play a role in the characteristic salt sensitivity and insulin resistance of obese patients with the cardiometabolic syndrome,[4] and RAAS inhibitors are considered preferred agents in these patients, having demonstrated the ability to lower BP while attenuating insulin resistance.[6] Given the frequency of salt-sensitive hypertension and corresponding volume expansion among patients with cardiometabolic syndrome, there is a rationale for use of low-dose diuretic therapy.[3] Data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) support that thiazide-like diuretics are appropriate as initial antihypertensive therapy in patients with cardiometabolic syndrome.[7–10] While diuretics have established efficacy in reducing BP and associated CV morbidity and mortality, they are known to produce adverse metabolic and inflammatory effects for which the mechanism(s) and influence on long-term outcomes are not well understood.[11–14] However, outcome studies to date have noted a marked decrease in CV morbidity and mortality when diuretics are used as monotherapy or in combination with other drugs.[10]

The Valsartan and Hydrochlorothiazide In Hypertensive Abdominally Obese (VITAE) trial[15] was a randomized double-blind study designed to examine whether treatment of obese hypertensive patients with a combination of the angiotensin receptor blocker (ARB) valsartan plus the diuretic hydrochlorothiazide (HCTZ) would achieve a greater reduction in systolic BP (SBP) with a more favorable metabolic profile relative to treatment with an HCTZ-based regimen. Results of the metabolic aspects of the trial have been published, supporting an enhanced glucose-stimulated insulin secretory response for valsartan/HCTZ relative to HCTZ monotherapy.[15] The overarching clinical question that formed the basis of the VITAE trial was whether initiating antihypertensive therapy with a RAAS blocker/diuretic combination would be more

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beneficial than diuretic monotherapy specifically in obese patients. The add-on use of the calcium channel blocker (CCB) amlodipine at week 8 in the HCTZ monotherapy arm also allows a comparison of the relative BP-lowering effects of valsartan/HCTZ vs amlodipine/HCTZ at the end of the 16-week study period. Additionally, given the well-recognized shortcomings of office BP measurements in reflecting a patient's true BP status[16] and the ability of 24-hour ambulatory blood pressure monitoring (ABPM) to provide a better reflection of CV risk,[17] a subset of VITAE patients participated in an ABPM substudy. It is important to assess whether any differences exist in terms of 24-hour BP lowering with the non-RAAS blocker–based approach (initial HCTZ with add-on amlodipine) vs the RAAS blocker–based approach (valsartan/HCTZ) used in VITAE, as both treatment strategies could be recommended for patients with comorbid obesity and hypertension. Herein, we report these findings as well as a comparison of office BP and ABPM findings in the ABPM substudy population.

METHODS

The VITAE study design has been described in detail elsewhere.[15] In brief, VITAE was a 16-week, double-blind, randomized, forced-titration, outpatient study conducted in men and women 40 years and older with both hypertension and central obesity. Central obesity was defined as waist circumference >40 inches in men and >35 inches in women (>35 inches and >31 inches in Asian American men and women, respectively), with hypertension determined by the mean of 3 sitting BP measurements and defined as mean sitting SBP (MSSBP) ≥150 mm Hg but <180 mm Hg and mean sitting diastolic BP (MSDBP) <110 mm Hg following a washout phase lasting for up to 4 weeks. Key exclusion criteria included (1) use of >3 antihypertensive agents prior to enrollment, (2) inability to discontinue antihypertensive medication safely for 2 to 4 weeks before randomization, (3) history of type 1 or 2 diabetes or fasting glucose ≥126 mg/dL at visit 1, (4) history or current signs or symptoms of chronic heart failure, and (5) hepatic or renal impairment.

After screening, antihypertensive medication was stopped and patients entered the 4-week washout period. Subsequently, eligible patients were randomized to initially receive either valsartan/HCTZ 160/12.5 mg or HCTZ 12.5 mg monotherapy. At week 4, doses were force-titrated to valsartan/HCTZ 320/25 mg and HCTZ 25 mg in their respective groups. At weeks 8 and 12, patients in the valsartan/HCTZ group remained at the same dose (320/25 mg) while patients in the HCTZ group received add-on amlodipine (5 mg and 10 mg at weeks 8 and 12, respectively). Downward titration of study drug doses was not permitted. All medications were taken once daily at the same time each morning.

Unless the protocol had not been correctly followed, patients developing severe hypertension (MSSBP ≥180 mm Hg and/or MSDBP ≥110 mm Hg) or hypotension (MSSBP <100 mm Hg and/or MSDBP <60 mm Hg with signs and symptoms of hypotension) at any time during the study were (unless the protocol was not followed) withdrawn.

Clinic BP Measurement

At each study visit, BP was measured to the nearest millimeter of mercury using a sphygmomanometer or digital device with an appropriately sized arm cuff. The measurements were done at trough (ie, immediately prior to the next dosing) and with patients sitting for ≥5 minutes. BP was recorded 3 times, repeated at 1- to 2-minute intervals, and the average was used for analyses. The arm with the highest BP at enrollment was used for all subsequent measurements.

The primary objective of VITAE was to compare the mean change in MSSBP from baseline to week 8 between valsartan/HCTZ and HCTZ monotherapy in the intent-to-treat (ITT) population (ie, all randomized patients who received ≥1 dose of study medication and had a valid baseline and ≥1 valid post-baseline assessment of an efficacy variable). Additional efficacy analyses reported herein for the overall study population were mean change in MSSBP from baseline to week 16 (supportive analyses of the primary efficacy variable), as well as the secondary efficacy variables of mean change in MSDBP from baseline to weeks 8 and 16.

ABPM

In a subset of the population, ABPM was performed 3 times during the study: week 0, week 8, and week 16. Following office BP measurements, patients were instructed to wear the ABPM device for 24 hours. ABPM devices were preset to collect readings every 15 minutes during the day (6 AM–10 PM) and every 30 minutes during the night (10 PM–6 AM). Patients were asked to return to the study site the following day (25–26 hours after the start of ABPM) to remove the device. At week 0, study medication was administered after removal of the device. At week 8, the current dose of study medication was administered before placement of the ABPM device, and the new dose level of study medication was administered after device removal. The last dose of study medication was given after placement of the ABPM device at week 16.

Analyses based on the evaluable ABPM substudy population (ie, all patients with a valid baseline and ≥1 post-baseline ABPM measurement) were of an exploratory nature and included changes from baseline to weeks 8 and 16 with respect to the following variables: 24-hour mean ambulatory SBP (MASBP), 24-hour mean ambulatory DBP (MADBP), and MASBP/MADBP during the last 6 hours of dosing.

Statistical Analysis

The target accrual was 392 patients (196 per group) based on 90% power to detect a 5-mm Hg difference

TABLE I. Baseline Demographic and Clinical Characteristics

	Overall Population		Ambulatory Substudy Population	
	Valsartan/HCTZ (n=206)	HCTZ[a] (n=206)	Valsartan/HCTZ (n=61)	HCTZ[a] (n=50)
Mean (SD) age, y	56.5 (8.6)	55.4 (8.5)	58.5 (8.2)	56.1 (8.5)
Age group, %				
≥65 y	16.5	12.6	23.0	14.0
Sex, %				
Men	39.8	28.2	50.8	40.0
Women	60.2	71.8	49.2	60.0
Race, %				
Caucasian	50.0	52.9	50.8	48.0
Black	32.5	28.6	26.2	22.0
Hispanic	13.6	16.5	19.7	30.0
Other	3.9	1.9	3.3	0
Antihypertensive therapy within 30 days prior to study, % yes	69.9	70.9	80.3	88.0
Diabetes status, %				
Normoglycemic	64.6	62.1	63.9	60.0
Prediabetic	31.6	31.1	32.8	30.0
Diabetic	3.9	6.8	3.3	10.0
Metabolic syndrome, %[b]	69.9	72.8	70.5	64.0
Mean (SD) eGFR, mL/min/1.73 m^2	72.3 (13.8)	73.4 (13.1)	73.5 (15.2)	74.4 (11.2)
Mean (SD) BMI, kg/m^2	34.8 (6.9)	35.2 (7.3)	33.2 (5.1)	33.6 (5.5)
Mean (SD) SBP, mm Hg	159.7 (7.9)	158.9 (7.6)	143.0 (13.0)[c]	140.0 (11.0)[c]
Mean (SD) DBP, mm Hg	94.9 (7.9)	93.6 (8.1)	85.6 (9.5)[c]	84.6 (7.4)[c]

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; SD, standard deviation. [a]Patients in this group received amlodipine starting at week 8. [b]One or more of the following 3 criteria were met: fasting plasma glucose ≥100 mg/dL, high-density lipoprotein cholesterol <40 mg/dL for men or <50 mg/dL for women, fasting triglycerides ≥150 mg/dL. [c]Ambulatory blood pressure measurements.

in the mean change in MSSBP between valsartan/HCTZ and HCTZ monotherapy at week 8, assuming a standard deviation of 14 mm Hg[18] and a drop-out rate of 15%. A total of 130 patients from selected study centers were recruited into the ABPM substudy.

Descriptive analyses were performed for baseline demographics, applying a 2-sample *t* test (continuous variables) or chi-square test (categorical variables) to test for homogeneity between the two treatments at baseline. Statistical analysis of the primary efficacy variable was conducted under a 2-sided alternative hypothesis, employing a significance level of .05. An analysis of covariance was used in estimating the treatment effect for the primary efficacy variable, with baseline MSSBP assessment as a covariate and treatment as factor in the model; similar analyses were conducted for the secondary and exploratory analyses of change in BP. For both the overall ITT and ABPM substudy populations, changes in BP from baseline were evaluated using a last-observation-carried-forward approach, replacing missing BP values with assessments made post-baseline (the baseline value was not carried forward). For the ABPM efficacy variables, mean BP reductions (over 24 hours, during the daytime [defined as 6 AM–10 PM] and nighttime [10 PM–6 AM], and for the last 6 hours of dosing) were calculated by averaging the patient's available hourly means (for which equal weight was assigned).

RESULTS

Baseline Characteristics

A total of 412 patients were randomly assigned to receive valsartan/HCTZ (n=206) or HCTZ (n=206), with 401 of these patients meeting the criteria for inclusion in the overall ITT population (n=197 valsartan/HCTZ, n=204 HCTZ). Of 130 patients enrolled into the ABPM substudy, 111 patients were evaluable: 61 patients randomized to valsartan/HCTZ and 50 patients to HCTZ.

Baseline demographic and clinical characteristics in the overall ITT and ABPM substudy populations are shown in Table I. The treatment groups were well matched except for a significantly higher proportion of men randomized to receive valsartan/HCTZ in the overall population (*P*=.013). In the ABPM substudy, although not statistically significant, the valsartan/HCTZ group was composed of more men and elderly patients (65 years and older) and fewer Hispanic patients compared with the HCTZ group.

Office BP vs ABPM Changes From Baseline

Week 8. From baseline to week 8 in the overall ITT population (Figure 1), the mean reductions were significantly greater with valsartan/HCTZ vs HCTZ monotherapy for both MSSBP (−28.6 mm Hg vs −21.5 mm Hg; least-squares mean difference [LSM_{diff}]=−6.9

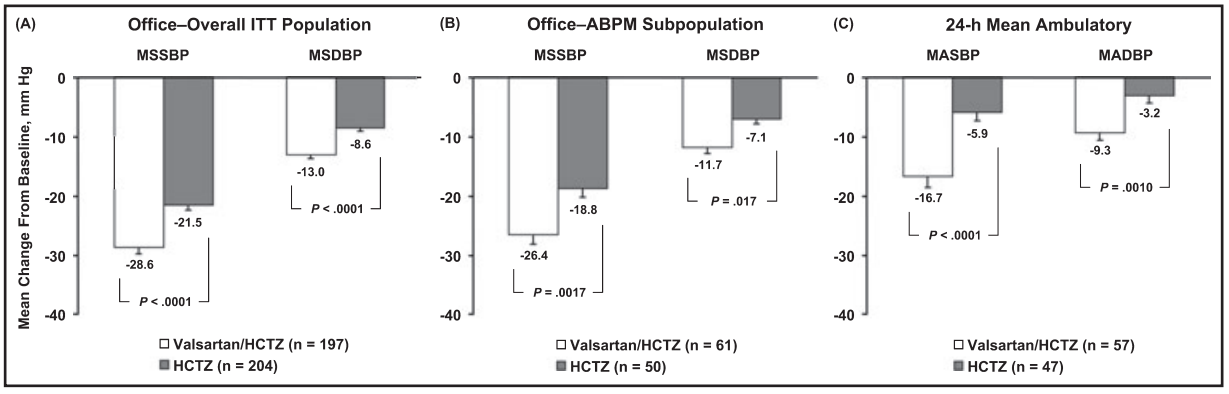

FIGURE 1. Mean±standard error change from baseline to week 8 in (A) office blood pressure for the overall intent-to-treat population, (B) office blood pressure for the intent-to-treat ambulatory substudy population, and (C) 24-hour blood pressure for the ambulatory substudy population. *P* values are based on least-squares mean differences. ABPM indicates ambulatory blood pressure monitoring; HCTZ, hydrochlorothiazide; ITT, intent-to-treat; MADBP, mean ambulatory diastolic blood pressure; MASBP, mean ambulatory systolic blood pressure; MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure.

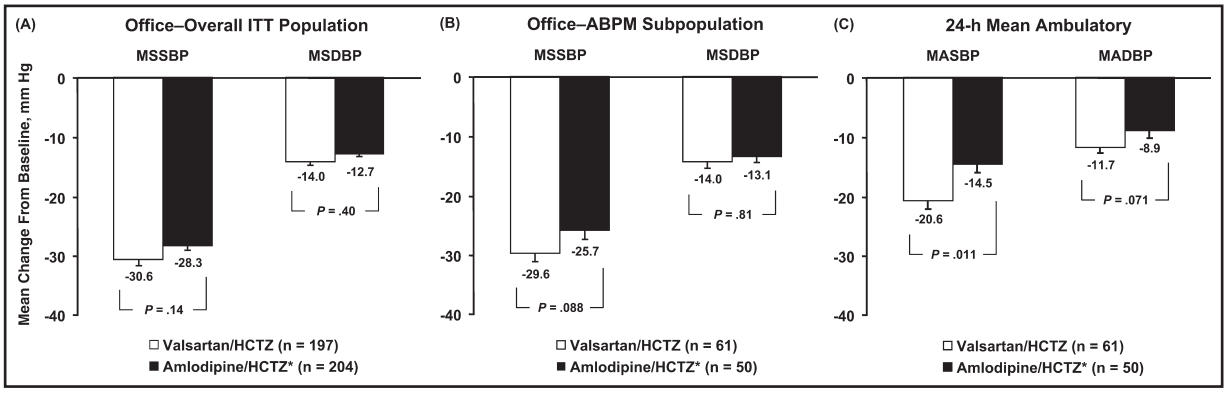

FIGURE 2. Mean±standard error change from baseline to week 16 in (A) office blood pressure for the overall intent-to-treat population, (B) office blood pressure for the intent-to-treat ambulatory substudy population, and (C) 24-hour blood pressure for the ambulatory substudy population. *P* values are based on least-squares mean differences. *Patients received amlodipine starting at week 8. ABPM indicates ambulatory blood pressure monitoring; HCTZ, hydrochlorothiazide; ITT, intent-to-treat; MADBP, mean ambulatory diastolic blood pressure; MASBP, mean ambulatory systolic blood pressure; MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure.

[95% confidence interval (CI), −9.6 to −4.1]; *P*<.0001) and MSDBP (−13.0 mm Hg vs −8.6 mm Hg; LSM_{diff}=−3.8 [95% CI, −5.4 to −2.2]; *P*<.0001; Figure 1A). Office BP results at week 8 specifically in the ABPM substudy population were consistent with those of the overall ITT population, with this subset experiencing significantly greater mean reductions with valsartan/HCTZ vs HCTZ monotherapy for MSSBP (−26.4 mm Hg vs −18.8 mm Hg; LSM_{diff}=−7.7 [95% CI, −12.5 to −3.0]; *P*=.0017) and MSDBP (−11.7 mm Hg vs −7.1 mm Hg; LSM_{diff}=−3.5 [95% CI, −6.3 to −0.6]; *P*=.017; Figure 1B).

As with the office BP study findings, in the ABPM substudy population (n=104), valsartan/HCTZ provided significantly greater mean reductions than HCTZ monotherapy in 24-hour MASBP (−16.7 mm Hg vs −5.9 mm Hg; LSM_{diff}=−9.5 [95% CI, −13.8 to −5.2]; *P*<.0001) and MADBP (−9.3 mm Hg vs −3.2 mm Hg; LSM_{diff}=−5.7 [95% CI, −8.9 to −2.4]; *P*=.0010; Figure 1C).

Week 16. At week 16 in the overall ITT population (Figure 2), the treatments (valsartan/HCTZ and amlodipine/HCTZ) provided similar mean reductions from baseline as measured by office BP, both MSSBP (−30.6 mm Hg vs −28.3 mm Hg; LSM_{diff}=−2.0 [95% CI, −4.8 to 0.7]; *P*=.14) and MSDBP (−14.0 mm Hg vs −12.7 mm Hg; LSM_{diff}=−0.7 [95% CI, −2.4 to 0.9]; *P*=.40; Figure 2A). The differences between the two treatments were not significantly different. Consistent with the office BP results in the overall ITT population, office BP results specifically for the ABPM substudy population showed that the valsartan/HCTZ and amlodipine/HCTZ groups were similar at week 16 with respect to mean reductions in MSSBP (−29.6 mm Hg and −25.7 mm Hg, respectively; LSM_{diff}=−4.1

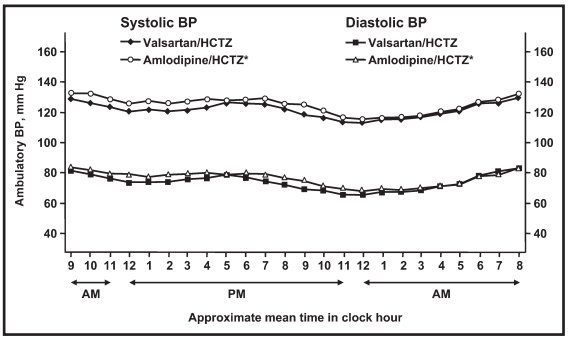

FIGURE 3. Hourly ambulatory blood pressure (BP) at the end of study in the ambulatory substudy population. *Patients received amlodipine starting at week 8. HCTZ indicates hydrochlorothiazide.

[95% CI, −8.7 to 0.6]; *P*=.088) and MSDBP (−14.0 mm Hg and −13.1 mm Hg, respectively; LSM_{diff}=0.4 [95% CI, −2.5 to 3.2]; *P*=.81; Figure 2B).

Using ABPM, however, significantly greater mean reductions in MASBP were observed with valsartan/HCTZ than with amlodipine/HCTZ (−20.6 vs −14.5 mm Hg; LSM_{diff}=−4.6 [but not different from the LSM difference of −4.1 mm Hg in office SBP between the two treatments; 95% CI, −8.1 to −1.1]; *P*=.011; Figure 2C). Although the reduction in 24-hour MADBP favored valsartan/HCTZ, the difference between that seen with amlodipine/HCTZ approached but did not reach statistical significance (−11.7 mm Hg vs −8.9 mm Hg; LSM_{diff}=−2.3 [95% CI, −4.8 to 0.2]; *P*=.071).

Additional ABPM Substudy Findings

The hourly MASBP/MADBP data at the end of study are shown in Figure 3. MASBP/MADBP reductions during the last 6 hours of the 24-hour dosing interval (Table II) were significantly different between valsartan/HCTZ and HCTZ monotherapy at week 8 but not between valsartan/HCTZ and amlodipine/HCTZ at week 16.

At the end of the study, valsartan/HCTZ was significantly more effective than amlodipine/HCTZ in reducing daytime SBP (−22.1 mm Hg vs −15.2 mm Hg; LSM_{diff}=−5.2 [95% CI, −9.0 to −1.4]; *P*=.0074), with the difference in nighttime SBP reduction of borderline significance (−18.1 mm Hg vs −12.6 mm Hg; LSM_{diff}=−3.8 [95% CI, −7.7 to 0.06]; *P*=.054). During both periods, corresponding DBP reductions with valsartan/HCTZ were not significantly greater than those with amlodipine/HCTZ (daytime: −12.4 mm Hg vs −9.4 mm Hg; LSM_{diff}=−2.5 [95% CI, −5.4 to 0.3]; *P*=.079; nighttime: −10.5 mm Hg vs −7.5 mm Hg; LSM_{diff}=−2.0 [95% CI, −4.5 to 0.5]; *P*=.11).

TABLE II. Ambulatory Substudy: Changes During the Last 6 Hours of the Dosing Interval

	Mean±SD During Last 6 Hours of Dosing, mm Hg	
	ASBP	ADBP
Baseline values per initial randomization		
Valsartan/HCTZ (n=61)	142.0±14.1	85.8±10.7
HCTZ (n=50)	139.8±12.2	85.1±9.3
Change from baseline to week 8		
Valsartan/HCTZ (n=57)	−19.0±14.6[a]	−11.9±10.0[a]
HCTZ (n=47)	−10.9±11.8[a]	−7.7±10.3[a]
LSM difference	−6.9 (*P*=.0024)	−3.7 (*P*=.030)
Change from baseline to week 16 (LOCF)		
Valsartan/HCTZ (n=61)	−18.1±13.6[a]	−10.5±9.6[a]
Amlodipine/HCTZ[b] (n=50)	−15.5±13.5[a]	−10.3±11.5[a]
LSM difference	−1.5 (*P*=.50)	0.2 (*P*=.90)

Abbreviations: ADBP, ambulatory diastolic blood pressure; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward; LSM, least-squares mean difference; ASBP, ambulatory systolic blood pressure; SD, standard deviation. [a]*P*<.0001 from baseline. [b]Patients received amlodipine starting at week 8.

DISCUSSION

The VITAE study was designed to evaluate the relative BP and metabolic effects of two different HCTZ-based regimens, namely HCTZ in combination with valsartan or HCTZ monotherapy for 8 weeks followed by add-on amlodipine for another 8 weeks (a metabolically neutral CCB). Given the entry criteria (requiring comorbid hypertension and obesity), the study population was dominated by patients with cardiometabolic syndrome. The metabolic findings[15] showed that the addition of valsartan to HCTZ mitigated the negative metabolic effects of HCTZ therapy throughout the duration of the 16-week study. Similar metabolic findings were observed in the ABPM subset (data not presented). Based on the analyses reported here, both study regimens were effective in reducing office and ABP, with significantly greater SBP reduction with valsartan/HCTZ vs amlodipine/HCTZ (at week 16) based on ABPM. Although other studies have confirmed the BP-lowering effects of combination thiazide diuretics with ARBs other than valsartan, angiotensin-converting enzyme inhibitors (ACEIs), direct renin inhibitors, or β-blockers in obese, hypertensive patients,[19–23] none have compared combining ARBs with HCTZ as an initial regimen vs addition of amlodipine, a metabolically neutral agent, with HCTZ in patients susceptible to the development of diabetes.

The prognostic value of ABPM-derived data has been well documented in numerous reports since the early 1980s,[24–33] with a correlation between 24-hour ambulatory BP, hypertension-related organ damage, and CV events reflecting the known relationship between BP variability and CV risk.[30,34,35] In the population-based Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, the risk of CV-related mortality among patients with cardiometabolic syndrome was increased to the greatest extent in the subset with both office and nonoffice (home monitoring

or 24-hour ABPM) BP elevations.[36] Clinical trials of antihypertensive therapy have shown an increasing focus on ABPM data, since 24-hour average BP is more closely associated with CV outcomes than office BP measurements[26,27,33,34,37] and provides a clearer distinction between treatments for parameters such as BP variability and duration of action.[38] Accumulating data support the efficacy of once-daily combination ARB/HCTZ therapy in reducing 24-hour ABP in various settings, including the treatment of stage 1 or 2 hypertension[39–41] or in more challenging clinical scenarios (eg, black,[42] elderly,[43,44] or high CV risk populations[45–48]).

In the current analysis, significantly greater BP lowering for valsartan/HCTZ vs amlodipine/HCTZ was evident only on examination of the ABPM data from the ambulatory substudy of VITAE (which evaluated changes in MASBP and MADBP as exploratory end points) and not in the office BP measurements. In addition to our study, the use of ABPM has shown differences in antihypertensive efficacy compared with clinic BP measures in other clinical trials as well. For example, Giles and colleagues[49] reported that 4 weeks of intensive treatment with amlodipine/valsartan (5/320 mg for 2 weeks, then 10/320 mg for 2 weeks) resulted in significantly greater reductions in 24-hour MASBP/MADBP compared with moderate treatment with the same agents (5/160 mg for 4 weeks), whereas no significant difference was noted using clinic BP. The future will definitely see increased use of ABPM as part of the evaluation in clinical trial settings to identify treatment differences, as apparent from several ongoing clinical trials registered on http://ClinicalTrials.gov. In our study, statistical significance in favor of valsartan/HCTZ was reached with respect to change in 24-hour and daytime MASBP, with a few additional differences in the ambulatory substudy population approaching significance (ie, the change in nighttime MASBP, change in 24-hour, daytime, and nighttime MADBP). Since trough clinic BP readings were performed at approximately 9 AM, perhaps the most relevant ABPM measure to compare with the office BP readings is the last 6-hour data. These measures yielded consistent results with no significant between-treatment differences at end of study. Our results show the importance of including a RAAS inhibitor as part of the treatment plan for obese hypertensive patients, many of whom have cardiometabolic syndrome (approximately 70% in VITAE). Further, they challenge the notion of initiating monotherapy in these patients. Patients with comorbid obesity and hypertension are characteristically difficult-to-treat and typically require multiple antihypertensive agents. The VITAE trial shows that better ABPM and metabolic outcomes can be achieved by initiating these patients on combination RAAS inhibitor/thiazide diuretic.

Our findings are consistent with previous studies reporting advantages with ARB/HCTZ over amlodipine/HCTZ in terms of ambulatory BP reduction.[41,43,44] In contrast, a previous study found no significant between-group differences in 24-hour, daytime, or nighttime ambulatory BP results following treatment with valsartan/HCTZ or amlodipine/HCTZ, perhaps owing to slow titration and/or use of half the maximum recommended dose of valsartan.[48]

Adverse event data for the overall population have been published that support safety and tolerability profiles for both study regimens.[15] The proportions of patients reporting ≥1 adverse event were 39.3% and 51.5% for those in the valsartan/HCTZ and amlodipine/HCTZ groups, respectively, with the difference largely attributable to more peripheral edema in the latter group (1.5% and 9.7%, respectively). The only other adverse events with an incidence >5% were fatigue in the valsartan/HCTZ group (5.3% vs 2.9% with amlodipine/HCTZ) and upper respiratory tract infection in the amlodipine/HCTZ group (6.8% vs 2.9% with valsartan/HCTZ).

Limitations

Interpretation of the results, both for the ABPM and overall populations, is confounded by the fact that patients in the amlodipine/HCTZ group only received full-dose amlodipine for the final 4 weeks of this 16-week study, having received HCTZ monotherapy for the first 8 weeks followed by amlodipine 5 mg (the usual starting dose) for the following 4 weeks. Based on data from other clinical trials, however, it appears that the maximal BP-lowering effects of amlodipine/HCTZ 10/25 mg are seen after about 2 to 3 weeks[50,51] and therefore support that the 4-week duration of treatment with amlodipine 10 mg was sufficient to allow for comparisons between the two treatment arms. However, because multiple factors (eg, demographics, sodium intake, and levels of psychosocial stress) can influence the BP response to antihypertensive medication, we cannot exclude the possibility that the treatment duration may have been too short for some patients to fully respond to amlodipine. Additional limitations stemming from the overall design of the VITAE trial were the lack of a valsartan monotherapy arm and the fact that comparisons of the combination regimens were feasible only at the end of the study, as the week 8 midpoint focused instead on comparing diuretic monotherapy with the RAAS blocker/diuretic combination. The ABPM substudy results are limited by the small sample size. Finally, because the VITAE study was designed to evaluate relatively short-term effects, it does not provide any insight into the sustainability of the observed BP and metabolic changes and their ultimate impact on long-term CV outcomes.

CONCLUSIONS

The 16-week VITAE study in obese hypertensive patients demonstrated lowering of BP in both treatment arms when assessed by office-monitoring or

ABPM. While office BP measurements showed no differences between the combinations at the end of the study, valsartan/HCTZ was more effective in lowering 24-hour SBP than amlodipine/HCTZ, as assessed using ABPM. The results of the ABPM substudy tended to favor valsartan/HCTZ and, when considered together with the metabolic data derived from VITAE, support the applicability of this ARB/diuretic combination to difficult-to-treat obese patients in whom cardiometabolic syndrome is highly prevalent.

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