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Article *in* Journal of Clinical Hypertension · January 2009

DOI: 10.1111/j.1751-7176.2008.00054.x · Source: PubMed

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Original Paper

Metabolic and Antihypertensive Effects of Combined Angiotensin Receptor Blocker and Diuretic Therapy in Prediabetic Hypertensive Patients With the Cardiometabolic Syndrome

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*Hypertensive patients with the cardiometabolic syndrome (CMS) are at increased risk for type 2 diabetes and cardiovascular disease. The authors examined effects of valsartan and hydrochlorothiazide (HCTZ) combined and alone on insulin sensitivity (using homeostasis model assessment–insulin resistance [HOMA-IR]), and inflammatory/metabolic biomarkers in prediabetic hypertensive persons with CMS. Eligible patients entered 16-week therapy with valsartan 320 mg/d (*n=*189), HCTZ 25 mg/d (*n=*190), or valsartan/HCTZ 320/25 mg/d (*n=*187). At the end point, there were no statistically significant differences in HOMA-IR among the 3 groups. HCTZ significantly increased hemoglobin A_{1c} and triglyceride concentrations and lowered serum potassium levels vs valsartan. HCTZ also increased plasma aldosterone and C-reactive protein levels. Blood pressure reduction and blood pressure control rates were highest with valsartan/HCTZ. There were no differences between combination valsartan/HCTZ or monotherapies on a measure of insulin sensitivity; however, the negative metabolic effects of HCTZ (increase in triglyceride and hemoglobin A_{1c} values) were absent with valsartan/HCTZ, indicating an ameliorating effect of valsartan on these measures.* J Clin Hypertens (Greenwich). *2008;10:894–903.* ©*2008 Le Jacq*

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Manuscript received February 20, 2008;
revised April 7, 2008; accepted April 7, 2008

doi: 10.1111/j.1751-7176.2008.00054.x

Diabetes is a major risk factor for both cardiovascular disease (CVD) and chronic kidney disease (CKD), and it is increasing in prevalence in both children and the adolescent population.[1] Predisposing factors for the development of diabetes include obesity, hypertension, dyslipidemia, and impaired fasting and postprandial glucose.[1]

All these factors are also associated with the cardiometabolic syndrome and place the hypertensive patient at an increased risk for CVD and CKD.[2,3] Patients with the cardiometabolic syndrome are commonly hypertensive; thus, the choice of antihypertensive therapy is of some importance since the metabolic status can be adversely impacted by certain drug therapies.

Antihypertensive agents such as thiazide diuretics, which stimulate the renin-angiotensin-aldosterone system (RAAS), have been associated with an increase in fasting glucose and insulin resistance.[4,5] For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the diuretic chlorthalidone was associated with increased fasting glucose and a higher incidence of new-onset diabetes.[6] Alternatively, recent trials have suggested that inhibitors of the RAAS reduce the incidence of new-onset diabetes.[4,7,8] This distinction among drug classes is not a trivial issue, since the development of diabetes during antihypertensive therapy may be associated with worse CVD and CKD outcomes compared with those in nondiabetic persons.[9,10]

The purpose of the present study was to evaluate the effects of 2 antihypertensive agents with disparate metabolic effects on markers of metabolic function in hypertensive patients susceptible to the development of diabetes. This study evaluated the effects of the angiotensin receptor blocker (ARB) valsartan vs hydrochlorothiazide (HCTZ) alone and in combination on peripheral insulin sensitivity using homeostasis model assessment–insulin resistance (HOMA-IR) and on inflammatory (eg, high-sensitivity C-reactive protein [hsCRP]) and metabolic biomarkers (eg, adiponectin) after 16 weeks of therapy in obese, prediabetic hypertensive patients.

METHODS

The Metabolic Assessment of Diovan's Efficacy in Comparison to Thiazide Therapy (MADE-ITT) study was a randomized 16-week double-blind, active-controlled, parallel-group titration study undertaken to evaluate the metabolic effects of valsartan compared with HCTZ therapy in obese hypertensive prediabetic patients with the cardiometabolic syndrome. The study also explored whether valsartan negated the metabolic effects induced by HCTZ during combination therapy.

Study Population

Patients aged 18 to 75 years entering the study were screened for diagnosis of the cardiometabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III to determine eligibility.[11] Patients eligible for inclusion had to be obese (waist circumference >40 in [male] or >35 in [female]) and hypertensive (mean sitting systolic blood pressure (MSSBP) ≥130 but ≤160 mm Hg and mean sitting diastolic blood pressure (MSDBP) ≥85 mm Hg but ≤100 mm Hg). In addition, patients had to meet ≥1 of the following criteria for the cardiometabolic syndrome: (1) fasting plasma glucose, 100–125 mg/dL (5.5–6.9 mmol/L); (2) serum triglycerides (TGs), >150 mg/dL; and (3) serum high-density lipoprotein cholesterol <40 mg/dL (men) or <50 mg/dL (women).

This study excluded patients with MSSBP levels >180 mm Hg or MSDBP levels >110 mm Hg at any visit. Patients unable to discontinue all antihypertensive medications safely for a period of 4 weeks prior to randomization who had known hypersensitivity to a study drug, or had any condition that would jeopardize the evaluation of efficacy or safety were excluded from the study. Pregnant or breast-feeding women and premenopausal female patients not using an effective form of contraception were also excluded.

Protocol

The study was conducted under the provisions of the Declaration of Helsinki and was approved by an appropriately constituted institutional review board from each site. Written informed consent was provided by each patient prior to conducting any study-related procedure. The study consisted of 3 periods: (1) a 2-week washout period during which antihypertensive medications were discontinued and patients were screened for their cardiometabolic syndrome status; (2) a 2-week single-blind run-in period in which eligible patients received placebo; and (3) patients meeting the blood pressure (BP) criteria for eligibility at the end of the placebo period entered a 16-week double-blind treatment period and were randomized into 1 of the 3 treatment groups: valsartan monotherapy 160 mg QD, valsartan/HCTZ combination therapy 160/12.5 mg QD, or HCTZ 12.5 mg QD (Figure 1). Two weeks following randomization, all patients were force-titrated to receive the next higher dose: the monotherapy arm of valsartan 160 mg to valsartan 320 mg; the combination valsartan/HCTZ 160/12.5 mg to valsartan/HCTZ 320/25 mg; and HCTZ 12.5 mg to HCTZ 25 mg. The treatment at these doses was maintained for the ensuing 14 weeks.

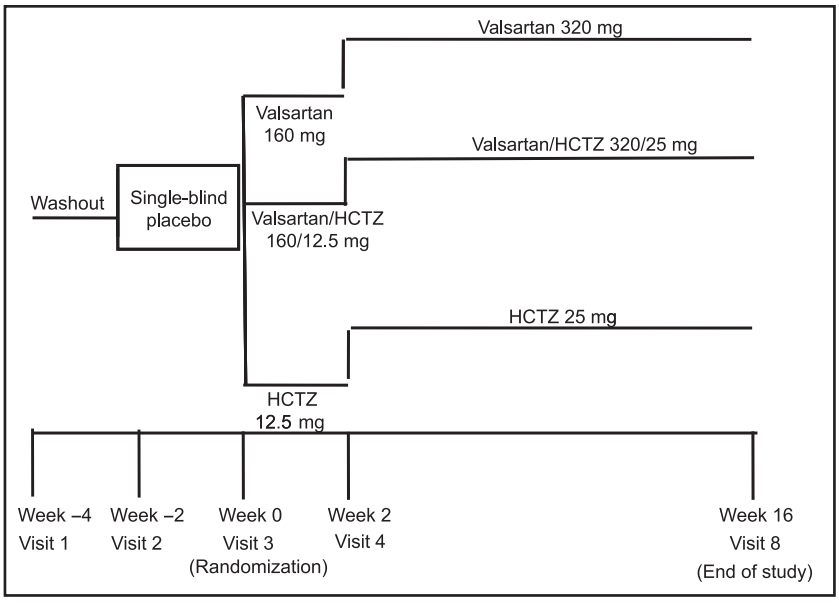

Figure 1. Study design of the Metabolic Assessment of Diovan's Efficacy in Comparison to Thiazide Therapy. There were 3 groups with 3 treatment periods: (1) screening/washout (if on prior antihypertensive therapy), (2) a 2-week single-blind period in which all patients received placebo, and (3) a 16-week double-blind period in which patients were randomized into 1 of the 3 treatment groups: valsartan monotherapy (160 mg QD), combination valsartan/hydrochlorothiazide (HCTZ) (160/12.5 mg QD), or HCTZ monotherapy (12.5 mg QD), with titration to valsartan 320 mg/d, valsartan/HCTZ 320/25 mg/d, and HCTZ 25 mg/d at week 2.

Anthropometric and BP Measurements

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Waist circumference was measured to the nearest 0.5 in, by placing the measuring tape snugly (but not compressing the skin) around the abdomen at the level of the umbilicus just above the uppermost lateral border of the right iliac crest and at normal minimal respiration with the patient in standing position and his/her hands by the side.

BP was measured in triplicate (at 1- to 2-minute intervals) at each visit with the use of a standard calibrated measuring device (mercury sphygmomanometer, aneroid sphygmomanometer, or a digital device using an appropriate-size cuff) with the patient seated after 5 minutes of rest. The mean of these readings was used for the visit measurement.

Laboratory Measurements

Prior to randomization, duplicate blood samples were collected for fasting plasma glucose and insulin, plasma aldosterone, hsCRP, interleukin 6 (IL-6), adiponectin, tumor necrosis factor α (TNF-α), and leptin. Urine samples were collected for the analysis of F_2-isoprostane 8-iso-prostaglandin ($F_{2\alpha}$-isoprostane). The baseline HOMA-IR value was calculated from the mean of 2 measurements conducted 2 weeks prior to randomization (week –2) and on the day of randomization (week 0). Blood samples were collected after 12 and 16 weeks of double-blind therapy for the analysis of fasting plasma glucose, insulin, and lipid levels and for the calculation of HOMA-IR at the end of the study. Blood and urine samples were collected at the final visit (week 16) for biomarker analysis and for measurement of hemoglobin A_{1c} (HbA_{1c}) and serum electrolytes.

Biochemical and Hormonal Assay

Serum insulin was measured by radioimmunoassay (RIA) (Immulite; Diagnostic Products Corporation, Los Angeles, CA), and plasma glucose was determined by the hexokinase method (Roche Diagnostics, Indianapolis, IN). Free fatty acids were measured enzymatically using Wako reagents on an automated chemistry analyzer (Roche Diagnostics). Aldosterone was measured by RIA (Coat-a-Count; Diagnostic Products Corporation). Serum levels of hsCRP were measured by immunoturbidimetry (Roche Diagnostics). IL-6 and plasma adiponectin were assayed using a commercially available enzyme immunoassay (EIA) microtiter plate (Quantikine; R&D Systems, Minneapolis, MN). Urinary excretion of the $F_{2\alpha}$-isoprostane was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Oxford Biomedical Research, Oxford, MI) and normalized by urinary creatinine concentration. Plasma TNF-α was measured using a quantitative sandwich

EIA kit (Quantikine; R&D Systems). Leptin was measured by an ELISA kit (Diagnostic Systems Laboratories Inc., Webster, TX).

Clinical End Points

The primary efficacy variable was the change in HOMA-IR value from baseline to study end point (week 16). The secondary objectives of this study were to evaluate the change from baseline to study end point in fasting plasma glucose and insulin, TG, nonesterified free fatty acid, and inflammatory and metabolic biomarker (ie, aldosterone, hsCRP, IL-6, $F_{2\alpha}$-isoprostane, adiponectin, TNF-α, leptin) levels in each treatment arm.

Statistical Analysis

A sample size of 507 patients randomized in a 1:1:1 ratio was required to ensure that the study had approximate 80% power to detect a between–treatment group (valsartan/HCTZ combination therapy vs HCTZ monotherapy) difference and 98% power when comparing valsartan vs HCTZ monotherapy using a 2-sided 5% significance level. A blinded pooled interim review of HOMA-IR showed a much higher variation than was originally assumed. Given the skewed distribution of the data, values were log-transformed before being submitted to statistical analysis.

Efficacy analyses were conducted for the intent-to-treat (ITT) population, which consisted of all randomized patients who received trial mediation and provided baseline efficacy data and had $\geq$1 postbaseline efficacy measure. Study end point was defined as the week-16 assessment, applying last observation carried forward to account for missing data. The baseline value for HOMA-IR was calculated from the mean of the available data obtained at 2 weeks prior to randomization (week 2) and the randomization visit (week 0). Baseline fasting values for glucose, insulin, HbA_{1c}, lipids, and all biomarkers was defined as the last value up to and including the day of randomization. HOMA-IR was calculated as a function of fasting plasma glucose and insulin: HOMA-IR=[fasting insulin (μU/mL)]$\times$[fasting plasma glucose (mmol/L)]/22.5, according to the method of Haffner and associates.[12]

The change from baseline to study end point in log HOMA-IR was analyzed using ANCOVA with treatment, center (pooled) as factors, and log baseline value as covariate. Model estimates were back-transformed, and the ratio of least-square means was calculated with 95% confidence interval and *P* value. A hierarchical testing procedure was used. Valsartan vs HCTZ was tested at a .05 significance level. If significant, then a second test was performed at the 2-sided .05 significance level comparing valsartan/HCTZ combination therapy vs HCTZ monotherapy. The logarithmic transformation of the secondary result for specific biomarkers (eg, hsCRP, IL-6, $F_{2\alpha}$-isoprostane, adiponectin, and TNF-α) were calculated and analyzed for each variable because of their skewed distribution. BP control, defined as values $<$140/90 mm Hg and $<$130/80 mm Hg, was analyzed by logistic regression including treatment, center (pooled), and baseline systolic and diastolic BP in the model. Furthermore, post hoc analyses were performed to evaluate treatment differences in BP reduction in patients with moderate obesity (waist circumference $\leq$44 in) and severe obesity (waist circumference $>$44 in); only descriptive statistics were used to identify patterns of association, since these analyses were not inferential in nature.

RESULTS

A total of 855 patients were enrolled into the single-blind period, with 566 (66.2%), meeting the prespecified eligibility criteria of cardiometabolic syndrome randomized into the double-blind period, of whom 530 (93.6%) were included in the ITT population (Figure 2). Four-hundred eighty patients completed the study, and adverse events (AEs) were the primary reason for discontinuation from the study (38%; 33/86). Baseline demographic characteristics were similar in the 3 treatment groups, with a mean systolic BP/diastolic BP of 142$\pm$9/91.3$\pm$5 mm Hg and a mean waist circumference of 44.6$\pm$5 in in the entire study group (Table I). The average age of randomized patients was 49.6 years; the majority were female (60.2%) and Caucasian (78.1%). Prior to the start of the single-blind run-in period, 430 patients (76%) were hypertensive (BP $>$140/90 mm Hg) and 195 patients (34%) were previously on antihypertensive medications. Antihypertensive agents used were angiotensin-converting enzyme (ACE) inhibitors (11%), ARBs (8%), β-blockers (9%), calcium channel blockers (7%), and diuretics (1%).

Efficacy Outcomes

There was a non–statistically significant ($P>.05$) increase in HOMA-IR value from baseline to study end point in all 3 treatment groups, with a slightly higher increase observed in the HCTZ monotherapy group (Table II). In contrast, fasting HbA_{1c} levels increased significantly ($P<.05$) from baseline to the end of the study in patients in the HCTZ

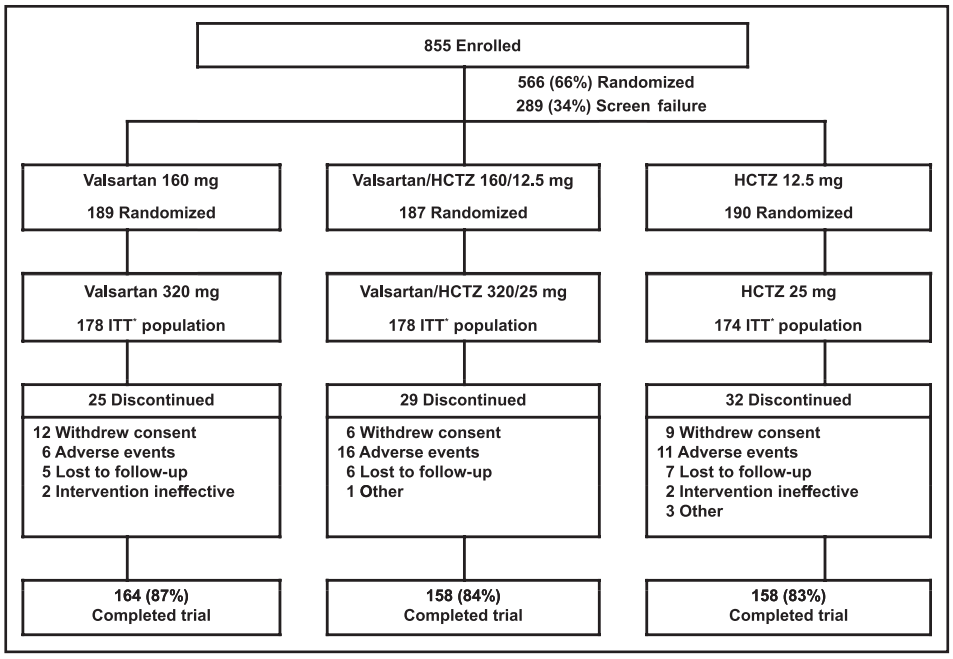

*Figure 2. Patient disposition. *The intent-to-treat (ITT) population included all randomized patients who received the randomized study drug, provided baseline efficacy data, and had at ≥1 postbaseline efficacy assessment of the primary variable.*

Table I. Baseline Demographics of All Randomized Patients

	Valsartan 320 mg	Valsartan/ HCTZ 320/25 mg	HCTZ 25 mg
No. of patients	189	187	190
Age, y[a]	50.0±11	50.2±11	48.8±11
Female, n (%)	118 (62)	112 (60)	111 (58)
Race, No. (%)			
Caucasian	154 (82)	142 (76)	146 (77)
Hispanic	19 (10)	24 (13)	22 (12)
African American	15 (8)	17 (9)	20 (11)
Other	1 (0.5)	4 (2)	2 (1)
Height, cm[a]	168.9±11	168.6±11	169.2±10
Weight, kg[a]	103.2±21	104.1±23	107.0±22
BMI, kg/m^2 [a]	36.2±7	36.4±7	37.4±7
Waist circumference,[b] in[a]	44.3±5	44.4±5	45.1±6
Systolic BP, mm Hg[a]	143.5±9	142.9±10	141.7±9
Diastolic BP, mm Hg[a]	91.5±5	91.1±5	91.4±5
LDL-C, mmol/L[a]	3.25±0.9	3.28±0.8	3.36±0.9
HDL-C, mmol/L[a]	1.23±0.3	1.19±0.3	1.20±0.3

Abbreviations: BMI, body mass index; BP, blood pressure; HCTZ, hydrochlorothiazide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. [a]Mean ± SD. [b]Waist circumference inclusion criteria for males and females was >40 in and >35 in, respectively.

treatment group (5.62%±0.5% to 5.82%±0.6%) as compared to patients treated with valsartan monotherapy (5.66%±0.5% to 5.75%±0.5%). Likewise, there was a 10% increase ($P<.05$) in fasting TGs from baseline to the end of the study in patients randomized to the HCTZ group vs patients in the valsartan arm (Table II).

HCTZ was associated with a lower ($P<.05$) serum potassium level (3.9±0.4 vs 4.26±0.4 mmol/L at baseline) compared to valsartan (4.2±0.3

Table II. HOMA-IR, Fasting Plasma Insulin, Glucose, HbA_{1c}, Triglycerides, and Free Fatty Acid Levels at Baseline and at End Point (Week 16)

	Valsartan 320 mg	Valsartan/HCTZ 320/25 mg	HCTZ 25 mg
HOMA-IR log (units), geometric mean ± SD			
Baseline	3.85±0.7	3.91±0.7	4.26±0.6
Week 16	4.14±0.8	4.23±0.6	4.73±0.7
Insulin (pmol/L), mean ± SD			
Baseline	132.5±98	138.4±178	141.3±111
Week 16	149.2±167	135.9±111	154.3±128
Glucose (mmol/L), mean ± SD			
Baseline	5.60±0.8	5.71±0.9	5.69±0.8
Week 16	5.77±0.9	5.82±1.3	5.91±0.9
HbA_{1c} (%), mean ± SD			
Baseline	5.66±0.5	5.67±0.6	5.63±0.5
Week 16	5.76±0.5	5.79±0.7	5.83±0.6[a]
Triglycerides (mmol/L), mean ± SD			
Baseline	2.0±0.04	1.9±0.04	1.9±0.04
Week 16	2.0±0.04	2.0±0.05	2.2±0.05[a]
Non-esterified free fatty acids (μmol/L), mean ± SD			
Baseline	525±538	480±483	486±500
Week 16	469±222	440±194	498±234

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; HCTZ, hydrochlorothiazide; HOMA-IR, homeostasis model assessment–insulin resistance index. [a]$P<.05$ vs valsartan.

Table III. Inflammatory and Metabolic Biomarker Levels at Baseline and at End Point (Week 16)

	Valsartan 320 mg	Valsartan/HCTZ 320/25 mg	HCTZ 25 mg
Aldosterone (ng/dL)			
Baseline	8.2±0.5	8.5±0.5	8.8±0.6
Week 16	7.4±0.4	11.1±0.5[a,b]	12.6±0.6[a,b]
hsCRP −log (mg/L)			
Baseline	3.9±8	4.3±9	3.5±7
Week 16	3.6±8	3.9±7	4.3±7[a,b,c]
IL-6 −log (ng/L)			
Baseline	2.2±2	2.2±3	2.1±2
Week 16	2.1±1	2.0±2	2.0±4
$F_{2\alpha}$-isoprostane −log (ng/mg)			
Baseline	1.0±1	0.9±1	1.0±1
Week 16	0.9±1	0.8±0.5	0.8±1
Adiponectin −log (ng/mL)			
Baseline	6.6±0.06	6.2±0.04	6.3±0.04
Week 16	6.5±0.05	6.2±0.04	5.8±0.04[a]
TNF-α −log (ng/L)			
Baseline	2.3±1	2.2±2	2.2±1
Week 16	2.1±1	2.2±1	2.1±1
Leptin (ng/mL)			
Baseline	84.5±62	89.7±60	89.0±59
Week 16	91.2±64	98.5±66	92.0±61

Abbreviations: HCTZ, hydrochlorothiazide; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor α. Values are mean ± SD. [a]$P<.05$ vs baseline. [b]$P<.05$ vs valsartan. [c]$P<.05$ vs valsartan/HCTZ.

vs 4.27±0.3 mmol/L at baseline). The serum potassium level in the valsartan/HCTZ combination treatment group was also reduced ($P<.05$) from baseline (4.05±0.4 vs 4.26±0.3 mmol/L at baseline). There were a total of 28 patients with hypokalemia (>20% decrease in serum potassium): 20

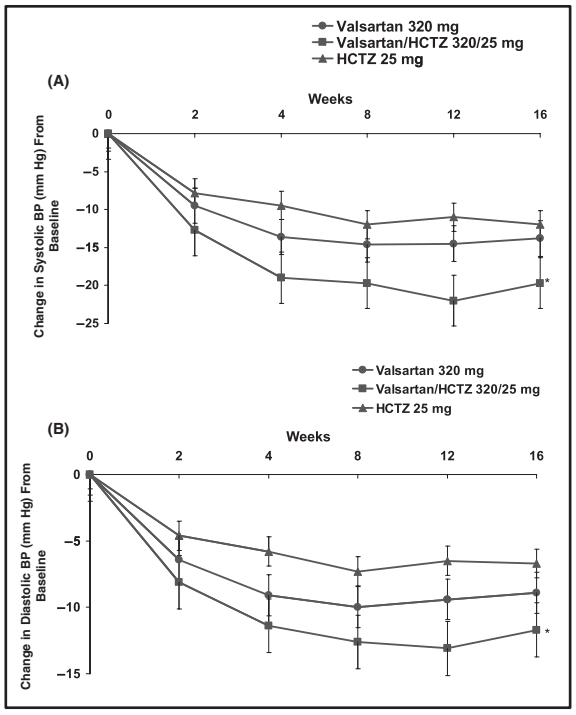

*Figure 3. (A) Change in mean systolic blood pressure from baseline during the study. (B) Change in mean diastolic blood pressure from baseline during the study. Results reported at week 16 are for last observation carried forward values. At week 16, reductions in BP were significantly larger (*P*<.0001) for combined valsartan/hydrochlorothiazide (HCTZ) 320/25 mg compared with valsartan 320 mg and HCTZ 25 mg monotherapy.*

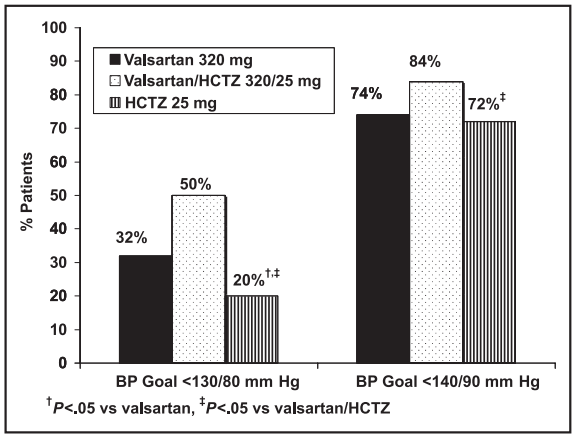

*Figure 4. Proportion of participants in whom the BP goals of <130/80 mm Hg and <140/90 mm Hg were reached at study end point (week 16). Significantly lower control rates were achieved in patients receiving hydrochlorothiazide (HCTZ) monotherapy (*P*<.05 vs valsartan; *P*<.05 vs valsartan/HCTZ).*

patients in the HCTZ treatment group, 6 patients in the valsartan/HCTZ combination group, and 2 in the valsartan group.

Aldosterone levels increased significantly from baseline to the end of the study in the valsartan/HCTZ and HCTZ treatment groups when compared with the valsartan treatment group (*P*<.05) (Table III). In the HCTZ treatment group, the hsCRP level was elevated by 16% (*P*<.05) from baseline levels to the end of study (4.3 vs 3.5 mg/L). In contrast, in patients treated with valsartan monotherapy or the valsartan/HCTZ combination, decreases in hsCRP levels by 9% and 5%, respectively, were observed from baseline levels to the end of the study. No change (*P*>.05) in IL-6, $F_{2\alpha}$-isoprostane, TNF-α, or leptin levels from baseline to week 16 was observed within any of the 3 treatment groups (Table III). Plasma adiponectin levels were significantly (*P*<.05) reduced at the end of the study compared to baseline in patients treated with HCTZ monotherapy (−0.5 ng/mL), but no changes were observed in patients receiving valsartan or valsartan/HCTZ combination therapy (Table III). There were no changes (*P*>.05) from baseline to the end of the study in the TNF-α and leptin biomarker levels within any of the 3 groups (Table III).

BP Efficacy

Patients randomized to valsartan/HCTZ combination therapy not unexpectedly showed greater reductions in BP (*P*<.0001) throughout and at the end of the study (mean systolic BP/diastolic BP change, −20/−12 mm Hg) when compared with the HCTZ (−12/−7 mm Hg) or valsartan (−14/−9 mm Hg) alone group (Figure 3A and Figure 3B). The BP target of <140/90 mm Hg was achieved in a significantly higher percentage of patients in the valsartan/HCTZ combination group (84% vs 72%, *P*=.002), and a more aggressive BP target of <130/80 mm Hg was reached in patients in that group (50% vs 20%, *P*<.0001) at the end of the study compared with patients in the HCTZ monotherapy group (Figure 4). The percentage of patients in valsartan group with a BP target of <140/90 mm Hg was similar to that in the HCTZ group (74% vs 72%); however, a BP target of <130/80 mm Hg was attained in 32% of valsartan patients (vs 20% HCTZ, *P*=.0017). Furthermore, when patients were stratified into 2 groups, moderate and severe abdominal obesity based on median waist circumference, HCTZ monotherapy was less effective in lowering systolic and diastolic BP than was valsartan monotherapy (−11/−6 vs −14/−9 mm Hg, respectively) in patients with severe abdominal obesity (median waist circumference >44 in, n=239). Of interest, in patients with

moderate abdominal obesity (median waist circumference ≤44 in, n=291), there was no difference in BP lowering between the HCTZ and the valsartan monotherapy groups (−14/−8 vs −14/−9 mm Hg, respectively). However, in both these groups, as with the findings for the entire population, the reduction in BP observed with combination valsartan/HCTZ was greater than with monotherapy (−19.3/−11.5 and −21/−12 mm Hg in the severely and moderately obese patients, respectively).

The overall incidence of AEs in patients during the double-blind phase was similar across the 3 treatment groups (~64% of patients reported an AE during the study). The most frequently reported AEs across all 3 treatment groups were dizziness (8.1%), headache (6.9%), and fatigue (5.5%). The valsartan/HCTZ group had the highest incidence of dizziness (10.7%) compared with the valsartan (6.9%) or HCTZ alone group (6.9%). The incidence of fatigue was also higher in the valsartan/HCTZ group (8.6%) compared with the valsartan (3.7%) or HCTZ alone group (4.2%). Headache was more common in the HCTZ group (11.6%) compared with in the valsartan (5.3%) or the valsartan/HCTZ group (3.7%).

DISCUSSION

Numerous studies have suggested that blockade of the RAAS with an ACE inhibitor or an ARB is an important therapeutic consideration to help delay the onset of diabetes in hypertensive patients.[7,13] In this study that evaluated the influence of RAAS blockade on insulin sensitivity in patients with the cardiometabolic syndrome in whom diabetes was likely to develop, we found that after 16 weeks of therapy there were no changes in insulin sensitivity in response to any of the 3 treatments: valsartan alone, HCTZ alone, or combined valsartan/HCTZ therapy. In this study, the dosage of valsartan used was 320 mg QD, the maximum approved dosage in the United States and Canada. The results are contrary to those of a previous study with valsartan (80 mg QD) that reported improvements in insulin sensitivity using HOMA-IR measurement in hypertensive patients.[14] Although generally believed to be the case, literature supporting RAAS blockade with an ACE inhibitor or ARB having a direct positive effect on measures of insulin sensitivity in prediabetic patients are limited. Our findings of the lack of an effect of an ARB, valsartan, to influence insulin sensitivity may have been due to insufficient time to develop, inactivation of the RAAS in some of the patients due to interpatient variability, or issues relating to the use of the HOMA-IR technique.

The use of the HOMA-IR technique to assess insulin sensitivity may not be the most sensitive indicator of improvements in insulin and glucose regulation. A large variation in fasting glucose and insulin values was observed in the present study of obese patients with the cardiometabolic syndrome. Perhaps the use of more specific and dynamic measures of insulin sensitivity (eg, hyperglycemic challenge or euglycemic hyperinsulinemic glucose clamp) may have helped to better examine the influence of RAAS blockade in prediabetic patients such as those we studied. In that regard, the recent results from the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study found reductions in glucose values in response to a hyperglycemic challenge after RAAS inhibition with ramipril, but it was not coupled with changes in fasting plasma glucose values.[15] Multiple studies have shown that RAAS blockade delays the onset of diabetes by preventing increases in fasting plasma glucose levels. Could it be that RAAS blockade may not have a direct positive effect on insulin sensitivity but rather works to prevent the worsening of hyperglycemia? This would suggest a different set of mechanisms related to the dynamic measure of insulin sensitivity (eg, peripheral adipose sensitivity to glucose) but not dependent on fasting measures of metabolic function (eg, hepatic insulin sensitivity).

The other interesting finding in this study was the lack of effect of HCTZ treatment on HOMA-IR. Previous studies comparing RAAS blockade to HCTZ therapy all showed worsening of the HOMA-IR index with HCTZ use.[16–18] The lack of an effect on fasting glucose and insulin values within the HCTZ group was opposed by nonfasting metabolic measures (eg, HbA_{1c} and TGs), which showed the typical negative effects associated with diuretic therapy. Patients receiving HCTZ also had higher reported incidences of hypokalemia. Hypokalemia may be an important factor eliciting the negative metabolic effects associated with diuretic therapy since it has been shown to reduce the pancreas's ability to secrete insulin and to worsen peripheral insulin sensitivity.[19,20] Other negative effects of HCTZ therapy, such as reduced lipoprotein lipase activity, may also explain some of the changes.[21] The failure of fasting glucose and insulin measures to detect metabolic changes with HCTZ in this patient population suggests that other tests, such as the oral glucose tolerance test, should be employed when comparing different antihypertensive therapies.

The elevation in plasma aldosterone in the HCTZ and valsartan/HCTZ groups is a classic

counterregulatory response to diuretic therapy. Despite the addition of valsartan to HCTZ, RAAS blockade was without a counterbalancing effect on plasma aldosterone levels, although valsartan monotherapy lowered aldosterone levels. It was interesting to note that despite no reduction in aldosterone levels, the reduction in plasma potassium was blunted in the valsartan/HCTZ group compared to HCTZ monotherapy. The disparate effects of valsartan and thiazide diuretic therapy on plasma aldosterone in this study may be one factor attributed to their differential metabolic effects.[22,23] As recently reviewed, there is emerging evidence that elevations in plasma aldosterone cause insulin resistance by increasing oxidative stress and inflammation in insulin-sensitive tissue.[22,23] Thus, the rise in plasma aldosterone levels with thiazide therapy may contribute to the increased propensity for new-onset diabetes with these drugs.[4] Among the mechanisms of metabolic adverse effects induced with diuretics, an increase in sympathetic activity with a consequent decrease in peripheral glucose utilization has also been reported.[19]

Of interest, HCTZ also raised plasma hsCRP values, but valsartan monotherapy lowered the levels. These results help to support the previous findings that found valsartan to lower hsCRP, while the combination of valsartan/HCTZ had a neutral effect.[24] The data from this study suggest that valsartan has an inhibitory effect and that HCTZ has a possible stimulatory effect on vascular inflammation to the extent that hsCRP levels reflect a direct inflammatory process. Aldosterone is known to have inflammatory effects and may have a modulating effect on the hsCRP response to these therapies, which may be relevant considering the rise in plasma aldosterone seen with HCTZ and valsartan/HCTZ therapies.[25] Plasma adiponectin, a measure of peripheral insulin sensitivity, was reduced by HCTZ in this study. Recently, diuretic therapy was found to be associated with a reduced adiponectin level, which may be due to its effect on carbohydrate metabolism or to a direct effect on adipose tissue function.[26]

Management of hypertension in obese patients with the cardiometabolic syndrome would appear to benefit most from diuretic therapy because of its effectiveness in essentially volume-dependent, low-renin hypertension. Diuretic therapy with HCTZ, however, did not reduce BP any more than valsartan monotherapy. In fact, there was a trend for BP reductions to be greater in patients receiving valsartan compared to HCTZ monotherapy, and this was most evident in the patients classified as having severe abdominal obesity (waist circumference >44 in). The reduced efficacy of HCTZ was also apparent in patients randomized to the combination of valsartan/HCTZ. Possible reasons for the reduced BP-lowering effect of HCTZ in severe obesity may be related to a number of factors, including poorer bioavailability of HCTZ (reduced absorption), reduced serum potassium levels (increased activation of the RAAS), and a lower effective plasma HCTZ concentration due to increased distribution space for the drug in the setting of significant obesity. Nonetheless, it appears that obesity is an important determinant of the BP-lowering response to HCTZ. Furthermore, the results suggest that HCTZ may have to be dosed higher (eg, $\geq$25 mg) in patients with severe obesity (grade III) to obtain the same clinical effect; thus, the use of HCTZ monotherapy as the initial agent of choice in obese hypertensive patients may not be ideal.

There is no specific BP target for prediabetic patients with the cardiometabolic syndrome, but it can be argued that these patients should be managed aggressively to a target of <130/80 mm Hg since the definition for hypertension in this high-risk patient population is a BP >130/85 mm Hg.[13] Approximately 24% of patients in this study had BP values <140/90 mm Hg at the baseline visit. When patients were evaluated for a BP control level of <130/80 mm Hg, valsartan/HCTZ was highly effective, with the goal reached in 50% of patients receiving this combination, whereas monotherapy with HCTZ only controlled 20% of patients' BP. It is recommended that combination therapy should be the initial approach in hypertensive patients with the cardiometabolic syndrome, as it will lead to earlier and greater reductions in systolic and diastolic BP without a significant increase in AEs.

CONCLUSIONS

The present data help to support more aggressive treatment strategies for the management of hypertension in prediabetic obese patients with the metabolic syndrome. The choice of which antihypertensive agent to use in patients susceptible to the development of diabetes is important to prevent worsening of the metabolic state and insulin resistance. In this study after 16 weeks of therapy, obese patients with the cardiometabolic syndrome reported greater reductions in BP with the combination of valsartan and HCTZ without any adverse metabolic effects when compared with valsartan monotherapy. In patients randomized to HCTZ therapy, there was a trend for reduced BP efficacy when compared with valsartan monotherapy. The

reduced antihypertensive response to HCTZ was more pronounced in patients with severe abdominal obesity. In light of the results of this study, it may be recommended that in hypertensive patients with severe obesity (grade III), HCTZ should not be used as first-line therapy, as recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, unless it is combined with another agent for further reductions in BP. In conclusion, results from this study support the initial use of combination antihypertensive therapy with an ARB and a diuretic for the management of hypertension in patients with the cardiometabolic syndrome, as it will help these patients reach their BP goals without worsening their metabolic status or burdening them with an excessive number of AEs.

Acknowledgments and disclosures: The authors wish to thank ***Kanaka Sridharan, MS, RPh****, and* ***Yogesh Mawal, PhD****, for their editorial assistance. This study was sponsored by Novartis Pharmaceuticals. DHZ is an employee at Novartis Pharmaceuticals Corporation, East Hanover, NJ. LK is an employee at Novartis Pharma AG, Basel, Switzerland, and provided statistical support for this study. JRS, WAH, SMH, PCD, VAF, and DAS are consultants for Novartis Pharmaceuticals Corporation, East Hanover, NJ.*

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