Published in final edited form as:

Am J Ther. 2013 January ; 20(1): 2–12. doi:10.1097/MJT.0b013e318230ae66.

Antihypertensive and Metabolic Effects of Angiotensin Receptor Blocker/Diuretic Combination Therapy in Obese, Hypertensive African American and Caucasian Patients

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Abstract

A clinical trial showed comparable blood pressure (BP) lowering by valsartan/hydrochlorothiazide and amlodipine/hydrochlorothiazide in obese hypertensives. Relative to amlodipine/hydrochlorothiazide, valsartan/hydrochlorothiazide reduced the hyperglycemic response to glucose challenge. An objective of this post-hoc analysis was to determine whether this benefit extended to African Americans and Caucasians. Treatments (valsartan/hydrochlorothiazide 160/12.5 mg force-titrated to valsartan/hydrochlorothiazide 320/25 mg at Week 4 or hydrochlorothiazide 12.5 mg force-titrated to hydrochlorothiazide 25 mg at Week 4 with amlodipine 5 mg and 10 mg added at Weeks 8 and 12, respectively) were administered once daily. Both treatments reduced clinic BP from baseline to all visits ($p < 0.0001$), regardless of race/ethnicity (126 African Americans, 212 Caucasians). In African Americans, there were no significant between-treatment differences in clinic or ambulatory BP lowering at Weeks 8 or 16. Caucasians responded better to valsartan/hydrochlorothiazide. In both racial/ethnic subgroups, the addition of valsartan but not amlodipine mitigated the hyperglycemic response to hydrochlorothiazide through enhanced insulin secretion. Valsartan/hydrochlorothiazide was as effective as amlodipine/hydrochlorothiazide in reducing BP in obese, hypertensive African Americans, and better than amlodipine/hydrochlorothiazide in Caucasians. In both racial/ethnic subgroups, addition of valsartan to hydrochlorothiazide reduced the negative metabolic effects associated with thiazide therapy.

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Conflicts of Interest: Author disclosures: Dr. Ofili has served as a consultant for Novartis Pharmaceuticals Corporation. Dr Ofili is also supported in part by the following research awards from the National Institutes of Health: PHS Grant UL1 RR025008, U54 RR026137, and 2R25RR017694-06A1 from the National Center for Research Resources (NCRR); and PHS Grant U01HL084891 from the National Heart Lung and Blood Institute. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of NCRR, NHLBI, or NIH. Drs. Zappe, Purkayastha, and Samuel are employees of Novartis Pharmaceuticals Corporation.

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Keywords

valsartan; hydrochlorothiazide; diuretic; prediabetic; obesity

Introduction

Distinct differences exist in cardiovascular and metabolic disease risk among racial/ethnic groups, including the prevalence of hypertension and diabetes. The most recent analysis of the National Health and Nutrition Examination Survey (1999–2004) data reported prevalence rates of hypertension and diabetes of approximately 40% and 15%, respectively, among African Americans compared with 27% and 6%, respectively, among Caucasians.¹ The higher prevalence rates of hypertension and diabetes among African Americans may be related, in part, to hereditary differences, environmental and dietary factors, as well as psychosocial stressors.^{2,3} African Americans also have a very high rate of uncontrolled hypertension (67%), despite increased awareness and treatment relative to Caucasians.¹ The management of hypertension in African Americans is further complicated by a higher prevalence of other risk factors such as obesity. Recent estimates indicate that 36% of African Americans are obese (vs 24% of Caucasians).⁴ Obesity is associated with more severe and treatment-resistant hypertension, which may be due, in part, to increased activation of the renin-angiotensin system (RAS).^{5,6}

Some evidence suggests that RAS inhibitors, when administered as monotherapy, may lower blood pressure (BP) less effectively in African Americans and obese hypertensive patients,⁷ and that African Americans may respond better to diuretics or calcium channel blockers (CCBs) than other antihypertensive classes.⁸ For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which included more than 10,000 African Americans, an angiotensin-converting enzyme (ACE) inhibitor was less effective than either a thiazide-type diuretic or a CCB.⁹ In the Blood Pressure-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA), a beta-blocker was less effective than a CCB.¹⁰ However, as noted in the recently updated International Society on Hypertension In Blacks (ISHIB) guidelines, the vast majority of African Americans will require multiple antihypertensive agents to achieve BP goals.¹¹ With the addition of an agent from an alternative/complementary antihypertensive class, the difference in treatment response to RAS blockade by race/ethnicity diminishes.^{11–15} A commonly recommended option for the treatment of hypertension is the use of a thiazide-type diuretic in combination with a RAS inhibitor or CCB,^{16,17} although a recent analysis of data from ASCOT-BPLA suggests that use of a RAS inhibitor as a second-line agent may not be an optimal treatment approach in African Americans.¹⁰ From a safety perspective, thiazide-type diuretics may be associated with adverse metabolic effects, particularly in patients with obesity or dysglycemia, whereas RAS inhibitors exert favorable metabolic effects and CCBs are generally regarded as metabolically neutral.^{18–22}

In the Valsartan and hydrochlorothiazide In hyperTensive Abdominally obEse patients (VITAE) trial²³ valsartan/hydrochlorothiazide and amlodipine/hydrochlorothiazide reduced BP to a similar extent in prediabetic, obese, hypertensive patients. However, of note, valsartan but not amlodipine attenuated the adverse metabolic effects of hydrochlorothiazide; patients treated with valsartan/hydrochlorothiazide had a reduced hyperglycemic response to glucose challenge relative to patients treated with amlodipine/hydrochlorothiazide.²³ Other studies have shown a significantly reduced risk of new-onset diabetes when valsartan was administered in combination with hydrochlorothiazide ($\pm$ other antihypertensive agents),²⁴ including in patients with impaired glucose tolerance.²⁵ These results are consistent with the metabolic profiles of these drug classes. This post-hoc

analysis of the VITAE trial reports clinic and ambulatory BP data, metabolic indices, and adverse events (AEs) for African American and Caucasian participants. Although the VITAE trial was not designed to compare these 2 racial/ethnic subgroups from a statistical perspective, our results provide some insight into addressing the question of whether the observed benefits of valsartan in reducing the negative metabolic effects of hydrochlorothiazide in the overall population extend to both African Americans and Caucasians.

Methods

The VITAE trial was a 16-week, double-blind, randomized, forced-titration study in nondiabetic patients with hypertension and abdominal obesity. The methods have been published elsewhere²³ and are briefly summarized here. This study was conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional review board at each site, and all patients provided informed written consent.

Patients

The study enrolled hypertensive outpatient men and women 40 years of age with central obesity (in men, waist circumference >40 in/102 cm; in women, >35 in/89 cm) and mean clinic sitting systolic BP (SBP) 150 mm Hg but <180 mm Hg and mean clinic sitting diastolic BP (DBP) <110 mm Hg.

Key exclusion criteria were: patients on more than 3 antihypertensive medications at the time of screening; patients unable to discontinue all prior antihypertensive medications safely during the washout phase; patients experiencing weight loss >10 pounds (4.5 kg) during the screening/washout phase; or documented history of Type 1 or 2 diabetes or fasting plasma glucose 126 mg/dL at screening. Other exclusion criteria included: history of pancreatic injury, pancreatitis, or impaired pancreatic function; life-threatening arrhythmia or symptomatic arrhythmia, chronic heart failure, or secondary hypertension; renal or hepatic disease, gout, malignancy, or severe autoimmune disease; and a serum potassium level <3.5 or >5.5 mEq/L at screening. Patients were also excluded if, within the month before screening, they had unstable angina pectoris or coronary artery disease requiring treatment with nitroglycerin or if, within the 6 months before screening, they had significant coronary artery disease or atherosclerotic vascular disease, stroke, transient ischemic attack, or myocardial infarction. Also excluded were female patients who were pregnant, nursing, or at risk of becoming pregnant.

Study Design

Eligible patients were randomized to either valsartan/hydrochlorothiazide 160/12.5 mg or hydrochlorothiazide 12.5 mg alone, following a washout phase of up to 4 weeks. At Week 4, doses were force-titrated to valsartan/hydrochlorothiazide 320/25 mg and hydrochlorothiazide 25 mg in their respective groups. At Weeks 8 and 12, patients in the valsartan/hydrochlorothiazide group remained at the same dose (320/25 mg), while patients in the hydrochlorothiazide group received add-on amlodipine 5 mg and 10 mg at Weeks 8 and 12, respectively. Thus, from the start of treatment through Week 8, patients received either combination therapy with valsartan/hydrochlorothiazide or monotherapy with hydrochlorothiazide. From Week 8 onwards, all patients received combination therapy (valsartan/hydrochlorothiazide or amlodipine/hydrochlorothiazide). Downward titration of study drug doses was not permitted. All medications were taken once daily at the same time each morning.

Blood Pressure Assessments

At baseline and every 4 weeks thereafter, BP was measured to the nearest millimeter of mercury using a sphygmomanometer and an arm cuff with dimensions adjusted according to arm circumference. The measurements were done at trough (ie, 24 hours after the last administration of the study drug) and with patients sitting for 5 minutes. BP was recorded 3 times, 2 minutes apart, and the average was used for analyses. The arm with the highest BP at enrollment was used for all subsequent measures.

Ambulatory BP measures were studied in a subset of patients. Twenty-four-hour ambulatory BP monitoring (ABPM) was conducted using a standard device (Model 90207, Spacelabs Healthcare, Issaquah, Washington, USA) at baseline, Week 8, and Week 16. Mean hourly ambulatory SBP and DBP were calculated for each patient at 1–24 postdosing hours. Each patient's postdosing hours (1–24) were determined relative to that patient's dosing time.

Metabolic Parameters

An oral glucose tolerance test (OGTT) was performed at baseline and Week 16 after an overnight fast to assess fasting and postprandial glucose and insulin levels. The insulinogenic index, an assessment of the insulin response relative to a glucose load, was also determined.²⁶ For the OGTT, plasma samples were measured at 0, 30, 60, 90, and 120 minutes after a 75-g glucose load, which was given in a fluid volume of 250–300 mL and orally consumed within a 5-minute period.

Adverse Events

All observed or volunteered AEs, including serious AEs, were recorded throughout the study period. Physical examinations were performed at screening, baseline, Week 4, Week 8, Week 12, and study end (Week 16 or discontinuation). Serum potassium was measured at baseline and study end.

Statistical Analysis

All results are summarized by race/ethnicity (African Americans, Caucasians) using the intent-to-treat (ITT) population. Descriptive and inferential analyses were performed for baseline demographics and for changes in BP and metabolic parameters. All statistical tests were conducted under a 2-sided alternative hypothesis, employing a significance level of 0.05. Baseline demographic characteristics were summarized and, within each racial/ethnic subgroup, a 2-sample t-test (continuous variables) or chi-squared test (categorical variables) was used to test for homogeneity between the 2 treatment groups.

To compare changes in BP and metabolic parameters between the 2 treatment groups within each racial/ethnic subgroup, an analysis of covariance (ANCOVA) was used with baseline assessment as a covariate and treatment as factor in the model. A t-test was used to assess the significance of within treatment changes from baseline. A last-observation-carried-forward approach was used for the BP analysis. The proportion of patients achieving goal BP (<140/90 mm Hg) at Weeks 8 and 16 was evaluated using the Cochran-Mantel-Haenszel test for treatment differences adjusting for pooled center.

Results

Baseline Characteristics

Demographic and clinical characteristics are shown by race/ethnicity and treatment group in Table 1. A total of 126 African Americans and 212 Caucasians were included in the analysis. At baseline, African Americans had a mean age of approximately 53 years, 78%

were women, 67% were normoglycemic (fasting plasma glucose <100 mg/dL), 63% had cardiometabolic syndrome (see definition in Table 1), and most were obese (mean body mass index [BMI], 37 kg/m²); mean sitting systolic blood pressure (MSSBP)/mean sitting diastolic blood pressure (MSDBP) was 160/95 mm Hg. In the Caucasian subgroup, mean age was about 58 years, 61% were women, 62% were normoglycemic, 75% had cardiometabolic syndrome, and mean BMI was 35 kg/m²; MSSBP/MSDBP was 160/94 mm Hg. Within each racial/ethnic subgroup, the only significant difference ($p<0.05$) between the 2 treatment groups was for gender among Caucasians (more men and fewer women were initially randomized to valsartan/hydrochlorothiazide compared with hydrochlorothiazide).

ABPM was available for 33 African Americans and 57 Caucasians (Table 1); mean 24-hour ambulatory SBP/DBP was 144/87 mm Hg in African Americans and 141/84 mm Hg in Caucasians.

Clinic Blood Pressure

Clinic MSSBP and MSDBP values are shown by race/ethnicity and treatment group over the course of the study in Figure 1. For both MSSBP and MSDBP, significant ($p<0.0001$) mean reductions from baseline to all study visits were observed within each of the treatment groups, regardless of race/ethnicity. In African Americans, the least-squares mean $\pm$ standard error (SE) reduction in MSSBP from baseline to Week 8 (ie, prior to the addition of amlodipine in the hydrochlorothiazide group) was comparable in the valsartan/hydrochlorothiazide and hydrochlorothiazide groups (-25.0 ± 2.0 vs -21.6 ± 2.0 mm Hg; $p=0.25$). Similarly, no significant difference was observed between reductions in valsartan/hydrochlorothiazide versus amlodipine/hydrochlorothiazide at Week 16 (-27.8 ± 2.0 vs -29.3 ± 2.0 mm Hg; $p=0.59$). In Caucasians, the least-squares mean $\pm$ SE reduction in MSSBP from baseline favored valsartan/hydrochlorothiazide versus hydrochlorothiazide at Week 8 (-31.6 ± 1.3 vs -22.1 ± 1.3 mm Hg; $p<0.0001$) and valsartan/hydrochlorothiazide versus amlodipine/hydrochlorothiazide at Week 16 (-33.0 ± 1.3 vs -29.0 ± 1.3 mm Hg; $p=0.027$). Among patients treated with valsartan/hydrochlorothiazide, MSSBP and MSDBP reductions from baseline to Week 16 were numerically greater in Caucasians than African Americans; whereas among patients treated with amlodipine/hydrochlorothiazide, the reductions were similar in both racial/ethnic subgroups (Figure 1).

Ambulatory Blood Pressure

ABPM results support the clinic BP findings. ABPM was conducted in a subset of patients (33 African Americans, 57 Caucasians). In African Americans, mean $\pm$ SE reductions from baseline in 24-hour mean ambulatory SBP/DBP were similar in the valsartan/hydrochlorothiazide and hydrochlorothiazide groups at Week 8 ($-15.0\pm4.6/-9.7\pm3.6$ mm Hg vs $-10.4\pm3.7/-6.4\pm3.0$ mm Hg; $p=0.53/p=0.38$) and valsartan/hydrochlorothiazide and amlodipine/hydrochlorothiazide groups at Week 16 (Figure 2). In Caucasians, the mean $\pm$ SE reductions from baseline in 24-hour ambulatory SBP/DBP were significantly greater with valsartan/hydrochlorothiazide versus hydrochlorothiazide at Week 8 ($-19.1\pm2.2/-9.5\pm1.3$ mm Hg vs $-3.5\pm1.9/-1.3\pm1.1$ mm Hg; $p<0.0001$) and with valsartan/hydrochlorothiazide versus amlodipine/hydrochlorothiazide at Week 16 (Figure 2). Among patients treated with valsartan/hydrochlorothiazide, ambulatory BP reductions from baseline to Week 16 were slightly greater in Caucasians than African Americans; whereas among patients treated with amlodipine/hydrochlorothiazide, the reductions tended to be numerically greater in African Americans than Caucasians.

Blood Pressure Goal

Clinic BP goal (<140/90 mm Hg) results were consistent with the above findings. The proportion of African Americans achieving the clinic BP goal was not significantly different

between valsartan/hydrochlorothiazide versus hydrochlorothiazide at Week 8 (60.0% vs 55.6%; $p=0.64$) or between valsartan/hydrochlorothiazide versus amlodipine/hydrochlorothiazide at Week 16 (67.3% vs 80.4%; $p=0.13$). The proportion of Caucasians achieving the same clinic BP goal was significantly greater with valsartan/hydrochlorothiazide versus hydrochlorothiazide at Week 8 (79.3% vs 52.5%; $p<0.0001$); no significant difference was seen between valsartan/hydrochlorothiazide versus amlodipine/hydrochlorothiazide at Week 16 (76.7% vs 78.8%; $p=0.75$).

Metabolic Parameters

Changes from baseline to end of study in fasting plasma glucose and insulin levels are shown in Table 2. In African Americans, the only significant finding was that the increase in fasting plasma glucose level was 5.8-mg/dL greater in the amlodipine/hydrochlorothiazide group than in the valsartan/hydrochlorothiazide group ($p=0.049$ for least-squares mean difference). In Caucasians, the mean fasting insulin level in the amlodipine/hydrochlorothiazide group increased by 4.4 uU/mL from baseline to end of study ($p=0.040$). No other significant findings were observed in either racial/ethnic subgroup (Table 2).

Mean postprandial glucose and insulin levels after OGTT are shown in Figure 3A and 3B, respectively. In African Americans and Caucasians, mean postprandial glucose levels after OGTT increased more from baseline in patients receiving amlodipine/hydrochlorothiazide compared with those receiving valsartan/hydrochlorothiazide, with some of the between-treatment group differences being statistically significant ($p<0.05$) (Figure 3A). The reduced hyperglycemic response associated with valsartan/hydrochlorothiazide therapy was due to an early increase in postprandial insulin levels in both racial/ethnic subgroups (Figure 3B).

The early insulin response, as reflected by insulinogenic index, was similar in both racial/ethnic subgroups. At 30 minutes, there was a greater mean increase in insulinogenic index from baseline in the valsartan/hydrochlorothiazide group ($0.7\text{--}0.9$ [$\mu\text{U/mL}$]/[mg/dL] across racial/ethnic subgroups) than in the amlodipine/hydrochlorothiazide group ($0.1\text{--}0.2$ [$\mu\text{U/mL}$]/[mg/dL]). In both racial/ethnic subgroups, the results were consistent with those observed in the overall population.

Adverse Events

All patients who received at least 1 dose of the study medication were included in the safety analysis. Throughout the entire study, AEs were experienced by 42.1% of African Americans. The most frequent AEs in this racial/ethnic subgroup (5% in either treatment group) were upper respiratory tract infection (1.5% valsartan/hydrochlorothiazide, 8.5% amlodipine/hydrochlorothiazide), peripheral edema (3.0%, 6.8%), and constipation (0%, 5.1%). AEs were reported by 50.0% of Caucasians during the study, the most common of which were peripheral edema (1.0% valsartan/hydrochlorothiazide, 14.7% amlodipine/hydrochlorothiazide), upper respiratory tract infection (2.9%, 7.3%), dizziness (6.8%, 0.9%), fatigue (5.8%, 3.7%), and rash (2.9%, 5.5%). The only reports of hypokalemia ($>20\%$ decrease) occurred in 4 (3.7%) Caucasians treated with amlodipine/hydrochlorothiazide.

Discussion

In this post-hoc analysis of VITAE, the BP-lowering effect of combination valsartan/hydrochlorothiazide was similar to that of amlodipine/hydrochlorothiazide in prediabetic, obese, hypertensive African Americans, with both regimens producing significant ($p<0.0001$) reductions in MSSBP/MSDBP from baseline to all time points and high rates of BP control ($<140/90$ mm Hg) at Week 16. Both treatments significantly ($p<0.001$) reduced 24-hour ambulatory SBP/DBP from baseline to Week 16 in the subset of African Americans

in whom ABPM was performed. We did not perform any statistical testing for racial/ethnic differences because our study was not designed to make such comparisons. However, whereas the antihypertensive effects (both clinic and ABPM) of valsartan/hydrochlorothiazide and amlodipine/hydrochlorothiazide were similar in African Americans, valsartan/hydrochlorothiazide provided significantly better BP-lowering efficacy than amlodipine/hydrochlorothiazide in Caucasians. The superiority of an angiotensin receptor blocker (ARB)/hydrochlorothiazide combination over amlodipine/hydrochlorothiazide was previously shown in ABPM studies involving predominantly Caucasian hypertensive populations.^{27,28} Despite the apparent reduced BP benefit of valsartan/hydrochlorothiazide in African Americans versus Caucasians in our study, the addition of valsartan was similarly able to lessen the hyperglycemic response to hydrochlorothiazide in both racial/ethnic subgroups through enhanced insulin secretion. Amlodipine had no such effect. Sowers and colleagues previously reported this observation for the overall population.²³

The widespread use of RAS inhibitors in African Americans has been impeded by evidence of smaller BP reductions when used as monotherapy or in the absence of a diuretic in African Americans versus Caucasians in some studies.²⁹ However, the importance of racial/ethnic differences in BP response to RAS inhibitor monotherapy are of questionable significance, particularly in light of the common need for combination therapy to achieve BP goal in this population. For example, to achieve BP target (mean arterial pressure 102 to 107 mm Hg or <92 mm Hg) in the African American Study of Kidney Disease and Hypertension (AASK), an average of 3 antihypertensive agents were required.³⁰ Current treatment guidelines^{11,17} acknowledge that the addition of antihypertensives such as diuretics or CCBs to RAS inhibitor therapy can help lessen or eliminate racial/ethnic disparities in BP-lowering effects. In our post-hoc analysis, the use of a diuretic with an ARB was effective in controlling BP in African Americans, although our data suggest that this combination may not have entirely negated racial/ethnic differences. Of note, as per the recently updated ISHIB consensus statement,¹¹ the combination of a RAS inhibitor plus diuretic is one of the preferred options for the treatment of African Americans whose BP is >15/10 mm Hg above target.¹¹ Our study population was representative of the general hypertensive population, although African Americans in our study did not have higher baseline MSSBP values relative to Caucasians. The younger age of African Americans versus Caucasians (~5 years) may have contributed to this finding.

Hypertension rarely exists in isolation, and is often observed with a constellation of other risk factors such as obesity, dyslipidemia, diabetes and renal disease, thus dramatically increasing the risk of cardiovascular events.³¹ Therefore, the potential beneficial and harmful effects of selected antihypertensive therapies on concomitant cardiovascular, renal, and metabolic conditions must be considered in concert with traditional concerns (eg, likelihood of drug interactions, patient's individual risk profile, ability to access medication, and race/ethnicity).³² The Seventh Report of the Joint National Committee (JNC 7) guidelines describe compelling indications for various antihypertensive agents¹⁷ and the recently updated ISHIB consensus statement¹¹ provide specific recommendations regarding advantages and disadvantages of antihypertensive classes in African Americans. These latter guidelines report that the benefits of RAS inhibitors in patients with a variety of comorbidities (eg, renal disease, diabetes, and congestive heart failure) extend to African Americans. Thus, RAS inhibitor combinations are appropriate for high-risk patients such as those enrolled in VITAE.

Recent re-evaluation of the ALLHAT study (N=42,418 high-risk hypertensives; 15,094 of whom were black)³³ has re-emphasized the use of diuretics as first-line therapy, despite the potential for negative metabolic effects. In ALLHAT, 11.6% of the chlorthalidone group

developed levels of fasting glucose consistent with diabetes mellitus (≥ 125 mg/dL) after 4 years. This represented a significantly greater proportion of patients compared with the amlodipine (9.8%; $p=0.01$) and lisinopril groups (7.8%; $p<0.001$). The positive metabolic effects of valsartan in our study are consistent with results from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE)²⁴ and Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trials.²⁵ In VALUE, a 23% higher risk ($p<0.0001$) of new-onset diabetes was reported for amlodipine-based therapy ($\pm$ hydrochlorothiazide and additional antihypertensives if needed) versus valsartan-based therapy ($\pm$ hydrochlorothiazide and additional antihypertensives if needed) in hypertensive patients at high cardiovascular risk.²⁴ In NAVIGATOR, the administration of valsartan in combination with other antihypertensive agents, including hydrochlorothiazide in about one third of patients, reduced the risk of new-onset diabetes by 14% over non-ARB therapy ($p<0.001$) in patients with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors.²⁵ Further, meta-analysis of data from 13 randomized, controlled trials demonstrated the protective effect of RAS inhibitors on the development of new-onset diabetes (26% reduction vs placebo or other agents [$p<0.001$]).³⁴ Thus, certain antihypertensive agents may be prodiabetic versus protective, making the selection of combination antihypertensive therapy very important, particularly in high-risk patients (eg, those who are obese, prediabetic, and/or have the cardiometabolic syndrome), regardless of race/ethnicity. The use of valsartan in combination with a diuretic in African Americans (and Caucasians) requiring initiation of therapy with 2 agents has the potential to mitigate the negative metabolic effects of diuretic therapy.

As mentioned earlier, our study was not designed to compare racial/ethnic differences in antihypertensive efficacy, metabolic parameters, or AE rates and thus no definitive conclusions can be made in this regard. Interpretation of our results is also limited by the short study duration (16 weeks), which did not allow monitoring for development of diabetes. Nevertheless, the metabolic data do show a protective effect of valsartan when added to a diuretic. It should be noted that amlodipine was only added to hydrochlorothiazide at Week 8 and the full dose (10 mg) was only administered for 4 weeks (ie, Weeks 12 to 16). The duration of this combination/dose was likely adequate to accurately reflect its BP-lowering effect, as it was previously shown to plateau at 4 weeks.³⁵

Conclusions

Valsartan/hydrochlorothiazide was as effective as amlodipine/hydrochlorothiazide in reducing BP in obese, hypertensive African Americans, and better than amlodipine/hydrochlorothiazide in Caucasians. In both racial/ethnic subgroups, addition of valsartan to hydrochlorothiazide reduced the negative metabolic effects associated with thiazide therapy.

Acknowledgments

The authors wish to thank Michael S. McNamara, MS, of Oxford PharmaGenesis, Inc., for editorial and writing assistance, funding for which was provided by Novartis Pharmaceuticals Corporation. The manuscript was drafted under the guidance of the lead author, Dr. Ofili. All authors reviewed and revised the draft and have approved the final version of the manuscript submitted for publication. The authors also wish to express their appreciation to Priscilla Igbo-Pemu, MD, of Morehouse School of Medicine for critical review of the manuscript and Susan Ritter, MS, of Novartis Pharmaceuticals Corporation for expert assistance in project management (ClinicalTrials.gov identifier: NCT00439738).

Source of Funding: Dr. Sowers has NIH and VA funding and has served as a consultant for Novartis Pharmaceuticals Corporation and Forest Pharmaceuticals. Research funding grants were provided to University of Missouri by Novartis Pharmaceuticals Corporation and Forest Pharmaceuticals.

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Figure 1.

Clinic mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) values throughout the study (last observation carried forward) by racial/ethnic and treatment group. Error bars represent standard error. HCTZ=hydrochlorothiazide; V=valsartan.

Figure 2.

Mean change from baseline to Week 16 (last observation carried forward) in 24-hour ambulatory blood pressure by racial/ethnic and treatment group. Error bars represent standard error. HCTZ=hydrochlorothiazide; MADBP=mean ambulatory diastolic blood pressure; MASBP=mean ambulatory systolic blood pressure; V=valsartan.

Figure 3.

Mean postprandial glucose (A) and insulin (B) at baseline and end of study after a 2-hour oral glucose tolerance test by racial/ethnic and treatment group. HCTZ=hydrochlorothiazide; V=valsartan.

Table 1
Demographic and clinical characteristics at baseline according to self-identified racial/ethnic and treatment group

	African Americans		Caucasians	
	V/HCTZ (n=67)	HCTZ* (n=59)	V/HCTZ (n=103)	HCTZ* (n=109)
Age, y				
Mean±SD	52.7±7.2	53.4±8.8	58.7±9.2	57.2±8.1
Range	40–69	41–82	40–85	40–78
<65, n (%)	63 (94)	54 (92)	77 (75)	90 (83)
65, n (%)	4 (6)	5 (8)	26 (25)	19 (17)
Sex, n (%)				
Men	17 (25)	11 (19)	47 (46)	35 (32)
Women	50 (75)	48 (81)	56 (54)	74 (68)
Prior antihypertensive medication, n (%) [†]	48 (72)	39 (66)	72 (70)	81 (74)
Diabetes status, n (%)				
Normoglycemia [‡]	47 (70)	37 (63)	66 (64)	65 (60)
IFG/prediabetes [§]	19 (28)	17 (29)	33 (32)	38 (35)
Diabetes	1 (1)	5 (8)	4 (4)	6 (6)
Cardiometabolic syndrome, [¶] n (%)	40 (60)	40 (68)	73 (71)	85 (78)
Mean±SD eGFR, mL/min/1.73 m ²	75.9±13.6	73.2±12.3	68.8±12.4	71.8±13.0
Mean±SD BMI, kg/m ²	35.9±7.0	37.3±7.7	34.9±6.8	35.1±7.6
Mean±SD waist circumference, cm	109.5±12.4	112.6±17.6	111.4±14.1	109.1±15.7
Mean±SD FPG, mg/dL	95.5±12.9 (n=67)	99.2±19.7 (n=58)	98.4±15.1 (n=103)	98.9±15.6 (n=108)
Mean±SD fasting insulin, uU/mL	23.6±32.3 (n=64)	20.0±19.5 (n=57)	17.8±14.4 (n=102)	17.3±13.8 (n=103)
Mean±SD LDL-C, mg/dL	109.1±29.7 (n=67)	109.0±29.5 (n=58)	105.8±26.5 (n=101)	115.7±33.5 (n=109)
Mean±SD HDL-C, mg/dL	55.1±14.1 (n=67)	51.4±11.8 (n=58)	49.8±13.8 (n=103)	50.5±12.2 (n=109)
Mean±SD triglycerides, mg/dL	103.2±41.3	116.4±60.6	157.2±98.3	152.9±61.7
Mean±SD MSSBP, mm Hg	159.6±8.4	159.6±7.8	159.9±7.8	159.7±7.9
Mean±SD MSDBP, mm Hg	96.1±6.5	94.6±8.8	94.6±8.2	93.3±8.2
Mean±SD 24-h ASBP, mm Hg	144.5±15.0 (n=19)	143.6±8.6 (n=14)	143.6±13.6 (n=33)	139.1±12.1 (n=24)
Mean±SD 24-h ADBP, mm Hg	85.7±11.4 (n=19)	87.3±7.0 (n=14)	85.6±10.0 (n=33)	82.9±8.2 (n=24)

ADBP=ambulatory diastolic blood pressure; ASBP=ambulatory systolic blood pressure; BMI=body mass index; BP=blood pressure; eGFR=estimated glomerular filtration rate; FPG=fasting plasma glucose; HCTZ=hydrochlorothiazide; HDL-C=high-density lipoprotein cholesterol; IFG=impaired fasting glucose; LDL-C=low-density lipoprotein cholesterol; MSDBP=mean sitting diastolic blood pressure; MSSBP=mean sitting systolic blood pressure; SD=standard deviation; V=valsartan.

Note: the only statistically significant difference between treatment groups (within each race subgroup) was for the sex distribution among Caucasians (p=0.043); ambulatory BP data were not compared statistically due to the limited sample sizes.

* Patients received amlodipine starting at Week 8.

[†] Use of antihypertensive medication during the 30 days prior to screening.

[‡] Fasting plasma glucose <100 mg/dL at baseline.

[§] Fasting plasma glucose <126 mg/dL and <100 mg/dL at baseline.

// Fasting plasma glucose 126 mg/dL at baseline.

¶ One or more of the following 3 criteria: FPG 100 mg/dL, HDL-C <40 mg/dL in men or <50 mg/dL in women, and fasting triglycerides 150 mg/dL.

Table 2
Change from baseline to EOS in metabolic measures by race/ethnicity and treatment group

	African American		Caucasian	
	V/HCTZ	HCTZ*	V/HCTZ	HCTZ*
Fasting plasma glucose				
Change from baseline to EOS, mg/dL	n=51	n=51	n=92	n=97
Mean±SD	0.9±12.0	4.4±19.3	−0.3±15.1	1.8±15.6
Median (range)	1.0 (−37–36)	5.0 (−73–64)	0.0 (−66–36)	3.0 (−73–55)
LS mean difference (95% CI)	−5.8 (−11.5, 0.0); p=0.049		−2.3 (−5.9, 1.2); p=0.19	
Fasting insulin				
Change from baseline to EOS, uU/mL	n=48	n=49	n=91	n=91
Mean±SD	6.2±46.4	2.6±18.8	2.9±17.4	4.4±20.1 [†]
Median (range)	1.95 (−105.8–226.0)	3.9 (−63.8–48.4)	2.0 (−92.0–100.5)	2.3 (−111.7–69.8)
LS mean difference (95% CI)	5.5 (−6.7, 17.7); p=0.37		−1.3 (−6.1, 3.4); p=0.59	

CI=confidence interval; EOS=end of study; HCTZ=hydrochlorothiazide; LS=least squares; SD=standard deviation; V=valsartan.

* Patients received amlodipine starting at Week 8.

[†] p=0.040 vs baseline.