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Moderate versus intensive treatment of hypertension using amlodipine/valsartan and with the addition of hydrochlorothiazide for patients uncontrolled on angiotensin receptor blocker monotherapy: results in racial/ethnic subgroups

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Abstract

Combination therapy may reduce racial/ethnic differences in response to antihypertensives. In this post-hoc analysis, we evaluated treatment response by race/ethnicity among hypertensive adults enrolled in a 12-week, double-blind study in which patients previously uncontrolled (mean sitting systolic blood pressure [MSSBP] 150 and <200 mm Hg) on angiotensin receptor blocker (ARB) monotherapy (other than valsartan) for 28 days or more (n = 728) were randomized to amlodipine/valsartan 10/320 mg (intensive) or 5/160 mg (moderate). Treatment-naïve patients (in previous 28 days) or those who failed on a non-ARB first underwent a 28-day run-in period with olmesartan 20 mg or 40 mg, respectively. Hydrochlorothiazide (HCTZ) 12.5 mg was added to both arms at week 4; optional up-titration to 25 mg at week 8 (if MSSBP >140 mm Hg). Intensive treatment provided greater BP lowering versus moderate treatment throughout the study, regardless of race/ethnicity (474 white, 198 African American, 165 Hispanic individuals). Least-square mean reductions from baseline to week 4 in MSSBP (primary outcome) ranged from 20.4 to 23.5 mm

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Hg (intensive) versus 17.5 to 19.0 mm Hg (moderate), across racial/ethnic subgroups. Both regimens were well tolerated. Amlodipine/valsartan/HCTZ combination therapy was efficacious across racial/ethnic subgroups. Maximal efficacy was obtained with intensive treatment.

Keywords

Racial differences; combination therapy

Introduction

The prevalence of hypertension in the United States is high across all racial/ethnic subgroups, ranging from approximately 26% in Hispanic individuals to 29% in white individuals to 43% in African American individuals based on 1999–2006 National Health and Nutrition Examination Survey (NHANES) data.¹ African Americans develop hypertension at an earlier age than other racial groups, and their average blood pressure (BP) tends to be higher.² These factors contribute to the increased cardiovascular and renal risk in this population, including a 1.8-times greater rate of fatal stroke and a 4.2-times greater rate of end-stage kidney disease relative to whites.² Regardless of race/ethnicity, BP control (< 140/90 mm Hg) has proven difficult to achieve. The poorest BP control rates in the United States are reported in Hispanic individuals (24%), with only slightly improved rates in African Americans (33%) and whites (37%)³

Some evidence suggests that antihypertensive agents may be differentially effective when given as monotherapy, depending on the race/ethnicity of the patient. For example, it has been reported that African Americans may respond better to calcium channel blockers (CCBs) or diuretics than to beta-blockers or renin-angiotensin system (RAS) inhibitors.^{4,5} This finding has been attributed to underlying pathophysiologic differences, including the greater propensity of African Americans versus whites to have low plasma renin activity (PRA).⁶ However, factors such as obesity or other co-morbid conditions are also likely to influence the BP-lowering efficacy of any given treatment.⁷ Many patients with hypertension have comorbid conditions such as obesity or diabetes and, regardless of race/ethnicity, will require 2 or more antihypertensive agents to achieve clinical practice guideline–recommended BP goals.^{8–10} Use of combination therapy with RAS agents along with CCBs or diuretics has been reported to reduce any differential effect of race/ethnicity on antihypertensive efficacy.^{4,8} In the 12-week EXforge Evaluation in Stage Two Hypertensives of African Descent (EX-STAND) study,¹¹ which exclusively enrolled African Americans with stage 2 hypertension (n = 572), combination amlodipine/valsartan reduced mean sitting systolic blood pressure (MSSBP) by 33.3 mm Hg at week 8 (primary time point) compared with a reduction of 26.6 mm Hg with amlodipine monotherapy ($P < .0001$). The BP goal (< 140/90 mm Hg) was achieved by 50% and 30% of patients, respectively ($P < .0001$). Additional BP-lowering effects were observed following the addition of optional hydrochlorothiazide (HCTZ) 12.5 mg at week 8.

The Exforge Target Achievement (EXTRA) study showed that an intensive-treatment strategy with amlodipine/valsartan provided significantly greater antihypertensive efficacy than a moderate-treatment strategy with the same agents. Here we report the findings by race/ethnicity (African American, white, and Hispanic individuals).

Methods

Methods for this study have been previously described in detail¹² and are briefly summarized here. The study protocol was approved by the ethics committee or institutional

review board at each center, and the study was conducted according to the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients

Men and women 18 years or older with a documented diagnosis of systolic hypertension (MSSBP ≥ 150 mm Hg and <200 mm Hg) were included. Participants were treatment naïve or had uncontrolled BP (as defined previously) on angiotensin receptor blocker (ARB) monotherapy (other than valsartan) or on any single antihypertensive agent other than an ARB. Exclusion criteria included the following: patients with type 2 diabetes (glycosylated hemoglobin [HbA1c] $>8.5\%$) uncontrolled with antidiabetic drugs; a history of dialysis or a history of nephrotic syndrome and estimated glomerular filtration rate less than 50 mL/min/1.73 m² (Modification of Diet in Renal Disease method) in the 3 months before screening; and other significant concomitant diseases. At screening, serum sodium concentrations had to be greater than or equal to 135 mEq/L and potassium levels had to be between 3.5 and 5.5 mEq/L (inclusive). Women were postmenopausal, surgically sterile, or using an adequate method of contraception.

Study Design

The 12-week, randomized, double-blind, parallel-group study was conducted at 140 centers in the United States. Patients previously uncontrolled on ARB monotherapy (other than valsartan) after 28 days or more (MSSBP ≥ 150 mm Hg and <200 mm Hg) were randomized directly to double-blind treatment. Patients who were naïve to antihypertensive therapy within the previous 28 days entered the open-label run-in phase, during which time they received olmesartan 20 mg for 28 days. Patients who failed on any single antihypertensive agent other than an ARB also entered the open-label run-in phase, during which time they received olmesartan 40 mg for 28 days. Thereafter, olmesartan-treated patients (20 mg or 40 mg) whose BP remained uncontrolled and who satisfied the other inclusion/exclusion criteria were randomized to double-blind treatment.

As shown in Figure 1, patients randomized to intensive treatment received amlodipine/valsartan 5/320 mg through week 2, amlodipine/valsartan 10/320 mg from week 2 to week 4, and amlodipine/valsartan/HCTZ 10/320/12.5 mg from week 4 to week 8. Patients randomized to moderate treatment received amlodipine/valsartan 5/160 mg through week 4 and amlodipine/valsartan/HCTZ 5/160/12.5 mg from week 4 to week 8. In both groups, physicians had the option of adding another 12.5 mg of HCTZ at week 8 (ie, total dose of HCTZ 25 mg) if patients had MSSBP higher than 140 mm Hg. Nonstudy antihypertensive agents, or other concomitant medications likely to interfere with the evaluation of study medication, were prohibited during the trial. Use of sildenafil or vardenafil was prohibited within 24 hours and tadalafil within 48 hours before any scheduled visit.

BP Assessments and Adverse Events

An automated BP monitor (Model #HEM-705CP; Omron, Schaumburg, IL) was used for office BP measurements, in accordance with the guidelines of the British Hypertension Society.¹³ At each visit, 3 replicate sitting BP measurements were obtained 2 minutes or more apart. The mean of these 3 measurements was used as the average sitting BP. Change from baseline to week 4 in MSSBP was the primary efficacy outcome.

All randomized patients who received 1 dose or more of the double-blind study drug were included in the safety analysis, which included assessments of adverse events (AEs) and serious AEs, vital signs, physical examinations, and standard laboratory tests (hematology, blood chemistry, and urine at screening only).

Study Objectives

In this post-hoc analysis, we report the change from baseline to each visit in MSSBP and mean sitting diastolic blood pressure (MSDBP) in self-identified white, African American, and Hispanic individuals as well as the proportion of patients in these subgroups achieving BP goals (<140/90 mm Hg). AE rates are also presented by racial/ ethnic subgroup.

Statistical Methods

Demographic and baseline characteristics for the subgroups described here were analyzed using a 2-sample *t* test, chi-square test, or Fisher exact test. Within-treatment changes from baseline to each visit in MSSBP and MSDBP were analyzed for the racial/ethnic subgroups using a paired *t* test, and between-treatment differences were analyzed using an analysis of covariance (ANCOVA) model. Based on this fitted model, a 2-sided 95% confidence interval (CI) for mean treatment difference between the treatment regimens and the associated *P* value were obtained. The least-squared means (LSM) of each treatment arm were also computed. Based on this ANCOVA, a 2-sided test was performed at the 5% significance level. A logistic regression model was used to evaluate the proportion of patients achieving BP goals. For all efficacy outcomes, a last-observation-carried-forward (LOCF) approach was used to impute for missing values after baseline (baseline not carried forward).

Results

Patients

Patient disposition for the overall study population was previously described.¹² Briefly, a total of 728 patients were randomized (*n* = 369 intensive treatment, *n* = 359 moderate treatment). Of the 728 randomized patients, 280 naïve patients were treated with olmesartan 20 mg (146 intensive treatment, 134 moderate treatment), 207 non-naïve patients (who failed on any single agent other than an ARB) were treated with olmesartan 40 mg (103 intensive treatment, 104 moderate treatment), and 241 non-naïve patients (uncontrolled on ARB monotherapy other than valsartan) were directly randomized to study drug (120 intensive treatment, 121 moderate treatment). Seventy patients discontinued the study prematurely (*n* = 33 [intensive], *n* = 37 [moderate]), primarily because of AEs (*n* = 9, *n* = 19), withdrawal of consent (*n* = 10, *n* = 9), or protocol deviations (*n* = 8, *n* = 6). The study population included 474 (65%) white (235 intensive treatment, 239 moderate treatment), 198 (27%) African American (105 intensive treatment, 93 moderate treatment), and 165 (23%) Hispanic individuals (84 intensive treatment, 81 moderate treatment).

Demographic and baseline characteristics for the racial/ ethnic subgroups are shown in Table 1. Across these subgroups, mean age ranged from approximately 51 to 57 years, most patients were obese (mean body mass index [BMI] of 31–35 kg/m²), and mean office sitting systolic/ diastolic BP ranged from about 163/91 to 165/98 mm Hg. Within each racial/ethnic subgroup, the only statistically significant between-treatment difference was a somewhat greater mean BMI among African Americans in the moderate-treatment group versus the intensive-treatment group (*P* = .043).

Changes From Baseline in MSSBP and MSDBP

Both treatments produced significant reductions from baseline to all time points in MSSBP and MSDBP (all *P* < .0001), regardless of racial/ethnic subgroup, and results were consistent with those of the overall population (Figure 2).

- White individuals: MSSBP/MSDBP was reduced from 163.0/94.3 mm Hg at baseline to 139.6/83.5 mm Hg at week 4, the primary time point, with intensive

treatment and from 163.4/94.4 mm Hg to 144.3/85.5 mm Hg with moderate treatment (Figure 3A). The LSM difference between treatment groups was -4.47 (95% CI: $-6.71, -2.22$)/ -1.99 (95% CI: $-3.37, -0.61$) mm Hg, in favor of a larger reduction with intensive treatment ($P = .0001/P = .0047$; Figure 2). Reductions from baseline to weeks 8 and 12 in both MSSBP and MSDBP were also significantly greater with intensive treatment (all $P < .01$; vs moderate treatment).

- African American individuals: MSSBP/MSDBP was reduced from 165.4/98.4 mm Hg at baseline to 145.1/ 88.9 mm Hg at week 4 with intensive treatment and from 163.7/96.8 mm Hg to 146.1/88.3 mm Hg with moderate treatment (Figure 3B). The LSM difference between treatment groups was -2.31 (95% CI: $-6.15, 1.53$)/ -0.69 (95% CI: $-3.18, 1.79$) mm Hg ($P = .24/P = .58$; Figure 2). At weeks 8 and 12, reductions from baseline in MSSBP and MSDBP were greater with intensive treatment than moderate treatment, but only the MSSBP differences achieved statistical significance (both $P < .05$).
- Hispanic individuals: MSSBP/MSDBP was reduced from 162.0/92.5 mm Hg at baseline to 138.1/81.4 mm Hg at week 4 with intensive treatment and from 164.2/91.1 mm Hg to 144.8/82.7 mm Hg with moderate treatment (Figure 3C). The LSM difference between treatment groups was -5.94 mm Hg (95% CI: $-9.92, -1.96$) for MSSBP ($P = .0037$) and -2.19 mm Hg (95% CI: $-4.83, 0.46$) for MSDBP ($P = .10$; Figure 2). At weeks 8 and 12, reductions from baseline in MSSBP and MSDBP were greater with intensive treatment than moderate treatment, but the only difference that reached statistical significance was for MSSBP at week 8 ($P = .030$).

BP Goal

At weeks 4 and 8, regardless of race/ethnicity, a significantly greater proportion of patients receiving intensive treatment achieved BP goal ($<140/90$ mm Hg) than those receiving moderate treatment (all $P < .05$; Figure 4). No statistically significant differences were observed at the other time points. In all racial/ethnic subgroups, the greatest BP-goal rates were achieved at week 8 in the intensive treatment group: 63.8% in white, 56.2% in African American, and 72.6% in Hispanic individuals. In African Americans, a BP lower than 130/80 mm Hg was achieved by week 12 in 21.9% and 19.4% of patients in the intensive and moderate arms, respectively.

Adverse Events

In the overall study population, AEs were reported by 134 patients (36.3%) in the intensive-treatment group and 135 (37.6%) in the moderate-treatment group.¹² In the racial/ ethnic subgroups, AE rates ranged from 22.4% to 37.7% in the intensive-treatment group and 23.5% to 38.3% in the moderate-treatment group (Table 2). The most frequent AE overall was peripheral edema; within each racial/ethnic subgroup, this AE was more common with intensive treatment than with moderate treatment. Hyperkalemia was reported as an AE in 1 white patient in the intensive-treatment group and hypokalemia in 1 African American patient in the moderate-treatment group. There were no specific AE reports of abnormal serum creatinine values.

Discussion

This post-hoc analysis shows that the BP-lowering effects of combination amlodipine/valsartan/HCTZ therapy extend across racial/ethnic subgroups (white, African American, and Hispanic individuals). Our study population had predominantly stage 2 systolic hypertension with all patients having been uncontrolled on ARB monotherapy. As in the

overall population,¹² at all clinic visits during therapy, both intensive and moderate treatment resulted in significant reductions from baseline in MSSBP and MSDBP in each racial/ethnic subgroup. LSM reductions from baseline to week 4 in MSSBP, the primary efficacy outcome, were 23.5, 20.4, and 23.4 mm Hg with intensive treatment and 19.0, 18.1, and 17.5 mm Hg with moderate treatment in white, African American, and Hispanic individuals, respectively. These results were comparable with results for the overall population (23.0 mm Hg and 19.2 mm Hg with intensive and moderate therapy, respectively). Reductions in MSSBP were significantly greater with intensive versus moderate treatment at all time points in the overall population and in the white subgroup; significant between-treatment differences were not evident at every time point in African American or Hispanic individuals perhaps owing to the more limited sample sizes in these populations. The proportion of patients achieving BP goal (<140/90 mm Hg) was significantly greater with intensive versus moderate treatment at weeks 4 and 8 in all racial/ethnic subgroups, as in the overall population. By week 12, between-treatment differences in goal attainment were no longer significant in the subgroups, despite a continued significant difference in the overall population. Both treatment approaches were well tolerated with no notable racial/ethnic differences.

The recently updated International Society on Hypertension in Blacks (ISHIB) guidelines recommend use of combination therapy with RAS inhibitor/CCB or RAS inhibitor/thiazide diuretic in black individuals with BP higher than 15/10 mm Hg above target. For those in need of further BP reduction, the addition of a thiazide diuretic or CCB to these combinations, respectively, is recommended.¹⁰ Like our study, previous subgroup analyses based on race/ethnicity (white, African American, and/or Hispanic individuals) have also demonstrated the efficacy and safety of combination amlodipine/valsartan ($\pm$ HCTZ) therapy for the treatment of hypertension. These studies have shown combination therapy to provide greater BP lowering and control than the monotherapy components^{15,16} and triple therapy (amlodipine/valsartan/HCTZ) to be better than dual therapy (amlodipine/valsartan, amlodipine/HCTZ, and valsartan/HCTZ).^{17,18} The number of black participants in these studies was small ($n = 237$ of the 3807 enrolled subjects; 0.4% to 10.4% of the total populations in the individual studies). In a study that enrolled 26% Hispanic individuals ($n = 588$), all of whom had stage 2 hypertension, triple therapy with amlodipine/valsartan/HCTZ lowered MSSBP by 42.7 mm Hg at end of study (week 8) compared with reductions of 32.0 to 37.3 mm Hg with the dual-therapy components (all $P < .01$) in the Hispanic subgroup.^{17,18} In addition, a greater proportion of Hispanic individuals achieved the BP goal (<140/90 mm Hg) with triple therapy (75%) than with the dual therapies (50% to 60%) (all $P < .01$).

The patients enrolled in our study failed initial ARB monotherapy and had comorbidities such as metabolic syndrome, diabetes, or chronic kidney disease (CKD), suggesting that this was a difficult-to-treat hypertensive population. Of the 198 self-identified African Americans included in our study (27% of overall population), 76 (38%) had metabolic syndrome, 20 (10%) had diabetes, 117 (59%) had stage 1 CKD, and 73 (37%) had stage 2 CKD. Although our sample size is limited, by week 12, only 22% of African Americans in the intensive arm and 19% in the moderate arm achieved the newly recommended ISHIB guideline BP goal of lower than 130/80 mm Hg for secondary prevention and, indeed, few patients achieved the newly recommended ISHIB guideline BP goal of lower than 135/85 mm Hg for primary prevention.¹⁰ This may be related, in part, to the relatively short treatment duration (12 weeks) and, as per the study design, the fact that uptitration from HCTZ 12.5 mg to 25.0 mg over the last 4 weeks was optional; in the overall population, only about one-third of patients in the intensive arm and one-half in the moderate arm received the higher HCTZ dose. Although the study populations were not identical, the findings from our study can be compared with those of the African American Study of

Kidney Disease and Hypertension (AASK) trial.¹⁹ After 2 years of treatment in the AASK trial, the BP goal of lower than 130/80 mm Hg was achieved in 12.3% of patients who took an average of 2.7 antihypertensive drug classes and 50.9% of patients who took an average of 3.5 antihypertensive drug classes. Thus, based on the characteristics of our study population, it appears that many patients may need more than 3 drugs to control BP.

Few publications have specifically reported on the BP-lowering effects of other CCB/ARB combinations based on race/ethnicity. Analysis of data from African Americans (n = 474) and other racial groups (n = 1449) in the Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) study demonstrated greater antihypertensive efficacy with combination amlodipine/olmesartan therapy (10/40 mg) versus olmesartan monotherapy (40 mg) in both subgroups.^{20,21} At end of study (week 8), which was the primary time point, BP reductions associated with combination therapy were 28.7/15.7 mm Hg in African Americans and 30.5/19.9 mm Hg in other racial groups (all $P < .0001$ vs olmesartan 40 mg). Approximately 38% of African Americans and 52% of those in other racial groups receiving combination therapy in COACH achieved the BP goal of lower than 140/90 mm Hg (<130/80 mm Hg if diabetic).²¹ This is consistent with the proportion of African American patients who achieved BP goal while receiving intensive amlodipine/valsartan combination therapy in our subgroup analysis (37.1% at week 4). The long-term efficacy of amlodipine/olmesartan ($\pm$ HCTZ) was confirmed in the 44-week open-label extension of COACH, during which 63% of African Americans and 68% of those in other racial groups achieved BP goal.²²

Although the current subgroup analysis supports the concept that combination therapy can help to overcome racial and ethnic differences in response to antihypertensive monotherapy, interpretation of our results must include consideration of the study's limitations, including that the study was not powered to make comparisons between racial/ethnic groups. In addition, some of the subpopulation sizes were relatively small (n = 198 African Americans [27%] and 165 Hispanic individuals [23%] vs 474 [65%] white). The consistent findings across several studies, however, lend further support for our conclusions.

As in the overall study population,¹² peripheral edema was more common with intensive treatment than with moderate treatment within each racial/ethnic subgroup in the current analysis. It is unclear if the study design, with its use of a rapid dose-titration of amlodipine in the intensive-therapy group, contributed to the increased incidence of peripheral edema observed with intensive therapy across populations. Evaluation of slower titration (eg, amlodipine/valsartan 5/160 mg with subsequent up-titration to 5/320 mg and then 10/320 mg followed by the addition of HCTZ) may be warranted. Also, it is not known if patients who were naïve to antihypertensive therapy within the 28 days before screening and who received olmesartan 20 mg once daily during the 28-day run-in period would have benefited from higher dose olmesartan monotherapy (40 mg) before the initiation of combination amlodipine/valsartan therapy. Olmesartan has been shown to provide dose-related BP reduction when administered in the 20- to 40-mg range.²⁰

In conclusion, results of this subgroup analysis confirm previous findings that the BP-lowering effects of combination ARB/CCB with diuretic therapy extend across the racial/ethnic subgroups analyzed (white, African American, and Hispanic subgroups), and that maximal efficacy is obtained with intensive (vs moderate) treatment.

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Figure 1. Study design. HCTZ, hydrochlorothiazide. From Oparil and colleagues.¹²

Figure 2.

Least-squared mean (LSM) reductions from baseline in mean sitting systolic blood pressure (MSSBP) during intensive treatment (amlodipine/valsartan 10/320 mg) versus moderate treatment (amlodipine/valsartan 5/160 mg). Hydrochlorothiazide (HCTZ) 12.5 mg was added to both treatments at week 4, with optional additional HCTZ 12.5 mg at week 8. Error bars represent standard error. Results are shown in the overall population and in white, African American, and Hispanic patients.

Figure 3.

Mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) during intensive treatment (amlodipine/valsartan 10/320 mg) versus moderate treatment (amlodipine/valsartan 5/160 mg). Hydrochlorothiazide (HCTZ) 12.5 mg was added to both treatments at week 4, with optional additional HCTZ 12.5 mg at week 8. Error bars represent standard error. Results are shown in (A) white patients, (B) African American patients, and (C) Hispanic patients.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; for intensive treatment vs moderate treatment.

Figure 4.

Proportion of patients achieving blood pressure goals (< 140/90 mm Hg) during intensive treatment (amlodipine/valsartan 10/ 320 mg) versus moderate treatment (amlodipine/valsartan 5/160 mg). Hydrochlorothiazide (HCTZ) 12.5 mg was added to both treatments at week 4, with optional additional HCTZ 12.5 mg at week 8. P values are based on logistic regression. Results are shown in white, African American, and Hispanic patients.

Table 1
Demographic and baseline characteristics by race/ethnicity (intent-to-treat population)

Characteristic	White Patients		African American Patients		Hispanic Patients	
	Intensive Treatment A/V 10/320 mg (n = 235)	Moderate Treatment A/V 5/160 mg (n = 239)	Intensive Treatment A/V 10/320 mg (n = 105)	Moderate Treatment A/V 5/160 mg (n = 93)	Intensive Treatment A/V 10/320 mg (n = 84)	Moderate Treatment A/V 5/160 mg (n = 81)
Age, years	55.7 (11.5)	56.4 (11.1)	50.8 (9.3)	51.8 (10.4)	53.5 (11.4)	56.5 (11.1)
Age ≥ 65 years, n (%)	53 (23)	50 (21)	7 (7)	11 (12)	10 (12)	18 (22)
Gender, n (%)						
Male	138 (59)	142 (59)	57 (54)	43 (46)	46 (55)	39 (48)
Female	97 (41)	97 (41)	48 (46)	50 (54)	38 (45)	42 (52)
Race/ethnicity, n (%)						
White	235 (100)	239 (100)	–	–	75 (89)	74 (91)
African American	–	–	105 (100)	93 (100)	3 (4)	1 (1)
Other	–	–	–	–	6 (7)	6 (7)
BMI, kg/m ² *	31.9 (6.7)	31.9 (6.6)	32.5 (7.7)	35.1 (10.5)	30.9 (5.9)	30.5 (4.9)
Metabolic syndrome, [†] n (%)	116 (49.4)	121 (50.6)	40 (38.1)	36 (38.7)	44 (52.4)	45 (55.6)
Diabetes, [‡] n (%)	34 (14.5)	49 (20.5)	11 (10.5)	9 (9.7)	14 (16.7)	19 (23.5)
Stage 1 CKD, [§] n (%)	106 (45.1)	124 (51.9)	60 (57.1)	57 (61.3)	46 (54.8)	53 (65.4)
Stage 2 CKD, [¶] n (%)	114 (48.5)	109 (45.6)	43 (41.0)	30 (32.3)	38 (45.2)	27 (33.3)
Office sitting SBP, mm Hg	163.0 (11.3)	163.4 (11.2)	165.4 (12.9)	163.7 (12.1)	162.0 (10.0)	164.2 (11.5)
Office sitting DBP, mm Hg	94.3 (11.1)	94.4 (10.9)	98.4 (11.6)	96.8 (9.2)	92.5 (10.7)	91.1 (10.1)

A/V, amlodipine/valsartan; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Values are mean (SD) unless otherwise noted.

* $P = .043$; for between-treatment difference in BMI within the African American subgroup. Within each subgroup, no other statistically significant between-treatment differences were observed.

[†] Based on the National Cholesterol Education Program's Adult Treatment Panel III report.¹⁴

[‡] Patients with medical history of diabetes, diabetic medication history, or fasting plasma glucose above 126 mg/dL and HbA1c at least 6.5% at screening.

[§] Kidney damage with normal or elevated estimated glomerular filtration rate (> 90 mL/min/1.73 m²).

[¶] Kidney damage with mild reduction in estimated glomerular filtration rate (< 60 to < 90 mL/min/1.73 m²).

Table 2
Number (%) of patients reporting adverse events* during the study by race/ethnicity (safety population)

Event	White Patients		African American Patients		Hispanic Patients	
	Intensive Treatment A/V 10/320 mg (n = 236)	Moderate Treatment A/V 5/160 mg (n = 240)	Intensive Treatment A/V 10/320 mg (n = 105)	Moderate Treatment A/V 5/160 mg (n = 94)	Intensive Treatment A/V 10/320 mg (n = 85)	Moderate Treatment A/V 5/160 mg (n = 81)
Any adverse event	89 (37.7)	92 (38.3)	38 (36.2)	33 (35.1)	19 (22.4)	19 (23.5)
Peripheral edema	26 (11.0)	14 (5.8)	4 (3.8)	2 (2.1)	7 (8.2)	2 (2.5)
Dizziness	10 (4.2)	11 (4.6)	7 (6.7)	2 (2.1)	2 (2.4)	2 (2.5)
Headache	5 (2.1)	7 (2.9)	4 (3.8)	3 (3.2)	2 (2.4)	4 (4.9)
Fatigue	5 (2.1)	3 (1.3)	2 (1.9)	3 (3.2)	1 (1.2)	0
Upper respiratory tract infection	6 (2.5)	2 (0.8)	0	2 (2.1)	1 (1.2)	0
Nasopharyngitis	1 (0.4)	1 (0.4)	4 (3.8)	1 (1.1)	0	0

A/V, amlodipine/valsartan.

* Reported by 2% of patients overall in any race/ethnic subgroup.