Original Paper

24-Hour Ambulatory Blood Pressure Response to Combination Valsartan/Hydrochlorothiazide and Amlodipine/Hydrochlorothiazide in Stage 2 Hypertension by Ethnicity: The EVALUATE Study

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Several studies reported racial/ethnic differences in blood pressure (BP) response to antihypertensive monotherapy. In a 10-week study of stage 2 hypertension, 320/25 mg valsartan/hydrochlorothiazide (HCTZ) reduced ambulatory BP (ABP) significantly more effectively than 10/25 mg amlodipine/HCTZ. Results (post hoc analysis) are described in Caucasians (n=256), African Americans (n=79), and Hispanics (n=86). Compared with clinic-measured BP (no significant treatment-group differences in ethnic subgroups), least-squares mean reductions from baseline to week 10 in mean ambulatory systolic BP (MASBP) and mean ambulatory diastolic BP (MADBP) favored valsartan/HCTZ over amlodipine/HCTZ in Caucasians (−21.9/−12.7 mm Hg vs −17.6/−9.5 mm Hg; P=.0004/P<.0001*). No treatment-group differences in MASBP/MADBP were observed in African Americans (−17.3/−10.6 vs −17.9/−9.5;* P=.76/P=.40*) or Hispanics (−17.9/−9.7 vs −14.2/−7.2;* P=.20/P=.17*). Based on ABP monitoring, valsartan/HCTZ is more effective than amlodipine/HCTZ in lowering ABP in Caucasians. In African Americans and Hispanics, both regimens are similarly effective.* J Clin Hypertens (Greenwich). *2010;12:833–840.*

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Prevalence of hypertension is high in all race/ethnic groups.[1,2] In the 2003–2004 National Health and Nutrition Examination Survey (NHANES), a national population-based observational study of the US adult population, the age-adjusted prevalence of hypertension was 28.5% among non-Hispanic white persons, 39.1% for non-Hispanic black persons, and 27.8% of Hispanic persons.[1] Although the rates of patients with hypertension who achieve goal blood pressure (BP) are increasing, most patients across all race/ethnic groups are not reaching

these targets, despite increased awareness and treatment.[1,2] According to 2003–2004 NHANES data, the percentages of all hypertensive patients (treated and untreated) who achieved goal BP were 35.4% in non-Hispanic whites, 28.9% in non-Hispanic blacks, and 26.5% in Hispanics. Control rates were 68.2%, 52.4%, and 56.6%, respectively, for those undergoing drug therapy. Over the years, control of BP has improved; however, racial and ethnic differences influencing response and BP control have not narrowed.[3,4] Although several studies conducted during the past few decades have speculated that race is a critical factor that influences differential effectiveness of a therapeutic regimen, recent studies have suggested that factors such as obesity or comorbid conditions also influence treatment responses in various race groups.[5]

Clinical evidence suggests that a decreased response in black persons to agents that act on the renin-angiotensin-aldosterone system (RAAS) may be related to the low plasma renin activity of this population.[6–8] In a recent NHANES survey, Hispanic persons had significantly higher rates of not being at goal BP, despite adherence to medications, salt restriction, and other lifestyle modifications.[9] However, based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which all patients had equal access to antihypertensive care and medications were provided at no cost, Hispanic white persons were 20% more likely than non-Hispanic white persons to attain BP goal.[10] Regardless of race or ethnicity, most patients with hypertension will require use of $\geq$2 agents to attain BP goal. For those with stage 2 hypertension, most guidelines recommend initiating treatment with two agents, one of which is a diuretic.[3,11–14] Diuretics are particularly useful because they enhance the effectiveness of RAAS inhibitors when used in combination, including in black patients with hypertension.[2]

We recently reported on a 10-week, multicenter, randomized, double-blind, parallel-group, forced-titration study (the Evaluation of Valsartan's Uniqueness and 24-Hour Blood Pressure Efficacy [EVALUATE] trial), which compared the effectiveness and safety of 320/25 mg valsartan/hydrochlorothiazide (HCTZ) and 10/25 mg amlodipine/HCTZ in a subset of patients with stage 2 systolic hypertension.[15] The overall results showed that valsartan/HCTZ lowered 24-hour mean ambulatory systolic BP (MASBP), the primary efficacy outcome, and 24-hour mean ambulatory diastolic BP (MADBP) by 3.8/2.7 mm Hg more than amlodipine/HCTZ at study end ($P<.01$). This article presents the findings of a post hoc subgroup analysis to assess race and ethnic variability in treatment response to valsartan/HCTZ and amlodipine/HCTZ in the EVALUATE study.

METHODS

Methods for the EVALUATE study have previously been described in detail.[15] Briefly, men and women 18 years or older with an established diagnosis of a subset of stage 2 systolic hypertension (systolic BP, 160–199 mm Hg; diastolic BP, <120 mm Hg) self-selected their race/ethnic category (Caucasian, African American, Asian, Hispanic, other) at screening; more than one selection was allowed. Patients were randomly assigned to receive double-blind treatment with either valsartan 160 mg (n=241) or amlodipine 5 mg (n=241). After 2 weeks, they were force-titrated to 160/12.5 mg valsartan/HCTZ or 10 mg amlodipine and to the maximum dose of 320/25 mg valsartan/HCTZ or 10/25 mg amlodipine/HCTZ at six weeks. Patients were then followed-up for an additional four weeks, for a total follow-up of 10 weeks after randomization. All treatments were administered once daily in the morning.

In this analysis, 24-hour ambulatory BP (ABP) and clinic BP were evaluated for the various race/ethnic subgroups (Caucasian, African American, Hispanic). A total of 61 enrolled patients were excluded from the subgroup analysis. Twenty-seven patients of other races/ethnicities were excluded because their numbers were too small for statistical relevance and 34 were excluded because they did not have at least one post-baseline assessment of the primary efficacy variable. The primary efficacy variable was change from baseline in 24-hour MASBP. Secondary variables included change from baseline in 24-hour MADBP, mean sitting systolic BP (MSSBP), and mean sitting diastolic BP (MSDBP). Secondary efficacy variables also included the proportion of patients who achieved ABP goal (<130/80 mm Hg) and clinic BP goal (<140/90 mm Hg). Mean daytime (6 AM to 10 PM) and nighttime (10 PM to 6 AM) ABPs were also analyzed.

Participants were seen at weeks 0 (baseline), 2, 6, and 10 for clinic BP measurements and assessment of interim adverse events (AEs). Twenty-four–hour ABP monitoring (ABPM) was conducted at weeks 0, 6, and 10 using a standard device and method.[15] ABP was automatically measured every 15 minutes during the 24-hour monitoring period, and data were processed by a central

Table I. Demographic and Baseline Characteristics by Race/Ethnicity

	Caucasian		African American		Hispanic	
	Valsartan/ HCTZ (n=131)	Amlodipine/ HCTZ (n=125)	Valsartan/ HCTZ (n=37)	Amlodipine/ HCTZ (n=42)	Valsartan/ HCTZ (n=44)	Amlodipine/ HCTZ (n=42)
Mean (SD) age, y	59.9 (9.7)	59.3 (10.6)	55.0 (9.5)	52.1 (8.9)	55.9 (9.3)	55.5 (10.9)
Age <65 y, %	67.2	69.6	83.8	97.6	84.1	88.1
Male sex, %	60.3	65.6	45.9	42.9	38.6	28.6
BMI >30 kg/m^2, No. (%)	62 (47.3)	61 (48.8)	25 (67.6)	21 (50.0)	26 (59.1)	24 (57.1)
MASBP (SD), mm Hg	146.8 (12.2)	145.5 (11.3)	149.1 (9.3)	147.2 (12.2)	151.3 (17.3)	144.2 (11.6)
MADBP (SD), mm Hg	86.9 (9.8)	85.8 (9.4)	89.0 (7.5)	90.3 (8.3)	88.0 (11.3)	85.3 (10.5)
Mean eGFR, mL/min/1.73 m^2	85.1	86.2	95.5	97.4	97.6	101.2
Antihypertensives within past 30 days, %	79.4	79.2	75.7	69.0	77.3	83.3

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; MADBP, mean ambulatory diastolic blood pressure; MASBP, mean ambulatory systolic blood pressure; SD, standard deviation.

laboratory. AEs were assessed throughout the study by questionnaire.

In each race and ethnic subgroup, the two treatment regimens were compared with respect to least-squares mean change from baseline to week 10 (last observation carried forward) in 24-hour, daytime, and nighttime MASBP and MADBP, as well as MSSBP and MSDBP. An analysis of covariance model was used with baseline measurement as the covariate and treatment and pooled center as factors. Within-treatment mean change from baseline was evaluated using a paired *t* test. In addition, between-treatment comparisons of the proportions of patients achieving the ABP goal (<130/80 mm Hg) and the clinic BP goal (<140/90 mm Hg) at week 10 were performed using the Cochran-Mantel-Haenszel chi-square test, adjusting for pooled center. In each race and ethnic subgroup, regression analysis was conducted to assess the relationship between various demographic and baseline characteristics and change from baseline to week 10 in 24-hour MASBP.

RESULTS

Demographic and Baseline Characteristics

Baseline characteristics of the overall study population (N=482) included 53% men, mean age of 57 years, mean body mass index (BMI) of 31 kg/m^2, mean clinic BP of 170.8/97.7 mm Hg, and mean ABP of 147.0/87.3 mm Hg.[15] This post hoc subgroup analysis contained 256 Caucasian, 79 African American, and 86 Hispanic persons. The demographic and baseline clinical characteristics of the patients who participated in this analysis are shown in Table I. Demographic and baseline characteristics of participants were similar to those of the overall study population. The African American patients were younger, had higher BP and BMI values, and were less likely than the Caucasian patients to be male or taking antihypertensive medications. The Hispanic patients were younger than the Caucasian patients, were more likely to be obese, and were more likely to be female (Table I).

ABP Measures

At week 6, following four weeks of therapy with 160/12.5 mg valsartan/HCTZ or 10 mg amlodipine, all race/ethnic groups achieved significant reductions from baseline in MASBP and MADBP ($P<.001$). The total study population achieved significantly greater week 6 MASBP/MADBP least-square mean reductions when treated with valsartan/HCTZ than with amlodipine (−16.0/−9.5 mm Hg vs −14.3/−7.6 mm Hg; $P<.0001/<.0001$), as did Caucasian patients (−16.3/−9.6 mm Hg vs −13.4/−7.1 mm Hg; $P=.018/.0023$). African American and Hispanic patients showed similar least-square mean reductions with valsartan/HCTZ and amlodipine (−12.5/−7.4 mm Hg vs −15.5/−8.0 mm Hg; $P=.19/.75$ and −18.1/−8.8 mm Hg vs −16.4/−7.5 mm Hg; $P=.50/.40$, respectively).

At week 10, valsartan/HCTZ and amlodipine/HCTZ also reduced 24-hour MASBP and MADBP for each race/ethnic subgroup, compared with baseline ($P<.0001$) (Figure 1). For MASBP/MADBP, there was a significant difference in least-squares mean change from baseline to week 10 between valsartan/HCTZ (−21.1/−12.5 mm Hg) and amlodipine/HCTZ (−18.1/−9.9 mm Hg) in

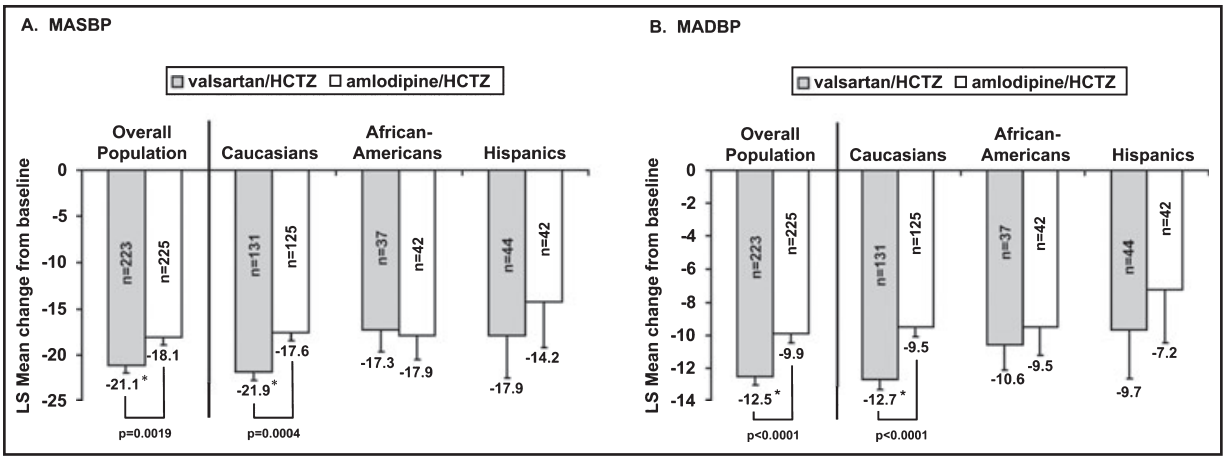

Figure 1. Change in (A) mean ambulatory systolic blood pressure (MASBP) and (B) mean ambulatory diastolic blood pressure (MADBP) from baseline to week 10 by race/ethnicity. HCTZ indicates hydrochlorothiazide; LS, least squares.

the overall study population (*P*=.0019/*P*<.0001). A similar difference was observed in Caucasian patients (−21.9/−12.7 mm Hg vs −17.6/−9.5 mm Hg; *P*=.0004/*P*<.0001). There was no statistical difference between valsartan/HCTZ and amlodipine/HCTZ within either the African American (−17.3/−10.6 mm Hg vs −17.9/−9.5 mm Hg; *P*=.76/*P*=.40) or Hispanic (−17.9/−9.7 mm Hg vs −14.2/−7.2 mm Hg; *P*=.20/*P*=.17) subgroups; however, Hispanic patients had numerically greater reductions in ABP with valsartan/HCTZ than with amlodipine/HCTZ. African American patients treated with amlodipine/HCTZ had numerically greater reductions in ABP than Hispanic patients treated with amlodipine/HCTZ; however, statistical comparisons were not made. Daytime and nighttime ABP findings were consistent with those described for 24-hour ABP (Table II).

In the overall population, the ABP goal (<130/80 mm Hg) was attained at a significantly higher rate with valsartan/HCTZ than with amlodipine/HCTZ (54.3% vs 42.7%; *P*=.022) (Figure 2). Similar results were observed in the Caucasian subgroup (57.9% vs 41.8%; *P*=.012). In contrast, no significant differences in goal attainment were seen between valsartan/HCTZ and amlodipine/HCTZ for either the African American or the Hispanic subgroup.

Clinical BP Measures

For clinical BP, no significant differences were observed between valsartan/HCTZ and amlodipine/HCTZ in changes from baseline to week 10 in either clinical systolic BP or diastolic BP (Table II). Similarly, in the overall study population and also within each race/ethnic subgroup, there were no significant differences between valsartan/HCTZ and amlodipine/HCTZ in the proportion of patients who reached the clinic BP goal (<140/90 mm Hg) at week 10; however, sample size was somewhat smaller in the African American and Hispanic subgroups (Figure 2).

Additional Analyses Evaluating the Relationship Between Demographic/Baseline Characteristics and 24-Hour BP

A regression analysis to evaluate the relationship between demographic/baseline characteristics and change from baseline in 24-hour MASBP is summarized in Table III. Reduction of MASBP was significantly correlated with severity of hypertension in African American patients (*P*=.0064) and with baseline estimated glomerular filtration rate (eGFR) in Hispanic patients (*P*=.017). There were no significant correlations between the evaluated factors and ABP change in Caucasian persons; however, a trend (*P*=.060) was observed between level of BP and treatment response for this subgroup.

Adverse Events

In the overall study population, the incidence of AEs was 39.0% with valsartan/HCTZ and 41.5% with amlodipine/HCTZ. The most common AEs were peripheral edema (3.3% vs 12.4%), dizziness (5.8% vs 0.8%), and headache (5.0% vs 5.4%). Laboratory findings did not notably differ between treatment groups except for serum potassium, which was reduced more in the amlodipine/HCTZ group than in the valsartan/HCTZ group (*P* <.0001 between treatments).[15] In the current analysis, AEs were reported by 42.7% of Caucasians, 29.3% of African Americans, and 37.0% of

Table II. Comparison Between Valsartan/HCTZ and Amlodipine/HCTZ for Their Effects on the Change From Baseline to Week 10 (LOCF) in Ambulatory, Daytime, Nighttime, and Clinic BP for the Overall Patient Population and for Each Race/Ethnic Subgroup

	Overall		Caucasian		African American		Hispanic	
	Valsartan/ HCTZ (N=223)	Amlodipine/ HCTZ (N=225)	Valsartan/ HCTZ (N=131)	Amlodipine/ HCTZ (N=125)	Valsartan/ HCTZ (N=37)	Amlodipine/ HCTZ (N=42)	Valsartan/ HCTZ (N=44)	Amlodipine/ HCTZ (N=42)
MASBP	−21.1 (0.8)[a]	−18.1 (0.8)	−21.9 (0.9)[b]	−17.6 (0.9)	−17.3 (2.4)	−17.9 (2.7)	−17.9 (4.7)	−14.2 (5.0)
MADBP	−12.5 (0.6)[c]	−9.9 (0.5)	−12.7 (0.6)[c]	−9.5 (0.6)	−10.6 (1.6)	−9.5 (1.7)	−9.7 (3.0)	−7.2 (3.2)
Nighttime MASBP	−18.4 (0.9)	−16.3 (0.9)	−18.9 (1.0)[d]	−15.7 (1.0)	−16.3 (3.1)	−17.2 (3.4)	−15.1 (5.5)	−13.4 (5.8)
Nighttime MADBP	−10.8 (0.6)[a]	−8.8 (0.6)	−10.8 (0.7)[a]	−8.4 (0.6)	−10.0 (2.1)	−9.5 (2.3)	−8.2 (3.3)	−6.7 (3.5)
Daytime MASBP	−22.4 (0.9)[b]	−18.9 (0.9)	−23.4 (1.0)[b]	−18.6 (1.0)	−17.5 (2.4)	−18.2 (2.7)	−19.7 (4.6)	−15.2 (5.0)
Daytime MADBP	−13.1 (0.6)[c]	−10.3 (0.6)	−13.3 (0.7)[b]	−10.1 (0.7)	−10.7 (1.8)	−9.6 (1.9)	−10.8 (3.1)	−7.6 (3.4)
Clinic SBP	−33.7 (1.3)	−33.0 (1.3)	−34.8 (1.4)	−32.7 (1.4)	−30.8 (4.1)	−36.5 (4.5)	−30.5 (6.9)	−28.6 (7.7)
Clinic DBP	−13.9 (0.7)	−14.0 (0.7)	−14.6 (0.8)	−14.1 (0.8)	−12.3 (2.4)	−15.2 (2.7)	−14.2 (3.5)	−13.4 (3.8)

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward; MADBP, mean ambulatory diastolic blood pressure; MASBP, mean ambulatory systolic blood pressure; SBP, systolic blood pressure. [a]$P<.01$; [b]$P<.001$; [c]$P<.0001$; [d]$P<.05$ vs amlodipine/HCTZ. Values are least-squares mean (standard error of the mean).

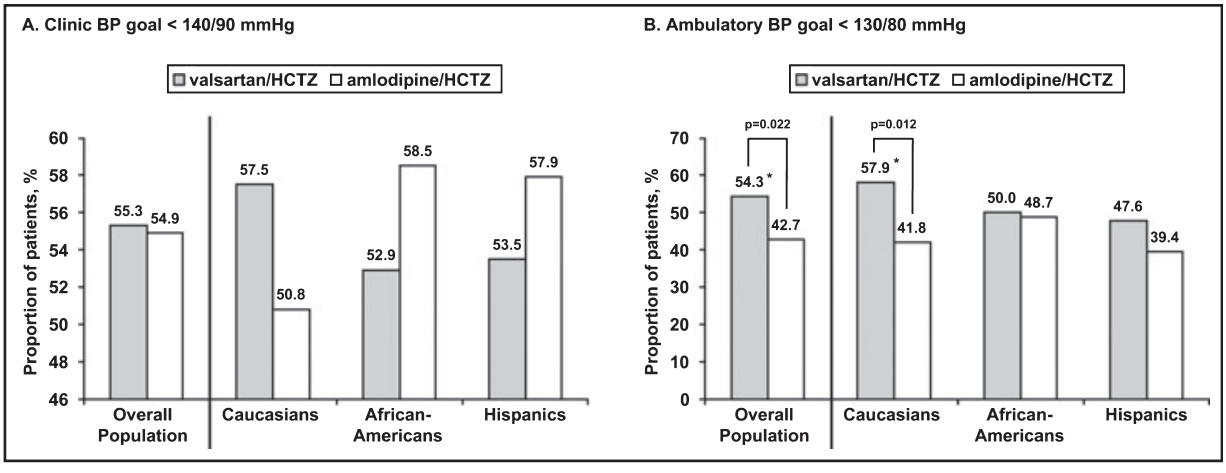

Figure 2. Proportion of patients achieving (A) clinic blood pressure (BP) goal (<140/90 mm Hg) and (B) ambulatory BP goal (<130/80 mm Hg) at week 10 by race/ethnicity. HCTZ indicates hydrochlorothiazide.

Hispanics who received valsartan/HCTZ and by 44.5%, 41.9%, and 33.3%, respectively, who were treated with amlodipine/HCTZ. As expected, a higher frequency of peripheral edema was noted in the amlodipine/HCTZ group (13.9% Caucasian, 9.3% African American, 13.3% Hispanic) than in the valsartan/HCTZ group (3.5% Caucasian, 4.9% African American, 2.2% Hispanic). Dizziness occurred with a higher frequency in the valsartan/HCTZ group (6.3% Caucasian, 4.9% African American, 6.5% Hispanic) than in the amlodipine/HCTZ group (1.5% Caucasian, 0% African American, 0% Hispanic). The frequency of headache was relatively low in Caucasians and African Americans, regardless of treatment (2.3–4.9%), but was higher in Hispanics (6.5% with valsartan/HCTZ; 15.6% with amlodipine/HCTZ).

DISCUSSION

This report assesses potential race/ethnic disparities by post hoc subgroup analysis of ABPM and clinic data on the antihypertensive response to two therapeutic regimens in the EVALUATE trial in Caucasian, African American, and Hispanic persons.

Table III. Relationship Between Demographic and Baseline Characteristics and Change from Baseline in 24-Hour Mean Ambulatory SBP

	Caucasian		African American		Hispanic	
Factor	Estimated Coefficient	*P* Value	Estimated Coefficient	*P* Value	Estimated Coefficient	*P* Value
Age	−0.099	ns	−0.042	ns	−0.047	ns
Sex	−3.56	ns	−1.55	ns	9.32	ns
BMI	2.66	ns	0.87	ns	−0.89	ns
BP severity	−1.88	Trend (.060)	−4.29	.0064	−1.46	ns
eGFR	0.0008	ns	−0.046	ns	−0.15	.017

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ns, not statistically significant; SBP, systolic blood pressure.

The overall results of the trial showed that the combination of valsartan/HCTZ was more effective in reducing MASBP (primary efficacy variable) than the combination of amlodipine/HCTZ.[15]

In this subgroup analysis, although all race/ethnic groups responded to both EVALUATE regimens with significant decreases in BP and showed similar responses to both regimens for clinic BP, heterogeneity in response among race/ethnic groups was seen with the more sensitive ABP. Decreases in MASBP/MADBP from baseline to week 10 with valsartan/HCTZ were −21.9/−12.7 mm Hg for the Caucasian group, −17.3/−10.6 mm Hg for the African American group, and −17.9/−9.7 mm Hg for the Hispanic group. In Caucasian patients, the effects of valsartan/HCTZ and amlodipine/HCTZ on MASBP and MADBP were consistent with findings in the overall study, in which significant differences in favor of valsartan/HCTZ were observed. Hispanic patients also experienced greater ABP reduction with valsartan/HCTZ than with amlodipine/HCTZ, but the difference between treatments was not statistically significant. However, in African Americans, similar ABP reduction was seen with both treatment groups. Within the limits of this post hoc analysis, these data therefore support an increased benefit for ABP lowering with valsartan/HCTZ over amlodipine/HCTZ for Caucasian patients, while suggesting that African American and Hispanic patients benefit from both drug regimens. Both treatments were well tolerated, although peripheral edema was more common with amlodipine-based therapy in all race/ethnic subgroups, as in the overall study.

Results of the regression analysis were interesting, showing that level of baseline BP correlated with treatment response in African American patients, baseline eGFR correlated with treatment response in Hispanic patients, and a trend for level of baseline BP and treatment response was seen in Caucasian patients. Additional studies will be necessary to understand the effect of these findings. Limitations of this study included its post hoc nature, and the smaller numbers of African American and Hispanic patients. This may have reduced the ability to see differences in effectiveness between drug regimens in these groups, particularly in Hispanic participants where the standard error of the mean suggests greater variability in treatment response.

Previous studies have been conducted to assess the effects of antihypertensive drug treatments on hypertension in patients of different race/ethnic groups. Although some evidence suggests that treatments may be differentially effective depending on the race/ethnic background of the patient, most of these results relate to the effects of monotherapy. One study of age–race subgroup response rates to a variety of antihypertensive drugs revealed racial disparities in response to these agents.[16] Examples included response rates (reduction from diastolic BP 100–110 mm Hg to <90 mm Hg) of 53% of older African Americans (older than 60 years), vs 29% of older Caucasians using HCTZ, and 81% of older African Americans, vs 53% of older Caucasians, using the calcium channel blocker (CCB) diltiazem. In that study, the response to single-drug therapy was significantly ($P<.001$) predicted by age–race subgroup. However, most studies, including a recent meta-analysis that evaluated whether African American and Caucasian persons have differential BP response to CCB monotherapy,[17] showed that BP response was qualitatively similar between races and that race was not likely a predictor of appropriateness of use of CCBs. These seemingly contradictory results may be accounted for, at least in part, by the choice of outcome measurements used in the different studies.

The EVALUATE trial confirms the lesser benefit of a diuretic/CCB combination in Caucasian

persons that has been seen in some, but not all, previous studies.[18–22] In EVALUATE, the diuretic/CCB combination seems to be at least as effective as a diuretic/angiotensin II receptor blocker (ARB) combination in African Americans. This may have been related to the greater effectiveness of monotherapy with CCBs and diuretics compared with β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and ARBs observed in African Americans.[12,16,23–25] Likewise, Hispanic patients responded similarly to the two treatments, possibly reflecting the positive response of this ethnic group to CCBs (including amlodipine) and to the diversity of racial background, geographic origin, and BP response of this population.[10,26,27] The lack of significant treatment-group differences observed in these groups may also have been related to the small number of African American and Hispanic persons evaluated, which were approximately three-fold lower than the number of Caucasian persons evaluated. In addition, African American and Hispanic EVALUATE patients were more likely than Caucasian patients to be obese (BMI >30 kg/m^2), which may also have affected their response to therapy.

Overall, race-based variability in response to antihypertensive therapy is not understood.[2] Two major potential contributing factors include differences in underlying pathophysiology and differences in prevalence of concomitant cardiovascular risk factors.[11] Some evidence shows that African American hypertensive patients exhibit lower renin levels than Caucasian patients and may be less affected by ACEIs.[28] In a recent systematic review, a number of issues were identified, ranging from methodologic disparities in reporting to studies in which race/ethnic demographic reporting was omitted.[5] Other issues, including the classification schemes for race/ethnic subgroups, which can vary among countries, and lifestyle factors that can differ between minorities within the United States and those in other countries may also contribute. More aggressive recruitment of minorities and more thorough reporting will help provide more accurate information about the response of such populations to antihypertensive agents and ultimately help to define the most appropriate antihypertensive treatment approaches in patients of particular race/ethnic origins.

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