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Research Article

Comparative efficacy and safety of combination aliskiren/amlodipine and amlodipine monotherapy in African Americans with stage 2 hypertension and obesity or metabolic syndrome

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Abstract

The renin-angiotensin system (RAS) is a common link between hypertension and comorbidities of obesity and metabolic syndrome (MetS). We evaluated the antihypertensive efficacy and safety of the combination direct renin inhibitor, aliskiren, with amlodipine versus amlodipine alone in self-identified African Americans with stage 2 hypertension in a subgroup of patients with obesity or MetS participating in the Aliskiren Amlodipine Combination in African AmEricans with Stage 2 HypertenSion (AACESS) trial. Subjects, newly diagnosed and treatment naive or taking three or fewer antihypertensive drugs with a mean sitting systolic blood pressure (msSBP) of 160–199 mm Hg were randomized to receive aliskiren/amlodipine 150/5 mg or amlodipine 5 mg for 1 week; force-titrated to aliskiren/amlodipine 300/10 mg or amlodipine 10 mg, for an additional 7 weeks. Overall, 292 obese (body mass index $\geq$30 kg/m^2) and 197 MetS subjects had baseline msSBP ranging from 167.0 to 167.5 mm Hg. Least-square mean reductions from baseline to 8 weeks in msSBP, the primary efficacy variable, were significantly higher with aliskiren/amlodipine than with amlodipine in both obese (−33.7 mm Hg vs. −27.9 mm Hg; $P < .001$) and MetS subjects (−36.4 mm Hg vs. −28.5 mm Hg; $P < .001$). Both treatments were well tolerated. Aliskiren/amlodipine 300/10 mg is more effective than amlodipine 10 mg in African Americans with stage 2 hypertension and obesity or MetS. J Am Soc Hypertens 2011;5(6):489–497.

Keywords: Direct renin inhibitor; calcium channel blocker; blood pressure; adverse events.

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Introduction

In the United States, the prevalence of hypertension in African Americans has remained at approximately 40% over the past decade compared with rates <30% in Caucasians and Hispanics.[1] Hypertension is more severe, develops at an earlier age, and leads to more target organ damage in African Americans than in Caucasians.[2] Moreover, hypertension in African Americans is often accompanied by obesity and/or metabolic syndrome (MetS),[3] which further increases cardiovascular (CV) risk in this population. Blood pressure (BP) goals are more difficult to achieve in subjects with these comorbidities versus those without them, with most individuals requiring a combination of antihypertensive agents.[4]

The updated International Society on Hypertension in Blacks (ISHIB) consensus statement recommends two-drug therapy when systolic BP (SBP) is >15 mm Hg and/or diastolic BP (DBP) is >10 mm Hg above goal (<135/85 mm Hg for primary prevention, <130/80 mm Hg for secondary prevention).[5] Primary prevention is applicable for subjects who have no target-organ damage, no history of CV disease, and no CV risk factors (specifically, MetS, Framingham risk score >20%, prediabetes, or diabetes mellitus [DM]), whereas secondary prevention is applicable for subjects with any of these characteristics. The statement further recommends use of a renin-angiotensin system (RAS) inhibitor plus either calcium channel blocker (CCB) or thiazide diuretic as the preferred initial combinations, the latter in edematous and/or volume overload states. The recommendation for RAS-based therapy stems from the wealth of clinical experience with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Direct renin inhibitors (DRIs) are the newest antihypertensive class to be indicated for the treatment of hypertension. Aliskiren, the first agent in this class, reduces plasma renin activity (PRA), unlike ACE inhibitors and ARBs, which increase PRA and thereby plasma levels of angiotensin I and angiotensin II.[6] This agent provides safe and effective BP lowering when administered alone or in combination with other agents, including a CCB (amlodipine) or thiazide diuretic (hydrochlorothiazide), although subjects studied to date have been predominantly Caucasian.[7,8] Previously, in the Aliskiren Amlodipine Combination in African AmEricans with Stage 2 HypertenSion (AACESS) study, we reported that combination aliskiren/amlodipine provided significantly greater BP lowering than amlodipine monotherapy in African Americans with stage 2 hypertension.[9] The objective of this post-hoc analysis of the AACESS study was to evaluate the antihypertensive efficacy and safety of these treatments in African Americans with hypertension and comorbid obesity or MetS.

Methods

Methods for the AACESS study have been previously described in detail[9] and are briefly summarized here. A research ethics board, ethics committee, or institutional review board at each center approved this study, and all subjects provided written informed consent before inclusion. The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice in conjunction with local regulations and the ethical principles of the current Declaration of Helsinki.

Subjects

Subjects were adult men or women who were self-identified as African Americans and who had newly diagnosed and treatment naïve stage 2 hypertension or were taking 3 or fewer antihypertensive drugs with a mean sitting systolic blood pressure (msSBP) ≥160 mm Hg and <200 mm Hg at randomization. Subjects with msSBP ≥200 mm Hg, mean sitting diastolic blood pressure (msDBP) ≥110 mm Hg, secondary hypertension, or a history of treatment with four or more antihypertensive agents were excluded. In addition, subjects could not have hypertension that was uncontrolled at screening (defined as msSBP >180 mm Hg on one or more antihypertensive agents) or refractory to treatment (>140/90 mm Hg on the maximum dose of three antihypertensive agents, including a diuretic). Subjects with CV disease, evidence of renal dysfunction, abnormal serum sodium or potassium, type I DM, or type II DM requiring insulin or associated with glycosylated hemoglobin >10% were also excluded. Premenopausal women who were pregnant, nursing, or not using two approved forms of contraception were not permitted to enter the study.

Study Design

This was an 8-week, prospective, multicenter (67 American centers), randomized, double-blind, parallel-group study. After screening, subjects underwent a 1- to 4-week washout period before being randomized 1:1 to receive either combination aliskiren/amlodipine 150/5 mg or amlodipine 5 mg alone for 1 week; subjects were then force-titrated to aliskiren/amlodipine 300/10 mg or amlodipine 10 mg, respectively, for 7 weeks (Figure 1).

Study drugs provided were aliskiren 150-mg tablets, amlodipine 5-mg capsules, and matching placebos. To ensure blinding, subjects were instructed to take 4 tablets/capsules of study drug per day with water in the morning between 7:00 a.m. and 10:00 a.m., except on the morning of clinic visits, when they were to be taken after the visit procedures were completed. Subjects were not permitted to take any nonstudy antihypertensives, nor were they permitted to take drugs that could affect BP, such as diuretics, certain classes of antidepressants and antipsychotics, oral corticosteroids, alpha adrenergic blockers, and antiarrhythmic drugs. Chronic use of sympathomimetic drugs or nonsteroidal

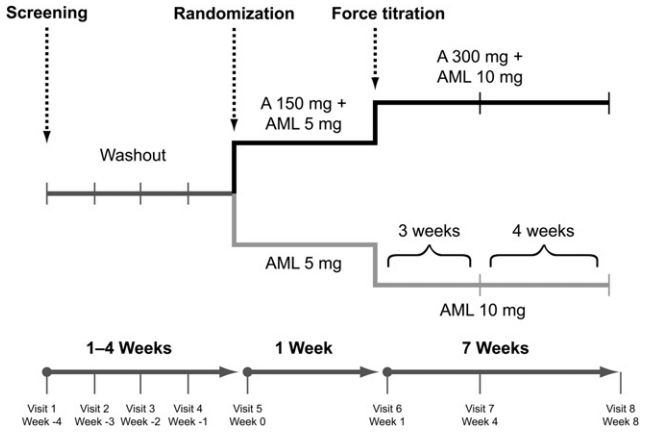

Figure 1. Study design.[9]

anti-inflammatory drugs was also prohibited. In addition, potassium supplements and salt substitutes containing potassium were not permitted, and phosphodiesterase type 5 inhibitors such as sildenafil, vardenafil, and tadalafil were not allowed within 48 hours before any scheduled visit.

BP Assessments

At all clinic visits, sitting BP was measured at trough (24 hours ± 3 hours postdose) using a calibrated standard mercury sphygmomanometer with the recommended cuff sizes.[10] After sitting for 5 minutes, three measurements of SBP and DBP were made at 1- to 2-minute intervals, and the mean of these numbers was recorded as the average clinic BP for that visit. The primary efficacy variable was the change from baseline to week 8 in msSBP; secondary variables included the change from baseline to week 8 in msDBP and the percentage of subjects achieving BP <140/90 mm Hg. The percentage of subjects achieving BP <135/85 mm Hg or <130/80 mm Hg was also determined, in accordance with the new ISHIB guideline recommendations.[5]

Safety Assessments

The safety population consisted of all randomized subjects who received at least one dose of study drug. Safety assessments consisted of recording all adverse events (AEs), serious AEs (SAEs), and discontinuations as well as performance of physical examinations and vital signs. Fasting blood and urine samples were obtained at screening, baseline, and week 8 for determination of hematology, blood chemistries, and urinalysis.

Subgroup Analyses

Subjects were classified as nonobese (baseline body mass index [BMI] <30 kg/m^2) or obese (baseline BMI ≥30 kg/m^2), and were further categorized into BMI subgroups for select analyses as follows: BMI 18.5–24.99, 25–29.99, 30–34.99, 35–39.99, and ≥40 kg/m^2. Subjects with MetS were identified based on the presence of two or more of the following baseline characteristics: waist circumference ≥102 cm for males or ≥88 cm for females, glucose ≥100 mg/dL to <126 mg/dL, high-density lipoprotein cholesterol <40 mg/dL for males or <50 mg/dL for females, and triglycerides ≥150 mg/dL.

Statistical Analysis

Baseline and safety data are presented for the full analysis set, consisting of all randomized subjects who received study drug. Demographics were compared between treatment groups using a two-sample *t*-test for continuous variables and Fisher's exact test for categorical variables. Paired *t*-tests were used to analyze the significance of BP changes from baseline within treatment groups. Differences between treatment groups were compared using an analysis of covariance (ANCOVA) with baseline BP as a covariate and treatment and pooled center as factors in the model. The least-square means of each treatment arm were also computed. Based on this ANCOVA analysis, a two-sided test was performed at the 5% significance level. A last observation carried forward approach was used to impute missing values postbaseline. The percentage of subjects achieving the various BP goals was analyzed using the Cochran-Mantel-Haenszel chi-square test stratifying for pooled center using data from the full analysis set and observed cases only. Select laboratory data (fasting blood glucose and urinary albumin excretion rate) were analyzed using an ANCOVA model. All statistical analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, NC) under the supervision of the Novartis trial statistician (D.P.).

Results

Subject Disposition and Baseline Characteristics

Subject disposition for the overall population was previously reported.[9] After screening of 729 subjects, 443 met study eligibility criteria and were randomized to treatment. Thirty-three subjects discontinued before the end of the study. Twelve subjects discontinued as a result of an AE (nine subjects in the aliskiren/amlodipine group, three in the amlodipine group), nine withdrew consent (four in the aliskiren/amlodipine group, five in the amlodipine group), seven were lost to follow-up (one in the aliskiren/amlodipine group, six in the amlodipine group), three were protocol deviators (all in the amlodipine group), and two did not achieve a satisfactory therapeutic effect (all in the amlodipine group). There were no apparent differences in the total frequency of subject discontinuations or the reasons for these discontinuations between obese and nonobese subjects or between subjects with and without MetS.

A total of 441 randomized subjects were categorized as obese or nonobese on the basis of their baseline BMI; 292 (66.2%) of these subjects were obese (BMI $\geq$30 kg/m^2) and 149 (33.8%) were nonobese (BMI <30 kg/m^2). In addition, 435 randomized subjects were evaluated for baseline MetS status; 197 (45.3%) met the criteria for MetS, whereas 238 (54.7%) did not. Demographic and baseline characteristics were well balanced between the treatment groups within the overall population[9] and within the obesity and MetS subgroups, with no statistically significant differences observed (Table 1). msSBP/msDBP ranges were 167–168/95–98 mm Hg across the subgroups presented here.

Changes from Baseline to Week 8 in msSBP and msDBP

In obese (BMI $\geq$30 kg/m^2) and nonobese (BMI <30 kg/m^2) subjects, msSBP and msDBP were reduced from baseline after 8 weeks of treatment with combination aliskiren/amlodipine or amlodipine monotherapy (all $P < .001$). As shown in Figure 2, reductions in msSBP were greater with combination therapy than monotherapy in the obese subgroup ($P < .001$). Further analysis of msSBP reductions showed similar results across BMIs of 30–34.99, 35–39.99, and $\geq$40 kg/m^2 (all $P < .05$) (Figure 2). In the nonobese subgroup, combination therapy resulted in numerically greater reductions in msSBP compared with monotherapy. At week 8, reductions from baseline in msDBP were greater with combination therapy than monotherapy in both obese (−14.2 vs. −10.3 mm Hg; $P < .001$) and nonobese (−13.2 vs. −9.8 mm Hg; $P < .05$) subjects.

In subjects with and without MetS, both treatment regimens reduced msSBP and msDBP from baseline to week 8 (all $P < .001$). Figure 3 shows that reductions in msSBP and msDBP were greater with combination therapy than monotherapy, regardless of MetS status (all $P < .05$). Differences between the treatment groups in favor of combination therapy were larger in subjects with MetS relative to those without MetS, particularly for msSBP (Figure 3); however, no statistical analysis was performed to compare results across subgroups.

BP Goals

At week 8, a greater percentage of subjects achieved the BP goal of <140/90 mm Hg on combination aliskiren/amlodipine versus amlodipine monotherapy in the obese (BMI $\geq$30 kg/m^2) subgroup (57.5% vs. 45.7%; $P < .05$) and MetS subgroup (55.4% vs. 42.4%; $P < .05$). No significant between-treatment group differences were observed in nonobese (BMI <30 kg/m^2) subjects (57.7% vs. 53.0%) or non-MetS subjects (58.7% vs. 51.4%).

The percentages of subjects achieving the BP goals of <135/85 mm Hg and <130/80 mm Hg at week 8 are shown in Figure 4. For the BP goal of <135/85 mm Hg, results numerically favored combination therapy over monotherapy across all subgroups, but the only significant difference was seen for the obese subgroup (40.3% vs. 26.8%; $P < .01$). Greater percentages of subjects in the combination therapy arm than monotherapy arm achieved the BP goal of <130/80 mm Hg, regardless of subgroup (all $P < .05$).

Safety

The most common AEs reported during the study were peripheral edema, headache, fatigue, and nausea, and the

Table 1
Demographics and baseline characteristics

Characteristic	Nonobese (<30 kg/m^2)		Obese ($\geq$30 kg/m^2)		Non-MetS		MetS	
	A/AML (n = 76)	AML (n = 73)	A/AML (n = 142)	AML (n = 150)	A/AML (n = 119)	AML (n = 119)	A/AML (n = 96)	AML (n = 101)
Age, y	53.7 (9.5)	53.8 (10.4)	53.0 (9.3)	51.7 (10.6)	53.3 (9.6)	52.1 (10.0)	53.1 (9.1)	52.6 (11.2)
Gender, n (%)								
Male	41 (53.9)	47 (64.4)	55 (38.7)	61 (40.7)	56 (47.1)	60 (50.4)	39 (40.6)	48 (47.5)
Female	35 (46.1)	26 (35.6)	87 (61.3)	89 (59.3)	63 (52.9)	59 (49.6)	57 (59.4)	53 (52.5)
Weight, kg	78.6 (11.5)	79.0 (12.8)	106.2 (20.2)	107.9 (23.1)	89.8 (19.8)	90.3 (21.2)	105.4 (21.5)	108.3 (24.3)
BMI, kg/m^2	26.4 (2.6)	26.4 (3.1)	37.7 (7.3)	37.6 (6.7)	31.4 (6.7)	31.3 (6.6)	36.8 (8.7)	37.1 (7.8)
Waist circumference, cm	90.4 (9.7)	89.5 (12.3)	110.4 (13.5)	110.6 (14.3)	98.3 (15.9)	97.8 (16.0)	110.1 (13.0)	110.8 (14.9)
Diabetes, n (%)	12 (15.8)	8 (11.0)	28 (19.7)	30 (20.0)	22 (18.5)	12 (10.1)	18 (18.8)	25 (24.8)
MetS, n (%)	17 (22.4)	15 (20.5)	79 (55.6)	86 (57.3)	0 (0.0)	0 (0.0)	96 (100.0)	101 (100.0)
msSBP, mm Hg	168.0 (7.8)	167.2 (7.3)	167.0 (8.3)	167.5 (8.4)	167.9 (8.8)	167.7 (8.2)	167.0 (7.7)	167.2 (8.0)
msDBP, mm Hg	97.2 (10.4)	96.9 (9.4)	95.5 (8.7)	97.4 (7.6)	96.0 (9.8)	98.1 (8.6)	96.4 (9.2)	96.4 (7.5)

A, aliskiren; AML, amlodipine; BMI, body mass index; circ, circumference; MetS, metabolic syndrome; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

All values are means (standard deviations) unless otherwise indicated.

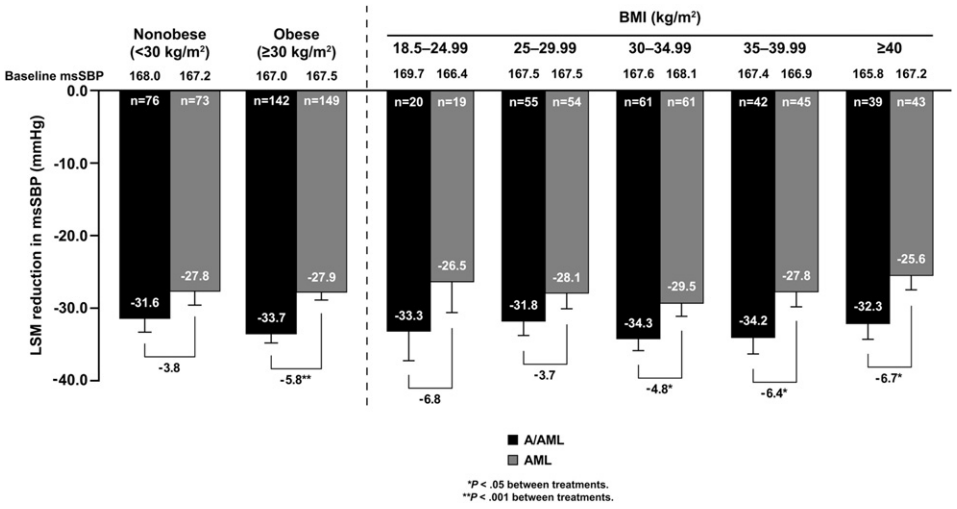

Figure 2. Least-square mean (LSM) reductions from baseline to week 8 in mean sitting systolic blood pressure (msSBP) in obese (body mass index [BMI] $\geq$30 kg/m^2) and nonobese (BMI $<$30 kg/m^2) subjects and across a range of baseline BMI values. Error bars represent standard error of the mean. A, aliskiren; AML, amlodipine.

frequency of these AEs was generally similar between the treatment groups both in the overall population and the subgroups analyzed (Table 2). The frequency of AEs was also generally similar between obese and nonobese subjects as well as between subjects with and without MetS, although more obese than nonobese subjects experienced peripheral edema; this was true of both the aliskiren/amlodipine and amlodipine groups (Table 2). There were few SAEs (unstable angina in the aliskiren/amlodipine group, pneumonia and back pain in the amlodipine group) and discontinuations because of AEs (nine in aliskiren/amlodipine group, three in amlodipine group) during the study, as previously reported.[9]

For all subgroups, no significant differences were observed between the two treatment groups with respect to changes from baseline to week 8 in fasting blood glucose levels or urinary albumin excretion rate (Table 3). Across the subgroups, least-square mean changes from baseline to week 8 in fasting blood glucose levels ranged from −0.1 to 6.7 mg/dL with combination aliskiren/amlodipine and 2.4 to 7.3 mg/dL with amlodipine monotherapy. Geometric mean ratios of the change from baseline to week 8 in urinary albumin excretion rate (combination therapy vs. monotherapy) were 0.800 (95% confidence interval [CI]: 0.475–1.349) in obese subjects, 1.007 (95%

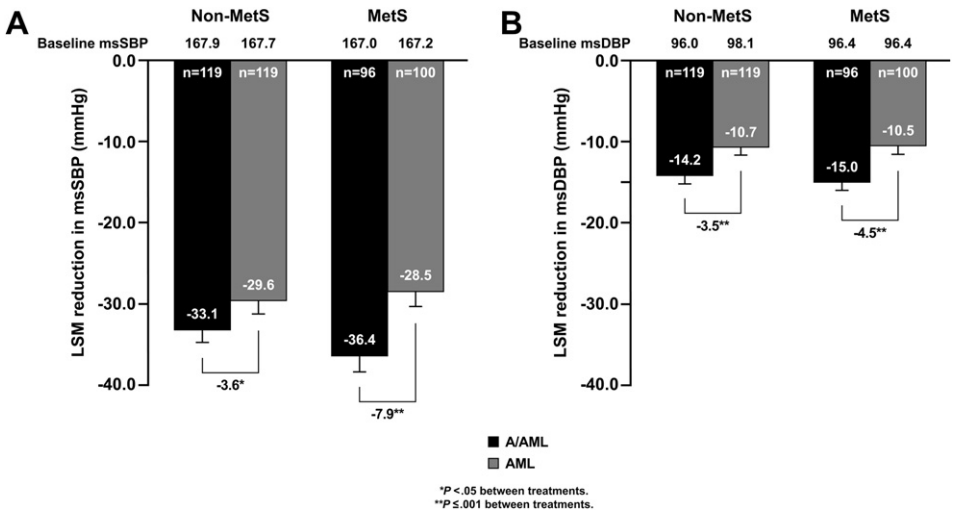

Figure 3. Least-square mean (LSM) reductions from baseline to week 8 in (A) mean sitting systolic blood pressure (msSBP) and (B) mean sitting diastolic blood pressure (msDBP) in subjects with and without the metabolic syndrome (MetS) at baseline. Error bars represent standard error of the mean. A, aliskiren; AML, amlodipine.

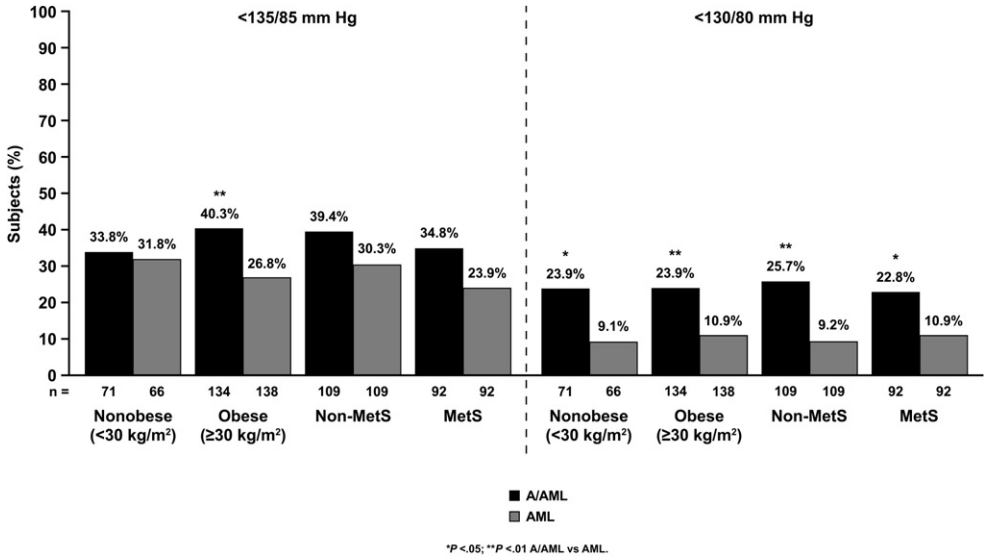

Figure 4. Percentage of subjects achieving blood pressure (BP) goals of <135/85 mm Hg and <130/80 mm Hg in nonobese (body mass index [BMI] <30 kg/m^2) and obese (BMI ≥30 kg/m^2) subjects and subjects with and without the metabolic syndrome (MetS). A, aliskiren; AML, amlodipine.

CI: 0.617–1.644) in nonobese subjects, 0.556 (95% CI: 0.307–1.009) in MetS subjects, and 1.140 (95% CI: 0.714–1.820) in non-MetS subjects.

Discussion

This post-hoc analysis of the AACESS study included self-identified African Americans with stage 2 hypertension and obesity or MetS and whose msSBP value was >15 mm Hg above goal (<135 mm Hg or <130 mm Hg). Regardless of subgroup, subjects experienced greater antihypertensive efficacy after treatment with combination aliskiren/amlodipine 300/10 mg compared with amlodipine 10 mg alone. msSBP and msDBP reductions from baseline to 8 weeks (primary time point), as well as the proportions of subjects achieving BP <130/80 mm Hg at 8 weeks, significantly favored combination therapy over monotherapy (all $P < .05$). The subgroup results presented here are similar to those reported for the overall population in which 8 weeks of treatment with combination aliskiren/amlodipine reduced BP by −34.1/−14.3 mm Hg while amlodipine alone reduced BP by −28.9/−10.5 mm Hg ($P < .001$ between treatments).[9] These data provide additional support for the guideline-recommended approach of treating this high-risk population with combination RAS inhibitor/CCB.[5]

Several other clinical studies, conducted largely in Caucasians with few African American participants (<5% overall), also support the use of combination aliskiren/amlodipine for the treatment of hypertension.[11–16] Braun-Dullaeus and colleagues used a study design and titration schedule identical to our study and found that combination aliskiren/amlodipine (n = 233) reduced msSBP by −37.7 mm Hg at 8 weeks, compared with −30.6 mm Hg on amlodipine alone (n = 230) ($P < .0001$).[15] Reductions in both treatment groups were greater than those in the overall AACESS population, by about 3.6 mm Hg with combination therapy and 1.7 mm Hg with monotherapy. Differences in the study populations may have contributed to this finding.

Table 2
Most common AEs (≥2% in either treatment group in overall population)

AE, n (%)	All Subjects		Nonobese (<30 kg/m^2)		Obese (≥30 kg/m^2)		Non-MetS		MetS	
	A/AML (n = 220)	AML (n = 223)	A/AML (n = 76)	AML (n = 73)	A/AML (n = 142)	AML (n = 150)	A/AML (n = 119)	AML (n = 119)	A/AML (n = 96)	AML (n = 101)
Total AEs	77 (35.0)	73 (32.7)	24 (31.6)	21 (28.8)	51 (35.9)	52 (34.7)	43 (36.1)	35 (29.4)	32 (33.3)	35 (34.7)
Peripheral edema	17 (7.7)	20 (9.0)	3 (3.9)	4 (5.5)	14 (9.9)	16 (10.7)	10 (8.4)	9 (7.6)	7 (7.3)	11 (10.9)
Headache	8 (3.6)	12 (5.4)	2 (2.6)	4 (5.5)	5 (3.5)	8 (5.3)	7 (5.9)	4 (3.4)	1 (1.0)	7 (6.9)
Fatigue	5 (2.3)	6 (2.7)	3 (3.9)	3 (4.1)	2 (1.4)	3 (2.0)	3 (2.5)	2 (1.7)	1 (1.0)	3 (3.0)
Nausea	7 (3.2)	4 (1.8)	3 (3.9)	2 (2.7)	4 (2.8)	2 (1.3)	5 (4.2)	3 (2.5)	2 (2.1)	1 (1.0)

A, aliskiren; AE, adverse event; AML, amlodipine; MetS, metabolic syndrome.

Table 3
Summary of fasting blood glucose and UAER results

Parameter	Nonobese (<30 kg/m^2)		Obese (≥30 kg/m^2)		Non-MetS		MetS	
	A/AML	AML	A/AML	AML	A/AML	AML	A/AML	AML
Fasting blood glucose, mg/dL								
Mean ± SD at baseline	99.9 ± 22.6 (n = 76)	98.3 ± 21.3 (n = 72)	108.7 ± 27.5 (n = 138)	104.3 ± 24.3 (n = 146)	103.1 ± 28.4 (n = 118)	97.0 ± 22.2 (n = 118)	108.5 ± 23.0 (n = 96)	108.6 ± 23.4 (n = 100)
Mean ± SD at week 8	105.1 ± 37.9 (n = 70)	103.5 ± 23.5 (n = 66)	110.3 ± 26.4 (n = 133)	108.2 ± 29.2 (n = 137)	105.3 ± 23.8 (n = 107)	99.3 ± 18.5 (n = 109)	112.8 ± 37.6 (n = 91)	116.3 ± 33.2 (n = 91)
LSM ± SE change	6.7 ± 3.6 (n = 68)	7.3 ± 3.8 (n = 65)	−0.1 ± 2.4 (n = 129)	2.4 ± 2.2 (n = 133)	5.4 ± 2.1 (n = 106)	2.7 ± 2.0 (n = 108)	1.0 ± 3.1 (n = 91)	4.3 ± 3.1 (n = 90)
UAER,* mg/24 h								
GM at baseline	11.6 (n = 25)	10.3 (n = 25)	13.7 (n = 30)	12.5 (n = 30)	11.7 (n = 30)	12.1 (n = 32)	15.0 (n = 24)	10.9 (n = 22)
GM at week 8	9.9 (n = 21)	9.5 (n = 21)	10.0 (n = 25)	10.5 (n = 31)	9.6 (n = 26)	9.5 (n = 32)	11.0 (n = 19)	11.4 (n = 19)
LSGM change	0.919 (n = 20)	0.912 (n = 20)	0.961 (n = 22)	1.200 (n = 26)	0.950 (n = 23)	0.833 (n = 28)	1.013 (n = 18)	1.820 (n = 17)
LSGM ratio (95% CI)	1.007 (0.617–1.644)		0.800 (0.475–1.349)		1.140 (0.714–1.820)		0.556 (0.307–1.009)	

A, aliskiren; AML, amlodipine; CI, confidence interval; GM, geometric mean; LSM, least-square mean; LSGM, least-square geometric mean; MetS, metabolic syndrome; SD, standard deviation; SE, standard error; UAER, urinary albumin excretion rate.

* Determined in the subset of subjects who participated in the ambulatory blood pressure monitoring substudy.

Participants in their study were predominantly Caucasian (70%) and Asian (27%); msSBP at baseline was about 4 mm Hg greater than in our study, and fewer obese subjects were enrolled (37% vs. 66%).

Other hypertension trials used different doses, titration schedules, and/or treatment durations compared with our study.[11–14,16] For example, a previous post-hoc analysis of a 52-week study evaluated BP response in the subset of 396 obese subjects (99% Caucasian; 67% had MetS).[14] Subjects were started on aliskiren 150 mg and force-titrated to aliskiren 300 mg, followed by the addition of amlodipine (5 mg and then 10 mg) to achieve BP <140/90 mm Hg. Subjects may have initiated treatment with the highest doses (aliskiren/amlodipine 300/10 mg) as early as week 18. At 52 weeks, combination aliskiren/amlodipine reduced msSBP by −19.9 mm Hg. The obese subjects in that study had lower BPs at baseline (msSBP ∼155 mm Hg), which may account for the less robust msSBP reductions relative to previously mentioned studies. Brown and colleagues reported the results of the Aliskiren and the Calcium Channel Blocker Amlodipine Combination as Initial Treatment Strategy in Stage I and II Hypertension (ACCELERATE) study, conducted in predominantly Caucasian (78%) hypertensive subjects with a mean BMI of ∼30 kg/m^2.[16] Over the initial 8 weeks, treatment with aliskiren/amlodipine 150/5 mg (n = 620), aliskiren 150 mg (n = 318), or amlodipine 5 mg (n = 316) reduced msSBP by about −21.5 mm Hg, −11.6 mm Hg, and −14.3 mm Hg, respectively. The magnitude of BP reduction remained numerically greatest in the initial combination-therapy group throughout the 32-week trial, despite the fact that all subjects were uptitrated to aliskiren/amlodipine 300/10 mg starting at 16 weeks. The larger reductions in BP observed in AACESS compared with the first 8 weeks of ACCELERATE can reasonably be attributed to the use of double doses of study medication and a baseline msSBP that was about 6–7 mm Hg higher.

Most recently, Ferdinand and colleagues employed a titration schedule in which subjects were uptitrated more slowly than in our study and received combination aliskiren/amlodipine 300/10 mg for only 4 weeks (ie, 3 weeks less than in our study).[17] This 8-week, randomized, double-blind study included 411 self-identified minority subjects (62% African American) with stage 2 hypertension (mean 167/95 mm Hg) and a high prevalence of comorbidities (69% MetS, mean BMI 32.3 kg/m^2). The reduction in msSBP/msDBP at end of study, the primary time point, was −29.5/−12.0 mm Hg.

The treatments in our study were well tolerated, both in obese and MetS subjects, and had similar effects on fasting blood glucose and urinary albumin excretion rate. The incidence of peripheral edema, a known side effect of amlodipine, was greater in obese (9.9% to 10.7%) versus nonobese (3.9% to 5.5%) subjects, regardless of treatment. This could possibly be related to the greater rate of

venous insufficiency that is generally observed in obese subjects.[18]

A limitation of our analysis was that it was post hoc. In addition, <35% of study participants were nonobese and some of the BMI subgroups comprised a limited number of subjects. This may have resulted in a lack of statistical power to detect some between-treatment differences within these subgroups. Nonetheless, numerical differences consistently favored combination therapy over monotherapy across all subgroups analyzed. A greater proportion of obese or MetS subjects achieved the BP goals on combination therapy than on monotherapy. We found that approximately one quarter of subjects treated with combination aliskiren/amlodipine were able to attain BP below the most stringent level (<130/80 mm Hg) recommended in the recent ISHIB consensus statement.[5] This finding is consistent with data from the African American Study of Kidney Disease and Hypertension (AASK) study in which 2 years of treatment resulted in 12% and 51% of subjects attaining BP <130/80 mm Hg while on an average of 2.7 and 3.5 antihypertensive drug classes, respectively.[19] Taken together, these data underscore the difficulty in adequately lowering BP in high-risk populations. The demographic and baseline characteristics of our study population suggest that the vast majority of individuals will require three or more antihypertensive agents.

Conclusions

In conclusion, combination aliskiren/amlodipine 300/10 mg is more effective than amlodipine 10 mg alone at lowering BP in African Americans with stage 2 hypertension and obesity or MetS. Both treatments are well tolerated. Our results support the use of combination RAS inhibitor/CCB for this high-risk population and, like previous studies, suggest that most subjects will require additional antihypertensive agents to achieve guideline-recommended BP levels.

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