



# Outcomes with Angiotensin-converting Enzyme Inhibitors vs Other Antihypertensive Agents in Hypertensive Blacks

Sripal Bangalore, MD, MHA,<sup>a</sup> Gbenga Ogedegbe, MD, MS, MPH,<sup>b,c</sup> Joyce Gyamfi, MS,<sup>b</sup> Yu Guo, MA,<sup>b</sup> Jason Roy, PhD,<sup>d</sup> Keith Goldfeld, DrPH,<sup>b</sup> Christopher Torgersen, MBA,<sup>b</sup> Louis Capponi, MD,<sup>e,f</sup> Christopher Phillips, MD, MPH,<sup>g</sup> Nirav R. Shah, MD, MPH<sup>h</sup>

<sup>a</sup>The Leon H. Charney Division of Cardiology, New York University School of Medicine, New York; <sup>b</sup>Department of Population Health, New York University School of Medicine, New York; <sup>c</sup>New York University Global Institute of Public Health, New York; <sup>d</sup>Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia; <sup>e</sup>New York City Health and Hospitals Cooperation, New York; <sup>f</sup>Department of Medicine, New York University School of Medicine, New York; <sup>g</sup>Morehouse School of Medicine, Atlanta, Ga; <sup>h</sup>Kaiser Foundation Hospital & Health Plan, Pasadena, Calif.

## ABSTRACT

**BACKGROUND:** Angiotensin-converting enzyme inhibitors are used widely in the treatment of patients with hypertension. However, their efficacy in hypertensive blacks when compared with other antihypertensive agents is not well established.

**METHODS:** We performed a cohort study of patients using data from a clinical data warehouse of 434,646 patients from New York City's Health and Hospitals Corporation from January 2004 to December 2009. Patients were divided into the following comparison groups: angiotensin-converting enzyme inhibitors vs calcium channel blockers, angiotensin-converting enzyme inhibitors vs thiazide diuretics, and angiotensin-converting enzyme inhibitors vs  $\beta$ -blockers. The primary outcome was a composite of death, myocardial infarction, and stroke. Secondary outcomes included the individual components and heart failure.

**RESULTS:** In the propensity score-matched angiotensin-converting enzyme inhibitors vs calcium channel blocker comparison cohort (4506 blacks in each group), angiotensin-converting enzyme inhibitors were associated with a higher risk of primary outcome (hazard ratio [HR], 1.45; 95% confidence interval [CI], 1.19-1.77;  $P = .0003$ ), myocardial infarction (HR, 3.40; 95% CI, 1.25-9.22;  $P = .02$ ), stroke (HR, 1.82; 95% CI, 1.29-2.57;  $P = .001$ ), and heart failure (HR, 1.77; 95% CI, 1.30-2.42;  $P = .0003$ ) when compared with calcium channel blockers. For the angiotensin-converting enzyme inhibitors vs thiazide diuretics comparison (5337 blacks in each group), angiotensin-converting enzyme inhibitors were associated with a higher risk of primary outcome (HR, 1.65; 95% CI, 1.33-2.05;  $P < .0001$ ), death (HR, 1.35; 95% CI, 1.03-1.76;  $P = .03$ ), myocardial infarction (HR, 4.00; 95% CI, 1.34-11.96;  $P = .01$ ), stroke (HR, 1.97; 95% CI, 1.34-2.92;  $P = .001$ ), and heart failure (HR, 3.00; 95% CI, 1.99-4.54;  $P < .0001$ ). For the angiotensin-converting enzyme inhibitors vs  $\beta$ -blocker comparison, the outcomes between the groups were not significantly different.

**CONCLUSIONS:** In a real-world cohort of hypertensive blacks, angiotensin-converting enzyme inhibitors were associated with a higher risk of cardiovascular events when compared with calcium channel blockers or thiazide diuretics.

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**KEYWORDS:** Angiotensin-converting enzyme inhibitors; Blacks; Hypertension

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Requests for reprints should be addressed to Sripal Bangalore, MD, MHA, The Leon H. Charney Division of Cardiology, New York University School of Medicine, 530 First Ave, SKI 9R/109, New York, NY 10016.

E-mail address: [sripalbangalore@gmail.com](mailto:sripalbangalore@gmail.com)

Major national and international hypertension guidelines recommend angiotensin-converting enzyme inhibitors as one of the first-line agents for the treatment of hypertension.<sup>1-3</sup> Despite the proven efficacy of angiotensin-converting enzyme inhibitors in lowering blood pressure,<sup>4-6</sup> there is uncertainty about their effectiveness among blacks.<sup>7</sup> In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), blacks treated with angiotensin-converting enzyme inhibitors demonstrated poorer blood pressure control (5/2 mm Hg higher blood pressure), 40% greater risk of stroke, 32% greater risk of heart failure, and 19% greater rates of cardiovascular disease than those randomized to diuretics.<sup>7-9</sup> In addition, studies have shown that blacks are more prone to develop adverse effects associated with angiotensin-converting enzyme inhibitors, including cough, angioedema,<sup>10,11</sup> and hyperkalemia.<sup>12</sup> Consequently, the National Institute for Health and Clinical Excellence clinical practice guidelines for hypertension recommend calcium channel blockers in lieu of angiotensin-converting enzyme inhibitors for hypertensive blacks as initial therapy. If a calcium channel blocker is not tolerated because of edema or other side effects, the guidelines recommend a thiazide-like diuretic in blacks.<sup>1</sup>

Given the low representation of blacks in hypertension clinical trials, there is an urgent need for more definitive data on the real-world therapeutic effectiveness of angiotensin-converting enzyme inhibitors vs other antihypertensive agents in hypertensive blacks. Our objective was to evaluate the effectiveness of angiotensin-converting enzyme inhibitors when compared with other antihypertensive agents in hypertensive blacks.

## MATERIALS AND METHODS

### Patient Population

Data from the New York City Health and Hospital Corporation's clinical data warehouse encompassing more than 1.8 million patients from its inception on January 2004 to December 2009 were chosen. The Health and Hospital Corporation consists of 11 acute care hospitals, 6 diagnostic and treatment centers, 4 long-term care facilities, a certified home health care agency, and more than 80 community health clinics, which provide care for approximately one fifth of all general hospital discharges and more than one third of emergency department and hospital-based clinic

visits in New York City. Approximately 35% of patients seen in the Health and Hospital Corporation system are black. The institutional review boards from the New York University School of Medicine and New York City Health and Hospital Corporation approved the study.

### CLINICAL SIGNIFICANCE

- In a cohort of 25,564 propensity score-matched hypertensive black patients, angiotensin-converting enzyme inhibitors were associated with a higher risk of primary outcome, myocardial infarction, stroke, and heart failure vs calcium channel blockers (4506 matched pairs) and a higher risk of primary outcome, death, myocardial infarction, stroke, and heart failure vs thiazide diuretics (5337 matched pairs).
- In this largest cohort of hypertensive blacks, angiotensin-converting enzyme inhibitors were associated with less benefit when compared with calcium channel blockers or thiazide diuretics.

### Inclusion and Exclusion Criteria

For the current study, hypertensive black patients who met the following inclusion criteria were selected: (1) hypertension diagnosis (identified through International Classification of Diseases, 9th Revision, Clinical Modification code for hypertension, or systolic pressure >140 mm Hg, or prescribed an antihypertensive agent on at least 2 occasions); and (2) prescribed an angiotensin-converting enzyme inhibitor/ $\beta$ -blocker/thiazide diuretic/calcium channel blocker at least 6 months after their first date of entry in the system (to prevent "healthy user" effect) and with at least 1 additional refill.

The exclusion criteria included (1) age <18 years or >90 years; (2) first medication prescription <6 months of entry into the system; (3) a history of heart failure, myocardial infarction, or stroke, because these are compelling indications for angiotensin-converting enzyme inhibitor use; (4) prescription of an angiotensin receptor blocker; and (5) patients with missing follow-up.

### Antihypertensive Use and Follow-up

We identified new users (an inception cohort) for each antihypertensive medication of interest<sup>13</sup> to prevent "healthy user" effects that result from studying patients who are not treatment naïve.<sup>14</sup> A 6-month time span after their first date of entry in the system and before the first prescription was required to ensure patients are new users, to eliminate selection bias.

Patient follow-up information, including blood pressure measurements, was obtained from the electronic health records (Misys, Raleigh, N.C). The study data were derived from structured fields and codes in the electronic health records, which contain all potential confounders to be included in the models. In addition, the database was linked with the New York State Vital Statistics to determine death during follow-up.

### Outcomes

The primary outcome was a composite of death, nonfatal myocardial infarction, and nonfatal stroke. Secondary

outcomes were the individual components of the primary outcome and heart failure.

## Statistical Analysis

All analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, NC). Three separate cohorts were identified: angiotensin-converting enzyme inhibitors vs calcium channel blocker, angiotensin-converting enzyme inhibitors vs thiazide diuretics, and angiotensin-converting enzyme inhibitors vs  $\beta$ -blockers.

**Propensity Score Matching.** Given the differences in baseline characteristics between participants in the 2 groups for each of the 3 cohorts (Tables 1-3), propensity score matching was used to identify a cohort of patients with similar baseline characteristics. The propensity score is a conditional

probability of having a particular exposure (eg, angiotensin-converting enzyme inhibitors vs calcium channel blocker) given a set of baseline measured covariates<sup>15,16</sup> and was estimated using a nonparsimonious multivariable logistic regression model<sup>17</sup> using angiotensin-converting enzyme inhibitor use as the dependent variable and all the baseline characteristics outlined in Table 1 as covariates. A caliper width of 0.2 times the standard deviation of logit of the propensity scores was used. Matching was performed using a 1:1 matching protocol without replacement (Greedy matching protocol). Absolute standardized differences were estimated for all the baseline covariates before and after matching to assess pre-match imbalance and post-match balance.<sup>18</sup> Absolute standardized differences <10% for a given covariate indicate a relatively small imbalance.<sup>18</sup>

We conducted each of the outcome analyses using the matched groups. Each outcome was operationalized in

**Table 1** Baseline Characteristics Before and After Propensity Score Matching for the Angiotensin-Converting Enzyme Inhibitor vs Calcium Channel Blocker Comparisons

Variables	Unmatched			Matched		
	ACEi (N = 11,144)	CCB (N = 6044)	ASD	ACEi (N = 4506)	CCB (N = 4506)	ASD
Age (y)	50.0 ± 12.8	50.5 ± 13.8	3.8%	50.9 ± 13.4	50.6 ± 13.8	2.2%
Female	57.4%	65.7%	17.2%	64.7%	64.2%	1.1%
BMI	32.3 ± 10.8	32.9 ± 11.3	5.0%	32.8 ± 11.6	32.9 ± 11.3	0.6%
Insurance	80.3%	79.5%	2.1%	78.8%	79.6%	2.1%
Baseline systolic pressure	143 ± 21	153 ± 22	47.7%	149 ± 21	150 ± 21	1.3%
Baseline diastolic pressure	82 ± 13	87 ± 13	33.3%	85 ± 13	85 ± 13	1.3%
Baseline heart rate	80 ± 14	80 ± 14	4.5%	80 ± 14	80 ± 14	0.7%
Diabetes mellitus	44.6%	17.6%	60.9%	24.1%	22.3%	4.3%
Atrial fibrillation	1.4%	0.5%	9.3%	1.2%	0.6%	6.0%
Cardiac dysrhythmias	3.0%	1.9%	6.9%	2.4%	2.1%	2.1%
Chronic pulmonary disease	0.2%	0.3%	0.6%	0.2%	0.2%	0.9%
Angina pectoris	1.4%	0.7%	6.9%	1.0%	0.9%	0.9%
Coronary artery disease	4.0%	1.8%	13.2%	2.2%	2.2%	0.6%
Diseases of mitral valve	0.1%	0.0%	3.1%	0.2%	0.0%	4.0%
Endocardial disease	0.0%	0.0%	1.2%	0.0%	0.1%	0.9%
Chronic kidney disease	1.5%	3.1%	11.2%	2.5%	2.6%	0.8%
Cancer	3.2%	5.2%	10.0%	4.6%	4.6%	0.1%
Connective tissue disease	1.0%	1.0%	0.5%	1.2%	1.1%	1.5%
Charlson score						
0	53.4%	76.1%	48.9%	71.6%	72.7%	2.3%
1-3	46.2%	23.1%	50.1%	28.1%	26.8%	2.8%
≥4	0.3%	0.7%	5.8%	0.3%	0.5%	3.4%
No. of hospitalization within 1 y	0.6 ± 1.1	0.4 ± 0.9	12.6%	0.47 ± 0.95	0.47 ± 0.89	0.2%
No. of days hospitalized within 1 y	3.7 ± 16.8	3.0 ± 10.8	4.9%	3.1 ± 14.8	3.0 ± 10.7	0.2%
No. of clinic visits within 1 y	10.6 ± 19.8	9.9 ± 16.8	3.7%	10.1 ± 19.9	9.9 ± 15.9	0.8%
No. of additional antihypertensive medication use						
0	93.8%	97.8%	20.3%	96.7%	97.3%	3.2%
1	4.3%	1.6%	16.1%	2.3%	2.0%	2.1%
2	1.3%	0.4%	9.6%	0.8%	0.6%	2.7%
≥3	0.6%	0.1%	7.3%	0.2%	0.2%	0.5%
BUN value	15.1 ± 7.1	15.9 ± 9.3	9.2%	15.5 ± 8.0	15.6 ± 8.6	1.5%
Creatinine value	1.0 ± 0.8	1.1 ± 1.2	11.8%	1.1 ± 1.0	1.1 ± 1.0	3.3%
GFR value	63.3 ± 14.9	66.7 ± 19.4	19.3%	66.0 ± 17.7	65.7 ± 18.4	1.7%

ACEi = angiotensin-converting enzyme inhibitor; ASD = absolute standardized differences; BMI = body mass index; BUN = blood urea nitrogen; CCB = calcium channel blocker; GFR = glomerular filtration rate.

**Table 2** Baseline Characteristics Before and After Propensity Score Matching for the Angiotensin-Converting Enzyme Inhibitor vs Thiazide Diuretic Comparisons

Variables	Unmatched			Matched		
	ACEi (N = 12,782)	Thiazide Diuretic (N = 7049)	ASD	ACEi (N = 5337)	Thiazide Diuretic (N = 5337)	ASD
Age (y)	51.1 ± 13.1	48.0 ± 12.6	24.0%	49.3 ± 13.1	49.1 ± 12.7	1.6%
Female	58.2%	66.8%	17.8%	63.6%	63.0%	1.4%
BMI	32.4 ± 11.0	33.0 ± 10.5	5.8%	32.8 ± 11.2	32.7 ± 10.6	1.0%
Insurance	81.6%	78.5%	7.6%	79.7%	79.2%	1.1%
Baseline systolic pressure	144 ± 21	148 ± 19	19.8%	148 ± 22	147 ± 19	1.3%
Baseline diastolic pressure	82 ± 13	85 ± 12	23.3%	85 ± 14	85 ± 12	0.1%
Baseline heart rate	80 ± 14	80 ± 13	4.9%	80 ± 14	79 ± 13	1.6%
Diabetes mellitus	44.6%	12.5%	76.1%	16.5%	16.0%	1.5%
Atrial fibrillation	1.5%	0.5%	9.9%	1.0%	0.6%	4.0%
Cardiac dysrhythmias	3.1%	1.8%	8.3%	2.2%	2.1%	0.8%
Chronic pulmonary disease	0.3%	0.1%	2.5%	0.2%	0.1%	0.9%
Angina pectoris	1.5%	0.6%	8.5%	0.7%	0.7%	0.2%
Coronary artery disease	4.2%	1.1%	19.1%	1.4%	1.4%	0.3%
Diseases of mitral valve	0.1%	0.0%	2.9%	0.2%	0.0%	4.1%
Endocardial disease	0.0%	0.0%	1.1%	0.0%	0.0%	1.1%
Chronic kidney disease	2.5%	0.5%	16.4%	0.5%	0.7%	1.7%
Cancer	4.1%	3.2%	4.8%	3.3%	3.1%	1.2%
Connective tissue disease	1.1%	0.6%	6.1%	0.7%	0.7%	0.2%
Charlson score						
0	52.3%	83.8%	71.6%	80.2%	80.4%	0.4%
1-3	47.2%	16.0%	71.3%	19.6%	19.3%	0.6%
≥4	0.5%	0.3%	3.9%	0.2%	0.3%	1.9%
No. of hospitalizations within 1 y	0.6 ± 1.1	0.3 ± 0.7	35.3%	0.3 ± 0.6	0.3 ± 0.8	1.5%
No. of days hospitalized within 1 y	3.8 ± 15.4	1.6 ± 10.3	16.5%	2.1 ± 8.75	2.0 ± 11.7	0.9%
No. of clinic visits within 1 y	11.1 ± 20.5	9.8 ± 18.6	6.7%	10.1 ± 20.3	9.9 ± 19.0	0.9%
No. of additional antihypertensive medication use						
0	80.1%	83.0%	7.6%	82.5%	82.5%	0.0%
1	19.4%	14.4%	13.4%	16.5%	16.1%	1.0%
2	0.4%	2.2%	15.9%	0.8%	1.1%	2.9%
≥3	0.1%	0.4%	5.3%	0.2%	0.3%	1.5%
BUN value	15.6 ± 8.0	14.2 ± 5.9	19.8%	14.6 ± 5.8	14.5 ± 6.2	1.5%
Creatinine value	1.1 ± 0.9	0.9 ± 0.4	18.1%	0.9 ± 0.4	1.0 ± 0.5	1.5%
GFR value	62.9 ± 15.8	63.9 ± 12.2	6.9%	63.6 ± 12.9	63.9 ± 12.5	3.0%

ACEi = angiotensin-converting enzyme inhibitor; ASD = absolute standardized differences; BMI = body mass index; BUN = blood urea nitrogen; GFR = glomerular filtration rate.

time-to-event fashion. Stratified Cox proportional hazards models, to account for matching, were fitted, with the treatment indicator variables as the exposure of interest. We reported hazard ratios (HRs) and 95% confidence intervals (CIs).

**Sensitivity Analysis.** Sensitivity analysis was performed to assess the robustness of the results using an inverse probability of treatment weights approach.<sup>19,20</sup> The advantage of the inverse probability of treatment weights approach is the use of all patients in the cohort, compared with propensity score matching in which only a subset of patients are matched. In the inverse probability of treatment weights approach, the Cox proportional model weighted observations using stabilized inverse probability weights, calculated as the marginal probability of being in the group divided by

the probability of being in the group conditional on the predictors. The probabilities were calculated using the logistic regression models. All reported *P* values are 2-sided and are not adjusted for multiple testing.

## RESULTS

### Angiotensin-Converting Enzyme Inhibitors vs Calcium Channel Blockers

Of the 434,646 patients with hypertension, 11,144 black patients taking angiotensin-converting enzyme inhibitors and 6044 black patients taking calcium channel blockers satisfied our inclusion criteria. The baseline characteristics of patients taking angiotensin-converting enzyme inhibitors vs calcium channel blockers are outlined in [Table 1](#).

**Table 3** Baseline Characteristics Before and After Propensity Score Matching for the Angiotensin-Converting Enzyme Inhibitor vs  $\beta$ -Blocker Comparisons

Variables	Unmatched			Matched		
	ACEi (N = 13,506)	$\beta$ -Blocker (N = 3057)	ASD	ACEi (N = 2939)	$\beta$ -Blocker (N = 2939)	ASD
Age (y)	50.9 $\pm$ 13.0	49.4 $\pm$ 14.7	11.0%	49.6 $\pm$ 13.5	49.5 $\pm$ 14.6	1.2%
Female	58.8%	63.3%	9.2%	61.7%	63.0%	2.7%
BMI	32.4 $\pm$ 10.9	32.1 $\pm$ 11.5	3.3%	32.0 $\pm$ 11.2	32.1 $\pm$ 11.5	1.3%
Insurance	80.9%	83.4%	6.7%	84.2%	83.3%	2.5%
Baseline systolic pressure	145 $\pm$ 21	138 $\pm$ 21	29.1%	139 $\pm$ 21	139 $\pm$ 21	0.3%
Baseline diastolic pressure	83 $\pm$ 13	80 $\pm$ 13	17.0%	81 $\pm$ 13	81 $\pm$ 13	0.2%
Baseline heart rate	80 $\pm$ 14	82 $\pm$ 15	11.8%	82 $\pm$ 16	82 $\pm$ 15	2.0%
Diabetes mellitus	43.4%	14.0%	68.7%	16.4%	14.5%	5.2%
Atrial fibrillation	1.4%	2.9%	11.0%	2.4%	2.8%	2.6%
Cardiac dysrhythmias	3.0%	5.8%	13.3%	5.5%	5.4%	0.3%
Chronic pulmonary disease	0.2%	0.2%	0.0%	0.2%	0.2%	0.8%
Angina pectoris	1.4%	1.7%	2.2%	1.5%	1.7%	1.1%
Coronary artery disease	3.9%	3.4%	2.4%	3.8%	3.5%	1.6%
Diseases of mitral valve	0.1%	0.2%	1.6%	0.1%	0.2%	1.8%
Endocardial disease	0.0%	0.0%	0.2%	0.0%	0.0%	2.6%
Renal disease	2.4%	1.2%	9.0%	1.5%	1.3%	2.0%
Cancer	4.0%	5.5%	7.1%	5.1%	5.4%	1.4%
Connective tissue disease	1.1%	0.6%	6.2%	0.7%	0.6%	2.1%
Charlson score						
0	53.5%	79.3%	56.7%	77.9%	79.1%	2.9%
1-3	46.0%	20.0%	57.5%	21.5%	20.3%	3.0%
$\geq$ 4	0.5%	0.7%	2.5%	0.6%	0.6%	0.4%
No. of hospitalizations within 1 y	0.6 $\pm$ 1.1	0.7 $\pm$ 1.1	11.3%	0.7 $\pm$ 1.3	0.7 $\pm$ 1.0	1.9%
No. of days hospitalized within 1 y	3.6 $\pm$ 15.7	5.6 $\pm$ 31.6	8.1%	5.5 $\pm$ 26.3	5.3 $\pm$ 21.5	0.7%
No. of clinic visits within 1 y	11.0 $\pm$ 20.2	9.9 $\pm$ 15.1	6.1%	9.8 $\pm$ 17.5	9.9 $\pm$ 15.3	0.6%
No. of additional antihypertensive medication use						
0	79.4%	75.9%	8.3%	77.4%	77.3%	0.2%
1	19.6%	17.5%	5.2%	18.3%	17.9%	1.1%
2	0.7%	5.0%	25.9%	3.1%	3.5%	2.1%
$\geq$ 3	0.3%	1.5%	12.7%	1.2%	1.3%	1.2%
BUN value	15.6 $\pm$ 7.9	14.6 $\pm$ 8.0	11.5%	14.9 $\pm$ 7.3	14.7 $\pm$ 8.2	2.8%
Creatinine value	1.1 $\pm$ 0.9	1.0 $\pm$ 0.8	6.6%	1.0 $\pm$ 0.7	1.0 $\pm$ 0.9	0.9%
GFR value	62.9 $\pm$ 15.7	65.5 $\pm$ 16.0	16.4%	65.7 $\pm$ 15.7	65.5 $\pm$ 16.1	0.9%

ACEi = angiotensin-converting enzyme inhibitor; ASD = absolute standardized differences; BMI = body mass index; BUN = blood urea nitrogen; GFR = glomerular filtration rate.

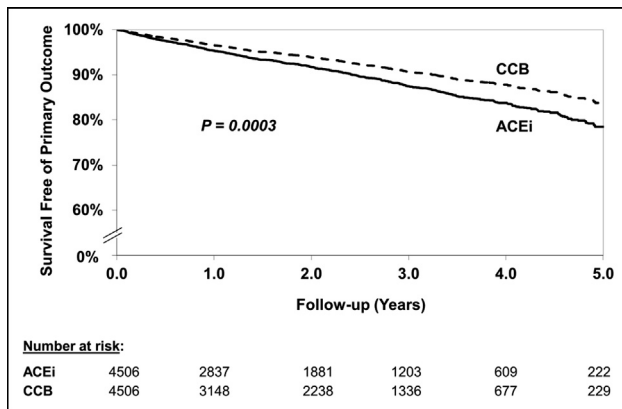
Propensity score matching matched 9012 black patients (4506 in each group) with a similar propensity score. Post-matching, the absolute standardized differences were  $<10\%$ , indicating similar baseline characteristics between the groups and an adequate match (Table 1).

Angiotensin-converting enzyme inhibitor use was associated with a higher risk of primary outcome (HR, 1.45; 95% CI, 1.19-1.77;  $P = .0003$ ) (Figure 1), myocardial infarction (HR, 3.40; 95% CI, 1.25-9.22;  $P = .02$ ), stroke (HR, 1.82; 95% CI, 1.29-2.57;  $P = .001$ ), and heart failure (HR, 1.77; 95% CI, 1.30, 2.42;  $P = .0003$ ) when compared with the group taking a calcium channel blocker (Table 4). The results were largely similar in the analysis adjusted for inverse probability of treatment weights, in which angiotensin-converting enzyme inhibitors were associated with a higher risk of primary outcome (HR, 1.18;

95% CI, 1.05-1.32;  $P = .01$ ) and heart failure (HR, 1.62; 95% CI, 1.34-1.95;  $P < .0001$ ), and a numerically higher risk of myocardial infarction (HR, 1.57; 95% CI, 0.93-2.63;  $P = .09$ ) and stroke (HR, 1.20; 95% CI, 0.97-1.48;  $P = .09$ ).

### Angiotensin-Converting Enzyme Inhibitors vs Thiazide Diuretics

Among the patients with hypertension, 12,782 black patients taking angiotensin-converting enzyme inhibitors and 7049 black patients taking a thiazide diuretic satisfied our inclusion criteria. The baseline characteristics of patients taking angiotensin-converting enzyme inhibitors vs patients taking a thiazide diuretic are outlined in Table 2. Propensity score matching matched 10,674 black patients (5337 in each group) with a similar propensity score. Post-matching, the



**Figure 1** Angiotensin-converting enzyme inhibitor vs calcium channel blocker: risk of primary outcome. ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker.

absolute standardized differences were <10%, indicating similar baseline characteristics between the groups and an adequate match (Table 1).

Angiotensin-converting enzyme inhibitors were associated with a higher risk of primary outcome (HR, 1.65; 95% CI, 1.33-2.05;  $P < .0001$ ) (Figure 2), death (HR, 1.35; 95% CI, 1.03-1.76;  $P = .03$ ), myocardial infarction (HR, 4.00; 95% CI, 1.34-11.96;  $P = .01$ ), stroke (HR, 1.97; 95% CI, 1.34-2.92;  $P = .001$ ), and heart failure (HR, 3.00; 95% CI, 1.99-4.54;  $P < .0001$ ) when compared with the group taking thiazide diuretics (Table 4). The results were largely similar in the analysis adjusted for inverse probability of treatment weights, in which angiotensin-converting enzyme inhibitors were associated with a higher risk of primary outcome (HR, 1.47; 95% CI, 1.30-1.66;  $P < .0001$ ), death (HR, 1.35; 95% CI, 1.17-1.56;  $P < .0001$ ), myocardial infarction (HR, 2.12; 95% CI, 1.19-3.78;  $P = .01$ ), stroke (HR, 1.56; 95% CI, 1.25-1.95;  $P < .0001$ ), and heart failure (HR, 2.73; 95% CI, 2.17-3.44;  $P < .0001$ ).

## Angiotensin-Converting Enzyme Inhibitors vs $\beta$ -Blockers

Among the patients with hypertension, 13,506 black patients taking angiotensin-converting enzyme inhibitors

and 3057 black patients taking a  $\beta$ -blocker satisfied our inclusion criteria. The baseline characteristics of patients taking angiotensin-converting enzyme inhibitors vs  $\beta$ -blockers are outlined in Table 3. Propensity score matching matched 5878 patients (2939 in each group) with a similar propensity score. Post-matching, the absolute standardized differences were <10%, indicating similar baseline characteristics between the groups and an adequate match (Table 1).

Angiotensin-converting enzyme inhibitors were associated with a similar risk of primary outcome ( $P = .45$ ), death ( $P = .72$ ), myocardial infarction ( $P = .06$ ), and stroke ( $P = .50$ ) but a higher risk of heart failure (HR, 2.38; 95% CI, 1.57-3.59;  $P < .0001$ ) when compared with the group taking  $\beta$ -blockers (Figure 3, Table 4).

## DISCUSSION

The results of the study with data derived from a real-world clinical practice cohort of hypertensive blacks showed that angiotensin-converting enzyme inhibitors were associated with worse cardiovascular outcomes when compared with calcium channel blockers or thiazide diuretics. However, the outcomes with angiotensin-converting enzyme inhibitors were largely similar to that of  $\beta$ -blockers (except worse outcomes for heart failure noted with angiotensin-converting enzyme inhibitors).

## Use of Angiotensin-Converting Enzyme Inhibitors for Blacks

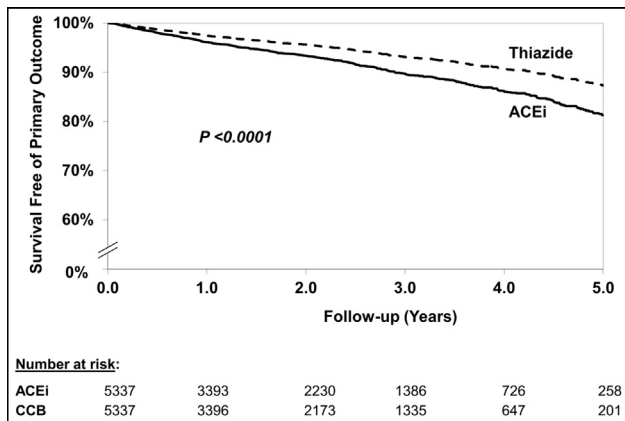
Black patients disproportionately experience hypertension<sup>21</sup> and have a significantly greater risk of hypertension-associated complications and target organ damage, including 1.8 times greater risk of stroke, 1.5 times greater risk of cardiovascular death, and 4.2 times greater risk of end-stage kidney disease when compared with whites.<sup>22-24</sup> Thus, effective antihypertensive therapy is particularly important in this high-risk group of patients.

Although angiotensin-converting enzyme inhibitors are commonly recommended as one of the first-line antihypertensive agents by national and international guidelines, the role of angiotensin-converting enzyme inhibitors in blacks has been questioned. Studies have shown that the

**Table 4** Primary and Secondary Outcomes in the Matched Cohort

Outcome	ACEi vs CCB		ACEi vs Thiazide Diuretic		ACEi vs $\beta$ -Blockers	
	HR (95% CI)	<i>P</i> Value	HR (95% CI)	<i>P</i> Value	HR (95% CI)	<i>P</i> Value
Primary outcome	1.45 (1.19-1.77)	.0003	1.65 (1.33-2.05)	<.0001	1.09 (0.88-1.35)	.45
Death	1.17 (0.92-1.49)	.20	1.35 (1.03-1.76)	.03	0.96 (0.76-1.21)	.72
Myocardial infarction	3.40 (1.25-9.22)	.02	4.00 (1.34-11.96)	.01	3.00 (0.97-9.30)	.06
Stroke	1.82 (1.29-2.57)	.001	1.97 (1.34-2.92)	.001	1.20 (0.71-2.04)	.50
Congestive heart failure	1.77 (1.30-2.42)	.0003	3.00 (1.99-4.54)	<.0001	2.38 (1.57-3.59)	<.0001

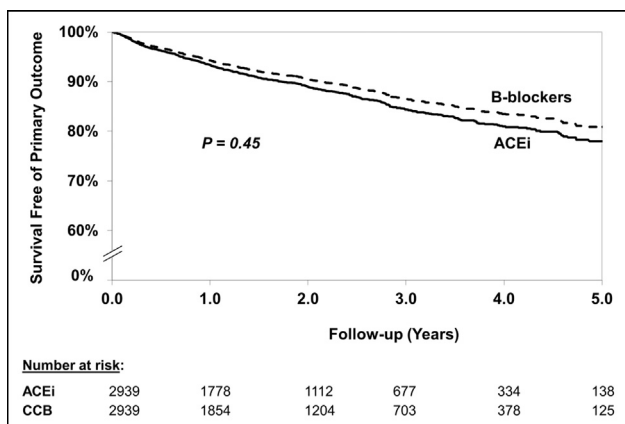
ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.



**Figure 2** Angiotensin-converting enzyme inhibitor vs thiazide diuretic: risk of primary outcome. ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker.

mean blood pressure response in blacks is usually less with angiotensin-converting enzyme inhibitors when compared with calcium channel blockers, thiazide diuretics, or  $\beta$ -blockers.<sup>25</sup> In fact, the percentage of patients attaining blood pressure target was lowest for angiotensin-converting enzyme inhibitors among both younger and older blacks when compared with calcium channel blockers, thiazide diuretics, or  $\beta$ -blockers.<sup>26</sup> The reason for this hypo-responsiveness is not clearly known. It has been hypothesized that this might be due to a high sodium intake in salt-sensitive blacks, in whom the response to angiotensin-converting enzyme inhibitors is somewhat blunted. Others have suggested that hypertension in blacks may not be an angiotensin II-dependent mechanism.<sup>27</sup> In addition, this increased salt sensitivity and volume also may explain the better blood pressure control with thiazide-like diuretics in blacks.<sup>28</sup>

Other studies have shown a significant increase in the risk of side effects associated with angiotensin-converting



**Figure 3** Angiotensin-converting enzyme inhibitor vs  $\beta$ -blockers: risk of primary outcome. ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker.

enzyme inhibitors in blacks. Black subjects taking angiotensin-converting enzyme inhibitors have a greater incidence of cough and a higher risk of angiotensin-converting enzyme inhibitors discontinuation due to cough than other races.<sup>29</sup> Likewise, black subjects are more prone to develop angiotensin-converting enzyme inhibitor-associated angioedema<sup>10,11</sup> and hyperkalemia.<sup>12</sup> As stated earlier, in ALLHAT, blacks treated with angiotensin-converting enzyme inhibitors demonstrated poorer blood pressure control with a significant increase in stroke, heart failure, and combined cardiovascular disease than those randomized to diuretics.<sup>7-9</sup> The limitation of prior analyses from subgroup analyses of randomized trials has been the small sample size of the subgroup. The results of the present study, with more than 25,564 black patients, is the largest series thus far and are largely consistent with the findings from ALLHAT. In our study, angiotensin-converting enzyme inhibitors were associated with a significantly higher risk of composite cardiovascular events, including an increased risk of death, myocardial infarction, stroke, and heart failure. The difference in outcomes in ALLHAT has been attributed at least in part to a lower attained blood pressure with diuretics when compared with angiotensin-converting enzyme inhibitors. However, this difference in outcomes persisted even after a time-dependent blood pressure adjustment in ALLHAT.

The results of our study lend credence to major specialty society guideline recommendations. As discussed earlier, the National Institute for Health and Clinical Excellence clinical practice guideline for hypertension recommends calcium channel blocker therapy in blacks.<sup>1</sup> Likewise, the International Society on Hypertension in blacks consensus statement recommends a dihydropyridine calcium channel blocker if monotherapy is used for black hypertensive patients.<sup>30</sup> Both guidelines recommend a thiazide-like diuretic, such as chlorthalidone, as a reasonable alternative to a calcium channel blocker, especially in patients who are intolerant to calcium channel blockers. The use of these 2 classes of drugs as initial antihypertensive therapy in blacks is also endorsed by the 2014 evidence base recommendation for hypertension by the panel appointed to the eighth Joint National Committee and by the European Societies of Hypertension and European Society of Cardiology.<sup>2,3</sup>

Although these data are true for monotherapy, studies have shown that angiotensin-converting enzyme inhibitors in combination with a thiazide diuretic or a calcium channel blocker produce a comparable reduction in blood pressure.<sup>31,32</sup> Moreover, outcomes data from the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial showed a superiority of a combination of angiotensin-converting enzyme inhibitors and calcium channel blocker when compared with angiotensin-converting enzyme inhibitors and hydrochlorothiazide even in the subset of black patients.<sup>33</sup> However, we did not test combination therapy in the current study.

## Study Limitations

This study assessed outcomes from a real-world cohort of hypertensive blacks without prior myocardial infarction, heart failure, or stroke; thus, the results cannot be extrapolated to other cohorts. The cohort included patients who self-identified as black and therefore may have missed Hispanic patients or Caribbean descent and others who did not self-identify as black. Although we used propensity score matching to account for measured confounders, this does not control for unmeasured confounders. Moreover, we did not have data on the reason for the choice of a particular antihypertensive therapy for a given patient.

## CONCLUSIONS

In this largest cohort of hypertensive blacks, the use of angiotensin-converting enzyme inhibitors was associated with worse cardiovascular outcomes when compared with the use of calcium channel blockers or thiazide diuretics. The data support the antihypertensive choice recommended by major national and international guideline committees for hypertensive blacks. These relationships should be considered when treating hypertensive blacks and should be tested in well-powered future randomized trials.

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