*Review Article*

# A Review of ACE Inhibitors and ARBs in Black Patients With Hypertension

Annals of Pharmacotherapy
1–9

DOI: 10.1177/1060028018779082
journals.sagepub.com/home/aop
SAGE

**Allison Helmer, PharmD, BCACP[1], Nicole Slater, PharmD, BCACP[1], and Sean Smithgall, PharmD, BCACP[1]**

## Abstract

**Objective:** To review current guidelines and recent data evaluating the efficacy and safety of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in black hypertensive patients. **Data Sources:** Articles evaluating race-specific outcomes in hypertension were gathered using a MEDLINE search with keywords *black, African American, ACE inhibitor, angiotensin receptor blocker, angiotensin system*, and *hypertension*. Studies published from 2000 through April 2018 were reviewed. **Study Selection and Data Extraction:** Six guidelines, 8 monotherapy publications, and 5 combination therapy publications included race-specific results and were included in the review. The authors individually compared and contrasted the results from each publication. **Data Synthesis:** Numerous monotherapy trials indicate that black patients may have a reduced blood pressure (BP) response with ACE inhibitors or ARBs compared with white patients. Conversely, additional studies propose that race may not be the primary predictor of BP response. Reduced efficacy is not observed in trials involving combination therapy. Some studies suggest increased cardiovascular and cerebrovascular morbidity and mortality with ACE inhibitor or ARB monotherapy in black patients; however, data are conflicting. **Relevance to Patient Care and Clinical Practice:** This article clarifies vague guideline statements and informs clinicians on the appropriate use of ACE inhibitors or ARBs for hypertension treatment in black patients through an in-depth look into the evidence. **Conclusions:** Potentially reduced efficacy and limited outcomes data indicate that ACE inhibitors or ARBs should not routinely be initiated as monotherapy in black hypertensive patients. Use in combination with a calcium channel blocker or thiazide diuretic is efficacious in black patients, and there are no data showing that this increases or decreases cardiovascular or cerebrovascular outcomes.

## Keywords

hypertension, ACE inhibitors, angiotensin II receptor antagonists, evidence-based practice, literature evaluation

## Introduction

Hypertension is one of the most common chronic disease states in the United States, affecting approximately 75 million American adults, with a higher prevalence in the black population.[1,2] Hypertension is generally more difficult to control in blacks, and cardiovascular and renal complications occur more frequently in this population compared with whites.[3] Increased stress and poor medication adherence in this population may contribute to this finding.[4] There is conflicting evidence on the efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in black hypertensive patients. Some of the proposed pathophysiological mechanisms for the decreased efficacy of ACE inhibitors and ARBs involve ethnic differences in metabolism as well as the renin-angiotensin-aldosterone system (RAAS). Genetic variants in cytochrome P450 2C9, which metabolizes some ARBs, that are more common in the white population compared with blacks may result in reduced ARB efficacy.[5-7] Additionally, studies have shown that genetic mutations resulting in baseline sodium retention can lead to naturally low renin levels in blacks.[8,9] In the western society, black patients with naturally low renin are more sensitive to the hypertensive effects of excess dietary sodium and reduced potassium intake because of the baseline negative feedback on their RAAS.[8,9] Excess sodium, along with visceral obesity, excess fructose, aging, and certain genetic mutations can lead to low-renin hypertension in blacks. The complications of a low-renin system are compounded further with salt sensitivity, a condition that increases the variability of sodium intake on blood pressure (BP) control and is more commonly found in

[1]Auburn University Harrison School of Pharmacy, Mobile, AL, USA

**Corresponding Author:**
Allison Helmer, Department of Pharmacy Practice, Auburn University Harrison School of Pharmacy, 650 Clinic Drive Suite 2100, Mobile, AL 36688, USA.
Email: amm0085@auburn.edu

blacks than whites.[8,9] Low-renin hypertension is a theorized reason for ACE inhibitor and ARB resistance in black patients because these medications exhibit their BP-lowering effects through RAAS deactivation. ACE inhibitors and ARBs remain widely used in the management of hypertension in black patients despite the proposed pathophysiological mechanism to their resistance; therefore, clinicians should understand the role in therapy of ACE inhibitors and ARBs when treating this population.

This review highlights ACE inhibitor and ARB therapy in blacks with respect to guideline recommendations, monotherapy and combination therapy with other antihypertensives, and clinical end points as well as adverse effects specific to ACE inhibitor therapy when used in blacks compared with other races. Ideally, a review of this topic should focus on clinical end points; however, most of the data specific to the black population evaluated surrogate end points (ie, BP reduction). For this reason, a large portion of the review highlights BP-lowering effects of ACE inhibitors and ARBs. Nonetheless, BP goals remain the mainstay of patient-specific management of hypertension, and clinicians should strive to help patients achieve these goals using evidence-based therapy.

## Data Sources

Authors sought to identify the most current literature evaluating the effectiveness and safety of ACE inhibitors and/or ARBs in black patients. Current hypertension treatment guidelines published in the United States, Canada, and Europe were identified. Because one purpose of this review is to understand the rationale behind race-related recommendations, articles cited in these guidelines specific to race-related outcomes were reviewed for inclusion. Additional articles evaluating race-specific outcomes in hypertension were gathered using a MEDLINE search with the keywords *black, African American, ACE inhibitor, angiotensin receptor blocker, angiotensin system*, and *hypertension*. Because of the large amount of published data over the past several decades and to focus on the most current data, the authors included articles published from 2000 through April 2018. This publication date restriction was lifted for articles concerning adverse effects of ACE inhibitors and ARBs in blacks because of the limited available research on this topic. Articles were included if they evaluated surrogate (ie, BP) and/or clinical outcomes in black patients taking ACE inhibitors or ARBs, either in the main study or as a subgroup analysis.

## Guideline Summary

Six hypertension guidelines were evaluated for specific recommendations related to blacks (see Table 1).[3,10-14] However, many guidelines have sparse, if any, recommendations specific to blacks. These recommendations commonly lack a grading of evidence or a clear reference to the studies used to support the recommendation. Most of the guidelines that were evaluated agree that calcium channel blockers (CCBs) or thiazide diuretics should be one of the primary medication classes started in blacks. If a thiazide diuretic is chosen as initial therapy, preference is given to chlorthalidone over hydrochlorothiazide (HCTZ) based on the results of the ALLHAT trial.[3,10,12,14] An ACE inhibitor or ARB should be utilized as secondary or alternative first-line therapies in black patients who cannot tolerate a CCB or thiazide or who have an indication specified on Table 1. When an ACE inhibitor or ARB is initiated in black patients, there is no preference as to which agent in the class should be selected.[3] Guidelines acknowledge that the majority of hypertensive patients, including black patients, will require more than 1 medication to control their BP, so the choice of initial therapy may not be as important.[3] The most recent guidelines released in 2017 further emphasize utilizing 2 or more agents to control BP in black patients, which coincides with the more stringent BP goal listed in Table 1.[10]

## BP-Lowering Effects of ACE Inhibitors or ARBs as Monotherapy in Black Patients

ACE inhibitors and ARBs can effectively lower BP in black patients[15]; however, numerous trials published over the past several decades have indicated that black patients may have a reduced BP response to ACE inhibitors compared with white patients. A recent meta-analysis of 13 trials compared BP differences in blacks and whites on ACE inhibitor monotherapy and found that after treatment, the mean BP in black patients was 4.6/2.8 mm Hg higher than that in white patients.[16] Study durations ranged from 4 to 18 weeks, with standardized mean doses ranging from 5 to 40 mg of enalapril per day. The majority of these trials were very small, conducted in the 1980s and 1990s, and many were cohort or open-label studies. Specific BP changes from the 2 larger, more recent studies included in this analysis are listed in Table 2.[17,18]

Numerous analyses have been conducted in racial subgroups of landmark hypertension trials, many of which included patients with diabetes, chronic kidney disease, and high cardiovascular risk as well as elderly patients. Most of these studies have found that ACE inhibitor or ARB treatment in black patients results in a reduced BP response compared with other antihypertensives.[19-25] Table 2 highlights the results of these trials. It is important to note that in most of these studies, the majority of patients, regardless of race, required additional therapy for BP control, so the effects of ACE inhibitor and ARB as monotherapy are somewhat unclear. Furthermore, when multiple agents were compared between black and white patients, BPs were typically higher in black patients after treatment regardless of

**Table 1.** Summary of Guideline Recommendations for Treatment of Hypertension in Blacks.

| Guideline | Goal BP | Preferred Therapy | Grading of Evidence[a] | Miscellaneous Recommendations |
|---|---|---|---|---|
| Recommendations that are specific to black patients | | | | |
| 2017 American College of Cardiology and American Heart Association[10] | <130/80 mm Hg | First line: CCB or thiazide<br>Second line: CCB, Thiazide, ACE inhibitor, or ARB<br>CKD or HF: ACE inhibitor or ARB | Strong level B-NR | Recommends 2 or more agents needed to control BP (Strong level C-LD) |
| 2014 American Society of Hypertension and International Society of Hypertension[11] | <140/90 mm Hg<br><150/90 mm Hg if 80 years or older and no diabetes or CKD | First line: CCB or thiazide<br>Second line: ACE inhibitor, ARB, or combine CCB and thiazide<br>CKD: ACE inhibitor<br>Diabetic: ACE inhibitor, ARB, CCB, or thiazide | None | For diabetics, if patient was started on CCB or thiazide, then add ACE inhibitor or ARB as second agent if needed |
| 2013 Eighth Joint National Committee[12] | <140/90 mm Hg regardless of age | General: thiazide or CCB | Moderate grade B | |
| | | Diabetic: thiazide or CCB | Weak grade C | |
| | | CKD with proteinuria: ACE inhibitor or ARB | Expert opinion | |
| | | CKD without proteinuria: ACE inhibitor, ARB, CCB, or thiazide | Expert opinion | |
| 2013 European Society of Hypertension and European Society of Cardiology (ESH/ESC)[13] | None | Diuretic (thiazide diuretic) or CCB[b] | None for blacks | Blood pressure effects of sodium restriction is greater in blacks[c] |
| 2011 National Institute for Health and Care Excellence (NICE)[14,d] | None | Step 1: CCB unless edema or intolerance<br>Step 2: ARB in preference to an ACE inhibitor in combination with a CCB | None | |
| 2010 International Society on Hypertension in Blacks[3] | <135/85 mm Hg | <145/90 mm Hg: Optional lifestyle for 3 months before pharmacotherapy<br>>145/90 mm Hg: Thiazide diuretic or CCB<br>>150/95 mm Hg: ACE inhibitor/ARB + CCB or ACE inhibitor/ARB + thiazide<br>Alternative: CCB + thiazide or thiazide + BB | None | Titrate ACE inhibitor every 6 weeks as opposed to every 2 weeks for higher BP control rates and fewer adverse drug events |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker, CKD, chronic kidney disease; HF, heart failure; RAAS, renin-angiotensin-aldosterone system.
[a]Explanations for individual guideline grading of evidence were not included in order to conserve space.
[b]Unchanged since the 2007 ESH/ESC guideline.
[c]Greater than an estimated 5 to 6 g/d.
[d]2016 Update to NICE only pertains to pregnancy recommendations.

agent used, suggesting that it may be harder to treat BP in black patients.

Although these studies have demonstrated that black patients may have a reduced BP response with an ACE inhibitor or ARB compared with nonblack patients, race may not be the primary predictor of BP response.[3,17,26] Mokwe et al,[17] studied the difference in response to quinapril between black and white patients. Although white patients generally responded better to quinapril (see Table 2), authors discussed the numerous confounders that may have contributed to differences in BP, which include age, gender, body size, and pretreatment BP.[17] Similarly, a review of 15 trials published in 2004 aimed to detect the similarity of BP response in blacks and whites.[26] The mean BP difference between blacks and whites taking an ACE inhibitor was comparable to that in previously reported studies (SBP 4.6 and DBP 3 mm Hg higher in blacks); however, there was significant overlap in treatment response among the entire study population. After treatment with an ACE inhibitor, 86% of SBP values and 81% of DBP values changed

**Table 2.** BP Changes With ACE Inhibitor or ARB Monotherapy.

| Trial | Study Groups | Baseline BP | | BP Change | | Notes |
|---|---|---|---|---|---|---|
| | | Black | White | Black | White | |
| Mokwe et al, 2004[17] | Quinapril 40-80 mg[a] | 159.9/95.6 | 152.2/94.9 | −10.6/−7.4 | −15.3/−9.8 | Quinapril titrated for BP ≥140/90 mm Hg; mean dose not provided. Results after 18 weeks. After adjustment for confounders, BP was only 2.3/1.9 mm Hg higher in blacks vs whites |
| | | Black | White | Black | White | |
| Cohn et al, 2004[18] | Perindopril 4-8 mg | 156.3/96.5 | 157/94.1 | −14.4/−9.1 | −18.2/−10.6 | 47.3% of blacks and 39.1% of whites increased to 8 mg at week 6. Results after 12 weeks. Open label, community-based trial. BP significantly reduced ($P < 0.001$) in both races |
| | | All Patients | | Black | White | |
| Flack et al, 2003[24] | Losartan 50-100 mg | 150.7/99.2 | | −5.3/−6.9 | −8.5/−8.4 | Racial subgroup analysis in which 63% of participants were black. Doses titrated for BP ≥140/90 mm Hg; mean doses not provided. Results after 16 weeks. BP reduction significantly greater with eplerenone vs losartan in blacks ($P < 0.001$ for SBP, $P = 0.001$ for DBP) but not whites |
| | Eplerenone 50-200 mg | 149.3/98.9 | | −13.5/−10.2 | −12.3/−11.1 | |
| | Placebo | 148.9/99.1 | | −3.7/−4.8 | −3.2/−6.4 | |
| | | Black | Nonblack | Black | Nonblack | |
| Wright et al, 2005[19] | Lisinopril 10-40 mg[a,b] | 146.2/84.9 | 146.5/83.7 | −6.8/−5.6 | −12/−8 | Racial subgroup analysis of ALLHAT in which 35% of participants were black. Doses titrated for BP ≥140/90 mm Hg; mean doses not provided. Results after 4 years |
| | Amlodipine 2.5-10 mg[a,b] | 146.1/84.7 | 146.3/83.5 | −8.8/−6.6 | −12.3/−8.7 | |
| | Chlorthalidone 12.5-25 mg[a,b] | 146.3/84.9 | 146.2/83.5 | −10.5/−6.6 | −12.3/−7.6 | |
| | | Black | Nonblack | Black | Nonblack | |
| Wright et al, 2008[21] | Metabolic syndrome | 146.2/84.4 | 146/83.5 | | | Subgroup analysis of ALLHAT in which participants were stratified by race and presence or absence of metabolic syndrome. Results after 6 years. BP reduction significantly greater ($P < 0.05$) with chlorthalidone vs lisinopril in blacks with and without metabolic syndrome and in nonblacks with metabolic syndrome |
| | Lisinopril 10-40 mg[b] | | | −8.3/−9.2 | −14.2/−11 | |
| | Amlodipine 2.5-10 mg[b] | | | −9.4/−9.2 | −11.9/−11.2 | |
| | Chlorthalidone 12.5-25 mg[b] | | | −11.4/−9.3 | −12.5/−10.2 | |
| | No metabolic syndrome | 146.2/85.4 | 146.8/83.7 | | | |
| | Lisinopril 10-40 mg[b] | | | −7.9/−7.6 | −13.6/−10.3 | |
| | Amlodipine 2.5-10 mg[b] | | | −10.9/−9.2 | −15.5/−11 | |
| | Chlorthalidone 12.5-25 mg[b] | | | −12.6/−9.2 | −14/−10.5 | |
| | | Black | | Black | | |
| Wright et al, 2002[22] | Ramipril 2.5-10 mg[a] | 151/96 | | −16/−14 | | BP analysis of AASK in which 100% of participants were black. Doses titrated to achieve MAP of 102-107 or ≥92 mm Hg; mean doses not provided. Results after at least 3 months of therapy |
| | Amlodipine 5-10 mg[a] | 150/96 | | −17/−15 | | |
| | Metoprolol 50-200 mg[a] | 150/95 | | −15/−14 | | |
| | | All Patients | | Black | Nonblack | |
| Julius et al, 2004[25] | Losartan 50-100 mg[a,c] | 174.3/97.9 | | −30.3/−17.3 | −31.1/−16.5 | Racial subgroup analysis of LIFE in which 6% of patients were black. Results after mean of 4.8 years. Only 11% and 12% of patients received monotherapy with losartan or atenolol, respectively, by the end of the study. Mean doses not provided |
| | Atenolol 50-100 mg[a,c] | 174.5/97.7 | | −29.1/−17.2 | −30.3/−17.5 | |
| | | All Patients | | Black | White | |
| Zanchetti et al, 2006[23] | Valsartan 80-160 mg[a,c] | 154.5/87.4 | | −4.54/−2.04 More with amlodipine | −2.1/−1.48 More with amlodipine | Racial subgroup analysis of VALUE in which 4.2% of participants were black. Mean doses at study end: valsartan 151.7 mg; amlodipine 8.7 mg. Results after mean of 4.2 years |
| | Amlodipine 5-10 mg[a,c] | 154.8/87.6 | | | | |

Abbreviations: ABPM, ambulatory BP monitoring; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DBP, diastolic BP; MAP, mean arterial pressure; SBP, systolic BP.
[a]Statistical analysis not performed for BP changes.
[b]Patients could have started atenolol, clonidine, reserpine, or hydralazine if needed for BP control.
[c]Patients could have started hydrochlorothiazide 12.5 to 25 mg if needed for BP control.

**Table 3.** BP Changes With ARB in Combination With Other Antihypertensives.[a]

| Trial | Treatment Groups | Baseline BP | BP Change | Notes |
|---|---|---|---|---|
| Flack et al, 2001[29] | Placebo | 151.4/99.8 | −2.3/−3.9 | BP efficacy study in which 100% of participants were black. Doses titrated every 4 weeks for DBP ≥90 mm Hg; mean doses not provided. BP reduction significantly greater with combination ($P < 0.01$) vs losartan monotherapy. Results after 12 weeks of therapy |
| | Losartan 50-100 mg | 150.9/99.9 | −6.4/−6.6 | |
| | Losartan 50-100 mg + HCTZ[b] 0-25 mg | 149.1/100.2 | −16.8/−10.8 | |
| Flack et al, 2009[30,b] | Amlodipine 10 mg | 170.5/98.2 | −26.6/−10.8 | BP efficacy study in which 100% of participants were black. Valsartan titrated at 4 weeks for SBP ≥130 mm Hg. BP reduction significantly greater with combination ($P < 0.0001$) vs amlodipine monotherapy. Results after 8 weeks of therapy |
| | Amlodipine 10 mg + valsartan 160-320 mg | 170.4/98.5 | −33.3/−13.6 | |
| McGill and Reilly, 2001[28] | Placebo | 150.4/101.2 | −0.1/−3.4 | Dose-response efficacy study in which 100% of participants were black. Patients received 0-25 mg of HCTZ and 0-160 mg of telmisartan, alone or in combination. Results reported for doses that showed maximum benefit of BP reduction significantly greater with combination ($P < 0.01$ compared with monotherapy). Results after 8 weeks of therapy |
| | Telmisartan 80 mg | 155.1/101 | −7.8/−4.6 | |
| | HCTZ 12.5 mg | 154.8/101.7 | −9.2/−5.2 | |
| | Telmisartan 80 mg + HCTZ 12.5 mg | 155/101.5 | −21.5/−13.3 | |

| | | Black | White | Black | White | |
|---|---|---|---|---|---|---|
| Oparil et al, 2010[27] | Amlodipine 5 mg + olmesartan 40 mg | 156.1/100.7 | 157.9/100.2 | −23.3/−16.7 | −31.2/−19.8 | Racial subgroup analysis of the CHANCE study in which 24.5% of participants were black. Results after 52 weeks. Statistical analysis not performed for BP changes |
| | Amlodipine 10 mg + olmesartan 40 mg | 158.1/100.9 | 161.5/101.2 | −27.5/−17.5 | −30.4/−19.2 | |
| | Amlodipine 10 mg + olmesartan 40 mg + HCTZ 12.5 mg | 161.1/102.4 | 167.2/102.1 | −31.5/−19.6 | −36/−21.8 | |
| | Amlodipine 10 mg + olmesartan 40 mg + HCTZ 25 mg | 172.3/103.6 | 173.2/102.9 | −36.4/−19.9 | −35.9/−19.6 | |

| | | Black | White | Black | White | |
|---|---|---|---|---|---|---|
| Smith et al, 2007[31] | | 149.7/100 | 155.5/99.1 | | | Racial and elderly subgroup analysis of 2 trials. In study 1, 10.4% of participants were black with only 0.4% in study 2. BP changes reported from study 1. Patients received amlodipine 0-5 mg, valsartan 0-320 mg, or the combination. Results reported for maximum trial doses. Statistical analysis not performed. Results after 8 weeks of therapy |
| | Amlodipine 5 mg | | | −10.1/−8.6 | −15/−11.2 | |
| | Valsartan 320 mg | | | −9.3/−7.7 | −18.0/−14.4 | |
| | Valsartan 320 mg + amlodipine 5 mg | | | −17.5/−17.9 | −23.0/−15.5 | |

Abbreviations: ARB, angiotensin receptor blocker; BP, blood pressure; DBP, diastolic BP; HCTZ, hydrochlorothiazide; SBP, systolic BP.
[a]No published trials comparing angiotensin-converting enzyme inhibitor monotherapy with combination therapy.
[b]HCTZ added at 4 weeks.

similarly when they were compared between racial groups. Authors suggest that clinical decisions for BP agents should be based on efficacy in individual patients, compelling indications, and cost rather than race.[26]

## BP-Lowering Effects of ACE Inhibitors or ARBs in Combination Therapy in Black Patients

Nearly two-thirds of patients with SBP between 140 and 159 mm Hg and DBP between 90 and 99 mm Hg on diagnosis of hypertension will require more than 1 agent to achieve control.[3] Combined with a higher prevalence of hypertension in blacks, it appears that most black patients will require more than just monotherapy to control their hypertension.[3,11] Few trials have assessed the effectiveness of combination antihypertensive therapy in black patients, with no trials evaluating combination therapy with ACE inhibitors. Most have compared BP changes with monotherapy versus combination therapy in black patients; only 2 studies have compared BP changes in black versus white patients.[27-31] See Table 3 for detailed results of these studies. As expected, the combination of an ARB with a thiazide or CCB provides significantly greater BP reduction than monotherapy with any agent or placebo. Although these trials only evaluated ARB therapy, it is likely that BP response would be similar with ACE inhibitors in combination with a thiazide or CCB given the similarity in the mechanism of action. Notably, the SBP reduction of ≥10 mm Hg with ARBs plus HCTZ compared with ARB monotherapy strengthens the hypothesis that ACE inhibitor or ARB may be more effective when combined with diuretics because of

their synergistic mechanism of action given the RAAS activation with diuresis.[8,28,32,33]

## Clinical End Points in Black Patients on ACE Inhibitors or ARBs

There are no randomized controlled trials with a large percentage of black participants that have a primary aim of assessing cardiovascular outcomes. The majority of clinical efficacy data in black patients taking ACE inhibitors comes from subgroup or post hoc analyses of large clinical trials or cohort studies. Several prespecified subgroup analyses comparing race categories have been conducted with results from the ALLHAT study.[19-21] This study compared chlorthalidone, lisinopril, and amlodipine in high-risk patients with elevated BP; roughly 35% of the population was black.[22,34] There was no significant difference in the primary composite end point of fatal coronary heart disease or nonfatal myocardial infarction in subgroup analyses comparing black with nonblack patients.[19-21,34] There were, however, significant differences in key secondary end points. The rates of combined coronary heart disease, combined cardiovascular disease, and stroke were significantly higher in black patients assigned to lisinopril.[19,20] In one subgroup analysis that stratified patients by presence or absence of metabolic syndrome, only black patients with metabolic syndrome had higher rates of these secondary end points.[21]

A recent cohort study compared cardiovascular outcomes in black and white patients with or without ACE inhibitor therapy.[31] Numerically, more black patients taking an ACE inhibitor experienced the primary outcome of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke; however, this difference was not statistically significant. There was no difference in the primary outcome in white patients with ACE inhibitor versus no ACE inhibitor therapy, nor was there a difference in outcomes comparing black and white patients on any treatment.[35] Another cohort study of black hypertensive patients compared outcomes in patients taking ACE inhibitors with CCBs, thiazide diuretics, and β-blockers.[36] The rate of the primary composite outcome of death, myocardial infarction, or stroke was significantly higher in those taking lisinopril compared with CCBs or thiazide diuretics.[36] Similar results were found in a subgroup analysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study which compared primary outcome results in black and nonblack patients with left ventricular hypertrophy. Black patients assigned to losartan had significantly higher rates of cardiovascular death, stroke, or myocardial infarction compared with black patients assigned to atenolol.[25] Alternatively, there was no difference in cardiac morbidity and mortality in the subgroup analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study comparing valsartan and amlodipine in high-risk black patients with hypertension.[23] The percentage of black patients in these studies was extremely low (6% in LIFE and 4.2% in VALUE), making it difficult to apply these results to the black population.[37,38] Although published literature evaluating cardiovascular outcomes in black patients is somewhat lacking, a trend from these subgroup analyses and cohort studies suggests that black patients may not be protected from cardiovascular outcomes using ACE inhibitor therapy to control their BP.

## Adverse Effects With ACE Inhibitors in Black Patients

It is hypothesized that black patients have an increased risk of adverse drug events, particularly angioedema, when exposed to an ACE inhibitor, compared with other races. Because the risk of angioedema seems to be linked to an increase in bradykinin, a mechanism unique to ACE inhibitors and not ARBs, the studies evaluating adverse effects have focused primarily on the ACE inhibitor class.[39,40] One study showed a 4.5 times greater increase (utilizing relative risk) in ACE inhibitor–induced angioedema in blacks compared with whites, with enalapril and lisinopril having a higher probability than captopril.[41] This increase in angioedema was mirrored by 2 additional studies; however, the individualized increase with specific ACE inhibitors was not duplicated or presented.[42,43] These studies were retrospective analyses of electronic medical records, with one of the studies only documenting adverse drug events that led to discontinuation of the ACE inhibitor.[41-43] A more recent prospective study evaluating enalapril showed an approximately 3-fold increase in risk of angioedema with blacks compared with whites.[44] This risk of angioedema may appear to be an exponential increase, but it should be kept in mind that the general population risk of ACE inhibitor–induced angioedema described in these studies is <1%.[42,44] There was no difference seen in blacks compared with other races in other common adverse effects of ACE inhibitors, including but not limited to cough, renal dysfunction, and hyperkalemia.[42]

## Relevance to Patient Care and Clinical Practice:

This article clarifies vague guideline statements and informs clinicians on the appropriate use of ACE inhibitors or ARBs in the hypertension treatment algorithm for black patients through an in-depth look into the evidence. Current literature indicates that the use of ACE inhibitors or ARBs as monotherapy in black patients may not lower BP as effectively as in white patients; however, clinicians should consider additional patient-specific factors to determine appropriateness of ACE inhibitor or ARB monotherapy, including pretreatment of BP and other compelling indications. When combination therapy is

warranted, combining ACE inhibitors or ARBs with a thiazide diuretic seems to provide the most benefit given their synergistic mechanism of action. Although some studies have found an increase in cardiovascular and cerebrovascular morbidity and mortality in black patients taking an ACE inhibitor or ARB as initial therapy, when compared with other agents, these data come from subgroup or post hoc analyses or cohort studies and should be viewed as hypothesis generating. Nonetheless, it is reasonable to consider alternative agents, such as CCBs or thiazides, as initial therapy in black patients requiring antihypertensive therapy. Currently, there are no published data assessing the effect of combination therapy on clinical end points specifically in black patients. There is no need to avoid ACE inhibitors or ARBs in combination with other antihypertensives in the black population. In terms of adverse events, the increased risk of angioedema should not limit the use of these medications in blacks but instead warrant a discussion with the patient regarding education on the signs and symptoms of angioedema before initiation.

## Conclusion

Much research has been done to assess the best hypertensive treatment approaches in black patients; however, there is a paucity of high-quality data. Although there are no published data assessing clinical outcomes specifically in black patients using ACE inhibitor or ARB monotherapy, evidence from subgroup analyses and cohort studies suggests that these patients may have higher rates of cardiovascular and cerebrovascular outcomes compared with those taking other antihypertensives. There is no evidence that adding an ACE inhibitor or ARB as a second-line agent increases or decreases cardiovascular or cerebrovascular outcomes. Until further research is completed, we cannot definitively say that ACE inhibitor or ARB use in black patients will lead to higher rates of cardiovascular outcomes; however, based on evidence of potentially reduced BP response and limited outcomes data, ACE inhibitors or ARBs should not routinely be initiated as monotherapy in black patients with hypertension. These agents in combination with a CCB or thiazide diuretic, however, have been shown to be efficacious in black patients, with perhaps the greatest efficacy when utilizing ACE inhibitors or ARBs in combination with a thiazide diuretic.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### References

1. Merai R, Siegel C, Rakotz M, et al. CDC grand rounds: a public health approach to detect and control hypertension. *MMWR Morb Mortal Wkly Rep*. 2016;65:1261-1264. doi:10.15585/mmwr.mm6545a3
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-e322. doi:10.1161/cir.0000000000000152
3. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in blacks: an update of the International Society on Hypertension in Blacks consensus statement. *Hypertension*. 2010;56:780-800. doi:10.1161/hypertensionaha.110.152892
4. Bosworth HB, Powers B, Grubber JM, et al. Racial differences in blood pressure control: potential explanatory factors. *J Gen Intern Med*. 2008;23:692-698. doi:10.1007/s11606-008-0547-7
5. Schwarz UI. Clinical relevance of genetic polymorphisms in the human CYP2C9 gene. *Eur J Clin Invest*. 2003;33(suppl 2):23-30.
6. Flaten HK, Monte AA. The pharmacogenomic and metabolomic predictors of ACE inhibitor and angiotensin II receptor blocker effectiveness and safety. *Cardiovasc Drugs Ther*. 2017;31:471-482. doi:10.1007/s10557-017-6733-2
7. Hallberg P, Karlsson J, Kurland L, et al. The CYP2C9 genotype predicts the blood pressure response to irbesartan: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol (SILVHIA) trial. *J Hypertens*. 2002;20:2089-2093.
8. Rayner BL, Spence JD. Hypertension in blacks: insights from Africa. *J Hypertens*. 2017;35:234-239. doi:10.1097/hjh.0000000000001171
9. Kurtz TW, DiCarlo SE, Pravenec M, Morris RC Jr. An appraisal of methods recently recommended for testing salt sensitivity of blood pressure. *J Am Heart Assoc*. 2017;6:e005653. doi:10.1161/jaha.117.005653
10. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127-e248. doi:10.1016/j.jacc.2017.11.006
11. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014;16:14-26. doi:10.1111/jch.12237
12. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520. doi:10.1001/jama.2013.284427
13. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159-2219. doi:10.1093/eurheartj/eht151

14. National Clinical Guideline Centre (UK). National Institute for Health and Care Excellence. *Hypertension in adults: diagnosis and management*. (CG127). 2016:1-25.
15. Johnson W, White WB, Sica D, et al. Evaluation of the angiotensin II receptor blocker azilsartan medoxomil in African-American patients with hypertension. *J Clin Hypertens (Greenwich)*. 2017;19:695-701. doi:10.1111/jch.12993
16. Peck RN, Smart LR, Beier R, et al. Difference in blood pressure response to ACE-inhibitor monotherapy between black and white adults with arterial hypertension: a meta-analysis of 13 clinical trials. *BMC Nephrol*. 2013;14:201. doi:10.1186/1471-2369-14-201
17. Mokwe E, Ohmit SE, Nasser SA, et al. Determinants of blood pressure response to quinapril in black and white hypertensive patients: the Quinapril Titration Interval Management Evaluation trial. *Hypertension*. 2004;43:1202-1207. doi:10.1161/01.hyp.0000127924.67353.86
18. Cohn JN, Julius S, Neutel J, et al. Clinical experience with perindopril in African-American hypertensive patients: a large United States community trial. *Am J Hypertens*. 2004;17:134-138. doi:10.1016/j.amjhyper.2003.09.017
19. Wright JT Jr, Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA*. 2005;293:1595-1608. doi:10.1001/jama.293.13.1595
20. Leenen FH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension*. 2006;48:374-384. doi:10.1161/01.HYP.0000231662.77359.de
21. Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2008;168:207-217. doi:10.1001/archinternmed.2007.66
22. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-2431.
23. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. *J Hypertens*. 2006;24:2163-2168. doi:10.1097/01.hjh.0000249692.96488.46
24. Flack JM, Oparil S, Pratt JH, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. *J Am Coll Cardiol*. 2003;41:1148-1155.
25. Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. *J Am Coll Cardiol*. 2004;43:1047-1055. doi:10.1016/j.jacc.2003.11.029
26. Sehgal AR. Overlap between whites and blacks in response to antihypertensive drugs. *Hypertension*. 2004;43:566-572. doi:10.1161/01.HYP.0000118019.28487.9c
27. Oparil S, Chrysant SG, Melino M, Lee J, Karki S, Heyrman R. Long-term efficacy of a combination of amlodipine and olmesartan medoxomil ± hydrochlorothiazide in patients with hypertension stratified by age, race and diabetes status: a substudy of the COACH trial. *J Hum Hypertens*. 2010;24:831-838. doi:10.1038/jhh.2010.16
28. McGill JB, Reilly PA. Combination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension. *Clin Cardiol*. 2001;24:66-72.
29. Flack JM, Saunders E, Gradman A, et al. Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension. *Clin Ther*. 2001;23:1193-1208.
30. Flack JM, Calhoun DA, Satlin L, Barbier M, Hilkert R, Brunel P. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared with amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. *J Hum Hypertens*. 2009;23:479-489. doi:10.1038/jhh.2008.153
31. Smith TR, Philipp T, Vaisse B, et al. Amlodipine and valsartan combined and as monotherapy in stage 2, elderly, and black hypertensive patients: subgroup analyses of 2 randomized, placebo-controlled studies. *J Clin Hypertens (Greenwich)*. 2007;9:355-364.
32. Weir MR, Smith DH, Neutel JM, Bedigian MP. Valsartan alone or with a diuretic or ACE inhibitor as treatment for African American hypertensives: relation to salt intake. *Am J Hypertens*. 2001;14(7, pt 1):665-671.
33. Izzo JL Jr, Jia Y, Zappe DH. Influence of age and race on 24-hour ambulatory blood pressure responses to valsartan, hydrochlorothiazide, and their combination: implications for clinical practice. *J Clin Hypertens (Greenwich)*. 2017;19:143-150. doi:10.1111/jch.12891
34. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997.
35. Ogedegbe G, Shah NR, Phillips C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitor-based treatment on cardiovascular outcomes in hypertensive blacks versus whites. *J Am Coll Cardiol*. 2015;66:1224-1233. doi:10.1016/j.jacc.2015.07.021
36. Bangalore S, Ogedegbe G, Gyamfi J, et al. Outcomes with angiotensin-converting enzyme inhibitors vs other antihypertensive agents in hypertensive blacks. *Am J Med*. 2015;128:1195-1203. doi:10.1016/j.amjmed.2015.04.034
37. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995-1003. doi:10.1016/s0140-6736(02)08089-3

38. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031. doi:10.1016/s0140-6736(04)16451-9
39. Nussberger J, Cugno M, Cicardi M. Bradykinin-mediated angioedema. *N Engl J Med*. 2002;347:621-622. doi:10.1056/NEJM200208223470820
40. Barreras A, Gurk-Turner C. Angiotensin II receptor blockers. *Proc (Bayl Univ Med Cent)*. 2003;16:123-126.
41. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther*. 1996;60:8-13. doi:10.1016/s0009-9236(96)90161-7
42. Morimoto T, Gandhi TK, Fiskio JM, et al. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. *J Eval Clin Pract*. 2004;10:499-509. doi:10.1111/j.1365-2753.2003.00484.x
43. Reichman ME, Wernecke M, Graham DJ, et al. Antihypertensive drug associated angioedema: effect modification by race/ethnicity. *Pharmacoepidemiol Drug Saf*. 2017;26:1190-1196. doi:10.1002/pds.4260
44. Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of angioedema associated with enalapril. *Arch Intern Med*. 2005;165:1637-1642. doi:10.1001/archinte.165.14.1637