Commentary

Underutilization of Angiotensin-Converting Enzyme Inhibitors in High-Risk Blacks: A Case of Missed Opportunities

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In this issue of *The Journal of Clinical Hypertension*, Dr Vasilios Papademetriou concludes that angiotensin-converting-enzyme (ACE) inhibitors are beneficial in high-risk African American patients with coronary artery disease (CAD).[1] ACE inhibitors have been consistently included in guidelines for treatment of patients at high risk for cardiovascular disease (CVD), including those with status post–myocardial infarction, heart failure (HF), and/or left ventricular dysfunction. However, possibly because of previous studies indicating less efficacy as monotherapy for the control of hypertension and the suggestion of less benefit in prior HF trials, these agents, along with angiotensin receptor blockers have been considered not as effective or even to be avoided in self-identified black patients. Although performed as a retrospective analysis of 810 African American men who underwent diagnostic coronary angiography, Dr Papademetriou and colleagues were able to demonstrate that, despite an unfavorable baseline profile, patients treated with ACE inhibitors had significantly lower mortality from CAD than those not taking ACE inhibitors (P=.006). Despite this finding, however, stroke mortality rates appeared similar with or without ACE inhibitors.

The underuse or avoidance of ACE inhibitors in high-risk African Americans is an unfortunate persistent pattern in the treatment of these patients. African Americans have one of the highest age-adjusted rates for hypertension and various comorbid conditions in the world, much higher than that seen in non-Hispanic whites. Relevant to the present study, African Americans have the highest coronary heart disease mortality rates in the United States among major racial/ethnic groups. They also experience high rates of left ventricular hypertrophy, HF morbidity and mortality, stroke morbidity and mortality, chronic kidney disease, and end-stage renal disease (ESRD).[2] Environmental factors are perhaps key to understanding the prevalence of elevated blood pressure (BP) across various populations of African descent. Rural West Africans and Afro-Caribbeans have less prevalent and severe hypertension compared with US blacks who have relatively higher body mass and sodium to potassium intake.[3] In fact, the high rate of poorly controlled hypertension and CVD has led to decreased life expectancy for both African American men and women when compared with the general population.

The Human Genome Project has unveiled that humans are essentially the same, with as great or greater genetic variation within, vs across, self-defined so-called racial groups. This challenges the validity of the term *race* in clinical research and

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conclusion-drawing on that basis. Furthermore, race as a determinant of drug efficacy has variable power as a predictor of response in any individual, and self-identified race alone must not guide clinical decisions regarding the class of antihypertensive drug used.[4] The mean difference between whites and blacks to various antihypertensive agents range from 0.6 to 3.0 mm Hg, with considerable overlap in response and careful analysis of multiple trials demonstrating variable responses among individuals within races for any given antihypertensive class.[5,6]

Furthermore, it is a myth that blacks always have low renin hypertension, and approximately half may have high to normal plasma renin activity (PRA). In a systematically measured PRA distribution in 4170 untreated multiethnic employed persons at a worksite-based hypertension treatment program, the majority of African American individuals did not have low renin hypertension.[7] Use of ACE inhibitors, when indicated, are necessary regardless of racial considerations since angiotensin II, the active component of the renin-angiotensin system (RAS), can be vasculotoxic and in hypertensive individuals is associated with increased cardiovascular morbidity and mortality.

For monotherapy, although thiazide-type diuretics and calcium channel blockers (CCBs) may indeed be more effective in many blacks, there is a wide variation of BP response to RAS blockade within African Americans, and adding diuretics or CCBs to RAS blockers removes apparent racial differences in response.[8] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest antihypertensive study ever performed, chlorthalidone was unsurpassed in its ability to lower BP and decrease major cardiovascular events compared with regimens based on lisinopril and amlodipine.[9] In addition, lisinopril was associated with a 40% increase in strokes in the black cohort vs chlorthalidone.[9] While this finding may appear to suggest less CVD protection with ACE inhibitors vs diuretics in the 15,133 black patients (35% of total patients) in ALLHAT, to a large extent these outcomes were affected by a 4- to 5-mm Hg lower systolic BP reduction in the lisinopril-based cohort vs the chlorthalidone-based treatment group. While adjustments for BP may not explain all of the differences in outcomes in ALLHAT, by design, a thiazide diuretic or long-acting CCB could not be combined with the lisinopril-based therapy. The combination of lisinopril with a diuretic or the CCB may have assisted with removing any racial differences in BP response and potentially diminished adverse outcomes in the lisinopril-treated black patients. Conversely, the African American Study of Kidney Disease and Hypertension (AASK) confirmed in 1094 African Americans with hypertensive nephropathy, especially with proteinuria, the benefit of RAS blocking with ramipril in protecting against renal disease compared with metoprolol succinate and amlodipine.[10]

One of the earliest studies that led to the concept that ACE inhibitors were less efficacious in high-risk blacks was the report, "Lesser Response to Angiotensin-Converting-Enzyme Inhibitor Therapy in Black as Compared With White Patients With Left Ventricular Dysfunction."[11] The authors concluded that despite similar demographic and clinical characteristics, black patients in a pooled analysis from the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trial had higher rates of death from any cause (12.2 vs 9.7 per 100 person-years) and hospitalization for HF (13.2 vs 7.7 per 100 person-years). Often underrecognized in SOLVD, however, were data showing that the black patients were slightly younger, had higher mean diastolic blood pressures (DBPs), were more likely to report having had financial distress in the 12 months before enrollment, and were less likely to have attended college than the matched white patients.[11] Furthermore, at 1 year, enalapril was associated with significant reductions from baseline in systolic blood pressure (SPB) and DBP among white patients and not black patients. Therefore, despite the effort to match patients, a close review of the SOLVD study revealed significant differences not only in baseline characteristics, but also in findings that black patients had lesser degrees of educational attainment, more financial distress, higher degrees of diabetes, and less use of certain medications, including aspirin and β-blockers.[11]

The recent Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) included 11,400 patients 55 years or older with SPB >160 mm Hg or currently taking antihypertensive therapy and with evidence of cardiovascular or renal disease or target organ damage.[12] Despite prior treatment for hypertension, only 37.5% had BP controlled to <140/90 mm Hg at baseline.[12] Without a washout period, combination treatment with the ACE inhibitor benazepril plus hydrochlorothiazide or the CCB amlodipine plus benazepril had similar excellent BP-lowering effects across the entire heterogeneous cohort at 18 months, including in African Americans (n=1361) who had SBP lowered from 145.1 mm Hg to 133.6 mm Hg ($P<.05$).[12]

In general, the reason for increased coronary heart disease and mortality, stroke morbidity and mortality, and ESRD in African Americans is not due to a lack of any one particular class of medication. There are multiple factors leading to CVD disparities and death in African Americans. Adverse lifestyle, including physical inactivity, inadequate potassium intake, high dietary sodium, disadvantaged socioeconomic status, decreased access to specialty care, and increased obesity (especially in black women), must be considered contributors to adverse cardiovascular outcomes in blacks. Furthermore, the presence of comorbid conditions, such as CAD, renal disease, and HF are essential in assisting clinicians with the choice of appropriate medicine. African Americans often have more severe and complicated hypertension and will not achieve control with monotherapy. Combination therapy, usually with a thiazide diuretic or long-acting CCB added to a RAS-blocking agent, especially may achieve successful BP goal attainment and target organ protection.[13] Control of BP is absolutely essential, regardless of a person's race or ethnicity.

"Of all the forms of inequality, . . ." wrote Martin L. King Jr, ". . . injustice in health care is the most shocking and inhumane."[14] The question clinicians and researchers must face is not whether blacks respond less to ACE inhibitor therapy but why the overwhelming degree of death and disability related to CVD in blacks is allowed to continue in one of the richest and most advanced societies in the history of humankind.

Disclosure: Dr Keith C. Ferdinand is a speaker and/or consultant for AstraZeneca; Bristol-Myers Squibb; Forest Laboratories, Inc; Merck; Novartis; and Pfizer Inc.

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