

# Cardiovascular Disease and African Americans: Why Determination of Race Is Inadequate for Research and Practice

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African Americans have been clearly shown to be at increased risk for cardiovascular disease (CVD), more prevalent and severe hypertension and increased rates of multiple cardiovascular conditions, including heart failure, fatal and nonfatal stroke, end-stage renal disease and death from myocardial infarction (MI). In response, recently completed clinical studies, including the African-American Rosuvastatin Investigation of Efficacy and Safety (ARIES)<sup>1</sup> and African-American Heart Failure Trial (A-HeFT),<sup>2</sup> have sought to specifically establish efficacy, safety and benefits of cardiovascular medications in self-identified blacks. Although the implication may therefore be that race or ethnicity could theoretically be utilized as a primary marker for research and practice, clinicians and researchers should continue to use evidence-based medicine whenever possible. The current concept of race itself remains flawed, and overreliance on this category may undervalue the benefit of other research, including the effects of socioeconomic status, geography, psychological stress and lifestyle. Furthermore, true genetic markers may go undetected if classification is simply left to the phenotype of skin color.

*Considering that race may be inadequate as a marker for CVD itself, should clinicians use race at all in evaluating or treating patients?*

While research using race as a marker for epidemiological differences has clearly revealed issues and led to important public health initiatives, in the final analysis, race itself is not a true biologic or genetic category. Race should not be the primary factor in assessing treatment plans in any individual. Although differences across populations have been noted in clinical trials, the difficulty of using the phenotype of race without any true genetic analysis is highlighted by the fact that, to a large extent, African Americans are a very heterogeneous population with varied ancestry of European and indigenous native-American genetic input. Furthermore, these race-based biologic differences will be increasingly blunted as populations merge. The adverse disparities in CVD may be influenced to similar degrees by cultural

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aspects, i.e., how patients live and healthcare disparities, how patients are treated by clinicians as well as the racial phenotype of self-identified African Americans.

The above concepts should not be to support the idea that there is absolutely no benefit in recognizing racial/ethnic differences in management of CV risk factors. Several clinical trials of African Americans have demonstrated a blunted response to monotherapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta-blockers for blood pressure lowering. Nevertheless, trials also confirm that blood pressure control may be more beneficial with thiazide diuretics and calcium channel blockers in patients who consume excess salt and/or have increased salt sensitivity and obesity, which describe a large portion of African Americans. For both blacks and whites, the racial gap in blood pressure is diminished with combination therapy; the apparent effects of racial difference may be related to unmeasured variables such as higher sodium intake and increased body mass index. Of course, the response of any given individual to a specific medicine cannot be predicted on self-identified race alone. For instance, in the African-American Study of Kidney Disease and Hypertension (AASK) trial,<sup>3</sup> ACE inhibitor-based therapy benefited blacks with hypertensive nephropathy, especially with proteinuria. Therefore, rather than withholding renin-angiotensin aldosterone system (RAAS)-blocking agents from black patients with compelling indications as defined by the JNC 7,<sup>4</sup> it is more reasonable to utilize combination therapy and larger doses to reach appropriate blood pressure goals in this population.<sup>5</sup>

*Are there any data to suggest African Americans have a different pathophysiology as related to cardiovascular conditions?*

The answer is unclear, and certainly there may be some benefit in attempting to identify unique pathophysiology more common in blacks than other populations. Research related to epithelial sodium channels, RAAS systems, polymorphisms of beta receptors, nitric oxide availability, endothelin-1 levels and transforming growth-factor  $\beta_1$  hyperexpression continues. Some data have suggested that blacks have increased response to sodium loading, perhaps due to more sodium absorption and sensitivity.<sup>6</sup> For instance, the T594M allele, described more commonly in persons of African origin than whites, may be a marker for salt-sensitive hypertension.<sup>7</sup> Blacks, also, may be at higher risk for the C825T encoding of the  $\beta_3$  subunit protein in response to these thiazide diuretics.<sup>8</sup> In our own A-HeFT trial,<sup>2</sup> we were able to demonstrate the benefit of the fixed-dose combination of isosorbide dinitrate (a nitric oxide donor) and hydralazine (an antioxidant), when added to conventional therapy, in decreasing death, first hospitalization from heart failure and improving quality of life for African Americans with systolic heart failure.

Unfortunately, overlooked in the often-vehement debate of the appropriateness of the initiation of a study of self-identified African Americans is the fact, as we noted in the primary paper, there is a clear need for future research to identify genotypic characteristics beyond self-identified race which would more accurately benefit from this type of therapy. Indeed, a recent paper on the results of the A-HeFT identified the effect of the aldosterone synthase promoter polymorphism in predicting outcomes in this population. The aldosterone synthase promoter-344C allele was linked to higher aldosterone levels and associated with poor event-free survival in blacks with heart failure. The Genetic Risk Assessment of Heart Failure in African Americans substudy highlights our desire to move beyond mere skin color in clinical research.<sup>9</sup>

*To what extent do environmental conditions explain disparities in CVD mortality in blacks?*

Racial/ethnic disparities are real, leading to decreased life expectancy for both black men and women perhaps driven to a large extent by environmental factors. Despite the reality that African Americans have more prevalent and severe hypertension and at earlier onset, the rates of high blood pressure and concomitant target organ damage vary widely across populations of the African diaspora. For instance, hypertension is less prevalent in rural African and Afro-Caribbean populations than in African Americans. This variance is probably due to environmental factors related to the impact of lifestyle differences, including high sodium intake, low potassium intake, increased obesity and inactivity.<sup>10</sup>

African Americans who live in the south are at highest risk for hypertension and its complications, particularly those in the southeastern area. Furthermore, in New York City, southern-born black residents have a higher prevalence of CVD and mortality than northern-born blacks.<sup>11</sup> Thus, within and across populations of African ancestry, geographical variations appear to have a significant impact and may also be markers for lifestyle and culture. In September 2006, published data from a powerful analysis, the Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States<sup>12</sup> confirmed remarkable differences in life expectancy in various groups in the United States, with the lowest being inner-city blacks. The authors of the Eight Americas study noted that the disparities across racial/economic groups are enormous, yet cannot be explained simply by isolating race, income or education status alone. The leading modifiable factors which contribute to the increased burden of disease are, in decreasing order: smoking, alcohol use, overweight/obesity status, high blood pressure, high cholesterol, low fruit/vegetable intake and physical inactivity. Illicit drug use and unsafe sex, commonly thought in our society to be the most irresponsible behaviors that lead to mortality burden, lag far behind the more common ac-

tivities such as smoking, alcohol use and poor diet. The racial death gap is real, as demonstrated in the results of this study. The life expectancy difference between high-risk African Americans versus Asian Americans, for example, is well more than a decade.

*How important is obesity as a cause in CVD in African Americans?*

One of the major contributors to the mortality burden in the United States is overweight/obesity. More than three-quarters of African-American females are obese or overweight,<sup>1</sup> and as many as 90% have no significant recreational/physical activity.<sup>13</sup> Patients who are overweight or obese have marked increased risk for hypertension. This therefore increases the risk of cardiovascular disease, stroke, type-2 diabetes and metabolic syndrome. However, the health consequences of this increased obesity status may be overlooked when considering self-determined race as the underlying cause for multiple conditions. Lifestyle factors also greatly contribute to the obesity epidemic in African Americans, especially women, such as environmental stresses related to racism, sedentary lifestyle, less-positive attitude toward weight loss activities, greater acceptance of overweight status and decreased likelihood of associating body size with health. Of major concern in other developing countries, including those with populations of African descent, is that there will be an increase in obesity and related cardiovascular diseases as they adopt a westernized, industrialized lifestyle. The combination of increasing obesity and excess sodium intake are prominent factors for the rates of specifically hypertension in self-identified African Americans.

*How important is socioeconomic status?*

Unfortunately, African Americans are more likely to be at lower socioeconomic status and at lower levels of education. Socioeconomic classifications and level of education play a potent role in determining CVD and mortality. More than half of all nonhigh-school graduates have multiple CVD risk factors. Furthermore, the percentage of a population with multiple risk factors decreases as the level of education increases, with slightly greater than one-fourth of all college graduates having multiple CVD risk factors. The correlation between level of education and income is also quite direct, with 53% of persons with an annual income of <\$10,000 having multiple risk factors as compared to 29% of those with incomes of >\$50,000. In the Eight Americas study, the lowest sociodemographic to complete high school and also with the lowest average income per capita were southern, low-income, rural blacks, followed by high-risk urban blacks with the second lowest rate of high-school completion and per capita income.<sup>12</sup> Multiple studies have confirmed the impact of psychogenic stress as a factor in hypertension and even coronary mortality.

African Americans are clearly affected by disproportionate levels of stress related to a socioeconomically disadvantaged status and perceived discrimination. Clinical trials have even demonstrated that stress reduction modalities such as transcendental meditation can benefit African Americans with hypertension, heart failure and perhaps the reduction of mortality.<sup>14,15</sup>

*In final analysis, should we even note self-identified race status in clinical practice and research?*

Yes. I do not propose an all-or-none situation regarding the utilization of self-identified race in clinical practice and research. There may be differences in genetics known and yet to be discovered that explain some of the increased risk for hypertension and other CVD in blacks and subtle, but significant, differences in response to various medications. We should continue to note patients' self-identified race status in clinical research and practice and continue to identify the many different reasons why African Americans have such significantly high rates in various diseases and increased mortality. Nevertheless, we must also avoid overlooking other measured and unmeasured variables which may affect cardiovascular morbidity and mortality.

Health disparities remain distressingly persistent in the United States but will not be overcome simply by identifying a person's self-identified race. We must address multiple barriers, including the control of risk factors; adverse lifestyle; bias in the healthcare system; socioeconomic inequality; and the imbalance in the application of life-saving, evidence-based medications to black patients. Perhaps the question is not "who gets cardiovascular disease?" but what is done once the diagnosis is made for secondary prevention and what efforts, in terms of lifestyle, are embraced by various populations to prevent the excessive morbidity and mortality related to the number-one cause of death in the United States. Inappropriate or excessive reliance on the phenotype of skin color as a guide for research or therapy may have the unexpected consequence of underrecognizing other important variables, including culture, lifestyle, socioeconomic status, psychological stress and bias within the healthcare system. Clinicians should avoid deprecating remarks regarding a patient's lifestyle and body habitus, thereby utilizing the presence of adverse environment factors as an explanation why therapeutic inertia is embraced.

Regarding the art of healing, no matter what scientific breakthroughs are noted in the future and despite increasing complexities of the healthcare delivery system, the essence of the modern physician will continue to be based on one-on-one patient care.

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