Perspective on Selected Issues in Cardiovascular Disease Research With a Focus on Black Americans

Michelle A. Albert, MD, MPH; Jose Torres; Robert J. Glynn, PhD; Paul M Ridker, MD, MPH

Case Presentation: Mr A is a healthy 38-year-old black male who comes to the clinic as a self-referral after a blood pressure check during “Health Day” at his job. Mr A is concerned because “high blood pressure” runs in his family. He reveals that his 58-year-old mother recently suffered a mild stroke and also takes water pills to reduce swelling in her legs. He denies any other health problems, is a non-smoker, and takes no medications. On physical examination, his supine blood pressure is 165/85, his heart rate is 74 bpm, and his weight is 72 kg. An ECG shows normal sinus rhythm at 76 bpm and evidence of left ventricular hypertrophy. A fasting lipid profile shows a total cholesterol level of 196 mg/dL, a low-density lipoprotein cholesterol (LDL-C) level of 120 mg/dL, a high-density lipoprotein cholesterol (HDL-C) level of 50 mg/dL, a triglyceride level of 130 mg/dL, and C-reactive protein level of 3.5 mg/L. What clinical strategy would be most appropriate for Mr A? What is the available scientific evidence to support your choice(s)?

Despite advances in the diagnosis and treatment of cardiovascular disease (CVD), morbidity and mortality from CVD is higher among black Americans than among white, Hispanic, and Asian Americans. Although black Americans are often considered to have less obstructive coronary heart disease than age-matched whites, the prevalence of traditional risk factors for CVD such as hypertension, diabetes mellitus, smoking, and obesity disproportionately affects black Americans. However, the relative importance of these risk factors and others, such as left ventricular hypertrophy, dyslipidemia, and novel risk determinants such as C-reactive protein and lipoprotein (a), on morbidity and mortality is unclear. At the population level, research efforts have focused primarily on the components of the Framingham Cardiovascular Risk Equation that were developed in a predominantly white cohort. Other important cardiovascular risk determinants that likely contribute to the disparity in CVD noted between ethnic groups include socioeconomic status, cultural issues, access to health care, and care provided by health professionals according to race/ethnicity.

Selected Traditional Risk Factors

Hypertension

Epidemiological studies have documented a strong relationship between hypertension and CVD among blacks. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that at least 33.5% of blacks and 28.9% of whites have hypertension and that black race was an independent predictor of hypertension. The development of hypertension and its relationship to CVD is multifactorial and likely includes both environmental and physiological/genetic components, including endothelial dysfunction, subendocardial fibrosis, and left ventricular hypertrophy (LVH). The relationship of LVH to cardiac death is of particular importance in blacks because of the higher prevalence of hypertension associated LVH in this ethnic group. Echocardiographic data from the Coronary Artery Risk Development in Young Adults study showed that LV mass was higher in blacks than in whites and correlated with systolic blood pressure. LVH in the presence of hypertension is associated with an increased risk of sudden cardiac death, probably due in part to complex ventricular arrhythmias, factors...
related to myocardial oxygen supply/demand, and subendocardial fibrosis.\textsuperscript{7,9} In one study that included only black males, among those men with hypertensive LVH, asymptomatic non-sustained ventricular tachycardia independently predicted subsequent cardiovascular events.\textsuperscript{10} These findings warrant further investigation, particularly because black Americans have a higher prevalence of out of hospital sudden cardiac death than other race/ethnic groups, an outcome that likely reflects both physiological and access-to-care issues.

Other work demonstrated that normotensive black and white youths with a family history of hypertension who had LVH at baseline were more likely to have greater blood pressure reactivity to stress at follow-up.\textsuperscript{11} This finding suggests possible important interactions between environmental stress and physiology that could result in deleterious cardiovascular consequences over the long-term. Further research evaluating the prevalence of LVH in normotensive and hypertensive blacks and the direct relationship to CVD mortality could be critical to improving our understanding and attenuating observed race related differences in hypertensive heart disease.

**Dyslipidemia**

Longitudinal population data that examine the distribution of lipid levels or the predictive power of these lipid values for coronary artery disease among various ethnic groups are limited. One such study—NHANES III—showed that blacks have lower non–HDL-C levels than whites or Mexican-Americans.\textsuperscript{12} Additionally, studies have indicated that blacks tend to have lower total cholesterol and triglyceride levels but higher HDL-C levels than whites.\textsuperscript{13,14} Meanwhile, a large multi-ethnic study suggested that HDL-C was more protective in white persons for coronary artery disease (CAD), but that there were no significant differences in the predictive capacity of LDL-C across ethnic groups.\textsuperscript{15} International data that evaluate the lipid profile of people of African descent are also consistent with the United States data regarding lower triglyceride and higher HDL-C levels.\textsuperscript{16} These findings are important and require further investigation, as a major target of CAD risk reduction involves education and lipid-lowering therapy. It may be that target lipid goals are different among blacks, or alternatively, that cardiovascular mortality benefit from triglyceride lowering or HDL-C increases would be substantial in high-risk individuals even if their triglyceride and HDL-C levels are within recommended target range. Evidence that supports the latter assertion is noted in the Heart Protection Study, where participants benefited significantly from simvastatin therapy regardless of whether they had triglyceride levels above or below 178 mg/dL or HDL-C levels above or below 42.9 mg/dL.\textsuperscript{17} Although some authors have recognized that these differences in lipid levels may contribute to the lower observed rates of coronary heart disease in persons of African heritage, it is interesting to note that whereas blacks in the United States also traditionally experience lower rates of CAD, they still have higher morbidity and mortality from CVD than other ethnic groups, a circumstance in which lipoprotein distribution potentially plays a role.

Until the publication of Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT), black American representation in major lipid lowering trials was generally less than 8%; therefore, limited data exist on any black–white differences in cholesterol lowering.\textsuperscript{18–20} Among blacks, ALLHAT-LLT demonstrated a 27% reduction in coronary events with pravastatin therapy compared with usual care, a finding that showed a greater benefit in this subgroup compared with the non-black population.\textsuperscript{21}

Despite differences in lipid parameters according to race/ethnicity, the clustering of certain CVD risk factors can result in a risk profile that arguably abolishes the effect of any lipid differences noted between blacks and whites. For example, a non-interventional outpatient study noted that among patients with type II diabetes, almost 50% of black patients compared with 42% of white patients had LDL-C levels above and HDL-C below the recommended goals, but blacks were still more likely than whites to have HDL-C or triglyceride levels within the recommended target range.\textsuperscript{22} In other data from the Bogalusa Heart Study, triglyceride levels were lower among black than white females despite their increased body mass index. Overall, although high triglyceride levels were positively associated with increased visceral fatness and insulin resistance, particularly at levels above 150 mg/dL, the combination of high triglyceride and low HDL-C levels tended to increase the likelihood of diabetes and hypertension and was present in 9% of white males, 3% of white females, 4% of black males, and 0% of black females.\textsuperscript{23} These data highlight several issues: (1) cardiovascular risk factors cluster to influence disease; (2) the contribution of triglycerides to CAD risk may vary by race/ethnicity; and (3) although improvement of LDL-C and HDL-C are important antiatherogenic targets, further research is needed to understand the observed differences in lipid levels and CAD outcomes by race/ethnicity. Specifically, data on the mechanisms of these differences, as well as the relationship/impact of these differences to other risk factors for CVD such as obesity, are necessary.

**Metabolic Syndrome**

The metabolic syndrome is present in almost 25% of Americans and the prevalence varies by ethnicity.\textsuperscript{24} Moreover, although the distribution of components of the metabolic syndrome might be similar across the 4 major race/ethnic groups in the United States, the relative contribution of the various components of the metabolic syndrome to CVD also varies by ethnicity.\textsuperscript{25} Among black women, blood pressure and dyslipidemia appeared to have the strongest associations with CVD, whereas obesity was more
tightly linked with CVD for Hispanic and white women. These findings require further investigation, as it is likely that these factors also cluster with other factors such as fibrinolytic and inflammatory parameters to influence cardiovascular risk.

Additionally, the relationship between obesity and its associated correlates with cardiovascular end points such as congestive heart failure and sudden death among blacks is unknown. Both are conditions that occur in higher frequency and account for a significant proportion of CVD burden among blacks. Individual analyses of these potential relationships might provide insight into the impact of the metabolic syndrome on CVD risk as well as the pathobiology of CVD in various ethnic groups. For example, it is possible that there exists a pathophysiological link between increased body mass index and sudden death via arrhythmias in addition to de novo CAD that varies by ethnicity. Such a hypothesis arises from data that demonstrate an association between increased LVH and characteristics of the insulin resistance syndrome, including insulin levels, systolic blood pressure, and waist girth. This hypothesis is also supported by autopsy data that indicate an excess of sudden cardiac death among older blacks compared with whites due to stable plaques, where the presence of stable plaque was associated with LVH and hypertension.26,27

**Novel Cardiovascular Risk Factors**

Little comparative information across race/ethnic groups in the United States is known about any relationship between novel risk factors of thrombosis and inflammation and CVD. For example, although multiple prospective studies show that C-reactive protein (CRP) is an independent predictor of vascular risk, rigorous prospective data in minority groups are virtually nonexistent. Most of the data regarding ethnicity and CRP relate to ethnic groups in Europe, where CRP levels were higher among the South Asian population compared with Europeans and lower in African-Caribbeans than Europeans in the United Kingdom.28–30 In the United States, data from NHANES, as well as from a study of black women <30 years old, suggest that CRP levels are higher in blacks than in their white counterparts.31,32 Although these data likely reflect both environmental and genetic factors, they are nonetheless disturbing, as both groups studied lacked clinical cardiovascular disease. Data on other inflammatory markers of atherosclerosis, such as adhesion molecules and interleukins, are also sparse.

Similarly, although elevated lipoprotein (a) (Lp[a]) levels are associated with incident CAD in whites, among black individuals, Lp(a) levels are higher and the data are conflicting regarding the strength of association for CAD.33–35 This discrepancy in risk is in part attributed to the epidemiological observation of lower LDL and higher HDL levels in black subjects as compared with white subjects. Additionally, some groups have argued that apolipoprotein (a) size is an important co-contributor to cardiovascular risk in black subjects.

Other data have suggested enhanced fibrinolytic potential in black individuals compared with white individuals. One study demonstrated that tPA antigen levels were higher in blacks, and subsequently higher coronary artery patency rates are noted after fibrinolysis.36 Additional data also show that PAI-1 levels were lower among blacks than among whites and Hispanics and that there was an association between the PAI-1 4G/5G polymorphism and serum levels of PAI-1, as well as with ethnicity.37 These data further emphasize the need for large-scale prospective data that investigate the interrelations between novel markers of thrombosis and inflammation and cardiovascular disease across ethnic groups.

**Socioeconomic Status**

The most frequently used measures of socioeconomic status (SES) in medical research are income, education level, and employment type. Among all ethnic groups, multiple studies demonstrate that lower SES is associated with worse cardiovascular status.38,39 Although over the last decade a solid black middle class has emerged, socio-demographic data indicate that overall blacks are among the poorest Americans, a factor that undeniably affects their health. Further, some data suggest that increasing income and education among some blacks correlates with improved health, whereas other data indicate that the health of income/education advantaged blacks still overall remains poor.40 For example, national data demonstrate that the infant mortality rate of educated black women, a sensitive measure of all cause morbidity and mortality, is 2 times higher than the rate for white women and is also higher than that of women from other race/ethnic groups.41 Likewise, cardiovascular mortality statistics in population cohorts that are comprised of persons of similar employment or insurance status indicate that black participants in those cohorts have higher cardiovascular mortality rates than white participants.42 These data suggest that in addition to the traditional cardiovascular risk factors, other variables such as race, neighborhood factors, and stress likely also impact SES and as such must be studied in conjunction with the former risk characteristics to understand outcomes.

Of the large epidemiological cohort studies that examine cardiovascular risk determinants, few collect information about stress or neighborhood factors. One interesting study reported that among black men living in disadvantaged neighborhoods, increased income and education were positively related to the insulin resistance syndrome, whereas among whites and black women, there was an inverse association between disadvantaged neighborhood status and the insulin resistance syndrome.43 Other data indicate that among black children, both lower family and neighborhood SES were associated with hostility and greater cardiovascular reactivity to stressors,
but among white children, only lower family SES was associated with increased cardiovascular reactivity, a factor related to increased left ventricular mass.44 Because SES is such a complex and difficult measure to capture, particularly in minority communities, one potential strategy might be to use an SES score that is composed of multiple variables, including and among others income, education, occupation status, community status/involvement, and violence. Although the latter strategy has been used in the social science community and in health population studies in Europe, comparative epidemiological or clinical trial data in the United States that utilize a combined measure of SES beyond education and income are sparse.

**Case Presentation Continued: Treatment**

Application of current Adult Treatment Panel III guidelines to Mr A’s case presentation would result in treatment of his hypertension most likely with diuretic and/or β-blocker therapy, as well as a recommendation for increased physical activity. According to the guidelines, Mr A has 2 major risk
factors for coronary heart disease: Hypertension and a family history of premature CHD. Despite the latter, his calculated Framingham 10-year estimate of cardiovascular risk is 1%. Although Mr A’s CRP level would be considered elevated, there are currently no firm guidelines that recommend treatment of the latter; however, there are available data that suggest CRP adds predictive data to the Framingham risk calculation.\textsuperscript{45,46}

Conclusion
Elimination of race/ethnic disparities in cardiovascular health is a solvable problem that will require a multifaceted approach. Although this article focused on CVD risk factor investigation, currently the most immediate strategy toward eliminating disparities and improving health of blacks in the United States involves provision of equal and affordable care to all race/ethnic groups, adherence to national cardiovascular guidelines, and the nurturing, recruitment, and retention of minority clinicians and researchers. In addition to these issues, aggressive effort must be put forth by researchers to recruit participants from minority groups into clinical trials and cohorts. This has proven difficult for many reasons, including lack of participant trust, lack of faith in the medical system, carryover from the Tuskegee experiment, and circumstances surrounding the continued racial divide in this country.\textsuperscript{47} The Table demonstrates the representation of blacks in some of the major randomized clinical trials.\textsuperscript{48}

Furthermore, as many of the precursors of cardiovascular disease are present in children and young adults, particularly in minority groups, public health strategies such as smoking cessation and increased physical activity should also target these groups.\textsuperscript{49} From a risk factor research perspective, not only must available data be used more effectively, but also novel questions for investigation and approaches to research operation may be required. For example, the composition and structure of research teams may need reconfiguration to include a multidisciplinary network of nurses, social workers, community advocates, and academic researchers instead of the traditional academic center-focused model. From a clinical perspective, individual physicians must strive to ensure that all of their patients achieve target levels of modifiable risk indicators regardless of race/ethnicity and that culturally sensitive educational tools are available for patient treatment.

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