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EDITORIAL

Identifying Differences: A Key Step in Precision Cardiovascular Disease Prevention

Mahmoud Al Rifai, MD, MPH; Salim S. Virani, MD, PhD; Vijay Nambi, MD, PhD

Understanding differences in pathobiology and response to treatment based on an individual's sex, race, and ethnicity are becoming ever more crucial as we strive to move away from the "one size fits all" management approach to one that is more precise and individualized.

See Article by Nonterah et al.

Several sex-specific contributors to cardiovascular risk have already been identified. The most recent cholesterol guidelines identified preeclampsia and premature menopause as risk-enhancing factors among women.[1] Similarly, South Asian (SA) ethnicity is now recognized as a risk enhancing factor. Along with identifying risk enhancers and risk factors, identifying pre- or subclinical atherosclerosis is an important tool to further refine and improve cardiovascular disease (CVD) risk stratification and enable shared decision making regarding preventive therapy.[1]

In this context, Nonterah et al present in this issue of the *Journal of the American Heart Association* (*JAHA*) their analyses using pooled data from multiple cohorts from multiple countries (n=34 025) representing various race and ethnic groups. They examined carotid intima-media thickness (cIMT) and explored the association of cardiovascular risk factors with cIMT.[2] Adjusted cIMT was highest among African Americans followed by Asian, European, Hispanic, and African populations. In analyses restricted to African populations, cIMT was highest among African Americans, followed by West Africans, South Africans, and East Africans. In each group, cIMT was higher among men compared with women. The authors evaluated the association between cardiovascular risk factors and cIMT in each race and ethnic group and identified some unique patterns. Compared with European populations, the magnitude of association of age, sex, and systolic blood pressure with cIMT was weaker in all races and ethnicities. Physical activity was inversely related to cIMT among European and African populations but directly related to cIMT among Asian populations. High-density lipoprotein cholesterol had the strongest inverse association with cIMT among African American and African populations followed by European populations, while it was not significant among Asian populations. Smoking, body mass index, and glucose had the strongest association with cIMT among Asian individuals.

The authors should be congratulated on this important work combining various cohorts with multiple race and ethnic groups from different countries. Importantly, they performed analyses in subgroups of African ethnicity in various regions of Africa and the United States. They conducted a 2-stage individual participant level data meta-analysis, which allowed them to perform

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Correspondence to: Vijay Nambi, MD, PhD, Baylor College of Medicine, 2002 Holcombe Blvd, Houston, TX 77030. Email: vnambi@bcm.edu

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valid comparisons of cIMT using adjusted means and to study its association with cardiovascular risk factors across different race and ethnic groups using standardized beta coefficients. Lastly, the authors used a standardized measurement of cIMT using the z-score and harmonized their covariates to limit bias.

However, the analyses do have some limitations. While the authors adjusted the analyses for age and other risk factors, it would have also been informative to present cIMT stratified by age given the strong association between age and cIMT. Furthermore, as with other analyses of this kind there are inherent limitations. Some variables were missing in some cohorts, which can result in non-random errors and residual confounding. For example, information about HIV infection was missing in non-African populations.[3] Furthermore, there was no information on diet, acculturation, social determinants of health (SDOH), exposure to particulate matter, medication use, genetic or inflammatory markers in any group. Participants were enrolled during different time points between 1990 and 2015, which may complicate data harmonization given temporal shifts in population level risk factors and medication use (although the authors did perform some secondary analyses to try to address some of these issues). Chinese and Hispanic individuals were recruited from the United States and not from representative countries. Furthermore, grouping all individuals of Asian descent can mask important heterogeneity in cardiovascular risk factors. For example, SA from Bangladesh, India, Pakistan, and Sri Lanka have been shown to have more carotid atherosclerosis compared with Chinese individuals.[4]

Another important consideration is the use of cIMT itself. As atherosclerosis is a sub-intimal process, measurement of cIMT with ultrasound has been used as a surrogate to identify early atherosclerosis. Prior studies have shown that cIMT (especially in concert with information about plaque presence) is directly associated with CVD risk factors and CVD risk and can improve risk discrimination and reclassification.[5] Although cIMT offers a number of advantages for assessing subclinical atherosclerosis burden including safety and ability to repeat measurements there are several disadvantages including reproducibility, alternate reasons for increased cIMT and, hence, has fallen out of favor. In the current analysis, the cIMT protocols (example imaging technique/angles used) were not homogenized across studies, plaque presence was not assessed and furthermore due to the time frame of the study technology will have changed.[5] Again, while the authors did perform additional secondary analyses based on when subjects were recruited, this will not completely resolve the limitations associated with cIMT measurements. Hence, despite a large sample size, one cannot completely discount the fact that differences in cIMT and associations with risk factors could still represent chance findings rather than true biological differences.

However, based on data such as presented in this study and other studies of biomarkers and subclinical atherosclerosis it is becoming clear that analyses of biomarkers/subclinical atherosclerosis and their association with CVD by race, ethnicity, and sex are essential to elucidate potential differences related to biology of disease (Figure). For example, it has been postulated that SA may have high-density lipoprotein particles that are dysfunctional, smaller, and possibly proatherogenic.[6] A prior study showed an inverse association between high-density lipoprotein cholesterol and cIMT among White individuals but a direct association among SA from India.[7] Interestingly, high-density lipoprotein cholesterol was directly associated with CAC density among SA.[8] Similarly, Black individuals of African descent and SA populations have higher lipoprotein(a) compared with White or East Asian individuals.[9] Data have also suggested that the prognostic value of NT-proBNP (N-terminal pro–B-type natriuretic peptide) may differ substantially by race and sex. Among both middle-aged and older individuals, NT-proBNP concentration was highest among White women and lowest among Black men.[10] These differences persisted after accounting for sociodemographic factors (including the area deprivation index) and left ventricular structure and function. However, at any level of NT-proBNP the risk of heart failure and death were greater in Black men. For example, the NT-proBNP values associated with a 5-year risk of 10% for heart failure and death were 76 pg/mL (95% CI, 53–107) for Black men, 116 pg/mL (95% CI, 95–125) for White men, 188 pg/mL (95% CI, 142–250) for Black women, and 402 pg/mL (95% CI, 312–597) for White women, respectively, suggesting that single cut-points to identify risk (example 125 pg/mL) can misclassify several individuals.

Genetic differences across races may also help guide our investigations and understanding as to why therapeutic response differs in certain subgroups. For example, pharmacodynamic studies have demonstrated that there may be genetic differences in

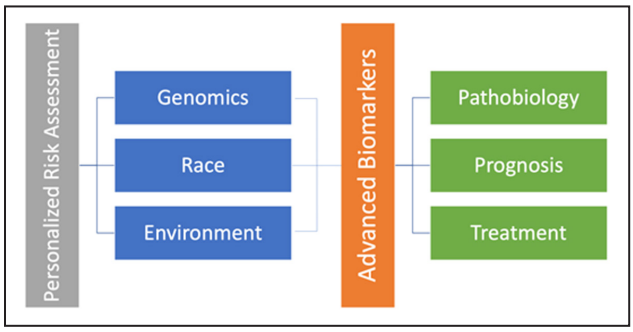

Figure. The utility of biomarkers for personalized cardiovascular risk assessment.

statin metabolism with East Asian individuals having a heightened response to statins. This might explain why lower statin doses can achieve similar reduction in low-density lipoprotein cholesterol in East Asian adults compared with higher doses in White individuals.[11] Similarly, the contribution of endothelial dysfunction and vascular homeostasis to heart failure in African Americans may explain why the combination of isosorbide dinitrate and hydralazine is uniquely effective in this group.[12] These important differences in response to treatment by race have been highlighted in a recent summary statement issued by the Food and Drug Administration to increase representation of underrepresented populations in drug trials.[13] Indeed, nearly 60% of the world's populations reside in Asia and 17% in Africa.

As important as understanding the contribution of biological differences between races and ethnicities to cardiovascular health is recognizing, acknowledging, and investigating the societal and environmental aspects influencing racial and ethnic differences in cardiovascular health and outcomes. Lack of proper access to health care and healthy choices (example, food deserts) can vary depending on a person's zip code and can result in health disparities.[14] For example, the southwestern and southeastern parts of the United States have the largest concentration of counties with social vulnerabilities and CVD mortality. Counties with higher social vulnerability index have a significantly higher mortality attributable to CVD and Black individuals in each social vulnerability index category had higher age-adjusted CVD mortality compared with White individuals. Cultural mistrust and physician distrust may lead to avoidance of medical care further exacerbating health disparities. There are also regional variations in the contribution of particulate matter pollution ($PM_{2.5}$) to life expectancy.[15] At any $PM_{2.5}$, life expectancy loss is larger in counties with lower income and higher poverty. Furthermore, cultural integration practices can change through measures of acculturation among foreign-born individuals. This can have important effects on cardiometabolic risk as immigrant populations settling in the United States can adopt a Western lifestyle.[16] For example, it is possible that in the current study, the higher cIMT that was observed among African American individuals compared with those from different regions of Africa may be due to environmental factors though this was not assessed in the present study. On the other hand, "globalization" of lifestyle is changing local practices and lifestyle which is already beginning to have an impact in cardiovascular health.

So where does the current analysis leave us? Currently, coronary artery calcium (CAC) which measures the burden of calcified coronary plaques using gated cardiac computed tomography scans is the test of choice (especially in middle age and older individuals) to help guide management decisions in the primary prevention of CVD. CIMT has fallen out of favor due to limitations as previously discussed. However, carotid ultrasound can also assess carotid plaque (which was not studied in this analysis) size and morphology which is thought to be superior to cIMT in CVD risk assessment and hence currently there is a greater focus on plaque quantification and qualification by ultrasound.[5] Hence, studies that evaluate the association of risk factors by sex, race, and ethnicity with carotid plaque and incident CVD will be valuable to perform to help us further explore the results of the current study. These analyses should also be replicated using CAC as a surrogate measure of atherosclerosis to provide further validation. CAC has already been shown to be associated with incident atherosclerotic cardiovascular disease in White, African American, Hispanic, and Chinese-American adults,[17] while SA men have been shown to have a similar CAC burden as White men but higher than other groups and SA women have a similar CAC burden compared with women of other races and ethnicities.[18]

Development of such sex, race, and ethnicity-specific associations will help us understand if there is any differential impact of various known and yet to be discovered risk factors on the incidence of CVD. Identifying these differences will then help us explore and study if more intensive targeted risk factor control will achieve improved residual risk reduction while minimizing potential harm from therapies. In parallel to understanding the impact of one's sex, race, and ethnicity, we should also focus on the environmental impact on CVD while trying to achieve health equity and reducing racial disparities in cardiovascular care.

In conclusion, while the current analysis has some strengths and limitations more such efforts that factor in genomics, SDOH, environmental factors, and other areas of interest such as metabolomics and proteomics are needed to understand their contribution to observed differences in biomarkers by race and ethnicity. Understanding these differences will help us develop a more individualized approach to the prevention and management of CVD that is more precise and personalized.

ARTICLE INFORMATION

Affiliations

Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, TX (M.A.R., S.S.V., V.N.); Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX (S.S.V., V.N.); and Division of Cardiovascular Research, Baylor College of Medicine, Houston, TX (S.S.V., V.N.).

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