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EDITORIAL

Bridging the Racial Disparity Gap in Lipid-Lowering Therapy

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There are significant variations in cardiovascular disease prevalence and outcomes, as well as in risk factors, including lipid profiles, among different races worldwide and in the United States.[1] Racial and ethnic minority groups account for 36% of the US population and are projected to increase to 53% by 2050: the 2 most rapidly growing of these are Hispanic and Asian-American populations, whose population is projected to increase to 110 and 30 million, respectively. Cardiovascular disease (CVD) burden among different races is heterogeneous: South Asian, Filipino, and Black individuals have more atherosclerotic CVD compared with non-Hispanic White individuals.[2,3] Despite dyslipidemia being more prevalent in certain ethnic minorities, they are prescribed lipid-lowering therapy less frequently than White individuals and are less likely to achieve optimal lipid targets (eg, women are less likely to be prescribed statin therapy in both primary and secondary prevention, especially Black women).[4,5] The same is true for younger Black men.[6] Furthermore, Hispanic adults have a higher prevalence of elevated low-density lipoprotein cholesterol (LDL-C), and both South Asian and Hispanic individuals have higher triglyceride and lower high-density lipoprotein cholesterol levels, and a higher prevalence of visceral adiposity, diabetes mellitus, and metabolic syndrome.[7] Black people have a higher prevalence of hypertension, stroke, heart failure, and cardiovascular mortality but are less likely to receive optimal preventive cardiovascular care.[8] In addition, differential effects of various lipid-lowering drugs can be seen in different ethnic groups because of variations in genetic background, sex, socioeconomic status, education level, drug metabolism, and environmental factors, such as diet, stress levels, alcohol consumption, cultural values, and medication adherence.[9] Two well-known examples of racial differences in statin blood levels, pharmacokinetics, and their efficacy and adverse effects are known to be caused by genetic variations (eg, the SLCO1B1*15 haplotype occurs at a frequency of 17% in Japanese versus 1% in Black individuals). This allelic variant results in reduced function of the organic anion transporter that regulates the hepatic uptake of simvastatin, resulting in higher serum levels and a higher rate of myopathy. Similarly, the 421C>A polymorphism in the drug efflux transporter, ATP-binding cassette G2 gene, results in a plasma concentration of rosuvastatin that is twice as high as in those with the normal variant. This polymorphism is seen more often in Asian patients than in White patients, which explains the lower doses of rosuvastatin needed in Asian patients for similar LDL-C lowering and cardiovascular event reduction.[10] Furthermore, there are differences in lipoprotein particle number and size and PCSK9 (proprotein convertase subtilisin/kexin type 9) levels and activity among different ethnicities, with higher circulating PCSK9 levels seen

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in Black versus White individuals.[11] Whether PCSK9 inhibitors resulted in different LDL-C lowering effects in different races had not been well examined up until recently, but emerging data show that these drugs are equally, if not more effective, in racial minorities. In a small pharmacodynamic/pharmacokinetic study of evolocumab in 143 patients, no differences in drug levels or effect were found between Asian and White individuals.[12]

Despite the fact that there is a higher prevalence of atherosclerotic CVD in racial minorities, White individuals, especially older White men, continue to be the dominant patient type in most cardiovascular trials. Data pertaining to minority races are thus obtained mostly through subgroup analyses, which are inherently limited because of small sample sizes, wider CIs, and lower precision. This underrepresentation of minorities unfortunately continues to be a common trend in many large cardiovascular trials that are being done presently by pharmaceutical companies.[13] In addition, in minority populations, there is less screening and fewer individuals are aware of their health status. Some Black people are mislabeled as having statin intolerance because they have elevated levels of creatinine kinase, which is racially mediated and does not usually denote myopathy. Adherence and access to lipid-lowering drugs also vary by race, geography, healthcare access, and perceived benefit, all of which are intertwined. In the cholesterol and pharmacogenetics study (CAP) study, the effectiveness of simvastatin was similar between White and Black individuals, and other small trials of statins and nonstatins specifically looking at other minorities have also demonstrated similar efficacy and safety in non-White individuals.[15]

With this background in mind, it is pertinent that in this issue of the *Journal of the American Heart Association* (*JAHA*), Daviglus et al now report the efficacy of the commercially available PCSK9 inhibitor, evolocumab, in LDL lowering in different ethnic/racial groups in >7500 patients.[16] They compiled pooled data from 15 randomized controlled trials of evolocumab versus placebo in 4 different minorities: Black, Asian, Hispanic, and non-White (American Indian, Hawaiian, mixed race) patients. The individual study designs and populations enrolled were heterogeneous, with ≈25% having known atherosclerotic CVD (ie, secondary prevention) and the remainder being primary prevention but with diabetes mellitus, familial hypercholesterolemia, or statin intolerance, or those not optimally controlled on statins. Study duration ranged from 12 weeks to 5 years; some studies had an open-label extension, in which after 1 year, all patients previously receiving placebo were transitioned to evolocumab. The placebo arm included either true placebo or ezetimibe comparator. The main result was that there were no significant differences in percentage LDL-C lowering, those with >50% LDL-C lowering, or percentage of patients who achieved LDL-C <70 mg/dL. There were also favorable accompanying changes in other lipid parameters, as expected from prior randomized controlled trial data, in White individuals (reductions in apolipoprotein B and non–high-density lipoprotein of ≈50% were seen, lipoprotein[a] ≈20%, triglycerides ≈8%, and an increase in high-density lipoprotein cholesterol of ≈7%). Treatment effects were directionally consistent and not statistically different across various patient characteristics, including race, sex, dosing schedules (weeks versus monthly injections), and statin intolerance status. Interestingly, patients with diabetes mellitus had a greater LDL-C reduction, especially among the Asian subgroup (LDL-C lowering of 69.6±20.2% occurred in 305 Asian patients versus 51.5±25.6% in 440 White patients; $P<0.001$). These results are thus reminiscent of the higher statin potency that has also been observed in Asian subjects. Furthermore, prior statin trials have shown that the effectiveness on cardiovascular outcomes is preserved across different races; in the Justification for the Use of statins in Primary prevention - an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of rosuvastatin in primary prevention, the degree of patient risk determined statin benefit, not ethnicity or sex.[17]

As noted, most individuals enrolled in randomized controlled trials of lipid-lowering therapy, including statins and PCSK9 inhibitors, have been White individuals from Western countries.[4] Of the 46 488 patients in 2 of the large PCSK9 monoclonal antibody drug trials, Further cardiovascular Outcomes Research with PCSK9 Inhibition In subjects With Elevated Risk (FOURIER) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY), ≈74% of patients were from North America or Europe and 80% were White individuals, 13% were Asian, 5% were Hispanic, and the remainder were Black individuals. However, because these large studies were underpowered to detect differences in PCSK9 efficacy between different races, the current report presents an individual-level meta-analysis of the available randomized controlled trials of evolocumab to see if any such differences existed; as mentioned, no significant differences in the LDL-C lowering effect were detected. This analysis does have a few shortcomings; similar data for the other commercially available PCSK9 drug, alirocumab, are not presented herein, although they have been published previously.[18] Also, the FOURIER results were not included in this analysis. A total of 85% of the 27 564 patients in that trial were White patients, with 80% enrolled from North America or Europe and only 7% in Latin America and 14% in the Asia-Pacific region. The forest plot for the primary composite outcome was not different when analyzed by geographic region or

race. Similar results were seen for alirocumab in the ODYSSEY trial (18 924 patients). Last, no outcomes data are presented given the individual study designs, which remains a shortcoming of this type of descriptive post hoc analysis.

Notwithstanding these limitations, these data will be useful in diminishing the treatment gap in racial disparities that exists in clinical practice; the findings herein will hopefully spur wider appropriate use of this class of drugs in primary and secondary prevention in racial/ethnic groups in which they are underused, such as in Hispanic and Black individuals, and thus are important from a public health perspective. In this regard, the American College of Cardiology and National Lipid Association have recognized certain races/ethnicities as being "risk modifiers" when assessing atherosclerotic CVD risk, and the National Lipid Association has led an initiative that focuses on reducing disparities in lipid-lowering therapy prescription by educating clinicians about the higher risk in minorities, such as South Asian individuals.[19,20] Multiple other professional and regulatory bodies, such as the American Heart Association, Food and Drug Administration, Institute of Medicine, and the Department of Health and Human Services, have also stressed the need for expanded inclusion of diverse ethnicities in trials that will provide more data and help lessen racial disparities.[21] By understanding the factors that are responsible for the reduced use and/or barriers to implementation of proven risk-reducing lipid therapies, recommendations can be formulated to bridge the racial divide in CVD prevention and management.

ARTICLE INFORMATION

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Disclosures

None.

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