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EDITORIAL COMMENT

# Potential for Bridging Treatment Gaps in Cardiovascular Health in Asia With Inclusive Clinical Trials*

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Asian individuals comprise nearly one-half of the global population and have well-documented increased cardiovascular disease risk; however, they represent a small minority of participants in cardiovascular research studies, raising key issues regarding equity. Widely used cardiovascular clinical risk prediction algorithms, such as the American Heart Association/American College of Cardiology Pooled Cohort Equations, did not include any Asian individuals in their derivation, and this has manifested with poorer performance of these risk predictors in these groups.[1-3] Similarly, genome-wide association studies, which are used to fuel mechanistic discovery and polygenic risk prediction, are also under-represented in Asians.[4,5] Historically, clinical trials conducted largely in Europe and North America have also had low enrollment of Asian populations, raising questions of generalizability of their results.[6] Numerous population specific factors, ranging from genetics to environmental exposures and lifestyle, can influence the effectiveness and safety of a drug in a given group. For example, studies in pharmacogenomics of clopidogrel have shown that Asian subgroups are more likely to have genetic predisposition of being poor or intermediate CYP2C19 metabolizers, potentially translating to higher risk of cardiovascular events compared with people of African or European ancestry.[7] National drug regulatory agencies around the world are increasing scrutiny of approval processes for new therapies to ensure that they meet safety and efficacy standards for their specific populations.

Recent years have seen a greater priority on conducting international trials. The original ORION-9, ORION-10, and ORION-11 trials were conducted in over a collective 3,600 participants across the United States, Europe, and South Africa and tested the effect of inclisiran–long-acting, short-chain siRNA directed against proprotein convertase subtilisin kexin type 9 (PCSK9)–protein-in lowering of low-density lipoprotein (LDL) cholesterol.[8,9] In this issue of *JACC: Asia*, Huo et al[10] present the ORION-18 study, which is the first large-scale clinical trial of inclisiran therapy in Asia. In total, 345 participants were randomized to receive inclisiran or placebo in 45 study sites across China, South Korea, Singapore, and Taiwan and were followed for almost a year. The authors report that administration of inclisiran resulted in a remarkable 60.5 mg/dL or 57.2% decrease in LDL cholesterol concentrations. They also found significant inclisiran-associated decreases in concentrations of total cholesterol, apolipoprotein B, non–high-density lipoprotein (HDL) cholesterol, and lipoprotein(a), along with increase in HDL cholesterol. In addition, they observed similar incidence of adverse events in both treatment and placebo arms. These results are in line with other global studies of inclisiran in patients with familial hypercholesterolemia or atherosclerosis.[11]

There is a growing need for deployment of additional lipid-altering therapies in Asia. As of 2019, approximately 58% of the 18.6 million cardiovascular deaths worldwide occurred in Asia.[12] Annual direct costs in the past decade caused by cardiovascular

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diseases in China, Japan, and Korea alone total almost $80 billion USD.[13] The prevalence of dyslipidemia with suboptimal control of LDL cholesterol has been growing in Asia over the past 3 decades, with an associated doubling to tripling of the number of deaths attributed to atherosclerotic cardiovascular disease.[14] The Asia Pacific Society of Cardiology recommends intensive control of LDL cholesterol to prevent disease in high-risk individuals.[15] However, the Pan-Asian CEPHEUS (Centralized Pan-Middle East Survey on the Under-Treatment of Hypercholesterolemia) study found that less than one-half of individuals in most of the studied Asian countries who were on lipid-lowering therapies met treatment goals.[16] Potential contributing factors to this include reluctance toward high-intensity statin therapy because of concern about side effects, unawareness of clinical guidelines, limited patient follow-up, and costs.[17] With its twice annual administration schedule, inclisiran may help bridge this treatment gap now that it has been shown to be well tolerated and efficacious at lowering LDL cholesterol in this target population.

This successful study of inclisiran therapy in East Asian countries sets the stage for future clinical trials. The authors plan to continue an open-label extension of this study for better understanding of safety and efficacy over a longer duration. In addition to effects on persistence of LDL cholesterol lowering, this may provide a window to examine cardiovascular events in this population. Analysis of event data from other international phase 3 trials showed significant reduction of composite major adverse cardiovascular events in inclisiran vs placebo arm, with OR of 0.74 (95% CI: 0.58-0.94).[18] Dedicated international randomized clinical trials testing efficacy of inclisiran in preventing cardiovascular outcomes are currently underway (NCT05030428, NCT03705234). As this study primarily focused on individuals in East Asian countries, future efforts directed at testing therapies in individuals from the Middle East or South Asia may be of benefit, particularly given the excess of atherosclerotic cardiovascular disease observed among the rapidly growing South Asian population.[19] Overall, this study offers valuable insights into the safety and efficacy of inclisiran in East Asian countries, laying the groundwork for more inclusive and region-specific clinical trials for cardiovascular therapies.

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