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EDITORIAL COMMENT

Global Benefit of SGLT2 Inhibitors in Heart Failure With Reduced Ejection Fraction*

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Heart failure (HF) is a global epidemic. In 2017, estimates suggested HF affected over 64 million people worldwide, a dramatic increase from 33.5 million in 1990.[1] HF as a disease state affects 1% to 2% of the adult population in developed countries, with growing impact in developing countries as well.[1,2] The annual global cost of HF is well over $108 billion, approximately 60% of which is related to direct medical costs.[3] The burden HF has on health care systems around the world simply cannot be stressed enough.

With such a broad international impact, HF has marked epidemiologic heterogeneity, both within and across countries.[4] International registry data confirm the regional differences in HF diagnosis, care, and outcomes, ranging from patients' disease awareness, underlying etiologies of HF, access and adherence to treatments, precipitants of HF exacerbations, structures of health care systems, mortality rates, and more.[5,6] As a result, global prospective research has started considering underlying recruitment across countries, suspected event rates based on location, and difference in regional demographics in order to create trials that are broadly applicable to the HF population at large.[7] And a shift is occurring, with HF trials increasingly conducted across multiple regions or internationally, compared with a decade prior.[8] Yet even within these large, international randomized clinical trials, where enrollment is guided by strict selection criteria, regional variation in patients' characteristics persist, including age, socioeconomic status, cultural background, comorbidities, and functional status; more notably, within individual trials, primary outcomes of interest such as HF hospitalization and mortality can vary purely based on geographic region.[9-11] Such differences mean that large clinical trials are often examined under the microscope for nuanced differences across regions, comorbidity status, baseline medication usage, and more in order to ensure novel medications are beneficial and safe across subpopulations.

The largest area of HF trial growth is Asia, both in terms of individual national HF trials as well as enrollment from Asia in multinational trials.[8] Asia is home to over 60% of the world's population; with over 4.7 billion people, the term *Asian* encompasses a highly heterogenous and diverse group of people.[12] These differences are reflected in the burden, management, and morbidity of HF. HF prevalence in Asian countries is comparable to Western countries; estimates range from 1.3% to 6.7% in South Asia, <1% to 6% in East Asia, and <1% to 2% in Southeast Asia.[13,14] Although these numbers are comparable to North America and Western Europe, the rate of increase is alarming. Nearly one-half of the global rise of HF from 1990 to 2017 occurred in China (29.9%) and India (16.6%).[1] Unsurprisingly, cohort studies suggest there is marked regional variation in HF patient characteristics, medication use, and mortality even within Asia, with the highest rates of comorbidities and all-cause mortality among HF patients in Southeast Asia, compared with East Asia and South Asia.[14-16] This indicates that *Asian HF* encompasses multiple phenotypes with marked regional and ethnic differences, and such diversity should be accounted for in clinical trials.[17]

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Given the burden of HF in Asia, novel medications for reduction in morbidity and mortality are actively investigated across the continent. One such medication, sodium glucose cotransporter 2 inhibitors (SGLT2is), have been shown to reduce worsening HF or cardiovascular death in patients with HF with reduced ejection fraction (HFrEF).[18-20] More specifically, the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure) trial asked the question of whether the SGLT2i dapagliflozin, compared with placebo, would reduce the composite endpoint of cardiovascular death or HF events in persons with HFrEF.[18] The findings were remarkable, with a significant reduction in the primary outcome of cardiovascular death, hospitalization for HF, or urgent HF visit (hazard ratio: 0.74; 95% CI: 0.65-0.85).[18] More notably, such results have been consistent across the age spectrum and by diabetes status, underlying health status, and baseline medication use.[18,21-23]

Whether these new HF medications are efficacious and safe across race/ethnicity subgroups and geographic regions are important questions to evaluate. Because race is a social construct, and there is no firm evidence for biological differences based on race, the expectation is that pharmaceuticals would be equally efficacious regardless of region or race/ethnicity; any variation may help clarify possible discrepancies in social determinants of health. Within that context, dapagliflozin was recently shown to both reduce the primary endpoint and improve HF symptoms similarly in Black and White patients, without a difference in adverse events.[24] The current study by Docherty et al,[25] published in this issue of *JACC: Asia*, furthers prior work to evaluate whether dapagliflozin is equally effective in patients enrolled in Asia, compared with those patients enrolled outside of Asia. The pertinent primary finding was that in DAPA-HF, patients from Asia had comparable reduction in rates of worsening HF events and mortality, compared with patients enrolled outside of Asia. This is despite a difference in underlying characteristics akin to those mentioned earlier; the population enrolled in Asia was younger (mean 63.3 years, compared with 67.2 years outside of Asia) and had lower body mass index (9.9% with body mass index $\geq$30 kg/m^2, compared with 42.9% outside of Asia), as well as lower prevalence of hypertension and chronic kidney disease. Furthermore, the risk of each component of the composite endpoint, as well as the risk of all-cause mortality, were similar among patients enrolled in Asia compared with those enrolled outside of Asia. In terms of symptom improvement, the proportion of patients with a significant improvement in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) was comparable between those enrolled in Asia and those enrolled outside of Asia, despite the better baseline score in the Asian population. Finally, the rate of adverse events was comparable between those enrolled in Asia and those enrolled outside of Asia.

The investigators should be commended for further disaggregating the data and investigating variation within Asia itself. Almost one-quarter of the trial was enrolled in Asia, with 99.8% of those enrollees identifying as Asian race; the investigators specifically stratified these patients into East Asia (n = 721, with 237 from China, 343 from Japan, and 141 from Taiwan), Southeast Asia (n = 138 from Vietnam), and South Asia (n = 237 from India). Based on this stratification, the heterogeneity across Asian HF patients was apparent, with differences in age, left ventricular ejection fraction, New York Heart Association functional classification, medical comorbidities, and medication and device use, based on the region of Asia evaluated. Despite these differences, the benefit of dapagliflozin on all outcomes was consistent across each region of Asia studied. Although this finding was the expectation, this work also highlights that additional efforts to increase representativeness of Asian patients in clinical trials are needed. Other trials, including those involving patients with HF with preserved ejection fraction, should further confirm the consistency of findings across Asian populations.

SGLT2is have come to the forefront of HF care and are now formally recommended by both the European Society of Cardiology and the American College of Cardiology for the treatment of HFrEF.[26,27] Treatment with an SGLT2i, along with the other pillars of HF treatment—an angiotensin receptor-neprilysin inhibitor, evidence-based beta-blocker, and a mineralocorticoid receptor antagonist—has been shown to lower the risk of HF admission or cardiovascular death by over 60% and all-cause mortality by just under 50%, compared with the old mainstays of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and beta-blocker.[28] In the United States alone, the addition of SGLT2is to standard of care could prevent 34,000 deaths among HF patients annually; the impact internationally would be far greater.[29] Given such a medication has an incremental cost-effectiveness ratio of $8 to $11,000 USD per quality-adjusted life-year, SGLTI2is are also considered cost-effective and of high value.[30]

SGLT2is should thus be maximally used for the heterogenous population of HF patients around the world; such an intervention would reduce HF morbidity and mortality and curb the growing HF epidemic.

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