

EDITORIAL COMMENT

Diabetes Mellitus in Patients With Heart Failure

Bad for All, Worse for Some*

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According to the recent World Health Organization global report, the population with diabetes mellitus (DM) has quadrupled since 1980 and reached 422 million persons in 2014 (1). Cardiovascular disease (CVD) remains the leading cause of death among patients with DM. Although the initial focus was on vascular disease in DM, the association between heart failure (HF) and DM has generated significant interest (2). Patients with DM are 2.5 times more likely to develop HF, and patients with HF who also have DM are at risk for worse outcomes (3). DM may adversely affect cardiomyocytes through not only accelerated atherosclerosis but also other direct cellular mechanisms. *Diabetic cardiomyopathy* is a recognized entity that can develop in the absence of known risk factors such as coronary disease, and it may be related to microvascular disease and metabolic derangements (4,5).

The epidemiology of CVD has been studied extensively in Western countries. However, similar data from other regions of the world are less robust. Therefore, the recommendations reflected in major cardiovascular practice guidelines are largely formulated on the basis of evidence obtained from studies conducted in the Western Hemisphere. Such recommendations may not always be generalizable to other

regions of the world where the epidemiology, risk factors, and outcomes of CVD may be different. The role of ethnicity in regional variation seen with CVD is intriguing and complex. A contemporary study of the risk factors of myocardial infarction across different populations was conducted in 2004 by Yusuf et al. (6). With data gathered from 52 countries, the INTER-HEART (A global case-control study of risk factors for acute myocardial infarction) study outlined 9 modifiable risk factors accounting for more than 90% of the risk of myocardial infarction. This study also demonstrated the variations in strength of association of these risk factors among different geographic regions across the 5 inhabited continents (6).

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The prevalence of patients with concomitant HF and DM is growing exponentially with aging of the population. The presence of each condition increases the risk for the other and results in poorer prognosis for patients with both HF and DM than for patients with either disease alone (7,8). Although the increasing prevalence of the simultaneous presence of these 2 conditions and the incremental impact on outcomes have been documented in published reports, regional differences have not been well described. In this issue of *JACC: Heart Failure*, however, Bank et al. (9) compare the prevalence, clinical risk factors, and prognostic impact of DM between Southeast Asian and white patients with HF. This well-designed observational study combines 2 contemporary cohorts of patients with HF from Singapore and from Sweden and seeks to evaluate the interaction between ethnicity and DM in predicting HF-related hospitalization and mortality rates.

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There are several noteworthy findings in this investigation. The investigators reconfirm the high prevalence of DM in patients with HF in general but also show a significantly higher prevalence of DM among Southeast Asian patients with HF compared with white patients with HF. In this study, South Asian patients with HF were 3 times more likely to have DM. Very intriguingly, Southeast Asian patients with DM were found to have significantly lower body mass index compared with their white counterparts. Although this finding could be simply attributed to the known difference in body fat composition between white and Southeast Asian general populations, Bank et al. (9) argue that it could also suggest significant variations in genetics as well as the molecular basis of DM between the 2 ethnicities. These hypothetical explanations can potentially have a profound impact on development of therapeutics for these patients across different ethnicities. These differences were also associated with patients' outcomes; Southeast Asian patients with HF and DM had a higher risk of the composite outcome of HF-related hospitalizations and all-cause mortality. No difference was observed in the all-cause mortality rate alone between the 2 ethnicities, and the difference was shown to be driven by the differential rate of hospitalizations for HF.

Asia is the largest continent on the globe and home to 60% of the world's current population. It is divided into 6 subregions including the Middle East, North Asia, Central Asia, East Asia, South Asia, and Southeast Asia. There is remarkable diversity among and within these regions in terms of demographics, as well as the epidemiology of and risk factors for CVD and HF. The number of persons with DM in Southeast Asia is comparable to that of United States and Europe combined, yet little is known about the ethnic and geographic differences in its association with HF-related outcomes. The study by Bank et al. (9) is a step toward characterizing the epidemiology of DM among patients with HF in Southeast Asia. Singapore, site of the Asian portion of the study population, is located in Southeast Asia and is a country that has enjoyed rapid economic growth in the last several decades, with a universal health care system ranked as one of the world's most efficient. It is home to people from various ethnic backgrounds including Chinese, Malay, Indian, and Eurasian. In the study by Bank et al. (9), all major ethnicities were proportionately represented in the HF cohort from Singapore. These data therefore may be generalizable to South Asia

and East Asia from a genetics perspective but not necessarily from an environmental influence perspective.

According to the Centers for Disease Control and Prevention, weight loss through increased physical activity and healthy eating decreases the risk of DM. It will be worthwhile to examine the ethnic variations in effectiveness of weight loss and exercise between Southeast Asians and whites, given the significant difference in their body mass index. Moreover, in the era of rapidly growing cardiovascular outcomes trials in patients with DM and with the emergence of new therapies demonstrating mortality benefit, a careful evaluation of regional differences is warranted. Most notably in this respect are the sodium-glucose cotransporter 2 (SGLT2) inhibitors, the first of which has shown a significant reduction in the risk of new-onset HF as well as improved outcomes among patients with prevalent HF (10). On the basis of these promising data, several trials with these newer agents are now being designed to target patients with HF primarily, and given the findings noted in the paper by Bank et al. (9), careful assessment of regional variations will be important. Finally, the investigators should consider a priori planned ethnicity-specific subgroup analysis in the design phase of these trials to enhance the credibility and interpretability of the results.

In summary, the study by Bank et al. (9) provides insight into the differences in epidemiology of DM and its impact among patients with HF between 2 different ethnic backgrounds. Parallel to other parts of the world, in Asia there is an ongoing rise in the prevalence of DM and HF. Future health policies need to be directed toward establishing targets for risk management and preventive strategies, to serve the Asian and Southeast Asian populations at risk more effectively. It is therefore of paramount importance to dissect the epidemiology of the relevant risk factors of DM and HF in these areas. The study by Bank et al. (9) is a major contribution to the path to accomplish this objective. The next steps are to elucidate the mechanisms behind these differences further and to develop and implement effective targeted interventions to improve outcomes for patients.

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