

STATE-OF-THE-ART PAPER

# Heart Failure Clinical Trials in East and Southeast Asia



## Understanding the Importance and Defining the Next Steps

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### ABSTRACT

Heart failure (HF) is a major and increasing global public health problem. In Asia, aging populations and recent increases in cardiovascular risk factors have contributed to a particularly high burden of HF, with outcomes that are poorer than those in the rest of the world. Representation of Asians in landmark HF trials has been variable. In addition, HF patients from Asia demonstrate clinical differences from patients in other geographic regions. Thus, the generalizability of some clinical trial results to the Asian population remains uncertain. In this article, we review differences in HF phenotype, HF management, and outcomes in patients from East and Southeast Asia. We describe lessons learned in Asia from recent HF registries and clinical trial databases and outline strategies to improve the potential for success in future trials. This review is based on discussions among scientists, clinical trialists, industry representatives, and regulatory representatives at the CardioVascular Clinical Trialist Asia Forum in Singapore on July 4, 2014. (J Am Coll Cardiol HF 2016;4:419-27)  
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**H**eat failure (HF) is a major public health problem worldwide (1,2). In Asia, aging populations and large increases in cardiovascular risk factors have contributed to a high burden of HF (3). HF patients from Asia differ in clinical characteristics from patients elsewhere and yet have similarly poor or even worse outcomes than

HF patients from the West (Table 1) (4). Given the diversity of countries in Asia (Online Appendix), clinical phenotypes and practice patterns vary widely, just as practice patterns vary across Europe and the Americas.

The last several decades have seen therapeutic advances for HF patients with reduced ejection

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## ABBREVIATIONS AND ACRONYMS

**ACEI/ARB** = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker

**CAD** = coronary artery disease

**GDMT** = guideline-directed medical therapy

**HFREF** = heart failure with reduced ejection fraction

**ICD/CRT** = implantable cardioverter-defibrillator/cardiac resynchronization therapy

**LOS** = length of stay

**MRA** = mineralocorticoid receptor antagonist

fraction (EF) (5), including recent trials of sacubitril/valsartan (6) and ivabradine (7) therapy. Older trials either did not include Asians or included small numbers of patients of Asian ethnicity from Western countries. Given the need to enroll large numbers to demonstrate outcome benefits as well as recent challenges with enrollment and cost in North American and certain European countries, contemporary trials have enrolled globally (8). Representation of patients from Asia was relatively low in many previous trials due to perceived and/or actual challenges to generalizability and trial infrastructure and conduct. Regulatory approval of HF drugs in Asian countries has largely relied on data extrapolated from Western

populations. More recently, Asian regulatory authorities have been requiring that study populations include Asians from Asia (9) in order to support approval.

We reviewed differences between HF patients from East and Southeast Asia (Online Appendix) and compared them to HF patients in the rest of the world. We focus on East and Southeast Asia because these regions within Asia have more robust registry and trial data available to date. We summarized observations within the context that heterogeneity exists even among regions within Asia. We describe lessons learned from HF datasets and outline strategies to improve future trials. This review is based on discussions among scientists, trialists, industry representatives, and regulators at the CardioVascular Clinical Trialist Asia Forum in Singapore on July 4, 2014. To identify additional relevant published data not discussed, we searched MEDLINE for articles published between January 1994 and December 2015 (see the Online Appendix for the search strategy).

## BURDEN OF HF

Limited data are available regarding the true incidence and prevalence of HF in Asia (3). Studies of hospitalized patients in Singapore, Malaysia, and Taiwan found that 3% to 7% of admissions were due to HF in the 1990s to early 2000s (10-12). In a community-based survey, the prevalence of HF in China among populations 55 to 74 years of age was 1.3%, with an estimated overall adult HF population >4 million (13). Similarly, in Japan, it is estimated that 1 million people have HF (14), which equates to a prevalence of ~1%. Although prevalence estimates in the general population are lower in Asia than in the West (1,15), this translates to a higher absolute burden

of disease in Asia because of larger population sizes. For example, even with conservative estimates of HF prevalence, the absolute number of individuals with HF in Asia is >20 million (16). Regarding HF hospitalizations, in Singapore there was a 38% increase from 1991 to 1998, which is approximately 5% per year (10). This matches the 5% yearly increase in all-cause hospitalizations from 2004 to 2012. However, in recent years, HF hospitalizations have been rising at 10% each year (17). Furthermore, the at-risk population is increasing at a faster rate in Asia than in other parts of the world, with aging of the population and increases in the prevalence of coronary artery disease (CAD), tobacco use, diabetes, and obesity. For instance, in 2007, there were 305,700 people older than 65 years of age in Singapore (6.7% of the population). This increased more than 30% to 404,500 in 2013 (7.5% of the population) (18). Thus, the burden of HF in Asia is expected to increase and be comparatively larger than that in the West over subsequent decades (14).

## HF PHENOTYPE

Data from trials and registries in Asia provide insights into the profile of HF in this region (Central Illustration). ADHERE-AP (Acute Decompensated Heart Failure Registry-Asia Pacific) was an acute HF registry that included 10,171 patients hospitalized with HF from 8 Asia-Pacific countries (Singapore, Thailand, Indonesia, Australia, Malaysia, the Philippines, Taiwan, and Hong Kong). HF patients in Asia-Pacific were younger than those from other regions. The median age was 67 to 70 years in Asia versus 70 to 75 years in the United States and Europe (4,19). Moreover, there was variation within different Asia-Pacific countries with the median age at presentation ranging from 53 years in the Philippines to 77 years in Australia and Hong Kong. These differences may be due, in part, to variations in risk factor profile, comorbidity burden, life expectancy, and standards of living (4). Thus, there may be nearly as much heterogeneity and regional variation within Asia-Pacific as between this geographic region and other world regions.

**HF CAUSES.** Compared with other regions where >50% of the population has ischemic HF, there is a lower prevalence of ischemic cardiomyopathy in Asia. For instance, in the ATTEND registry (Acute decompensated heart failure syndromes) consisting of 4,841 acute HF patients enrolled in Japan, 31% of patients had ischemic, 19% had valvular, 18% had hypertensive, and 32% with “other/unspecified” causes (20). A chronic HF registry of 1,078 Japanese patients

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