ORIGINAL RESEARCH

Regional Variation of Mortality in Heart Failure With Reduced and Preserved Ejection Fraction Across Asia: Outcomes in the ASIAN-HF Registry

Michael R. MacDonald, MB ChB, BSc (Hons); Wan Ting Tay, MAppStat; Tiew-Hwa Katherine Teng, MPH, PhD; Inder Anand, MD, PhD; Lieng Hsi Ling, MBBS, MD; Jonathan Yap, MBBS, MPH; Jasper Tromp, MD, PhD; Gurpreet S. Wander, MD, DM; Ajay Naik, MD, DM; Tachapong Ngarmukos, MD; Bambang B. Siswanto, MD, PhD; Chung-Lieh Hung, MD; ASIAN-HF investigators;* A. Mark Richards, MD, PhD; Carolyn S. P. Lam, MBBS, PhD

Background—Data comparing outcomes in heart failure (HF) across Asia are limited. We examined regional variation in mortality among patients with HF enrolled in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry with separate analyses for those with reduced ejection fraction (EF; <40%) versus preserved EF (≥50%).

Methods and Results—The ASIAN-HF registry is a prospective longitudinal study. Participants with symptomatic HF were recruited from 46 secondary care centers in 3 Asian regions: South Asia (India), Southeast Asia (Thailand, Malaysia, Philippines, Indonesia, Singapore), and Northeast Asia (South Korea, Japan, Taiwan, Hong Kong, China). Overall, 6480 patients aged >18 years with symptomatic HF were recruited (mean age: 61.6±13.3 years; 27% women; 81% with HF and reduced rEF). The primary outcome was 1-year all-cause mortality. Striking regional variations in baseline characteristics and outcomes were observed. Regardless of HF type, Southeast Asians had the highest burden of comorbidities, particularly diabetes mellitus and chronic kidney disease, despite being younger than Northeast Asian participants. One-year, crude, all-cause mortality for the whole population was 9.6%, higher in patients with HF and reduced EF (10.6%) than in those with HF and preserved EF (5.4%). One-year, all-cause mortality was significantly higher in Southeast Asian patients (13.0%), compared with South Asian (7.5%) and Northeast Asian patients (7.4%; $P<0.001$). Well-known predictors of death accounted for only 44.2% of the variation in risk of mortality.

Conclusions—This first multinational prospective study shows that the outcomes in Asian patients with both HF and reduced or preserved EF are poor overall and worst in Southeast Asian patients. Region-specific risk factors and gaps in guideline-directed therapy should be addressed to potentially improve outcomes.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov/. Unique identifier: NCT01633398. **(*J Am Heart Assoc.* 2020;9: e012199. DOI: 10.1161/JAHA.119.012199.)**

Key Words: epidemiology • heart failure • mortality

Downloaded from http://ahajournals.org by on August 17, 2021

Heart failure (HF) is a rapidly growing, global public health problem that imposes a severe burden of morbidity and mortality.[1] Worldwide, >38 million people have HF,[2] at an estimated cost of US$100 billion in 2012.[3] With explosive population growth in the past century, Asia is currently home to 4.4 billion people (60% of the world's population), and its population is projected to reach 5.2 billion by 2050. Exponential population growth, urbanization, sedentary lifestyle, and an

From the Changi General Hospital, Singapore (M.R.M.); National Heart Centre Singapore, Singapore (W.T.T., T.-H.K.T., J.Y., J.T., C.S.P.L.); School of Population & Global Health, University of Western Australia, Perth, Australia (T.-H.K.T.); Veterans Affairs Medical Center, Minneapolis, MN (I.A.); Cardiovascular Research Institute, National University Heart Centre, Singapore (L.H.L., A.M.R.); Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands (J.T.C., C.S.P.L.); Dayanand Medical College and Hospital, Ludhiana, India (G.S.W.); Care Institute of Medical Sciences, Ahmedabad, India (A.N.); Ramathibodi Hospital, Bangkok, Thailand (T.N.); National Cardiovascular Center Universitas Indonesia, Jakarta, Indonesia (B.B.S.); Mackay Memorial Hospital, Taipei, Taiwan (C.-L.H.); University of Otago, New Zealand (A.M.R.); Duke-National University of Singapore Medical School, Singapore (C.S.P.L.).

*A complete list of the ASIAN-HF investigators can be found in the Appendix at the end of the article.

Correspondence to: Carolyn S. Lam, MBBS, PhD, National Heart Centre Singapore, 5 Hospital Dr, Singapore 169609, Singapore. E-mail: carolyn.lam@duke-nus.edu.sg

Received February 12, 2019; accepted August 28, 2019.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Clinical Perspective

What Is New?

- This study describes large interregional differences in the characteristics and outcomes of patients with heart failure in Asia.
- Heart failure with reduced ejection fraction carries higher mortality than heart failure with preserved ejection fraction in Asia, and patients from Southeast Asia have the poorest outcomes.

What Are the Clinical Implications?

- The results of this study will allow us to target region-specific risk factors and gaps in guideline-directed therapy to improve patient outcomes.

aging population together with increasing rates of obesity, hypertension, and diabetes mellitus, all of which predispose to HF, have contributed to a "tsunami" of cardiovascular disease, including HF, in Asia. Asia is highly heterogeneous, with countries at different stages of economic development. Population-based data suggest that socioeconomically deprived persons are likely to develop HF at an earlier age than affluent individuals.[4] Limited data from Southeast Asian countries also suggest a higher prevalence of HF compared with other Asian countries.[5] This is of increasing concern, especially as the burden of HF is predicted to be highest in the poorest countries least equipped to deal with the onslaught.[2]

Most outcomes data in HF come from European and North American populations, with scant information from Asia, restricted to a few individual Asian countries.[6,7] In affluent Western populations, 5-year mortality rates in HF patients from population-based studies rival those of major cancers at 50–60%.[2] The limited data from low- and middle-income countries suggest their mortality rates may be even higher.[6,8] Furthermore, studies have suggested that Asian patients present with HF on average at least a decade earlier than their white counterparts, with two thirds presenting with multimorbidity.[9] The INTER-CHF (International Congestive Heart Failure) study recently reported marked regional differences in mortality in patients with HF that persist even after adjustment for known cardiac and noncardiac predictors, suggesting distinctive heterogeneity of the Asian HF phenotype.[6] Adding to this complexity, HF subtypes (ie, with reduced ejection fraction [rEF] or preserved ejection fraction [pEF]) are heterogeneous syndromes. Epidemiological data on outcomes in these HF subtypes in Asia are scarce, limited to single-center or national data.[10] The degree of regional variation in HF outcomes and the underlying reasons for such variations are uncertain. Research into factors underpinning regional disparities is necessary to enable targeted action to improve population-level outcomes. We therefore examined the regional variation in all-cause and cause-specific mortality among all patients with HF enrolled in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry with separate subanalyses in HF patients with rEF (HFrEF) and with pEF (HFpEF).

Methods

Study Population

The study data and materials used to conduct the research cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure because of the legal restrictions imposed by multinational jurisdictions. ASIAN-HF is a prospective observational multinational registry of Asian patients aged >18 years with symptomatic HF (at least 1 episode of decompensated HF in the previous 6 months, resulting in a hospital admission or treatment in an outpatient clinic) recruited from 46 medical centers across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand), following informed consent.[11] Investigation sites (46 in total with >220 investigators; Appendix) covered a broad spectrum of medical, cardiology, and HF specialty units, admitting patients with acute HF and conducting outpatient follow-up of patients with chronic HF. Site selection in ASIAN-HF was based on the size of the country, the geographic location of the site within the country, the patient population served, HF patient volume, and availability of expertise in echocardiography. A mix of private and public hospitals and tertiary, university, and cardiovascular specialty hospitals in capital and provincial cities were included. Ethics approvals conforming to the Declaration of Helsinki were obtained from the relevant human ethics committees at all sites. Patients were excluded if they had severe valve disease as the primary cause of HF, had life-threatening comorbidity with life expectancy of <1 year, were unable or unwilling to give consent, or were concurrently participating in a clinical therapeutic trial. Asian patients were recruited in 2 stages: those with HF and rEF (HFrEF; EF <40% on baseline echocardiography) were enrolled between October 1, 2012, and December 31, 2015, with overlapping recruitment of those with HF and pEF (HFpEF; EF ≥50% on baseline echocardiography) between September 9, 2013, and October 31, 2016. Recruitment of patients with HFpEF started later than the recruitment of patients with HFrEF, for funding reasons; however, the delay was only 1 year (October 1, 2012, versus September 9, 2013). For the majority of the recruitment period (until October 6, 2016), there was overlap in recruitment of both types of HF. We do not anticipate that there were substantial shifts in epidemiology or treatment of

Downloaded from http://ahajournals.org by on August 17, 2021

patients with HFrEF or HFpEF during this year that would have biased regional patterns of multimorbidity, although this cannot be entirely excluded. All patients included in the ASIAN-HF registry were required to have a validated clinical diagnosis of HF (based on symptoms and signs according to The Framingham Heart Study criteria with decompensation within 6 months) and left ventricular (LV) EF <40% and ≥50% for HFrEF and HFpEF, respectively.[12] A previous hospitalization for HF was defined as any previous hospitalization for HF during 6 months before inclusion requiring intravenous or oral diuretic treatment. Patients treated for an episode of decompensation in an outpatient clinic were generally treated with additional or high dosages of oral diuretics for short periods, failing which intravenous diuretics would be administered, usually in a hospital setting. Criteria for recruitment of patients were standardized across sites. Patients with HFpEF and a previously recorded LVEF <50% were excluded. In addition, 99.5% of HFpEF patients had structural or functional abnormalities meeting the 2016 European Society of Cardiology criteria for diastolic dysfunction (E/e' ≥13, E' medial/lateral <9 ms, left atrial enlargement or LV hypertrophy.[1,13]

The collection and processing of echocardiographic data have been reported previously.[11] Echocardiography was performed at each center according to internationally accepted guidelines.[14] Left atrial size, LV diastolic function, stroke volume, and cardiac output were documented in addition to LVEF and LV dimensions. The Cardiovascular Imaging Laboratory of the National University Health System, Singapore, provided oversight and imaging protocol guidelines and quality assurance of the echocardiograms. Echocardiographic measurements were performed at the site level with standardized protocols provided by the echocardiography laboratory in Singapore.

Demographics (including socioeconomic status), clinical signs and symptoms, functional status, date of HF diagnosis, duration of HF, prior cardiovascular procedures or investigations, clinical and lifestyle risk factors, medical history, comorbidities, quality of life, and blood chemistry were documented at recruitment. Standard 12-lead ECG and transthoracic echocardiography were also recorded at baseline. Coronary artery disease was defined as the angiographically documented presence of significant coronary obstruction, history of myocardial infarction, or prior revascularization. Hypertension was defined as any past or current history of hypertension, and diabetes mellitus was defined as having a prior diagnosis of diabetes mellitus. Estimated glomerular filtration rate was calculated using the MDRD (Modification of Diet in Renal Disease) study equation, and chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Atrial fibrillation (AF), peripheral arterial vascular disease, previous stroke, and chronic obstructive pulmonary disease were identified by medical history.

Geographic regions were defined according to United Nations classification as follows: Northeast Asia included South Korea, Japan, Taiwan, Hong Kong, and China; South Asia included India; and Southeast Asia included Thailand, Malaysia, Philippines, Indonesia, and Singapore. National income level as defined by the World Bank was used to categorize countries as *high*, *middle*, and *low income*.[9]

All data were captured prospectively in an electronic database, with registry operations and data management handled by Quintiles Outcomes as the contract research organization appointed by the academic executive committee.

Outcomes

The primary outcome of interest was all-cause mortality at 1 year. In all, 5875 (90.7%) patients had outcome data available, whereas 605 (9.3%) patients were lost to follow-up. The cause of death was adjudicated by an independent committee, using the US Food and Drug Administrations standardized event definitions.[15] Two members of the end point committee independently reviewed the death data collected from the case report forms; the third member reviewed cases in which adjudicated causes of death were discordant between the first 2 members. After the third review, if there was still discordance, the events were adjudicated at a meeting of the end point committee. As such, ascertainment of mortality does not vary between sites.

Causes of death were classified as *cardiovascular*, *noncardiovascular*, or *unknown/presumed cardiovascular* in those with insufficient information on cause of death. Specific mode of cardiovascular death was further classified as *sudden death*, *HF death*, *acute myocardial infarction*, *stroke*, *cardiovascular hemorrhage*, or *procedural or other cardiovascular death*.

Statistical Analyses

Standard descriptive statistics were used to describe baseline characteristics by nation and geographic region for patients with HFrEF and HFpEF separately. Differences in the baseline characteristics were assessed with ANOVA and χ^2 tests for continuous and categorical factors, respectively. Univariable and multivariable Cox proportional hazards models were used to assess factors associated with risk of mortality at 1 year, with geographical region as the key factor of interest. We tested for interaction in the univariable models with the specific main effects by geographical region and HF type on 1-year all-cause mortality outcomes and presented stratified results only if interactions were significant. Factors associated with mortality (P<0.1) in univariable models and/or clinically important factors (demographics, clinical signs, concomitant comorbidities, pharmacotherapy, or device therapy) were included for adjustment of the multivariable models. South Asia was

Downloaded from http://ahajournals.org by on August 17, 2021

used as the reference region because it had the lowest death rate and the least heterogeneity. Analyses were then repeated and stratified by geographical region (in the presence of significant interaction) to assess differences in the risk factors for 1-year mortality. The Cox proportional hazards assumption was confirmed using log-log plots and the Schoenfeld residuals test. The overall assessment of explained risk and relative importance of a subset of factors in the Cox proportional hazards models was calculated using the explained risk statistic and interpreted similarly to the coefficient of determination R^2 in the normal linear model.[16] Patients who were lost to follow-up or had incomplete data on adjusted risk factors were excluded from survival analysis. All analyses were 2-tailed, and $P<0.05$ was considered statistically significant. Analyses were performed in Stata v14 (StataCorp), and explained risk statistics were calculated in R software v3.4.1.

Results

Overall, 6480 patients (mean age: 61.6±13.3 years; 27% women; 81% HFrEF) were enrolled from 46 centers across 11 Asian regions. All patients had a documented episode of decompensated HF requiring hospitalization or equivalent outpatient treatment within the 6 months before enrollment. In addition, 42% of patients were enrolled as inpatients recruited after initial treatment of acute symptoms and following stabilization. Vital status was available for 5851 (90.3%) patients who completed 1 year of follow-up. Table 1 describes the baseline characteristics of the entire cohort by HF group and geographic region. Detailed baseline characteristics at a country level are listed in the Appendix.

Demographics

Demographics varied considerably by geographical region. Regardless of ejection fraction, Northeast Asian participants were the oldest, followed by Southeast then South Asian participants. Patients with HFrEF were on average 8 years younger than the patients with HFpEF (Table 1). Among the patients with HFrEF, older cohorts were more likely to be female; 25.2% of patients in Northeast Asia were female, in comparison to 17.7% in Southeast Asia. Approximately half of the patients with HFpEF were women in all 3 regions. The Philippines had the youngest cohort (20% female), aged 55.8 years, in stark contrast to the patients from Hong Kong, who were almost 17 years older (46.8% female) at 72.9 years.

Comorbidity

Prevalence of comorbidities was high throughout Asia, but marked regional variation was evident. Regardless of HF group, Southeast Asia had the highest prevalence of diabetes mellitus, stroke, hypertension, CKD, and coronary artery disease despite a relatively low mean age. In both HFrEF and HFpEF, ischemic etiology of HF was twice as common in Southeast Asia as in Northeast and South Asia. In keeping with the higher prevalence of comorbidities, Southeast Asian patients also had the highest body mass index (kg/m^2) at 25.7 and 28.2 in patients with HFrEF and HFpEF, respectively. Between countries, patients from the Philippines had the highest body mass index at 26.9, and those from Japan had the lowest at 23.0. Across all regions, HFpEF patients had higher body mass indexes than those with HFrEF. South Asians had distinctly lower prevalence of AF (4.2% [versus 22.8% average prevalence in other geographical regions] in HFrEF and 7.2% [versus 23.6% average prevalence in other regions] in HFpEF) and chronic obstructive pulmonary disease.

Pharmacological and Device Therapy

Despite the lack of evidence-based HF therapies for HFpEF patients, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and β-blockers were usually prescribed in both HFrEF and HFpEF patients (Table 1). Southeast Asia had the highest rates of ACEI and ARB use (77.3% and 70.2%, respectively) and β-blocker use (81.8% and 78.9%, respectively), whereas mineralocorticoid receptor antagonists were most frequently prescribed in Northeast Asia for 61.7% and 26.6% of HFrEF and HFpEF patients, respectively. Marked variation in pharmacological treatment was observed at the country level—for example, Indonesia had the lowest usage (61.7%) of β-blockers but the highest (85.8%) of ACEIs/ARBs; Japan had highest usage of β-blockers (89.5%) but moderate usage (78.4%) of ACEIs/ARBs. There was wide variability in device implantation across countries and regions, with Japan having the highest rate.

Outcomes

One-year outcome data were available for 93% of patients in South Asia, 86% in Southeast Asia, and 93% in Northeast Asia. One-year crude all-cause mortality for the whole population was 9.6%, with a higher mortality rate for patients with HFrEF than HFpEF (10.6% and 5.4%, respectively; $P<0.001$). In almost all countries, participants recruited as inpatients had almost twice (13.4% versus 6.8%) the 1-year mortality of those recruited as outpatients. Figures 1 through 3 and Tables 2 and 3 detail 1-year outcomes.

Among patients with HFrEF, Southeast Asia had the highest crude all-cause mortality at 13.6% compared with 8.9% and 8.3% in Northeast Asia and South Asia, respectively. The high mortality in Southeast Asia was largely driven by a

Downloaded from http://ahajournals.org by on August 17, 2021

Downloaded from http://ahajournals.org by on August 17, 2021

Table 1. Baseline Characteristics by Geographic Region and HF Group

	Overall				HFrEF				HFpEF			
	Northeast Asia	South Asia	Southeast Asia	*P* Value	Northeast Asia	South Asia	Southeast Asia	*P* Value	Northeast Asia	South Asia	Southeast Asia	*P* Value
n	2201	1688	2591		1658	1436	2182		543	252	409	
Demographic variables												
Age, y, mean (SD)	64.9 (14.4)	59.0 (12.6)	60.6 (12.2)	<0.001	62.7 (14.5)	58.3 (12.5)	59.3 (11.9)	<0.001	71.6 (11.7)	63.4 (12.5)	67.4 (11.6)	<0.001
Female	692 (31.4)	467 (27.7)	591 (22.8)	<0.001	417 (25.2)	349 (24.3)	387 (17.7)	<0.001	275 (50.6)	118 (46.8)	204 (49.9)	0.600
Enrolled as inpatient	965 (43.8)	496 (29.4)	1286 (49.6)	<0.001	840 (50.7)	393 (27.4)	1057 (48.4)	<0.001	125 (23.0)	103 (40.9)	229 (56.0)	<0.001
Clinical variables												
NYHA class III/IV	809 (43.1)	499 (35.5)	595 (24.0)	<0.001	690 (46.7)	454 (37.2)	524 (25.2)	<0.001	119 (30.1)	45 (24.6)	71 (17.7)	<0.001
Body mass index, kg/m^2, mean (SD)	24.2 (4.7)	25.4 (5.1)	26.0 (5.8)	<0.001	23.8 (4.5)	25.0 (4.8)	25.7 (5.6)	<0.001	25.7 (5.4)	28.1 (6.1)	28.2 (6.2)	<0.001
Heart rate, bpm, mean (SD)	78.0 (16.3)	81.4 (16.3)	78.4 (15.6)	<0.001	78.8 (16.9)	81.5 (15.8)	79.2 (15.7)	<0.001	75.7 (13.9)	81.1 (19.1)	74.5 (14.5)	<0.001
Systolic BP, mm Hg, mean (SD)	120.2 (20.7)	118.3 (20.2)	123.4 (21.9)	<0.001	116.8 (19.5)	115.9 (18.6)	121.3 (20.9)	<0.001	130.5 (20.8)	132.3 (23.5)	134.6 (23.5)	0.021
Diastolic BP, mm Hg, mean (SD)	71.1 (13.2)	74.1 (11.0)	72.4 (13.1)	<0.001	70.9 (13.2)	73.7 (10.8)	72.6 (13.1)	<0.001	71.8 (13.2)	76.4 (12.0)	71.3 (13.0)	<0.001
eGFR, mean (SD)	67.0 (26.6)	72.1 (31.9)	59.8 (26.4)	<0.001	68.1 (26.7)	72.4 (31.5)	60.4 (25.5)	<0.001	63.4 (26.0)	70.0 (35.6)	57.3 (29.8)	<0.001
Duration of HF												
<1 y	977 (44.4)	766 (45.7)	1208 (50.4)		733 (44.2)	662 (46.1)	981 (48.3)		244 (44.9)	104 (43.3)	227 (62.0)	
1–5 y	594 (27.0)	648 (38.7)	727 (30.3)		429 (25.9)	538 (37.5)	647 (31.8)		165 (30.4)	110 (45.8)	80 (21.9)	
5–10 y	353 (16.0)	165 (9.8)	329 (13.7)		265 (16.0)	147 (10.2)	291 (14.3)		88 (16.2)	18 (7.5)	38 (10.4)	
≥10 y	276 (12.6)	97 (5.8)	134 (5.6)	<0.001	230 (13.9)	89 (6.2)	113 (5.6)	<0.001	46 (8.5)	8 (3.3)	21 (5.7)	<0.001
Ischemic etiology of HF	667 (30.3)	587 (34.9)	1586 (62.0)	<0.001	534 (32.2)	536 (37.3)	1400 (65.0)	<0.001	133 (24.5)	51 (20.9)	186 (46.0)	<0.001
Coronary artery disease	777 (35.3)	788 (47.1)	1410 (55.1)	<0.001	633 (38.2)	734 (51.1)	1261 (58.5)	<0.001	144 (26.5)	54 (22.9)	149 (36.7)	<0.001
AF	694 (31.5)	77 (4.6)	508 (19.8)	<0.001	501 (30.2)	60 (4.2)	380 (17.6)	<0.001	193 (35.5)	17 (7.2)	128 (31.3)	<0.001
Hypertension	1206 (54.8)	639 (38.2)	1717 (67.0)	<0.001	797 (48.1)	544 (37.9)	1378 (64.0)	<0.001	409 (75.3)	95 (40.3)	339 (82.9)	<0.001
Prior stroke	165 (7.5)	30 (1.8)	239 (9.3)	<0.001	119 (7.2)	26 (1.8)	193 (9.0)	<0.001	46 (8.5)	4 (1.7)	46 (11.2)	<0.001
PAD	82 (3.7)	24 (1.4)	97 (3.8)	<0.001	70 (4.2)	22 (1.5)	87 (4.0)	<0.001	12 (2.2)	2 (0.8)	10 (2.5)	0.350
COPD	235 (10.7)	79 (4.7)	228 (8.9)	<0.001	181 (10.9)	68 (4.7)	185 (8.6)	<0.001	54 (9.9)	11 (4.7)	43 (10.5)	0.029
Diabetes mellitus	739 (33.6)	601 (35.9)	1316 (51.3)	<0.001	525 (31.7)	533 (37.1)	1062 (49.3)	<0.001	214 (39.4)	68 (28.8)	254 (62.1)	<0.001
Renal artery stenosis	19 (0.9)	6 (0.4)	30 (1.2)	0.019	16 (1.0)	6 (0.4)	25 (1.2)	0.064	3 (0.6)	0 (0.0)	5 (1.2)	0.170
Cancer	152 (6.9)	8 (0.5)	56 (2.2)	<0.001	108 (6.5)	5 (0.3)	49 (2.3)	<0.001	44 (8.1)	3 (1.3)	7 (1.7)	<0.001

Continued

DOI: 10.1161/JAHA.119.012199

Downloaded from http://ahajournals.org by on August 17, 2021

Table 1. Continued

	Overall				HFrEF				HFpEF			
	Northeast Asia	South Asia	Southeast Asia	*P* Value	Northeast Asia	South Asia	Southeast Asia	*P* Value	Northeast Asia	South Asia	Southeast Asia	*P* Value
Smoking, ever	983 (44.7)	291 (17.4)	1362 (53.2)	<0.001	850 (51.3)	280 (19.5)	1231 (57.1)	<0.001	133 (24.5)	11 (4.7)	131 (32.1)	<0.001
Alcohol, ever	727 (33.0)	245 (14.7)	725 (28.3)	<0.001	633 (38.2)	234 (16.3)	650 (30.2)	<0.001	94 (17.3)	11 (4.7)	75 (18.4)	<0.001
CKD	771 (40.3)	381 (37.0)	1160 (54.0)	<0.001	564 (39.0)	336 (36.5)	931 (52.6)	<0.001	207 (44.3)	45 (41.3)	229 (60.4)	<0.001
ECG rhythm												
Sinus rhythm	1084 (54.4)	1228 (78.8)	1812 (74.0)	<0.001	854 (53.6)	1079 (80.0)	1556 (75.6)	<0.001	230 (57.4)	149 (71.0)	256 (65.8)	<0.001
AF/flutter	408 (20.5)	61 (3.9)	362 (14.8)		280 (17.5)	45 (3.3)	272 (13.2)		128 (31.9)	16 (7.6)	90 (23.1)	
Other rhythms/unknown	501 (25.1)	269 (17.3)	273 (11.2)		458 (28.8)	224 (16.6)	230 (11.2)		43 (10.7)	45 (21.4)	43 (11.1)	
Left bundle-branch block	200 (10.0)	283 (18.1)	244 (10.0)	<0.001	190 (11.9)	274 (20.3)	230 (11.2)	<0.001	10 (2.5)	9 (4.3)	14 (3.6)	0.440
Medication or device use												
ACEI	862 (40.0)	639 (40.9)	1336 (54.1)	<0.001	780 (47.4)	616 (43.7)	1177 (56.4)	<0.001	82 (16.2)	23 (14.9)	159 (41.5)	<0.001
ARB	741 (34.4)	517 (33.1)	613 (24.8)	<0.001	472 (28.7)	459 (32.6)	492 (23.6)	<0.001	269 (53.1)	58 (37.7)	121 (31.6)	<0.001
ACEI or ARB	1546 (71.8)	1134 (72.6)	1882 (76.2)	0.002	1203 (73.0)	1053 (74.7)	1613 (77.3)	0.011	343 (67.7)	81 (52.6)	269 (70.2)	<0.001
β-Blocker	1682 (78.1)	990 (63.3)	2010 (81.3)	<0.001	1353 (82.1)	914 (64.9)	1708 (81.8)	<0.001	329 (64.9)	76 (49.4)	302 (78.9)	<0.001
Mineralocorticoid receptor antagonist	1151 (53.4)	868 (55.5)	1203 (48.7)	<0.001	1016 (61.7)	832 (59.0)	1150 (55.1)	<0.001	135 (26.6)	36 (23.4)	53 (13.8)	<0.001
Loop diuretic	1519 (70.5)	1242 (79.5)	2092 (84.7)	<0.001	1241 (75.3)	1157 (82.1)	1788 (85.6)	<0.001	278 (54.8)	85 (55.2)	304 (79.4)	<0.001
Diuretic	1586 (73.6)	1268 (81.1)	2106 (85.2)	<0.001	1256 (76.3)	1169 (83.0)	1795 (86.0)	<0.001	330 (65.1)	99 (64.3)	311 (81.2)	<0.001
Digoxin	523 (24.3)	500 (32.0)	532 (21.5)	<0.001	486 (29.5)	488 (34.6)	489 (23.4)	<0.001	37 (7.3)	12 (7.8)	43 (11.2)	0.110
Ivabradine	34 (1.6)	316 (20.2)	144 (5.8)	<0.001	34 (2.1)	303 (21.5)	134 (6.4)	<0.001	0 (0.0)	13 (8.4)	10 (2.6)	<0.001
Device therapy												
None	1702 (77.4)	1559 (93.2)	2339 (91.3)	<0.001	1209 (73.0)	1336 (93.0)	1952 (90.6)	<0.001	493 (90.8)	223 (94.1)	387 (94.9)	0.015
ICD only	133 (6.0)	46 (2.7)	103 (4.0)		115 (6.9)	38 (2.6)	101 (4.7)		18 (3.3)	8 (3.4)	2 (0.5)	
Pacemaker only	72 (3.3)	16 (1.0)	48 (1.9)		45 (2.7)	12 (0.8)	30 (1.4)		27 (5.0)	4 (1.7)	18 (4.4)	
Biventricular pacer only	57 (2.6)	17 (1.0)	19 (0.7)		55 (3.3)	15 (1.0)	19 (0.9)		2 (0.4)	2 (0.8)	0 (0.0)	
Biventricular pacer and ICD	236 (10.7)	35 (2.1)	54 (2.1)		233 (14.1)	35 (2.4)	53 (2.5)		3 (0.6)	0 (0.0)	1 (0.2)	
Sociodemographics												
Education												
None/primary education	664 (30.8)	460 (27.5)	630 (35.6)	<0.001	398 (24.5)	386 (27.1)	556 (35.1)	<0.001	266 (49.8)	74 (29.8)	74 (39.8)	<0.001
Secondary education	697 (32.3)	485 (29.0)	729 (41.2)		578 (35.6)	430 (30.2)	655 (41.4)		119 (22.3)	55 (22.2)	74 (39.8)	
Preuniversity	374 (17.3)	209 (12.5)	175 (9.9)		294 (18.1)	177 (12.4)	157 (9.9)		80 (15.0)	32 (12.9)	18 (9.7)	

Continued

DOI: 10.1161/JAHA.119.012199

Table 1. Continued

	Overall				HFrEF				HFpEF			
	Northeast Asia	South Asia	Southeast Asia	*P* Value	Northeast Asia	South Asia	Southeast Asia	*P* Value	Northeast Asia	South Asia	Southeast Asia	*P* Value
Degree or higher	347 (16.1)	451 (26.9)	199 (11.3)		288 (17.8)	402 (28.2)	189 (11.9)		59 (11.0)	49 (19.8)	10 (5.4)	
Decline to respond	74 (3.4)	69 (4.1)	35 (2.0)		64 (3.9)	31 (2.2)	25 (1.6)		10 (1.9)	38 (15.3)	10 (5.4)	
Marital status				<0.001				<0.001				<0.001
Single	206 (9.6)	28 (1.7)	146 (8.3)		165 (10.2)	26 (1.8)	139 (8.8)		41 (7.7)	2 (0.8)	7 (3.8)	
Married	1621 (75.2)	1570 (93.8)	1417 (80.2)		1246 (76.8)	1336 (93.7)	1274 (80.6)		375 (70.2)	234 (94.4)	143 (76.9)	
Separated/divorced	82 (3.8)	9 (0.5)	77 (4.4)		66 (4.1)	6 (0.4)	70 (4.4)		16 (3.0)	3 (1.2)	7 (3.8)	
Widowed	204 (9.5)	60 (3.6)	119 (6.7)		115 (7.1)	53 (3.7)	93 (5.9)		89 (16.7)	7 (2.8)	26 (14.0)	
Decline to answer	43 (2.0)	7 (0.4)	8 (0.5)		30 (1.8)	5 (0.4)	5 (0.3)		13 (2.4)	2 (0.8)	3 (1.6)	

Data presented are mean (SD) or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PAD, peripheral arterial disease.

21.4% mortality rate in Indonesia and 14.3% in the Philippines, despite these 2 countries having the youngest populations. Japan, with a relatively elderly population, had the lowest 1-year mortality rate at 4.4%.

Overall, the most common cause of death among patients with HFrEF (54%) was known cardiovascular death, with a further 34% of deaths having a presumed cardiovascular or unknown cause, whereas 12% of deaths were noncardiovascular. Sudden death and HF death accounted for at least 80% of cardiovascular deaths. Among patients with HFpEF, cardiovascular and noncardiovascular deaths accounted for half and a quarter of deaths, respectively.

Associations With Mortality

Table 4 demonstrates the variables associated with 1-year mortality in the entire ASIAN-HF cohort. In unadjusted analyses, multiple variables were associated with death. After adjustment, clinical and demographic features associated with death within 1 year included enrollment as an inpatient (hazard ratio [HR]: 1.49; 95% CI, 1.19–1.86), HFpEF (HR: 0.54; 95% CI, 0.37–0.80), New York Heart Association (NYHA) class III/IV (HR: 1.99; 95% CI, 1.60–2.47), body mass index (HR: 0.95; 95% CI, 0.93–0.97), systolic blood pressure (HR: 0.90; 95% CI, 0.85–0.95), AF (HR: 1.33; 95% CI, 1.05–1.67), and CKD (HR: 1.58; 95% CI, 1.27–1.97). Treatment with an ACEI/ARB and treatment with a β-blocker were both independently associated with better survival, with HRs of 0.61 (95% CI, 0.50–0.76) and 0.66 (95% CI, 0.52–0.83), respectively. However, use of mineralocorticoid receptor antagonists was not associated with outcomes, and use of diuretics was associated with worse outcomes (HR: 1.96; 95% CI, 1.37–2.82). There were a number of interactions with regional status in the univariable models. AF was associated with poor prognosis in South Asian patients (HR: 2.79; 95% CI, 1.31–5.94) and Northeast Asian patients (HR: 1.55; 95% CI, 1.07–2.25) but not in Southeast Asian patients, in whom it was not significantly associated with mortality. There was also a significant interaction between enrollment as an inpatient and region. Inpatient enrollment was associated with higher mortality than outpatient enrollment in Northeast and South Asia but not in Southeast Asia. Southeast Asia had almost double the adjusted risk of mortality of the other 2 regions (HR: 1.94; 95% CI, 1.42–2.66). The relationship between geographical region and outcomes was not significantly affected by HF type ($P_{interaction}$=0.075), such that Southeast Asia had higher risk of mortality compared with South and Northeast Asia for both HFrEF and HFpEF.

Table 5 shows the contribution of each demographic, clinical, medication/device, and regional variable that contributed to the relative amount of the risk of death at 1 year. These known variables accounted for only 44.8% of the risk of

Downloaded from http://ahajournals.org by on August 17, 2021

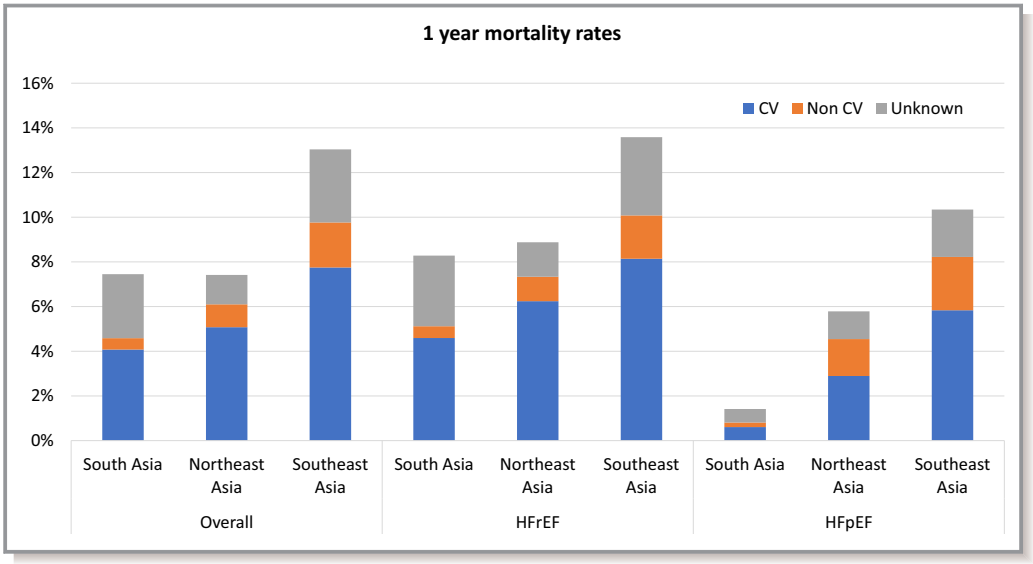

Figure 1. One-year mortality and cause of death by region and heart failure group. CV indicates cardiovascular; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

death and consisted of 3.9% demographic, 21.9% clinical, 7.0% medication/device, and 5.8% regional variables. The relative contributions were similar in HFrEF, comprising 3.8% demographic, 18.2% clinical, 7.8% medication/device, and 5.3% regional variables. In HFpEF, however, known variables accounted for 49.0% of the risk of death, mostly contributed by demographics and region.

Discussion

The ASIAN-HF study is the first multinational prospective registry to present outcomes data for patients with HF by regions and HF subtypes across Asia. Crude 1-year all-cause mortality was 9.6% in the overall cohort. However, we observed significant regional differences in patient characteristics, treatment, and mortality. Asian patients with HFrEF had worse 1-year outcomes than those with HFpEF, despite being significantly younger. Patients from the lowest income countries presented at the youngest ages but had the poorest outcomes. Southeast Asia had the highest rate of comorbidities, and patients from this region were almost twice as likely to die during the first year of follow-up in comparison to patients from South and Northeast Asia. Despite the considerable regional variations in demographics, comorbidity, and treatment, these measured factors explain less than half of the interregional variation in mortality, with unmeasured factors accounting for the bulk of the varying mortality risk. Notably, region was as or more important than demographics in predicting mortality in both HFrEF and HFpEF patients.

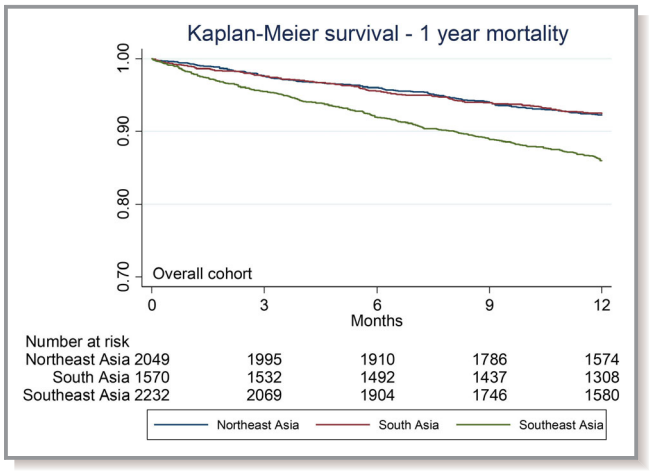

Figure 2. Kaplan–Meier curves for mortality by region.

Few other studies have explored the outcomes of patients with HF in Asia at national and regional levels.[10] The INTER-CHF study was a prospective HF cohort study conducted in 108 centers worldwide.[6] In addition to enrolling patients from the Middle East, Africa, and South America, INTER-CHF also enrolled 2660 patients from 4 Asian countries: China, India, Malaysia, and the Philippines. Unlike ASIAN-HF, INTER-CHF did not report outcomes in the different HF subtypes. The 1-year mortality rate in Southeast Asia (Malaysia and Philippines) in INTER-CHF was 15%, which is comparable to the mortality in our own Southeast Asian cohort (covering 5 countries) at 13%. However, the INTER-CHF mortality rates for China (7.3%) and India (23.3%) do not accord with our data; this is attributed to marked differences in patient characteristics of both studies. In ASIAN-HF, we found almost double the mortality rate in China (13.6%) and a far lower mortality

Downloaded from http://ahajournals.org by on August 17, 2021

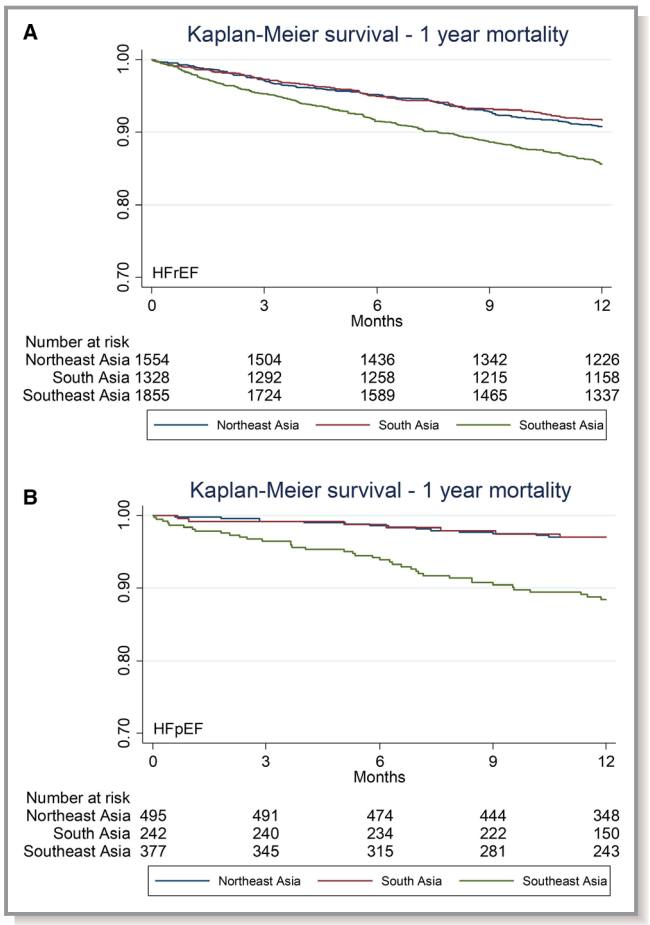

Figure 3. Kaplan–Meier curves for mortality by heart failure group. **A**, Heart failure with reduced ejection fraction (HFrEF). **B**, Heart failure with preserved ejection fraction (HFpEF).

rate in India (7.7%). The mortality variation in China may well be explained by the differing proportions of patients with HFrEF and inpatients in each study; in INTER-CHF, 27% of Chinese patients had HFrEF and 35% were recruited as inpatients. In contrast, the corresponding proportions of China's participants in ASIAN-HF were 98.8% with HFrEF and 91.3% recruited as inpatients. Higher mortality in the INTER-CHF population from India may be partly explained by a sicker population, with patients more likely to be enrolled as inpatients, to have more NYHA III/IV class HF, and to use fewer ACEIs/ARBs and β-blockers compared with ASIAN-HF participants.

The SWEDE-HF (Swedish Heart Failure) registry had enrollment criteria similar to the ASIAN-HF registry, so it is a useful comparator to represent non-Asian populations. Crude 1-year mortality rates for patients with EF <40% (n=23 400) and EF ≥50% (n=9640) were 15% and 17%, respectively. These rates are higher than those in the ASIAN-HF cohort but may partly reflect the older age of the Swedish cohort, with a mean age of 72 years for HFrEF and 77 years for HFpEF patients, in comparison to mean ages of 60 and

Table 2. One-Year Mortality Rates

	Overall					HFrEF					HFpEF				
		All-Cause Death	Cardiovascular Death	Non Cardiovascular Death	Unknown/Presumed Cardiovascular Deaths		All-Cause Death	Cardiovascular Death	Non Cardiovascular Death	Unknown/Presumed Cardiovascular Deaths		All-Cause Death	Cardiovascular Death	Non Cardiovascular Death	Unknown/Presumed Cardiovascular Deaths
	N	n (%)	n (%)	n (%)	n (%)	N	n (%)	n (%)	n (%)	n (%)	N	n (%)	n (%)	n (%)	n (%)
ASIAN-HF	5851	560 (9.6)	341 (60.9)	74 (13.2)	145 (25.9)	4737	500 (10.6)	270 (54.0)	60 (12.0)	170 (34.0)	1114	60 (5.4)	32 (53.3)	14 (23.3)	14 (23.3)
By geographical region															
South Asia	1570	117 (7.5)	64 (54.7)	8 (6.8)	45 (38.5)	1328	110 (8.3)	61 (55.5)	7 (6.4)	42 (38.2)	242	7 (2.9)	3 (42.9)	1 (14.3)	3 (42.9)
Northeast Asia	2049	152 (7.4)	104 (68.4)	21 (13.8)	27 (17.8)	1554	138 (8.9)	97 (70.3)	17 (12.3)	24 (17.4)	495	14 (2.8)	7 (50.0)	4 (28.6)	3 (21.4)
Southeast Asia	2232	291 (13.0)	173 (59.4)	45 (15.5)	73 (25.1)	1855	252 (13.6)	151 (59.9)	36 (14.3)	65 (25.8)	377	39 (10.3)	22 (56.4)	9 (23.1)	8 (20.5)
By enrollment status															
Inpatient	2472	331 (13.4)	215 (64.9)	42 (12.7)	74 (22.4)	2062	297 (14.4)	198 (66.7)	33 (11.1)	66 (22.2)	410	34 (8.3)	17 (50.0)	9 (26.5)	8 (23.5)
Outpatient	3379	229 (6.8)	126 (55.0)	32 (14.0)	71 (31.0)	2675	203 (7.6)	111 (54.7)	27 (13.3)	65 (32.0)	704	26 (3.7)	15 (57.7)	5 (19.2)	6 (23.1)

ASIAN-HF indicates Asian Sudden Cardiac Death in Heart Failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Downloaded from http://ahajournals.org by on August 17, 2021

Table 3. One-Year Cause-Specific Mortality Rates

	Overall			HFrEF			HFpEF		
	South Asia	Northeast Asia	Southeast Asia	South Asia	Northeast Asia	Southeast Asia	South Asia	Northeast Asia	Southeast Asia
No. of cardiovascular deaths	64	104	173	61	97	151	3	7	22
Specific cause of cardiovascular death									
Sudden death	41 (64.0)	43 (41.3)	49 (28.3)	41 (67.2)	41 (42.3)	47 (31.1)	0 (0.0)	2 (28.6)	2 (9.1)
HF death	18 (28.1)	52 (50.0)	41 (23.7)	17 (27.9)	47 (48.4)	39 (25.8)	1 (33.3)	5 (71.4)	2 (9.1)
AMI death	4 (6.3)	5 (4.8)	14 (8.1)	3 (4.9)	5 (5.2)	11 (7.3)	1 (33.3)	0 (0.0)	3 (13.6)
Stroke death	1 (1.6)	2 (1.9)	7 (4.0)	0 (0.0)	2 (2.1)	6 (4.0)	1 (33.3)	0 (0.0)	1 (4.6)
Cardiovascular hemorrhage death	0 (0)	1 (1.0)	4 (2.3)	0 (0.0)	1 (1.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (9.1)
Procedure death	0 (0)	1 (1.0)	2 (1.2)	0 (0.0)	1 (1.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other cardiovascular death	0 (0)	0 (0)	56 (32.4)	0 (0.0)	0 (0.0)	44 (29.1)	0 (0.0)	0 (0.0)	12 (55.5)

Data are shown as n (%) except as noted. AMI indicates acute myocardial infarction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

68 years, respectively, in ASIAN-HF participants. Other notable differences in the populations were a far higher proportion of patients with AF in the Swedish cohort, at 51% in those with HFrEF and 63% in those with HFpEF. In addition, the Swedish cohort had a higher proportion of female participants, with 29% of HFrEF patients and 55% of HFPEF patients being female.[17]

We previously described the interregional differences in clinical and echo characteristics and outcomes of patients with HFpEF in the ASIAN-HF population. We found that in patients with HFpEF, Southeast Asian patients had the highest rate of comorbidities and LV hypertrophy and the poorest outcomes. We extend this study in a number of ways by (1) presenting mortality rates for HFrEF and comparing these with HFpEF, (2) investigating differences in adjudicated causes of death in patients with HFrEF and HFpEF, and (3) studying differences in predictors of clinical outcomes between patients with HFrEF and HFpEF from Asia. A similar pattern of comorbidity clustering occurs in HFrEF patients, with particularly high rates of comorbidities and mortality in Southeast Asia. Mortality rates are almost double in HFrEF patients despite their being significantly younger.

After multivariable analysis we found that the relationship between certain key factors and mortality was modified by regional status. Enrollment as an inpatient was associated with significantly worse outcomes in Northeast and South Asia but not in Southeast Asia. This may reflect that inpatients in Southeast Asia may not be as sick as inpatients in Northeast and South Asia, or perhaps be due to disproportionately higher enrollment of inpatients from Singapore and Malaysia, where there is good tertiary care. Interestingly, in patients from South Asia, AF was associated with a far greater risk of death than in other regions. This result is particularly intriguing, given the markedly lower prevalence of AF in the South Asian population, and further study is warranted.

At a national level, Indonesia had the highest rate of all-cause death at 22.6%, with the second highest in Hong Kong at 19.8%—an interesting finding, given that Indonesia had the youngest population in the cohort (mean age: 57 years) and Hong Kong had the oldest (mean age: 79 years). It is notable that Indonesia also had the highest rates of coronary artery disease (62%) and smoking (66.4%) and a high prevalence of CKD but the lowest uptake of implantable cardioverter-defibrillators and cardiac resynchronization therapy–defibrillators and β-blockers. The finding of poor outcomes in young patients in Asia was reported previously from a subgroup analysis of the PARADIGM-HF trial that compared patient characteristics and outcomes among different global geographic regions, including 1487 patients with HFrEF from the Asia Pacific region.[18] Patients in the Asia Pacific region were on average 10.5 years younger than their western European counterparts at enrollment and had one of the highest rates of all-cause mortality and cardiovascular death globally, before and after adjustment for clinical characteristics. Poorer outcomes in younger Southeast Asian populations may reflect later presentation and more advanced disease but also the lower life expectancy seen in lower income countries such as Indonesia and the Philippines, which have vast geographic spread and less developed healthcare infrastructure.

We found marked divergence in both drug and device utilization across Asia. Device utilization in Northeast Asia was more than 3-fold that seen in Southeast and South Asia, with particularly high rates of device usage in Japan. The disparity in device utilization across geographical regions was recently described in a pan-Asian analysis from ASIAN-HF.[19]

Downloaded from http://ahajournals.org by on August 17, 2021

Table 4. Variables Associated With All-Cause Mortality At 1 Year

	Univariable Analysis		Multivariable Analysis		Interaction With Region			
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	$P_{interaction}$	Northeast Asia	South Asia	Southeast Asia
Demographic variables								
Age, per 10 y	1.13 (1.06–1.21)	<0.001	1.07 (0.98–1.18)	0.148	0.002	1.08 (0.93–1.26)	0.94 (0.77–1.15)	1.17 (1.02–1.33)
Female	0.81 (0.67–0.99)	0.038	0.97 (0.74–1.27)	0.834	. . .	. . .	. . .	. . .
Enrolled as inpatient	2.12 (1.79–2.51)	<0.001	1.47 (1.17–1.84)	0.001	0.001	1.88 (1.21–2.93)	1.86 (1.11–3.12)	1.20 (0.89–1.62)
HF hospitalization in past 6 mo	1.87 (1.59–2.21)	<0.001	1.47 (1.20–1.80)	<0.001	0.062	. . .	. . .	. . .
Clinical variables								
HFpEF	0.51 (0.39–0.67)	<0.001	0.55 (0.37–0.83)	0.004	. . .	. . .	. . .	. . .
NYHA class III/IV	2.26 (1.91–2.68)	<0.001	1.93 (1.54–2.42)	<0.001	. . .	. . .	. . .	. . .
Body mass index, kg/m^2	0.94 (0.93–0.96)	<0.001	0.95 (0.93–0.97)	<0.001	. . .	. . .	. . .	. . .
Heart rate, per 5 bpm	1.02 (1.00–1.05)	0.074	1.02 (0.99–1.05)	0.201	. . .	. . .	. . .	. . .
Systolic BP, per 10 mm Hg	0.89 (0.86–0.93)	<0.001	0.91 (0.86–0.97)	0.002	. . .	. . .	. . .	. . .
Diastolic BP, per 10 mm Hg	0.87 (0.81–0.93)	<0.001	. . .	. . .	. . .	. . .	. . .	. . .
Duration of HF, y	1.20 (1.11–1.31)	<0.001	1.16 (1.04–1.29)	0.006	. . .	. . .	. . .	. . .
Ischemic etiology of HF	1.64 (1.38–1.95)	<0.001	. . .	. . .	. . .	. . .	. . .	. . .
Coronary artery disease	1.53 (1.30–1.81)	<0.001	1.14 (0.91–1.42)	0.265	. . .	. . .	. . .	. . .
AF	1.44 (1.19–1.74)	<0.001	1.35 (1.06–1.71)	0.013	0.019	1.55 (1.07–2.25)	2.79 (1.31–5.94)	1.15 (0.84–1.57)
Hypertension	1.11 (0.94–1.31)	0.218	. . .	. . .	. . .	. . .	. . .	. . .
Prior stroke	1.38 (1.03–1.85)	0.029	0.99 (0.70–1.40)	0.975	. . .	. . .	. . .	. . .
PAD	2.28 (1.63–3.20)	<0.001	1.41 (0.92–2.17)	0.117	. . .	. . .	. . .	. . .
COPD	1.33 (1.01–1.74)	0.039	0.88 (0.63–1.24)	0.479	. . .	. . .	. . .	. . .
Diabetes mellitus	1.37 (1.16–1.61)	<0.001	1.06 (0.85–1.31)	0.621	. . .	. . .	. . .	. . .
Renal artery stenosis	2.34 (1.29–4.26)	0.005	. . .	. . .	. . .	. . .	. . .	. . .
Cancer	1.12 (0.73–1.73)	0.607	. . .	. . .	. . .	. . .	. . .	. . .
Smoking, ever	1.33 (1.13–1.57)	0.001	0.99 (0.78–1.25)	0.930	. . .	. . .	. . .	. . .
Alcohol, ever	1.05 (0.87–1.27)	0.596	. . .	. . .	. . .	. . .	. . .	. . .
CKD	1.97 (1.64–2.37)	<0.001	1.57 (1.26–1.97)	<0.001	. . .	. . .	. . .	. . .
Left bundle-branch block	0.96 (0.74–1.25)	0.758	. . .	. . .	. . .	. . .	. . .	. . .
Medications/device use								
ACEI or ARB	0.55 (0.46–0.65)	<0.001	0.61 (0.49–0.75)	<0.001	. . .	. . .	. . .	. . .
β-Blocker	0.63 (0.52–0.75)	<0.001	0.66 (0.52–0.83)	<0.001	. . .	. . .	. . .	. . .
Mineralocorticoid receptor antagonist	0.89 (0.75–1.05)	0.161	0.90 (0.72–1.11)	0.325	. . .	. . .	. . .	. . .
Diuretic	2.01 (1.54–2.64)	<0.001	1.87 (1.30–2.69)	0.001	. . .	. . .	. . .	. . .
Digoxin	1.35 (1.13–1.62)	0.001	. . .	. . .	. . .	. . .	. . .	. . .
ICD/CRT-D	0.92 (0.69–1.22)	0.558	0.75 (0.53–1.08)	0.119	. . .	. . .	. . .	. . .

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy–defibrillator; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PAD, peripheral arterial disease.

Downloaded from http://ahajournals.org by on August 17, 2021

Table 5. Explained Risk Analysis

1-y Mortality	Overall*		HFrEF*		HFpEF†	
	Value (%)	SE (%)	Value (%)	SE (%)	Value (%)	SE (%)
Demographic variables+clinical variables+ medication or device use+region	44.8	2.9	42.7	3.2	49.0	7.9
Only demographic variables	3.9	1.6	3.8	1.7	20.4	9.7
Only clinical variables	21.9	3.2	18.2	3.2	11.5	7.8
Only medications/device use	7.0	2.0	7.8	2.2	. . .	. . .
Only region	5.8	1.9	5.3	2.0	21.8	8.8

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
*Adjusted for demographic variables (age, sex, inpatient enrollment), clinical variables (New York Heart Association class, body mass index, heart rate, systolic blood pressure, duration of heart failure, coronary artery disease, atrial fibrillation, prior stroke, peripheral arterial disease, chronic obstructive pulmonary disease, diabetes mellitus, smoking, chronic kidney disease), medication or device use (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, mineralocorticoid receptor antagonist, diuretic, implantable cardioverter-defibrillator/cardiac resynchronization therapy–defibrillator) and regional variables.
†Adjusted for demographic (age, inpatient enrollment), clinical (New York Heart Association class, body mass index, duration of heart failure), and regional variables.

The ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) study[20] previously reported low rates of guideline-directed medical therapy and very low rates of implantable cardioverter-defibrillator utilization in a small group of patients (n=439) from the Asia Pacific region (India, Singapore, Israel, Philippines, Turkey, Taiwan). Implantable cardioverter-defibrillator usage was 5.7% in Asia Pacific in comparison to 38% in North America, and patients from the Asia Pacific region had the highest 1-year all-cause mortality rate at 26.7%, in comparison to 7.3% in North America. The largest driver of regional differences in mortality was sudden cardiac death, with a 10.3% 1-year rate of sudden cardiac death in Asia compared with 1.6% in North America.

The clear interregional differences in mortality seen in ASIAN-HF were only partly explained by differences in patient demographics, comorbidities, and treatment. These measured variables account for less than half of the variation in mortality risk after multivariable adjustment. The majority of regional variation in mortality arises from unmeasured factors that likely include differences in healthcare infrastructure, delayed presentation to healthcare facilities, access to and delivery of health care, and the quality of healthcare, as shown by the poorest countries having the greatest mortality. Other important variables such as genetic, cultural, and environmental factors may also be operative. Consequently, efforts at unraveling and addressing these unmeasured factors, including improvements in national and regional healthcare infrastructure and organization, may have great potential for enhancing survival outcomes in Asian HF patients. With pharmacological management and device therapy explaining only 7% of variation in the risk of mortality in the fully adjusted model in chronic patients with HF, primary prevention of HF through attention to its key risk factors or antecedents (eg. coronary artery disease, hypertension, diabetes mellitus, and CKD) is key to reducing the burden of HF in Asia.

Limitations

There is a potential bias in site selection (with a clear bias to reputable, academically inclined centers with expertise in echocardiography and resources to devote to research activities) and willingness of patients to participate in a prospective registry. Priority was given to sites that could provide high-quality data with as little missing data as possible. Therefore, the experience of our centers likely represents the best practice achievable in our multinational observational registry. Our results may therefore underestimate the true outcome burden of HF across Asia. Underreporting bias is also a possibility. To minimize this, every effort was made to ensure protocol standardization and adherence, including on-site investigator training, regular monitoring (both in person and remote), and centralized database management. Variation in reporting of cause of death across the different sites precluded the ascertainment of the cause of death in a significant proportion of cases, with subsequent substantial percentage variation in the category of death with unknown cause. However, in the absence of official pan-Asian population-based data, ASIAN-HF provides the best information available on HF to date across a broad swathe of Asia.

Conclusions

These first multinational prospective outcomes data on patients with HF across 11 Asian regions show that patients from Southeast Asia (particularly low-income countries with the youngest patients) had the poorest outcomes regardless of LVEF. Region-specific risk factors and gaps in guideline-directed therapy should be addressed, along with exploration of potential regional differences in healthcare systems, access to device therapy, and genetic and environmental factors.

Downloaded from http://ahajournals.org by on August 17, 2021

Appendix

ASIAN-HF Executive Committee

Professor A. Mark Richards (as Chairman), Cardiovascular Research Institute, National University of Singapore, Singapore. Email: mdcarthu@nus.edu.sg. Professor Carolyn S. P. Lam (as Principal Investigator), National Heart Centre Singapore, Duke-NUS Medical School, Singapore. Email: carolyn.lam@duke-nus.edu.sg. Professor Inder Anand (as Director, Publications Committee), University of Minnesota Medical School, VA Medical Center Minneapolis and San Diego, USA. Email: anand001@umn.edu. Dr Chung-Lieh Hung, Mackay Memorial Hospital, Taipei, Taiwan. Email: jotaro3791@gmail.com. Professor Lieng Hsi Ling (as Director, Echo Core Laboratory), Cardiovascular Research Institute, National University of Singapore, Singapore. Email: lieng_hsi_ling@nuhs.edu.sg. Dr Houng Bang Liew, Queen Elizabeth II Hospital, Clinical Research Center, Sabah, Malaysia. Email: hbliew22@gmail.com. Dr Calambur Narasimhan, Care Hospital, Hyderabad, India. Email: calambur@hotmail.com. Dr Tachapong Ngarmukos, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. Email: tachaponis.nga@mahidol.ac.th. Dr Sang Weon Park, SeJong General Hospital, Seoul, South Korea. Email: swparkmd@gmail.com. Dr Eugenio Reyes, Manila Doctors Hospital, Manila, Philippines. Email: eugenereyes@yahoo.com. Professor Bambang B. Siswanto, National Cardiovascular Center Universitas Indonesia, Jakarta, Indonesia. Email: bambbs@gmail.com. Professor Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan. Email: wshimizu@nms.ac.jp. Professor Shu Zhang, Fuwai Cardiovascular Hospital, Beijing, People's Republic of China. Email: zsfuwai@vip.163.com.

Country and Site Investigators

China

Fuwai Hospital: Shu Zhang (Country PI), Xiaohan Fan, Keping Chen. Ruijin Hospital, Shanghai Jiaotong university: Liqun Wu, Yucai Xie, Qi Jin, Tianyou Ling. The First Affiliated Hospital With Nanjing Medical University: Xinli Li, Fang Zhou, Yanli Zhou, Dongjie Xu, Haifeng Zhang. Zhongshan Hospital Fudan University: Yangang Su, Xueying Chen, Shengmei Qin, Jingfeng Wang, Xue Gong, Zhaodi Wu.

Hong Kong

Chinese University of Hong Kong: Cheuk Man Yu (Country PI).

India

CARE Hospital: Calambur Narasimhan (Country PI), B K S Sastry, Arun Gopi, K Raghu, C Sridevi, Daljeet Kaur. Care Institute of Medical Sciences: Ajay Naik, Keyur Parikh, Anish Chandarana, Urmil Shah, Milan Chag, Hemang Baxi, Satya Gupta, Jyoti Bhatia, Vaishali Khakhkhar, Vineet Sankhla, Tejas Patel, Vipul Kapoor. Hero Dayanand Medical College Heart Institute: Gurpreet Singh Wander, Rohit Tandon. Medanta-The Medicity: Vijay Chopra, Manoj Kumar, Hatinder Jeet Singh Sethi, Rashmi Verma, Sanjay Mittal. Sir Ganga Ram Hospital: Jitendra Sawhney, Manish Kr. Sharma. Westfort Hi-Tech Hospital Ltd: Mohanan Padinhare Purayil.

Indonesia

Rumah Sakit Jantung dan Pembuluh Darah Harapan Kita: Bambang Budi Siswanto (Country PI). RS Dr Hasan Sadikin: Pintoko Tedjokusumo, Erwan Martanto, Erwinanto. R S Khusus Jantung Binawaluya: Muhammad Munawar, Jimmy Agung Pambudi. RS Siloam Karawaci: Antonia Lukito, Ingrid Pardede, Alvin Thengker, Vito Damay, Siska Suridanda Danny, Rarsari Surarso.

Japan

Nippon Medical School: Wataru Shimizu (Country PI), National Cerebral and Cardiovascular Center: Takashi Noda, Ikutaro Nakajima, Mitsuru Wada, Kohei Ishibashi. Kinki University Hospital Cardiovascular Center: Takashi Kurita, Ryoubun Yasuoka. Nippon Medical School Hospital: Kuniya Asai, Kohji Murai, Yoshiaki Kubota, Yuki Izumi. Toho University Omori Medical Center: Takanori Ikeda, Shinji Hisatake, Takayuki Kabuki, Shunsuke Kiuchi, Tokyo Women's Medical University: Nobuhisa Hagiwara, Atsushi Suzuki, Dr Tsuyoshi Suzuki.

Korea

SeJong General Hospital: Sang-Weon Park (Country PI), Suk Keun Hong, SookJin Lee, Lim Dal Soo, Dong-Hyeok Kim. Korea University Anam Hospital: Jaemin Shim, Seong-Mi Park, Seung-Young Roh, Young Hoon Kim, Mina Kim, Jong-Il Choi. Korea University Guro Hospital: Jin Oh Na, Seung Woon Rha, Hong Seog Seo, Dong Joo Oh, Chang Gyu Park, Eung Ju Kim, Sunki Lee,

Severance Hospital, Yonsei University Health System: Boyoung Joung, Jae-Sun Uhm, Moon Hyoung Lee, In-Jeong Cho, Hui-Nam Park. Chonnam National University Hospital: Hyung-Wook Park, Jeong-Gwan Cho, Namsik Yoon, KiHong Lee, Kye Hun Kim. Korea University Ansan Hospital: Seong Hwan Kim.

Malaysia

Hospital Queen Elizabeth II: Houng Bang Liew (Country PI), Sahrin Saharudin, Boon Cong Beh, Yu Wei Lee, Chia How Yen, Mohd Khairi Othman, Amie-Anne Augustine, Mohd Hariz Mohd Asnawi, Roberto Angelo Mojolou, You Zhuan Tan, Aida Nurbaini Arbain, Chii Koh Wong. Institut Jantung Negara:

Downloaded from http://ahajournals.org by on August 17, 2021

Razali Omar, Azmee Mohd Ghazi, Surinder Kaur Khelae, David S.P. Chew, Lok Bin Yap, Azlan Hussin, Zulkeflee Muhammad, Mohd. Ghazi Azmee. University Malaya Medical Centre: Imran Zainal Abidin, Ahmad Syadi Bin Mahmood Zhudi, Nor Ashikin Md Sari, Ganiga Srinivasaiah Sridhar, Ahmad Syadi Mahmood Zuhdi. Muhammad Dzafir Ismail. Sarawak General Hospital Heart Centre: Tiong Kiam Ong, Yee Ling Cham, Ning Zan Khiew, Asri Bin Said, Alan Yean Yip Fong, Nor Hanim Mohd Amin, Keong Chua Seng, Sian Kong Tan, Kuan Leong Yew.

Philippines

Manila Doctors Hospital: Eugenio Reyes (Country PI), Jones Santos, Allan Lim. Makati Medical Center: Raul Lapitan, Ryan Andal, Philippine Heart Center: Eleanor Lopez.

Singapore

National Heart Centre Singapore: Carolyn S.P. Lam (Country PI), Kheng Leng David Sim, Boon Yew Tan, Choon Pin Lim, Louis L.Y. Teo, Laura L. H. Chan. National University Heart Centre: Lieng Hsi Ling, Ping Chai, Ching Chiew Raymond Wong, Kian Keong Poh, Tan Tock Seng Hospital: Poh Shuan Daniel Yeo, Evelyn M. Lee, Seet Yong Loh, Min Er Ching, Deanna Z.L. Khoo, Min Sen Yew, Wenjie Huang. Changi General Hospital-Parent: Kui Toh Gerard Leong, Jia Hao Jason See, Yaozong Benji Lim, Svenszeat Tan, Colin Yeo, Siang Chew Chai. Singapore General Hospital-Parent: Fazlur Rehman Jaufeerally, Haresh Tulsidas, Than Aung. Khoo Teck Puat Hospital: Hean Yee Ong, Lee Fong Ling, Dinna Kar Nee Soon.

Taiwan

Mackay Memorial Hospital, Taipei, Taiwan: Chung-Lieh Hung (Country PI), Hung-I Yeh,Jen-Yuan Kuo, Chih-Hsuan Yen. National Taiwan University Hospital: Juey-Jen Hwang, Kuo-Liong Chien, Ta-Chen Su, Lian-Yu Lin, Jyh-Ming Juang, Yen-Hung Lin, Fu-Tien Chiang, Jiunn-Lee Lin, Yi-Lwun Ho, Chii-Ming Lee, Po-Chih Lin, Chi-Sheng Hung, Sheng-Nan Chang, Jou-Wei Lin, Chih-Neng Hsu. Taipei Veterans General Hospital: Wen-Chung Yu, Tze-Fan Chao, Shih-Hsien Sung, Kang-Ling Wang, Hsin-Bang Leu, Yenn-Jiang Lin, Shih-Lin Chang, Po-Hsun Huang, Li-Wei Lo, Cheng-Hsueh Wu. China Medical University Hospital: Hsin-Yueh Liang, Shih-Sheng Chang, Lien-Cheng Hsiao, Yu-Chen Wang, Chiung-Ray Lu, Hung-Pin Wu, Yen-Nien Lin, Ke-Wei Chen, Ping-Han Lo, Chung-Ho Hsu, Li-Chuan Hsieh.

Thailand

Ramathibodi Hospital: Tachapong Ngarmukos (Country PI), Mann Chandavimol, Teerapat Yingchoncharoen, Prasart Laothavorn. Phramongkutklao Hospital:Waraporn Tiyanon. Maharaj Nakorn Chiang Mai Hospital: Wanwarang Wongcharoen, Arintaya Phrommintikul.

Acknowledgments

The contributions of all site investigators and clinical coordinators are duly acknowledged. The lead author affirms that this article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Authors' Contributions

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors critically reviewed and contributed to the intellectual content of the article. Lam, MacDonald, and Anand were involved with the conception of the study. Initial data preparation was done by Tay, who performed the statistical analyses. MacDonald drafted the article. Teng contributed to part of the draft article and undertook revisions of the final article. Lam, MacDonald, Richards, Ling, and Anand provided the clinical expertise. Lam, MacDonald, and Yap adjudicated all mortality and causes of death. All authors have read and approved the final version of the article.

Sources of Funding

The ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) study is supported by grants from the National Medical Research Council of Singapore; Agency for Science, Technology, and Research; Biomedical Research Council; Asian Network for Translational Research and Cardiovascular Trials program; Boston Scientific Investigator-Sponsored Research Program; and Bayer. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

Disclosures

None relevant to the present work. Lam is supported by a Clinician Scientist Award from the National Medical Research Council Singapore. Lam has received research support from Boston Scientific, Medtronic, and Vifor Pharma and has consulted for Bayer, Novartis, Takeda, Merck, Astra Zeneca,

Downloaded from http://ahajournals.org by on August 17, 2021

Janssen Research & Development, and Menarini. She has served on the clinical end point committee for DC Devices. Richards is supported by a Senior Translational Research (STaR) award from the National Medical Research Council of Singapore; holds the New Zealand Heart Foundation Chair of Cardiovascular Studies; has received research support from Boston Scientific, Bayer, AstraZeneca, Medtronic, Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics; and has consulted for Bayer, Novartis, Merck, AstraZeneca, and Roche Diagnostics.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
2. Braunwald E. The war against heart failure: the Lancet lecture. *Lancet*. 2015;385:812–824.
3. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol*. 2014;171:368–376.
4. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;391:572–580.
5. Lam CSP. Heart failure in Southeast Asia: facts and numbers. *ESC Heart failure*. 2015;2:46–49.
6. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanas F, Prabhakaran D, Badr A, Elmaghawry M, Damasceno A, Tibazarwa K, Belley-Cote E, Balasubramanian K, Islam S, Yacoub MH, Huffman MD, Harkness K, Grinvalds A, McKelvie R, Bangdiwala SI, Yusuf S; Inter-CHF Investigators. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health*. 2017;5:e665–e672.
7. Reyes EB, Ha JW, Firdaus I, Ghazi AM, Phrommintikul A, Sim D, Vu QN, Siu CW, Yin WH, Cowie MR. Heart failure across Asia: same healthcare burden but differences in organization of care. *Int J Cardiol*. 2016;223:163–167.
8. Mentz RJ, Roessig L, Greenberg BH, Sato N, Shinagawa K, Yeo D, Kwok BW, Reyes EB, Krum H, Pieske B, Greene SJ, Ambrosy AP, Kelly JP, Zannad F, Pitt B, Lam CS. Heart failure clinical trials in east and Southeast Asia: understanding the importance and defining the next steps. *JACC Heart Fail*. 2016;4:419–427.
9. Lam CS, Teng TK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto BB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. *Eur Heart J*. 2016;37:3141–3153.
10. MacDonald MR, Wee PP, Cao Y, Yang DM, Lee S, Tong KL, Leong KT. Comparison of characteristics and outcomes of heart failure patients with preserved versus reduced ejection fraction in a multiethnic Southeast Asian cohort. *Am J Cardiol*. 2016;118:1233–1238.
11. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur J Heart Fail*. 2013;15:928–936.
12. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1983;22(4 Suppl A):6A–13A.
13. Tromp J, Teng THK, Tay WT, Hung CL, Narasimhan C, Ngarmukos T, Reyes E, Siswanto B, Yu C, Zhang S, Yap J, MacDonald M, Leineweber K, Richards AM, Zile M, Anand I, Lam CSP. Heart failure with preserved ejection fraction in Asia. *Eur J Heart Fail*. 2019;21:23–36.
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
15. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MTT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 cardiovascular and stroke endpoint definitions for clinical trials. *Circulation*. 2018;137:961–972.
16. Heller G. A measure of explained risk in the proportional hazards model. *Biostatistics*. 2012;13:315–325.
17. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2017;19:1624–1634.
18. Kristensen SL, Martinez F, Jhund PS, Arango JL, Belohlavek J, Boytsov S, Cabrera W, Gomez E, Hagege AA, Huang J, Kiatchoosakun S, Kim KS, Mendoza I, Senni M, Squire IB, Vinereanu D, Wong RC, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJ. Geographic variations in the PARADIGM-HF heart failure trial. *Eur Heart J*. 2016;37:3167–3174.
19. Chia YMF, Teng TK, Tan ESJ, Tay WT, Richards AM, Chin CWL, Shimizu W, Park SW, Hung CL, Ling LH, Ngarmukos T, Omar R, Siswanto BB, Narasimhan C, Reyes EB, Yu CM, Anand I, MacDonald MR, Yap J, Zhang S, Finkelstein EA, Lam CSP. Disparity between indications for and utilization of implantable cardioverter defibrillators in Asian patients with heart failure. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003651.
20. Greene SJ, Fonarow GC, Solomon SD, Subacius H, Maggioni AP, Bohm M, Lewis EF, Zannad F, Gheorghiade M; ASTRONAUT Investigators and Coordinators. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: findings from the ASTRONAUT trial. *Eur J Heart Fail*. 2015;17:591–600.

Downloaded from http://ahajournals.org by on August 17, 2021