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

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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.

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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
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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. Limited data from Southeast Asian countries also suggest a higher prevalence of HF compared with other Asian countries. 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.

Most outcomes data in HF come from European and North American populations, with scant information from Asia, restricted to a few individual Asian countries. In affluent Western populations, 5-year mortality rates in HF patients from population-based studies rival those of major cancers at 50–60%. The limited data from low- and middle-income countries suggest their mortality rates may be even higher. 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. 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. 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. 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. 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

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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. 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 m². 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 χ² 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
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MARKED regional variation was evident. Regardless of HF

Prevalence of comorbidities was high throughout Asia, but

55.8 years, in stark contrast to the patients from Hong Kong,

Philippines had the youngest cohort (20% female), aged

the patients with HFpEF were women in all 3 regions. The

comparison to 17.7% in Southeast Asia. Approximately half of

female; 25.2% of patients in Northeast Asia were female, in

younger than the patients with HFpEF (Table 1). Among the

patients with HFpEF, older cohorts were more likely to be

female; 81% HFrEF) were enrolled from 46 centers across 11

Asian regions. All patients had a documented episode of

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/m²) 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
Table 1. Baseline Characteristics by Geographic Region and HF Group

| Demographic variables | Overall | HFpEF | HFpEF |
|-----------------------|---------|-------|-------|
|                       | Northeast | South Asia | Southeast | P Value | Northeast | South Asia | Southeast | P Value |
| **n**                 | 2201     | 1688   | 2591   |        | 1658     | 1436      | 2182      |        |
| **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 |
| **Female**            | 692 (31.4) | 467 (27.7) | 591 (22.8) | <0.001 | 417 (25.2) | 349 (24.3) | 387 (17.7) | <0.001 |
| **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 |

| Clinical variables | Overall | HFpEF | HFpEF |
|-------------------|---------|-------|-------|
|                   | Northeast | South Asia | Southeast | P Value | Northeast | South Asia | Southeast | P Value |
| **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 |
| **Body mass index, kg/m², 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 |
| **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 |
| **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 |
| **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 |
| **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 |

| Duration of HF | Overall | HFpEF | HFpEF |
|---------------|---------|-------|-------|
|               | Northeast | South Asia | Southeast | P Value | Northeast | South Asia | Southeast | P Value |
| **<1 y**      | 977 (44.4) | 766 (45.7) | 1208 (50.4) |        | 733 (44.2) | 662 (46.1) | 981 (48.3) |        |
| **1–5 y**     | 594 (27.0) | 648 (38.7) | 727 (30.3) |        | 429 (25.9) | 538 (37.5) | 647 (31.8) |        |
| **5–10 y**    | 353 (16.0) | 165 (9.8) | 329 (13.7) |        | 265 (16.0) | 147 (10.2) | 291 (14.3) |        |
| **≥10 y**     | 276 (12.6) | 97 (5.8) | 134 (5.6) | <0.001 | 230 (13.9) | 89 (6.2) | 113 (5.6) | <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 |
| **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 |
| **AF**        | 694 (31.5) | 77 (4.6) | 508 (19.8) | <0.001 | 501 (30.2) | 60 (4.2) | 380 (17.6) | <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 |
| **Prior stroke** | 165 (7.5) | 30 (1.8) | 239 (9.3) | <0.001 | 119 (7.2) | 26 (1.8) | 193 (9.0) | <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 |
| **COPD**      | 235 (10.7) | 79 (4.7) | 228 (8.9) | <0.001 | 181 (10.9) | 68 (4.7) | 185 (8.6) | <0.001 |
| **Diabetes mellitus** | 739 (33.6) | 601 (35.9) | 1316 (51.3) | <0.001 | 525 (31.7) | 533 (37.1) | 1062 (49.3) | <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 |
| **Cancer**    | 152 (6.9) | 8 (0.5) | 56 (2.2) | <0.001 | 108 (6.5) | 5 (0.3) | 49 (2.3) | <0.001 |

Continued
|                          | Overall | HF/EF | HFP EF |
|--------------------------|---------|-------|--------|
|                          | 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 |
| Alcohol, ever            | 727 (33.0) | 245 (14.7) | 725 (28.3) | <0.001 | 633 (38.2) | 234 (16.3) | 650 (30.2) | <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 |
| 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 |
| AF/flutter                | 408 (20.5) | 61 (3.9) | 362 (14.8) | <0.001 | 280 (17.5) | 45 (3.3) | 272 (13.2) | 0.017 |
| Other rhythms/unknown    | 501 (25.1) | 269 (17.3) | 273 (11.2) | <0.001 | 458 (28.8) | 224 (16.6) | 230 (11.2) | 0.017 |
| Left bundle-branch block | 200 (1.0) | 283 (18.1) | 244 (10.0) | <0.001 | 190 (11.9) | 274 (20.3) | 230 (11.2) | <0.001 |
| 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 |
| ARB                      | 741 (34.4) | 517 (33.1) | 613 (24.8) | <0.001 | 472 (28.7) | 459 (32.6) | 492 (23.6) | <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 |
| β-Blocker                | 1682 (78.1) | 990 (63.3) | 2010 (81.3) | <0.001 | 1353 (82.1) | 914 (64.9) | 1708 (81.8) | <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 |
| Loop diuretic            | 1519 (70.5) | 1242 (79.5) | 2092 (84.7) | <0.001 | 1241 (75.3) | 1157 (82.1) | 1788 (85.6) | <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 |
| Digoxin                  | 523 (24.3) | 500 (32.0) | 532 (21.5) | <0.001 | 486 (29.5) | 488 (34.6) | 489 (23.4) | <0.001 |
| Ivabradine               | 34 (1.6) | 316 (20.2) | 144 (5.8) | <0.001 | 34 (2.1) | 303 (21.5) | 134 (6.4) | <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 |
| ICD only                 | 133 (6.0) | 46 (2.7) | 103 (4.0) | <0.001 | 115 (6.9) | 38 (2.6) | 101 (4.7) | 0.003 |
| Pacemaker only           | 72 (3.3) | 16 (1.0) | 48 (1.9) | <0.001 | 45 (2.7) | 12 (0.8) | 30 (1.4) | 0.003 |
| Biventricular pacemaker only | 57 (2.6) | 17 (1.0) | 19 (0.7) | <0.001 | 55 (3.3) | 15 (1.0) | 19 (0.9) | 0.003 |
| Biventricular pacer and ICD | 236 (10.7) | 35 (2.1) | 54 (2.1) | <0.001 | 233 (14.1) | 35 (2.4) | 53 (2.5) | 0.003 |
| 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 |
| Secondary education      | 697 (32.3) | 485 (29.0) | 729 (41.2) | <0.001 | 578 (35.6) | 430 (30.2) | 655 (41.4) | <0.001 |
| Preuniversity            | 374 (17.3) | 209 (12.5) | 175 (9.9) | <0.001 | 294 (18.1) | 177 (12.4) | 157 (9.9) | 0.003 |

Table 1. Continued
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
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.

Few other studies have explored the outcomes of patients with HF in Asia at national and regional levels. The INTER-CHF study was a prospective HF cohort study conducted in 108 centers worldwide. 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...
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

**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).

Table 2. One-Year Mortality Rates

|                | Overall | HFrEF | HFpEF |
|----------------|---------|-------|-------|
|                | Unknown | Non   | Cardiac-vascular Death | Cardiovascular Death | All-Cause Death | Mortality 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 (5.4) | 32 (53.3) | 14 (23.3) | 13 (23.3) |
| By geographical region |         |       |       |       |           |           |           |           |           |           |       |       |           |           |
| South Asia     | 1570    | 117 (7.5) | 64 (45.4) | 8 (6.2) | 45 (30.5) | 1328 (110 (8.3)) | 61 (55.5) | 7 (6.4) | 42 (33.8) | 292 (2.9) | 1 (14.3) | 3 (20.4) | 4 (21.4) | 3 (21.4) |
| By enrollment status |       |       |       |       |           |           |           |           |           |           |       |       |           |           |
| Inpatient      | 2472    | 104 (15.4) | 104 (66.4) | 21 (15.2) | 34 (24.7) | 2062 (257 (15.2)) | 24 (17.4) | 405 (14.8) | 7 (2.9) | 66 (6.4) | 66 (10.3) | 9 (22.1) | 8 (20.5) |
| Outpatient     | 3379    | 229 (6.8) | 126 (55.0) | 32 (14.0) | 74 (31.0) | 2675 (171 (6.5)) | 111 (45.0) | 70 (26.0) | 704 (26.3) | 33 (9.9) | 17 (50.0) | 9 (26.3) | 5 (10.2) | 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.
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. In addition, the proportion of patients with AF in the Swedish cohort, at 51%, was notably higher than in other regions.

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 and comparing these with HFpEF, Southeast Asian patients had the highest rate of comorbidities and LV hypertrophy and the poorest outcomes.

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. 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.

### Table 3. One-Year Cause-Specific Mortality Rates

|                      | Overall | Northeast Asia | Southeast Asia | HFrEF | Northeast Asia | Southeast Asia | HFpEF | Northeast Asia | Southeast Asia |
|----------------------|---------|----------------|----------------|-------|----------------|----------------|-------|----------------|----------------|
| No. of cardiovascular deaths | 64      | 104            | 173            | 61    | 97             | 151            | 3     | 7              | 22             |

| Specific cause of cardiovascular death | Overall | Northeast Asia | Southeast Asia | HFrEF | Northeast Asia | Southeast Asia | HFpEF | Northeast Asia | Southeast Asia |
|---------------------------------------|---------|----------------|----------------|-------|----------------|----------------|-------|----------------|----------------|
| 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) | 0 (0.0) |
| Procedure 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.
Table 4. Variables Associated With All-Cause Mortality At 1 Year

| 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 | 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/m²                                 | 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.
The ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) study\textsuperscript{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 swath 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.
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Appendix

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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.

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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, Ruslichek LM, Rutschitzka 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, Molsen H, Hedgcock D, Crespillo AP, Allinson M, Hemingway H, Cleland JG, McMurray JVF, 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. Int J Cardiol. 2016;223:163–167.

6. Dokainish H, Teo K, Zhu J, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siiswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. Eur J Heart Fail. 2013;15:928–936.

7. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siiswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. Eur J Heart Fail. 2013;15:928–936.

8. Ko AS, Tay WT, Eng TKH, Vedin O, Benson L, Dahlström U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail. 2018;20:1624–1634.

9. Kristensen SL, Martinez F, Jhund PS, Arango JL, Belohlavek J, Boytsov S, Cabrera W, Gomez E, Hagehe AA, Huang J, Kiatchoosakun S, Kim KS, Mendoza I, Senni M, Squire IB, Vinereanu D, Wong RC, Gong J, Lefkowitz MP, Rokala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJV. Geographic variations in the PARADIGM-HF heart failure trial. Eur J Heart Fail. 2017;19:3153–3174.

10. Chia YMF, Teng TK, Tan ESJ, Tay WT, Richards AM, Chin CWL, Shimizu W, Park SW, Hung CL, Ling LH, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. Eur J Heart Fail. 2016;18:314–3153.

11. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siiswanto 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, Siiswanto 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, Alfaijah 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 JV. 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, Fab F, Morrow DA, Targum SH, Sias CA, Hai MT, Jaff MR, Joffe HV, Cutler JE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfeld 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 (STCRI). 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, Eng TKH, 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.