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RESEARCH ARTICLE

Heart failure with reduced ejection fraction: comparison of patient characteristics and clinical outcomes within Asia and between Asia, Europe and the Americas

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Aims Nearly 60% of the world's population lives in Asia but little is known about the characteristics and outcomes of Asian patients with heart failure with reduced ejection fraction (HFrEF) compared to other areas of the world.

Methods and results We pooled two, large, global trials, with similar design, in 13 174 patients with HFrEF (patient distribution: China 833, India 1390, Japan 209, Korea 223, Philippines 223, Taiwan 199 and Thailand 95, Western Europe 3521, Eastern Europe 4758, North America 613, and Latin America 1110). Asian patients were younger (55.0–63.9 years) than in Western Europe (67.9 years) and North America (66.6 years). Diuretics and devices were used less, and digoxin used more, in Asia. Mineralocorticoid receptor antagonist use was higher in China (66.3%), the Philippines (64.1%) and Latin America (62.8%) compared to Europe and North America (range 32.8% to 49.6%). The rate of cardiovascular death/heart failure hospitalization was higher in Asia (e.g. Taiwan 17.2, China 14.9 per 100 patient-years) than in Western Europe (10.4) and North America (12.8). However, the adjusted risk of cardiovascular death was higher in many Asian countries than in Western Europe (except Japan) and the risk of heart failure hospitalization was lower in India and in the Philippines than in Western Europe, but significantly higher in China, Japan, and Taiwan.

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A complete list of the PARADIGM-HF and ATMOSPHERE investigators is provided in the online supplementary *Appendix S1*.

Conclusion Patient characteristics and outcomes vary between Asia and other regions and between Asian countries. These variations may reflect several factors, including geography, climate and environment, diet and lifestyle, health care systems, genetics and socioeconomic influences.

Keywords Heart failure • Asia

Introduction

Although heart failure is a global problem afflicting approximately 30 million people worldwide, little is known about how the characteristics of affected individuals, clinical outcomes and response to treatment vary outside Europe and North America.[1] Yet, nearly 60% of the world's population lives in Asia, with China and India alone constituting about 37% of the global population. The future importance of Asia in relation to the globalization of clinical trials has been highlighted recently and the differences in individual characteristics between Asian and other patients, and among Asian patients, have begun to be described, although largely in hospitalized individuals apart from the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) study and most recently, the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry.[2–8] Little, however, is known about ambulatory patients with heart failure in the two largest countries in Asia and long-term clinical outcomes have not been compared within Asia and between Asia and the rest of the world. The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) trials were the largest and most globally representative trials ever conducted in patients with heart failure and reduced ejection fraction (HFrEF).[9,10] These two trials had almost identical inclusion and exclusion criteria and a common control group treated with enalapril. We have pooled these two recent trial datasets to examine clinical characteristics and patient outcomes in Asian countries compared to the other major regions of the world.

Methods

Design of included trials and participants

The inclusion and exclusion criteria of the two trials were almost identical.[11,12] Briefly, patients were eligible at screening if they were ≥18 years of age, had New York Heart Association (NYHA) functional class II–IV, left ventricular ejection fraction (LVEF) ≤35% (changed from ≤40% initially in PARADIGM-HF by amendment), elevated natriuretic peptides (cut-off level independent of atrial fibrillation), and took an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), along with a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (MRA), if indicated. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure <95 mmHg (<90 mmHg in ATMOSPHERE), estimated glomerular filtration rate (eGFR) <30 (<35 in ATMOSPHERE) mL/min/1.73 m^2 and potassium >5.4 (>5.2 in ATMOSPHERE) mmol/L. The trial was approved by ethics committees at all 1043 participating centres in 47 countries in PARADIGM-HF and 789 centres in 43 countries in ATMOSPHERE, and all patients provided written informed consent.

On trial entry, ongoing therapy with an ACE inhibitor or ARB was stopped and patients entered a sequential run-in, first receiving enalapril followed by sacubitril/valsartan in PARADIGM-HF and enalapril followed by the combination of enalapril plus aliskiren in ATMOSPHERE. Patients tolerating both run-in periods were randomly assigned to double-blind therapy with sacubitril/valsartan or enalapril in a 1:1 ratio in PARADIGM-HF or enalapril, aliskiren or both drugs in a 1:1:1 ratio in ATMOSPHERE.[9,10]

Outcomes

The primary outcome of both trials was a composite of death from cardiovascular causes or heart failure hospitalization. In the present study, we investigated the association between country/region and risk of the primary outcome, each of its components and all-cause mortality. All endpoints were adjudicated by the same clinical endpoint committee according to pre-specified criteria.

Countries/regions of interest

The Asian countries which enrolled at least 90 patients in the two trials were China (including Hong Kong), India, Japan, Korea, Philippines, Taiwan and Thailand; these were compared to the regions of Western Europe (reference region), Eastern Europe, North America and Latin America.

In both trials, patients were asked to self-identify their race (as one of: Caucasian, Black, Asian, Native American, Pacific Islander, or other) and ethnicity (as one of: Hispanic/Latino, Chinese, Indian, Japanese, mixed ethnicity, other or unknown). Only Caucasians were included in the analysis of non-Asian regions (Caucasians constituted 76% of all individuals in these regions).

Statistical analysis

Baseline characteristics are presented as means with standard deviations or medians with interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Differences in baseline characteristics according to country/region at baseline were assessed using the chi-square test for categorical variables and either ANOVA or the Kruskal–Wallis test for continuous variables.

Incidence rates for the outcomes of interest are presented per 100 patient-years. Relative hazard ratios (HR) with 95% confidence intervals of outcomes according to country/region were calculated using Cox proportional hazard models using Western Europe as the reference group. Final models included adjustment for randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination of enalapril and aliskiren), and the following baseline characteristics: age, sex, heart rate, systolic blood pressure, body mass index (BMI),

N-terminal pro B-type natriuretic peptide (NT-proBNP), LVEF, eGFR and NYHA class. The primary outcome and its composites were also tested for competing risks of death using Fine–Gray sub-distribution hazard model. We also carried out a sensitivity analysis by adjusting for variables in the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score.[13]

Analyses were performed using Stata version 14.0 (Stata Corp., College Station, TX, USA). Two-sided *P*-values < 0.05 were considered significant.

Results

Of the 13 174 patients included in this analysis, 833 (6.3%) were resident in China, 1390 (10.6%) in India, 209 (1.6%) in Japan, 223 (1.7%) in Korea, 223 (1.7%) in the Philippines, 199 (1.5%) in Taiwan, and 95 (0.7%) in Thailand; 3521 (26.7%) participants lived in Western Europe (reference region), 4758 (36.1%) in Eastern Europe, 613 (4.7%) in North America, and 1110 (8.4%) in Latin America (*Table 1*). All patients enrolled in China and Japan were of Chinese or Japanese ethnicity, respectively; those in the other Asian countries were of 'other' or 'mixed' Asian ethnicity except for Taiwan where 167 were of Chinese ethnicity and 32 of 'other' Asian ethnicity.

Baseline characteristics: patients in Asia compared with those elsewhere

Except for those in Japan (mean age 63.9 years), Asian patients were considerably younger on average (55.0–61.2 years) than Western European (mean age 67.9 years) and North American patients (66.6 years).

Asian patients had a lower BMI (range 22.9–25.6 kg/m^2) than those in other regions (e.g. 27.8 kg/m^2 in Western Europe and 29.8 kg/m^2 in North America) and a lower systolic blood pressure than in Europe (although not lower than in North or Latin America). With the exceptions of India, Taiwan and the Philippines, Asian patients had a lower prevalence of diabetes than those in Europe and North America (although not Latin America); the same pattern was seen for hypertension (although this was as common in Latin America as in Europe and North America).

Chronic obstructive pulmonary disease (COPD) was much less common in most Asian countries (Taiwan was the notable exception) than in Europe and North America (but not Latin America). This was despite current smoking being a lot more common in many Asian countries. As with COPD, renal disease was much less common in most Asian countries (except Taiwan), and Latin America, compared with Europe and North America. The prevalence of atrial fibrillation (on an electrocardiogram) was lower in most Asian countries and strikingly lower in India (2.5%) than in Europe or the Americas (14.8–36.7%).

Looking at heart failure characteristics, an ischaemic aetiology was less common in most Asian countries (e.g. 33.3% in China) than in other regions, although was as common in India (69.7%) and the Philippines (66.4%) as in Europe (57.4% in Western and 70.9% in Eastern Europe) and North America (71.8%). Asian patients were generally less severely functionally limited, according to NYHA class, except those in China and India. Consistent with this, patients in Asian countries had higher (better) Kansas City Cardiomyopaty Questionnaire (KCCQ) scores than in Europe and the Americas. LVEF was generally lower in patients in Asian countries compared with Europe and, to a lesser extent, North America. NT-proBNP levels were at least as high in China (1470 pg/mL) and the Philippines (2241 pg/mL) (and nearly as high in India and Thailand) as in Europe (1381 pg/mL Western Europe, 1454 pg/mL in Eastern Europe) and the Americas but markedly lower in other Asian countries (e.g. median 1263 pg/mL in Taiwan and 943 pg/mL in Korea). History of pre-randomization heart failure hospitalization varied markedly across the world with the greatest variation within Asia, from 43.7% in India to 76.9% in Taiwan (the range in Europe and the Americas was 58.8–68.2%) (*Table 2*).

In terms of symptoms and signs, patients in Asia generally (Taiwan being the exception) had less evidence of congestion (oedema, raised jugular venous pressure) than those in Europe and North America (with Latin America again more like Asia). Pre-trial use of an ARB (rather than ACE inhibitor) was higher in most Asian countries (ranging from 13.8% in China to 53.4% in the Philippines) than in Europe and the Americas (10.4–11.4%), with the exceptions of Japan (4.8%), Thailand (8.4%) and India (10.0%).

In terms of laboratory and other investigations, creatinine and haemoglobin varied considerably among countries/regions without a definite pattern. The lowest average haemoglobin was in India (127 g/L) and highest in the Philippines (143 g/L), compared with 139–142 g/L in Europe and the Americas. Left bundle branch block was less prevalent in most Asian countries than elsewhere. Consistent with this, average QRS duration was shorter in Asia than in the other regions (although QRS duration was shorter in Eastern Europe than in the other non-Asian regions).

On examination of treatments used, diuretics were less commonly taken by patients in most Asian countries, compared with elsewhere (with the exceptions of India and Japan). Conversely, use of digoxin was much more common (except in Japan). Beta-blocker use was uniformly high globally, although was lower in India, the Philippines and Taiwan than elsewhere. MRA prescription varied greatly, with the highest use in China (66.3%) the Philippines (64.1%) and Latin America (62.8%) compared with other countries and regions (range 32.8–49.6% in Europe and North America). Use of anticoagulants was lower in most Asian countries (as low as 5.1% in India and 7.8% in China). Device use was low overall but much less in all Asian countries than in Western Europe and North America (device use was also uncommon in Latin America and Eastern Europe) (*Table 3*).

Outcomes: patients in Asia compared with those elsewhere

With respect to the primary composite outcome, patients in Taiwan (17.2 per 100 patient-years), China (14.9), and Thailand (13.8) had a higher event rate than those in Europe (10.4 in Western and 12.3 in Eastern Europe) and the Americas (12.8 in North and 12.6 in Latin America) and the adjusted risk was significantly higher in these Asian countries than in Western Europe, the reference region. However, the picture was quite

Table 1 Baseline characteristics according to country in Asia and in non-Asian regions

	Western Europe (*n* = 3521, 26.7%)	Central/ Eastern Europe/Russia (*n* = 4758, 36.1%)	North America (*n* = 613, 4.7%)	Latin America (*n* = 1110, 8.4%)	China (*n* = 833, 6.3%)	India (*n* = 1390, 10.6%)	Japan (*n* = 209, 1.6%)	Korea (*n* = 223, 1.7%)	Philippines (*n* = 223, 1.7%)	Taiwan (*n* = 199, 1.5%)	Thailand (*n* = 95, 0.7%)
Age, years	67.9 (9.9)	64.9 (10.1)	66.6 (10.7)	63.3 (10.9)	57.2 (11.9)	56.4 (11.8)	63.9 (11.5)	59.1 (10.7)	55.0 (12.1)	61.2 (15.1)	57.0 (13.6)
Age group, *n* (%)											
≤40 years	33 (0.9)	69 (1.5)	7 (1.1)	26 (2.3)	73 (8.8)	145 (10.4)	8 (3.8)	20 (9.0)	29 (13.0)	21 (10.6)	15 (15.8)
41–55 years	351 (10.0)	724 (15.2)	94 (15.3)	242 (21.8)	271 (32.5)	477 (34.3)	32 (15.3)	61 (27.4)	87 (39.0)	50 (25.1)	22 (23.2)
56–70 years	1594 (45.3)	2443 (51.3)	274 (44.7)	548 (49.4)	373 (44.8)	629 (45.3)	100 (47.8)	100 (44.8)	85 (38.1)	64 (32.2)	42 (44.2)
>70 years	1543 (43.8)	1522 (32.0)	238 (38.8)	294 (26.5)	116 (13.9)	139 (10.0)	69 (33.0)	42 (18.8)	22 (9.9)	64 (32.2)	16 (16.8)
Female sex, *n* (%)	621 (17.6)	1113 (23.4)	87 (14.2)	283 (25.5)	143 (17.2)	328 (23.6)	30 (14.4)	50 (22.4)	46 (20.6)	30 (15.1)	22 (23.2)
Per capita income, USD (IQR)	46 530.9 (35 370.3–51 574.5)	15 543.7 (13 613.6–18 191.6)	52 787.0 (52 413.7–52 787.0)	12 976.6 (12 216.9–12 976.6)	7077.8	1452.2	40454.4	25890	2760.3	39600	6171.3
Healthcare spending* (IQR)	11.0 (9.2–11.2)	7.1 (6.5–7.5)	16.9 (10.7–16.9)	7.9	5.4	4.5	10.2	7.2	4.6	–	4.0
SBP, mmHg	123.2 (18.3)	127.4 (15.3)	117.0 (15.0)	119.9 (15.1)	117.1 (16.6)	117.6 (14.7)	118.7 (19.1)	112.9 (14.8)	118.1 (17.6)	120.6 (17.1)	122.2 (18.0)
HR, b.p.m.	68.7 (11.8)	73.6 (12.6)	69.0 (10.9)	70.3 (11.5)	72.8 (11.8)	77.1 (9.9)	71.5 (12.2)	72.0 (14.7)	75.0 (12.4)	77.6 (13.0)	73.3 (14.3)
BMI (IQR)	27.8 (25.1–31.2)	28.7 (25.7–32.5)	29.8 (26.4–34.2)	27.6 (24.8–30.9)	24.4 (22.0–27.1)	22.9 (20.4–25.5)	23.8 (21.5–26.2)	23.9 (22.3–26.6)	24.2 (21.3–26.6)	25.6 (23.0–28.1)	23.1 (20.4–26.3)
Medical history, *n* (%)											
Hypertension	2132 (60.6)	3970 (83.4)	485 (79.1)	768 (69.2)	390 (46.8)	509 (36.6)	113 (54.1)	79 (35.4)	135 (60.5)	143 (71.9)	42 (44.2)
Diabetes	1167 (33.1)	1502 (31.6)	295 (48.1)	307 (27.7)	207 (24.8)	465 (33.5)	59 (28.2)	55 (24.7)	71 (31.8)	82 (41.2)	28 (29.5)
Atrial fibrillation (Hx)	1531 (43.5)	2356 (49.5)	246 (40.1)	300 (27.0)	186 (22.3)	58 (4.2)	59 (28.2)	83 (37.2)	44 (19.7)	70 (35.2)	22 (23.2)
Atrial fibrillation (ECG)	881 (25.0)	1748 (36.7)	91 (14.8)	219 (19.7)	152 (18.2)	35 (2.5)	37 (17.7)	58 (26.0)	30 (13.5)	40 (20.1)	17 (17.9)
Unstable angina	403 (11.4)	703 (14.8)	136 (22.2)	69 (6.2)	58 (7.0)	81 (5.8)	16 (7.7)	20 (9.0)	3 (1.3)	43 (21.6)	14 (14.7)
Myocardial infarction	1640 (46.6)	2374 (49.9)	392 (63.9)	319 (28.7)	187 (22.4)	530 (38.1)	82 (39.2)	45 (20.2)	61 (27.4)	57 (28.6)	31 (32.6)
Stroke	305 (8.7)	449 (9.4)	56 (9.1)	78 (7.0)	54 (6.5)	30 (2.2)	21 (10.0)	14 (6.3)	22 (9.9)	16 (8.0)	10 (10.5)
COPD	567 (16.1)	738 (15.5)	153 (25.0)	71 (6.4)	31 (3.7)	58 (4.2)	7 (3.3)	8 (3.6)	19 (8.5)	36 (18.1)	4 (4.2)
Renal disease	538 (15.3)	919 (19.3)	164 (26.8)	65 (5.9)	19 (2.3)	22 (1.6)	20 (9.6)	9 (4.0)	23 (10.3)	55 (27.6)	5 (5.3)
ECG											
LBBB, *n* (%)	784 (22.3)	990 (20.8)	106 (17.3)	278 (25.0)	115 (13.8)	223 (16.0)	14 (6.7)	23 (10.3)	22 (9.9)	25 (12.6)	12 (12.6)
RBBB, *n* (%)	250 (7.1)	388 (8.2)	37 (6.0)	119 (10.7)	38 (4.6)	100 (7.2)	16 (7.7)	9 (4.0)	11 (4.9)	13 (6.5)	7 (7.4)
QRS duration, ms (IQR)	120 (100–153)	106 (90–130)	128 (104–162)	110 (80–140)	109 (96–128)	98 (80–120)	109 (98–134)	106 (96–122)	96 (80–114)	108 (96–130)	108 (98–132)
Current smoker	535 (15.2)	662 (13.9)	108 (17.6)	94 (8.5)	188 (22.6)	99 (7.1)	40 (19.1)	56 (25.1)	25 (11.2)	53 (26.6)	14 (14.7)
Alcohol intake											
<1 drink/day	2706 (76.9)	4281 (90.0)	539 (87.9)	1020 (91.9)	736 (88.4)	1342 (96.7)	163 (78.0)	199 (89.2)	184 (82.5)	186 (93.5)	88 (92.6)
1–2 drinks/day	661 (18.8)	432 (9.1)	61 (10.0)	86 (7.7)	65 (7.8)	34 (2.4)	38 (18.2)	16 (7.2)	21 (9.4)	8 (4.0)	5 (5.3)
>2 drinks/day	154 (4.4)	45 (0.9)	13 (2.1)	4 (0.4)	32 (3.8)	12 (0.9)	8 (3.8)	8 (3.6)	18 (8.1)	5 (2.5)	2 (2.1)
Haemoglobin, gm/L (IQR)	139 (129–150)	142 (131–152)	139 (129–148)	140 (130–150)	142 (131–153)	127 (117–137)	136 (127–146)	138 (127–149)	143 (128–153)	140 (126–154)	129 (117–145)
Potassium, mEq/L	4.5 (0.4)	4.5 (0.5)	4.4 (0.5)	4.5 (0.5)	4.3 (0.4)	4.4 (0.5)	4.3 (0.4)	4.5 (0.4)	4.3 (0.4)	4.2 (0.5)	4.2 (0.4)
eGFR, mL/min/1.73 m^2	65.8 (19.1)	70.0 (19.5)	61.7 (17.7)	71.7 (23.5)	80.4 (21.0)	77.5 (29.5)	71.3 (18.0)	77.7 (22.5)	68.3 (19.2)	68.0 (21.0)	69.1 (18.4)
eGFR <60 mL/min/m^2, *n* (%)	1408 (40.0)	1449 (30.5)	316 (51.6)	354 (31.9)	134 (16.1)	320 (23.0)	58 (27.8)	49 (22.0)	78 (35.0)	74 (37.2)	33 (34.7.7)

Values are expressed as mean (standard deviation), unless otherwise indicated.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HR, heart rate; Hx, history of; IQR, interquartile range; LBBB, left bundle branch block; RBBB, right bundle branch block; SBP, systolic blood pressure; USD, United States Dollars.

*Percentage of gross domestic product spent on healthcare.

Table 2 Heart failure characteristics according to country in Asia and in non-Asian regions

	Western Europe (*n* = 3521, 26.7%)	Central/ Eastern Europe/ Russia (*n* = 4758, 36.1%)	North America (*n* = 613, 4.7%)	Latin America (*n* = 1110, 8.4%)	China (*n* = 833, 6.3%)	India (*n* = 1390, 0.6%)	Japan (*n* = 209, 1.6%)	Korea (*n* = 223, 1.7%)	Philippines (*n* = 223, 1.7%)	Taiwan (*n* = 199, 1.5%)	Thailand (*n* = 95, 0.7%)
HF aetiology											
Ischaemic	2022 (57.4)	3373 (70.9)	440 (71.8)	449 (40.5)	277 (33.3)	969 (69.7)	89 (42.6)	85 (38.1)	148 (66.4)	87 (43.7)	36 (37.9)
Time since HF diagnosis											
<1 year	851 (24.2)	1243 (26.1)	114 (18.6)	323 (29.1)	377 (45.3)	790 (56.9)	76 (36.4)	107 (48.0)	109 (48.9)	73 (36.7)	45 (47.4)
1–5 years	1174 (33.3)	2040 (42.9)	167 (27.2)	441 (39.7)	311 (37.3)	485 (34.9)	64 (30.6)	67 (30.0)	85 (38.1)	69 (34.7)	40 (42.1)
>5 years	1495 (42.5)	1474 (30.9)	332 (54.2)	346 (31.2)	145 (17.4)	113 (8.1)	69 (33.0)	49 (22.0)	29 (13.0)	57 (28.6)	10 (10.5)
Previous hospitalization for HF	2069 (58.8)	3245 (68.2)	365 (59.5)	622 (56.0)	636 (76.4)	607 (43.7)	151 (72.2)	143 (64.1)	127 (57.0)	153 (76.9)	60 (63.2)
KCCQ clinical summary score (IQR)	80.2 (63.5–91.7)	70.8 (54.7–85.0)	78.1 (62.5–90.6)	86.5 (72.9–95.0)	91.7 (83.3–97.9)	83.3 (68.8–93.8)	93.8 (85.5–100.0)	–	80.2 (69.4–96.4)	–	–
LVEF, %, mean (SD)	28.9 (6.0)	30.8 (5.4)	26.7 (7.0)	28.5 (5.8)	29.5 (4.9)	27.9 (5.6)	28.5 (5.5)	27.0 (6.6)	28.1 (6.2)	28.1 (6.0)	26.2 (6.0)
NT-proBNP, pg/mL (IQR)	1381 (787–2580)	1454 (780–2740)	1494 (801–2885)	1302 (712–2547)	1470 (718–3109)	1260 (669–2628)	921 (550–1548)	943 (545–1765)	2241 (1126–4806)	1263 (719–2647)	1288 (724–2674)
NYHA class*											
I–II	2762 (78.5)	2555 (53.7)	492 (80.5)	1011 (91.2)	677 (81.4)	1080 (77.7)	198 (94.7)	203 (91.0)	211 (94.6)	178 (89.5)	94 (99.0)
III	742 (21.1)	2123 (44.7)	115 (18.8)	97 (8.8)	144 (17.3)	300 (21.6)	11 (5.3)	20 (9.0)	12 (5.4)	21 (10.6)	1 (1.1)
IV	13 (0.4)	77 (1.6)	4 (0.7)	1 (0.1)	11 (1.3)	10 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea on effort	3067 (87.3)	4499 (94.6)	463 (75.9)	954 (86.0)	558 (67.1)	1270 (91.4)	62 (29.7)	151 (67.7)	104 (46.6)	141 (70.9)	52 (54.7)
Orthopnoea	208 (5.9)	244 (5.1)	87 (14.3)	45 (4.1)	2 (0.2)	68 (4.9)	0 (0.0)	7 (3.1)	22 (9.9)	4 (2.0)	3 (3.2)
Paroxysmal nocturnal dyspnoea	137 (3.9)	331 (7.0)	23 (3.8)	25 (2.3)	13 (1.6)	84 (6.0)	1 (0.5)	5 (2.2)	5 (2.2)	6 (3.0)	1 (1.1)
Oedema	599 (17.0)	1470 (30.9)	188 (30.8)	156 (14.0)	51 (6.1)	206 (14.8)	12 (5.7)	6 (2.6)	18 (8.1)	51 (25.6)	5 (5.3)
Third heart sound	116 (3.3)	473 (9.9)	59 (9.7)	68 (6.1)	8 (1.0)	416 (29.9)	13 (6.2)	4 (1.8)	26 (11.7)	32 (16.1)	3 (3.2)
Jugular venous distension	177 (5.0)	623 (13.1)	49 (8.0)	136 (12.3)	19 (2.3)	123 (8.8)	8 (3.8)	6 (2.7)	2 (0.9)	8 (4.0)	4 (4.2)

Values are expressed as *n* (%), unless otherwise indicated.

HF, heart failure; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire, LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

*11 missing.

Table 3 Use of drugs and devices at baseline according to country in Asia and in non-Asian regions

	Western Europe (*n* = 3521, 26.7%)	Central/ Eastern Europe/Russia (*n* = 4758, 36.1%)	North America (*n* = 613, 4.7%)	Latin America (*n* = 1110, 8.4%)	China (*n* = 833, 6.3%)	India (*n* = 1390, 10.6%)	Japan (*n* = 209, 1.6%)	Korea (*n* = 223, 1.7%)	Philippines (*n* = 223, 1.7%)	Taiwan (*n* = 199, 1.5%)	Thailand (*n* = 95, 0.7%)
Diuretic	2845 (80.8)	3887 (81.7)	486 (79.3)	877 (79.0)	573 (68.8)	1188 (85.5)	163 (78.0)	165 (74.0)	96 (43.0)	146 (73.4)	68 (71.6)
Digitalis	681 (19.3)	1417 (29.8)	161 (26.3)	300 (27.0)	425 (51.0)	658 (47.3)	32 (15.3)	83 (37.2)	100 (44.8)	57 (28.6)	38 (40.0)
Beta-blocker	3292 (93.5)	4485 (94.3)	594 (96.9)	1038 (93.5)	779 (93.5)	1181 (85.0)	194 (92.8)	202 (90.6)	181 (81.2)	168 (84.4)	88 (92.6)
MRA	1436 (40.8)	2362 (49.6)	201 (32.8)	697 (62.8)	552 (66.3)	468 (33.7)	82 (39.2)	91 (40.8)	143 (64.1)	70 (35.2)	32 (33.7)
Pre-trial use of ACEI	3175 (90.2)	4289 (90.1)	554 (90.4)	997 (89.8)	718 (86.2)	1260 (90.6)	209 (100.0)	186 (83.4)	105 (47.1)	142 (71.4)	86 (90.5)
Pre-trial use of ARB	386 (11.0)	494 (10.4)	70 (11.4)	116 (10.5)	115 (13.8)	139 (10.0)	10 (4.8)	38 (17.0)	119 (53.4)	57 (28.6)	8 (8.4)
Anticoagulants	1609 (45.7)	1853 (38.9)	235 (38.3)	236 (21.3)	65 (7.8)	71 (5.1)	108 (51.7)	69 (30.9)	25 (11.2)	29 (14.6)	20 (21.1)
Statins	2350 (66.7)	2634 (55.4)	481 (78.5)	416 (37.5)	246 (29.5)	765 (55.0)	108 (51.7)	88 (39.5)	129 (57.8)	61 (30.7)	60 (63.2)
Aspirin	1746 (49.6)	2451 (51.5)	428 (69.8)	546 (49.2)	433 (52.0)	619 (44.5)	109 (52.2)	119 (53.4)	125 (56.1)	110 (55.3)	58 (61.1)
Prior PCI	1068 (30.3)	936 (19.7)	258 (42.1)	161 (14.5)	122 (14.6)	162 (11.7)	62 (29.7)	48 (21.5)	3 (1.3)	54 (27.1)	19 (20.0)
Prior CABG	767 (21.8)	723 (15.2)	240 (39.2)	80 (7.2)	34 (4.1)	165 (11.9)	21 (10.0)	12 (5.4)	7 (3.1)	19 (9.5)	4 (4.2)
Pacemaker	744 (21.1)	408 (8.6)	204 (33.3)	98 (8.8)	62 (7.4)	11 (0.8)	17 (8.1)	3 (1.3)	0 (0.0)	14 (7.0)	1 (1.1)
ICD/CRT-D	1199 (34.1)	412 (8.7)	328 (53.5)	30 (2.7)	29 (3.5)	1 (0.1)	24 (11.5)	1 (0.4)	0 (0.0)	9 (4.5)	6 (6.3)
CRT-P/CRT-D	460 (13.1)	172 (3.6)	138 (22.5)	16 (1.4)	49 (5.9)	5 (0.4)	12 (5.7)	0 (0.0)	0 (0.0)	7 (3.5)	1 (1.1)

Values are expressed as *n* (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; D, defibrillator; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; P, pacemaker; PCI, percutaneous coronary intervention.

different when the components of the composite were examined separately. The adjusted risk of cardiovascular death was higher in India, China, the Philippines, Thailand and Taiwan, than in Western Europe, whereas the risk of this outcome tended to be lower in patients in Japan (*Table 4*). A broadly similar pattern was observed for all-cause mortality (with a significantly lower all-cause mortality in Japan than in Western Europe). Conversely, the risk of hospital admission was significantly lower in India and in the Philippines than in Western Europe, whereas this risk was significantly higher in China, Japan, and Taiwan (*Table 4*, *Figure 1* and online supplementary *Table S1*).

Discussion

Together, the patients enrolled in PARADIGM-HF and ATMOSPHERE comprise the largest, most contemporary and most geographically, racially and ethnically diverse cohort of patients with HFrEF enrolled in clinical trials, with participants from 55 countries. In the present analyses we focused on 3172 patients enrolled from seven countries in Asia, including 1390 from India and 833 from China. We believe this to be the only report describing long-term non-fatal and fatal outcomes in HFrEF patients in Asia and comparing these with other regions of the world.

Although our analysis was by country, it should be noted that this geographical division of patients was largely synonymous with their categorization by race and ethnicity. For example, all patients in China, India and Japan were reported to be of Asian race but to have Chinese, Indian or Japanese ethnicity, respectively. All patients in the remaining Asian countries were described as of Asian race and, in most cases, 'other' ethnicity. The one exception was Taiwan where most patients described themselves as having Chinese ethnicity. Very small numbers of participants in the comparator regions were of Asian race.

We found substantial differences among patients within countries in Asia and between Asia and elsewhere. This was true for both clinical characteristics at baseline and for clinical outcomes. However, the differences within Asia were not consistent and varied for different characteristics. For example, patients in many Asian countries were considerably younger than in Europe and North America. However, patients in Japan and Taiwan were older than in other Asian countries. There are two other large studies of Asian patients with heart failure.[8,14] The International Congestive Heart Failure Study (INTER-CHF) included consecutive patients with a clinical diagnosis of heart failure from outpatient clinics and inpatient hospital wards at participating centres in India ($n = 858$), China ($n = 991$) and South-East Asia (defined as Malaysia, and the Philippines, $n = 811$), as well as patients in Africa ($n = 1294$), Latin America ($n = 869$), and the Middle East ($n = 1000$).[14] The average age of patients in India, China, South-East Asia and Latin America, was 56, 66, 57 and 67 years, respectively. However, the proportion of patients with heart failure with preserved ejection fraction (HFpEF) in these countries/regions varied considerably (47%, 63%, 61% and 47%, respectively), which is important for interpretation of age as patients with HFpEF are generally older than patients with HFrEF (and we studied only patients with HFrEF).[15] Despite this, the age of patients in all these countries/regions were similar in the two studies, except for China (patients in INTER-CHF in China were older than in our study). The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry enrolled symptomatic HFrEF in- or outpatients (with at least one episode of decompensated heart failure in the previous 6 months that resulted in a hospital admission or was treated in an outpatient clinic) at 46 medical centres in 11 Asian countries/territories: China ($n = 477$)/Hong Kong ($n = 50$), India ($n = 1436$), Indonesia ($n = 290$), Japan ($n = 540$), Korea ($n = 317$), Malaysia ($n = 541$), Philippines ($n = 91$), Singapore ($n = 1066$), Taiwan ($n = 274$), and Thailand ($n = 194$). The mean age in these countries was 57.0/67.7, 57.8, 55.8, 64.9, 63.3, 57.4, 54.3, 60.7, 63.3, and 60.0 years, respectively.[8] This age profile and ranking within Asian countries was very similar to what we found in our analysis. Genetic differences, stage of epidemiological transition, environmental factors, foetal programming, socioeconomic status and other factors are thought to account for the increasing prevalence and early development of cardiovascular disease in low and middle-income countries. South Asians may be especially prone to the premature development of cardiovascular diseases because of their high frequency of insulin resistance, in part related to pattern of fat distribution (abdominal obesity).[16–18] Atrial fibrillation was generally less frequent in Asian countries, especially India, possibly because it is a particularly age-related condition, or potentially because of ethnic or genetic differences.[19,20] The particularly low prevalence of atrial fibrillation in India (2.5% in our study) does not reflect ascertainment bias (as it was based on electrocardiographic analysis) and was also found in the ASIAN-HF registry (4.2%; frequency of atrial fibrillation was not reported in INTER-CHF).[8] Conversely, India and the Philippines differed from other Asian countries in their high prevalence of diabetes (but not higher BMI) whereas the Philippines and Taiwan had a higher prevalence of hypertension (but not a higher blood pressure) than other Asian countries.

LVEF varied little among Asian countries or between Asia and elsewhere whereas NT-proBNP varied much more, with several Asian countries (Japan and Korea and, to a lesser extent, India and Taiwan) having notably lower median concentrations than elsewhere which in some of these countries may be attributed to younger age, lower prevalence of atrial fibrillation and better renal function.[18,21] This did not seem to be explained by difference in LVEF or NYHA class distribution and we know of no other obvious explanation. Unfortunately, neither the ASIAN-HF registry nor INTER-CHF reported NT-proBNP.[8,14]

Patients in Asian countries generally had a higher heart rate than in Western Europe and North America and this was not readily explicable by either prevalence of atrial fibrillation or rate of beta-blocker treatment, although beta-blocker dosing may be lower in Asian countries. Heart rate was not recorded in INTER-CHF and, although the ASIAN-HF registry does not provide a direct comparison with other regions, heart rate was generally higher than in similar studies from elsewhere.[8,14]

Interestingly, peripheral oedema was reported less frequently in Asian patients and this was not obviously explained by differences in diuretic therapy but could relate to climatic conditions or MRA therapy, the use of which was higher in China and the

Table 4 Cardiovascular outcomes of interest according to country in Asia and in non-Asian regions

	Western Europe (*n* = 3521, 26.7%)	Central/ Eastern Europe/ Russia (*n* = 4758, 36.1%)	North America (*n* = 613, 4.7%)	Latin America (*n* = 1110, 8.4%)	China (*n* = 833, 6.3%)	India (*n* = 1390, 10.6%)	Japan (*n* = 209, 1.6%)	Korea (*n* = 223, 1.7%)	Philippines (*n* = 223, 1.7%)	Taiwan (*n* = 199, 1.5%)	Thailand (*n* = 95, 0.7%)
Primary outcome											
Events, *n* (%)	949 (27.0)	1371 (28.8)	181 (29.5)	317 (28.6)	290 (34.8)	356 (25.6)	69 (33.0)	59 (26.5)	51 (22.9)	88 (44.2)	31 (32.6)
Events per 100 patient-years (95% CI)	10.4 (9.7–11.0)	12.3(11.7–3.0)	12.8 (11.0–4.8)	12.6 (11.3–4.0)	14.9 (13.3–6.8)	10.4 (9.4–11.6)	10.4 (8.2–13.2)	9.1 (7.0–11.7)	11.5 (8.8–15.2)	17.2 (14.0–21.2)	13.8 (9.7–19.6)
Unadjusted HR	1.00 (ref)	1.19 (1.09–1.29)	1.24 (1.06–1.46)	1.18 (1.04–1.34)	1.44 (1.26–1.64)	1.01 (0.89–1.14)	1.02 (0.79–1.30)	0.90 (0.69–1.17)	1.13 (0.85–1.50)	1.67 (1.34– 2.08)	1.30 (0.91–1.85)
Adjusted HR*	1.00 (ref)	1.20 (1.10–1.32)	1.09 (0.92–1.28)	1.38 (1.21–1.57)	1.76 (1.52–2.02)	1.13 (0.97–1.30)	1.24 (0.97–1.58)	1.12 (0.85–1.46)	1.28 (0.95–1.74)	1.86 (1.50–2.30)	1.51 (1.05–2.18)
Heart failure hospitalization											
Events, *n* (%)	643 (18.3)	740 (15.6)	137 (22.3)	159 (14.3)	193 (23.2)	113 (8.1)	51 (24.4)	36 (16.1)	20 (9.0)	67 (33.7)	23 (24.2)
Events per 100 patient-years (95% CI)	7.0 (6.5– 7.6)	6.7 (6.2–7.1)	9.7 (8.2–11.4)	6.3 (5.4–7.4)	9.9 (8.6–11.5)	3.3 (2.8–4.0)	7.7 (5.9–10.2)	5.5 (4.0–7.7)	4.5 (2.9–7.0)	13.1 (10.3–6.7)	10.2 (6.8–15.4)
Unadjusted HR	1.00 (ref)	0.90 (0.81–1.00)	1.36 (1.13–1.63)	0.82 (0.69–0.98)	1.35 (1.15–1.58)	0.44 (0.36–0.54)	1.16 (0.87–1.54)	0.82 (0.59–1.14)	0.58 (0.37–0.92)	1.88 (1.46–2.42)	1.40 (0.93–2.12)
Adjusted HR*	1.00 (ref)	0.91 (0.81–1.02)	1.14 (0.94–1.38)	0.93 (0.78–1.11)	1.65 (1.38–1.96)	0.51 (0.41–0.66)	1.45 (1.09–1.94)	1.01 (0.71–1.42)	0.64 (0.40–1.03)	1.94 (1.47–2.56)	1.63 (1.06–2.49)
CV death											
Events, *n* (%)	537 (15.3)	899 (18.9)	98 (16.0)	238 (21.4)	180 (21.6)	299 (21.5)	29 (13.9)	39 (17.5)	42 (18.8)	47 (23.6)	21 (22.1)
Events per 100 patient-years (95% CI)	5.4 (4.9-5.8)	7.4 (7.0–7.9)	6.2 (5.1–7.5)	8.8 (7.7–10.0)	8.2 (7.1–9.5)	8.5 (7.5–9.5)	3.8 (2.6–5.4)	5.5 (4.0–7.5)	9.0 (6.7–12.2)	7.7 (5.8–10.3)	8.6 (5.6–13.1)
Unadjusted HR	1.00 (ref)	1.42 (1.2–1.58)	1.20 (0.97–1.48)	1.62 (1.39–1.89)	1.56 (1.32- 1.84)	1.61 (1.39–1.85)	0.68 (0.46–0.98)	1.03 (0.75–1.42)	1.87 (1.36–2.57)	1.42 (1.06–1.92)	1.60 (1.04–2.46)
Adjusted HR*	1.00 (ref)	1.48 (1.32–1.66)	1.08 (0.87–1.34)	1.96 (1.68–2.29)	1.89 (1.58–2.27)	1.76 (1.49–2.09)	0.77 (0.53–1.12)	1.27 (0.92–1.78)	2.14 (1.52–3.00)	1.57 (1.17–2.10)	1.87 (1.18–2.96)
All-cause death											
Events, *n* (%)	717 (20.4)	1065 (22.4)	131 (21.4)	297 (26.8)	192 (23.0)	317 (22.8)	35 (16.7)	41 (18.4)	48 (21.5)	57 (28.6)	24 (25.3)
Events per 100 patient-years (95% CI)	7.1 (6.6–7.7)	8.8 (8.3–9.4)	8.2 (6.9–9.8)	10.9 (9.8–12.3)	8.8 (7.6–10.1)	9.0 (8.0–10.0)	4.6 (3.3–6.3)	5.8 (4.2–7.8)	10.3 (7.8–13.7)	9.4 (7.2–12.2)	9.8 (6.6–14.6)
Unadjusted HR+	1.00 (ref)	1.25 (1.14–1.38)	1.19 (0.99–1.44)	1.55 (1.35–1.77)	1.23 (1.05–1.44)	1.26 (1.10–1.44)	0.61 (0.43–0.85)	0.79 (0.58–1.08)	1.55 (1.16–2.08)	1.30 (0.99–1.70)	1.37 (0.92–2.06)
Adjusted HR*+	1.00 (ref)	1.32 (1.19–1.46)	1.11 (0.92–1.35)	1.89 (1.64–2.18)	1.51 (1.27–1.79)	1.41 (1.21–1.64)	0.68 (0.48–0.96)	0.98 (0.71–1.36)	1.80 (1.33–2.44)	1.41 (1.07–1.85)	1.63 (1.07–2.48)

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Both models adjusted for treatment and region at baseline.

HR denotes sub-distribution HR with 95% CI within brackets, except where + denotes HR.

*Adjusted for randomized treatment, age, sex, heart rate, systolic blood pressure, body mass index, left ventricular ejection fraction, New York Heart Association class, N-terminal pro brain natriuretic peptide and estimated glomerular filtration rate.

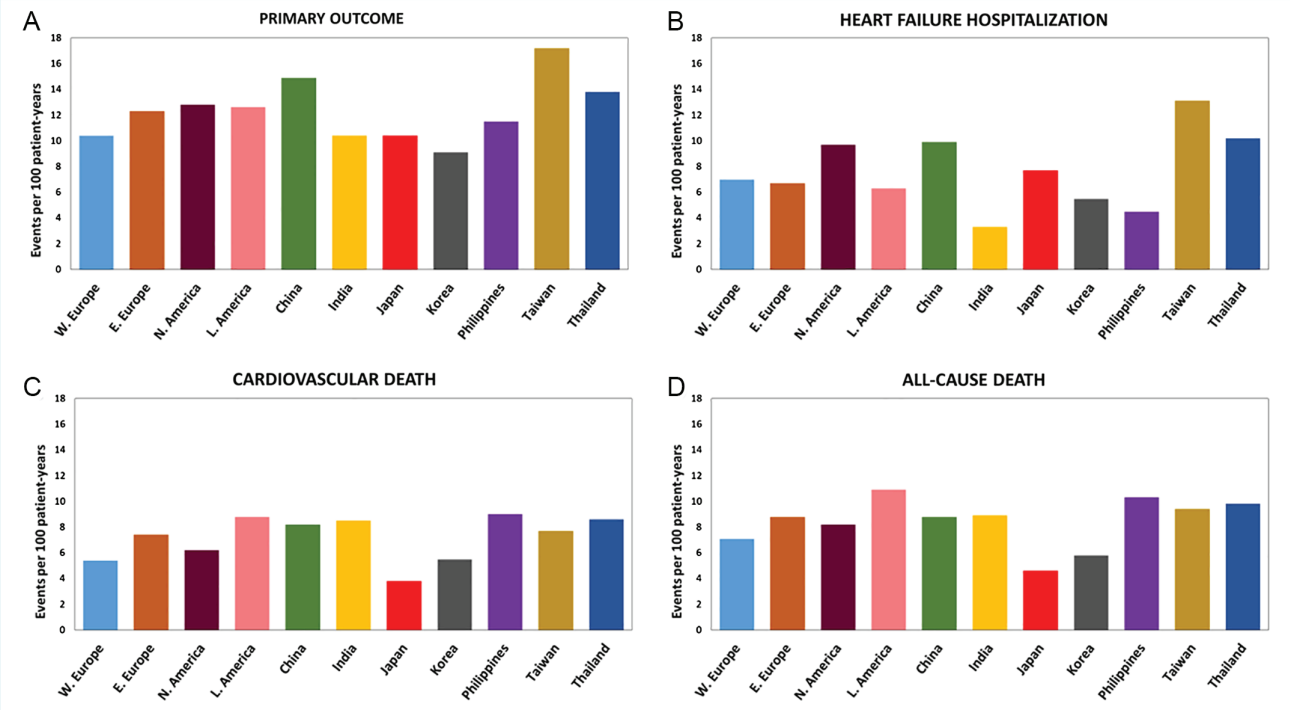

Figure 1 Cardiovascular outcomes of interest, shown as rates per 100 patient-years (unadjusted). (*A*) Primary composite outcome (cardiovascular death or heart failure hospitalization). (*B*) Heart failure hospitalization. (*C*) Cardiovascular death. (*D*) All-cause death.

Philippines than in any other Asian country and higher than in any other region, except Latin America (which also reported a low prevalence of oedema). The strikingly low use of diuretics found in the Philippines in the present study was supported by both the ASIAN-HF registry and INTER-CHF. The high use of MRAs in China (and the Philippines in the ASIAN-HF registry) was also confirmed by each of these studies (and high use in Latin America too by INTER-CHF).[8,14] In China, this may be related to national programmes to promote the use of spironolactone.[22]

There were other notable differences in treatment patterns, with some Asian countries reporting much higher use of digoxin than others (and elsewhere), despite a low prevalence of atrial fibrillation. Digoxin use was not reported in the ASIAN-HF registry and was difficult to interpret in INTER-CHF given the mix of patients with HFrEF and HFpEF. However, low use of anticoagulants in India and China corroborated the low prevalence of atrial fibrillation in the two countries (neither ASIAN-HF nor INTER-CHF reported use of anticoagulants). Device use was uniformly low in Asia (as in Eastern Europe and Latin America), with only Japan reporting above 10% use, likely reflecting economic considerations as much as clinical ones. Device use was not reported in INTER-CHF and was generally low in the ASIAN-HF registry, with the exception of Japan.[8,14]

Appropriate versions of the KCCQ were available for four of the seven Asian countries we studied (India, China, Japan and Philippines). In one previous study, Indians had a higher mean overall summary score (64.8) compared with Chinese who lived in a number of Asian countries (mean score 60.1) and Japanese and Koreans (reported as a single group) had the highest score (67.3).[23] While we found the highest median KCCQ clinical summary score in patients enrolled in Japan, we found a reverse ranking for patients in India and China compared with this prior study. Clearly, there is a huge gap in our knowledge of patient reported outcomes in different parts of Asia and compared with the rest of the world.

A particular strength of the present study is the availability of information on long-term fatal and non-fatal outcomes. Here the differences within Asia and between Asia and elsewhere were stark. For example, the highest and lowest heart failure hospitalization rates, globally, were found in Asian countries (Taiwan and India, respectively). We know of no previous comparison of heart failure hospitalization rates in ambulatory HFrEF patients in Asia (and between Asia and elsewhere).

The low rate of hospitalization in India was especially striking, being a third to half that in Europe and North America and about a quarter of the rate in Taiwan. This was not explained by a particularly high competing risk of death. Younger age, shorter duration of heart failure and a higher KCCQ score (better quality of life) may be relevant, as well as differences in access to, or utilization of, hospital care in some countries (such as India). This clearly has implications for clinical trials using heart failure hospitalization as part of a composite outcome.

Conversely, the high hospitalization rates in other Asian countries were not explained by a lower risk of death. In fact, Asian countries generally had high mortality rates with two notable exceptions, namely Japan and Korea, which had the lowest and second lowest mortality rates globally. These low rates reflect

the known long life expectancy in these two countries, especially Japan.[24] It is of interest to compare our findings in relation to mortality with other studies which included patients from Asia. The only study to do this that we know of was INTER-CHF, which included consecutive patients with a clinical diagnosis of heart failure from outpatient clinics and inpatient hospital wards at participating centres in India ($n = 858$), China ($n = 991$) and South-East Asia ($n = 811$).[14] The 1-year mortality was 23.3% in India, 7.3% in China and 15.0% in South-East Asia (non-fatal outcomes were not collected). However, the proportions of patients enrolled as an in-patient (i.e. at higher risk of death) differed considerably (45%, 35%, and 23%, respectively) as did the proportion of patients with HFrEF (53%, 27%, and 39%, respectively). Clearly, these differences make comparison with our dataset impossible but highlight the need for better understanding of mortality and morbidity rates in Asia.

Our study has a number of strengths and weaknesses. Comparison of countries within Asia (and comparing countries in Asia with other regions) is extremely complex, reflecting many influences including geography, climate and other environmental factors, diet and lifestyle, type of health care system, race/ethnicity, cultural influences, genetics and economic considerations. Using information from clinical trials also has disadvantages and advantages. Patients in trials are selected and not necessarily representative of patients in the population in general, especially those living in non-urban areas with inadequate access to health facilities. Compared to epidemiological studies, however, the common inclusion and exclusion criteria used in trials result in a more homogeneous study population, overall. This allows a more 'like-with-like' comparison between countries. This difference from epidemiological studies is highlighted by the mix of inpatients and outpatients and patients with HFrEF and HFpEF in INTER-CHF.[14] Patients in trials are usually characterized in more detail than in epidemiological studies as illustrated here by measurement of NT-proBNP, for example. Event ascertainment in trials is also vigorous and consistent across countries. However, our study has other limitations, including the absence of information on patients from other key regions, namely Africa and the Middle East.

In summary, although patient characteristics and outcomes vary markedly between Asia and other global regions there are equally striking variations among Asian countries (e.g. the highest and lowest heart failure hospitalization rates, globally, were found in Asian countries). These findings highlight the need to better understand the explanations for the differences in mortality and morbidity rates across Asia and have implications for the globalization of clinical trials.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cardiovascular outcomes of interest according to country in Asia and in non-Asian regions with additional adjustment for variables from Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score.

Appendix S1. List of PARADIGM-HF and ATMOSPHERE Principal Investigators.

Conflict of interest: none declared.

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