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Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study

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Summary

Background Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), β blockers, and mineralocorticoid receptor antagonists (MRAs) are of proven benefit and are recommended by guidelines for management of patients with heart failure and reduced ejection fraction (HFrEF). We aimed to examine the first prospective multinational data from Asia on prescribing patterns of guideline-directed medical therapies and analyse its effect on outcomes.

Methods In the prospective multinational ASIAN-HF registry (with enrolment from 46 centres in 11 countries in Asia), we enrolled patients aged 18 years or older, with symptomatic heart failure (stage C, with at least one episode of decompensated heart failure in the past 6 months that resulted in admission to hospital or was treated in an outpatient clinic) and left ventricular systolic dysfunction (ejection fraction ≤40% on baseline echocardiography, consistent with 2016 European Society of Cardiology guidelines). We excluded patients with heart failure caused by severe valvular heart disease, life-threatening comorbidity with a life expectancy of less than 1 year, who were unable or unwilling to give consent, or who had concurrent participation in a clinical trial. Patients were followed up for 3 years for the outcomes of death and cause-specific admittance to hospital. Primary outcomes were uptake of guideline-directed medical therapies (as proportions) by therapeutic class, achieved doses as proportions of guideline-recommended doses, and their association with 1-year composite outcome of all-cause death or admittance to hospital because of heart failure. This study is registered with ClinicalTrials.gov, number NCT01633398.

Findings Between Oct 1, 2012, and Dec 31, 2015, we enrolled 5276 patients with HFrEF (mean age 59·6 years [SD 13·2], 77% men, body-mass index 24·9 kg/m² [5·1], 33% New York Heart Association class III or IV). Follow-up data were available for 4544 (90%) of 5061 eligible patients taking medication for heart failure, with median follow-up of 417 days (IQR 214–735). ACE inhibitors or ARBs were prescribed to 3868 (77%) of 5005 patients, β blockers to 3975 (79%) of 5061, and MRAs to 2998 (58%) of 5205, with substantial regional variation. Guideline-recommended dose was achieved in only 17% of cases for ACE inhibitors or ARB, 13% for β blockers, and 29% for MRAs. Country (all three drug classes), increasing body-mass index (ACE inhibitors or ARBs and MRAs), and in-patient recruitment (ACE inhibitors or ARBs and β blockers) were associated with attainment of guideline-recommended dose (all p<0·05). When adjusted for indication bias, increasing drug doses, from low dose (1–<25% of guideline-recommended dose) upwards were associated with lower hazards of a 1-year composite outcome for ACE inhibitors or ARBs and β blockers compared with non-users. The lowest adjusted hazards were in the group that attained guideline-recommended doses above 50% (hazard ratio [HR] 0·54, 95% CI 0·50–0·58 for ACE inhibitors or ARBs [50–99·9%]; HR 0·47, 0·46–0·50 for β blockers, and HR 0·77, 0·72–0·81 for MRAs [≥100%]).

Interpretation Guideline-directed medical therapies at recommended doses are underutilised in patients with HFrEF. Improved uptake and uptitration of guideline-directed medical therapies are needed for better patient outcomes.

Introduction

Current evidence-based guidelines for best practice[1,2] recommend that patients should be treated to trial-directed doses for angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs) and β blockers, as first-line therapy, and mineralocorticoid receptor antagonists (MRAs), as second-line therapy, in the management of patients with heart failure with reduced ejection fraction (HFrEF). Despite this, many patients with heart failure either do not receive these

Research in context

Evidence before this study

We searched Medline and EMBASE from Jan 1, 1985 up to the start of ASIAN-HF (Oct 1, 2012) for relevant articles published in English on prescribing patterns and doses of evidence-based medications for heart failure with reduced ejection fraction (HFrEF) in Asia or Asians. Search terms were "heart failure" AND "medications" OR "therapy" AND "doses" OR "target dose" OR "up-titration" OR "titration" AND "Asians" OR "Asia". We did an additional search for each therapeutic class using "angiotensin-converting enzyme (ACE) inhibitors", "angiotensin receptor blockers (ARBs)", "beta-blockers", and "mineralocorticoid receptor antagonists (MRAs)" in place of "medications" or "therapy". We found no cohort studies on prescribing patterns and doses of guideline-directed medical therapy for heart failure across multinational regions within Asia. We found no such studies when we extended the search to March 31, 2017. The search showed a scarcity of evidence from Asia, with only ten relevant studies, which were mainly small, single-centre studies. There are few data on Asian ethnicities from randomised controlled trials. In the TRANSCEND and ONTARGET trials, Asians, despite having a lower body-mass index than non-Asians, tolerated both telmisartan (80 mg/day) and ramipril (10 mg/day) better than did non-Asians. Similarly, higher dose controlled-release carvedilol (40 mg/day), when compared with 20 mg/day immediate-release carvedilol, was safe and well tolerated in a separate small Japanese study. Studies have also showed that bisoprolol fumarate (even at half the targeted doses) and low dose (5 mg/day) carvedilol had beneficial effects in Asians with heart failure and left ventricular systolic dysfunction. A comparison study of the pharmacokinetics and pharmacodynamics of oral perindopril in normotensive Chinese and Caucasian volunteers showed that time to maximum concentration after 4 mg was administered was significantly shorter for the Chinese subgroups than it was for the Caucasian subgroups. Similarly, C_{max} and the area under the curve were increased after 4 mg was given to the Chinese participants, who had lower mean bodyweight than did the Caucasian participants.

Added value of this study

This study is the first prospective, multinational registry of real-world data on prescription patterns and doses attained of guideline-directed medical therapies in patients with HFrEF across most of Asia (11 regions). In the absence of such evidence in large multinational Asian populations, the current analysis represents the best available evidence for clinicians treating HFrEF in Asia. We acknowledge causality, including drug efficacy, cannot be established from observational studies, which require evidence from randomised controlled trials for definitive answers.

Implications of all the available evidence

There is striking regional variation in the patterns of prescription and dosage of ACE inhibitors or ARBs, β blockers and MRAs for HFrEF across Asia. Gaps in the administration of guideline-directed medical therapy were monotherapy (only ACE inhibitors, ARB, or β blocker prescribed instead of combined therapy) and widespread underdosing. The scientific literature increasingly points to an earlier onset of heart failure in Asian than in western populations. With pharmacotherapy being the mainstay in the management of heart failure, our findings have major implications for clinicians, health policy makers, and health-care providers, and support active advocacy for the conscientious initiation and uptitration of evidence-based medications to improve the outcomes of patients in Asia with HFrEF.

guideline-directed medical therapies or receive doses considerably below the guideline-recommended doses.[3–5] A pan-European study reported that there was widespread underdosing of ACE inhibitors or ARBs and β blockers despite encouraged uptitration. Undertreatment with doses that are less than 50% of guideline-recommended dose for ACE inhibitors or ARBs and β blockers is associated with poorer prognosis.[6,7]

In Asia, rapidly ageing demographics and the increasing prevalence of cardiovascular diseases and metabolic disorders are driving an epidemic of heart failure.[8] Adding to the complexities of the heterogeneous populations, emerging data suggests heightened sensitivity to, and pharmacokinetic variability of, cardiovascular drugs in patients from Asia.[9–12] This background, together with smaller body size and weight, explains why prescribed doses are lower for Asians than they are for their western counterparts.[9,13–15] Prospective multinational data from Asia on prescribing patterns of guideline-directed medical therapy and association of doses with outcomes have, thus far, been scarce. We studied prescribing patterns of evidence-based heart failure pharmacotherapy and their association with clinical outcomes in a population with heart failure from a large region in Asia.

Methods

Study design and participants

The ASIAN-HF registry, as previously described,[16,17] is a contemporary prospective multinational registry of patients in Asia aged 18 years or older, with symptomatic heart failure (stage C, with at least one episode of decompensated heart failure in the past 6 months that resulted in admission to hospital or was treated in an outpatient clinic) and left ventricular systolic dysfunction (ejection fraction ≤40% on baseline echocardiography, consistent with 2016 European Society of Cardiology guidelines[1]). We excluded patients with heart failure caused by severe valvular heart disease, life-threatening comorbidity with life expectancy of less than 1 year, who were unable or unwilling to give consent, or who had concurrent participation in a clinical trial. Patients who met eligibility criteria and provided informed consent were enrolled from 11 countries in Asia (South Korea, Japan, Taiwan, Hong Kong, China, India, Thailand,

Malaysia, Philippines, Indonesia, and Singapore) at different stages of economic development.

We recruited participants between Oct 1, 2012, and Dec 31, 2015. At investigation sites (46 in total with >220 investigators), which included medical, cardiology, and specialty heart failure units, patients with acute heart failure were admitted and patients with chronic heart failure were followed up as outpatients. Sites in ASIAN-HF were selected on the basis of the size of the country, geographical location of the site within the country, patient population served, heart failure patient volume, and availability of expertise in echocardiography.[17] We included a mix of private and public hospitals and tertiary, university, and specialist cardiovascular hospitals in capital cities and provincial cities (appendix).

Consecutive patients at each site were screened to determine eligibility based on inclusion and exclusion criteria.[17] Screening logs were encouraged but were not available from all sites. Every effort was made to ensure protocol standardisation and adherence, including translation of languages specific to each region, on-site investigator training, regular monitoring (both in-person and remote), and centralised database management.

Ethics approvals were obtained from the local institutional review committee of each participating centre and all participants gave informed consent. The establishment of the registry and this study conform to the ethical guidelines in the Declaration of Helsinki.

Data collection and medications

Demographic and clinical data were collected at baseline, including socioeconomic status, clinical signs and symptoms, functional status, date of diagnosis with heart failure, duration of heart failure, prior cardiovascular procedures or investigations, clinical and lifestyle risk factors, medical history, comorbidities, quality of life, blood chemistry, standard 12-lead ECG, and transthoracic echocardiography. Patients were followed up for 3 years for the outcomes of death and cause-specific admittance to hospital. Causes of death or admittance to hospital were adjudicated by a central event adjudication committee using prespecified criteria.

Case report forms included a complete record of all concomitant medications, dosage patterns, maximum doses achieved (yes or no, based on assessment by investigators), reasons if not achieved (eg, side-effects or intolerance, still uptitrating, cost, and other, with a text field). Medications were identified by therapeutic class, including ACE inhibitors, ARBs, β blockers, MRAs (appendix), and others (digoxin, ivabradine, and loop and thiazide diuretics). Data on patients' medication were collected at baseline and throughout the follow-up period, including changes in drugs and doses. Maximum total daily doses attained during follow-up were calculated as a percentage of the guideline-recommended doses for daily maintenance of the individual heart failure medications (appendix). Doses were grouped into

categories (0%, 1–24%, 25–49%, 50–99%, and ≥100%) on the basis of similar proportions in each of these categories and the predominance of doses that are less than 50% of the guideline-recommended doses.

Outcomes

Primary outcomes were uptake (as proportions) by therapeutic class, achieved doses as a proportion of guideline-recommended dose, and their association with 1-year composite outcome of all-cause death or admittance to hospital because of heart failure. 1-year all-cause mortality, cardiovascular-related deaths, and admittance to hospital because of heart failure were secondary outcomes.

Statistical analysis

We analysed data from each of the five groups (separated by percentage of guideline-recommended dose) using standard descriptive statistics including, as appropriate, mean plus standard deviation and median plus interquartile ranges or numbers and proportions. We tested differences between groups using the Kruskal-Wallis test (for continuous variables) or the χ^2 test (for categorical variables), and the Cochran-Armitage test for linear trends across the ordinal categories of percentage of guideline-recommended dose.

To correct for treatment indication bias in outcome analysis, all analyses for the effects of successful uptitration of ACE inhibitors or ARB, β blockers, and MRAs were inversely weighted for the probability of receiving the given treatment. We defined successful uptitration as the achievement of at least 100% of the dose recommended by the European Society of Cardiology.[1] We modelled the probability of achieving uptitration for a particular treatment in a given patient by logistic regression using lasso penalisation to obtain parsimonious logistic models comprising a few predictor variables derived from an initial comprehensive list of 29 clinical variables (appendix). To find the optimal lambda in our lasso regression, we performed ten cross validations to increase robustness.[18,19]

We imputed missing data via random forest regression models in the MICE package using the R statistical program (version 3.2.4).[20] Five imputed datasets were created. We did 10-fold cross validation to ensure optimal penalty parameters and used all analyses for each imputed dataset. Final probability weights were calculated by the mean per patient across imputation sets. We used multivariable Cox regression models to examine the association of percentage of guideline-recommended dose prescribed (0%, 1–24%, 25–49%, 50–99%, ≥100%) by therapeutic class with a 1-year composite outcome of all-cause mortality or admittance to hospital because of heart failure, with 0% (non-users) as the reference. We also analysed the interaction of dose categories by medication class and geographical blocs (northeast, south, and southeast Asia) with a composite outcome. We checked the proportionality hazards assumption for Cox models
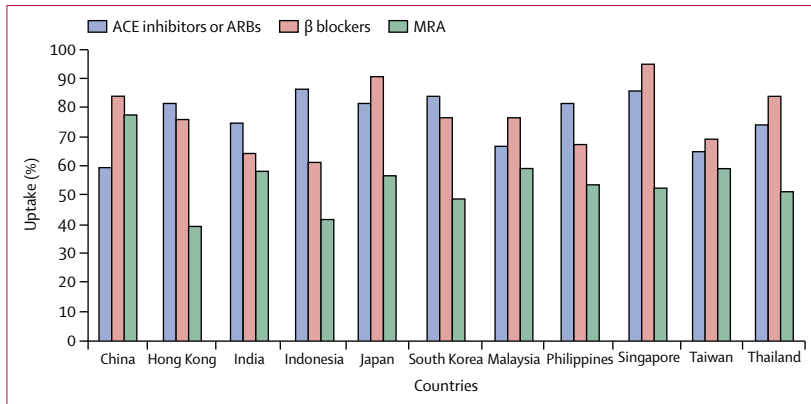
Figure 1: Regional variation in uptake
ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blockers. MRA=mineralocorticoid receptor antagonists.

using statistical tests and graphical diagnostics on the basis of the Schoenfeld residuals. The Cox multivariable and logistic regression models were restricted to the same set of reduced variables, with a minimum of ten events for each variable in the model.[21,22]

Since hypotension, bradycardia, and renal dysfunction often restrict the achievement of guideline-recommended dose in clinical practice,[1] we did a subgroup analysis (with or without hypotension [defined as systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg], bradycardia [defined as heart rate <60 bpm], and renal disease) to examine usage and dosage patterns of ACE inhibitors or ARBs, β blockers, and MRAs.

We did sensitivity analyses using 100% guideline-recommended dose as a reference, and did additional tests confined to data from patients recruited as outpatients and assessed associations between achievement of guideline-directed medical therapies doses and the combined outcome of all-cause mortality and admittance to hospital because of heart failure. Multiple imputation might introduce bias depending on the model.[23] Although multiple chained equations provide for an effective tool to account for missing data, bias cannot be excluded. Therefore, we did additional sensitivity analyses, in which we analysed our non-imputed data separately, to account for this potential bias.

We used Stata version 14 (Stata Corp, College Station, TX, USA) and R statistical program (version 3.2.4) for all statistical analyses. All p values are two-sided, with a 5% significance level.

Role of the funding source
The funders of the study had no role in study design, site selection, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

Results
Between Oct 1, 2012, and Dec 31, 2015, we enrolled 5276 patients with HFrEF (mean age 59·6 years [SD 13·2], 77% men). The mean left ventricular ejection fraction (LVEF) was 27% (7), 33% were New York Heart Association (NYHA) class III or IV, and mean BMI was 24·9 kg/m² [5·1]). 5061 (96%) of 5276 were prescribed at least one class of guideline-directed medical therapies. ACE inhibitors or ARBs were prescribed to 3868 (77%) of 5005 patients, β blockers to 3975 (79%) of 5061, and MRAs to 2998 (58%) of 5205, digoxin to 1464 (31%) of 4763, ivabradine to 447 (10%) of 4585, and loop and thiazide diuretics to 4221 (83%) of 5067.

China had the lowest uptake for ACE inhibitors or ARBs (286 [60%] of 477), but had the highest uptake for MRAs (372 [78%] of 477; figure 1). Indonesia had the highest uptake for ACE inhibitors or ARBs (236 [87%] of 272) and the lowest uptake of β blockers (167 [61%] of 272). The guideline-recommended combination of ACE inhibitors or ARB and β blockers was prescribed in only 2914 (55%) of the overall ASIAN-HF cohort (5276). The high-income countries—for example, Singapore (757 [71%] of 1066), Hong Kong (35 [70%] of 50), Korea (207 [65%] of 317), and Japan (340 [63%] of 540), but not Taiwan (127 [46%] of 274)—were more likely to prescribe the dual first-line medications than were lower income countries (p<0·001). In China, however, 317 (66%) of 477 patients received the combination therapy of β blockers with MRA.

Only 127 (2%) of the cohort (5276) had hypotension and 324 (6%) had bradycardia; 442 (11%) of 4187 patients with measurements of serum creatinine or estimated glomerular filtration rate (eGFR) at baseline had severe renal dysfunction (including renal failure). The difference in the proportions of participants achieving the guideline-recommended doses for ACE inhibitors or ARB or β blockers was not significant in patients with hypotension (vs no hypotension, p=0·834 for ACE inhibitors or ARBs; p=0·830 for β blockers) or bradycardia (vs no bradycardia, p=0·380 for ACE inhibitors or ARBs; p=0·224 for β blockers), probably because of the small numbers of patients. However, patients with severe chronic kidney disease (eGFR <30 mL/min per 1·73 m²) and renal failure (eGFR <15 mL/min per 1·73 m²) had reduced uptake of ACE inhibitors or ARBs and MRAs (both p<0·001). For β blockers, only those with renal failure had decreased uptake. In general, as expected, fewer patients with severe chronic kidney disease or renal failure achieved the guideline-recommended dose than did those with less severe disease.

Considerable underdosing of ACE inhibitors or ARBs, β blockers, and MRA was observed (figure 2). Recommended doses of ACE inhibitors or ARBs were reached in only 17% of patients, compared with 13% for β blockers, and 29% for MRAs. Reasons given for not achieving the guideline-recommended dose included already at maximum tolerated dose (2414 [57%] of 4231 patients), still considering uptitration (986 [23%]), and

side-effects or intolerance (831 [20%]). Cost was not reported as a reason for not achieving the guideline-recommended dose. In those whom the maximum tolerated dose was achieved, the median doses against the guideline-recommended dose were 50% (IQR 25–100%) for ACE inhibitors, 33% (IQR 25–50%) for ARBs, 25% (13–50%) for β blockers, and 80% (50–100%) for MRA. The median doses against the guideline-recommended dose for ACE inhibitor and MRA were comparatively higher than that in the overall cohort.

Patient characteristics, stratified by dose, are given in the table. Country (all three drug classes), increasing body-mass index (ACE inhibitors or ARBs and MRAs), and in-patient recruitment (ACE inhibitors or ARBs) were associated with attainment of guideline-recommended dose (all p<0·05; appendix). Other independent factors associated with attainment of 100% guideline-recommended dose by therapeutic class are summarised in the appendix.

The most commonly prescribed ACE inhibitors were enalapril (716 [30%] of 2422 patients on ACE inhibitors), perindopril (691 [29%]), and ramipril (687 [28%]), accounting for 57% (2094 of 3653) of all evidence-based ACE inhibitors or ARB used. Losartan potassium (429 [32%] of 1349 patients on ARBs), valsartan (425 [32%]), and candesartan cilexetil (300 [22%]) were the most commonly prescribed ARBs, accounting for 32% (1154 of 3653) of all ACE inhibitors or ARBs prescribed. Figure 2A shows the mean achieved doses (as a percentage of guideline-recommended dose) of ACE inhibitors or ARBs by country. The median prescribed dose was 33% (IQR 16–50%) of the guideline-recommended dose. Among the 11 countries, prescribed doses for ACE inhibitors or ARBs were highest in South Korea (87 [28%] of 312 people achieved guideline-recommended dose) and Indonesia (72 [28%] of 254; figure 2A). By contrast, prescribed doses were lowest in China (9 [2%] of 473), Thailand (6 [4%] of 166), and Japan (25 [5%] of 529; figure 2A). A full guideline-recommended dose of ACE inhibitors or ARBs was less common in older in-patients with longer length of stay, those with severe chronic kidney disease and atrial fibrillation (p$_{trend}$<0·001; table), and those in NYHA classes III and IV (data not shown).

Carvedilol (37%), bisoprolol fumarate (30%), and metoprolol (11%) were the most commonly prescribed β blockers. The median prescribed dose was 25% (IQR 13–50%) of the guideline-recommended dose, with 65% of patients being prescribed doses that were less than 50% of guideline-recommended doses. There was regional variation in mean doses of β blocker (figure 2B), with the highest doses in Malaysia and Thailand. Japan had high uptake (91%) of β blockers (figure 1) but had the lowest achieved doses (figure 2B), with 41% of patients receiving less than 25% of the guideline-recommended dose. Despite low doses of β blockers, mean heart rate was lowest in patients from Japan (72·6 beats per min [SD 14·1]); as expected, heart rates in
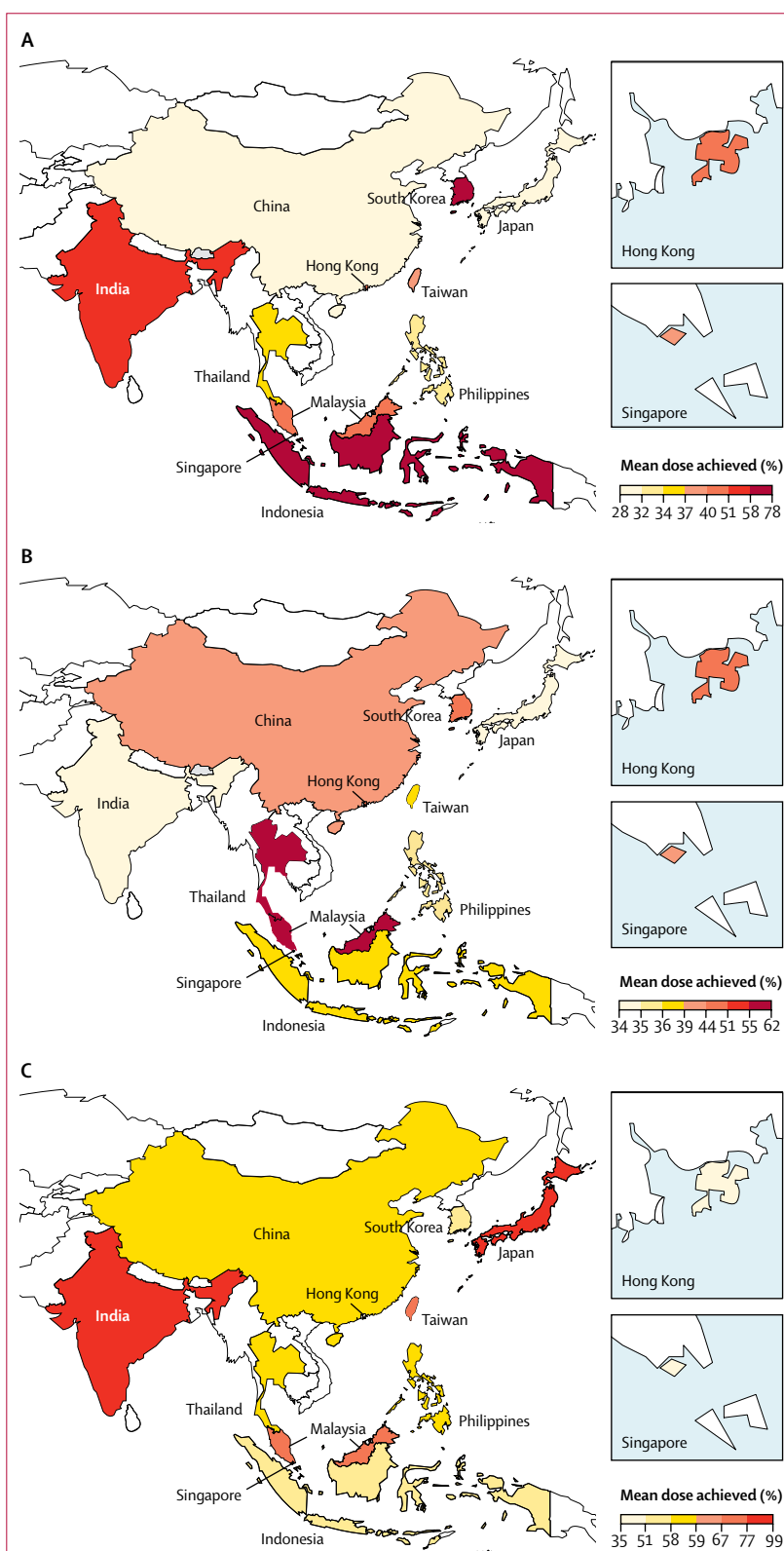

Figure 2: **Mean doses achieved by region**
(A) Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. (B) β blockers. (C) Mineralocorticoid receptor antagonists. Achieved doses were calculated as a percentage of the dose recommended by guidelines.

	Observations available, n	Percentage achieved of guideline-recommended dose					p value	p trend
		0	1–24%	25–49%	50–99%	≥100%		
Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists								
Number of participants	5005	1418	911	1074	992	610	..	..
Median age, years (IQR)	4991	62 (54–71)	60 (52–68)	60 (50–68)	59 (51–66)	60 (51–66)	<0·001	<0·001
Female sex	5005	333 (23%)	192 (21%)	227 (21%)	209 (21%)	134 (22%)	0·523	0·233
Median body-mass index, kg/m² (IQR)	4799	23·8 (21·1–26·7)	23·7 (21·2–26·7)	24·2 (21·7–27·2)	25·0 (22·1–28·2)	24·8 (22·3–28·2)	<0·001	<0·001
Median systolic blood pressure, mm Hg (IQR)	4983	117 (104–130)	110 (100–123)	116 (103–130)	120 (109–130)	120 (109–130)	<0·001	<0·001
Median diastolic blood pressure, mm Hg (IQR)	4983	70 (63–80)	69 (60–78)	70 (63–80)	72 (67–80)	73 (65–81)	<0·001	<0·001
Median heart rate, beats per min (IQR)	4979	78 (68–89)	76 (68–87)	78 (70–88)	78 (70–89)	78 (69–89)	0·016	0·096
Median LVEF, % (IQR)	5005	29% (23–34)	26% (20–33)	28% (22–33)	27% (22–33)	27% (22–32)	<0·001	0·592
Ischemic cause of heart failure, n (%)	5000	660 (47%)	422 (46%)	511 (48%)	461 (47%)	270 (44%)	0·034	0·016
Enrolment type (in-patient status), n (%)	5004	819 (58%)	434 (48%)	418 (39%)	323 (33%)	174 (29%)	<0·001	<0·001
Median length of stay, days (IQR)	2151	8·0 (4·0–14·0)	6·0 (3·0–14·0)	6·0 (3·0–11·0)	5·0 (3·0–10·0)	6·0 (3·0–11·0)	<0·001	0·109
Medical history, n (%)								
Coronary artery disease	4998	752 (53%)	456 (50%)	539 (50%)	476 (48%)	287 (47%)	0·073	0·005
Atrial fibrillation or flutter	4998	299 (21%)	229 (25%)	174 (16%)	123 (12%)	76 (12%)	<0·001	<0·001
Hypertension	4997	785 (55%)	417 (46%)	524 (49%)	511 (52%)	341 (56%)	<0·001	0·780
Peripheral arterial or vascular disease	4996	59 (4%)	46 (5%)	25 (2%)	28 (3%)	14 (2%)	0·002	0·002
Diabetes	4999	596 (42%)	339 (37%)	437 (41%)	400 (40%)	236 (39%)	0·200	0·362
Chronic kidney disease*	4004	676 (57%)	244 (40%)	263 (38%)	228 (36%)	158 (39%)	<0·001	<0·001
Chronic obstructive pulmonary disease	4997	144 (10%)	66 (7%)	94 (9%)	70 (7%)	39 (6%)	0·012	0·003
Current or ex-smoker	4996	606 (43%)	451 (50%)	503 (47%)	431 (43%)	260 (43%)	0·002	0·792
Sinus rhythm	4758	852 (60%)	564 (62%)	742 (70%)	714 (72%)	449 (74%)	<0·001	<0·001
Highest education level, n (%)								
No formal education/Primary	1296	386 (28%) of 1338	183 (28%) of 664	272 (30%) of 897	288 (33%) of 878	167 (29%) of 569	<0·001	<0·001
Secondary	1600	477 (36%) of 1338	224 (34%) of 664	348 (39%) of 897	321 (37%) of 878	230 (41%) of 569	..	..
Pre-university (polytechnic, equivalent)	609	235 (18%) of 1338	98 (14%) of 664	116 (13%) of 897	97 (11%) of 878	63 (11%) of 569	..	..
Degree or higher	841	240 (18%) of 1338	159 (24%) of 664	161 (18%) of 897	172 (20%) of 878	109 (19%) of 569	..	..
β blockers								
Number of participants	5061	1150	1325	1229	868	489	..	..
Median age, years (IQR)	5047	61 (53–71)	62 (53–70)	60 (51–68)	59 (51–67)	58 (49–66)	<0·001	<0·001
Female sex	5061	286 (25%)	312 (24%)	235 (19%)	180 (21%)	95 (19%)	0·003	0·001
Median body-mass index, kg/m² (IQR)	4852	23·8 (21·2–26·7)	23·7 (21·0–26·6)	24·3 (21·8–27·3)	24·9 (22·2–28·3)	25·1 (22·3–28·2)	<0·001	<0·001
Median systolic blood pressure, mm Hg (IQR)	5038	118 (102–130)	114 (102–129)	115 (105–130)	120 (106–131)	120 (107–133)	<0·001	<0·001
Median diastolic blood pressure, mm Hg (IQR)	5038	70 (64–80)	70 (71–80)	70 (62–80)	71 (65–80)	71 (64–80)	<0·001	<0·001
Median heart rate, beats per min (IQR)	5035	80 (70–94)	78 (69–88)	76 (68–87)	77 (68–86)	78 (69–87)	<0·001	<0·001
Median LVEF, % (IQR)	5061	29% (23–29)	28% (21–33)	27% (21–33)	27% (22–34)	28% (22–33)	<0·001	0·391
Ischemic cause of heart failure, n (%)	5056	544 (47%)	596 (45%)	605 (49%)	389 (45%)	229 (47%)	0·019	0·208
Enrolment type (in-patient status)	5060	555 (48%)	651 (49%)	491 (40%)	328 (38%)	164 (34%)	<0·001	<0·001
Median length of stay, days (IQR)	2171	7·0 (4·0–13·0)	7·0 (3·0–13·0)	6·0 (3·0–12·0)	6·5 (4·0–12·0)	6·0 (3·0–11·0)	0·088	0·564
Medical history, n (%)								
Coronary artery disease	5054	559 (49%)	654 (49%)	661 (54%)	419 (48%)	248 (51%)	0·062	0·311
Atrial fibrillation or flutter	5053	190 (17%)	234 (18%)	208 (17%)	175 (20%)	105 (22%)	0·045	0·011
Hypertension	5053	543 (47%)	655 (50%)	646 (53%)	476 (55%)	294 (60%)	<0·001	<0·001
Peripheral arterial or vascular disease	5052	28 (2%)	60 (5%)	41 (3%)	27 (3%)	19 (4%)	0·065	0·509

(Table continues on next page)

	Observations available, n	Percentage achieved of guideline-recommended dose					p value	p_{trend}
		0	1–24%	25–49%	50–99%	≥100%		
(Continued from previous page)								
Diabetes	5055	454 (39%)	484 (37%)	511 (42%)	357 (41%)	239 (49%)	<0·001	<0·001
Chronic kidney disease*	4051	436 (49%)	356 (39%)	358 (44%)	268 (44%)	169 (48%)	<0·001	0·800
Chronic obstructive pulmonary disease	5053	139 (12%)	99 (7%)	85 (7%)	55 (6%)	27 (6%)	<0·001	<0·001
Current or ex-smoker	5052	450 (39%)	604 (46%)	578 (47%)	398 (46%)	248 (51%)	<0·001	<0·001
Sinus rhythm	4808	744 (65%)	872 (66%)	838 (68%)	577 (66%)	325 (66%)	<0·001	<0·001
Highest education level, n (%)								
No formal education/primary	1315	383 (35%) of 1096	321 (29%) of 1114	273 (27%) of 1003	214 (28%) of 737	124 (28%) of 427	<0·001	0·031
Secondary	1612	379 (35%) of 1096	409 (37%) of 1114	406 (40%) of 1003	266 (35%) of 737	152 (36%) of 427	..	..
Pre-university (polytechnic, equivalent)	605	133 (12%) of 1096	159 (14%) of 1114	145 (14%) of 1003	102 (14%) of 737	66 (15%) of 427	..	..
Degree or higher	845	201 (18%) of 1096	225 (20%) of 1114	179 (18%) of 1003	155 (21%) of 737	85 (19%) of 427	..	..
Mineralocorticoid receptor antagonists								
Number of participants	5205	2279	156	813	1101	856	..	..
Median age, years (IQR)	5189	62 (54–71)	57 (52–64)	59 (51–68)	59 (51–67)	61 (52–69)	<0·001	<0·001
Female sex	5205	520 (23%)	26 (17%)	149 (18%)	248 (23%)	200 (23%)	0·027	0·004
Median body-mass index, kg/m² (IQR)	4935	24·1 (21·6–27·3)	25·2 (22·6–28·3)	24·1 (21·3–27·0)	24·3 (21·6–27·3)	24·2 (21·7–27·3)	<0·001	0·904
Median systolic blood pressure, mm Hg (IQR)	5143	120 (110–132)	117 (104–129)	114 (102–130)	115 (102–130)	119 (106–130)	<0·001	<0·001
Median diastolic blood pressure, mm Hg (IQR)	5143	71 (64–80)	70 (60–80)	70 (62–80)	70 (62–80)	70 (64–80)	<0·001	0·380
Median heart rate, beats per min (IQR)	5140	78 (69–88)	75 (67–86)	78 (68–89)	77 (68–88)	78 (70–88)	0·021	0·015
Median LVEF, % (IQR)	5205	29% (23–35)	25% (20–30)	27% (21–33)	27% (21–32)	27% (21–32)	<0·001	0·503
Ischemic cause of heart failure, n (%)	5161	1192 (53%)	94 (61%)	381 (47%)	495 (45%)	264 (31%)	<0·001	0·426
Enrolment type (in-patient status), n (%)	5203	1004 (44%)	88 (56%)	528 (65%)	395 (36%)	257 (30%)	<0·001	<0·001
Median length of stay, days (IQR)	2246	6·0 (3·0–12·0)	4·0 (3·0–7·0)	7·0 (4·0–13·0)	6·0 (3·0–12·0)	8·0 (4·0–14·0)	<0·001	<0·001
Medical history, n (%)								
Coronary artery disease	5160	1215 (54%)	95 (61%)	387 (48%)	526 (48%)	359 (42%)	<0·001	<0·001
Atrial fibrillation or flutter	5161	387 (17%)	20 (13%)	169 (21%)	230 (21%)	122 (14%)	<0·001	0·015
Hypertension	5158	1292 (58%)	95 (61%)	416 (51%)	550 (50%)	320 (37%)	<0·001	<0·001
Peripheral arterial or vascular disease	5160	80 (4%)	8 (5%)	43 (5%)	25 (2%)	21 (2%)	0·002	0·001
Diabetes	5160	987 (44%)	80 (52%)	300 (37%)	452 (41%)	264 (31%)	<0·001	<0·001
Chronic kidney disease*	4132	879 (54%)	7 (41%)	194 (37%)	356 (41%)	167 (31%)	<0·001	0·004
Chronic obstructive pulmonary disease	5161	194 (9%)	14 (9%)	81 (10%)	83 (8%)	59 (7%)	0·165	0·024
Current or ex-smoker	5158	1004 (45%)	96 (62%)	469 (58%)	497 (45%)	262 (31%)	<0·001	<0·001
Sinus rhythm	4904	1483 (65%)	118 (76%)	571 (70%)	682 (62%)	561 (66%)	<0·001	<0·001
Highest education level, n (%)								
No formal education/Primary	1331	582 (30%) of 1921	3 (9%) of 32	184 (30%) of 613	303 (29%) of 1042	259 (31%) of 823	<0·001	0·132
Secondary	1639	677 (35%) of 1921	20 (63%) of 32	256 (42%) of 613	385 (37%) of 1042	301 (37%) of 823	..	..
Pre-university (polytechnic, equivalent)	614	252 (13%) of 1921	2 (6%) of 32	110 (18%) of 613	142 (14%) of 1042	108 (13%) of 823	..	..
Degree or higher	847	410 (21%) of 1921	7 (22%) of 32	63 (10%) of 613	212 (20%) of 1042	155 (19%) of 823	..	..

Some percentages do not sum to 100% because of rounding. LVEF=left ventricular ejection fraction. *Defined as an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m².

Table: Baseline characteristics by percentage achieved of guideline-recommended doses

Japan were lower than in India, Indonesia, Taiwan, and Hong Kong (all >80 beats per min), where uptake of β blockers was lower than it was in Japan. Patients who achieved 100% or more of the guideline-recommended dose for β blockers were most often younger, in NYHA classes I and II (data not shown), and were more likely to have a high BMI, atrial fibrillation, diabetes, or hypertension (p_{trend}<0·001; table), but were less likely to be admitted to hospital or have clinical signs or symptoms of more severe heart failure (eg, peripheral
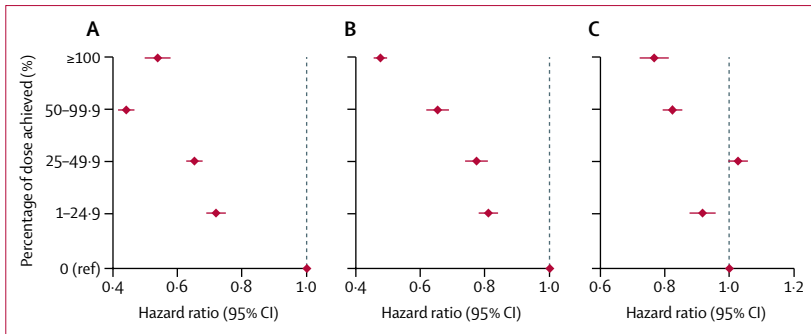
Figure 3: Association of doses achieved with 1-year composite outcome of all-cause deaths or hospitalisation for heart failure
(A) Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. (B) β blockers. (C) Mineralocorticoid receptor antagonists. Achieved doses were calculated as a percentage of the dose recommended by guidelines. We used inverse probability weighting to adjust for indication bias.

oedema, pulmonary rales; data not shown) or chronic obstructive pulmonary disorder.

Patients who achieved 100% of guideline-recommended dose for MRAs were more likely to be older, have higher systolic blood pressure, or be hypertensive (all p_{trend}<0·001), but less likely to have atrial fibrillation, diabetes, and chronic kidney disease (p<0·001; table). MRAs were prescribed in 2998 (58%) of 5205 patients. Spironolactone was the most commonly prescribed MRA (2845 [95%] of 2998 patients on MRAs). Uptake of MRAs was highest in China (372 [78%] of 477) and lowest in Hong Kong (20 [40%] of 50) and Indonesia (112 [41%] of 272; figure 1). The median prescribed dose was 50% (IQR 40–100) of the guideline-recommended dose. Mean MRA doses were highest in India and Japan and lowest in Singapore (figure 2C). The overall prevalence of hyperkalaemia at recruitment was 2% cohort, with a higher propor-tion of hyperkalaemia in non-MRA users (58 [3%] of 1980 patients with serum potassium records) compared with those prescribed MRAs (41 [1%] of 2928, p=0·001).

Follow-up data were available for 4544 (90%) of 5061 eligible patients taking medication for heart failure, with median follow-up of 417 days (IQR 214–735). Compared with the reference group (0%, non-users), after adjustment, there was a dose-dependent reduction (p_{trend}≤0·001) of hazards of 1-year composite endpoint with increasing doses of ACE inhibitors or ARBs and β blockers (all p<0·001; figure 3). Patients who received at least 100% of guideline-recommended dose had better outcomes (hazard ratio [HR] 0·77, 95% CI 0·72–0·81 for MRAs; HR 0·47, 0·46–0·50 for β blockers) than did those who received lower doses (figure 3). Notably, patients who achieved 50–99·9% of recommended doses for ACE inhibitors or ARBs had the best outcomes (0·44, 0·42–0·47; p<0·001 vs non-users; figure 3). When compared with those who achieved at least 100% of recommended doses (in a separate sensitivity analysis), patients who achieved 50–99·9% of recommended doses had a reduced hazard ratio (0·82, 0·76–0·89; p<0·001) for the 1-year

combined endpoint. For MRAs, only doses above 50% of guideline-recommended doses were associated with a reduced hazard of the combined outcome (figure 3). The reduced HR (<1) in the 1–24·99% of guideline-recommended dose of MRA could be due to chance or confounding, given the small size of this subgroup (156 patients vs ≥813 patients in other subgroups).

In multivariable models, patients with HFrEF from southeast Asia had almost double the risk of death at 1 year (HR 1·9, 95% CI 1·4–2·6) compared with patients from northeast and south Asia. Although there was no interaction between region and outcomes for ACE inhibitors or ARBs and MRAs, region did modify the association between β blockers and combined outcome. β blockers at all doses were associated with reduced hazard of the combined outcome in northeast and south Asia, whereas only attainment of guideline-recommended dose of β blockers was associated with reduced hazard of the combined outcome in southeast Asia. Stratified HRs from the weighted model, however, showed no differences across regions, with the same beneficial pattern for all three therapeutic classes (appendix).

We restricted our sensitivity analyses to non-imputed samples. The achievement of guideline-recommended dose for ACE inhibitors or ARBs (HR 0·22, 95% CI 0·19–0·24), β blockers (0·13, 0·12–0·15), and MRAs (0·49, 0·45–0·53) remained associated with a survival benefit for the combined outcome. In sensitivity analyses restricted to outpatients, differences in uptake and doses between countries persisted. Outpatients that received at least 100% of guideline-directed medical therapy with ACE inhibitors or ARB (HR 0·56, 95% CI 0·37–0·85) or β blockers (HR 0·48, 0·30–0·79) had a survival benefit for the primary combined outcome.

When all-cause mortality, cardiovascular mortality, and admittance to hospital because of heart failure at 1-year were examined separately, results for the composite outcome were similar (appendix).

Discussion

The ASIAN-HF registry provides real-world data on prescription of guideline-directed medical therapies in patients with HFrEF from 46 centres in 11 countries across Asia. There was substantial regional heterogeneity in the uptake and dose prescribing patterns of ACE inhibitors or ARBs, β blockers, and MRAs. Identified gaps in admini-stration of guideline-directed medical therapies were monotherapy given instead of combined therapy and widespread underdosing, with recommended target doses achieved in only 17% of those given ACE inhibitors or ARBs, 13% of those given β blockers, and 29% of those given MRAs. Notably, there was a graded relationship between increased achieved doses of guideline-directed medical therapy and reduced risk of deaths or admittance to hospital because of heart failure. Even small doses (<25% of guideline-recommended dose) of ACE inhibitors or ARBs and β blockers were associated with improved

outcomes compared with no dose or non-usage in the overall cohort. However, only attainment of guideline-recommended dose of β blockers were associated with better outcomes in patients from southeast Asia, where outcomes are poor. Our findings support guideline recommendations to start evidence-based therapies in those who are not receiving any therapy, and to uptitrate the doses of ACE inhibitors or ARBs and β blockers to the maximum tolerated, to achieve maximum benefits in patients in Asia with HFrEF.

The widespread underdosing of ACE inhibitors or ARBs and β blockers found in our study is consistent with that reported in a pan-European study,[6] despite encouraged uptitration, where full doses of guideline-directed medical therapy were achieved in 22% of patients given ACE inhibitors or ARB and in 12% for β blockers. The reduced proportion of patients achieving guideline-recommended doses of ACE inhibitor in our Asian cohort, compared with the European cohort, might be related to the higher prevalence of persistent cough with ACE inhibitor reported among people from Asia;[10,24,25] although this reasoning would not explain differences in prescription of ARB. Additionally, in the ONTARGET study,[26] a subgroup of Asians tolerated both telmisartan and ramipril better than non-Asians did, although the absolute risk of cough in Asians was higher (6·1% vs 3·9% in non-Asians) among those who discontinued ramipril. Patients in the European cohort had a mean age of 68 years (SD 12) and mean body-mass index of 28 kg/m² (5·5), thus were older and heavier than our Asian cohort. This finding suggests that underdosage of guideline-directed medical therapy in HFrEF could not be fully ascribed to the common perception that smaller body size was the dominant reason for low doses in Asians, since doses prescribed were similarly low in Europeans of larger body size.

Despite similarities in the underutilisation of guideline-directed medical therapy worldwide, geographical region within Asia had the most pronounced association with variation in attainment of recommended doses of guideline-directed medical therapy in ASIAN-HF. We were unable to determine the reasons for the differences in prescription patterns but made some notable observations with regards to regional socioeconomic status. For uptake of guideline-directed medical therapy, patients in high-income countries—such as Singapore, Hong Kong, Korea, and Japan—were more likely to be prescribed dual first-line medications compared with lower income countries, consistent with PURE[27] and INTER-CHF;[28] however, socioeconomic status did not affect uptitration of guideline-directed medical therapy, and patients in Japan were prescribed the lowest doses of β blockers whereas those in lower income regions, such as India and Thailand, were prescribed the highest doses. Patients' educational status was not predictive of attainment of guideline-recommended dose; we speculate that physician factors or country-specific factors (eg, differences in health-care systems, local manufacturing

capability, health policies, delivery and quality of cardiac care) might have influenced prescription patterns. Notably, the high uptake of spironolactone in China could be attributed to a nationwide quality assessment evaluation programme,[29] presumably driven partly by the low cost of spironolactone (US$0·08 per day).

The case for achieving target high doses of ACE inhibitors or ARB in HFrEF has been established from prospective clinical trials, albeit not specifically among patients in Asia. The HEAAL trial[30] compared low-dose versus high-dose (50 mg vs 150 mg; 33–100% of guideline-recommended doses) losartan potassium in patients with HFrEF and reported that high-dose losartan potassium favoured a combined endpoint of all-cause mortality or admittance to hospital because of heart failure (p=0·027). In the ATLAS trial,[31] over 46 months of follow up, high doses of lisinopril, 32·5–35·0 mg/day (93–100% of guideline-recommended doses), led to a significant reduction (12%) in the composite outcome of death or admittance to hospital because of heart failure compared with low doses of 2·5–5·0 mg/day of lisinopril (7–14% of guideline-recommended dose). According to 2016 European Society of Cardiology guidelines,[1] the recommended initial dose of carvedilol in the management of HFrEF is 6·25 mg/day, uptitrating to 50 mg/day as maintenance if tolerated. Reduced doses were tested in the Japanese randomised, placebo-controlled double blind MUCHA trial,[32] where carvedilol at doses of 5–20 mg/day led to reductions of 71–91% in risk of death or admittance to hospital because of heart failure or cardiovascular event, albeit to a smaller extent than did 20 mg/day. In another study among Japanese patients with dilated cardiomyopathy, a mean maintenance dose of 14 mg/day (SD 7) carvedilol increased LVEF from 28% (SD 7) to 39% (9) over 6 months,[33] consistent with the benefits reported by MUCHA.[32] These results are also consistent with our observation of graded survival benefit with higher doses of β blockers, even at low doses (<25–50% guideline-recommended dose).

The use of MRAs to treat HFrEF is well established.[1,34] Our findings showed low doses of MRAs (<50%) were associated with more harm than was seen in those who did not receive MRAs, suggesting a possible threshold effect of higher doses, but perhaps also reflecting the frailer nature of patients who are unable to tolerate full doses of MRA. Our observational study was not designed to investigate the dose-dependent effects of MRAs. Although prevalence of hyperkalaemia was low in our cohort, more research is needed to define MRA-associated risks in Asia, particularly in light of the low cost of spironolactone and its uniquely high use in China.

We acknowledge that observational data cannot definitively establish causality or drug efficacy. Randomised controlled trials are required for definitive answers. Although we used inverse probability weighting to account for potential bias by indication, residual

confounding of unmeasured factors might affect our results. Furthermore, our data is observational and might be affected by possible selection bias with regard to the centres invited to participate and is, for this reason, hypothesis-generating rather than comprehensive regional data. Priority was given to sites that could provide high-quality data with as little missing data as possible. Although our data does not include population-based data throughout the 11 Asian regions examined in ASIAN-HF, every effort was made to minimise loss to follow-up, and our approach probably represents the best practice that could be feasibly achieved in our multinational observational registry. Given all the constraints of the large geographical areas with diverse socioeconomic factors and availability of health care, our data represent a best case scenario that underestimates the broader deficiencies in medical prescribing in each region. We further acknowledge our lack of data on adherence to medications. In the absence of any other such real-world evidence from a large multinational Asian population, the current data and findings are probably the best available evidence for clinicians caring for HFrEF in Asia.

Our findings suggest the need for interventions to increase the prescribing rates or initiation of first-line guideline-directed medical therapy in Asians with HFrEF, particularly those in low-income and middle-income countries. Strategies that warrant consideration include the establishment of programmatic approaches to the management of heart failure, targeted education for physicians to strengthen evidence-based practices, provision of initiatives in populous Asia to support overworked physicians with an excessive number of cases, and increased patient awareness of the importance of guideline-directed medical therapy at targeted doses.

In summary, we observed substantial regional variation in guideline-directed medical therapy and uptake among patients with HFrEF across Asia. Identified gaps in administration of such therapy were monotherapy (instead of combined therapy) and widespread under-dosing of medications. Increased achieved doses of ACE inhibitors or ARBs and β blockers were associated with improved outcomes, as we expected. Although smaller doses of ACE inhibitors or ARBs and β blockers conferred some benefit, guideline-recommended doses led to maximum benefit. These first prospective multinational data from Asia suggest that efforts to improve uptake and uptitration of guideline-directed medical therapies are warranted.

Contributors
CSPL, T-HKT, WTT, and IA conceived the study. T-HKT, CFX, and WTT prepared the initial data. JT, WO, and WTT performed the statistical analyses. T-HKT drafted the manuscript. CSPL, AV, AMR, and IA provided clinical expertise. CSPL, MRM, and JJLY adjudicated all data on mortality and causes of death. All authors critically reviewed and approved the final version of the manuscript.

Declaration of interests
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