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STATE-OF-THE-ART PAPER

Heart Failure Clinical Trials in East and Southeast Asia

Understanding the Importance and Defining the Next Steps

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ABSTRACT

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

Heart failure (HF) is a major public health problem worldwide (1,2). In Asia, aging populations and large increases in cardiovascular risk factors have contributed to a high burden of HF (3). HF patients from Asia differ in clinical characteristics from patients elsewhere and yet have similarly poor or even worse outcomes than HF patients from the West (**Table 1**) (4). Given the diversity of countries in Asia (Online Appendix), clinical phenotypes and practice patterns vary widely, just as practice patterns vary across Europe and the Americas.

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

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ABBREVIATIONS AND ACRONYMS

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

CAD = coronary artery disease

GDMT = guideline-directed medical therapy

HFrEF = heart failure with reduced ejection fraction

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

LOS = length of stay

MRA = mineralocorticoid receptor antagonist

fraction (EF) (5), including recent trials of sacubitril/valsartan (6) and ivabradine (7) therapy. Older trials either did not include Asians or included small numbers of patients of Asian ethnicity from Western countries. Given the need to enroll large numbers to demonstrate outcome benefits as well as recent challenges with enrollment and cost in North American and certain European countries, contemporary trials have enrolled globally (8). Representation of patients from Asia was relatively low in many previous trials due to perceived and/or actual challenges to generalizability and trial infrastructure and conduct. Regulatory approval of HF drugs in Asian countries has largely relied on data extrapolated from Western populations. More recently, Asian regulatory authorities have been requiring that study populations include Asians from Asia (9) in order to support approval.

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

BURDEN OF HF

Limited data are available regarding the true incidence and prevalence of HF in Asia (3). Studies of hospitalized patients in Singapore, Malaysia, and Taiwan found that 3% to 7% of admissions were due to HF in the 1990s to early 2000s (10–12). In a community-based survey, the prevalence of HF in China among populations 55 to 74 years of age was 1.3%, with an estimated overall adult HF population >4 million (13). Similarly, in Japan, it is estimated that 1 million people have HF (14), which equates to a prevalence of ~1%. Although prevalence estimates in the general population are lower in Asia than in the West (1,15), this translates to a higher absolute burden of disease in Asia because of larger population sizes. For example, even with conservative estimates of HF prevalence, the absolute number of individuals with HF in Asia is >20 million (16). Regarding HF hospitalizations, in Singapore there was a 38% increase from 1991 to 1998, which is approximately 5% per year (10). This matches the 5% yearly increase in all-cause hospitalizations from 2004 to 2012. However, in recent years, HF hospitalizations have been rising at 10% each year (17). Furthermore, the at-risk population is increasing at a faster rate in Asia than in other parts of the world, with aging of the population and increases in the prevalence of coronary artery disease (CAD), tobacco use, diabetes, and obesity. For instance, in 2007, there were 305,700 people older than 65 years of age in Singapore (6.7% of the population). This increased more than 30% to 404,500 in 2013 (7.5% of the population) (18). Thus, the burden of HF in Asia is expected to increase and be comparatively larger than that in the West over subsequent decades (14).

HF PHENOTYPE

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

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

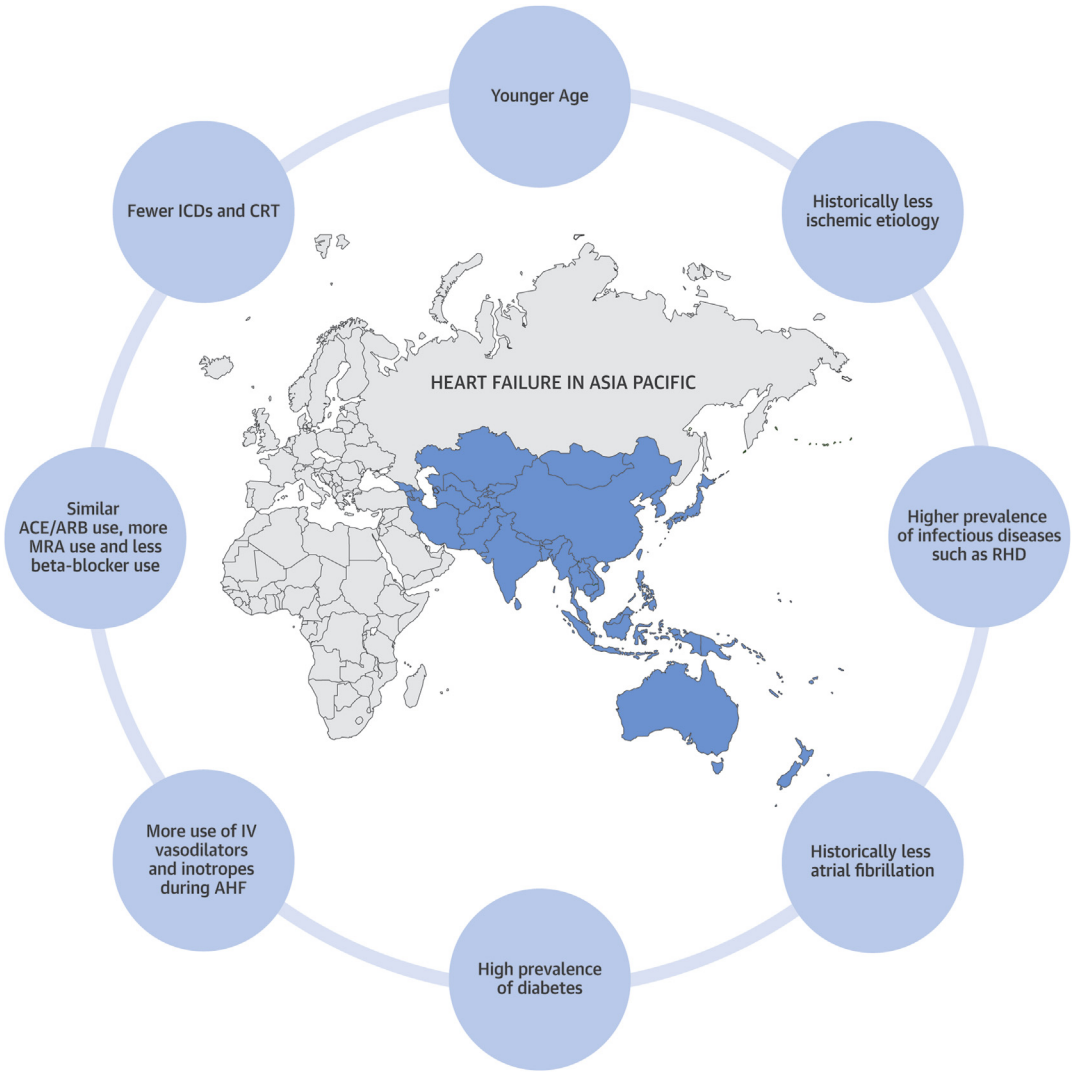
TABLE 1 Comparison of Clinical Characteristics and Outcomes in Asia to Other Regions

	CHART-1 (19)	CHART-2 (19)	JCARE-CARD (69)	ATTEND (20)	KorAHF (31)	Tseng (12)	ADHERE-AP (4)	ADHERE (30)	OPTIMIZE-HF (70,71)	EHFS II (72)
	2000–2004	2006–2010	2004–2005	2007–2011	2011–2012	2005	2006–2008	2001–2004	2003–2004	2004–2005
	Japan	Japan	Japan	Japan	Korea	Taiwan	AP Region	United States	United States	Europe
	Stage C/D	Stage C/D	AHF	AHF	AHF	AHF	AHF	AHF	AHF	AHF
	N = 1,078	N = 4,735	N = 2,549	N = 4,841	N = 2,066	N = 2,692	N = 10,171	N = 105,388	N = 48,612	N = 3,580
	26 hospitals	24 hospitals	164 hospitals	52 hospitals	10 centers	insured patients	43 hospitals	274 hospitals	259 hospitals	133 hospitals
Age, yrs	69 ± 13	69 ± 12	71 ± 13	73 ± 14	69 ± 14	73 ± 13	67	72 ± 14	73 ± 14	70 ± 13
Males	65%	68%	60%	58%	55%	55%	57%	48%	48%	61%
Ischemia cause	26%	47%	32%	31%	38%	32%	50%	57%	46%	54%
LVEF ≥50%	51/51%	57/69%	42 ± 18	-	40 ± 18	-	53% (LVEF<40%)	34 ± 16/46% (>40%)	39 ± 18	38 ± 15/34% (LVEF ≥45%)
Diabetes	20%	23%	30%	34%	36%	28%	45%	44%	25%	33%
Atrial fibrillation	42%	31%	35%	40%	27%	-	24%	31%	31%	39%
Renal dysfunction	50%	47%	12%	-	-	13%	22%	30%	20%	17%
BMI, kg/m^2	23.0 ± 3.7	23.8 ± 3.9	22.4 ± 4.1	-	-	-	-	-	-	26.8
SBP, mm Hg	126 ± 19	126 ± 19	117 ± 18	146 ± 37	136 ± 31	-	57% with SBP 90–140	144 ± 33	143 ± 33	135 (110–160)
HR, beats/min	75 ± 14	72 ± 15	70 ± 12	99 ± 29	91 ± 26	-	-	-	87 ± 22	95 (77–114)
Creatinine/eGFR	–/61 ± 31	–/61 ± 24 (stage C)	1.4/52 ± 25	1.4 ± 1.6	1.5 ± 1.6	-	>1.5 mg/dl in 41%	1.8 ± 1.6	1.8 ± 1.8	-
BNP/NT-proBNP, pg/mL	273 ± 353	191 (C), 454 (D)	375 ± 474	707 (362–1,284)	-	-	-	840 (430–1,730)	800 (403–1,660)	-
Chronic HF therapies										
ACEI/ARB	57%/13%	45%/32%	37%/44%	31%/46%	65%	51%	63%	41%/12%	40%/12%	80%
Beta-blocker	28%	49%	49%	67%	44%	25%	41%	48%	53%	61%
MRA	~21%	~22%	42%	-	40%	-	31%	20%	7%	48%
Digoxin	48%	24%	31%	-	24%	32%	34%	28%	23%	31%
CRT/ICD	1.5%	2.9% (C), 15.8% (D)	1.6%/2.0%	2.3%/3.4%	1.3%/1.4%	-	–/1.6%	-	5%	9.1% pacemaker
Inpatient therapies										
IV diuresis	-	-		76%	72%	76% (all diuretic)	85%	92%	-	84%
IV vasodilation	-	-		78%	40%	-	14% (IV nitrate)	9%	14%	38%
IV inotrope therapy				19%	32%	-	15%	15%	7%	>11%
In-hospital mortality	-	-	3.9% (rEF) 6.5% (pEF)	6.4%	5.2%	3.9%	4.8%	4.0%	3.8%	6.7%
Length of stay, days	-	-	36 (rEF) 31 (pEF)	30 ± 39/21 (14–32 days)	8	15.8 ± 42.7	6.0	4.3	6.4	9 (6–14 days)
30-day mortality	-	-	-	-	1.2%	-	-	-	8.6% at 60–90 days	-
Short-term rehospitalization	-	-	-	-	6% HF rehospitalization at 30 days	-	-	-	29.6% at 60–90 days	-

Values are mean ± SD, median (IQR), or %. If details were not provided in the primary manuscript, this is represented by a "–" sign. If multiple relevant details are provided in the same section, these are separated with a "/" symbol.

ACEI = angiotensin-converting enzyme inhibitor; AHF = acute heart failure; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CRT = cardiac resynchronization therapy; GFR = glomerular filtration rate; HR = heart rate; ICD = implantable cardioverter-defibrillator; IV = intravenous; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; pEF = preserved ejection fraction; rEF = reduced ejection fraction; SBP = systolic blood pressure.

CENTRAL ILLUSTRATION **HF Phenotype and Treatment in Asia Compared With Other Regions**



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ACE/ARB = angiotensin-converting enzyme/angiotensin receptor blocker; AHF = acute heart failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; RHD = rheumatic heart disease.

reported that ischemia was the underlying cause in 26% of cases (19). These observations are notable given the high prevalence of CAD risk factors, including >40% of the Asian population with a smoking history and 45% with diabetes. Younger age may partially explain the discordance between risk factor burden and ischemic prevalence. Recent data suggest that ischemia-driven HF is increasing in Asia. For instance, in Japan, the prevalence of CAD increased from 26% to 47% from 2000 to 2010 (19).

COMORBIDITIES. Atrial fibrillation (AF) and diabetes were previously less common in Asia than in other regions, but current trends suggest that both are increasing. Historically, the incidence of AF was lower in the Asian population (21) than in individuals in North America and Western Europe (22). However, from 2001 to 2012, there was a >20-fold increase in AF incidence in China (21). These observations are likely due to the aging of the population as well as comorbidities such as rheumatic heart

disease, lung disease, and diabetes (21). The recent increase in AF incidence in Asia is markedly higher than in North America/Europe (23,24), suggesting that AF may play an even more critical role in HF in Asia in the future (25). Importantly, these observations may also be related to increased disease ascertainment in Asia.

Similarly, diabetes in Asia has increased in recent years due to changes in lifestyle involving physical inactivity and diet changes (26). For instance, in Malaysia, obesity increased from 12% to 15% and diabetes increased from 12% to 15% from 2003 to 2011 (27). Regional changes in lifestyle and diet were strongly associated with diabetes. Similar findings have been seen in other Asian countries (28). Data from the International Diabetes Federation indicate that the Western Pacific and South East Asia regions have the highest levels of diabetes at 138 and 72 million, respectively (29); these numbers are expected to increase more than 40% by 2035. China and India have the largest current and projected populations of people living with diabetes, at 98 and 65 million, respectively, in 2013, growing to 143 and 109 million, respectively, by 2035. Thus, diabetes and obesity will likely become increasingly prevalent in the Asian HF population, which has important implications on clinical management. Other cardiovascular and noncardiovascular comorbidities such as sleep disordered breathing, renal dysfunction, lung disease, depression, and frailty also influence HF management in Asia but are less well characterized than in other world regions.

HF MANAGEMENT

In-hospital management of acute HF in ADHERE-AP included intravenous (IV) diuretic therapy in 85% of patients and IV inotrope therapy in 15%. IV diuretic use was comparable to North America and Western Europe (~85% to 90%); however, IV inotrope use tends to be higher in Asia than in the United States (4). Similarly, the Japanese ATTEND registry showed high IV inotrope use (19%) and frequent use of IV vasodilators (>70%) (20) compared with only 10% to 15% vasodilator use in the United States (30). IV vasodilator use was also higher in Korea (40%) (31). These variations in practice patterns were observed despite a relatively similar percentage of patients presenting with systolic blood pressure <90 mm Hg (4) and similar admission systolic blood pressure (2) compared with U.S. patients. These management differences may have important prognostic implications, as even short-term inotrope use is associated with increased mortality (32).

Uptake of guideline-directed medical therapy (GDMT) in Asia has exhibited a distinct pattern. In ADHERE-AP, compared with ADHERE, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) was similar, whereas use of mineralocorticoid receptor antagonists was higher in Asia, and use of beta-blockers lower (4). These observations may be related to perceptions of drug tolerability in Asian populations. Importantly, significant regional differences in prescription of GDMT exist even within Asia, with higher rates in Japan (20) and lower use in developing countries (2). Trial datasets such as the ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) and ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trials demonstrated similar differences in a comparison of Asia-Pacific to other regions (33,34). Factors associated with underutilization of medications in Asia include rural residency, less-specialized health care providers, and fewer comorbid conditions (35). Analyses have also assessed chronic HF patients of Asian descent who now reside in Western countries. For instance, Chinese individuals with HF living in Canada reported lower use of ACEIs than non-Asians (36). Importantly, data suggest that the use of GDMT in Asia has increased in recent years. For instance, in Japan, ACEI/ARB and beta-blocker use increased from 69% and 28%, respectively, to 72% and 49%, respectively, from 2000 to 2010 (19).

PHARMACOLOGIC DIFFERENCES. Few data are available regarding differences in dosing, tolerability, or adherence in Asia compared with other regions. Nonetheless, geographic differences in the efficacy of GDMT may exist (37). Distinct HF phenotypes among Asians support assessment of differences in the pharmacokinetics and pharmacodynamics for GDMT. Previous studies have demonstrated genetic variations between the renin-angiotensin aldosterone system in Chinese and that in Caucasian populations involving polymorphisms in the ACE and angiotensinogen genes (38,39). Several small studies have suggested that ACEIs demonstrate a pharmacologic profile in Asians that is different from that in Caucasians, including differences in volume of distribution and drug clearance as well as effects on renin-angiotensin aldosterone system levels and blood pressure (40,41). Chinese patients may experience more coughing from ACEIs than Caucasians (38). Similarly, ethnic differences in genetics and pharmacologic response for beta-blockers have been identified. For instance, polymorphisms in hepatic metabolizing proteins that are commonly seen in

Asian populations affect beta-blocker concentrations and clearance (42). Given the small sample size of previous studies and the relative paucity of data pertaining to differences in pharmacological response in Asians (43), future research is needed to clarify the clinical relevance of these findings. Perspectives related to differential pharmacological responses in Asians are highlighted in the 2011 Japanese guidelines (44). For 32% (44 of 137) of the drugs approved in Japan between 2001 and 2007, the maximum recommended dose was less than one-half that in the United States (45). For example, the dosage of carvedilol is recommended to be increased up to 100 mg/day, if tolerated, in the United States and Europe, whereas the maximum approved dosage in Japan is 20 mg/day. Without robust pharmacodynamic studies and dose titration studies that document consistent differences among Asian populations, compared with other world regions, whether the differences in dosages are appropriate remains largely unknown.

DEVICE THERAPY. ASTRONAUT and ASCEND-HF reported markedly lower use of implantable cardioverter-defibrillators (ICD) in Asia-Pacific than in other regions (33,34). In ASTRONAUT, only 5.7% of Asian-Pacific patients had an ICD compared with 38.2% in North America, despite similar EF and symptom class. CHART-2 (Chronic Heart Failure Analysis and Registry in the Tohoku District) reported that only 6.6% of Asians with reduced left ventricle EF (LVEF) received a primary prevention ICD (46). It has been suggested that limited accessibility and affordability are primary reasons for low implantation (47). Poorly defined sociocultural norms, conservative value systems, and ethnicity- or religion-specific health beliefs may also play a role.

Other considerations include continued controversy regarding the risk of sudden cardiac death (SCD) in Asians. In the United States, the incidence of SCD was reported to be lower among Asian Americans compared with Caucasians (48). A Japanese study found that Asians who were eligible by MADIT-II criteria but did not undergo ICD implantation had significantly lower risk of SCD and even better overall survival than the historical Western MADIT-II population (49). On the other hand, when MADIT-II criteria were applied to a Chinese cohort, those fulfilling criteria were found to be at similar risk of SCD compared with the original Western MADIT-II population (50). Acknowledging that previous studies were limited by retrospective design and referral and selection bias, the ongoing prospective ASIAN-HF study was designed (51).

OUTCOMES

Regional differences in HF outcomes have been described (33,52–54). In ADHERE-AP, the median hospital length of stay (LOS) for HF was 6 days, and in-hospital mortality was 4.8% compared with 4 days and 4.0%, respectively, in ADHERE. This may be attributed, in part, to the ADHERE-AP cohort having an increased severity of disease due to larger enrollment from tertiary hospitals. In the Japanese ATTEND registry, median LOS was 21 days, and in-hospital mortality was 6.4% (20). Japanese patients often participate in in-patient disease management programs that increase LOS. Differences in HF disease severity, clinical practice patterns, reimbursement, and participation in disease management programs have been hypothesized to at least partially explain these observations. In contrast, trial data from ASTRONAUT demonstrated similar LOS in North America and Asia-Pacific (33), highlighting differences between trial and registry patients.

Limited data are available regarding post-discharge outcomes in Asia. In Korea, 30-day and 180-day all-cause mortality were 1.2% and 9.2%, respectively, whereas HF readmission rates were 6% and 24%, respectively, at those time points (31). These figures are lower than in other regions in Asia. In ASTRONAUT, the 30-day all-cause mortality and HF hospitalization in Asia-Pacific were 2.7% and 12.5%, respectively, with 12-month rates of 26.7% and 25.1%, respectively (33). Mortality rates in Asia-Pacific were higher than in other regions, but hospitalization rates were lower. In ASTRONAUT, Asia-Pacific enrollment location was independently associated with a ≥3-fold increase in mortality compared with that in North America. The rate of SCD at 12 months in the Asia-Pacific region (10.3%) was more than double that in any other world region. These observations can be interpreted in the context of a study of 1,719 HF patients in Singapore, where 1-year mortality was 16%, and 4.5% of subjects had an ICD and/or cardiac resynchronization therapy (CRT), which was associated with clinical outcomes (55).

ASIAN REPRESENTATION IN TRIALS

Prior large-scale outcome trials of current HF with reduced EF (HFrEF) GDMT did not routinely enroll Asians. Specifically, none of the landmark ACEI trials (CONSENSUS, SOLVD, SAVE, AIRE, TRACE) or beta-blocker trials (COPERNICUS, CIBIS-II, MERIT-HF) included patients from Asia (5). In contrast, 2 of the 3 MRA trials enrolled patients from Asia. RALES enrolled patients from Japan (56), and EMPHASIS

enrolled in Hong Kong, Korea, India, Singapore, and the United Arab Emirates (57). Similarly, trials assessing ivabradine and LCZ-696 had greater representation from Asian countries. SHIFT enrolled 532 patients (8.2%) in China, India, Malaysia, and South Korea (7), and PARADIGM-HF enrolled 1,509 patients (18%) in China, Philippines, Singapore, South Korea, Taiwan, and Thailand (6). In addition to these trials, which form the basis of GDMT, ASCEND-HF (58) and ASTRONAUT (33) enrolled 1,762 patients (25%) and 439 patients (27%) from Asia-Pacific, respectively. However, earlier large-scale HF trials, including PROTECT (59) and EVEREST (60), did not enroll in Asia.

ASIA-SPECIFIC STUDIES

Relatively few Asia-specific studies in HF patients have been conducted. MAIN-CHF-II was a randomized trial of bisoprolol versus carvedilol for 32 weeks in 59 Japanese HFrEF patients (61). The study had been stopped earlier after off-label use of bisoprolol was approved in Japan. Importantly, the dosing strategy targeted significantly lower doses than the landmark trials with the drugs. Bisoprolol was started at 0.625 mg daily with up-titration to 5 mg versus 1.25 mg with up-titration to 10 mg in CIBIS-II (62). Similarly, carvedilol was started at 2.5 mg/day and up-titrated to 20 mg/day versus 3.125 mg twice daily with up-titration to 25 mg twice daily in COPERNICUS (63).

SUGAR was an observational study of HFrEF patients in Korea, which assessed the association between prescription of GDMT and outcomes (64). Patients who were prescribed GDMT tended to have reduced mortality and rehospitalization at 90 days and 12 months compared to similar patients who did not receive GDMT. With a sample size of 1,319 patients, this analysis was likely underpowered, yet consistent benefits were observed for ACEI/ARBs and beta-blockers. Additional observational studies have supported benefits of beta-blockers in elderly Japanese patients (65). Another analysis assessed carvedilol use in Japanese patients with either preserved or reduced EF (66). Similar observational analyses of ACEI/ARBs in HFrEF patients have been performed in Asian populations. For instance, the JCARE-CARD investigators demonstrated similar clinical outcomes when comparing ACEI and ARBs in chronic HFrEF patients in Japan (67). However, the lack of control groups, the inclusion of reduced and preserved EF patients, and the observational nature of these studies limit interpretation of results.

The ongoing RELAX-AHF-ASIA trial is exclusively enrolling patients in Asia (NCT02007720). This trial is targeting enrollment of 1,520 patients within Asia in parallel to the overall international RELAX-AHF-2 trial with target enrollment of 6800 patients (NCT01870778).

FUTURE DIRECTIONS

Given the differences in phenotype and medical management as well as potential differences in pharmacological response to HF medications in Asia, we suggest several design considerations for future trials to improve applicability to Asian populations. Importantly, early-phase pharmacokinetic and dose-ranging studies are needed in Asian populations. Subsequently, we propose a developmental strategy whereby trials are conducted in Asian countries simultaneously with efforts in other regions, rather than the historical model where Asian countries were included only after initial efforts in Europe/North America. Patients from Asia may be included as a pre-specified subgroup of trials or in separate region-specific trials.

In the former strategy, trials are designed to include pre-specified targets of numbers and percentages to be enrolled in Asia, in order for meaningful conclusions to be drawn within this pre-specified subgroup. This strategy applies uniform protocols in Asia and elsewhere, with post hoc statistical techniques to adjust for baseline differences and assess for interaction between region/ethnicity and drug response.

In the latter strategy, there may be sufficient interest in international or within-region differences in response to a given compound, or anticipated differences in clinical settings or practice patterns, to warrant a dedicated trial in Asia. Such a trial may run in parallel with trials in the rest of the world, but with the Asian trial uniquely designed to account for Asia-specific patient and practice characteristics. For example, the RELAX-ASIA trial accounted for regional differences in patient management pathways for acute HF, and included region-specific renal function cutoffs. Lower age and BMI cutoffs may also be needed for HF trials in Asia.

Differences in background therapy may influence trial design. As an example, the heart rate–reducing agent ivabradine is approved for use in chronic HFrEF patients in sinus rhythm with a heart rate of ≥70 beats/min on maximally tolerated beta-blocker dosage. Use of the drug is dependent on the interpretation of maximally tolerated beta-blocker dosage, which may vary across world regions with

potentially lower dosing used in Asian countries. Data are needed to clarify tolerability and target dosing of HF drugs in Asian populations. One strategy to address this evidence gap is to develop region-specific databanks of administrative, registry, and trial data. With the rapid growth and evolving health care systems in many of these countries, several of these databases are being developed (68).

HF trial development and conduct must acknowledge that Asia covers a diverse group of nations, each with unique patient, sociocultural, and medical practice backgrounds that may affect trial design. There is a need to collect blood samples to assess potential genetic differences that might alter responsiveness to drugs or devices, as in the ongoing ASIAN-HF registry (51). Moreover, sociocultural norms of aging, health beliefs, and receptivity to medical intervention differ within and between regions. LOS varies, thus influencing the utility of using 30-day rehospitalization as an outcome measure in trials. Dedicated HF programs and outpatient clinics allow close follow-up in some nations (e.g., Singapore) but not others (e.g., parts of China and India), where it may be challenging to follow patients from rural communities. Processes for ethics approval and requirements for regulatory approval also vary widely and must be taken into consideration for optimal design of trials in Asia.

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KEY WORDS Asia, heart failure, trials

APPENDIX For supplemental tables, please see the online version of this article.