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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 similarly poor outcomes compared to the rest of the world. Representation

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of Asians in landmark HF trials has been variable. In addition, HF patients from Asia demonstrate clinical differences from other geographic regions. Thus, the generalizability of some clinical trials results to the Asian population remains uncertain. In this manuscript, we review differences in the HF phenotype, 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 between scientists, clinical trialists, industry representatives and regulatory representatives at the CardioVascular Clinical Trialist Asia Forum on July 4, 2014.

Keywords

Heart failure; Asia; Trials

INTRODUCTION

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 having similarly poor or even worse outcomes compared to HF patients from the West (Table)([4]). Given the diversity of countries in Asia (Appendix), clinical phenotypes and practice patterns vary widely, just as practice patterns vary across Europe or the Americas.

The last several decades have seen therapeutic advances for HF patients with reduced ejection fraction (EF)([5]) including recent trials of sacubitril/valsartan([6]) and ivabradine([7]). 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]). The representation of patients from Asia was relatively low in many prior trials due to perceived and/or actual challenges with generalizability as well as 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 review differences in HF patients from East and Southeast Asia (See Appendix) compared to the rest of the world. We focus on East and Southeast Asia given that these regions within Asia have more robust registry and trial data available to date. We summarize observations within the context that heterogeneity exists even between regions within Asia. We describe lessons learned in HF datasets and outline strategies to improve future trials. This review is based on discussions between 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 from January 1994 to December 2015 (see Appendix for 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 3–7% 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 55–74 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 the prevalence estimates in the general population are lower in Asia compared to 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 about 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 above 65 years in Singapore (6.7% of the population). This increased >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 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 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 67–70 years in Asia vs 70–75 years in the US/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 variation in risk factor profile, comorbidity burden, life expectancy and standard 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 Etiology—Compared to other regions where >50% have ischemic etiology, there is a lower prevalence of ischemic cardiomyopathy in Asia. For instance, in the ATTEND registry of 4,841 acute HF patients enrolled in Japan, 31% of patients had ischemic etiology, 19% valvular, 18% hypertensive and 32% with “other/unspecified”([20]). A chronic HF registry of 1078 Japanese patients reported that ischemia was the underlying etiology in 26%([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 compared to other regions but current trends suggest that both are increasing. Historically, the incidence of AF was lower in the Asian population([21]) compared with individuals in North American 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 larger 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 >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 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 non-cardiovascular 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 IV diuretics in 85% of patients and IV inotrope use in 15%. IV diuretic use was comparable to North America and Western Europe (~85–90%); however, IV inotrope use tends to be higher Asia compared to the US([4]). Similarly, the Japanese ATTEND registry showed high IV inotrope use (19%) as well as frequent use of IV vasodilators (>70%)([20]) as compared with only 10–15% vasodilator use in the US([30]). IV vasodilator use was also higher in Korea (40%)([31]). These variations in practice pattern were observed despite a relatively similar percentage of patients presenting with systolic blood pressure (SBP)<90 mmHg([4]) and similar admission SBP([2]) compared to US 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 as compared with ADHERE, ACE-I/ARB use was similar while MRA use was higher in Asia and beta-blocker use 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

and ASCEND-HF trials demonstrated similar differences when comparing Asia-Pacific to other regions([33,34]). Factors associated with underutilization of medications in Asia include rural residence, less-specialized healthcare 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 ACE-Is compared with non-Asians([36]). Importantly, data suggest that the use of GDMT in Asia has increased in recent years. For instance, in Japan, ACE-I/ARB and beta-blocker use increased from 69% and 28%, respectively, to 72% and 49% 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/dynamics for GDMT. Previous studies have demonstrated genetic variations in the renin-angiotensin aldosterone system (RAAS) in Chinese and Caucasian populations involving polymorphisms in the ACE and angiotensinogen genes([38,39]). Several small studies have suggested that ACE-Is demonstrate a different pharmacologic profile in Asians compared to Caucasians including differences in volume of distribution and drug clearance as well as effects on RAAS levels and blood pressure([40,41]). Chinese patients may experience more cough from ACE-Is compared to 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 prior studies and the relative paucity of data on differences in pharmacologic response in Asians([43]), future research is needed to clarify the clinical relevance of these findings. Perspectives related to differential pharmacologic responses in Asians are highlighted in the 2011 Japanese guidelines([44]). For 32% (44/137) of the drugs approved in Japan between 2001 and 2007, the maximum recommended dose was less than half the US dose([45]). For example, the dose of carvedilol is recommended to be increased up to 100 mg/day if tolerated in the US/Europe, whereas the maximum approved dose in Japan is 20 mg/day. Without robust pharmacodynamic studies and dose titration studies that document consistent differences amongst Asian populations as compared to other world regions, it remains largely unknown whether the differences in dosing are appropriate.

Device Therapy—ASTRONAUT and ASCEND-HF reported markedly lower use of implantable cardioverter defibrillators (ICD) in Asia-Pacific compared to other regions([33,34]). In ASTRONAUT, only 5.7% of Asian-Pacific patients had an ICD compared to 38.2% in North America despite similar EF and symptom class. CHART-2 reported that only 6.6% of Asians with reduced 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 US, the incidence of SCD was reported to be lower among Asian Americans compared to 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 prior studies were limited by retrospective design, 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 length of stay (LOS) for HF hospitalization 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 inpatient disease management programs which 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, while HF readmission rates were 6% and 24% at these timepoints([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%([33]). The mortality rates in Asia-Pacific were higher than in other regions but hospitalization rates were lower. In ASTRONAUT, Asia-Pacific enrolling location was independently associated with a more than 3-fold increase in mortality compared to North America. The rate of SCD at 12 months in the Asia-Pacific region (10.3%) was more than double any other world region. These observations can be interpreted in the context of a study of 1719 HF patients in Singapore where 1-year mortality was 16% and 4.5% had an ICD/CRT which was associated with clinical outcomes([55]).

Asian Representation in Trials

Prior large-scale outcomes trials of current HFrEF GDMT did not routinely enroll Asians. Specifically, none of the landmark ACE-I trials (CONSENSUS, SOLVD, SAVE, AIRE, TRACE) or beta-blocker trials (COPERNICUS, CIBIS-II, MERIT-HF) included patients from Asia([5]). In contrast, two of the three 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 1509 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 1762 (25%) and 439 (27%) patients from Asia-Pacific, respectively. However, earlier large scale HF trials including PROTECT([59]) and EVEREST([60]) did not enroll in Asia.

Asian-Specific Studies

Relatively few Asia-specific studies in HF patients have been conducted. MAIN-CHF-II was a randomized trial of bisoprolol vs. carvedilol for 32 weeks in 59 Japanese HFrEF patients([61]). The study was 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 uptitration to 5mg vs. 1.25 mg with uptitration to 10 mg in CIBIS-II([62]). Similarly, carvedilol was started at 2.5 mg/day and uptitrated to 20 mg/day vs. 3.125 mg twice daily with uptitration 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 not receiving GDMT. With a sample size of 1319 patients, this analysis was likely underpowered, yet consistent benefits were observed for ACE-I/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 ACE-I/ARBs in HFrEF patients have been performed in Asian populations. For instance, the JCARE-CARD investigators demonstrated similar clinical outcomes when comparing ACE-I 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 (clinicaltrials.gov identifier:NCT02007720). This trial is targeting enrollment of 1520 patients within Asia in parallel to the overall international RELAX-AHF-2 trial with target enrollment of 6800 patients (clinicaltrials.gov identifier:NCT01870778).

Future Directions

Given the differences in phenotype and medical management as well as potential differences in pharmacologic response to HF medications in Asia, we suggest several design considerations for future trials in order to improve applicability to Asian populations. Importantly, early phase pharmacokinetic and dose ranging studies are needed in Asian populations. Subsequently, we propose a development 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/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 impact 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 ≥70 bpm on maximally tolerated beta-blocker dosing. The use of the drug is dependent on the interpretation of maximally tolerated beta-blocker dose 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 impact 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 different 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/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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Appendix 1. Medline (via PubMed) search strategy

To identify additional relevant published data not discussed at the CVCT Asia Forum, we searched MEDLINE (via PubMed) through December 2015. We used Medical Subject Headings and key words, focusing on the most relevant terms for this topic. We manually searched reference lists of pertinent reviews, including studies and background data to find any relevant citations that our searches might have missed. We imported all citations into an EndNote X7 database. One reviewer (J.P.K.) screened and evaluated the retrieved records to select relevant studies.

Search	Add to builder	Query	Items found	Time
#2	Add	Search **(#1) AND english[Filter]**	2478	11:54:01
#1	Add	((“heart failure”[MeSH Terms] OR (“heart”[All Fields] AND “failure”[All Fields]) OR “heart failure”[All Fields]) AND ((“asia”[MeSH Terms] OR “asia”[All Fields]) OR ((“asia”[MeSH Terms] OR “asia”[All Fields]) AND pacific[All Fields]) OR (“hong kong”[MeSH Terms] OR (“hong”[All Fields] AND “kong”[All Fields]) OR “hong kong”[All Fields]) OR (“japan”[MeSH Terms] OR “japan” [All Fields]) OR (“macau”[MeSH Terms] OR “macau”[All Fields]) OR (“mongolia” [MeSH Terms] OR “mongolia” [All Fields]) OR (“china”[MeSH Terms] OR “china”[All Fields]) OR (“korea”[MeSH Terms] OR “korea”[All Fields]) OR (“brunei”[MeSH Terms] OR “brunei”[All Fields]) OR (“myanmar”[MeSH Terms] OR “myanmar”[All Fields] OR “burma”[All Fields]) OR (“myanmar”[MeSH Terms] OR “myanmar”[All Fields]) OR (“cambodia” [MeSH Terms] OR “cambodia”[All Fields]) OR (“timor-leste” [MeSH Terms] OR “timor-leste” [All Fields] OR (“east”[All Fields] AND “timor”[All Fields]) OR “east timor” [All Fields]) OR (“indonesia”[MeSH Terms] OR “indonesia”[All Fields]) OR (“laos”[MeSH Terms] OR “laos”[All Fields]) OR (“alaysia”MeSH Terms] OR “alaysia”All Fields]) OR (“hilippines”[MeSH Terms] OR “hilippines”[All Fields]) OR (“ingapore”[MeSH Terms] OR “ingapore”All Fields]) OR (“hailand”MeSH Terms] OR “hailand”All Fields]) OR (“ietnam”MeSH Terms] OR “ietnam”All Fields]) OR (“fghanistan”MeSH Terms] OR “fghanistan”All Fields]) OR (“angladesh”MeSH Terms] OR “bangladesh”[All Fields]) OR (“bhutan”[MeSH Terms] OR “bhutan”[All Fields]) OR (“india”[MeSH Terms] OR “india”[All Fields]) OR (“indian ocean islands”[MeSH Terms] OR (“indian”[All Fields] AND “ocean”[All Fields] AND “islands”[All Fields]) OR “indian ocean islands”[All Fields] OR “maldives”[All Fields]) OR (“nepal”[MeSH Terms] OR “nepal”[All Fields]) OR (“pakistan”[MeSH Terms] OR “pakistan”[All Fields]) OR (“sri lanka”[MeSH Terms] OR (“sri”[All Fields] AND ”lanka”[All Fields]) OR “sri lanka”[All Fields]))) AND ((“clinical trial”[Publication Type] OR “clinical trials as topic”[MeSH Terms] OR “clinical trial”[All Fields]) OR (“clinical trials as topic”[MeSH Terms] OR (“clinical”[All Fields] AND “trials”[All Fields] AND “topic”[All Fields]) OR “clinical trials as topic”[All Fields] OR “trial”[All Fields]) OR (“registries”[MeSH Terms] OR “registries”[All Fields] OR “registry”[All Fields]) OR cohort[All Fields] OR observational[All Fields])	3038	11:53:00

Appendix 2. Southeastern Asian Countries

South Eastern Asia	Other Regions of Asia
Southern Asia:	**Central Asia:**

South Eastern Asia	Other Regions of Asia
Afghanistan	Kazakhstan
Bangladesh	Kyrgyzstan
Bhutan	Tajikistan
India	Turkmenistan
Maldives	Uzbekistan
Nepal	**Western Asia:**
Pakistan	Armenia
Sri Lanka	Azerbaijan
Eastern Asia:	Bahrain
Hong Kong	Cyprus
Japan	Georgia
Macau	Iraq
Mongolia	Iran
North Korea	Jordan
People's Republic of China	Kuwait
Republic of China	Lebanon
South Korea	Oman
Southeastern Asia:	Palestinian territories
Brunei	Qatar
Burma (Myanmar)	Saudi Arabia
Cambodia	Syria
East Timor	Turkey
Indonesia	United Arab Emirates
Laos	Yemen
Malaysia	
Philippines	
Singapore	
Thailand	
Vietnam	

ABBREVIATIONS

HFrEF	heart failure with reduced ejection fraction
CAD	coronary artery disease
GDMT	guideline-directed medical therapy
ACE/ARB	angiotensin converting enzyme inhibitor/angiotensin receptor blocker
MRA	mineralocorticoid receptor antagonist
ICD/CRT	implantable cardioverter defibrillator/cardiac resynchronization therapy
RAAS	renin angiotensin aldosterone system
LOS	length of stay

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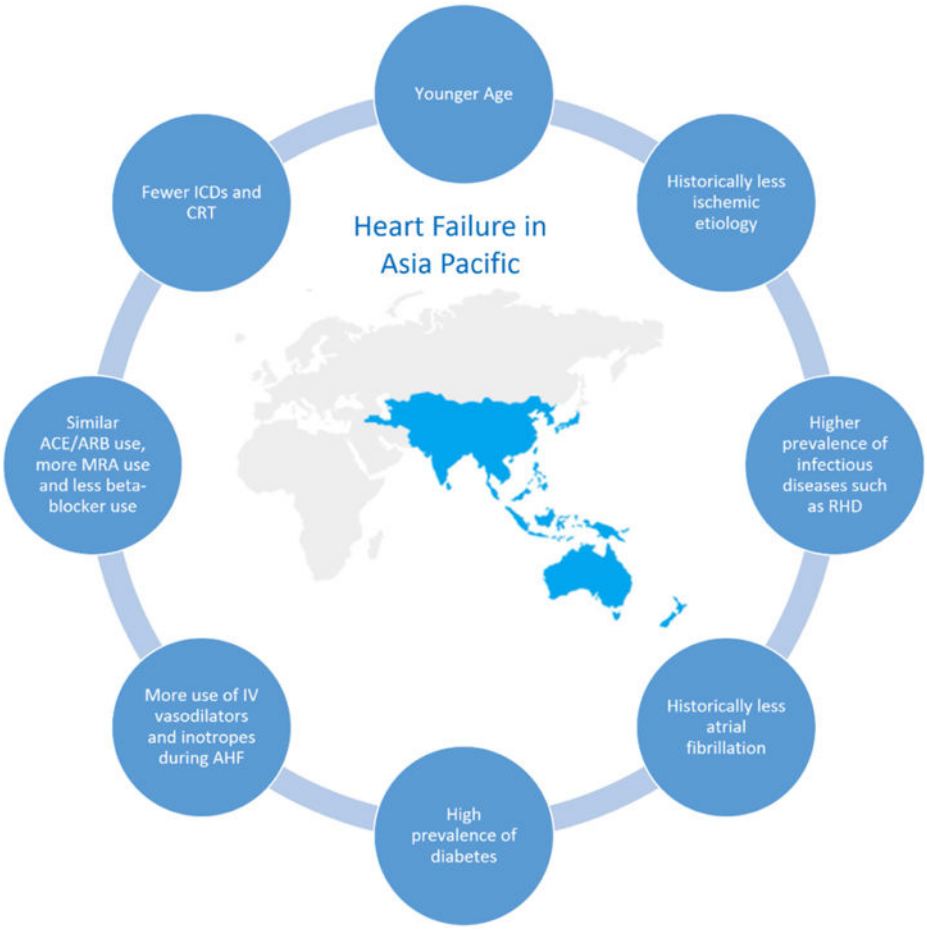

Central Illustration.
HF phenotype and treatment in Asia compared with other regions.

Table

Comparison of clinical characteristics and outcomes in Asia compared with 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)
Study population	2000–04 Japan Stage C/D N=1078 26 hospitals	2006–10 Japan Stage C/D N=4735 24 hospitals	2004–05 Japan AHF N=2549 164 hospitals	2007–11 Japan AHF N=4841 52 hospitals	2011–12 Korea AHF N=206 6 10 centers	2005 Taiwan AHF N=2692 Insured patients	2006–08 AP Region AHF N=10171 43 hospitals	2001–04 US AHF N=105388 274 hospitals	2003–04 US AHF N=48612 259 hospitals	2004–05 Europe AHF N=3580 133 hospitals
Age, yr	69 ± 13	69 ± 12	71 ± 13	73 ± 14	69 ± 14	73 ± 13	67	72 ± 14	73 ± 14	70 ± 13
Male Sex	65%	68%	60%	58%	55%	55%	57%	48%	48%	61%
Ischemic etiology	26%	47%	32%	31%	38%	32%	50%	57%	46%	54%
LVEF/≥50%	51/51%	57/69%	42 ± 18	–	40 ± 18	–	53% (LVEF<4 0%)	34 ± 16/46% (>40%)	39 ± 18	38 ± 15/34% (LVEF≥4 5%)
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, mmHg	126±19	126±19	117±18	146±37	136±31	–	57% with SBP 90–140	144±33	143±33	135 (110–160)
HR, bpm	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	–	>1.5mg/d L in 41%	1.8±1.6	1.8±1.8	–
BNP/NT- proBNP, pg/mL	273±353	191 (C), 454 (D)	375±474	707 (362–1284)	–	–	–	840 (430–1730)	800 (403–1660)	–
Chronic HF therapies										
ACE/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
In patient therapies										
IV diuretic	–	–		76%	72%	76% (all diuretic)	85%	92%	–	84%
IV vasodilator	–	–		78%	40%	–	14% (IV nitrate)	9%	14%	38%
IV Inotrope				19%	32%	–	15%	15%	7%	>11%

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	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])
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)	8	15.8±42.7	6.0	4.3	6.4	9 (6–14)
30-day Mortality	–	–	–	–	1.2%	–	–	–	8.6% at 60–90 days	–
Short-term rehospitalizati on	–	–	–	–	6% HF rehosp at 30-day	–	–	–	29.6% at 60–90 days	–

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