Review Article

Understanding the Epidemiology of Heart Failure to Improve Management Practices: An Asia-Pacific Perspective

JEYAMALAR RAJADURAI, MBBS,[1] HUNG-FAT TSE, MBBS, MD, PhD,[2] CHAO-HUNG WANG, MD, PhD,[3] NING-I YANG, MBChB,[3] JINGMIN ZHOU, MD,[4] AND DAVID SIM, MBBS[5]

Subang Jaya, Malaysia; Hong Kong and Shanghai, China; Taoyuan, Taiwan; and Singapore

ABSTRACT

Heart failure (HF) is a major global healthcare problem with an estimated prevalence of approximately 26 million. In Asia-Pacific regions, HF is associated with a significant socioeconomic burden and high rates of hospital admission. Epidemiological data that could help to improve management approaches to address this burden in Asia-Pacific regions are limited, but suggest patients with HF in the Asia-Pacific are younger and have more severe signs and symptoms of HF than those of Western countries. However, local guidelines are based largely on the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association guidelines, which draw their evidence from studies where Western patients form the major demographic and patients from the Asia-Pacific region are underrepresented. Furthermore, regional differences in treatment practices likely affect patient outcomes. In the following review, we examine epidemiological data from existing regional registries, which indicate that these patients represent a distinct subpopulation of patients with HF. In addition, we highlight that patients with HF are under-treated in the region despite the existence of local guidelines. Finally, we provide suggestions on how data can be enriched throughout the region, which may positively affect local guidelines and improve management practices. (*J Cardiac Fail 2017;23:327–339*)

Key Words: Asia-Pacific, heart failure, epidemiology, management.

Heart failure (HF) has an estimated global prevalence of approximately 26 million and is a leading cause of morbidity and mortality and therefore is a global health care problem.[1,2] In Asia-Pacific regions, HF is associated with a significant socioeconomic burden, representing a major cause of hospital admissions and readmissions, loss of work and productivity, and death.[3–6] In Western countries, extensive information is available on the epidemiology and management of HF because of established disease-specific registries[7–12] and clinical guidelines.[13,14] In contrast, reliable data on disease prevalence and incidence of HF in Asia-Pacific regions are lacking and it is likely that region-wide differences in treatment practices affect patient outcomes. An accurate account of HF in this region is critical and has the potential to influence clinical management, which may improve patient outcomes over the short and long term.

In this narrative review, current understanding of the epidemiology of HF in Asia-Pacific regions is discussed (supported by data from local disease registries and regional clinical trials) to characterize how patients from these regions may differ from Western countries. We review current clinical management practices and local guidelines throughout the region, highlighting ways in which regional data and management practices can be enhanced to improve patient outcomes.

Search Strategy

We searched PubMed for English-language articles reporting on the epidemiological data and current management

From the [1]Department of Cardiology, Subang Jaya Medical Centre, Subang Jaya, Malaysia; [2]Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [3]Heart Failure Research Center, Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung; Chang Gung University College of Medicine, Taoyuan, Taiwan; [4]Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China and [5]Department of Cardiology, National Heart Centre Singapore, Singapore.

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Reprint requests: Jeyamalar Rajadurai, MBBS, Department of Cardiology, Subang Jaya Medical Centre, Subang Jaya, Malaysia. Tel: +60 3 5639 1212; Fax: +60 3 5639 1209. E-mail: rjeyacardio@gmail.com

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practices of adults with HF in Asia-Pacific regions published between January 2000 and August 2016 using the following search criteria: Asia/Asia Pacific, heart failure/chronic heart failure/acute heart failure (including heart failure with reduced or preserved ejection fraction). The search results were first evaluated by title and/or abstract for relevant publications, particularly registry, observational, and controlled studies. Full articles were reviewed for those citations identified for inclusion in the manuscript, the majority of which were published after 2010. We also examined the official websites of national HF societies to identify local HF guidelines.

The Epidemiology of HF in Asia-Pacific Regions

Prevalence of HF

Approximately 5.7 million (2.2%) adults aged ≥20 years in the United States have HF.[15] In contrast to Western countries, there are large gaps in information relating to HF in Asia.[16] According to the America Heart Association (AHA), current estimates of HF prevalence in this region range from 1.26% to 6.7%.[15] Looking specifically at individual countries and areas within Asia, the enormity of the problem becomes clear. For example, in China alone, approximately 4.2 million people have HF, whereas in India prevalence estimates vary widely between 1.3 and 23 million, and in Southeast Asia, 9 million people are estimated to have HF.[17–19] Additionally, based on the incidence of de novo HF in the United States (10 of 1000 people aged ≥65 years, per year),[15] it has been predicted that more than 0.37 million Japanese individuals aged ≥65 years will develop new-onset HF in 2025.[20] With the aging population and the rising prevalence of various cardiovascular (CV) risk factors, such as hypertension and diabetes, it is evident that a significant number of people will continue to develop HF every year in the region.[16,21–23] Data available from the few regional studies indicate a prevalence of HF among hospitalized patients of 3.4% to 6.7%,[20,24] and in common with evidence from Western populations, studies suggest that hospitalization for HF is increasing in the region.[25,26] Further detail by type of HF is required to characterize the region-specific burden of disease. The following overview provides a summary of the current epidemiological data of acutely decompensated HF (ADHF) and chronic HF (HF with reduced ejection fraction [HFrEF] and HF with preserved ejection fraction [HFpEF]) in the Asia-Pacific.

ADHF

Patients with ADHF commonly present in the emergency setting and require urgent management. Admission to hospital for ADHF is a powerful predictor of readmission and postdischarge death in patients with chronic HF.[27,28] Therefore, identification and appropriate management of these patients is crucial for improving outcomes.

Despite an increase in the prevalence of ADHF, there are still limited data on its epidemiology, treatment, and prognosis in the Asia-Pacific region. As shown in Table 1, regional data are available from the Acute Decompensated Heart Failure Registry-International Asia-Pacific (ADHERE-AP),[29] the Thai Acute Decompensated Heart Failure Registry,[30] the Acute Decompensated Heart Failure Syndromes (ATTEND) registry,[31] the Korean Acute Heart Failure registry,[32] and the Taiwan Society of Cardiology—Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry,[33] which can be compared with data from the United States (Acute Decompensated Heart Failure National Registry [ADHERE]),[9] Europe (EuroHeart Failure Survey II [EHFS II]),[34] and the United Kingdom National Heart Failure Audit (UKNHFA).[35]

Overall, patients from the Asia-Pacific were similar to Western populations, but with some notable differences. With the exception of patients enrolled in the ATTEND registry (mean age 73 years), the mean ages of patients with ADHF in the Asia-Pacific (64–69 years) are lower than that of Western registries (69–78 years), including the Get With The Guidelines-HF registry conducted in the United States (2005–2014; N = 117,761).[36] A known history of HF was reported in similar proportions of patients across the registries (50%–75%),[9,29,30,32,34,35] aside from ATTEND and TSOC-HFrEF (36% and 40%, respectively).[31,33] Overall, in both Asian and Western registries, a history of ischemic heart disease was relatively common, although some variation was observed (31%–58%; Table 1).[9,29–35] However, incidence of valvular heart disease was lower in regional registries compared with the EHFS II study (Table 1).[9,29–35] Intraregional variation in comorbidity rates could help explain these differences.

Despite some differences in patient characteristics, the burden of in-hospital morbidity/mortality in the Asia-Pacific is similar to Western registries. With the exception of Japanese patients (in which median hospital length of stay was 21 days), hospital stay was similar in Asia-Pacific registries compared with ADHERE, EHFS II, and UKNHFA (median length of stay 6–8 days vs 4–9 days, respectively).[9,29–35] The range in length of hospital stay may be a result of differences between national health insurance systems, hospital location (eg, metropolitan vs rural), and hospital teaching/academic status.[37,38] In-hospital mortality in Asia-Pacific registries was also generally comparable to those in western registries, despite more patients requiring mechanical ventilation in the Asia-Pacific region (Table 1).

Data from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial (ASCEND-HF), covering 5 geographical regions including North America, Western Europe, and the Asia-Pacific, are consistent with registry findings; for example, patients from the Asia-Pacific were younger (62 years) compared with those from North America (67 years) and Europe (74 years), and hypertension was the most common comorbidity irrespective of region studied.[39] Moreover, median length of hospital stay was 5 days for patients in the Asia Pacific and North America, but was slightly greater in Western Europe (8 days).

Chronic HF

Table 2 summarizes the baseline clinical characteristics of patients enrolled in chronic HF registries across the

Table 1. Baseline Characteristics and Clinical Treatment of Patients with Acute Decompensated HF Enrolled in Regional Registries

Study	ADHERE-AP[29]	Thai-ADHERE[30]	ATTEND[31]	KorAHF[32]	TSOC-HFrEF[33]	ADHERE[9]	EHFS II[34]/UKNHFA[35]
Geography (time frame)	8 countries in the Asia-Pacific (2006–2008)	Thailand (2006–2007)	Japan (2007–2012)	Republic of Korea (2011–2012)	Taiwan (2013–2014)	United States (2001–2004)	Europe/United Kingdom (2004–2005)/(2014–2015)
Patients (n)	10,171	1612*	4842	2066	1509	159,168	3580/56,915 cases (N = 41,461)
Mean age (y)	66	64	73	69	64	72	70/78
Male (%)	57	50	58	55	72	48	61/55
Mean LVEF (%)	NR	NR	NR	40	28	38	38/NR
LVEF <40 (%)	53	40	53	56	100	51	66†/NR
Known HF history	64	67	36	50	40	76	63/NR
NYHA I/II/III/IV (%)	NR	NR/15/16/70	<2/16/38/44	NR/NR/41/41‡	NR/12/NR§/NR§	NR	NR/NR/19/45/37
Etiology (%)							
Ischemic heart disease	50	47	31	38	44	58	54/51‖ and 40¶
Valvular heart disease	NR	19	19	13	8	*NR*	34/23‖ and 33¶
Hypertensive	NR	12	18	6	5	*NR*	11/NR
Cardiomyopathy	NR	14	13	15	33**	*NR*	19/NR
Comorbidities (%)							
Hypertension	64	65	69	59	35	74	63/52‖ and 61¶
Dyslipidemia	*NR*	51	37	*NR*	20††	*NR*	*NR*/NR
Diabetes mellitus	45	47	34	36	44	*NR*	33/33‖ and 33¶
Chronic kidney disease	22‡‡	19§§	*NR*	14§§	32	30§§	17§§/NR
Atrial fibrillation	24	24	40‖‖	27	26	31	39‖‖ /21‖ and 22¶
COPD	*NR*	8¶¶	10***	11***	11¶¶	31¶¶	19/17‖ and 19¶
Previous stroke or TIA	13	12	14	15	9	*NR*	13/NR
In-hospital management (%)							
IV diuretics	85	96	76	72	63	87	84/NR
IV nitrates	14	22	35	40	NR	9	38/NR
IV inotropic agents	15	23	19	32	37	8	30†††NR
Mechanical ventilation/intubation	9	20	8	14	13	3	5/NR
Discharge medication (%)							
RAAS inhibitors	63	48	70–75‡‡‡	65	62	83	80§§§/91‖
β-blockers	41	25	67	44	60	80	61/86‖
Aldosterone antagonists	31	17	40–50‡‡‡	40	49	33	48/52‖
Diuretics	*NR*	73	80–85‡‡‡	NR	82	87	90/98‖

(*continued on next page*)

Table 1. (*Continued*)

Study	ADHERE-AP[29]	Thai-ADHERE[30]	ATTEND[31]	KorAHF[32]	TSOC-HFrEF[33]	ADHERE[9]	EHFS II[34]/UKNHFA[35]
Digitalis	34¶¶¶	26¶¶¶	10–15‡‡‡	NR	26	38¶¶¶	31/23‖¶¶¶
Calcium channel blockers	NR	NR	25–30‡‡‡	NR	NR	NR	15/NR
Statins	NR	NR	30–35‡‡‡	NR	NR	NR	42/NR
ICD	1.6	3****	3.4	1.4††††	1.0††††	NR	1.2††††/NR
CRT	4.2	3****	2.3	1.3††††	1.0††††	NR	2.7††††/NR
Outcomes (%)							
Median length of hospital stay (d)	6	8	21	8	8	4	9/9
In-hospital mortality (%)	5	6	6	6	2	4	7/9.6

*2041 admissions.
†LVEF <45%.
‡Reported as severity of dyspnea.
§88% of patients had severe HF (NYHA class III or IV).
‖Heart failure reduced ejection fraction.
¶Heart failure preserved ejection fraction.
**Dilated cardiomyopathy.
††Atherogenic dyslipidemia.
‡‡Chronic renal insufficiency (>177 μmol/L/>2.0 mg/dL or on dialysis.
§§Chronic renal failure/insufficiency.
‖‖Atrial fibrillation or atrial flutter.
¶¶COPD or asthma.
***Chronic respiratory disease.
†††IV positive inotropes were administered as follows: dopamine (11%); dobutamine (10%); levosimendan (4%); noradrenaline (3%) and adrenaline (2%).
‡‡‡Data have been approximated.
§§§Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.
¶¶¶Digoxin.
****CRT or ICD.
††††During hospitalization.

ADHERE, acute decompensated heart failure national registry; ADHERE-AP, acute decompensated heart failure registry-international Asia-Pacific; ARIC, Atherosclerosis Risk in Communities Study Community Surveillance; ATTEND, acute decompensated heart failure syndromes registry; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EHFS II, EuroHeart failure survey II; HF, heart failure; ICD, implantable cardioverter defibrillator; IV, intravenous; KorAHF, Korean acute heart failure registry; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; RAAS, renin angiotensin aldosterone system; Thai-ADHERE, Thai acute decompensated heart failure registry; TIA, transient ischemic attack; TSOC-HFrEF, Taiwan Society of Cardiology—Heart Failure with reduced Ejection Fraction registry; UKNHFA, United Kingdom National Heart Failure Audit.

Table 2. Baseline Characteristics and Clinical Treatment of Patients Enrolled in Regional Chronic HF Registries

Study	ASIAN-HF[16]	Yu et al.[40]	CHART-1[41]	KorHF[42]	CHF-REF[43]	CHART-2[41]	HEARTS[44]	INTER-CHF*[45]	ADHERE[9]	EHFS II[34]/ UKNHFA[35]
Geography (time frame)	11 countries in Asia (2012–2015)	China (2000–2010)	Japan (2000–2004)	Republic of Korea (2004–2009)	China (2005–2009)	Japan (2006–2010)	Dubai (2011–2012)	4 countries in Asia (2012–2014)	United States (2001–2004)	Europe/United Kingdom (2004–2005)/(2014–2015)
Patients (n)	5276	12,450	1006	1527	2154	3676	504	2661	159,168	3580/56,915 cases (N = 41,461)
Mean age(y)	60	62	69	69	64	70	63	60	72	70/78
Mal (%)	78	58	64	56	79	66	65	59	48	61/55
Mean LVEF (%)	28 (median)	NR	50	29	37	56	NR	NR	38	38/NR
LVEF <40 (%)	100	NR	54†	100	100	37†	54	59‡	51	66§/NR
Known HF history	64.1‖	NR	NR	31	NR	NR	82	28‖	76	63/NR
NYHA I/II/III/IV (%)	13/52/29/6	<1/23/50/ 27	NR/78/21/1	*NR*/*NR*/60/60¶	0/41/34/25	*NR*/86/14/1	NR	13/45/29/13	NR	NR/NR/19/45/37
Etiology (%)										
Ischemic heart disease	47	28	27	40	*NR*	48	NR	48	58	54/51** and 40††
Valvular heart disease	NR	18	*NR*	13	NR	NR	NR	13	NR	34/23** and 33††
Hypertensive	NR	32	NR	NR	NR	NR	NR	14	NR	11/NR
Cardiomyopathy	NR	27	33	22	NR	18	NR	10	NR	19/NR
Comorbidities (%)										
Hypertension	52	NR	46	42	57	87	72	59	74	63/52** and 61††
Dyslipidemia	NR	NR	16	NR	24	78	23	26	*NR*	*NR*/NR
Diabetes mellitus	40	NR	19	31	17	35	66	28	*NR*	33/33** and 33††
Chronic kidney disease	*NR*	NR	NR	7‡‡	NR	NR	NR	7	30‡‡	17‡‡/NR
Atrial fibrillation	18	NR	42	21§§	16	42	21	NR	31	39§§/21** and 22††
COPD	8‖‖	NR	NR	3	23	NR	17¶¶	NR	31¶¶	19/17** and 19††
Previous stroke or TIA	6	NR	NR	8	5	NR	13	10	NR	13/NR
Medication (%)										
RAAS inhibitors	75	51	69	68	66	73	73	68	55***	80/91**
β-blockers	79	44	29	41	68	51	81	61	58	61/86**
Aldosterone antagonists	59	53	19	38	75	27	49	44	16	48/52**
Diuretics	82	69	77	NR	74	56	91	62	65	90/98**
Digitalis	NR	48	49	NR	58†††	25	7	28	19†††	31/23**†††
Calcium channel blockers	NR	NR	29	NR	46	38	15	NR	11	15/NR
Statins	NR	NR	NR	NR	43	36	67	NR	47	42/NR
ICD	14‡‡‡	NR	1.6‡‡‡	NR	2.2‡‡‡	2.8‡‡‡	NR	NR	5.4§§§	1.2§§§/*NR*
CRT	14‡‡‡	NR	1.6‡‡‡	NR	5.8	2.8†††	NR	NR	NR	2.7§§§/NR

*INTER-CHF was conducted in 16 countries across Africa, Asia, Middle East and South America (only data for Asia are presented in the table).
†LVEF <50%.
‡41% of patients had preserved ejection fraction (defined as LVEF ≥50%).
§LVEF <45%.
‖Previous hospitalization for HF (in past year for INTER-CHF).
¶Reported as 60% (NYHA class III–IV).
**Heart failure reduced ejection fraction.
††Heart failure preserved ejection fraction.
‡‡Chronic renal insufficiency.
§§Atrial fibrillation or atrial flutter.
‖‖Chronic respiratory disease.
¶¶COPD or asthma.
***Total calculated percentage of patients treated with angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers and renin inhibitors.
†††Digoxin.
‡‡‡CRT-D or ICD.
§§§During hospitalization.
ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; CHART, Chronic Heart Failure Analysis and Registry in the Tohoku District; CHF-REF, Chinese Chronic HF with reduced ejection fraction; HEARTS, Heart Function Assessment Registry Trial in Saudi Arabia; INTER-CHF, INTERnational Congestive Heart Failure; other abbreviations as in Table 1.

Asia-Pacific[16,40–45] compared with patients enrolled in registries in the United States (ADHERE)[9] and Europe (EHFS II/UKNHFA).[34,35] In general, patients were younger than those in Western countries, as shown in the recent Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) and INTERnational Congestive Heart Failure (INTER-CHF) registry studies, in which mean age was 60 years.[16,45] The majority of patients with HF in the Asia-Pacific were male and aside from 3 studies that recruited patients with a left ventricular (LV) ejection fraction (LVEF) <40% only,[16,42,43] the prevalence of HFrEF was 37% to 59% (Table 2). Furthermore, patients with HF in regional registries were predominately New York Heart Association class II/III.[16,40–45]

Ischemic heart disease was the major cause of HF in Asia-Pacific populations (27%–48%), which is not too dissimilar to that observed in Western populations (40%–58%).[9,16,34,35,40–42,45] Despite some inconsistencies, comorbidities such as hypertension and diabetes were highly prevalent in Asian patients with HF (Table 2).[16,41–45] Notably, some registry populations (Heart Function Assessment Registry Trial in Saudi Arabia [HEARTS]) were highly heterogeneous, containing subpopulations from other regions and ethnic groups.[44]

Several global HF trials have examined geographic variations in clinical profile, management, and postdischarge outcomes.[46,47] Similar to the registry data, notable differences were recorded in the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial for patient age (58 years in the Asia-Pacific and 65–68 years in the United States/Western Europe); furthermore, evidence-based therapies were most frequently used in Western regions.[47] Of note, this study found that the risk of death was greater in the Asia-Pacific compared with North America.

A Focus on HFpEF

Despite clear guidance on the definition, diagnosis, and treatment of HFrEF vs HFpEF,[13,14] there are limited epidemiological data on HFpEF in Asia-Pacific populations. The majority of data is accessible through chronic HF registries, predominately in Japanese populations (eg, Chronic Heart Failure Analysis and Registry in the Tohoku District [CHART] studies). In these studies, the prevalence of HFpEF ranged from 50% to 70% of the total HF population,[48–50] higher than that reported in multiethnic studies in Singapore (38.3%)[51] and the INTER-CHF study of 5813 patients from Africa, Asia, the Middle East, and South America (26% of the total population and 41% of 2661 Asian participants).[45] Further, the prevalence of HFpEF in Japan is higher than in Western registries (51%–69% vs 36%–47%, respectively),[49,52–54] and continues to increase (46% vs 63% in CHART-1 [2000–2005] and CHART-2 [2006–2010], respectively),[41] which is in contrast to the modest increase in prevalence recorded in the Framingham studies (33% in 2000 vs 39% in 2010).[55] The underlying reasons for the difference in rates are unclear at present; however, lifestyle factors are likely to have a major impact on disease prevalence (both HFpEF and HF in general).[41]

Large-scale studies, including the Japanese Cardiac Registry of Heart Failure in Cardiology, have demonstrated that, compared with patients with HFrEF, Japanese patients with an LVEF >50% are significantly older and are more likely to be female with higher systolic blood pressure and lower heart rate.[48,50] Patients with HFpEF were also more likely to have a history of hypertension, renal failure, anemia, and atrial fibrillation compared with patients with HFrEF, in which hyperlipidemia, sustained ventricular tachycardia or ventricular fibrillation, and prior coronary revascularization were more common.[48] These data are supported by observations from the multiethnic study in Singapore[51] and in a population-based study conducted in northeast China.[56] In this latter study of 2230 patients, the prevalence of HFpEF was greater in women than men (4.9% vs 1.8%, respectively; $P < .01$) and increased with age in both sexes; furthermore, although men with HFpEF had a higher prevalence of hypertension, obesity, and history of heart disease, women with HFpEF tended to have hypertension, history of stroke, hyperuricemia, and reduced renal function.[56]

Several studies have reported that all-cause mortality in Japanese patients with HFpEF is not significantly different to that in patients with HFrEF (ranging from ~20% to 25% in both populations).[41,48,57] In contrast, Yap et al. reported a lower 2-year all-cause mortality rate in patients with HFpEF compared with patients with HFrEF in a broad spectrum of Asian ethnicities (27% vs 37%, respectively).[51] Encouragingly, data from the CHART-2 study suggest that the 3-year incidence rates of all-cause and CV deaths of patients with both HFrEF and HFpEF are improving.[41]

Current HF Diagnostic and Treatment Patterns in the Asia-Pacific

Our review of the epidemiological data for HF has revealed considerable inter- and intraregional variations, which include differences in the underlying causes of HF and the prevalence of comorbidities within the region, the age of patients hospitalized for HF, and length of hospital stay between Asia-Pacific and Western countries. Possible explanations include genetic and disease-modifying factors (eg, risk factors for CV disease and comorbidities), but also contrasting approaches to management.[58,59] In the Asia-Pacific region overall, the diagnosis of HF is usually made on clinical grounds. In the ADHERE-AP registry, measurement of natriuretic peptide levels was performed in few patients hospitalized for ADHF; brain natriuretic peptide (BNP) was assessed in 7.8% and N-terminal pro B-type natriuretic peptide (NT-proBNP) was assessed in 8.5% of cases.[29] Use of echocardiography was higher; LV function was assessed in approximately one-half of patients.[29] In contrast, echocardiography was performed in 94.5% of patients in the TSOC-HFrEF registry, and NT-proBNP, BNP, and troponin levels determined in 22.7%, 32.4%, and 64.4% of cases, correspondingly.[33] In the Korean

HF registry, 76.6% and 79.8% of patients hospitalized for ADHF were assessed for natriuretic peptide levels or LV function, respectively, to support a clinical diagnosis.[42] In patients with stable HF in the outpatient setting, assessment of LV function is considerably lower. In Australian primary care clinics, echocardiography was performed in approximately 22% and 64% of outpatients with a suspected or known diagnosis of HF, respectively.[60]

The use of intravenous diuretics to relieve volume overload in patients admitted to the hospital with ADHF in Asia-Pacific registries was common (63%–96%), similar to the ADHERE and EHFS II registries (87% and 84%, respectively) (Table 1). Administration of intravenous nitrates and use of inotropic agents in the region were higher than reported in ADHERE, but comparable to EHFS II registries (Table 1). In addition, more patients required mechanical ventilation (8%–20%, compared with 3%–5% in the Western registries). This suggests that patients admitted to the hospital with ADHF in Asia-Pacific regions may present with more clinically severe conditions.

Despite evidence that adherence to pharmacological treatment guidelines results in improved clinical outcomes,[61,62] the reported use of pharmacotherapy is generally lower in Asia-Pacific countries compared with patients with HF enrolled in Western registries (Tables 1 and 2). There were fewer patients discharged on evidence-based HF treatment in Asia-Pacific registries. The use of renin angiotensin aldosterone system (RAAS) inhibitors ranged from 51% to 75% in the region, lower than that reported in ADHERE (83%), EHFS II (80%), and UKNHFA (91%) (Table 2).[9,16,34,35,40–42,44,45] β-blocker use varied widely in Asia-Pacific registries (Table 2), although recent data from ASIAN-HF (79%) and INTER-CHF (61%) were more comparable to Western studies (61%–86%) (Table 2).[9,16,34,35,40–45] Of interest, higher proportions of patients with HFrEF (90%) and HFpEF (83%) enrolled in the Swedish HF Registry (2005–2012; N = 41,976), received β-blockers,[63] compared with other European studies, despite limited evidence of the benefit of β-blockers in HFpEF.[13]

The use of aldosterone antagonists ranged widely throughout the region. Low use (19%) was reported in the Japanese CHART-1 study, which was comparable to 16% of patients prescribed aldosterone antagonists before hospital admission in the Get With The Guidelines-HF registry in the United States (2005–2014; N = 117,761);[36] in other studies, reported use ranged from 27% to 53%, which was comparable with other Western registries (33%–59%).[9,16,34,35,40–42,44,45] High use of aldosterone antagonists (75%) was reported in the Chinese Chronic HF with Reduced Ejection Fraction (CHF-REF) study.[43] Of note, the aldosterone antagonist spironolactone was primarily used because eplerenone is not approved for use in many countries in the region.

A relatively higher proportion of patients (48%–58%) was prescribed digitalis in China and Japan (according to CHART-1, CHF-REF, and the large registry conducted in China by Yu et al.),[40,41,43] compared with other Asia-Pacific countries (7%–28%).[41,44,45] The role of digitalis in the treatment of HF is less certain,[13] and use is less common in the United States and Europe, with 19% to 38% of patients reported to receive digitalis in the ADHERE, Get With The Guidelines-HF, EHFS II, and UKNHFA registries.[9,34–36]

In general, prescription of diuretics (mainly loop diuretics) was similar between patients with HF in the Asia-Pacific (56%–91%) and the United States and Europe (65%–98%; Table 2). Device use (defibrillator, pacemaker, or cardiac resynchronization therapy) was low in the region (2%–6%), which was consistent with EHFS II (1%–3%),[34] but lower than that reported in more recent studies in Europe (use ranging from 5% to 18%) and America (5.1%–5.4%).[64,65] By contrast, device use was considerably greater in the ASIAN-HF registry (14.3%).[16]

Recent data from a multiethnic Asian population indicated that patients with HFpEF were less likely to receive angiotensin-receptor-blockers/angiotensin-converting-enzyme inhibitors (60% vs 74%), diuretics (78% vs 87%), mineralocorticoid receptor antagonists (8% vs 22%), β-blockers (50% vs 65%), and statins (61% vs 72%) than patients with HFrEF (all $P < .001$).[51] This was supported by Takada et al., who reported that Japanese patients with LVEF >50% were less likely to receive RAAS inhibitors (70% vs 80%, $P < .001$), loop diuretics (31% vs 57%, $P < .001$), aldosterone antagonists (14% vs 34%, $P < .001$), or β-blockers (40% vs 65%, $P < .001$) than patients with LVEF <50%. The use of statins was consistent in both populations in this study.[50]

Finally, treatment patterns across the Asia-Pacific region vary not only by country but also by setting. In general, patients with HF managed by cardiologists in hospitals compared with those managed by general practitioners in primary care were more likely to be treated at target doses of RAAS inhibitors and β-blockers (Table 3).[66–70]

Progress Toward Improvements in Data Quality and Management Practices in the Asia-Pacific

Epidemiological data from the Asia-Pacific region are relatively limited compared with data from Western populations, despite the existence of some registries. However, our review of the epidemiological and treatment data available for the region underlines the need to improve the quality of data collected on patients as well as management practices to reduce inequalities within and between countries.

Regional Studies

Available registry data indicate that patients with HF from the Asia-Pacific represent a distinct population compared with their Western counterparts (Tables 1 and 2). Clinical trials provide the means to further capture and understand baseline characteristics of patient populations across different countries and regions. Although trial inclusion and exclusion criteria may limit the generalizability to some extent, such information would provide insights that could lead to improvements in local management practices. However, it is widely recognized that patients from Asia-Pacific countries are underrepresented in global HF clinical trials.[71]

Table 3. Regional Management of Patients with HF in Primary Care vs at a Specialized Unit

Study	Krum et al., 2001[66]	JCARE-GENERAL GP-HF[67]	JCARE-GENERAL Hospital-HF[67]	Yao et al., 2011[68]	Ho et al., 2014[69]	Mao et al., 2014[70]
Geography (time frame)	Australia (1998)	Japan (2004–2005)	Japan (2004–2005)	Australia (2006–2011)	Australia (2006–2011)	Taiwan (2010–2012)
Study design	Prospective multicenter	Prospective multicenter	Prospective multicenter	Retrospective analysis of medical records at a single center	Retrospective analysis of medical records at a single center	Prospective single center
Population	Outpatients with known or suspected HF presenting to a primary care physician	Outpatients with stable HF managed by primary care physicians in general practice	Outpatients with stable HF managed by cardiologists in hospital	Patients hospitalized for HF	Patients with documented HF attending a multidisciplinary clinic in tertiary hospital	Patients with documented HF attending a multidisciplinary clinic in tertiary hospital
Patients (n)	2905	1405	1280	667	255	349
Mean age (y)	NR	77	71	76	81	60
Male (%)	NR	38	55	53	47	70
Assessment of LV function (%)	64 (known HF); 22 (suspected HF)	NR	NR	36	NR	100
LVEF <40 (%)	NR	NR	NR	50*	43†	66‡
Medication (%)						
RAAS inhibitors	59§	51	69	58	97	92
β-blockers	12	18	38	35	93	77
Aldosterone antagonists	8	NR	NR	12	NR	NR
Diuretics	63	58	66	72	NR	NR
Digitalis	31‖	41	45	19‡	NR	NR
Calcium channel blockers	10	41	33	11	NR	NR
Statins	NR	NR	NR	22	NR	NR

*LVEF <45%.
†Systolic HF.
‡Mao CT, Liu MH, Hsu KH, Fu TC, Wang JS, Huang YY, et al. Unpublished data.
§ACEI.
‖Digoxin.
ACEI, angiotensin-converting-enzyme inhibitor; JCARE-GENERAL, Japanese cardiac registry of heart failure in general practice; LV, left ventricular; other abbreviations as in Table 1.

Enrollment of Asian patients ranged from 1% to 27% in recent landmark trials such as Metoprolol Randomized Intervention Trial in congestive Heart Failure (MERIT-HF), Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT), Randomized Aldactone Evaluation Study (RALES), Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure (EMPHASIS-HF), PARADIGM-HF, Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEEAL), Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), and ASCEND-HF, in which white patients predominated.[39,46,47,72] Other large HF trials, including Studies of Left Ventricular Dysfunction Treatment (SOLVD-T) and Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added, have not included any Asian patients.[59,72]

There is an urgent need for increased representation of patients from Asia and the Pacific in future clinical trials and international registries.[71] However, important progress is being made in this respect as evidenced by the initial patient characteristics data from the ASIAN-HF registry of 5276 patients with HFrEF from 11 countries (China, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Republic of Korea, Singapore, Taiwan, and Thailand).[16] Implementation of diagnostic tools in the region, specifically echocardiography, which was shown to be underused on patients in ADHERE-AP compared with data from Western registries,[29,73] is being examined. Furthermore, ASIAN-HF will explore the controversy over sudden cardiac death and use of implantable devices in the region. According to Western data, sudden cardiac death accounts for ~50% of deaths in patients with HF [74]; however, some studies have suggested a lower incidence in Asian patients, and recent trials have provided inconclusive data on the benefit of implantable devices.[75–78] It is anticipated that data from ASIAN-HF will address the ambiguity surrounding sudden cardiac death and device use in the region allowing physicians to make informed decisions on treatment intervention.[73]

Regionally specific data will also be generated as part of the Asian Network for Translational Research and Cardiovascular Trials (ATTRaCT) initiative, which will investigate the underlying CV disease pathophysiology of HF in Asia with the aim of identifying target diagnostic tools and therapies. Further regional trials of note include the Singapore Heart Failure Outcomes and Phenotypes and Prospective Evaluation of Outcome in Patients with Heart Failure with Preserved Left Ventricular Ejection Fraction (PEOPLE) studies. These are the first studies determining the epidemiology, outcomes and inter-ethnic differences in patients with HFpEF in Singapore (n = 1250) and New Zealand (n = 1073), respectively.[79]

Data of relevance for the region will also be generated by the International Registry to Assess Medical Practice with Longitudinal Observation for Treatment of Heart Failure (REPORT-HF), a global, prospective, observational study that will characterize patient outcomes following an index hospitalization for HF.[80] It is anticipated that approximately 20,000 patients with new-onset HF will be enrolled in >300 sites in 40 countries with a follow-up period of 3 years.

The studies discussed previously will significantly enhance epidemiological data in the region; however, fundamental improvements to the number of Asian-Pacific patients represented in global trials including clinical and observational studies are essential to fully understand future regional trends and the overall disease burden. Dedicated regional clinical trials, designed specifically to account for patient characteristics and clinical practices may also be warranted.[71] One such example is the ongoing RELAXin in Acute Heart Failure in Asia (RELAX-AHF-ASIA) trial, which has been designed to account for specific management pathways for acute HF in the region.[81]

Several barriers to patient enrollment currently exist, including (1) poor awareness of HF and knowledge of the clinical trial process, (2) reluctance to participate due to cultural/social beliefs, and (3) poor access to hospitals/medical centers (particularly for rural/remote patients). Strategies to improve patient education would be effective in tackling the first 2 barriers; the third barrier would most likely require intervention by organizations with the medical sphere to improve local infrastructure.

In parallel, improvements to study centers throughout the region will be required to support increased numbers of enrolled patients. These include (1) enhanced medical and administrative resources in local academic centers (eg, availability of diagnostic tools and trained support staff), (2) increased number of participating centers in global trials, (3) improved recognition of centers currently participating in global trials, and (4) closer relationships between academic establishments and pharmaceutical organizations (effectively demonstrated by The Agency for Science, Technology and Research and The National University Heart Centre, Singapore).[79] A coordinated effort on behalf of physicians, academic establishments, pharmaceutical companies, and local government will be required to successfully accomplish these goals.

Differences between Regional Guidelines and European Society of Cardiology (ESC) or American College of Cardiology Foundation (ACCF)/AHA Guidelines

Many countries in the Asia-Pacific region have published practical guidelines on the diagnosis and treatment of HF to drive improvements in management practices.[82–89] These guidelines are based mainly on evidence derived from clinical trials conducted in Europe and the United States[2]; as a result, guidelines published by Asia-Pacific countries are somewhat overlapping.[82,83,85,86,88–90]

Although regional guidelines are largely consistent with ESC and ACCF/AHA guidelines in terms of pharmacological therapy, varying emphases are placed on wider management aspects. The Japanese Circulation Society guidelines (published in 2013), along with a simple set of guidelines for chronic HF, emphasize the importance of determining targets in the treatment and management of patients.[89]

In China, the guidelines (published in 2014) emphasize the usefulness of BNP and NT-proBNP in the diagnosis and evaluation of patients with HF and the importance of optimizing standard medical therapy for 3 to 6 months before implantation of a cardiac resynchronization device, the recommendation of which has been updated to include patients with New York Heart Association class II HF and a left-branch bundle block pattern QRS width ≥150 ms. Australian guidelines published in 2011 highlight evidence to support nonpharmacological management (eg, benefits of regular physical activity) alongside pharmacological management of patients with HF.[90]

Malaysian guidelines (published in 2014) provide similar recommendations to those for China, but in addition address HF in patients who are pregnant, as well as in infants and children, which are patient groups rarely mentioned in other guidelines.[85] The need for a multidisciplinary approach to the management of patients with HF is also highlighted. Furthermore, in Singapore, HF guidelines published in 2004 provide recommendations not only for health care professionals on diagnostic approaches, pharmacological, and surgical therapy (including mechanical devices),[87] but also have published detailed guidelines for clinical pharmacists[88] with information on therapy initiation, titration and how to monitor, prevent, and manage possible side effects.

Finally, the Taiwan Society of Cardiology guidelines (published in 2012) recognize that social and ethnocultural differences between Chinese and Western populations may confound the management of Chinese patients with HF.[85] For instance, recommendations regarding the use of warfarin suggest that the maintenance dose proposed in Western guidelines may not be suitable for Taiwanese patients with HF as a result of interindividual and interethnic differences.[85] This should also be considered by other Asian countries. However, although detailed recommendations for cardiac rehabilitation and palliative care are provided, recommendations are not accompanied by classifications and levels of evidence to guide clinical decision making, as in the ESC and ACCF/AHA guidelines.

Multidisciplinary Disease Management Programs

A key feature of current ESC and ACCF/AHA guidelines is the focus on multidisciplinary disease management programs,[13,14] which have been shown to reduce hospitalization, improve quality of life, and prolong survival,[91–95] yet are mentioned in few regional guidelines.[85,86,88–90]

In the Asia-Pacific, preliminary evidence suggests that multidisciplinary disease management programs are effective in reducing all-cause mortality and HF-related rehospitalizations in high-density populations with nationalized health care and easy access to cardiologists.[70] Additionally, there are several hospital-based HF clinics that currently offer various outreach services (eg, home visits, telephone support). Using telephone support and telemetry provides the opportunity to advise patients with symptoms to seek immediate help, allowing for earlier intervention, which may reduce or prevent hospital admissions and all-cause mortality.[96] However, there are very few specialized clinics in the community, resulting in limited access to specialists and additional resources that are more easily accessible in hospitals. Home visits or home-based HF clinics have been shown to reduce recurrent hospital stays and are associated with significantly less total health care expenditure per quality-adjusted life years compared with community-based intervention.[97]

Limitations

This is a narrative review of currently published data, including observational registry studies, controlled trials, and treatment guidelines. As is typical with such publications, discussions include historical data and are somewhat limited to methodological flaws introduced in the reviewed studies. Moreover, there is a potential for bias resulting from lack of a clear systematic methodology. However, in the current paper, the majority of articles included were published after 2010 and, of particular note, comparison of key findings (Tables 1 and 2) are based on registry data from heterogeneous sources. A systematic review could have provided a more reliable and accurate picture of heart failure in the Asia-Pacific compared with Western regions and may have identified common methodological weaknesses and errors in the reviewed data. Nevertheless, given the heterogeneous nature of the studies discussed, a narrative approach is considered to be of most value.

Summary and Conclusions

HF is a global health care problem, a leading cause of morbidity and mortality in the Asia-Pacific, and has recently been described as a "pandemic." [20] Analysis of recent clinical trials and disease registries highlight several regional trends: (1) patients with HF in the Asia-Pacific are younger and present with more severe signs and symptoms of HF than those of Western countries; (2) ischemic cardiomyopathy, valvular heart disease, hypertension, and diabetes are common etiological and comorbid factors that will have a greater impact on health care systems in the future; (3) patients receive lower-than-recommended levels of treatment despite the existence of local clinical guidelines; and (4) intraregional variation exists. Although current ongoing observational studies, including ASIAN-HF, which has recently highlighted the significant heterogeneity among Asian patients with HFrEF,[16] will address the lack of regional epidemiological data and positively influence local clinical guidelines, a significant effort will be required to address the underrepresentation of Asian-Pacific patients in global trials. Further resources are needed to better characterize patients, drive improvements in local clinical practice, and inform local guidelines to improve the outlook for patients in the region.

Disclosures

Jeyamalar Rajadurai, Hung-Fat Tse, Chao-Hung Wang, Ning-I Yang, and Jingmin Zhou declare that they have no

conflicts of interest. David Sim has received speaker honoraria from Novartis.

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