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REVIEW ARTICLE

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An overview of hypertension and cardiac involvement in Asia: Focus on heart failure

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Abstract

Cardiovascular Disease (CVD) is the leading cause of deaths worldwide, contributing to about 30% of all deaths. Half of the cases of CVD are estimated in Asia, the world's most populous continent. Hypertension, a major modifiable risk factor for

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CVD, results in more deaths than any other CV risk factors in the Asian regions. The total number of patients with hypertension is likely to grow as the population ages. The proportion of the elderly population aged 65 years or more in Asia is expected to increase from 7.4% in 2015 to 10.9% in 2030. It is important to note that more than half (54%) of the world's population live in Asia. Aside of being the biggest single risk factor for global deaths, hypertension is also an important precursor and most common risk factor of heart failure (HF). An increase in HF prevalence is clearly related to the rapid epidemiological transition caused by changes in lifestyle in Asian countries. However, the availability of data on HF burden and health care delivery is limited in Asia compared with Europe and North America. This reality has driven the working group of Asian experts for example the HOPE Asia Network to concentrate on hypertension as risk factors for CVD, with the mission to improve the management of hypertension resulting in organ protection toward a goal of achieving "ZERO" CV event in Asia. This paper aims to give an overview regarding the heart problems caused by hypertension in Asia, focus on HF.

1 | INTRODUCTION

With the rapid increase in the aging population, the prevalence of hypertension and related CV morbidity in Asian patients continues to rise, resulting in a socio and economic burden in this region.[1] CVD has many risk factors, like elevated blood pressure (BP), high serum cholesterol levels, diabetes mellitus (DM), obesity, and tobacco use.[2] In an analysis of data from the Asia Pacific Cohort Studies Collaboration, Asian participants with high BP had a 4.5 higher risk of CVD compared with those normotensive participants. The relation between CV risk and hypertension was significantly stronger for Asian participants compared with participants from Australia and New Zealand.[3]

The distribution of each risk factor, like hypertension, differs not only between Asia and the other countries of the world but also within Asia itself.[4] The INTERHEART study has shown that the joint distribution of those risk factors account for 80% of CVD.[5] In the Asia-Pacific region, 66% of deaths from CVD could be attributed to hypertension.[6] Hypertension has also been reported as the leading CV risk factor in Indonesia, explaining 20%-25% of all coronary artery disease (CAD) and 36%-42% of all strokes.[7] Interestingly, the awareness, proportion of those with well controlled BP, and hypertension-mediated organ damage (HMOD) also vary among countries in Asia, as reported in global BP screening campaign initiative of International Society of Hypertension in Asian countries.[8-11]

Epidemiological studies showed that cardiac damage by hypertension is one of the most important HMOD. The consequences of hypertensive heart disease (HHD) are heart failure, coronary artery disease (CAD), and arrhythmias.[12] The Framingham study demonstrated that hypertension was the major precursor in the development of HF, shown by other epidemiological studies as well.[13-15] The Framingham study with patients followed up for 14 years, showed that a 20 mm Hg increase of systolic BP was associated with a 50% increase of HF and hypertension alone or in combination with CAD proceeded to the development of HF in 70% of both male and female participants in this study.[16]

There are significant ethnic differences in the determinants of hypertension and the risk of hypertension-related demographics of CVD.[1,17-19] In Asian countries, stroke and nonischemic HF are more common than in the Western countries. Stroke and HF are also more related to hypertension than CAD or renal disease.[20]

2 | HYPERTENSION AND HEART FAILURE IN ASIA: THE BURDEN

The risk of hypertension increases with age as well as HF. Life expectancy continues to rise globally, resulting in an increase in the elderly population.[21,22] The increase in the prevalence of hypertension and HF in Asian countries is related to the changes in lifestyle.[23] Hypertension is also the leading preventable cause of premature death worldwide. [24,25] There are various characteristics of hypertension unique to the Asian population. The phenotypes of CVD, stroke, and HF closely associated with BP are common in Asia. The association between high BP and CVD is stronger in Asian countries than in Western countries. Stroke is more common than CAD in Asian people, and the reverse is true in the Western population.[20] Comparable with the global trend, the single most attributable cause of mortality in South-East Asia, including Indonesia, is hypertension.[26] A systematic review of data from 33 Asian countries reported an overall hypertension prevalence of 27% (range from 13.6% to 47.9%).[27] In Indonesia, accordingly, RISKESDAS 2018 (Basic Health Research, conducted by the Indonesian Government) showed a hypertension prevalence of 34.1% while the prevalence of RISKESDAS 2013 was 25.8%.[28] The Indonesian Family Life Survey (IFLS-5), published in

August 2018, interviewed and examined participants in a national population-based cross-sectional study of 29 965 individuals aged 18 years and older, mean age 43.3 years, showed a prevalence of hypertension of 33.4% (male 31% and female 35.4%).[29] The Asia Pacific Cohort Studies Collaboration showed that the association between BP and CVD was stronger in Asian participants than in white participants from Australia and New Zealand.[3,30]

The number of HF patients has been increasing rapidly and are estimated to be 26 million worldwide.[31,32] Most of the published studies reported a prevalence between 1% and 2% of the adult population,[33,34] and the prevalence of HF in Asia was generally similar to the global values (1% to 3%).[23] Values >5% were reported from Indonesia and Taiwan.[23] The Asian-HF patients appeared to be younger than the European and American HF patients. The etiologies of HF were also reported in this study. Ischemic heart disease (IHD) is reported as the most common cause of HF in almost all countries/regions, except Hongkong, where HHD is the most common cause of HF. Vascular risk factors like hypertension, diabetes, and dyslipidemia were common in HF patients in all countries/regions, particularly in Malaysia (75%, 67%, and 52%, respectively) and Singapore (69%, 55%, and 65%, respectively). The highest number of HF hospitalizations was in Taiwan, with 40.000 hospitalizations annually. In some countries/regions, more than a fifth of total hospitalizations is because of HF.[23]

3 | HEART FAILURE WITH REDUCED VS PRESERVED EJECTION FRACTION (HFREF VS HFPEF)

HF exists in two different forms: HFrEF and HFpEF.[35,36] Across Asia, 44% of the physicians use left ventricular ejection fraction (LVEF) >50% to distinguish between the two forms of HF. HFpEF constitutes half of the HF population in the Western population; a little is known regarding the prevalence of HFpEF in Asians. Lansang et al[37] reported that HFrEF was the predominant form of Acute HF presenting to the cardiologic centers in Asia. Among the 12 Asian countries/regions studied, HFpEF was reported to be common only in Hongkong (55%) and Japan (50%) consistent with the findings in the United States (US). From the 12 Asian countries/regions, the proportion of elderly in the population was also the highest in Japan and Hongkong, comparable to Germany and the US.[38]

The Asian-HF registry by Carolyn S. P. Lam and other HF investigators in Asia (published in 2016) studied 5276 HF patients with reduced ejection fraction (40% or less) from 11 Asian regions (China, Hongkong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand) with a mean age of 59.6 ± 13.1 years. Sixty-four percent of patients had 2 or more comorbid conditions, hypertension 51.9%, CAD 50.2%, and diabetes 40.4%. South-East Asians, including Indonesians, had the highest prevalence of CAD (51.9% vs. 38.2% in Northeast Asians). Compared with Chinese ethnicity, Malays and Indians had higher odds of CAD, while Koreans and Japanese had lower odds. The prevalence of hypertension and diabetes mellitus was highest in South-East Asians (64.2% and 49.3% respectively).[39] Jasper Tromp et al and the ASIAN-HF investigators showed the results of 1204 HF patients with HFpEF (LVEF of 50% or higher) from Northeast Asia (Hongkong, Taiwan, China, Japan, and Korea, n = 543), South Asia (India, n = 252), and South-East Asia (Malaysia, Thailand, Singapore, Indonesia, and Philippines, n = 409). Mean age was 68 ± 12 years. This prospective multinational study showed that Asians with HFpEF were relatively young (one third under the age of 65 years) and lean (only one fifth are obese) compared to those from the Western population. The Asian population had a high comorbidity burden and 70% of patients had two or more comorbidities, mostly hypertension (71%), followed by anemia (57%), chronic kidney disease (50%), diabetes (45%), CAD (29%), atrial fibrillation (29%), and obesity (26%). This study also showed that South Asians were the youngest with more obesity and anemia, but with the lowest prevalence of atrial fibrillation. South-East Asians have the highest prevalence of all comorbidities, except AF, with the most concentric remodeling LVH and the worst outcome. Northeast Asians were the oldest and had the most AF and eccentric LVH. Regarding ethnicity, Indian and Malay patients with HFpEF were younger than Chinese, Japanese, and Koreans patients, but had a higher prevalence of obesity, diabetes, chronic kidney disease (CKD), and anemia and the worst outcome among the ethnicities.[40]

The Asian-HF registry showed a prevalence of HF with reduced EF (HFrEF) and HFpEF, 52% and 71%, respectively.[41] The other registries regarding HFpEF showed a prevalence between 64% and 91%.[42-48] Data from the HF Registry, Indonesia, confirmed by the above mentioned Asian-HF Registry, showed that Indonesia had the highest HF risk factor burden (hypertension, diabetes mellitus, and CAD). The risk factors of the Indonesian HF registry in the National CV Center (NCVC), compared with the Asia-Pacific and US registry, showed for hypertension 54.8%, 60.2%, and 74%, respectively, CAD 49.9%, 47.4%, and 57%, respectively, and diabetes mellius 31%, 36.2%, and 44%, respectively. Among 38 296 patients hospitalized in NCVC between 2015 and 2018, 55.7% had hypertension or diabetes mellitus or HF, indicating the significant burden of these comorbidities.[49]

HFpEF from the ASIAN-HF registry compared with the Western registries of patients with HFpEF showed similar rates of comorbidities in patients such as hypertension, diabetes mellitus, and CKD. The South-East Asians had a high prevalence of diabetes mellitus (62%), and atrial fibrillation was lower compared to Western cohorts (Table 1). The lower prevalence of atrial fibrillation in the ASIAN-HF registry might be because of the lower age and obesity, which is consistent with the findings that the oldest Asian ethnic group of Japanese and Korean patients had the highest prevalence of atrial fibrillation among ethnicities. Compared to Western registries (GWTG-HF, SWEDE-HF, ADHERE-HF, and OPTIMIZE-HF) and studies in the primarily Western population (TOPCAT, I-PRESERVED, and CHARM PRESERVED), Asian patients with HFpEF were younger than, except TOPCAT and I-PRESERVED, in which age was similar. Despite the younger

TABLE 1 Comparison to heart failure with reduced and preserved ejection fraction from Asian vs. non-Asian registries

Registry	Asian-HF[1]		GWTG-HF[2]		ADHERE-HF[3]		OPTIMIZE-HF[4]
LVEF	HFrEF (EF ≤ 40%)	HFpEF (EF ≤ 50%)	HFrEF (EF ≤ 40%	HFpEF (EF ≤ 50%)	HFrEF (EF ≤ 40%	HFpEF (EF ≥ 40%)	HFrEF (EF < 40%)
N	5276	1204	15 716	18 897	25 865	26 322	20 118
Enrolment type	In/outpatient		Inpatient		Inpatient		Inpatient
Age (year)	59.6 (13.1)	68.4 (12.3)	79 (72-85)	82 (75-87)	69 (14.4)	73 (13.2)	70.4 (14.3)
Men (%)	78.2	50.4	60	32.7	60	38	62
NYHA class I/II/III/IV (%)	13/52/29/6	17/59/21/3	NA	NA	NA	NA	NA
Body mass index (kg/m2)	24.9 (5.1)	27.1 (6.0)	NA	27.4 (23.3-33.0)	NA	NA	NA
Medical history (%)							
Hypertension	52	71	73	81	69	77	66
Coronary artery disease	50	29	58	45	59	50	54
Diabetes mellitus	40	45	39	41	40	45	39
Chronic kidney disease	45	50	21	20	26	26	NA
Atrial fibrillation	10	29	36	41	17	21	28
Valvular heart disease	NA	NA	13	16	22	21	NA

age, Asians with HFpEF had a high prevalence of comorbidities, especially CKD, diabetes mellitus, and hypertension. The overall prevalence of CAD was lower than the Caucasian population. Obesity-related HFpEF is an important HFpEF phenotype.[50] Studies have shown that 83% of patients with HFpEF were overweight or obese.[50,51] Asian patients with HFpEF had lower rates of increased/high BMI.[52,53] Regardless of the lower rates of obesity, the prevalence of diabetes mellitus was high in the Asian HFpEF population in the ASIAN-HF study. Data from studies suggest that regarding obesity and HFpEF, metabolic derangement plays an important role in HFpEF rather than pure mechanical overload caused by body weight (obese) per se.[40]

4 | MULTIMORBIDITY IN PATIENTS WITH HF

Multimorbidity (two or more comorbidities) is increasing in patients with HF.[54-56] With the growing aging population worldwide without exception the growing Asian elderly, the Asian population age-related multimorbidity is as well on the rise. In Asia, with the most rapidly growing population in the world, multimorbidity is found in two-thirds of patients with HF.[39] Clustering of comorbidities in individuals will have an impact on patient's outcome. The individualized treatment approach is thus of importance.[57-59] The ASIAN-HF Registry was very informative regarding the multimorbidity in 6480 patients with chronic HF (1204 patients with HFpEF) from 11 Asians regions, enrolled between 2012 and 2016. The median number of comorbidities was 3% and 81% of patients had two or more comorbidities in addition to HF. Among all comorbidities, hypertension (55%) was most common, followed by CAD (46%) and CKD (45%). Five multimorbidity groups were identified in this study, that is, elderly/atrial fibrillation, metabolic (obese, diabetes mellitus, and hypertension), young ischemic (ischemic etiology), and lean diabetes mellitus (with a low prevalence of obesity). These are the characteristics of the findings from the elderly/atrial fibrillation, which showed the highest prevalence of atrial fibrillation (67.6%) or stroke (19.8%), high CKD (63.6%), more often HFpEF, and concentric remodeling mostly in Chinese, Japanese, and Koreans ethnicities or from high-income regions. The metabolic group showed the highest prevalence of obesity (45.1%) combined with a high prevalence of hypertension (87.8%) and diabetes mellitus (63.5%), relatively young and more often with HFpEF and concentric remodeling, primarily in Malay ethnicity, in addition to Singapore, Philippines, and Taiwan ethnicities. The young group showed a low proportion of all comorbidities, more often HFrEF with eccentric hypertrophy, primarily in Indian or Chinese ethnicity/low-income region, also in Japan, Korea, and Thailand ethnicities. The ischemic group showed an ischemic etiology of HF (71%). The lower prevalence of diabetes mellitus (43%) but the highest prevalence of CAD (88%) and higher prevalence of anemia (69%), compared to the young group, have more often HFrEF with eccentric hypertrophy. Indians, Indonesians, and Malaysians belong to this group. Patients in the lean diabetic group have a high prevalence of diabetes mellitus (97%), despite a low prevalence of obesity (22%). They also had a high prevalence of hypertension (95%), while CKD shows a prevalence of

	TOPCAT[5]	I-PRESERVE[6]	CHARM-Preserved[7]	SWEDE-HF[8]	EHFS[9]	U.S Veteran[10]	Olmsted County[11]
HFpEF (EF> 50%)	HFpEF (EF ≥ 45%)	HFpEF (EF ≥ 45%)	HFpEF (EF> 40%)	HFpEF (EF ≥ 50%)	HFrEF (EF < 40%)	HFrEF (EF < 40%)	HFrEF (EF < 40%)
10 072	3445	4133	3023	9140	3658	6599	985
	In/outpatient	In/outpatient	In/outpatient	In/outpatient	Inpatient	Outpatient	In/outpatient
75.6 (13.1)	69 (10)	72 (7)	67 (11)	77.5 (10)	67 (13)	69.5 (10.3)	72.4
32	48	40	60	45.4	71	96.4	56.9
NA	3/63/33/1	0/21/76/3	0/61/37/2	16/45/ 35/3	NA	NA	NA
NA	32 (7)	30 (5)	29 (6)	27.5 (6.1)	NA	NA	29.0
77	91	88	64	64	50	62	69
32	59	48	60	44	69	NA	37
41	32	27	28	26	28	40	28
NA	39	31	NA	55	NA	NA	NA
32	35	29	29	60	23	35	NA
NA	NA	NA	NA	NA	NA	NA	NA

89%, anemia of 78.5%, and CAD of 76%, most often with HFpEF and concentric hypertrophy. These patients were commonly of Malay ethnicity and high-income regions.[40]

These findings showed an expected association between the metabolic group and HFpEF as well as the ischemic group and HFrEF. The very most interesting finding is the association of the lean diabetes mellitus group with the greatest extent of concentric remodeling LVH and diastolic dysfunction, even more than in the obese diabetes mellitus metabolic group in HFpEF. This provides clinical evidence of cardiometabolic disturbance as the important stimulants leading to cardiac dysfunction apart from the until now regarded influence of weight gain per se.[40,60] These findings will have a great impact on the HF approach in a specific Asian population, as opposed to weight loss as a therapeutic strategy in the Western population.[40,61]

Overall, it has been accepted that hypertension is a significant risk for the development of HF. The true prevalence of hypertension-related HF is however still underestimated because of the common practice of attributing HF mainly to CAD and less attention to the precursor causes of the CAD, and the direct hemodynamic consequences of hypertension to the myocardium.[62]

5 | SUMMARY

- The prevalence of hypertension and HF and hypertension-related HF in Asia is expected to further increase due to the increase in the aging population and epidemiological transition.
- The CVD risk factors generally act similar in the Western and Asian countries, but the distribution of these risk factors, for example hypertension, seems to differ between Asia and the rest of the world. But what is of interest is that it differs even within the Asia regions itself.
- Approach to hypertension and HF related to hypertension that takes Asian characteristics need to be considered to develop effective prevention of CVD and hypertension-mediated organ damage in the Asian Countries/regions. To achieve this, more studies to clarify Asian-specific characteristics for the management of hypertension and hypertension-related HF are needed.

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CONFLICT OF INTEREST

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