Hypertensive Heart Failure in Asia

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Abstract
Hypertension (HT) is an important risk factor for heart failure (HF). The prevalence of HT among the HF population is higher in Asia than in other regions around the world. In Asia, HT is the most common cause of HF after ischemic heart disease. Hypertensive HF (HHF) results from structural and functional adaptations of the heart, which lead to left ventricular (LV) hypertrophy (LVH). Hypertensive LVH can cause ventricular diastolic dysfunction and becomes a risk factor for myocardial infarction, which is a well-known cause of LV systolic dysfunction. Asymptomatic systolic and diastolic LV dysfunction easily progress to clinically overt HF with other precipitating factors. Although the precise pathophysiology of HHF is still unclear, we have known that HHF can be reversed by effective control of blood pressure (BP). Thus, HT control is essential not only for primary prevention but also for the secondary prevention of HF. Here, we reviewed the epidemiology, pathophysiology, outcome, and implication of BP management in HHF patients, especially in the Asian population.

Background
Heart failure (HF) is a clinical syndrome that has a huge impact on the hospitalization and mortality of the patients [1, 2]. Indeed, 1-year all-cause death rates among HF patients in South Asia, Northeast Asia, and Southeast Asia reach 7.5, 7.4, and 13%, respectively, according to the Asian sudden cardiac death in HF registry (ASIAN-HF) [3]. Also, several HF reports suggest higher mortality in Asian people than in Westerners [4].

Hypertension (HT) is a significant modifiable risk factor for cardiovascular disease (CVD), particularly HF [5–7]. The causative association of HT with HF has been continuously observed since the first report from the Framingham heart study [6]. This study presents the lifetime risk of HF based on subjects’ age and blood pressure (BP). HT doubled the new-onset HF in men and tripled in women after adjusting other risk factors [6]. In the same manner, HT was proven to contribute to existing HF development by 39% in men and 59% in women [6].

Chronic exposure to high BP leads to various alterations in the structure of the myocardium, the heart’s conduction system, and coronary vascularization [8]. These changes refer to hypertensive heart disease conditions [8]. Hypertensive heart disease is characterized by a prolonged increase in left ventricular (LV) filling pressure.
and diastolic dysfunction. The increase in left atrium size in this setting results in impaired LV compliance followed by LV systolic dysfunction in the hypertrophic ventricle [9]. Further LV myocardial damage by myocardial ischemia and arrhythmias accelerates the development of hypertensive HF (HHF) [8].

The American College of Cardiology Foundation and American Heart Association regard HT as a preceding factor for HF and denominate HT without structural heart disease state as stage A HHF [5]. As for stage B HHF, the cardinal sign of systemic arterial HT is LV hypertrophy (LVH) [5, 9]. In addition to LVH, subclinical coronary artery disease (CAD) and silent myocardial infarction (MI) are common in hypertensive patients [5, 8, 10]. The clinical symptoms of stage C HHF patients do not differ from those of patients with HF of other causes. HT is present in most patients who develop HF, especially in HF patients with preserved LV ejection fraction (HFrEF) [5, 8]. Stage D HHF refers to patients with chronic HF that continuously progress and develop severe symptoms despite adequate management, including guideline-directed medical therapy [5].

**Epidemiology of HHF in Asia**

Most of the HF epidemiologic data up to date came from Europe and North America [11]. There are few data on the epidemiology of HF or the relationship between HF and HT in Asia. In Korea, the prevalence of HF among general population was reported as 1.53% [12]. However, the prevalence continuously increased approximately 2 folds from 2002 to 2013. The prevalence of HF in Taiwan and China was reported as 6% [11] and 1.3% [13], respectively. The prevalence of HF in Japan was relatively low (<1%) than in other Northeast Asia regions [13, 14]. The prevalence of HF in Southeast Asia showed variable prevalences such as 5% in Indonesia, 0.4% in Thailand, and 1–2%, in the Philippines [11].

The characteristics of HF in various registries were summarized in Table 1. According to the Asian Sudden Cardiac Death in HF registry (ASIAN-HF) and the Acute Decompensated HF Registry International-Asia Pacific (ADHERE-AP), Asian-HF patients were almost a decade younger compared to patients in Europe and North America [3, 15, 16]. In the ASIAN-HF registry, Northeast Asian-HF patients are generally older, and the mean body mass index was lower than those of South Asian and Southeast Asian. The oldest HF patients were from Hong Kong, with an average of 73 years old, while the youngest was from the Philippines of 56 years [3]. Similar to the ASIAN-HF registry, ADHERE-AP is an observational study from 8 Asia-Pacific countries between 2006 and 2008. Among HF patients, 40% had HT. In conjunction with ASIAN-HF, data from Southeast Asia registries, such as the Dysfunction Established and Registered adult symptomatic HF (The DEAR Heart) from Philippines, and Indonesia, and Thailand as part of the ADHERE-AP registry showed that Southeast Asian-HF patients were younger than other regions [17–19]. In contrast, the Korean Acute HF Registry (KorAHF), the Acute Decompensated HF Syndrome registry (ATTEND) from Japan, and Asian-HF registry from Northeast Asia showed the mean onset of HF relative older than other Asian regions [15, 20, 21]. ATTEND registry compared hypertensive and nonhypertensive in hospitalized HF patients after matched age and sex data. The HF patients with HT were older and had more comorbidities such as diabetes mellitus (DM) [21].

Regarding sex, women had lower prevalence of HF than men in the general Asian registries (Table 1). The prevalence of HFrEF was similar between both sex, whereas HF with reduced LV ejection fraction (HFrEF) were more common in men in all 3 Asian regions, especially in the Southeast Asia region where men showed two-thirds higher prevalence [3, 15, 21]. Interestingly according to the KorAHF, the prevalence of HF is higher in women, by 1.72 than 1.34% in men [12]. This result is similar to the finding from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with HF (OPTIMIZE HF) and the Acute Decompensated HF National Registry (ADHERE) from North America [22, 23].

The proportion of HT among the comorbidities of HF varies among Asian countries (Table 1). According to HF cohort registries in Asia, the HT proportion as a comorbidity of HF was between 55 and 69.4%. The highest was 69.4% in Japan, followed by 64.8% in Thailand, 64% in the Philippines, 62.2% in Korea, 57.8% in India, and 54.8% in Indonesia [17–21, 24]. Similarly, HT is also more prevalent among Western HF population, as data from the European Society of Cardiology HF Long-Term Registry (ESC-HF-LT) reported 65.6% and Acute Decompensated HF National Registry (ADHERE) reported 73.9% of the comorbid proportion. The comorbidities among HF patients are described in Figure 1. HT is the most common chronic noncommunicable disease among HF patients in Asia, Europe, and North America (35–69%), followed by DM and atrial fibrillation (AF).
The following table summarizes the characteristics of HF registries:

| Registry          | ASIAN-HF [15] | KorAHF [20] | ATTEND [21] | TSOC-HFrEF [26] | ADHERE-AP [16] | THFR [24] | DEAR heart [17] | INTER-CHF [25] | ESC-HF-LT [72] | ADHERE [23] |
|-------------------|---------------|-------------|-------------|-----------------|-----------------|-----------|-----------------|-----------------|----------------|-------------|
| Region            | Asia          | South Asia  | Northeast Asia | Southeast Asia | Northeast Asia | Asia      | Indonesia      | Thailand        | Pacific Asia    | Asia-Pacifc |
| Country           | Korea         | Japan       | Taiwan      | Indonesia       | Thailand        | India     | Philippines    | Overall         | India           | China       |
| Years             | 2012–2015     | 2011–2014   | 2013–2013   | 2007–2011       | 2013–2014       | 2011–2013 | 2013–2014      | 2011–2013       | 2011–2014       | 2011–2014   |
| Sample size       | 5,766         | 1,436       | 1,658       | 2,182           | 5,625           | 1,078     | 1,509          | 1,687           | 2,401           | 10,171      |

**Demographic**

| Age, years (SD)  | 59.6 (13.1)  | 57.8 (12.5) | 62.1 (14.5) | 59.9 (11.9) | 68.5 (14.5) | 73 (13.8) | 64 (15.8) | 60 (14) | 64 (13.7) | 66 (15) |
| BMI, kg/m²        | 24.9 (4.8)   | 25.0 (4.5)  | 23.9 (5.6)  | 25.7 (3.9)   | 23.3 (N/A)   | N/A       | N/A       | N/A       | N/A       | N/A       |

**Comorbidity**

| HT, %             | 51.9          | 37.9        | 48.1        | 64.2          | 62.2          | 69.4      | 34.5      | 54.8      | 64.8      | 64 (N/A) |
| DM, %             | 40.4          | 37.1        | 31.8        | 49.3          | 40            | 33.8      | 44        | 31.2      | 47.3      | 45        |
| AF, %             | 17.9          | 4.2         | 30.2        | 17.40         | 28.50         | 39.6      | 26        | 14.6      | 24        | 24        |

**Etiology**

| Ischemic, %       | 47            | 37          | 32          | 65            | 37.6          | 31.1      | 44        | 49.9      | 44.70     | N/A       |
| HT, %             | N/A           | N/A         | N/A         | N/A           | 4.0           | 17.7      | 4.8       | 54.8      | 12.2      | N/A       |

**Outcome**

| In-hospital mortality, % | N/A | N/A | N/A | N/A | 4.8 | 6.4 | 2.4 | 6.7 | 5.5 | 48 | 8 | 10 | N/A | N/A | N/A | N/A | 4.90 | 3.7 |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|-----|-----|-----|-----|------|----|
| LOS, days                | N/A | N/A | N/A | N/A | 9.0 | 30.0 | 8.0 | 7.1 | 7.5 | 6  | 6.0 | 10.0 | N/A | N/A | N/A | N/A | 4.3  | 3.9 |

**Notes:** HF, heart failure; ADHERE, acute decompenated heart failure registry international; ASIAN-HF, Asian sudden cardiac death in heart failure registry; ATTEND, the acute decompenated heart failure syndromes registry; TSOC-HFrEF, the Taiwan society of cardiology-heart failure with reduced ejection fraction; N/A, information not available; LOS, length of stay.
HT is reported as the most important cause of HF in Hong Kong and Indonesia, accounting for 70 and 55% of all HF patients, respectively [11, 19]. The prevalence of HT as HF etiology in other regions of Asia such as Japan, China, Thailand, Philippines, Taiwan, and Korea was reported as 17.7, 14, 12.2, 6, 4.8, and 4%, respectively [16–18, 20, 21, 25, 26]. It is not always easy to define coincident HT as a cause of HF. Many registries do not suggest the definition of HHF in their method section, and only present the prevalence of coincident HT among HF patients or prevalence of HT as HF etiology. In that case, we only reported the proportion of HT as comorbid and cause of HF that presented in some cohort registries.

**Pathophysiology and Clinical Characteristic of HHF**

The natural course of the HF development among HT patients is well described in the Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) Study [9]. PAMELA study is an epidemiological study designed with the original purpose of determining the normal values of home BP and ambulatory BP monitoring. However, this study showed a valuable natural history of HT progressing to HF. Although the baseline BP level and HT prevalence of the study population were similar to general population, many patients developed LVH after 10 years of follow-up. Especially in hypertensive and prehypertensive patients, there were more than 2-fold increase in LVH [9].

HT increases LV afterload, which is exacerbated by chronicity, severity of BP, and systemic vascular resistance resulting in LV remodeling [27, 28]. This pressure overload causes mechanical stress as a hemodynamic factor. Along with this process, other factors contribute to the progression of HF, namely neurohormonal, cytokine, comorbidities, race, and genetic factors [29]. Paulus and Tschöpe [30] conceived a new concept for the development of HF that occurs in HFP EF patients. It begins with the induction of a systemic inflammatory process due to the patient’s comorbid conditions such as HT and obesity. The systemic pro-inflammatory state causes inflammation of the coronary artery endothelium, reducing nitric oxide and protein kinase G activity leading to fibrosis and hypertrophy of cardiomyocytes in the left ventricle. Thereby increased LV stiffness and impaired LV relaxation eventually lead to LV diastolic dysfunction [30]. Diastolic dysfunction may antedate LVH [31] and induce parallel addition of new myofibril, leading to compensatory changes such as relatively increased LV mass and wall thickness [27].

The pathophysiology of HHF is illustrated in Figure 2. Aortic stiffening with HT causes LV diastolic dysfunction.
in patients with HHF and also rise in central SBP that promotes increase in afterload and myocyte size [32]. In contrast, increased aortic stiffness also reduces diastolic BP (DBP) and compromise coronary perfusion, thus further aggravating subendocardial ischemia and myocardial fibrosis leading to HFpEF condition (Pathway 1) [32]. HFpEF more commonly occurs than HFrEF in HT patients (Pathway 1) [33, 34]. Neurohormones play a role in the LV geometric remodeling in either eccentric or concentric LVH by causing myocyte hypertrophy.

Differences in renin activity levels affect LV remodeling in hypertensive patients. Researchers found that patients with concentric LVH had high renin activity [35] and the opposite for eccentric LVH [36]. Demographic differences also affect the relationship between HT and type of LV remodeling. Women are more likely to exhibit concentric LVH, while men are more likely to exhibit eccentric LVH [37]. Levy et al. [38], along with the Framingham heart study (FHS), found that in both sexes, the increase in SBP was significantly associated with LVH. After adjusting with CAD risk factor, LVH was significantly associated with MI (Pathway 2). In the combined analysis of 4 prospective community-based cohorts, including the FHS, the Prevention of Renal and Vascular Endstage Disease (PREVEND), the Cardiovascular Heart Study (CHS), and the Multi-Ethnic Study of Atherosclerosis (MESA), hypertensive patients who experienced MI (Pathway 2 and pathway 3) may more frequently develop HFpEF (Pathway 4), and more prevalent develop to HF with reduced ejection fraction (HFrEF) (Pathway 5) [29, 39–42]. HT also can be associated with arrhythmia, primarily AF (Pathways 6 and 7) [43]. Increased secretion of angiotensin II induces the proliferation of fibroblast, predisposing

**Fig. 2.** Pathophysiology of hypertensive heart failure. HT progresses to LVH. Along with this process, the patient’s condition can directly develop to symptomatic HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF) (Pathway 1). Hypertensive patients with progression to LVH (Pathway 2) or without LVH (Pathway 3) who suffer MI may develop to HFpEF (Pathway 4), and more prevalent develop to HF with reduced ejection fraction (HFrEF) (Pathway 5). HT is associated with a variety of cardiac arrhythmias, most AF. Arrhythmias may occur in hypertensive patients, commonly with LVH progression than without LVH (pathway 6 and 7). AF is more common to develop HFpEF (pathway 8) than to HFrEF (pathway 9). HFpEF patients who commonly suffer MI and poor risk factor control develop HF with reduced ejection fraction (HFrEF). HFrEF patients with successful risk factor control and treated with evidence-based medication may improve to HFpEF condition. A thicker arrow shows a more common pathway compared with a thinner arrow. HT, hypertension; LVH, left ventricular hypertrophy; AF, atrial fibrillation; MI, myocardial infarction.
factor of AF [44]. AF is more prevalent among patients with HFP EF (Pathway 9) than those with HFrEF (Pathway 8) [43]. If MI occurs in HFP EF patients, they might develop HFrEF [29].

Dunlay et al. [45], in their community-based cohort study in Olmsted County, analyzed longitudinal changes in EF in HFP EF and HFrEF patients. 39% of the HFP EF patients experienced further EF reduction to < 50% and thus developed HFrEF, and a similar proportion of HFrEF patients (39%) had improved EF to ≥ 50% during the follow-up period [45]. In those with reduced EF, EF decreased by 5.8% over 5 years with bigger reduction in older patients and patients with CAD. In contrast, in HFrEF patients, EF by 6.9% over 5 years and more in younger patients, female sex, those treated with evidence-based medication, and those without CAD [45]. Among HFP EF patients, a reduction of 5% in EF was associated with a 7% increase in mortality. Conversely, in HFrEF patients, an increase of 5% in EF was associated with a 12% mortality reduction [45]. This finding is consistent with other studies on HF patients with improved ejection fraction (HFrEF), such as the Val-HeFT trial [46] and KorAHF study [47]. After 12 months of follow-up, in the Val-HeFT trial, 9.1% of patients from HFrEF group moved to the HFrEF (EF > 40%) subgroup and 31.3% of HFrEF patients from the KorAHF study improved and moved to HFrEF group [46, 47]. Patients in HFrEF group were significantly better in mortality and prognosis than those who persistently remained in HFrEF group in these studies [46, 47]. In the ASIAN-HF study, HFP EF patients showed better mortality outcomes than HFrEF patients [3].

**Outcome and Therapeutic Implication of HHF**

HF is associated with grave prognosis. According to HF registries data in Asia, the length of stay in hospital ranged from 6 to 30 days, and in-hospital mortality ranged 2.4–10% (Table 1). Non-Asian registries showed fewer in-hospital deaths of 3.7–4.9% and shorter length of stay (4.3 days) [23, 48]. The 1-year mortality rate in the Southeast Asia region was similarly reported in the ASIAN-HF study and INTER-CHF study, as around 13–15% [3, 25]. In contrast, data from South Asia and Northeast Asia registries showed lower mortality of 7.5 and 7.4%, respectively [3]. In the KorAHF registry, post-discharge 30-day mortality was 3.3% [20]. 1-, 2-, and 3-year mortality was 18.2%, 27.6%, and 34.7%, respectively [20]. In ATTEND registry from Japan, 1-year all-cause death rate was 18.4%, and cardiac death rate was 11.5% [21].

The independent predictors of morbidity and mortality in HF patients include age, comorbidities, SBP, renal function, serum sodium, hemoglobin, natriuretic peptide concentration, troponin, QRS duration, and evidence-based medication utilization [49]. Data from ADHERE (Acute Decompensated HF National Registry) and OPTIMIZE-HF registries found SBP and renal function at admission were among the best discriminators between hospital survivors and nonsurvivors [22, 23]. The OPTIMIZE-HF registry found that 8 factors, including age, weight, SBP, sodium, serum creatinine, and comorbid disease states, could predict the combined endpoint of death or readmission with a c-index of 0.72 [22].

BP control target becomes the most crucial discussion among HT experts for primary prevention of HF development [5, 50] and secondary prevention of death or repeated hospitalization in established HF patients [2, 51–54]. The recent European guidelines strongly suggest that lowering office SBP/DBP to < 140/90 mm Hg is beneficial for all patients groups but recommend further reduction of SBP/DBP under 130/80 mm Hg in high-risk patients, including patients with HF [51]. The 2017 ACC/American Heart Association HT guideline recommends a BP target of < 130/80 mm Hg in adults with known CVD or moderate-to-high CVD risk as primary prevention [55]. The Korean Society of HT guideline, a representative guideline for the Asian population, recommends BP target of < 140/90 mm Hg for uncomplicated HT in the general population including the elderly, and more strict BP target of < 130/80 mm Hg is recommended for those who previously suffered from cerebrovascular disease, chronic kidney disease with albuminuria, diabetes, and CVD [56].

Management of HT in patient with HHF is challenging. In the KorAHF registry, BP and HF mortality showed inverse J-curve shape relationship. The mortality was the lowest with BP of 132/74 mm Hg and increased with further decrease in BP toward 130/70 mm Hg [57]. This finding is consistent with the recommendations of The Korean Society of HT guidelines, which reports an optimal BP is 130/80 mm Hg in HHF patients [56]. However, the evidence describing optimal BP in patients with HF is limited.

The effect of the BP-lowering in primary prevention of HF is presented in Table 2. According to the Systolic Blood Pressure Intervention Trial (SPRINT), 9,361 random people with SBP over 130 mm Hg without DM were randomly assigned to intensive SBP control group (target SBP < 120 mm Hg) or standard control group (target SBP < 140 mm Hg). After a mean follow-up of 3.3 years, the mean
SBP in the intensive arm and the standard arm were 121.5 and 134.6 mm Hg, respectively. Intensive BP-lowering markedly reduced the incidence of the primary outcome by around 40%, with 38% reduction of acute decompensated HF; 27% reduction of all-cause death [8, 50]. In the Hypertension in the Very Elderly Trial (HYVET), BP-lowering agents reduced HF development by 64% compared to placebo. A meta-analysis of 35 HT randomized control trials by Thomopoulos et al. [59] showed 37% relative risk reduction in HF primary prevention by antihypertensive agents use. SBP, DBP, and pulse pressure reduction all had significant and robust correlation with HF prevention [59]. These findings highlight the importance of BP control in the prevention of HF development. While the BP-lowering strategy from the SPRINT trial showed clear benefit, the Asian population was not included in the study, leaving the necessity for different BP threshold in Asian patients. Therefore, further studies in Asian hypertensive patients should be warranted for establishing optimal BP for the prevention of HHF.

Besides HF prevention, BP-lowering was beneficial for controlling precursors of HHF. In the substudy of the SPRINT trial, intensive BP control significantly reduced AF incidence by 26% compared to the standard BP control [60]. Losartan Intervention For Endpoint reduction (LIFE) trial showed that losartan, an angiotensin receptor blocker, reduced LV mass index greater than atenolol, a β-blocker. The LV mass index difference between 2 groups was consistent up to 5-year follow-up, with comparable magnitude among annual examination [61]. BP remained similarly low throughout the whole follow-up period, suggesting that antihypertensive agents had long-lasting LVM reducing effects. Angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers were more effective in reducing LVM than β-blockers [62], as well.

The benefit of HF medications with BP-lowering property in HF patients is summarized in Table 3. The ValHeFT trial compared the effectiveness of valsartan versus placebo in HF patients. Valsartan showed better result, reducing the relative risk for AF by 37% [63]. Standard HF therapy is effective in patients with HFrEF but does not reduce morbidity or mortality in patients with HFpEF [52–54, 64–66]. In a meta-analysis by Pinho-Gomes et al. [67], HF medications with BP-lowering properties significantly decreased cardiovascular mortality and HF hospitalization by 10%. Secondary prevention of HHF is not targeting BP reduction but targeting LV reverse remodeling, relief of subjective discomfort, improving functional status, and preventing repeated hospitalization or death [2, 5, 53, 54, 66].

Not all hypertensive medications share beneficial effects for HF. Angiotensin receptor blockers, ACEIs, β-blockers are effective both in primary prevention [59,
and secondary prevention of HF, constituting the important components of guideline-directed management and therapy of HF [2, 5]. Diuretics are beneficial for symptom relief and for primary prevention of HF, but it is not clear whether they have a role in secondary prevention [2, 69]. Alpha-blockers do not have a role in HF prevention, but rather have adverse effect in HF prevention, especially for the secondary prevention [70]. Calcium channel blockers are effective BP-lowering medications, but they may increase fluid retention and should be cautiously used in HHF patients [2, 5, 71, 72].

**Summary**

Among HF patients in Asia, HT is the most prevalent comorbidity and is the common cause of HF. Asian HHF patients are younger than those in the Western countries, with the majority of male patients. The pathophysiology of HHF is complex, which is influenced by many factors (e.g., mechanical stress as a hemodynamic factor, neurohormonal, and comorbidities). HT control is essential for both primary and secondary prevention of HHF. The optimal BP in HHF remains unclear yet, and further research is needed to determine the target BP for primary and secondary prevention of HHF, particularly in Asian population.

**Conflict of Interest Statement**

The authors declare no conflicts of interest regarding the review article.

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