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REVIEW ARTICLE

Special Issue: Current evidence and perspectives for hypertension management in Asia

Blood pressure in heart failure management and prevention

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Abstract

Hypertension is a leading cause of heart failure and other cardiovascular diseases. Its role in the pathogenesis of heart failure with reduced ejection fraction (HFrEF) differs from that in heart failure with preserved ejection fraction (HFpEF). Moreover, rigorous blood pressure control may reduce the incidence of heart failure. However, once heart failure develops, prognosis is affected by blood pressure, which may differ between patients with and without heart failure. Therefore, the association between guideline-directed medical therapy (GDMT) for heart failure and its uptitration must be considered for blood pressure management and should not be overlooked. Heart failure medications affect the blood pressure and efficacy per baseline blood pressure value. This review discusses the potential mechanisms by which hypertension leads to HFrEF or HFpEF, the impact of hypertension on incident heart failure, and the recommended approaches for blood pressure management in patients with heart failure.

Keywords Blood pressure · DASH diet · Heart failure · Hypertension · Pharmacotherapy

Introduction

Heart failure, a clinical syndrome with a poor prognosis, is closely associated with cardiovascular/noncardiovascular comorbidities [1–4]. Hypertension is an important modifiable risk factor for all-cause morbidity and mortality, various diseases, and end-organ dysfunction, particularly in the cardiovascular system [5, 6]. Currently, patients with hypertension alone are considered "at risk for heart failure" [7]. However, once heart failure is established, the association between blood pressure (BP) and heart failure prognosis becomes complex. A high baseline BP is not necessarily harmful in patients with chronic heart failure [8–10]. Furthermore, most medications used in guideline-directed medical therapy (GDMT) improve the prognosis of patients with heart failure, which somewhat impacts BP. This review summarizes the impact of hypertension on incident heart failure and hypertension as a modifiable risk factor for heart failure and suggests BP management in patients with heart failure.

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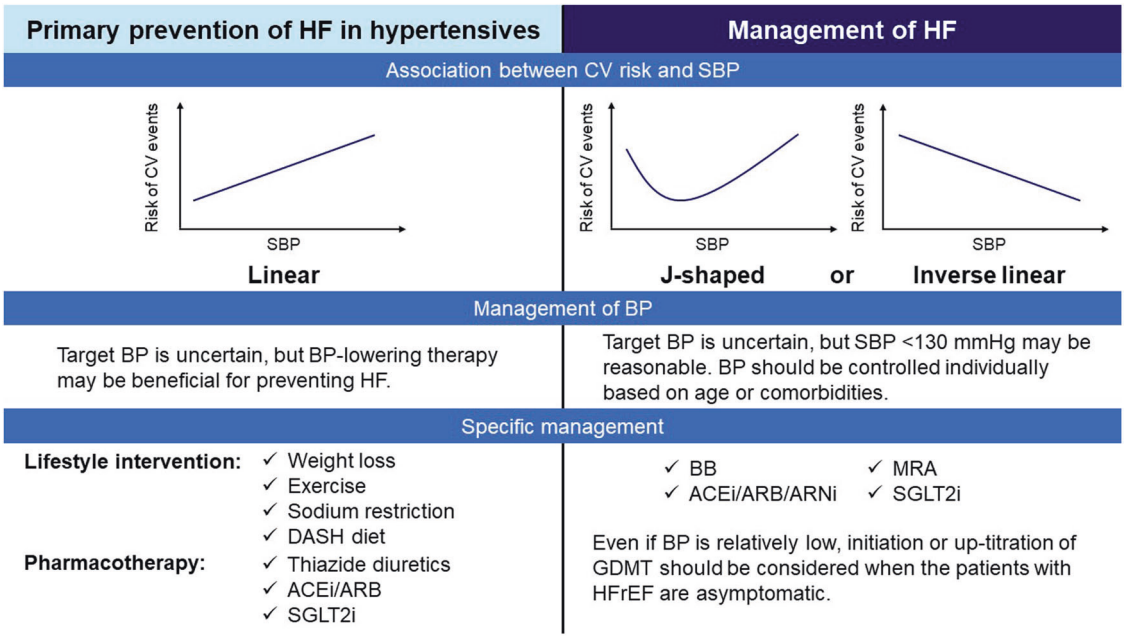
Blood pressure and heart failure incidence

Hypertension and incident heart failure

The prevalence of hypertension has increased over the past few decades and will continue to rise [11–13]. According to the Global Burden of Disease 2019 study, the number of adults affected by hypertension worldwide increased from 2.18 billion in 1990 to 4.06 billion in 2019 [14]. Furthermore, the number of patients with hypertension may

Graphical Abstract

Comparison between patients with and without heart failure regarding blood pressure The association between CV events and SBP is linear in patients without heart failure; however, it becomes J-shaped or inverse linear in those with heart failure. The management of BP, including optimal BP or pharmacotherapy, differs between the two populations. ACEi angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blockers; ARNi angiotensin receptor-neprilysin inhibitors, BB beta-blockers, BP blood pressure, CV cardiovascular, DASH Dietary Approaches to Stop Hypertension, GDMT guideline-directed medical therapy, HF heart failure, HFrEF heart failure with reduced ejection fraction, MRA mineralocorticoid receptor antagonists, SBP systolic blood pressure, SGLT2i sodium-glucose cotransporter 2 inhibitors.



Point of View

- Clinical relevance
  Although the association between blood pressure and heart failure is not fully understood, the importance of lifestyle modification or initiating/untratitrating guideline-directed medical therapy should be recognized.
- Future direction
  Further studies focusing on appropriate thresholds of blood pressure in patients with heart failure based on age, comorbidities, and race are needed.
- Consideration for the Asian population
  Since the association between blood pressure and heart failure may be different between Asian and Western populations, race-specific management of blood pressure may be needed.

increase with age: the elderly population (>65 years) in Asia is expected to increase from 7.4% in 2015 to 10.9% in 2030 [15]. Approximately half of the Chinese adult population aged 35–75 years has hypertension [16]. In Japan, almost one-third of the population is hypertensive, 50% are treated, and approximately 25% are controlled at the target BP [17].

Hypertension (high BP) is associated with adverse cardiovascular events independent of other risk factors [18–20], and heart failure is a major consequence. Observations from the Framingham cohort revealed that the cumulative incidence of heart failure was higher in patients with hypertension [21]. A national health claims database, including over 2 million Japanese individuals without a history of cardiovascular diseases, revealed that higher baseline BP was significantly associated with greater heart failure incidence (normal BP, 2.99 per 1000 person-years; stage 1 hypertension, 5.00 per 1000 person-years; and stage 2 hypertension, 9.53 per 1000 person-years) [22]. In another observational study of 4851 young adults (<40 years) from the US without cardiovascular disease, hypertension was an independent risk factor for future heart failure incidence (normal BP, 0.30 per 1000 person-years; stage 1 hypertension, 0.97 per 1000 person-years; and stage 2 hypertension, 2.66 per 1000 person-years) [23].

Notably, the association between BP and cardiovascular diseases may be stronger in the Asian than in the Western population: data from the Asia Pacific Cohort Studies Collaboration revealed that the association between BP and other cardiovascular diseases was stronger in Asians than in Caucasians from Australia and New Zealand [24, 25]. Furthermore, important hypertension features in Asia include a high prevalence of heart failure as a complication of hypertension, a strong association between elevated BP and incident cardiovascular disease rates, and high salt sensitivity [26]. Thus, the benefits of lowering BP in Asians may be greater than those in Caucasians because the effect of reducing BP on incident heart failure is greater than that for coronary artery disease [27]. In this context, appropriate BP management could be essential for preventing heart failure, particularly in Asians.

Hypertension and HFpEF and HFrEF incidence

Currently, two major phenotypes represent heart failure: heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). The association of hypertension with incident HFpEF may be stronger than with incident HFrEF [28–30]. Moreover, HFpEF is an essential final expression of advanced hypertensive heart disease [31]. In a combined study involving the Framingham Heart Study (FHS), Prevention of Renal and Vascular End-stage Disease (PREVEND) Study, and Multi-Ethnic Study of Atherosclerosis (MESA), hypertension accounted for 47% of all new HFpEF cases in individuals aged 65–74 years [32]. Nevertheless, hypertension is also significantly associated with incident HFrEF [28–30, 32] and is responsible for 43% of all new HFrEF cases [32].

Hypertension leading to HFrEF or HFpEF depends on individual patient characteristics such as age, ethnicity, or history of myocardial infarction. Furthermore, the association between isolated arterial hypertension and cardiac remodeling has been established. The classic model of hypertensive heart disease suggests that the left ventricle grows to maintain cardiac output, compensating for persistent cardiac pressure overload, leading to concentric hypertrophy [33]. Notably, left ventricular concentric hypertrophy is more of an independent risk factor for HFpEF than for HFrEF [34]. A contributing factor may be the shared pathophysiological mechanisms between hypertension and HFpEF. In addition to cardiac hypertrophy, diastolic dysfunction (abnormal active relaxation and increased passive stiffness) is an essential hallmark of HFpEF [35]. The FHS observed a significant association between left ventricular diastolic dysfunction and incident HFpEF [36]. A suggested cause of diastolic dysfunction is myocardial fibrosis due to age-associated increased systemic inflammation and oxidative stress [37–39]. This pathophysiological process may be associated with vascular stiffening-related hypertension [40]. This suggests that HFpEF and hypertension have a close relationship characterized by cardiac hypertrophy following pressure overload and may share underlying pathophysiological processes related to aging, inflammation, and vascular and myocardial stiffening.

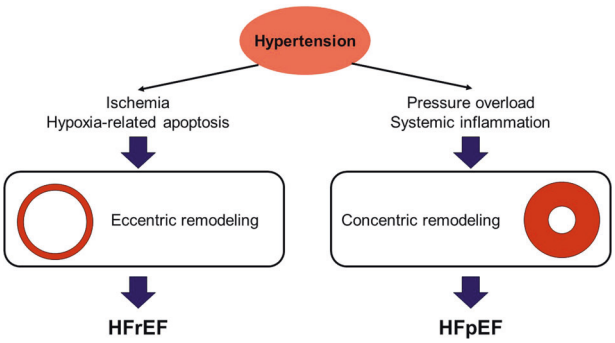


Fig. 1 Possible mechanism of association between hypertension and HFrEF/HFpEF. Eccentric remodeling caused by ischemia or hypoxia-related apoptosis may lead to HFrEF. Concentric remodeling due to pressure overload or inflammation may cause HFpEF. The mechanism differs between EF phenotypes. EF ejection fraction, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction

Hypertension also leads to eccentric hypertrophy [41], an independent risk factor for HFrEF but not HFpEF. In some cases, the naturally developing concentric hypertrophy may be advantageous [41]. The possible causes of patients with hypertension developing concentric or eccentric hypertrophy are complex [41, 42]. Ethnicity seems to influence this process, especially in black males at a higher risk of developing concentric than eccentric hypertrophy [43]. Similarly, patients with obesity and diabetes with hypertension are at a higher risk of concentric than eccentric hypertrophy [35], possibly due to the compounding systemic inflammation associated with both conditions [44]. In contrast, young males with coronary artery disease are at a higher risk of developing eccentric than concentric hypertrophy [41, 45]. A mechanism shared with HFrEF might be cell loss following hypoxia-related apoptosis [46].

Therefore, these data suggest that hypertension can lead to HFrEF and HFpEF. However, the pathways leading to them differ markedly. Pressure overload and systemic inflammation might lead to concentric remodeling in patients with hypertension predisposed to HFpEF. Conversely, concomitant coronary artery disease can predispose patients to eccentric remodeling, leading to HFrEF (Fig. 1).

Preventing heart failure in patients with hypertension by lifestyle interventions

Patients with hypertension are at risk of heart failure (stage A) and requiring intervention to mitigate this risk [7]. A

meta-analysis of Western populations revealed that being overweight mostly contributed to hypertension and that physical inactivity, high sodium intake, and low potassium intake were important contributors to hypertension [47]. Thus, lifestyle interventions appear to be a reasonable approach for preventing hypertension and the subsequent incidence of heart failure. A meta-analysis, including 25 randomized controlled trials of weight reduction and BP changes, revealed that a 1 kg body weight decrease lowered systolic BP (SBP) and diastolic BP (DBP) by 1.05 (95% confidence interval [CI], 0.66–1.43) mmHg and 0.92 (95% CI, 0.55–1.28) mmHg, respectively [48]. Another randomized interventional study showed that weight loss intervention through group meetings and individual counseling on dietary change, physical activity, and social support was significantly associated with long-term BP reduction (36 months' difference, −1.3 mmHg; 95% CI, −2.4–−0.3 mmHg) and lower hypertension incidence compared to the usual care group (risk ratio, 0.81; 95% CI, 0.70–0.95) [49]. Sodium restriction is also an essential factor for preventing heart failure. A randomized control trial revealed that reduced sodium intake (1.8 g/day) lowered the BP more than the absence of sodium restriction (−3.4 ± 0.8 mmHg vs. −0.8 ± 0.8 mmHg, $P < 0.001$) [50]. A meta-analysis revealed that a low-sodium diet measured by urinary sodium excretion significantly lowered SBP compared with a high-sodium diet in populations with hypertension and normotension [51]. The Dietary Approaches to Stop Hypertension (DASH) diet, a diet rich in potassium, calcium, magnesium, dietary fiber, and protein with reduced saturated and total fat, is a well-validated approach to lowering BP [52, 53]. Appropriate exercise is strongly recommended as a lifestyle intervention in patients with hypertension. Numerous studies have also revealed the beneficial effect of aerobic exercises in lowering BP [54–56]. Additionally, combining these interventions may be more beneficial for lowering BP than each intervention alone. For instance, combining sodium restriction and the DASH diet was more effective for lowering BP than either intervention alone [53, 57]. Another randomized controlled trial revealed that the DASH diet and increased walking were associated with lower BP than dietary recommendations based on American Diabetes Association guidelines [58]. Therefore, a comprehensive lifestyle intervention approach for preventing heart failure is important.

These lifestyle interventions have potential mechanisms for preventing heart failure other than lowering BP [59]. Weight loss, physical exercise, and a DASH diet reduce adipose tissue, which secretes adipocytokines, including tumor necrosis factor, resistin, and leptin. These secretions are associated with incident heart failure [60–62]. Weight loss, physical exercise, and a DASH diet also improve insulin resistance and inflammation profiles [63–65], which are strongly associated with the incidence of heart failure [60, 66, 67]. Moreover, weight reduction likely reduces the activation of the renin-angiotensin-aldosterone system [68, 69]. These mechanisms may contribute to preventing the incidence of heart failure.

Preventing heart failure in patients with hypertension by pharmacotherapy

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the prognostic impact of BP-lowering agents (chlorthalidone, amlodipine, and lisinopril) in patients with hypertension and coronary risk factors [70]. At five years, chlorthalidone (133.9 ± 15.2 mmHg) lowered SBP slightly more than amlodipine (134.7 ± 14.9 mmHg, $P = 0.03$) and lisinopril (135.9 ± 17.9 mmHg, $P < 0.001$). In addition, the 6-year heart failure rate was significantly lower in patients receiving chlorthalidone (7.7%) than in those treated with amlodipine (10.2%) or lisinopril (8.7%), implying that thiazide diuretics may be more effective than angiotensin-converting enzyme inhibitors (ACEis) and calcium channel blockers (CCBs) in preventing heart failure. In the ALLHAT subanalysis, chlorthalidone was associated with a lower incidence of both HFrEF and HFpEF than amlodipine and a lower incidence of HFpEF than lisinopril [71]. Additionally, the primary preventive effect of beta-blockers for heart failure is negative [72]. A meta-analysis revealed that diuretics are the most effective for preventing heart failure, followed by ACEi/angiotensin II receptor blockers (ARB) [73]. Another meta-analysis revealed possible beneficial effects of diuretics and ACEis for primary heart failure prevention [74]. This study revealed that diuretics reduced the risk of heart failure incidence compared to CCBs, beta-blockers, and alpha-blockers. ACEi was superior to CCB regarding heart failure risk [74]. In addition, recent subanalyses of randomized controlled trials reported sodium-glucose cotransporter 2 inhibitors (SGLT2i) to effectively prevent the incidence of heart failure in patients with diabetes without a history of heart failure [75–77]. Various mechanisms have been reported, one of which is its BP-lowering effect [78]. Thus, diuretics, ACEi/ABR, and SGLT2i may prevent heart failure in patients with hypertension.

The timing of pharmacotherapy is controversial; the Japan Ambulatory Blood Pressure Monitoring Prospective (JAMP), a nationwide, multicenter, prospective, observational study involving 6359 patients without cardiovascular disease, reported nighttime SBP to be significantly associated with heart failure but not daytime SBP [79]. This reinforces the importance of controlling nighttime SBP. The Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC), randomized, open-label,

Table 1 Randomized interventional trials evaluating the impact of blood pressure lowering therapy on clinical outcomes

Trial name (year)	Main inclusion patients	Sample size	BP measurement	Target BP	HR of heart failure events
HOT (1998)	- 50–80 years - Hypertension with DBP 100–115 mmHg.	18,790	Oscillometric semi-automated office BP	DBP ≤ 90 mmHg vs. DBP ≤ 85 mmHg vs. DBP ≤ 80 mmHg	Not evaluated.
Cardio–Sis (2008)	- ≥55 years - Non–DM - SBP ≥ 150 mmHg with at least 1 additional cardiovascular risk factor	1111	Auscultated office BP	Usual control (<140 mmHg) vs. Tight control (<130 mmHg)	HR 0.42 (0.11–1.63)
ACCORD–BP (2010)	-≥40 years - Type 2 DM	4733	Automated office BP	Intensive therapy (<120 mmHg) vs. Standard therapy (<140 mmHg)	HR 0.94 (0.70–1.26)
SPRINT (2015)	-≥50 years - Non-DM - SBP 130–180 mmHg with at least 1 additional cardiovascular risk factor	9361	Automated office BP	Intensive treatment (<120 mmHg) vs. Standard treatment (<140 mmHg)	HR 0.62 (0.45–0.84)
STEP (2021)	- 60–80 years - SBP 140–190 mmHg	8511	A validated automated home BP	Intensive treatment (110–130 mmHg) vs. Standard treatment (130–150 mmHg)	HR 0.27 (0.08–0.98)

BP bloop pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *HR* hazard ratio, *SBP* systolic blood pressure

controlled study of 2156 individuals with hypertension, showed that bedtime treatment with ≥1 BP-lowering medication had a significantly lower risk of cardiovascular events, including heart failure [80]. However, the Treatment in Morning versus Evening (TIME), a recent randomized, open-label, controlled study including 24,610 patients with hypertension, reported that the risk of cardiovascular events, including heart failure, was comparable between evening doses of the usual antihypertensive medication (8:00 p.m. to 12:00 p.m.) and morning dosing (6:00 a.m. to 10:00 a.m.) [81]. The bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed), a randomized, open-label, blinded end-point study, is currently investigating whether, compared to morning administration, bedtime administration of anti-hypertensive medications reduces cardiovascular events (NCT02990663) [82].

The impact of BP-lowering therapy on heart failure incidence

Several randomized interventional trials have evaluated the impact of BP-lowering treatments on heart failure (Table 1). In 1998, the Hypertension Optimal Treatment (HOT) study investigated the optimal target diastolic BP (DBP) in 18,790 patients with hypertension [83]. It demonstrated that future cardiovascular events did not differ between patients in the ≤90 mmHg, ≤85 mmHg, and ≤80 mmHg target DBP groups. However, incident heart failure was excluded as an outcome. The Studio Italiano Sugli Effetti CARDIOvascolari del Controllo Della Pressione Arteriosa SIStolicatrial (Cardio-Sis), a randomized open-label trial involving 44 centers in Italy, compared the clinical benefits of tight (SBP target <130 mmHg) and usual control (SBP target <140 mmHg) of BP in 1111 nondiabetic patients with hypertension [84]. Patients with tight control were less frequently hospitalized for heart failure than those with usual control; however, this was not significant and partially underpowered. Moreover, the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial evaluated the clinical efficacy of an intensive BP-lowering strategy in patients with type 2 diabetes with high cardiovascular event risk [85]. The heart failure event rate did not differ between patients receiving intensive (target SBP < 120 mmHg) and those receiving standard therapies (target SBP < 140 mmHg) (0.73%/year vs. 0.78%/year). The Systolic Blood Pressure Intervention Trial (SPRINT) conducted on patients without diabetes evaluated whether a low SBP target strategy (<120 mmHg) prevented cardiovascular events compared with a standard target strategy (<140 mmHg) [86]. The prespecified primary endpoint was a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. The trial was terminated early because a

significant benefit for the primary endpoint was observed in patients with a lower target SBP. Regarding heart failure, an intensive strategy was significantly associated with a lower incidence than a standard target strategy. A possible reason for the association difference between intensive and standard treatments is that the SPRINT trial included "HFpEF" as a heart failure event [86]. In contrast, other trials did not mention the ejection fraction as a heart failure definition [87–89]. Therefore, SPRINT might provide a more precise heart failure definition than other studies, especially regarding HFpEF, which seems more relevant to high BP than HFrEF [28–30]. Furthermore, the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) study on an elderly (60–80 years of age) population [90] allocated patients with hypertension to intensive (target SBP 110–<130 mmHg) or standard (target SBP 130–<150 mmHg) hypertension treatment. This trial revealed that intensive therapy was associated with a lower heart failure incidence than standard treatment. A meta-analysis of 123 randomized trials revealed that as the BP decreased by 10 mmHg, the heart failure risk decreased by 28% [27]. BP-lowering therapy might be beneficial for preventing heart failure; however, the optimal BP target is yet to be determined, and the impact of clinical factors, including age or comorbidities, on the target BP should be discussed.

BP management and incident heart failure by age

In older individuals

Hypertension is the leading risk factor for cardiovascular diseases, including heart failure, and the prevalence increases with age; however, optimal BP management in older individuals remains inconclusive. The Hypertension in the Very Elderly Trial (HYVET) is a multinational, randomized, double-blind, placebo-controlled trial that examined diuretic indapamide effects on individuals aged ≥80 years with a sustained SBP of ≥160 mmHg. BP management with indapamide to 150/80 mmHg revealed a 64% reduction in heart failure rate with fewer reported serious adverse events in the active treatment group [91]. Intensive antihypertensive treatment achieving BP ≤ 140/90 mmHg in Chinese patients >70 years resulted in reduced heart failure mortality by 62.7% compared with standard antihypertensive treatment achieving BP ≤ 150/90 mmHg [92]. Older individuals may benefit more from intensive BP control than younger individuals. In the SPRINT, intensive BP management (target SBP < 120 mmHg) in patients ≥75 years (28.2% of all the participants) achieved a greater reduction in the primary cardiovascular endpoint, including heart failure, than in those <75 years with cardiovascular event risk, yet the interaction remained nonsignificant [86].

However, the results of the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study opened a discussion on the intensity of BP management in older individuals and reported that the incidence of heart failure was not significantly different after 2 years of strict BP management (<140 mmHg) and moderate BP control (140–150 mmHg) in individuals aged ≥70 and <85 years [93]. The results of clinical trials have been controversial due to differences in targeted BP, patient characteristics, and achievement of BP differences between the intensive and standard treatment groups. In the same SPRINT data, a secondary analysis reported increased heart failure risk for those with lower DBP, particularly for patients aged ≥75 years with a history of cardiovascular disease before enrollment [94]. However, the recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend aggressive lowering of BP levels to <130/80 mmHg even in older individuals, considering their high cardiovascular risks and generally acceptable tolerability to antihypertensive medications [95]. Guidelines from the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) [96], the Japanese Society of Hypertension (JSH) [97], and the National Institute for Health and Care Excellence (NICE) [98] recommend higher BP targets for those >80 years (≥75 years in the JSH guideline) but with suggestions for further BP reduction when necessary and tolerable.

In younger individuals

Elevated BP in mid-to-late life (the late 40 s to 70 s) is a risk factor for incident heart failure. A higher average BP over 25 years of mid-to-late life in the Atherosclerosis Risk in Communities (ARIC) study indicated increased incident heart failure risk [99]. With the recognition of longer lifetime gain [100] and the financial impact on medical expenses in preventing subsequent cardiovascular diseases in younger individuals [101], long-term BP management is more emphasized. There is no clear evidence of intensive BP management benefits in younger versus older individuals for preventing major cardiovascular diseases [102]; however, recent guidelines generally recommend aggressive BP management for patients aged <80 years.

Hypertension in younger individuals (20–40 years) is also a risk factor for cardiovascular diseases, including heart failure [103]. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, the cumulative SBP, estimated as the area under the curve of 15 years of BP trend during young adulthood, was also associated with a subsequent heart failure incidence [104]. However, BP management efficacy in very young patients with hypertension remains ambiguous without randomized studies assessing cardiovascular outcomes. Lifestyle intervention,

careful follow-up, and pharmacological intervention via shared decision-making are common approaches for hypertension in young individuals.

Management of BP in patients with heart failure

The association between BP and prognosis in patients with heart failure

Previous studies indicated that high BP was a significant prognostic factor and that the relationship between baseline BP and prognosis was linear in the general population [19, 105]. Thus, guidelines strongly recommend BP-lowering therapy for those with high BP in the general population [96, 97, 106]. However, once heart failure develops, the association between BP and prognosis seems to differ from that in the general population [107–111]. The relationship between systolic BP and clinical outcomes was J-shaped or an inverse linear relationship. Patients with lower BP and chronic heart failure have low survival rates regardless of reduced or preserved EF [9, 10, 107–109, 112]. Nevertheless, most medications proven to improve heart failure prognosis have a BP-lowering effect, thereby making the association between BP and prognosis complex; however, there are no trials regarding optimal BP management in patients with heart failure [97]. In the following sections, we discuss the management of BP in HFrEF and HFpEF and the impact of GDMT on BP and prognosis.

BP management in patients with heart failure based on ejection fraction phenotypes

No randomized controlled trial has evaluated the optimal BP target and BP-lowering agents in patients with heart failure. Therefore, recent guidelines were extrapolated from the results of different patient groups. A summary of recent guidelines for BP management in patients with heart failure is presented in Table 2. The 2018 ESC/ESH guidelines for hypertension state that BP-lowering therapy should start at BP < 140/90 mmHg in patients with HFrEF [96]. Specific target BP was not recommended; however, avoiding a BP < 120/70 mmHg is suggested regardless of the heart failure phenotype. In the 2021 ESC guidelines for heart failure, a target BP was not specified; nonetheless, it was mentioned that age and comorbidities could help personalization [113]. In contrast, the ACC/AHA guidelines for hypertension indicated a target SBP of <130 mmHg for HFrEF and HFpEF [106]. The updated 2022 ACC/AHA guidelines recommend that patients with heart failure and hypertension should be managed according to the ACC/AHA for hypertension [7]. In Japan, the JSH guidelines suggested SBP control at 110–130 mmHg for HFrEF and <130 mmHg for HFpEF per the AHA statement regarding hypertension management in chronic heart failure [114]. The target BP of 130 mmHg for HFpEF was determined based on a meta-analysis of 10 randomized controlled trials with HFpEF, which reported that SBP < 130 mmHg might be associated with a lower incidence of heart failure hospitalization [115]. However, the same meta-analysis also suggested SBP < 130 mmHg to be related to renal dysfunction [115]. Therefore, the threshold has been controversial, and no robust evidence exists.

Previous substudies of randomized controlled trials/large registries of patients with heart failure have studied the impact of heart failure medications on BP. A subanalysis of the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF), comparing the efficacy of sacubitril/valsartan versus valsartan in patients with HFpEF, indicated that an SBP of 120–129 mmHg had the lowest cardiovascular event risk [109]. Another substudy of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMZE-HF), a large registry of patients hospitalized with heart failure, revealed that discharge SBPs of <130 mmHg for HFrEF and <120 mmHg for HFpEF were significantly associated with a higher incidence of all-cause mortality compared to their counterparts [116, 117]. However, since reverse causality may impact the relationship between BP and prognosis in patients with heart failure, the optimal BP is unclear, and BP control should be individualized according to the patient's characteristics, including age and comorbidities.

BP and GDMT in patients with heart failure

The current guidelines strongly recommend that patients with HFrEF be put on four kinds of medications well proven to improve these patients' prognoses: beta-blockers, renin-angiotensin-aldosterone system inhibitors (ACEi, ARB or sacubitril/valsartan), mineralocorticoid receptor antagonists (MRA), and SGLT2i. Furthermore, recent studies have revealed that switching the medication from conventional treatment consisting of a beta-blocker and ACEi/ARB to four contemporary drugs, including beta-blockers, sacubitril/valsartan, MRA, and SGLT2i, is associated with lowering all adverse outcomes, including all-cause mortality [118]. However, registry data indicated that the clinical implementation of such drugs has not been successful [119, 120]. The reason for this is multifactorial; nonetheless, low BP limits the use or titration of these recommended medications [121–123]. However, it is important to consider whether prescribing guideline-recommended medications due to low BP can be justified,

Table 2 Recent guideline recommendations of BP management in patients with HFrEF and HFpEF

Guidelines (Year)	Target BP for HFrEF	Target BP for HFpEF	Treatment strategy for BP in HFrEF	Treatment strategy for BP in HFpEF
Europe				
ESC/ESH guidelines for hypertension (2018)	- When BP > 140/90 mmHg, antihypertensive drug therapy should be started. - Avoiding 120/70 mmHg would be better.	- Same as for HFrEF.	Class I: ACEi/ARB, BB, MRA, Diuretics Class IIb: Dihydropyridine CCB - Non-dihydropyridine CCB, alpha-blockers, and centrally acting agents should not be used.	- The strategy for HFrEF might also be the one to adopt in HFpEF.
ESC guidelines for heart failure (2021)	- BP target is uncertain. - Age and comorbidities can help to personalize target BP.		1st line: Neurohormonal antagonists, Diuretics 2nd line: Dihydropyridine CCB Contraindication: Non-dihydropyridine CCB, centrally acting agents	- The strategy used in HFrEF should be considered in HFpEF.
USA				
ACC/AHA guidelines for hypertension (2017)	<130/80 mmHg	<130 mmHg	Class I: ACEi/ARB/ARNI, BB, MRA, Diuretics Class III: Non-dihydropyridine CCB	Class I: Diuretics, ACEi/ARB, BB - MRA would be the preferred choice. - Nitrates should be avoided.
AHA/ACC/HFSA guidelines for heart failure (2022)	- Target BP is unknown. - Refer to ACC/AHA guidelines for hypertension.		Refer to ACC/AHA guidelines for hypertension.	
Japan				
JCS/JHFS guidelines for heart failure (2017)	SBP 110–130 mmHg		Class I: ACEi/ARB, BB, MRA, Diuretics Class IIa: Long-acting dihydropyridine CCB - Other types pf CCB should be avoided.	- No evidence for HFpEF. - BP should be controlled individually according to underlying conditions.
JSH guidelines for hypertension (2019)	- SBP 110–130 mmHg is recommended, but BP should be controlled individually.	SBP < 130 mmHg	1st line: ACEi/ARB, BB, MRA, Diuretics 2nd line: Long-acting dihydropyridine CCB	- Diuretics with useful drugs (ACEi/ARB, BB, MRA) are suggested.

ACC American College of Cardiology, *ACEi* angiotensin-converting enzyme inhibitors, *AHA* American Heart Association, *ARB* angiotensin II receptor blockers, *ARNI* angiotensin receptor neprilysin inhibitors, *BB* beta-blockers, *BP* blood pressure, *CCB* calcium channel blockers, *ESC* European Society of Cardiology, *ESH* European Society of Hypertension, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HFSA* Heart Failure Society of America, *JCS* Japanese Circulation Society, *JHFS* Japanese Heart Failure Society, *JSH* Japanese Society of Hypertension, *MRA* mineralocorticoid receptor antagonists, *SBP* systolic blood pressure

given that those with low BP are particularly at a high risk of adverse events. Several substudies from randomized controlled trials examined the impact of baseline BP on heart failure medications. Table 3 summarizes data on baseline BP, hypotension incidence, and associated changes in BP observed in pivotal double-blind, randomized clinical trials that have proven the efficacy of heart failure medications currently recommended by guidelines. More studies have recently provided evidence on how heart failure medications impact BP and their prognostic implications.

Beta-blockers' impact on prognosis in relation to baseline BP was examined in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study cohort [124]. In this study, treatment with carvedilol was associated with a greater decline in BP than was the placebo; however, this decline in SBP was not consistent regardless of the baseline SBP, which is a significant determinant of the effects of carvedilol on BP. Among patients with a baseline SBP of 85–95 mmHg, the SBP was not reduced and instead increased relative to placebo in this subgroup. Most importantly, the absolute risk reduction of adverse events significantly increased as the baseline SBP decreased (P for interaction = 0.03).

A subanalysis of the Valsartan Heart Failure Trial (Val-HeFT) study examined the interaction between baseline SBP and the prognostic impact of valsartan in HFrEF and the association between changes in SBP at 4 months of randomization and prognosis [125]. They observed that the favorable effect of valsartan did not interact with baseline SBP, implying that valsartan improved the prognosis of patients with HFrEF and low BP. Moreover, valsartan lowered SBP by 4 mmHg more than placebo; however, this reduction in SBP was observed in those with preserved SBP and not in the lowest quartile group of baseline SBP. Interestingly, further analysis revealed that although the SBP increased in patients in the lowest quartile of baseline SBP in the valsartan and placebo groups, this increase in SBP was significantly higher in the placebo group than in the valsartan group, implying that this phenomenon cannot be explained only by mean regression.

Similar findings were reported for sacubitril/valsartan. Treatment with sacubitril/valsartan lowered the SBP more in patients with HFrEF than in those treated with enalapril in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) [126]. In the subanalysis using the PARADIGM-HF cohort stratified by baseline SBP, the SBP increased in patients with lower baseline SBP and decreased in those with higher baseline SBP [108]. However, the SBP increase was less, and the SBP decrease was greater in the sacubitril/valsartan group than in the enalapril group. Additionally, the prognostically beneficial effect of sacubitril/valsartan did not significantly correlate with baseline SBP and was observed in all the baseline SBP categories. Another subanalysis of PARADIGM-HF evaluated the association between SBP drop and prognosis [127]. In this study, treatment with sacubitril/valsartan resulted in significantly more hypotensive events after randomization than treatment with enalapril, and hypotensive events led to a higher incidence of primary endpoints (cardiovascular death or heart failure hospitalization). However, this was considerably stronger in the enalapril group than in the sacubitril/valsartan group. In PARAGON-HF, the study run-in phase was set up to evaluate patient tolerability for enalapril and sacubitril/valsartan before randomization and whether the beneficial effect of sacubitril/valsartan differs between those who experienced hypotension during the run-in phase and those who did not [127]. As a result, no interaction was observed between the two populations, and treatment with sacubitril/valsartan was superior to enalapril therapy in those who experienced hypotension during the run-in phase [127].

MRA is one of the least prescribed guideline-directed medications for HFrEF [119, 120]. In addition to the hyperkalemia concern, its impact on BP is a reason for unwillingness to prescribe it, considering recent trial results indicating that MRA is a powerful antihypertensive agent as an adjunct for resistant hypertension [122, 128, 129]. In a study combining the Randomized Aldactone Evaluation Study (RALES) and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) datasets [130], MRA effects on BP, the interaction between changes in BP and the prognostic impact of MRAs in patients with HFrEF were explored. After 9 months of treatment, the SBP increased in those with lower baseline SBP and decreased in those with higher baseline SBP. Moreover, MRA treatment was associated with less increase and a greater decrease in the lower and higher baseline SBP groups than in the placebo group, respectively. The number of patients who experienced hypotension was similar between the MRA and placebo groups (4.6% vs. 3.9%, $P = 0.25$). A lower baseline SBP was associated with a higher incidence of hypotension; however, there was no interaction between baseline SBP and treatment on hypotension incidence. The beneficial effect of MRAs was consistent across the baseline SBP spectrum, implying that MRA improves the prognosis of patients with HFrEF regardless of baseline SBP. Regarding finerenone, a novel selective nonsteroidal MRA, the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF), a first phase III study on patients with heart failure, is currently ongoing [NCT04435626].

SGLT2i reduces SBP in patients with type 2 diabetes by 3–4 mmHg, and the impact of SGLT2i on BP [131], the interaction between changes in SBP, and the prognostic

Table 3 Clinical implication of blood pressure in randomized-control trials evaluating the effect of heart failure medications

Drug class	Trial name (year)	Sample size	Randomization	Baseline BP (active arm vs. control)	Exclusion/Inclusion criteria on BP	Hypotension (active arm vs. control)	Other findings
Beta blocker	COPERNICUS (2001)	2289	Carvedilol vs. Placebo	123 vs. 123 mmHg	SBP < 85 mmHg	1.9% vs. 1.6% ($P = 0.57$)	At the final up-titration visit, SBP was decreased from baseline by a mean of 4.6 mmHg in the carvedilol group and by 2.4 mmHg in the placebo group ($p = 0.001$). However, this difference was no longer apparent after eight months of randomization. Fewer patients in the carvedilol group than in the placebo group required the permanent discontinuation of treatment because of adverse effects of for reasons other than death ($P = 0.02$).
	CIBIS II (1999)	2647	Bisoprolol vs. Placebo	129.2 vs. 130.2 mmHg	SBP < 100 mmHg	3 patients vs. 11 patients ($P = 0.03$)	No statistically significant difference in permanent treatment withdrawals ($P = 0.98$).
	MERIT-HF (1999)	3991	Metoprolol XL vs. Placebo	130.0 vs. 129.5 mmHg	SBP < 100 mmHg	0.6% vs. 0.2%	SBP decreased less in the metoprolol CR/XL group than in the placebo group (−2.1 vs. 3.5 mmHg, $P = 0.013$). There was no difference between groups in the change of diastolic blood pressure (−2.6 vs 2.3 mmHg, $P = 0.38$).
ACEi	SOLVD (1991)	2569	Enalapril vs. Placebo	125.3 vs. 124.5 mmHg	N/A	14.8% vs. 7.1% ($P < 0.001$)	Systolic and diastolic blood pressures were significantly lower in those treated with enalapril compared to placebo, by 4.7 and 4.0 mmHg, respectively. Treatment with enalapril was associated with significantly more dizziness and fainting (57% in enalapril vs. 50% in placebo).
	CONSENSUS (1987)	253	Enalapril vs. Placebo	118 vs. 121 mmHg	N/A	Not described.	A significant decrease in SBP was greater in the enalapril group (−20 mmHg) than the placebo group (−11 mmHg) ($P < 0.01$).
ARB	ELITE II (2000)	3152	Losartan vs. Captopril	134 vs. 134 mmHg	SBP < 90 mmHg or DBP > 95 mmHg	There were no significant differences in lowering of BP (Percentages were not shown).	Significantly fewer patients taking losartan discontinued treatment because of adverse effects ($P < 0.001$).
	Val-HeFT (2001)	5010	Valsartan vs. Placebo	123.0 vs. 124.0 mmHg	N/A	1.3% vs. 0.8% ($P = 0.124$)[a]	SBP was reduced to a greater extent with valsartan than placebo (5.2 mmHg in valsartan vs. 1.2 mmHg in placebo at 4 M).
	CHARM-added (2003)	2548	Candesartan vs. Placebo	124.7 vs. 125.6 mmHg	N/A	4.5% vs. 3.1% ($P = 0.079$)[a]	SBP lowered from baseline 4.6 mmHg more in candesartan group ($P = 0.007$).

Table 3 (continued)

Drug class	Trial name (year)	Sample size	Randomization	Baseline BP (active arm vs. control)	Exclusion/Inclusion criteria on BP	Hypotension (active arm vs. control)	Other findings
MRA	RALES (1999)	1663	Spironolactone vs. Placebo	123 vs. 122 mmHg	N/A	Not described.	There was no significant difference between the two groups in blood pressure during the study.
	EMPHASIS-HF (2011)	2737	Eplerenone vs. Placebo	124 vs. 124 mmHg	SBP > 180 mmHg and/or DBP > 110 mmHg	3.4% vs. 2.7% ($P = 0.32$)[a]	SBP decreased more in the eplerenone group than in the placebo group (2.5 vs. 0.3 mmHg, $P = 0.001$).
S/V	PARADIGM-HF (2014)	8442	S/V vs. Enalapril	122 vs. 121 mmHg	SBP < 100 mmHg at screening or <95 mmHg after screening	Symptomatic: 14.0% vs. 9.2% ($P < 0.001$) Symptomatic & SBP < 90 mmHg: 2.7% vs. 1.4% ($P < 0.001$)	The mean SBP at 8 months was 3.2 mmHg lower in the S/V group compared to enalapril ($P < 0.001$).
	PARAGON-HF (2019)	4822	S/V vs. Valsartan	130.5 vs. 130.6 mmHg	SBP > 180 mmHg or SBP 150–180 mmHg if taking 2 or less antihypertensive drugs, or SBP < 105 mmHg or symptomatic hypotension at visit 103 or visit 201	Hypotension (SBP < 100 mmHg): 15.8% vs. 10.8%	The mean SBP at 8 months was 4.5 mmHg (95% CI, 3.6 to 5.4) lower in the S/V group.
SGLT2i	DAPA-HF (2019)	4744	Dapagliflozin vs. Placebo	122.0 vs. 121.6 mmHg	SBP < 95 mmHg	0.3% vs. 0.5%	The mean SBP at 8 months was 1.27 mmHg lower in dapagliflozin group compared to placebo ($P = 0.002$).
	EMPEROR-reduced (2020)	3730	Empagliflozin vs. Placebo	122.6 vs. 121.4 mmHg	SBP ≥ 180 mmHg or SBP < 100 mmHg	Hypotension: 9.4% vs. 8.7% Symptomatic hypotension: 5.7% vs. 5.5%	Changes in SBP at 52 weeks from baseline were −2.4 mmHg in empagliflozin group and −1.7 mmHg in placebo group. Absolute difference was −0.7 (95% CI, −1.8 to 0.4) mmHg.
	EMPEROR-preserved (2021)	5988	Empagliflozin vs. Placebo	131.8 vs. 131.9 mmHg	SBP ≥ 180 mmHg or SBP < 100 mmHg	10.4 % vs. 8.6%	Changes in SBP at 52 weeks from baseline were −1.8 mmHg in empagliflozin group and −0.6 mmHg in placebo group. Absolute difference was −1.2 (95% CI, −2.1 to −0.3) mmHg.

[a]Only events leading to drug discontinuation

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *BP* blood pressure, *CI* confidence interval, *DBP* diastolic blood pressure, *MRA* mineralocorticoid receptor antagonist, *SBP* systolic blood pressure, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *S/V* sacubitril/valsartan

impact of SGLT2i in patients with heart failure are of clinical relevance. In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) group, compared with placebo, dapagliflozin significantly lowered SBP; nonetheless, this change was significantly correlated with baseline SBP [132]. In patients in the lowest baseline SBP category, the SBP slightly increased, whereas it decreased in patients with higher baseline SBP. In contrast, treatment with dapagliflozin lowered SBP regardless of the baseline SBP (less increase in patients with lower baseline SBP and more decrease in patients with higher baseline SBP). Low SBP resulted in a higher rate of drug discontinuation but without a significant difference in the discontinuation rate between dapagliflozin and placebo across all SBP spectra. Notably, a favorable effect of dapagliflozin on the primary outcome (composite of cardiovascular death and worsening heart failure) and all-cause death was observed regardless of baseline SBP. These findings were consistent with those in another large-scale, double-blind, randomized study that tested the efficacy of SGLT2i in patients with HFrEF [133]. Additionally, empagliflozin attenuated the eGFR slope decline regardless of the baseline SBP and reduced the risk of the renal composite outcome to a greater extent in patients with lower SBP, although the P value for the interaction trend was significant.

Interestingly, these GDMTs consistently increased BP after their initiation. There are several possible explanations for this association. First, the "regression to the mean" should be considered in this setting. Second, the effect of lowering atrial impedance and reverse remodeling may contribute to an increase in BP. All GDMTs mentioned earlier are associated with left ventricular reverse remodeling in patients with heart failure [134–139]. Last, the hypotensive group may have been modified for antihypertensive or other heart failure medications after the implementation of GDMT.

Available evidence on the interplay between BP and the prognostic impact of class I recommendation heart failure drugs (beta-blockers, ACEi/ARB, sacubitril/valsartan, and SGLT2i) is not consistent. However, all studies invariably demonstrated that the prognostic impact of such drugs is independent of baseline BP and not diminished even in those with relatively low BP. Given the prognostic effect of these drugs, all should be prescribed whenever possible. Additionally, a pharmacological approach attempting to introduce multiple drugs targeting several neurohormonal blocking pathways even at low doses, rather than sequentially introducing multiple drugs for heart failure, seems preferable in improving the outcome of patients with heart failure. However, this strategy's clinical and prognostic implications have not been tested in patients with heart failure whose BP is low and need to be elucidated in future studies.

Perspective of Asia

Compared to Westerners, Asians may present a closer association between blood pressure and cardiovascular events [25]; thus, stricter blood pressure control may be essential. Further studies on specific management, including the optimal threshold of BP according to age, race, or comorbidities, are warranted.

Conclusions

Hypertension is a risk factor for developing HFrEF and HFpEF, and lifestyle interventions and antihypertensive drugs are efficient for preventing heart failure incidence. Once heart failure is established, the association between BP and heart failure becomes complex, in which lower BP incurs worse outcomes. Optimal management of BP, including targeted BP or medical therapy, has not been fully identified via clinical trials. Meanwhile, recent guidelines suggested that patients with heart failure should be carefully managed based on age, comorbidities, and heart failure phenotype. However, previous randomized controlled trials of heart failure medications revealed consistent efficiency in improving the outcomes of patients with heart failure, regardless of the baseline BP. There have not been large randomized controlled trials revealing optimal BP management in patients with heart failure; therefore, clinicians should try intensifying GDMT as much as possible, even in cases with relatively low BP, to improve their outcomes.

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Compliance with ethical standards

Conflict of interest J.T. was supported by the National University of Singapore Start-up grant, the tier 1 grant from the Ministry of Education and the CS-IRG New Investigator Grant from the National Medical Research Council; received consulting or speaker fees from Daiichi-Sankyo, Boehringer Ingelheim, Roche Diagnostics and Us2.ai; and owns patent US-10702247-B2 unrelated to the present work. Y.M. received an honorarium from Otsuka Pharmaceutical Co, Novartis Pharma K.K., Bayer, Inc., and AstraZeneca and collaborative research grants from Pfizer Japan, Inc., Otsuka Pharmaceutical Co, EN Otsuka Pharmaceutical Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. T.M. is an Associate Editor of Hypertension Research. The other authors have no other conflicts of interest to declare.

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