**Management of Blood Pressure in Heart Failure**

Ana-Catarina Pinho-Gomes [1,2], Kazem Rahimi[1,2]

[1] The George Institute for Global Health, University of Oxford, Oxford, United Kingdom

[2] Deep Medicine, Oxford Martin School, University of Oxford, Oxford, United Kingdom

**Key words:** Heart failure; Hypertension; Blood pressure; Antihypertensive agents

Word count: 3,000

Corresponding author:

Ana-Catarina Pinho-Gomes

The George Institute for Global Health

University of Oxford

Hayes House, 75 George Street, OX1 2BQ

Oxford, United Kingdom

ana.pinho-gomes@georgeinstitute.ox.ac.uk

**Abstract**

Hypertension is a common comorbidity in patients with heart failure and most drugs that have demonstrated to improve prognosis in this population have the potential to reduce blood pressure. Nonetheless, the relationship between blood pressure and clinical outcomes and the relevance of blood pressure reduction in heart failure remains unclear. This narrative review summarises the evidence currently available to guide blood pressure treatment in this patient group and highlights key questions for further research. In patient with heart failure with reduced ejection fraction, guidelines consensually recommend treating hypertension with drugs that have compelling indications in heart failure, with a target blood pressure of 130/80 mmHg. In patients with heart failure with preserved ejection fraction, guidelines acknowledge that the optimal treatment strategy remains unclear and thus recommend adopting a similar treatment strategy to patient with reduced ejection fraction. In any case, low blood pressure should not deter up-titration of drugs otherwise indicated to improve prognosis in heart failure, provided that patients tolerate drugs without adverse events. In absence of evidence for modification of treatment efficacy and safety by baseline blood pressure, it is likely that treatment may actually lead to higher absolute risk reduction in patients with the lowest blood pressure. Special considerations and treatment adjustments are needed in the elderly as well as in patients with diabetes, chronic kidney disease and atrial fibrillation. More evidence is needed on blood pressure management in patients with heart failure in general, in whom the increasing burden of multimorbidity adds further complexity to treatment.

## I. Hypertension and heart failure

Hypertension, commonly defined as blood pressure (BP) above 140/90 mmHg, is the leading risk factor for developing heart failure (HF),[1] and the prevalence of hypertension as comorbidity in patients with established HF has been estimated to range from 25 to 70% in epidemiological studies in different regions across Europe.[2] Elevated BP is more common in HF with preserved ejection fraction (HFpEF) than in HF with reduced ejection fraction (HFrEF), with a prevalence of up to 90% in the former.[3, 4, 5] However, the poorly understood association between BP and clinical outcomes in HF creates a challenge for managing BP in this population. Contrary to the well-established linear association between elevated BP and cardiovascular events in the general population,[6] observational studies have reported a J-shaped relationship between SBP and all-cause and cardiovascular mortality in patients with HF, in particular among those with HFrEF (Figure 1).[7, 8, 9] This 'paradoxical' association has raised the question as to whether a very low systolic BP (SBP) itself might be harmful or whether it is simply a marker of poorer health. Proponents of the former hypothesis have argued that in observational analyses patients with SBP below 110 mmHg had an increased risk of HF hospitalisation even though they were on maximum guideline-recommended medical therapy,[10] and that in some analyses the associations were present despite no evidence for more advanced HF or greater burden of known comorbidities among those with low BP.[11] On the other hand, low BP may be a surrogate marker for more severe heart dysfunction and lower cardiac output, which are the actual causes of the adverse clinical outcomes rather than BP itself.[12, 13] This hypothesis is supported by trials of cardiac devices, in which resynchronisation therapy significantly increased BP and reduced mortality and HF hospitalisation, with a higher relative risk reduction in patients with low baseline BP in whom BP increased likely due to device-induced improvement in cardiac function.[14] The associations between BP and clinical outcomes in patients with HFpEF are even more uncertain, with conflicting reports from observational studies on whether low SBP and/or diastolic BP (DBP) carry an adverse prognosis.[15, 16]

Clinical trials are ideally suited to assess whether low BP is a cause or consequence of poor health. However, in patients with HF, there is no compelling evidence from clinical trials on this question. Although meta-analyses[17, 18] of hypertension trials in patients without HF have shown that decreasing BP significantly reduces the risk of fatal and non-fatal cardiovascular outcomes, with no effect heterogeneity across a range of baseline BP categories, the extent to which those findings are applicable to HF patients and whether the relationship holds true when baseline BP is very low remain unclear. This is in part because meta-analyses of antihypertensive drugs have typically excluded HF trials even when trials tested the effect of drugs with BP-lowering properties.[19] This exclusion has been justified by the absence of BP reduction in some HFrEF trials despite improved clinical outcomes,[20, 21, 22] and no or harmful effects of some drugs (e.g. calcium channel blockers (CCBs), alpha-blockers) on cardiovascular risk in patients with HFrEF despite their known BP-lowering properties in the general population.[23, 24, 25] In the same vein, contradictory evidence suggested that mineralocorticoid receptor antagonists (MRA) either did not reduce BP in patients with HFpEF, or reduced BP but this effect had no impact on clinical outcomes contrary to what had been demonstrated in the general population.[26, 27]

Therefore, it remains to be established whether the observed J-shaped relationship between BP and clinical outcomes in patients with HF is causal and it has been suggested that pulsatile haemodynamic parameters (particularly pulse wave velocity (PWV)) may more accurately reflect ventricular-vascular interaction and estimate prognosis in HF.[28] Indeed, higher PWV as a marker of increased arterial stiffness has been associated with poor prognosis independently of left ventricular ejection fraction (LVEF), with conflicting findings on whether high PWV is associated with low or high brachial BP.[29, 30] However, measurement of PWV is not yet routinely available in clinical practice and thus BP management still relies on brachial BP measurements despite its paradoxical and controversial relationship with clinical outcomes. This creates a dilemma for physicians, who have to strike the balance between prescribing life-saving HF treatment with drugs that may reduce BP, and the potentially harmful effects of low BP itself in the HF population. In this scenario, this narrative

review aims to summarise the best evidence currently available on BP management in HF and to highlight critical questions deserving further research.

## II. Guideline-recommended treatment for hypertension in HF

Although guidelines state that 'blood pressure control is an element of the holistic management of patients with HF',[31] they acknowledge that there have been no trials in the HF population purposefully comparing different antihypertensive drugs and treatment goals. Therefore, recommendations have been extrapolated from evidence in other high-risk populations, in whom intensive BP reduction showed greater protection from cardiovascular events, albeit with a potential increase in side effects.[32, 33] Overall, HF and hypertension guidelines recommend titration of drugs that have compelling indications for management of HF and also reduce BP to attain a BP reduction consistent with a target of 130/80 mmHg, as in patients without HF (Table 1 and Figure 2). However, the ideal BP target in HF is yet to be established as the more intensive target, in comparison to the conventional 140/90 mmHg, has not been tested in randomised clinical trials (RCTs) in the HF population.[34, 35] The recommendations are thus tempered with caution to acknowledge the uncertainty regarding the extrapolation of recommendations from hypertensive patients in the general population to patients with HF, who are considerably different from them. On one hand, the range of BP in HF patients is overall lower than that of the general population and thus it is unclear whether further treatment-induced BP reduction in those patients actually happens or influences clinical outcomes.[36, 37] On the other hand, clinical outcomes for which the protective effect of antihypertensives has been demonstrated in the general population may be less relevant in patients with HF, in whom atherosclerotic events like stroke and myocardial infarction[38, 39] are relatively less common.[40, 41, 42]

The complexity of BP management in patients with HF is further exacerbated by the well-recognised diversity and complexity of HF syndrome. In an attempt to create more homogenous HF groups, a binary classification based on left ventricular ejection fraction (LVEF) has been historically

used with separation of patients into HFrEF or HFpEF subtypes. This classification has been recently superseded by the addition of a third category of HF with mid-range LVEF (HFmEF), defined as LVEF in the range of 40-49%,[43, 44] with LVEF below or above that range classified as HFrEF and HFpEF, respectively.[31] Although the diversity of the HF syndrome seems consensual, the appropriateness of patient classification into categories based on arbitrary cut-offs of LVEF has been questioned,[45] and it has been argued that HFrEF and HFpEF represent similar processes along one disease continuum rather than distinct disease entities.[46, 47, 48] Regardless of the ongoing controversy, the classification based on LVEF is clinically useful because it distinguishes between populations that differ on underlying aetiologies, demographics, comorbidities and, most importantly, on response to treatment,[49, 50] including BP management.[51] For instance, MRAs improved prognosis in patients with HFrEF[52] but not in patients with HFpEF,[53] with significant interaction between LVEF and treatment effect.[54] As LVEF has also been shown to significantly interact with BP,[55] it is likely that antihypertensive treatment effect varies across the spectrum of LVEF. Therefore, HF guidelines make recommendations for BP management separately for HPrEF and HFpEF,[31] and this classification, which remains the mainstay in research and in clinical practice, is thus adopted in this review.

## III. Heart Failure with reduced Ejection Fraction

Although all the agents that have proven to reduce cardiovascular and total mortality in HFrEF (Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin-receptor blockers (ARBs), beta-blockers (BBs), Angiotensin receptor-neprilysin inhibitor (ARNI) and MRAs) have the potential to decrease BP, whether BP reduction actually happens and mediates their beneficial effects remains controversial. Indeed, clinical trials of those agents with BP-lowering properties in patients with HFrEF suggested that (1) BP increased in the treatment arm only;[11, 36] (2) BP did not change in any of the study arms;[21] or (3) BP decreased in both study arms, but this reduction did not modify treatment effect (Table 2).[56, 57] These conflicting results raised the question as to whether

BP reduction contributes to the positive effects of guideline-recommended drugs that have BP-lowering properties, or on the contrary it has detrimental effects that are offset by the benefits of neurohumoral modulation.[58] Although the contribution of BP to the benefits of guideline-recommended drugs in HFrEF remains unclear, the importance of treating elevated BP in this population is consensually recognised by HF and hypertension guidelines, with both recommending drugs that have proven to improve prognosis in HFrEF as first-line therapy (Table 1). Dual renin-angiotensin-aldosterone system (RAAS) blockade with ACEI and ARB is though contra-indicated due to the risk of renal adverse events.[59] Non-dihydropyridine CCBs and alpha-blockers should also be avoided because of their negative inotropic effect. Similarly, centrally-acting agents (like moxonidine) were shown to increase mortality in HFrEF and are therefore contraindicated.[60] Hydralazine and dihydropyridine CCBs are additional BP-lowering agents that have been shown to be safe in HFrEF, albeit without improving prognosis.[61, 62]

Contrary to the consensus on recommended drug regimens, the ideal BP targets remain unclear due to lack of evidence. For patients with HFrEF and elevated BP, the most recent ESC/EHS hypertension guidelines advise a conservative BP target below 130/80 mmHg but never lower than 120/70 mmHg,[34] whilst other guidelines do not specify a BP target but instead recommend drug up-titration to the dosages shown to improve clinical outcomes in RCTs, provided that patients tolerate without developing adverse events.[31, 35] On the other hand, patients in whom baseline BP is already below this target, treatment with drugs with BP-lowering treatment is still recommended to improve prognosis rather than to decrease BP. However, concerns about further BP reduction often lead to overzealous treatment in those patients, which may be not only unnecessary but also harmful. Indeed, the relative benefit of drugs with BP-lowering properties appears consistent across the spectrum of baseline BP,[36, 57] and patients with the lowest baseline BP experience a greater absolute risk reduction, due to their intrinsically higher risk of cardiovascular events and HF hospitalisation.[63, 64] Furthermore, evidence currently available supports the safety of BP reduction in the high-risk population of patients with low baseline BP. These patients have the

highest rate of treatment discontinuation due to adverse events, particularly hypotension, irrespective of being treated with active drug or placebo, which suggests that treatment discontinuation may be related to the severity of the underlying illness rather than to treatment with the active drug.[12] However, the perception that patients with low baseline SBP have a higher risk of adverse events has justified not only their exclusion from many key trials in HF,[20, 65] but also clinicians' reluctance to prescribe those life-saving drugs. Paradoxically, the sickest patients who might potentially gain from treatment are least likely to be treated due to concerns about side effects, which seem common causes of non-compliance with dose recommendations and treatment discontinuation, particularly regarding RAAS inhibitors.[66, 67] Despite the trade-off between the risk of worsening renal function and the combination of multiple RAAS inhibitors, maintaining guideline-recommended target doses of those agents is pivotal to achieve the intended benefits on mortality and HF hospitalisations.[68] In conclusion, although the optimum BP target in patients with HFrEF remains to be established, aiming for BP below 130/80 mmHg is recommended, and concerns about further BP reduction should not deter clinicians from complying with guideline-recommended doses irrespective of baseline BP.

## IV. **Heart Failure with preserved Ejection Fraction**

As no treatment has convincingly shown to reduce morbidity or mortality in patients with HFpEF or HFmrEF thus far, the main aims of treatment are to alleviate symptoms and improve quality of life.[69] Despite the limited evidence available on treatment of hypertension in patients with HFpEF, guidelines recommend RAAS inhibition, with ACE inhibitor or ARB and especially MRA as first choice (Table 1). Although diuretics are important in all patients with HF to control fluid retention, guidelines emphasise that they are essential components of the treatment regimen of all patients with hypertension and HFpEF.[70] However, close monitoring is essential because inappropriately low or high doses of diuretics can result in fluid overload or volume depletion, respectively, and the latter can increase the risk of hypotension, renal impairment and electrolyte

disturbances. Whilst nitrates are not recommended because they do not improve quality of life and may actually worsen functional status,[71] for all other common antihypertensive agents, including BBs, alpha-blockers and CCBs, the lack of evidence precludes making recommendations on their efficacy and safety. Therefore, the ultimate recommendation regarding choice of antihypertensive medication is shared decision-making, considering patient's preferences and circumstances as well as clinician's judgement.

BP management in patients with HFpEF is further complicated by the myriad comorbidities that are common in those patients. Indeed, multimorbidity, defined as the presence of two or more diseases in the same patient,[72] is present in the majority of patients with HFpEF and carries a poor prognosis.[73, 74, 75] It is estimated that 55% of patient with HFpEF have 5 or more cardiac and noncardiac chronic diseases,[76, 77] with on average one more comorbidity than patients with HFrEF.[78] Furthermore, in patients with HFpEF, hospitalisations and deaths are more likely to be non-cardiovascular than in patients with HFrEF,[79] which reinforces the importance of treating associated comorbidities, including hypertension.[5] However, comorbidity and particularly multimorbidity add further complexity to antihypertensive treatment, because drugs with BP-lowering properties that would be otherwise recommended may cause unintentional harm on other comorbidities.[80, 81, 82, 83, 84, 85]

## V. Special populations

### a. Advanced age

Advanced age itself should not be a barrier to treatment, as there is no evidence that protection against major cardiovascular events afforded by different drug classes varies substantially with age,[86, 87, 88] even in the very old and frail.[89] Evidence also does suggest an increased risk of adverse events,[90, 91] or a negative impact on patient-reported outcomes,[92] and functional status,[93] even when more intensive BP targets were pursued. Furthermore, antihypertensive treatment may reduce the risk of dementia.[94, 95, 96] However, therapeutic adjustments may be required due to

their limited ability to preserve BP homeostasis and maintain vital organ perfusion, and to the presence of comorbidities, which tend to accrue over time and may interfere with antihypertensive drugs.[97] Guidelines recommend a more careful approach (Table 3) and acknowledge that any BP reduction is likely to be worthwhile and protect from major cardiovascular events and mortality, even if recommended BP targets are impossible to achieve.[98, 99]

### b. Diabetes Mellitus

Although treatment for HFrEF seems to be similarly effective at reducing mortality and morbidity irrespective of the presence of diabetes,[100] adjustments may be needed as different drugs within each class vary in their ability to influence metabolism and glycaemic control.[101] Moreover, novel antidiabetic agents, particularly the selective inhibitors of sodium glucose cotransporter 2 in the kidney, have shown to reduce BP by several mmHg, even in patients concomitantly taking other antihypertensive drugs.[102, 103] Guidelines recommendations are similar for HF patients with and without diabetes (Table 3),[34] but emphasise that the initial treatment regimen should include an ACEI or ARB, which have been shown to reduce albuminuria and retard the progression of diabetic nephropathy more effectively than other drug classes.[104]

### c. Chronic Kidney Disease

As lowering BP reduces renal perfusion pressure, a transient 10-20% decrease in eGFR is expected and common when antihypertensive treatment is initiated, particularly with RAAS inhibitors.[105, 106] However, treatment discontinuation is usually not warranted as the eGFR decline tends to stabilise after a few weeks, may not actually reflect true renal injury,[107, 108] and does not reduce treatment benefit.[109] On the contrary, a marked decline in renal function is unexpected and mandates temporarily withdrawal of nephrotoxic drugs, including RAAS inhibitors, and careful evaluation of potential causes, such as hyper- or hypovolaemia, concomitant medication, and concurrent illness.[34] CKD can also interfere with the efficacy of antihypertensive drugs in

patients with HF. Diuretics, particularly thiazides, are less effective in patients with very low eGFR and hence higher doses or replacement by loop-diuretics may be required.[110, 111] Guideline-recommended treatment for hypertension in patients with CKD is similar to the remaining patients with HF (Table 3), as the risks and benefits of reducing SBP to below 130 and 120 mmHg remain uncertain.[112, 113, 114]

### d. Atrial fibrillation

AF is the most common arrhythmia in patients with HF, and hypertension is the most common comorbidity in both[115] and significantly increases the risk of adverse cardiovascular events. Antihypertensive treatment seems to reduce the risk of new-onset AF by 25% in patients with HF, with a null effect in patients without AF and no evidence for class-specific effects.[116] The scarce evidence regarding recurrent AF suggests that RAAS inhibitors may reduce the risk of AF recurrence when combined with antiarrhythmics.[117] Despite the limited evidence available, guidelines recommend RAAS inhibitors as antihypertensive agents to prevent AF in patients with HF (Table 3). Beta-blockers or non-dihydropyridine calcium antagonists (e.g. diltiazem and verapamil) are recommended in patients with high ventricular rate, but the latter should be avoided in patients with HFrEF.[118] As hypertension substantially increases the risk of intracerebral haemorrhage, achieving a BP goal of <130/80 mmHg is highly recommended in patients receiving oral anticoagulants.

## VI. Conclusion

Guidelines consensually recommend treating hypertension in patients with HF with drugs that have compelling indications in this population, whilst avoiding agents with demonstrated harmful effects. Although acknowledging the current uncertainty, a target of 130/80 mmHg is recommended with a word of caution regarding BP below 120/70 mmHg. However, BP levels should not deter up-titration of drugs otherwise indicated to improve prognosis in HF, provided that patients tolerate without

adverse events. Moreover, there is no evidence supporting safety concerns regarding use of drugs with BP-lowering properties in patients with low baseline BP, who actually reap the most absolute benefit from treatment due to their higher absolute risk of cardiovascular events. Special considerations regarding BP control are crucial in the elderly as well as in patients with diabetes and CKD. Further evidence on management of hypertension in HF is warranted as current guidelines rely on extrapolation of findings from high-risk hypertensive patients in the general population, who are not necessarily similar to patients with HF. Understanding the relative merits of different drugs as well as the optimal BP target in patients with HF is paramount considering that the already challenging management of BP in HF patients is expected to become even more complex thanks to the rapidly growing burden of multimorbidity in the HF population.

**Contributorship Statement**

ACPG contributed to planning and writing this review article. KR supervised ACPG and reviewed the manuscript. ACPG is responsible for the overall content of this review.

**Funding Statement**

This project was supported by the Oxford Martin School grant for the Deep Medicine programme, the National Institute of Health Research (NIHR) Oxford Biomedical Research Centre and the British Heart Foundation.

**Competing interests**

No competing interests to be declared.

**Acknowledgements**

No acknowledgements to be reported.

**References**

1 Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)* 2017;**390**:1345-422.

2 Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *European heart journal* 2003;**24**:442-63.

3 Kajimoto K, Sato N, Takano T. Relation of left ventricular ejection fraction and clinical features or co-morbidities to outcomes among patients hospitalized for acute heart failure syndromes. *The American journal of cardiology* 2015;**115**:334-40.

4 Nichols GA, Reynolds K, Kimes TM, et al. Comparison of Risk of Re-hospitalization, All-Cause Mortality, and Medical Care Resource Utilization in Patients With Heart Failure and Preserved Versus Reduced Ejection Fraction. *The American journal of cardiology* 2015;**116**:1088-92.

5 Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *Journal of the American College of Cardiology* 2012;**59**:998-1005.

6 Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet (London, England)* 2002;**360**:1903-13.

7 Lip GY, Skjoth F, Overvad K, et al. Blood pressure and prognosis in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. *Clinical research in cardiology : official journal of the German Cardiac Society* 2015;**104**:1088-96.

8 Schmid FA, Schlager O, Keller P, et al. Prognostic value of long-term blood pressure changes in patients with chronic heart failure. *European journal of heart failure* 2017;**19**:837-42.

9 Raphael CE, Whinnett ZI, Davies JE, et al. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart (British Cardiac Society)* 2009;**95**:56-62.

10 Desai RV, Banach M, Ahmed MI, et al. Impact of Baseline Systolic Blood Pressure on Long-Term Outcomes in Patients With Advanced Chronic Systolic Heart Failure (Insights from the BEST Trial). *The American journal of cardiology* 2010;**106**:221-7.

11 Bohm M, Young R, Jhund PS, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. *European heart journal* 2017;**38**:1132-43.

12 Ather S, Chan W, Chillar A, et al. Association of systolic blood pressure with mortality in patients with heart failure with reduced ejection fraction: a complex relationship. *American heart journal* 2011;**161**:567-73.

13 Messerli FH, Rimoldi SF, Bangalore S. The Transition From Hypertension to Heart Failure: Contemporary Update. *JACC Heart failure* 2017;**5**:543-51.

14 Ather S, Bangalore S, Vemuri S, et al. Trials on the effect of cardiac resynchronization on arterial blood pressure in patients with heart failure. *The American journal of cardiology* 2011;**107**:561-8.

15 Tsujimoto T, Kajio H. Low diastolic blood pressure and adverse outcomes in heart failure with preserved ejection fraction. *International journal of cardiology* 2018.

16 Tsimploulis A, Lam PH, Arundel C, et al. Systolic Blood Pressure and Outcomes in Patients With Heart Failure With Preserved Ejection Fraction. *JAMA cardiology* 2018.

17 Xie W, Zheng F, Evangelou E, et al. Blood pressure-lowering drugs and secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Journal of hypertension* 2018.

18 Turnbull F, Neal B, Pfeffer M, et al. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *Journal of hypertension* 2007;**25**:951-8.

19 Law MR, Wald NJ, Morris JK, et al. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *Bmj* 2003;**326**:1427.

20 Hjalmarson A, Goldstein S, Fagerberg B, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet (London, England)* 1999;**353**:2001-7.

21 Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *New England Journal of Medicine* 1996;**334**:1349-55.

22 Sakata Y, Shiba N, Takahashi J, et al. Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. *European heart journal* 2015;**36**:915-23.

23 Levine TB, Bernink PJ, Caspi A, et al. Effect of mibefradil, a T-type calcium channel blocker, on morbidity and mortality in moderate to severe congestive heart failure: the MACH-1 study. Mortality Assessment in Congestive Heart Failure Trial. *Circulation* 2000;**101**:758-64.

24 Udelson JE, DeAbate CA, Berk M, et al. Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. *American heart journal* 2000;**139**:503-10.

25 Cohn JN, Archibald DG, Ziesche S. Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration Cooperative Study. *New England Journal of Medicine* 1986;**314**:1547-52.

26 Bazoukis G, Thomopoulos C, Tse G, et al. Is there a blood pressure lowering effect of MRAs in heart failure? An overview and meta-analysis. *Heart failure reviews* 2018.

27 Bazoukis G, Thomopoulos C, Tsioufis C. Effect of mineralocorticoid antagonists on blood pressure lowering: overview and meta-analysis of randomized controlled trials in hypertension. *Journal of hypertension* 2018;**36**:987-94.

28 Weber T, Chirinos JA. Pulsatile arterial haemodynamics in heart failure. *European heart journal* 2018;**39**:3847-54.

29 Regnault V, Lagrange J, Pizard A, et al. Opposite predictive value of pulse pressure and aortic pulse wave velocity on heart failure with reduced left ventricular ejection fraction: insights from an Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) substudy. *Hypertension (Dallas, Tex : 1979)* 2014;**63**:105-11.

30 Meguro T, Nagatomo Y, Nagae A, et al. Elevated arterial stiffness evaluated by brachial-ankle pulse wave velocity is deleterious for the prognosis of patients with heart failure. *Circ J* 2009;**73**:673-80.

Full list of references provided as Supplementary File.

**Table 1: Summary of recommendations for management of elevated blood pressure in the context of heart failure**

| Guidelines | HFrEF | HFpEF |
|---|---|---|
| **ESC/ESH Hypertension Guidelines 2018[34]** | Threshold BP ≥140/90 mmHg if not already on treatment<br>Target unclear but wise to avoid <120/70 mmHg (unless patients tolerate and needed for reasons other than BP)<br>1st line: BB, ACEI/ARB, ARNI and MRA<br>2nd line: diuretics and dihydropiridine CCB<br>Non-dihydropiridine CCB, alpha-blockers, and centrally acting agents (moxonidine) should not be used | Same thresholds and targets for HFrEF<br>Optimal treatment strategy is not known, but the strategy recommended for HFrEF patients might be adopted in HFpEF patients<br>Multimorbidity may further complicate BP management |
| **ESC HF Guidelines 2016[31]** | BP targets recommended in general population are applicable to HF<br>1st line: ACEI/ARB, BB, and MRA<br>2nd line: thiazide/loop diuretic<br>3rd line: hydralazine or dihydropiridine CCB<br>Avoid non-dihydropiridine CCB and moxonidine | BP targets recommended in general population are applicable to HF<br>Non-dihydropiridine CCBs are believed to be safe in HFpEF |
| **AHA Hypertension Guidelines 2017[119]** | Clinical trials evaluating goal BP reduction and optimal BP-lowering agents in HF and concomitant hypertension have not been performed. Recommendations based on extrapolations from patients at high risk of cardiovascular disease. | |

| | | |
|---|---|---|
| | Threshold BP ≥130/80 mmHg<br>Target BP <130/80 mmHg<br>Avoid non-dihydropyridine CCB | Threshold ≥130/80 mmHg<br>Target BP <130/80 mmHg<br>1st line: Diuretics for management of volume overload<br>2nd line: ACEI/ARB or MRA<br>3rd line: uncertain BB, CCB, alpha-blockers<br>Avoid nitrates. |
| **AHA HF Guidelines 2013[120] and 2017[121]** | 2013 Recommendations do not consider hypertension as an important comorbidity in HF!<br>2017 Recommendations based on extrapolations from patients at high risk of cardiovascular disease ('threshold now associated with improved clinical outcomes but not yet proven by RCTs in a population with HF') | |
| | Target SBP <130 mmHg | Target SBP <130 mmHg<br>1st line: ACEI/ARB, MRA and maybe ARNI<br>2nd line: Uncertain BB, CCB, alpha-blockers<br>Avoid nitrates |
| **Hypertension Canada Guidelines 2018[35]** | No mention to HFrEF vs HFpEF<br>Target not specified: titrate to dosages found to be effective in RCT as tolerated/until adverse events arise<br>1st line: ACEI/ARB, BB and MRA (if needed)<br>2nd line: loop diuretic (maybe thiazide)<br>3rd line: hydralazine plus isosorbide dinitrate if ACEI/ARB not tolerated<br>4th line: ACEI+ARB or dihydropyridine CCB<br>5th line: ARNI instead of ACEI/ARB if symptomatic despite optimal guideline-recommended treatment | |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; BP, blood pressure; CCB, calcium-channel blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure

**Table 2: Contradictory findings reported by clinical trials of drugs with blood pressure lowering properties in patients with heart failure**

| Trial | Author | Year | Control | Intervention | HF type | Achieved BP | All-cause mortality | CV mortality | HF hospitalisation |
|---|---|---|---|---|---|---|---|---|---|
| **COPERNICUS[122]** | Packer et al. | 2002 | Placebo | Carvedilol | HFrEF | ↓ | ↓ | NA | ↓ |
| **SOLVD[123]** | SOLVD Inv | 1991 | Placebo | Enalapril | HFrEF | ↓ | ↓ | ↓ | ↓ |
| **MERIT-HF[124]** | MERIT-HF Inv | 1999 | Placebo | Metoprolol | HFrEF | ↑ | ↓ | ↓ | NA |
| **Val-HeFT[125]** | Cohn et al. | 2001 | Placebo | Valsartan | HFrEF | ↓ | ↔ | NA | ↓ |
| **A-HeFT[126]** | Taylor et al. | 2004 | Placebo | ISD/HZ | HFrEF | ↓ | ↓ | NA | ↓ |
| **CHARM-Added[39]** | McMurray et al. | 2003 | Placebo | Candesartan | HFrEF | ↓ | ↔ | ↓ | ↓ |
| **CHARM-Alternative[127]** | Granger et al. | 2003 | Placebo | Candesartan | HFrEF | ↓ | ↔ | ↔ | ↓ |
| **EMPHASIS-HF[52]** | Zannad et al. | 2011 | Placebo | Eplerenone | HFrEF | ↓ | ↓ | ↓ | ↓ |
| **PARADIGM-HF[128]** | McMurray et al. | 2014 | Enalapril | Sacubitril/Valsartan | HFrEF | ↓ | ↓ | ↓ | ↓ |
| **PRAISE 2[61]** | Packer et al. | 2013 | Placebo | Amlodipine | HFrEF | ↓ | ↔ | ↔ | ↔ |
| **PRECISE[129]** | Packer et al. | 1996 | Placebo | Carvedilol | HFrEF | ↔ | ↓ | ↓ | NA |
| **PEP-CHF[130]** | Cleland et al. | 2006 | Placebo | Perindopril | HFpEF | ↓ | ↔ | ↔ | ↔ |
| **I-PRESERVE[131]** | Massie et al. | 2008 | Placebo | Irbesartan | HFpEF | ↓ | ↔ | ↔ | ↔ |
| **TOPCAT[132]** | Pitt et al. | 2014 | Placebo | Spironolactone | HFpEF | ↔ | ↔ | ↔ | ↓ |
| **CHARM-Preserved[133]** | Yusuf et al. | 2003 | Placebo | Candesartan | HFpEF | ↓ | ↔ | ↔ | ↔ |
| **SENIORS[134]** | Flather et al. | 2005 | Placebo | Nebivolol | Mix | ↓ | ↔ | ↔ | ↔ |

BP, blood pressure; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available; ↓ Lower in intervention arm; ↔ similar in control and intervention arms; ↑ higher in intervention arm

**Table 3: Summary of guideline-based recommendations for special populations**

| Special population | Blood pressure treatment recommendations |
|---|---|
| **Old age** | - Start with monotherapy and the lowest available doses if combination therapy is required [98]<br>- Loop diuretics and alpha-blockers are contra-indicated because of their association with injurious falls, but all other drugs can be used [135]<br>- Aim for conservative BP targets (BP below 140/80 mmHg) and avoid treated SBP below 130 mmHg in ambulatory patients over 75-years old [99]<br>- More intensive BP reduction to less than 120 mmHg may afford additional risk reduction [136] |
| **Diabetes mellitus** | - Start with ACEI or ARB together with a dihydropyridine CCB or diuretic but avoid dual RAAS blockade as it increases the risk of renal adverse events [104]<br>- Aim for BP below 130/80 mmHg), and consider further BP reduction if tolerated but avoid BP below 120/70 mmHg [34]<br>- Consider the impact of antidiabetic drugs on BP [102, 103] and the impact of antihypertensive drugs on glycaemic control [101] |
| **Chronic kidney disease** | - Start with ACEI or ARB together with a dihydropyridine CCB or diuretic, but avoid dual RAAS blockade as it increases risk of renal adverse events [137]<br>- Aim for BP below 130/80 mmHg and consider further BP reduction if tolerated (up to 120 mmHg) [112, 113, 114]<br>- Higher doses of diuretics may be required in CKD, and thiazides [110] should be replaced by loop-diuretics when eGRF if eGFR<30 ml/min/1.73m$^2$ [111]<br>- Lifestyle measures, particularly sodium restriction, are key to control BP in patients with concurrent HF and CKD [138]<br>- Transient decrease in eGFR is expected and common initially, [105, 106] but marked/continuous decline requires investigation [34]<br>- Prefer 5-alpha-reductase inhibitors to alpha-adrenergic blockers as these promote sodium and water retention [31, 139, 140] |

| | |
|---|---|
| **Atrial fibrillation** | - Start with ACEI or ARB as they may prevent recurrent or new-onset AF in patients with HF [117]<br>- BB and non-dihydropyridine CCB are recommended in patients with fast ventricular rate but the latter are contraindicated in patients with HFrEF [118]<br>- Aim for BP below 130/80 mmHg in patients taking oral anticoagulants to prevent intracerebral haemorrhage [34] |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CCB, calcium-channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system

**Figure legends**

**Figure 1:** Relationship between Systolic Blood Pressure and Clinical Outcomes in Patients with Heart Failure. Observational studies showed a J-shaped relationship between systolic blood pressure and clinical outcomes (all-cause and cardiovascular mortality, heart failure hospitalisation) in heart failure, particularly for patients with reduced ejection fraction. However, the exact causes of the higher risk of patients with lower blood pressure remain unclear and they seem unrelated to treatment with drugs with blood pressure lowering properties. The limitations of observational studies mean that this relationship may be due to residual confounding or reverse causality. On the other hand, the benefits of blood pressure reduction in patients with heart failure are not completely understood, and it has been argued that mechanisms other than blood pressure reduction (e.g., neurohumoral modulation) are the key mediators of the risk reduction afforded by guideline-recommended drugs, like angiotensin-converting inhibitors and beta-blockers. HF, heart failure; RAAS, renin angiotensin aldosterone system

**Figure 2:** Diagram summarizing the recommendations on management of blood pressure in patients with heart failure, including special populations within heart failure: old age, diabetes mellitus and/or chronic kidney disease. *Non-dihydropyridine CCBs are contra-indicated due to negative inotropic effect. Please see text for further details. AB, alpha-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist