Hypertension and Heart Failure

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KEYWORDS

- Hypertension • Heart failure • LVH • HFpEF • HFrEF • Heart failure drug therapy

KEY POINTS

- Hypertension leads to heart failure through pathologic left ventricular hypertrophy (LVH) and diastolic dysfunction. A subset of these patients ultimately develops systolic heart failure owing to ischemia, genetic polymorphisms, or other insults to the cardiac myocytes.
- LVH represents the inciting event in the development of heart failure owing to hypertension.
- Early screening and intervention are keys to preventing hypertensive heart failure. Even after the onset of LVH, prompt initiation of therapy may still lead to reversal of remodeling.
- Once heart failure develops, the outlook declines significantly. Treatment should be in accordance with current guidelines for heart failure.

INTRODUCTION

Hypertension is the leading risk factor for numerous cardiovascular diseases, including stroke, coronary artery disease, atrial fibrillation, and peripheral vascular disease. In particular, hypertension contributes significantly to the incidence of heart failure, a condition responsible for 1 in 9 annual deaths in the United States and approximately $30.7 billion in annual health care costs.[1,2] Hypertension is highly prevalent in the heart failure population. In the Framingham study, 91% of patients with new heart failure had underlying hypertension.[3] History of hypertension has also been noted in up to 70% of patients in the PARADIGM-HF trial.[4] Hypertension appears to have a dose-dependent impact on heart failure incidence.[5] In all, hypertension is the single greatest risk factor for heart failure at a population level, owing to its high prevalence.[3] Hypertension is also a leading cause of myocardial infarction, the second greatest risk factor. Hypertensive heart disease is therefore a major concern to anyone caring for heart failure patients.

PATHOPHYSIOLOGY

In the most widely accepted model of hypertensive heart failure, chronic pressure overload leads to the development of left ventricular hypertrophy (LVH). Progressive hypertrophy and fibrotic changes in the heart lead to progressive diastolic dysfunction ultimately leading to elevated left-sided filling pressures and diastolic heart failure. Eventually, a subset of patients progresses to systolic dysfunction in the presence of chronic volume and pressure overload.[6]

Multiple mechanisms appear to contribute to this disease progression. Chronic pressure overload appears to lead to alterations in gene expression resulting in both myocyte hypertrophy and alterations in the extracellular matrix. At the myocyte level, increased microtubule density initially leads to improved contractility and left ventricular mass.[7] In the later stages, derangements within the cardiac myocyte lead to impaired relaxation and increased stiffness. Abnormal calcium handling, microtubule disarray, and hyperphosphorylation of

titin protein have been implicated in this pathologic process.[8,9] Increased collagen turnover owing to enzymes called membranometalloproteases is also linked to increased fibrotic remodeling and ultimately the development of both diastolic and systolic dysfunction in hypertensive patients.[10,11] The microvasculature may also play a role; both microvascular resistance and reactivity are impaired in hypertension and may contribute to the development of both systolic and diastolic heart failure.[12,13]

Increased neurohormonal stress also appears to play a powerful role in remodeling, and ultimately, heart failure (**Fig. 1**).[14] Elevated levels of renin and aldosterone have been implicated in the development of LVH and fibrotic remodeling.[15,16] Polymorphisms in these pathways may be partially responsible for the variability in remodeling seen in different patient populations.

STAGES OF HYPERTENSIVE HEART FAILURE

Based on the pathophysiologic mechanisms described above, Messerli and colleagues[6,17] proposed the following stages in the evolution of hypertensive heart disease (**Fig. 2**):

- Degree I: Hypertension without LVH
- Degree II: Asymptomatic hypertension with LVH
- Degree III: Symptomatic heart failure with preserved ejection fraction (HFpEF)

- Degree IV: Symptomatic heart failure with reduced ejection fraction

These stages draw similarities from the American College of Cardiology/American Heart Association (ACC/AHA) stages in which those with stage A possess risk factors without overt disease; stage B patients have underlying structural heart disease, and stage C/D patients are those with overt, clinical heart failure.

LEFT VENTRICULAR HYPERTROPHY

Chronic pressure overload resulting in LVH appears to be the inciting event in the cascade ultimately leading to hypertensive heart failure. Concentric hypertrophy represents, at least initially, an attempt by the left ventricle to maintain wall stress in response to elevated systemic pressures in accordance with Laplace's law (**Fig. 3**).

Classically, LVH was diagnosed by electrocardiography (ECG); however, although specific, ECG criteria appear to lack sensitivity for this finding.[18] When more sensitive modalities such as cardiac MRI are used, the prevalence of LVH in the population ranges from 9% to 13%.[19]

The link between hypertension and the incidence of LVH is well established and has been demonstrated using multiple imaging modalities, including ECG, echocardiography, and cardiac MRI.[20,21] Hypertension appears to result in LVH in a dose-dependent fashion with even prehypertensive
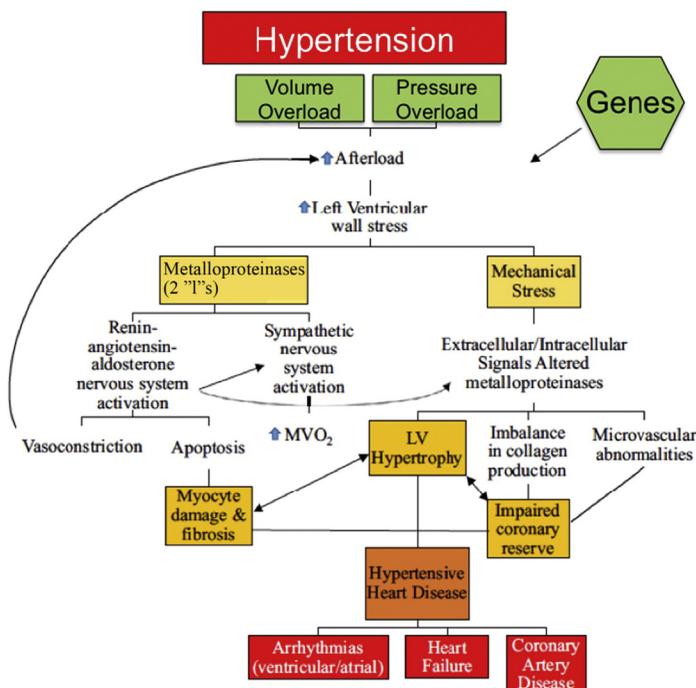
Fig. 1. Cellular pathways contributing to LVH in hypertensive heart disease. Both physical and neurohormonal stresses contribute to alterations in gene expression resulting in myocyte hypertrophy and pathologic remodeling. LV, left ventricular; MVO$_2$, Myocardial oxygen consumption. (*From* Shenasa M, Shenasa H. Hypertension, left ventricular hypertrophy, and sudden cardiac death. Int J Cardiol 2017;237:61; with permission.)
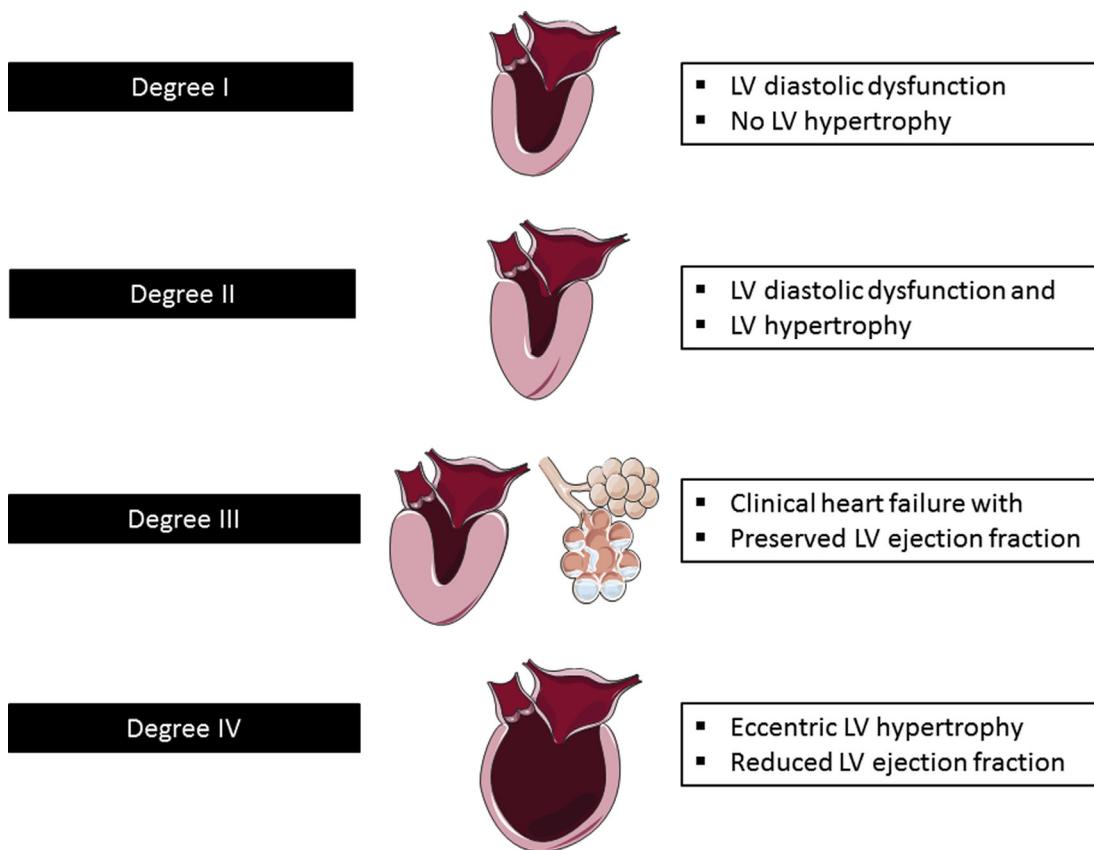
Fig. 2. Stages of hypertensive heart disease. (*From* Messerli FH, Rimoldi SF, Bangalore S. The Transition From Hypertension to Heart Failure: Contemporary Update. JACC Heart Fail 2017;5(8):546; with permission.)

patients at risk for remodeling.[21–23] This correlation appears to be much stronger when ambulatory or workplace blood pressure monitoring is used as compared with physician's office measurements.[24]

It should be noted that other factors besides blood pressure also modulate the development of LVH. Not all patients with hypertension develop LVH and not all LVH occur secondary to hypertension. In a review of major trials by Devereux and colleagues,[24] the prevalence of LVH among hypertensive patients was only 23% to 48%. In addition, LVH was seen in 0% to 10% of normal subjects. In regression models, hypertension only explained 50% to 68% of the variance in left ventricular

mass.[21,25] Race appears to play a significant role. On average, blacks have significantly higher left ventricular mass and are over twice as likely to develop LVH as their white counterparts.[18,19] These racial differences suggest the possible role of genetics in the remodeling process. This is supported by sibling studies from the Framingham cohort, which demonstrated a significant heritable component of hypertrophy in response to hypertension.[26] Last, classical cardiovascular risk factors, such as diabetes, active smoking, and obesity, also significantly contribute to LVH irrespective of blood pressure.[21,27,28] Thus, this process appears to be multifactorial in nature.

FROM REMODELING TO HEART FAILURE

Although initially adaptive, LVH in response to hypertension ultimately becomes pathologic. There are clear differences in the pattern of hypertrophy in patients with LVH owing to hypertension when compared with those with physiologic hypertrophy, such as in athletes. In a study by Galderisi and colleagues,[29] patients with hypertensive hypertrophy

$$T = \frac{PR}{2t}$$

T = wall tension
P = pressure
R = radius
t = wall thickness

Fig. 3. Law of Laplace.

had significantly lower global longitudinal strain and greater degrees of diastolic dysfunction than age-matched competitive athletes despite lower mean left ventricular mass. As discussed above, impairments in active myocyte relaxation and extracellular fibrosis appear to contribute to the process. In addition, left ventricular mass inversely correlates with cardiac index in hypertensive patients, which also argues against a physiologic benefit to this pattern of hypertrophy.[24]

Regardless of how it occurs, once LVH develops, the risk of developing heart failure increases dramatically.[21,30] This remains true for both HFpEF and heart failure with reduced ejection fraction (HFrEF), even when controlling for known heart failure risk factors, such as age, gender, blood pressure, myocardial infarction, and diabetes.[30] This relationship appears to be dose dependent. In a study by de Simone and colleagues,[30] each 1% increase in left ventricular mass above the normal range on echocardiogram was associated with a 1% increased incidence of heart failure after controlling for risk factors, such as prior myocardial infarction. Several studies have shown that elevations in biomarkers, such as N-terminal-prohormone brain natriuretic peptide (NT-proBNP) and troponin, may identify patients with LVH at higher risk of heart failure and death.[31,32]

DIASTOLIC DYSFUNCTION

Following left ventricular remodeling, ongoing pressure overload leads to diastolic dysfunction, a finding that heralds the transition to symptomatic heart failure. At this stage, abnormalities in myocyte relaxation and progressive extracellular fibrosis lead to impaired ventricular filling. This ultimately leads to elevation in left atrial pressure and dyspnea. As discussed above, this process is mediated by both pressure overload and neurohormonal influences.

Diastolic dysfunction is common in hypertensive patients with LVH and appears to precede changes in systolic function.[33–35] Increased left ventricular mass is not just associated with echocardiographic changes but clinical heart failure as well. It is therefore not surprising that hypertension is highly prevalent in patients with HFpEF in major clinical trials.[36,37] In subanalysis of HFpEF patients from the CHARM and I-PRESERVE trials, the presence of LVH was also associated with increased risk of major adverse events in this population.[38]

Once clinical HFpEF has manifested, there is minimal hope for reversing the disease process. Despite advances in treatment of HFrEF, therapeutic options for HFpEF remain limited. At present, no medical intervention has been shown to alter mortality in HFpEF and very few medications appear to alter the disease process at all. This highlights the importance of the early detection and treatment of hypertension and LVH before onset of HFpEF.

HEART FAILURE WITH REDUCED EJECTION FRACTION

Eventually, a subset of patients with longstanding hypertension progresses to develop systolic dysfunction and clinical HFrEF. Unlike those who develop HFpEF, these patients appear to develop disproportionate myocyte loss rather than hypertrophy. Myocyte death leads to increased wall stress and the shift toward a dilated cardiomyopathy phenotype.[13] Interestingly, eccentric hypertrophy appears to be as common as concentric hypertrophy in patients with hypertension.[39] The pattern of hypertrophy may be influenced, in part, by variable levels of pressure and volume overload. Indeed, patients with eccentric hypertrophy have lower systolic blood pressure and systemic vascular resistance than their concentric counterparts.[38] Those with eccentric hypertrophy are also more likely to develop HFrEF than those with concentric hypertrophy.[40] Conversely, in the same study, the pattern of hypertrophy did not appear to impact the risk of developing HFpEF.

The combination of LVH with elevated biomarkers, such as NT-proBNP and troponin, may identify a subgroup of patients at particularly high risk of developing symptomatic HFrEF as compared with HFpEF.[32] This finding also supports the contribution of low-grade myocardial injury in the development of systolic dysfunction. Moreover, these biomarkers may identify higher-risk patients in whom intensified treatment may prevent progression.

Unlike in HFpEF, defining how hypertension causes systolic heart failure is more complex. It is clear that hypertension is a strong risk factor for the development of systolic dysfunction.[41] In addition, there is evidence that systolic strain is abnormal in hypertensive patients; these abnormalities in strain appear to be proportional to increases in wall stress, suggesting a relationship between afterload and systolic performance.[24,42,43] However, in epidemiologic studies, hypertension does not appear to be a common sole cause of HFrEF.[44] In addition, there is a paucity of evidence of a direct progression from HFpEF to HFrEF in these patients.

In a review, Borlaug and Redfield[45] propose the idea of a "second hit" leading to accelerated myocyte dysfunction in the background of hypertensive

remodeling. Hypertensive heart disease that progresses for a long time before a second hit may closely resemble HFpEF. Such a second hit may occur from myocardial infarction, medications (eg, anthracyclines), toxins (eg, alcohol or cocaine), or genetic polymorphisms. The longer that concentric hypertrophy develops before the onset of HFrEF, the more a patient's phenotype is likely to overlap HFpEF. Ischemia is by far the most common insult. In the Framingham cohort, 42% of hypertensive heart failure patients had preceding myocardial infarction.[3] In addition, LVH and hypertension are potent risk factors for coronary artery disease, creating a synergistic risk profile.[46,47] In a review article, Levy and colleagues[48] propose myocardial infarction as an obligate step in the incidence of systolic heart failure in their population. This likely applies to many but not all patients. In large observational studies, nearly half of patients with hypertensive heart disease appear to progress to systolic dysfunction in the absence of coronary artery disease.[3,49] Other mechanisms, such as toxins, genetic factors, or environmental exposures, may be responsible for accelerated myocyte loss leading to HFrEF.

Decreased renin-angiotensin-aldosterone activity and accelerated collagen breakdown have also been linked to dilated hypertrophy in hypertensive patients.[50,51] Overall, the authors agree with the concept that HFpEF represents the natural trajectory of uncontrolled hypertensive heart disease, with a second insult likely being required in order to develop HFrEF (Fig. 4).

Similar to HFpEF, once HFrEF develops in patients with hypertensive heart disease, the prognosis becomes markedly worse. Despite significant advances in therapy for systolic heart failure, the estimated 4-year survival for a patient with symptomatic New York Heart Association (NYHA) class II–III heart failure is only 60%; survival is markedly worse for those with NYHA class IV symptoms.[52,53]
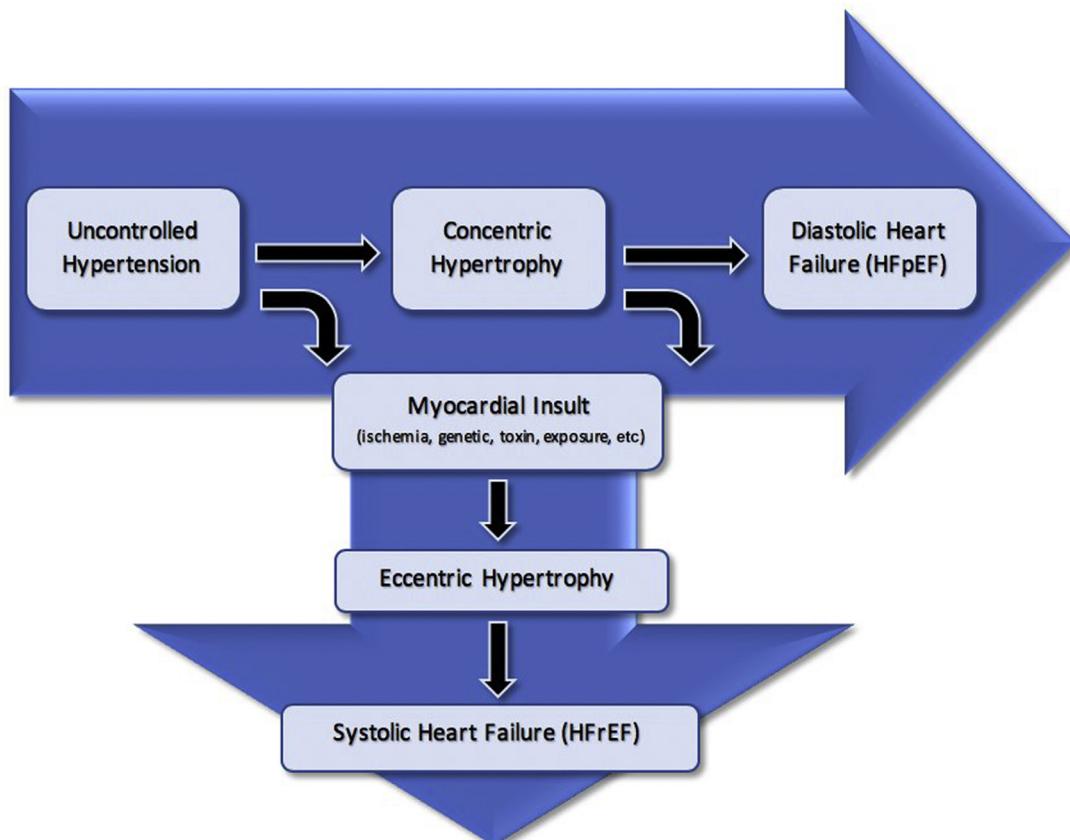
Fig. 4. Proposed mechanism for the development of hypertensive heart failure. The natural progression of heart failure owing to hypertension is concentric hypertrophy leading to diastolic heart failure. A subset of patients will develop systolic heart failure, generally through a second insult leading to myocyte loss. (*Modified from* Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011;123(18).)

ADVANCED HEART FAILURE WITH REDUCED EJECTION FRACTION

In patients with end-stage systolic heart failure owing to hypertension, blood pressure may paradoxically be low. In their review article, Messerli and colleagues[6] coin the term "decapitated hypertension" to refer to the lower mean blood pressures frequently seen in hypertensive heart failure patients with reduced EF. This finding of low blood pressure may confound the diagnosis of hypertensive heart disease in patients with HFrEF. Elevation in blood pressure after initiation of goal-directed medical therapy may be a clue to underlying hypertensive heart disease.

Some have postulated a possible protective role of high blood pressure in patients with reduced ejection fraction. This finding is supported by the observation that lower pretreatment blood pressure is associated with an increased risk for mortality.[54–56] Improvements in blood pressure may also herald clinical improvement in response to common heart failure therapies.[57,58] However, it is unclear if this relationship is correlative or causative in nature, because lower pretreatment blood pressures may identify sicker patients with a greater degree of left ventricular dysfunction. This theoretic protective effect should by no means be used as evidence to support withholding guideline-directed medical therapy with antihypertensives, which represent the cornerstone of therapy in HFrEF.

TREATMENT

The most effective method of treating hypertensive heart failure is primary prevention before the onset of pathologic remodeling and heart failure. Treatment of blood pressure has been shown to reduce LVH and reduce the risk of developing heart failure.[59] This benefit also appears to be dose dependent.[60] Multiple agents have shown benefit in large randomized trials. Thiazide diuretics, angiotensin-converting-enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARB), and dihydropyridine calcium channel blockers (CCB) appear to be the most effective agents at reducing heart failure risk as compared with other agents, such as alpha- and beta-blockers.[61–63] This is in line with current hypertension guidelines that list these as first-line agents.[64] In a large meta-analysis, thiazide diuretics appeared to confer the lowest risk of heart failure of the 3 agents.[65] In addition, in a Cochrane Review, ACEi/ARBs outperformed CCBs with respect to heart failure endpoints.[66] Thus, thiazides are likely the ideal agent for heart failure prevention followed by ACEi/ARBs. For primary prevention, blood pressure targets should be in accordance with the ACC/AHA Eighth Joint National Committee (JNC-8) guidelines.[65]

In patients at elevated cardiovascular risk, strong consideration should be given for more stringent blood pressure control. The landmark SPRINT trial demonstrated a reduction in major adverse cardiac events with intensive blood pressure control (systolic blood pressure <120 mm Hg) in hypertensive patients at increased cardiovascular risk.[67] This benefit was accompanied by greater reductions in LVH and new heart failure incidence.[68] In addition, a greater number of intensively treated patients had resolution of LVH, which fits with the observed dose-dependent relationship between blood pressure and LVH discussed above. Based on these findings, the JNC-8 guidelines were updated to support a blood pressure target of 130/90 mm Hg in patients at high cardiovascular risk (atherosclerotic cardiovascular disease >10%), a recommendation that these authors strongly support.[65]

Biomarkers may also be useful in identifying an at-risk patient population that may benefit from more aggressive therapy. In the STOP-HF trial, patients with multiple risk factors for heart failure were screened for risk using B-type natriuretic peptide (BNP).[69] Those with elevated biomarkers underwent echocardiography and were referred for collaborative care involving a cardiologist. Compared with a control population that was not screened, the use of BNP screening showed a trend toward reduction in heart failure and asymptomatic left ventricular systolic dysfunction. Although it did not reach significance, this is an interesting proof-of-concept study; further research is warranted, particularly in patients with hypertension and LVH.

Once LVH has developed, aggressive efforts should be taken to control blood pressure in the hopes of halting or reversing the remodeling process. Antihypertensive therapy has been shown to lead to reduction in left ventricular mass by echocardiography, with corresponding reduction in risks of adverse events.[70–73] ACEi, ARBs, and CCBs appear to be most effective at reducing LVH.[74] Once developed, the hypertrophy process may take years to improve.[75] Given the above SPRINT findings and the known associated with LVH, one wonders whether hypertensive patients with LVH would also benefit from more intensive blood pressure control in the absence of other indications. Further studies are needed to address this important question.

Once heart failure has developed, treatment should be in accordance with available heart failure guidelines.[76] In patients with HFpEF, spironolactone and ACEi/ARBs can be considered for

the management of hypertension based on some suggesting benefit at decreasing heart failure hospitalizations. Based on results from the SPRINT trial, recent heart failure guidelines advocate for stringent blood pressure control with a blood pressure target of less than 130/80 mm Hg.

For patients in all stages of systolic heart failure, ACEi/ARBs and beta-blockers represent the cornerstone of antihypertensive therapy based on high-quality, randomized controlled data. The combination of these agents carries a class I indication in patients with systolic dysfunction regardless of NYHA class.[77] The evidence for ACEi/ARB originated from several trials, most notably the SOLVD, CONSENSUS, Val-HEFT, and CHARM trials.[77–80] In these trials, ACEi/ARB were initiated at lower doses and titrated to reach the maximum tolerated dose based on symptoms and renal function. Evidence for beta-blockers arose from the COPERNICUS and MERIT-HF trials.[81,82] As with ACEi/ARBs, these agents were titrated to maximally tolerated dosages based on symptoms and heart rate. For those with NYHA class II–IV who are maximally titrated on the above medications and have acceptable renal function, the use of aldosterone antagonists is a class I indication.[83] Hydralazine and long-acting nitrates should also be considered in African Americans with NYHA class III–IV heart failure already on an ACEi/ARB, beta-blocker, and a mineralocorticoid antagonist.[84] More recently, with the publication of the PARADIGM-HF trial, angiotensin-neprilysin inhibitors (ARNI) have been shown to reduce mortality in patients with HFrEF and NYHA class II–III symptoms despite above agents.[4] These promising data were reflected in the 2017 updated heart failure guidelines, which assigned a class I recommendation for the use of ARNIs, ACEi, or ARBs in this population.[77] Given the success of ARNI in HFrEF, there are now ongoing trials evaluating the use of these agents in patients with HFpEF. With regards to blood pressure targets, the most recent ACC/AHA heart failure guidelines advocate for treating to achieve a blood pressure less than 130/80 mm Hg.[77] However, as discussed above, in most of the landmark systolic heart failure trials, these medications were titrated to maximum tolerated dosages rather than a blood pressure cutoff.

Recently, the concept of heart failure with mid-range EF (HFmrEF) has been increasingly recognized and was described as its own distinct heart failure subset in the most recent European Society of Cardiology Heart Failure Guidelines.[85] This group comprises nearly one-quarter of all heart failure patients and suffers similar morbidity and mortality as patients with HFpEF and HFrEF.[86,87] Despite this, HFmrEF is largely underrepresented in large clinical trials.[88] One factor that complicates this is the group's heterogeneity, because it appears to be composed of patients with stable systolic function, HFrEF patients with recovering EF, and HFpEF patients in decline.[89,90] Much of the available data comes from subgroup analysis of major heart failure trials, which included patients with HFmrEF. Based on subgroup analysis from the CHARM and TOPCAT trials, candesartan and spironolactone appeared to reduce major adverse heart failure events in patients with HFmrEF.[91,92] Similar benefits were also seen with beta-blockers based on meta-analyses in patients with HFmrEF.[93] Although there have been insufficient data to provide strong guideline recommendations, it is the opinion of these authors that these agents should be preferentially used based on the evidence available. Further research is indicated to determine optimal management strategies in this population.

RISK FACTOR MODIFICATION

In all stages of treatment, it is imperative to prevent coronary artery disease. Coronary artery disease is highly prevalent among hypertensive patients, particularly those with LVH.[47,48] In addition, as discussed above, myocardial infarction is likely the most common accelerant to systolic heart failure in patients with hypertensive heart disease. This should be accomplished by appropriate initiation of antiplatelet, lipid-lowering, and antihypertensive medications in patients who have or are at risk for developing coronary artery disease. Efforts to address diabetes, obesity, sleep apnea, and salt intake may also help to prevent pathologic remodeling and reduce the future risk of heart failure.[94–97]

SUMMARY

Hypertensive heart disease describes a spectrum of illness spanning from uncontrolled hypertension to the ultimate development of heart failure. The inciting event in hypertensive heart disease is the development of LVH, a process that may be reversible if recognized early and treated aggressively. LVH appears to be a pathologic process ultimately leading to fibrosis, impaired left ventricular compliance, and ultimately, diastolic heart failure. A subset of patients ultimately develops systolic heart failure, generally because of a subsequent insult leading to accelerated myocyte loss. Once developed, heart failure owing to hypertension is often irreversible and results in significant morbidity and mortality. Once heart failure is diagnosed, patients should be treated in accordance with available heart failure guidelines.

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