

Mechanisms and management of hypertensive heart disease: from left ventricular hypertrophy to heart failure

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Hypertensive heart disease (HHD) is a spectrum of abnormalities that represents the accumulation of a lifetime of functional and structural adaptations to increased blood pressure (BP) load. Left ventricular hypertrophy (LVH), increasing vascular and ventricular stiffness, and diastolic dysfunction are prominent intermediate features of this syndrome that operate in parallel with ischemic heart disease and ultimately cause heart failure (HF) if inadequately treated. Outcomes in HHD and HF are improved by antihypertensive drugs at any stage of the condition. This review describes an integrated model of the natural history, pathogenesis, and drug treatment of hypertensive heart disease that is consistent with the recommendations of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [1,2], including an important modification to the HF guideline published by the American College of Cardiology (ACC) and the American Heart Association (AHA) [3] that includes LVH and diastolic dysfunction as treatable conditions within the HHD-HF continuum.

Demographics of hypertensive heart disease

Hypertension

Hypertension, in common with other cardiovascular risk factors, is affected by the aging process. The contribution of hypertension to cardiovascular disease (CVD) morbidity and mortality is greater than any

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other CVD risk factor. In the report of the Prospective Trialists' group [4], each 20/10 mm Hg increase in BP doubles the risk of ischemic heart disease and stroke over the range of 115/75 to 185/115 mm Hg in individuals from 40 to 90 years of age. The slope of the relationship between hypertension and CVD is about twice as steep as the comparable slope of the cholesterol-CVD relationship. Approximately one fourth of the American population is hypertensive, including over half of individuals over the age of 65 [5].

Left ventricular hypertrophy

Increased left ventricular (LV) wall thickness and mass are associated continuously with the level of BP and age. Without increased systolic BP, however, clinically significant increases in LV mass probably do not occur with advancing age. Chronic systolic hypertension thus seems to be the principal cause of LVH [6,7], although genetic factors may cause LVH in the absence of hypertension. Prevalence rates of LVH are somewhat difficult to establish precisely because they are affected so strongly by the duration and severity of hypertension. It has been suggested that prevalence rates for LVH have declined in the United States as a result of more widespread use of effective antihypertensive drugs [8]. Prevalence rates of LVH also are very sensitive to the method and detection criteria used. In the largest population studies, the ECG has been the main tool for the detection and evaluation of LVH. Echocardiography is far more sensitive than ECG in detecting LVH but is used less often due to cost and expertise requirements [6,9,10]. In general, echocardiographically determined LVH (echo-LVH) prevalence ranges from about 20% to 60% in hypertensive individuals. As with other forms of target organ damage, LVH is more prevalent in African Americans [11,12].

LVH is an independent cardiovascular risk factor that is as potent as age or systolic BP in predicting future myocardial infarction, stroke, sudden cardiac death, or HF [13]. The presence of ECG-determined LVH (ECG-LVH) roughly doubles the risk of subsequent cardiovascular events or death [13,14], largely irrespective of race, sex, or history of prior coronary artery disease. Increased ECG voltage also correlates with increased incidence of HF episodes [15]. In studies of echo-LVH, the risk factor-adjusted relative risk of CVD is about 50% greater for each increase of 50 g/m² in echocardiographically determined LV mass index in men or women [13]. Overall, LVH increases CVD mortality by about 75% in men and roughly doubles it in women, with similar impact on all-cause mortality [6,16–19].

Left ventricular hypertrophy, blood pressure, and markers of cardiovascular disease

LVH serves as an integrated surrogate for cumulated BP load and, perhaps, is best described as being proportional to the “area under the

lifetime BP curve.” Consistent with this idea is the strong association of LV mass and mean 24-hour ambulatory BP [20,21]. Progressive increases in LV mass also are found in proportion to the degree of obesity or dysglycemia [11,22]. Vascular changes such as increased systemic arterial stiffness (pulse pressure/stroke volume ratio) [23] and certain indices of carotid arterial stiffness are associated with LVH [24]. Another important correlate of LV mass at any age is albuminuria [12,25–27], a marker of microvascular pressure load and damage. LVH also is associated with ventricular stiffness, impaired relaxation, congestive HF, coronary artery disease, cardiac dysrhythmias [28], increased QT dispersion on ECG [29], and sudden death [30].

Heart failure

The final phase of HHD is overt HF. This syndrome afflicts an increasing burden on patients and health care expenses, especially in the Medicare-insured population. HF accounts for over 1 million hospitalizations annually, and about one third of those hospitalized will die within 1 year [31]. In the Framingham Heart Study, hypertension accounted for 39% of HF cases in men and 59% in women [6,16–19]. Overall, about 20% of individuals with HF have antecedent ECG-LVH and 60% to 70% demonstrate echo-LVH [32]. About one third to one half of the patients who present with pulmonary edema have “preserved systolic function,” with ejection fraction $\geq 40\%$. In long-standing hypertension, most individuals demonstrate some impaired ventricular relaxation (diastolic dysfunction) [32]. HF prevalence rates are increased further by concomitant conditions such as diabetes or chronic kidney disease. The natural history of diastolic dysfunction differs from systolic dysfunction, in that annual mortality is approximately one half that of systolic dysfunction [33–36]. In both conditions, however, hospitalization occurs with approximately equal frequency [33–36].

Pathogenesis of hypertensive heart disease

The pathogenesis of HHD involves a stepwise progression from hypertension to LVH to diastolic dysfunction (HF with preserved systolic function) and, eventually, to ventricular dilation and cardiac failure (Fig. 1). The clinical presentation of HHD is strongly dependent on demographic factors (such as age, sex, race), comorbid diseases (such as obesity, diabetes mellitus, or coronary arterial disease), and type of drug therapy in addition to duration and severity of hypertension. An important parallel route to HF involves loss of cardiac myofibrils from ischemic heart disease, which leads directly to segmental wall motion abnormalities and systolic dysfunction (see Fig. 1). Systolic dysfunction and diastolic dysfunction may be mutually causally related and often coexist in the same individual.

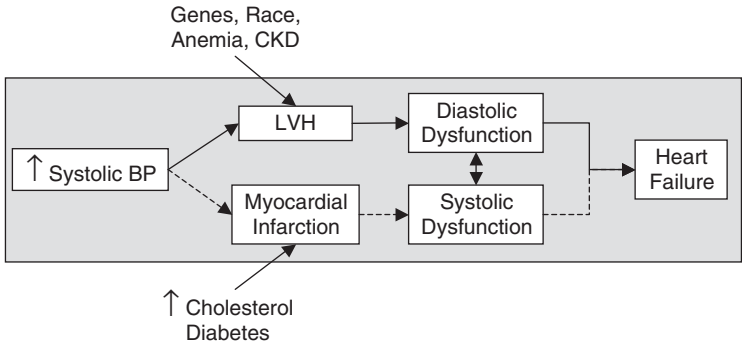


Fig. 1. The spectrum of hypertensive heart disease and major exacerbating conditions. Hypertensive heart disease is a spectrum of conditions (*large box*) that culminates in HF if not treated adequately. The major pathway (*solid arrows*) includes LVH and diastolic dysfunction. Hypertension also exacerbates coronary artery disease and myocardial infarction, which cause systolic dysfunction (*broken arrows*). Systolic and diastolic dysfunction have a complex cause–effect relationship (*double-ended arrow*) and often coexist. CKD, chronic kidney disease.

Cardiomyocyte adaptations and types of left ventricular hypertrophy

As with any muscle exposed to a chronic load, the response of the myocardium to chronic increased stretch (either preload or afterload) is hypertrophy. The pattern of hypertrophy, however, differs with the stimulus [10]. Eccentric hypertrophy occurs when increased cardiac preload causes individual myofibrils to lengthen as a result of physical conditioning with normal ventricular function (the athletic heart), in response to chronic volume overload (chronic kidney disease or obesity), or with reduced ventricular function during disease-mediated ventricular dilation. In each of these situations, increased end-diastolic volume is an adaptation that initially uses Starling forces to create a favorable energy expenditure profile to sustain cardiac stroke volume and normal ventricular ejection fraction. With continuous volume overload, however, there can be a series of maladaptive changes that lead to further ventricular dilation.

In contrast, concentric hypertrophy occurs when there is an increase in the circumferential diameters of myofibrils due to increased cardiac afterload, as occurs with systolic hypertension or aortic stenosis. Early in the course of concentric hypertrophy, myocardial wall thickening allows ventricular function and ejection fraction to keep pace with increased afterload. The thickened wall intrinsically is less efficient and the force of contraction per gram of muscle is reduced progressively. Eventually, end-diastolic pressure begins to rise and ventricular dilation may ensue. Eccentric and concentric hypertrophy can occur in the same individual, however, and LVH and HF commonly result from combined pressure and volume overload.

Cardiac load and left ventricular hypertrophy

Cardiac preload (the degree of cardiomyocyte stretch at the end of diastole) is determined by ventricular filling pressure and end-diastolic volume. Cardiac afterload (the pressure generated by the interaction of cardiac contraction and total vascular impedance) is the critical determinant in the development of concentric LVH. Central systolic BP, a surrogate for cardiac afterload, is the most critical determinant of concentric LVH. As demonstrated in Fig. 2, the vascular contribution to cardiac afterload is the integrated sum of three main components: systemic vascular resistance; early systolic “ventricular-vascular coupling” (dependent on cardiac emptying and aortic stiffness); and late-systolic pressure augmentation caused by the summation of the incident wave with reflected pressure waves. Inertance caused by the column of blood to be pumped is a fourth determinant of afterload, but this factor is relatively constant and can be ignored for practical purposes. Aortic stiffness and systolic hypertension are exacerbated in women and other individuals with intrinsically smaller aortas that intrinsically are stiffer [37]. Combined preload and afterload reduction is essential for optimal therapy of LVH and HHD.

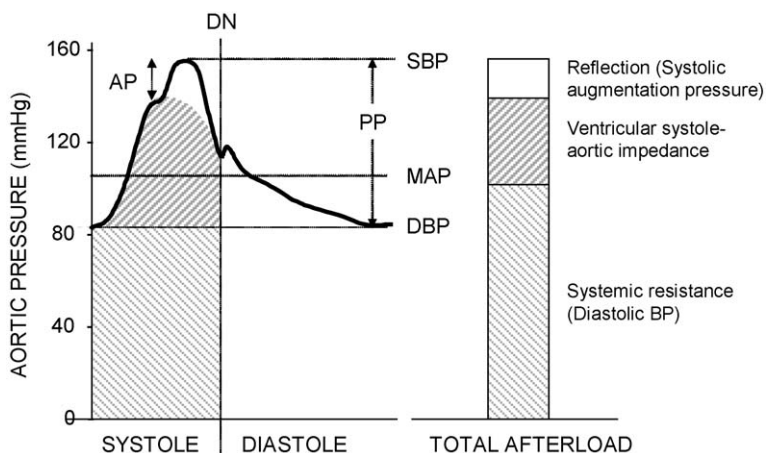


Fig. 2. Components of the central pulse wave and cardiac afterload. Left-hand panel demonstrates a typical aortic pulse contour in an older or hypertensive individual. Pulse pressure (PP) is the maximal pulsatile difference between systolic BP (SBP) and diastolic BP (DBP), whereas mean arterial pressure (MAP = $DBP + 1/3 PP$) or DBP represents the static component of afterload. Other components of PP and cardiac afterload include the interaction between cardiac stroke volume and aortic impedance during early systole (“ventricular-vascular coupling”) and systolic augmentation pressure (AP) caused by wave reflection from distal blood vessels during late systole. Total cardiac afterload is the integral of the systolic pulse contour. Relative contributions of systemic resistance (diastolic BP), ventricular-vascular coupling (aortic stiffness), and wave reflection (AP) are depicted in approximate proportions in the bar graph of total afterload in the right-hand panel. Dicrotic notch (DN) is the division between systolic and diastolic.

Nonhemodynamic factors and myocardial fibrosis

Pressor hormones such as norepinephrine, angiotensin II, and endothelin can exert direct growth-promoting influences on cardiomyocytes [38,39], even in tissue culture. There has been much debate over the importance of trophic factors such as angiotensin II on LVH. Although hypertrophy is believed to be mediated largely by AT₁ receptors, recent work suggests that AT₂ receptor stimulation also is necessary for hypertrophy [40]. It also has been claimed that agents that reduce in impact of angiotensin II are especially effective in inducing the regression of LVH [41], but lowering of central systolic BP is the most important consideration in allowing regression of LVH. Interstitial protein build-up and myocardial fibrosis increasingly appear to be significant contributors to ventricular stiffening, impaired cardiac relaxation, reduced diastolic filling, atrial hypertrophy, and eventually, elevated LV end-diastolic pressure. Aldosterone is believed to be an important promoter of LVH, particularly because it appears to stimulate the deposition of collagen and other interstitial proteins [42,43].

Genetic–environmental interactions in left ventricular hypertrophy

There is considerable interindividual variation in the response of the heart to hypertension, and not all individuals with similar BP elevations develop LVH. Twin and cohort studies have yielded heritability estimates for LV mass that range from about 20% to 70%, independent of body size, BP, sex, or age. Heritability of LV mass is particularly strong in African Americans [44]. Despite the observation that LVH arises predominantly as an acquired characteristic secondary to chronic systolic hypertension, a genetic component is suggested by the finding that diastolic filling abnormalities occur in the offspring of individuals with LVH [45]. Genetic susceptibility to the expression of LVH [44,46] has been proposed to occur by way of a variety of genes that secondarily cause LVH, pleiotropic genes that control hypertension and LV mass, and unique LV hypertrophy genes. Polymorphisms in sarcomeric proteins have been reported in severe, monogenic forms of hypertrophy, and there is a locus on chromosome 11 that cosegregates with LVH [46].

Mechanisms for increased risk in left ventricular hypertrophy

Explanations for the increased CVD risk associated with LVH include progressive impairment in coronary blood flow and flow reserve, increased coronary vascular resistance, perivascular fibrosis, arterial stiffness, and endothelial dysfunction with exacerbation of coronary atherosclerosis. Progressive contraction of intravascular volume and cardiac preload, in conjunction with increasing arterial pressure and vascular resistance, may

alter the rheology and viscosity abnormalities of the coronary microcirculation in patients with LVH further.

Progression to heart failure

The two major interacting pathways that lead to premature death from HF are diastolic dysfunction and systolic dysfunction (see Fig. 2). These two conditions often coexist, but the sequence of appearance may differ. Systolic dysfunction commonly occurs as a result of myocardial infarction or diffuse cardiomyopathy. Diastolic dysfunction may occur in the absence of systolic dysfunction, but when systolic dysfunction already exists, there almost always is some degree of impaired diastolic function. When diastolic dysfunction exists in the absence of systolic dysfunction, it usually is found in the elderly patient with long-standing hypertension without high cholesterol or coronary artery disease (usually women) [47]. Clinical presentations of systolic and diastolic HF are remarkably similar and include increased sympathetic activation, severely reduced exercise capacity, and impaired quality of life [47]. Elevated ventricular filling pressures are transmitted directly to the pulmonary capillaries and are believed to contribute to increasing dyspnea. Right-heart overload, exercise intolerance, and pulmonary edema can occur with diastolic dysfunction if LV end-diastolic pressure increases out of proportion to end-diastolic volume. Systolic and diastolic dysfunction often can be distinguished only by measuring LV function with echocardiography or radionuclide angiography.

Mechanisms that lead to ventricular dilation in individuals with decompensating LVH are not completely understood at present. In patients with systolic dysfunction, neurohormonal activation (sympathetic nervous and renin-angiotensin-aldosterone systems) causes vasoconstriction, salt and water retention, and progressive ventricular dilation and remodeling—all of which are maladaptive responses that create a vicious cycle that worsens cardiac performance. As cardiac function declines, there is no further increase in LV mass, suggesting increased apoptosis [48]. In the myocardium, the altered gene expression pattern that accompanies the transition from LVH to HF includes an overall decrease in contractile proteins [42]. At the same time, interstitial protein synthesis continues, leading to myocardial stiffness, impaired diastolic relaxation, and reduced exercise tolerance [49]. Ultimately, there is reduced myofibrillar efficiency, ventricular dilation, and HF [10]. A wide variety of other genetic and molecular mechanisms involving myocytes and interstitial proteins is under active investigation [50].

Concomitant large and small blood vessel changes exacerbate the progression from LVH to HF. The aorta becomes stiffer [51,52], with impairment of ventricular-vascular coupling and increased cardiac afterload. If atherosclerotic epicardial coronary disease also is present, then there may be areas of intermittent segmental flow compromise. With coronary

occlusion and myocardial infarction, regional myofibrillar dropout leads to segmental wall motion abnormalities and maladaptive ventricular remodeling, usually with ventricular dilation, interstitial fibrosis, and hypertrophy of surviving myocytes [53]. Coronary flow reserve is diminished by LVH and is eroded further by progressive ventricular dilation [54].

Therapy for hypertensive heart disease

Therapy for HHD is best appreciated within the contexts of the JNC 7 [1,2] and the 2001 ACC/AHA HF guideline [3] that stress the importance of antihypertensive therapy based on clinical evidence and the natural history of the condition. Originally, HHD was not fully integrated into the ACC/AHA guideline, but it is clear that HHD fits perfectly within the overall context as outlined.

Prevention (stage A individuals)

The goal of therapy in stage A (those at risk for HF) is vigorous risk factor reduction, with BP control most important. Stage A individuals should be encouraged to pursue vigorous lifestyle changes, especially weight control and aerobic exercise to control BP and other risk factors such as dyslipidemia and dysglycemia (Table 1) [2]. Physical activity improves cardiac function and reduces BP and cardiac afterload by way of a variety of mechanisms, including reduced arterial stiffness [55]. Drug treatment for hypertension is recommended for individuals with BP $\geq 140/90$ mm Hg in the general population or $\geq 130/80$ mm Hg in individuals with diabetes or chronic kidney disease [1,2]. Emphasis is placed on reaching treatment goals, which usually requires a combination of agents [1,2]. With respect to specific drug classes, diuretic-based antihypertensive therapy allows approximately a 50% reduction in HF occurrence [56]. Angiotensin-converting enzyme (ACE) inhibitors and β -blockers also are efficacious [2], whereas calcium antagonists and α -blockers seem to be less effective in preventing HF [57,58].

Combined prevention/treatment (stage B and left ventricular hypertrophy)

The specific treatment objective for stage B patients with “asymptomatic HF” is to alleviate, retard, or reverse maladaptive cardiac and vascular remodeling, thereby preventing or delaying overt HF. Fastidious BP control remains the cornerstone of therapy in stage B, along with other risk factor management. Stage B should include LVH because many experts believe that regression of LVH is an important therapeutic target. Heart Outcomes Prevention Evaluation (HOPE) study data demonstrate that an ECG voltage decline is associated with a significant reduction in CVD events [59]. In a meta-analysis of four studies of antihypertensive therapy, patients with

Table 1

Heart failure staging, clinical characteristics, and drug therapy especially pertaining to hypertension

| Heart failure stage | Clinical characteristics (risk factors/symptoms) | Recommended therapy ^a |
|---------------------|--|---|
| A | | |
| High risk for HF | Hypertension | Aggressive management of hypertension, with lifestyle modifications and drug therapy as needed |
| B | | |
| Asymptomatic HF | LVH ^b Systolic dysfunction | Aggressive management of hypertension, with drug combinations including at least one of the following: ACE inhibitors Beta-blockers ARBs ^c Thiazide diuretics ^d |
| C | | |
| Symptomatic HF | Shortness of breath Fatigue Reduced exercise tolerance | Drugs effective for HF and hypertension, including the following: ACE inhibitors/ARBs β-Blockers Aldosterone antagonists Loop diuretics (for symptoms) |
| D | | |
| End-stage HF | Marked refractory symptoms at rest despite maximal medical therapy | Drugs as in stage C; other modalities as needed |

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; FH, family history; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association.

^a Recommended drugs as in JNC 7, with modification.

^b LVH and diastolic dysfunction were not included in the staging algorithm in the 2001 ACC/AHA HF guideline.

^c ARBs were not included in the JNC 7 recommendations or the ACC/AHA guideline but are supported by data from the Losartan Intervention for Endpoint Reduction [65] and CHARM [33–36] studies.

^d Thiazide diuretics included based on Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [58] results.

Data from Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252; and Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Fedman AM, Francis GS, et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2001;104:2996–3007.

echo-LVH regression experienced a 59% CVD risk reduction compared with those without regression or with subsequent development of LVH [60]. Because increased cardiac afterload is the primary stimulus for concentric LVH, almost any therapeutic regimen that reduces systolic BP induces a degree of LVH regression [61]. Direct vasodilators are exceptions because drugs such as hydralazine and minoxidil do not reverse LVH despite effective BP lowering [61].

Whether all antihypertensive drug classes are equally effective in promoting LVH regression or altering the natural history of HHD is less clear. Some investigators have proposed that the prohypertrophic effects of angiotensin II form the basis for preferred status of ACE inhibitors and angiotensin receptor blockers (ARBs) in LVH regression; however, calcium antagonists and diuretics, which tend to stimulate angiotensin II, are only marginally worse (about 10%) than ACE inhibitors or ARBs in allowing LVH regression [41]. In the HOPE trial, ACE inhibitor therapy prevented the development or persistence of ECG-LVH more than placebo, an effect that was initially attributed to the drug itself [62]. New data, however, have revealed that the ACE inhibitor lowers ambulatory BP to a much greater degree than the investigators initially reported [63], and it is likely that BP lowering alone explained the differences in LVH in HOPE. In the Losartan Intervention for Endpoint Reduction in Hypertension study, the ARB (losartan) achieved greater echo-LVH regression [64] and better overall outcomes (less stroke but similar CVD mortality) than the comparison β -blocker (atenolol) [65,66].

Optimal therapy of stage B HF still is unclear because of the relative lack of direct clinical studies in this area. On balance, ACE inhibitors [2,58,67,68], β -blockers [2], and ARBs [33–36] appear to be reasonable choices in any stage B patient with systolic dysfunction or LVH. Combination of ACE inhibitors and ARBs in stage B patients appears to achieve no additional benefit [69]. The role of thiazide diuretics in stage B HF is somewhat less clear. There is no doubt that thiazides prevent the onset of symptomatic HF based on the Systolic Hypertension in the Elderly Program and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial studies [58,70]. Thiazides, however, have not been specifically tested in LVH or diastolic dysfunction and, therefore, it is not known whether they provide optimal outcomes in all stages of HHD. Aldosterone antagonists also may be beneficial in stage B but lack clinical trial evidence.

Overt heart failure (stages C–D)

Certain agents are recommended by JNC 7 for the treatment of hypertension and HF as a “compelling indication.” A compelling indication is a high-risk condition associated with hypertension for which there is clinical trial evidence of a specific outcome benefit for a given class of

antihypertensive drugs [2]. As with any compelling indication, the practitioner is directed to treat the compelling indication first and then to achieve appropriate target BP using additional agents as needed. The treatment goals for patients with symptomatic HF are to alleviate symptoms, prevent hospitalization, slow or reverse progressive LV remodeling, and decrease mortality. BP care in advanced HF deserves an additional comment. By the time that HF has reached an advanced stage, most individuals no longer exhibit hypertension. In those who do, aggressive BP reduction is of particular importance because of the exquisite sensitivity of the failing ventricle to increased cardiac afterload. Accordingly, it often is necessary to reduce systolic BP by as much as possible, even to values well below 120 mm Hg if the patient is not symptomatic (usually orthostatic hypotension or severe fatigue).

A complete discussion of the therapy of overt HF is beyond the scope of this review and has been covered in existing guidelines [2,3]. For systolic dysfunction, drug therapy is the cornerstone of management. Drugs that meet JNC 7 requirements as compelling indications for the treatment of hypertension and HF can be classified broadly as neurohormonal blockers (ie, drugs that block the sympathetic and renin-angiotensin-aldosterone systems). Included in this category are ACE inhibitors, ARBs, β -blockers, and aldosterone antagonists. The number of antineurohumoral agents needed to provide optimal therapy for stage C–D HF is unclear. All β -blocker studies have been performed with a background of digitalis and ACE inhibitor. Marginal outcome benefits have been reported for the ACE inhibitor–ARB combination in stage C HF [34], but it is highly possible that higher ACE inhibitor doses would have achieved the same benefits. Loop diuretics are indispensable in managing symptoms related to volume overload and in the aggressive control of BP in some individuals. Older treatments such as digitalis may improve symptoms but do not impact survival favorably. Additional modalities such as implantable defibrillators, counterpulsation devices, and organ transplantation are used occasionally in the most advanced or complex cases.

The foregoing discussion indicates that diastolic dysfunction is a component of stage B–D HF. At present, there is no recommended treatment for diastolic dysfunction because of the relative paucity of clinical trial evidence. Nevertheless, in the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity-Preserved Trial of diastolic dysfunction, ARB-based therapy was associated with an 11% trend toward improvement in CVD outcomes, especially HF hospitalization [36]. Other therapies have not been tested in diastolic dysfunction specifically, but it is believed by some experts that rate slowing with β blockade or nondihydropyridine calcium antagonists is useful because of improved ventricular filling. Digitalis glycosides and other inotropic agents generally are not recommended because cardiac contractility is not impaired.

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