

Update in the Approach to and Management of Heart Failure

Jill M. Gelow, MD, MPH, and James C. Fang, MD

Abstract: Heart failure (HF) is a prevalent and morbid chronic disease that patients experience in stages. Progression through the stages of HF can be slowed with optimal medical therapy. Although HF remains a clinical diagnosis made at the bedside, measurement of serum brain natriuretic peptide (BNP) can help in the diagnosis when there is uncertainty. The initial workup for patients with newly diagnosed HF is directed at identifying the underlying cause of left ventricular dysfunction. An assessment of hemodynamic status, determined by a careful physical examination, can be used to direct therapy.

Angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers remain the two most important therapies for patients with chronic HF. Aldosterone antagonists improve mortality but require close monitoring for severe hyperkalemia. Angiotensin-receptor blockers (ARBs) are excellent alternatives to ACEIs for ACEI-intolerant patients. Digoxin, a second line agent in HF, improves symptoms without mortality benefit. Successful management of HF requires aggressive management of comorbid conditions and careful follow up to slow disease progression, optimize functional status, and improve longevity.

Key Words: heart failure, left ventricular dysfunction, angiotensin-converting enzyme inhibitors, beta blockers, aldosterone antagonists, angiotensin-receptor blockers, digoxin

Heart failure (HF) is an important public health problem. Nearly five million people in the United States are currently diagnosed with heart failure and approximately 500,000 new cases are diagnosed every year. HF accounts for 15 million office visits per year and is the most common reason for hospitalization among elderly adults.¹

Despite advances in treatment, HF remains a deadly disease. The 10-year mortality following an initial HF diagnosis is 90% and in 2001, 53,000 patients died as a result of heart failure as a primary cause. HF is also costly. In 2005, 27.9

billion dollars were spent on HF in the U.S.; 2.9 billion dollars are spent annually on HF medications alone.¹

In this review, advances to the approach and management of heart failure as a consequence of systolic dysfunction are discussed. For a discussion of “diastolic” heart failure (ie, when systolic function is preserved), the reader is referred to a contemporary review of this topic.²

Staging in Heart Failure: A New Paradigm

HF should be viewed as a chronic progressive condition that patients experience in stages rather than defined solely by functional capacity. HF has traditionally been categorized by the New York Heart Association (NYHA) functional classification that stratifies patients based upon the degree of activity needed to elicit symptoms of HF (Table 1). However, this system of classification is limited because HF patients commonly experience waxing and waning functional class through the course of their condition. To better describe the spectrum and progressive nature of HF, a new classification of HF has been proposed to complement the existing NYHA classification system. This new system considers HF as a continuum that begins before HF symptoms develop and di-

Key Points

- Heart failure is a prevalent and morbid disease.
- Brain natriuretic peptide (BNP) can help in the diagnosis of heart failure when there is clinical uncertainty.
- Angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers are the two most important therapies for patients with chronic heart failure.
- Aldosterone antagonists require close monitoring for the development of severe hyperkalemia.
- Angiotensin-receptor blockers (ARBs) are an excellent alternative to ACEIs for ACEI-intolerant patients.
- Digoxin is a second line agent in heart failure and primarily improves symptoms without mortality benefit.
- Heart failure requires careful longitudinal follow up to slow disease progression, optimize functional status, and improve longevity.

From Division of Cardiovascular Medicine, University Hospitals, Cleveland, OH.

Reprint requests to James C. Fang, MD, University Hospitals, 11100 Euclid Avenue, LKS 3001, Cleveland, OH 44106. Email: jfang@partners.org

Accepted April 3, 2006.

Copyright © 2006 by The Southern Medical Association

0038-4348/0-2000/9900-1346

Table 1. New York Heart Association (NYHA) functional classification of heart failure

NYHA class	Description
Class I	No. symptoms
Class II	Symptoms with modest activity
Class III	Symptoms with minimal activity
Class IV	Symptoms at rest

rects attention to risk factors that predispose patients to the development of structural heart disease.

Accordingly, the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines describe four stages of HF (Fig. 1).¹ Stage A includes patients at high risk for developing HF (ie, hypertension) but without evidence of structural heart disease. Stage B describes patients with evidence of structural heart disease, such as left ventricular hypertrophy or left ventricular dysfunction, but without symptoms of HF. Stage C refers to patients with structural heart disease who have past or current symptoms of HF. Stage D is reserved for patients with medically refractory end-stage HF requiring advanced therapies for management. This staging system also highlights the concept that progression through the stages of HF can be slowed or even halted with the introduction and maintenance of optimal medical therapy at every stage. Furthermore, patients with Stage C or D heart failure may readily move between NYHA classes

depending on the dynamic circumstances of their underlying disease, treatment regimen, and exogenous factors.¹

The Primary Evaluation in Heart Failure

Left ventricular systolic dysfunction can be caused by a wide spectrum of diseases and conditions (Table 2). Coronary artery disease accounts for approximately 50% of HF cases. The largest portion of nonischemic cases of systolic dysfunction are idiopathic. Many patients with idiopathic cardiomyopathy likely have unrecognized familial cardiomyopathies. In a recent study, approximately 20% of first- and second-degree relatives of patients with an idiopathic cardiomyopathy had echocardiographic abnormalities suggestive of left ventricular dilation or dysfunction.³

The diagnostic workup for patients newly presenting with HF is directed at identifying the underlying cause of left ventricular dysfunction. History taking should be thorough and should explore alcohol and/or illicit drug use as well as familial conditions. A detailed physical examination is directed toward hemodynamic status and potential systemic diseases that may result in heart failure, such as atherosclerosis. Initial laboratories should include a complete blood count, electrolytes, kidney function, urinalysis, glycosylated hemoglobin, fasting lipids, liver and thyroid function tests.¹ Basic testing should also include an electrocardiogram, echocardiogram and an objective assessment of functional capacity. A thorough evaluation for ischemia should always be performed unless the patient is not a candidate for revascu-

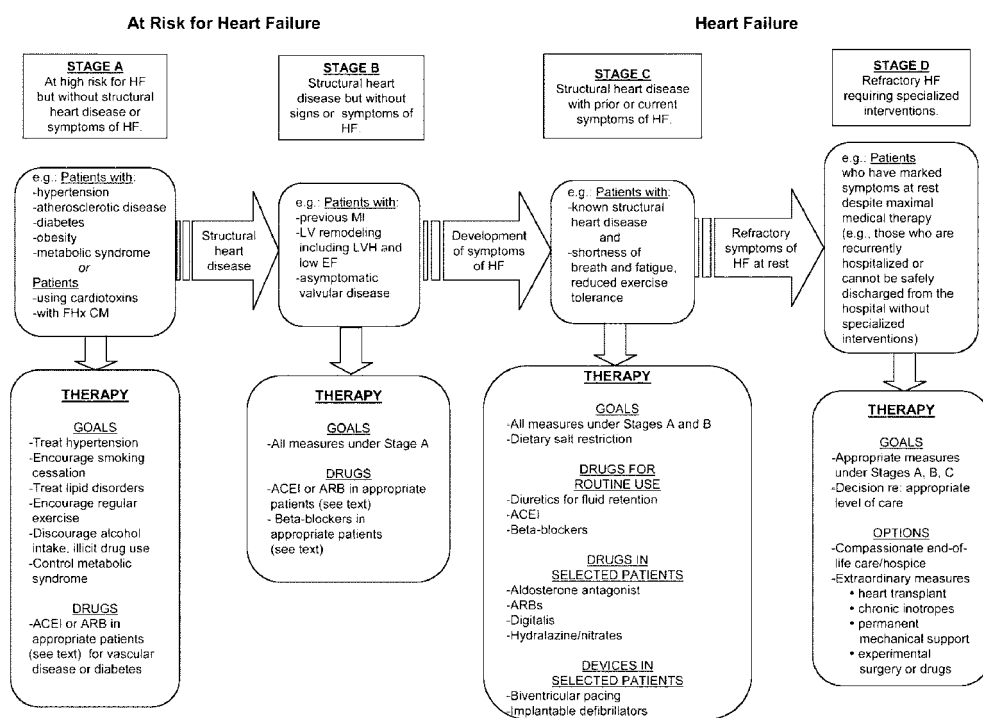


Fig. 1 Stages in the development of heart failure and recommended treatment options by stage.¹ *FHx CM, family history of cardiomyopathy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Etiologies of systolic dysfunction

Coronary artery disease	Amyloid
Idiopathic	Cocaine
Valvular	Sarcoid
Hypertension	Thyroid disease
Familial	Hemochromatosis
Tachycardia	Uncontrolled alcohol
Viral	HIV
Postpartum	

HIV, human immunodeficiency virus.

larization. Further testing, including iron studies, HIV, metanephrines, left and right heart catheterization and endomyocardial biopsy, may be indicated in selected patients.¹

Prognosis should be routinely assessed when evaluating a patient with heart failure. Although there are many independent predictors of prognosis (such as serum sodium and left ventricular size), NYHA class and left ventricular ejection fraction (EF) remain the two most important and intuitive predictors of survival in HF.^{4,5} Mortality from HF increases linearly with NYHA class; the 2-year mortality for NYHA class I, II, III and IV patients is approximately 10%, 20%, 30% and 40%, respectively.¹ Clinical class is best determined quantitatively using tests such as the 6-minute walk, a Bruce protocol exercise treadmill test, or an assessment of oxygen consumption (which is often limited to specialized heart failure centers). For example, patients who cannot walk further than 100 m in 6 minutes have an extremely high 1-year mortality.⁴ Using EF in addition to functional capacity, HF prognosis can be further refined. Among patients with NYHA class III or IV symptoms, patients with an EF >30% have a better survival rate without urgent transplantation than patients with an EF <30%.⁵ The 2-year survival without urgent transplantation for patients with class III or IV HF and an EF <25% is approximately 50%.⁵

Assessment of hemodynamic status is a primary goal of the initial physical examination in patients with heart failure and can be used as a starting point to direct therapy. Patients can be classified into one of four hemodynamic profiles at the bedside, based on filling pressures (“dry or wet”) and cardiac output or end organ perfusion (“warm or cold”), the two primary axes of hemodynamic status (Fig. 2).⁶ The majority of HF patients present with symptoms and signs consistent with the “warm and wet” profile B. These patients have elevated filling pressures in the presence of adequate perfusion.⁶ Initial treatment for patients with profile B largely focuses on preload reduction through diuresis and/or vasodilation. A smaller proportion of HF patients present with elevated filling pressures and evidence of poor perfusion (profile C), a picture compatible with cardiogenic shock. These patients are classified as “cold and wet” and often require aggressive therapy with vasodilators and inotropes to improve perfusion before initiation of successful diuresis.⁶ These hemodynamic profiles have prognostic implications as well. For example, profile C (“cold and wet”) patients have an extremely high mortality among patients referred for HF management.⁷

Brain Natriuretic Peptide

HF is traditionally identified using bedside signs and symptoms that have been incorporated into various criteria for its diagnosis. For example, the Framingham criteria defines HF if two major or one major and one minor clinical criterion are present (Table 3).⁸ However, in clinical practice, the history may be vague and the physical examination unreliable, limiting the use of such criteria. In these situations, biomarkers, such as brain natriuretic peptide (BNP), can be useful adjuncts to the diagnosis of HF.

BNP is a cardiac neurohormone secreted from the ventricles in response to pressure and volume overload. BNP results in natriuresis, diuresis, vascular smooth muscle relaxation, and inhibition of the renin-angiotensin system (RAS).⁹

Fig. 2 Hemodynamic assessment of heart failure.⁶ *Diagram of a 2 × 2 table of hemodynamic profiles for patients presenting with heart failure. ACE inhibitor: angiotensin-converting enzyme inhibitor.

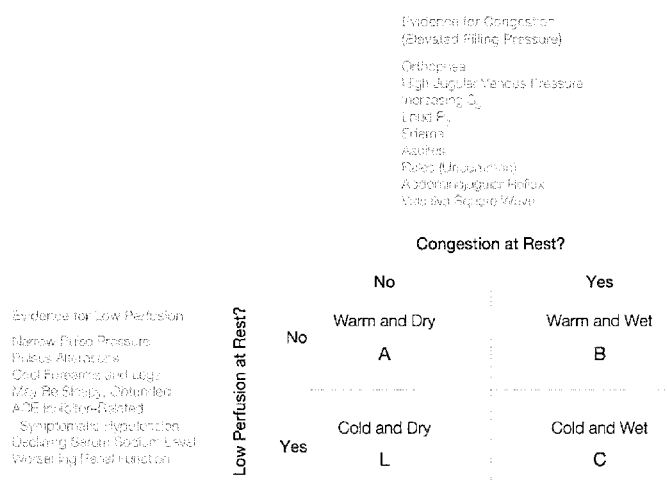


Table 3. Framingham criteria for the diagnosis of heart failure⁸

Major criteria	Minor criteria
Orthopnea	Ankle edema
Paroxysmal nocturnal dyspnea	Night cough
Rales	Exertional dyspnea
Cardiomegaly	Hepatomegaly
Acute pulmonary edema	Pleural effusion
JVD >16 cm	Tachycardia (>120 beats/minute)
Hepatojugular reflex	Decreased vital capacity by one-third
Circulation time greater than 25 seconds	Weight loss with HF treatment

Diagnosis of congestive HF equals 2 major or 1 major plus 1 minor criteria. JVD, jugular venous distension; HF, heart failure.

Pro-BNP, a 108 amino acid prohormone, is cleaved into BNP and an N-terminal fragment (NT-proBNP) after being released from cardiac myocytes. Both BNP and NT-proBNP can be measured in clinically available assays.⁹

The measurement of BNP and NT-proBNP is currently used for a variety of purposes including screening for left ventricular dysfunction, the diagnosis of heart failure, and as a prognostic/treatment guide. When considering BNP as a clinical tool it is important to remember that BNP levels are variable and must be interpreted within the clinical context. BNP levels increase with age, female gender, renal failure and NYHA class.^{10,11} In contrast, BNP levels decrease in obesity, with treatment of heart failure, and are lower in HF with preserved ejection fraction (EF).¹²⁻¹⁴ These issues may limit its helpfulness in unselected populations. BNP was found to have limited utility as a screening tool to identify left ventricular hypertrophy and left ventricular dysfunction among 3,532 members of the Framingham Offspring study.¹⁵ BNP may be more useful as a screening test for structural heart disease among populations with a high prevalence of disease.¹⁶

Although the usefulness of BNP as a screening test remains in question, the role of BNP in the diagnosis of HF is better defined. Measurement of BNP has been shown to be useful in situations where there is diagnostic uncertainty regarding the etiology of acute dyspnea. In a population of emergency room patients presenting with acute dyspnea, a BNP cutoff of 100 pg/mL was 90% sensitive, 76% specific and 83% accurate for diagnosing HF. A BNP level of 50 pg/mL had a 96% negative predictive value for HF.¹⁷ In this population, BNP was more accurate in determining the cause of dyspnea than any other history, examination or laboratory finding.¹⁷ In addition to diagnosing acutely symptomatic HF, BNP levels have been used to guide HF therapy.¹⁸

BNP levels also provide prognostic information. A study of 3,346 patients without known HF followed for five years

found that elevated baseline BNP levels were associated with increased risk of all-cause death and cardiovascular events.¹⁹ In chronic HF, BNP is an independent predictor of sudden death among patients with a left ventricular EF <35%.²⁰ How BNP changes over time may also be relevant. In the Valsartan Heart Failure Trial (Val-HeFT), patients with the greatest decrease in BNP levels from baseline had the lowest morbidity and mortality. In contrast, patients with the greatest increase in BNP had the highest morbidity and mortality.²¹ NT-proBNP also appears to have similar clinical utility and has the advantage of greater stability over time when plasma samples are stored and its measurement is not confounded by the concomitant use of recombinant IV BNP (nesiritide).

Heart Failure Treatment

Prevention of HF is critical (Fig. 1). Treatment of patients with stage A HF should focus on modification of risk factors that lead to myocardial injury and structural heart disease, including hypertension, coronary artery disease and diabetes mellitus.¹ Angiotensin-converting enzyme inhibitor (ACEI) therapy should be initiated in high-risk patients for prevention of stroke, myocardial infarction and death.²² After myocardial injury has resulted in structural heart disease (ie, stages B, C, and D), the primary goals of HF management are to improve symptoms, slow disease progression, and lower mortality. These goals are accomplished through identification and treatment of causes of myocardial injury, optimization of the hemodynamic profile, and neurohormonal antagonism. The remainder of this review will focus on the pharmacologic strategies that are employed to accomplish these goals. Stage D patients are medically refractory to pharmacologic agents and often require specialized therapy with inotropes, cardiac resynchronization therapy (CRT), ventricular assist device implantation (VAD) and/or transplantation. Excellent reviews on the treatment of stage D patients⁶ and the role of device therapy in HF,²³ including biventricular pacing and defibrillators, are available and are beyond the scope of this update.

Diuretics

Diuretics are one of the cornerstones of treating symptomatic HF. Loop diuretics (furosemide, torsemide and bumetanide), the most common class of diuretics used in HF management, act by inhibiting the Na⁺ K⁺ 2Cl⁻ cotransporter in the thick ascending limb of the loop of Henle, where the majority of the sodium filtered at the glomerulus is reabsorbed. In contrast, the thiazide-based diuretics (metolazone, hydrochlorothiazide and chlorthalidone) inhibit the Na⁺ Cl⁻ cotransporter in the distal convoluted tubule. Thiazide diuretics can be used to augment diuresis when administered 30 minutes before a loop diuretic by preventing the compensatory distal reabsorption of sodium when the loop of Henle has been blocked by a loop diuretic. Combination therapy with a loop and thiazide diuretic must be initiated with caution as it

increases the risk of hypokalemia, hyponatremia and renal insufficiency.²⁴ Furthermore, the use of diuretics may paradoxically lead to greater neurohormonal activation and decreases in renal perfusion.²⁵ These issues are especially relevant since most diuretics have not been shown to improve survival in prospective randomized placebo-controlled trials.

Certain potassium-sparing diuretics inhibit the action of aldosterone in the cortical collecting duct and block sodium channels in the collecting duct. Overall, these drugs are weak diuretics but can be useful in counterbalancing hypokalemia induced by loop and thiazide diuretics. However, in contrast to the loop and thiazide diuretics, two particular agents in this class, spironolactone and eplerenone, have been studied in prospective randomized trials. Their beneficial effects are likely a result of their aldosterone antagonism rather than their diuretic action. Aldosterone is especially deleterious in HF. Aldosterone is released from the adrenal cortex in response to angiotensin II, ACTH and potassium and results in sodium and water retention as well as the loss of potassium and magnesium. Aldosterone also activates the sympathetic nervous system, inhibits the parasympathetic nervous system, causes endothelial and baroreceptor dysfunction, and produces myocyte and vascular fibrosis.

Two large randomized trials of aldosterone antagonists in HF have demonstrated their benefits.^{26,27} The RALES (Randomized Aldactone Evaluation Study) trial randomized chronic NYHA class III/IV HF patients with an EF <35% to spironolactone or placebo. Spironolactone (average dose 26 mg per day) decreased the risk of death by 30% ($p = <0.0001$) compared with placebo over a mean 24-month follow-up period.²⁶ At the other end of the HF spectrum, EPHEUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) studied patients with a myocardial infarction in the prior 3 to 14 days, HF, and an EF <40%. Patients randomized to treatment with eplerenone, a more specific aldosterone receptor antagonist, had a 15% reduction ($P = 0.0005$) in the risk of death from all causes when compared with placebo.²⁷

It is important to note for clinical practice that in both RALES and EPHEUS, patients with an elevated baseline creatinine (Cr >2.5 mg/dL) or serum potassium (>5.0 mEq/dL) were excluded. Equally important, laboratory follow up of potassium and renal function were measured at frequent intervals. Although there was no difference in the occurrence of severe hyperkalemia between spironolactone and placebo in the RALES trial,²⁶ there was a significant increase in hospitalizations for hyperkalemia and associated mortality in clinical practice after its publication.²⁸ Furthermore, EPHEUS found patients treated with eplerenone were more likely than the placebo control group to develop severe hyperkalemia (5.5% versus 3.9%, $P = 0.002$).²⁷

In general, aldosterone antagonists should be considered in most patients with chronic symptomatic HF as long as hyperkalemia (potassium >5.0 mmol/L) and renal insufficiency (creatinine >2.5 mg/dL) are not present. All patients

should be monitored closely for the development of severe hyperkalemia and/or renal insufficiency. Eplerenone, a selective aldosterone antagonist, can be useful for patients unable to tolerate the side effect profile of spironolactone, which includes gynecomastia and impotence.²⁷

Angiotensin-converting Enzyme Inhibitors

The renin-angiotensin system (RAS) plays a critical role in the pathogenesis of HF. ACEIs decrease the conversion of angiotensin I to angiotensin II, the key product of the RAS cascade. Angiotensin II increases peripheral resistance, leads to sodium retention, and has mitogenic and pro-oxidant properties. Angiotensin II also interacts with other neurohormonal pathways integral to the pathophysiology of HF, such as the adrenergic and natriuretic peptide systems. In addition to inhibiting the production of angiotensin II, ACEIs decrease the breakdown of bradykinin. Bradykinin promotes natriuresis and vasodilation in the vascular endothelium. Paradoxically, bradykinin is also responsible for producing the side effects of cough and angioedema associated with ACEI use.

The benefits of ACEIs in heart failure have been repeatedly demonstrated in thousands of patients in clinical trials that date back to the late 1980s. For example, in the first CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial, patients with class IV HF randomized to enalapril experienced a 40% reduction in mortality compared with a placebo, which surprisingly was evident in six months. Patients treated with enalapril also had an improvement in NYHA class, a reduction in heart size, and a decreased need for other HF medications.²⁹ Subsequent studies have confirmed the mortality benefit of ACEIs for patients with left ventricular dysfunction across all NYHA classes of HF (Table 4).^{29–33}

Despite the well-established benefits of ACEIs in HF, this medication class remains underutilized. National prescribing data suggests that only 28% of HF patients in the year 2000 were prescribed an ACEI.³⁴ Furthermore, ACEIs are frequently prescribed in lower doses than the target doses used in clinical trials, likely decreasing the benefit to the patient. The ATLAS study randomized 3,164 patients with class II-IV HF and an EF <30% to low dose (2.5–5.0 mg) or high dose (32.5–35 mg) lisinopril.³⁵ Patients treated with high-dose lisinopril had a 12% reduction ($P = 0.002$) in the risk of death or hospitalization for any reason, a 15% reduction in all-cause mortality and hospitalization for HF ($p = <0.001$) and 24% fewer hospitalizations for HF ($P = 0.002$) than patients treated with low dose lisinopril.³⁵ Although downward dose titration may be required when beta blockers are added to the medical regimen, HF patients should be treated with the target doses of ACEIs used in clinical trials (Table 5).

HF patients unable to tolerate ACEI therapy due to circulatory-renal limitations (symptomatic hypotension, progressive renal dysfunction or hyperkalemia) have severe disease

Table 4. Selected trials of angiotensin-converting enzyme inhibitors in heart failure

Trial (year)	N	NYHA class	Treatment group mortality	Control group mortality	Hazard ratio	P value
CONSENSUS I ²⁹ (1987)	253	IV	26%	44%	0.66	<i>P</i> = 0.002
V-HeFT II ³⁰ (1991)	804	I-III	18%	25% (Isordil/hydralazine)	0.72	<i>P</i> = 0.016
SOLVD treatment ³¹ (1991)	2569	II/III	35%	40%	0.84	<i>P</i> = 0.0036
SOLVD ³² prevention (1992)	4228	I	15%	16%	0.91	<i>P</i> = ns
SAVE ³³ (1992)	2231	Post-MI (EF <40%)	20%	25%	0.81	<i>P</i> = 0.019

MI, Myocardial infarction; EF, ejection fraction.

and are at increased risk of death within the next year.³⁶ In a study of 259 consecutive inpatient HF admissions at an academic medical center, ACEIs were discontinued in 23% due to circulatory-renal limitations. Mortality in this group during 8.5 months of follow up was 57% compared with only 22% among patients tolerating ACEI therapy at discharge (*P* = 0.0001), even when other comorbidities were considered.³⁶

Beta Blockers

HF is a state of excessive sympathetic activity. The initial adrenergic response to myocardial injury is acutely beneficial because it maintains cardiac output by increasing contractility and heart rate. However, over time, chronic sustained adrenergic activity leads to disease progression through ventricular remodeling, arrhythmogenesis, apoptosis, and cytokine activation. Beta blockers counteract the disproportionate sympathetic nervous system activity in chronic HF.³⁷

β -blocker therapy in chronic HF patients leads to a striking reduction in mortality. The benefits of β -blocker therapy are independent of baseline heart rate, change in heart rate, and final heart rate.³⁸ A meta-analysis of 18 clinical trials showed that beta blockers reduced the risk of death or hospitalization for HF by 37% (*P* < 0.001).³⁹ Beta blockers also improve functional class and EF. However, caution should be exercised when initiating β -blocker therapy in chronic HF since there may be an acute reduction in left ventricular systolic function which can result in clinical deterioration.⁴⁰ For this reason, initiation of beta blockade remains contraindicated in acutely decompensated HF. In such patients, initiating ACEI therapy before beta blockade remains appropriate. ACEIs can hemodynamically stabilize decompensated HF through vasodilation, allowing subsequent initiation of β -blocker therapy once the patient becomes compensated.⁴¹ In ambulatory patients with compensated mild to moderate chronic HF, it may be safe to consider a beta blocker first approach to therapy.⁴²⁻⁴⁴ However, the overall goal should be to maintain chronic HF patients on both ACEIs and beta blockers since the greatest benefits are with long-term combination therapy.

Which beta blocker to use in chronic HF has been debated. Beta blockers differ in their adrenergic, vasodilator, and ancillary properties, which are putative reasons why one

agent might be preferable to another.³⁷ For example, carvedilol and bucindolol are nonselective beta blockers with intrinsic vasodilator activity. In contrast, metoprolol succinate and bisoprolol selectively block the β -1 receptor. Clinical HF trials also imply that these differences are relevant. Although carvedilol, metoprolol succinate, and bisoprolol lowered mortality in randomized placebo-controlled trials, bucindolol did not (Table 6).⁴⁵⁻⁴⁸ Furthermore, in COMET (the only head-to-head trial of β -blocker therapy in chronic HF), all-cause mortality was decreased for patients treated with carvedilol 25 mg twice daily when compared with metoprolol tartrate 50 mg twice daily over a 5-year period (34% versus 40%, *P* = 0.0017).⁴⁹ However, there was no difference between the groups in the composite endpoint of mortality or all-cause hospital admissions (*P* = 0.122).⁴⁹

Yet, the superiority of carvedilol may not be that simple. Metoprolol tartrate (Lopressor), the metoprolol formulation in COMET, and metoprolol succinate (Toprol XL), the approved formulation for HF, are similar but not equivalent. For example, the dose of metoprolol tartrate [Lopressor] used in COMET (50 mg twice daily) is not equivalent to the target dose of metoprolol succinate [Toprol XL] used in the MERIT-HF study (200 mg once daily) that demonstrated the effectiveness of metoprolol succinate in HF.^{46,49}

In the end, the choice of an agent should be driven by its proven effectiveness in a clinical trial and other patient-specific issues. For instance, one might favor metoprolol succinate for its once daily dosing and cost and may be a better choice for patients with dizziness, asthma or lower baseline blood pressures. In contrast, carvedilol has shorter dosing

Table 5. Target doses of recommended angiotensin-converting enzyme inhibitors

Drug	Dose	Frequency
Lisinopril	20-40 mg	q.d.
Captopril	50 mg	t.i.d.
Ramipril	10 mg	q.d.
Enalapril	10 mg	b.i.d.

Table 6. Trials of beta blockers in heart failure

Trial (year)	Agent	NYHA Class II/III/IV%	Treatment group mortality	Placebo group mortality	Hazard ratio	P value
Copernicus ⁴⁵ (2001)	Carvedilol	“severe”	13%	20%	0.65	<i>P</i> = 0.0014
MERIT HF ⁴⁶ (2001)	Metoprolol XL	41/56/3	7%	11%	0.66	<i>P</i> = 0.00009
CIBIS-II ⁴⁷ (1999)	Bisoprolol	0/83/17	12%	17%	0.66	<i>P</i> < 0.0001
BEST ⁴⁸ (2001)	Bucindolol	0/92/8	30%	33%	0.90	<i>P</i> = 0.10

intervals that allow for easier titration and may be better for patients with hypertension (because of its alpha antagonism) and/or diabetes (since it improves insulin sensitivity).⁵⁰ Appropriate target dosing is also vital and can only be addressed for those agents used in clinical trials of HF where the most effective dose of an agent is known.

Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) antagonize the effects of angiotensin II directly at the level of the angiotensin II subtype 1 receptor and thus may provide more complete blockade of the RAS system than ACEIs. This action may be important because angiotensin II levels return to pretreatment levels after several weeks despite the use of an ACEI. In addition, angiotensin II is generated by non-ACE pathways that may not be blocked by circulating ACEIs. ARBs are also better tolerated since they lack bradykinin potentiation, the mechanism of ACEI-related cough and angioedema. Recent clinical trials of ARBs in HF have specifically addressed issues of tolerability, superiority, and combination therapy with ACEIs.

Data from the multinational SPICE registry of patients with EF <35% found that 9% of registry patients were not on an ACEI because of intolerance. The most common reason for ACEI intolerance was cough.⁵¹ The SPICE trial assessed ARB tolerability by randomizing 270 patients previously in-

tolerant to ACEIs to candesartan or placebo. At the completion of 12 weeks, more than 85% of patients were able to tolerate candesartan, which was similar to tolerance of the placebo.⁵² Subsequent studies have confirmed the improved tolerability of ARBs.

Several studies comparing ACEIs to ARBs in patients with chronic HF have shown no difference in mortality or HF hospitalization and it appears that ARBs are not superior but not inferior to ACEIs (Table 7).^{53–56} ARBs have also been used in conjunction with ACEIs in patients with chronic HF. In CHARM,⁵⁷ a chronic HF trial, and VALIANT,⁵⁸ a post myocardial infarction trial, there were statistically significant reductions in HF hospitalizations for patients treated with both ACEIs and ARBs when compared with ACEIs alone (Table 7). Of note, patients receiving combination therapy with valsartan and captopril in the VALIANT trial had more adverse drug-related events.^{53–58}

In summary, ARBs can be considered excellent alternatives for patients unable to tolerate ACEI therapy, an ACC/AHA class I indication for ARB use in chronic HF.¹ Adding an ARB to an ACEI and beta blocker may have additional benefits but blood pressure may be limiting and the triple combination has been associated with increased adverse events. Currently, the use of an ARB in this fashion is considered a class IIa recommendation by the ACC/AHA.¹ Fi-

Table 7. Trials of angiotensin-receptor blockers in heart failure

Trial (year)	NYHA Class (N)	Study design	Mortality	HF hospitalizations
ELITE I ⁵³ (1997)	NYHA Class II–IV (722)	Losartan vs. Captopril	Losartan better <i>P</i> = 0.035	No difference
ELITE II ⁵⁴ (2000)	NYHA Class II–IV (3152)	Losartan vs. Captopril	No difference	No difference
Val-HeFT ⁵⁵ (2001)	NYHA Class II–IV (5010)	Valsartan vs. Placebo	No difference	Valsartan better <i>P</i> = 0.001
CHARM-alternative ⁵⁶ (2003) ^a	NYHA Class II–IV (2028)	Candesartan vs. Placebo	No difference	Candesartan better <i>P</i> = 0.0001
CHARM-added ⁵⁷ (2003) ^b	NYHA Class II–IV (2548)	Candesartan vs. Placebo	No difference	Candesartan better <i>P</i> = 0.014
VALIANT ⁵⁸ (2003)	Acute MI/CHF (14808)	Valsartan vs. Valsartan + Captopril vs. Captopril	No differences	Valsartan + Captopril better <i>P</i> = 0.007

^aAll patients ACEI intolerant.

^bAll patients on an ACEI in addition to study therapy.

MI, myocardial infarction; CHF, congestive heart failure; NYHA, New York Heart Association; HF, heart failure.

nally, ARBs may also be important in other HF subgroups, such as patients with “diastolic” HF as recently demonstrated in the CHARM program.²

Digoxin

Digoxin is among the oldest drugs used for HF treatment. Today, digoxin is second line therapy for the management of HF, ie, an ACC/AHA class IIa indication for HF.¹ Traditionally, digoxin was thought to improve HF by acting as a positive inotrope. More contemporary work suggests that the benefit of digoxin in chronic HF is more likely related to neurohormonal effects that improve autonomic dysregulation. Digoxin inhibits sympathetic outflow from the central nervous system, decreases plasma norepinephrine levels, and increases parasympathetic activity.⁵⁹

Treatment with digoxin improves symptoms and functional status and results in fewer hospitalizations but does not change mortality among patients with HF. The RADIANCE study evaluated the effect of withdrawing digoxin from stable HF patients who were also being treated with diuretics and ACEIs. The relative risk of developing worsening HF in the withdrawal group was 5.9 (95% CI 2.1–17.2). Functional capacity, quality of life scores and ejection fraction were also significantly decreased in the digoxin withdrawal group.⁶⁰ The mortality benefit of digoxin was explored in the DIG trial, a study of chronic HF patients without atrial fibrillation and optimally treated with ACEIs and diuretics. In this study, 6,800 patients with an EF <45% were randomized to treatment with digoxin or placebo. Although patients treated with digoxin were less likely to be hospitalized for any reason ($P = 0.01$) and less likely to be hospitalized for worsening HF ($P < 0.001$), there was no difference in mortality between the two groups ($P = 0.80$).⁶¹ Of greater concern, a post hoc analysis revealed a significantly increased risk of death among women treated with digoxin.⁶²

The clinical practice of titrating digoxin to “therapeutic” serum drug levels also does not appear warranted. The PROVED⁶³ and RADIANCE⁶⁴ trials showed no correlation between serum drug concentration at the time of randomization and worsening of HF symptoms. Patients with low serum digoxin concentrations (≤ 0.9 ng/mL) were no more likely than patients with moderate (0.9–1.2 ng/mL) or high (> 1.2 ng/mL) serum digoxin concentrations to experience worsening HF, suggesting that lower target serum digoxin concentrations are appropriate in patients with HF.⁶⁴ In general, the maximum daily digoxin dose for male patients older than age 70 and women should be 0.125 mg per day, assuming normal renal function. Digoxin doses of 0.25 mg should be reserved for male patients younger than 70 with normal renal function. Digoxin levels should primarily be used to confirm clinically suspected drug toxicity rather than for dose titration for therapeutic efficacy.

Isordil and Hydralazine

V-HeFT I was the first trial to show a benefit of combination therapy with isosorbide dinitrate and hydralazine in patients with mild to severe HF.⁶⁵ Post hoc analysis from the V-HeFT I⁶⁵ and V-HeFT II³⁰ trials suggested that African-American patients experienced a particular benefit to this combination of drugs. In addition to its vasodilator properties, hydralazine may act as an antioxidant that can improve the bioavailability of exogenously donated nitric oxide from isosorbide. A-HeFT randomized 1,050 African-American patients with NYHA class III or IV HF already treated with an ACEI or ARB, beta blocker and aldosterone antagonists to therapy with isosorbide dinitrate (target dose of 40 mg three times a day) and hydralazine (target dose 75 mg three times a day) in a combination tablet or placebo. Mortality in the placebo group (10.2%) was significantly higher than in the group receiving isosorbide dinitrate and hydralazine (6.2%), prompting early termination of the study ($P = 0.02$).⁶⁶ Combination therapy with isosorbide dinitrate and hydralazine can be considered for patients with NYHA class III or IV HF already on RAS antagonists and beta blockers.

Comprehensive Heart Failure Management

Successful management of HF requires far more than the selection of evidence-based pharmacologic therapies. Diet, exercise, daily monitoring of weight, medication compliance and treatment of comorbidities are important components of comprehensive HF management. Outpatient care of HF patients can improve with the use of well-designed disease management programs. A systematic review of 11 randomized trials showed that disease management programs for HF were successful in reducing hospitalizations (RR = 0.87, 95% CI: 0.79–0.96).⁶⁷

Summary

Heart failure is a prevalent and morbid disease that moves through stages. It remains a clinical diagnosis made at the bedside but the measurement of serum BNP can help in the diagnosis when there is diagnostic uncertainty. Other clinical uses for BNP are currently being evaluated. ACEIs and beta blockers remain the two most important therapies for patients with chronic HF. Whenever possible, ACEIs and beta blockers should be titrated to the target doses used in clinical trials. Aldosterone antagonists confer additional mortality benefit but require close monitoring for the development of severe hyperkalemia and renal dysfunction. ARBs are an excellent alternative to ACEIs for ACE-intolerant patients and can be used as add-on therapy in those patients already optimized on ACEIs and beta blockers if blood pressure is not limiting. Digoxin is a second line agent in HF and primarily improves symptoms without mortality benefit. Finally, it is important to understand that HF is a systemic illness that is complicated by important comorbidities such as sudden death, atrial fibrillation, sleep apnea, and thromboembolic complications. HF

requires aggressive management of comorbid conditions and careful longitudinal follow up to slow disease progression, optimize functional status, and improve longevity.

References

- Hunt SA., American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46:1116–1143.
- Fang JC, Givertz MM. *Diastolic Heart Failure: Treatment of Advanced Heart Disease*. Baughman KL, ed. New York, Taylor and Francis, 2006,pp 229–247.
- Mahon N, Murphy RT, MacRae CA, et al. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease. *Ann Intern Med* 2005;143:108–115.
- Bittner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction: SOLVD Investigators. *JAMA* 1993;270:1702–1707.
- Stevenson LW, Couper G, Natteson B, et al. Target heart failure populations for newer therapies. *Circulation* 1995;92(9 Suppl):II-174–II-181.
- Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA* 2002;287:628–640.
- Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;41:1797–1804.
- McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971;285:1441–1446.
- Vuolteenaho O, Ala-Kopsala M, Ruskoaho H. BNP as a biomarker in heart disease. *Adv Clin Chem* 2005;40:1–36.
- Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–982.
- McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis for the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003;41:571–570.
- Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *J Am Coll Cardiol* 2006;47:85–90.
- Rousseu MF, Gurne O, Duprez D, et al. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: results from the RALES neurohormonal substudy. *J Am Coll Cardiol* 2002;40:1596–1601.
- Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction: results from the Breathing Not Properly Multinational study. *J Am Coll Cardiol* 2003;41:2010–2017.
- Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA* 2002;288:1252–1259.
- Nakamura M, Tanaka F, Sato K, et al. B-type natriuretic peptide testing for structural heart disease screening: a general population-based study. *J Card Fail* 2005;11:705–712.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergent diagnosis of heart failure. *N Engl J Med* 2002;347:161–167.
- Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355:1126–1130.
- Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655–663.
- Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002;105:2392–2397.
- Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the valsartan heart failure trial (Val-HeFT). *Circulation* 2003;107:1278–1283.
- HOPE Investigators. Effects of an angiotensin-converting-enzymes inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–153.
- Desai AS, Koplan B. *The Role of ICDs in Advanced Heart Failure: Treatment of Advanced Heart Disease*. Baughman KL, ed. New York, Taylor and Francis, 2006.
- Rosenberg J, Gustafsson F, Galatius S, et al. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. *Cardiovasc Drugs Ther* 2005;19:301–306.
- Gottlieb SS, Skettino SL, Wolff A, et al. Effects of BG9719 (CVT-124), an A1-adenosine receptor antagonist, and furosemide on glomerular filtration rate and natriuresis in patients with congestive heart failure. *J Am Coll Cardiol* 2000;35:56–59.
- Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709–717.
- Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321.
- Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543–551.
- Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS): the Consensus Trial Study Group. *N Engl J Med* 1987;316:1429–1435.
- Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303–310.
- Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure: SOLVD Investigators. *N Engl J Med* 1991;325:293–302.
- Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejections fractions: SOLVD Investigators. *N Engl J Med* 1992;327:685–691.
- Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial: the SAVE Investigators. *N Engl J Med* 1992;327:669–667.
- Stafford RS, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. *J Am Coll Cardiol* 2003;41:56–61.
- Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure: ATLAS Study Group *Circulation* 1999;100:2312–2318.
- Kittleson M, Hurwitz S, Shah MR, et al. Development of circulatory-

- renal limitations to angiotensin-converting inhibitor identifies patients with severe heart failure and early mortality. *J Am Coll Cardiol* 2003; 41:2029–2035.
37. Brislow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101:558–569.
 38. Lechat P, Hulot JS, Escolano S, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic HF in CIBIS II trial. *Circulation* 2001;103:1428–1433.
 39. Lechat P, Packer M, Chalon S, et al. Clinical effects of beta-adrenergic blockage in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184–1191.
 40. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treatment with beta-adrenergic blockade. *J Am Coll Cardiol* 1995;25:1154–1161.
 41. Fang JC. Angiotensin-converting enzyme inhibitors or β -blockers in heart failure: does it matter who goes first? *Circulation* 2005;112:2380–2392.
 42. Remme WJ, Riegger G, Hildebrandt P, et al. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction: the Carvedilol and ACE-inhibitor Remodeling Mild Heart Failure Evaluation Trial (CARMEN). *Cardiovasc Drugs Ther* 2004;18:57–66.
 43. Sliwa K, Norton GR, Kone N, et al. Impact of initiating carvedilol before angiotensin-converting enzymes inhibitor therapy on cardiac function in newly diagnosed heart failure. *J Am Coll Cardiol* 2004;44:1825–1830.
 44. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effects on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III trial. *Circulation* 2005;112:2426–2435.
 45. Packer M, Fowler MB, Coats AJ, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe heart failure. *N Engl J Med* 2001;344:1651–1658.
 46. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure: MERIT-HF Study Group. *Lancet* 1999;353:2001–2007.
 47. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999;353:9–13.
 48. The Beta Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;344:1659–1657.
 49. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): a randomized control trial. *Lancet* 2003;362:7–13.
 50. Jacob S, Rett K, Wicklmayr M, et al. Differential effects of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. *J Hypertens* 1996;14:489–494.
 51. Bart BA, Ertl G, Held P, et al. Contemporary management of patients with left ventricular systolic dysfunction: results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) registry. *Eur Heart J* 1999;20:1182–1190.
 52. Granger CB, Ertl G, Kuch J, et al. Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzymes inhibitors. *Am Heart J* 2000;139:609–617.
 53. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747–752.
 54. Pitt B, Pool-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial: the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582–1587.
 55. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–1675.
 56. Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic congestive heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;262:772–776.
 57. McMurray JJ, Ostergren J, Sewdberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-added trial. *Lancet* 2003;362:767–771.
 58. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril or both in myocardial infarction complicated by heart failure, left ventricular dysfunction of both. *N Engl J Med* 2003;349:1893–1906.
 59. Krum H, Bigger JT Jr, Goldsmith RL, et al. Effect of long-term digoxin therapy on autonomic function in patients with congestive heart failure. *J Am Coll Cardiol* 1995;25:289–94.
 60. Packer M, Gheorghide M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors: RADIANCE STUDY. *N Engl J Med* 1993;329:1–7.
 61. The effect of digoxin on mortality and morbidity inpatients with heart failure: the Digitalis Investigation Group. *N Engl J Med* 1997;336:525–533.
 62. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;347:1403–1411.
 63. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial: PROVED Investigators Group. *J Am Coll Cardiol* 1993;22:955–962.
 64. Adams KF Jr, Gheorghide M, Uretsky BF, et al. Clinical benefit of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; 39:946–953.
 65. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative study. *N Engl J Med* 1986;314:1547–1552.
 66. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; 351:2049–2057.
 67. McAlister FA, Lawson FM, Teo KK, et al. A systematic review of randomized trials of disease management programs in heart failure. *Am J Med* 2001;110:378–384.