

Slowing Heart Failure Progression: Optimal Treatment of Mild Heart Failure

Barry H. Greenberg, MD

A major cause of morbidity and mortality in the United States and other industrialized nations, heart failure is a progressive disease characterized by increasing cardiac dysfunction. Despite improvements in therapy, mortality rates remain unacceptably high. Even in those persons whose heart failure is judged to be mild, the mortality rate is approximately 50% in 5 years.¹

Recent advances in the understanding of heart failure have shifted the focus of treatment from palliative therapies designed to relieve symptoms to the use of agents able to delay disease progression. Physicians are now able to reduce morbidity and mortality by more aggressively treating patients as early as possible in the course of their disease. Thus, a paramount goal of treating heart failure should be to prevent the transition from asymptomatic or mildly symptomatic left ventricular dysfunction to more advanced heart failure.²

After briefly reviewing the epidemiology and pathophysiology of heart failure, this article will focus on its diagnosis and management, paying particular attention to new trends in pharmacologic therapy. The role of risk factors in the development of heart failure will be considered, as will specific steps to prevent progression of heart failure in patients who have had a myocardial infarction. The article will conclude with a discussion of the importance of early detection and treatment in preventing progression of heart failure.

EPIDEMIOLOGY

According to recent surveys, heart failure is pandemic in the United States and other industrialized nations. Among older adults, the incidence of heart failure approaches 10 per 1000 after age 65 years.³ As previously stated, heart failure is a leading cause of morbidity and mortality in these countries, with a mortality rate of approximately 50% within 5 years in patients with mild heart failure. Heart failure is also the leading cause of hospitalization in patients age 65 years and older.

Whereas conditions such as myocardial infarction and stroke are becoming less common, heart failure is unique among the major cardiovascular disorders in that

its incidence and prevalence continues to increase. There are 2 major reasons for this trend: (1) because prevalence of heart failure increases with age, recent shifts in population demographics predict that the frequency of heart failure will also increase; (2) the ability to treat patients with a variety of other cardiovascular conditions has resulted in improved survival of patients with some degree of cardiac damage, and these patients are at increased risk for developing heart failure in the future.

PATHOPHYSIOLOGY

Heart failure is a complex syndrome that develops as a consequence of diverse conditions that affect cardiac function, including myocardial infarction, hypertension, and exposure to myocardial toxins. The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are activated in response to any initial damage to the myocardium. This neurohormonal activation occurs in response to a decrease in cardiac output (**Figure 1**) and has an initial compensatory effect, because it tends to augment cardiac pump function. However, over time, prolonged neurohormonal stimulation of the heart has deleterious effects. Increases in left ventricular volume and mass occur, and the ventricle assumes a more spherical shape. This process, known as *cardiac remodeling*, leads to impaired cardiac function and the development of heart failure⁴; neurohormonal activation is now recognized as a major promoter of remodeling. Consequently, inhibiting increased neurohormonal activation early in the course of the disease and slowing (or reversing) the process of cardiac remodeling potentially may enable physicians to alter disease progression.

DIAGNOSIS

Diagnosis of the syndrome of heart failure is generally based on clinical assessment of the patient, often

Dr. Greenberg is a Professor of Medicine and the Director of the Heart Failure/Cardiac Transplantation Program, UCSD Medical Center, San Diego, CA.

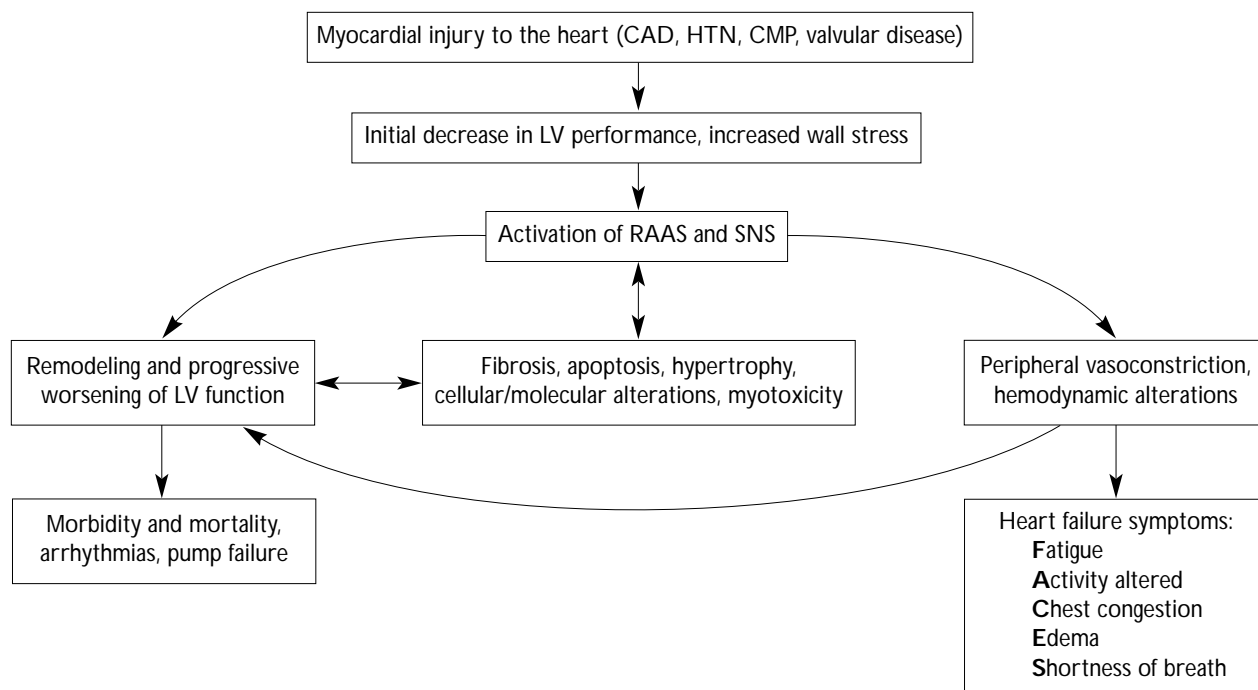


Figure 1. Algorithm schematically representing the progression of heart failure. CAD = coronary artery disease; CMP = cardiomyopathy; HTN = hypertension; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

by a primary care physician. Early detection of the disease is vital. However, the ability to judge the presence of heart failure may be poor when the signs and symptoms of the condition are mild or absent. Recognizing mild heart failure in the elderly can be particularly difficult, because the clinical presentation is often distorted by concomitant illness. Nevertheless, simple office-based techniques—such as thorough medical history taking, careful performance of a physical examination, and use of relevant tests (eg, chest radiography, electrocardiography)—are essential to the early identification of heart failure. Information from the medical history (eg, history of diabetes mellitus, hypertension, previous myocardial infarction) can alert the physician that the patient is at increased risk for heart failure. Moreover, a history of previous myocardial infarction, the presence of a conduction abnormality (eg, left bundle branch block) detected on electrocardiography, or evidence of cardiomegaly seen on chest radiography all point toward a diagnosis of heart failure.

Initial symptoms may be subtle and nonspecific. Patients may report fatigue and inability to perform activities that they previously could, often choosing to abandon these activities because of their symptoms. The onset of shortness of breath usually progresses

from exercise-related symptoms to breathlessness on mild exertion. The development of paroxysmal nocturnal dyspnea that awakens a patient from sleep and can be relieved only by elevating the head is a good early indicator that heart failure is likely present.

Physical findings early in the course of the disease can also be quite subtle. However, evidence of neck vein distention, pulmonary rales or wheezes, dullness at the lung bases indicating a pleural effusion (particularly on the right side), an S_3 , and evidence of pedal edema should alert the examiner to the possibility of heart failure.

Measurement of left ventricular ejection fraction is an integral part of the evaluation of patients with suspected heart failure. Echocardiography is most commonly used for this purpose. Not only can echocardiography determine the presence and extent of systolic pump function abnormalities, but it also provides information about the cardiac valves, pericardium, and cardiac muscle itself that can be used, in many instances, to help define the cause of the heart failure.

Evaluation of symptoms and their intensity using, for example, the New York Heart Association (NYHA) classification scheme (Table 1) can help categorize the severity of heart failure and subsequently monitor the

effects of treatment. Patients with NYHA class I (mild) heart failure have no limitation of physical activity, so heart failure is frequently underdiagnosed in this population because of the lack of overt symptoms. Of note, the American College of Cardiology and the American Heart Association have recently released a new classification scheme for heart failure.⁵ However, there is only a limited relationship between presence of symptoms and disease prognosis.⁶

MANAGEMENT STRATEGIES

Standard therapy for mild heart failure generally consists of administration of diuretics when volume overload is present, followed by the addition of an angiotensin-converting enzyme (ACE) inhibitor. Based on recent evidence from large-scale clinical trials, β -blockade is now also regarded as standard therapy in heart failure.² Digoxin is often prescribed to treat residual symptoms once diuretics, ACE inhibitors, and β -blockers have achieved their optimal results or to help control heart rate in patients with atrial fibrillation.

The value of ACE inhibition in heart failure has been recognized for many years. ACE inhibitors relieve symptoms, reduce the number of hospitalizations, and significantly improve survival compared with placebo.⁷ The doses of various ACE inhibitors approved to treat heart failure or left ventricular dysfunction in the United States are listed in **Table 2**. However, the use of ACE inhibitors alone results in incomplete blockade of neurohormonal activation, thus further enabling heart failure progression. Hence, mortality rates in patients with heart failure continue to be high with the use of ACE inhibitors alone.

The use of β -blockers for the treatment of heart failure was contraindicated for many years because of the negative inotropic effects of these drugs. The results from recent large-scale clinical trials, however, indicate that β -blockade is a vital addition to ACE inhibition and diuretic therapy in patients with mild-to-moderate heart failure, irrespective of etiology.⁸⁻¹⁰ There is now compelling evidence that treatment with β -blockers, which inhibit sympathetic activity, reduces the risk of disease progression in these patients; a decrease of approximately 37% in the combined risk of death and hospitalization in patients with heart failure has been reported when they receive β -blockers in addition to ACE inhibition.¹¹

A variety of β -blockers are available; they are distinguished on the basis of their ability to inhibit sympathetic activity to varying extents because of differences in their pharmacologic profiles (eg, selective β_1 blockers such as metoprolol and bisoprolol, nonselective β_1 - and

Table 1. NYHA Classification of Heart Failure

Class I
Asymptomatic
Class II
Slight limitations of physical activity, asymptomatic at rest
Class III
Marked limitation of physical activity, asymptomatic at rest
Class IV
Shortness of breath at rest

NYHA = New York Heart Association.

β_2 -blockers such as propranolol). In addition, carvedilol combines nonselective β -blockade with blockade of the α_1 receptor, thereby providing the most comprehensive antagonism of sympathetic activity.¹² The results of ongoing studies, such as the Carvedilol or Metoprolol Evaluation Trial, are expected to clarify whether there is a difference in the impact of these various pharmacologic agents on outcome in heart failure. The doses of β -blockers approved for the treatment of heart failure in the United States are listed in **Table 3**.

It is now believed that ACE inhibitors and β -blockers, but not digoxin or diuretics, slow heart failure progression and the worsening of underlying cardiac function.¹³ This belief is based on insights into the pathophysiology of heart failure that have shown the critical role played by the RAAS and SNS in causing disease progression by stimulating cardiac remodeling. In clinical trials, agents that block the effects of activation of the RAAS and SNS not only block remodeling but also have been shown to block disease progression. Diuretics and digoxin, although effective in decreasing symptoms and improving exercise capacity, have little or no effect on remodeling and disease progression.

ROLE OF RISK FACTORS IN HEART FAILURE PROGRESSION

General Considerations

Recognition of risk factors is essential because left ventricular dysfunction may be present long before the characteristic signs and symptoms of heart failure are recognized. A study of men and women randomly sampled in Glasgow, Scotland, showed left ventricular systolic dysfunction in 2.9% of the population.¹⁴ Of these affected persons, approximately 50% were asymptomatic; although the disease was progressing and remodeling had occurred, clinical symptoms of dysfunction had yet to develop.¹⁴

Table 2. ACE Inhibitors Approved to Treat Heart Failure and LV Dysfunction

Agent	Heart Failure	LV Dysfunction	Dosage
Captopril	Yes	Yes (after an MI)	6.25–50 mg tid
Enalapril	Yes	Yes (if asymptomatic)	2.5–10 mg bid
Fosinopril	Yes	No	20–40 mg qd
Lisinopril	Yes	No	5–20 mg qd
Quinapril	Yes	No	10–20 mg bid
Ramipril	Yes	Yes (after an MI)	5 mg bid
Trandolapril	Yes	Yes (after an MI)	1–4 mg qd

ACE = angiotensin-converting enzyme; bid = twice daily; HF = heart failure; LV = left ventricular; MI = myocardial infarction; qd = once daily; tid = 3 times daily.

Coronary Artery Disease and Hypertension

Approximately 87% of heart failure cases result from either coronary artery disease or hypertension.¹⁵ Estimates from 1995 indicated that approximately 41.5% of all deaths in the United States were attributable to cardiovascular diseases, far exceeding deaths from cancer, accidents, and HIV.³ Additionally, cardiovascular disease was the primary diagnosis reported in more than 5.8 million patients discharged from short-stay hospitals; of these patients, 65% were age 65 years or older.³

Treatment directed at underlying etiologies (eg, reducing elevated cholesterol levels, lowering blood pressure) has been shown to be effective in reducing the number of cardiovascular events (and, by extension, heart failure) in at-risk populations.^{16–18} In patients with elevated cholesterol levels, primary and secondary prevention with pravastatin and simvastatin, respectively, reduced the risk for death from cardiovascular events.^{16,17} A meta-analysis of primary prevention study data showed that lowering blood pressure over the course of 3 to 5 years effectively prevented progression to severe hypertension, left ventricular hypertrophy, and heart failure. The incidence of stroke and myocardial infarction was also decreased.¹⁸

Diabetes Mellitus

Diabetes mellitus is another recognized risk factor in heart failure, not only because it is associated with hypertension and obesity but also because it appears to damage the myocardium directly.¹⁵ Aggressive control of diabetes mellitus should, therefore, be a principal goal in preventing heart failure.

Postmyocardial Infarction Populations

Patients who survive a myocardial infarction are at high risk for developing left ventricular dysfunction and progressing to heart failure. Between 30% and

50% of adults with heart failure have a previous history of myocardial infarction.¹⁵ Heart failure progression in patients who have had a myocardial infarction involves cardiac remodeling, which again is promoted by activation of the SNS and RAAS. In patients with extensive damage to the heart as a result of 1 or more myocardial infarctions, progressive increases in left ventricular volume develop in order to compensate for the reduction in stroke volume that occurs as a result of such injury.¹⁹ This expansion in chamber size is accompanied by increases in overall muscle mass (known as *eccentric hypertrophy*) and conformational changes as the ventricle becomes more spherical. The net effect of these changes in cardiac structure and shape is a deterioration in cardiac function and, ultimately, the development of heart failure.⁴

The value of inhibiting neurohormonal activation in a post-myocardial infarction population has been apparent for many years. Short-term β -blockade has been shown to reduce infarct size when β -blockers are administered intravenously early after myocardial infarction.²⁰ A recent meta-analysis studying use of β -blockers in post-myocardial infarction patients reported reductions in mortality of between 28% and 40%.²¹ ACE inhibition after myocardial infarction has also been shown to reduce not only the risk of death from all causes and but also the progression to heart failure.²² A meta-analysis studying use of ACE inhibitors in post-myocardial infarction patients concluded that early intervention (ie, within 3–16 days of infarction) can slow disease progression and improve survival rates.²³ Despite this abundance of convincing information about the value of β -blockers and ACE inhibitors for patients who have survived a myocardial infarction, these agents are still underused—particularly by primary care physicians—in patients most likely to benefit from them.²⁴

The combination of ACE inhibitor and β -blocker therapy after a myocardial infarction may provide further benefits. A retrospective analysis of data from the Survival and Ventricular Enlargement study showed that the use of β -blockade with ACE inhibition in post-myocardial infarction patients was associated with decreases in both cardiovascular mortality and incidence of severe heart failure.²⁵ In addition, in a small-scale study, intravenously (followed by orally) administered carvedilol begun early after myocardial infarction significantly reduced cardiovascular events compared with placebo.²⁶ However, because only retrospective and/or meta-analysis data are available to support the benefits of β -blockade in patients who have left ventricular dysfunction after a myocardial infarction, further studies are either ongoing or completed, including the large-scale Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction Trial; this study is investigating the effectiveness of β -blockade with carvedilol in patients after myocardial infarction who have left ventricular dysfunction, with or without symptoms of heart failure.

MANAGING HEART FAILURE TO SLOW DISEASE PROGRESSION

Neurohormonal activation occurs early in the natural history of heart failure and is often present well before patients develop symptoms related to ventricular dysfunction.²⁷ In cases of mild heart failure, some data suggest that the SNS is activated but that other neurohormonal systems might not be. This preferential activation is thought to contribute to arrhythmias and, most likely, to the progression of heart failure; it also has been linked to mortality in patients with mild heart failure.²⁸

At first glance, administration of additional drugs may seem to be unwarranted in patients with mild heart failure whose condition appears to be well compensated by ACE inhibitors and diuretics. However, these patients are at high risk for progressive clinical deterioration, and their mortality remains unacceptably high. Consequently, there is sound rationale for the early use of β -blockers in these patients to slow disease progression.

β -blockade (using carvedilol, bisoprolol, or metoprolol) added to standard therapy with an ACE inhibitor and diuretics has been shown to reduce heart failure morbidity and mortality.^{8–10} In addition, there is evidence that β -blockers effectively prevent disease progression. The addition of carvedilol to ACE inhibitor-based therapy in patients with mild, but well-compensated, heart failure reduced clinical progression of the disease

Table 3. β -Blockers Approved to Treat Heart Failure

Agent	Recommended Initial Dose	Target Dose
Carvedilol (Coreg*)	3.125 mg bid	6.25–25 mg bid [†]
Metoprolol succinate (Toprol-XL*)	12.5–25 mg qd	200 mg qd

*Brand name.

[†]50 mg bid for patients who weigh more than 87 kg (191.4 lb).

bid = twice daily; HF = heart failure; qd = once daily.

by 48%; fluctuation between NYHA classes was also stabilized, irrespective of the cause of heart failure.²⁹

Contrary to former concerns about use of β -blockers, recent clinical trials have shown that β -blockade is generally well tolerated in patients who are clinically stable at initiation of therapy.^{8–10} Interestingly, in studies of β -blockade in patients with mild heart failure, the most frequent reasons for withdrawal from the trials were symptoms of worsening heart failure and fatigue, both of which were more common in the placebo group (ie, in patients receiving ACE inhibition alone) than in patients also receiving β -blockers.²⁹

Because ischemic heart disease is the most common cause of heart failure in the United States and other developed nations, the long-term effects of β -blockers in patients with this disorder are of particular interest. The Australia/New Zealand Heart Failure Collaborative Group Study enrolled only those patients with mild-to-moderate heart failure related to ischemic heart disease.³⁰ Compared with the placebo group (ie, patients on ACE inhibitor-based therapy alone), patients who also received carvedilol had sustained improvements in cardiac function; left ventricular ejection fraction improved significantly over 18 months of treatment ($p < 0.0001$).³⁰ Carvedilol also reduced the rate of death and hospital admission and resulted in avoidance of at least 1 serious cardiac event among every 12 to 14 patients with mild (but chronic) stable heart failure.

Left ventricular dimensions and ejection fraction provide a good indication of the extent of structural changes (ie, remodeling) that the heart has undergone. If the parameters do not increase after administration of a particular drug (ie, if the drug attenuates remodeling), the drug most likely slows disease progression by not allowing further deterioration. By the same token, an agent that decreases cardiac dimensions most likely has the property of reversing the

remodeling process. A substudy of the Studies of Left Ventricular Dysfunction Treatment Trial showed that chronic administration of enalapril prevented progressive left ventricular dilation and systolic dysfunction and improved left ventricular ejection fraction compared with placebo in patients with mild-to-moderate heart failure.³¹ Similarly, data from an echocardiographic substudy of the Australia/New Zealand Collaborative Group that examined patients with mild heart failure of ischemic etiology show that administration of carvedilol significantly decreased the left ventricular end-diastolic and end-systolic volume index and increased left ventricular ejection fraction compared with placebo (ie, administration of ACE inhibitors only); these improvements were apparent by 6 months and maintained at 12 months.³² Such results imply that, although ACE inhibition attenuates remodeling (ie, slows deterioration),³³ carvedilol slows disease progression, possibly through the reversal of the left ventricular dilation that has already occurred, even in cases of mild heart failure.³²

ROLE OF THE PRIMARY CARE PHYSICIAN IN THE MANAGEMENT OF MILD HEART FAILURE

Primary care physicians play a critical role in the prevention of progression to heart failure. The presence of risk factors for heart failure (eg, hypertension, myocardial infarction, diabetes mellitus) should be recognized and addressed when possible. As the population ages, heart failure is likely to become even more prevalent, and the need for early disease detection and effective management by primary care physicians will be increasingly important—especially in the setting of mild heart failure. Patients with mild heart failure are at high risk for future disease progression and are at continued risk of morbidity and mortality despite standard treatment, including administration of diuretics, digoxin, and ACE inhibitors. Based on firm evidence showing an improved clinical course in heart failure patients who receive β -blockers, there is now a compelling argument for primary care physicians to initiate β -blocker therapy in patients with mild heart failure.

CONCLUSION

Heart failure mortality can be curbed. Indeed, mortality rates for heart failure are falling for the first time; recent data from the Centers for Disease Control and Prevention show that age-adjusted death rates in US adults age 65 years or older declined by an average of 1.1% annually from 1988 to 1995.³⁴ Moreover, there is now considerable evidence that long-term benefits can be obtained by preventing disease progression. The

use of β -blockers and ACE inhibitors early in the course of the disease should be part of the standard therapy for cases of mild heart failure. **HP**

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