Heart Failure: Recent Advances in Prevention and Treatment

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The most important advance in heart failure treatment during the past decade has been the recognition that medications inhibiting neurohormonal activation relieve symptoms, reduce hospitalizations, and prolong survival in patients with heart failure from left ventricular systolic dysfunction. Recent trials with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, aldosterone antagonists, and ß-blockers have provided valuable information regarding the uses, dosing, and extent of therapeutic benefits of neurohormonal inhibition.
[Rev Cardiovasc Med. *2000;1(1):25-33, 54*]

Key words: Aldosterone antagonists • Angiotensin-converting enzyme inhibitors • β-Blockers • Heart failure, congestive • Neurohormones

Heart failure affects an estimated 4.6 million persons in the United States, with approximately 550,000 new cases diagnosed each year.[1] Heart failure causes substantial morbidity and mortality, accounting for 1 million hospitalizations a year.

There has been intensive research into the pathophysiology of this disease. Neurohormonal activation is now thought to play a key role in the initiation and progression of heart failure (Figure 1). Researchers have conducted many clinical trials to assess the impact of medical therapies on patient outcomes. As a result, many therapeutic options are available to manage heart failure.

The most important therapeutic advance during the past decade has been the recognition that agents inhibiting neurohormonal activation relieve symptoms, reduce hospitalizations, and prolong survival in patients with heart failure from left ventricular systolic dysfunction. Neurohormonal inhibition has also been shown to prevent the development of heart failure in patients at risk.

Despite the demonstration of marked benefits in numerous clinical trials, there has been significant variability in the extent to which neurohormonal inhibitors are used and the patient populations in which they are employed. There have been questions regarding which patient populations benefit, how patients should receive the medications, what are the most appropriate doses, and what is the most effective combination of agents. A number of recent trials have helped to address many of these questions and to better define the extent of therapeutic benefits of neuro-

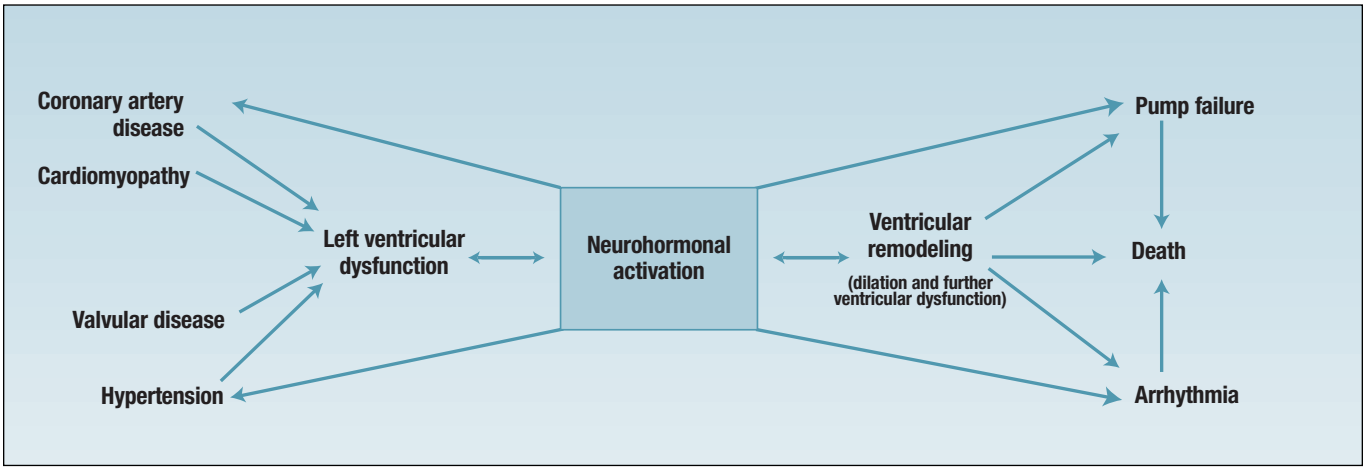

Figure 1. Pathophysiology of heart failure. Activation of neurohormonal systems, including the renin-angiotensin-aldosterone system, sympathetic nervous system, and endothelin system, drives the development and progression of heart failure through a variety of mechanisms.

hormonal inhibition in preventing and treating heart failure.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have produced hemodynamic, symptomatic, and functional benefits in patients with heart failure.[2] These agents decrease ventricular remodeling and decrease the rate of heart failure progression. These benefits have been produced with a low risk of adverse reactions.

Numerous trials have demonstrated that ACE inhibitors reduce morbidity and mortality in patients with left ventricular dysfunction, regardless of the severity of symptoms of heart failure (Table 1). The survival benefit from an overview of controlled trial data (32 trials in 7105 patients) ranges from 12% to 33%.[2] These benefits were demonstrated to be caused by mechanisms beyond the hemodynamic effects of ACE inhibitors. Both the UCLA Hydralazine-Captopril (Hy-C)[3] trial and the Veterans Affairs Cooperative Vasodilator-Heart Failure Trial II (VeHFT-II)[4] showed better survival with ACE inhibitors than with regimens of hydralazine and nitrates producing similar hemodynamic effects.

Patients with myocardial infarction, even in the absence of heart failure symptoms, have been shown to benefit from ACE inhibitors.[5] These observations have led to the recommendation that ACE inhibitors be given to all patients with left ventricular systolic dysfunction, with or without symptoms of heart failure, as long as they are well tolerated.[6,7]

Despite expert opinion and numerous practice guideline recommendations for ACE inhibitor use, a substantial proportion of patients with heart failure are not receiving ACE inhibitors.[8] When they are used, the ACE inhibitor dosages prescribed are often substantially smaller than the neurohormonal target dosages used in the large-scale clinical trials that defined their benefits.

The Assessment of Treatment With Lisinopril and Survival (ATLAS) study[9] was designed to determine whether the low doses of ACE inhibitors frequently used in clinical practice were as effective as the higher doses used in clinical trials. This study randomized 3164 patients with the New York Heart Association (NYHA) class II to IV heart failure and with ejection fractions of 30% or lower to the ACE inhibitor lisinopril at either a low dose (2.5 to 5 mg daily) or a high dose (32.5 to 35 mg daily). Compared with low-dose patients, patients treated with the high-dose ACE inhibitor had a 12% lower relative risk of death or hospitalization (83.8% vs 79.7%, $P = .002$) and 24% fewer hospitalizations for heart failure ($P = .002$). There was a nonsignificant 8% lower relative risk of death (44.9% vs 42.5%, $P = .128$) with the higher dose. Patients who received the high dose did not experience a greater improvement in NYHA functional class. Dizziness and renal insufficiency were observed more frequently in the high-dose group, but these adverse reactions could generally be managed by changes in dose of the ACE inhibitor or concomitant medications. The number of patients needing to discontinue double-blind therapy was therefore small and did not differ between the groups. Cough and worsened heart failure oc-

curred less frequently in the high-dose patients.

These findings indicate that patients with heart failure are better served by treatment with intermediate- or high-dose ACE inhibitors, if tolerated. This trial lends further support to the concept of titrating ACE inhibitors to a target dose, as opposed to symptom relief or blood pressure response. Although the ATLAS study had no placebo arm, when compared with results of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial,[10] its results do suggest that low-dose ACE inhibitor therapy has substantial benefits over no treatment. Therefore, patients with heart failure are better off receiving low-dose ACE inhibitor treatment, if that is the only dose tolerated, than receiving no treatment.

The ability of ACE inhibitors to prevent heart failure and decrease vascular events in patients with reduced systolic function and in those with acute myocardial infarction (MI) suggested the possibility that these benefits would apply more broadly.[5,11] The Heart Outcomes Prevention Evaluation (HOPE) trial[12] studied 9297 patients (55 years or older) who had evidence of vascular disease or diabetes plus 1 other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure. These patients were randomized to receive ramipril (10 mg once daily) or matching placebo for a mean of 5 years. Treatment with ramipril substantially reduced the risk of new-onset heart failure (9.1% vs 11.6% in the placebo group; relative risk, 0.77; $P < .001$). There were significant reductions in the rates of death from cardiovascular causes (6.1% vs 8.1%; relative risk, 0.74; $P < .001$), MI (9.9% vs 12.3%; relative risk, 0.8; $P < .001$), and stroke (3.4% vs 4.9%; relative risk, 0.68; $P < .001$). Drug therapy also affected overall mortality from all causes. Death from any cause was reduced to 10.4% with drug therapy, as compared with 12.2% with placebo (relative risk, 0.84; $P = .005$). This trial demonstrated an ACE inhibitor's striking ability to reduce the rates of death, MI, heart failure, and stroke in a broad range of high-risk patients even when left ventricular systolic function is not reduced and blood pressure is not elevated.

The results of the HOPE trial have considerable implications for clinical practice, since they indicate that virtually all patients with a history of cardiovascular disease, not just those who have had an acute MI or who have heart failure, benefit from ACE inhibition. ACE inhibitor therapy should be instituted in all patients at risk for heart failure, including patients with coronary artery and other atherosclerotic vascular disease, hypertension, diabetes, and left ventricular dysfunction, unless contraindications exist (Table 2).

Table 1

New York Heart Association Functional Classification for Heart Failure

Class	Functional impairment
I	Patients with left ventricular dysfunction but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.
II	Patients with left ventricular dysfunction resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue or dyspnea.
III	Patients with left ventricular dysfunction resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue or dyspnea.
IV	Patients with left ventricular dysfunction resulting in inability to carry on any physical activity without symptoms. Symptoms of cardiac insufficiency are present at rest. If any physical activity is undertaken, symptoms worsen.

Angiotensin Receptor Antagonists

Despite the convincing evidence that the renin-angiotensin-aldosterone system plays a major role in the pathogenesis and progression of heart failure and the demonstrated benefit of ACE inhibitors, the exact mechanisms by which ACE inhibitors mediate their beneficial effects are still in question. In addition to blocking production of angiotensin II through the converting-enzyme pathway, ACE inhibitors also block the breakdown of bradykinin.[5,13] Bradykinin reduces vasomotor tone by enhancing the release of vasodilator substances from the vascular endothelium. It also has been shown to have antiproliferative properties. In some experiments, the favorable effects of the ACE inhibitors on cardiac remodeling can be blocked with bradykinin receptor antagonists. Although the relative importance of increased brady-

Table 2
Neurohormonal Antagonists Used for Heart Failure Management

Generic name	Trade name
ACE inhibitors	
Benazepril	Lotensin
Captopril	Capoten
Enalapril	Vasotec
Fosinopril sodium	Monopril
Lisinopril	Prinivil/Zestril
Moexipril HCl	Univasc
Perindopril erbumine	Aceon
Ramipril	Altace
Trandolapril	Mavik
Angiotensin receptor antagonists	
Candesartan	Atacand
Eprosartan mesylate	Teveten
Irbesartan	Avapro
Losartan potassium	Cozaar
Telmisartan	Micardis
Valsartan	Diovan
Aldosterone antagonist	
Spironolactone	Aldactone
β-Adrenergic antagonists	
Bisoprolol fumarate	Zebeta
Carvedilol	Coreg
Metoprolol	Lopressor
Metoprolol CR/XL	Toprol XL

ACE, angiotensin-converting enzyme.

kinin is not entirely clear, it is possible that it contributes to the clinical benefits of these agents.

Angiotensin receptor antagonists represent an alternative pharmacologic approach to blocking the renin-angiotensin system.[14] Selective blockers of the type 1 angiotensin II (AT_1) receptor are available. Because formation of angiotensin II can take place through alternative pathways as well as through the converting-enzyme route, AT_1 receptor blockers would block angiotensin II that is generated through this alternative pathway, which would not be altered by the administration of an ACE inhibitor (Figure 2). It is possible that shunting of angiotensin II from the AT_1 to the AT_2 receptor, which has antigrowth properties, might represent another potential benefit of the receptor blockers. These agents do not, however, block the breakdown of bradykinin.

Angiotensin receptor antagonists have been shown to have effects similar to those of the ACE inhibitors in terms of improving hemodynamic variables and cardiac function in patients with heart failure. There is more limited and incomplete evidence from clinical trials regarding their impact on morbidity and mortality.

The Evaluation of Losartan in the Elderly (ELITE) study[15] randomized 722 ACE inhibitor–naive patients (aged at least 65 years) with NYHA class II to IV heart failure and ejection fractions 40% or lower to losartan titrated to 50 mg once daily or captopril titrated to 50 mg 3 times daily, for 48 weeks. The primary end point, the frequency of persistent increases in serum creatinine level, was the same in both groups (10.5%). Fewer losartan patients discontinued therapy as a result of adverse experiences. Death and/or hospital admission for heart failure was reduced 32%. This risk reduction was primarily a factor of a decrease in all-cause mortality (4.8% vs 8.7%; relative risk 0.54; 95% confidence interval [CI], 0.95 to 0.31; P = .035). Admissions of patients with heart failure were the same in both groups, as was improvement in NYHA functional class from baseline.

The Randomized Evaluation of Strategies of Left Ventricular Dysfunction (RESOLVD) pilot study[16] compared the effects of candesartan, enalapril, and a combination of the 2 in a cohort of 768 patients with symptomatic heart failure from left ventricular systolic dysfunction. Patients received either candesartan (4, 8, or 16 mg), candesartan (4 or 8 mg) plus 20 mg of enalapril, or 20 mg of enalapril alone for 43 weeks. The goal was to compare the effects of the drugs and the combination of agents on exercise performance, ventricular function, quality of life, neurohormones, and tolerability.

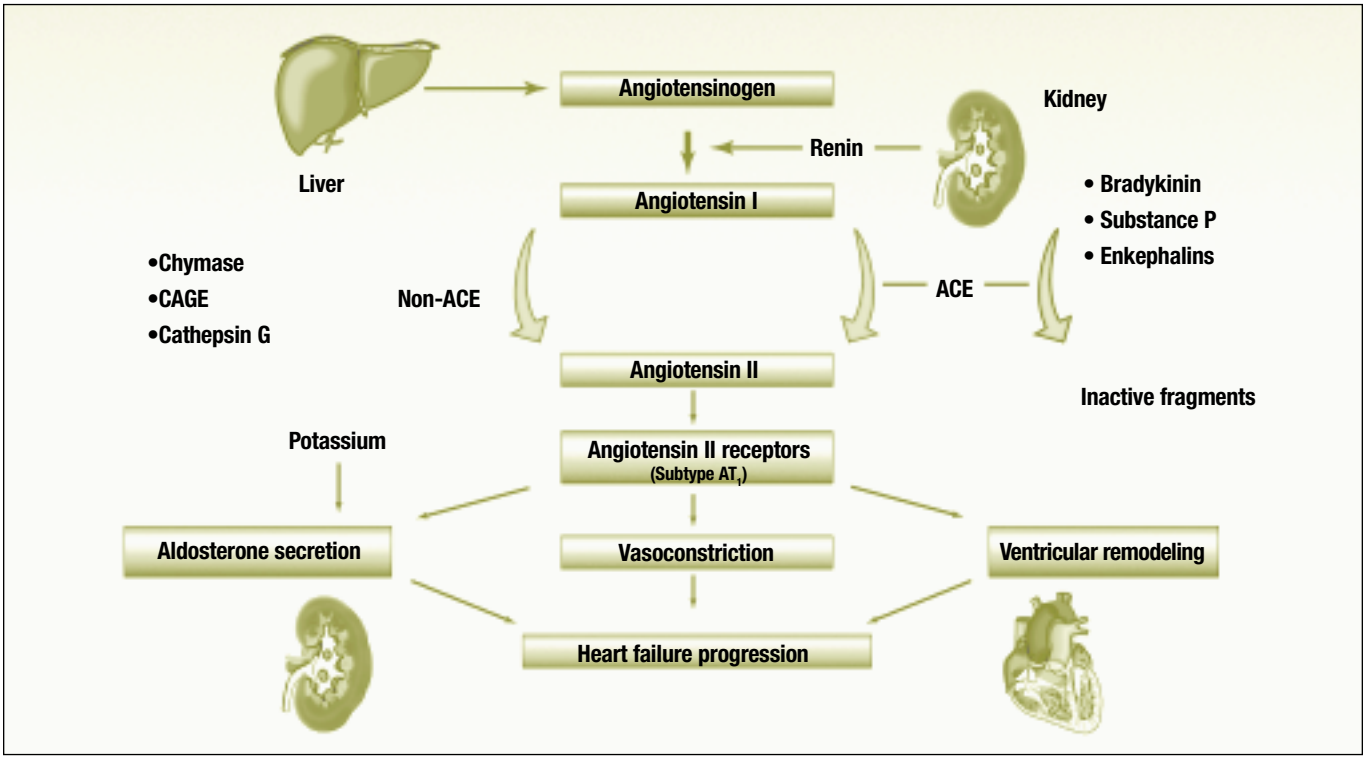

Figure 2. The renin-angiotensin-aldosterone pathway. Activation pathways for the formation of angiotensin II and aldosterone that contribute to the pathophysiology of heart failure. (ACE, angiotensin-converting enzyme; CAGE, chymostatin-sensitive angiotensin II–generating enzyme; AT_1, type 1 angiotensin II.)

The main findings were the absence of any appreciable difference among treatments in exercise performance, NYHA functional class, or quality of life. There was a trend toward a greater number of events in either the candesartan alone or combination groups, compared with the enalapril-alone group. Mortality up to week 43 was 6.1% for candesartan alone, 8.7% for the candesartan-enalapril combination, and 3.7% for enalapril alone (P = .15). For hospitalizations alone, the 3-way comparison was significant, favoring enalapril alone (P = .048). The combination of candesartan and enalapril prevented increases in left ventricular volumes that occurred with either of the drugs alone. Combination therapy also appeared to have favorable effects on the neurohormonal profile of these patients, with reductions seen in aldosterone levels and in levels of brain natriuretic peptide.

Enthusiasm about the results of the ELITE I trial prompted the ELITE II trial, which randomized 3152 patients with a similar design,[17] but with mortality as the primary end point. The results of this trial were preliminarily presented at the 71st Scientific Sessions of the American Heart Association. Unlike the first trial, ELITE II showed mortality of 15.9% with captopril versus 17.7% with losartan, which was not statistically significantly different (relative risk 1.12; 95% CI, 0.95 to 1.25; P = .16). The death and hospitalization rates were similar (44.9% and 47.7%, respectively). This failure to show a significant difference in mortality and the trend favoring ACE inhibitors in this study may have been a factor of the relatively low dose of losartan studied in this trial or may indicate that angiotensin receptor blockers confer no added benefit over ACE inhibitors in heart failure. Consequently, ACE inhibitors remain the therapy of choice for patients with heart failure. Angiotensin receptor antagonists should be reserved for those patients with absolute contraindications to or intolerable side effects from ACE inhibitors.

The pharmacologic differences between the ACE inhibitors and AT_1 receptor blockers, however, raise the possibility that combination therapy with both classes of drug could offer benefits beyond those seen with either agent alone. Theoretically, this approach would provide greater inhibition of angiotensin II activation of the AT_1 receptor than would treatment with an ACE inhibitor alone, while

Table 3
Major Placebo-Controlled Trials of β-Blocker Therapy in Patients With Heart Failure

Study	Number of patients	LVEF (%)	Annual mortality	Relative risk
US Carvedilol Heart Failure study[21] (varied dosing)	1094	22	Placebo vs carvedilol, 12.0% vs 4.2%	0.35
CIBIS II[23] (bisoprolol, 10 mg)	2647	28	Placebo vs bisoprolol, 13.2% vs 8.8%	0.66
MERIT-HF[24] (metoprolol, CR/XL 200 mg)	3991	28	Placebo vs metoprolol, 11.0% vs 7.2%	0.66

LVEF, left ventricular ejection fraction; CIBIS II, Cardiac Insufficiency Bisoprolol Study; MERIT-HF, Metroprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.

maintaining the beneficial effects of increased bradykinin levels. This combination approach is being tested in at least 2 ongoing trials.

Aldosterone Antagonists

Until recently, aldosterone antagonists had been used infrequently in patients with heart failure. It was believed that ACE inhibitors would suppress the formation of aldosterone, that aldosterone antagonists had relatively weak diuretic effects, and that with these agents there was the potential for serious hyperkalemia.[18] Experimental studies a decade ago, however, suggested that aldosterone plays an important role in the pathophysiology of heart failure.[19]

In patients with congestive heart failure, plasma aldosterone concentrations may reach 20 times the normal level because of both increased production and decreased hepatic clearance. Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, and baroreceptor dysfunction. It also impairs vascular compliance. There was also evidence to suggest that ACE inhibitors only transiently suppress the production of aldosterone.

The Randomized Aldactone Evaluation Study (RALES)[18] was designed to test the hypothesis that aldosterone antagonism with spironolactone would significantly reduce the risk of death among patients who had severe heart failure and who were receiving standard therapy, including an ACE inhibitor. In this study, 1663 patients with NYHA class III to IV heart failure and ejection fraction of 35% or less who were treated with an ACE inhibitor, a loop diuretic, and (in most cases) digoxin were randomized to receive 25 mg of spironolactone daily or placebo. Patients were excluded if they had a serum creatinine level of more than 2.5 mg/dL or serum potassium level of more than 5 µg/dL. Serum potassium levels were monitored closely during this trial, especially during initiation.

This trial was discontinued early, since the risk of death was reduced from 46% to 35% with spironolactone (relative risk, 0.7; 95% CI, 0.6 to 0.82; $P < .001$). There was a lower risk of both death from progressive heart failure and sudden death. In addition, the frequency of hospitalization for worsening heart failure was 35% lower in the spironolactone group, and these patients had a significant improvement in the symptoms of heart failure, as shown by the NYHA functional class ($P < .001$). The incidence of serious hyperkalemia was low in both groups of patients (1% vs 2%).

The fact that the aldosterone antagonist reduced the risk of both morbidity and death among heart failure patients who were receiving an ACE inhibitor emphasizes the point that standard doses of an ACE inhibitor do not effectively suppress the production of aldosterone. Since patients' blood pressure, heart rates, and body weights did not substantially change and there were no clinically important differences in serum potassium levels, it can be inferred that much of the survival benefit was due to neurohormonal antagonism as opposed to hemodynamic effects.

RALES indicates that the beneficial effects of aldosterone receptor antagonists in patients with heart failure are additive to those of ACE inhibitors. This observation suggests that the standard of care for the treatment of patients with moderate or severe symptomatic heart failure with a serum creatinine level of 2.5 mg/dL or higher should include spironolactone. This trial also raises the possibility that patients with milder heart failure, asymptomatic left ventricular dysfunction, MI, coronary artery disease, or hypertension (ie, other conditions in

which ACE inhibitors are beneficial) may also benefit from aldosterone blockade. Additional clinical trials will be necessary to assess the safety and effectiveness of aldosterone blockade in these patient populations.

β-Adrenergic Antagonists

Activation of the sympathetic nervous system is common in patients with heart failure and can contribute to progressive myocyte dysfunction, cell loss, and ventricular remodeling. The rationale for β-blocker use in heart failure, based on the hypothetical neurohormonal pathogenesis of heart failure, has evolved during the past 2 decades.[20] Clinical and experimental studies have revealed that β-adrenergic blockade in myocardial failure can improve myocyte functin and reduce left ventricular chamber size. Small clinical trials suggesting that patients with heart failure may benefit from β-blocker therapy set the stage for larger trials.

The US Carvedilol Heart Failure study[21] enrolled 1094 patients with chronic heart failure in a double-blind, placebo-controlled, stratified program in which patients with heart failure were randomly assigned to receive either placebo or the nonselective β- and α-blocker carvedilol. Mortality was reduced from 7.8% in the placebo group to 3.2% with carvedilol, a 65% reduction (95% CI, 0.2 to 0.61, $P < .001$). Carvedilol therapy was accompanied by a 27% reduction in the risk of hospitalization for cardiovascular causes and a lower risk of worsening heart failure symptoms (21% vs 16%). A meta-analysis of the 18 double-blind, placebo-controlled trials of β-blockade in patients with chronic heart failure published up to 1997 showed that this therapy increased left ventricular ejection fraction by 29% and reduced the risk of death by 32%.[22] The mean annual mortality rate was reduced from 9.7% to 7.5%.

In 1999, 2 more large-scale studies were published: Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[23] and Metroprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).[24] Results of these studies are consistent with each other and with previous meta-analysis (Table 3).

In CIBIS-II, 2647 patients aged 18 to 80 years who were receiving diuretics and ACE inhibitors were assigned placebo or bisoprolol, a selective antagonist of β_1-adrenergic receptors.[23] Bisoprolol was started at 1.25 mg/d and was progressively increased to a maximum of 10 mg/d. The trial was stopped after a mean follow-up of 1.3 years, because the bisoprolol patients showed a 34% reduction in mortality (11.8% with bisoprolol vs 17.3% with placebo; 95% CI, 0.54 to 0.81; $P < .0001$). There was a 44% reduction in sudden deaths and a 20% reduction in hospital admissions.

MERIT-HF included 3991 patients with heart failure, aged 50 to 80 years, in NYHA class II to IV and with an ejection fraction of less than 40% who were receiving standard therapy with ACE inhibitors and diuretics.[24] Patients were initially given metoprolol CR/XL 12.5 mg (NYHA class III or IV) or 25 mg once daily (NYHA class II), and the doses were increased over 8 weeks toward the target dose of 200 mg once daily. Treatment with long-acting metoprolol conferred a 34% reduction in mortality (relative risk, 0.66; 95% CI, 0.53 to 0.81; $P = .0062$). Annual mortality was reduced from 11.0% to 7.2%. There were significant reductions in both sudden deaths and deaths from worsening heart failure.

The results of the Australia/New Zealand (ANZ) Heart Failure trial[25] and of the SOLVD prevention trial suggest that even patients with mild heart failure and asymptomatic left ventricular dysfunction benefit from β-blockers. The Multicenter Oral Carvedilol Heart-failure Assessment (MOCHA)[26] demonstrated a dose-related reduction in mortality among patients with moderate chronic heart failure. Even at the lowest dosage of carvedilol studied (6.25 mg twice daily), mortality was reduced from 15.5% with placebo to 6.0% ($P < .05$).[25] At the 25-mg twice-daily dosage, mortality was 1.1% ($P < .001$ for linear dose response).

It appears that as with ACE inhibitors, patients with heart failure derive benefit from even low doses of β-blockers, but additional benefits accrue by titration to target doses. The benefits of β-blockers are additive, if not synergistic, with ACE inhibitors. Based on the available evidence, titration to target doses of both an ACE inhibitor and a β-blocker, if tolerated, is the recommended course of treatment for patients with heart failure.

Patients with severe class IV heart failure had generally been excluded from published trials, and experience in such patients was limited. Results of the β-Blocker Evaluation of Survival Trial (BEST),[27] which evaluated bucindolol in 2708 patients with class III or IV heart failure, were preliminarily reported at the 71st Scientific Sessions of the American Heart Association. BEST failed to demonstrate a significant reduction in mortality (33.0% with placebo vs 30.2% with bucindolol; relative risk, 0.9; $P = .015$). Recently, bucindolol has been shown to have intrinsic sympathomimetic activity, so this trial result may have more to do with the β-blocker studied than with

Main Points

- Agents that inhibit neurohormonal activation can relieve symptoms, reduce hospitalizations, and prolong survival in patients with heart failure from left ventricular systolic dysfunction.
- All patients with or at risk for heart failure are candidates for angiotensin-converting enzyme inhibitor therapy.
- β-Blockers are indicated for all patients with stable class I to IV heart failure from left ventricular systolic dysfunction, unless there is a contraindication or intolerance.
- An aldosterone antagonist should be used for patients with class III or IV heart failure from left ventricular systolic dysfunction, unless contraindicated.

the patient population.[28]

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial evaluated carvedilol in patients with class IV heart failure. This trial was terminated 1 year early by the data safety and monitoring committee because of a significant reduction in mortality with carvedilol.

The results of the US Carvedilol Trial and COPERNICUS raise the possibility that carvedilol may provide greater benefit than other selective agents, perhaps because of more complete sympathetic blockade, vasodilator effects, and other ancillary actions. The results of CIBIS-II and MERIT-HF indicate that there is also significant survival benefit with selective β-blockers.

The Carvedilol and Metoprolol European Trial (COMET) is evaluating the relative effects of metoprolol and carvedilol on outcomes in 3000 patients with class II to IV heart failure. Currently, treatment with carvedilol, bisoprolol, or metoprolol can be recommended.

β-Blocker therapy is indicated in all patients with stable class I to IV heart failure due to left ventricular systolic dysfunction, unless contraindications exist or intolerance has been demonstrated.[6] Treatment should be started with low doses and increased gradually over weeks or months. The benefits of β-blocker treatment for heart failure are now clearly established, and this therapy should be integrated into routine clinical practice.

Other Neurohormonal Inhibitors

Medications in various stages of development that inhibit other aspects of neurohormonal systems are being evaluated as possible therapies for patients with heart failure. They include endothelin receptor antagonists, neutral endopeptidase inhibitors, imidazoline receptor agonists, and synthetic natriuretic peptides. Results of some of these trials have been surprising. Moxonidine, which is a selective α-adrenergic and imidazoline receptor agonist, was evaluated as a potential heart failure therapy. Moxonidine selectively stimulates imidazoline receptors located in the medulla that centrally inhibit sympathetic outflow, resulting in a decrease in plasma norepinephrine. A trial of this agent was halted prematurely after 53 deaths occurred in patients randomized to moxonidine, compared with 29 in the placebo group among the first 2000 patients who were enrolled.[29]

Endothelin receptor antagonists, such as bosentan, which is a mixed endothelin-1 type A and type B receptor antagonist, have been shown to prevent the progression of left ventricular dysfunction and attenuate left ventricular chamber remodeling in animal models of heart failure.[30] In preliminary studies in patients with heart failure, there have been favorable acute hemodynamic effects and an improvement in clinical status over 6 months.

Vasopeptidase inhibitors simultaneously inhibit both neutral endopeptidase (NEP) and ACE. Simultaneous inhibition of NEP and ACE increases natriuretic and vasodilatory peptides, including atrial natriuretic peptide, brain natriuretic peptide of myocardial cell origin, and C-type natriuretic peptide of endothelial cell origin, and increases the half-life of other vasodilator peptides, including bradykinin and adrenomedullin.[31]

Omapatrilat is 1 such agent and was evaluated in a trial involving 573 patients with heart failure who were treated with either 40 mg of omapatrilat or 20 mg of the ACE inhibitor lisinopril for 24 weeks.[32] Exercise tolerance, the study's primary end point, improved in both treatment groups. Compared with lisinopril-treated patients, 45% fewer omapatrilat-treated patients discontinued treatment, were hospitalized, or died of worsening heart failure, (16 vs 29; relative risk, 0.55; $P < .04$). A new study, the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) will evaluate omapatrilat's ability to prolong survival and reduce hospitalization for heart failure, as compared with the ACE inhibitor

enalapril, in 4420 patients at more than 600 sites.

Evidence-Based Optimal Management

Evidence of heart failure's progressive nature and continued high mortality have stimulated an intensive search for new therapeutic options. A better understanding of the role that neurohormonal activation plays in heart failure progression and the results of large-scale clinical trials have led to major advances in medical management (Figure 3).

The following recommendations for heart failure management can be made:

- ACE inhibitor therapy is indicated in all patients with or at risk for heart failure, including patients with coronary artery and other atherosclerotic vascular disease, patients with hypertension, patients with diabetes, and patients with left ventricular dysfunction, unless contraindications exist.
- Aldosterone antagonism is indicated in all patients with class III or IV heart failure from left ventricular systolic dysfunction, unless contraindications exist. Patients with less severe heart failure may also benefit.
- β-Blocker therapy is indicated in all patients with stable class I to IV heart failure from left ventricular systolic dysfunction, unless contraindications exist or intolerance has been demonstrated. Treatment should be started with low doses and increased gradually over weeks or months.

These therapies are readily available but continue to be underused. As the development and evaluation of new therapies for heart failure proceed, significant efforts should be made to ensure that the existing clinical trial results are better translated into routine clinical practice. ■

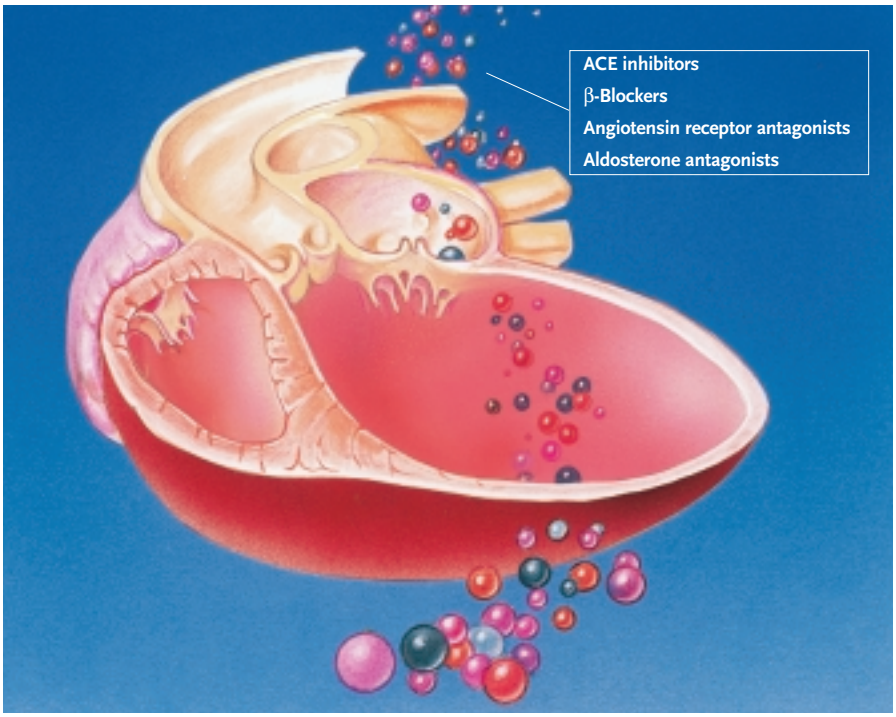

Figure 3. Current options for medical treatment for patients with heart failure from left ventricular dysfunction include angiotensin-converting enzyme inhibitors, aldosterone antagonists, angiotensin receptor antagonists, and β-blockers.

Acknowledgments

The author thanks Michele Hamilton, MD, for her review of this manuscript and Stephanie Kagimoto for administrative assistance.

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