



Improving care of chronic heart failure: Advances from drugs to devices

RANDALL C. STARLING, MD, MPH*

Section of Heart Failure and Cardiac Transplant Medicine, Kaufman Center for Heart Failure, Department of Cardiovascular Medicine, Cleveland Clinic

■ ABSTRACT

The right combination of drugs and surgical treatment can improve systolic function and prevent, attenuate, or reverse heart failure. Patient education and disease management programs can reduce hospitalizations. Optimal treatment for each patient is guided by a thorough evaluation and use of functional classification and disease staging systems.

A 48-YEAR-OLD WOMAN is referred to us with dyspnea on exertion after climbing one flight of stairs. More than a year earlier, she had been treated in a hospital emergency department and found to have an ejection fraction of 15% to 20% and 4+ mitral regurgitation. After a catheterization found her coronary arteries to be normal, she was placed on quinapril and a diuretic.

As we began treating her, she was referred for evaluation for transplantation and consideration for biventricular pacing or mitral valve repair. However, she was not taking a beta-blocker, so we started her on a low dose (3.125 mg) of carvedilol. We also referred her to a nurse practitioner–heart failure specialist for education, disease management, and titration of the carvedilol.

Six months later, she had reached her target dose of carvedilol of 25 mg twice daily. She remained on quinapril and the diuretic, and had also started spironolactone. She required neither a transplant nor mitral repair.

In fact, her ejection fraction had improved to 50%, and the dimension of her left ventricle had decreased, from 6.3 cm to 4.7 cm. The mitral regurgitation had vanished.

■ PROGRESS IN HEART FAILURE

The marked improvement in this woman's heart failure is not an isolated case. We see this often in patients who are treated aggressively with medical therapy.

Medical therapy, notably the use of beta-blockers, has revolutionized the care of heart failure patients. In addition, patient education and disease management programs can help reduce the frequent and expensive hospitalizations of heart failure patients.

Even those patients with more advanced heart failure have a variety of surgical and device options that were not available in the past.

Still, all these new options raise a number of difficult issues. Given the growing polypharmacy, what is the optimal drug therapy for which patients? How can the growing healthcare costs be controlled? And how will the many new devices fit into the therapeutic options for patients?

■ DRUG THERAPY IS GUIDED BY FUNCTIONAL CLASS

The choice of drugs in the treatment of heart failure can be guided by the New York Heart Association (NYHA) functional class (TABLE 1).¹ Recently, the American College of

**Beta-blockers
have
revolutionized
heart failure
treatment**

*The author has indicated that he has received grant or research support from Acorn Cardiovascular corporation, and is a consultant for Novartis. This paper discusses therapies that are experimental or not approved by the US Food and Drug Administration for the use under discussion. Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the authors but are not peer-reviewed.

TABLE 1

General guidelines for use of drugs in each New York Heart Association functional class

Class I	Angiotensin-converting enzyme (ACE) inhibitor
Class II	ACE inhibitor, beta-blocker, diuretic
Class III	ACE inhibitor, beta-blocker, spironolactone,* digoxin, diuretic
Class IV	ACE inhibitor, beta-blocker, spironolactone,* digoxin, diuretic

*Spironolactone should be reserved for those with severe heart failure who remain symptomatic despite standard therapy with an ACE inhibitor, a beta-blocker, digoxin, and a diuretic, or those with hypokalemia and an intolerance for potassium supplements.

TABLE 2

**Not available for online publication.
See print version of the
*Cleveland Clinic Journal of Medicine***

**ARBs have not
proven
superior
to ACE
inhibitors**

Cardiology (ACC) devised another classification system, also with four stages, to emphasize the idea of considering heart failure before it occurs in patients with hypertension, diabetes, and coronary artery disease. (TABLE 2).²

Most patients with heart failure receive an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker, a diuretic, and digoxin. Evidence suggests that angiotensin II receptor blockers (ARBs) convey no survival benefit over ACE inhibitors. Therefore, ARBs are recommended for use only in patients who cannot tolerate ACE inhibitors because of angioedema or intractable cough.^{3,4}

Give ACE inhibitors almost always: High or low dose is the question

As demonstrated in more than 7,000 patients in more than 30 placebo-controlled trials, ACE inhibitors alleviate symptoms, improve functional class, and decrease risk of death and

the combined risk of death or hospitalization. These drugs are now recommended for patients in all functional classes of heart failure unless the patient cannot tolerate them or this class of drugs is otherwise contraindicated.

The Studies of Left Ventricular Dysfunction (SOLVD) prevention trial⁵ showed that ACE inhibitors may prevent disease progression. They should be used even in patients with structural heart disease but no symptoms; patients with symptoms should continue to take ACE inhibitors even if they do not achieve complete relief.

The optimal dosage remains contentious. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial⁶ showed that, compared with low doses, high doses of these drugs do not reduce the mortality rate but are more effective at reducing hospitalizations and slowing progression of heart failure. However, common sense suggests that modest doses may



be appropriate in patients who are receiving increasing doses of additional important medications (eg, beta-blockers) that can have antihypertensive effects.

ACE inhibitors plus spironolactone in severe heart failure

The Randomized Aldactone Evaluation Study (RALES)⁷ fueled interest in using the combination of an ACE inhibitor and spironolactone. In this study of 1,663 patients, the addition of spironolactone reduced the mortality rate by 30%. However, it is important to observe several points:

- Enrollment in the study was completed before beta-blockers were in common use for heart failure; only 18% of the patients in the study were receiving them.
- The study included patients with severe heart failure; 72% were in NYHA class III and 27% were in NYHA class IV.
- Patients with elevated levels of creatinine and potassium were excluded.
- The target dose of spironolactone was low. This dose was derived from a pilot study, which determined that only a low dose was needed to achieve an advantageous sodium balance.

This study generated no evidence that spironolactone is advantageous in patients with NYHA class I or II heart failure. Thus, spironolactone should be reserved for those with severe heart failure who still have symptoms despite standard therapy with an ACE inhibitor, a beta-blocker, digoxin, and a diuretic, or those with hypokalemia who cannot tolerate potassium supplements.

ACE inhibitor plus an ARB?

The Valsartan in Heart Failure (Val-HeFT) study,⁸ in 5,010 patients with moderate to severe heart failure, showed that the addition of the ARB valsartan to standard therapy reduced the combined end point of all-cause mortality, hospitalizations for heart failure, cardiac arrest or resuscitation, or intravenous inotropic or vasodilator therapy by 13.3%. Furthermore, treatment with valsartan also resulted in improvement in NYHA functional class, ejection fraction, and quality of life.

However, valsartan did not decrease the mortality rate, and post hoc analysis showed

that valsartan had an adverse effect in those receiving both an ACE inhibitor and a beta-blocker.

This finding has led to the consensus that the combination of an ACE inhibitor, an ARB, and a beta-blocker should not be used because it produces too much neurohormonal blockade. It also led the Cardiorenal Advisory Board of the US Food and Drug Administration (FDA) to require a warning on valsartan packaging that, while it is approved for treatment of heart failure in patients who cannot tolerate ACE inhibitors, it should not be used in combination with both ACE inhibitors and beta-blockers.

Other studies now in progress are expected to yield more information on using a combination of these drugs and on their effect on remodeling after myocardial infarction (MI).

Beta-blockers:

A true revolution in heart failure care

Beta-blockers have revolutionized the care of patients with heart failure and represent one of the most exciting advances in the last 15 years. They reduce total mortality and slow left ventricular remodeling, improve ejection fractions by 8 to 10 units, and reduce the size of the heart. Studies of more than 10,000 patients in more than 20 placebo-controlled trials strongly support the use of carvedilol, bisoprolol, or metoprolol in nearly all patients with NYHA class II or III heart failure.

What about class IV? Although current guidelines suggest that patients with NYHA class IV failure should not receive a beta-blocker, the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study,⁹ with 2,289 patients, showed that carvedilol reduced the mortality rate by 35% compared with placebo, even in patients with severe heart failure.

The only patients in whom beta-blockers have not been studied are those with NYHA class I failure; a large trial is planned to address that group.

Which beta-blocker to use remains controversial.¹⁰ Metoprolol and carvedilol are the only ones approved for this indication, and carvedilol is thought to be ideal because it is a nonselective vasodilator with antioxidant and antiendothelin properties.

An ARB should not be added to an ACE inhibitor plus a beta-blocker

The best candidates for beta-blockers are stable with mild to moderate heart failure and optimal fluid status. It is important that the drugs be initiated at a low dose and slowly and carefully adjusted upward every 2 to 4 weeks.

■ SURGICAL AND MECHANICAL INTERVENTIONS

Beta-blockers and biventricular pacing were not part of our routine clinical armamentarium until recently. Many patients with heart failure had no options beyond cardiac transplantation. And the waiting list for cardiac transplantation is expanding, while the number of heart transplants performed in the United States has plateaued.

Experience with partial left ventriculectomy (the Batista procedure) spawned tremendous interest in new surgical procedures for the treatment of heart failure.¹¹ In addition, the recognition that wall stress and sphericity could be altered surgically and would impact future structural and biological changes generated further interest and the development of therapies. A growing body of evidence in both animals and humans indicates that surgically deployed devices can change the structure and the biology of the ventricle.

Contemporary medical therapy is highly effective and must be given before and after surgical treatments. Beta-blockers and ACE inhibitors can independently promote reverse remodeling (improved ejection fraction and reduced chamber dimensions). Also, new-onset cardiomyopathy should be effectively treated medically and the patient observed before surgical therapy is considered, as marked improvement in ventricular performance and anatomy often can occur.¹²

The goal today is to avoid or delay cardiac transplantation whenever feasible, as its limitations are well recognized. If a surgical procedure can improve quality of life and delay the need for cardiac transplantation, it should be undertaken. Patients can live many years with abnormal ventricles after surgical optimization in conjunction with contemporary medical and device therapy.

Biventricular pacing

Biventricular pacing is a good option for patients who are receiving optimal drug therapy but remain symptomatically impaired with left bundle branch block. This method, approved by the FDA in 2001, is safe and well tolerated. It also improves quality of life, functional class, exercise capacity, and structure and function of the heart.¹³

This technique is meant to correct inter-ventricular conduction delays in patients with left bundle branch block that lead to abnormal filling patterns of both ventricles. Resynchronization of the filling of both ventricles shortens the QRS duration.

The procedure consists of placing a standard pacemaker with an additional third pacemaker lead via the coronary sinus to the lateral wall of the left ventricle to control when it is activated and bring the other side of the left ventricle into synchrony.

The Cleveland Clinic has been very involved in clinical trials of this technology. The 6-month Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial¹⁴ recruited patients with advanced heart failure, a widened QRS complex, reduced ejection fraction, and cardiomegaly. Patients in this study had been receiving stable medical therapy and a beta-blocker for more than 3 months before they were randomly assigned to the therapy or the control group; this precaution ruled out any improvement due to medical therapy.

The 6-minute walk time, oxygen consumption, and total exercise time improved in patients who received biventricular pacing, as did the quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire. NYHA functional class also improved; 90% of the patients had been in class III at the beginning of the study, and 52% were reassigned to class II at the end.

Data also suggested a tendency toward reduction of the size of the left ventricle and diastolic diameter. An increase in the ejection fraction was observed, although it was not statistically significant.¹⁴

More trials are examining pairing biventricular pacing with an implantable cardiac defibrillator.

**Beta-blockers
have not yet
been tested
in class I
heart failure**



Left ventricular assist devices

Left ventricular assist devices (LVADs) achieved favorable results in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH).¹⁵ The patients, most of whom required inotropic therapy and were not candidates for cardiac transplantation, were given either a LVAD or medical therapy and followed for 2 years.

The LVAD reduced death from any cause by 48%. The survival rate at 1 year was 52% with the LVAD vs 25% with medical therapy; at 2 years, it was 23% vs 8%. This statistic translates into 270 deaths prevented per 1,000 patients; in contrast, about 70 lives per 1,000 are saved each year with ACE inhibitors or beta-blockers.

Infection and device mechanical failure were major factors in the poor 2-year survival rate. The rate of neurologic events was 4.35 times as great in the LVAD group, but 76% of patients were free of serious neurologic events without routine anticoagulation.

In November 2002, the FDA approved the use of the Thoratec HeartMate LVAD for patients with severe end-stage heart failure (NYHA class IV/ACC stage D) who are on optimized medical therapy, are not eligible for heart transplantation, and have an anticipated life expectancy of less than 2 years. The Novacor LVAD, the AbioCor total artificial heart, and the Jarvik 2000 are currently undergoing clinical trials.

Cardiac support device

The Acorn Cardiac Support Device, a mesh device sewn on the surface of the heart, has been shown in animal and human studies to provide diastolic support, reduce wall stress, and allow recovery of ventricular function, leading to higher ejection fractions and a slight reduction in the size of the heart.¹⁶ NYHA functional class improves. The device can adhere to the surface of the heart without causing fibrosis.

The Cleveland Clinic is involved in a multicenter randomized study to determine the efficacy of this device in patients with advanced heart failure that is symptomatic despite excellent medical treatment. Recruitment for this surgical trial is expected to end in early 2003.

Myosplint

The Mycor Myosplint changes the shape of the left ventricle, leading to improved ventricular function. It has been shown in animal studies to improve the structure of the heart and to reduce wall stress.¹⁷ Clinical trials of this device are under way in the United States and Europe.

Dor procedure

After an MI, regions of the heart not involved in the MI become dysfunctional due to changes in the chamber dimensions, resulting in increased wall stress. Vincent Dor, a cardiovascular surgeon, showed that removal of the "scarred" regions improved the areas of the heart that were not involved in the MI.

Endoventricular "patch plasty," also known as ventricular restoration and the Dor procedure, has been performed at The Cleveland Clinic in more than 250 patients with anterior MI and adverse remodeling. Performed during a bypass procedure, the Dor procedure consists of suturing the area between normal muscle and scar tissue to exclude the area of dysfunctional chamber (infarct exclusion surgery) where blood had been merely swirling around.¹⁸ The result is a more muscular cavity without the bulging area of scar tissue.

The Dor procedure appears to alter the natural history of readmissions for heart failure, improve functional class, and result in long-lasting improved structure of the heart. The National Institutes of Health has just approved the \$40 million Surgical Treatment for Ischemic Heart Failure (STITCH) study, which will be conducted at centers around the country and is designed to determine the added benefit of ventricular restoration vs coronary artery bypass alone.

■ KEEPING PATIENTS OUT OF THE HOSPITAL

The hospital readmission rate for patients with heart failure is dismal, with 30% to 40% of patients returning to the hospital within 90 days. Patient education and disease management programs can reduce that readmission rate and improve patients' quality of life. Studies have shown that patients who were

Mechanical and surgical treatments can improve the structure and biology of the ventricle



educated about their condition and given rapid access to a health care provider if their symptoms changed were 60% to 80% less likely to go back into the hospital.^{19–22}

In such programs, typically run by nurse clinicians, patients are instructed how to maintain fluid balance by restricting sodium, weighing themselves daily, and adjusting diuretic doses. They are also educated about the symptoms and signs of heart failure progression and the need to continue medication even when they have no symptoms. An

education program recently was started at The Cleveland Clinic; although no data have been published, initial results have been encouraging.

In conclusion, successful treatment of heart failure requires specialized expertise in diagnosis and management and a multidisciplinary approach to patient education and follow-up. Utilization of the latest heart failure guidelines results in improved quality of life and survival that was unobtainable just a few years ago.

REFERENCES

1. **The Task Force on Heart Failure of the European Society of Cardiology.** Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995; 16:741–751.
2. **Hunt SA, Baker DW, Chin MH, et al.** ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001; 38:2101–2113.
3. **Heart Failure Society of America (HFSA) practice guidelines.** HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. *J Card Fail* 1999; 5:357–382.
4. **Pitt B, Poole-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.
5. **Konstam MA, Kronenberg MW, Rousseau MF, et al.** Effects of the angiotensin-converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. *Circulation* 1993; 88:2277–2283.
6. **Sculpher MJ, Poole L, Cleland J, et al.** Low doses vs. high doses of the angiotensin-converting inhibitor lisinopril in chronic heart failure: a cost-effectiveness analysis based on the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. The ATLAS Study Group. *Eur J Heart Fail* 2000; 4:447–454.
7. **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.
8. **Cohn JN, Tognoni G.** A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345:1667–1675.
9. **Packer M, Coats AJS, Fowler MB, et al for the Carvedilol Prospective Randomized Cumulative Survival Study Group.** Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344:1651–1658.
10. **Kukin ML.** Are all β -blockers the same for heart failure? *Congest Heart Fail* 2000; 6:153–157.
11. **Starling RC, McCarthy PM, Buda T, et al.** Results of partial left ventriculectomy for dilated cardiomyopathy: hemodynamic, clinical and echocardiographic observations. *J Am Coll Cardiol* 2000; 36:2098–2103.
12. **McNamara DM, Holubkov R, Starling RC, et al.** Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation* 2001; 103:2254–2259.
13. **Cazeau S, LeClercq C, Lavergne T, et al.** Effects of multi-site biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001; 344:873–880.
14. **Abraham WT, Fisher WG, Smith AL, et al for the MIRACLE Study Group.** Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346:1845–1853.
15. **Rose EA, Gelijns AC, Moskowitz AJ, et al.** Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001; 345:1435–1443.
16. **Konertz WF, Shapland JE, Hotz H, et al.** Passive containment and reverse remodeling by a novel textile cardiac support device. *Circulation* 2001; 104(suppl 1):I-270–I-275.
17. **McCarthy PM, Takagaki M, Ochiai Y, et al.** Device-based change in left ventricular shape: a new concept for the treatment of dilated cardiomyopathy. *J Thorac Cardiovasc Surg* 2001; 122:483–490.
18. **Athanasuleas CL, Stanley AW Jr, Buckberg GD, et al.** Surgical anterior ventricular endocardial restoration (SAVER) in the dilated remodeled ventricle after anterior myocardial infarction. RESTORE group. Reconstructive Endovascular Surgery returning Torsion Original Radius Elliptical Shape to the LV. *J Am Coll Cardiol* 2001; 37:1199–1209.
19. **Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM.** A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995; 333:1190–1195.
20. **West JA, Miller NH, Parker KM, et al.** A comprehensive management system for heart failure improves clinical outcomes and reduces medical resource utilization. *Am J Cardiol* 1997; 79:58–63.
21. **Fonarow GC, Stevenson LW, Walden J, et al.** Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol* 1997; 30:725–732.
22. **Krumholz HM, Amatruda J, Smith GL, et al.** Randomized trial of an education and support intervention to prevent readmission of patients with heart failure. *J Am Coll Cardiol* 2002; 39:83–89.

ADDRESS: Randall C. Starling, MD, MPH, Department of Cardiovascular Medicine, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

Patient
education and
disease
management
can reduce
hospital
readmission
rates