Beyond Angiotensin-Converting Enzyme Inhibitors and β-Blockers: Nonpharmacologic Therapy for Chronic Heart Failure
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ABSTRACT

PURPOSE: This article reviews nonpharmacologic treatment options for patients with chronic heart failure (HF).

EPIDEMIOLOGY: HF is the fastest growing cardiovascular problem in the United States, driven both by the demographics of aging and the partial short-term successes of newer therapies for acute cardiovascular conditions.

REVIEW SUMMARY: Though there is still much room for improvement in the appropriate utilization of angiotensin-converting enzyme (ACE) inhibitors and β-blockers in patients with HF, other nonpharmacologic therapies also should be considered. Select HF patients with ejection fractions less than 35% will benefit from implantable cardioverter/defibrillators or biventricular pacemakers. The effects of exercise training currently are being studied. Surgical options for some HF patients include revascularization, valve repair, destination ventricular assist devices, and transplantation. Furthermore, new therapies such as stem cell replacement are undergoing preliminary studies.

TYPE OF AVAILABLE EVIDENCE: Randomized, placebo-controlled multicenter clinical trials; retrospective single-center and multicenter surgical outcomes studies; national registry data review; unstructured review.

GRADE OF AVAILABLE EVIDENCE: Fair to good.

CONCLUSION: Although the β-blockers and ACE inhibitors have the strongest evidence of mortality benefit for the typical HF patient, emerging data from recent clinical trials indicate that clinicians now have other options to help selected HF patients live longer and feel better. (Adv Stud Med. 2006;6(1):16-23)

Heart failure (HF) is the only major cardiovascular disease increasing in incidence and prevalence. The overall prevalence of HF in the United States is 2.3%, a percentage that rises sharply with age—from less than 1% in those under 44 years of age, to 2% to 6% in those between 55 and 74 years of age, to 10% in those older than 75 years. HF currently affects 4.9 million Americans and approximately 550 000 additional new cases of HF are diagnosed every year. Even a decade ago, the chronic disorder was thought to be the underlying reason for 12 to 15 million office visits and more than 6 million hospital-days each year. Based on a predicted doubling of the US population older than age 65 by 2030, the prevalence of HF will likely increase by 2 to 3 times over this period and the burden of disease will continue to swell.

The direct medical costs already attributable to HF are estimated at $25.3 billion per year, with about 58% of this total going toward hospitalization. The median length of stay for each
HF admission is 4.3 days and actual cost per patient per admission is likely much higher than the $5456 per discharge estimated as the average Medicare payment for HF inpatients in 1999. Clearly, the increasing costs of managing HF patients are related to the increasing rates of hospitalization, which rose from 377,000 discharges in 1979 to 970,000 in 2002.

Unfortunately, the increased spending and inpatient care for HF patients has not translated into reductions in mortality. From 1992 to 2002, deaths from HF increased by 35% (vs an overall 8% increase in deaths from any cause). In 2001, total mortality stood at 264,900 deaths per year and Framingham data show 5-year mortality in men and women with HF to be 59% and 45%, respectively. About 3 of every 4 men or women under the age of 65 with HF will die within 8 years of diagnosis. In another clear sign of the failure of current approaches to management, almost half of older adult patients hospitalized for HF are readmitted within 6 months. Clinical trials over the past 2 decades document the significantly improved care now available to patients with HF. The solid evidence of large trials has prompted implementation of guidelines for improved cardiovascular care. Despite these guidelines, the use of these agents still is not ideal. In the recent report from ADHERE (Acute Decompensated Heart Failure National Registry), which tracks patients hospitalized for HF, only 66.1% of patients thought to be eligible for an angiotensin-converting enzyme (ACE) inhibitor were discharged on one. Similarly, only 48% of the patients were on β-blockers. The Joint Commission on Accreditation of Health Care Organizations (JCAHO) has now established performance standards for HF care and a recent survey revealed that only 66% of the patients were in compliance with the ACE-inhibitor-at-discharge guidelines, with only a minor difference in compliance between academic and nonacademic hospitals. All of this serves to remind us that although the ACE inhibitors and β-blockers remain the top evidence-based choices for improving survival in most HF patients without contraindications, actual practice patterns show that there is still much room for improvement in full utilization of these 2 "standard" agents. In fact, many health systems and hospitals are developing their own quality improvement programs to set goals and encourage compliance with ACE-inhibitor and β-blocker standards.

The 1-year and 5-year mortality rates in patients with more severe HF remain very high, even in patients receiving "the standard of care" as outlined in Table 1. The OPTIME (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study was a randomized comparison of intravenous milrinone and placebo in addition to standard therapy in 951 patients admitted with an acute exacerbation of HF. The trial reflected the prevailing late-1990s view that inotropes were beneficial to improve cardiac function, improve symptoms and quality of life, and reduce the length of stay and readmissions. Unfortunately, OPTIME showed absolutely no benefit with milrinone, with exactly the same percentage of patients (35%) in either group deceased or readmitted within 60 days. There also was a trend towards an increase in mortality at 60 days with milrinone compared with placebo (10.3% and 8.9%, respectively).

The evidence for pharmacologic therapy for chronic HF was recently reviewed. But what else can clinicians do for their HF patients? This article reviews emerging evidence from major randomized trials involving nonpharmacologic HF therapies. Newer approaches are desperately needed, and this article will highlight evidence showing how it may be possible to improve survival over time.

**EXERCISE**

Exercise has been described as a near-perfect “drug” for lowering lipids, reducing blood pressure and body weight, increasing inotropism, and decreasing chronotropism. However, getting patients to commit to a regimen of exercise is even more difficult than achieving adherence to medications. But, should we really be pushing our patients with HF to exercise? Is it safe? Does it improve functional capacity or survival?

Two studies asking those questions came to different conclusions. In the first, 99 patients with stable chronic HF were randomized to exercise training (3 times/week for 8 weeks, and then 2 times/week for 1 year) or usual care and monitored for a year.

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**Table 1. Therapy Options in Heart Failure**

<table>
<thead>
<tr>
<th>To Improve Mortality</th>
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<tbody>
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<td>Angiotensin-converting enzyme inhibitors</td>
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<td>Angiotensin II inhibitors</td>
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<td>β-blockers</td>
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<td>Spironolactone (NYHA class III, IV)</td>
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<td>Implantable cardioverter-defibrillators</td>
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<table>
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<tr>
<th>To Improve Symptoms</th>
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<td>Digitalis</td>
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<td>Biventricular pacing devices</td>
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NYHA = New York Heart Association.
Exercise training was associated with lower mortality (9 deaths in trained group vs 20 in nontrained, \( P = .01 \)) as well as reduced hospitalizations (5 readmissions vs 14, \( P = .02 \)). Improvements in functional capacity, quality of life, and scintigraphically documented peak flow and thallium scores also were demonstrated. The other randomized-controlled study involved 181 patients with New York Heart Association (NYHA) functional class I to III HF.\(^{21}\) Compared with the control group, those who engaged in 3 months of supervised training and 9 months of home-based training showed significant improvements in peak oxygen uptake and arm and leg strength but no differences in cardiac function, quality of life, or mortality. To clarify the potential value of exercise training in HF patients and its safety, the National Institutes of Health (NIH) currently is sponsoring a national multicenter trial called ACTION (A CHF Trial Investigating Outcomes of Exercise Training) that will enroll patients with class II to IV HF.

**Implantable Cardioverter-Defibrillators and Cardiac Resynchronizers**

Arrhythmia-related sudden death is a common cause of mortality in patients with reduced left ventricular function. Sudden cardiac death (SCD) occurs in HF patients about 6 to 9 times more often than in the overall population\(^1\) and the incidence is 5% to 12% in those with class III to IV HF.\(^{22}\) Antiarrhythmics such as amiodarone have limited impact on reducing SCD.\(^{23}\) Recently, the MADIT-2 (Multicenter Automatic Defibrillator Implantation Trial) study was presented.\(^{24}\) The investigators studied patients with an ejection fraction (EF) <30%, an average age of 64 ± 10, who were predominantly male (84%). They found that placement of an implantable cardioverter-defibrillator (ICD) reduced the risk of mortality by 41%. Growing evidence of ICD efficacy caused placements of implantable defibrillators to increase from 46 000 in 2001 to 63 000 in 2002 and the trend continues.\(^1\)

The most recent ICD study with implications for the HF patient was SCD-HeFT (Sudden Cardiac Death - Heart Failure Trial), which compared shock-only single-lead ICDs, amiodarone, and placebo in 2521 patients with ischemic or nonischemic HF (EF <35%) of NYHA class II or III.\(^{25}\) In this study, the average patient age was 60, 24% were female, and 23% were nonwhite. This trial showed that ICDs significantly reduced all-cause mortality by 23% over a 5-year period (hazard ratio 0.77; 97.5% confidence interval, 0.62 to 0.96, \( P = .007 \)). By contrast, amiodarone had no effect on survival vs placebo (Figure 1). For the first time, the ICD survival benefit was documented in both the ischemic and nonischemic subgroups of HF patients.

Many HF patients have conduction delay that leads to dyssynchrony between the contraction of the septum and the left ventricular free wall. Biventricular pacing can coordinate left ventricular contraction and potentially improve cardiac function and quality of life.\(^{26}\) The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial of more than 453 patients with moderate to severe HF showed that a biventricular pacemaker significantly improved exercise capacity, increased EF, and reduced hospitalizations compared with a control group using unactivated pacers.\(^{27}\)

The larger and more recent COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial tested the hypothesis that a biventricular pacemaker with or without a defibrillator would reduce the risk of death and hospitalization among patients with advanced HF and conduction delays.\(^{28}\) Compared with optimal pharmacologic therapy alone, patients receiving cardiac resynchronization therapy had a significantly lower risk of death (Figure 2). The combined risk of death or hospitalization due to HF was reduced by 34% in the pacemaker group \( (P < .002) \) and by 40% in the pacemaker-defibrillator group \( (P < .001) \). This was followed by the recently presented CARE-HF (Cardiac Resynchronization - Heart Failure) trial.\(^{29}\) Eight hundred thirteen patients were randomized to medical therapy vs resynchronization. There was a 36% decrease in deaths in the resynchronization arm. Additionally, the
investigators found improvements in EF, a reduction in HF symptoms, and an improvement in quality of life. Overall, the defibrillator probably offers a greater mortality benefit to HF patients, but the biventricular pacemaker undoubtedly improves symptoms, reduces hospitalizations, and, at least in one study, prolongs survival independently of a defibrillator.

Based on results such as these, the Centers for Medicare & Medicaid Services (CMS) have approved placement of ICDs in patients with an EF of less than 35% and class II or III symptoms; if the patient has a nonischemic cardiomyopathy, he or she must have had symptoms for at least 9 months. This waiting period is recommended to identify those individuals with underlying conditions, such as myocarditis or peripartum cardiomyopathy, who may recover their left ventricular function spontaneously. The CMS indications for insertion of a biventricular pacemaker are: wide QRS (≥0.13), class II to IV HF, on optimum medical therapy, and an EF <35%.30 At this time, all patients with NYHA class II to IV HF symptoms and an EF <35% should be considered for this life-saving and symptom-improving therapy.

SURGERY

The HF patients who might benefit from surgery tend to fall into 2 groups: first, those with severe disease that is refractory to medical management and may require transplantation; and second, those with specific underlying heart ailments that can be targeted with procedures such as valve repair, revascularization, or pacemaker or defibrillator implantation. As surgical techniques improve, the guidelines for surgical approach-
including death, need for assist device, or listing for transplant) that were essentially equivalent to those seen in 293 similar patients treated medically (Figure 3). At this time, the indications to refer someone with chronic HF for mitral valve repair are unclear and referral should be considered on a case-by-case basis.

Coronary artery disease contributes to more than half of all HF cases. With improved techniques and better patient selection, surgery has become a more viable option for ischemic patients to prevent HF but the exact role of revascularization in managing HF and improving survival remains controversial. Data from the mid-1980s, for example, implied that patients with the most severe ischemia (ie, 3-vessel disease) received the greatest benefit from coronary artery bypass graft (CABG) operations in terms of long-term survival. More recently, however, data from a single cardiovascular center’s 25-year catheterization experience was reviewed to evaluate outcomes in 1391 patients with coronary artery disease, NYHA class II symptoms, and EF <40%. In this retrospective analysis, the benefit of bypass over medical therapy was apparent in HF patients regardless of the severity of coronary disease (Figure 4). To help answer this important question about the value of surgery in patients with HF, the NIH is now sponsoring an international multicenter randomized study comparing various bypass operations and left ventricular reconstructions with medical therapies alone.

In 2001, the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial compared left ventricular assist devices (LVADs) vs medical therapy in patients not eligible for heart transplantation. To be eligible for the trial patients had to have NYHA functional class IV symptoms, an EF <25%, and a peak oxygen consumption <12 mL/kg/min or be on continuous inotropic infusions of milrinone or dobutamine. Excluding factors for transplantation included age, malignancy, or other medical contraindications to transplantation such as diabetes mellitus with evidence of end organ dysfunction. The mean age was 67 and 80% were male. The use of LVADs was associated with a 48% reduction in the risk of death compared with medical therapy. Although this was quite promising, even the treated group had a high mortality, and at 1 year only 52% of the LVAD patients were living, with only 23% living at 2 years. LVADs were associated with an increased number of infections, strokes, peripheral emboli, bleeding, and prolonged hospital stays. Because of the high morbidity associated with these devices, the investigators tried to determine what group of patients most benefited from this therapy. Further analyses have shown that the patients who were dependent on inotropic drugs received most benefit from implantation of an LVAD with an improvement in survival from 24% to 49% at 1 year. The medical therapy group not receiving inotropes had no difference in survival compared with those receiving an LVAD. Based on this study, LVADs were approved by Medicare for “destination therapy” (meaning patients would go home with the device with no plans for other therapies vs LVADs as a “bridge to transplant”).

Since the publication of the REMATCH trial, LVAD devices and surgical techniques have improved. A recent study analyzing the current outcomes of patients receiving LVADs has demonstrated an improved 1-year survival of 61% in destination LVAD patients treated at high-volume centers. Although outcomes are improv-

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Figure 4. Coronary Artery Bypass Graft Surgery Improves Survival in Patients With Heart Failure and Ejection Fractions <40%: Retrospective Data (N = 1391; Catheterization 1969-1994)
ON THE HORIZON

Cell transplantation is being aggressively studied as a potential new therapy for patients with chronic HF. Various donor cell types, including skeletal myoblasts, unfractionated bone marrow cells, endothelial progenitor cells, mesenchymal stem cells, and cardiac stem cells, are being studied. Additionally, various delivery methods are being evaluated including intravenous delivery, percutaneous delivery through the left ventricle, and direct delivery via a thoracotomy. Although multiple studies are ongoing, the current results are quite preliminary. Menasche et al. implanted skeletal myoblasts into 10 patients at the time of CABG and found that the NYHA function class improved from 2.7 ± 0.2 to 1.6 ± 0.1 and the EF improved from 24% ± 1% to 32% ± 1%.

Unfortunately, this was associated with death in 1 patient and ventricular arrhythmias in 4. Smits et al. injected skeletal myoblasts percutaneously into 5 patients with HF after an anterior myocardial infarction (MI). They also found an improvement in EF of about 5%; 1 patient had ventricular tachycardia. More recently, Siminiak et al. found that 10 patients receiving percutaneous skeletal myoblasts had an improvement in EF of 3% to 8%.

One group has examined the use of delivering autologous bone marrow stem cells via intracoronary infusion after MI. In a randomized study of 60 patients, EF increased by 6.7% in the bone marrow group vs 0.7% in the control group. Of interest, they did not see an increased incidence of arrhythmias. At this time the use of stem cells is restricted to clinical trials. Although the initial reports are quite promising, this field is still in its infancy and many issues remain to be answered, including whether these cells migrate from the heart to other body areas, are tumorigenic, and/or are proarrhythmic, if the effects are long lasting, and whether the early improvements in EF translate into long-term improvements in morbidity and mortality.

CONCLUSION

β-blockers and ACE inhibitors remain the cornerstones of therapy for HF, and other drugs can help extend life or relieve symptoms in carefully selected patients. However, there is an expanding range of nonmedical options for patients with HF (Table 2), including not only revascularization, valve procedures, and transplants, but also a growing range of novel ventricular procedures and device-based procedures (eg, passive restraint devices, left ventricular reduction surgery, new LVADs, or total artificial hearts) that may have an increasingly important role in combination therapy for HF management in years to come.

Prior to undergoing peer review, this article was developed with the assistance of a staff medical writer. The named author had final approval of the article and all its contents.

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