Treating Advanced Heart Failure Is Cost Effective

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — With no medical therapy, patients with stage C and D heart failure face a 2-year mortality risk of 35%, Lee Goldberg, M.D., said at the 100th International Conference of the American Thoracic Society.

But clinicians can reduce the 2-year mortality in this population of patients by 12%-24% if they treat patients with the available medical therapies.

"The number needed to treat to save one life is four patients," said Dr. Goldberg of the heart failure/transplant program at the University of Pennsylvania Health System, Philadelphia.

"So it's extremely cost effective to treat heart failure patients. Many of the medical therapies we have are underutilized—especially in patients who are less symptomatic," Dr. Goldberg said.

He reviewed the following treatments, commonly used in patients with stage C and D heart failure:

► **Diuretics.** Although there are no clinical trial data proving their efficacy in this patient population, diuretics are the most commonly prescribed drugs for patients with advanced heart failure.

"But we know from epidemiologic data that diuretics don't change the natural history of heart failure," Dr. Goldberg said. "Morbidity and mortality after taking them doesn't change very much."

Loop diuretics are the most commonly used type, although many centers augment them with thiazide diuretics.

"I would titrate to signs and symptoms of volume overload," he advised. "Many disease management programs have action plans of sliding-scale diuretics to help patients control their volume status. It keeps them out of the hospital and keeps them safe, but it doesn't prolong their life, and it doesn't change the [heart] remodeling process."

The symptomatic benefits of diuretics occur more rapidly than those of other drugs, and diuretics are the only class of drugs that adequately control chronic fluid retention.

Adverse effects may include volume depletion and renal insufficiency. Metabolic effects may include electrolyte imbalance, hyperuricemia, and hyperglycemia.

► **ACE inhibitors.** There are "buckets of data" on the use of these agents in advanced heart failure. ACE inhibitors interfere with the renin-angiotensin system and enhance the action of kinins. "They alleviate symptoms, reduce death, and reduce hospitalizations," Dr. Goldberg said. "So they hit all three of our goals [in treating these patients]: heart remodeling, symptoms, and mortality."

These drugs are typically given to all patients with systolic dysfunction. "A lot of people believe they should also be used in diastolic dysfunction, but we don't have good data for that yet," he said.

Adverse effects may include hypotension, azotemia, hyperkalemia, cough, and angioedema.

Unanswered questions include the issue of whether there is a class effect. "The answer is probably yes," he said. Also, it is not known whether there is a significant interaction with aspirin. "Most of us are comfortable using both aspirin and ACE inhibitors," said Dr. Goldberg, also of the University of Pennsylvania.

► **β-Blockers.** These drugs inhibit the adverse effects of the sympathetic system, and they delay and reverse heart remodeling. "The No. 1 way to increase the ejection fraction in patients with heart failure is to actually put them on a β-blocker," Dr. Goldberg said.

β-Blockers are currently given to all patients with systolic heart failure in the absence of fluid overload. Adverse effects may include hypotension, bradycardia, and worsening heart failure.

The ideal target dose for β-blockers has not been determined. This is one remaining question about this class of drugs. "There is probably not a class effect," he said. "It appears that the long-acting β-blockers and nonselective β-blockers may have an advantage over the shorter-acting and selective ones."

Many medical therapies are underutilized, especially in patients who are less symptomatic.

DR. GOLDBERG

► **Angiotensin II–receptor blockers.** These drugs block the effect of angiotensin II at the receptor site. They delay heart remodeling and reduce symptoms, and they have been shown to reduce hospitalizations and deaths. ARBs are currently given to patients who can't tolerate ACE inhibitors—specifically, the side effects of angioedema and cough.

The Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial showed some improvement in the efficacy of ARBs when used with ACE inhibitors. However, patients in Val-HeFT who took ARBs with an ACE inhibitor and a β-blocker had worse outcomes. This association was not found in CHARM.

Adverse effects may include hypotension, azotemia, hyperkalemia, and cough.

► **Digoxin.** This drug has no impact on mortality, but it does appear to improve symptoms. Dr. Goldberg cautioned that digoxin carries a high risk of renal insufficiency and an increased risk of drug interactions.

He recommends using the lowest possible dose of the drug and maintaining drug levels below 1.0 ng/mL.

A recent study of heart failure patients found that digoxin had no effect on quality of life, compared with placebo, in terms of perceived health, functioning, depression, anxiety, anger, and the 6-minute walk test (J. Card. Fail. 2003;9:4-12).

► **Aldosterone antagonists.** Trials of these agents show improved mortality for class IIIB or class IV patients, but not in heart failure patients with less severe disease, Dr. Goldberg said.

The role of these drugs with β-blockers is not well defined, and they are contraindicated if patients are on both an ACE inhibitor and an ARB due to a risk of hyperkalemia.

► **Nitrates.** The Vasodilator-Heart Failure Trial (V-HeFT) demonstrated that nitrates in combination with hydralazine are not as effective as ACE inhibitors, yet they are better than placebo.

The African-American Heart Failure Trial (A-HeFT) showed that nitrates and hydralazine improved mortality when used with ACE inhibitors and β-blockers, but their value when added to traditional therapy is unknown in other racial groups. ■

Cardiac Resynchronization Cuts Mortality in Heart Failure

BY MITCHEL L. ZOLER
Philadelphia Bureau

ORLANDO — Cardiac resynchronization therapy was, for the first time, proved to cut mortality in patients with severe heart failure in a controlled study with 813 patients.

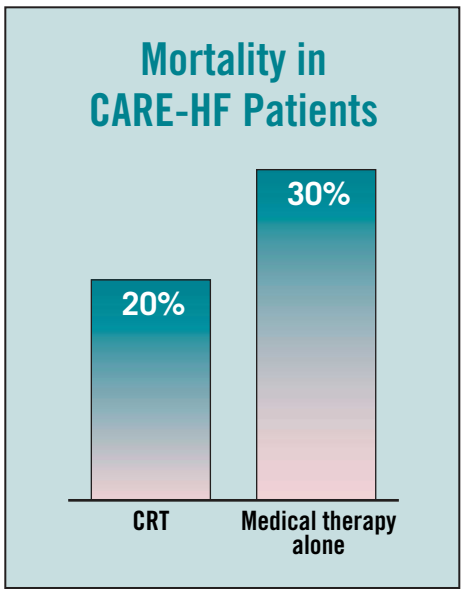
With an average follow-up of almost 2.5 years, the results of the Cardiac Resynchronisation Heart Failure Study (CARE-HF) also substantially extended the period that cardiac resynchronization therapy (CRT) has been shown to benefit patients. And the results showed that CRT devices produce a marked improvement in serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of left ventricular dysfunction.

"About 15%-20% of patients returned to normal or near-normal cardiac function," John G.F. Cleland, M.D., reported at the annual meeting of the American College of Cardiology.

But the study left unanswered a major, lingering question about using CRT devices for treating heart failure: Do patients get incremental benefit from a combined CRT-defibrillator device, or is a CRT-pacemaker device enough? All of the CRT devices used in the new study had pacemaker function only.

"In some patients, a CRT-defibrillator is indicated, because they're at high risk for sudden death, but for many patients a CRT alone is the preferred choice because defibrillators can add a mortality risk," said Dr. Cleland, chairman of the department of cardiology at Castle Hill Hospital in Kingston-upon-Hull, England.

The CARE-HF trial enrolled patients with New York Heart Association (NYHA) class III or IV heart failure, a left ventricular ejection fraction of 35% or less, a left ventricular end-diastolic dimension of at least 30 mm, and a QRS interval of at least 120 msec. Patients with a QRS interval of less than 150 msec also had to meet at least two of three more criteria of cardiac dyssynchrony.



The study was done at 82 European centers and was funded by Medtronic Inc., the company that makes the devices used in the study. Dr. Cleland has been a consultant to and a speaker for Medtronic.

About 38% of patients had ischemic heart disease, about 45% had dilated cardiomyopathy, and the remainder had other causes of heart disease. About 95% of patients were treated with an ACE inhibitor or angiotensin receptor blocker, about 72% were treated with a β-blocker, and about 55% were treated with spironolactone. Patients were randomized to treatment with optimized medical therapy only, or medical therapy plus implantation of a CRT pacemaker device. The primary end point of the study was combined rate of death from any cause, or an unplanned hospitalization for a major cardiovascular event.

After an average follow-up of 29 months, the primary end point occurred in 39% of patients who received CRT devices, compared with 55% of patients treated with medical therapy only, a statistically significant difference, reported Dr. Cleland. (Results were published concurrent with his presentation at http://content.nejm.org/cgi/reprint/NEJMoa050496.pdf.)

Death occurred in 20% of patients in the CRT group and 30% of patients treated with drugs only, also a statistically significant difference. Sudden death occurred in 38 of 120 patients who died in the medical therapy group, and in 29 of the 82 patients who died in the CRT group.

After 18 months of treatment, 31% of patients in the CRT group had NYHA class I heart failure, 45% had class II heart failure, and 24% continued to have class III or IV heart failure. In the medical therapy group, 13% improved to NYHA class I heart failure, 37% had class II disease, and 50% continued to have class III or IV disease. ■