VA PRACTICE Matters

February, 2004 VOL. 9 ISSUE 1

Treating Chronic Heart Failure

- *Approximately 5 million American adults are affected by chronic heart failure (CHF), with 550,000 new cases occurring each year.*
- *Prevalence approaches 10% of the population older than age 75.*
- *CHF is the most common cause for hospitalization within the Medicare population.*
- *After hospitalization for CHF, 40% of the patients are readmitted within 3 months.*
- *Annual health care costs exceed $24 billion, with the majority spent on hospitalizations.*
- *Within the VA health care system, in 2001 there were more than 311,000 veteran patients with a diagnosis of CHF, and more than 110,000 hospitalizations.*
- *In FY 2002, VA costs for CHF care were estimated at $2.4 billion.*

MDRC
MANAGEMENT DECISION AND RESEARCH CENTER
VA HSR&D
Health Services Research & Development Service

A publication of the Management Decision and Research Center
A program within the Department of Veterans Affairs Health Services Research and Development Service

BACKGROUND

Chronic heart failure (CHF) is a highly prevalent and costly disease, especially in the elderly – 1 in every 10 elderly persons has this condition.[1] Almost one-half of CHF patients are readmitted to the hospital within six months of discharge, and approximately two-thirds of veterans with CHF die within five years of their initial hospitalization. Hospital and health care resource use associated with CHF is high, with heavy utilization of both inpatient and outpatient services.

While CHF can be cured only rarely, the goal is to maintain the quality of life and independent living, and to improve life expectancy. Approaches to the CHF patient should include disease counseling and education, dietary and exercise recommendations, and a wide range of pharmacological treatment options.

Diagnosis

Common presentations of patients with CHF include: shortness of breath, decreased exercise tolerance, fatigue, and fluid retention. However, many patients have asymptomatic left ventricular dysfunction (LVD) and are diagnosed only incidentally.

Initial evaluation in patients suspected of having heart failure should include an in-depth history and physical exam. A detailed history is critical for determining the precipitating factor(s) leading to decompensation (e.g., medication or dietary non-adherence, use of concomitant medications, etc.). The physical exam should focus on the assessment of fluid status, including serial weights, evaluation of jugular venous pressure (JVP), checking for peripheral edema, and listening to the lungs and heart for the presence of rales and an S3 gallop, respectively, as well as cardiac murmurs that might indicate valvular abnormalities. Physical findings help not only in diagnosis, but may also aid in prognosis.[2]

A two dimensional echocardiogram, using Doppler flow studies, is useful in determining the presence of structural disease while assessing the extent of LVD, and potentially delineating the etiology, such as valvular disease or coronary artery disease (CAD). It should be emphasized, however, that an echocardiogram is predominantly useful for assessing left ventricular function that can add to the probability of a patient's symptoms being attributed to heart failure, but LVD and normal left ventricular function can both be present with and without symptoms of heart failure. Thus, the diagnosis of CHF remains a clinical entity based on symptoms and the physical exam.

The New York Heart Association (NYHA) functional classification system has withstood the test of time as a simple but effective system to provide important prognostic information and to aid the clinician in determining appropriate therapy. According to the NYHA system, Class I patients are those with impaired LV function, but who have no limitation with ordinary physical activity. Class II patients have slight limitation of physical activity. Those with Class III symptoms are comfortable at rest but have symptoms with less than ordinary activity, and Class IV patients are unable to participate in any physical activity without symptoms.

In addition, a blood test for B-type natriuretic peptide (BNP) is emerging as an important marker for diagnosis of heart failure in some patients and clinical settings. The sensitivity and specificity are both > 90%.[3] Further, BNP correlates with the extent and prognosis of CHF.

CHF CLASSIFICATIONS AND TREATMENT

The importance of patient self-management cannot be overstated. Appropriate dietary counseling should be given with particular emphasis on sodium restriction. Patients should be advised to follow a moderate exercise regimen, consisting of walking for at least 20-30 minutes for a minimum of three times per week, and advanced as tolerated. Daily weight measurement can aid in detecting early signs of fluid accumulation and may guide in flexible diuretic dosing. Finally, the importance of maximizing adherence to medical therapy to avoid hospitalization should be emphasized.

The new classification for CHF underscores the progressive nature of the disease, and emphasizes opportunities for early intervention and prevention. This new approach to CHF has been incorporated in guidelines published jointly by the American College of Cardiology and the American Heart Association.[6] Four stages of heart failure have been defined – Stages A through D.

Stage A

Patients at this ("pre-CHF") stage have risk factors associated with the development of CHF but do not have any identifiable structural or functional cardiac abnormalities. The goal of treatment for stage A patients is the prevention of structural changes in the heart by identifying and aggressively treating patients at risk of developing overt heart failure. This includes treating hypertension, CAD, and diabetes. Studies have demonstrated that the incidence of CHF can be reduced by half with *effective treatment of hypertension*.[7] Other recommendations include the treatment of lipid disorders, and avoidance of habits that may increase the risk of CHF such as – smoking, excessive alcohol consumption, and illicit drug use.

Angiotensin converting enzyme (ACE) inhibitors decrease morbidity and mortality in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension and associated cardiovascular risk factors.

Stage B

Patients who demonstrate LVD in the absence of symptoms are considered to be in Stage B (NYHA Class I), which also includes patients with a history of myocardial infarction. Such patients are at high risk of developing symptomatic CHF. The goal of therapy in Stage B is to reduce the risk of additional injury and to prevent the progression of LVD.

ACE inhibitors are considered the standard of care in patients with LVD, whether or not they have experienced a myocardial infarction, and in patients with or without LVD who have a recent or remote history of myocardial infarction. Use of ACE inhibitors in this stage of CHF reduces the frequency of hospitalization.[8] Beta-blockers, which are used for angina, arrhythmias, and hypertension, also reduce mortality in patients with a history of myocardial infarction. Valve replacement or repair for patients who have significant valvular disease is also highly recommended.[6]

Stage C

Stage C patients have LVD and current or previous symptoms (NYHA Class II-III). These patients should be treated with all therapies listed in Stage A and B, including ACE inhibitors, beta-blockers, and treatment of risk factors. In the Studies of Left Ventricular Dysfunction (SOLVD) and other similar trials with symptomatic CHF, ACE inhibitors conferred a 20-25% reduction in mortality.[8] Three large beta-blocker trials, enrolling approximately 10,000 patients with CHF, showed a 35% survival benefit in patients with CHF Stages C and D.[9-11] Close follow-up is needed to guide specific therapy, such as the use of diuretic medications in patients with signs of fluid retention.

While digitalis does not increase survival rates, it does lead to improvement in symptoms and a reduction in hospitalization, and continues to be useful, especially in more symptomatic CHF patients. Spironolactone is recommended for patients with advanced symptoms, preserved renal function, and normal potassium.

Exercise training and angiotensin receptor blockers (ARB's) may be helpful for patients in Stage C who do not tolerate ACE inhibitors, but this has not been proven unequivocally.[6, 12-14]

Stage D

These patients have advanced structural heart disease and remain symptomatic at rest, despite optimal medical therapy (NYHA Class IV). All recommendations for heart failure therapy for previous stages also apply to Stage D. Patients developing end-stage and refractory heart failure should have careful follow-up, with particular

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attention to the management of fluid retention. Referral to a heart failure program with expertise in the management of refractory heart failure can also help patients at this stage. All efforts should be attempted to correct reversible causes of heart failure, such as revascularization in patients with signs of ischemia, or performing valvular repair or replacement. Referral for cardiac transplantation and implantation of devices in eligible patients should be made (see below).

Improving Treatment

Despite substantial evidence of excellent pharmacologic benefit to prevent and treat heart failure, as well as agents that reduce mortality in patients with symptoms, the under-utilization of appropriate therapy remains surprisingly large. Surveys show ACE inhibitors are used in only slightly more than 50% of patients, and beta-blockers in only about 35% of patients. Thus, there is a great need for:

- improved education,
- easier access and referral to specialists, and
- establishment of specialized heart failure programs.

When patients are treated under these programs, studies show marked improvement in the use of appropriate medications, quality of life, and survival.

While ACE inhibitors and beta blockers have emerged as standards of care for patients with CHF due to potent effects on mortality, hospitalizations, and symptoms, studies suggest that these agents are still widely under-utilized. However, mortality for CHF patients remains over 7-8% annually even with optimal treatment, so studies to evaluate newer approaches for treating CHF are needed and continue.

New Drug Therapies

Angiotensin Receptor Blockade

While ACE inhibitors block the conversion of angiotensin I to angiotensin II, other "ACE-independent" pathways can still lead to the production of angiotensin II. Angiotensin-receptor blockers (ARBs) block the actions of angiotensin II at the level of the receptor, regardless of the path by which angiotensin II is produced. The Evaluation of Losartan in the Elderly (*ELITE-II*) Trial compared the effects of an ACE inhibitor (enalapril) with an ARB (losartan), and the ACE inhibitor was marginally superior to the ARB in this study.[1,5]

Val-HeFT

A slightly different approach was taken in the Valsartan in CHF Trial (Val-HeFT), in which 5,010 patients with CHF were randomized to conventional therapy (ACE inhibitor, digoxin, diuretics), or conventional therapy plus the ARB valsartan.[16] While valsartan did not alter mortality, the risk of hospitalization for CHF was decreased compared to placebo. The benefits were not seen in patients also taking a beta-blocker. In the small group of patients not taking ACE inhibitors, valsartan decreased mortality.

CHARM

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study examined the use of the ARB candesartan in 7,601 patients with CHF. This study had three distinct "arms." CHARM-Alternative, which enrolled patients intolerant to ACE inhibitors, confirmed findings from Val-HeFT that ARB's reduce morbidity and mortality in patients intolerant to ACE inhibitors, with good tolerability. CHARM "Added" examined the use of candesartan in patients already taking an ACE inhibitor and, in contrast to Val-HeFT, found that the ARB further reduced morbidity and mortality. The "Preserved" arm studied patients with CHF with ejection fractions (EF) > 40%, and found no reduction in mortality, but a beneficial effect of the ARB on CHF hospitalization of borderline statistical significance. Current guidelines recommend ARBs in patients who cannot tolerate ACE inhibitors, but the CHARM results suggested added benefits of candesartan in CHF patients whether or not they were taking either ACE inhibitors or beta-blockers, regardless of EF.

Aldosterone Inhibition

One of the mechanisms for the toxic effects of sustained renin angiotensin aldosterone system activation is through the increased production of

aldosterone. Elevated aldosterone levels have several adverse consequences in patients with CHF.[17, 18] Given this background, aldosterone antagonists have been evaluated in CHF patients.

RALES

In the Randomized Aldactone Evaluation Study (RALES) 1,663 patients with current or recent advanced CHF were randomized to receive conventional therapy (ACE inhibitors, loop diuretics, digoxin and in some cases beta-blockers), or conventional therapy plus low dose spironolactone, an aldosterone antagonist. Low dose spironolactone was associated with a 30% reduction in the risk of death and a 35% reduction in hospitalization for worsening CHF compared to placebo. Because spironolactone use may lead to hyperkalemia, it is not recommended in patients with hyperkalemia or significant renal insufficiency. After beginning at a dose of 12.5 - 25 mg daily, serum potassium should be checked at one week and at one month after the initiation of therapy. This is recommended in patients with current or recent NYHA Class IV patients.

EPHESUS

Spironolactone often has unwanted progestational and antiandrogenic side effects that may limit its chronic use. Newer mineralocorticoid receptor antagonists (e.g., eplerenone) have been developed for more selective aldosterone antagonism resulting in a much lower incidence of the sex hormone related side effects.[19,20] The recently completed Eplerenone Post-AMI CHF Efficacy and Survival Study (EPHESUS) compared the effect of eplerenone (25-50 mg daily) plus standard therapy to placebo plus standard therapy (including ACEIs and beta-blockers) in 6,632 patients with recent acute myocardial infarction, depressed left ventricular systolic function, and CHF or diabetes.[21] Eplerenone reduced mortality by 15%.

Thus the role of aldosterone antagonists has been established in patients with advanced CHF, as well as in post myocardial infarction patients with left ventricular systolic dysfunction. No data are available currently that demonstrates benefit of these agents in patients with moderately severe CHF.

Alternatives to Pharmacologic Approaches

Even good pharmacotherapy for patients with CHF does not normalize life expectancy, and significant numbers of patients continue to have sub-optimal quality of life. Therefore, alternatives to pharmacologic approaches have been tested over the past few years.

Implantable Cardiodefibrillators (ICD's)

Between 40-60% of patients with CHF die suddenly, most often from tachyarrhythmias (disturbance in heart rhythm resulting in rapid heart beat). While beta-blockers reduce mortality from sudden death, they do not eliminate the risk entirely. Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)[22] studied the effect of implantable cardiodefibrillators (ICD's) on the primary prevention of mortality in 1,232 patients with a prior myocardial infarction and a left ventricular ejection fraction of $\leq$30% (70% of the patients were receiving an ACE inhibitor, BB, or both). The ICD group showed a 31% reduction in all-cause mortality compared to controls. While the investigators stated that the effect was consistent regardless of the QRS interval, the data suggested that the effect was greatest in those patients with the widest QRS intervals, leading the Centers for Medicare and Medicaid Services (CMS) to approve coverage for ICDs in patients meeting this more stringent criteria, i.e., QRS > 120msec. Representatives from major cardiology organizations have hotly contested this decision.

Biventricular Pacing in CHF (BiV)

Patients with advanced CHF often have enlarged hearts, slowed electrical activation, and ventricles that do not contract in a synchronized manner. Approximately 30% have intra-ventricular conduction defects of varying severity. Biventricular pacing (BiV), or resynchronization therapy, attempts to improve the pattern of LV activation, normalize the delay between atrial and ventricular systole, and improve mechanical efficiency of the failing heart.

Small, short-term trials targeted advanced CHF

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CLINICAL OPINION

Over the past two decades, remarkable advances have occurred in the management of chronic heart failure (CHF). Several warrant highlighting.

- *1983:* First multi-center controlled trial demonstrating efficacy of an ACE inhibitor
- *1986:* V-HeFT—first demonstration of improved survival in CHF
- *1987:* CONSENSUS—first demonstration of survival benefit from ACE inhibitor,
- *1995:* First large controlled trial of a heart failure management program published
- *1996:* First multi-center trial demonstrating improved survival with beta-blockers,
- *1999:* RALES—first demonstration of survival benefit with aldosterone blockade
- *2001-2003:* Evolving evidence of reduced morbidity and mortality with devices (cardiac resynchronization, left ventricular assist devices, and implantable cardiodefibrillators)

Outcomes of CHF patients are improving. Annual mortality rates of mild to moderate CHF patients in trials have declined from 15-20% to 7%. Improvements are also apparent in epidemiological and cohort studies. However, this is not a time for complacency. As statistics illustrate, mortality, morbidity, and health care resource utilization remain unacceptably high. I would like to emphasize three specific challenges that must be addressed successfully if we are to reduce the burden of CHF.

First, the discrepancies between *what can be achieved* and *what occurs in practice* must be reduced. This is the goal of VA's Quality Enhancement Research Initiative (QUERI). QUERI's mission is to facilitate the systematic implementation of clinical research findings and evidence-based recommendations into routine clinical practice. Thus for CHF-QUERI – one of eight condition-specific QUERI groups – the first step is to ensure that all appropriate patients receive ACE inhibitors, beta-blockers, and aldosterone antagonists, as well as appropriate management of volume status. While provider education remains a cornerstone of changing practice, it is clearly not sufficient. Promising approaches include greater

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KEY RECOMMENDATIONS

- Treatment for CHF should include disease counseling and education, dietary and exercise recommendations, and a wide range of pharmacological treatment options.
- CHF patients should be administered angiotensin converting enzyme (ACE) inhibitors at appropriate doses.
- Patients intolerant of ACE inhibitors should receive an angiotensin receptor blocker (ARB).
- CHF patients should be prescribed a beta-blocker, shown in clinical trials to be effective at appropriate doses
- Patients with advanced CHF, and those with HF following a myocardial infarction (MI) should receive an aldosterone antagonist.
- ARB's should be strongly considered for patients who remain symptomatic or who have been hospitalized.
- Bi-ventricular pacing should be reserved for those patients with LBBB who remain symptomatic despite optimal medical therapy.
- Implantable cardiodefibrillators (ICDs) should be strongly considered in patients with a history of MI and low ejection fraction.

ACKNOWLEDGEMENTS

This issue of *VA Practice Matters* on *Treating Chronic Heart Failure* was written by Mark Dunlap, MD, Clinical Coordinator for the Chronic Heart Failure Quality Enhancement Research Initiative (CHF QUERI); Rebecca Beyth, MD, Research Coordinator for CHF QUERI; Anita Deswal, MD, Member of the CHF QUERI Executive Committee and Cardiologist at the VAMC in Houston, TX; Barbara Kimmel, MS, MSc, Administrative Coordinator and Acting Implementation Research Coordinator for CHF QUERI; Barry Massie, MD, Director of the Coronary Care Unit and Director of the Heart Failure and Hypertension Unit at the VAMC in San Francisco, CA; and Jahandar Saleh, MD, Research Fellow in the Department of Cardiology at UCLA/VA Greater Los Angeles Health Care System. Robert L. Jesse, MD, National Program Director for Cardiology, Richmond, VAMC, and John G. Demakis, MD, Director of HSR&D, reviewed the issue and provided comments. This issue was edited by Geraldine McGlynn, MEd, and Diane Hanks, MA, with HSR&D's Information Dissemination Program.

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patients with EF of <20% and LBBB (left bundle branch block). These trials mostly showed improvements in the magnitude and synchrony of contraction. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, more than 400 patients were randomized to either BiV pacing or placebo pacing (i.e. implant with no pacing).[23] Patients with moderate to severe CHF were enrolled with EF ≤ 35%, QRS duration ≥ 130 msec, and on medical therapy optimized by the investigator. More than 90% of patients were receiving an ACE inhibitor, though < 60% were taking beta-blockers. The BiV group showed improvements in exercise tolerance, quality of life, and degree of CHF, as well as reductions in hospitalizations and length of stay at six months. Based primarily on these data, the FDA has recently approved BiV for adjunctive treatment of patients with moderate to severe CHF, who, in spite of medical therapy, remain symptomatic and have dysynchrony.

The recently completed Comparison of Medical Therapy, Pacing and Defibillation in Heart Failure (COMPANION) trial studied the use of BiV compared to combined BiV and ICD to optimal medical therapy in patients with moderate to severe CHF (EF < 35%, and QRS interval of > 120 ms).[24] In this non-blinded trial, the results pointed to a mortality benefit in the combined BiV and ICD group, with a reduction in hospitalizations from BiV alone.

Devices—summary

Since not all patients with current criteria for BiV improve following implantation of the device, an important dilemma is identifying patients who would benefit the most from BiV, in addition to aggressive medical therapy with ACE inhibitors and beta-blockers. Additionally, complications, sometimes serious, can occur with the specialized lead placement required. At this time, selection criteria for these patients needs to be better defined. Referral to a Cardiologist is indicated for patients who might be candidates, including CHF with continued Class III or IV symptoms, especially in patients with a wide QRS complex. ICD's are indicated in CHF patients with a high risk of sudden death, including ischemic cardiomyopathy and EF ≤ 35%, especially with a wide QRS complex. These indications may change with publication of new studies, some of which are anticipated this year.

Clinical Opinion Continued from page 6

involvement of specialists even at early stages of the process, use of multidisciplinary interventions, and facilitating patient self-care.

Second, in the face of an increasing number of potentially effective interventions (e.g. new medications, devices, etc.) we must determine which ones offer optimal management in which potential candidates, and at what cost and benefit. And third, we must address a glaring gap in our knowledge. For example, approximately 40% of CHF patients who have preserved systolic function, which includes the majority of women and those over age 75, there are no proven effective therapies.

Great strides have been made in the management of heart failure. Now is the moment to address the difficult challenge of translating these advances into better care and outcomes for our patients.

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