From Hypertension to Heart Failure: Update on the Management of Systolic and Diastolic Dysfunction

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The aging of the population of the United States (US) will bring with it higher numbers of patients with coronary heart disease and heart failure (HF). Because HF already imposes severe economic and medical burdens on our health care system, it is imperative to optimize primary and secondary prevention of cardiovascular (CV) disease.

In most cases, HF develops as a result of either long-standing hypertension or a myocardial infarction (MI). Other than cardiac death, HF represents the last stage in the progression of CV disease, which begins with CV risk factors such as hypertension, dyslipidemia, obesity, and smoking. These risk factors lead to the development of left ventricular (LV) hypertrophy or an MI (or both), which lead to LV dysfunction and, finally, to HF. The prognosis of HF is poor, the 5-year survival rate being approximately 25%. Heart failure may be due to either LV systolic or diastolic dysfunction, the latter having a normal ejection fraction.

Because CV disease is progressive, interventions are possible at all stages along the CV continuum. β-Blockers (βB) are recommended agents at several stages of CV disease. Large-scale trials have shown that βB significantly reduce risks for morbidity and mortality in patients with HF. Ongoing studies should help to clarify further the optimal cardioprotective therapies in patients with HF. Am J Hypertens 2003;16:18S–22S © 2003 American Journal of Hypertension, Ltd.

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years of age, for example, found that LV function was normal in 63% of the 269 participants with HF. Although the mortality risk was lower among the HF patients with normal LV systolic function, there was a higher number of absolute deaths among them because of the higher prevalence, compared to subjects with HF and impaired LV systolic function.6

Implications for Treatment

Left ventricular remodeling is a key mechanism in the progression of systolic and diastolic dysfunction.7 Reversal of LV remodeling, with a return to more normal ventricular dimensions, has been seen as a result of therapy with angiotensin-converting enzyme (ACE) inhibitors, β-blockers (BB), and cardiac resynchronization.7 The ability to reverse LVH in HF patients is an important surrogate endpoint, indicating the potential usefulness of antihypertensive or cardioprotective therapy.

Primary and secondary prevention of CV disease cannot be achieved through antihypertensive therapy alone, however, but must also encompass treatment of other common CV risk factors. One study in 2489 men and 2856 women found, for example, that about 28% of CHD events in men and 29% in women were attributable to blood pressure levels of ≥130/85 mm Hg after adjustment for other factors.8 This analysis also showed that 27% of CHD events in men and 34% in women were attributable after adjustment to an elevated total cholesterol level (ie, ≥200 mg/dL).

Evaluating Heart Failure

In clinical practice, the functional status of patients with HF is most commonly assessed using the New York Heart Association (NYHA) classification,9 based on the degree of physical activity needed to elicit HF symptoms:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
- Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea.
- Class IV: Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

A new classification of HF was developed to emphasize the progression of the disease and the role of neurohormonal activation in the pathogenesis of LV remodeling10 (Table 3). Diminished arterial or peripheral perfusion in HF triggers activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS).11 Chronic activation of these compensatory neurohormonal responses over time contribute to the progression of HF. β-Blockers, which suppress SNS activation,
and ACE inhibitors, which inhibit RAAS activity, are highly beneficial at each stage of HF\textsuperscript{10} (Fig. 2).

### \( \beta \)-Blockers in Heart Failure

The primary aims of HF therapy are to improve symptoms and to prolong life by slowing disease progression.\textsuperscript{12} Chronic use of \( \beta \)B in patients with HF has been shown in several large-scale studies to improve signs and symptoms of HF and to reduce mortality. The first evidence of the beneficial effects of \( \beta \)-blockade on survival in patients with HF came from a pooled analysis from four separate placebo-controlled trials involving a total of 1094 subjects with mild, moderate, or severe HF (EF \( \leq 35\% \)). In this pooled analysis, the \( \beta \)B carvedilol demonstrated significant reductions in the risk of all-cause mortality and of CV hospitalizations as compared with placebo.\textsuperscript{13}

To investigate further the impact of \( \beta \)B on survival in patients with HF, the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) was conducted in 2647 patients with NYHA Class III or IV HF (LV EF \( \leq 35\% \)) who were receiving standard therapy with diuretics and ACE inhibitors.\textsuperscript{14} Subjects were randomly assigned to the \( \beta \)B bisoprolol 1.25 mg (\( n = 1327 \)) or placebo (\( n = 1320 \)) once daily, with drug treatment progressively increased to a maximum of 10 mg/day. Mean follow-up was 1.3 years, and the primary endpoint was all-cause mortality. Secondary endpoints included all-cause hospitalizations, CV mortality or CV hospitalizations, and premature withdrawals from treatment. After a mean follow-up of 1.3 years, the \( \beta \)B bisoprolol was associated with a 34\% risk reduction for all-cause mortality as compared with placebo (\( P < \) .0001).

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study evaluated the effect of \( \beta \)B on survival in 2287 patients with severe HF who were clinically euvolemic, had an EF of <25\% and were receiving standard HF therapy with diuretics and ACE inhibitors.\textsuperscript{15} In this double-blind trial, subjects were randomized either to carvedilol 3.125 mg twice daily (titrated up to 25 mg twice daily, \( n = 1156 \)) or to placebo (\( n = 1133 \)), with mean follow-up of 10.4 weeks. The \( \beta \)B carvedilol reduced the risk of death by 35\% (\( P = .0014 \)) (Fig. 3), and the combined risk of death or hospitalization by 24\% (\( P < .001 \)) as compared with placebo.

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) was conducted to investigate whether the \( \beta \)B extended-release (ER) metoprolol succinate would improve survival in patients with HF.\textsuperscript{16} The MERIT-HF enrolled 3991 patients with NYHA Class II to Class IV HF, who had an EF of \( \leq 40\% \) and were receiving standard therapy with diuretics and ACE inhibitors. In this double-blind study, subjects were randomized to either ER metoprolol succinate 12.5 mg (titrated up to 200 mg once daily, \( n = 1990 \)), or to placebo (\( n = 2001 \)). The co-primary endpoints were all-cause mortality, and death or hospitalization for any reason. The study was stopped early because of a significant reduction in mortality. Therapy with ER metoprolol succinate achieved a 34\% reduction in all-cause mortality as compared with placebo (\( P = .0006 \)) (Fig. 4).

A post hoc analysis investigating results by mode of
death found that the leading cause of mortality was sudden death, and that treatment with ER metoprolol succinate reduced the risk of sudden death by 41% (P = .0002). Additional subgroup analyses of MERIT-HF found that ER metoprolol succinate therapy achieved similar risk reductions in all-cause mortality and all-cause hospitalization in diabetic and nondiabetic patients, in the <65-year-old and ≥65-year-old age groups, and in both men and women. Furthermore, in the subgroup of patients with severe HF (NYHA Class III/IV) and EF of <25% (n = 795), treatment with ER metoprolol succinate significantly reduced all mortality endpoints, including a 39% risk reduction in total mortality (P = .009) (Fig. 5).

Heart Failure With Preserved Systolic Function

Although the management of HF in patients with poor systolic function has been well studied, the optimal therapeutic strategies for diastolic HF are less well known. Theoretical treatments, based on our knowledge of the complex pathophysiology of this condition, include relieving volume overload with diuretics, reducing heart rate with βB, and general control of hypertension. The ongoing Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program is being conducted to evaluate the effects of the angiotensin II receptor blocker candesartan as compared with placebo, in a broad spectrum of HF patients, including those with a normal EF. Results are expected later this year.

Conclusions

Heart failure is a major public health problem. It may develop either as a result of long-standing hypertension or of cardiac damage resulting from an acute MI. Risk factors for developing HF should be identified and treated even before patients show any evidence of structural heart disease. Left ventricular function should be evaluated in all patients with HF to detect those with systolic dysfunction. Patients with evidence of fluid retention should receive diuretic therapy until euvolemia is achieved. Angiotensin-converting enzyme inhibitors and BB are recommended at all stages of HF to reduce the risk of morbidity and mortality. Ongoing studies will further illuminate potential therapies in HF patients with preserved systolic function.

References


