Heart failure (HF) remains a dynamic field. Treatment continues to be refined and improved and, at last, there is evidence that the increased survival demonstrated in randomized clinical trial cohorts has been translated to the unselected general population. Beyond angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, two more classes of drug, the angiotensin receptor blockers and aldosterone antagonists, were unequivocally demonstrated to have a survival benefit during 2003. This year also establishes a new era in device therapies, which also improve outcomes in patients with HF.

IMPROVING CLINICAL OUTCOMES IN HF

In a population-based study, Blackledge et al. (1) reported improving 30-day and 1-year survival after a first admission to hospital with HF in the English county of Leicestershire over the period 1993 to 2001. Postdischarge cardiovascular mortality fell by over 50%. Also of note, hospital admission rates increased from 1993 to 1998 but plateaued thereafter. These encouraging findings with respect to survival, first admissions, and readmissions mirror prior observations from Scotland, the Netherlands, the U.S. (Framingham, Massachusetts, and Northeast Ohio), and, more recently, Sweden and Canada (Ontario) (2–7). These consistent trends (Figs. 1 and 2) have been interpreted to reflect the population impact of the incremental survival and other benefits of ACE inhibitors, spironolactone, and beta-blockers. Indeed, the improvements in outcomes noted in these observational studies temporally correlate with the widespread uptake of ACE inhibitors and, to a lesser extent, spironolactone; it is only in the most recent studies that beta-blockers could have begun to have had an effect. It will be of interest to see if these findings can be replicated in additional countries and whether the trends identified continue as the full effect of beta-blockade becomes apparent.

HF WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

An encouraging development that accelerated in 2003 was the shift to a broader focus of HF incorporating the substantial proportion of patients with signs and symptoms occurring in the absence of any major reduction in left ventricular systolic function (8–13). The pathophysiology and even terminology related to this latter, heterogeneous type of HF, however, remains controversial. Most of the recently reported epidemiologic and hospital cohort studies made no attempt to assess diastolic function, instead describing these patients as having HF with preserved systolic function (PSF). Zile (14) has argued that detailed evaluation would confirm diastolic dysfunction in most of these patients, though, to date, this has only been verified in small numbers of highly selected individuals. Some paradoxes also remain; HF-PSF is much more frequent in women than men, yet two population-based epidemiologic studies published in 2003 found that indexes of diastolic dysfunction were more common in men than women. Indeed, diastolic dysfunction was also remarkably common in older individuals generally, even in the absence of clinical HF (12,13). Redfield et al. (12) found that, of those age 75 years or older, 53% had mild, 15% moderate, and 3.4% severe diastolic dysfunction. Is the finding of diastolic dysfunction in a breathless elderly patient, therefore, a very specific finding? Others have drawn attention to vascular rather than myocardial differences between these two types of HF (15). The nonspecific nature of the signs and symptoms of HF and the complexity of performing and interpreting measures of diastolic function emphasize the great need for a simple and agreed upon diagnostic test for HF-PSF. Without a quantitative, reproducible, and clinically applicable measure of diastolic function, left ventricular ejection fraction will continue to serve as the distinguishing feature. B-type natriuretic peptides (BNP) provide additional underpinning for the clinical diagnosis of HF. The Breathing Not Properly study was one of the first to address this important question (16). Using a “gold standard” of a clinical diagnosis made by two independent cardiologists unaware of BNP levels, Maisel et al. (15) tested how BNP performed. Unfortunately, there was a significant overlap in BNP concentrations between patients with non-cardiac breathlessness and those with HF-PSF, especially women. Clearly, more studies of this type are needed, perhaps using a different “gold standard” or natriuretic peptide (e.g., N-terminal pro-BNP).
Whatever the underlying pathophysiology and optimal diagnostic approach, evidence continues to accumulate that HF-PSF is a common and important syndrome. Smith et al. (10) have added to the growing array of studies showing that, while HF-PSF is associated with a lower mortality than HF with reduced systolic function, it still leads to a comparable degree of functional limitation and morbidity as measured by admission to hospital. Fortunately, there has also been a drive to conduct major prospective randomized outcome studies to evaluate new treatments in this type of HF. The first of these to report was Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved, one of the three component trials of the CHARM program (see the following text) (17). In this study, candesartan was compared with placebo in 3,023 patients with HF and a left ventricular ejection fraction higher than 0.40. During a median of 37 months, candesartan treatment did not lead to a statistically significant reduction in the primary end point of cardiovascular death or hospital admission for HF (22% vs. 24%, hazard ratio 0.89, p = 0.118). Compared with placebo, however, candesartan did reduce the proportion of patients requiring admission to hospital for HF by 18% (p = 0.017) and the total number of admissions for HF by 29% (p = 0.014). This trial did demonstrate that the annual mortality rate of 5.4 %, although less than the patients with reduced left ventricular ejection fraction (11.2%), was higher than the general population, and that recurrent hospitalization for cardiovascular reasons was common.

RANDOMIZED TRIALS OF THERAPEUTIC INTERVENTIONS IN CHRONIC HF WITH REDUCED SYSTOLIC FUNCTION

Pharmacologic. ANGIOTENSIN RECEPTOR BLOCKERS. The CHARM program confirmed and extended the findings of the Evaluation of Losartan in the Elderly (ELITE)-2 and Valsartan Heart Failure Trial (Val-HeFT) in patients with
HF and reduced systolic function (18–20). In 2,028 patients previously intolerant of an ACE inhibitor, compared with placebo during 34 months of follow-up, candesartan reduced the primary end point of cardiovascular death or hospital admission for HF from 40% to 33% (hazard ratio 0.77, \( p = 0.0004 \)) in CHARM-Alternative (18). In CHARM-Added, 2,548 patients all treated with an ACE inhibitor (and, in 55% of cases a beta-blocker as well), candesartan reduced the incidence of the same end point from 42% to 36% (hazard ratio 0.85, \( p = 0.011 \)) during 41 months of follow-up (19). This finding is consistent with recent evidence of incremental and favorable remodeling effects with “triple therapy” (21). In both these low ejection fraction trials, candesartan reduced all-cause mortality from 31% to 28% (hazard ratio 0.88, \( p = 0.018 \)). The benefits of candesartan were consistent across a wide range of subgroups and irrespective of background therapy, including ACE inhibitor, beta-blocker, and spironolactone, whether used individually or in any combination (20). Candesartan was also effective when added to either high- or lower-dose ACE inhibitor treatment.

**BETA-BLOCKERS.** The greatest advance in the treatment of HF since the introduction of ACE inhibitors was the demonstration in three landmark prospective, randomized, placebo-controlled trials of an approximately 33% relative reduction in all-cause mortality (and similarly impressive reductions in hospital admissions) with the addition of a beta-blocker. Of note, these benefits were identified early, and all three trials were terminated prematurely, after about one year’s follow-up. The effective agents used were bisoprolol (in Cardiac Insufficiency Bisoprolol Study [CIBIS]-2), carvedilol (in the Effect of Carvedilol on Survival in Severe Chronic Heart Failure [COPERNICUS] trial), and a slow-release formulation of metoprolol (succinate) in Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF); each had an almost identical size of treatment effect (22–24).

Of note, in the Beta Blocker Evaluation of Survival Trial (BEST), another beta-blocker, bucindolol, was not clearly shown to have these benefits (25). The results of Carvedilol Or Metoprolol European Trial (COMET), a rare type of randomized trial comparing two active treatments within the same drug class, were reported in 2003; COMET compared carre-
dilol to a short-acting formulation of metoprolol (tartrate), different from that used in MERIT-HF (which used metoprolol succinate) (26). This large (n = 3,029), long-term (mean follow-up 58 months) trial demonstrated that carvedilol led to a 17% relative risk reduction in all-cause mortality from 40% to 34% (p = 0.0017) compared with short-acting metoprolol tartrate. The interpretation of this remarkable difference between two beta-blockers has been controversial. Some have interpreted the COMET as demonstrating the advantages of the different molecular actions of carvedilol, namely nonselective (beta-1 and -2) adrenoceptor blockade, alphaadrenoceptor blockade, and perhaps other effects, over metoprolol (which is a relatively beta-1 adrenoceptor antagonist). Others have criticized the COMET on the basis of comparing different intensities of beta-1 adrenoceptor antagonism, as a consequence of the unproven formulation of metoprolol used (the only sizable prior study with metoprolol tartrate, the Metoprolol in Dilated Cardiomyopathy [MDC] trial, used two or three times daily dosing and achieved a mean dose of metoprolol tartrate of 108 mg compared with 85 mg in the COMET). Other evidence suggests that 50-mg metoprolol tartrate prescribed twice daily does not give equivalent beta-blockade to metoprolol succinate 200 mg taken once daily, as the reduction in heart rate in the metoprolol group in the COMET was slightly less than in the MERIT-HF. One definite conclusion from the COMET, however, is that short-acting metoprolol tartrate, used only twice daily, is an inferior treatment to carvedilol in chronic heart failure (CHF).

**Devices. CARDIAC RESYNCHRONIZATION THERAPY (CRT).** Another intervention that may revolutionize the treatment of CHF is atrioventricular pacing (27–30). It is estimated that about a quarter of patients with CHF have increased QRS duration (>120 ms). This is a marker of dyssynchrony of right and left ventricular activation, which causes inefficient pump function. Atrioventricular pacing recoordinates ventricular contraction. In 2003, follow-up reports from the first controlled trials of this new therapy confirmed improvements in symptoms, quality of life, and functional capacity, and showed additional mechanistic benefits such as reduced left ventricular remodeling, reduced mitral regurgitation, and increased heart rate variability (27–29). An interesting meta-analysis suggested that CRT also reduces hospital admissions for HF and death from progressive pump failure but perhaps not all-cause mortality (30). The recently reported Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial supports this conclusion and also shows that CRT reduces the clinically important composite outcome of death or hospital admission for any reason by 19% (p = 0.014) although the benefits were not as great as in patients having both CRT and an implantable cardioverter-defibrillator (ICD) (31). The results of the second major outcome study of CRT in CHF, Cardiac Resynchronization in Heart Failure (CARE-HF) study, are due in 2005 and eagerly awaited (32). A number of other issues remain to be resolved with CRT. There is concern that a broadened QRS may not offer the best means of identifying patients with ventricular dyssynchrony. Consensus has yet to be reached on whether CRT therapy alone or a combined CRT-ICD device should be implanted (or in whom these different therapeutic modalities are indicated). The recent COMPANION trial and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) argue powerfully for wider use of ICD therapy in CHF (31).

**INEFFECTIVE TREATMENTS IN CHF.** The history of clinical trials in CHF is littered with failures as well as successes. Two examples of the former were published in 2003. The adverse Mortality Effect of Central Sympathetic Inhibition with Sustained-Release Moxonidine in Patients with Heart Failure (MOXCON) trial showed that not all antiadrenergic therapies are beneficial in CHF (as also shown by V-HeFT 1 with the alpha-adrenoceptor prazosin) and once again raised the vexed issue of dose selection (33). The anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial showed that one type of anticytokine therapy does not improve outcome in CHF, and the recent publication of the results of Randomized Etanercept Worldwide Evaluation (RENEWAL) trial revealed a similar finding with a different inhibitor (34,35). These studies serve to emphasize two points. First, our understanding of sophisticated, inter-related, biologic systems is limited, and it cannot be assumed that activation of such a system in CHF is necessarily disadvantageous. Second, it is also clear that effects of inhibitors of these systems, especially when complex molecular therapies are used, are not easy to predict. The recent experience with endothelin receptor antagonists and dual neutral endopeptidase-ACE inhibitors serves to reinforce all of these issues about dose and biologic complexity.

**HF AFTER ACUTE MYOCARDIAL INFARCTION.**

Clinical evidence of acute HF, even if transient, early after acute myocardial infarction identifies a patient at high risk of short- and longer-term adverse cardiovascular outcomes. The same is true for left ventricular systolic dysfunction without acute HF and, especially, if both of these problems are present. The recent findings of international registries have clearly illustrated this risk in contemporary cohorts of patients with acute coronary syndromes where pulmonary congestion was associated with up to a four-fold excess of death (36,37). The key role of early, sustained ACE inhibition in improving prognosis in these patients remains undisputed (38). The importance of concomitant beta-blockade was recently reinforced by the Carvedilol Post-Infarct Survival Controlled Evaluation (CAPRICORN) (39). Recently, two further therapeutic questions were answered. One was whether an angiotensin receptor blocker would be as, or more, effective than a proven dose of a proven ACE inhibitor and whether combination ACE inhibitor-angiotensin receptor blocker treatment would be better than ACE inhibitor monotherapy, as in CHF (see
the preceding text) (40). The second question was whether the addition of an aldosterone blocker to an ACE inhibitor and beta-blocker would further improve outcome in these patients (41).

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) showed that the angiotensin receptor blocker valsartan used in a dose of up to 160 mg twice a day (as in Val-HeFT) was as effective in reducing risk of death and other major cardiovascular outcomes as the proven dose of captopril (50 mg three times a day) used in the Survival and Ventricular Enlargement (SAVE) study (and, subsequently, in ELITE-2 and Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL]) (40). Valsartan 80 mg twice a day, added to this dose of captopril, did not, however, lead to any further reduction in risk of the primary or secondary end points in the VALIANT (though the combination did lead to more intolerance). The possible explanations for this difference between the effects of combination ACE inhibitor-angiotensin receptor blocker therapy in CHF and acute myocardial infarction are discussed elsewhere (41,42).

In the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS), of patients with acute myocardial infarction with both acute HF and reduced left ventricular ejection fraction, the addition of the aldosterone blocker eplerenone led to a 15% relative risk reduction in all-cause mortality and a reduction in hospital admission for HF. These benefits were achieved despite high baseline use of ACE inhibitors and beta-blockers, demonstrating the incremental advance for these patients at especially high risk after acute myocardial infarction (39). The prior observation, in the Randomized Aldactone Evaluation Study (RALES), that spironolactone, added to an ACE inhibitor, improves survival in severe HF reinforces the findings of EPHESUS (43).

**ACUTE DECOMPENSATED HF**

There has been a recent explosion of interest in what has become known as “acute decompensated HF,” a term probably describing a mixture of syndromes including acute de novo HF and acute on-chronic HF (44). The clinical community is still struggling with how best to evaluate treatments in this type of HF (45,46). Since many are designed to be given intravenously for only a short period, it is difficult to know whether long-term outcomes can be improved. Several drugs including the endothelin receptor antagonist tezosentan (47) and the arginine vasopressin antagonist tolvaptan (48) have been shown to have favorable hemodynamic, neurohumoral renal, and other actions in acute HF. However, to date, none of these therapies has been shown to improve short-term survival or other clinical outcomes in patients presenting with acute HF. Large-scale outcome trials with these agents are now underway, adding to completed studies with “inodilators” and nesiritide (49,50).

**THE IMPORTANCE OF COMORBIDITY IN HF**

Heart failure is most commonly caused by coronary heart disease, hypertension, or both. Consequently, many patients have other complications of atherosclerosis and hypertension. Often these elderly individuals have related comorbidity, such as diabetes (51,52) and other conditions sharing a common etiology (e.g., smoking-related chronic pulmonary disease). Some comorbidities are complications of HF or the combination of HF, its underlying etiology, and advanced age (e.g., renal impairment) (53,54), stroke, atrial fibrillation (55,56) and ventricular arrhythmias. The causes of others have yet to be fully elucidated (e.g., anemia, obstructive sleep apnea, and cachexia) (57). The importance of certain comorbidities as independent predictors of poor outcome has been highlighted in 2003. This recognition has also led to the view that these might themselves be therapeutic targets. The clearest example of this is anemia (58–61). Four recent studies found that low hemoglobin or hematocrit is a powerful prognostic factor in HF (58–61). In a small, single-blind, randomized, controlled trial, Mancini et al. (62) showed that correcting anemia with erythropoietin resulted in clinical improvement and an increase in exercise capacity. At least one prospective outcome trial using erythropoietic therapy is now planned. Another notable development, related to comorbidity, was recognition of the problems thiazolidinediones can cause, related to fluid retention, when given to treat diabetes in patients with HF (63).

Two studies published in 2003 add to prior evidence that continuous positive airway pressure improves ventricular function and well-being and reduces neurohumoral activity in patients with obstructive sleep apnea (64,65). At least one large trial is now testing the effect of continuous positive airway pressure on mortality and morbidity in HF.

**ORGANIZING AND IMPROVING THE DELIVERY OF CARE**

Based on the results of randomized controlled trials, the treatment of patients with HF continues to improve and has been summarized in a number of authoritative, evidence-based guidelines. The challenge of developing these treatments, however, is matched by the challenge of ensuring these are widely adopted into clinical practice (66). In 2003, it was again shown that organized, nurse-led, multidisciplinary care aids this goal (67), though whether all patients gain from this intervention remains uncertain (68). New technology, such as home-telemonitoring, may also have a role to play in improving chronic disease management (69,70).

Determining efforts to implement guidelines can improve treatment locally and nationally, as illustrated in the Italian Health Service (71,72).
SUMMARY AND CONCLUSIONS

Highlighting some of the important aspects of the recent progress in the diagnosis and management of patients with HF serves to underscore both the globalization of the problem in our aging populations and the collaborative effort needed in order to develop new treatments for it. The benefits observed in randomized controlled trials, at last, seem to have been realized in nontrial populations. The persistently high mortality and morbidity in HF, however, provide a continuing impetus to find additional pharmacologic and device treatments that will improve the quality and duration of life beyond what is currently available. The bar is set high though, with expectations raised by the success of optimal conventional therapy, success that may be increasingly difficult to exceed. However, the rate of generation of new knowledge is dramatic, greatly expanding the range of potential therapeutic approaches, and offering a realistic promise of continued meaningful progress in this important field.

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