The second part of this review deals with newer, nonneurohumoral, pharmacological approaches to congestive heart failure (CHF) and nonpharmacological interventions in heart failure patients with low left ventricular ejection fraction (LVEF) as well as potential treatments for CHF with preserved LV systolic function. An algorithm summarizing current, evidence-based therapy is also provided.

Anticytokine and Immunomodulating Therapy

Cytokines, such as tumor necrosis factor, are produced in increased amounts in a variety of tissues in patients with CHF.1 Higher plasma cytokine concentrations are associated with a worse prognosis.2 Experimentally, cytokines depress myocardial contractility, cause myocyte death, and induce heart failure.3 There is some evidence that anticytokine interventions improve ventricular function and clinical status in CHF.2,3 Two parallel trials (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines [RENAISSANCE] and Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction Trial [RECOVER], pooled as the Randomized Etanercept Worldwide Evaluation [RENEWAL] program) examining the effect of the anti–tumor necrosis factor agent etanercept on morbidity and mortality in CHF, however, were recently discontinued because of futility (Table). Even more recently, a placebo-controlled phase II trial with an alternative anti–tumor necrosis factor chimeric monoclonal antibody, infliximab, was stopped early because of higher rates of mortality and hospitalization in the active-therapy group. Whether this means that the cytokine hypothesis is invalid, that etanercept and infliximab were the wrong drugs to use (or were used incorrectly), that inappropriate patients were chosen, or that the study designs were flawed is unknown.

Matrix Metalloproteinase Inhibitors

The constitution of the cardiac extracellular matrix depends on the balance in activity of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases.4,5 End-stage heart failure is associated with increased collagenase activity (increased expression of MMP-1 and MMP-9) and reduced expression of tissue inhibitors of metalloproteinases.5 Experimentally, MMP inhibition reduces ventricular dilatation, although theoretical concerns remain about this therapeutic approach in patients.5

Antithrombotic Therapy

At present, there is no indication for warfarin in patients with CHF in sinus rhythm, although there are obvious theoretical reasons why antithrombotic therapy might be of benefit. The place of aspirin in patients with coronary heart disease and CHF has been challenged because of a possible interaction with ACE inhibitors (whereby aspirin attenuates the effects of ACE inhibitors).6 Unfortunately, the only outcome data available to address this issue come from retrospective analyses of the large ACE inhibitor trials. By far the largest such analysis, pooling the 3 long-term postinfarction trials with the 2 Studies of Left Ventricular Dysfunction (SOLVD) trials, did not identify any significant treatment interaction between aspirin and ACE inhibitors.6 Clopidogrel has an antiplatelet effect comparable to that of aspirin but does not interact with ACE inhibitors. To attempt to clarify the optimum antithrombotic strategy in patients with CHF, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial is comparing open-label warfarin (target INR 2.5 to 3.0) with double-blind aspirin (162 mg QD) or clopidogrel (75 mg QD) in ~4500 patients with NYHA class II to IV CHF and an LVEF ≤0.35. The primary end point is a composite of death, nonfatal MI, and nonfatal stroke. Until the results of WATCH are available, low-dose aspirin remains the antiplatelet agent of choice in patients with CHF and atherosclerotic disease and should usually be coprescribed with an ACE inhibitor.

Metabolic Interventions

The concept of CHF as a state of myocardial “energy starvation” has been advocated by Katz.7 Ranolazine is a partial fatty acid oxidation inhibitor that has demonstrated efficacy in patients with angina pectoris.8 A morbidity/mortality trial with ranolazine is being considered in CHF.

Inotropic Therapy

Previous experience with orally administered inotropic agents was unfavorable. Mortality was increased by drugs with...
Selective A<sub>1</sub> adenosine receptor blockade may induce diuresis and natriuresis in CHF without reducing glomerular filtration rate. As such, this therapeutic approach could be of great value in CHF patients with azotemia, a problem group growing in size.

**Targeting Pharmacological Therapy?**

Patients with CHF may currently be prescribed many different antifailure therapies (diuretics, ACE inhibitors, β-blockers, spironolactone, digoxin) and potentially several more in the future. They may also take multiple treatments for concomitant problems. This polypharmacy is a cause of concern, not least from the adherence point of view. There is growing interest in the notion of targeting therapy either on the basis of biological mechanisms or genetic makeup. Differential ethnic or racial responses to therapy may reflect either or both of these factors. This subject has been the focus of much recent interest and the source of considerable controversy, with suggestions that African Americans may respond less well to ACE inhibitor therapy and better to hydralazine and isosorbide dinitrate combination therapy. There is conflicting evidence about racial or ethnic background and response to β-blocker therapy. The African American Heart Failure Trial (A-HeFT) will randomize 600 black men and women with NYHA class III to IV CHF to placebo or hydralazine and isosorbide dinitrate and evaluate clinical status and ventricular function.

**Tailoring Pharmacological Therapy?**

In addition to knowing which therapies to give to patients, we also need to understand better how to decide how much treatment patients require. Trials to date have usually had “target” doses of treatment, and these are the doses also recommended in clinical practice. It has recently been suggested that plasma natriuretic peptide concentrations might provide a simple biochemical means of tailoring therapy. In addition to knowing which therapies to give to patients, we also need to understand better how to decide how much treatment patients require. Trials to date have usually had “target” doses of treatment, and these are the doses also recommended in clinical practice. It has recently been suggested that plasma natriuretic peptide concentrations might provide a simple biochemical means of tailoring therapy.

**Frameworks for Implementation of Pharmacological Therapy**

A consistent finding across many countries is that evidence-based therapy for CHF (and other conditions) is frequently underused. Even when therapy is prescribed, patients may be nonadherent, probably in part because they are poorly educated about their condition and its treatment. For these and other reasons, better approaches to the organized and systematic care of patients with CHF have been sought. A number of randomized trials have shown that nurse- or pharmacist-led, multidisciplinary intervention can improve medium-term outcomes in CHF (mainly by reducing hospital admissions). Although to date, the greatest effect seems to be seen with home-based interventions, a number of questions remain unanswered about these new approaches. What

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**Anemia as a Treatment Target?**

There has been much recent interest in the finding that a high proportion of patients with CHF are anemic and that correction of this anemia with iron supplementation and erythropoietin may improve symptoms and morbidity. Larger-scale clinical trials are being considered.
is the optimal timing, intensity, and duration of such interventions? Do these interventions have long-term benefits? Are they cost-effective? What are the exact mechanisms of their beneficial effects? Are programs of this type associated with improved survival?

**Treatments Targeted at Coronary Artery Disease and Its Consequences in CHF**
Many, if not the majority, of patients with CHF have underlying coronary artery disease, and as alluded to above, existing, successful therapies may exert some of their beneficial effects by preventing new acute coronary events (see Part I). There is also much interest in specifically addressing recurrent ischemia and hibernation as therapeutic targets in CHF. Pharmacological and interventional strategies are under investigation.

**Pharmacological Reversal of Myocardial Hibernation**
A surprisingly high proportion of patients with CHF and coronary artery disease have substantial areas of hibernating myocardium.24–26 The Carvedilol Hibernation Reversible ISchaemia Trial: MArker of Success (CHRISTMAS) study is attempting to determine whether the presence or absence of hibernating myocardium predicts improvement in LVEF in patients treated with carvedilol, ie, comparing the changes in LVEF in the randomized nonhibernating versus hibernating groups.26

**Percutaneous and Surgical “Revascularization” in Patients With Coronary Artery Disease and CHF**
The safety and efficacy of myocardial revascularization, especially surgical revascularization, is uncertain in CHF.25 A number of small and uncontrolled series have suggested that patients with large areas of viable myocardium may have a low interventional risk and a large potential benefit from revascularization.25 Consequently, 2 clinical trials are currently planned to address the impact of mechanical revascularization on outcome in such patients. One is the Heart Failure Revascularization Trial–United Kingdom (HEART-UK) study, comparing percutaneous or surgical revascularization with optimal medical therapy, which will recruit \( \approx 800 \) patients and have a minimum follow-up of \( \approx 5 \) years and a primary end point of all-cause mortality.25 A planned US trial, Surgical Treatment for IsChemic Heart failure (STICH), intends to address 2 hypotheses, one being the revascularization hypothesis and the other an “LV reconstruction hypothesis.”27 The latter concerns the possibility that surgical remodeling to achieve optimum LV shape and size will also reduce morbidity and mortality in these patients.

**Nonpharmacological Therapy for Low-LVEF CHF: Exercise Training, Devices, and Surgery**

**Exercise Training**
The short-term benefits of exercise training on functional capacity, symptoms, neurohumoral activity, muscle performance, and baroreceptor function are well recognized. To date, however, a definitive randomized trial studying the effect of exercise prescription on morbidity and mortality is awaited.28

**Biventricular (Multisite) Pacing**
Patients with CHF often have abnormal electrical activation of the myocardium, reflected as a prolonged PR interval and/or QRS duration of the surface ECG. This electromechanical dyssynchrony may lead to suboptimal atrioventricular coupling, uncoordinated ventricular contraction, and presystolic mitral regurgitation. Biventricular or multisite pacing may “resynchronize” cardiac contraction and reduce these abnormalities.29

Two relatively small, short-term trials, the Multisite STImulation in Cardiomyopathy (MUSTIC) and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) studies, have suggested that biventricular pacing can improve symptoms and exercise capacity in patients with prolonged QRS duration.30,31 Biventricular pacing may also lead to LV reverse remodeling and a reduction in mitral regurgitation. Long-term morbidity/mortality trials are either planned or under way, including the Comparison Of Medical therapy and Pacing ANd DefibrillatION in Chronic Heart Failure (COMPANION) and Cardiac REsynchronisation in Heart Failure (CARE-HF) trials.29

**Implantable Cardioverter-Defibrillators**
The Antiarrhythmics Versus Implantable Defibrillators (AVID) and Multicentre Automatic Defibrillator Implant Trial (MADIT) demonstrated that implantable cardioverter-defibrillators (ICDs) reduce mortality in patients with a low LVEF and spontaneous or inducible ventricular arrhythmias. Post hoc analysis of both trials suggested that the greatest benefit was obtained in patients with the lowest LVEF.32,33 Other primary and secondary prevention studies with ICDs are in general agreement with these findings, including the MADIT-II trial, which was recently stopped prematurely because of overwhelming evidence of a survival benefit in the ICD group. Consequently, there is interest in the role of ICDs in patients with CHF. One large study, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), is comparing ICD therapy with amiodarone treatment in \( \approx 2500 \) patients with NYHA class II to III CHF and an LVEF \( \leq 0.35 \). The primary end point is all-cause mortality.32,33 COMPANION (see above) is a 3-way comparison of medical therapy; medical therapy plus biventricular pacing; and medical therapy, biventricular pacing, and an ICD.29

**Ventricular Assist Devices, Pumps, and Total Artificial Hearts**
There is renewed interest in mechanical support for, or replacement of, the failing heart as a stand-alone therapy, rather than as a bridge to transplantation. A detailed review of this topic is beyond the scope of this review. The Randomized Evaluation of Mechanical Assistance for Treatment of Chronic Heart failure (REMATCH), however, showed that implantation of an LV assist device can improve survival in transplant-ineligible patients with end-stage CHF, but at the expense of frequent infective and hemorrhagic complications.34 Recently, the first implantations of a newly config-
Molecular Approaches to Treatment: Cell and Gene Therapy for CHF

Multiple recent reports suggest that there is an exciting potential for gene therapy and cell therapy both in preventing and in treating CHF. Similarly, new molecular pathways, such as those that cause programmed cell death (apoptosis) may also be important future treatment targets. At present, however, these remain at an exploratory stage and cannot be detailed here. They do, however, offer the possibility of revolutionizing therapy for CHF. for example, by allowing fibrotic scar tissue to be replaced by new myocytes.

Current Recommendations for the Treatment of Low-LVEF CHF

The Figure summarizes the current treatment of patients with low-LVEF CHF, emphasizing the key role of ACE inhibitors and β-blockers and highlighting some of the concomitant problems that either reflect the cause of CHF (eg, coronary heart disease) or arise as a complication of CHF (eg, atrial and ventricular arrhythmias). This algorithm also maps the focus of many of the investigational approaches summarized in the preceding text.

### Treatments for Preserved-LVEF CHF

As mentioned above, a substantial minority of patients with the clinical syndrome of CHF appear to have “preserved” LV systolic function (or at least a relatively normal LVEF). Sometimes these patients are considered to have diastolic dysfunction, although there is no agreed-upon definition of this, and the precise cardiac problem in these patients is variable and often undefined. Because many of these patients have underlying atherosclerotic arterial disease, hypertension, diabetes mellitus, LV hypertrophy, and atrial fibrillation, however, it is hoped that inhibitors of the renin-angiotensin-aldosterone system and sympathetic nervous system might be of benefit. Three morbidity/mortality trials enrolling patients with normal LVEF CHF are under way, and one is planned. One arm of the CHARM program (CHARM...
Preserved) has fully recruited 3025 patients with an LVEF of >0.40, randomized to placebo or candesartan.47 Another trial, I-PRESERVE, is also planning to compare placebo with an angiotensin-receptor antagonist (irbesartan) in patients with CHF despite preserved LV systolic function. The Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) study intends to enroll ~1000 patients >70 years of age with CHF and no major LV systolic dysfunction (LVEF <0.40 or wall motion index <1.4).48 Patients will receive double-blind treatment with placebo or perindopril. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors (SENIORS) trial is randomizing patients ≥70 years of age with CHF, many of whom will have a normal LVEF, to treatment with either placebo or nebivolol. There will undoubtedly be more trials in this previously neglected minority of patients with CHF.

Challenges Ahead

Many other important questions cannot be discussed here in detail. We still do not understand some of the most basic aspects of drug development and trial design. Selecting a dose, or range of doses, to test remains a relatively arbitrary process and may have resulted in problems with a number of the therapies discussed above. There is also the clinically pressing problem of adding yet more treatments to a patient’s existing therapy. Targeting therapy has been mentioned earlier, but will the sponsors of large trials, the pharmaceutical industry, encourage this? Can we ethically find ways of comparing proven therapies with new ones (even though that may mean that patients do not receive the former during the trial)? The Carvedilol ACE inhibitor Remodelling Mild heart failure EvaluatioN (CARMEN) study, comparing the effect of carvedilol alone, enalapril alone, and the combination of both agents on LV function in 450 patients with an LVEF <0.39 is one of few studies addressing this challenge.49 What other moral and ethical problems will molecular and genetic advances bring (embryonic stem cell research has already been contentious)? Will conventional clinical trials with a mortality end point become enormously large and prohibitive? Will more expensive and more effective therapies be added to existing ones? We may need to think of not only new approaches to trial design but also new end points for trials, perhaps refocusing on patient well-being rather than just adverse clinical events.50

Conclusions

The past 20 years have seen enormous progress in our understanding of the pathophysiology of CHF and its treatment. Pathophysiological progress has suggested therapeutic approaches, and the successes and failures of clinical trials have refined pathophysiological concepts as well as the science of trial design and conduct. The next 2 decades will present at least as many challenges as the past 2 and perhaps less prospect of the same enormous breakthroughs with pharmacological agents. Nevertheless, our patients with CHF can still expect further improvement in their quantity and quality of life.

Note Added in Proof

Both OVERTURE and ENABLE have recently completed and reported. There was no significant difference in mortality between the omapatrilat and enalapril groups in OVERTURE. Bosentan was not superior to placebo in ENABLE. Both of these trials were presented at the “late-breaking trials hot-line” at the American College of Cardiology Meeting in March 2002 (Atlanta, Ga).

References


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