New Therapeutic Options in Congestive Heart Failure: Part I

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The need for new treatments for congestive heart failure (CHF) is clear. Population morbidity and mortality, although they are improving, remain high.1,2 In this article, we review potential future therapies for CHF, building on our understanding of pathophysiological mechanisms and insights gained from previous studies of therapeutic interventions. The focus is on ambulatory CHF associated with left ventricular (LV) systolic dysfunction, although heart failure with preserved systolic function is also discussed. Given the broad scope of this review, individual areas can be addressed only briefly. The first part of this review deals with the pathophysiological basis of therapy and the use of neurohumoral antagonists in CHF with low LV ejection fraction (LVEF).

Pathophysiological Basis of Treatment

Although the pathophysiology of CHF has recently been reviewed in detail, it is important to mention key concepts as the basis of therapy.3,4

Neurohumoral Pathways

Over the past 20 years, the “neurohumoral hypothesis” has evolved to focus less on the impact of these pathways on the blood vessels and kidneys and more on the heart (Figure 1, and see below).5 This in part reflects the benefit of β-blockers and spironolactone, treatments that are not vasodilators.6–10 New peptides, such as the endothelins, and other mediators that are not conventional endocrine, autocrine, or paracrine factors, such as cytokines and free radicals, have also been postulated to play a role in CHF.11,12 These, in turn, are now thought to set into motion pathophysiological processes, such as apoptosis, that had not yet been recognized when the neurohumoral model was originally postulated (Figure 1B).13 The interaction between primitive neurohumoral reflexes designed to maintain blood volume and vital organ perfusion and hemostasis has been belatedly recognized.14

We also have moved beyond merely trying to inhibit or antagonize factors thought to have detrimental effects (eg, angiotensin II). It is now recognized that CHF is also characterized by augmentation of neurohumoral pathways with potentially favorable actions in CHF (the natriuretic peptides).15 CHF can be thought of as a state of neurohumoral imbalance, in which the activity of potentially harmful pathways outweighs that of favorable ones.

Therapeutic interventions might therefore be targeted not just at inhibiting undesirable pathways but also at augmenting desirable ones. In other words, neurohumoral modulation may become more important in the future than the neurohumoral inhibition that we have focused on in the past.

Remodeling

The phenotypic and genotypic changes characterizing cardiac hypertrophy and failure involving both the cardiomyocytes and extracellular matrix contribute to impaired relaxation as well as contraction.16,17 They may also impair coronary flow reserve, indirectly exacerbating both systolic and diastolic function, especially if there is concomitant coronary artery disease.15–17 The physiological response to chronically increased wall stress, hypertrophy, may also lead to a state of energy starvation.18

Thus, there is no single factor but rather a complex interrelated, multifactorial cascade, involving hemodynamic, nonhemodynamic, genetic, energetic, and neurohumoral alterations that leads to the progression of heart failure (Figure 1B). These diverse, intertwining contributors provide multiple opportunities for therapeutic intervention.

Other Pathophysiological Considerations in CHF

Although the neurohumoral paradigm of CHF has deservedly been the focus of attention over the past 2 decades, and the LV remodeling paradigm more recently, other pathophysiological mechanisms may be important in CHF. Although these could ultimately be related to neurohumoral processes, they may still be subject to more direct therapeutic interventions.

Myocardial Ischemia and Infarction

Most patients with CHF caused by LV systolic dysfunction have coronary artery disease. The concept of “hibernating myocardium” has matured in the past decade.19 Hibernating myocardium is muscle with a blood flow so severely restricted that it is unable to contract, although it does remain viable at least for a period of time. Restoration of coronary flow restores normal contractility, whereas continued hibernation may ultimately lead to cell death. Clearly, the issue in...
CHF is whether revascularization might substantially improve LV systolic function in patients with significant areas of hibernation. The definition and best means of detecting hibernation are discussed extensively elsewhere. There are, as yet, few data on the prevalence of important myocardial hibernation in patients with CHF. Although some small case series describe the effect of revascularization on LV function in such patients, the results of this type of treatment have not been studied in any systematic way. Fortunately, North American and European trials are getting under way (see below).

Acute coronary events increase the risk of death and hospitalization with worsening heart failure in patients with CHF. ACE inhibitors and β-blockers may exert their beneficial effects in part by reducing coronary events. Antiplatelet therapy may do likewise, although the role of aspirin is controversial (see below). Although HMG-CoA reductase inhibitors (statins) have not been specifically studied in patients with CHF, they might also be expected to reduce coronary events, as they do in other patients with coronary artery disease.

Atrial Arrhythmias
Recent clinical trials (please see Appendix for acronyms of trial names) have brought to our attention the potentially important role of atrial fibrillation (AF) in the progression of CHF (even though AF was not the focus of these trials). Both the CHF-STAT and the DIAMOND-HF studies found that development of AF was associated with an increased risk of hospitalization because of worsening CHF. There is conflicting evidence from other studies as to whether AF is also an independent predictor of death. Both CHF-STAT and DIAMOND-HF, however, suggest that pharmacological maintenance of sinus rhythm may reduce the risk of hospitalization with CHF. The predictors of AF development and the mechanisms of such development are certainly worthy of more attention. Similarly, prospective evaluation of anti-AF therapies merits study, given the findings of CHF-STAT and DIAMOND-HF. AF may also bring about ventricular systolic dysfunction by causing a tachycardiomypathy.

Ventricular Arrhythmias
Many of the patients with CHF who die suddenly probably suffer a lethal ventricular arrhythmia. Although antiarrhythmic drug therapy has had, at best, a neutral effect on mortality in CHF (or even increased mortality), there is hope that implantable cardioverter-defibrillators will improve prognosis. This hypothesis is currently being tested in a number of trials (see below).

Renal Dysfunction and Anemia
Renal dysfunction and anemia are common in CHF, may be related, and predict a poor prognosis. There is now interest that treatments specifically aimed at these abnormalities may improve outcome.

Depression
Similarly, depression appears to be an independent prognostic marker in CHF, as in other forms of heart disease, and may be a future therapeutic target.

Treatments for Low-LVEF CHF

Neurohumoral Antagonists

Inhibitors of the Renin-Angiotensin System
ACE inhibitors. Two landmark trials, CONSENSUS and SOLVD-T, showed convincingly that ACE inhibitors reduce morbidity and mortality in all grades of CHF. Another trial, V-HeFT II, showed an ACE inhibitor to be superior to direct-acting vasodilators. Further studies demonstrated that ACE inhibitors could also improve survival and reduce the risk of major cardiovascular events in patients with impaired LV systolic function (SAVE, TRACE) or heart failure (AIRE) after myocardial infarction. SAVE and the prevention arm of SOLVD also showed that ACE inhibition could delay or prevent the onset of overt, symptomatic CHF in asymptomatic patients.

These trials also showed that ACE inhibitors reduce the risk of myocardial infarction, emphasizing the potentially complex actions of these drugs and the multiple pathophysiological mechanisms driving the progression of CHF. ACE inhibitors also reduce the risk of AF.

The anti-infarction effect of ACE inhibitors has recently been confirmed in the HOPE study, and the vasculoprotective actions of these drugs are being evaluated further in the PEACE and EUROPA trials.

Although they are considered here as renin-angiotensin system inhibitors, the possibility that ACE inhibitors exert their actions, in part, through non-angiotensin II–related mechanisms has recently gained support.
Angiotensin Receptor Blocker
The more recent advent of specific angiotensin II type 1 receptor (AT1R) blockers (ARBs) provides the treating physician with a much more focused and specific pharmacological means of inhibiting the renin-angiotensin system. These agents act at the AT1R. In theory, the action of non–ACE-generated angiotensin II should be blocked by these agents and obviously not by ACE inhibitors. The effect of angiotensin II at other ATRs should also be unaffected (and, indeed, enhanced by the reflex increase in angiotensin II after AT1R blockade). The other ATR identified in humans, the AT2R, is postulated to have potentially desirable actions, eg, induction of nitric oxide release. Conversely, as ACE equates to kininase II (which degrades bradykinin), ACE inhibitors may have a greater effect on bradykinin metabolism than ARBs. Whatever the theoretical pharmacological merits of these 2 therapies, the ELITE-2 study did not confirm its hypothesis that the AT1R blocker losartan was superior to captopril in reducing mortality in elderly patients with CHF. Many explanations for this finding can be advanced: ARBs are not better than ACE inhibitors, the dose of losartan was too low, bradykinin is an important contributor to the action of ACE inhibitors, etc.

Instead of a direct comparison of ACE inhibitors with ARBs, the Val-HeFT investigators took a different approach, evaluating whether the addition of the ARB valsartan to conventionally managed patients with heart failure would result in a clinical benefit. As would be anticipated, a vast majority of conventionally treated patients are taking an ACE inhibitor. In Val-HeFT, 93% of the patients were taking an ACE inhibitor, 36% a β-blocker, and 86% a diuretic. In patients with symptomatic heart failure and depressed LVEF, the addition of valsartan to this regimen did not improve mortality but did reduce the end point of mortality plus nonfatal morbid events, which were predominantly hospitalizations for heart failure, by 13%. Despite the hazards of subgroup analyses, it did not appear that this benefit was uniformly observed. It appears that the small proportion of patients not receiving an ACE inhibitor experienced more pronounced benefit, whereas those already taking a combination of an ACE inhibitor plus a β-blocker tended toward a negative effect with the addition of the ARB. Again, the subgroup analysis must be interpreted cautiously; at this point, however, the add-on hypothesis of more complete inhibition with use of multiple agents does not appear to be confirmed. This is, fortunately, an area under active clinical investigation, with several large trials well under way. The Candesartan cilexetil (candesartan) in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) trial has 3 components (Table). One component is specifically addressing the concept of the ARB used alone in ACE-intolerant patients, as in the small percentage of patients in Val-HeFT who were not being treated with an ACE inhibitor. Another component of CHARM was designed to address the add-on hypothesis, with 2548 patients treated with an ACE inhibitor randomized to the addition of the ARB candesartan in addition to the ACE inhibitor and other therapies. It should be noted that >50% of these patients are also taking a β-blocker. The third arm of CHARM is evaluating the use of an ARB in an important and understudied population of heart failure patients, those with signs and symptoms of heart failure, a past hospitalization for cardiovascular event, and a measured LVEF >40% (see below).

Two major studies of ARBs in infarct patients will undoubtedly help clarify the potential clinical value of this mode of inhibiting the renin-angiotensin system. The Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study, like the Evaluation of Losartan in the Elderly-II (ELITE-II), is a direct comparison of the ARB losartan with the proven ACE inhibitor captopril. This study is designed to demonstrate whether one of these modes is superior or whether they can be considered clinically comparable in terms of improving survival in high-risk post–myocardial infarction patients. The Valsartan in Myocardial Infarction Trial (VALIANT) is an even larger study that is simultaneously addressing whether the ARB valsartan can be considered superior to or as good as the proven ACE inhibitor captopril in high-risk myocardial infarction patients. In addition, the trial is prospectively designed with equal statistical power to address the question of whether the combination of valsartan and captopril is superior to captopril alone in reducing mortality in this patient population. Collectively, these trials have all completed their randomization phase and are now in the active follow-up phase. It can be anticipated that in the years 2002 and 2003, all of these studies will be completed, providing a robust framework in which to view the clinical utility of ARBs.

Aldosterone Antagonists
Aldosterone, under the control of potassium and adrenocorticotropic hormone, as well as angiotensin II, escapes during chronic ACE inhibition and may have a number of detrimental effects in CHF (eg, causing potassium and magnesium wastage, baroreceptor dysfunction, and myocardial fibrosis). In one trial, the addition of low-dose (mean 26 mg) spironolactone, an aldosterone antagonist, to conventional therapy with a diuretic, digoxin, and in a minority of cases, β-blockers, improved symptoms, reduced hospitalization, and prolonged survival in patients with severe CHF. The place of aldosterone antagonists in patients with less severely symptomatic CHF is unknown but should be explored.

Fortunately, the role of aldosterone antagonism is being examined in postinfarction heart failure in the EPESUS study.

Inhibitors of the Sympathetic Nervous System
β-Blockers
There is even more overwhelming evidence than with ACE inhibitors that β-blockers reduce morbidity and mortality in all grades of CHF. The unexpected findings of the US Carvedilol Program were confirmed in the second Cardiac Insufficiency Bisoprolol Study (CIBIS II) and the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF), trials recruiting patients with predominantly NYHA class II to III CHF. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study extended these benefits to patients with more severe CHF, a
finding supported by post hoc analyses of CIBIS II and MERIT-HF. One large trial, the Beta-blocker Evaluation of Survival Trial (BEST), showed only a trend in favor of survival. This study used bucindolol and raised questions about potential racial differences in responsiveness to this agent (see below).

Elderly patients, however, have been underrepresented in these trials, and the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors (SENIORS) intends to enroll 2000 patients 70 years old with CHF and either a documented LVEF 0.35 or a hospital admission with CHF within the previous 12 months. The treatment comparison is placebo and nebivolol. It is expected that half of the patients will have a normal LVEF (see below). The primary end point is death or cardiovascular hospitalization. Survival benefits have now been demonstrated with 3 different β-blocking agents. An ongoing study, the Carvedilol Or Metoprolol European Trial (COMET), is also directly comparing 2 previously proven therapies, one a β1-selective nonvasodilating antagonist and the other a nonselective antagonist with vasodilating activity caused by a concomitant α1-antagonist action (Table).

It is of interest that these impressive benefits of β-blockers were obtained, for the most part, in patients who were already receiving ACE inhibitors. With the combination of heart failure and myocardial infarction in post–myocardial infarction studies collectively, we can now feel comfortable with the fact that the combination therapy is most effective. Historically, the β-blocker post–myocardial infarction trials were done before the use of ACE inhibitors, although the recent CAPRICORN Study has examined the addition of carvedilol to background ACE inhibitor therapy in patients with postinfarction LV systolic dysfunction. With the clinical trials of ACE inhibitors, their benefits were found to be additive to those of β-blockers after myocardial infarction. Conversely, ACE inhibitors were proved to be of clinical value in heart failure before β-blockers. Testing of the β-blockers was done, for the most part, in the presence of ACE inhibitors. Patients treated with both an ACE inhibitor and a β-blocker have the best prognosis (Figure 2). It is of interest that at this time, the addition of an angiotensin-receptor blocker to the treatment of patients already taking an ACE inhibitor and a β-blocker does not appear to confer additional benefit. This, however, is an area of active investigation (see above).

Other Antia-adrenergic Therapies

Moxonidine. Moxonidine, like clonidine, is a centrally acting inhibitor of sympathetic outflow. Despite encouraging neu-
Natriuretic Peptides and Drugs That Augment Plasma Natriuretic Peptide Concentrations

Atrial and brain natriuretic peptides (ANP and BNP) are circulating peptides produced principally by the atria and ventricles, respectively. Both peptides increase sodium and water excretion, suppress renin and aldosterone secretion, and lead to venous and arterial dilatation.\textsuperscript{15,61} They may also favorably influence autonomic function and have direct and indirect antimotif effects in the heart and blood vessels.\textsuperscript{61} Infused ANP and BNP have beneficial hemodynamic, neurohumoral, and renal actions in patients with CHF.\textsuperscript{62,63} ANP and BNP are metabolized (along with other peptides) by NEP.\textsuperscript{15,61} Orally acting NEP inhibitors augment plasma concentrations of these peptides.\textsuperscript{62,63} Early studies showed that the lead compound in this class, candoxatril, improved hemodynamics, symptoms, and exercise time when given alone or in conjunction with an ACE inhibitor (in both cases with conventional background diuretic and digoxin therapy).\textsuperscript{62--64} Candoxatril did not, however, lower blood pressure effectively in hypertensives, probably because NEP also metabolizes angiotensin II and possibly other vasoconstrictors (ie, NEP inhibition increases the amount of these vasoconstrictors).
The development of candoxatril was not pursued in CHF. That of another NEP inhibitor, ecadotril (sinorphan), was also stopped because of an apparent excess of death resulting from pancytopenia.65 Molecules that are combined inhibitors of NEP and other enzymes (eg, ACE, ECE), however, are in active development in CHF (see below).

**Combined NEP/ACE Inhibitors**

A number of these molecules have been described, and one, omapatrilat, has been compared with an ACE inhibitor (lisinopril) in a moderate-size short-term study (IMPRESS).66 Omapatrilat is also currently under evaluation in a major mortality trial (OVERTURE), in which it is being compared with enalapril (Table). Clearly, the philosophy behind this sort of intervention is to simultaneously suppress a harmful neurohumoral system, the renin-angiotensin-aldosterone system, while augmenting a beneficial one (the NP system). Given that NEP may also metabolize angiotensin II and bradykinin, there is some pharmacological synergy from the dual action of this molecule.67 Acute augmentation of bradykinin levels with dual NEP/ACE inhibitors has also led to concerns that angioneurotic edema may be more common and more severe than with simple ACE inhibitors. The recently completed OCTAVE in hypertension and the ongoing OVERTURE Study in CHF should clarify the extent of this risk.

Other dual NEP/ACE inhibitors are under clinical development.68,69 Additional molecules with multiple neurohumoral actions have been developed, including dual NEP/ECE inhibitors and triple-enzyme, NEP/ACE/ECE, inhibitors.60,70

**Arginine Vasopressin Antagonists**

Arginine vasopressin (AVP) is a powerful vasoconstrictor and potent antidiuretic agent.71 Plasma AVP concentrations are increased in CHF to levels known to have systemic hemodynamic and other biological effects. Less is known about the association between AVP concentrations and the severity of CHF and between these concentrations and prognosis.

AVP acts via V1 receptors, found on the blood vessels and myocardium, and V2 receptors, responsible for the action of the peptide on water reabsorption in the renal tubule.

Nonpeptide, orally active, selective V1 and V2 and mixed V1/V2 receptor antagonists have recently been developed and are in the early phase of clinical development.72 Acute administration of a V1 receptor antagonist has been shown to have favorable hemodynamic actions, and V2 receptor antagonists have been shown to induce diuresis and improve hyponatremia.71,72

**Note Added in Proof**

Both OVERTURE and ENABLE have recently been 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.

**Appendix**

**Clinical Trial Acronyms**

A-HeFT, African American heart failure trial; AIRE, Acute Infarction Ramipril Efficacy study; AVID, Antiarrhythmics Versus Impiantable Defibrillators; BEST, Beta-blocker Evaluation Survival Trial; CAPRICORN, Carvedilol Post-infarct survival ConRolled evaluation; CARMEN, Carvedilol ACE inhibitor Remodelling Mild heart failure Evaluation; CARE-HF, Cardiac Resynchronisation in Heart Failure; CIBIS, Cardiac Insufficiency Bisoprolol Study; CHARM, Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity; CHF-STAT, Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy; CHRISTMAS, Carvedilol Hibernation Reversible Ischemia Trial; Marker of Success; COMET, Carvedilol Or Metoprolol European Trial; COMPANION, Comparison Of Medical therapy and Pacing ANd Defibrillation in Chronic Heart Failure; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol ProspEcific RandoMized Cumulative Survival Trial; DIAMOND, Danish Investigations of Arrhythmias and Mortality ON Dofetilide; ECHO, The Echo Cardiography and Heart Outcome Study; ELITE, Evaluation of Losartan In The Elderly; ENABLE, ENdothelin Antagonist Bosentan for Lowering cardiac Events; ENC, Enrasentan CO-operative Randomized evaluation; EPHESUS, EPeReneon Post-AMI for Heart failure Efficacy and Survival Study; ESSENTIAL, the studies of oral enoximone therapy in advanced heart failure; EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HEART UK, Heart Failure Revascularization Trial-United Kingdom; HOPE, Heart Outcomes Prevention Evaluation; IMPRESS, Inhibition of metalloproteinase by BMS-186716 in a randomized exercise and studies study: MADIT, Multicenter Autonomic Defibrillator Implantation Trial; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in, congestive Heart failure; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MOXCON, MOXonidine in CONgestive heart failure; MUSTIC, MultiSite Stimulation in Cardiomyopathies; OCTAVE, Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril; OPTIMAAL, Optimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan; OVERTURE, Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; PEACE, Prevention of Events with Angiotensin Converting Enzyme; PEP-HF, Perindopril for elderly people with chronic heart failure; RALES, Randomized Aldactone Evaluation Study; REACH, Research on Endothelin Antagonism in Chronic Heart failure; RECOVER, Research into Etanercept CytOkine Antagonism in VEntricu-lar dysfunction trial; REMATCH, Randomized Evaluation of Mechanical Assistance for Treatment of Chronic Heart; RENAISSANCE, Randomized Etanercept North American Strategy to Study ANtagonism of CytokinEs; RENEWAL, Randomized Etanercept Worldwide evALuation; REVIVE, Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short-Term Treatment of Decompensated Heart Failure; SAVE, Survival and Ventricular Enlargement Study; SC-D-HeFT, Sudden Cardiac Death in Heart Failure; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors; SOLVD, Studies of Left Enlargement Study; SCD-HeFT, Sudden Cardiac Death in Heart Failure; STICH, Surgical Treatment for IsChemic Heart Failure; TRACE, TRAndolapril Cardiac Elevation; VAL-HeFT, Val-HeFT, Valsrartan in Heart Failure Trial; V-HeFT, Vasodilator Heart Failure Trial; VALIANT, VALsartan In Acute myocardial iNfarction Trial; WATCH, Warfarin Antiplaque Therapy in Chronic Heart failure.

**References**


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Circulation. 2002;105:2099-2106
doi: 10.1161/01.CIR.0000014763.63528.9D
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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