Limitations of Current Medical Therapies for the Treatment of Heart Failure

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The medical treatment of heart failure has evolved over the past 40 years, from the primary use of diuretics and digitalis in the 1960s to the use of inotropic agents and vasodilators in the 1970s. More recently, the focus has been on the neurohormonal system, specifically the renin-angiotensin-aldosterone system and the sympathetic nervous system. Drugs that inhibit or block these systems (eg, angiotensin-converting enzyme inhibitors and ß-blocking drugs) are the primary agents recommended in recent heart failure guidelines. However, the actual percent reduction in mortality associated with the use of these agents has been relatively modest. This article will review the results and limitations of medical therapy for heart failure. Our understanding of the pathogenesis of heart failure may be incomplete, and alternative strategies, including mechanical devices, may play an increasing role in the treatment of heart failure in the future.

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As the postwar generation of Americans continues to age, the incidence and prevalence of heart failure has increased significantly.[1] The medical treatment of this syndrome has evolved over the past 40 years, from the primary use of diuretics and digitalis—used largely in an attempt to ameliorate signs and symptoms of volume overload in the 1950s and 1960s—to the use of inotropic agents and vasodilators in the 1970s. More recently, the focus has been on the neurohormonal system, specifically the renin-angiotensin-aldosterone

Table 1
Landmark ACE Inhibitor Mortality Trials

Study	Drug	Dosing	Survival Benefit	Study Duration
SAVE[20]	Captopril	12.5–50 mg tid	$P \leq .019$	2–5 years
AIRE[21]	Ramipril	2.5–5 mg bid	$P \leq .002$	Up to 4.5 years
CONSENSUS II[22]	Enalaprilat IV	5–20 mg bid	$P \leq .260$	14 months
SOLVD[23]	Enalapril	2.5–10 mg bid	$P \leq .001$	37 months
TRACE[24]	Trandolapril	1–4 mg qd	$P \leq .001$	2–4 years

ACE, angiotensin-converting enzyme.

system (RAAS) and the sympathetic nervous system.[2–4] A number of randomized, prospective, placebo-controlled trials have demonstrated the unequivocal benefit of drugs that inhibit or block these systems (eg, angiotensin-converting enzyme [ACE] inhibitors and β-blocking drugs) in the treatment of heart failure of all levels of severity. These two classes of drugs are the primary agents recommended in recent heart failure guidelines.[5] However, the actual percent reduction in mortality associated with the use of these agents has been relatively modest (see below). Recently, data from animal models of heart failure and from clinical studies have identified several substances (eg, tumor necrosis factor [TNF], endothelin-1, neutral endopeptidase) that are strongly correlated with severity of heart failure. This has generated new hypotheses and potential targets for drug therapy, leading to a number of new drugs to be tested in randomized, clinical trials (see below). Unfortunately, none of these new agents has demonstrated a favorable impact on survival in patients with heart failure. This review will examine the results and limitations of medical therapy for heart failure.

There are a number of intrinsic problems with any form of drug therapy, not just that for heart failure, including patient compliance, drug absorption, side effects, drug-drug interactions, and cost. In addition, many patients may be receiving agents that have demonstrated efficacy for the treatment of heart failure (eg, ACE inhibitors, β-blockers) but in doses well below those demonstrated to be effective in clinical trials.

There is some evidence that suggests that patients in the general population do not fare as well as those enrolled in clinical trials.

The prevalence of heart failure is clearly increasing, as is the number of deaths associated with the disease.[1] The practice of medicine has also evolved to focus on evidence-based practice (ie, guided by the results of large, prospective, randomized trials). Some evidence suggests that patients in the general population do not fare as well as those enrolled in clinical trials.[6] Because of their typically large sample size, most clinical trials offer the feature of minimizing the chances of random error in their findings. However, relatively modest absolute differences in outcomes can result in robust statistical differences. Other factors, such as race,[7–9] sex,[10] age[11] and, potentially, disease etiology[12] may also significantly influence the responsiveness of a given population to heart failure drug therapy.

ACE Inhibitors

The ability of ACE inhibitors to improve survival in patients with heart failure has been demonstrated in numerous randomized, prospective, placebo-controlled trials, including thousands of patients. These trials have included patients with Stage A to Stage D heart failure, such as the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[13] the Valsartan Heart Failure Trial (Val-HeFT),[14] Val-HeFT II,[15] the Studies of Left Ventricular Dysfunction Treatment and Prevention (SOLVD),[16] and the Heart Outcomes Prevention Evaluation (HOPE) trial, as well as post-myocardial infarction patients with decreased ejection fraction, such as the Acute Infarction Ramipril Efficacy (AIRE) trial, Survival and Ventricular Enlargement (SAVE) trial, and Trandolapril Cardiac Evaluation (TRACE) trial.[17,19-21] Although the per-

cent reduction in mortality has been highly significant, the actual reduction in mortality with ACE inhibitors has averaged only 3%–4%.

Francis and colleagues[18] confirmed the importance of the RAAS in the pathogenesis of heart failure. In this study, examination of blood samples from patients enrolled in the SOLVD Study[18] demonstrated a significant correlation between elevations of neurohormones (including norepinephrine, atrial natriuretic factor, renin, and arginine vasopressin) and worsening severity of heart failure, compared with control patients.

The overwhelming body of evidence demonstrating a survival advantage with ACE inhibition in patients with heart failure (Table 1)[22-24] led the U.S. Food and Drug Administration to mandate the use of an ACE inhibitor, digitalis, and a diuretic as maintenance therapy in any trial testing a new drug for the treatment of heart failure.

Several investigators have examined the role of the dose of ACE inhibitors and were somewhat surprised to find that doses as high as 40 mg/d or 60 mg/d of enalapril were associated with persisting elevations of neurohormone levels prior to next dose.[25-26] This observation led to a body of research demonstrating that there are indigenous substances, including caspase and cathepsin, that are able to convert angiotensin I to angiotensin II by an alternate pathway when the primary pathway is blocked by the use of ACE inhibitors, thereby leading to increased levels of angiotensin II (and subsequently aldosterone) and propagation of the heart failure syndrome (Figure 1).[27-36] This understanding led to the design of drugs that selectively block the angiotensin receptor, typically the AT_1 subtype (which leads to vasoconstriction and, thereby, enhances the effect on the AT_2 receptor, which leads to vasodilation). These are known as angiotensin receptor blockers (ARBs).

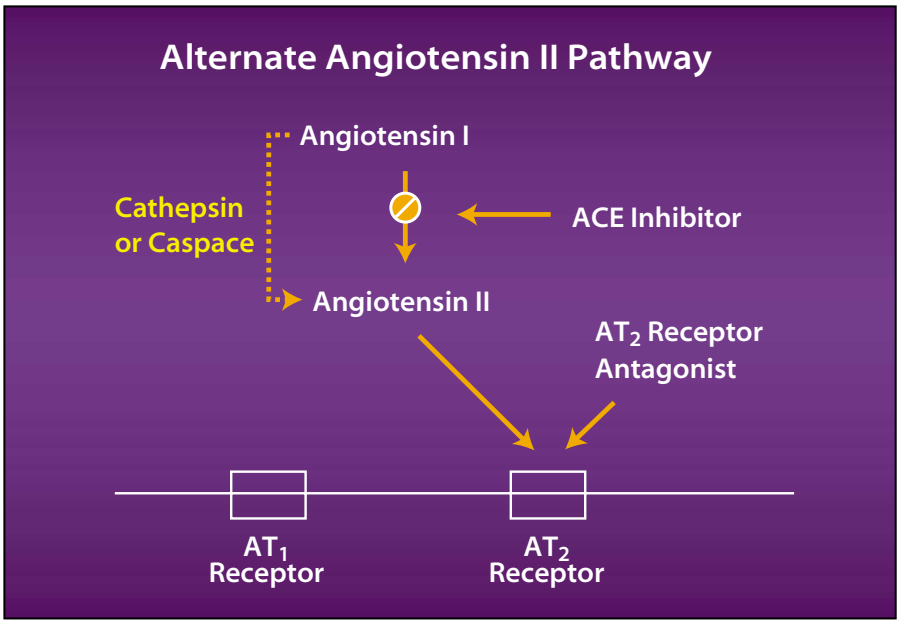

Figure 1. *Angiotensin-converting enzyme (ACE)–independent angiotensin II production. Approximately 70%–80% of all angiotensin II in the normal human heart (from autopsy) is made by cardiac chymase (from mast cells). In diseased human heart and coronary arteries (from heart transplant), approximately 70%–80% of angiotensin I to angiotensin II is converted by cardiac chymase. See references 25–34.*

Patients unable to take an ACE inhibitor who were randomized to the ARB arm of the Val-HFT study showed a reduction in mortality similar to that seen in ACE inhibitor trials.

Angiotensin Receptor Blockers

The initial clinical trial of ARBs in heart failure patients was designed to compare the nephrotoxicity of the ARB losartan with the ACE inhibitor captopril (Evaluation of Losartan in the Elderly [ELITE]).[37] Unexpectedly, this trial demonstrated a significant survival advantage in favor of the ARB. This surprising finding led to the larger ELITE II trial,[38] which also compared an ACE inhibitor with an ARB but, unlike ELITE I, was adequately powered to assess survival as the primary end point. ELITE II demonstrated an almost identical all-cause mortality between the two agents, but a small trend in favor of the ACE inhibitor over the ARB in all end points examined. More recently, the strategy of adding an ARB to an ACE inhibitor was examined in the Val-HeFT study[14]. This trial demonstrated no difference in mortality for patients taking an ACE inhibitor, digitalis, and diuretics who were randomized to the ARB valsartan or placebo. There was, however, a significant reduction in hospitalization associated with the addition of valsartan compared with placebo, leading to a positive (statistically significant) outcome for the combined end point. Patients unable to take an ACE inhibitor who were randomized

Table 2
Major Trials of Beta-Blockade in Heart Failure

Study	Patients (N)	Follow-Up, y	Target Dosage, mg/d	Mean Dosage Achieved, mg/d	Effects on Outcomes
CIBIS[45]	641	1.9	5	3.8	All-cause mortality: NS
CIBIS-II[46]	2647	1.3	10	7.5	All-cause mortality: 34% reduction ($P < .0001$)
MDC[41]	383	1	100–150	108	Death or need for transplant (primary end point): NS
MERIT-HF[44]	3991	1	200	159	All-cause mortality: 34% reduction ($P = .0062$)
U.S. Carvedilol Trials[42,43]*	1094	7.5 months	50–100	45	All-cause mortality†: 65% reduction ($P = .0001$)
ANZ[69]	415	1.5	50	41	Death or all-cause hospitalization: 26% reduction ($P = .02$)

NS, not significant; ANZ, Australia-New Zealand Study. See text for other expanded trial names.
*Carvedilol is the only agent with β-blockade approved by the U.S. Food and Drug Administration for the treatment of mild-to-moderate heart failure.
†Not a planned end point.

to the ARB arm showed a reduction in mortality similar to that seen in ACE inhibitor trials, in an actual reduction of 4.5%, reconfirming the importance of the RAAS in heart failure. One unexpected finding was that patients who were taking a β-blocker plus an ACE inhibitor had a significantly increased risk of mortality when randomized to also receive the ARB.

Diuretics

Diuretics have been shown to have a number of adverse effects, including volume depletion, electrolyte disturbance, and increased risk of arrhythmia. One positive trial of a diuretic for the treatment of heart failure was the Randomized Aldactone Evaluation Study (RALES),[39] which examined the use of spironolactone. This trial, which included Class III and IV heart failure patients receiving an ACE inhibitor and digitalis, was stopped early due to a demonstrated survival benefit. The mechanism of benefit in this trial using only 25 mg of spironolactone may have been in maintaining a higher average, less arrhythmogenic, serum potassium level. However, hyperkalemia can be a serious problem in some patients taking an ACE inhibitor and spironolactone.

ß-Blockers

The concept of using a β-blocker drug in the management of patients with heart failure was long thought to be counterintuitive, given the demonstrated negative inotropic and chronotropic effects of this class of drugs in physiologic testing in animal models of heart failure. However, Cohn and colleagues[40] demonstrated the adverse impact of increased stimulation of the sympathetic nervous system in patients with heart failure, showing a high inverse correlation between the level of circulating plasma norepinephrine and survival. The initial β-blocker trial in heart failure patients was the Metoprolol Dilated Cardiomyopathy (MDC) trial,[41] which examined only younger patients with non-ischemic cardiomyopathy. Although it just missed demonstrating statistical significance in being associated with reduced mortality ($P = .07$), use of metoprolol was associated with significant improvement in exercise capacity, functional capacity, and ability to have patients removed from a heart transplant list. More recently, a body of evidence has accumulated regarding newer β-blockers, including the combination α- and β-blocker drug carvedilol.[42,43] The U.S. Carvedilol Trial[43] examined more than 1000 patients with Class II–IV heart failure symptoms and ejection fractions less than 35% who were receiving

ACE inhibitors, digitalis, and diuretics. All patients underwent exercise testing, were stratified based on their exertional capacity, and were then randomized to additionally receive either placebo or carvedilol. Patients randomized to carvedilol had a 65% relative reduction in mortality and a 7.4% absolute reduction in all-cause mortality. This survival advantage was in addition to that expected to be derived from the use of ACE inhibitors. The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) trial,[44] which examined the use of long-acting metoprolol in a similar cohort of patients, demonstrated a 35% relative reduction in mortality and an actual reduction of 4.5%. A similar benefit of β-blockers was demonstrated in the Cardiac Insufficiency Bisoprolol Study (CIBIS)[45] and CIBIS II[46] trials (Table 2).

The first trial that failed to demonstrate a benefit of β-blockers in heart failure patients was the Beta-Blocker Evaluation of Survival Trial (BEST),[47] which examined the β-blocker bucindolol. This trial was somewhat different from the two previous β-blocker trials in that it examined more Class III and IV heart failure patients and, importantly, enrolled a two-to-three-fold greater percentage of African Americans. Examination of reasons for the failure to demonstrate a benefit in this trial led to the observation that African American patients, who have a much higher incidence of hypertension as the cause of heart failure (which is often a low renin state and not particularly responsive to β-blockers) showed no benefit from the use of bucindolol.[7–9] Conversely, the Caucasian population in this trial had a relatively favorable outcome. These data caution against the extrapolation of trial data to all patients with heart failure. More recently, the use of carvedilol in patients with Class III or IV heart failure was further explored in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial,[48–50] which showed an absolute reduction in mortality of approximately 5%. ß-blockers do not alter the circulating levels of catecholamines; they only block their physiologic effect at the receptor. It is noteworthy that the SR Moxonidine for Congestive Heart Failure (MOXCON) trial,[51] which examined the use of moxonidine, a central acting agent that reduces circulating norepinephrine levels rather than just blocking β receptors, was stopped early due to increased mortality in the patients receiving moxonidine.

Numerous studies examining the role of calcium channel blockers in the treatment of heart failure have uniformly failed to demonstrate any survival advantage.

Digitalis

Digitalis is the drug of longest clinical use in the management of patients with heart failure. The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)[52] and Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE)[53] trials demonstrated that withdrawal of digitalis in patients with reduced ejection fraction and symptomatic heart failure led to a significantly increased risk of recurrent heart failure compared with placebo. This led to the multicenter, multinational, National Institutes of Health–sponsored Digitalis Investigation Group (DIG) trial.[54] Patients who were receiving an ACE inhibitor and diuretic were randomized to digitalis or placebo. This trial demonstrated absolutely no difference in survival associated with the use of digitalis compared with placebo in patients with Class II–III heart failure. Examination of cause of death showed that digitalis was associated with reduced hospitalization and death from heart failure but an almost identical increase in the risk of sudden death.

Calcium Channel Blockers

The concept of using vasodilators to lower systemic vascular resistance and decrease myocardial work in patients with heart failure seemed a reasonable hypothesis. However, numerous studies examining the role of calcium channel blockers in the treatment of heart failure have uniformly failed to demonstrate any survival advantage. Most recently, the V-HeFT III trial[55] which examined felodipine, and the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial[12] which examined amlodipine, similarly showed no beneficial effect on survival. However, subgroup analysis of the PRAISE trial[12] demonstrated a significant benefit in response to amlodipine in patients with non-ischemic etiology, compared with an adverse effect in patients with ischemic etiology. This was not a post hoc analysis but a predefined subset analysis, and it demonstrates the potential variability in response to some drugs for treatment of heart failure.

Investigational Agents/Trials

Tumor Necrosis Factor

The role of inflammation in the

pathogenesis of heart failure has been suggested by a number of investigators, based on several animal models.[5,56,57] Torre-Amione and colleagues[58] examined the levels of TNF-α in patients enrolled in the SOLVD treatment trial and showed a linear correlation between increasing levels of TNF-α and progressively severe heart failure. Similarly, by cut-point analysis, there was a highly significant increase in mortality in heart failure patients with moderate or greater elevations of TNF-α levels.

A pilot trial demonstrated a significant benefit of a humanized monoclonal antibody directed against the soluble TNF-α receptor.[59] This led to the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial in North America and the Research into Etanercept Antagonism in Ventricular Dysfunction (RECOVER) trial in Europe, examining the use of a subcutaneous injection of the antibody three times a week in patients with Class II–IV heart failure.[60,61] Despite all of the encouraging preliminary evidence, both trials were stopped prior to completion for failure to show efficacy.

Endothelin Receptor Antagonists

Another molecule that has been shown to be elevated in direct correlation with the severity of heart failure is the vasoconstrictor substance endothelin. Several randomized, clinical trials of selective and nonselective endothelin receptor antagonists have been completed (Resource Utilization Among Congestive Heart Failure [REACH],[62] Enrasentan Cooperative Randomized Evaluation [ENCOR], Heart Failure ET(A) Receptor Blockade Trial [HEAT],[63] and Randomized Intravenous Tezosentan for the Treatment of Pulmonary Edema [RITZ][64]). Unfortunately, none of these trials was able to demonstrate a survival benefit with this class of drugs in patients with heart failure.

Vesnarinone

Patients with heart failure die largely of either congestive failure or arrhythmic death. Vesnarinone is a drug with combined type C anti-arrhythmic properties as well as phosphodiesterase inhibitor–type inotropic properties. Preliminary trials in patients with heart failure demonstrated a significant reduction in mortality at the lower of two doses (60 mg/d vs 120 mg/d) that were examined. The higher dose was associated with increased mortality. This led to the large-scale, randomized, double-blind, placebo-controlled Vesnarinone Trial (VEST),[65] which compared the original low dose (60 mg) and an even lower dose (30 mg) with placebo. The study was stopped prematurely due to increased mortality in both of the vesnarinone active-treatment arms.

Omapatrilat

Another drug with an attractive profile is omapatrilat. This drug inhibits the renin-angiotensin system and is also a neutral endopeptidase inhibitor that inhibits the breakdown of circulating natriuretic peptides. The pilot trial of omapatrilat, Inhibition of Metallo Protease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure (IMPRESS),[66] showed a benefit in patients with chronic heart failure. However, this agent was recently examined in the large, prospective, randomized, Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial.[67,68] Unfortunately, like all of the above agents, this trial was stopped prematurely owing to lack of efficacy.

Several other agents have failed to show benefit in patients with heart failure, including enoximone, ibopamine, and flosequinan. However, a number of new therapies are currently under investigation, including vasopressin antagonists, calcium-sensitizing inotropic agents, immune-modulating therapy, as well as indirect therapy, such as treatment of anemia (common in heart failure patients) with erythropoietin stimulants or analogs. It remains to be demonstrated whether these promising agents and strategies will offer any proven benefit or will join the list of other promising strategies that have failed to show a survival benefit in patients with heart failure.

Despite all of the encouraging preliminary evidence, the RENAISSANCE and RECOVER trials were stopped prior to completion for failure to show efficacy.

Conclusion

Perhaps mortality is not the only end point that should be examined in trials of agents for the treatment of heart failure. Many trials have used the combined end point of hospitalization or worsening heart failure. However, using the "gold standard" of survival, only ACE inhibitors and β-blockers have been able to demonstrate consistent survival advantage over time, and they remain the cornerstone of current guidelines for the treatment of heart failure.[5] Addition of an ARB may not have added benefit in terms of survival advantage over an ACE inhibitor and β-blocker, but it serves

as an effective alternative for patients unable to receive ACE inhibitors.

Collectively, this information suggests that our understanding of the pathogenesis of heart failure is incomplete and that alternative strategies, including mechanical devices, may play an increasing role in the treatment of heart failure in the future. Devices such as biventricular pacemakers eliminate the problems of drug compliance and drug interaction and, although clearly more expensive and more invasive, may also offer some advantage by improving ventricular function and leading to reverse remodeling. It is clear that new strategies are needed to treat the ever-increasing population of patients with heart failure. ■

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Main Points

- Devices such as biventricular pacemakers eliminate the problems of drug compliance and drug interaction and may offer some advantage by improving ventricular function and leading to reverse remodeling.
- Although the percent reduction in mortality with angiotensin-converting enzyme (ACE) inhibitors in heart failure has been highly significant, the actual reduction in mortality with these agents has averaged only 3%–4%.
- Addition of an angiotensin receptor blocker for treatment of heart failure may not have added benefit in terms of survival advantage over an ACE inhibitor and β-blocker, but it serves as an effective alternative for patients unable to receive ACE inhibitors.
- Diuretics have been shown to have a number of adverse effects, including volume depletion, electrolyte disturbance, and increased risk of arrhythmia.
- Evidence has accumulated regarding newer β-blockers: patients in the U.S. Carvedilol Trial randomized to carvedilol had a 7.4% absolute reduction in all-cause mortality; patients randomized to metoprolol in MERIT-HF demonstrated an actual reduction in mortality of 4.5%; similar benefit of β-blockers was demonstrated in the CIBIS and CIBIS II trials. However, in BEST, patients with Class III or IV heart failure who were randomized to the β-blocker bucindolol did not show a survival advantage.
- The DIG trial demonstrated absolutely no difference in survival associated with the use of digitalis compared with placebo in patients with Class II or III heart failure, and examination of cause of death showed that digitalis was associated with reduced hospitalization and death from heart failure but an almost identical increase in risk of sudden death.
- Numerous studies examining the role of calcium channel blockers in the treatment of heart failure have uniformly failed to demonstrate any survival advantage.
- Recently, data from animal models of heart failure and from clinical studies have identified several substances (eg, tumor necrosis factor, endothelin-1, neutral endopeptidase) that are strongly correlated with severity of heart failure. This has generated new hypotheses and potential targets for drug therapy, leading to a number of new drugs to be tested in randomized, clinical trials. Unfortunately, none of these new agents have demonstrated a favorable impact on survival in patients with heart failure.

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