Management of Heart Failure: a Brief Review and Selected Update

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KEYWORDS

• Heart failure • Treatment

Clinical trials in heart failure (HF) are designed to identify effective and safe therapies that reduce mortality and improve symptoms. In the past few decades, many novel mechanistic targets have been proposed, and physicians now have an abundance of proven therapies. The early drug development experience from the late 1970s through the 1990s was highly successful, but more recently it has become increasingly difficult to demonstrate efficacy and safety in the development of new drugs for HF.[1]

As pharmacologic targets become more complex, so also do clinical trials. The vasodilator strategy described years ago is still appropriate today, and neurohormonal blockade has proven remarkably durable over time. It is becoming more challenging, however, to investigate new therapeutic targets, design drugs that affect the target, and move on to a clinical trial. Regulatory agencies require one or two large mortality trials, and they do not accept surrogate endpoints such as left ventricular (LV) remodeling or reduced B-type natriuretic peptide (BNP) as primary endpoints. Clinical trials today tend to be multicentered, randomized, placebo-controlled, double-blinded, and require large sample sizes to demonstrate meaningful difference between therapies, all of which makes them very expensive. Control groups are treated with effective drugs, making it more difficult to show survival benefit.

"One size does not fit all" is a frequent claim of clinicians. In this era in medicine, therapy is likely to be increasingly tailored to the individual patient. It is now widely recognized that a medication that benefits one patient may be ineffective in another. Trialists, however, still tend to homogenize their patient samples to reduce the variance of response. In doing so, the sample size of patients can be made smaller (ie, less expensive), but the homogenized sample of patients may ultimately not be very representative of "real world" patients. The elderly and those with serious comorbid conditions, such as renal insufficiency and lung disease, are frequently excluded from clinical trials. This has created problems.

This article first reviews what the authors consider to be the landmark trials that have brought us to where we are today (**Table 1**, a–d). The authors describe and analyze some more novel targets and therapeutic agents, as well as their respective performance in clinical trials. Further, the authors speculate about the future.

LANDMARK CLINICAL TRIALS

Table 1 highlights studies that have created the modern framework on which today's conventional therapy for chronic HF rests. In the 1980s, the Pfeffers and many others developed the concept that the core lesion of chronic HF is progressive left ventricular remodeling.[2] In response to myocardial injury, perverse loading conditions, cardiac inflammation, altered myocardial gene expression, or infiltrative processes within the myocardium, the heart tends to progressively hypertrophy, dilate, and eventually manifests reduced LV systolic function.[3] Some, but not all of these changes in LV geometry and performance are driven by

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Table 1
Review of trials

Trial	Study Drug	Patients	Primary Endpoint	Difference Between Treatments
a. ACE Inhibitors				
CONSENSUS[4] NYHA IV	Enalapril versus placebo	253	-All cause mortality	*P* = .003 in favor of enalapril
SOLVD[5] Reduced EF and HF	Enalapril versus placebo	2569	-All cause mortality	*P* = .0036 in favor of enalapril
SAVE[6] Post-MI Study	Captopril versus placebo	2231	-All cause mortality -Mortality from CV causes -CV morbidity -CV morbidity and mortality -HF -Hospitalization to treat HF	Favors captopril (*P* = .019)
AIRE[7] Post-MI Study	Ramipril versus placebo	1986	-All cause mortality	*P* = .002 in favor of ramipril
ATLAS[8] Chronic HF	Lisinopril low versus high dose	3164	-All cause mortality	*P* = .128 in favor of high dose treatment
HOPE[9] High risk patients	Ramipril versus placebo	9541	-MI -Stroke -Death from CV causes	Favors ramipril p = <0.001
EUROPA[10] Stable CAD	Perindopril versus placebo	12,218	-CV mortality -Non-fatal MI -Resuscitated cardiac arrest	Trend in favor of perindopril *P* = .10
PEACE[11] Stable CAD	Trandolapril versus placebo	8290	-Death from CV causes -Non fatal MI -Revascularization	Trend in favor of trandolapril *P* = .43
PEP-CHF[12] Elderly	Perindopril versus placebo	852	-Total mortality -Unplanned heart failure hospitalization	Trend in favor of perindopril *P* = .545
b. β-blockers				
MDC[13] Idiopathic dilated cardiomyopathy	Metoprolol versus placebo	383	-All cause mortality -Clinical deterioration requiring cardiac transplantation.	Trend in favor of metoprolol *P* = .058

ANZ Carvedilol[14] Chronic HF	Carvedilol versus placebo	415	-Changes in LV ejection fraction. -Changes in treadmill exercise duration.	$P \leq .0005$, (LV ejection fraction) and $P \geq 0.5$ (treadmill exercise duration). In favor of carvedilol
US Carvedilol[15] Chronic HF	Carvedilol versus placebo	1094	-All cause mortality	$P < .001$ in favor of carvedilol
CIBIS-II[16] NYHA III-IV.	Bisoprolol versus placebo	2647	-All cause mortality	$P \leq .0001$ in favor of bisoprolol
MERIT-HF[17] Chronic HF	Metoprolol CR/XL versus placebo	3980	-Vital status -CV death -Death from HF -Sudden death	$P = .0062$ in favor of the beta-blocker
BEST[18] NYHA III-IV.	Bucindolol versus placebo	2708	-All cause mortality	Trend in favor of bucindolol ($P = .16$)
COPERNICUS[19] NYHA III-IV.	Carvedilol versus placebo	2289	-All cause mortality	$P = .0014$ in favor of carvedilol
COMET[20] Chronic HF	Carvedilol versus Metoprolol	3029	-All cause mortality or admission to hospital	$P = .0017$ in favor of carvedilol
CIBIS-III[21] Chronic HF	Bisoprolol versus Enalapril In drug naïve patients	1010	-Combined all cause mortality or hospitalization	Bisoprolol and enalapril similar
SENIORS[22] Elderly	Nebivolol versus placebo	2128	-Death or cardiovascular hospital admission	Trend in favor of nebivolol $P = .039$
c. ARBs				
ELITE II[23] Symptomatic HF-elderly	Losartan versus Captoril	3152	-All cause mortality	Trend in favor of losartan $P = .16$
Val-HeFT[24] Chronic HF	Valsartan versus placebo (most patients already on ACE inhibitor)	5010	-Mortality -Mortality and morbidity	Valsartan similar to ACE inhibitor
OPTIMAAL[25] Post-MI study	Losartan versus Captopril	5477	-All cause mortality	$P = .07$ in favor of losartan
CHARM-Alternative[26] HF patients intolerant to ACE inhibitors	Candesartan versus placebo	2028	-All cause mortality or -Hospital admission for CHF	$P \leq .0001$ in favor of candesartan
CHARM-Added[27] HF patients on ACE inhibitors	Candesartan versus placebo	2548	-All cause mortality or -Hospital admission for CHF	$P = .105$ trend in favor of adding candesartan to ACE inhibitors
CHARM-Preserved[28] HF with preserved EF	Candesartan versus placebo	3023	-All-cause mortality or -Hospital admission for CHF	$P = .051$ trend in favor of adding candesartan

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Table 1
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Trial	Study Drug	Patients	Primary Endpoint	Difference Between Treatments
VALIANT[29] Post-MI study	Valsartan versus Captopril versus combination of both.	14,703	-All cause mortality	All groups have similar effects
d. Vasodilators				
V-HeFT-I[30] Chronic HF	Prazosin versus hydralazine and isosorbide dinitrate versus placebo	642	-Mortality	$P = .046$ in the hydralazine and isosorbide dinitrate treatment grouptable_head
V-HeFT–II[31] Chronic HF	Hydralazine and isosorbide dinitrate versus Enalapril	804	-Mortality -Peak VO2 -LVEF -Plasma norepinephrine levels	favors enalapril ($P \leq .05$) at 2 years
PRAISE II[32] NYHA III-IV	Amlodipine versus placebo	1652	-All cause mortality	Amlodipine and placebo similar; no harm from amlodipine
VMAC[33] Acute HF	Nesiritide versus nitroglycerine versus placebo	489	-Self-evaluation of dyspnea -Changes in PCWP	$P = .03$ for dyspnea in favor of nesiritide
A-HeFT[34] African-American with HF	Bidil versus placebo. Bidil = combination of isosrbide dinitrate and hydralazine.	1050	-All-cause mortality -Hospitalization for HF -Change of quality of life	Favors Bidil ($P = .01$)
e. Others				
DIG[35] Chronic HF	Digoxin versus placebo	3397	-All cause mortality	$P = .80$, digoxin and placebo similar
RALES[36] NYHA III-IV	Spironolactone versus placebo	1663	-All cause mortality	$P \leq .001$, favors spironolactone
EARTH[37] Chronic HF	Darusentan versus placebo. Darusentan= endothelin receptor blocker	642	-Change in LVESV -6-min walk test -Quality of life	No significant difference between placebo and darusentan

ENABLE-1 & 2[38] NYHA IIIb-IV	Bosentan versus placebo Bosentan = endothelin receptor blocker	1613	-Death and -Hospitalization for heart failure	$P = .8976$ (not published)
EPHESUS[39] Post-MI study	Eplerenone versus placebo	6632	-Time to death from any cause and -Time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia	favors eplerenone ($P = .008$)
MOXCON[40] Chronic HF	Moxonidine versus placebo Moxonidine = sympatholytic agent.	1934	-All cause mortality	Stopped early by DSMB due to excess fatalities from monoxidine group
RENAISSANCE/RECOVER)[41] Chronic HF	Etanercept versus placebo Etanercept = TNFα blocker	925/1123	-Clinical status at 24 weeks	No significant difference
VERITAS[42] Acute HF	Tezosentan versus placebo Tezosentan = endothelin receptor blocker	1435	-All cause mortality -Worsening HF	Stopped early by DSMB due to low probability of achieving a significant treatment effect

Abbreviations: EF, ejection fraction; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PCWP, pulmonary capillary wedge pressure; Peak VO2, peak oxygen uptake.

neurohormonal activation, including excessive sympathetic activity and heightened activity of the renin-angiotensin-aldosterone system (RAAS). Chronic blockade of these systems with β-adrenergic blocking drugs and agents that inhibit the RAAS such as angiotensin converting enzyme (ACE) inhibitors, aldosterone receptor blockers, and angiotensin receptor blockers (ARBs) reduces progressive LV remodeling and improves patient survival. These agents, along with diuretics, constitute the core treatment for chronic HF today.

Despite many successful clinical trials, the annual mortality for HF remains about 8%–10% per year (down from about 20% per year 30 years ago), and there is an ongoing quest to find newer, safer, and more efficacious drugs. This has been a difficult road because new treatment strategies must be now tested on top of effective therapy.[1] Demonstrating a meaningful incremental improvement in survival by adding additional drugs has been challenging in the face of treatment with baseline β-blockers, ACE inhibitors, ARBs, and aldosterone receptor blockers. Recently, new devices such as cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICDs) have accounted for more success in improving patient survival than new drugs. Moreover, there have been almost no new drugs introduced for the treatment of acute HF, as there is the vexing problem as to which clinical endpoints to measure and how to measure them. Lastly, it has become apparent that diuretic therapy is not uniformly effective in acute HF, and new strategies to reduce salt and water retention are being explored.

NEWER MEDICAL THERAPIES

Levosimendan for Acute HF

Intravenous inotropes are still widely used to improve hemodynamic parameters in patients with acute decompensated HF, but these agents have never demonstrated a survival benefit. In fact, inotropic agents almost uniformly increase mortality.[43] Levosimendan, a calcium sensitizer, is a new class of inotropic drug that has been evaluated and is used primarily in Europe. It has a different mechanism of action than the currently more widely used inotropes such as dobutamine and milrinone. The drug induces positive inotropy by binding to the calcium saturated N-terminal domain of cardiac troponin C, thus stabilizing and prolonging the lifespan of the molecule without impairment in filament relaxation. Levosimendan seemingly does not increase myocardial oxygen consumption despite increasing myocardial contractility. Other benefits of the drug include peripheral and coronary vasodilation and antiischemic effects mediated by opening of ATP-dependent potassium channels. Levosimendan is highly bound to plasma protein and is metabolized by the liver, rendering the half-life to be quite long (80 hours). The active moiety is likely not the levosimendan molecule but a degradation product. One of the drawbacks of levosimendan is prolonged hypotension, which can be prevented by keeping LV filling pressures adequate. Levosimendan is used in Europe but is not approved in the United States.[44]

Several clinical studies evaluating the efficacy and safety of levosimendan have been performed. They have demonstrated improvement in acute hemodynamic parameters and symptoms, with a trend toward prolonging short-term survival (Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure due to an Acute Myocardial Infarct [RUSSLAN], Levosimendan Infusion versus Dobutamine [LIDO] and Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure [CASINO] trials). However, these trials were relatively small trials performed in Europe and they were generally of short duration.

Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) was a large randomized, double-blind study conducted in Europe that compared levosimendan to dobutamine. The study included 1327 patients with acute decompensated HF and a left ventricular ejection fraction (LVEF) <30% who were followed for 180 days after randomization. The primary endpoint of this study was all-cause mortality. At 30 and 180 days, there was no difference between the two groups ($P = .29$ and .40 respectively). After 5 days, BNP was lower in the levosimendan group compared with dobutamine (46% reduction versus 13% reduction respectively). The study showed evidence of regional heterogeneity in results, suggesting that differences in clinical practice may have influenced outcome.[45] Traditionally, comparator studies such as SURVIVE have a difficult time demonstrating a robust and clear ''winner,'' and this may be particularly the case in acute HF where there is ambiguity about which clinical outcome to measure and when to measure it, making interpretation even more difficult.

The Second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE-2) compared levosimendan versus placebo in 600 patients with acute decompensated HF unresponsive to conventional therapy who were followed up for 90 days after randomization. The primary endpoint of this study was a composite outcome

including changes in symptoms, death or worsening HF over 5 days. There was no significant reduction in mortality between the two groups (15.1% versus 11.6% [P = .210]). In the levosimendan group, there was 33% improvement in patient symptoms, and 30% fewer patients worsened compared with placebo (P = .015). The length of stay was 2 days shorter (P = .001) and BNP levels were lower in the levosimendan group. There were 10 more deaths at 90 days in the levosimendan arm, but this difference was not statistically significant because of the small sample size. Another observation was that the levosimendan group had more hypotension and atrial fibrillation than the control group. The lack of positive survival data is disappointing,[46] and, to date, the levosimendan portfolio has not been forwarded to the Food and Drug Administration for approval in the United States.

Nesiritide for Acute Heart Failure

Nesiritide is an approved form of human B-type natriuretic peptide synthesized by using recombinant DNA techniques. It is prescribed for patients who have acute HF. Nesiritide has modest natriuretic properties and is a systemic vasodilator. It has been widely used in the United States but not in the rest of the world. Its high-tech production makes the drug relatively expensive. Nesiritide was quickly adopted in the United States soon after its approval, but its use has waned over time, in part due to concerns raised about its efficacy and safety.[47] It produces its pharmacologic effects by binding to the guanlylate cyclase receptor on endothelial and smooth muscle cells in the arteries and veins. Like all vasodilators, nesiritide can increase cardiac output and reduce LV filling pressure. It has a long half-life (18 minutes) relative to nitrates and nitroprusside, and has no positive inotropic action. However, it can produce prolonged hypotension, especially if the patient is volume depleted. Nesiritide tends to inhibit neurohormonal activity and blocks proliferative/fibrotic response to injury in the heart in vitro, but the importance of these effects is understudied in patients. The pivotal clinical study leading to approval of nesiritide was done in the United States (Vasodilation in the Management of Acute CHF-VMAC).[33] This study demonstrated improvement in dyspnea in a large, randomized, controlled setting and on this basis nesiritide was approved for use in acute HF. It was rapidly adopted by clinicians, indicating a perceived need for such therapy. Eventually, pooled analysis of several studies suggested a possible increased risk of worsening renal function (RR 1.54, 95% CI, 1.20-1.99; P = .001). A recent large study of serial infusions of nesiritide for chronic severe HF (ie, The Second Follow-up Serial Infusions of Nesiritide- FUSION II) has not replicated this risk.[48] The FUSION II study used intermittent infusions of nesiritide versus placebo in a prospective, randomized, parallel, multicenter, double-blind, placebo-controlled trial in patients with advanced HF (NYHA class III-IV) and a LVEF <40%. The trial was performed on an outpatient basis. Treatment with nesiritide and placebo was allocated using a 2:1 ratio and the treatments were administered once or twice weekly. A total of 911 patients were randomized (306 patients in the placebo group and 605 patients in the nesiritide group). The primary endpoint was time to all-cause mortality or first occurrence of hospitalization for cardiovascular and/or renal causes through week 12. All cause mortality and cardiorenal hospitalization were similar in both groups (P = .98 and 0.95 respectively).[49,50] There were no apparent safety concerns.

A large mortality study with nesiritide, ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) is now underway and its results are awaited.

Vasopressin Antagonists for Chronic Heart Failure

Inappropriately excessive circulating plasma vasopressin levels occur in patients with chronic HF.[51] These levels might contribute to increased vascular resistance and to positive water balance observed in patients with HF. There are at least two vasopressin receptors types in the body. The V1 (V_{1a}, V_{1b}) receptors are located in vasculature and subserve intense vasoconstriction. V2b receptors are located in the distal nephron segments of the kidneys and mediate water re-absorption. Because the goal of most HF drugs is to alleviate symptoms of fluid congestion, removal of excessive water (but not salt) via aquaresis could lead to improvement in hyponatemia and reduce pulmonary and tissue congestion. This was the basis of development of vasopressin antagonists.

Tolvaptan, is an oral, selective vasopressin V2-receptor antagonist that facilitates an aquaresis of mainly electrolyte-free water. There is an associated improvement in hyponatremia, as observed in the very large Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial.[52,53] This placebo-controlled study evaluated the short- and long-term effects of tolvaptan versus placebo in optimally treated patients hospitalized with acute HF. The primary endpoints for the EVEREST program were all-cause mortality and cardiovascular death or

hospitalization for HF. Candidates for this trial were patients with an LVEF of 40% or less hospitalized for HF. Additional endpoints were a composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge. A total of 4133 patients were randomized. Tolvaptan improved serum sodium levels at hospital discharge in patients who were hyponatremic at baseline. At discharge, mean reduction from baseline was grater in the tolvaptan group than placebo (55.6 mg per day versus 42.9 mg per day; p=0.002). Despite the improvements in signs and symptoms of HF, there was no benefit in global clinical status at day 7 or at hospital discharge. Moreover, long-term tolvaptan treatment had no effect on all-cause mortality (P = .68) or the combined endpoints of cardiovascular mortality or subsequent hospitalization for worsening HF (P = .55). It also failed to show any favorable effect on cardiac remodeling, a surrogate endpoint usually associated with improvement in survival.[54] There is no question that these new aquaretic agents, including tolvaptan, conivaptan and other novel arginine vasopressin antagonists provide short-term improvement in hyponatremia and promote water loss. Whether they are useful in improving the long-term natural history of HF is open to question. More clinical investigation will be necessary.

MECHANICAL INTERVENTIONS AND DEVICES

Ultrafiltration

Diuretics have been used to treat HF since the 1950s. However, diuretic refractoriness can occur in patients with acute HF, despite large doses of loop diuretics and metolazone. The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial[55] is the first randomized comparison of intravenous loop diuretic therapy versus ultrafiltration in hypervolemic patients hospitalized with acute HF. It was designed as a prospective, randomized, multicenter trial. There was no ejection fraction inclusion criterion. All patients received conventional HF therapy. The duration and rate of acute fluid removal was at the discretion of the treating physician. The primary endpoint was weight loss and patient's dyspnea assessment 48 hours after randomization to ultrafiltration or medical therapy. The trial also included several secondary endpoints. One hundred patients were enrolled in each arm and followed for 90 days or until death. At 48 hours following randomization, ultrafiltration produced more weight loss than conventional medical therapy (5.0 $\pm$ 3.1 Kg versus 3.1 $\pm$ 3.5 Kg; P = .001), but dyspnea assessment indicated similar scores in both groups. Fewer patients required vasoactive medications for hypotension in the ultrafiltration group than the conventional group (P = .015). Somewhat surprisingly, there was no correlation between the 48-hour dyspnea score and the 48-hour weight or fluid loss. Changes in serum creatinine were similar in both groups at the end of the trial and changes were not reflected by the amount of fluid that was removed. However, serum creatinine did increase more during ultrafiltration more than with loop diuretics, but it returned to baseline by the end of the ultrafiltration treatment, and thus was not an adverse event. The rise in creatinine during ultrafiltration may be related to how aggressively fluid is removed, which varied from center to center. The patients in the ultrafiltration group required less diuretic, were rehospitalized fewer times (P = .037), and had fewer emergency department visits due to symptoms of congestion after release from the hospital. There were nine deaths in the ultrafiltration group compared with eleven in the diuretic arm. There was a very small number of adverse events secondary to the technical aspects of ultrafiltration (bleeding, clotted filters, infection). Ultrafiltration was associated with a 44% reduction in the percentage of patients rehospitalized for HF, and more than 50% reduction in the number and length of HF rehospitalizations and in the occurrence of unscheduled medical visits for HF. Length of index hospitalization stay was comparable (6.3 $\pm$ 4.9 days versus 5.8 $\pm$ 3.8 days; P = .979). These results clearly demonstrate the potential of an alternative therapeutic modality for patients admitted to the hospital with acute decompensated HF. However, the filters are expensive and personnel must be trained to use the technique. It is not entirely clear if bedside ultrafiltration can be easily used outside the setting of an intensive care unit, which would possibly offset the cost of the filters. The additional costs will have to be offset by reduced hospitalization stay and re-admissions to hospital. More experience will be useful in determining how and when to use this new strategy.

Cardiac Resynchronization Therapy

Another example of device innovation is biventricular pacing. Dyssynchrony in myocardial contraction commonly occurs in patients with HF and left bundle branch block, leading to impaired LV function and worsening mitral regurgitation. CRT restores more normal contraction to the LV wall while improving overall heart function. Longitudinal follow-up data suggest that CRT induces reverse remodeling as early as 3 months after

implantation. Experimental data show that restoration of more normal contraction is accompanied by improvement in local loading conditions leading to changes in myocyte protein synthesis.[56] CRT should be considered only after conventional pharmacologic treatment has been optimized. Published data suggest that about 70% of patients receiving a biventricular pacemaker improve clinically.[57] Proper patient selection is perhaps the most important issue key to success with this therapeutic modality, and is a subject of ongoing discussion, but is still under intense study.[58]

Indications for CRT include: EF <35%, NYHA class III; QRS-interval of more than 130 msec; medically refractory, LV end diastolic diameter of 55 mm or more; and dyssynchrony on echocardiogram. Studies performed the last few years have demonstrated that CRT in addition to an ICD can lower the composite endpoint of death and hospitalization (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION] trial[59]). The European Cardiac Resynchronization — Heart Failure (CARE-HF) trial was a multicenter, randomized, controlled mortality trial that compared a population of patients who had systolic dysfunction (LVEF <35%), HF symptoms (NYHA class III-IV), and dyssynchrony by echocardiography with two different treatment strategies: 1) conventional drug therapy and 2) conventional drug therapy plus cardiac resynchronization. Patients were required to have a QRS-duration of more than 120 msec on the electrocardiogram. Those randomized to a device received a Medtronic InSync or InSync III device (Bi-ventricular pacemaker). Patients were followed for a mean of 29.4 months. The primary endpoint was a composite of all-cause mortality or an unplanned hospitalization for a major cardiovascular event. All patients received optimal medical therapy and 409 were additionally randomized to receive a biventricular pacer. Nearly 85% of the study population was on β-blockers. By the end of the study, 224 medically treated patients reached the primary endpoint compared with 159 in the resynchronization group ($P < .001$). Mortality was strikingly reduced. Unplanned hospitalization was also less in the device group than in the medically treated group ($P < .002$). CRT significantly reduced death, hospitalization for worsening HF, and symptoms/NYHA classification, while improving quality of life and echocardiographic parameters. The data suggest that for every nine devices implanted, one can prevent one death and three hospitalizations for major cardiovascular events. Biventricular pacing has proved to be a powerful tool in the management of HF. In the United States, it is usually performed in conjunction with implantation of an ICD, but in Europe this is not the case. Patients with class IV HF make up a small subset of these CRT studies, and to date, CRT cannot be considered a form of "rescue" therapy for the critically ill class IV patient. However, more stable class IV patients may occasionally benefit from CRT.

SUMMARY

Patients with HF are clearly receiving better treatment today than was the case 20 years ago. However, the mortality, morbidity, and costs of caring for patients with HF remain substantial. Four new trends are emerging in the development of new therapies: (1) pharmacogenomics is beginning to identify more clearly who the responders and nonresponders might be; (2) designer drugs, including new natriuretic peptides, that include the most effective moieties of several molecules are being hybridized to create highly creative new drugs that may favorably alter specific pathophysiologic components of HF; (3) in the future, small interference ribonucleotides (si RNAs) may be used to silence or activate specific genes that regulate the synthesis of proteins known to alter the clinical course of HF; and (4) stem cell therapy may emerge to stabilize or even reverse the failing heart and some of its associated signs and symptoms. Clinicians may look back some day at how primitive our current armamentarium of drugs and devices, such as intra-aortic balloon pumps, LV assist devices, defibrillators and CRT, might appear. Many challenges remain, but as long as HF is a major public health problem, medical practitioners can expect even more highly creative and innovative therapeutic approaches to the problem.

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