Management of Chronic Heart Failure: What Do Recent Clinical Trials Teach Us?

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Though understanding and development of new therapies for heart failure (HF) have increased dramatically in recent years, the condition still takes a huge toll in terms of both morbidity and mortality and it is essential to continue with the quest for more effective HF treatments. Clinical trials provide the most precise scientific data regarding efficacy of HF therapies. Over the past 2 decades, about 100 large-scale clinical trials have significantly impacted treatment practices with respect to HF patients. The latest have shown benefit in the use of certain ß-blockers, aldosterone-receptor blockers, and the implantation of biventricular pacing-cardioverter defibrillator devices, generally in conjunction with an aggressive medical therapy regimen. This information should be integrated into existing guidelines for HF patient treatment as the search for greater efficacy in controlling and reversing this disease state continues.
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Chronic heart failure (HF) remains a substantial challenge to the clinical cardiologist. Though understanding and development of new therapies for HF have improved dramatically in recent years, the condition still takes a huge toll in terms of both morbidity and mortality. Recently published data from the Framingham cohort indicate that, irrespective of age, men and women have an almost equal (20%) likelihood of developing congestive HF

over a lifetime.[1] This statistic could drop to 11% to 14%, for men, if myocardial infarction (MI) could be prevented. These numbers are sobering, as are the Framingham cohort mortality data, stratified for era of HF diagnosis.[2] The 5-year mortality rate for men in the Framingham study, who were diagnosed with congestive HF between 1950 and 1969, was 70%. This drops substantially if the diagnosis was made between 1990 and 1999, but the 5-year mortality rate remains extraordinarily high at 59%. It is essential, then, to continue with the quest for more effective HF treatments.

It is fortunate that large numbers of HF patients have been studied in carefully designed clinical trials studying morbidity and mortality. Though clinical trials cannot answer all questions, they are the best means for providing objective information that can mold practice patterns in the prescription of drugs, devices, and surgical procedures for HF patients.[3] So-called evidence-based medical practices rely heavily on clinical trial findings. Indeed, the vast majority of clinical practice guidelines are based on clinical trials performed in HF patients.

Table 1
Clinical Trials in Heart Failure: Pros and Cons

Pros	Cons
• Most precise science	• "Art of medicine" not studied
• Define benefits of interventions	• Cannot address all questions
• Define risks of interventions	• Surgical procedures difficult to study
• Clarify risk/benefit ratios	• Trials are inflexible by design
• Describe patients likely to benefit	• Long duration of trials ignore intercurrent advances
• Determine "number needed to treat" with specific intervention	• Trial participants not like real-world patients
	• Ascertainment bias great
	• Expensive
	• Focus on easily counted endpoints (death) rather than quality of life

Table 1 reviews some of the pros and cons of clinical trials performed in HF patients. These factors should be kept in perspective when reviewing the recent studies and addressing new treatment guidelines. Certainly, clinical trials provide the most precise scientific data regarding efficacy of HF therapies. They can define both risks and benefits of interventions so that appropriate risk/benefit ratios can be constructed. They also describe patients likely to benefit in certain circumstances and allow clinicians to determine "the number needed to treat" for a specific intervention to give beneficial results with respect to morbidity and mortality.

On the other hand, clinical trials do not generally give insight into the art of medicine. Furthermore, some important clinical questions cannot be addressed in clinical trials. Surgical procedures are particularly difficult to study because of the many nuances of technique that vary among institutions and operators. Clinical trials, by design, are inflexible and their long duration generally precludes introduction of intercurrent advances that may occur. They have also been criticized because ascertainment bias is often elevated by trial participants who do not always look like real-world patient populations. This is particularly true in the arena of HF, where clinical trial populations tend to be younger, more often have systolic left ventricular dysfunction, and tend to exclude women, children, and minorities. Finally, clinical trials are expensive and usually focus on easily counted endpoints (such as death or hospital admission) rather than the important parameter of quality of life.

Though clinical trials cannot answer all questions, they are the best means for providing objective information that can mold practice patterns in the prescription of drugs, devices, and surgical procedures for HF patients.

Over the past 2 decades, about 100 large-scale clinical trials have significantly impacted treatment practices with respect to HF patients. A dizzying array of acronyms characterizes these studies. Generally speaking, clinical trials in HF have explored the use of angiotensin-converting enzyme (ACE) inhibitors (generally and in the post-MI setting), ß-blockers, angiotensin-receptor blockers (ARBs), calcium channel blockers, other vasodilators, inotropes, anti-arrhythmic agents, and device strategies including implantable cardioverting defibrillation (ICD) devices and biventricular cardiac resynchronizing pacemakers. Surgical interventions, immunomodulation, exercise,

Table 2
Recent Clinical Trials Impacting Heart Failure Therapeutic Practice

Trial Acronym	Clinical Setting	Drug or Intervention
COMET	CHF	carvedilol vs metoprolol
COPERNICUS	NYHA III-IV HF	carvedilol vs placebo
CAPRICORN	Post MI HF	carvedilol vs placebo
BEST	Chronic HF	bucindolol vs placebo
Val-HeFt	CHF	valsartan vs placebo
VALIANT	Post MI HF	valsartan vs captopril
CHARM-Alternative	CHF-ACEI intolerant	candesartan vs placebo
CHARM-Added	CHF-on ACEI	candesartan vs placebo
CHARM-Preserved	CHF-LVEF ≥40%	candesartan vs placebo
CHARM Programme	CHF overall	candesartan vs placebo
EPHESUS	post-MI HF	eplerenone
OVERTURE	CHF	omapatrilat vs enalapril
DIAMOND-CHF	CHF	dofetilide vs placebo
MACH-I	CHF	mibefradil vs placebo
MOXCON	CHF	moxonidine vs placebo
MADIT-II	post-MI HF	ICD
SCD-HeFt	CHF	ICD vs placebo vs amiodarone
MIRACLE	CHF	CRT
MIRACLE-ICD	CHF	CRT/ICD
COMPANION	CHF	CRT vs CRT/ICD vs Med Rx

CHF, chronic heart failure; MI, myocardial infarction; CRT, cardiac resynchronization therapy (biventricular pacing); ICD, implantable cardioverting defibrillator. See text for trial acronym definitions.

and anticoagulation therapies are other areas that have been studied carefully. Past clinical trials have been used to shape society guidelines formulating treatment recommendations.[3] Common themes of guidelines for HF management based on clinical trials include the importance of identifying and aggressively treating ischemia in patients with HF, using ACE inhibitors in all patients with left ventricular systolic dysfunction who can tolerate them, using ARBs in ACE inhibitor-intolerant patients when left ventricular systolic dysfunction is present, using ß-blockers in stable patients with mild to moderate symptoms and no significant congestion, avoiding agents with incomplete benefit/risk profiles, diagnosing and addressing underlying or precipitating disorders, prescribing non-pharmacologic therapies including exercise and diet modification, and stressing the importance of educating patients, family, and caregivers. Recently performed clinical trials will undoubtedly force clinicians to further modify existing guidelines.

Recent Clinical Trials

Table 2 lists several recent clinical trials that have impacted therapeutic practice in patients with chronic HF. They can be loosely grouped into trials focusing on ß-blockers, ARBs, ICDs, and cardiac resynchronization therapies (CRT) with biventricular pacing. Several trials have examined other agents, including aldosterone antagonists, calcium channel blockers, central ß-blockers, and a combination neutral endopeptidase/angiotensin-converting enzyme converter. All are interesting and shed light on the direction that HF therapeutics is taking.

ß-Blocker Trials

Review of the overall ß-blocker experience adds to our already robust knowledge base, which supports the aggressive use of these agents in patients with HF. The Carvedilol or Metoprolol European Trial (COMET) was a fascinating study comparing short-acting metoprolol in fairly low doses versus carvedilol in stable chronic HF patients.[4] This study, in the end, demonstrated that carvedilol was better than short-acting metoprolol with respect to mortality reduction. Results suggested superiority of a nonselective vasodilating ß-blocker in mild to moderate HF. Some have argued, however, that the longer-acting sustained release preparation of metoprolol used at higher doses would have been a more appropriate control. It is important to realize, though, that when COMET was designed, studies with sustained release metoprolol were not available. Clearly, this study demonstrates that short-acting metoprolol in the doses used was inferior to carvedilol.

The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) Trial tested carvedilol versus placebo in 2289 New York Heart Association (NYHA) Functional Class IIIB or Class IV congestive HF patients.[5] All-cause mortality was the primary endpoint. This was a particularly important study because it studied ß-blocker therapy in the most severely ill HF patients, whereas

until recently, ß-blockers had been considered contraindicated in this group. This study demonstrates that, as long as patients were not terribly congested, a 35% mortality reduction could be seen with carvedilol use, and supports an extended indication for ß-blockers, particularly carvedilol, in very ill HF patients.

The CAPRICORN (Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction) Trial was a double-blind, placebo-controlled, mortality endpoint trial of carvedilol added to optimal MI treatment, when left ventricular ejection fraction measured lower than 40%, and systolic blood pressure measured higher than 90 mm Hg in early post-MI readings.[6] All-cause mortality risk reduction was 0.77 (P = .031) and suggested that ß-blockers, even in the modern era, reduced mortality post-MI. This adds substantive evidence supporting the use of ß-blockers, particularly carvedilol, in the treatment of MI when thrombolytics, ACE inhibitors, statin therapy, and aspirin are prescribed.

Not all clinical HF trials studying beta blockers have demonstrated mortality reduction in HF patients. The BEST (Beta Blocker Evaluation of Survival) Trial studied the beta blocker bucindolol and suggested that only slight, non-statistically significant reduction in morbidity and mortality was achieved.[7] Either bucindolol is a ß-blocker not associated with benefit in HF, or the population studied was resistant to this specific drug. There were more women and minorities, as well as a shift toward more severely ill patients, in this particular clinical trial, which perhaps explains the results.

Aldosterone-Receptor Blocker Trials

Studies focused on ARBs have recently been completed and demonstrate several fascinating observations. The Valsartan Heart Failure Trial (Val-HeFT) was a double-blind, placebo-controlled, multicenter trial of valsartan in over 5000 patients. Val-HeFT included subjects already taking ACE inhibitors (92%) and ß-blockers (35%) with all-cause mortality and combined mortality and morbidity as the endpoints.[8] This large trial suggested that valsartan could reduce a combined endpoint of mortality and hospital admission for HF, but there was no impact on overall mortality. Interestingly, the beneficial impact was primarily found in the 7% of patients not taking an ACE inhibitor due to intolerance. Further, a subset of patients on both ACE inhibitors and ß-blockers experienced increased adverse events when valsartan was added to this set of agents.

The findings of CHARM, particularly when juxtaposed with the findings of VaL-HeFT, suggest that angiotensin-receptor blocking drugs, specifically valsartan and candesartan, are valuable agents in patients with HF who are intolerant of ACE inhibitors.

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) was another study exploring valsartan's role in HF, but was specifically limited to post-MI patients (N = 9249) and compared valsartan with captopril therapy.[9] There was no difference between captopril and valsartan therapies with respect to the assigned endpoints. ACE inhibitors probably remain the first choice in post-MI HF, but the angiotensin-receptor blocker valsartan seems a reasonable alternative, particularly in patients intolerant of ACE inhibitors.

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program was a large study of 7601 patients.[10-14] In actuality, there were 3 underlying clinical trials,[11-13] the overall analysis (CHARM Programme Analysis),[14] and a separate analysis of the 2 trials of patients with ejection fractions lower than 40%. The CHARM-Alternative Trial was a study performed in patients intolerant of ACE inhibitors with an ejection fraction lower than 40%.[11] The CHARM-Added Trial studied candesartan added to a regimen of ACE inhibitor therapy, again in patients with an ejection fraction lower than 40%.[12] The CHARM-Preserved Trial was performed in congestive HF patients having an ejection fraction greater than 40%.[13] This was the first large-scale clinical trial specifically designed to address HF in the setting of so-called diastolic dysfunction. CHARM demonstrated an overall 9% decrease in mortality with a 21% decrease in congestive HF hospitalizations—both statistically significant observations when an analysis was performed adjusted for baseline variables. In the individual trials, there was a highly significant reduction in cardiovascular death and congestive HF hospitalizations in both ACE inhibitor-intolerant patients and those taking an ACE inhibitor. In patients with ejection fractions greater than 40%, no mortality reduction was noted. However, congestive HF hospitalizations were decreased. The findings of CHARM, particularly when juxtaposed with the findings of VaL-HeFT, suggest that angiotensin-receptor blocking drugs, specifically valsartan and candesartan, are valuable agents in patients with HF who are intolerant of ACE inhibitors. This holds true for individuals already taking an

ACE inhibitor and receiving background therapy with a ß-blocker or even an aldosterone antagonist.

The Eplerenone Neurohormonal Efficacy and Survival (EPHESUS) Study was another post-MI trial in HF patients comparing the aldosterone antagonist eplerenone to placebo in 6632 patients.[15] During a mean followup of 16 months there was a significant mortality reduction (relative risk = 0.85; P = .008) suggesting that adding eplerenone to routine therapies post-MI produces added benefit.

Trials with Other Medical Therapies

Not all contemporary clinical trials have been positive. The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) Trial studied the combined ACE inhibitor-neutral endopeptidase inhibiting compound, omapatrilat, and suggested a neutral effect in HF when compared to an ACE inhibitor alone.[16] The Danish Investigations of Arrhythmia and Mortality on Dofetilide-Congestive Heart Failure (DIAMOND-CHF) Trial was a double-blind, placebo-controlled, clinical trial of dofetilide in symptomatic congestive HF when severe left ventricular dysfunction was present, with mortality the primary endpoint.[17] In 1518 patients studied over 18 months, there was no difference in mortality, with dofetilide decreasing HF hospital admissions and converting atrial fibrillation more often, but with a 3.3% incidences of torsade in the dofetilide group. It appears that dofetilide, in the long term, has a neutral effect on mortality but with a possibly significant pro-arrhythmic side effect.

This discovery is emblematic of the results of many arrhythmia trials in HF. The Mortality Assessment in Congestive Heart Failure I (MACH-I) Trial studied mibefradil, a t-type calcium channel blocker, compared with placebo in 2390 patients. Results indicated that this drug actually increased mortality by 11% compared to placebo.[18] Calcium channel blockers remain a concern in congestive HF with mibefradil likely adversely interacting with drugs that prolong the QT interval. Finally, the Moxonidine in Congestive Heart Failure (MOXCON) Trial was a mortality-endpoint trial planned for greater than 4000 NYHA Functional Class II to IV HF patients with an ejection fraction lower than 40%. It was terminated early because moxonidine was associated with an increase in mortality.[19] Moxonidine is a potent central ß-blocking antihypertensive agent and reasons for adverse outcomes are not entirely clear. Nonetheless, this re-emphasizes the importance of studying drugs in a clinical trial setting to uncover problematic outcomes.

Trials in Pacing and Cardiac Resynchronization Therapies

The final group of recently completed trials impacting HF focus on ICDs and pacing. All of these studies were executed with intensive background medication therapies. Some trials had more ACE inhibitor and ß-blocker use than others, but clearly it was the combination of medical therapies and mechanical interventions that was important. The Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) studied the routine implantation of an ICD (without preparatory electrophysiologic study) in patients with ejection fractions of less than 30% and prior MI.[20] There was a marked reduction in death (the trial was stopped early with a hazard ratio = 0.69; P = .016) with a slight increase in HF hospitalizations. This landmark study suggested that ICD insertion should be considered routinely in all post-MI patients with reduced left ventricular ejection fraction.

The recently presented Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) compared best medical treatment strategies to routine amiodarone therapy and a third arm of routine ICD implantation in patients with either ischemic or non-ischemic HF.[21] Preliminary results suggest a highly statistically significant reduction in mortality with ICD therapy (hazard ratio = 0.77; P = .007) compared to placebo or amiodarone. Clearly ICD implantation in patients with substantive HF should now be a consideration. Though these trials focused on mortality, other efforts have looked at reduction in morbidity, particularly hospital admissions for congestive HF. To achieve this aim, cardiac resynchronization has been used in patients with wide QRS complexes (generally greater than 120 to 130 ms) and some studies have explored the combination of a biventricular pacing-ICD device. The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Trial studied biventricular pacing alone with exercise and quality of life endpoints in NYHA Functional Class III and IV patients with a wide QRS but no indication for a pacemaker.[22] Exercise performance and quality of life were improved. The Multicenter InSync Randomized Clinical Evaluation-Implantable Cardioverter Defibrillator (MIRACLE-ICD) Trial was a virtually identical study, but focused on patients with indications for ICD implantation.[23] Exercise performance and quality of life endpoints were similar. Pooled analysis of these trials suggests a reduction in the combined endpoint of hospitalizations for HF and mortality. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial evaluated over 1500 patients receiving biven-

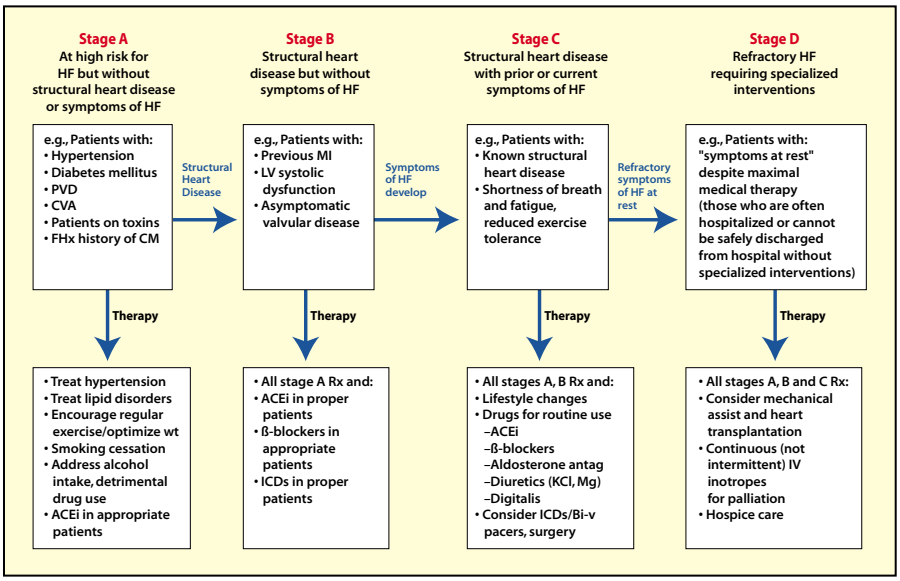

Figure 1. *Heart failure diagnosis and management: suggested modifications to the ACC/AHA Guidelines. ACEi, angiotensin-converting enzyme inhibitor; Bi-v, biventricular; CM, cardiomyopathy; HF, heart failure; ICD, internal cardiac defibrillator; KCl, potassium chloride; LV, left ventricle; Mg, magnesium; MI, myocardial infarction; PVD, peripheral vascular disease.*

tricular pacing, combined biventricular pacing and ICD, and a regimen of predetermined "best medical therapy."[24] This study demonstrated a robust reduction in mortality at the 12-month follow-up point with both cardiac resynchronization therapy and cardiac resynchronization therapy with an ICD (36% and 40% reductions respectively). When one focuses on death alone as an endpoint, biventricular pacing compared to best medical therapy showed no statistically significant difference. However, treatment with biventricular pacing plus ICD device did. The compendium of these clinical intervention studies suggests that utilization of a biventricular pacing device coupled with an ICD is, perhaps, superior when an aggressive underlying medication treatment protocol is utilized in patients with HF and systolic left ventricular dysfunction.

Treating Patients with Heart Failure

Based on recently completed clinical trials, the last American College of Cardiology/American Heart Association Guidelines for Therapy in HF can be modified as shown in Figure 1.[3] Specifically, in patients who are Stage B (structural heart disease without symptoms of HF), use of ICDs in individuals with prior MI and significant left ventricular systolic dysfunction could be important, in addition to adding ACE inhibitors and ß-blockers. In Stage C, along with all measures outlined for Stages A and B patients, clinicians can now consider utilizing angiotensin-receptor blockers (specifically valsartan and candesartan), particularly in those patients with reduced left ventricular systolic function and ACE inhibitor intolerance. Also, the angiotensin-receptor blocking agent candesartan could be considered beneficial when added to an ACE inhibitor in patients with depressed ejection fraction as well as in indi-

Main Points

- Recently published data from the Framingham cohort indicate that, irrespective of age, men and women have an almost equal (20%) likelihood of developing congestive heart failure (HF) over a lifetime. For men diagnosed between 1990 and 1999, the 5-year mortality rate remains extraordinarily high at 59%.
- The COMET study demonstrated that carvedilol was better than short-acting metoprolol with respect to mortality reduction.
- While not all ß-blocker trials have shown positive results in the treatment of heart failure, COMET, COPERNICUS, and CAPRICORN all found added benefit from carvedilol therapy, even in post-MI patients and those with severe (New York Heart Association Class IIIB or IV) HF.
- Recent trials of angiotensin II-receptor blockers have shown them to be a viable alternative therapy for patients intolerant of angiotensin-converting enzyme (ACE) inhibitors and that they may also help in some cases when combined with ACE inhibitors.
- Recent trials suggest that utilization of a biventricular pacing device coupled with an internal cardiac defibrillator is, perhaps, superior to medications alone in patients with HF and systolic left ventricular dysfunction, when an aggressive underlying treatment protocol is prescribed.

viduals with preserved systolic left ventricular function and HF. Aldosterone antagonists should be added to the protocol in Stage C patients and, again, implantation of an ICD or utilization of biventricular pacing strategies should be considered in appropriately selected patients.

Summary

Recent clinical trials have given us additional data regarding therapeutic strategies in HF patients and, undoubtedly, present guidelines will be substantially modified as we move into the future. Nonetheless, many questions and challenges still remain. ■

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