The Challenge of Optimal Heart Failure Management: Present and Future

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HEART FAILURE FROM PATHOPHYSIOLOGY TO OPTIMAL MANAGEMENT: THE PACE OF CHANGE

The fact that medicine is a fast-moving science could not be better illustrated than by the succession, over the past several decades, of theories invoked to explain the pathophysiology of heart failure and define its optimal treatment. In the 1950s, heart failure was considered as a form of kidney disease and its pathophysiological mechanism was split into two categories: “forward heart failure,” or inability of the heart to pump blood at a sufficient rate to meet oxygen demand at rest or at exercise, and “backward heart failure,” which referred to the ability of the heart to pump blood at a sufficient rate only when heart filling pressures were abnormally high. Back then, state-of-the-art treatment consisted of digitalis, diuretics, and bed rest.

Ten years later, heart failure started being considered as a cardiovascular disease in its own right. From a pathophysiological point of view, it was described as resulting from excess afterload or diminished inotropic response. Accordingly, treatment sought to address both the heart muscle (positive inotropic drugs) and the blood vessels (vasodilators).

We did not have to wait long before a completely different theory became accepted, with heart failure now being understood as a neurohormonal disease. This was further refined in the 1980s, when it was realized that the neurohormonal response characterizing heart failure was not compensatory, but in fact detrimental. Also around this time, evidence-based medicine—an offshoot of oncology—started pervading the rest of medicine, and in particular cardiology. Prognosis became the central therapeutic goal over and above mere symptom relief. The therapeutic consequence of this was that the 1980s were the advent of neurohormonal antagonists such as the angiotensin-converting enzyme (ACE) inhibitors and β-blockers, and of training programs for the failing patient.
Thus, within a limited time span of just thirty years, we went from bed rest to physical training, from positive inotropes to negative inotropes (β-blockers) and from vasodilators to neurohormonal antagonists (ACE inhibitors). But of course, the story hasn’t stopped there, and if anything the pace of change over the past ten years has been growing faster still, as several new exciting concepts have made their way into the field of heart failure. This issue of Dialogues explores them in detail, and attempts to show how they will impact the future.

The first and perhaps most important concept relates to the role of heart rate and the discovery that a heart rate of ≥70 bpm is linked to a worse prognosis in patients with left ventricular dysfunction. This, as well as findings from registries and surveys worldwide showing that many patients continue to have increased heart rates >70 bpm despite β-blocker therapy, led to the role of heart rate–reducing therapy being tested in a landmark clinical trial, SHIFT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial). These developments are covered in the Lead article by Karl Swedberg as well as in the first Expert Answer article by Michel Komajda, both of whom were principal investigators in SHIFT, and we are much honored by their contribution to this issue of Dialogues. But other therapeutic approaches than drug treatments also have an important role to play in heart failure, and Kenneth Dickstein, in the second Expert Answer, discusses another major point: the recognition that the adverse effects of ventricular desynchronization can benefit from the use of cardiac resynchronization therapy (CRT) devices and how advances in technology have meant that ever-smaller pacemakers can be used to both resynchronize the mechanical activity of the ventricle and function as defibrillators. Finally, in the third Expert Answer, Martin Cowie shows us how a more precise understanding of the pathophysiology of heart failure based on the distinction between systolic heart failure (decreased left ventricular ejection fraction, more frequent in younger patients) and diastolic heart failure (normal ejection fraction, more frequent in elderly patients) is helping us to be more effective in diagnosing heart failure patients, and above all, treating them.
Contemporary trends in the pharmacological management of heart failure

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This review attempts a catalogue raisonné of the treatment paradigms developed over the past 20 years that have substantially reduced the disability, morbidity, and mortality associated with the syndrome of chronic heart failure. Compensatory adjustments of the circulation to myocardial injury include an increase in hemodynamic resistance, but also, and importantly, the activation of neurohormonal systems, primarily the renin-angiotensin-aldosterone system (RAAS) and sympathetic adrenergic nervous system. Reduced stroke volume is offset by increased peripheral resistance and to some extent by an increase in heart rate. These compensatory mechanisms are now targeted by therapeutic intervention based on RAAS inhibition using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists, and on sympathetic inhibition using β-blockers, initiated by titration to minimize the risk of an introductory negative inotropic effect. Elevation of the resting heart rate above 70 bpm despite recommended therapy is a modifiable risk factor and an indication to add heart rate reduction as a treatment target above and beyond neurohormonal blockade. Direct sinus node inhibition using a pure heart rate–reducing agent is thus a promising new strategy in patients remaining symptomatic with an elevated heart rate, especially those whose comorbidity renders them intolerant of β-blockers.

Myocardial dysfunction progresses to the clinical syndrome of chronic heart failure via a complex series of neurohormonal and hemodynamic interactions resulting in a cardiovascular phenotype characterized by fluid overload, low cardiac output, or a combination of both. Treatment paradigms developed over the past 20 years have been extremely successful in reducing mortality and morbidity thanks to the elaboration and implementation of diagnostic and treatment guidelines.

Although symptom relief (such as that achieved by diuretics) is a treatment goal, its relationship to survival is often nonlinear. Interventions may improve symptoms, but have a negative or neutral effect on survival, while those that improve survival (eg, β-blockers) may have neutral effects on important clinical markers such as exercise tolerance. The pathophysiology of the disconnect between organ function and symptom severity remains unelucidated and is just one of the uncertainties complicating the management of heart failure.

This review discusses contemporary approaches to the pharmacological management of patients with heart failure and left ventricular (LV) systolic dysfunction based on the experience accumulated over a period of major progress.

SELECTED ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
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<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>CHD</td>
<td>coronary heart disease</td>
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<td>LV</td>
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<td>reduced nicotinamide adenine dinucleotide</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>RAAS</td>
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Keywords: β-blocker; chronic heart failure; heart rate; left ventricular dysfunction; neurohormonal activation; renin-angiotensin-aldosterone system; sympathetic nervous system

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PATHOPHYSIOLOGY

Cardiovascular sensors, including those in the kidney, recognize the compromised circulatory output resulting from myocardial insults such as infarction, hypertrophy, cardiomyopathy, and inflammation. Compensatory adjustments include an increase in hemodynamic resistance, but also, and importantly, neurohormonal activation encompassing the renin-angiotensin-aldosterone system (RAAS) and sympathetic (adrenergic) nervous system. The degree of such activation correlates with outcome.2

Myocardial function also adjusts. Preload increases to compensate for the reduction in systolic function, and the myocardium undergoes remodeling.3 Changes in myocardial function are reflected in the release of myocardial peptides acting on both the circulation and kidneys.4 Reduced stroke volume is compensated to some extent by an increase in resting heart rate together with background RAAS and adrenergic nervous system activation. Reduction in cardiac output triggers an increase in peripheral vascular resistance. When the failing myocardium is exposed to this afterload, a “preload mismatch” develops as there is a need for a paradoxical reduction of afterload.5 The discovery that we could inhibit both neurohormonal activation and remodeling greatly advanced our understanding of the potential mechanisms behind reduced morbidity and mortality (Figure 1).

The combination of renal dysfunction and increased ventricular filling pressures causes fluid to accumulate peripherally as well as centrally,6 producing the characteristic symptoms of heart failure. Elucidation of fundamental factors such as RAAS and adrenergic nervous system activation, remodeling, preload mismatch, heart rate, and symptom development has been in-

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structural in the successful management of patients with heart failure. However, even if much of the relationship between symptoms and cardiovascular function can be explained mechanistically, there remains a major gap in understanding how cardiovascular function translates into symptoms.7

**Diuretics**

Diuretics are key drugs in handling the congestion associated with heart failure. Furosemide is the most thoroughly tested loop diuretic, but bumetanide and torsemide are common alternatives. Most long-term studies have involved a small number of patients and used a variety of drugs and doses; chronic neuroendocrine effects are less well studied. Oral furosemide is associated with reduced norepinephrine levels and marked increases in plasma renin activity, angiotensin, and aldosterone.8 Recent comparison has shown that oral administration is as effective as continuous intravenous infusion.9

**Clinical management.** Diuretics reduce symptoms in heart failure. By increasing urinary electrolyte excretion, they are prone to induce metabolic abnormalities such as hypokalemia, hypernatremia, hypocalcemia, hypomagnesemia, and metabolic alkalosis.11 Potassium-sparing diuretics, such as amiloride or aldosterone, reduce the need for potassium supplementation. However, ACE inhibitors act synergistically with potassium-sparing diuretics, which may cause hyperkalemia; diabetics with proteinuria and renal tubular acidosis are at particularly high risk. The addition of a potassium-sparing diuretic to a loop diuretic may further increase diuresis, but in the case of spironolactone, the therapeutic effects in heart failure are likely mediated by aldosterone blockade rather than direct diuresis. Additionally, the effect of a loop diuretic can be augmented by other diuretics acting at different sites in the nephron, especially if clinically apparent diuretic resistance has developed. A loop diuretic becomes especially effective when administered less than 30 minutes after a thiazide.

**Long-term Vasodilator Therapy**

**Nitrates and hydralazine**

Hydralazine was available as an antihypertensive agent when vasodilator therapy was adopted as a therapeutic strategy in heart failure. Adding a nitrate to hydralazine is more effective than hydralazine alone in reducing filling pressures.12 However, despite the focus on direct venodilation and arterial vasodilation, current hypotheses as to the mechanism involved focus on the nitrate component as a nitric oxide donor and hydralazine as an agent that mitigates nitrate tolerance via a complex pathway mediated by reduced nicotinamide adenine dinucleotide (NADH) oxidase. This mechanism may explain the difference in clinical effect between African-Americans and whites inferred from the first two Vasodilator-Heart Failure Trials (V HeFT).

The African-American Heart Failure Trial (A HeFT) randomized 1050 self-identified African-Americans in New York Heart Association (NYHA) class III or IV heart failure to hydralazine + nitrate or placebo three times daily.13 The primary end point was a composite of mortality, quality of life measured on the Minnesota Living with Heart Failure Questionnaire, and time to first hospitalization. Each component was statistically significant in favor of combined therapy, in particular mortality, which declined by 43% (P=0.01). The magnitude of this change paralleled or exceeded that of almost all other double-blind placebo-controlled trials.
and as such represented a significant achievement. However, the results were not widely accepted by clinicians, probably because of thrice-daily administration and difficulties in interpreting the importance of race.

**Calcium channel blockers**

Calcium channel blockers have a very limited role in heart failure. The second-generation calcium channel blocker felodipine caused vasodilation and an increase in cardiac output, but the effect on survival was neutral.\(^\text{14}\)

Amlodipine, a third-generation calcium channel blocker, was the subject of the Prospective Randomized Amlo-
dipine Survival Evaluation (PRAISE) trial in over 1100 patients with NYHA III-IV heart failure.\(^\text{15}\) Overall effect on mortality and the composite end point of mortality + hospitalization was neutral, but there were significantly fewer end point events in the nonischemic group treated with amlodipine than in the placebo group (22% vs 35%; \(P=0.001\)). As a consequence, PRAISE II randomized patients with nonischemic NYHA class IIIB or IV heart failure (n=1652) to amlodipine or placebo.\(^\text{16}\) There was no significant difference in all-cause or cardiac mortality or cardiac event rates between the two groups. PRAISE I and II, along with the felodipine trials, suggest therapeutic neutrality; however, amlodipine and felodipine are probably safe to use for concomitant angina or hypertension in patients with heart failure if other proven drugs, such as ACE inhibitors and β-blockers, are ineffective or poorly tolerated.

**NEUROHORMONAL ANTAGONISTS**

**Angiotensin-converting enzyme inhibitors**

ACE inhibitors were introduced for the treatment of heart failure 25 years ago. They have prolonged sur-
vival in multiple landmark studies in patients at risk of heart failure and those with clinically manifest disease, from NYHA class I through IV.\(^\text{17}\) All current guidelines recommend their use in patients with sys-
tolic dysfunction.

- **Survival trials.** The first major trial, the COoperative North Scandinavian ENalapril SUrvival Study (CON-
SUS), included 253 patients in NYHA class IV ran-
domized to placebo or enalapril. At 6 months’ follow-
up (primary end point), overall mortality was reduced by 27% (\(P=0.003\))\(^\text{18}\) (Figure 2A). In the Studies Of Left

Ventricular Dysfunction (SOLVD), 2569 patients with NYHA class II-III heart failure received placebo or enalapril on top of conventional heart failure therapy (Figure 2B).\(^\text{19}\) After an average follow up of 41.4 months, enalapril significantly reduced mortality from 40% to 35% (\(P=0.0036\)), most notably in terms of deaths attrib-
uted to progressive heart failure. It also reduced hospitalizations for heart failure and improved symp-
toms and quality of life as assessed by questionnaire.

The Survival And Ventricular Enlargement (SAVE) trial randomized 2231 early post–myocardial infarction (MI) patients with LV ejection fraction (LVEF) ≤40%, but no overt heart failure or symptomatic myocardial ischemia, to captopril or placebo\(^\text{20}\) (Figure 2C); the ACE inhibitor reduced all-cause mortality by 19% (\(P=0.019\)). Similarly, the TRAndolapril Cardiac Evaluation [TRACE] study randomized 1749 patients with left ventricular (LV) dysfunction to trandolapril or placebo started 3 to 7 days post-MI onset; trandolapril reduced all-cause mortality by 22% (\(P<0.001\)). Likewise, the Acute Infarction Ramipril Efficacy (AIRE) study randomized 2006 patients in clinical heart failure 3 to 10 days post-MI onset to ramipril or placebo; ramipril reduced all-cause mortality by 27% (\(P=0.002\)) after a mean follow-up of 15 months. These studies provide incontrovertible cumulative support for the use of ACE inhibitors in post-MI patients with LV dysfunction.

- **Dose and class effects: clinical questions remain.** Uncertainty about the importance of ACE inhibitor dose and class effects stimulated debate and clinical evaluation. The Assessment of Treatment with Lisinopril And Survival (ATLAS) trial compared two dose ranges of lisinopril. Patients with heart failure (n=3164) and LVEF <30% were randomized to a low dose of lisino-

pril (2.5-5.0 mg/day) or a high dose (32.5-35 mg/day) for a median 45.7 months.\(^\text{21}\) Mortality was 8% lower on the high dose (\(P=0.128\)). The hazard ratio for the combined end point of all-cause mortality or all-cause hospitalization was 0.88 (\(P=0.002\)). Side effects and tolerability were similar in both groups. However, the high withdrawal rate and crossover to open-label ther-

apy make interpretation difficult.

- **Clinical perspective.** These findings indicate that pa-

tients with systolic heart failure should generally be titrated up from low doses of an ACE inhibitor, but sug-

gest that the difference in efficacy between intermedi-
ate and high doses is likely to be small. Patients should be titrated to the dose levels achieved in the clinical trials. The value of dose levels exceeding 20 mg/day of lisinopril or enalapril remains uncertain, but can be viewed as supported in part by the ATLAS results.
Prevention trials. Several trials, including SAVE and the prevention arm of SOLVD, showed that ACE inhibitors reduce the incidence of heart failure and/or the number of hospitalizations. There have been three landmark studies in patients at risk for heart failure: the Heart Outcomes Prevention Evaluation (HOPE), the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), and Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE). Taken together, these trials suggest that ACE inhibitors help to prevent heart failure.

Clinical perspective. All patients with documented LV systolic dysfunction (LVEF <35%-40%) should receive long-term ACE inhibition unless contraindicated (eg, by systolic blood pressure <80 mm Hg, marked renal dysfunction, a history of angioneurotic edema, or marked valve stenosis), titrated from a low dose up to the levels used in clinical trials.

Angiotensin II receptor blockers

Val-HeFT. As ACE inhibition does not fully block angiotensin II synthesis, blockade was postulated to be more effective at the angiotensin II receptor (AT1) level. The major series of angiotensin receptor blocker (ARB) studies began with the Valsartan
Heart Failure Trial (Val-HeFT), which randomized 5010 NYHA class II-IV patients with LVEF <40% to valsartan or placebo, 93% were receiving background ACE-inhibitor therapy. Although there was no effect on all-cause mortality, there was a significant 13% reduction in the other primary end point, mortality or hospitalization (P=0.009).

- The CHARM Program. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) program addressed a broad spectrum of heart failure patients. Its three component arms included patients with LV systolic dysfunction (LVEF ±40%) in two studies (CHARM-Patients with LV dysfunction intolerant to ACE inhibitors [CHARM-Alternative] and CHARM-Patients with LV dysfunction already taking ACE inhibitors [CHARM-Added]), and patients with preserved LV function (LVEF>40%) in one study (CHARM-Patients with preserved LV function [CHARM-Preserved]). The primary outcome in each was cardiovascular death or hospital admission for heart failure. CHARM-Overall pooled the three trials and assessed the effect on all-cause mortality.

CHARM-Alternative included 2028 symptomatic heart failure patients intolerant of ACE inhibitors due to cough, symptomatic hypotension, or renal dysfunction. Candesartan significantly reduced cardiovascular death or hospital admission for heart failure by 23% (P=0.0004); the rate of discontinuation of the study drug was similar to that of placebo. In CHARM-Added (n=2548), candesartan plus ACE inhibition significantly reduced the composite primary outcome of cardiovascular death or hospital admission for heart failure by 15% (P=0.011), as well as the total number of hospital admissions for heart failure (P=0.014). CHARM-Preserved (n=3023) reported a nonsignificant 11% reduction in cardiovascular death or worsening heart failure (P=0.12). Hospitalizations for heart failure reported by investigators were reduced by 15% (P=0.017). Across all patients with symptomatic heart failure (n=7599), irrespective of background ACE inhibition or β-blockade, candesartan reduced all-cause mortality by 9% (P=0.055), and by 12% (P=0.018) among those with LV systolic dysfunction. In the latter group, the effects on mortality were seen early, with hazard ratios of 0.67 and 0.82 (both P<0.001) at 1 and 2 years, respectively. Hospital admissions for heart failure also fell by a significant 21% (P<0.001).

- Angiotensin receptor blockers and background therapy. Post-hoc analysis of the Val-HeFT trials suggested that background β-blockade attenuated the treatment effect of valsartan. However, CHARM-Added found the effect of candesartan to be similar regardless of background β-blockade. Overall, based on Val-HeFT and in particular CHARM-Added, the effects of valsartan and candesartan were additive on top of background ACE inhibition, with reductions in the composite primary outcome in both trials.

- Clinical perspective. The ARB trials prove that this class of drug can be used to treat patients with symptomatic systolic heart failure who fail to tolerate ACE inhibitors. Treatment effect is at least equal to that of ACE inhibition. There is also an added, albeit modest, effect on morbidity and mortality on top of that achieved by ACE inhibitor therapy.

Aldosterone antagonists

Aldosterone plays an important role in the pathophysiology of heart failure, increasing sodium resorption and potassium release. It also activates the sympathetic nervous system, stimulates myocardial and vascular fibrosis, and is a component of the circulating RAAS.

- Trial findings. Although aldosterone antagonists have diuretic effects, they differ from other diuretics in being neuroendocrine antagonists. They thus have the potential to be effective in the long-term treatment of heart failure. The Randomized ALdactone Evaluation Study (RALES), published in 1999, randomized 1663 patients in NYHA class III-IV to spironolactone or placebo; 95% of the patients were taking ACE inhibitors, and 11% β-blockers. The trial was discontinued after a mean follow-up of 24 months when interim analysis showed spironolactone to reduce all-cause mortality by 30% (P<0.001), due mostly to lower risk from sudden cardiac death.

Subsequently (2005), in a different population (early post-MI with LV dysfunction or heart failure), the selective aldosterone antagonist eplerenone was shown to reduce all-cause mortality and cardiovascular deaths, with effects most noticeable within 30 days after MI. This early effect suggests that the benefit may be mediated more by protection against hypokalemia than through inhibition of aldosterone. Serious hyperkalemia was more common with eplerenone than with placebo (5.5% vs 3.9%), and the incidence of hypokalemia was more than halved (from 8.4% to 3.1%).

More recently (2011), the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) was similarly discontinued after...
analysis showed that eplerenone reduced the primary end point, cardiovascular death or hospitalization for heart failure, by 37% ($P<0.001$), all-cause mortality by 24% ($P=0.008$), and all-cause hospitalization by 23% ($P<0.001$).36

- **Clinical implications.** Given the range, consistency and amplitude of their benefits, aldosterone antagonists should be considered in all patients with heart failure and systolic dysfunction.

**β-Adrenergic blockade**

Clinicians have generally been cautious in using β-blockers in heart failure despite possible benefits being suggested back in the early 1970s.37,38 Rigorous clinical trial data gathered during the last 15 years have incontrovertibly confirmed a role for β-blockers in mild, moderate and severe heart failure.

- **Hemodynamic and neurohormonal effects.** β-Blockade has markedly different effects in the short as opposed to longer term. Intravenous administration rapidly lowers heart rate, contractility, and blood pressure, with an ensuing fall in cardiac output, intraventricular volumes, stroke volume, and LVEF are unaffected. Longer-term oral administration (3-12 months), on the other hand, improves myocardial performance, shown by increases in LVEF, cardiac output, and exercise capacity. Like ACE inhibitors, β-blockers attenuate LV remodeling.39,40

- **Effects on survival.** An early study of β-blockade in heart failure showed a decrease in mortality compared with historical controls.37 Not until 1993, with the publication of the Metoprolol in Dilated Cardiomyopathy (MDC) trial in 383 patients, did additional clinical outcome information become available, revealing a 34% reduction versus placebo in the combined end point of mortality and need for heart transplantation ($P=0.058$).41

Four trials subsequently transformed views about the importance of β-blockade in symptomatic patients with systolic dysfunction: the US Carvedilol trial42 (Figure 3A, page 92), Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS)43 (Figure 3B), Cardiac Insufficiency Bisoprolol Study II (CIBIS II)44 (Figure 3C), and Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF)45 (Figure 3D) were all stopped prematurely because of clear evidence of benefit. In contrast, in the Beta-blocker Evaluation of Survival Trial (BEST) trial, the effects of the nonselective β-blocker bucindolol in 2708 patients in NYHA class III-IV heart failure were modest compared with placebo and statistically nonsignificant.46 Several meta-analyses testify to the consistent effect of β-blockade. In a total of more than 10 000 randomized patients, overall mortality was reduced by 35%, interestingly, the analysis revealed no difference in benefit between high and low doses.47 Another meta-analysis revealed a direct relationship between heart rate and mortality: for every 5 bpm reduction in heart rate, mortality declined by 18%.48

- **Comparison of β-blockers.** Given the variability in clinical data and the known differences between β-blockers in terms of receptor blockade, half-lives, and lipophilicity, it is reasonable to assume that not all β-blockers are appropriate in heart failure. Only three β-blockers are currently recommended (bisoprolol, metoprolol succinate, and carvedilol), although a case can be made for nebivolol. Are there differences between these agents? The data are confined to comparisons of metoprolol tartrate and carvedilol.

The issue was explored in the Carvedilol Or Metoprolol European Trial (COMET) in 3042 patients in NYHA class II to IV heart failure with a prior cardiovascular admission. At mean follow-up of 58 months (longer than in the placebo-controlled trials because both arms received active therapy), the primary end point, all-cause mortality, was 34% with carvedilol vs 40% for metoprolol (hazard ratio 0.83 [95% confidence interval 0.74-0.93], $P=0.0017$), suggesting that carvedilol extends survival compared with metoprolol.49

- **Clinical perspective.** The COMET results were widely debated: was this a real difference or an artefact related to the dose or formulation of metoprolol? At the very least, the results suggest that the concept of class effect is dubious, especially when interpreting COMET in the light of the BEST data, which did not parallel the outcomes described in the four major β-blocker trials.46 The recommendation is therefore to prescribe the same dose of any β-blocker shown to be effective in those four trials.

- **β-blockers in the post–myocardial infarction setting: preventing heart failure.** Data from several of the older large post-MI trials suggested that β-blockers would be beneficial in patients with symptomatic heart failure. These findings were first extended prospectively in the CArvedilol Post InfaRction survival CoNTRol in left ventricular dysfuncctioN (CAPRICORN) study conducted versus placebo in 1995 patients with recent MI
and signs of LV dysfunction (LVEF ≤40%). The design was conceptually similar to that of SAVE, AIRE, TRACE, and the Eplerenone Post-AMI Heart failure Efficacy and Survival Study (EPHESUS). There was no effect on the primary end point of mortality or cardiovascular hospitalization, but the reduction of 23% in all-cause mortality was significant ($P=0.03$). Risk reduction was similar in magnitude to that found in previous post-MI trials with β-blockers.

**Clinical perspective: drug titration and intolerance.**

Titration is required when initiating a β-blocker owing to the initially negative inotropic effect. Clinical trial experience indicates that this procedure is normally well tolerated. However, patients with a combination of marked hypotension and tachycardia, and/or in severe decompensation, may not tolerate a β-blocker. Clinical euvolemia is a crucial condition for successful initiation or uptitration. In patients with significant
bronchospasm, β-blockers should be used with caution, with preference given to a selective β-blocker. However, chronic obstructive airways disease is not in itself a contraindication to β-blockade.

HEART RATE MANAGEMENT

High heart rates are associated with reduced myocardial function in experimental settings. Various pathophysiologic mechanisms account for the negative impact of tachycardia on cardiovascular and myocardial function.\(^\text{51}\)

When myocardial function is reduced, as in heart failure with systolic dysfunction, the myocardium is starved of energy. High heart rates compound the problem by inducing progressive mechanical dyssynchrony and reduced inotropy.\(^\text{52}\) It was long hypothesized that the main benefit of β-blockers lay in their ability to modulate heart rate. However, these drugs have several other effects on the cardiovascular system, even if their importance is still unclear.

In 2008, a meta-regression analysis of 35 β-blocker trials conducted in a total of 22,926 patients over a mean follow-up of 9.6 months provided further evidence of the relationship between myocardial function (LVEF), outcome (all-cause mortality), and heart rate.\(^\text{53}\) It revealed correlations between all-cause annualized mortality and heart rate (adjusted \(r=0.51, P=0.004\)), and also between changes in heart rate and changes in LVEF (adjusted \(r=0.48, P=0.001\)), becoming tighter still (adjusted \(r=0.60, P=0.0004\)) when the analysis was confined to trials in >100 patients. The conclusion was that the magnitude of heart rate reduction may be more important than achieving the target dose.

This was confirmed in 2009 by meta-regression analysis of 23 β-blocker trials reporting all-cause mortality in a total of 19,209 patients.\(^\text{48}\) The degree of heart rate reduction was the only significant variable of prognostic importance. For every 5 bpm reduction, the risk of death decreased by 18%. No significant relationship was observed between all-cause mortality and dose.

These data are consistent with those from the MorBidity-mortality EvAlUaTion of the \(I_1\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study.\(^\text{54}\) Patients were aged ≥55 years, in sinus rhythm, with resting heart rates ≥60 bpm, and LVEF values <40%. Analyses of baseline heart rate as a continuous variable showed that every increase of 5 bpm was matched by an 8% increase in cardiovascular death (\(P=0.0005\)), a 16% increase in hospital admission for heart failure (\(P<0.0001\)), a 7% increase in admission for fatal and nonfatal MI (\(P=0.052\)), and an 8% increase in coronary revascularization (\(P=0.034\)).

The follow-up Systolic Heart failure treatment with \(I_1\) inhibitor ivabradine Trial (SHIFT) analyzed baseline heart rate in relation to outcome in heart failure patients in sinus rhythm with LVEF <35% on recommended \(β\)-blocker trial reporting all-cause mortality in a total of 19,209 patients.\(^\text{48}\) Division of the placebo group into quintiles of baseline heart rate revealed the highest incidence of the primary composite end point (cardiovascular death or hospitalization for worsening heart failure) and its components in patients with high heart rates. Patients with the highest baseline heart rate (≥87 bpm) had over twice the risk of the primary composite end point than those with the lowest heart rate (\(P<0.0001\)). In the placebo group, analysis with heart rate as a continuous variable showed that for every beat increase in heart rate, risk of a primary composite end point event increased by 3% (\(P<0.0001\)).

• Pure heart rate reduction. The evidence strongly suggests that the main benefit of β-blockade is heart rate reduction. Ivabradine reduces the heart rate by acting on the sinus node via a mechanism completely different from that of a β-blocker. SHIFT randomized 6,505 patients in symptomatic heart failure to ivabradine or placebo for 23 months. All were in sinus rhythm on stable background therapy, with LVEF ≤35%, heart rate ≥70 bpm, and at least one hospital admission for heart failure in the previous 12 months. The primary composite end point, cardiovascular mortality or hospitalization for heart failure, was reduced by 18% in the ivabradine group (\(P<0.0001\)). The effects were driven mainly by hospitalizations for worsening heart failure, which were reduced by 26% (\(P<0.0001\)), and deaths due to heart failure (\(P=0.014\)). Patients with the highest heart rate at baseline obtained the greatest benefit from ivabradine.

• Clinical perspective. A heart rate >70 bpm despite recommended therapy should be considered as a modifiable risk factor and an indication to initiate specific rate-lowering therapy. It requires treatment over and above neurohormonal blockade.

ANTIARRHYTHMIC DRUGS IN HEART FAILURE

Although progressive pump dysfunction is a common cause of death in heart failure, sudden death is probably more common still, being responsible for 25% to 50% of all deaths.\(^\text{57-60}\) Most are due to ventricular ar-
rhythmias rather than primary asystole (although terminal bradycardia is common in patients dying of pump dysfunction). Antiarrhythmic therapy is thus a central issue in heart failure.

Although frequent and complex ventricular arrhythmias are predictive of sudden death, LV dysfunction is a more powerful predictor still. Unfortunately, most antiarrhythmics depress LV function. They can also have paradoxical proarrhythmic effects, especially in the presence of LV dysfunction, prolonged QT, and the metabolic abnormalities, such as low potassium and magnesium, that often accompany acute or chronic diuretic therapy.

The landmark Cardiac Arrhythmia Suppression Trial (CAST) studied the efficacy of antiarrhythmic drugs in post-MI patients with LV dysfunction and complex ventricular arrhythmias. Patients responding to drug testing with attenuated arrhythmia were randomized to encainide, flecainide, or moricizine. The results showed an increase in mortality in patients treated with the first two of these agents. There followed an increased interest in amiodarone, a class III antiarrhythmic with little or no negative inotropic effect. However, despite promising, albeit mixed, results in smaller studies, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) suggested that the drug had no impact on survival when used for primary prevention of sudden death in patients with LV dysfunction and heart failure.

The intensity of ongoing activity can be appreciated by visiting www.clinicaltrials.gov which in late March 2011 showed that no fewer than 830 open intervention trials had been registered, promising a profusion of interesting new data on heart failure in the near future.

CONCLUDING REMARKS

Neurohormonal blockade in heart failure with LV systolic dysfunction requires the initiation of a drug combination based on three components: an ACE inhibitor and/or ARB, a β-blocker, and an aldosterone antagonist. Because these agents need to be titrated over time, they should be initiated using a structured transdisciplinary approach. Recent experience suggests that this core strategy should include the addition of a pure heart rate-reducing agent in patients remaining symptomatic with an elevated heart rate.

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The Challenge of Optimal Heart Failure Management: Present and Future

*Expert Answers to Three Key Questions*

1. What are the main challenges of heart rate–reducing therapy in heart failure?
   
   *M. Komajda*

2. What are the differences in treating systolic and diastolic heart failure?
   
   *M. R. Cowie*

3. What are the challenges in cardiac resynchronization therapy in heart failure?
   
   *K. Dickstein*
Elevated heart rate is a risk factor in chronic heart failure. Heart rate reduction by means of β-blocker therapy is associated with improved outcomes. However, in real life conditions, many heart failure patients remain with increased heart rate due to suboptimal dosing of β-blockers because of poor tolerability and/or physician reluctance to use these agents. SHIFT (Systolic Heart failure treatment with If inhibitor ivabradine Trial) has shown that addition of the If current inhibitor ivabradine, a selective heart rate–reducing agent devoid of any other significant pharmacological properties, on top of the best possible recommended therapy including β-blockers at the maximum tolerated dosage, improved outcomes in heart failure patients with low ejection fraction and heart rate ≥70 bpm.

Since the mainstay of recommended medications in heart failure is the combination of angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers in case of intolerance) and of a β-adrenergic blocker agent, it is logical to start this review article by the advantages and disadvantages of β-blockers in the management of heart rate in CHF.

Rationale of β-blocker therapy in CHF

β-Blocks are a cornerstone of pharmacological therapy of CHF. Several large randomized controlled studies have confirmed that β-adrenergic blockers reduce morbidity and mortality in CHF with reduced ejection fraction and the marked improvement in outcomes appears to be proportional to the magnitude of heart rate reduction2 and not to the β-blocker dosage. A meta-analysis of β-blocker trials also suggests that heart rate reduction may reverse remodeling and therefore prevent progression of the disease.3 However, since β-blockers have multiple mechanisms of action, it was not known until the publication of the results of SHIFT (Systolic Heart failure treatment with If inhibitor ivabradine Trial) whether a selective heart rate reduction obtained by a heart rate–reducing agent devoid of any other significant pharmacological properties would be beneficial in CHF.

Keywords: β-blocker; chronic heart failure; digoxin; heart rate; ivabradine; outcome; side effect

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**β-BLOCKERS IN CHF: THE REAL LIFE SITUATION**

Recent international surveys suggest that the prescription rate of β-blockers in CHF with reduced ejection fraction is improving compared with surveys conducted in the early 2000s, but that the dosage used in daily practice remains approximately half the target dose recommended by international guidelines.4-6 The underuse and insufficient uptitration of β-blocker therapy in real life has multiple causes: (i) physicians’ reluctance to change their practice due to a long-standing contraindication in heart failure in relation to the negative inotropic effect before large trials evidenced benefit in the late 90s; and (ii) limited tolerability due to bradycardia, hypotension, or pulmonary side effects.

β-Blockers are not a uniform class of drugs and distinctions exist in their pharmacological profile, including β₁-cardioselectivity or vasodilatory properties. These vasodilatory properties are more marked with β-blockers such as carvedilol, which has both α- and β-adrenergic blocking effects. Tolerability, for its part, may be limited in the heart failure population, which is typically an elderly population with a mean age of 70 years or more and prone to multiple comorbidities.

As a result, underdosing is a general observation even in contemporary surveys and clinical trials: thus, in the recently published heart failure pilot survey including 3226 patients with CHF from 12 European countries, the average dosage of β-blockers remained too low.7 Indeed, only 21% to 37% of patients were at target dose of carvedilol, bisoprolol, or metoprolol. In SHIFT, where investigators were encouraged to uptitrate as much as possible the β-blockers, only 26% of patients were able to reach the target dose recommended by the European Society of Cardiology (ESC), while 56% reached half of the target dose. 11% of this population did not receive this class of heart failure medication.8 The main reason for nonprescription was the existence leading to treatment withdrawal.9 In contrast, hypotension/fatigue/drowsiness/vertigo were observed in more than 20% of the patients and bradycardia was the most common reason for titration failure and was more commonly observed with bisoprolol. The CIBIS-ELD trial (Cardiac Insufficiency Bisoprolol Study in Elderly), clearly demonstrates that uptitration of β-blockers in the elderly heart failure population is a major challenge since only 25% of the patients reached the primary objective, ie, reaching and maintaining guideline-recommended target doses after 12 weeks’ treatment, and none of the two β-blockers tested in this study was superior with regard to tolerability.

The situation is particularly challenging in the very elderly population: among the 2780 octogenarians enrolled in Euro Heart Failure Survey, 24% were receiving β-blockers and only 9% were taking high doses of β-blockers.10 In this study, age was an independent predictor of nonprescription of β-blockers, suggesting that physicians’ reluctance of pulmonary disease, (chronic obstructive pulmonary disease, COPD) or asthma, and this finding is in line with the modeling analysis performed in the Euro Heart Failure Survey where the presence of COPD was the most powerful predictor of nonprescription of β-blocker therapy, probably for fear of bronchoconstriction.4

In a recent trial comparing the tolerability of two widely used β-blockers, carvedilol and bisoprolol, in an elderly heart failure population, pulmonary side effects including clinical symptoms or a significant change ≥20% in 1 s forced expiratory volume (FEV1) were observed more commonly with carvedilol (10%) than with bisoprolol (4%), but appeared not to be dose-limiting or leading to treatment withdrawal.9
played a role in this situation. In the second Euro Heart Failure Survey, the prescription rate of β-blockers improved since 53% of patients were taking these drugs. However, high doses of β-blockers were used in only 12% of these patients, here again suggesting poor tolerability and/or physicians’ reluctance to provide high doses of this heart failure medication to elderly patients. This is all the more unfortunate as, in this analysis, β-blocker prescription was associated with better outcome.

The uptitration scheme of β-blockers in heart failure (“start low, go slow”) is another limitation to reaching target doses in real life: international guidelines recommend uptitration over 8 to 12 weeks. This time-consuming process may discourage prescribers from going up to the highest tolerated dosage.

As a result of these practical difficulties in uptitrating β-blockers, heart rate remains often elevated in daily life situations: three contemporary surveys conducted in France, Italy, and the Heart Failure Pilot Survey conducted by the ESC in 12 countries show that approximately half of the patients enrolled remain with a heart rate >70 bpm and approximately 1/3 with a heart rate >75 bpm despite the fact that β-blockers were prescribed to approximately 80% of the patients (Figures 1 and 2).

IVABRADINE AND HEART RATE LOWERING IN CHF

The main conclusions of SHIFT are that: (i) elevated heart rate ≥70 bpm is a risk factor for poor cardiovascular outcome in heart failure with low ejection fraction; (ii) the addition of the selective heart rate-reducing If current inhibitor ivabradine improves outcomes in this condition when added on top of recommended medications, including β-blockers. It is therefore tempting to propose the addition of this novel agent to baseline heart failure medications whenever heart rate remains elevated ≥70 bpm.

This strategy used in SHIFT was associated with good tolerability, since the rate of asymptomatic and symptomatic bradycardia was 6% and 5%, respectively, and the rate of treatment discontinuations was 1% for each of these two adverse events in the ivabradine arm. The good tolerability of the addition of ivabradine to the background heart failure medication is also reflected by the fact that close to 70% of the patients enrolled in SHIFT could reach and were maintained on the target dosage of 7.5 mg twice daily, while fewer than 10% had to be downtitrated to the lowest dosage, ie, 2.5 mg twice daily. Another advantage of combining ivabradine with β-blockers to reduce heart rate is the fact that, unlike β-blockers, this compound is devoid of effects on the blood pressure. It is therefore proposed to use ivabradine in combination with β-blocker therapy in the many heart failure patients who remain with an increased heart rate despite attempts to uptitrate β-blockers to the maximal tolerated dose, and as a substitute to β-blockers in patients who do not tolerate this drug. Indeed, in the 10% of SHIFT patients who were not on β-blocker therapy, the magnitude of the effect of ivabradine tended to be more important than in those on β-blockers, although the interaction was not significant.

WHAT IS THE IDEAL HEART RATE IN HEART FAILURE?

The analysis of the rate of the primary outcome in SHIFT (cardiovascular mortality or heart failure hospitalizations) based on the heart rate achieved 28 days after initiation of ivabradine shows that the lowest incidence was observed in patients with a heart rate <60 bpm.

Therefore, it is reasonable to recommend that a heart rate <60 bpm should be reached in heart failure patients in order to reduce cardiovascular risk as much as possible.
BY HOW MUCH SHOULD HEART RATE BE REDUCED?

There is no clear answer to this question. However, since cardiac output is the product of heart rate by stroke volume, a drastic reduction in heart rate could lead to a significant reduction in cardiac output. It may therefore be proposed to reach a heart rate between 50 to 60 bpm in order to minimize cardiovascular risk without inducing untoward effects.

Measuring heart rate at rest under standardized conditions is therefore a simple, but important, clinical procedure in CHF. It is crucial to identify patients who remain with a markedly elevated heart rate, since they are at particularly high risk of cardiovascular events and since the benefit on outcomes resulting from the addition of ivabradine is particularly important, as shown by the subgroup analysis based on the median value of heart rate at baseline in SHIFT: patients who had a baseline heart rate >77 bpm (the median value of heart rate in our population) had a greater benefit than those with a baseline heart rate below the median value.

Digoxin in patients in sinus rhythm

Since only one large outcome trial (DIG, Digitalis Intervention Group) was carried out with digoxin in patients in sinus rhythm with ejection fraction <45% and before β-blockers were widely used, the level of evidence is low (level B). In this trial, digoxin did not reduce all-cause mortality, though it reduced hospital admissions by 28%. One disadvantage of digoxin is its narrow efficacy/toxicity window. Atrial arrhythmias and severe ventricular arrhythmias can occur, particularly in the presence of hypokalemia. It is therefore critical to monitor serum electrolytes and renal function since digitalis is eliminated by the kidneys and to reduce the dosage (usually 0.25 mg once daily) in elderly patients or in case of renal dysfunction. Digoxin plasma concentration may be useful to monitor digoxin treatment or when toxicity is suspected. Finally, some widely used drugs, such as amiodarone, diltiazem, or verapamil, may increase plasma digoxin levels.

Patients with permanent atrial fibrillation

Atrial fibrillation is present in approximately 30% of patients with CHF. In this particular situation, the pharmacological options are β-blockers or digitalis; ivabradine is not recommended due to its mechanism of action (I current inhibitor in the sinoatrial node).

The ESC Guidelines recommend digitalis to reduce heart rate in heart failure with atrial fibrillation, although the level of evidence is low (class of recommendation IIa, level of evidence C). In this situation, digoxin is useful to control ventricular rate in patients with rapid atrial fibrillation. In the long term, the ESC Guidelines favor β-blockers as the preferred treatment to control heart rate either alone or in combination with digoxin.

Finally, in patients with relatively preserved ejection fraction (>40%), verapamil or diltiazem may be used alone or in combination with digoxin to control ventricular rate.

CONCLUSION

Heart rate is an important marker of poor prognosis in CHF. Reduction of elevated heart rate when elevated to below 60 bpm by combining ivabradine, a new heart rate-reducing agent with β-blocker therapy improves outcomes in heart failure with low ejection fraction. This medical strategy should be considered in all patients with heart failure with low ejection fraction whose heart rate remains >70 bpm in resting conditions despite β-blocker therapy at the maximally tolerated dose.

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What are the differences in treating systolic and diastolic heart failure?

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Heart failure is a syndrome triggered by underlying cardiac dysfunction. The characterization of the underlying dysfunction is crucial to a proper diagnosis and informs the management plan. Clinical guidelines encourage physicians to determine whether the underlying cardiac dysfunction is ventricular, valvular, arrhythmic, or pericardial, or a combination of these. In a substantial minority of patients with heart failure, imaging of the heart reveals a normal left ventricular ejection fraction (LVEF). This has been variously described as “diastolic heart failure,” “heart failure with preserved systolic function,” or, arguably the most accurate term, “heart failure with normal ejection fraction” (HFNEF).

Epidemiological studies suggest that up to 50% of patients with heart failure have a normal ejection fraction. The proportion is highest in the elderly, and as the world population ages rapidly the size of this problem is likely to increase steeply. Current published literature suggests that the mortality rate and hospitalization rate are not dissimilar to those found among people with heart failure due to systolic dysfunction. The evidence base for

In a substantial minority of patients with heart failure, the ejection fraction is normal (“diastolic heart failure”). The evidence base for treatment of such patients is less robust than that for patients with systolic heart failure, with few large randomized trials. International guidelines make few recommendations: fluid retention should be controlled with judicious use of diuretics, ventricular rate in atrial fibrillation should be controlled (and consideration given to returning to sinus rhythm), and identification and treatment of hypertension and myocardial ischemia is considered worthwhile. This approach contrasts markedly with the firm evidence-based recommendations for the use of neurohormonal antagonists (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and aldosterone antagonists) for mortality and morbidity benefit in patients with systolic heart failure.

**Keywords:** atrial fibrillation; diastolic heart failure; diuretic; ejection fraction; evidence-based guidelines; neurohormonal antagonist; systolic heart failure; treatment

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_SeleCted abbreviations and acronYms_

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity</td>
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<tr>
<td>DIG</td>
<td>Digitalis Investigators Group</td>
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<tr>
<td>EMPHASIS-HF</td>
<td>Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>HFNEF</td>
<td>heart failure with normal ejection fraction (“diastolic heart failure”)</td>
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<td>I-PRESERVE</td>
<td>Irbesartan in Heart Failure with Preserved Ejection Fraction Study</td>
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<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>PEP-CHF</td>
<td>Perindopril in Elderly People with Chronic Heart Failure</td>
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<tr>
<td>SENIORS</td>
<td>Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalizations in Seniors with heart failure</td>
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<td>SHIFT</td>
<td>Systolic Heart Failure treatment with the L inhibitor ivabradine Trial</td>
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the treatment of systolic heart failure is large and based on many high-quality randomized clinical trials; in contrast, the evidence base for diastolic heart failure (HFNEF) is much smaller and less definitive. This gap in the evidence base is increasingly recognized as a problem.

This article summarizes the main differences between treating heart failure in patients with a low ejection fraction and those with a normal ejection fraction, with a review of the key clinical trials and international guidelines.

**THE TREATMENT OF SYSTOLIC HEART FAILURE**

The evidence base for the treatment of systolic heart failure is large and well codified in international guidelines\(^1,2\): there is little disagreement among clinicians on how such heart failure should be treated. This evidence base has been used in several countries to draw up standards of care with which to benchmark hospital and community heart failure services.\(^3,6\) In the United Kingdom, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and \(\beta\)-blockers, among this group of patients, is used as part of a payment for performance framework for primary care doctors (The Quality and Outcomes Framework).\(^7\)

The algorithm for the treatment of systolic heart failure in the most recent guidelines from the European Society of Cardiology (ESC) is shown in Figure 1.\(^1\)

Antagonism of the neurohormonal activation found in the heart failure syndrome is key to success, with a

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**Figure 1.** Algorithm for the treatment of heart failure due to systolic heart failure in the most recent European Society of Cardiology (ESC) guidelines.

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CRT-D, cardiac resynchronization therapy device; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device.

central role for ACE inhibitors (or angiotensin receptor blockers if such agents are not tolerated), β-blockers, and aldosterone antagonists. For patients with broad QRS complex on the ECG, cardiac resynchronization therapy is also now considered standard therapy for those with systolic dysfunction who remain symptomatic despite optimal drug therapy. An implantable cardioverter defibrillator is also considered indicated for those with severe systolic dysfunction, particularly if there is a history of coronary artery disease, and no other serious comorbidity, or for survivors of failed sudden death.

For patients in sinus rhythm, SHIFT (Systolic Heart Failure treatment with the I1 inhibitor ivabradine Trial), using this pure heart-rate lowering drug, has recently demonstrated an important impact on the combined end point of cardiovascular mortality and heart failure hospitalization in patients with systolic heart failure (18% relative risk [RR] reduction, \( P<0.0001 \)) with the largest benefit seen in heart failure hospitalization (26% RR reduction, \( P<0.0001 \)). Total mortality was not affected, but deaths from heart failure were reduced by 26% (\( P=0.014 \)).

EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) results suggest that the role for eplerenone (an aldosterone antagonist) will increase—there was an important impact on all-cause mortality (24% reduction, \( P=0.008 \)) and all-cause hospitalization (23% reduction, \( P<0.001 \)) in patients with systolic dysfunction who remained mildly symptomatic despite therapy with diuretic, ACE inhibitor, and β-blockade.

For those with atrial fibrillation, consideration is given to both rhythm and rate control, and thromboembolism prophylaxis with oral anticoagulation. Diuretic therapy is used in most patients with systolic heart failure. Current thinking is to use as little as is necessary to control symptoms and signs of fluid retention, with the dose often reduced as the dose of neurohormonal antagonists is optimized. Where symptoms fail to respond to the general approach described above, the guidelines suggest that a specialist should consider adding other agents such as nitrates and hydralazine, or an angiotensin receptor blocker to an ACE inhibitor, or digoxin in those in sinus rhythm.

Identification, and treatment, of relevant comorbidities such as anemia, chronic lung disease, and diabetes is also considered important, as is the identification of precipitants of worsening heart failure such as poor compliance with treatment or lifestyle measures, arrhythmia, and concomitant medication, eg, nonsteroidal anti-inflammatory agents. For a small minority, surgical approaches may be appropriate—such as revascularization for hibernating myocardium, treatment of concomitant valve disease, aneurysmectomy, transplantation, or ventricular assist device therapy.

THE TREATMENT OF DIASTOLIC HEART FAILURE

The situation for heart HFNEF (“diastolic heart failure”) is very different. There are few large randomized trials, and much of the evidence is empiric. Recent guidelines have been drawn up to assist physicians in diagnosing HFNEF, with the combined use of echocardiography and measurement of plasma natriuretic peptide concentration. Once the diagnosis has been confirmed, the therapy that is employed (on an empiric basis) is often very similar to that used for patients with systolic heart failure, as the syndrome of neurohormonal activation overlaps significantly with systolic heart failure. This article reviews the clinical trial evidence base, the recommen-
dations from key guidelines, and concludes with a pragmatic approach that is used by many physicians in day-to-day practice.

Review of the large randomized trials of treatment of diastolic heart failure

- **PEP-CHF.** In the PEP-CHF trial (Perindopril in Elderly People with Chronic Heart Failure), 850 patients aged 70 years or over with chronic heart failure and an echocardiogram that excluded significant valve disease or systolic dysfunction, but was compatible with diastolic dysfunction, were randomized to the ACE inhibitor perindopril 4 mg per day, or placebo, in addition to standard therapy. There was no significant reduction in the primary end point of all-cause mortality or unplanned heart failure hospitalization (hazard ratio [HR], 0.92; \( P = 0.55 \)) (Figure 2), but there was considerable crossover from the placebo group to open-label ACE-inhibitor treatment during the trial (presumably related to the clinicians’ belief that it was unethical to not use an ACE inhibitor in such patients, despite the lack of trial evidence), and a lower than anticipated event rate. These two factors resulted in very low power to detect a clinically important difference in outcome for the two groups. However, a reduction in one component of the primary end point, hospitalization for heart failure, and an improvement in symptoms and exercise capacity, in the first year, were observed with perindopril, suggesting that it may be of benefit in this population.

- **CHARM-Preserved.** In the CHARM-Preserved Trial (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), 3023 patients with heart failure and an ejection fraction >40% were randomized to the angiotensin receptor blocker candesartan, with a target dose of 32 mg once per day, or placebo, in addition to “standard” therapy. There was an 11% statistically nonsignificant (\( P = 0.12 \)) decrease in the primary end point of cardiovascular death or heart fail-

\[
\text{Hazard ratio } 0.89 \\
\text{(95% CI } 0.77-1.03), \ P = 0.118 \\
\text{Adjusted hazard ratio } 0.86, \ P = 0.051
\]

**Figure 3.** Time to cardiovascular death or heart failure hospitalisation in the CHARM-Preserved Study.

CHARM-Preserved (Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity in patients with left ventricular ejection fraction > 40% treated or not with an angiotensin-converting enzyme inhibitor).

ure hospitalization, driven almost entirely by the reduction in heart failure hospitalization (HR, 0.85; P=0.07, reaching statistical significance only after adjustment for baseline differences in characteristics in the two groups HR, 0.86; P=0.05) (Figure 3, page 109). Taking only investigator-defined heart failure hospitalizations (rather than those agreed by the end point committee), there was a 21% reduction in the total number of hospitalizations (P=0.01) during the trial.

• I-PRESERVE. The Irbesartan in Heart Failure with Preserved Ejection Fraction Study, the angiotensin receptor blocker irbesartan at a dose of up to 300 mg once per day or placebo was added to “standard” therapy for 4128 patients with heart failure and an ejection fraction ≥45%.13 There was no difference in the primary end point of all-cause mortality or cardiovascular hospitalization (Figure 4, page 109), or in any of the other predefined end points. The therapy considered “standard” by the clinicians recruiting patients to this study, published in 2008, and in CHARM-Preserved published in 2003, is shown in Table I.

Table 1. Drug therapy of diastolic heart failure at baseline.
Patients randomized in the CHARM-Preserved12 (published 2003) and I-PRESERVE13 (published 2008) studies, reflecting the treatment pattern for such patients at the recruiting centers.

<table>
<thead>
<tr>
<th>Drug</th>
<th>CHARM-Preserved</th>
<th>I-PRESERVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>56%</td>
<td>59%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>75%</td>
<td>83%</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Digoxin*</td>
<td>28%</td>
<td>14%</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>31%</td>
<td>40%</td>
</tr>
<tr>
<td>Other vasodilator (including nitrate)</td>
<td>38%</td>
<td>&gt;27%</td>
</tr>
<tr>
<td>Oral anticoagulant*</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Antiplatelet drug</td>
<td>63%</td>
<td>59%</td>
</tr>
<tr>
<td>Lipid-lowering drug†</td>
<td>42%</td>
<td>31%</td>
</tr>
</tbody>
</table>

* In both studies 29% of patients had a history of atrial fibrillation.
† Etiology was labeled “ischemic” in 56% of patients in CHARM-Preserved, and in 25% of patients in I-PRESERVE.

Review of subgroup analyses from other randomized trials

• DIG. The Digitalis Investigators Group Ancillary Trial included patients in sinus rhythm with diastolic heart failure (ejection fraction >45%).14 There was no difference in mortality in this group, but there was evidence at 24 months of some benefit in terms of the primary end point of heart failure mortality or heart failure hospitalization, but these effects were nonsignificant at the end of the study period (Figure 5). Total hospitalizations were not reduced, however, due to an increase in hospitalizations for unstable angina canceling out the reduction in heart failure hospitalizations.

• SENIORS. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalizations in Seniors with Heart Failure included a small number of patients with an ejection fraction >40% (but very few with ejection fraction >50%), and reported no statistical evidence of a difference in effect on the primary end point of all-cause mortality or...
What are the differences in treating systolic and diastolic heart failure? - Cowie

Cardiovascular hospitalizations (HR for nebivolol compared with placebo of 0.86, 95% confidence interval [CI], 0.74-0.99, \( P=0.04 \)) \(^{15}\)

- Ongoing trials. The effect of spironolactone, sildenafil, and an endothelin antagonist in diastolic heart failure are being examined currently in phase 3 trials.

**CURRENT GUIDELINES ON THE TREATMENT OF DIASTOLIC HEART FAILURE**

The current recommendations for the treatment of patients with diastolic heart failure in the ESC guidelines are confined to two paragraphs in a document of 54 pages.\(^1\) The recommendation is that diuretics should be used to control sodium and water retention and relieve breathlessness and edema. Adequate treatment of hypertension and myocardial ischemia is also highlighted, along with the “control” of the ventricular rate in atrial fibrillation, with mention of a potential role for verapamil, based on two very small studies.\(^{16,17}\) CHARM-Preserved and PEP-CHF are mentioned, but without firm recommendations on whether the drugs used in these studies should be used routinely in such patients.

The North American guidelines are only slightly more detailed. The current guidance is shown in Table II.\(^{18}\) Most recently, the National Institute for Health and Clinical Excellence (NICE) published a partial update to its guidance on the treatment of heart failure.\(^{19}\) It considered that there was no clear evidence of benefit for drug treatment in heart failure with preserved ejection fraction, but advised that drug treatment for comorbid conditions (such as hypertension, ischemic heart disease, and diabetes mellitus) should be optimized.

### Table II. Current North American guidelines for the treatment of diastolic heart failure.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control systolic and diastolic heart failure, in accordance with published guidelines</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Control ventricular rate in patients with atrial fibrillation</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Use diuretics to control pulmonary congestion and peripheral edema</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Revascularization is “reasonable” in patients with CAD with symptomatic or demonstrable myocardial ischemia judged to have an adverse effect on cardiac function</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Restoration and maintenance of sinus rhythm in patients with AF “might” be useful to improve symptoms</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of BB, ACEI, ARBs, or calcium antagonists in patients with controlled hypertension “might” be effective to minimize symptoms of HF</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>The use of digoxin to minimize symptoms of HF is not well established</td>
<td>Iib</td>
<td>C</td>
</tr>
</tbody>
</table>

**CURRENT CLINICAL APPROACH TO THE TREATMENT OF DIASTOLIC HEART FAILURE**

In the absence of a large and convincing evidence base for the treatment of patients with heart failure and normal ejection fraction (diastolic heart failure), most clinicians take a pragmatic approach informed by our current understanding of the underlying pathology and the frequent coexistence of other disease processes.\(^{18}\) The empiric approach that is adopted can be summarized as below:

1. Treat the fluid congestion
   - **Symptom relief** by judicious use of diuretics to lower left ventricular end-diastolic pressure and left atrial pressure, without compromising cardiac output;
   - **Use of nitrates** to further reduce ventricular preload and thus ventricular filling pressures may be useful.

2. Treat the underlying or aggravating conditions
   - **Underlying ischemia** (if this is the mechanism of diastolic dysfunction)—consider medical therapy ± revascularization;
   - **Hypertension** (frequently coexists with diastolic heart failure)—its treatment may help reduce left ventricular hypertrophy (in the medium term) and afterload, thus improving hemodynamics.

3. Empiric pharmacological therapy of diastolic dysfunction, in an attempt to improve ventricular re-
laxation and filling by slowing heart rate or improving the intrinsic properties of ventricular muscle. This is usually achieved by use of β-blockers or rate-limiting calcium antagonists to reduce heart rate and increase time for ventricular filling. Improved ventricular relaxation may also occur with regression of hypertrophy with the longer-term use of β-blockers, renin-angiotensin-aldosterone blockers, and rate-limiting calcium antagonists.

4. For patients in atrial fibrillation, return to sinus rhythm or, at least, rate control can have a major symptomatic benefit. Anticoagulation should also be considered in this group.

5. Lifestyle measures. Although the evidence base is almost nonexistent for lifestyle measures for diastolic heart failure, most physicians consider avoidance of excessive dietary salt or fluid intake, and regular exercise, as advisable. In practice, many disease management programs have excluded patients with nonsystolic heart failure, but this is changing rapidly as the unmet needs of this large population are becoming clearer and more pressing.

CONCLUSIONS

Heart failure is frequently caused by diastolic dysfunction of the left ventricle (or “heart failure with normal ejection fraction”). Although the evidence base for therapy to improve prognosis, reduce the risk of hospitalization, and improve quality of life, is very thin compared with that for systolic heart failure, in day-to-day practice the therapy is very similar to that of systolic heart failure. Diuretics are used to control fluid retention, and there is a low threshold for the use of renin-angiotensin blockers such as ACE inhibitors or angiotensin receptor blockers, particularly if there is co-existing hypertension or diabetes mellitus. Control of heart rate and maintenance of sinus rhythm is also considered important. The willingness to accept side effects of therapy is perhaps less than for systolic heart failure, as the evidence for benefit is less good. Further trials are ongoing, which may help to clarify the role of other agents.

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Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. 

Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. 

18. Redfield MM. 
Recognising and managing the patient with heart failure and preserved ejection fraction. 

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What are the challenges in cardiac resynchronization therapy in heart failure?

Kenneth Dickstein, MD, PhD
University of Bergen - Stavanger University Hospital - NORWAY

This paper briefly reviews the current guideline recommendations on the use of cardiac resynchronization therapy (CRT) devices in heart failure and focuses on the challenges that need to be addressed. Two essential issues are immediately apparent. The first regards encouraging implementation of evidence-based guidelines. The second concerns identifying the important gaps in evidence that exist with regard to patient selection and implantation techniques. In practice, clinicians must make decisions in evaluating patients for device implantation who do not fulfill the conventional criteria, but may still respond favorably with improvements in symptoms and outcomes.

The management of patients with heart failure (HF) represents a substantial economic burden and hospitalization is responsible for over 50% of this expense. The initial expense of device implantation must be weighed against measures of short- and long-term efficacy with regard to survival, morbidity, and quality of life.

The clinical effects of long-term cardiac resynchronization therapy (CRT) have been evaluated in a large number of randomized multicenter trials, using CRT pacemakers (CRT-P) or CRT-ICD (implantable cardioverter/defibrillator) devices (CRT-D). Randomized clinical trials (RCTs) evaluating CRT with or without an ICD in patients with symptomatic HF provide consistent evidence of progressive and sustained reverse remodeling. The devices significantly alleviate symptoms, increase exercise capacity, lower the rate of hospitalization, and prolong survival.

The effective use of limited health care resources necessitates identification of the characteristics of the patient population most likely to benefit from CRT. Treatment strategy should target these patients for device implantation. A device that can substantially reduce hospitalizations and prolong survival with...
improved symptoms in the large population of patients with symptomatic heart failure should represent an efficient use of health care resources.

**UPDATED CRT PRACTICE GUIDELINES: CHALLENGES RECENTLY ADDRESSED**

Practice guideline recommendations represent evidence-based medicine based on the outcomes in the cohort of patients described by the inclusion criteria in the protocols of RCTs. The current European Society of Cardiology (ESC) Heart Failure Guidelines were published in 2008 and the Pacing Guidelines were published in 2007. The Focused Update on the use of Devices in Heart Failure 2010 modified the recommendations according to the most recent clinical trial evidence. These updated recommendations are summarized in Table 1 and an overview of the evidence from the RCTs along with the appropriate references is presented in Tables II (page 116) and III (page 117).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D is recommended to reduce morbidity and mortality</td>
<td>NYHA function class III/IV, LVEF ≤ 35%, QRS ≥ 120 ms, SR, Optimal medical therapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression</td>
<td>NYHA class II symptoms, LVEF ≤ 35%, QRS ≥ 150 ms, SR, Optimal medical therapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered to reduce morbidity</td>
<td>Permanent atrial fibrillation, NYHA III/IV, LVEF ≤ 35%, QRS ≥ 130 ms, Pacemaker dependency induced by AV nodal ablation</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered to reduce morbidity</td>
<td>Permanent atrial fibrillation, NYHA III/IV, LVEF ≤ 35%, QRS ≥ 130 ms, Slow ventricular rate and frequent pacing</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>CRT-P/CRT-D is recommended to reduce morbidity</td>
<td>Class I indication for pacemaker, NYHA class III/IV, LVEF ≤ 35%, QRS ≥ 120 ms</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered to reduce morbidity</td>
<td>Class I indication for pacemaker, NYHA class III/IV, LVEF ≤ 35%, QRS &lt; 120 ms</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>CRT-P/CRT-D may be considered to reduce morbidity</td>
<td>Class I indication for pacemaker, NYHA class II, LVEF ≤ 35%, QRS &lt; 120 ms</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>LVAD may be considered as destination treatment to reduce mortality</td>
<td>Ineligible for cardiac transplantation, NYHA III/IV symptoms, LVEF ≤ 25%, Peak VO2 &lt; 14 mL/kg/min</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

**Table I. Summary of indications for devices in patients with heart failure.**

Abbreviations: a, class of recommendation; b, level of evidence; CRT, cardiac resynchronization therapy; CRT-P, cardiac resynchronization therapy with pacemaker function; CRT-D, cardiac resynchronization therapy with defibrillator function; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SR, sinus rhythm.

Reproduced from reference 6: Dickstein K et al. Eur J Heart Fail. 2010;12(11):1143-1153. © European Society of Cardiology/Published by Oxford University Press.

**Patients in NYHA class III**

There is consistency in the CRT Class I Recommendation with Level of Evidence A for patients with New York Heart Association (NYHA) class functional class III-IV symptoms, left ventricular dysfunction, and a wide QRS complex across all the European and American guidelines. Treatment has been shown...
to reduce morbidity, as evidenced by fewer hospitalizations and prolonged survival. CARE-HF (CArdiac RESynchronization in Heart Failure) found a 40% relative risk reduction in the primary end point of all-cause death or cardiovascular hospitalization and a 52% reduction in HF hospitalizations. The number needed to treat (NNT) to prevent a primary end point was 9.

Patients in NYHA class IV

COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) enrolled 218 NYHA class IV patients. Patients were required to be “ambulatory,” with no scheduled or unscheduled admissions for HF during the last month, with a life expectancy of >6 months. Time to all-cause mortality or first all-cause hospitalization was significantly improved by both CRT-P and CRT-D as compared with optimal medical treatment. However, no benefit was observed on all-cause mortality alone. These data support the use of CRT to improve morbidity (but not mortality) in ambulatory class IV patients.

Patients in NYHA class II

CPT in patients presenting with no or only mild manifestations of HF, a depressed left ventricular ejection fraction (LVEF), and a wide QRS complex, has been addressed in 4 trials, MIRACLE ICD II (Multicenter InSync ICD [implantable cardioverter-defibrillator] RAndomized CLinical Evaluation–II).13 MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial—Cardiac resynchronization Therapy),19 REVERSE (RESynchronization revErses Re-modeling in Systolic left vEntricular dysfunction),21 and RAFT (RESynchronization/defibrillation for Ambulatory heart failure Trial).20 The results confirm that CRT lowers the risk of HF-related adverse clinical events and morbidity as evaluated by rehospitalization. Further studies are needed to determine whether survival is increased by CRT-D in patients with mild symptoms. In prespecified subgroup analyses of data collected in MADIT-CRT19 and REVERSE,21 the patients whose QRS duration was ≥150 ms derived the greatest benefit from CRT. This finding was further supported by the results in RAFT. In a context of limited resources, it would be prudent to target the population most likely to respond favorably. In patients with mild symptoms and a QRS width of 120 to 150 ms, clinicians may wish to assess other criteria associated with a favorable outcome such as dyssynchrony determined by echocardiography, LV dilatation, left bundle branch block (LBBB), non-ischemic cardiomyopathy, or recent NYHA class III symptoms.

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**Table II. Inclusion criteria in the controlled randomized trials.** Study acronyms: see table at beginning of article.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>NYHA class</th>
<th>LVEF (%)</th>
<th>LVEDD (mm)</th>
<th>SR/AF</th>
<th>ORS (ms)</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC-SR7</td>
<td>58</td>
<td>III</td>
<td>&lt;35%</td>
<td>&gt;60</td>
<td>SR</td>
<td>&gt;150</td>
<td>No</td>
</tr>
<tr>
<td>MIRACLE8</td>
<td>453</td>
<td>III,IV</td>
<td>&lt;35%</td>
<td>&gt;55</td>
<td>SR</td>
<td>&gt;130</td>
<td>No</td>
</tr>
<tr>
<td>MUSTIC AF9</td>
<td>43</td>
<td>III</td>
<td>&lt;35%</td>
<td>&gt;60</td>
<td>AF</td>
<td>&gt;200</td>
<td>No</td>
</tr>
<tr>
<td>PATH CHF10</td>
<td>41</td>
<td>III,IV</td>
<td>&lt;35%</td>
<td>NA</td>
<td>SR</td>
<td>&gt;120</td>
<td>No</td>
</tr>
<tr>
<td>MIRACLE ICD11</td>
<td>369</td>
<td>III,IV</td>
<td>&lt;35%</td>
<td>&gt;55</td>
<td>SR</td>
<td>&gt;130</td>
<td>Yes</td>
</tr>
<tr>
<td>CONTAK CD12</td>
<td>227</td>
<td>II,IV</td>
<td>&lt;35%</td>
<td>NA</td>
<td>SR</td>
<td>&gt;120</td>
<td>Yes</td>
</tr>
<tr>
<td>MIRACLE ICD II13</td>
<td>186</td>
<td>II</td>
<td>&lt;35%</td>
<td>&gt;55</td>
<td>SR</td>
<td>&gt;130</td>
<td>Yes</td>
</tr>
<tr>
<td>PATH CHF II14</td>
<td>89</td>
<td>III,IV</td>
<td>&lt;35%</td>
<td>NA</td>
<td>SR</td>
<td>&gt;120</td>
<td>Yes/No</td>
</tr>
<tr>
<td>COMPANION15</td>
<td>1520</td>
<td>III,IV</td>
<td>&lt;35%</td>
<td>NA</td>
<td>SR</td>
<td>&gt;120</td>
<td>Yes/No</td>
</tr>
<tr>
<td>CARE HF66</td>
<td>814</td>
<td>III,IV</td>
<td>&lt;35%</td>
<td>&gt;30 (indexed to height)</td>
<td>SR</td>
<td>&gt;120</td>
<td>No</td>
</tr>
<tr>
<td>CARE HF extension 20062</td>
<td>813</td>
<td>III,IV</td>
<td>≤35%</td>
<td>&gt;30 (indexed to height)</td>
<td>SR</td>
<td>&gt;120</td>
<td>No</td>
</tr>
<tr>
<td>REVERSE 200817,18</td>
<td>610</td>
<td>I,II</td>
<td>&lt;40%</td>
<td>&gt;55</td>
<td>SR</td>
<td>&gt;120</td>
<td>Yes/No</td>
</tr>
<tr>
<td>MADIT CRT19</td>
<td>1800</td>
<td>I,II</td>
<td>&lt;30%</td>
<td>NA</td>
<td>SR</td>
<td>&gt;130</td>
<td>Yes</td>
</tr>
<tr>
<td>RAFT20</td>
<td>1798</td>
<td>II,III</td>
<td>&lt;30%</td>
<td>NA</td>
<td>SR/AF</td>
<td>&gt;130/200*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; SR, sinus rhythm; AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; NA, not available; NYHA, New York Heart Association (classification of heart failure); “patients in atrial fibrillation.
### NYHA class III/IV with permanent atrial fibrillation

Randomized studies of CRT to date have been almost exclusively restricted to patients in sinus rhythm. However, a recent ESC CRT survey\(^2^2\) indicates that approximately 1 out of 5 patients receiving CRT in Europe has permanent atrial fibrillation (AF). Patients with symptomatic HF, AF, and an LVEF $\leq 35\%$ may satisfy the criteria for ICD implantation. The presence of QRS prolongation and an LBBB pattern in such patients would favor implantation of a CRT-D. There is consensus that complete ventricular capture is required in order to maximize the clinical benefit of CRT and improve the prognosis of patients with permanent AF. Pharmacological treatment is frequently inadequate in controlling ventricular rate, especially during exercise.\(^2^3\) Hybrid therapy, combining CRT with atrioventricular ablation (resulting in 100% effective biventricular stimulation) has been shown to confer improvements in left ventricular function and exer-

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**Table III.** End points, design and main findings of the randomized controlled trials evaluating CRT in heart failure.

<table>
<thead>
<tr>
<th>Study</th>
<th>End points</th>
<th>Design</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC-SR(^7)</td>
<td>6-MWT, QOL, pVO(_2), hosp</td>
<td>Single-blinded, controlled, crossover, 6 months</td>
<td>CRT-P improved: 6-MWT, QOL, pVO(_2); reduced hosp</td>
</tr>
<tr>
<td>MIRACLE(^8)</td>
<td>NYHA class, QOL, pVO(_2)</td>
<td>Double-blinded, controlled, 6 months</td>
<td>CRT-P improved: NYHA, pVO(_2), 6-MWT</td>
</tr>
<tr>
<td>MUSTIC AF(^9)</td>
<td>6-MWT, QOL, pVO(_2), hosp</td>
<td>Single-blinded, controlled, crossover, 6 months</td>
<td>CRT-P (high dropout rate): improved all, reduction of hosp</td>
</tr>
<tr>
<td>PATH CHF(^1^0)</td>
<td>6-MWT, pVO(_2)</td>
<td>Single-blinded, controlled, crossover, 12 months</td>
<td>CRT-P improved: 6-MWT, pVO(_2)</td>
</tr>
<tr>
<td>MIRACLE ICD(^1^1)</td>
<td>6-MWT, QOL, hosp</td>
<td>Double-blinded, ICD vs CRT-D 6 months</td>
<td>CRT-D improved all from baseline (not ICD)</td>
</tr>
<tr>
<td>CONTAK CD(^1^2)</td>
<td>Mortality + Hosp HF + VA, pVO(_2), 6MWT, NYHA class, QOL, LVEDD + LVEF</td>
<td>Double-blinded, ICD vs CRT-D 6 months</td>
<td>CRT-D improved: pVO(_2), 6-MWT; reduced LVEDD and increased LVEF</td>
</tr>
<tr>
<td>MIRACLE ICD II(^1^3)</td>
<td>VE/CO(_2), pVO(_2), NYHA, QOL, 6-MWT, LV volumes/EF</td>
<td>Double-blinded, ICD vs CRT-D 6 months</td>
<td>CRT-D improved: NYHA, VE/CO(_2); volumes, LVEF</td>
</tr>
<tr>
<td>COMPANION(^1^5)</td>
<td>(1) All-cause death or hosp for major CV event (2) Death from any cause</td>
<td>Double-blinded, controlled, OPT, CRT-D, CRT-P, about 15 months</td>
<td>CRT-P/CRT-D reduced (1)</td>
</tr>
<tr>
<td>CARE-HF(^1^6)</td>
<td>(1) All-cause death or hosp (2) Mortality</td>
<td>Double-blinded, controlled, OPT, CRT-P, 29 months</td>
<td>CRT-P reduced (1) and (2)</td>
</tr>
<tr>
<td>REVERSE(^1^8)</td>
<td>(1) Percent worsened by clinical composite end point (2) LVESt (3) HF hosp (4) Mortality</td>
<td>Double-blinded, controlled, OPT, CRT-P + ICD, 12months</td>
<td>Primary end point NS CRT-P/ CRT-D reduced (2) and (3) hosp, but not (4)</td>
</tr>
<tr>
<td>MADIT –CRT(^1^9)</td>
<td>(1) Heart failure events or death (2) Mortality (3) LVESt</td>
<td>Controlled, CRT-P, CRT-D, 2.4 years</td>
<td>CRT-D reduced (1) and (3), but not (2)</td>
</tr>
<tr>
<td>RAFT(^2^0)</td>
<td>(1) All-cause death (2) Hosp</td>
<td>Controlled, double-blinded CRT-D, CRT-P, 40 months</td>
<td>CRT-D reduced (1) and (2)</td>
</tr>
</tbody>
</table>

Abbreviations: 6-MWT, 6-minute walk test; CRT-P, cardiac resynchronization therapy with biventricular pacemaker; CRT-D, cardiac resynchronization therapy with biventricular pacemaker with a defibrillator; HF, heart failure; hosp, hospitalizations; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESt, left ventricular stroke volume index; NYHA, New York Heart Association (classification of heart failure); OPT, optimal pharmacological treatment; pVO\(_2\), peak oxygen consumption; QOL, quality of life; VE/CO\(_2\), ventilation/carbon dioxide ratio. Study acronyms: see table at beginning of article.
cise capacity. Meta-analyses provided evidence that patients with heart failure and AF treated with CRT received the same survival benefit to those achieved in patients with sinus rhythm only when atrioventricular ablation was performed shortly after CRT implantation.

NYHA class III/IV and conventional pacemaker indication

Prospective randomized controlled studies specifically addressing the issue of CRT in patients with a narrow QRS complex are currently lacking. However, there are several retrospective relatively large observational series demonstrating the clinical benefit of upgrading to CRT in patients with chronic right ventricular pacing, ventricular dysfunction, and NYHA class III symptoms, regardless of QRS duration.

It is important to consider that both the underlying bradycardia and right ventricular pacing induced ventricular dyssynchrony may contribute to symptoms of HF. The detrimental effects of right ventricular pacing on symptoms and left ventricular function in patients with HF of ischemic origin have been demonstrated. It is reasonable to consider CRT for the improvement of symptoms, which should aim at avoiding chronic right ventricular pacing in such patients. Importantly, CRT may permit initiation and adequate uptitration of β-blocker treatment in these patients.

**UNMET CHALLENGES: IMPLEMENTATION ISSUES**

Health care resources are limited and frequently budgets will not permit implantation of devices in all patients that satisfy the conventional recommendations described above. Priorities must be established and local administrative policies will decide the extent of available resources. Ultimately, clinicians will decide how these resources should best be distributed to the heterogeneous population of patients with HF. CRT presents challenges that differ from the pharmacological management of these patients. In clinical practice, drug therapy represents a relatively small initial expense that persists during chronic therapy. Drug therapy is routinely initiated, uptitrated, and fine-tuned by primary care hospital-based physicians, frequently in cooperation with an outpatient nurse-led heart failure management program. The initial expense is usually modest and treatment can be readily modified or discontinued as appropriate.

In contrast, device therapy requires a substantial initial investment and necessitates a broad cooperation between a number of players and requires identifying appropriate candidates, adequate evaluation of the patient with imaging techniques, available implantation expertise, and an infrastructure for adequate follow-up. Effective device treatment including implantation and follow-up will usually involve the patient, a primary care physician, a cardiologist, an electrophysiologist, and specially trained nurses.

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**Patient selection criteria for CRT**

- Chronological/biological age?
- Major comorbidities?
- LVEF >35%?
- QRS width between 120-150 ms and NYHA II class?
- Right bundle branch pattern/atrial fibrillation?
- Role of imaging techniques to detect mechanical dyssynchrony/viable myocardium/mitral insufficiency?
- Heart failure, ICD indication with QRS <120 ms?
- Heart failure, RV pacing indication with QRS <120 ms?
- NYHA I functional class?
- Which factors predict a poor response?

**CRT Implantation Issues**

- CRT-P or CRT-D?
- Indications for upgrade of a previous device?
- Importance of operator experience/lead placement?
- Role of imaging techniques to determine optimal lead placement?
- Skills in optimal AV, VV programming?
- Adequate follow-up program?
- Health resource utilization and cost/benefit ratio?

*Table IV. List of issues concerning cardiac resynchronization therapy needing to be addressed in future clinical research.*

**Abbreviations:** AV, atrioventricular; CRT-P, cardiac resynchronization therapy with biventricular pacemaker; CRT-D, cardiac resynchronization therapy with biventricular pacemaker with a defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association (classification of heart failure); RV, right ventricular.

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**UNMET CHALLENGES: SELECTION CRITERIA ISSUES**

Clinicians responsible for managing patients with HF must frequently make treatment decisions without adequate evidence or consensus expert opinion. *Table IV* is a short-list of selected, common patient selection and implantation issues concerning CRT with limited evidence that deserve to be addressed in future clinical research.
Which factors in patient selection predict a favorable response?

Unfortunately, there is no consensus among investigators concerning which clinical or functional criteria best indicate a favorable response following implantation of a CRT device. A recent review of 26 of the most cited publications on predicting response to CRT demonstrated that response was defined using 17 different criteria.

Defining a “responder” is a challenging area in clinical research. Symptoms, functional capacity, cardiac function, and clinical outcomes including both morbidity and mortality represent important efficacy parameters. Although an elusive goal, the HF community should strive to develop a standard composite end point.

Role of imaging techniques to detect mechanical dyssynchrony/viable myocardium

RCTs have uniformly selected patients for inclusion based on evidence of electrical dyssynchrony as evidenced by QRS prolongation. Although intuitively attractive, there is no currently convincing evidence that selection based on echocardiography or other imaging techniques demonstrating mechanical dyssynchrony can be recommended. This may be due to the large number of different measurements assessed by these techniques as well as the lack of consensus regarding evaluation of the criteria indicating reverse remodeling. In practice, clinicians most frequently will search for evidence of left ventricular dyssynchrony with echocardiography and consider these results prior to a decision concerning eligibility for CRT.

LV remodeling and clinical outcomes

It makes biological sense that improvement in symptoms and outcomes with effective CRT would be accompanied by improved ventricular function and reductions in chamber volumes. Paired echocardiographic studies were obtained in nearly all patients in MADIT-CRT and analyzed at a core laboratory. Consistent with the echocardiographic studies from CARE-HF and REVERSE, substantial improvements in left ventricular size and function, LVEF, right ventricular function, left atrial size, and mitral regurgitation severity were observed in patients treated with CRT compared with ICD only.

Although these findings were consistent across all subgroups, the improvements in volumes were greatest in patients with a QRS width ≥150 ms, patients with LBBB, patients with nonischemic etiology, and in female patients. These findings were strongly concordant with, and predictive of, the primary outcome of death or an HF event, and suggest a compelling cardiac structural and functional mechanism by which CRT therapy prevents the progression of disease by reverse left ventricular remodeling. It represents an important challenge for clinical researchers to identify which characteristics of cardiac function and which imaging techniques would best predict the likelihood of substantial reverse remodeling following CRT.

NYHA class I

MADIT-CRT and REVERSE enrolled a small proportion of asymptomatic patients, only 15% and 18%, respectively. Neither study showed a significant reduction in all-cause mortality or HF event rate by CRT as compared to ICD alone. There is no current evidence that CRT would improve outcomes in asymptomatic patients. However, due to the lower event rate in this population, the trials evaluating NYHA I patients have not been adequately powered to evaluate the efficacy of long-term CRT on clinical outcomes.

Choice of device

CRTs improve symptoms as well as reducing morbidity and mortality. ICDs improve survival. Randomized trials in mildly symptomatic patients (NYHA II) have predominantly compared CRT-D vs ICD in populations with an indication for ICD. There is no evidence currently supporting the use of CRT-P in mildly symptomatic patients. Importantly, the significantly younger age, lower comorbidity, longer life expectancy, and higher proportion of sudden cardiac death relative to overall mortality...
of patients presenting in NYHA class II compared with classes III or IV would support the implantation of CRT-D. CARE-HF demonstrated convincing results regarding morbidity and mortality for CRT-P alone in patients with NYHA class III/IV symptoms. Current guidelines do not indicate a preference between CRT-P or CRT-D in patients with NYHA III/IV symptoms who are not considered definite candidates for an ICD. Clinicians consider a number of factors when choosing which device is most appropriate in a given patient. Another frequent decision that clinicians face concerns the indications for upgrading a previously implanted device (ICD/pacemaker) to a CRT-P or CRT-D.

QRS morphology: LBBB vs RBBB

In CARE-HF, baseline LBBB duration predicted a favorable outcome. By multivariable analysis, right bundle branch block (RBBB) was a predictor of unfavorable outcome. The 5% of patients with RBBB had a particularly high event rate.

In MADIT-CRT, improvement in outcomes was restricted to patients with QRS ≥150 ms and typical LBBB, and women with LBBB had a particularly favorable response.

Atrial fibrillation

Although there are now guidelines concerning patients with heart failure and AF, these are class II recommendations with second-tier evidence levels. RCTs have not included adequate numbers of patients with AF to clearly define outcomes. The efficacy and necessity of atrioventricular node ablation in patients with a rapid ventricular response not adequately controlled by drugs needs to be established in large prospective RCTs.

Mitral insufficiency

The contribution of papillary muscle dyssynchrony to the severity of mitral insufficiency is difficult to assess by ECG or echocardiography prior to implantation. Reductions in volumes and reverse remodeling during chronic therapy also complicate evaluation of improvement of mitral valve function.

Both clinical and trial evidence have demonstrated substantial reductions in the severity of myocardial infarction. However, we have not identified imaging techniques that would predict, prior to implantation, a significant reduction in the degree of mitral insufficiency with symptomatic improvement following CRT.

UNMET CHALLENGES: IMPLANTATION ISSUES

Importance of operator experience and lead placement

A central issue related to the success of CRT concerns the importance of operator expertise and experience. Electrophysiologists at centers with large volumes of device implantation use less time per procedure. Implantations performed electively are associated with shorter durations of hospitalizations. Whether this results in improved outcome is not established. The relationship between a successful posterolateral placement of the LV lead with adequate capture and a favorable response has been demonstrated.

The most sensitive imaging technique for assessing successful resynchronization during the procedure is echocardiography. Which measurements best predict response remain to be identified.

Skills in optimal atroventricular (AV) and interventricular (VV) programming

The importance of programming following implantation and during follow-up cannot be overestimated. Although recommendations with regard to the various imaging techniques employed to optimize programming following implantation in the individual patient exist, this aspect of CRT implantation is often neglected. Ongoing trials to evaluate various automated programs should lead to a consensus regarding the most effective techniques and facilitate this process. The physician responsible for this essential, postimplantation fine-tuning during follow-up should be adequately trained.

Adequate follow-up program

Follow-up of patients following implantation includes adjustment of pharmacological therapy, which frequently will change over time. It may be possible to introduce or up titrate medication that was not tolerated previously. Specifically, up titration of β-blocker therapy is frequently possible following CRT implantation. An effective follow-up program should be multidisciplinary, usually including a specially trained nurse, clinical cardiologist, and electrophysiologist.

Health resource utilization and cost/benefit ratio

This essential aspect of device therapy in HF must receive attention and routines for capturing information relevant to this issue should be developed. Although CRT-P/ CRT-D implantation involves a substantial initial expense, the cost/ benefit ratio improves during chronic therapy in patients with improved
What are the challenges of cardiac resynchronization therapy in heart failure? - Dickstein

Functional capacity and reduced morbidity. Guidelines have traditionally not adequately addressed this important issue, in that RCTs do not routinely report such information. The primary publications report results based on the prespecified end points. Rigorous assessment of health resource utilization in the various subsets of populations receiving devices remains a major unmet challenge.

**CONCLUSIONS**

CRT in patients with symptomatic HF, systolic dysfunction, and electrical dyssynchrony has been shown to substantially improve symptoms and clinical outcomes. However, adequate implementation of current guidelines remains a challenge. Future clinical research should address the gaps in the evidence with regard to selection of the patient population most likely to respond favorably as well as which aspects of implantation and follow-up are essential for the most effective use of limited resources.

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Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial.
I suppose I was always destined to be a doctor. Genes certainly played a role in the matter. We have always had doctors in the family, ever since my ancestors came to Malta from France in 1751. Six of my seven uncles were doctors, my maternal grandfather, Salvatore, was a chest physician, and my paternal great-great-grandfather, Lorenzo, became the first professor of ophthalmology in Malta and, with his son Charles, also an eye surgeon, founded the philanthropic Ophthalmic Institute in 1908.

DR KILDARE, ARPEGGIOS, AND FIRST PAINTINGS

Of course Dr Kildare burst onto our TV screens in 1961 when I was a susceptible 4-year-old and Richard Chamberlain, who played the part, instantly became my hero. That year was a great turning point in my life. My father Gilbert, who was a pharmacist, took up a new post in the then Dowty Rubber Company and was asked to go to Cheltenham to study rubber technology for a year.

With my parents abroad, I spent this happy time with my paternal grandfather, a musician and artist, and he instilled in me a love for both these fields which has flourished in me till today. Granddad Bertie was immensely patient, disciplined, and obsessed with the minutiae of life. We spent many long hours perfecting those scales and arpeggios on the piano, as well as copying paintings his cousin had created, down to every detail. Today I tell my patients that it is a joy for me to stitch evenly and we owe it to my...
MEDICAL STUDIES—CARDIAC SURGERY BECKONS

Before long I was faced with a career choice, such as it was in Malta in the early seventies. If one opted out of Holy Orders then there was medicine, law, or architecture. That was it. As I had just completed my art and philosophy A levels, I took up a crash course in the sciences and enrolled in the medical course of the then Royal University of Malta in 1974. Sadly, Malta was going through a mini “cultural revolution” and in 1977 I left the island with 50 of my student colleagues to complete my studies abroad. After two years at Westminster Medical School I sat my conjoint exam and started the long and tortuous course all young doctors went through in those days, working hard to secure a reference for the next 6-month appointment. As fate would have it I was at the Hammersmith in 1980 when I inadvertently walked into the cardiac theater and observed professor Hugh Henry Bentall perform an elective cardiac arrest prior to a mitral valve replacement. As I watched the ECG turn to a straight line I felt a great urge to dash into that chest and start cardiac massage. Fortuitously, the large crowd of assistants physically obstructed me. When the surgeon removed the cross clamp and the heart resumed its rhythm I was so mesmerized that I decided there and then that cardiac surgery was for me.

I spent the next ten years in London working all hours with the fathers of coronary surgery. I can only describe this time as one of hardship, but also of immense clinical exposure. Surgical firms were akin to army units with strict hierarchical organization. One
assisted, obeyed, and learnt, until, without warning, one would be thrown in at the deep end. I recall very clearly being left to close a Dubost atrial incision, and this brought back dreadful memories of my first unsupervised episiotomy repair. Or the time my boss went on vacation and left me to perform my first solo bypass with junior help.

ARCHITECTURAL INCLINATIONS, RAYNE INSTITUTE, AND TRANSPLANTS

It was during these long evenings in hospital on call rooms that I resumed my interest in buildings, and researched the works of the great Italian architects, particularly Brunelleschi, Bramante, and Palladio. Then, in 1987 after a short spell with Norman Shumway in Palo Alto, California, and with Jack Copeland in Tucson, Arizona, I helped set up the transplant program with my teacher and mentor Stephen Edmondson at St Bartholomew’s hospital.

Having time on my hands I relished the opportunity to combine this work with full time research at the Rayne Institute under the direction of Professor Hearse.

This was a time of immense change where I was exposed to an ethic of free thought, innovation, and open discussion. My first year with rabbits was taxing and bore little fruit. Together with Alison Cave we described the mechanism of bypass-induced pulmonary hypertension, and also performed the first orthotopic heart transplants in this species. Year two was vastly more productive when I was able to study early reperfusion in my newly described blood-perfused rat heart model.
Long experiments provided fertile ground for sketching experimental preparations and much reading into my favorite subject of Italian Mannerist architecture.

I guess I was considered somewhat of an outsider as a surgeon in this mecca of scientists, but this experience was one I look back on with great pride and affection. All researchers delivered a Saturday morning lecture, normally related to ongoing laboratory work, but mine, on the history of roof construction, was very well received. This exciting stint was cut short by a senior registrar appointment in Sheffield, where I continued my training in cardiothoracic surgery and transplantation. In 1994, I was lucky to spend a year as senior resident at the University of Washington. From my chief, Professor Ed Verrier, I learnt a myriad surgical techniques, but what I truly admired in this great surgeon was his ability to lead.

Subsequently it was nigh impossible for me to settle back in the north of England and I jumped at the chance of setting up the first cardiothoracic unit in my birthplace after an absence of 17 years. Practicing here in Malta must be a unique experience in that the work encompasses pediatric thoracic, adult cardiac, thoracic, and esophageal procedures, as well as the occasional transplant. My initial worry was that I would be underworked on a sunny island with a healthy Mediterranean diet, but add the cigarettes, stress, junk food, one of the highest incidences of diabetes, overpopulation, and three cars to every four people, and it soon becomes obvious why my phone rings incessantly. Patients have open access to me and sometimes I feel my role can be aptly described as a parish priest with a medical background.

Of course it is easy to become isolated here, but regular contact with UK and Italian colleagues makes one feel an integral part of the small community of cardiothoracic surgeons that we are. The first years were an exercise in development: purchasing equipment, training staff, and convincing them we could do it. Being the only consultant...
on the island was extremely taxing, but conditions improved when, 7 years into my post, two of my trainees shared the workload as independent surgeons. Vacations became easier and with them, a resurgence of sketching that had sadly all but disappeared over the years. Frequent trips around the Mediterranean are now carefully planned architectural itineraries and

BIOGRAPHICAL SKETCH

Cardiothoracic Surgeon Alexander Manché, MPhil. FRCS(CTh), FETCS, MOM (Westminster Medical School; St Thomas’ Hospital; University of Washington, Senior Lecturer University of Malta). Senior Surgeon Cardiac Services, Mater Dei Hospital, Malta. Developed the blood-perfused rat heart model and went on to describe the dynamics of early reperfusion in this preparation. Contributed to an understanding of lung injury during cardiopulmonary bypass. Went on to set up cardiothoracic surgery in Malta. Has mentored many young doctors and hundreds of foreign students who spend their elective days in Malta. A strong believer in apprenticeship and mentoring in cardiac surgery. Author of over 50 papers and a regular contributor to seminars of preventive medicine. Deputy Chairman of the National Commission for Higher Education. Member of jazz band and piano accompanist to operatic singers. Avid traveler, architecture, and art addict.

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I never fail to derive immense pleasure from the beauty and harmony of the various monuments. My considerable collection of architectural photographs should provide ample material, but I am sure to be additionally inspired to paint these buildings with the sun beating down my back. Coupled with this, my ambition to become a full time architectural guide, doing Rome, Florence, and Venice, with piano playing in my spare time.....
The Challenge of Optimal Heart Failure Management: Present and Future

Summaries of Ten Seminal Papers

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1. Effects of enalapril on mortality in severe congestive heart failure. Results of the CONSENSUS…

2. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions

3. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction…

4. Effect of metoprolol CR/XL in chronic heart failure: MERIT-HF
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    K. Swedberg et al; SHIFT Investigators. Lancet. 2010

Selection of seminal papers by Karl Swedberg, MD, PhD
Department of Emergency and Cardiovascular Medicine
Sahlgrenska Academy - University of Gothenburg - SWEDEN
Chronic heart failure (CHF) has developed into epidemic proportions during the second half of the 20th century. Life expectancy has increased by 2 to 3 decades over the course of the last century, and with this has come the HF epidemic, not least due to the aging population, and also improved survival from acute myocardial infarction. However, up to the second half of the 1980s, life expectancy from CHF was grim, with 50% mortality within 1 year of diagnosis following an admission with acute decompensation of CHF. Against this malignant background, numerous efforts had been made to improve prognosis with diuretics and nitrate-based vasodilators without significant impact.

CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study) was the first study that changed the landscape of pharmacological therapy for CHF, and ushered in the paradigm of neurohormonal blockade as a therapeutic strategy, which influenced the hard endpoints of mortality and hospitalization. Conducted across 35 Scandinavian hospitals, 253 patients with acute decompenated HF (NYHA Class IV symptoms) were randomized in a double-blinded manner to receive enalapril, starting at 5 mg twice daily (2.5 mg in high-risk patients), with uptitration to a target of 20 mg bid, or placebo. Patients were required at baseline to have dilated hearts and be stabilized upon medical therapy with diuretics, digoxin, and other vasodilators, but were excluded if they had experienced a recent myocardial infarction.

Remarkably, the trial was halted when mean follow-up was still less than 1 year (188 days) by the ethical review panel due to the significant reduction in the enalapril arm. Enalapril treatment reduced the primary end point of all-cause mortality in absolute terms by 18% at 6 months and 16% at 12 months, translating as 40% and 31% relative risk reduction at these time points, respectively. The magnitude of this therapeutic benefit had only been seen in the contemporary thrombolysis trials of the 1980s, and this trial ensured that angiotensin-converting enzyme (ACE) inhibitors have been written into every guideline for advanced congestive cardiac failure. Interestingly, the difference in mortality at 12 months was due to an absolute difference of 20 patients between the study arms. But the denominator was small (126 and 127 patients) by the scale of later trials, and the survival curves clearly show an early divergence, which continues through the follow-up period.

In addition to reducing mortality, enalapril treatment also significantly improved symptoms, with 42% patients receiving enalapril improving by at least one NYHA class score, versus 22% in the placebo arm. These figures demonstrate not only the benefit of ACE inhibitors upon symptoms in this debilitating condition, but also the importance of the placebo effect, particularly with close monitoring in research trial participants, reinforcing the critical importance of blinding and randomization in clinical trials.

An interesting observation was that the mortality benefit was almost entirely due to death from progressive pump failure (50% relative risk reduction [RRR]), whereas no benefit upon sudden cardiac death (SCD) was observed. Initially it was concluded that ACE inhibitors do not reduce SCD. However, this result probably reflects this patient population with New York Heart Association (NYHA) class IV symptoms, where SCD does occur, but at a low rate (10%) relative to death from pump failure, and hence the trial was underpowered to demonstrate benefit on SCD in the time frames reported.

Subsequent 10-year follow-up was reported by the investigators, with the benefit of enalapril lasting for at least 4 years, and placebo arm survivors received the benefits of ACE inhibition as they were commenced upon enalapril after unblinding. However, attrition in this patient population with advanced heart failure was relentless, with only 5 patients alive at 10 years. More work was required!
Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions

SOLVD Investigators


The SOLVD (Study of Left Ventricular Dysfunction) investigators studied the influence of angiotensin-converting enzyme (ACE) inhibitors in heart failure (HF) patients with milder symptoms than those included in CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study). The SOLVD investigators screened 39,924 patients with HF and a reduced left ventricular ejection fraction (LVEF) before enrolling 2569 patients in the treatment trial for patients with symptomatic HF and reduced ejection fraction (=87% in New York Heart Association [NYHA] II or III), and a further 4228 patients with asymptomatic left ventricular dysfunction (LVEF <35%) into the SOLVD-Prevention study.

It is interesting to reflect upon the SOLVD-Prevention study from a 2011 viewpoint. In the 1980s and 1990s, having HF symptoms was a critical element for diagnosis. Hence the strategy to “prevent” HF was in essence prevention of the complications of chronic HF, expressed as death, hospitalization, or symptom development. While still contentious, perhaps contemporary HF specialists may consider this strategy “stabilization” rather than “prevention,” unless the heart recovers normal function. The large numbers in SOLVD-Prevention also reinforce the disconnect between symptoms and LVEF in patients with chronic HF, highlighting the limitations of using either, or any other clinical parameter, in isolation as a single stratifying value to categorize HF patients.

SOLVD-Prevention randomized this patient group to enalapril 2.5 mg twice daily, up titrated to 10 mg twice daily, or placebo. An interesting observation in light of the evolution of trial design was that all patients in both study arms received a test dose of the active study drug for 1 week. Few if any trials would employ such a strategy in 2011, particularly due to risk of unblinding, but tolerance to the drug, particularly regarding concerns of ACE inhibitor–induced hypotension, dictated that this was deemed an appropriate strategy. Although presented as a trial in asymptomatic patients, a third were reported to be in NYHA class II, with, by definition, limiting symptoms on moderate exertion.

SOLVD-Prevention reported strong trends toward a reduction in mortality (8%), and in particular cardiovascular mortality secondary to progressive pump failure (12%), in the enalapril treated arm, but these were not statistically significant, and therefore one has to conclude that, at least in the duration of follow-up (mean 37.4 months), there was no mortality benefit in this asymptomatic HF population with reduced LVEF. However, there was a significant reduction in HF hospitalization, and when presented a reduction in death or HF hospitalization the beneficial effect of enalapril was statistically different, with a 3.9% absolute risk reduction (20% relative risk reduction) at follow-up. It is interesting to contrast these reductions with those achieved in CONSENSUS of advanced symptomatic HF, and SOLVD treatment with moderately symptomatic heart failure, and reflect the graded benefit of ACE inhibitors on the heart failure populations with increasing symptom severity.

This trial also evaluated progression to development of HF symptoms, reported as HF development in light of contemporary definitions as discussed above. Enalapril significantly reduced the proportion of patients developing HF symptoms (29.8% vs 38.6%), and the time to symptom development (median time 8.3 months in the placebo arm was extended to 22.3 months for the same number of events in the enalapril arm).

Analogous to the CONSENSUS trial, the 12-year follow-up of the SOLVD trial demonstrated that the benefit of ACE inhibition lasts for several years, but that by 12 years the enalapril and placebo arms had met, with <5% survival. A final comment is that in an era which preceded the Internet and modern electronic record keeping, remarkably, only 7/4228 patients were lost to follow up, reflecting the efficient organization of this large multicenter international trial for which the investigators must be commended.
Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial


**SAVE** (Survival And Ventricular Enlargement) is a wonderful example of translational biology from the basic science laboratory to the clinic with a major impact on the hard end points of mortality and hospitalization in heart failure (HF). In the 1980s, Marc and Janice Pfeffer, in the research laboratory of Eugene Braunwald, first developed the rat model of surgical myocardial infarction (MI), and then characterized postinfarction left ventricular (LV) remodeling and the adverse pathophysiological sequelae. These adverse remodeling changes were mirrored in patient populations surviving after acute MI, which were becoming an ever-increasing patient population after the successful introduction of thrombolysis. Braunwald and the Pfeffers demonstrated that treating infarcted rats with the angiotensin-converting enzyme (ACE) inhibitor captopril attenuated the adverse post-MI LV remodeling, with improved survival, and Braunwald demonstrated similar observations upon LV dimensions in patients.

The SAVE trial also selected to treat patients early after acute MI, recognizing the importance of a “preventative” strategy. The SAVE trial recruited patients within 3 days post infarction with reduced left ventricular ejection fraction (LVEF <40%), and randomized eligible patients to captopril therapy, starting at 12.5 mg tds, and uptitrating to a target of 50 mg tds during follow-up. The investigators screened eligible patients with a 6.25-mg test dose, with only 19/2250 patients excluded for symptomatic hypotension or unstable angina. This was the basis of the “captopril trial” strategy for commencing angiotensin-converting enzyme (ACE) inhibitors, which has since disappeared from routine clinical practice, predominantly due to greater clinical experience, and perhaps also the use of less potent ACE inhibitors initiated at relatively lower starting doses.

Follow-up was exemplary in this pre-Internet era, with only 6 out of 2231 enrolled patients, spread across 112 hospitals in the USA and Canada, who were lost to follow-up. Captopril treatment resulted in a 5% absolute risk reduction (ARR) in mortality at mean of 42 months follow-up, translating into a 19% relative risk reduction (RRR). The benefit was attributable to reduction in cardiovascular death from progressive HF, and in accordance with CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study) and SOLVD (Studies Of Left Ventricular Dysfunction), there was no reduction in sudden cardiac death. Progression of the HF syndrome, with requirement for open-label ACE inhibitors, identified a high-risk subgroup in this trial population. Early treatment with captopril significantly reduced the proportion of patients progressing into this high-risk group (5% ARR, 37% RRR). This morbidity benefit also translated into a 3% ARR or 22% RRR for hospitalization with congestive HF. Progression of the HF syndrome, with requirement for open-label ACE inhibitors, identified a high-risk subgroup in this trial population. Early treatment with captopril significantly reduced the proportion of patients progressing into this high-risk group (5% ARR, 37% RRR). This morbidity benefit also translated into a 3% ARR or 22% RRR for hospitalization with congestive HF. These benefits were consistent across multiple subgroups (age, previous MI, degree of left ventricular dysfunction, MI territory, β-blocker, and aspirin use). As frequent in trials of HF and MI, the minority of women enrolled (18%) lead to nonsignificant differences due to statistical underpowering.

The remodeling hypothesis was evaluated with follow-up radionuclide scans in 95% patients. A nonsignificant (P=0.168) reduction in progressive LV remodeling, when defined as >9% reduction in LVEF, was reported. However this may underestimate the benefit as patients with the most severely depressed LVEF at baseline (eg, <25%) are unlikely to survive a further reduction of 9% points.

A further interesting observation, given that the pathophysiological hypothesis was to target post-MI HF, was a significant reduction in new acute MI events (25% RRR) in the captopril-treated group. The potential mechanisms are multiple, but this observation initiated the evaluation of ACE inhibitors for treatment of patients with atherosclerosis but without HF, resulting in the subsequent HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) trials.

The SAVE trial established early ACE inhibition in the treatment of post MI HF, and together with the CONSENSUS and SOLVD trials established ACE inhibitors in the treatment of HF as a class 1 indication.
Metoprolol is a lipophilic β₁-selective antagonist with no intrinsic sympathomimetic activity, though less selective than bisoprolol. The tartrate preparation was developed first, but a single dose was insufficient to provide stable 24-hour β-blockade, and therefore a twice-daily dosing regimen was recommended. Metoprolol succinate was developed as a slow release, longer-acting, once-daily preparation. The metoprolol succinate dose required to produce equivalent blood metoprolol concentrations is 33% higher than that of metoprolol tartrate. This is important as different heart failure (HF) trials have used different preparations, and comparisons of the data have to be made carefully.

The MERIT-HF study (MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure) compared metoprolol succinate controlled-release/extended release (CR/XL) once daily and placebo in a double-blinded study of 3991 patients. The entry criteria included HF with New York Heart Association (NYHA) class II-IV symptoms, and left ventricular ejection fraction (LVEF) <40%. Patients were randomly assigned metoprolol CR/XL 12.5 mg (NYHA III-IV) or 25.0 mg once daily (NYHA II) or placebo. The target dose was 200 mg once daily and doses were uptitrated over 8 weeks.

The MERIT-HF trial was stopped early, with a mean follow-up period of 1 year, due to a significant mortality reduction in the metoprolol succinate–treated group versus placebo (7.2% vs 11.0% ARR; 3.8% RRR 34%). There was a significant reduction in sudden cardiac death (RRR, 0.59) and death due to worsening heart failure (0.51). MERIT-HF, together with CIBIS II (Cardiac Insufficiency Bisoprolol Study II), were the first trials to demonstrate reduction in sudden “arrhythmic” death in HF patients, as the ACE inhibitor and amiodarone trials had been neutral for this end point.

Metoprolol reduced the number of hospitalizations due to worsening heart failure (317 vs 451, P<0.001) and number of days in hospital due to worsening heart failure (3401 vs 5303 days, P<0.001).

Somewhat at odds with the CIBIS II data, there did not seem to be a dose-related effect of the benefits with metoprolol succinate. However, those patients who could only tolerate a low dose had similar reduction in heart rate to the high-dose group. This may reflect the heterogeneity of β-adrenergic receptor sensitivity in HF patients. The absolute degree of heart rate lowering from baseline was not correlated with mortality benefit, an interesting finding in view of results from the recent SHIFT (Systolic Heart Failure Treatment with the I Inhibitor Ivabradine Trial). This may reflect the multiple mechanisms of benefit imparted by β-blockers in HF, with differing thresholds for beneficial effects on the ventricular cardiomycocytes versus the conducting system, and hence heart rate lowering is a useful, but not absolute, surrogate of β-blocker benefits to the failing heart.

A subgroup of 41 patients was followed with serial cardiac magnetic resonance imaging assessments during the study. The treatment group demonstrated significant improvements with reduction in both left ventricular (LV) end-diastolic and end-systolic volumes, and a mean improvement in LVEF of 8% in the metoprolol CR/XL group (29% to 37%; P=0.005). There were no significant changes in the placebo group. This demonstrated that β-blockers can initiate reverse remodeling in chronic HF patients.

Another similarity with the CIBIS II results was the benefit of metoprolol in patients with the most severe cardiac impairment and symptoms. In a subgroup of NYHA class III/IV patients (mean LVEF 19%), there was a mortality reduction of 39% (P=0.008) and hospitalizations with worsening cardiac failure reduced by 45%. In addition, benefit was seen in the elderly (mortality reduction 37% in patients over 65 years), and patients with diabetes mellitus.

MERIT-HF, CIBIS II, and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) established β-blockers as central therapeutic strategy for chronic HF (class I indication in all HF guidelines), finally reversing the deeply ingrained prejudice of avoiding β-blockers in the HF population.
In 1975, Waagstein et al first proposed the use of β-blockers in heart failure (HF). However, the cardiological community reacted with skepticism, not aided by a series of subsequent studies that produced contradictory or inconclusive results. During the 1980s, the excessive sympathetic activation and reduction of β-adrenergic receptor (βAR) density in cardiac failure patients was identified, leading researchers to hypothesize that antagonism of this system might be beneficial. The MERIT-HF (METoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure) and CIBIS (Cardiac Insufficiency Bisoprolol Study) trials were the first large trials to confirm irrefutably the beneficial effects of β-blockers in patients with chronic HF.

Bisoprolol is the most selective clinically β1AR antagonist. The initial CIBIS trial (641 patients) demonstrated a non-significant reduction in both mortality (20%) and hospital admissions (30%) in patients receiving bisoprolol. The CIBIS II trial was designed to be powered to answer the question of benefit, and was a double-blind, randomized trial of 2647 patients with stable, but severe chronic cardiac failure. The patients all had left ventricular ejection fraction (LVEF) <35%, New York Heart Association (NYHA) class III-IV symptoms, and were treated with angiotensin-converting enzyme (ACE) inhibitors and diuretics. The mean LVEF was 27%, 50% of patients had documented coronary artery disease, and 12% had dilated cardiomyopathy. The active arm received bisoprolol once daily, with a starting dose of 1.25 mg, titrated by doubling every 1 to 4 weeks up to 10 mg daily or maximum tolerated dose. The average dose taken was 8.6 mg daily, with the target dose of 10 mg daily reached in 43% cases.

The CIBIS II trial was stopped at 2 years due to the significant reduction in mortality in the bisoprolol-treated group from 17.3% to 11.8% (absolute risk reduction [ARR] 5.5%, relative risk reduction [RRR] 36%). There was a significant reduction in sudden cardiac deaths, but deaths due to "pump failure" and myocardial infarction where not reduced significantly. Intriguingly, one third of the difference in deaths between the groups was unexplained (26 of 72).

There were significantly fewer hospitalization events in the bisoprolol-treated group (ARR 6%), including a reduction in admissions for worsening heart failure, hypotension, and ventricular tachyarrhythmias. Interestingly, bisoprolol reduced the mortality of patients in sinus rhythm (ARR 6%), but not those in atrial fibrillation. There was also a trend toward a greater benefit for women with cardiac failure receiving bisoprolol, although as they were the minority (20% cases), this did not reach statistical significance.

Bisoprolol lowered both baseline heart rate and heart rate variability, and both were significantly related to survival and hospitalization for worsening heart failure, the lowest basal heart rate and the greatest heart rate control being associated with best survival and reduction of hospital admissions. Bisoprolol provided benefit across all the high-risk groups such as elderly, diabetics, patients with chronic renal failure and NYHA class IV patients, reversing the previous held belief that β-blockers were less beneficial or even harmful in these high-risk subgroups. The cost-benefit analysis showed that bisoprolol reduced the cost of care for cardiac failure patients by 5% to 10% independent of the country and health service assessed.

The final post-hoc analysis demonstrated a dose-related effect of benefit. Those on the highest dose (10 mg od) had a 70% reduction in mortality, and those on moderate dose (5 mg or 7.5 mg od) a 51% mortality reduction, relative to those on the lowest doses (1.25 mg and 2.5 mg od), though all were superior to placebo. Patients who withdrew from the bisoprolol group due to drug intolerance had a higher mortality. CIBIS II emphasized the importance of titration of β-blockers in HF patients in real-world cardiology practice, and persisting with lower doses in the patients intolerant of highest target doses.
The effect of spironolactone on morbidity and mortality in patients with severe heart failure

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ALES (Randomized ALdactone Evaluation Study) was a landmark study published in 1999, which established aldosterone antagonism as a central tenet in the management of chronic heart failure (HF). RALES was conducted in an era after publication of the angiotensin-converting enzyme (ACE) inhibitor trials, and contemporary teaching was that ACE inhibitors also reduced aldosterone production as part of their therapeutic effect. The RALES investigators had previously recognized that in reality ACE inhibitors only transiently suppress aldosterone production, and the breakthrough of aldosterone production presented a new therapeutic target in the ACE-inhibitor–treated patient.

Aldosterone promotes renal sodium and water retention, with kaliuresis, but also has direct effects upon the myocardium. Specifically, aldosterone increases extracellular fibrosis, a pathophysiological process enhanced in the failing heart. In the 1990s, spironolactone was an established treatment of salt and water retention in liver failure, but at high “diuretic” doses (200+ mg daily). Hyperkalemia was a recognized complication of both spironolactone, at these high doses, and ACE inhibitors, and there was understandable concern of combining the two treatments. The RALES investigators performed phase 1 and 2 studies, reporting that low spironolactone doses (12.5-50 mg) were tolerated in patients taking ACE inhibitors without hyperkalemia, and there was understandable concern of combining the two treatments. The RALES investigators performed phase 1 and 2 studies, reporting that low spironolactone doses (12.5-50 mg) were tolerated in patients taking ACE inhibitors without hyperkalemia, and there was understandable concern of combining the two treatments. The RALES investigators performed phase 1 and 2 studies, reporting that low spironolactone doses (12.5-50 mg) were tolerated in patients taking ACE inhibitors without hyperkalemia, and there was understandable concern of combining the two treatments.

The RALES investigators enrolled 1663 patients in 195 centers across 15 countries, demonstrating the amazing logistical efforts to perform a phase 3 clinical trial. This is all the more remarkable without a large pharmaceutical company supporting the trial financially, given the lack of intellectual property for spironolactone. The patients enrolled had advanced symptomatic HF with mean left ventricular ejection fraction of 25% to 26% and almost all (>99%) patients were in New York Heart Association (NYHA) class III or IV. A total of 95% enrolled patients were treated with ACE inhibitors at baseline.

Spironolactone (25 mg once daily) reduced all-cause mortality by 11% at 24 months, which was a 30% relative risk reduction on top of ACE inhibition, confirming the investigators’ hypothesis that breakthrough aldosterone production in the ACE-inhibitor–treated patient was a detrimental pathophysiological pathway. The mortality benefit was primarily due to cardiovascular death reduction, and in contrast to the ACE inhibitor trials, both heart failure progression and sudden cardiac death were reduced significantly.

This reduction in sudden “arrhythmic” death is intriguing, and raises the question of what are the antiarrhythmic mechanism(s) of aldosterone blockade. Aldosterone promotes myocardial collagen deposition and fibrosis, which electrophysiologically can contribute to conduction slowing or block and unmask the increased repolarization heterogeneity in the failing heart, both of which predispose to wavefront reentry. Aldosterone also directly increases calcium leak from the sarcoplasmic reticulum, which may be a subcellular origin of triggered arrhythmias. Finally, although not formally a diuretic dose, mean serum potassium levels were higher in the spironolactone-treated arm (0.30 mmol/L). Hypokalemia is proarrhythmic, stimulating \( I_{Kr} \) channel internalization, action potential (and QT) prolongation, and is common in HF patients treated with loop diuretics. Preventing hypokalemia in this patient population may have a significant impact on sudden arrhythmic death.

Spironolactone caused gynecomastia or breast discomfort in 10% of men, leading to the development of eplerenone as a more selective aldosterone antagonist for HF patients. However, spironolactone is a cheap drug, and the RALES trial has had an enormous effect on the global HF population as patients can receive this effective treatment without the prohibitive costs of a novel “in patent” drug.
Carvedilol has a greater array of pharmacological effects than metoprolol and bisoprolol. It is an antagonist of $\beta_1$, $\beta_2$, and $\alpha_1$-adrenergic receptors, and also has antioxidant effects, beneficial effects on insulin sensitivity, anti-apoptotic activity, reduces hypokalemia, and alters the HERG component of the $I_{Kr}$ channel.

Carvedilol was initially assessed with caution in heart failure (HF) patients with minimal symptoms in the late 1980s and early 1990s in the small US Carvedilol Heart Failure Studies. On the basis of these studies carvedilol received a Food and Drug Administration license for HF treatment in the USA, but the European regulatory authorities required a larger randomized double-blinded placebo-controlled trial, and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) was designed to meet these requirements.

COPERNICUS assessed the effect of carvedilol in a more severe group of HF patients compared with the MERIT-HF (MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure) and CIBIS (Cardiac Insufficiency BIsoprolol Study) trials, which also addressed an important concern regarding the use of $\beta$-blockers in the most symptomatic HF patients with severely impaired ventricles. A total of 2289 clinically stable patients with New York Heart Association (NYHA) class III or IV symptoms, left ventricular ejection fraction (LVEF) <25%, and treatment with ACE inhibitors (or angiotensin receptor blockers [ARBs]) and diuretics, were randomized to carvedilol or placebo. The starting dose was 3.125 mg bid, doubled fortnightly to a target dose of 25 mg bid. Mean age was 63.4 years and 80% of patients were male. A total of 67% patients had ischemic heart disease as their cause of cardiac failure, and average LVEF was 19%, confirming COPERNICUS as a trial of more severe cardiac failure than CIBIS II or MERIT-HF.

The trial was stopped early after a prespecified boundary end point had been reached. The mean follow-up was 10.4 months. There were 190 deaths in the placebo group (18.5% cumulative risk) versus 130 deaths in the carvedilol group (11.4%) (absolute risk reduction [ARR] 7.1% relative risk reduction [RRR] 35% at 12 months). Mode of death was not reported in the COPERNICUS trial, but the subsequent COMET (Carvedilol Or Metoprolol European Trial) would support both antiarrhythmic effect and prevention of heart failure progression as benefits with carvedilol treatment.

Total hospitalizations were reduced by 24%, with the impact on admission with worsening HF significant, reducing from 23.7% to 17.1% with carvedilol. This corresponded to 40% reduction in the number of days admitted to hospital, which had a significant impact on quality of life in this high-risk patient group with a poor prognosis. These benefits were independent of sex, age, LVEF and ischemic versus non-ischemic etiology. It was subsequently reported that this reduced rate of hospital admissions led to an estimated overall reduction in the cost of patient care by 11.1% in the British National Health Service.

Carvedilol was well tolerated in this advanced HF population, with 65% of patients reaching target dose. Due to drug intolerance, 14.8% of patients withdrew from the carvedilol arm (18.5% in the placebo arm). A low systolic blood pressure at entry to the study was associated with a reduced likelihood to tolerate maximal carvedilol doses, but this high-risk patient group also received the greatest benefit from the carvedilol that they could tolerate.

A substudy demonstrated that carvedilol lowered N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, with an elevated NT-proBNP level being a sensitive marker for adverse prognosis in HF patients.

The absolute mortality benefits with carvedilol seen in COPERNICUS are greater than those reported in the $\beta$-blocker arms of CIBIS II and MERIT-HF. Whether this reflects the sicker population, or the superiority of carvedilol as the $\beta$-blocker of choice in HF, is a point for discussion. The subsequent COMET trial demonstrated superiority for carvedilol over metoprolol, but the argument of carvedilol versus bisoprolol continues in 2011.
The CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) program is in some respects the “mega-trial of megatrials.” CHARM is the largest trial program ever undertaken in heart failure (HF) patients, with three trials rolled into one, allowing an overall analysis in addition to the three parts. The CHARM investigators compared the angiotensin receptor blocker (ARB) candesartan with placebo in three HF patient populations with mild-to-moderate symptoms (>97% in New York Heart Association [NYHA] classes II and III).

The combined analysis in the CHARM-Overall program (7599 patients) showed that candesartan treatment reduced all-cause mortality by 1.6% (P = 0.055) at median 37 months, which became statistically significant after a prespecified covariate analysis (P = 0.03). Each substudy contained a different cohort of HF patients, and therefore I will evaluate each on its own merits.

CHARM-Alternative randomized 2028 HF patients with reduced left ventricular ejection fraction (LVEF) of <40%, intolerant of angiotensin-converting enzyme (ACE) inhibitors, to candesartan or placebo. At a median of 33.7 months, there was a 7% absolute risk reduction of cardiovascular (CV) death or hospitalization (33% vs 40% P = 0.0004). The reduction in CV hospitalization was significant (7.8% P < 0.0001), whereas the mortality reduction was not (3.2% P = 0.07). These findings replicated those reported in Val-HeFT (Valsartan Heart Failure Trial), whereas valsartan reduced hospitalization, but not mortality, in ACE-inhibitor-intolerant patients. These two trials have placed ARBs as class 1 indication for treatment of HF with reduced LVEF in ACE-inhibitor-intolerant patients.

CHARM-Added randomized 2548 patients with HF and reduced LVEF who were treated with optimal ACE-inhibitor doses to treatment with candesartan or placebo. Analogous to CHARM-Alternative, candesartan reduced the combined primary end point of death or hospitalization, although to a lesser degree (38% vs 42% P = 0.01). In contrast to CHARM-Alternative, there was a significant reduction in both CV hospitalization (3.8% absolute risk reduction [ARR], P = 0.014) and mortality (4.6% ARR, P = 0.02). This is an interesting finding for several reasons. It is curious that patients enrolled on ACE inhibitor treatment in CHARM-Added had similar outcomes to those without ACE inhibitors enrolled in CHARM-Alternative (primary end point in placebo arms 40 and 42%), despite superior baseline therapy. This may possibly be explained by the sicker population enrolled in CHARM-Added—they were symptomatic despite ACE inhibitors, with 73% of patients in NYHA class III vs 48% in CHARM-Alternative, and in CHARM-Added mean LVEF, systolic blood pressure, and spironolactone prescribing were lower (LVEF: 28.0% vs 30%, systolic blood pressure: 125 vs 130 mm Hg, spironolactone: 17% vs 23%). Whether these small differences are sufficient to account for the paradoxically equal event rate in these two CHARM studies is open to debate.

CHARM-Added also refuted a clinical concern raised by the Val-HeFT trial regarding triple therapy with ACE inhibitors, ARBs, and β-blockers. In Val-HeFT, patients receiving these three agents had higher mortality than those taking two alone, raising concerns that excessive neurohormonal blockade may be deleterious. In the CHARM-Added trial, the benefits were seen in patients taking ACE inhibitors, β-blockers, and candesartan (triple therapy). Serendipitously, only 55% of patients were taking β-blockers in CHARM-Added, providing sufficient statistical power to conclude that triple therapy was beneficial, and not harmful.

CHARM-Preserved was the first trial to investigate the benefit of ARBs in patients with heart failure and milder levels of LV systolic dysfunction (LVEF >40%). Almost one third of patients enrolled had LVEF >60%, a subgroup now defined as HF with preserved ejection fraction (HFP EF). Candesartan reduced CV hospitalizations (2.4% ARR, P = 0.04 after covariate adjustment), whereas mortality was unchanged (11.2% vs 11.3%). Subsequent trials have shown that HFP EF is a difficult clinical problem, with few studies demonstrating positive outcomes with pharmacological intervention. The reduction in hospitalization seen in CHARM-Preserved is hence an important finding.
Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure


SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) was a pivotal heart failure (HF) trial published in 2005 that has molded the care of HF patients in two critical ways. Firstly, SCD-HeFT identified that in patients with significantly reduced left ventricular systolic function and mild-to-moderate symptoms, primary prevention of cardiac death with an implantable cardioverter-defibrillator (ICD) significantly reduced mortality. Secondly, SCD-HeFT confirmed that chronic prophylactic treatment with amiodarone had no benefit in this population. These represent two major landmarks for HF management.

The trial investigators recruited 2251 patients with New York Heart Association (NYHA) class II or III symptoms and stable HF with reduced left ventricular ejection fraction (LVEF) (inclusion criterion LVEF <35%, median 25%) due to ischemic or nonischemic cardiomyopathy from multiple centers across the USA and Canada. Patients were randomized to amiodarone, ICD, or placebo in a permuted-block randomization strategy to ensure equal distribution of ischemic and nonischemic, and NYHA class II and III, patients in each study arm. Patients were followed up for a median of 45.5 months, with the vital status of all 2251 patients reported at follow-up.

Single-lead ICD therapy resulted in an absolute risk reduction (ARR) in mortality of 7% over 5 years compared with placebo (relative risk reduction [RRR], 23%, *P*=0.007). This benefit appeared from 18 months post enrollment, suggesting that the benefit is dependent upon the long-term attrition of SCD in this patient population, and the development of electrical instability is a dynamic process, rather than a static, fixed risk.

A number of findings have made this trial even more interesting to practicing clinicians caring for HF patients. A total of 31% of patients in the ICD group received shocks, with 21% appropriate, and presumably life-saving in the context of the settings used, and 10% inappropriate. The annual rate of appropriate shocks was 5%, which may reflect the natural incidence of malignant ventricular tachyrhythmias in this patient population. However, it also confirmed that the benefits of ICDs come at a price, given the psychological and physical trauma of inappropriate shocks.

This trial was published after the MADIT I and II trials (Multicenter Automatic Defibrillator Implantation Trials), confirming the benefit of ICDs in the postinfarction HF population. SCD-HeFT helped to answer uncertainties regarding ICD use in dilated cardiomyopathy patients raised by the DEFINITE (DEFibrillators in Non-Ischemic cardiomyopathy Treatment Evaluation) trial, which reported a nonsignificant trend toward benefit from ICD in the dilated cardiomyopathy population (*P*=0.08). SCD-HeFT reported benefit in both ischemic and nonischemic populations, confirming the view that the DEFINITE trial was underpowered, and also had a slightly lower risk population (1-year mortality in dilated cardiomyopathy patients 14% in SCD-HeFT vs 10% in DEFINITE).

Perhaps the most provocative finding was the interaction with NYHA symptom class. In the milder symptom group (NYHA class II) there was an 11% absolute risk reduction in mortality (46% RRR), which was highly significant, whereas in the NYHA class III patients there was no reduction in mortality with ICD therapy. This supports the observations from MUSTT (Multicenter UnSustained Tachycardia Trial) and epidemiological studies that SCD represents a greater proportion of deaths in congestive HF patients with impaired systolic function, but low symptom burden, who are potentially more active, compared with a higher rate of “pump failure” death in patients with higher symptom burden (NYHA class III and IV) for which ICD therapy may not be expected to reduce mortality.

SCD-HeFT has made primary prevention ICD therapy a class 1 indication in HF patients, but with cardiac resynchronization therapy developing in parallel, the use of single-lead ICD devices in this patient population has become exceedingly rare. Given that SCD-HeFT is the cornerstone trial for ICD therapy in HF, perhaps revisiting SCD-HeFT will also ensure more complex dual- and triple-lead devices are implanted for the correct indications.
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

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Systolic Heart Failure treatment with the If inhibitor Ivabradine Trial (SHIFT), published last year, was the first trial for 10 years that showed a benefit from adding a new drug to contemporary pharmacological heart failure (HF) therapy. It also confirmed elevated heart rate (HR) in HF patients in sinus rhythm as a cardiovascular risk factor.

The SHIFT investigators recruited 6558 stable HF patients across 37 countries with New York Heart Association (NYHA) class II-IV symptoms, reduced left ventricular ejection fraction (LVEF ≤35%), and a sinus HR ≥70 beats per minute (bpm). HF patients were randomized to the selective If current inhibitor ivabradine or placebo. The requirement for a higher resting heart rate was critical, given the previous results from the BEAUTIFUL trial (morBidity-mortality EvaLUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) where individuals with HR <70 bpm were enrolled, potentially neutralizing benefit with respect to ivabradine treatment.

Over a median follow up of 22.9 months, ivabradine treatment resulted in a significant 5% reduction in the primary end point of cardiovascular death or hospitalization for worsening HF (24% vs 29%, P<0.0001), with the end point driven by a significant reduction in HF hospitalization (relative risk reduction [RRR] 26%). There was no significant reduction in all-cause death or cardiovascular death, but deaths from HF were significantly reduced (RRR, 26%). The benefits were consistent across all prespecified subgroups and were greatest in patients with a resting HR >77 bpm, and ivabradine was well tolerated, with few adverse events.

Ivabradine treatment significantly lowered sinus HR in the treatment arm, with a net reduction of 10.9 bpm detectable at 28 days, reducing to 8.1 bpm by the end of follow up.

This trial has raised debate regarding the role for ivabradine therapy in modern cardiology practice, and in particular for HF patients receiving guideline-recommended therapies, including β-blockade. Investigators were asked to prescribe according to their routine practice except for β-blockers, for which they were repetitively asked to use the highest dose tolerated. Indeed, only 23% of patients recruited were at target dose for a licensed β-blocker for HF, and 49% at >50% target dose. This, therefore, reflects real-world β-blocker usage. In the subgroup of patients receiving at least 50% of the target dose of β-blocker, effects on cardiovascular outcomes were not significant apart from hospital admission for heart failure, which was significantly reduced by 19%. This finding might have been related to the lower event rate in this subgroup (13% per year for the primary end point) than in the overall population, reducing the power of this secondary analysis.

The low prevalence of cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) devices (1% and 4%, respectively), was attributed to study design (sinus rhythm had to be present ≥40% of the time and the pacing threshold had to be <60 bpm), which led to the exclusion of some patients with pacemakers. Given the significant reduction in morbidity and mortality with device therapy, further studies are required to determine if HF patients with CRT and/or ICDs will obtain additional benefit from ivabradine therapy.

No differences in sudden cardiac death were observed, which could be attributable to the effect of the background β-blocker treatment (used in 89% of patients), which has intrinsic electrophysiological effects and is known to affect sudden cardiac death.

This trial reflects the evolution of HF trial design with the primary end point encompassing CV mortality and hospitalization, whereas in the angiotensin-converting enzyme inhibitor and β-blocker trials, all-cause mortality was the single primary end point.

In summary, the benefit of ivabradine in patients with HF and high resting sinus heart rates (>70 bpm) was established in SHIFT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial), and in my opinion ivabradine should be considered in HF patients in sinus rhythm with elevated heart rate who have an intolerance to high β-blocker doses.
The Challenge of Optimal Heart Failure Management: Present and Future

Bibliography of One Hundred Key Papers

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