

# Advances in systolic heart failure

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## Abstract

Heart failure due to systolic dysfunction has enormous global impact. Medical management based on an understanding of the pathophysiology of the disease as well as its neurohormonal mechanisms has greatly advanced over the past 25 years. Below is a review of recent and emerging data on epidemiology and diagnosis of heart failure due to systolic dysfunction and the current and future management techniques to ameliorate this disease. At the end, we will highlight three significant trials in the field in 2009 that will impact heart failure care: STICH, MADIT-CRT, and HeartMate II.

## Introduction and context

Heart failure (HF) is a major public health problem. Incidence, prevalence, and risk have been found to be high in both Europe and the US [1,2]. The Rotterdam study [1] found that a man and a woman at age 55 have, respectively, a 33.0% and 28.5% chance of developing HF during their remaining lifetime, whereas the Framingham Heart Study reported lifetime risks at age 50 of 20.9% for men and 20.5% for women. The Rotterdam study further showed that the prevalence of HF increased with age; in 1998, 0.9% of subjects 55-64 years old had HF compared with 17.4% of those 85 years old or older. Approximately 5.7 million Americans have been diagnosed with the disease [3], and each year an additional 550,000 patients are diagnosed for the first time [4].

This increasing clinical burden is expected to be matched with an increasing financial burden. By means of a prevalence-based approach, the economic burden of HF in the UK was estimated to be £905.3 million in 2000, a 26% increase over 1995 estimates and equivalent to 1.91% of the total National Health Service expenditure [5]. It is estimated that, in 2009, over \$37.2 billion was spent on costs of HF in the US [3]. Medicare spends more dollars for the diagnosis and treatment of HF than for any other diagnosis, as HF is the most frequent Medicare diagnosis-related group [4]. Hospital

discharges for HF increased by 171% from 1996 to 2006 [1]. In 2005, the number of 'total mention' deaths from HF in the US was 292,000, which is higher than in 1995 (287,000) [3]. HF is declared on 1 in 8 death certificates [1]. Although considerable advances have been made in the management of HF over the past few decades, HF remains a major public health issue with high prevalence and poor outcomes.

An understanding of the pathophysiology and natural history of HF underpins the therapeutic approaches used to achieve the goals of treatment, which are to relieve symptoms, to avoid hospital admission, and to prolong life. On the basis of a large number of randomized controlled trials, drugs are the mainstay of treatment for all patients with HF and reduced left ventricular systolic function. Device therapy and transplant surgery have carved out a respectable place in the field over the past decade.

Diuretics are essential for relief of dyspnea and signs of sodium and water retention; they are needed in virtually all patients with symptomatic HF. These are best used flexibly and in the minimum dose needed to maintain euvolemia and avoid electrolyte disorders (hypokalemia and hyponatremia), gout, and renal dysfunction. In advanced HF, high doses of loop diuretics and thiazide or thiazide-like diuretic (metolazone) might be needed

to maintain 'dry weight'. Despite the widespread use of diuretics, no evidence exists to date to show that these agents prolong survival, and their use could activate key neurohormonal systems such as the renin angiotensin aldosterone system (RAAS) [6,7].

RAAS is important for progression of the HF disease process; conversely, attenuation of this system has yielded considerable benefit in the management of systolic HF. Angiotensin-converting enzyme inhibitors (ACEIs), by reducing the production of angiotensin II and possibly by blocking the degradation of bradykinin, exert many biological effects that lead to improvement in symptoms, fewer admissions to the hospital, and prolonged survival in HF; as a consequence, they are recommended for all patients with systolic dysfunction. Reduced mortality was also noted with ACE inhibition in people with recent myocardial infarction and left-ventricular systolic dysfunction, but without HF symptoms [8,9]. The main causes of intolerance are cough, symptomatic hypotension, and renal dysfunction, which are exacerbated by overdiuresis and nonsteroidal anti-inflammatory drugs.

Angiotensin receptor blockers (ARBs) seem to be a reasonable alternative for patients unable to tolerate ACE inhibition secondary to cough [10]. However, the use of ACE inhibition in addition to ARBs remains uncertain. Several studies that looked at the combination of ACEIs and ARBs in HF patients are worth mentioning. The Valsartan Heart Failure Trial (Val-HeFT) included patients with a left ventricular ejection fraction (LVEF) of less than 40% and New York Heart Association (NYHA) class II-IV; 92% were on ACEIs and 35% were on beta blockers [11]. All patients were randomly assigned to valsartan versus placebo. Overall mortality was similar in the two groups. Rates of death from any cause during the entire trial were 19.7% in the valsartan group and 19.4% in the placebo group ( $P = 0.8$ ). Combined endpoint of death from any cause, hospitalization for HF, cardiac arrest with resuscitation, and intravenous therapy was statistically significant ( $P = 0.009$ ); however, it was driven mainly by a decline in hospitalization rate for HF (13.8% in the valsartan group and 18.2% in the placebo). Patients were further subdivided into subgroups based on their background therapy (ACEIs and beta blockers). Among those who were receiving both drugs at baseline, valsartan had an adverse effect on mortality ( $P = 0.009$ ) and was associated with a trend toward an increase in combined endpoints of mortality and morbidity ( $P = 0.1$ ) [11]. The Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity trial (CHARM-Added) was the only study that showed a reduction in cardiovascular

mortality (absolute risk reduction [ARR] of 3.6%) for combination therapy; it also showed reduced hospitalization for HF (ARR of 4%) [12]. However, the all-cause mortality was not different between the groups. Given the available data, it is safe to conclude that combination treatment in HF patients should be used with caution. Both Val-HeFT and CHARM-Alternative confirm that ARBs are appropriate substitutes for ACEIs when cough is the reason for intolerance [10,11].

By contrast, use of the aldosterone receptor antagonist spironolactone in patients with advanced disease (class III or IV systolic HF) yielded clear-cut survival benefits additional to background ACE inhibition, although only a few people were receiving beta blockers [13]. Furthermore, the selective aldosterone receptor antagonist eplerenone was of benefit in individuals with systolic HF early after myocardial infarction [14]. Careful attention to the development of hyperkalemia during initiation is an essential safety measure when using aldosterone antagonists. Furthermore, potassium supplements should be discontinued until the potassium levels reach equilibrium after several months of usage.

Beta blockers are a cornerstone of systolic HF management. Chronic activation of the sympathetic nervous system – the cardiac effects of which are attenuated by beta blockers – has a key role in HF disease progression, including fibrosis, necrosis, apoptosis, and arrhythmogenesis. The beneficial effects of beta blockers have largely been studied as additional to background ACE inhibition, and therefore both are judged to be mandatory treatment. These effects have been shown with bisoprolol, carvedilol, and extended-release metoprolol in patients with stable systolic HF across a broad range of disease severities.

Beta blockers in HF patients should be initiated at low doses and gradually up-titrated to the target dosages proven effective in the major mortality trials (carvedilol 25 mg twice daily, bisoprolol 10 mg daily, or metoprolol succinate 200 mg daily) [15-17]. Researchers in the Cardiac Insufficiency Bisoprolol Study III (CIBIS III) raised the hypothesis that the order of initiation of ACEIs and beta blockers might not be vital to outcomes provided that eventually the patient is receiving appropriate doses of both classes of drug in a timely manner [18].

The combination of hydralazine and isosorbide dinitrate was the first treatment shown to improve survival in HF, but a subsequent study showed that it was less effective than an ACEI in direct comparisons. A strategy of adding a vasodilator combination to conventional treatment, including an ACEI, a beta blocker, and

spironolactone, was shown to reduce mortality and admissions to hospital for HF in African-American patients, although this conclusion was based on a small number of events [19].

## Recent advances

### **Surgical Treatment for Ischemic Heart Failure (STICH) trial**

Although cardiac transplantation remains the ultimate surgical strategy for HF, the poor availability of suitable donor organs renders this option epidemiologically insignificant. Other surgical approaches to HF include revascularization for ischemic HF, mitral valve repair to address functional mitral regurgitation associated with pathological ventricular remodeling, and surgical reconstruction of the size and shape of the failing left ventricle (LV) to render it more effective to pump. With the exception of the recently published Surgical Treatment for Ischemic Heart Failure (STICH) trial [20], most of these surgical techniques have not been adequately tested. The STICH trial, funded by the National Heart, Lung, and Blood Institute, is a multicenter international randomized trial addressing two specific primary hypotheses: (a) coronary artery bypass grafting (CABG) with intensive medical therapy improves long-term survival compared with survival with medical therapy alone, and (b) in patients with anterior left ventricular dysfunction, surgical ventricular reconstruction to a more normal left ventricular size plus CABG improves survival free of subsequent hospitalization for cardiac cause when compared with CABG alone. Subjects meeting the broad inclusion criteria of coronary artery disease (CAD) amenable to CABG with an LVEF of 0.35 or less without a specific exclusion were segregated into three strata, depending on investigator-determined suitability for continued medical therapy alone and eligibility for surgical ventricular restoration (SVR). Eligibility for medical therapy alone was defined by the investigator but generally excluded patients with intraluminal left main coronary artery stenosis of 50% or more or severe disabling angina (Canadian Cardiovascular Society [CCS] class III) unresponsive to nonsurgical interventions. Eligibility for SVR is defined as dominant LV akinesia or dyskinesia amenable to SVR. Stratum A subjects are defined as suitable for medical therapy with or without CABG, and consenting patients are randomly assigned in a 1:1 ratio to medical therapy alone or medical therapy with CABG. Stratum B subjects, defined as eligible for all three treatment options, are randomly assigned in a 1:1:1 ratio to medical therapy alone, medical therapy with CABG, or medical therapy with CABG and SVR. Subjects eligible for CABG and SVR are

randomly assigned in a 1:1 ratio to stratum C to either CABG or CABG with SVR.

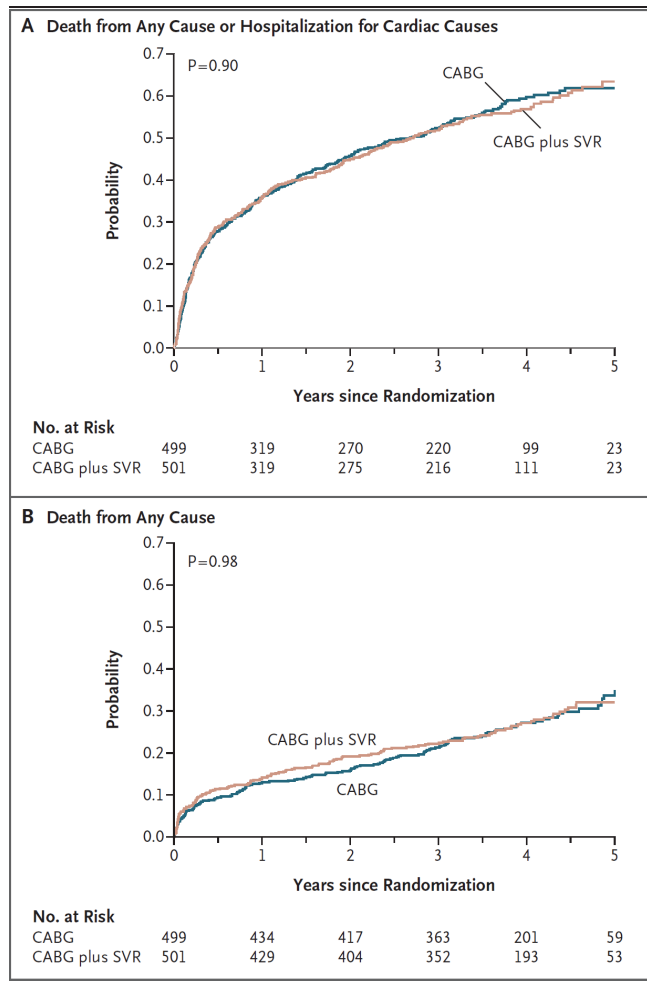
Enrollment is now complete in both STICH hypotheses. The primary outcome of the second hypothesis was recently reported. This study included 1000 patients (from 96 clinical centers) who were randomly assigned to undergo either CABG alone (499 patients) or CABG with SVR (501 patients). The patients were closely matched in demographic and clinical characteristics. The median age was 62 years, and 147 of the 1000 patients were women. The median left ventricular function was 28%, and the median left ventricular end systolic volume index (LVESVi) was 82 mL per square meter of body surface area. Multivessel CAD was present in 64% of patients in each group. Although standard HF treatment was recorded at baseline and was encouraged throughout the trial, no information about the rates of its use over time is provided. All patients were followed up for 48 months (minimum of 30 months). The two strategies were equally successful in improvement of patients' symptoms, with an average improvement in CCS class of 1.7 classes ( $P = 0.84$ ) and an average of 1 NYHA class ( $P = 0.7$ ). Equivalent improvement in the 6-minute walk test, obtained at baseline and 4-month follow-up, was demonstrated between the two groups (48 m among patients who were assigned to CABG and 52 m among patients assigned to CABG and SVR;  $P = 0.8$ ).

There was a greater reduction in LVESVi with combined procedure (16 mL per square meter of body surface area) when compared with CABG alone (5 mL per square meter of body surface area).

The primary outcome of death from any causes or hospitalization for cardiac causes was the same in CABG alone (59%) when compared with CABG with SVR (58%) (Figure 1). Death occurring within 30 days after the procedure did not differ significantly between the two study groups. Subgroup analysis showed no individual variables interacting significantly with the study group assignment.

The first STICH trial hypothesis is addressing an important question of revascularization of patients with CAD and LV systolic dysfunction. Although specific clinical problems in this population, such as severe angina, are used to decide on revascularization strategies, the vast majority of patients with ischemic cardiomyopathy (ICM) have limited or no angina and fall into a gray zone where clear evidence for adding CABG to optimal medical therapy is either absent or outdated.

**Figure 1. Kaplan-Meier estimates of outcomes [20]**



**(A)** The probability of the primary outcome (death from any cause or hospitalization for cardiac causes), which did not differ significantly between the two groups. The primary outcome occurred in 292 patients (59%) assigned to undergo coronary artery bypass grafting (CABG) alone and in 289 patients (58%) assigned to undergo CABG with surgical ventricular reconstruction (SVR) (hazard ratio 0.99, 95% confidence interval [CI] 0.84-1.17). **(B)** The probability of death from any cause, which occurred in 141 patients (28%) assigned to undergo CABG and in 138 patients (28%) assigned to undergo CABG with SVR (hazard ratio 1.00, 95% CI 0.79-1.26). Reproduced with permission from [20]. Copyright © 2009, Massachusetts Medical Society. All rights reserved.

**Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)**

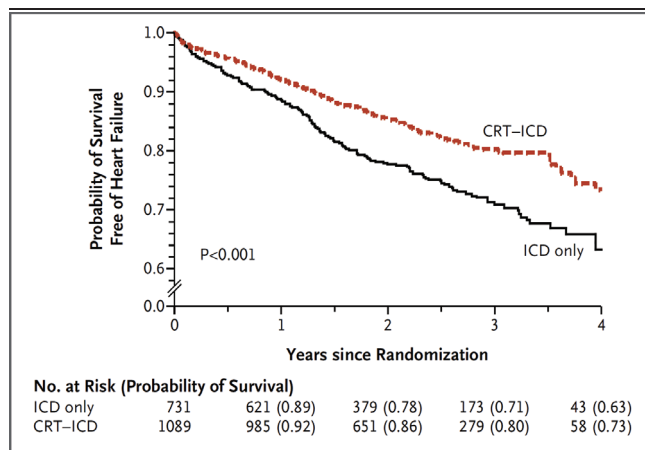
Recent guidelines recommend cardiac resynchronization therapy (CRT) in patients with an LVEF of less than 35%, NYHA class III-IV symptoms, and a QRS duration of greater than 0.12 seconds [4]. This represents a subgroup of HF patients with abnormal cardiac conduction and possible ventricular dyssynchronous contraction [4]. Dyssynchronous contraction results in suboptimal

ventricular filling, reduced LV dP/dt (rate of rise in LV pressure), prolonged duration and severity of mitral regurgitation, and paradoxical septal wall motion [4]. Studies have shown that HF patients with ventricular dyssynchrony have an increase in mortality [4]. CRT is a biventricular pacemaker device that electrically paces the right and left ventricles in a synchronized mode and thus may improve ventricular contraction and diminish secondary mitral regurgitation [4]. CRT in conjunction with optimal medical therapy has been shown to significantly improve quality of life, functional class, exercise capacity and distance, and ejection fraction (EF), as well as reduce HF hospitalizations by 32% and all-cause mortality by 25% (in a meta-analysis) [4]. It was unknown whether these devices would be beneficial in asymptomatic or mildly symptomatic patients.

MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) investigated whether CRT-D (CRT + implantable cardioverter defibrillator [ICD] device) would reduce all-cause mortality and HF events (need for intravenous diuretic therapy as an outpatient or augmented HF regimen during hospitalization) in patients who qualify for ICD but are NYHA class I or II [21]. Inclusion criteria were age of more than 21 years, an LVEF of not more than 30%, stable optimal medical therapy, a QRS of at least 130 ms, normal sinus rhythm, and NYHA class I or II (ICM) or class II (nonischemic cardiomyopathy). In a 3:2 ratio, 1820 patients were randomly assigned to either CRT-D (1089) or ICD (731) alone. ICD devices were optimized to minimize right ventricular pacing. Successful device implantation occurred in 98.4% of patients, and 95.4% were in their originally assigned arm. The groups were well matched at baseline, and for the entire study group, ICM occurred in about 55% of patients, approximately 10% had NYHA class III/IV symptoms more than 3 months prior to enrollment, mean LVEF was 24%, with a mean 6-minute walk distance of about 361 ms, 70% had left bundle branch block, and 64% had a QRS width of at least 150 ms. Medical therapy was optimized with 93% receiving beta blockers, 97% ACEIs or ARBs, 31% aldosterone antagonist, 74% diuretics, 67% statin, and 7% amiodarone.

The trial was terminated early after a mean follow-up of 2.4 years because of a significant difference in the combined primary endpoint. Death or nonfatal HF events were 17.2% for CRT-D versus 25.3% for ICD (hazard ratio 0.66, 95% confidence interval [CI] 0.52-0.84;  $P = 0.001$ ) (Figure 2). Reduced HF events (13.9% versus 22.8%,  $P < 0.001$ ) drove the primary endpoint to significance, with no difference in all-cause mortality

**Figure 2. Kaplan-Meier estimates of the probability of survival free of heart failure [21]**



There was a significant difference in the estimate of survival free of heart failure between the group that received cardiac resynchronization therapy plus an implantable cardioverter defibrillator (CRT-ICD) and the group that received an ICD only (unadjusted  $P < 0.001$  by the log-rank test).

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(6.8% versus 7.3%,  $P = 0.99$ ). In subgroup analysis, women and patients with a QRS duration of 150 ms or more showed a greater benefit. Improvement of LVEF occurred compared with baseline in the CRT-D arm (0.11 versus 0.03,  $P < 0.001$ ) as measured by echocardiography in a subgroup of patients. LVESV and LVEDV (left ventricular end diastolic volume) decreased significantly compared with baseline in the CRT-D arm (57 versus 18 mL and 52 versus 15 mL, respectively;  $P < 0.001$ ). More frequent device-related adverse outcomes occurred in the CRT-D arm compared with the ICD arm in the 30 days after implantation [21].

Among criticisms of the study are that approximately 10% of patients qualified for CRT with NYHA class III or IV more than 3 months prior to random assignment. Also, patients were assessed by investigators who were not blinded to the patients' device and thus there was a possible bias toward the CRT-D arm [22]. However, there was a blinded independent clinical events adjudication committee.

MADIT-CRT results reveal that CRT-D reduced the primary combined endpoint of death or HF events as compared with ICD alone with optimal medical management in NYHA class I and II patients, driven largely by a reduction in HF events [21]. While these effects may have been exaggerated due to the early termination of follow-up, it is also likely that a longer

follow-up in these NYHA I/II patients would have shown a beneficial effect on mortality. As a result of this and other studies, device therapy has begun to play an even greater role in the management of HF patients.

#### **Continuous-flow left ventricular assist device**

Despite current treatments with optimal medical and device therapy including CRT, a number of HF patients will proceed to refractory HF. Continuous intravenous inotropic assists in the short term only, and transplants are offered to a very small percentage of HF patients. Thus, more permanent solutions with mechanical circulatory support devices such as left ventricular assist devices (LVADs) are being evaluated. In 2002, the landmark REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial was the first to randomly assign nontransplantable end-stage HF patients to optimal medical management or LVAD plus optimal medical management [23]. A 48% risk reduction in death from any cause was found in the LVAD group as compared with medical therapy alone [23]. One-year survival rate was 52% with LVAD and 23% at 2 years versus 25% in the medically treated patients at 1 year and only 8% at 2 years [23].

The older pulsatile-flow LVAD used in REMATCH was compared with the new continuous-flow HeartMate II device in the Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device ('HeartMate II') trial. The continuous-flow device has fewer moving parts, is much smaller, and has less mechanical breakdown than the pulsatile-flow LVAD. Patients with advanced HF (EF of less than 25%, peak oxygen consumption of less than 14 mL/kg per minute or less than 50% of the predicted value, and NYHA class IIIB or IV symptoms for at least 45 of the 60 days before enrollment), refractory to optimal medical management (dependence on an intra-aortic balloon pump for 7 days or inotropes for at least 14 days before enrollment), and ineligible for transplantation were evaluated [24]. Random assignment occurred in a 2:1 ratio to undergo implantation of a continuous-flow device, HeartMate II (134 patients), or the currently approved pulsatile-flow device HeartMate XVE (66 patients). The primary composite endpoint was survival free from disabling stroke and reoperation to repair or replace the device at 2 years. Secondary endpoints were survival, frequency of adverse events, quality of life, and functional capacity.

The two treatment groups had similar preoperative characteristics, including a median age of 64 years (range of 26-81) and a mean LVEF of 17%, and almost 80% had received intravenous inotropic agents, more

than 20% were fitted with an intra-aortic balloon pump, and greater than 60% failed CRT. The primary composite endpoint occurred more frequently in patients with continuous-flow devices (62 of 134 [46%]) than with pulsatile-flow devices (7 of 66 [11%];  $P < 0.001$ ). Patients with continuous-flow devices had greater actuarial survival rates at 2 years (58% versus 24%;  $P = 0.008$ ). Estimated 1- and 2-year survival rates were 68% (95% CI 60-76%) and 58% (95% CI 49-67%), respectively, with the continuous-flow device and 55% (95% CI 42-69%) and 24% (95% CI 1-46%) with the pulsatile-flow device. The better durability of the Heart-Mate II continuous-flow device was the primary determinant of the significant positive endpoint. One-third of patients with pulsatile-flow LVAD required pump replacements, one required urgent transplantation, and three required device explantation. About 10% of patients with continuous-flow LVAD required pump replacements due to breakage of the percutaneous lead, pump thrombosis, or outflow elbow disconnection. Major adverse events were significantly reduced in patients with a continuous-flow LVAD, including device- and non-device-related infection, right HF, respiratory failure, renal failure, and cardiac arrhythmia. The incidence of stroke did not differ significantly between groups. There was a significant improvement in quality of life and functional capacity in both groups.

Limitations of the study include the potential bias despite random assignment of the devices because both patient and physician were aware that the device was being implanted [25]. The study failed to report the number of patients screened. It also did not report the postoperative mortality [25].

Overall, the study found that continuous-flow LVAD in patients with advanced HF significantly improved the probability of survival-free device failure at 2 years as compared with a pulsatile device [24]. Most importantly, the study demonstrated that the survival of patients with a continuous-flow device is twice that of the REMATCH trial pulsatile-flow group at 2 years, thus illustrating that newer technology and improved medical treatment have enhanced the survival of refractory HF patients in the past decade [24].

### Implications for clinical practice

Medical therapy with optimal doses of ACEI and beta blocker based on patient tolerability and clinical trial evidence is essential for HF therapy. The judicious use of diuretics, in conjunction with a low sodium diet, helps to manage the volume overload of this condition. Patients must follow appropriate lifestyle recommendations: no smoking, moderate exercise, avoidance of nonsteroidal

anti-inflammatory drugs, and avoidance of alcohol. The careful addition of aldosterone antagonists or ARBS (or both) can improve outcomes. Finally, the appropriate use of bypass surgery and devices (ICDs, CRT-D, and LVADs) can beneficially impact morbidity and mortality for HF patients.

### Abbreviations

ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARR, absolute risk reduction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHARM, Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy + implantable cardioverter defibrillator device; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVESVi, left ventricular end systolic volume index; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; NYHA, New York Heart Association; RAAS, renin angiotensin aldosterone system; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; STICH, Surgical Treatment for Ischemic Heart Failure; SVR, surgical ventricular restoration; Val-HeFT, Valsartan Heart Failure Trial.

### Competing interests

The authors declare that they have no competing interests.

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**Changes Clinical Practice**F1000 Factor 9.6 *Exceptional*

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**F1000 Factor 8.3 *Exceptional***

Evaluated by Larry Allen 26 Nov 2009, Carolyn Lam 22 Dec 2009, Mariell Jessup 21 Jan 2010, Paul Pagel 26 Jan 2010, Alain Vuylsteke 23 Feb 2010

25. Fang J: **Rise of the machines — left ventricular assist devices as permanent therapy for advanced heart failure.** *N Engl J Med* 2009, **361**:2282-5.