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# Algorithm for Treatment of Advanced Heart Failure

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## Introduction

## Epidemiology

Heart failure (HF) is a growing epidemic in the United States with steadily increasing prevalence. According to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2012 update, HF prevalence was 5.7 million in the United States based on the National Health and Nutrition Examination Survey (NHANES) 2005–2008 data for Americans  $\geq 20$  years, with projected crude prevalence of 6.6 million (2.8 %) in 2010 for adults  $\geq 18$  years. Further, it is estimated that by 2030, an additional 3 million people will have HF, which is a 25 % increase in prevalence compared to 2010. HF incidence

approaches 10 per 1,000 after 65 years of age with a lifetime risk of developing HF of 1 in 5 at 40 years of age in both genders [1].

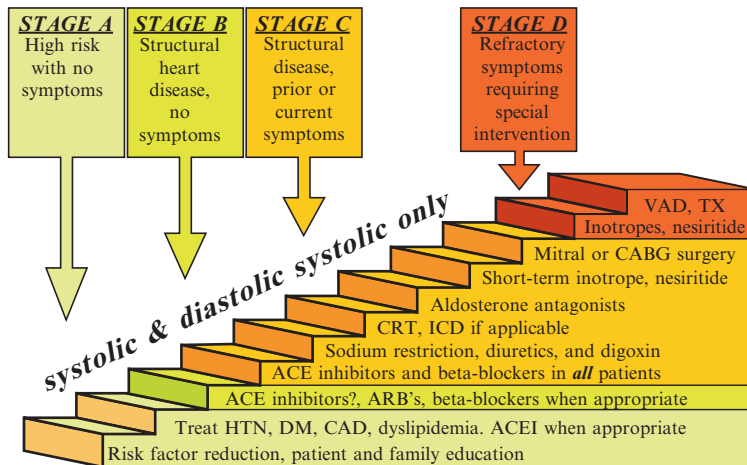
Hospital discharges for HF were only mildly increased from 1999 to 2009, with first-listed diagnoses of 975,000 and 1,094,000, respectively. In 2009, HF resulted in 3,041,000 office visits, 668,000 emergency room visits, and 293,000 outpatient department visits [1]. In 2008, any mention of HF in mortality was 281,437, and death directly attributable to HF was 56,830. Currently, one in nine deaths in the United States mentions HF on the death certificate. Even though survival after HF diagnosis has improved, the death rate remains unacceptably high at approximately 50 % within 5 years from time of index diagnosis. It is a major public health concern due to its tremendous societal and economic burden, with a projected direct and indirect cost in the United States of \$37.2 billion in 2009 [2], which is expected to further increase to \$44.6, \$57.0, \$74.1, and \$97.0 billion by 2015, 2020, 2025, and 2030, respectively [1].

In the international community, the epidemiological transition in less industrialized countries is associated with a reduced risk of mortality from communicable diseases and increased risk of death from cardiovascular diseases including HF [3]. As a consequence of improved management in acute coronary syndromes and improved longevity of the population, the number of patients with HF is growing. The prevalence and incidence in industrialized countries are estimated

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**Fig. 2.1** Heart failure staging system (Adapted from Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the

2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005 Sep 20;112(12):e154–235)

to be approximately 1.5 % and 0.15 % of the population, respectively [4, 5]. An estimated 10 % of persons with HF have advanced disease. In the United States and Europe alone, with  $\geq 700$  million inhabitants and  $\geq 7$  million patients with HF, the prevalence of advanced HF, constituting between 1 % and 10 % of the HF population, is estimated to total between 70,000 and 700,000 patients [6].

## Definition of Heart Failure

The clinical syndrome of HF is defined as the final common pathway that results from any structural or functional cardiac disorder that impairs the ventricle from either filling with (diastolic dysfunction) or ejecting blood (systolic dysfunction). The diverse causes of HF range from disorders of the pericardium, myocardium, endocardium, or great vessels. Despite the fact that the majority of patients with HF have symptoms secondary to impaired systolic function, it is important to recognize that symptoms may also arise due to abnormal filling [7]. The over-

all prognosis of HF with preserved ejection fraction (HF-PEF) is less well defined, with certain observational series suggesting improved outcomes compared to HF with reduced ejection fraction (HF-REF) [8–10], while other series have shown similar mortality for HF-PEF and HF-REF [11, 12].

## Stages of Heart Failure

The terminology of HF in its advanced stages is not very precise. The terms advanced, severe, congestive, refractory, and end-stage HF are used in largely interchangeable ways. The term end-stage HF reflects the impaired prognosis associated with it and has been incorporated into the recent staging system for HF (Fig. 2.1) [4], which complements the New York Heart Association (NYHA) classification of HF. This staging system has the advantage of including asymptomatic stages (risk factors, structural heart disease), thereby underscoring the importance of preventive medicine and reflecting the progressive nature of the HF syndrome. It bears resemblance with the

classification of tumors, a similarly malignant group of conditions. In other words, a HF patient may progress from stage A to stage D but cannot reverse to stage A again. However, treatment may result in a patient reversing from NYHA class IV to class III due to improved symptoms.

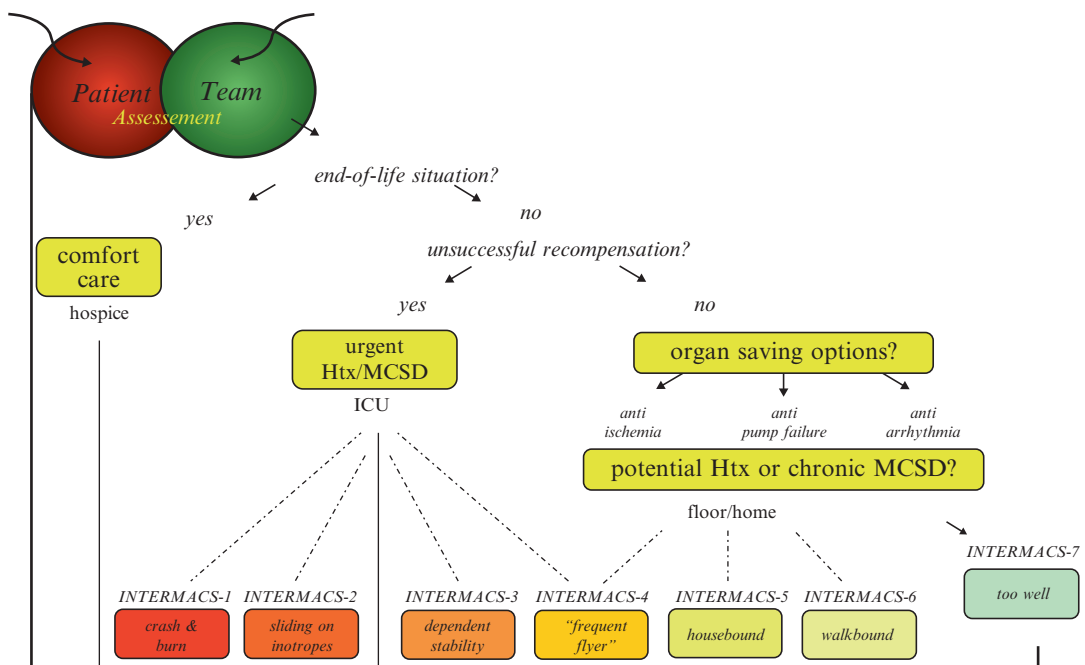
## Importance of Algorithms

In order to define and guide the optimal management of HF patients in varying clinical scenarios, treatment algorithms have become an essential cornerstone of clinical practice. These modalities are valued for their ability to help streamline clinical decision making based on disease severity. However, oversimplification of an algorithm may lead to its inapplicability in complex clinical situations. Therefore, treatment algorithms should be based on current guidelines derived from large randomized controlled clinical trials and individualized based on the assessment of a clinical situation.

In the field of heart failure, there are five main sets of guidelines developed by (1) European Society of Cardiology (ESC 2012), (2) American College of Cardiology/American Heart Association (ACC/AHA 2009), (3) Heart Failure Society of America (HFSA 2010), (4) Canadian Cardiovascular Society (CCS 2012), and (5) International Society of Heart and Lung Transplantation (ISHLT 2007). The algorithm described in Fig. 2.2 is based on these guidelines as well as current randomized controlled trials.

## Initial Assessment

The algorithm starts with the encounter between the HF patient and the primary medical team, consisting of cardiologist, general internist, and nurse, who have exhausted all lifestyle and medical options without success. In this setting of acute decompensation and progression towards advanced heart failure, a phase known to be associated with a



**Fig. 2.2** Management algorithm in heart failure (Adapted from Deng MC, Naka Y. Mechanical Circulatory Support Therapy for Advanced Heart Failure. London: Imperial College Press; 2007)

high risk of death, a referral to a designated cardiac transplantation center for evaluation is undertaken. The initial assessment is not a complete cardiac transplantation evaluation but rather addresses the following main questions:

- How severe is the heart failure condition?
- Are there reversible causes?
- Are there risk factors limiting the overall prognosis?

After the initial assessment, a structured management algorithm (Fig. 2.2) is applied in order to recompensate the patient. If recompensation cannot be achieved, cardiac transplantation evaluation is initiated with the option of mechanical circulatory support device (MCS) as either bridge to recovery (BTR), transplant (BTT), or destination therapy (DT). At anytime during management, a situation may arise in which the patient may not benefit from any of the modern therapies because of multiorgan failure or other conditions, leading to a patient preference for *comfort care* facilitating a humane form of death instead of prolongation of suffering [13, 14].

## Risk Stratifiers

In order to plan effective treatment strategies and transplant programs, it is important to be able to objectively measure the prognosis of patients. An ideal test needs to be accurate (i.e., have a high specificity and sensitivity), reproducible, safe, and inexpensive.

The *6-min walk test* can be performed by almost all patients with chronic heart failure without the need for specialized equipment. This test was first used in heart failure patients by Guyatt and colleagues in 1985 [15] and has subsequently gained widespread acceptance as a measure of exercise capacity in clinical trials and transplant programs. Zugck et al. showed that the walk test provided information on the combined end point of death and/or hospital admission due to worsening heart failure that was similar to peak oxygen uptake in patients with dilated cardiomyopathy [16]. The authors concluded the test correlated closely with peak oxygen uptake ( $pVO_2$ ) and could predict individual  $pVO_2$  when deter-

mined serially in the same patient. Opasich and colleagues also compared the prognostic role of the 6-min walk test to  $pVO_2$  and NYHA functional class. Although the test was found to be able to predict survival in univariate analysis, this was not the case when  $pVO_2$  or NYHA class were included in multivariate models, indicating that the walk test is not an independent prognostic indicator [17]. Whether the test is an accurate and independent predictor of prognosis in chronic heart failure, however, is the subject of some debate [18].

## Peak Oxygen Uptake

Based on the groundbreaking work of Mancini and coworkers [19], a team at UCLA assessed the role of  $pVO_2$  in reevaluation of candidates awaiting heart transplantation. All ambulatory transplant candidates with initial  $pVO_2 \leq 14$  mL/kg/min were identified. Of 107 such patients listed, 68 survived without early deterioration or transplantation to undergo repeat exercise. In 38 of the 68 patients,  $pVO_2$  increased by  $\geq 2$  mL/kg/min to a level  $\geq 12$  mL/kg/min after  $6 \pm 5$  months, together with an increase in anaerobic threshold, peak oxygen pulse, and exercise heart rate reserve and a decrease in heart rate at rest. Increased  $pVO_2$  was accompanied by stable clinical status without congestion in 31 of 38 patients, and these 31 were taken off the active waiting list. At 2 years, actuarial survival rate was 100 %, and survival rate without relisting for transplantation was 85 %. The authors concluded that an algorithm with scheduled reevaluation of exercise capacity and clinical status allowed identification of patients who became “too well” during follow-up. They estimate that 29 % of ambulatory transplant candidates could be removed from the waiting list with excellent early survival despite low  $pVO_2$  on initial testing, allowing deferral of transplantation in favor of more compromised candidates [20].

In order to refine risk stratification in ambulatory cardiac transplantation candidates and estimate their survival probability without transplantation and thus the potential benefit from transplantation, the group at the University of Pennsylvania and Columbia University between

1987 and 1995 developed the first independently validated prognostication tool, entailing high-, medium-, and low-risk stratum [21]. The multivariable proportional hazards survival model was developed with the use of data on 80 clinical characteristics from 268 ambulatory patients with advanced heart failure (derivation sample). Invasive and noninvasive models (with and without catheterization-derived data) were constructed. Stratum-specific likelihood ratios were used to develop three prognostic-score risk groups. The noninvasive model performed well, and increased performance was not attained by the addition of catheterization-derived variables.

Prognostic-score risk groups derived from the noninvasive model in the derivation sample effectively stratified the risk of an outcome event in both the derivation and validation samples (1-year event-free survival for derivation and validation samples, respectively: low risk [Heart Failure Survival Score or HFSS 8.10–10.47] 93 % and 88 %; medium risk [HFSS 7.20–8.09] 72 % and 60 %; high risk [HFSS 5.51–7.19] 43 % and 35 %). The authors concluded that selection of candidates for cardiac transplantation may be improved by use of this noninvasive risk-stratification model [21]. The beauty of this score does not reside only in its powerful predictive value but also on its easy bedside implementation by the equation:

$$\begin{aligned} \text{HFSS} = & [(0.69 \times \text{CAD} : \text{YES} = 1 \text{ NO} = 0) \\ & + (0.022 \times \text{HR}) + (-0.046 \times \text{LVEF}) \\ & + (-0.026 \times \text{mBP}) + (0.61 \times \text{IVCD} : \text{YES} = 1 \text{ NO} = 0) \\ & + (-0.055 \times \text{VO}_2) + (-0.047 \times \text{Na})] \end{aligned}$$

CAD coronary artery disease; HR heart rate; LVEF left ventricular ejection fraction; mBP mean blood pressure; IVCD interventricular conduction delay; VO<sub>2</sub> peak oxygen consumption Na sodium. gathered

Event-free survival rates for the medium- and high-risk strata were much worse than would be expected after cardiac transplantation; the low-risk stratum had an event-free survival rate that was better than would be expected with transplantation. Based on this excellent prognostication tool,

patients with HFSS low risk would be considered too well for cardiac transplantation [21]. Risk stratification of hospital-bound cardiac transplantation candidates who are inotrope- or left ventricular assist-device-dependent can be improved by inclusion of further parameters [22].

After the introduction of  $\beta$ -blocker therapy and given the large survival benefit conferred by  $\beta$ -blocker therapy, it was unclear whether the HFSS and pVO<sub>2</sub> were still valid predictors. The fact that  $\beta$ -blockers considerably improved survival while having an inconsistent effect on pVO<sub>2</sub> may explain why pVO<sub>2</sub> did not accurately predict outcomes in patients taking  $\beta$ -blockers. Given the better prognosis for patients with heart failure receiving  $\beta$ -blockade and absence of effect on exercise performance, the clinical guideline value for pVO<sub>2</sub> has probably decreased to the extent that a pVO<sub>2</sub>  $\leq$  10 mL/kg/min is a more appropriate target. However, recalibration of the HFSS was not necessary since there were no particular differences in the HFSS pre- or post- $\beta$ -blocker therapy or its parameters (other than heart rate). The authors conclude that in the  $\beta$ -blocker era, clinicians can continue to rely on the HFSS to accurately predict prognosis in patients with severe heart failure and that pVO<sub>2</sub> may have diminished in value [23].

The predictive accuracy of the HFSS has been noted to be suboptimal in some validation data sets [24]. As a result, the Seattle Heart Failure Model (SHFM) was developed and validated as a multivariate risk model to predict 1-, 2-, and 3-year survival in heart failure patients with the use of easily obtainable characteristics relating to clinical status, therapy (pharmacological as well as devices), and laboratory parameters. The SHFM was derived from a cohort of 1,125 heart failure patients in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1) with the use of a multivariate Cox model. For medications and devices not available in the derivation database, hazard ratios were estimated from published literature. The model was prospectively validated in five additional cohorts totalling 9,942 heart failure patients. The accuracy of the model was excellent, with predicted versus actual 1-year survival rates of 73.4 % versus 74.3 % in the derivation cohort and

90.5 % versus 88.5 %, 86.5 % versus 86.5 %, 83.8 % versus 83.3 %, 90.9 % versus 91.0 %, and 89.6 % versus 86.7 % in the five validation cohorts. Overall receiver operating characteristic area under the curve was 0.729 (95 % CI, 0.714–0.744). The model also allowed estimation of the benefit of adding medications or devices to an individual patient's therapeutic regimen. The authors concluded that the SHFM provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacological, device, and laboratory characteristics [24].

In a study by Kalogeropoulos and colleagues [25], the SHFM was utilized to predict a composite end point of death, left ventricular assist device (LVAD), and urgent transplantation. However, 98 % of the events in the original SHFM study were death. This fact raises important issues. A higher rate of LVAD implantation and/or urgent transplantation might lead to higher overall event rate. Considering that this patient population was sicker as compared with the original SHFM cohort, it is not surprising that a larger proportion of patients underwent these procedures in their study (16 % vs. 2 %). Thus, miscalibration might not be due to SHFM performance but rather to the SHFM being more accurate for mortality prediction alone rather than a combined outcome. Indeed, when assessing the model performance restricting the outcome to death alone, the model performance improved significantly. Unlike mortality, the timing for urgent transplantation or LVAD implantation can vary between institutions and physicians. With regard to race-based differences, the SHFM needed to be recalibrated by using race-specific coefficients (0.77 for whites and 1.15 for blacks, as estimated in this cohort).

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## **Nonsurgical Management of Heart Failure**

### **Recompensation**

The evolution of treatment options for advanced HF patients over the last several decades has been impressive. It includes medical therapies (positive

inotropes, vasodilators, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers,  $\beta$ -blockade, aldosterone antagonists), defibrillator implantation, resynchronization therapy, heart transplantation, and most recently MCSDs. The comparison of outcomes between different therapies for advanced HF has been challenging. For example, heart transplantation has never been tested in a randomized clinical trial because of the obvious survival advantage in the 1970s in comparison to medical therapy. It is unclear whether this remains true with the recent improvement in HF therapies. Moreover, MCSD is rapidly evolving with advances in technology leading to smaller devices with decreased morbidity. Therefore, the clinical decision-making algorithm is subject to continuing debate and consensus processes, as exemplified by the guideline development initiative of the International Society for Heart and Lung Transplantation [26].

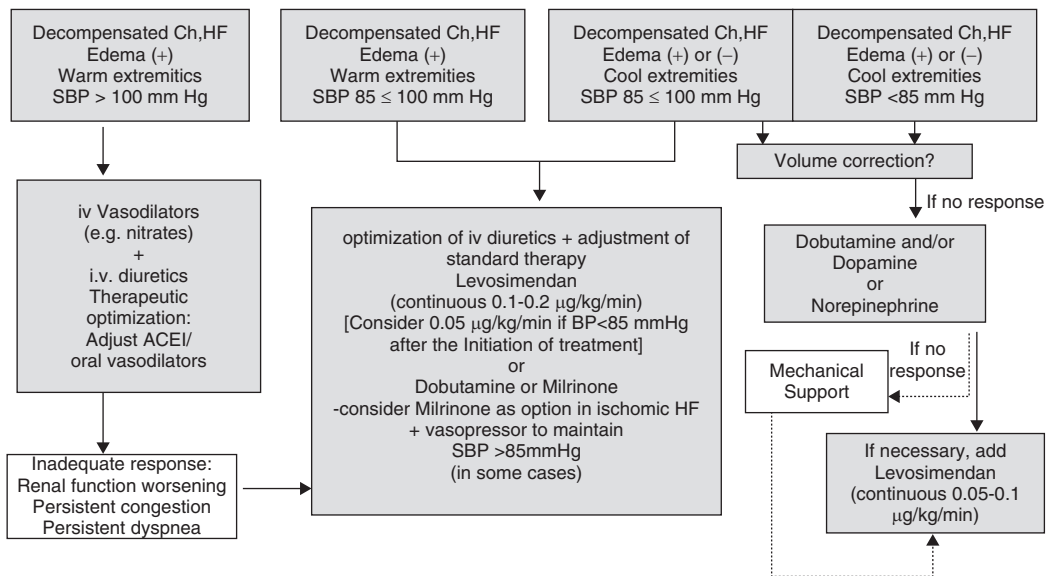
### **Neurohormonal Blockade**

In increasing stages of HF, the adrenergic system, renin-angiotensin-aldosterone system (RAAS), antidiuretic hormone system, and the atrial natriuretic peptide system are chronically activated. These chronic neurohormonal changes lead to compensatory elevation of preload, heart rate, contractility, and cardiac hypertrophy. NYHA class IV is characterized by a flattening and rightward shift of the cardiac function curve to a point where reduced cardiac output does not fulfill the metabolic requirements of the body and capillary wedge pressure reaches a level at which pulmonary edema ensues or both happen [27].

### **Positive Inotropes/Vasodilators**

In the context of refractory acute HF, characterized by peripheral hypoperfusion, renal dysfunction, and marked hypotension present in less than 10 % of acute decompensated HF patients, inotropic agents (classically  $\beta$ -adrenergic agonists and phosphodiesterase inhibitors) have been used as a short-term bridge to cardiac surgery,

## Inotrope Treatment Algorithm in Acutely Decompensated Chronic Heart Failure



**Fig. 2.3** Stepwise approach to use of inotrope therapy

transplantation, or prolonged infusions via improvement of central hemodynamics. The goals outlined for the utilization of inotropes are as follows: (1) provide rapid relief of congestive symptoms and (2) restoration of end-organ perfusion. If the myocardial insult is deemed reversible, inotropic therapy can be transitioned to organ-saving options. However, if end-organ perfusion cannot be achieved, then mechanical circulatory support (e.g., intra-aortic balloon pump) may be required to transition to possible urgent ventricular assist device or heart transplant [28]. A stepwise approach to the use of inotropic therapy is outlined in Fig. 2.3.

Inotropic agents increase myocardial contractility via increase in intracellular cyclic adenylyl monophosphate levels (cAMP). This results in an increase in calcium release from the sarcoplasmic reticulum, thereby increasing the contractile force generation. The phosphodiesterase inhibitors such as milrinone and enoximone inhibit phosphodiesterase III, the enzyme that catalyzes the breakdown of cAMP, whereas the  $\beta$ -adrenergic agonists such as dobutamine and dopamine

stimulate adenylyl cyclase which increases cAMP production. Dopamine has a dose-dependent mechanism of action:  $\leq 2$  mcg/kg/min (dopaminergic receptor activity), 2–5 mcg/kg/min ( $\beta$ -adrenergic receptor activity), and  $\geq 5$  mcg/kg/min (alpha adrenergic agonist activity). Both milrinone and dobutamine have similar overall hemodynamic effects with key potential distinctions. Milrinone appears to lower filling pressures to a greater extent than dobutamine. It also has a more profound effect of lowering systemic vascular resistance and blood pressure. On the other hand, dobutamine may result in tachycardia with higher heart rates than milrinone [29]. Therefore, the individual clinical setting should dictate which type of inotrope is used (Table 2.1).

Despite short-term hemodynamic and symptomatic improvement, long-term mortality appears to be increased with the use of intravenous and oral inotropes for the treatment of chronic heart failure. Positive inotropes such as vesnarinone [30–34] and vasodilators such as epoprostenol did not demonstrate a survival benefit and, in fact, showed an adverse mortality

**Table 2.1** Inotrope selection in various clinical settings

Clinical scenarios	Inotrope
Hypotension	Dobutamine or dopamine
Increased mean pulmonary artery pressure	Milrinone
Tachycardia	Milrinone
Renal hypoperfusion	Dopamine, dobutamine, or milrinone

effect [35]. Over the past years, a large clinical development program with the phosphodiesterase III inhibitor, enoximone, yielded promising preliminary results in the phase II results of Oral Enoximone in Intravenous Inotrope-Dependent Subjects (EMOTE) [36]. However, the phase III studies of Oral Enoximone Therapy in Advanced Heart Failure (ESSENTIAL) trial demonstrated a lack of statistically significant differences in time to all-cause mortality or cardiovascular hospitalization [37].

A novel class of inotropic drugs known as calcium-sensitizing agents, such as levosimendan, had generated excitement due to their ability to induce contractility via enhanced troponin C affinity for calcium and stabilization of the calcium-induced conformation of troponin C. The two phase III trials on levosimendan, “Survival in Patients with Acute Heart Failure in Need of Intravenous Inotropic Support” (SURVIVE) [38] and “Second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Survival in the Short-Term Treatment of Decompensated Heart Failure” (REVIVE-II) [39], demonstrated that levosimendan was superior to dobutamine or placebo, respectively, regarding clinical improvement and neurohormonal modulation but failed to demonstrate superiority with regard to 6-month mortality.

Another potential intravenous therapy which promotes vasodilation, salt and water excretion, and improved diastolic filling properties in order to relieve congestion and reduce cardiac filling pressures is nesiritide, a recombinantly produced intravenous formulation of human B-type natriuretic peptide. Rapid and sustained beneficial hemodynamic effects of nesiritide were demonstrated by Mills et al. [40] in NYHA class II–IV patients over a 24-h infusion period and 4 h post-infusion.

Effects on clinical outcomes beyond improvement in symptoms and hemodynamics are not clear. In a meta-analysis [41], Sackner-Bernstein and coworkers expressed the opinion that the use of nesiritide could increase the risk of short-term (30-day) mortality. The three trials included in their analysis were the Nesiritide Study Group Efficacy Trial (NSGET) [42], Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) [43], and the Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially as Outpatients with Nesiritide (PROACTION) [44]. Another meta-analysis showed that the cumulative short-term (30 days) and long-term (180 days) mortality in patients who received nesiritide combined with or without the use of inotropes [45] was not statistically increased [46].

Based on this conflicting meta-analysis data, an international, multicenter, randomized, double-blind, placebo-controlled study, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF), has assessed the safety and efficacy of nesiritide. ASCEND-HF randomized 7,141 patients hospitalized with acute HF within 24 h of hospitalization to receive IV nesiritide or placebo in addition to standard therapy. Although there was a trend toward improvement in dyspnea (measured on the 7-point Likert scale) at 6 and 24 h with nesiritide, the prespecified level for significance was not met. Further, there was no difference between the composite end point of 30-day death and HF hospitalization. It was also shown that nesiritide had no impact on worsening of renal function, which had been a prior concern. The authors concluded that nesiritide cannot be recommended for routine use in patients with acute decompensated HF [47].

Adjunctive intravenous therapy which targets the elevated vasopressin (AVP) levels that activate vasoconstriction and left ventricular hypertrophy/remodeling via V1A/V1B receptors and water retention via V2 receptors have also been studied. Both these mechanisms contribute toward acute decompensation of HF. The utilization of intravenous conivaptan, an AVP-receptor antagonist which binds to both V1A and V2 receptors, has



demonstrated favorable changes in hemodynamics, with statistically significant reduction in pulmonary capillary pressure and right atrial pressure, and urine output without affecting blood pressure or heart rate [48]. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial randomized 4,133 patients hospitalized with HF to oral tolvaptan (selective for V2) or placebo, in addition to standard therapy. Although tolvaptan improved dyspnea, body weight, and edema, there was no significant difference in all-cause mortality or the composite end point of cardiovascular death or HF hospitalization [49]. Thus, vasopressin receptor antagonists may be considered in the management of refractory hyponatremia in HF patients but has no impact on mortality.

## RAAS Blockade

Multiple studies have demonstrated the benefit derived from renin-angiotensin system blockade via angiotensin-converting-enzyme inhibitors (ACE-I), including improvements in symptoms, survival, rate of hospitalization, and reverse remodeling. ACE-I decrease the conversion of angiotensin I to angiotensin II, thereby reducing the maladaptive effects of angiotensin II. Furthermore, there is a decrease in the breakdown of bradykinin which promotes vasodilation in the vascular endothelium and promotes natriuresis [7]. At this time, it is unclear if all the different ACE-I demonstrate a similar extent of survival benefit. There is conflicting results from meta-analysis [50], observational studies [51], and comparative trials [52–54]. Moreover, low- versus high-dose enalapril has been studied with no significant differences in survival or clinical and hemodynamic variables [55].

With regard to trial data, the first randomized prospective medical trial demonstrating a survival benefit with ACE-I from a medical treatment in advanced heart failure was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS-I) trial [56]. Two hundred fifty-six patients in NYHA class IV heart failure were randomized to enalapril or placebo. This trial

demonstrated improved survival in the enalapril cohort. This study is unique in being the first heart failure trial in unselected NYHA class IV patients but also in examining extended survival, with sustained benefit for at least 4 years [57]. The subsequent Studies of Left Ventricular Dysfunction (SOLVD) study in 1991 randomly assigned 2,569 patients with symptomatic NYHA class II to III HF and ejection fraction  $\leq 35\%$  to either placebo or enalapril, with reduction in all-cause mortality in the enalapril cohort [58].

Despite the inhibition of the angiotensin-converting enzyme with ACE-I, there is evidence of increased plasma levels of aldosterone. Aldosterone has pleiotropic effects, resulting in increased sodium retention, constriction of systemic arterioles, stimulation of cytokine production, inflammatory-cell adhesion, activation of macrophages as well as stimulation of growth of fibroblasts, and the synthesis of type I and III fibrillar collagens involved in scar formation [59]. Mortality reduction was noted with the addition of aldosterone inhibitors, as evidenced by the Randomized Aldactone Evaluation Study (RALES) trial, in which 1,663 NYHA class III–IV HF patients who had severe heart failure and a left ventricular ejection fraction (LVEF) of  $\leq 35\%$  and who were being treated with an ACE-I, a loop diuretic, and in most cases digoxin were randomly assigned to receive 25 mg of spironolactone daily or placebo. After a mean follow-up period of 24 months, there was a 46% mortality rate in the placebo group and a 35% mortality rate in the spironolactone group [60]. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial demonstrated that eplerenone also significantly reduces mortality in post-myocardial infarction (MI) patients with HF or diabetes mellitus with LVEF  $\leq 40\%$  [61]. More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial studied eplerenone in HF patients with LVEF  $\leq 30\%$  (or 30–35% if QRS duration  $\geq 130$  ms) with milder NYHA class II symptoms. In this population, aldosterone antagonism was also associated with improved survival [62].

Another class of medication utilized in RAAS blockade is angiotensin II type 1 receptor blockers (ARB). In the Valsartan Heart Failure Trial (Val-HeFT) study, valsartan significantly reduced the combined end point of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure compared to placebo. This difference was predominantly driven by a 24 % reduction in the rate of HF hospitalizations, without a clear benefit for survival alone. However, the post hoc observation of an adverse effect on mortality and morbidity in the subgroup receiving combined valsartan, an angiotensin-converting-enzyme (ACE) inhibitor, and a  $\beta$ -blocker raised concern about the potential safety of this specific combination [63].

Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) addressed whether the angiotensin-receptor blocker (ARB) candesartan improved outcomes in HF patients in two complementary parallel trials (CHARM-Alternative, for patients who could not tolerate ACE-I, and CHARM-Added, for patients who were receiving ACE-I). NYHA II–IV HF patients with LVEF of  $\leq 40\%$  were randomized to candesartan or placebo. The study drug was discontinued in CHARM-Alternative because of adverse effects in 23.1 % of patients in the candesartan group and 18.8 % in the placebo group; the reasons included increased creatinine, hypotension, and hyperkalemia. The authors concluded that candesartan significantly reduces all-cause mortality, cardiovascular death, and heart failure hospitalizations in patients with HF and LVEF  $\leq 40\%$  when added to standard therapies including ACE-I,  $\beta$ -blockers, and an aldosterone antagonist. However, routine monitoring of blood pressure, serum creatinine, and serum potassium is warranted [64]. Thus, ARB are a reasonable alternative to ACE inhibitors as first-line agents for HF. ARB or ACE-I are useful to prevent HF in selected stage A and B patients, and candesartan can improve outcomes in patients with impaired cardiac function who are intolerant of ACE-I [64].

Other landmark trials including Evaluation of Losartan in the Elderly (ELITE II) [65], Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)

[66], and Valsartan in Acute Myocardial Infarction (VALIANT) [67] that have assessed ARB in comparison to ACE-I for treatment of HF have shown no clear benefit of one pharmacologic agent over the other for mortality in HF-REF patients. Studies that have looked at the addition of ARB to background therapy, including the aforementioned Val-HeFT [63], CHARM-Added [68], and VALIANT [67], that already includes ACE-I have also not shown any clear benefit of ARB in addition to ACE-I in reducing mortality in HF-REF.

### **$\beta$ -Adrenergic Blockade**

The cornerstone of heart failure treatment is neurohormonal blockade of the RAAS and adrenergic systems. According to the European guidelines, ACE inhibition is the first line of therapy, with the initiation of  $\beta$ -blockers (BB) once the patient is clinically stable and ACE inhibitors have been optimized. This paradigm of treatment has resulted in some degree of controversy, pertaining to whether adrenergic blockade should be the front-runner in medical therapy as opposed to ACE inhibition due to its greater impact on sudden death and its initial presence in the sequence of maladaptive neurohormonal activation [69].

The Carvedilol and ACE-Inhibitor Remodeling Mild Heart Failure Evaluation (CARMEN) and the Cardiac Insufficiency Bisoprolol Study (CIBIS) III studies challenged the concept of ACE inhibitors as first-line treatment in CHF. CARMEN explored the need for combined treatment of ACE-I and  $\beta$ -blocker, as well as the order of introduction of these therapies in HF patients with mild, chronic symptoms. They found that combination therapy is superior to ACE-I alone for left ventricular (LV) remodeling as assessed by LV end-systolic volume index on transthoracic echocardiography. When assessing whether introduction of enalapril or carvedilol first had an impact on outcomes, they found that introduction of carvedilol first had a nonsignificant trend toward benefit. The authors concluded that introduction of beta-blockade should not be delayed [70].

CIBIS III was designed to assess the effectiveness of bisoprolol for 6 months followed by combination therapy with enalapril compared to enalapril for 6 months followed by combination therapy with bisoprolol. HF patients with stable mild to moderate symptoms demonstrated non-inferiority of initial initiation of bisoprolol or enalapril in only the intention-to-treat sample for a combined end point of all-cause mortality or hospitalization. However, there was notably more frequent HF events (defined as requiring hospitalization or occurring in the hospital) observed in the bisoprolol group [71]. As a result, first-line treatment with either ACE inhibitors or BB should be based on personalized medicine.

The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) study group investigated whether metoprolol succinate controlled release/extended release (CR/XL) once daily, in addition to standard therapy, would lower mortality in patients with decreased ejection fraction (EF) and HF symptoms. The study randomized approximately 2,000 NYHA class II–VI patients with chronic HF and with LVEF  $\leq 40\%$  to either metoprolol succinate or placebo. All-cause mortality, sudden death, and death from worsening HF were lower in the metoprolol group [72].

The CIBIS study group investigated the efficacy of bisoprolol, a  $\beta_1$ -selective adrenoceptor blocker, in decreasing all-cause mortality in chronic HF. In a multicenter trial in Europe, they randomized 2,647 NYHA III–IV patients with LVEF  $\leq 35\%$  receiving standard therapy with diuretics and ACE-I to bisoprolol or placebo. CIBIS-II was stopped early because bisoprolol showed a significant mortality benefit. Treatment effects were independent of the severity or cause of heart failure. The authors concluded that  $\beta$ -blocker therapy had benefits for survival in stable heart failure patients [73].

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial demonstrated the beneficial effects of carvedilol, a mixed  $\beta_1$ -,  $\beta_2$ -, and  $\alpha_1$ -blocker, on mortality in NYHA class IV patients with chronic HF, with reduction in 1-year mortality from 19.6% to 11%, when compared to placebo. All subgroups

including those with the most advanced HF showed the same beneficial direction of effect [74]. The Carvedilol or Metoprolol European Trial (COMET) reported a significant survival benefit for carvedilol when compared to metoprolol tartrate in patients with mild-to-severe chronic heart failure [75]. However, the implications of COMET are not fully clear, as critics have argued that the target dosing of metoprolol tartrate (50 mg twice daily) and carvedilol (25 mg twice daily) was not equivalent, with the carvedilol dose being substantially higher [76]. Further, others have argued that long-acting metoprolol succinate should have been directly compared to carvedilol rather than the shorter-acting metoprolol tartrate to achieve more steady-state  $\beta$ -blockade over each 24-h period.

## Oral Vasodilators

Hydralazine increases intracellular cyclic guanosine monophosphate (cGMP) to promote smooth muscle relaxation, primarily in the arterioles with reduction in afterload. Nitrates act on the nitric oxide pathway to activate guanylate cyclase and increase cGMP, with predominant venodilation at low doses and vasodilation at higher doses. The original Vasodilator-Heart Failure Trial (V-HeFT) study randomized HF-REF patients who were on background digoxin and diuretic to receive additional therapy with placebo, prazosin ( $\alpha_1$ -blocker), or combination of isosorbide dinitrate-hydralazine (ISDN-HYD). They found that mortality was lower in the ISDN-HYD cohort compared to placebo at 2 years. Prazosin demonstrated no benefit compared to placebo. Thus, it appeared that ISDN-HYD has potential benefit in chronic HF [77]. However, it should be kept in mind that these patients were not on a background therapy of ACE-I and  $\beta$ -blockade. Subsequently, V-HeFT II randomized 804 patients to either ISDN-HYD or enalapril on background therapy of digoxin and diuretics. The study showed that enalapril resulted in significantly improved survival compared to ISDN-HYD in HF patients [78].

However, there appeared to less benefit of ACE-I compared to ISDN-HYD in African

American patients in V-HeFT II. This led to the African American Heart Failure Trial (A-HeFT), which randomized 1,050 NYHA class III–VI HF patients self-described as African American to fixed-dose ISDN-HYD or placebo in addition to standard background therapy that included neurohormonal blockade (including ACE-I, ARB,  $\beta$ -blockers, aldosterone antagonists on the discretion of their regular physicians). The study was terminated early due to significantly improved survival in the ISDN-HYD arm. ISDN-HYD was also associated with improved quality of life. This suggests that there are additional mechanisms of heart failure progression, perhaps decreased NO bioavailability not treated by standard neurohormonal blockade, which are favorably impacted by combined ISDN-HYD [79].

Pulmonary hypertension (PH) is present in 68–78 % of patients with chronic severe LV systolic dysfunction (LVSD) and is commonly associated with right ventricular (RV) dysfunction. Pulmonary vascular resistance (PVR) and RV performance are important determinants of exercise capacity and prognosis in patients with LVSD. The hypothesis that sildenafil, an effective therapy for pulmonary arterial hypertension, would lower PVR and improve exercise capacity in patients with HF complicated by PH was tested in a group of 34 symptomatic HF patients with PH. The patients were randomized to 12 weeks of treatment with sildenafil (25–75 mg orally three times daily) or placebo. Patients underwent cardiopulmonary exercise testing before and after treatment, with greater improvement in  $pV_{O_2}$  for the sildenafil group. Sildenafil reduced PVR and increased cardiac output with exercise without altering pulmonary capillary wedge or mean arterial pressure, heart rate, or systemic vascular resistance. The ability of sildenafil to augment  $pV_{O_2}$  correlated directly with baseline resting PVR and indirectly with baseline resting right ventricular ejection fraction (RVEF). Sildenafil also improved 6-min walk distance and Minnesota Living with Heart Failure score. The sildenafil cohort experienced fewer HF hospitalizations but had a higher incidence of headache without incurring other serious adverse events. Thus, phosphodiesterase 5

inhibition with sildenafil may improve exercise capacity and quality of life in patients with systolic HF with secondary PH [80].

## Antiarrhythmic Therapy

Despite a steady decline in the risk of death from pump failure, many patients remain at high risk for sudden cardiac death (SCD). It accounts for one third to one half of the deaths in patients with HF [81]. Severity of HF is associated with higher overall mortality and higher rate of SCD [72]. Patients with HF are at risk of ventricular arrhythmias, ranging from asymptomatic ventricular premature beats to sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), which can develop into malignant form and can lead to SCD. Some studies have shown arrhythmias not to be the only cause of SCD [82]. Regardless, prevention of arrhythmias remains the key strategy for reducing the risk of SCD.

Most clinical trials of implantable cardioverter/defibrillator (ICD) therapy have demonstrated the superiority of ICD to conventional medical therapy in reducing overall mortality. Most of the antiarrhythmic medications, along with their antiarrhythmic effect, are associated with pro-arrhythmic effects limiting their use as an adjunct to the ICD therapy. Currently, the only antiarrhythmics considered safe for use in HF patients with ventricular arrhythmias are amiodarone and dofetilide. Early trials with amiodarone including the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA) trial [83] found a significant benefit to mortality and SCD, while the Veterans Affairs Congestive HF Survival Trial of Antiarrhythmic Therapy (CHF-STAT) trial [84] found no benefit in terms of mortality or SCD. Thus, amiodarone is not routinely used in the absence of significant arrhythmias. Other studies have demonstrated increased mortality with sotalol [85] and dronedarone [86] in HF-REF. Radiofrequency ablation and surgical options can also be considered in selected patient populations. In patients with prior MI, the border zone of the infarct is frequently the site of the reentrant circuit, and these sites are often amenable to ablation.

Since most HF patients receive  $\beta$ -blocker therapy, some studies have shown that using  $\beta$ -adrenergic blockers in patients with reduced systolic function and HF symptoms leads to significant reductions in overall mortality rates, which is in part related to reduced SCD. The reduced rate of SCD was 3.9 % versus 6.6 % in MERIT-HF [72] and 3.6 % versus 6.3 % in CIBIS-II [73].

## Implantable Cardioverter/Defibrillator

Because of the survival benefit of ICDs as compared with medical therapy, ICDs are the treatment of choice for the primary and secondary prevention of malignant arrhythmias which lead to SCD.

### Secondary Prevention

Based on the results of three major clinical trials: Cardiac Arrest Study Hamburg (CASH) [87], Canadian Implantable Defibrillator Study (CIDS) [88], and The Antiarrhythmics Versus Implantable Defibrillators (AVID) [89], which compared ICD to pharmacologic therapy in SCD survivors and other high-risk patients with sustained VT, patients who have survived SCD or had sustained VT are recommended to get an ICD because of their high risk for the development of malignant arrhythmia and SCD. Similarly, all patients who have syncope with either spontaneous or induced sustained VT also should get an ICD. It is unclear whether all patients with unexplained syncope should undergo ICD placement. According to the Heart Rhythm Society guidelines, ICD implantation is recommended if there is significant LV dysfunction due to non-ischemic cardiomyopathy in patients with unexplained syncope [90]. On the other hand, patients with ischemic cardiomyopathy and LV dysfunction (LVEF  $\leq 30$  %) qualify for an ICD even in the absence of syncope [91].

### Primary Prevention

In asymptomatic patients, there is a mortality benefit with prophylactic use of ICD therapy. Multicenter Automatic Defibrillator Implantation

Trial (MADIT) I was the first trial to show that an ICD has a role in primary prevention of SCD. However, the trial enrolled a subselective cohort of patients with prior MI, nonsustained VT, LVEF  $\leq 35$  %, and inducible sustained monomorphic VT [91]. The Multicenter Unsustained Tachycardia Trial (MUSTT) trial showed that patients with prior MI, asymptomatic nonsustained VT, LVEF  $\leq 40$  %, and inducible sustained VT had reduced sudden cardiac death with ICD implantation for primary prevention [92]. MADIT II was subsequently carried out to expand the population compared to earlier studies, enrolling patients with LVEF  $\leq 30$  % more than 30 days post-MI. Unlike the earlier studies, electrophysiologic testing and presence of nonsustained VT were not required for enrollment. Patients were randomized to ICD or medical therapy, with the trial terminated early due to significant reduction in all-cause mortality for the ICD cohort, due to reduction in sudden cardiac death [93].

The Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial included all HF patients with LVEF  $\leq 35$  % and NYHA class II–III, regardless of ischemic or non-ischemic etiology. Patients were randomized to either ICD implantation, amiodarone, or placebo. At 5 years, mortality was significantly improved with ICD therapy in both ischemic and non-ischemic cardiomyopathy. Amiodarone had no impact on survival [94]. The decision to use ICD therapy in asymptomatic patients with non-ischemic cardiomyopathy can be challenging. Different risk prediction methods (e.g., microvolt T-wave alternans) [95] have been used to predict the risk of arrhythmia, without the identification of any clear risk stratifiers. Some patients might die because of arrhythmia despite ICD therapy, which may be related to heart failure severity or frequency of appropriate and inappropriate shocks received from ICD versus no shocks, as was demonstrated from the SCD-HeFT trial results [96].

The most recent AHA/ACC guidelines [97] for primary prevention with ICD recommend implantation for (1) LVEF  $\leq 35$  % due to prior MI, who are at least 40 days post-MI and NYHA class II–III; (2) LVEF  $\leq 35$  % in non-ischemic dilated cardiomyopathy who are NYHA class

II–III; (3) LVEF  $\leq 30\%$  due to prior MI, who are at least 40 days post-MI and NYHA class I; and (4) LVEF  $\leq 40\%$  due to prior MI, with nonsustained VT and inducible VF or VT at electrophysiological study.

### Cardiac Resynchronization Therapy (CRT)

A growing body of evidence suggests that the use of implantable devices to resynchronize ventricular contraction may be a beneficial adjunct in the treatment of chronic heart failure. One third of patients with chronic heart failure have electrocardiographic evidence of a major intraventricular conduction delay, which may worsen left ventricular systolic dysfunction through asynchronous ventricular contraction. Uncontrolled studies suggest that multisite biventricular pacing improves hemodynamics and well-being by reducing ventricular asynchrony.

The Multisite Stimulation in Cardiomyopathies (MUSTIC) trial showed that CRT in NYHA class III HF-REF patients with QRS  $\geq 150$  ms resulted in improvement in 6-min walk distance, quality of life, and  $p\text{VO}_2$ , with reduced hospitalizations [98]. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, patients with NYHA class III–IV HF from either ischemic or non-ischemic cardiomyopathy, LVEF  $\leq 35\%$ , LVEDD  $\geq 55$  mm, and QRS duration of  $\geq 130$  ms were randomized to CRT or conventional therapy. Patients randomized to CRT had an improvement in 6-min walk distance, quality of life, functional class, time on treadmill during exercise testing, and ejection fraction. Further, CRT reduced hospitalization compared to control [99]. The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial randomized NYHA class III–IV patients with LVEF  $\leq 35\%$  and QRS  $\geq 120$  ms to receive optimal pharmacologic therapy (diuretics, ACE-I,  $\beta$ -blockers, and spironolactone) alone or in combination with CRT with either a pacemaker or a pacemaker-defibrillator. CRT with either pacemaker or pacemaker-defibrillator resulted in reduction of the primary end point of time to all-cause mortality or

hospitalization by 34% and 40%, respectively, when compared to pharmacologic-only therapy. The authors concluded that CRT decreases the combined risk of death from any cause or first hospitalization and, when combined with an ICD, significantly reduces mortality [100]. The Cardiac Resynchronization Heart Failure (CARE-HF) study randomized patients with NYHA class III–IV HF, LVEF  $\leq 35\%$ , and cardiac dyssynchrony to CRT or standard pharmacologic therapy. CRT reduced time to all-cause mortality or cardiovascular hospitalization [37], with reduction in mortality that persisted to an extended follow-up of 38 months [101]. Further, CRT reduced the interventricular mechanical delay, the end-systolic volume index, and the area of the mitral regurgitant jet; increased the LVEF; and improved symptoms and the quality of life. The authors concluded that in patients with heart failure and cardiac dyssynchrony, cardiac resynchronization improves symptoms and the quality of life as well as reducing complications and the risk of death. The beneficial effects of CRT in this group of patients were impressive, considering that these patients were receiving optimal medical therapy with diuretics,  $\beta$ -blockers, spironolactone, ACE-I, or ARB at the time of enrollment. The results showed that for every nine devices implanted, one death and three hospital stays were prevented [37].

Other studies have explored the use of CRT in patients with milder HF symptoms. Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) demonstrated that in NYHA class I–II symptoms with LVEF  $\leq 40\%$  and QRS  $\geq 120$  ms, CRT resulted in a reduction in HF hospitalization, with improvement of ventricular structure and function. However, the REVERSE study did not examine the impact of CRT on mortality in these patients with milder HF symptoms [102]. The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) randomized patients with NYHA class II–III HF, with LVEF  $\leq 30\%$ , intrinsic QRS  $\geq 120$  ms, or paced QRS  $\geq 200$  ms to ICD alone compared to ICD plus CRT. With CRT, there was a reduction in a combined end point all-cause mortality or HF hospitalization. Independently, there was a reduction in mortality alone. However, there was

increased rate of device-related complications in the CRT cohort [103]. The recent MADIT-CRT trial explored the use of CRT in patients with NYHA class I–II HF, LVEF  $\leq 30\%$ , and QRS  $\geq 130$  ms, showing a reduction in a composite of all-cause mortality and nonfatal HF event, but was predominantly driven by a 41% reduction in risk of HF events. There was no difference in risk of death alone [104]. The 2012 AHA/ACC class I recommendation for CRT includes patients with LVEF  $\leq 35\%$ , sinus rhythm, left bundle branch block (LBBB) morphology with QRS  $\geq 150$  ms, and NYHA class II–IV symptoms. Class IIa indications include expanded criteria including LBBB with QRS duration of 120–149 ms, non-LBBB with QRS  $\geq 150$  ms, and in patients with atrial fibrillation if they require ventricular pacing [105].

After CRT implantation, optimization may be considered. Mullens and colleagues evaluated 75 ambulatory patients with CRT with persistent advanced HF symptoms and/or adverse reverse remodeling referred for CRT optimization. Eighty-eight percent of patients had significantly better echocardiographic indexes of LV filling and LV ejection with optimal setting of their CRT compared with VVI (ventricular pacing, ventricular sensing, inhibition) setting. Most patients had identifiable reasons for suboptimal response, including inadequate device settings (47%), suboptimal medical treatment (32%), arrhythmias (32%), inappropriate lead position (21%), or lack of baseline dyssynchrony (9%). Device settings or therapies were modified in 74% of cases, with a decrease in adverse events [106].

Other studies have sought to determine the effects of CRT on quality of life (QoL). CARE-HF showed that CRT improved QoL (measured with European Quality of Life-5 Dimensions and Minnesota Living with Heart Failure questionnaires) at each timepoint of 3 months, 18 months, and study-end with median follow-up of 29.6 months, mostly due to improved physical functioning. Thus, CRT improves QoL with sustained effects [107].

Further studies have examined the impact of CRT on patients with narrower QRS than the standard criteria. The evaluation of CRT in narrow QRS

patients with mechanical dyssynchrony from a multicenter study (ESTEEM-CRT) trial evaluated CRT in patients with QRS  $\leq 120$  ms, NYHA class III, LVEF  $\leq 35\%$ , and mechanical dyssynchrony (standard deviation of time to peak velocity of 12 segments more than 28.7 ms) as a multicenter, non-randomized, unblinded feasibility trial to determine the effects CRT in this population. Patients with CRT had improvement in QoL and NYHA functional class at 6 months. There was no improvement in  $p\text{VO}_2$ , LVEF, left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV). Mechanical dyssynchrony remained unchanged [108]. One important limitation of this study was the nonblinded single arm design, suggesting that symptom improvement may have been related to a placebo effect.

The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) study sought to determine if CRT benefits individuals with QRS  $\leq 130$  ms. They randomized 172 NYHA class III HF patients with LVEF  $\leq 35\%$ , QRS  $\leq 130$  ms, and evidence of mechanical dyssynchrony on echocardiography undergoing ICD to either CRT or no CRT, with a primary end point of increase in  $p\text{VO}_2$  of 1.0 cc/kg/min by cardiopulmonary testing at 6 months. They found that there was no difference with CRT in the total cohort. In a subcohort of individuals with QRS  $\geq 120$  ms, there was apparent benefit with CRT. CRT does not appear to result in improvement in  $p\text{VO}_2$  in HF patients with narrow QRS intervals [109]. It is estimated, however, that approximately 15% of patients with CHF meet the current indications for CRT. Moreover, clinical trials have demonstrated that approximately 30–40% of these patients are considered nonresponders clinically or based on echocardiographic remodeling [110]. Therefore, the actual number of patients who benefit from CRT is quite small relative to that of the entire CHF patient population.

ESTEEM-CRT and RethinQ suggest that perhaps echocardiographic tissue Doppler failed to identify patients who would respond to CRT with a narrow QRS and mechanical dyssynchrony or that this patient population does not actually benefit from CRT. Interestingly, when baseline

characteristics are compared between the ESTEEM-CRT and RethinQ patient populations, it is evident that the patients in the RethinQ study appeared to be more sick with a lower baseline peak  $\text{VO}_2$  and larger LVESV and LVEDV. In addition, there was a higher percentage of non-ischemic patients in the RethinQ patient population as compared with that of the ESTEEM-CRT. Regardless, neither trial identified patients with a narrow QRS and echocardiographic evidence of dyssynchrony who benefited from CRT. In light of these data, the question remains whether or not tissue Doppler is the appropriate diagnostic tool for identifying dyssynchrony in this patient population or whether it is a technology searching for an application. It has been suggested that “Until other technologies for evaluating mechanical dyssynchrony emerge and demonstrate efficacy in large-scale randomized clinical trials, patients with narrow QRS should not receive CRT” [111].

## Surgical Management of Heart Failure

### Coronary Revascularization Therapy

High-risk revascularization may constitute the treatment of choice in the subgroup of advanced HF patients with ischemic cardiomyopathy, LVEF  $\leq 35\%$ , viable myocardium, and vessels suitable for grafting. Different trials have suggested the benefit of revascularization in advanced heart failure if angina [112–117] is present. There are several key questions in the management of patients with symptomatic heart failure, left ventricular dysfunction, and coronary artery disease (CAD) amenable to coronary artery bypass grafting (CABG):

- Does surgical coronary revascularization in addition to aggressive medical management confer long-term mortality, morbidity, QoL, or cost benefit beyond aggressive medical management alone?
- Does surgical ventricular shape restoration in combination with CABG improve outcome compared to coronary revascularization alone and medical therapy alone [118]?

To assess the effect of CABG on future risk of death in patients with HF-REF, mortality and modes of death in 5,410 patients with ischemic LV dysfunction from the Studies of Left Ventricular Dysfunction (SOLVD) trials were retrospectively evaluated. Outcomes of patients with and without prior CABG were compared, and stratification by baseline LVEF ( $\leq 0.25$ ,  $0.25-0.30$ , and  $\geq 0.30\%$ ) was performed. Prior CABG was associated with a 25% reduction in risk of death and a 46% reduction in risk of sudden death independent of LVEF and severity of symptoms [119]. The Veteran Affairs Cooperative Study of Surgery and the Coronary Artery Surgery Study (CASS) confirmed these findings, showing a higher survival rate in HF-REF after CABG compared to medical therapy [120]. The benefits appear to be transient and last shorter than 11 years, with benefit diminished after graft closure. Low-risk patients had no survival benefit with CABG [121].

The Surgical Treatment of Ischemic Heart Failure (STICH) trial was an international randomized controlled clinical trial evaluating the use of CABG on heart failure patients with CAD [122]. In the primary study, 1,212 patients with LVEF  $\leq 35\%$  were randomized to CABG compared to medical therapy alone. Over a median follow-up of 56 months, there was no significant difference between CABG compared to medical therapy alone for all-cause mortality (HR 0.86, 95% CI: 0.72–1.04,  $p=0.12$ ). Secondary outcomes appeared to favor CABG compared to medical therapy alone, including cardiovascular mortality. There was significant crossover of the study groups, with 17% of the medical group receiving CABG and 9% of patients assigned to CABG not undergoing surgery. An as-treated analysis showed an apparent benefit of CABG compared to medical therapy alone at 1 year ( $p \leq 0.001$ ) [122].

Recent studies have confirmed that CABG on patients with severely depressed LVEF gave a satisfactory survival rate, approaching that of cardiac transplantation. Selection of patients for high-risk myocardial revascularization involves considerations about potential systemic comorbidities like chronic pulmonary disease, renal



failure requiring dialysis, cancer, or severe advanced diabetes. Myocardial dysfunction in patients with ischemic cardiomyopathy may be due to impaired blood flow leading to oxygen supply/demand imbalance. This condition can result in myocardial stunning and/or hibernation (which may be reversible after CABG) or scarring. Myocardial stunning follows an acute episode of cardiac ischemia and leads to reversible reduced systolic and diastolic function. Hibernation was described in the late 1980s, and is characterized by decreased myocardial function concomitant with a reduction in blood supply. The identification of viable myocardium usually allows confirmation of contractile reserve, preserved metabolic activity, and myocyte membrane integrity and is associated with convincing improvements in left ventricular function after coronary revascularization. The techniques employed to identify the presence of hibernation include positron emission tomography (PET) with fluorodeoxyglucose (FDG), which is limited by its high costs and availability. Myocardial viability can be demonstrated by dobutamine stress echocardiography and by its predictive biphasic response, characterized by an initial improvement in myocardial contractility at low doses of dobutamine infusion, followed by a decrease at high doses. Nevertheless, the most promising imaging technique seems to be magnetic resonance with gadolinium enhancement because it can reveal scar or viable muscle. Both hibernating and stunned myocardium contribute to progressive systolic dysfunction, remodeling, and the development of HF. Rahimtoola et al. [123] have recently suggested a unifying concept of hibernation and remodeling with emphasis on the importance of early revascularization. In fact, remodeling appears to progress over time, and the ability to reverse the process may be time-sensitive [124].

It has long been suggested that if no viable myocardium is present, the prospect of improvement with revascularization is reduced and, thus, cardiac transplantation should be considered for appropriate candidates [125–128]. Recently, a substudy from the STICH trial assessed the impact of myocardial viability on outcomes after CABG versus medical therapy for ischemic heart disease

in 601 HF-REF patients who underwent viability testing with either single photon emission computed tomography (SPECT) or dobutamine echocardiography at the discretion of the recruiting investigators. It demonstrated that viability at baseline did not appear to be associated with all-cause mortality over 5 years and had no interaction with the effectiveness of CABG or medical therapy. The presence of viability did not identify patients with differential survival from CABG compared to medical therapy [129]. The STICH viability substudy must be interpreted with caution due to the loss of true randomization as a sub-cohort and the fact that the main STICH study had a negative end point, making any further analyses exploratory. Also, the interpretation may either be that viability is not associated with improved survival after CABG but can also be viewed that the lack of viability should not exclude CABG.

### **Mitral Valve Repair**

Severe mitral regurgitation (MR) is a frequent complication of end-stage cardiomyopathy that contributes to HF and predicts a poor survival. A group at University of Michigan, Ann Arbor, studied the intermediate-term outcome of mitral reconstruction in 48 NYHA class III–IV patients with severe 4+ mitral regurgitation (LVEF  $16\% \pm 3\%$ ) who underwent annuloplasty with improvement to mild MR in 7 and no MR in 41 patients. One- and two-year actuarial survivals were 82% and 71%. HF hospitalizations post-MR repair decreased, NYHA functional class improved, and LV volume and sphericity decreased, while LVEF and cardiac output increased [130]. Another group explored the outcomes in a series of 40 patients with LVEF  $\leq 35\%$  and moderate to severe secondary MR who underwent mitral valve replacement or repair. They found that at mean follow-up of 50+34 months, patients had improved NYHA class and improved LVEF, without any difference in survival after mitral valve repair or replacement and with no difference in mortality compared to age- and period-matched controls who underwent cardiac transplantation instead [131].

## Ventricular Reconstruction

There has been significant interest in ventricular reconstruction, with the theory that improving LV geometry will theoretically improve function and may translate to better outcomes. Surgical anterior ventricular endocardial restoration (SAVER) involves the exclusion of noncontracting segments in the dilated remodeled LV after anterior myocardial infarction. An international study was performed, with 439 patients undergoing SAVER and followed for 18 months. Concomitant procedures included CABG in 89 %, mitral valve repair in 22 %, and mitral valve replacement in 4 % of patients. After SAVER, there was improvement in LVEF and reduction in LV end-systolic volume index. In-hospital mortality was 6.6 %, with 18-month survival of 84 % in the total cohort [132].

A study at the Cleveland Clinic followed the echocardiographic changes and functional outcome from mitral valve repair combined with partial left ventriculectomy (the Batista procedure) in 57 patients, primarily (95 %) transplant candidates with idiopathic dilated cardiomyopathy. Forty percent of patients were hospitalized on inotropes, with all patients previously NYHA class IV (36.8 % improved to class III by time of surgery). At 3 months, there was improvement in LV end-diastolic diameter (from  $8.1 \pm 1.0$  cm to  $6.3 \pm 0.9$  cm), LVEF (from  $13.6 \pm 6$  % to  $23 \pm 7.7$  %), improvement in NYHA functional class, and improved  $p\text{VO}_2$ . Actuarial survival at 1 year was 82.1 %, and freedom from death, relisting for transplantation, and need for LVAD support was 58 % [133].

The Reconstructive Endoventricular Surgery Returning Torsion Original Radius Elliptical Shape (RESTORE) to the LV study tested how surgical ventricular restoration affects early and late survival in a registry of 1,198 post-anterior infarction HF patients with LVEF  $\leq 35$  % between 1998 and 2003. Concomitant procedures included CABG in 95 %, mitral valve repair in 22 %, and mitral valve replacement in 1 %. LVEF improved from  $29.6 \pm 11.0$  % preoperatively to  $39.5 \pm 12.3$  % postoperatively ( $p \leq 0.001$ ), and NYHA functional class also improved in the majority of

patients. Overall 30-day survival was 94.7 %, and 5-year survival was 68.6 %. Based on these results, it was felt that surgical ventricular restoration improves LV function [134].

In a substudy of the previously mentioned STICH trial, the use of surgical ventricular reconstruction in addition to CABG compared to CABG alone was examined [135]. They found that patients undergoing CABG with surgical ventricular reconstruction had a reduction in 19 % of end-systolic volume index, while those undergoing CABG alone had a decrease of 6 % in end-systolic volume index ( $p < 0.001$ ). However, there was no significant difference in the primary outcome of all-cause mortality or cardiac hospitalization ( $p = 0.90$ ). Symptoms of patients in each treatment arm were followed, and patients in both groups had improvement of 1.7 CCS angina class ( $p = 0.84$ ) and approximately 1 NYHA HF class ( $p = 0.70$ ). There was also no significant difference in median distance by 6-min walk test ( $p = 0.80$ ). Thus, even though surgical vascular reconstruction appeared to reduce LV volume, this did not translate to clinically meaningful outcomes [135].

## Mechanical Circulatory Support Device Implantation

Recompensation after development of advanced HF includes appropriate neurohormonal blockade. Specifically, targets include the adrenergic system, RAAS, antidiuretic hormone system, and the atrial natriuretic peptide system, which are chronically activated in increasing stages of advanced heart failure. If a patient is deemed unsuccessfully recompensated despite maximal tolerated medical therapy, revascularization, and CRT, then one needs to risk stratify the patient for possible urgent heart transplant or MCS.

Risk stratification of patients with end-stage congestive heart failure is a critical component of the selection process in identifying the best treatment for a given patient. For example, for patients with refractory HF, the choice between optimal medical therapy, heart transplantation, and chronic mechanical circulatory support has to be

made. Accurate identification of individuals most likely to survive without a transplant would facilitate more efficient use of scarce donor organs.

Advanced heart failure therapy with MCS/D is currently being practiced in approximately 200 selected hospitals out of  $\geq 3,000$  in the USA alone. In order to provide equitable and high-quality access to MCS/D therapy, a referral network has to be in place. This network requires a structure similar to the referral network for heart transplantation and includes the local general practitioner, internist and cardiologist, the local and regional hospital, and the tertiary care center. The referral is often initiated by the local or regional colleagues who are taking care of a patient at a stage of the advanced heart failure syndrome that is not sufficiently responsive to medical therapy. Upon contacting the tertiary care center, patient history information is shared between the two hospitals. If the patient is deemed to likely benefit from evaluation for mechanical circulatory support, the transfer is initiated.

### **Advanced Heart Failure Transfer Decision Making**

The decision of a local center to ask for transfer of a patient to a center providing MCS/D therapy or cardiac transplant is followed by an evaluation and decision of the accepting MCS/D/cardiac transplant center. This evaluation is critically important. A transfer is in the interest of a patient who has a higher chance of longevity and good quality of life with more advanced therapies but not for a patient who is either too well or too ill for these potential options.

### **Tertiary Center Outreach Team**

The MCS/D/cardiac transplant center may organize an outreach team on call. This team can perform the evaluation in the transfer-requesting hospital. This approach is advantageous for (1) the patient (minimizing unnecessary transfers), (2) the transferring hospital (maximizing educational decision-making experience), and (3) the MCS/D/cardiac transplant center (minimizing medically unnecessary resource consumption and maximizing networking in the region).

### **Decision-Making Algorithm**

The decision-making algorithm is initiated when the patient is referred for evaluation into an established MCS/D/cardiac transplant center [136–139]. Referral takes place to a designated center when the treating cardiologist or internist has exhausted all lifestyle and medical options without success in the setting of decompensation and progression of advanced heart failure (AHF), a phase known to be associated with a high risk of death. Anytime during management, if a patient is felt to be too end stage to benefit from any of the modern therapies because of multiorgan failure or other comorbidities, there should be ongoing discussions regarding comfort care as a way to facilitate a humane form of death instead of prolongation of suffering [13, 14]. A structured management algorithm should be applied to recompensate the patient and initiate neurohormonal blockade and lifestyle changes, or if recompensation cannot be achieved and the patient is not a suitable candidate for cardiac transplantation, destination MCS/D therapy should be considered. In 2005, the International Society Heart Lung Transplantation (ISHLT) organized a consensus conference to provide clinical evidence and expert opinion and experience-based guidelines for consideration of MCS/D implantation [26]. More recently in 2013, ISHLT released an executive summary for the use of mechanical circulatory support devices [140]. Care must be taken in MCS/D-centers to adhere to evidence-based destination-MCS/D-implantation guidelines and not to inadvertently drift to other patient-selection criteria, either patients who are less sick or patients who are sicker than the original Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) cohort and therefore would have a survival/QoL benefit that would be difficult to predict [6] (see Fig. 2.2).

### **Patient Selection for MCS/D**

Despite the potential for explosive growth for MCS/D in the future with the aging population, there are no definitive patient-selection criteria for ventricular assist device (VAD) use. Patient

selection must take into account the (1) appropriateness for device therapy based on patient condition and (2) risk to the patient.

The landmark REMATCH trial randomized patients with NYHA class IV HF on maximal medical therapy for 90 days, LVEF  $\leq 25\%$ , and with  $pVO_2 \leq 12$  mL/kg/min (later expanded to 14) who were ineligible for cardiac transplantation to a pulsatile, first-generation LVAD compared to optimal medical management. LVAD implantation significantly improved survival compared to medical therapy (relative risk 0.52 with 95% confidence interval of 0.34–0.78;  $p=0.001$ ). Quality of life was also improved in the LVAD group [141].

Given this clear benefit in the selective REMATCH cohort, it could be suggested that this population should be eligible for LVAD. However, this excludes a large proportion of patients with advanced HF, including those who are functionally better than NYHA class IV, LVEF better than 25%, or who are not yet excluded from transplant candidacy. Despite this gap, no consensus guidelines for MCS or VAD candidacy have been established [142]. Rather, patients continue to be evaluated for VAD implantation across most centers in the USA on a case-by-case basis. Typical inclusion criteria include patients unable to be weaned from inotropic support, who develop intolerance to medical therapies, have poor functional capacity, and cannot be restored to a reasonable NYHA class despite maximal medical therapy.

More recent studies with MCS have been aimed at newer generations of VAD and development of the total artificial heart (TAH). For example, it was demonstrated that the Heartmate II (Thoratec Corporation, Pleasanton, CA), a second-generation continuous-flow VAD, can be successfully utilized for hemodynamic support as a bridge to cardiac transplantation [143] and that it appears to improve survival free from disabling stroke and reoperation, as well as actuarial survival rates, at 2 years as compared to the first-generation pulsatile devices [144]. It has also been demonstrated that TAH may be a viable alternative to patients as a bridge to transplant in critically ill patients with biventricular failure [145].

The centers for Medicare and Medicaid services (CMS) have requirements in place for reimbursement for MCS. However, criteria for VAD use in the post-cardiotomy setting or as bridge to cardiac transplantation are not well defined. For destination therapy, current CMS criteria mirror the inclusion criteria from the REMATCH trial [81]. A recent review by Wilson et al. tackles this problem and includes an extensive list of indications, relative contraindications, and absolute contraindications to VAD implantation [142]. The recommendations incorporate a combination of REMATCH inclusion criteria, CMS reimbursement requirements, case series, anecdotal reports, published literature, and experience from general clinical practice.

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## Heart Transplantation

Based on the initial evaluation and failure of re-optimization measures, a patient may be designated as a “potential transplant candidate,” who could be placed on a national “potential transplant candidate list.” This algorithm combines the psychological benefit for the patient of being accepted by the program with an ongoing openness to a diversity of advanced HF treatment modalities, not committing to transplantation as the only therapeutic option. If the initial evaluation reveals hemodynamic instability and therefore cardiac transplant evaluation and listing is completed, follow-up may still lead to stabilization without transplantation enabling delisting in individual cases.

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