Optimal Pharmacologic and Non-pharmacologic Management of Cardiac Transplant Candidates: Approaches to Be Considered Prior to Transplant Evaluation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006

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1. OPTIMAL PHARMACOLOGIC AND NON-PHARMACOLOGIC MANAGEMENT OF CARDIAC TRANSPLANT CANDIDATES

Recommendations for Pharmacologic Management of Patients With Compensated Heart Failure

Class I:

1. In patients with severe heart failure and fluid retention, loop diuretics should be used and adjusted to achieve symptom control and/or euvolemia (*Level of Evidence: C*).
2. In cases of diuretic resistance, precipitating factors or alternative causes of fluid retention should be investigated and excluded (Table 1) (*Level of Evidence: C*).
3. Diuretic resistance should be treated with an increase in dose or frequency of loop diuretics, change to a loop diuretic with better bioavailability, addition of a thiazide diuretic, or intravenous administration (bolus or continuous infusion) of a loop diuretic (*Level of Evidence: C*).
4. All neurohormonal antagonists used in the management of patients with heart failure with low left ventricular ejection fraction (LVEF) should be those shown to be effective in clinical trials and they should be used at maximally tolerated or target dosages (Table 2) (*Level of Evidence: A*).
5. All patients with heart failure and low LVEF should have a trial of angiotensin-converting enzyme (ACE) inhibitors unless there are unequivocal contraindications (*Level of Evidence: A*).
6. Angiotensin receptor blockers (ARBs) should be used as an alternative to ACE inhibitors in patients who cannot tolerate ACE inhibitors due to cough or angioedema (*Level of Evidence: A*).
7. All patients with heart failure and low LVEF should have a trial of β-blockers unless there are unequivocal contraindications (*Level of Evidence: A*).
8. In patients with atrial fibrillation, control of the heart rate should be done and conversion may be performed (*Level of Evidence: C*).
9. Patients with heart failure and low LVEF should be anti-coagulated with warfarin if they have a history of an embolic event, atrial fibrillation or evidence of a new left ventricular (LV) thrombus (*Level of Evidence: A*).
10. In carefully selected advanced heart failure patients with low LVEF, aldosterone antagonists should be added to maximally tolerated ACE inhibitors and β-blockers. However, this approach requires frequent monitoring of serum potassium and renal function (*Level of Evidence: B*).

Class IIa:

1. In patients with pre–renal azotemia or fluid retention resistant to diuretic therapy, it is reasonable to use hemofiltration or dialysis (*Level of Evidence: C*).
2. In heart failure patients with low LVEF, it is reasonable to add ARBs to the combination of maximally tolerated ACE inhibitors and β-blockers (*Level of Evidence: B*).
3. In heart failure patients with low LVEF, it is reasonable to continue maximal ARB therapy rather than changing to an ACE inhibitor (*Level of Evidence: C*).
4. In patients with heart failure and low LVEF, it is reasonable to consider a combination of hydralazine and nitrates when progressive renal dysfunc-

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Table 1. Precipitating Factors or Alternative Causes of Edema in Heart Failure

- Non-compliance with diuretic (and other) medication
- Non-compliance with salt and fluid restriction
- Non-steroidal anti-inflammatory drug usage
- Glitazones
- Intrinsic renal disease
- Hypoproteinemia
- Calcium channel antagonists
- Acute impairment of left ventricular function (new-onset ischemia, arrhythmias such as atrial fibrillation)

Adapted with permission from Nieminen et al.[1]

tion or hyperkalemia limits therapy with an ACE inhibitor (ACEI) or ARB (*Level of Evidence: C*).

5. In patients with heart failure and low LVEF, it is reasonable to consider the addition of a hydralazine and nitrate combination or nitrates alone for patients with persistent symptoms despite recommended therapy with neurohormonal antagonists and diuretics for fluid retention (*Level of Evidence: B*).
6. In patients with persistent, severe heart failure and low LVEF, who are on maximal therapy with ACEIs, β-blockers and diuretics, it is reasonable to use digoxin therapy to reduce symptoms, decrease hospitalizations, or control heart rate in atrial fibrillation. Drug-level monitoring is strongly recommended. Target trough levels should be <1.0 ng/ml (*Level of Evidence: C*).

Recommendations for Non-pharmacologic Management of Patients With Compensated Heart Failure

Class I:

1. In heart failure patients with fluid retention, salt and fluid intake should be restricted (*Level of Evidence: C*).
2. In addition to optimal medical therapy, regular exercise should be advised in patients with chronic stable heart failure to improve functional capacity (*Level of Evidence: A*).
3. Patients with advanced heart failure should be cared for by a multidisciplinary team, and seen at regular intervals (*Level of Evidence: A*).
4. Right heart catheterization should be performed to assess pulmonary vascular resistance (PVR) in heart transplant candidates (*Level of Evidence: B*).
5. Hemodynamic assessment using an indwelling pulmonary catheter should be used for assessment and management in patients with cardiogenic shock (*Level of Evidence: C*).
6. Patients with heart failure should be approached regarding their wishes for resuscitative care and their wishes should be documented in a living will or other advanced medical directive (*Level of Evidence: C*).

Class IIa:

1. It is reasonable to consider a formal sleep evaluation for all patients with a history suggestive of sleep apnea prior to consideration of cardiac transplantation (*Level of Evidence: C*).
2. In patients with ischemic heart failure and low LVEF, it is reasonable to consider coronary artery bypass grafting (CABG) (*Level of Evidence: C*).
3. It is reasonable to use brain natriuretic peptide (BNP) or N-terminal pro–B-type (NT-pro-BNP) levels and trends over time in the management of patients with heart failure (*Level of Evidence: B*).
4. Short-term hemodynamic monitoring with a pulmonary artery catheter may be used to assess and manage patients with advanced heart failure (*Level of Evidence: B*).

Table 2. Standard Drugs That Antagonize the Neurohormonal Systems

Drug	Class	Starting dose	Target dose from clinical trial
Captopril	ACE inhibitor	6.25–12.5 mg tid	50 mg tid
Enalapril	ACE inhibitor	2.5–5 mg bid	10–20 mg bid
Ramipril	ACE inhibitor	2.5 mg bid	5 mg bid
Trandolapril	ACE inhibitor	1 mg qd	4 mg qd
Carvedilol	α_1 non-selective β-blocker, anti-oxidant properties	3.125 mg bid	25 mg bid (50 mg bid, if weight >85 kg [187 lb])
Metoprolol succinate	β_1-selective β-blocker	12.5–25 mg qd	200 mg qd
Bisoprolol	β_1-selective β-blocker	1.25 mg qd	10 mg qd
Candesartan	ARB	4–8 mg qd	32 mg qd
Losartan	ARB	12.5 mg qd	50 mg qd
Valsartan	ARB	20 mg bid	160 mg bid
Eplerenone	Selective aldosterone receptor blocker	25 mg qd	50 mg qd
Spironolactone	Aldosterone receptor blocker	12.5–25 mg qd	25–50 mg qd

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bid, twice daily; d, day; qd, once daily; tid, three times daily.

Class IIb:

1. In patients with heart failure and low LVEF, ventricular restoration surgery or mitral valve repair may be considered (*Level of Evidence: C*).

Class III:

1. Candidacy for transplantation must not be contingent upon clinical trial participation (*Level of Evidence: C*).

Recommendations for Management of Patients With Decompensated Heart Failure

Class I:

1. In patients with decompensated heart failure and adequate blood pressure, intravenous vasodilators should be considered before inotropic therapy (*Level of Evidence: C*).
2. In patients with decompensated heart failure and hypoperfusion in spite of adequate filling pressures, inotropic or pressor therapy should be used (*Level of Evidence: C*).
3. The need for continued inotropic therapy should be frequently re-assessed (*Level of Evidence: C*).
4. Long-term use of inotropic therapy should only be used as a pharmacologic bridge to transplantation or for palliation (*Level of Evidence: C*).
5. The use of vasoconstrictive agents should be reserved for those patients who are in refractory cardiogenic shock (*Level of Evidence: C*).

1.1. Diuretics

In chronic heart failure, neuroendocrine systems are activated to compensate for reduced perfusion of vital organs (e.g., activation of the sympathetic nervous system and renin–angiotensin–aldosterone system [RAAS] and secretion of vasopressin, cytokines and endothelin). Activation of these systems leads to fluid retention. Clinical correlates to fluid retention in heart failure are dyspnea and pulmonary edema (LV failure) as well as peripheral edema and ascites (right ventricular [RV] failure). Repeated decompensation or failure to control fluid retention are important symptomatic criteria for the decision to list a patient for heart transplantation.[1]

Measures to control or avoid fluid retention in patients with heart failure include fluid and salt intake restriction and the use of diuretic drugs. Fluid status should be monitored roughly by daily weights. Limited fluid intake (1.5 to 2 liters/day for severe heart failure) limits edema formation and avoids hyponatremia. Diuretic drugs improve dyspnea, exercise tolerance and cardiac performance by reducing LV filling pressures and decreasing dynamic mitral regurgitation. Insufficient diuresis may impair the efficacy of ACEIs. Excessive dehydration should be avoided because it may lead to hypotension, further activation of RAAS, and renal insufficiency. Thiazide diuretics, which block sodium and water re-absorption in the distal convoluted tubule, cause only mild water diuresis; their primary effect in heart failure is sodium excretion with a subsequent effect on hypertension.[1] Loop diuretics (furosemide, bumetanide or torsemide) inhibit sodium uptake in the ascending loop of Henle by blocking the sodium–potassium–chloride transporter. Loop diuretics are the most potent diuretics, have a short duration of action, and are used in the treatment of patients with chronic heart failure or an acute exacerbation of heart failure, as well as in the setting of renal failure in patients with heart failure. As diuretics may induce further activation of the RAAS, diuretics should always be combined with an ACEI or ARB.

In advanced stages of heart failure (New York Heart Association [NYHA] Class III or IV) diuretics form the mainstay of symptomatic therapy, affording unquestionable relief from dyspnea, peripheral edema and ascites. Although the effects of diuretics on symptom control are well established, the impact of diuretic therapy on prognosis (mortality) in heart failure is far less clear as large, placebo-controlled mortality trials have not been performed with diuretics. In the Torsemide in Congestive Heart Failure (TORIC) trial, a significant survival advantage was demonstrated for patients treated with torsemide vs furosemide, possibly due to additional anti-aldosterone action and better absorption of torsemide.[2]

In advanced heart failure, diuretic resistance, defined as failure to induce clinically sufficient diuresis even with large doses of loop diuretics, may develop. Diuretic resistance is associated with an adverse prognosis,[3] and it may be caused by delayed absorption of the diuretic, reduced secretion into the renal tubule, post-diuretic (rebound) salt retention, and compensatory hypertrophy of the distal tubule.[4] Management includes: exclusion of precipitating factors (Table 1); salt and volume restriction; increased dosing of diuretics; intravenous application of diuretic; combination therapy of loop diuretic with thiazide or metolazone[5,6]; and institution of inodilatory therapy with dopamine, dobutamine or milrinone.

Acute exacerbation of fluid retention represents the most common form of acute decompensation ("wet" decompensation) in patients with heart failure, leading to increased hospitalization, morbidity and cost. Diuretic resistance, further compromise of LV function, or intercurrent illness may represent precipitating factors. Rapid restoration of euvolemia, usually via intensified diuretic therapy, achieves symptomatic relief. In therapy-resistant cases hemofiltration or hemodialysis may be required.

1.2. Neurohormonal Antagonists

Activation of the RAAS and the adrenergic system has a pivotal role in the progression of heart failure.[7–9] These systems are activated by increased myocardial stretch and peripheral hypoperfusion and cause vasoconstriction, hydrosaline retention, myocardial hypertrophy and fibrosis, fetal gene expression and accelerated cell death. Their importance is shown by their independent prognostic value and, more importantly, by the beneficial effects of their long-term pharmacologic inhibition. Hence, the administration of neurohormonal antagonists is the basis of the current medical treatment of chronic heart failure.[10–12] The impact of neurohormonal antagonists on prognosis is so important that no patient should undergo heart transplantation if not previously treated with or shown to be intolerant of neurohormonal antagonists. As the beneficial effects of neurohormonal antagonists are progressive and may need at least 4 months to become significant,[7] it is recommended to wait for such a time interval, if possible, before making a decision regarding heart transplantation candidacy in a patient not previously treated.

It is also important to note that neurohormonal antagonists are not short-term life-saving agents. They are administered for their long-term beneficial effects on outcome. In the short term, their administration may be associated with worsening of symptoms and hemodynamic variables, so that their initiation may be poorly tolerated or even contraindicated in patients with unstable clinical conditions.[7,13–15]

1.2.1. Angiotensin-converting enzyme inhibitors. The main mechanisms of action of the ACEIs include inhibiting LV remodeling and myocardial dysfunction, as well as reducing ischemic events in patients with concomitant coronary artery disease (CAD). The beneficial effects of ACEIs on symptoms, hospitalization rate and mortality have been consistently shown in large, placebo-controlled, randomized trials.[16,17] These effects are independent from the baseline characteristics of the patients, except that they are of greater magnitude in patients with more severe LV dysfunction and symptoms.[12,16–17]

Patients with severe heart failure have a lower tolerance to ACEI administration. Lower cardiac output and peripheral hypoperfusion are associated with a greater activation of the RAAS, with a corresponding increased likelihood of renal failure and hypotension when this system is blocked.[14,18] However, a mild 10% to 20% increase in serum creatinine after the initiation of ACEI therapy should not be considered a contraindication to the continuation of treatment. Similarly, hypotension should be a contraindication to treatment only if symptomatic.[10,12,18–20]

Even if initiation and titration of ACEI therapy may be more difficult in patients with advanced heart failure, it must be pointed out that the beneficial effects of ACEIs on prognosis are similar in patients with renal failure[21] and greater in those with more severe heart failure.[8,17] Conversely, hemodynamic intolerance to ACEIs is associated with a worse prognosis.[22]

1.2.2. ARBs. ARBs block the effects of angiotensin II on Type I angiotensin II receptors. These receptors mediate most, if not all, of the untoward effects of angiotensin II. Thus, as opposed to ACEIs, their efficacy cannot be decreased by the activation of non–ACE-dependent angiotensin II synthetic pathways. Hence, ARBs provide a more effective blockade of the Type I angiotensin receptors. Unlike the ACEIs, ARBs do not increase kinin levels. This property accounts for the increased tolerability of ARBs (lack of kinin-mediated side effects), but it may also lower their efficacy, because kinins have been associated with beneficial effects such as peripheral vasodilation and inhibition of myocardial hypertrophy and fibrosis.[23,24] The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative Trial has shown that the administration of an ARB improves prognosis in those heart failure patients who are intolerant of an ACEI.[25] These data are consistent with previous studies in patients with chronic heart failure[26] or with post-infarction LV dysfunction or heart failure.[27]

The major trials addressing the issue of combined therapy with ARBs and ACEIs in heart failure have been the Valsartan Heart Failure Trial (Val-HeFT)[28] and CHARM.[29] In the Val-HeFT trial, the administration of valsartan to patients receiving ACEI therapy was associated with an 18.2% lower incidence of hospitalizations for heart failure; however, there was no effect on mortality. The CHARM-Added trial showed that the administration of candesartan to patients with severe heart failure (NYHA Class III or IV) or moderately symptomatic heart failure (NYHA Class II), but with a recent (<6 months) cardiovascular hospitalization, was associated with a reduction in the primary end-point (cardiovascular death or heart failure hospitalization) and a reduction in both cardiovascular death and heart failure hospitalizations. In contrast to the Val-HeFT trial, the beneficial effects of ARB use in the CHARM-Added trial were also observed in the patients on concomitant ACEI and β-blocker therapy. The differences between the two studies are likely influenced by the inclusion of patients with more advanced heart failure and poorer prognosis in the CHARM trial.

ARBs should be administered with the same precautions as ACEIs. They lack the kinin-mediated effects of ACEIs, but may cause renal failure and hypotension by the same mechanism as ACEIs.[10,12]

1.2.3. Aldosterone antagonists. In the Randomized Aldactone Evaluation Study (RALES), administration of spironolactone 25 to 50 mg/day was associated with a

35% reduction in mortality, a concomitant decrease in heart failure hospitalizations, and an improvement in symptoms.[30] The Eplerenone in Patients with Heart Failure Due to Systolic Dysfunction Complicating Acute Myocardial Infarction (EPHESUS) trial showed the beneficial effects of the selective aldosterone antagonist eplerenone in patients with recent myocardial infarction (MI) and LV dysfunction or heart failure.[31] Aldosterone antagonists should therefore be considered in all candidates for heart transplantation.

To minimize the risks of hyperkalemia and renal failure,[32] aldosterone antagonists are generally contraindicated in patients with renal insufficiency (serum creatinine >2.5 mg/dl) or hyperkalemia (serum potassium >5.5 mEq/liter). Careful and frequent monitoring of these laboratory evaluations is required after the initiation of an aldosterone antagonist, and then periodically, at least every 1 to 3 months.[10,12,33]

1.2.4. β-blockers. Large, randomized trials have consistently shown that β-blocker therapy is associated with a significant reduction in mortality and hospitalization rate. The magnitude of this effect is greater than that found in ACEI trials, with a 34% to 35% reduction in mortality, a 33% to 35% reduction in the heart failure hospitalization rate, and an 18% to 20% reduction in all-cause hospitalizations.[34–36] These beneficial effects have been observed in patients with more advanced heart failure[37–39] and become evident relatively early, 1 to 2 months after initiation of therapy, as soon as minimal effective doses of the β-blockers are reached.[39]

The incidence rates of worsening heart failure and intolerance to β-blocker administration are higher in patients with more severe heart failure.[40–42] However, these patients may benefit even more from β-blockade as they also have higher levels of cardiac sympathetic stimulation. Therefore, it is mandatory that β-blocker therapy be attempted even in patients with more advanced heart failure. Treatment should always be initiated at the lowest possible dose, with very slow and careful dose increases. The failing heart is critically dependent on adrenergic stimulation, and is therefore particularly sensitive to the negative inotropic effects of β-blockade.[7,10,12,15]

β-blockers are a heterogeneous class of agents.[7,13,43] Differences in their pharmacologic characteristics may have an effect on outcome.[44] Therefore, only the agents shown to be clearly beneficial for survival in placebo-controlled trials should be administered. These include bisoprolol, carvedilol, metoprolol succinate, and, in the elderly, nebivolol.[12,33,45]

β-blocker therapy may worsen the symptoms and signs of congestion in patients with acute decompensated heart failure (ADHF). Therefore, starting β-blocker therapy in these patients is contraindicated.[1,10,12] However, if acute decompensation develops in patients already on long-term β-blocker treatment, retrospective analyses have shown that the permanent reduction or withdrawal of β-blocker therapy may be an independent predictor of poor outcome.[46,47] The β-blocker dose should, therefore, be reduced or withdrawn only temporarily, if ever, with treatment restarted at the previous maintenance doses as soon as the patient's condition stabilizes.

1.3. Other Oral Pharmacotherapy

1.3.1. Hydralazine and nitrates. The major benefit of ACEIs in preventing disease progression is attributed to their neurohormonal inhibition rather than to direct hemodynamic effects. However, ACEIs do have vasodilatory activity, both through inhibition of angiotensin II production and through increase of bradykinin levels. This action may be increasingly important as the disease progresses and systemic vasoconstriction and mitral regurgitation increase. During mild or moderate heart failure, the mortality benefit of ACEIs is greater than that achieved by the combination of the direct vasodilators hydralazine and nitrates. For therapy in patients with hemodynamic compromise undergoing evaluation for transplantation, a regimen containing ACEIs was associated with better survival than a regimen containing hydralazine and nitrates without ACEIs, although nitrates were frequently added to the ACEI regimen to produce hemodynamic stabilization.[48] The hydralazine and nitrate combination is a reasonable alternative to ACEI use in patients who no longer tolerate ACEIs due to circulatory–renal limitations of hypotension, progressive renal dysfunction or hyperkalemia, for which risk increases as heart failure becomes more severe. In patients with mild-to-moderate heart failure who cannot take ACEIs due to cough or angioedema, ARBs provide the more convenient alternative.

Addition of the hydralazine and nitrate combination to ACEIs and β-blockers has been shown to decrease mortality and hospitalizations and improve survival in an ambulatory population of self-described African Americans with moderate to severe symptoms of heart failure.[49] Previous smaller studies indicated improved exercise capacity and symptoms from nitrates added to ACEIs in patients with moderately symptomatic heart failure. Therefore, it is reasonable to consider addition of the hydralazine and nitrate combination for any patient with persistent symptoms despite optimization of other therapies.

Hypertension should be vigorously treated at all stages of heart failure, including refractory heart failure. Reversible causes of secondary hypertension should be investigated when hypertension is severe. After ACEIs, β-blockers and ARBs, hydralazine and nitrates are reasonable agents to consider for further blood pressure control. Thiazides can also be useful as added agents for control of hypertension, but care is needed to avoid

excessive diuresis in combination with loop diuretics. Although an excess risk of cardiac disease has been associated with most calcium channel blockers, this has not been the case with amlodipine. Therefore, the use of amlodipine may be considered if hypertension cannot otherwise be controlled.

1.3.2. Digitalis. Digitalis is the oldest recognized therapy for heart failure. However, its clinical usefulness has long been controversial because studies of its efficacy have been lacking. Two trials, utilizing a withdrawal design, showed that fewer patients with NYHA Class II or III heart failure who were maintained on digoxin worsened with respect to clinical symptoms. More patients who remained on digoxin had an improvement in LVEF and exercise capacity as compared with patients having digoxin withdrawn.[50,51] A comparison of oral milrinone, digoxin and their combination in a trial enrolling patients with NYHA Class II or III heart failure showed that digoxin was superior to placebo and milrinone for enhanced exercise capacity and clinical status.[52] Unfortunately, these studies provided no information about the effects of digoxin on survival.

The Digitalis Investigation Group (DIG) trial was a large, randomized, placebo-controlled study that enrolled 6,800 patients with chronic heart failure and sinus rhythm to evaluate the role of long-term digoxin on mortality and morbidity.[53] No effects on all-cause mortality or cardiovascular mortality were observed; the treated patients demonstrated a clinical improvement and a decreased risk of death from worsening heart failure (11.6% on digoxin vs 13.2% on placebo, $p < 0.06$). In a further post hoc analysis of the DIG trial, gender differences in the effects of digoxin in heart failure were investigated. Women randomized to digoxin showed a worse prognosis than those randomized to placebo, with a higher risk of death related to cardiovascular causes.[54]

Digoxin is usually considered standard therapy in patients with heart failure and atrial fibrillation, although β-blockers may be more effective in the control of ventricular response during exercise or in the presence of increased sympathetic tone.[55] The suitability of the combined use of digitalis and β-blockers is currently an important question, as the earlier trials with digitalis were in heart failure patients who were only rarely treated with β-blockers. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial was designed to evaluate the role of a β-blocker in survival of patients with severe heart failure.[56] Among 2,289 randomized patients, at baseline, 61% to 78% were treated with digitalis. Eichhorn et al assessed the effect of combined therapy with digoxin and β-blockers (carvedilol) in a retrospective analysis including 1,509 patients enrolled in the U.S. Carvedilol Heart Failure Program and Australia–New Zealand Heart Failure Research Collaborative Group Carvedilol (ANZ-Carvedilol) trials.[57] Among the patients enrolled, 669 were taking digoxin and carvedilol, 234 carvedilol alone, and 423 patients who were sicker than those included in other groups were treated with digoxin. The combined treatment did not add benefit in terms of either hospitalization or the combined end-point of death and hospitalization. These results do not preclude the combined use of β-blockers and digitalis, but the drug combination has no clear benefit in patients doing well on β-blocker therapy.

Digitalis has narrow therapeutic range. The risk of toxicity increases in relation to worsening renal and hepatic function, reduced drug redistribution volume, and concomitant use of other drugs. It is reasonable to expect that patients with severe heart failure being considered for cardiac transplantation will obtain symptomatic benefit from digoxin. Otherwise, digitalis glycosides are not indicated in ADHF, except in the presence of atrial fibrillation, or in heart failure patients with preserved systolic function.

1.4. Exercise

One of the hallmarks of chronic heart failure is the development of exercise intolerance that can lead to a more sedentary lifestyle and progressive deconditioning. Exercise intolerance is due to cardiovascular as well as peripheral abnormalities associated with the syndrome of heart failure. These include reduced cardiac output with exercise, limited stroke volume, increased resting heart rate, reduced heart rate variability, reduced β-adrenergic responsiveness, abnormal autonomic balance, endothelial dysfunction, primary skeletal muscle changes and neurohormonal abnormalities.[58–61]

The use of exercise training or cardiac rehabilitation is a well-accepted and recommended modality in select groups of patients, such as those with ischemic heart disease, particularly after a re-vascularization procedure.[62–64] Exercise training in patients with heart failure has not been as widely used until recently. There have been many small, randomized studies that have documented the benefits of exercise training in heart failure patients. Patients with heart failure who participate in structured exercise training have shown improvement in maximal and sub-maximal exercise capacity, quality-of-life scores, inspiratory muscle strength and respiratory endurance; reversal of some of the autonomic imbalances associated with physical deconditioning; increased peak oxygen consumption; improved endothelium-dependent vasodilation of skeletal muscle vasculature; decreased plasma norepinephrine level; improved skeletal myopathy of chronic heart failure; and reduced hospitalizations for heart failure.[65–76]

There have been very few adverse events associated with supervised exercise training in heart failure pa-

tients.[77,78] Rather, studies have shown improved clinical outcomes and measures in LV remodeling, cost effectiveness, and a reduction in mortality.[79–83]

In general, the majority of exercise training studies performed in patients with heart failure excluded patients with advanced symptoms (NYHA Class IV) from participation. Although it seems intuitive that the better conditioned a patient is when undergoing a major surgical procedure (such as heart transplantation), the fewer the complications and the better the outcome, there are, to date, no clinical trials to substantiate this association in patients with advanced heart failure awaiting transplantation.

1.5. Sleep Disorders

Daytime fatigue and impaired physical performance in advanced heart failure may be an indicator of sleep-disordered breathing. There is a growing awareness of sleep-disordered breathing as a frequently occurring, often unrecognized, but potentially treatable risk factor for worsening of advanced heart failure. Sleep-disordered breathing is categorized as either obstructive sleep apnea (OSA) or central sleep apnea (CSA). OSA is characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep, which disrupts normal ventilation and is typically associated with snoring and daytime sleepiness.[84] CSA (Cheyne–Stokes respiration) is a form of periodic breathing in which apneas and hypopneas alternate with ventilatory periods having a waxing–waning pattern of tidal volume. Unlike OSA, CSA likely arises as a consequence of heart failure, delayed circulation time, increased chemoreceptor sensitivity to carbon dioxide, input into the respiratory center from other brain centers, and from peripheral receptors that might have pathophysiologic importance.[85–87] It is not clear whether CSA is simply a reflection of severely compromised cardiac function, or whether it exerts independent pathologic effects on the failing myocardium.

Both OSA and CSA are common in patients with heart failure. In the two largest case series of patients with heart failure undergoing polysomnography, OSA was detected in 166 of 450 (37%) and 9 of 81 (11%) patients studied. CSA is also highly prevalent in patients with chronic heart failure, present in 30% to 40% of patients in the largest reported series.[88,89]

In patients with heart failure, the presence of OSA has the potential to worsen ventricular dysfunction. Inspiration against an occluded upper airway generates exaggerated negative intrathoracic pressure, leading to both an increase in LV after-load and a decrease in pre-load, resulting in reduction of stroke volume.[90,91] Sympathetic outflow produces intermittent hypertension, further increasing after-load.[92] These hemodynamic effects as well as activation of adrenergic,[92] inflammatory and other mechanisms induced by repetitive nocturnal hypoxia would reasonably be expected to worsen prognosis in heart failure. However, definitive data about the effects of OSA on the natural history of treated or untreated heart failure are lacking. In contrast, CSA has been shown to be associated with an increased risk of death or cardiac transplantation.[93,94] However, it remains uncertain whether it is because Cheyne–Stokes respiration is a reflection of very poor cardiac function or whether its presence constitutes an additive adverse influence on outcomes via neurohormonal activation, surges in blood pressure and heart rate, and a greater propensity to lethal arrhythmia.[95,96]

Currently, the standard method for the diagnosis of sleep apnea is polysomnography conducted in a sleep laboratory, which is an expensive and not universally available procedure. However, the development and validation of less expensive and more readily available techniques, such as ambulatory monitoring, may make widespread screening for sleep apnea feasible in patients with heart failure.

Therapeutic approaches have focused on correction of the pathologic breathing pattern. Various respiratory interventions during sleep have been tried, including nasal oxygen,[97] continuous positive airway pressure (CPAP),[98–106] bi-level positive airway pressure (BIPAP) and adaptive pressure support servo-ventilation.[107–109] In patients with OSA, CPAP decreases LV after-load by increasing intrathoracic pressure, augments stroke volume, and reduces cardiac sympathetic activity.[98,104,105] It also decreases pre-load by impeding venous return and reduces LV end-diastolic volume.[90,100,102] A substantial improvement in both LVEF and functional class after treatment with CPAP has been demonstrated.[100,103]

In studies on patients with CSA, the long-term nightly use of CPAP over a period of 1 to 3 months has been shown to increase LVEF[103] as well as reduce mitral regurgitation, atrial natriuretic peptide (ANP)[105,106] and nocturnal and daytime sympathetic nervous system activity.[104,105] It has also been shown to improve quality of life.[103] A randomized, controlled clinical trial was conducted in 66 patients with chronic heart failure with and without CSA. The patients were randomized to nightly CPAP or control. The results showed that, over a 5-year follow-up period, patients in the CSA group who complied with CPAP had a significant reduction in the combined rate of mortality and cardiac transplantation.[110] However, in the largest trial to date (>250 patients), there was no improvement in mortality in those randomized to CPAP. In fact, early mortality was observed.[111]

1.6. Intravenous Support

In patients with acute exacerbation of chronic heart failure, intravenous therapy remains a cornerstone of current therapeutic regimens. Selection of treatment should be based on the patient's volume status and cardiac output. If volume overload with peripheral or pulmonary congestion is predominant, diuretics and vasodilators are the first line of therapy. If hemodynamic compromise with hypoperfusion and hypotension, despite optimal dosing of diuretics and vasodilators, is predominant, institution of positive inotropic support is generally indicated to achieve symptomatic relief.

1.6.1. Intravenous vasodilators. *1.6.1.1. Nitrates/sodium nitroprusside.* At low doses, nitrates induce only venodilation, resulting in reduced pre-load. At higher doses, nitrates also induce dilation of arteries, with consequent reduction of after-load. Their effectiveness in the treatment of acute heart failure, when combined with diuretics, has been well established. The major drawbacks of intravenous nitrate use include the rapid development of tolerance and the potential for severe hypotension.[112,113]

Sodium nitroprusside is a potent vasodilator. The use of nitroprusside generally requires invasive arterial monitoring. Long-term use (>3 days) is not advisable because of the potential risk of thiocyanate and cyanide toxicity, especially in patients with renal and hepatic failure. Nitroprusside can be beneficial in patients with severely increased after-load—for example, when due to marked hypertension, or in patients with pronounced acute mitral or aortic valvular regurgitation.

1.6.1.2. Nesiritide. Nesiritide, a recombinant human brain natriuretic peptide (BNP), relaxes smooth muscle cells. This leads to venous and arterial vasodilation, thereby reducing pre- and after-load, resulting in increased cardiac output without direct (positive) inotropic effect.[114–117] Nesiritide has been approved in the USA for the management of ADHF. Compared with intravenous nitroglycerin, nesiritide produced faster relief of dyspnea and a quicker and more pronounced reduction in elevated pulmonary capillary wedge pressure (PCWP). This benefit was sustained over 24 hours.[118] Nesiritide suppresses both the RAAS and the sympathetic nervous system. Therefore, the vasodilatory effect is not accompanied by pronounced neurohormonal activation.[119] This property is one of the reasons why nesiritide is postulated to be less arrhythmogenic than dobutamine.[120,121] BNP has a natriuretic and diuretic effect,[122] but in severe advanced heart failure up to 50% of patients seem to be resistant to its natriuretic effects.[123]

Currently, there is no conclusive evidence that nesiritide improves kidney function.[124] In fact, recent concern has focused on the possibility that nesiritide may worsen kidney function.[125] Nesiritide is generally well tolerated and hypotension is the most common side effect. Intravenous administration of nesiritide should be done with caution and under close blood pressure monitoring.[126] Its short-term safety relative to standard diuretic and vasodilator therapies is currently not well defined.[127]

In a randomized, open-label, pilot study, the safety and tolerability of outpatient serial infusions of nesiritide in 210 patients with decompensated heart failure was assessed. Cardiovascular and renal adverse events were not increased in the nesiritide group compared with the usual-care group. By investigator assessment, the nesiritide group showed a significant improvement in clinical status compared with the usual-care group, but there were no statistically significant differences in deaths or hospitalizations among groups.[128] A large, randomized trial is currently underway, but at the present time there are no compelling data to recommend the use of nesiritide in a long-term, intermittent manner for either in-hospital or out-of-hospital patients.

1.6.2. Intravenous inotropes. Most inotropes increase the intracellular level of cyclic adenosine monophosphate (cAMP), either by receptor stimulation (β-adrenergic agonists) or by decreasing cAMP breakdown (phosphodiesterase inhibitors). A new class of inotropes affects intracellular calcium mechanisms by increasing the sensitivity of contractile proteins to calcium (calcium sensitizers).[129–131] The mechanism of available inotropes (with the possible exception of digoxin) appears to favor short-term hemodynamic benefit at the expense of accelerating the underlying disease progression.[132–134] This effect is at least in part due to the fact that an enhancement of contractility is usually associated with an increase in myocardial oxygen consumption.[135] To date, inotropic therapies have failed to provide a mortality or morbidity benefit.[136–138]

1.6.2.1. Adrenergic agonists. The most powerful way to increase contractility in the human heart is the use of a β-adrenergic receptor agonist. Although, in the failing human heart, β-adrenergic pathways undergo desensitization,[139–141] the vast majority of patients with advanced heart failure still exhibit a substantial inotropic response to β-agonists.[142] Their administration should be carefully monitored and the lowest possible effective doses used.

1.6.2.1.1. Dopamine. Dopamine is not routinely recommended as a positive inotropic agent. Low doses of dopamine may be helpful for improving renal perfusion. Consideration should be given to using higher doses of dopamine in clinical settings where an increase in peripheral resistance is necessary, such as sepsis or iatrogenic overvasodilation.

In acute shock with critical hypoperfusion, immediate institution of inotropic therapy is mandatory until definitive therapy can be implemented. First-line therapy should usually be dopamine in medium to high doses. If this is not sufficient, epinephrine should then be used. If pronounced vasodilation is present, norepinephrine might be considered.

Dopamine mediates its effects by dose-dependent activation of different adrenergic receptors. At low doses, the activation of vascular dopamine receptors predominates, causing dilation of renal, mesenteric and coronary arteries, with a resultant increase in diuresis. This effect may be useful in promoting renal blood flow and maintaining diuresis in patients who become refractory to diuretics, especially when caused by marginal renal perfusion. At intermediate doses, the cardiac effects of dopamine are based on β_1-adrenergic receptor activation. At still higher doses, dopamine effects vasoconstriction through activation of α-receptors in the periphery.[143–146]

1.6.2.1.2. Dobutamine. Dobutamine is recommended for treatment of patients with low cardiac output and substantially reduced blood pressure, provided that they are not receiving concomitant β-blocker therapy. Concomitant use of β-blockers with dobutamine may attenuate the benefit of either agent.[147,148]

Dobutamine induces mild vasodilation in combination with a significant increase in contractility, leading to an augmentation of stroke volume and cardiac output.[149–151] Dobutamine may decrease β-receptor sensitivity, and prolonged infusion over 96 hours has been associated with a decrease in hemodynamic effect by as much as 50%.[152] It is mandatory to taper off dobutamine as opposed to abrupt discontinuation.[153,154] Dobutamine treatment significantly increases the number of serious ventricular arrhythmias,[155] although this might be less pronounced for patients with normal sinus rhythm.[156]

1.6.2.2. Phosphodiesterase inhibitors. In patients with preserved systolic blood pressure, phosphodiesterase inhibitors are preferred over dobutamine, especially in patients with concomitant β-blocker use. Phosphodiesterase inhibitors (milrinone, enoximone) increase intracellular cAMP by mechanisms not involving adrenergic receptors, producing both inotropic and vasodilatory actions.[157–161] Because they act independent of adrenergic receptors, they are still effective despite the down-regulation of β-adrenergic receptors in patients with chronic heart failure.[141,162] Short-term administration of phosphodiesterase inhibitors may improve myocardial performance and the clinical condition of patients with chronic heart failure.[160,163]

Combining phosphodiesterase inhibitors with dobutamine results in the additive effects of myocardial performance, including a reduction in PCWP and pulmonary artery pressure.[164–166] Favorable hemodynamic responses to phosphodiesterase inhibitors are enhanced by either carvedilol or metoprolol.[147,148,167] In fact, phosphodiesterase inhibitors may permit the concomitant safe introduction of β-blockers,[168–171] but this approach remains to be verified in a controlled trial.[172]

1.6.2.3. Levosimendan. Levosimendan might be helpful in patients with peripheral hypoperfusion secondary to systolic dysfunction without severe hypotension. Levosimendan enhances contractility primarily by binding to troponin C and increasing myofilament sensitivity to calcium without impairment of myocardial relaxation. Levosimendan also causes vasodilation by opening adenosine triphosphate (ATP)-sensitive potassium channels and inhibiting phosphodiesterase.[173–176] The hemodynamic effects of levosimendan, including significant increases in stroke volume and cardiac index and decreases in pulmonary arterial pressures, PCWP and arterial pressure,[176–179] were maintained during a 48-hour infusion and for at least 24 hours after discontinuation,[180] and were not attenuated by β-blockers.[181] Levosimendan is generally well tolerated, with the most common adverse events being rate and rhythm disorders, headache and hypotension.[182]

1.6.3. Long-term continuous inotropic treatment. For some patients on inotropic support, weaning of inotropic support is not possible, primarily because of the recurrence of symptomatic hypotension, congestive symptoms or the worsening renal function early after discontinuation of inotropic therapy. In these acutely inotrope-dependent patients, institution of a continuous infusion of the inotropic agent may be considered. As most studies have consistently shown an increase in mortality using long-term inotropes, this treatment option is used as a pharmacologic bridge to heart transplantation or mechanical support.[183–187] In patients with end-stage (Class D) heart failure, where no other therapeutic alternatives are feasible, long-term inotropic support may be considered for symptomatic relief at the end of life, taking into account the individual patient preferences while balancing the potential symptomatic benefit with the potential risks.[188–195]

1.6.4. Long-term intermittent inotropic treatment. Intermittent use of inotropic support has been described to increase quality of life and hemodynamics in observational reports,[196] but there are no controlled studies to support the benefit of intermittent infusions of positive inotropic substances to outpatients.[191,197–204] Indeed, published studies with control groups suggested that this approach may also increase mortality.[205,206] All oral agents with positive inotropic actions studied so far have significantly increased mortality or have been associated with a trend toward increased mortality, primarily as a result of markedly more occurrences of sudden death.

Although acute hemodynamic improvement with these agents is often pronounced, evidence of sustained clinical benefit is lacking.[207–212]

1.7. Investigational Approaches

Before transplantation is considered, a thorough search for reversible or surgically amenable cardiac disease should be completed and optimal medical management implemented. Patients should either have failed to improve with non-investigational therapies or have clear contraindications to the use of the specific therapy. Confidence that the medical therapy is optimal is increased when the therapy is directed or administered by heart failure specialists.

Investigational therapy should not be mandated before transplantation, no matter how promising. Doing so violates key ethical principles and fails to protect human participants at various stages in the research process. Listing for transplantation and transplantation should not be contingent upon clinical trial participation. Such coercion is incompatible with ethical standards. However, inviting potential heart transplant candidates to participate in clinical research trials that may delay or even prevent the need for transplantation is entirely appropriate, provided fully informed consent is secured.

Treatments intended to stabilize the circulation while patients await heart transplantation (e.g., continuous or intermittent intravenous inotropic agents or mechanical circulatory support [MCS]) are not currently considered investigational and should be used when hemodynamically indicated. Treatments that are considered investigational include: MCS instead of transplantation in an otherwise suitable transplant candidate; MCS as a temporary platform for myocardial recovery or regeneration strategies; passive cardiac restraint or support devices to prevent adverse cardiac remodeling; reparative surgery; enhanced external counterpulsation (EECP); and cell transplantation.

New MCS devices are being examined in clinical trials. Permanent MCS may conceivably become as desirable as transplantation. Some existing as well as newer MCS devices may allow pharmacologic interventions, stem cell therapy or cell transplantation for treatment of end-stage heart failure.[213]

In addition to MCS, a wide array of surgical options is currently available for the treatment of congestive heart failure. These range from traditional to high risk and include coronary artery bypass grafting (CABG) to passive cardiac support devices that may prevent adverse LV remodeling and favorably impact the natural history of heart failure.[214–216]

EECP has been shown to be beneficial for the treatment of refractory angina in patients with LV dysfunction, but its benefit in congestive heart failure (CHF) itself is less clear.[217,218] Cell-based myocardial repair and regeneration provides an opportunity to treat the injury-induced myocardial cell loss that prompts the cascade of events leading to heart failure.[219–224]

1.8. Reparative Surgery

1.8.1. High-risk bypass surgery. In the early days of surgical re-vascularization, some survival benefit was shown for re-vascularization over then current medical therapy in patients with 3-vessel disease or left main CAD and impaired LV function. However, the 5-year survival of patients with LVEF <35% was only about 50%.[225] In the modern era, survival is better, but the leading cause of death—29% of patients in one study[226]—is still heart failure. Demonstration of the existence of reversible perfusion defects or echocardiographic enhancement of contractility of akinetic myocardium with positive inotropy might theoretically lead to better selection of re-vascularization candidates in the future, but thus far it has failed to adequately select for tissue that is capable of recovery. Using more advanced techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET) scanning to demonstrate myocardial viability may possibly enhance selection in the future.

Stand-alone surgical re-vascularization is currently being prospectively studied in a randomized trial comparing standard medical therapy vs CABG alone or CABG plus surgical ventricular restoration (SVR) in patients with ischemic heart failure. The Surgical Treatment for Ischemic Heart Failure (STICH) multicenter trial is funded by the National Heart, Lung, and Blood Institute (NHLBI) and began enrolling patients in 2002. The goal of the STICH trial is to determine whether a benefit over medical therapy can be found for coronary re-vascularization and whether this benefit can be enhanced by ventricular restoration surgery.[227]

1.8.2. Surgical ventricular restoration. The SVR (or Dor) procedure is a surgical technique designed to reshape the left ventricle by excluding antero-apical and septal regions of asynergy in patients with heart failure after anterior myocardial infarction.[228] It is designed to create a more elliptical chamber by excluding scar tissue in either akinetic or dyskinetic segments.[229] SVR is often referred to as "the Dor procedure"; however, Dr Dor's technique is but one of a variety of surgical techniques that have been employed to reshape the left ventricle. A group of cardiologists and surgeons from 12 centers (the Reconstructive Endoventricular Surgery Returning Torsion Original Radius Elliptical Shape to the Left Ventricle [RESTORE] group) recently reported on their registry with 5-year follow-up involving 1,198 patients undergoing the SVR procedure between 1998 and 2003.[230] Concomitant procedures included CABG in 95%, mitral valve repair in 22% and mitral valve replacement in 1%. The group demon-

strated a 30-day surgical mortality of only 5.3% and overall 5-year survival of 68.6 ± 2.8%. Five-year freedom from hospital re-admission for heart failure was 78%. Pre-operatively, 67% of the patients were NYHA Functional Class III or IV and, post-operatively, 85% were NYHA Class I or II. The investigators concluded that the operation improves ventricular function and is highly effective in the treatment of ischemic cardiomyopathy, with an excellent 5-year outcome. The results of this registry have served as a benchmark for the ongoing STICH trial.

1.8.3. Mitral repair. Clinical improvement has been reported after mitral valve repair or replacement in a number of patients with significant mitral regurgitation that was considered due to the geometric effects of LV dilation.[231] However, no controlled studies have evaluated the effect of this surgical approach on long-term ventricular function or survival. A recent retrospective observational analysis from the investigators most enthusiastic about the procedure used a "propensity score" or conditional probability of a theoretically eligible patient having the surgery to look at the effect of surgical annuloplasty on long-term mortality. They found no improvement in long-term survival (or the combined end-point of mortality or urgent transplantation) in the surgical group and no difference between groups with ischemic or non-ischemic underlying etiology for heart failure.[232]

Whether this lack of benefit has to do with the surgery simply not working or whether a different surgical approach would work is unknown. There could be other, more sophisticated approaches in addition to annuloplasty, including sub-annular 3-dimensional repair of the mitral geometry.[233] For now, it seems that isolated mitral valve repair, not associated with re-vascularization or ventricular restoration, should not be routinely performed in patients with advanced LV dysfunction and heart failure.

1.9. Methods to Maximize Therapy: Biomarkers and Hemodynamics

Clinical trials have established the benefit of neurohormonal blockade in chronic heart failure using ACEIs, β-blockade, aldosterone antagonists and ARBs.[234] These trials have generally specified a target dose for the drug studied and therapeutic effects are usually dose-related.[235] Consequently, therapeutic guidelines require that drug doses be titrated up to target levels.[234] However, dose-limiting adverse effects frequently occur in patients with advanced heart failure, limiting the applicability of this approach. In addition, it is now apparent that some groups of patients respond more favorably to specific classes of drugs.[49,236] Thus, decisions about prioritizing and tailoring drug therapy for the individual patient remain in the realm of physician discretion. Furthermore, those patients with very advanced heart failure are often unable to tolerate such therapy at all and become candidates for inotropic therapy despite its limited benefit and serious limitations.[131,194] Bio-markers such as BNP and invasive measurement of hemodynamic parameters may assist with the adjustment of medical therapy in such patients. These markers have a more clearly defined role in case selection for transplantation and MCS.

1.9.1. Bio-markers. BNP is primarily released from ventricular myocardium. BNP is produced as a pro-hormone, pro-BNP, which is enzymatically cleaved into BNP and the aminoterminal portion of the pro-hormone (NT-pro-BNP).[237] Circulating levels of BNP and NT-pro-BNP are increased in heart failure, reflecting increased filling pressures and wall tension together with ventricular remodeling and hypertrophy. Both BNP and NT-pro-BNP have been used as diagnostic and prognostic markers in heart failure.[238–240] During treatment, peptide levels usually fall. Persistently high levels are associated with a worse prognosis and are a reason for considering transplantation.[241] Changes must be interpreted in light of the within-patient variability of BNP and NT-pro-BNP measurements.[242] In a small controlled trial, BNP levels were used to guide drug therapy and this strategy was compared with treatment based on routine clinical assessment; patients managed with the aim of reducing BNP levels received more diuretics and vasodilators than patients in the control group and experienced less cardiac events during follow-up.[243]

Release of troponin T into the circulation is a sensitive marker of myocardial injury.[244] Troponin T levels are frequently elevated in both stable and ADHF patients. Persistently elevated levels are associated with a worse prognosis.[245,246] In patients with ischemic cardiomyopathy, an acutely elevated troponin level may indicate an ischemic event. Troponin T and BNP provide independent prognostic information and may be combined to improve risk stratification.[245,247]

1.9.2. Hemodynamic data. Hemodynamic measurements form an important part of assessment for both heart transplantation and MCS. Hemodynamic assessment provides prognostic information[248]; however, in patients with ambulatory heart failure, this information is not independent from the information obtained from non-invasive assessment.[249,250] Thus, right heart catheterization is not routinely indicated for assessment of heart failure severity. Invasive hemodynamic assessment has been used to tailor intravenous vasodilator and diuretic therapy in advanced heart failure. Achievement of a normal cardiac index and LV filling pressure after treatment with a vasodilator and diuretics appears to place patients in a low-risk category.[251,252] However, care must be taken to ensure that this favorable hemodynamic state can be maintained after transitioning the patient to oral therapy. This requires the use of an indwelling pulmonary

artery catheter and can lead to complications such as infection, arrhythmia and thromboembolism.

Pulmonary artery catheters are also sometimes used to assess a patient's hemodynamic response to therapy with inotropic agents. However, treatment with inotropic agents does not improve the prognosis of heart failure and can cause serious complications. Therefore, it should be reserved for cases that are refractory to other approaches.[131,194] Such treatment should be directed toward maintaining adequate perfusion of the kidneys and other vital organs, relieving symptomatic hypotension, or promoting diuresis in cases of refractory fluid overload. Inotropes should not be introduced or escalated solely for the purpose of normalizing the patient's cardiac index or other hemodynamic parameters. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial demonstrated that there was no advantage to the routine use of pulmonary artery catheters in patients with ADHF.[253]

Right heart catheterization is an essential part of transplant assessment and is used principally to assess PVR and thus to assess the risk of right heart failure immediately after transplantation.[254] Risk stratification in patients with an increased PVR may be improved by the use of either vasodilators or inotropes to provide a dynamic assessment of the pulmonary circulation.[255–257] Information from right heart catheterization may contribute to case selection, donor–recipient matching and postoperative care planning.

In patients presenting with end-stage heart failure or cardiogenic shock, right heart catheterization data should be routinely used to confirm that hypotension is cardiac in origin (low cardiac index combined with a high LV filling pressure) and not due to hypovolemia or vasodilation related to prior therapy or sepsis. Cardiogenic shock requires urgent resuscitation with inotropes, often an intra-aortic balloon pump (IABP), and occasionally temporary circulatory support.[258] In some cases, such treatment can maintain, or bridge, patients to more long-term treatment, either implantation of an LVAD or, if a donor organ is available, urgent transplantation.[259,260]

1.10. Disease Management Programs

Heart failure disease management programs provide multidisciplinary and intensive education, monitoring (telephone, facsimile, clinic, internet) and support that are not feasible within a typical medical practice. They implement and follow clinical practice guidelines, potentially improving utilization rates of evidence-based medical therapies. Given the most common precipitant of admission for heart failure is medication and dietary non-adherence,[261] by increasing adherence, disease management programs are thought to reduce hospital admission and improve outcomes. Early clinical data suggest that intensive nurse-led multidisciplinary interventions could reduce non-compliance and improve outcomes, reducing hospitalizations and length of hospital stay.[262,263] The benefits appeared to be greater if multidisciplinary involvement occurred within specialized heart failure clinics vs those based solely on telephone follow-up interventions.

McAlister et al published a review of 29 randomized clinical trials addressing multidisciplinary management programs in heart failure. Although there was a great deal of heterogeneity among the trials, programs using a specialized multidisciplinary team had an overall reduction in mortality (relative risk [RR] = 0.75), hospitalization for heart failure (RR = 0.74) and all-cause hospitalizations (RR = 0.81). There was no mortality benefit seen in those studies that employed telephone intervention or enhanced patient self-care intervention, suggesting that face-to-face interaction with a multidisciplinary team is required for mortality benefit.[264] Similar reductions in hospitalizations were seen in the elderly, with a significant improvement in quality of life noted.[264]

There have been clear discrepancies regarding the effectiveness of disease management programs, as a few significant trials have failed to show a benefit.[265] In general, these studies involved patients with NYHA Class I or II heart failure, who may not have exhibited the same benefit with multidisciplinary intervention. Factors that influence outcomes include: target population (mild, moderate or severe heart failure); the intensity of the intervention (frequency); composition of the multidisciplinary team (registered nurse [RN], advanced practice nurse [APN], pharmacist, physician) and type of intervention (face-to-face, telephone, facsimile, internet); and timing of initiation either before or after hospital discharge for heart failure, among others. Overall, approaches that involve access to a specialized heart failure clinic with specially trained interdisciplinary staff appear to have the greatest impact.[264,266,267]

1.11. End-of-Life Issues

Mortality from heart failure is due to sudden cardiac death, bradyarrhythmias or tachyarrhythmias or progressive heart failure, typically gradual in nature but on occasion rapidly progressive. Patients who develop progressive heart failure frequently die in an intensive care setting, receive major intervention and life support, and are much less likely to die at home or receive palliative care assessment. Although there are multiple prognostic markers in heart failure, predicting life expectancy is notoriously challenging, especially given the cyclic nature of the disease.

Recent technological advances have led to the use of defibrillators, re-synchronization pacemakers and MCS devices as viable treatment options for patients with heart failure. This has led to increased complexity of care and

decisionmaking at the end of life. As a result, advanced care planning for patients with heart failure must be addressed earlier in the course of the disease and before the end of life, which would allow patients the opportunity to review the issues surrounding death from heart failure, before the development of an acute exacerbation.

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