Advanced Heart Failure

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This is to acknowledge that Dr. Drazner has disclosed a financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Drazner will be discussing "off-label" uses in his presentation.

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Interests:

Left ventricular hypertrophy
Heart failure
Ventricular assist devices
Cardiac transplantation

Chronic heart failure (CHF) is a significant public health problem. In the United States, the estimated prevalence is close to 6.5 million among those ≥18 years and is expected to rise to close to 10 million by the year 2030 (1). Increasingly, there has been focus on the subset of CHF patients with the highest severity of illness. A variety of names have been used to characterize this group of patients including "advanced heart failure," "refractory heart failure," or "end-stage heart failure." In the American Heart Association/American College of Cardiology classification of 4 stages (A through D) of heart failure (2), this group of patients is categorized as "Stage D" heart failure. The thesis that these patients deserve unique attention is supported by the new board certification offered by the American Board of Internal Medicine in "Advanced Heart Failure and Transplant Cardiology." If for no other reason, it is clear that patients with advanced heart failure warrant attention given that they consume huge economic resources: one estimate from the medical arm of a randomized trial investigating left ventricular assist devices (LVADs) was that the medical costs per patient in the final 2 years of life were $156,000 with 50% ($78,900) occurring in the final 6 months of life (3,4).

With rapid advances in the field LVADs offering new therapeutic options for patients with advanced heart failure, it is timely to review this clinical syndrome. Further, since most patients in the United States with heart failure are cared for by general practitioners including internists, rather than cardiologists (5), Internal Medicine Grand Rounds is a particularly appropriate venue for this discussion.

The objectives of this discussion are three-fold. The first objective is to define advanced heart failure with a focus on the natural history of this syndrome. The second objective is to discuss easily identifiable clinical risk factors which are associated with adverse outcomes. The goal of this objective is to enable physicians to recognize patients with advanced heart failure before such patients have progressed to a critical, often non-salvageable state of illness. The third objective is to describe therapeutic options for patients with advanced heart failure.

1. Epidemiology

There is no consensus definition for the syndrome of advanced heart failure. It remains uncertain whether to define advanced heart failure based solely on the presence of severe symptoms and poor quality of life or to define it based on an expected poor prognosis (6). Given the absence of a standard definition for epidemiological purposes, the prevalence of advanced heart failure is uncertain. In a 1999 registry of patients in France, the crude incidence of advanced heart failure (defined as at least one hospitalization for heart failure in last year, NYHA class III or IV, radiological and/or clinical signs of pulmonary congestion and/or peripheral edema, LVEF <30% or cardiothoracic ratio >60%) was 225 per million in the general population (7). There was a striking association of age and gender with incidence, with rates ranging from 6 per million in women aged <30 years to 1,480 per million in men aged 70 to 80 years. In a population-based sample of Olmstead County, Minnesota (8), the prevalence of stage D heart failure (defined as a history of heart failure with a Goldman Specific Activity Scale (9) class IV functional status [< 2 METS]) in residents ≥45 years of age was 0.2%. In 2010, there were 122,000,000 people over the age of 45 in the United States (10), yielding an estimate of approximately 250,000 patients with stage D/advanced heart failure in this country. This estimate

is consistent with that based on a projection that 5% of patients with chronic heart failure have advanced symptoms (11).

2. Defining Advanced Heart Failure

2A. The New York Heart Association classification

The New York Heart Association classification (12) assigns 4 classes to patients with heart failure:

Class I (asymptomatic): no symptoms with ordinary activities.

Class II (mild CHF): slight limitation of physical activity; symptoms with ordinary physical activity.

Class III (moderate CHF): marked limitation of physical activity; symptoms with less than ordinary activity.

Class IV (severe CHF): inability to carry on any physical activity without symptoms; symptoms may be present even at rest.

Patients with advanced heart failure fall within the spectrum of NYHA class III or IV. However, there are many limitations of the present NYHA classification including subjectivity in its definitions (e.g., what is less than ordinary activity?) undoubtedly contributing to poor inter-observer reproducibility (9,13). Further, the NYHA system does not provide a fine enough gradation of patients with severe symptoms. For example, patients who are in cardiogenic shock requiring mechanical support, those who are symptomatic at rest, or those who get dyspneic with activities of daily living would all be classified as NYHA class IV. Similarly, NYHA class III represents a broad spectrum of severity of illness. To address the latter limitation, the designation NYHA class IIIB has increasingly been used to denote patients who have a severity of illness between traditional NYHA class III and class IV. In fact, NYHA class IIIB, despite the absence of a well-accepted definition, has been used in the Food and Drug Administration's approved indication for the HeartMate II left ventricular assist device (14). Recently, Dr. Jennifer Thibodeau and other members of the UT Southwestern advanced heart failure section have proposed a modification of the NYHA classification which may improve its utility in describing patients with advanced heart failure (Table 1).

Table 1. Conventional and newly proposed modification of the NYHA classification (15)

Onset of symptoms	Standard NYHA class	Revised NYHA class
At rest	IV	IV-Rest
Activities of daily living (such as dressing, bathing, walking to adjacent room)	IV	IV-ADL
Walking on level ground < 1 block*	III	IIIB
Walking on level ground 1-2 blocks* or 1 flight of stairs	III	III

*Qualified in revised classification as: walking at least at a medium pace (2-3 mph) and without stopping. A block is approximately 500 feet.

2B. Beyond NYHA Classification

The initial effort to categorize the syndrome of advanced heart failure came in 1998 when Adams and Zannad published a paper entitled "Clinical definition and epidemiology of advanced heart failure" (16). In their diagnostic criteria, they required patients to have a left ventricular ejection fraction (LVEF) <30% and be NYHA class III-IV or have a peak oxygen consumption (VO2) <14 ml/kg/min. They provided 4 additional criteria which "contribute to the diagnosis": 1. trial of standard therapy for 3 months (at that point, ACE-inhibitor, digoxin, diuretics) 2. plasma norepinephrine >900 pg/ml 3. noninvasive evidence of pulmonary hypertension as indicated by tricuspid regurgitation velocity > 2.5 msec and 4. hyponatremia (serum Na <130 mmol/L). There are a number of limitations with this initial definition including that patients with preserved ejection fraction and diastolic heart failure (e.g., restrictive cardiomyopathy) are excluded and that measurement of norepinephrine is rarely performed in the clinical setting.

A more recent and comprehensive definition of advanced heart failure was provided by the Study Group on Advanced Heart Failure in the European Society of Cardiology in 2007 (Table 2) (17).

Table 2. European Society of Cardiology Definition of Advanced Heart Failure

1. NYHA class III or IV
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction shown by at least one of the following: A. LVEF<30% B. Pseudonormal or restrictive mitral inflow pattern C. Mean PCWP >16 mm Hg and/or RAP >12 mm Hg by PA catheterization d. High BNP or NT-proBNP plasma levels in the absence of non-cardiac causes
4. Severe impairment of functional capacity shown by one of the following: A. Inability to exercise B. 6 minute walk distance distance <300m or less in females and/or patients ≥75 years C. Peak V02 <12 to 14 ml/kg/min
5. History of ≥1 HF hospitalization in past 6 months
6. Presence of all the previous features despite "attempts to optimize" therapy including diuretics, renin-angio-aldo blockers, beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated

This definition improves upon the original Adams and Zannad definition by allowing for the inclusion of patients with preserved ejection fraction, by broadening the criteria for impaired functional capacity, by requiring at least one recent heart failure hospitalization, and by updating the requirement that patients fail all modern therapies including beta-blockers and cardiac resynchronization therapy (CRT).

Another advanced heart failure classification has been developed by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) group. INTERMACS, a

mandated registry for centers implanting Food and Drug Administration (FDA) approved, durable left ventricular assist devices in the United States, is a joint collaboration among the National Heart, Lung and Blood Institute, the Centers for Medicare and Medicaid Services (CMS), the FDA, United Network for Organ Sharing (UNOS), industry, clinicians, and scientists. One of the first major advances of INTERMACS was to define 7 profiles within the spectrum of advanced heart failure (Table 3) (18).

Table 3. INTERMACS Profiles of Advanced Heart Failure

Profile*	Profile Description	Descriptive label
1	Critical cardiogenic shock	Crash and burn
2	Progressive decline	Sliding fast on inotropes
3	Stable but inotrope-dependent	Stable on inotropes
4	Resting symptoms on oral therapy at home	Rest symptoms
5	Exertion intolerant	Housebound
6	Exertion limited	Walking wounded
7	Advanced NYHA III	Advanced class III

*Modifier options: Profiles 3-6 can be modified with the designation FF (frequent flyer) for patients with recurrent decompensations leading to frequent (generally at least 2 in last 3 months or 3 in last 6 months) emergency department visits or hospitalizations for intravenous diuretics, ultrafiltration or brief inotropic therapy. Other modifier options include A (arrhythmia) which should be used in the presence of recurrent ventricular tachyarrhythmias contributing to the overall clinical course (e.g., frequent ICD shocks or requirement of external defibrillation, usually more than twice weekly); or TCS (temporary circulatory support) for hospitalized patients profiles 1-3.

INTERMACS profiles 1 – 3 have rapidly entered the lexicon of standard clinical practice. In contrast, profiles 4 – 7, which have been modified since their initial description (18), have not yet had the same utility. A classification system which describes the entire spectrum of advanced heart failure incorporating the proposed UT Southwestern revised NYHA classification in conjunction with INTERMACS Profiles 1 – 3 is shown (Figure 1) (15).

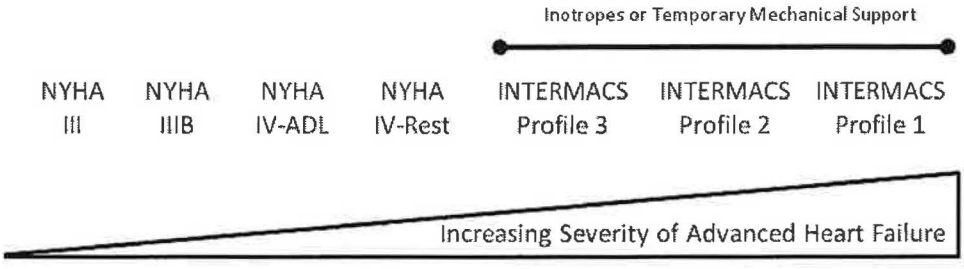

Figure 1. UT Southwestern Proposed Classification of the Advanced Heart Failure Spectrum. From (15).

3. Clinical features of advanced heart failure

3A. Natural history of patients with advanced heart failure

Patients with advanced heart failure have a high expected mortality within one year. In 2003, Dr. Ray Hershberger and colleagues demonstrated a one-year mortality of approximately 90% for patients who are dependent upon continuous intravenous infusions of inotropes (Figure 2) (19).

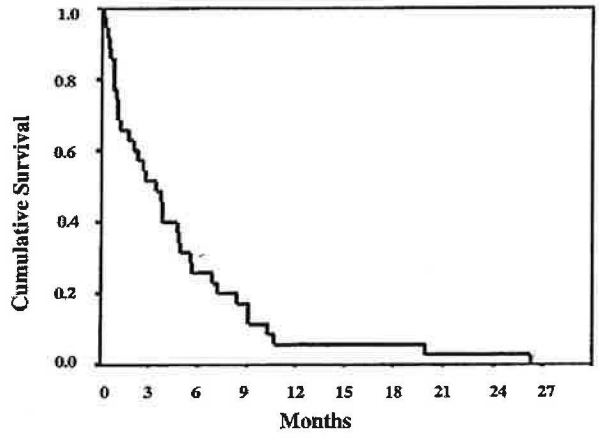

Figure 2. All cause survival in patients with advanced heart failure who are inotrope-dependent. From (19).

This bleak outcome was confirmed in the medical treatment arm of the INTrEPID (Investigation of Nontransplant-Eligible Patients Who are Inotrope Dependent) trial which demonstrated a one-year mortality of 89% (20) and in the REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure) trial where those dependent upon inotropes who were not randomized to LVAD therapy had a one-year mortality of 76% (21). Both trials required an attempt to wean off inotropes before labeling a patient as inotrope dependent. In INTrEPID, two inotrope weaning trials were mandated at least 7 days apart, with failure defined as systemic hypotension, exacerbation of CHF symptoms, deterioration of end-organ function, CI $\leq$2.2 L/min/m^2 or PCWP >20 mm Hg (20). In REMATCH, intravenous inotrope dependence also required a weaning trial. Here, failure to wean could include hypotension (SBP <80 mm Hg), worsening renal function, and/or deterioration in heart failure defined by increased symptoms and objective findings (21). Another confirmation of poor outcomes in those dependent upon inotropes comes from the Cleveland Clinic which reported that subjects discharged home on inotropes from their advanced heart failure center had a one-year mortality ranging from 50% (milrinone) to 65% (dobutamine) (22).

When one moves upstream in the spectrum of advanced heart failure and considers patients who are not inotrope-dependent, the one-year mortality has been shown to be ~20% to 60% in various selected systolic heart failure trials (Figure 3) (4, 21, 23-27).

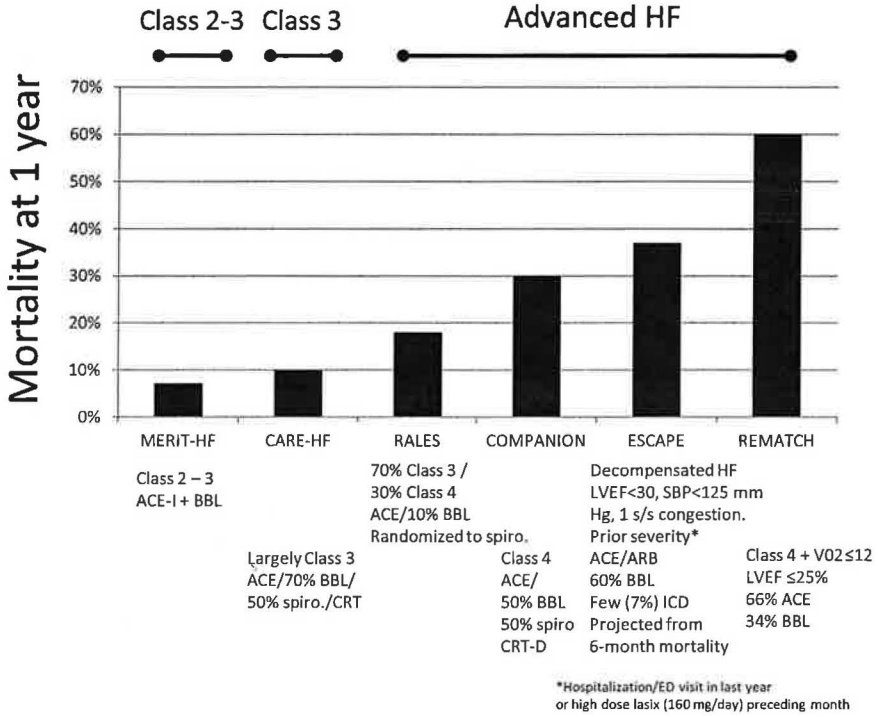

Figure 3. Composite 1-year mortality from systolic heart failure trials enrolling moderate to advanced heart failure in those NOT inotrope dependent. From (4, 21, 23-27).

Summary

Advanced heart failure describes a spectrum of illness among patients with NYHA class III or IV symptoms. The syndrome is associated with a very poor prognosis. The requirement for chronic intravenous inotrope infusion appears to be an important harbinger of a particularly guarded prognosis: in clinical studies, those not on inotropes had a one-year mortality ranging from 20% to 60%, while those dependent upon continuous intravenous inotropes had a one-year mortality ranging from 50% to 90%.

Certainly, patients dependent upon chronic infusions of inotropes warrant referral to an advanced heart failure center for consideration of "advanced therapies" (LVAD and/or cardiac transplantation). The next focus will be on identifying easily recognizable clinical characteristics which can be useful in risk-stratifying patients with chronic heart failure who are not inotrope-dependent.

3B. Simple clinical findings useful to risk stratify patients with advanced heart failure who are not inotrope-dependent

Assessing prognosis is an important part in clinical decision making, especially when considering therapies which can convey substantial risk such as LVADs. Physicians may be overoptimistic in assessing prognosis of patients with advanced medical illness (28). There have been many tools developed to improve risk assessment in patients with heart failure. The Heart Failure Survival Score was the first well-validated model to be broadly considered by the advanced heart failure community (29). The score's limitation is that it requires measurement of peak oxygen consumption by a cardiopulmonary stress test. Thus, it is less likely to be used by physicians as a tool for when to refer a patient to an advanced heart failure center (where cardiopulmonary stress testing is usually done) and more likely to be applied after patient

referral. The Seattle Heart Failure Model is another tool which has been well validated in patients with chronic heart failure (30). The unique features of this model are that it is publicly available with an interactive data entry screen (Figure 4) and that it does not require any specialized testing such as right heart catheterization or cardiopulmonary stress testing, offering the opportunity to make it broadly applicable.

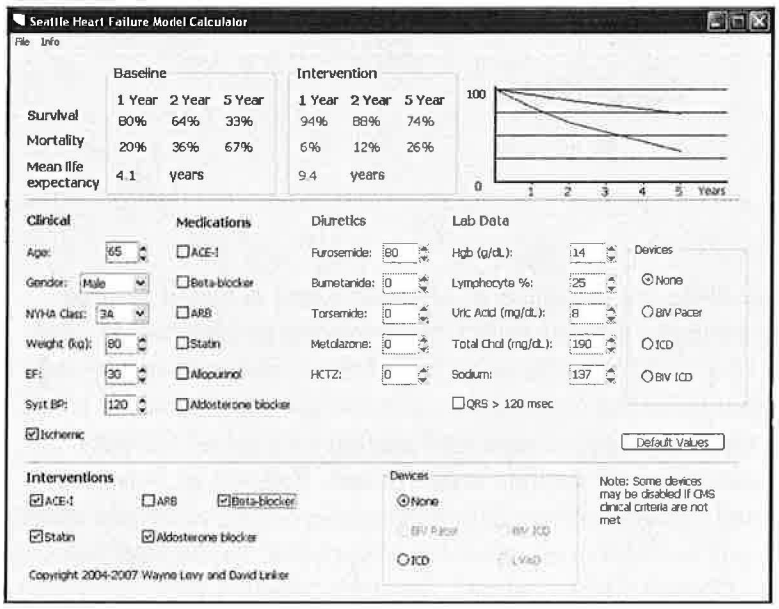

Figure 4. Seattle Heart Failure Model interactive data entry screen. Available at http://depts.washington.edu/shfm

However, the Seattle Heart Failure Model, which was developed and validated in patients with chronic systolic heart failure, appears to offer somewhat suboptimal discrimination and calibration in patients with advanced heart failure (31,32).

In the last several years, it has become apparent that there are a number of clinical events which convey substantial prognostic value in patients with advanced heart failure. These will be reviewed sequentially.

3B. i. Achieving clinical stability

Inability to achieve "clinical stability" is associated with adverse outcome. One measure of clinical stability is NYHA class: in the COMPANION trial, the 2-year mortality rate was significantly higher in NYHA IV (55%) as compared to NYHA III (20%) subjects (4). Another measure of clinical stability is the hemodynamic profile estimated by history and physical examination. As advocated by Dr. Lynne Stevenson, patients are categorized into one of four groups depending upon the absence or presence of elevated left-ventricular filling pressures (dry or wet) and adequacy or inadequacy of perfusion (warm or cold) (Figure 5) (33).

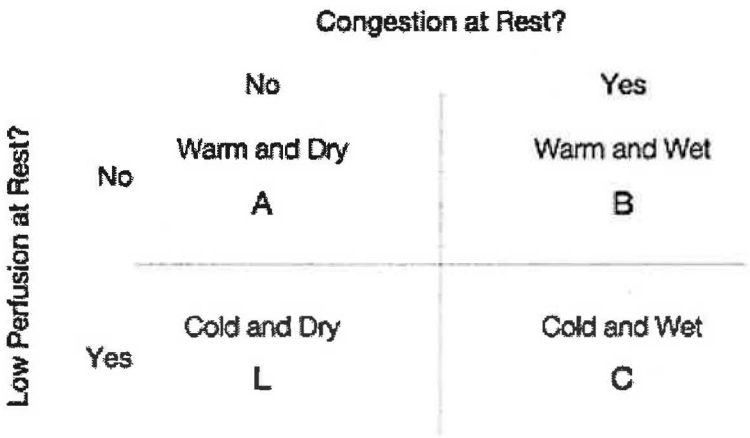

Figure 5. Stevenson classification of heart failure based on clinical estimates of hemodynamics. From (33).

From the history and physical examination, the presence of orthopnea and elevated jugular venous pressure have been shown to have the highest utility for detecting an elevated PCWP, while an overall clinical assessment of a "cold" profile (e.g., based on narrow pulse pressure and cool lower extremities) has been shown to be the best marker of a low cardiac index (34). In the Stevenson classification, Profile A (warm and dry) would be a marker of clinical stability representing relief of congestion and an adequate cardiac index at rest. Patients in Stevenson profile B (warm and wet) have elevated left ventricular filling pressures but an adequate cardiac index, while those in profile C (cold and wet) have elevated left ventricular filling pressures and inadequate cardiac index. In a series of hospitalized patients, Stevenson profile upon admission was associated with subsequent one-year mortality: profile A (~10%), B (~30%), and C (~40%) (35). In the ESCAPE trial ("Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness"), the hemodynamic profile estimated at discharge conveyed more prognostic information than did the admission profile. Subjects who wet or cold at admission but ended up warm and dry at discharge (i.e., had achieved Profile A at discharge) had a comparable risk to those subjects who were Profile A both at admission and discharge. In contrast, subjects who were either wet or cold at discharge (i.e., had not achieved Profile A status), as compared to those who were Profile A at discharge, had a hazard ratio of 1.5 (1.1 to 2.1) for the primary endpoint (number of days alive outside the hospital at 6 months) despite adjustment for other prognostic variables in ESCAPE (6-minute walk, baseline systolic blood pressure, and baseline blood urea nitrogen) (34).

Just as in the hospital, a repeat assessment of clinical stability in the weeks following discharge also appears to provide prognostic information. In a series of 146 patients with advanced heart failure discharged from a hospitalization during which they had been NYHA class IV, a congestion score was calculated at the 4 to 6 week follow-up clinic visit based on 5 clinical markers (1 point for each: orthopnea, JVD, increased weight of at least 2 lbs compared to the previous week, need to increase diuretic dose at post-discharge clinic visit, and edema). There was a striking relationship between the presence of markers of congestion in the early discharge period and subsequent 2-year mortality (congestion scores of 0, 1-2, or 3-5 were associated with a 2-year mortality of 13%, 33%, and 59%, respectively, $p<0.001$) (36).

In summary, patients who cannot achieve clinical stability (i.e., they continue to have evidence of congestion or inadequate perfusion as assessed by clinical evaluation, or NYHA IV symptoms) are at substantially increased risk of adverse events. Serial assessment of patients (both from admission to discharge and following discharge) adds prognostic value to an initial assessment.

3B. ii. Recurrent heart failure hospitalization

There were more than one million hospitalizations for a primary diagnosis of heart failure in the United States in 2004 (37). Although recent data demonstrated a 30% reduction in the rate of heart failure hospitalizations in the Medicare population from 1998 to 2008 (38), hospitalizations remain common. Further, rehospitalization after an index admission occurs commonly: approximately 25% at 30 days and 50% at 6 months (39). Importantly, hospitalization for decompensated heart failure appears to punctuate an inflection point in the trajectory of the natural history of patients with chronic heart failure. In the CHARM (Candesartan in Heart Failure: Reduction in Mortality and morbidity) trials, a first hospitalization was associated with an unadjusted HR of 4.55 (95% CI 4.1 to 5) and an adjusted HR of 3.2 (2.8 to 3.5) for mortality (40).

The association of heart failure hospitalization and subsequent outcome is readily evident given that **the one-year mortality following admission for acutely decompensated heart failure is ~30%.** The one-year mortality was 25% in a VA population (41), ~30% in the EFFECT-HF cohort (heart failure cohort of the Enhanced Feedback for Effective Cardiac Treatment Study, a prospective Canadian registry) (42), 28% in ADHERE-LM (the Acute Decompensated Heart Failure National Registry Longitudinal Module, a prospective multicenter registry in the US of patients with class III and IV symptoms who were hospitalized at least 2 times in the prior year for HF) (43), and 32% in the Medicare population in 2008 (38), suggesting that even one hospitalization places a patient within the spectrum of advanced heart failure.

Although there are multivariable risk models which can stratify patients at hospital discharge (41,44), **for practitioners it may be particularly worthwhile to focus on those patients who are re-hospitalized for heart failure, given that outcomes following recurrent hospitalizations are very poor** (40,45,46). In an observational experience from British Columbia conducted between 2000 and 2004 in which 14,374 patients were hospitalized for heart failure, there was an association between the number of heart failure hospitalizations and subsequent mortality (Figure 6) (46). Patients with at least 2 re-hospitalizations had a 50% mortality in the following year. As a control, these investigators demonstrated that re-hospitalization for a non-cardiac cause did not substantially increase subsequent mortality.

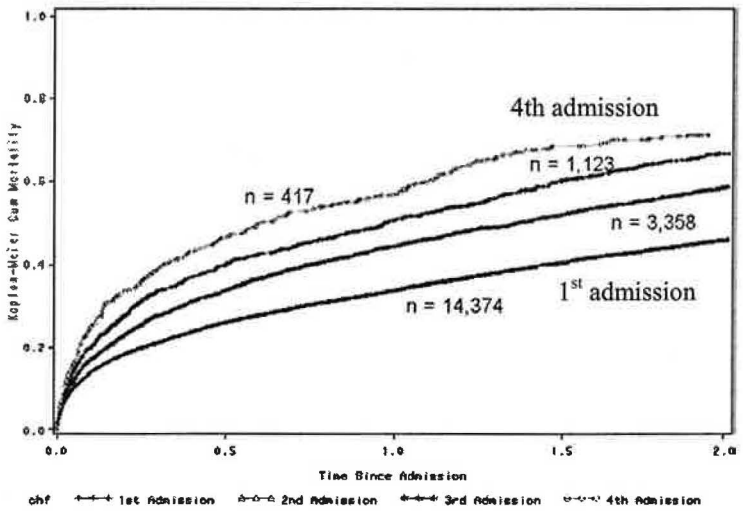

Figure 6. Association of number of hospitalizations and subsequent mortality in patients with heart failure. From (46).

A similar association of recurrent hospitalization and subsequent mortality was demonstrated in the EFFECT-HF study (45) and the CHARM trials (40). The CHARM investigators also demonstrated that mortality risk was associated with increased duration of the hospitalization and was greatest in the early period following discharge. The association of hospitalizations and mortality was further underscored in a review of 160 patients with advanced systolic heart failure who died: in the 6 months before death, approximately 75% had been in the hospital at least once (32% had one HF hospitalization and 42% had 2+ hospitalizations) (47).

3B. iii. Cardiorenal syndrome

Renal dysfunction is associated with an increased risk of mortality in patients with chronic heart failure, acutely decompensated heart failure, and advanced heart failure.

Chronic heart failure

In the DIG trial (Digitalis Intervention Group, n=6800, chronic heart failure, predominantly NYHA class II and III, mean follow-up 3 years), renal dysfunction as assessed by estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) was inversely associated with all-cause mortality: mortality 31% (eGFR >60); 46% (eGFR 30 to 60); 62% (eGFR <30). Further, these associations persisted in multivariable models adjusted for important covariates including NYHA class and LVEF (48). In the CHARM trials (chronic heart failure, predominantly NYHA class II or III, median follow-up 34 months), eGFR had an adjusted hazard ratio of 1.9 (95% CI 1.4, 2.6; $p<0.001$) for all-cause mortality (49).

Acutely decompensated heart failure

In ADHERE (a population of approximately 65,000 heart failure patients hospitalized in the United States), an admission BUN ≥43 mg/dL and a serum creatinine ≥2.75 mg/dL, when present in concert with a systolic blood pressure <115 mm Hg, was associated with ~20% in-hospital mortality (10-fold that when the SBP was ≥115 mm Hg and the BUN was <43 mg/dL) (50). In the EVEREST trial (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan enrolling patients with LVEF ≤40% hospitalized for decompensated heart failure), one-year mortality was ~45% in those with a baseline eGFR <30 mL/min/1.73 m^2

versus ~15% in those with a baseline eGFR ≥90 mL/min/1.73 m^2 (51). Similarly, in the OPTIME-CHF trial (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure enrolling 949 patients hospitalized with acute on chronic systolic heart failure), baseline BUN was a strong marker of death at 60 days: 3.3% in quartile 1 BUN (median BUN 14 mg/dL, IQR 12-16) vs. 21% in quartile 4 (median 56 mg/dL, IQR 46-68) (52).

Advanced heart failure

In a series of 48 subjects with advanced heart failure (NYHA III or IV) admitted to a heart failure service, development of aggravated renal dysfunction (defined as ≥ 25% in serum creatinine to a level ≥2 mg/dL which occurred in 10 subjects) was associated with mortality after approximately one year of follow-up: 60% vs. 10% in those with stable renal function, p=0.002 (53). In the ESCAPE trial, worsening renal function (increased serum creatinine ≥0.3 mg/dL) was not associated with outcome at 6 months although both baseline eGFR (HR 1.2 per 10 ml/min decrement, 95% CI 1.11-1.29, p<0.001) and discharge eGFR (HR 1.28 per 10 ml/min decrement, 95% CI 1.14 to 1.4, p<0.001) were associated with 6-month mortality (54).

In summary, renal dysfunction is a strong marker of an increased risk of death in patients with chronic heart failure, those hospitalized with acutely decompensated heart failure, and those with known advanced heart failure.

3B. iv. Need for high diuretic doses

As patients with chronic heart failure develop progressive illness, diuretic doses are often escalated in an attempt to achieve euvolemia. Dr. Milton Packer and colleagues assessed the association of the dose of loop diuretic with mortality in a retrospective analysis of the PRAISE trial (Prospective Randomized Amlodipine Survival Evaluation study, 1153 patients, LVEF <30%, NYHA IIIB/IV, median follow-up 14 months) (55). They dichotomized diuretic dose at the median (80 mg furosemide or 2 mg bumetanide) and demonstrated that those receiving above the median (mean dose 175 ± 3 mg furosemide/day) versus below the median furosemide dose (mean dose 53 ± 0.9 mg furosemide/day) were at significantly increased risk of mortality (adjusted HR 1.37, p=0.004). In particular, subjects on both high diuretic dose and low ACE-inhibitor dose were high risk with a one-year mortality of ~40%. Subjects who required supplemental metolazone in addition to loop diuretics were also at increased risk of death (adjusted HR 1.37, p=0.02). In another study of 1354 patients with advanced heart failure followed at UCLA, diuretic dose again was demonstrated to be associated with all-cause mortality both in unadjusted (see Figure 7) and adjusted analyses (HR 4 [95% CI 1.9 to 8.4] for quartile 4 vs. quartile 1) (56).

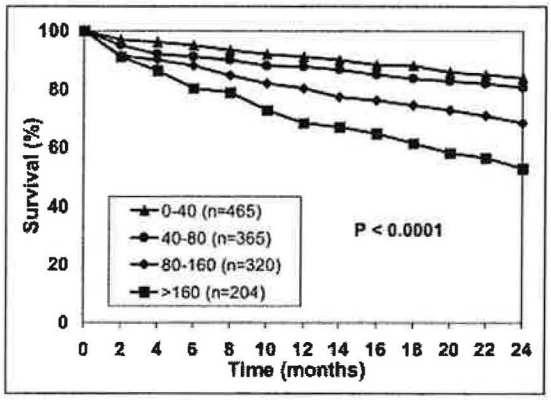

Figure 7. Association of diuretic dose with survival in advanced heart failure. Subjects treated with >160 mg/day of furosemide had the highest one-year mortality (31%). From (56).

In summary, patients with chronic heart failure requiring furosemide equivalent dose ≥160 mg a day and/or supplemental metolazone should be considered to be at increased risk of death.

3B. v. Intolerance to ACE-I or BBL

Patients admitted to the cardiomyopathy service at Brigham and Women's Hospital were stratified based on whether they were receiving ACE-inhibitor therapy at discharge. Subjects who had developed hypotension or progressive renal dysfunction leading to ACE-inhibitor discontinuation were said to have developed a "circulatory-renal limitation" (CRL). As shown in Figure 8, this single event identified patients with ~50% one-year mortality (57).

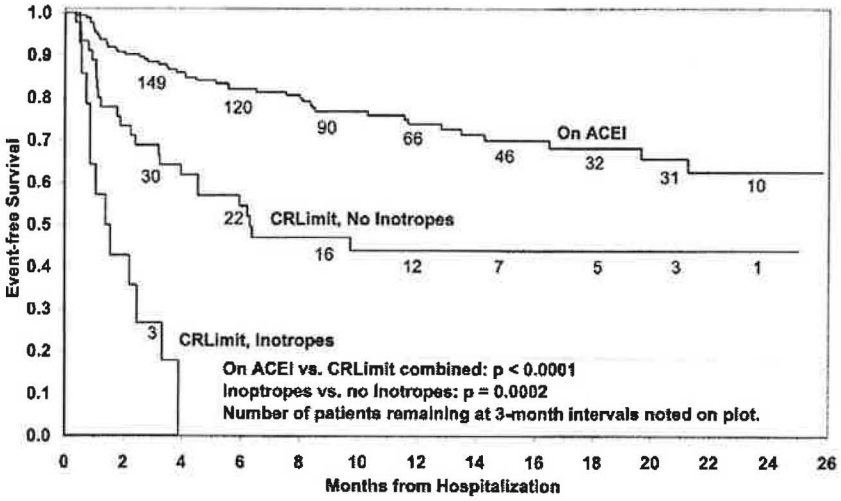

Figure 8. Kaplan-Meier plot of survival without LVAD or transplant. N=173 (ACE-I); n=45 (circulatory-renal limitation, [CRL] without inotropes); n=14 (CRL with inotropes). From (57).

Patients who do not tolerate beta-blockers also appear to be at high risk of adverse outcomes. In OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure), subjects who had beta-blockers withdrawn during hospitalization had a subsequent 90-day mortality rate of 25%, which was significantly higher than the 90-day mortality rate of 8.7% in subjects who had their beta-blockers continued [adjusted HR 2.3 (95% CI: 1.2 to 4.6, p=0.013)] (58).

3B. vi. Cardiac cachexia

The inability to defend one's body weight is associated with a poor prognosis in many medical conditions (59). In heart failure, cachexia occurs due to complex, poorly understood pathways including activation of neurohormonal and inflammatory pathways (60,61), possibly mediated through intestinal abnormalities allowing translocation of endotoxin (lipopolysaccharide) (62,63). That cachexia is associated with increased mortality in HF was first demonstrated in 1997 in a series of 171 heart failure patients who were predominantly NYHA class II-III; subjects (n=28) who lost more than 7.5% of their previous nonedematous weight over a period of at least 6 months, as compared to those who did not, had a higher one-year mortality (39% vs. 13%, respectively) (64). This association was confirmed in retrospective analyses of the SOLVD and V-HeFT II study where a weight loss of ≥6% was independently associated with mortality despite adjustment of other risk factors including NYHA class and LVEF (adjusted HR 2.1, 95% CI 1.8-2.5, p<0.001) (65).

3B. vii. Bad news from the electrophysiologist: ICD shocks and "non-responder" to biventricular pacing

Device therapy including implantable cardioverter-defibrillators and cardiac resynchronization therapy have become commonplace in patients with systolic heart failure. With deployment of these therapies, it has become evident that patient response to such therapies provides prognostic information.

ICD shocks

Approximately one-third of patients receive a shock within four years of ICD implantation (66). The MADIT II investigators (Multicenter Automatic Defibrillator Implantation Trial) were the first to report that an ICD shock was an adverse prognostic factor. In that trial, an appropriate ICD shock was associated with a significant increase in the risk of development of heart failure (67). In the SCD-HeFT trial (Sudden Cardiac Death in Heart Failure, median follow-up 45.5 months, 269 of 811 patients with ICD had a shock, 128 of which were appropriate shocks), an appropriate ICD shock was associated with an increased risk of death in multivariable analysis (HR 5.7, 95% CI 4 to 8, p<0.001) and there appeared to be a dose effect with increasing number of shocks (see Figure 9) (66).

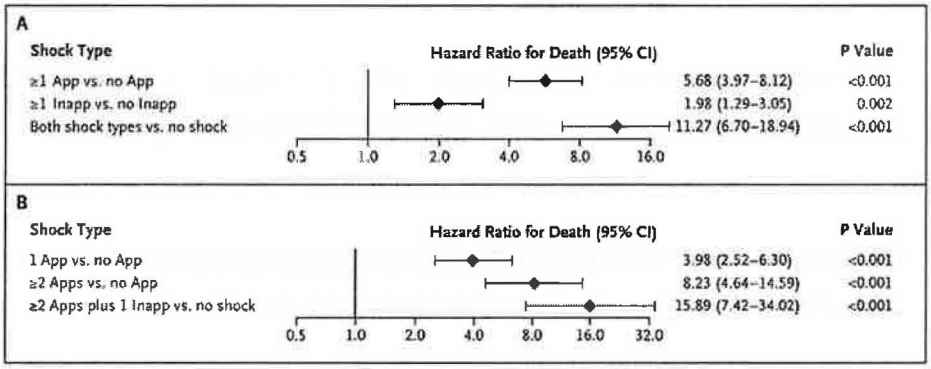

Figure 9. The association of ICD shocks with mortality. Panel A. Shock types Panel B. Number of shocks. App=appropriate; Inapp=inappropriate. From (66).

Among subjects with an inappropriate shock, the risk of death was also increased [HR 1.98 (1.3-3, p=0.002)], though not to the magnitude following an appropriate shock. The risk of death persisted (HR 3) among those who survived more than 24 hours post-appropriate ICD shock. Further, in NYHA class III subjects, the one-year mortality after a shock was 36% (66). Although it is not certain whether the ICD shock contributes to the clinical deterioration, or is simply a marker of clinical deterioration, this event represents a transition in the expected natural history of a patient with heart failure (68). In a review paper addressing the management of heart failure patients who received an ICD shock, Dr. Joseph Mishkin emphasized that such patients should be considered high-risk and have close multidisciplinary surveillance including involvement of a primary care physician, electrophysiologist, and heart failure specialist (69).

"Non-responder" to cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT, also called biventricular pacing) has emerged as an important therapy in patients with systolic heart failure who have a wide QRS (at least 120 msec) on the electrocardiogram (70). CRT is associated with improvements in functional class, quality of life, LVEF, and survival. However, there is considerable inter-individual variability in the response to CRT therapy such that approximately one-third of patients do not benefit from this therapy (71). Assessment of response to cardiac resynchronization therapy can be measured in a number of ways, including improvement in NYHA class, but in many studies is assessed by a reduction in left ventricular volume measured by echocardiography ("reverse remodeling"). Although one cannot predict with certainty who will either have a robust echocardiographic response ("hyper-responder") or not have any measurable response ("non-responder"), a number of baseline features do have predictive value, the most important of which favoring response include a left bundle branch block pattern with a very wide QRS duration (e.g., ≥150 msec). Additionally, patients with a nonischemic cardiomyopathy are more likely to respond to CRT than those with ischemic cardiomyopathy (71).

Individuals who receive CRT and do not have reverse remodeling are at an increased risk of death as compared to those who do have reverse remodeling (72,73). In NYHA III or IV patients who undergo CRT, evidence for lack of reverse remodeling (i.e., no reduction or an increase in LV chamber dimensions) at 6 months portends that they will remain within the spectrum of advanced heart failure and have a guarded prognosis.

Table 4. Clinical events which identify heart failure patients at high risk for adverse outcomes

Clinical finding	Detailed information about clinical finding
Lack of clinical stability	· Inability to walk 1 block on the level ground due to dyspnea/fatigue (NYHA IIIB) · Dyspnea/fatigue with dressing or bathing requiring rest (NYHA IV) · Clinical assessment suggests congestion and/or low cardiac index
Rehospitalization for CHF	Repeated (≥ 2) hospitalizations for heart failure in the last year
Renal dysfunction	Progressive renal insufficiency (especially when approaching stage 4 CKD)
High doses of diuretic	Need for furosemide equivalent dose >160 mg a day and/or use of supplemental metolazone
Weight loss	Body weight loss ≥6% without other cause (cardiac cachexia; not resolution of volume overload)
ACEi or BBL intolerance	·Intolerance to ACE-inhibitors due to hypotension and/or worsening renal function ·Intolerance to Beta-blockers due to worsening heart failure or hypotension
Bad news from EP	· Non-responder to cardiac resynchronization therapy ·Recurrent ICD shocks

3B. Summary

A number of easily recognizable clinical parameters (Table 4) can allow physicians to identify subjects with advanced heart failure. The presence of these factors should prompt consideration of referral to an advanced heart failure center if the patient does not have major comorbidities which would limit candidacy for advanced therapies such as LVAD or transplantation.

4. Therapeutic options

4A. Current therapies

The components of an initial evaluation of an advanced heart failure patient are shown (Table 5).

Table 5. Initial approach to a patient with advanced heart failure

Confirm severity of illness
Reassess "evidence based" medical and device regimen
"Buy time" for new-onset heart failure
Look for reversible factors – including relief of congestion
Assess stability of rhythm and device
Inotropes are last resort

When patients are referred to an advanced heart failure center, an initial evaluation is undertaken to confirm their severity of illness. The absence of any of the other factors (besides NYHA IIIB/IV symptoms) listed in Table 4 raises questions as to whether the patient has advanced heart failure. Another important determination is to confirm that heart failure is the cause of the patient's symptoms. For example, in a NYHA IV-Rest patient, a Stevenson A profile, especially in the presence of a low natriuretic peptide level (when patient is not obese), would suggest their symptoms are disproportionate to the objective clinical findings. Additionally, in a patient who has concomitant heart and lung disease, it can be challenging to determine the cause of their dyspnea. In both situations, a formal cardiopulmonary stress test can be helpful and is often used in the early evaluation at an advanced heart failure center.

Second, a reassessment should be conducted to ensure that all "evidenced-based" therapies (Figure 10) have been attempted (74).

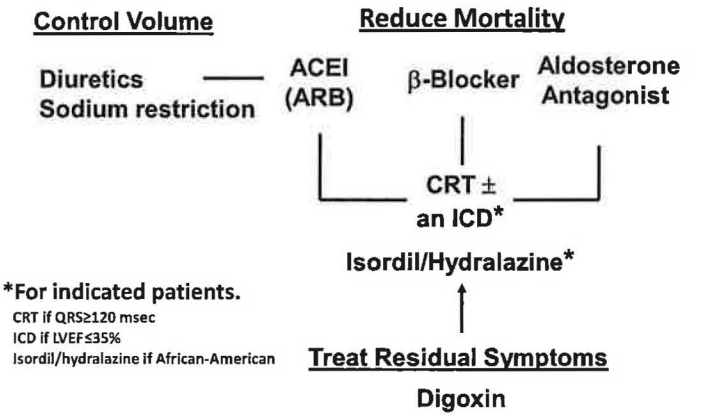

Figure 10. Treatment algorithm for systolic heart failure.

All attempts should be made to treat with agents that have been shown to improve survival. In particular, in subjects who have not been challenged with beta-blockers (if they can be rendered clinically euvolemic) or CRT (in those with wide LBBB), implementation of these therapies can have profound effects on ventricular function and outcome. Although digoxin does not improve mortality, it does reduce risk of hospitalization from progressive heart failure (75) and may be more beneficial when its trough levels are kept in the 0.5 to 0.8 ng/mL range (76-78).

Third, the temporal nature of the illness is important to consider as patients with "new-onset heart failure" (often defined as onset within 6 months) can have substantial recovery of myocardial function over time (79). Even patients who present with fulminant myocarditis requiring temporary mechanical support can recover (80). Thus, if at all possible, before considering LVAD or transplantation, all efforts should be made to "buy some time" for the patient with recent onset heart failure to see if reverse remodeling can occur.

Fourth, patients should be evaluated for reversible factors which can impact clinical stability: including ongoing alcohol use, thyroid disturbances, valvular abnormalities, poorly controlled hypertension, ischemia, and untreated sleep apnea. When renal insufficiency is present, other processes which can detrimentally impact renal function should be considered (e.g., urinary obstruction). A major factor which should be considered in all patients is inadequately treated volume overload, as this is the major cause of ongoing symptoms in patients with advanced heart failure and therefore is a potential therapeutic target (33). Upon referral to our advanced heart failure center, we commonly discover that patients are consuming large amounts of daily sodium, sometimes in part due to a lack of knowledge about the importance of sodium restriction, and sometimes due to a lack in the skills needed to implement a sodium restriction (i.e., reading a *Nutrition Facts* label) (81). Other approaches to relieve congestion include escalation of diuretic therapy and education in a "flexible diuretic regimen." Here, patients are instructed to weigh daily each morning (before breakfast, after voiding, wearing the same amount of clothes: e.g., undergarments or naked) and to increase their diuretics if they gain more than 2 lbs in a day (or 5 lbs in a week). The intent is to mobilize volume (as reflected by the small weight gain) before the patient becomes so overloaded that they are resistant to oral diuretics (perhaps in part due to lack of absorption with gut edema) and present to the emergency department or are hospitalized. Weight gain often precedes decompensation in heart failure patients (82).

Fifth, it is important to assess the stability of the heart rhythm and pacemaker/ICD. Potential rhythm disturbances such as bradycardia, atrial tachycardia (which can be mistaken for sinus tachycardia), atrial fibrillation/flutter, and ventricular ectopy should be considered. Treatment of many of these can improve LVEF and lead to clinical stability (83-86). In addition, interrogation of the pacemaker/ICD should be undertaken. Such assessment may identify chronic RV pacing which can lead to worsening heart failure (87-89), loss of LV capture or other malfunction of biventricular pacing (90,91), and atrial dysrhythmias not recognized on the surface electrocardiogram.

Sixth, inotropes do not improve outcomes in patients with heart failure. Indeed, the dismal prognosis for patients with inotropes has previously been described (see Section 3A and

Figure 2). Thus, inotropes should be used as a last resort and after a low cardiac index impacting end-organ function has been demonstrated.

The important question then is what therapeutic options are available for a patient with persistent advanced heart failure after the above evaluation is concluded?

4. A. i. Therapy guided by invasively measured hemodynamics

In the late 1980s-1990s, a series of observational studies suggested that therapy "tailored" to invasively measured hemodynamics could stabilize patients with advanced heart failure and potentially obviate the need for transplantation (92-94). In this approach, patients would be admitted to the hospital and have a right heart catheter placed. For those with elevated left ventricular filling pressures (as measured by the pulmonary capillary wedge pressure, PCWP) and a high systemic vascular resistance (SVR) in concert with a low cardiac index (CI) (i.e., Stevenson profile C), an intravenous vasodilator with or without inotrope was given and then followed by aggressive diuresis targeting a PCWP <16 mm Hg. Subsequently, the intravenous inotrope/vasodilator was weaned off while doses of ACE-inhibitor (usually captopril), isordil, and hydralazine were uptitrated to maintain the targeted SVR (1000-1200 dyne-sec-cm^{-5}). Dr. Milton Packer has demonstrated that captopril is better tolerated than enalapril in a comparable patient population of advanced heart failure (95).

A strategy of guiding therapy in advanced heart failure with the pulmonary artery catheter (PAC) was tested in the ESCAPE study conducted between 2000 and 2003 (24). The trial was designed to randomize 500 subjects with advanced heart failure to a clinical evaluation arm or a PAC + clinical evaluation arm. The trial was terminated early by the Data and Safety Monitoring Board due to futility after 433 subjects were enrolled. The primary outcome, the number of days alive outside the hospital at 6 months, was no different in the two arms as shown (Figure 11).

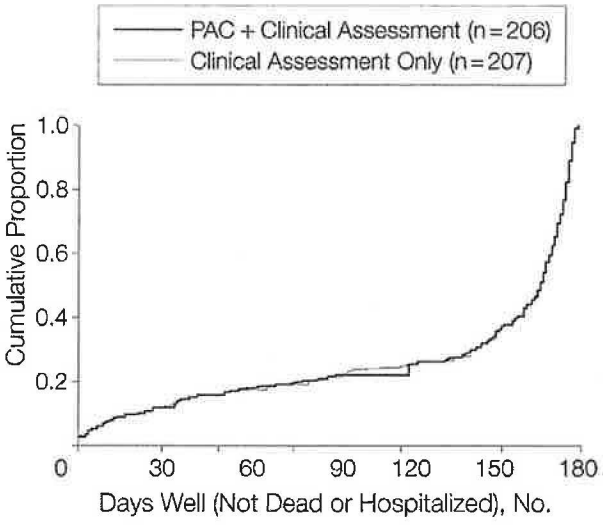

Figure 11. Cumulative primary outcome from the ESCAPE trial. Primary outcome was number of days alive outside the hospital at 6 months. PAC=pulmonary artery catheter. From (24).

The ESCAPE trial demonstrated there is no justification for routine right heart catheterization in patients with advanced heart failure. Given the paucity of data demonstrating benefit of PACs, there has been a dramatic reduction in their use in the United States (65%

reduction from 1993 to 2004) for all medical conditions, including heart failure patients (96). However, right heart catheterization continues to be routinely performed in many advanced heart failure centers as they consider the need for continuous intravenous inotropes, LVAD, or cardiac transplantation.

4 A. ii. LVAD

There have been major advances in the field of mechanical support of the failing heart over the last decade. Strategies include "bridge to transplant" (to keep patients alive and functional while awaiting a suitable donor) and "destination therapy" (in patients who are not transplant candidates). The REMATCH trial, published in 2001, demonstrated that in patients with end-stage failure, destination therapy with a LVAD (the HeartMate XVE) could improve survival beyond the best available medical therapy (23). As such, this landmark trial should be considered to be "proof-of-concept." However, although the LVAD outcomes were better than those in the medical arm (2-year survival, 23% vs. 8%), they remained suboptimal. That fact, coupled with the bulk and noise of HeartMate XVE, likely prevented the medical community from broadly embracing this therapy.

More recently, second-generation LVADs have entered the medical arena. These are smaller, quieter, continuous flow devices which often result in the absence of pulsatile flow in the LVAD recipient. The HeartMate II has been approved in the United States both for bridge to transplant and destination therapy based on two pivotal trials (97,98). In addition to improved survival, the LVAD was also associated with improved functional class and quality of life (99). There are a number of important potential complications associated with these devices including RV failure, gastrointestinal bleeding (often from arteriovenous malformations), infection (e.g., driveline), aortic insufficiency, and stroke (100-103). In particular, the published stroke rate was 13% per patient year (98). Candidates for LVAD therapy are screened carefully to ensure their post-LVAD risks will be acceptable. For example, patients who cannot tolerate systemic anticoagulation or those with poor compliance who may not care for the driveline site should not be offered LVAD therapy. Despite these potential complications, the progress in the survival of end-stage heart failure patients who receive a HeartMate II for destination therapy, as compared to the medical treatment arm in REMATCH, is remarkable (Figure 12) (104).

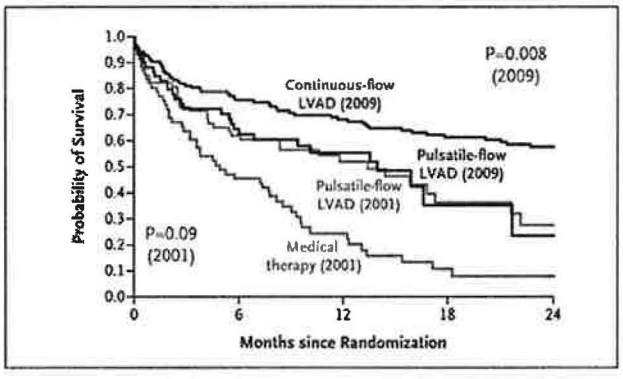

Figure 12. Composite of survival curves from REMATCH (lighter lines) and the more recent destination trial (darker lines) which compared the pulsatile HeartMate XVE to the continuous flow HeartMate II. Note that the survival curves for the pulsatile device experience in the two trials are nearly superimposed despite the intervening 8 years. Also note the dramatic improvement in survival when comparing the recent continuous flow LVAD to the REMATCH medical therapy arm. From (104).

The field of mechanical support continues to advance quickly. Already 3rd generation, smaller, centrifugal pumps have completed clinical trials and are awaiting regulatory approval. HeartWare reported an ~90% one-year survival in its HVAD bridge to transplant trial (105). In addition to technological advances, better patient selection may improve outcomes. One possible strategy is to implant patients with less advanced heart failure because patients who are INTERMACS 3 or 4 have better survival following LVAD implant than those who are INTERMACS 1 or 2 (106). There is an ongoing trial (REVIVE-IT) testing LVAD therapy in NYHA class III patients (107,108).

An important question to consider is whether we have reached the "tipping point" (109) in the acceptance of LVAD therapy. Specifically, are the survival rates (68% at 1 year and 58% at 2 years) sufficient, and the associated comorbidities acceptable, such that physicians will routinely refer patients with advanced heart failure for this therapy? There are conflicting opinions as to whether a large increase in LVAD utilization would be appropriate (11,103). The publicity provided from the LVAD implant in former Vice President Dick Cheney (110) may influence these decisions. A favorable experience in patients older than 70 years of age has been published (111). Cognitive function appears stable or improved from baseline, and comparable to that seen with a pulsatile LVAD (112). In 2010, there already was a 10-fold increase in the use of destination LVADs as compared to that seen in 2009 (before the HeartMate II was approved) (103).

LVADs are expensive. The mean 1-year Medicare payment for inpatient care in recipients of LVADs between the years 2000 and 2005 was $178,714 (± sd $142,549) (113). Post-REMATCH, the cost for the index hospitalization for a HeartMate XVE implant was $128,000 (114). As described on page 3, the cost of medical therapy in the last two years of life is also high in this population ($156,000) (3). Recently, the HeartMate II five-year cost was reported to be $360,407 with an incremental cost-effectiveness ratio/quality-adjusted life year (ICER/QALY) of $198,184 (115). Although the ICER/QALY was above a commonly used threshold of $50,000, it was much lower than that reported with the HeartMate XVE ($802,700) (115). These data suggest that with ongoing improvements in LVAD technologies, this therapy will ultimately be cost effective. Given the estimated number of patients with advanced heart failure (e.g., ~250,000 as reviewed above), there are important economic implications related to LVAD therapy in this country.

4A. iii. Cardiac transplantation

Cardiac transplantation remains the "gold-standard" for treatment of patients with advanced heart failure. However, cardiac transplantation is constrained by the number of donor hearts available. In the United States, approximately 2200 recipients are transplanted annually, a number which has essentially been stable since 1991 (n=2127 then) (116). Thus, in the current organ procurement system, transplantation cannot be the solution for advanced heart failure from a public health perspective. Because of the limited supply, donor hearts are viewed as "precious resources" and efforts are made to maximize the benefits accrued from them. Potential candidates are screened closely for comorbidities which may negatively influence the post-transplant outcome (117).

Patients who undergo transplantation have significantly improved survival as compared to patients with advanced heart failure. The median survival is approximately 11 years post transplant. For those who survive the first year, the median survival is 14 years (118). In addition, transplantation restores quality of life: approximately 75% of recipients at year one report having few disease symptoms and a normal healthy lifestyle, and at 5 years, 50% of recipients aged 25 to 55 years are working full (~40% of recipients) or part time (118).

4A. iv. Palliative care

As described in a recent position statement concerning the use of palliative care in patients with heart failure, its aims are "to prevent and relieve suffering and to promote the best quality of life for patients and their families" (119). The 2009 Focused Update of the AHA/ACC 2005 Guidelines for the Management of Heart Failure in Adults provided a class 1 (level of evidence C) recommendation that patients and families should be educated about options for formulating/implementing advanced directives and the role of palliative and hospice care services as they approach end of life (74). In a systematic literature search, suboptimal communication between advanced heart failure patients and their physicians was noted, including the reluctance of many providers to discuss end-of-life issues (120). The need for close collaboration between heart failure specialists and palliative care physicians has been emphasized (120,121). There has been a dramatic shift in the use of hospice in patients with heart failure. In 229,543 Medicare patients with heart failure who died between 1/1/2000 and 12/31/2007, the use of hospice increased from 19% to approximately 40% (122).

4B. Future therapies

There clearly remains a need for additional therapies for patients with advanced heart failure. Promising emerging therapies include miniaturized LVADs which are fully implantable (123,124), the total artificial heart (125,126) and stem cell therapy (127,128). Recent data suggest that a cardiac myosin activator, omecamtiv mecarbil, can improve cardiac function in heart failure patients (129,130), though the experience with this agent is in its early stages. Finally, a recent small (n=39) phase II randomized trial in humans called CUPID (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) demonstrated that sarcoplasmic reticulum Ca^{2+}-ATPase delivered by intracoronary adeno-associated virus type 1 was associated with improvements in a number of clinical parameters including a reduction in subsequent hospitalizations (131) although larger studies are needed.

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