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Advanced Chronic Heart Failure and Heart Transplantation

A Guide to Clinical Decision-Making

FIRST EDITION

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Advanced Chronic Heart Failure and Heart Transplantation

A Guide to Clinical Decision-Making

FIRST EDITION

To the memory of my father

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Preface

Due to recent advances in treatment of acute coronary syndromes, chronic heart failure remains the only cardiovascular disease, which is steadily increasing in incidence and represents a major global healthcare problem. Left ventricular dysfunction for patients with heart failure is usually progressive, even when no new myocardial insult can be identified; this eventually results in the advanced stages of heart failure marked by worsening symptoms that require multiple and frequently prolonged hospitalizations. The syndrome is usually treated with appropriate medical therapies; the clinical diagnosis advanced heart failure is made only when such therapies have failed. Strategies for treating advanced heart failure aim to improve symptoms, limit disease progression, and improve the health, wellbeing, and patient survival. Despite the recent advances in medical management and novel devices in the field, heart transplantation remains the therapeutic 'golden standard' in this patient cohort.

The aim of this book is to better define the role of heart transplantation in treatment of advanced chronic heart failure in the recent era and to directly compare it to the main alternative treatment modalities (optimal medical management, cardiac resynchronization therapy, left ventricular assist devices). Using a patient-based approach this manual first selectively analyses the main indications and contraindications for heart transplantation (Part 1), and then aims to define risk factors and preventive strategies to tailor immunosuppressive management in heart transplant recipients (Part 2).

The inspiration for this book came from Dr. Branislav Radovancević, my recently deceased mentor, friend and a world-renown transplant physician, to whom I owe my deepest gratitude for introducing me into the clinical arena of advanced heart failure and heart transplantation. The manual was written during my visiting professorship at Stanford University School of Medicine, where I received extensive support and excellent guidance from Professor Sharon A. Hunt. Finally, this book could not have been written without the help of many colleagues from Ljubljana University Medical Center Advanced Heart Failure and Transplantation Program, who allow the principles of this book to be transferred into daily practice.

Bojan Vrtovec

PART I:

**PATIENTS WITH ADVANCED CHRONIC
HEART FAILURE**

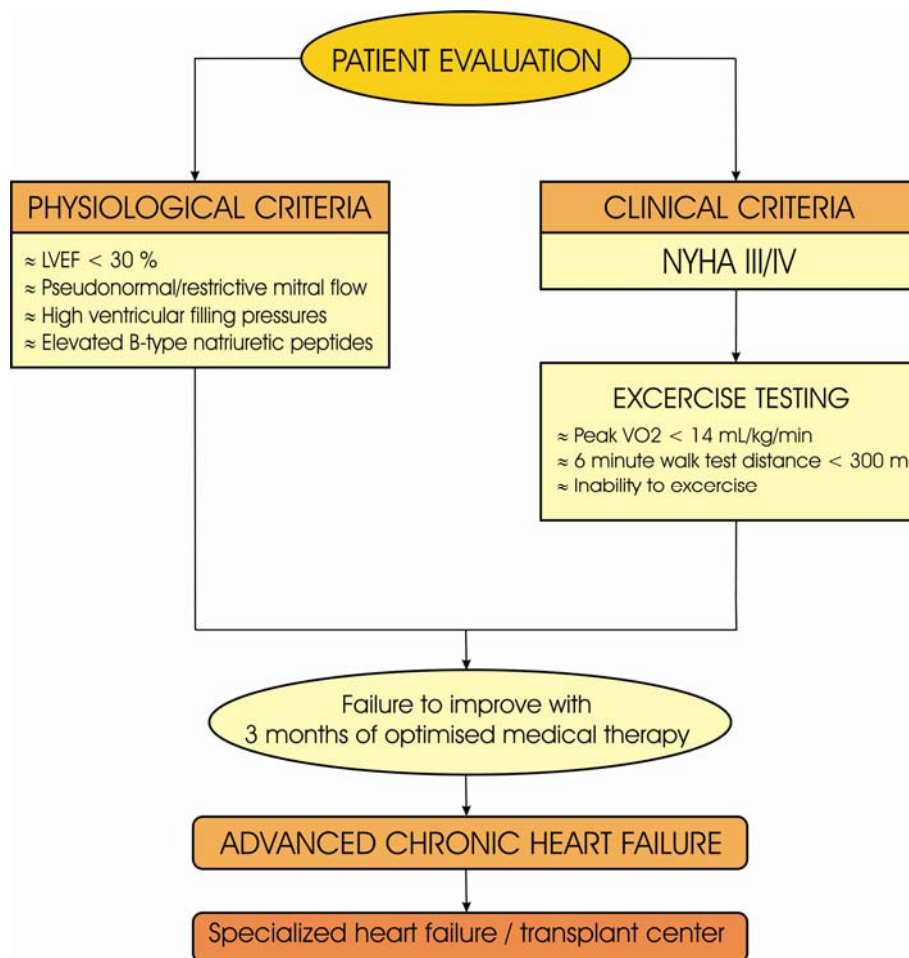
Chapter 1:

Diagnosis of Advanced Chronic Heart Failure

Advanced chronic heart failure is defined as Stage D heart failure according to the latest ACC/AHA heart failure guidelines (1). It designates patients with refractory heart failure who might be eligible for specialized, advanced treatment strategies or cardiac transplantation, or for end-of-life care, such as hospice.

In the definition of advanced chronic heart failure both physiological and clinical criteria seem required. “Advanced” connotes being far along in a course. From the physiological viewpoint being far along in the course of heart failure may imply the presence of severe cardiac dysfunction, whereas from the clinical perspective marked signs and symptoms of volume overload or fatigue would be characteristic. Thus, the definition of advanced heart failure unites classical physiological and clinical criteria (2) (Figure 1).

Figure 1. Diagnosis of advanced chronic heart failure



To make the definition of advanced chronic heart failure clinically useful, specific degrees of symptoms and cardiac dysfunction whose presence is indicative not only of severe disease but also of poor outcome during follow-up should be delineated.

Physiological Criteria

Advanced chronic heart failure was traditionally defined by objective evidence of severe cardiac dysfunction as shown by severely depressed left ventricular ejection fraction, which may be accompanied by right ventricular dysfunction. However, nearly one-half of patients presenting with heart failure have preserved left ventricular ejection fraction, and they experience an overall prognosis and pattern of functional decline similar to that of patients with heart failure and reduced ejection fraction (3). This signifies that the degree of systolic dysfunction is not a clinically useful parameter when determining the degree of heart failure progression, and that other parameters have to be considered. In fact, it is likely that the clinical syndrome of heart failure may result from a combination of disorders of the pericardium, myocardium, endocardium, great vessels, and kidneys (1,4).

Therefore, although left ventricular ejection fraction provides an easily available and well-established noninvasive method to identify patients with systolic dysfunction (5), it should not be viewed as a sole physiologic criterion for defining advanced chronic heart failure.

In a recent position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology, severe cardiac dysfunction is defined by the presence of at least one of the following: left ventricular ejection fraction < 30%, pseudonormal or restrictive mitral inflow pattern at Doppler-echocardiography; high left and/or right

ventricular filling pressures or elevated B-type natriuretic peptides (6). Although this approach may offer a better definition of physiologic criteria, the diagnosis of advanced chronic heart failure still largely relies on clinical criteria.

Clinical Criteria

The clinical definition of advanced chronic heart failure is based on NYHA class 3 or 4 symptoms, severely impaired exercise capacity, and a history of at least 1 hospitalization due to heart failure in the past 6 months despite optimal medical therapy (6).

NYHA functional class provides a simple clinical assessment that may be surprisingly useful. This categoric system is traditionally based on the degree of difficulty with shortness of breath and fatigue that patients have at rest or during activity. It assigns patients to 1 of 4 functional classes: patients may have symptoms of heart failure at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels of exertion that would limit normal individuals (class I). Advanced heart failure is characterized by NYHA functional class III or IV, implying symptoms during minimal activity or at rest, respectively.

Even advanced heart failure is punctuated by periods of more severe signs and symptoms followed by periods of compensation. Often, patients with a history of functional class 4 will respond to augmented therapy with significant lessening of symptoms. Therefore, a 3-month persistence of at least NYHA III symptoms seems to be a justifiable requirement for the diagnosis of advanced chronic heart failure (2).

Additional objective criteria for advanced heart failure can be obtained using exercise studies. Exercise testing typically includes measurement of expired gases to better characterize functional

capacity. A peak oxygen consumption of <14 ml/kg/min would appear to be a reasonable diagnostic criterion for advanced heart failure, and a diagnosis of advanced heart failure would be unreasonable if peak VO_2 was >18 ml/kg/min (7).

However, cardiopulmonary exercise testing is a time consuming and costly diagnostic tool, which requires sophisticated equipment and specially trained personnel. Alternatively, exercise capacity can also be determined by the 6-minute walk test. This test simply measures the distance covered by strong walking on a hallway level within 6 minutes. Part of the rationale for using the 6 minute walk test rather than the bicycle or treadmill exercise is that it is a more natural form of exercise that may better reflect daily activity. The results of the 6-minute walk test are concordant with changes in symptoms, suggesting that it may be used as supportive evidence for symptom benefit. The test may be of greater value in patients with more advanced heart failure, where it may function as a maximal exercise test. In these patients a severe impairment of functional capacity is demonstrated by either inability to exercise or a 6-minute walk test distance less than 300 m (8).

Patients who have met the working definition for advanced heart failure can respond dramatically to medical treatment. The response to optimization of pharmacologic and nonpharmacologic therapy may be sufficiently favorable that the diagnosis of advanced heart failure is no longer warranted. Therefore, a 3-month trial of maximized medical therapy according to the latest clinical guidelines (1) should be performed before the diagnosis of advanced heart failure is assigned. A history of at least 1 heart failure hospitalization in the past 6 months despite maximal medical therapy can further confirm the diagnosis (6). Once the diagnosis of advanced chronic heart failure is assigned, a referral to a specialized heart failure/cardiac transplantation center in potentially eligible patients is recommended (1).

Part I: Diagnosis of Advanced Chronic Heart Failure

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Chapter 2:

Evaluation of Indications for Heart Transplantation

In a specialized center, the evaluation of patients with advanced chronic heart failure patient is based on integrated approach that includes the assessment of candidacy for heart transplantation and alternate treatment modalities, such as cardiac resynchronization therapy (CRT) or mechanical circulatory support (LVAD).

Current indications for heart transplantation listing in patients with advanced chronic heart failure are presented in Table 1 (1). The evaluation process and listing practices for heart transplantation have evolved significantly over the past years. Increasing therapeutic options for these patients have contributed to longer periods of stability before transplantation. When applying currently accepted criteria for heart transplant candidacy, the majority of patients referred for a transplant are never listed, and those who are listed are not often listed immediately after the initial evaluation (2).

Table 1. Indications for Heart Transplantation in Advanced Chronic Heart Failure

<p><u>ABSOLUTE</u></p> <ul style="list-style-type: none">• Refractory cardiogenic shock• Documented dependence on IV inotropic support to maintain adequate organ perfusion• Peak VO_2 less than 10 ml/kg/min with achievement of anaerobic metabolism• Recurrent life-threatening ventricular arrhythmias refractory to all therapeutic modalities <p><u>RELATIVE</u></p> <ul style="list-style-type: none">• Peak VO_2 11 to 14 ml/kg/min (or 55% of predicted) and major limitation of the patient's daily activities

Since the decision-making for patients with advanced heart failure is rapidly changing, specialized advanced heart failure programs must evaluate the increasingly complex medical and device therapies available to determine the most optimal management plan for individual patients. This is particularly true for ambulatory patients with advanced heart failure, in whom the survival benefit of heart transplantation may be comparable to other treatment modalities. To further stratify these patients, several predictive factors have been studied to calculate heart failure prognosis scores. According to the ISHLT guidelines (3) in circumstances of ambiguity a Heart Failure Survival Score (HFSS) may be considered to add discriminatory value to determining prognosis and guide listing for transplantation for ambulatory patients (Table 2). Although the components of HFSS have each been separately identified and validated as valid prognostic measures in ambulatory patients with advanced heart failure, the HFSS was

Table 2. Components of Heart Failure Survival Score (HFSS)

- Peak VO₂
- Ischemic heart failure etiology
- Left ventricular ejection fraction
- Serum sodium
- Mean blood pressure at rest
- Resting heart rate
- QRS duration ≥120 milliseconds (left bundle branch block, right bundle branch block, non-specific intraventricular conduction delay or ventricularly paced rhythm)

developed before the widespread use of beta-blockers, spironolactone, biventricular pacemakers, and mechanical circulatory support. Since the value of HFSS in the setting of modern therapies for advanced chronic heart failure may be somewhat limited, the clinical decision –making still largely relies on determination of exercise capacity, as measured by peak VO₂.

Peak VO₂

Peak VO₂ has been shown to be an important prognostic measurement in the evaluation of patients with heart failure and is used to monitor the progress of the condition. Although it may be influenced by noncardiac factors such as age, sex, motivation, anemia, and muscle deconditioning, it is still the most widely used predictor of outcome in ambulatory patients who have severe heart failure (4).

Patients with advanced chronic heart failure and peak VO₂ ≤14 ml/kg/min have been shown to have significantly higher mortality when compared to those with peak VO₂ >14 ml/kg/min (5). However, recent advances in medical management may also

change the predictive value of peak VO₂ in this cohort.

Patients with chronic heart failure with peak exercise oxygen consumption ≤ 14 ml/kg/min and who were treated with beta-blockers have been shown to have significantly better outcomes compared with similarly functionally impaired patients who were not treated with blockers. This benefit was consistent whether patients had ischemic or non-ischemic cardiomyopathy, irrespective of the end-point used, and despite relatively low doses of beta-blocker therapy (6). The beneficial effects of beta-blockers were also evident in each stratum of peak VO₂ ≤ 14 ml/kg/min with the greatest difference in events between the subgroups of patients with a peak VO₂ between 10 and 12 ml/kg/min and 12 and 14 ml/kg/min (7).

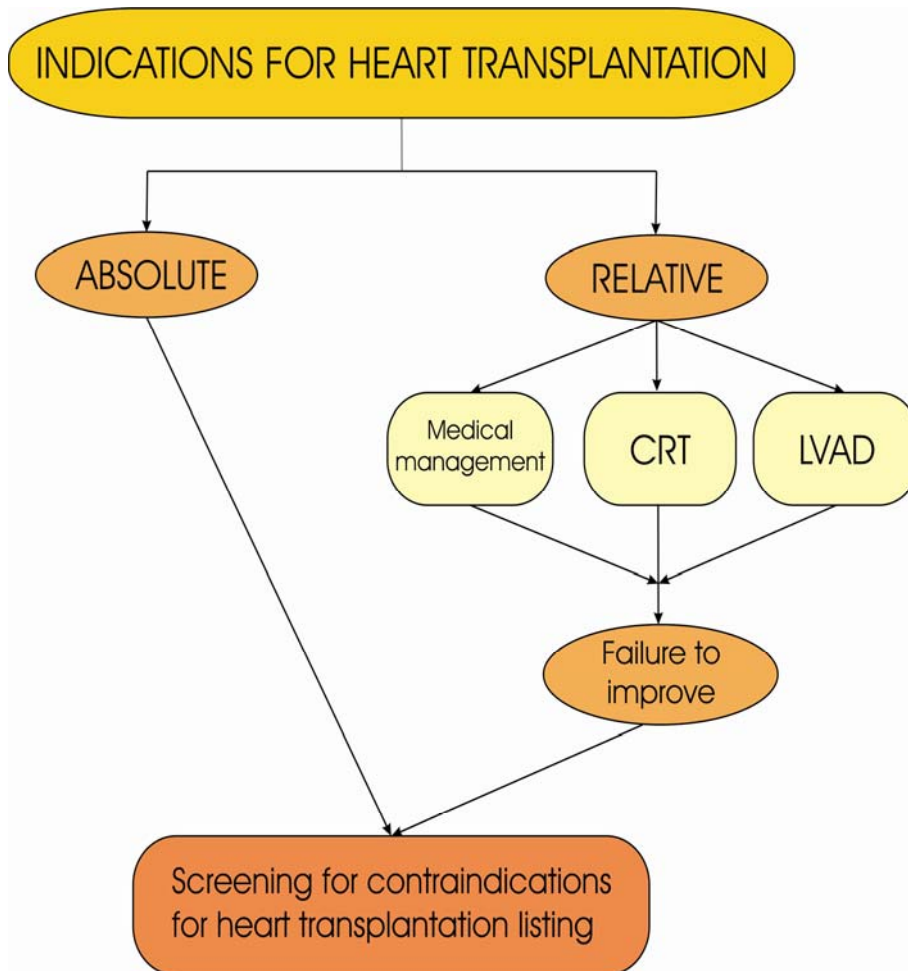
Based on these data it appears that beta-blockers may significantly improve outcome of patients with peak VO₂ ≤ 14 ml/kg/min. Thus, current peak VO₂ listing criteria may not be valid for all patients with advanced chronic heart failure and in addition to other transplant listing criteria, the use of beta-blocker therapy should be considered.

Evaluation of Alternative Treatment Modalities

Before the studies for heart transplantation listing are performed, all patients with advanced chronic heart failure should undergo a comparative assessment of potential benefit with alternative treatment modalities including medical management, LVAD and CRT (Figure 2).

Comparative studies have demonstrated that one-year event-free survival in patients considered for heart transplantation improved in the current era, regardless of initial peak VO₂: 64% versus 48%

Figure 2. Evaluation of advanced chronic heart failure patients



Part I: Evaluation of Indications for Heart Transplantation

for peak VO₂ of <10 ml/min/kg, and 81% versus 70% for peak VO₂ of 10 to 14 ml/min/kg. Overall, patients with peak VO₂ of 10 to 14 ml/min/kg demonstrate survival rates that comparable to those after transplantation (1). Thus, a peak VO₂ less than 10 ml/kg/min is considered an absolute indication for heart transplantation, while in patients with peak VO₂ above 10 ml/kg/min additional risk stratification may be warranted.

Results of recent studies suggest that exercise performance after implantation of LVAD in patients with end-stage heart failure, who underwent intensive postoperative rehabilitation, is sufficient for activities of normal daily life. An increase in maximal exercise performance from 8 to 12 weeks could be demonstrated, most likely due to postoperative convalescence and systematic strenuous training (8). Although LVAD support does increase exercise capacity, the magnitude of improvement is less than after heart transplantation (9). Although it appears that functional capacity post-LVAD may be improved by higher maximum LVAD rate and output, in patients from The LVAD Working Group Recovery Study they found no relationship between functional capacity improvement and peak LVAD flow or LVEF, suggesting that peripheral factors may play an important role (10).

Typically, before implantation of the device, patients have been bedridden on multiple positive inotropic agents or temporary mechanical support. The pre-implant VO₂ of these patients is, therefore, essentially resting oxygen consumption. Therefore, although LVAD implantation has been shown increase exercise capacity (11), the peak VO₂ value in patients with advanced chronic heart failure cannot be used as a parameter to determine candidacy for LVAD support.

In an analysis of data form the InSync/InSync ICD Italian Registry

the authors compared the effect of CRT between patients with mild symptoms of HF with its effect in those with moderate to severe heart failure (NYHA class III or IV) (12). The results of this study indicate that CRT induced similar improvements in ventricular function in the 2 groups, whereas the improvement in functional status was significantly lower for patients in NYHA class II than for those in class III or IV. Similarly, a sub-study of the COMPANTION trial that included NYHA class III or IV heart failure patients with a peak $VO_2 \leq 22$ mL/kg/ min found that CRT improved exercise capacity, functional status, and quality of life in this patient cohort (13). Furthermore, pre-implant peak VO_2 has been shown to predict clinical events (time to death, time to death or first hospitalization, or time to death and first heart failure hospitalization) after CRT implantation.

Based on the existing data it appears that peak VO_2 may be significantly improved with CRT, which suggests that this therapy should be considered in the setting of pre transplant candidate selection. However, since patients with lower pre-implant peak VO_2 also have inferior outcome after CRT this therapy may not be a suitable option to improve the outcome in this cohort. Furthermore, the effects of CRT are limited to patients with evidence of ventricular dyssynchrony and thus cannot be applied to general population of patients with advanced chronic heart failure.

Based on the current data it appears that alternate therapies, in particular optimization of medical therapy can considerably alter the outcome of patients with advanced heart failure and Peak $VO_2 < 14$ mL/kg/min. Therefore, a trial of beta blocker therapy appears warranted in all heart transplant candidates with Peak VO_2 between 10 and 14 mL/kg/min. Since pre-implant Peak VO_2 also predicts the outcome after CRT it may be a valid criterion for patient selection with this regard. However, due to its limited

predictive value in patients undergoing LVAD support, it should not be used for decision-making in this setting.

Pre-Transplant Screening

Patients in whom heart transplantation is considered superior to alternate treatment modalities should undergo pre-transplant screening according to the grid recommended by International Society of Heart and Lung Transplantation (3). The studies required for all patients are presented in Table 3, and the additional studies recommended for selected patients are presented in Table 4. In addition to the studies performed at the time of pre-transplant evaluation, follow-up assessment should be performed regularly to allow for adequate response to potential contraindications for heart transplantation listing.

Table 3. Required Pre-Transplant Studies in All Patients

History and Physical, Body weight	Baseline+Q3Months
Assessment of heart failure severity	
• Cardiopulmonary exercise test	Baseline+Q1Year
• Echocardiogram	Baseline+Q1Year
• Right heart catheter	Baseline+Q6Months
• Coronary angiography	Baseline
• ECG	Baseline+Q1Year
Evaluation of multi-organ function	
• Routine lab work (BMP, CBC, LFT)	Baseline+Q3Months
• PT/INR	Baseline+Q3Months

Table 3. cont.

• Urinalysis	Baseline+Q3Months
• GFR (MDRD quadratic equation)	Baseline+Q3Months
• Urine sample for protein excretion	Baseline+Q3Months
• PFT with Arterial blood gasses	Baseline
• CXR (PA and lateral)	Baseline+Q1Year
• Abdominal ultrasound	Baseline
• Stool for occult blood 3x	Baseline+Q1Year
• Immunocompatibility	
• ABO , Repeat ABO	Baseline
• HLA tissue typing	Baseline
• PRA and flow cytometry	Baseline+Q2Months (PRA>10%, VAD, transfusion)
Infectious serology and vaccination	
• Hepatitis B surface Ag	Baseline
• Hepatitis B surface Ab	Baseline
• Hepatitis B core Ab	Baseline
• Hepatitis C Ab	Baseline
• HIV	Baseline
• Rapid Plasma Reagin	Baseline
• HSV IgG	Baseline
• CMV IgG	Baseline
• Toxoplasmosis IgG	Baseline
• EBV IgG	Baseline
• Varicella IgG	Baseline
• PPD	Baseline
General consultation	
• Social work, Psychology	Baseline
• Financial	Baseline

Table 4. Recommended Pre-Transplant Studies in Selected Patients

Evaluation of multi-organ function	
• Carotid Doppler and lower extremity arterial ultrasounds (history or coronary artery disease, smoking, or >50 y)	Baseline
• Pulmonary Function Testing (smoking, amiodarone use)	Baseline
• DEXA scan (>50 y)	Baseline
• Dental examination (poor oral hygiene)	Baseline+Q1Year
• Ophthalmologic examination (diabetic)	Baseline+Q1Year
Preventive and malignancy	
• Colonoscopy (men > 50 y)	Baseline
• Mammography (> 40 y)	Baseline+Q1Year
• Gyn/Pap (>18 y sexually active)	Baseline+Q1Year
• PSA and digital rectal exam (men > 50 y)	Baseline+Q1Year

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Chapter 3:

Evaluation on Contraindications for Heart Transplantation

Traditionally, a number of comorbidities have been considered important in excluding a patient from heart transplantation (Table 5). Due to recent improvements of post-transplant management, most transplant physicians and surgeons would now agree that many of these are primarily relative contraindications that require discussion and individual patient exemptions (1). The aim of pre-transplant comorbidity screening is not only to define absolute and relative contraindications for transplantation, but also to find alternative treatment modalities which may be beneficial in an individual patient either as bridge-to-listing or as destination therapy (Figure 3).

Recipient Age

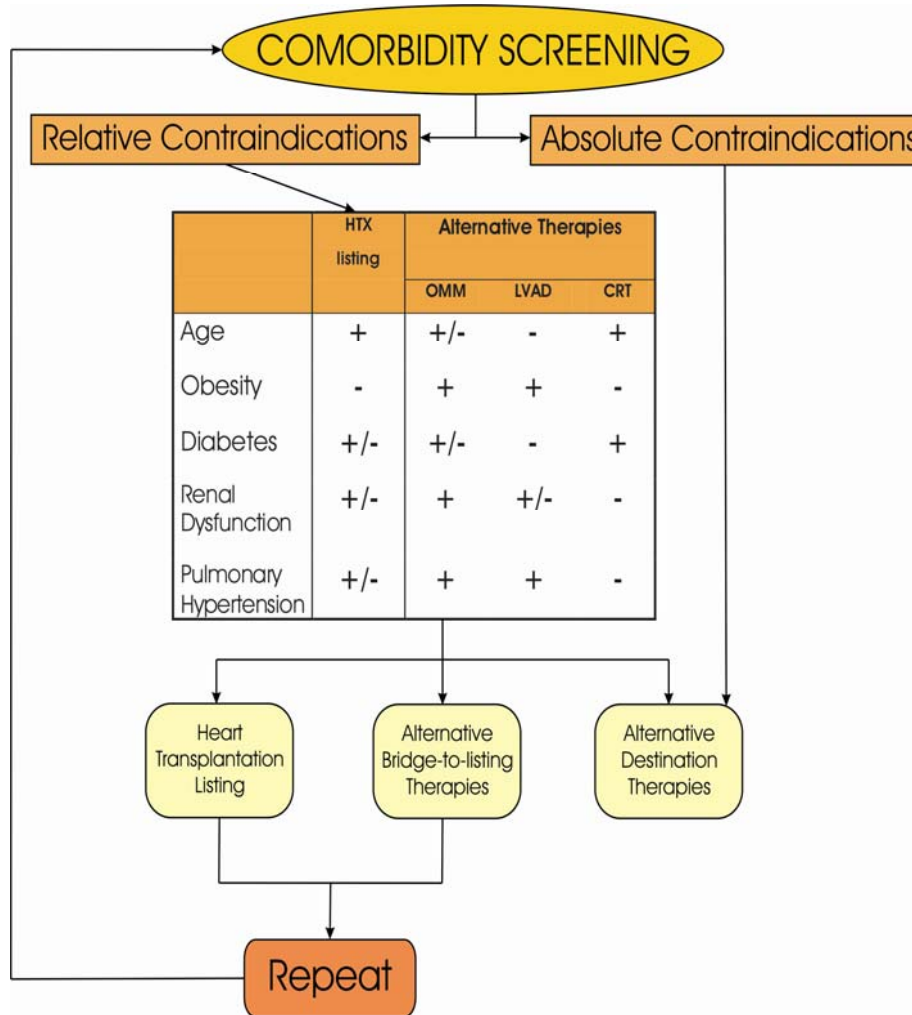
Heart failure affects over 5% of those aged 65-75 and 10-20% of those aged >80, and levels are likely to rise in the wake of

Table 5. Traditional Contraindications for Heart Transplantation

- Age
- Obesity
- Insulin-dependent diabetes with end-organ damage
- Irreversible renal dysfunction
- Irreversible hepatic dysfunction
- Coexistent systemic illness with a poor prognosis
- Irreversible pulmonary arterial hypertension
- Irreversible pulmonary parenchymal disease
- Acute pulmonary parenchymal disease
- Severe peripheral and/or cerebrovascular disease
- Irreversible renal dysfunction
- Active peptic ulcer disease
- Active diverticulosis or diverticulitis
- Active infection
- Coexisting neoplasm

improved therapies for hypertension and myocardial infarction. In this group, heart failure is often multifactorial with the most common causes being hypertension and coronary heart disease, and accompanied by various disorders associated with aging. Up to 40% of patients older than 65 years have more than 5 non-cardiac comorbidities. The most common non-cardiac conditions are chronic obstructive pulmonary disease, diabetes, osteoarthritis, thyroid disease, Alzheimer's disease/dementia, depression, chronic renal failure, cancer, and osteoporosis. Since these co-morbidities significantly affect survival in heart failure, the outcome assessment of elderly heart failure patients should include a careful co-morbidity screen (2).

Figure 3. Evaluation of contraindications for heart transplantation



OMM, optimal medical management; HTX, heart transplantation; LVAD, left ventricular assist device; CRT, cardiac resynchronization therapy.

Heart Transplantation

In the past, older patients have been excluded from consideration for transplantation. Advances in post-transplant care have improved outcomes in older patients (>60 years) and many centers have demonstrated that the survival in selected patients from older age groups is comparable to that of younger transplant recipients.

When evaluating the long-term results of heart transplantation in patients older than 60 years, actuarial survival at 1, 5, and 10 years was reported to be 88%, 83% and 50% versus 83%, 69% and 51% in the younger patients, respectively (3). A 10-year follow-up of cardiac transplant recipients older than 65 years of age demonstrated survival rates comparable to those of younger patients (4). Ten-year survival was similar in all groups (<60 years: 53.7%; 60 to 64 years: 53.1%; >65 years: 60.2). Patients older than 70 years of age have also been reported to have acceptable outcome (5): the actuarial survival rates at 1 year and 4 years were not statistically different between patients >70 years and younger patients (1-year survival: 93.3% vs. 88.3%; 4-year survival: 73.5% vs 69.1%).

In addition, some data suggest that older patients have less donor organ rejection, which most likely represents immunosenescence in this older population (3). The survival rates in these patients indicate that age above 60 years per se should not be considered a contraindication to heart transplantation. However, special care must be taken in the pretransplant evaluation of patients older than 60 years to identify concomitant medical conditions that might limit survival after transplantation.

Alternative Treatment

Prior to heart transplantation listing of elderly patients, particularly those with significant comorbidities, alternative destination strategies should be considered

Medical Management

Despite these staggering figures and increasing incidence there remains a reluctance to prescribe heart-failure medications that have proven efficacious in clinical trials in the elderly patient population (6). This reluctance may in part be due to fear of decreased efficacy in older patients, based on most large-scale, randomized trials enrolling patients from a disproportionately younger cohort. Additionally, there may be concerns that the elderly might not be able to tolerate these medications as well as younger patients. These concerns may be based on the presence of multiple co-morbidities, complicating medication dosing and compliance together with altered pharmacokinetics and pharmacodynamics in the elderly.

Due to reasons outlined above, the effects of medical management on the outcome of elderly patients with advanced heart failure remain unsatisfactory. In a study of Medicare beneficiaries hospitalized with heart failure, patients 67 to 74 years of age had a median survival from 2.3 to 3.6 years, in patients aged 75 to 84 years median survival ranged from 1.7 to 2.6 years, whereas in patients 85 years of age or older, median survival ranged from just 1.1 to 1.6 years (7). In a prospective study evaluating the outcome of patients older than 80 years who were hospitalized for heart failure they found that the 5-year survival in elderly patients was 19%, dramatically lower than the survival of age- and sex-matched general population (48%) (8). Similarly, a cohort of 6478 patients (mean age 77.2 years) with

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definite heart failure diagnosed from General Practitioners had a 15.9 times (men) or 14.7 times (women) higher 1-year mortality compared to the age-matched population (9).

Despite the trend of improved implementation of patient management guidelines, the role of optimal medical therapy in improving the outcomes of elderly patients with advanced heart failure remains poorly defined. Thus, in patients without significant co-morbidities, alternate treatment strategies may be considered.

Mechanical Circulatory Support

As the use of left ventricular assist devices (LVADs) is more widely available as accepted therapy for patients with refractory heart failure, it could also represent a good treatment option for the elderly group of advanced heart failure patients. However, the sub-analysis of the outcome of these patients does not yet appear to justify this approach.

In a study evaluating the effects of age in patients receiving Novacor support they observed a trend toward a higher mortality with increasing age (10). In patients older than 60 years, actuarial survival at 1 year post-LVAD implantation was 26.2% versus 42.2% in the overall population. Older patients showed a higher risk of infections, embolic strokes, and respiratory complications. Similarly, in univariate analysis for risk factors for 90-Day in-hospital mortality after LVAD implantation as destination therapy in the post-REMATCH era, patients older than 65 years had a 2.8-fold higher risk of mortality, compared to the remaining cohort (11). In patients undergoing Heartmate LVAD implantation, advanced age was determined to be an independent predictor of both early death (<30 days) and poor bridge to transplantation (12). Advanced age predisposed toward early death by 1.9 times

for every additional 10 years of age.

These data suggest that elderly patients have worse outcome after LVAD implantation when compared to younger cohorts. This may be partly due to constraints associated with this therapy, including the need for extensive surgical dissection, the requirement that the recipient have a large body habitus, the presence of a large-diameter percutaneous lead, and limitations in long-term mechanical durability that frequently require subsequent operations for device exchange. It appears that most of these setbacks have been overcome with a use of a smaller, continuous-flow technology in a study that enrolled patients with a mean age of 50 years (13). Further studies are needed to define whether or not this treatment approach could also improve the outcome of elderly patient cohorts.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy has been shown to improve exercise capacity and quality of life and to reduce heart failure hospitalizations and mortality in patients with advanced chronic heart failure and signs of ventricular dyssynchrony. The COMPANION trial (14) used CRT with and without prophylactic ICD back-up in 1520 patients with advanced heart failure and bundle branch block in addition to optimized medical therapy. A subgroup analysis in COMPANION demonstrated a similar benefit of CRT for patients below and above the age of 65 years. Similarly, the Cardiac Resynchronization-Heart Failure (CARE-HF) (15) study demonstrated a similar benefit for patients below and above the age of 66.4 years.

The lack of the effects of ageing on the outcome after CRT implantation has also been confirmed in several smaller studies.

In a single center study evaluating the effects of age on 1-year outcome after CRT, the frequency of combined end point of hospitalization for heart failure and/or all cause mortality was no different in the older (age >70, 31%) and younger subjects (age <70, 37%), respectively (16). In a study enrolling patients with moderate to severe heart failure and QRS duration >120 ms with left bundle branch block configuration, the one-year survival was similar in patients aged <70 years (90%) and those aged >70 years (83%). In addition, the number of nonresponders was comparable between the patients aged <70 years (25%) and those aged >70 years (22%) (17).

In the analysis of the Insync/Insync ICD Italian Registry they evaluated the outcome of patients older than 80 years. In the study population, the 1-year mortality was 13% in the <80 years group and 15% in the > or =80 years group. There was a higher all-cause mortality among > or =80 years patients, with a trend towards higher sudden cardiac death (SCD), but similar non-SCD (18).

These data suggest that the outcomes of CRT in elderly patients are comparable to the ones in general patient cohort, suggesting that CRT may be a good treatment option for patients with advanced age. However, ageing appears to be associated with narrowing of QRS complex duration (19,20). Since QRS duration is one of the key determinants of electrical dyssynchrony, the numbers of elderly patients fulfilling the criteria for CRT implantation may be somewhat lower than in general heart failure population.

Obesity

Body mass index (BMI) is calculated according to the equation: BMI= weight [kg]/ height [m²]. Patients with BMI under 18.5 kg/m²

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are considered underweight, and those with BMI higher than 30 kg/m² are defined as obese. The diagnosis of obesity in heart failure may be somewhat more difficult than in general population. It is possible that obese patients with dyspnea but without actual heart failure are incorrectly categorized as having heart failure. On the other hand, the presence of peripheral edema in heart failure patients further challenges the traditional diagnosis of obesity in this patient cohort (21).

Heart Transplantation

Obese patients have a greater risk of morbidity and mortality after open-heart surgery (22). This is manifested in poor wound healing, increased risk of infection, lower-extremity thrombosis and pulmonary complications.

In a study investigating the effects of pre-transplant extremes in body weight on post-transplant outcome, patients who were morbidly obese demonstrated nearly twice the 5-year mortality of normal-weight or overweight recipients (53% vs. 27%, respectively). An increase in mortality for morbidly obese was seen already at 30 days post-transplant (12.7% versus a 30-day mortality rate of 7.6% in normal-weight recipients). Furthermore, morbidly obese recipients experienced a shorter time to high-grade acute rejection as well as an increased annual high-grade rejection frequency when compared with normal-weight recipients (23). Similarly, the survival analysis of patients participating in the Cardiac Transplant Research Database, demonstrated that preoperative obesity is associated with decreased survival in all patients after heart transplantation. Being obese preoperatively was associated with increased infection after heart transplant in males and females younger than 55 years and in patients with ischemic heart disease (24).

Overall, it appears that obesity (BMI >30 kg/m²) is associated with poor outcome after cardiac transplantation. Therefore, for severely obese patients, weight loss should be mandatory before heart transplantation listing.

Alternative Treatment

Since heart transplantation may not be a preferable treatment option in morbidly obese patients, other treatment modalities may be considered either as bridge-to candidacy or destination therapy in these population.

Medical Management

Among outpatients with stable heart failure, higher BMI values are independently associated with a lower risk of death and death due to worsening heart failure, such that overweight and obese patients have better survival rates compared with patients at a healthy weight (25). Advanced chronic heart failure is commonly associated with cardiac cachexia, a wasting syndrome characterized by significant weight loss in the absence of peripheral edema (26). Hence, the deleterious effects of cachexia, not the salutary ones of obesity, could primarily drive the inverse association of BMI with survival.

An analysis of heart failure patients from the SOLVD trial demonstrated that any weight loss (independent of the patients' weight at baseline) is related to poor survival and that medical therapy can reverse weight loss and thereby contribute to improved outcome (27). Similarly, several recent studies have shown that in patients with established heart failure, obesity is not associated with increased mortality, but rather is associated with improved survival. Potential mechanisms for cardioprotection in

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obesity include a diminished activation of the neurohumoral system, an enhanced protection against endotoxin/inflammatory cytokines, and an increased nutritional and metabolic reserve (28).

Current evidence from clinical trial on both chronic and acute heart failure (29) suggests that patients with higher BMI may indeed have better survival compared to the remaining cohort. Although the underlying mechanisms remain to be defined, obese patients with advanced heart failure appear to have good outcomes when treated with optimal medical therapy alone.

Mechanical Circulatory Support

Nutritional disorders, both cachexia and obesity, are common among those with end-stage heart failure and nutritional evaluation is a routine part of pre-LVAD protocol. After LVAD implantation there is a significant degree of weight loss in the first postoperative month, which persists up to 90 days after implantation (30). Although this weight loss may partly reflect the reductions in oedema, it might also be a reflection of inflammatory activation and the inability of LVAD support to reverse the cachexia of advanced heart failure.

In a group of patients who underwent LVAD placement either as bridge-to transplant or destination therapy higher BMI did not adversely affect 12-month survival after LVAD implantation. However, patients with higher BMI tended to have a greater risk of re-operations and renal complications (31). On the other hand, serum albumin levels lower than 3.3 g/dL were associated with higher 90-day mortality in patients undergoing LVAD support in the post-REMATCH era (11). Therefore, it appears that poor nutrition rather than obesity may be of paramount importance when considering an implantation of LVAD.

Malnutrition and obesity in the LVAD patient contribute to a host of post-operative problems, such as infection and limited functional capacity, which compromise long-term outcomes. Comprehensive pre-operative evaluation of the LVAD patient should include a nutrition assessment and formalized plan to initiate and advance nutrition support while addressing the metabolic imbalances associated with heart failure (32).

Cardiac Resynchronization Therapy

Data on potential role of obesity in patients undergoing CRT are lacking; however there is some evidence that intra-ventricular dyssynchrony may correlate with visceral adiposity and proinflammatory cytokine levels, and that the reduction of body weight may be associated with improved dyssynchrony (33). Although this could suggest that obese patients may benefit more from CRT, the existing data are non-conclusive.

Diabetes

Diabetes is associated with a specific metabolic cardiomyopathy. The risk for development of heart failure in diabetic patients is markedly increased, independently from coronary artery disease and hypertension (each 1% increase in HbA1c is associated with 8% increased risk of developing heart failure). In diabetic patients there is accumulation of collagen and other glycation end-products in the myocardium leading to an increased myocardial stiffness and resulting in abnormal diastolic function. In addition to hyperglycemia, increased turnover of free fatty acids and impaired uptake of glucose in the myocardium are all important factors leading to a disturbed cardiac function (34).

Heart Transplantation

In heart transplant candidates with diabetes, the areas of concern include the presence of autonomic dysfunction and end-organ damage, both worsening with corticosteroid therapy after heart transplantation. At both short-term and long-term post-transplant follow-ups, diabetics showed a statistically significant risk of severe infection. This was evident during the first 90 days after surgery and also at 4 years (35). Diabetic patients also have a higher risk for post-transplant renal failure, however, no definite link between diabetes and incidence of rejections and cardiac allograft vasculopathy was found (36).

Data from the ISHLT registry demonstrated that diabetic patients have an approximately 20% to 40% increase in 1- and 5-year mortality (37). Furthermore, the presence of diabetes mellitus at the time of heart transplantation has also been shown to adversely affect long-term (10 year) post-transplant survival (38). In an analysis of The United Network of Organ Sharing database, post-transplantation survival among patients with uncomplicated diabetes was not significantly different than that among nondiabetics. However, when stratified by disease severity, recipients with more severe diabetes had significantly worse survival than non-diabetics (39).

Based on the available evidence it appears that diabetic patient may represent a rather heterogeneous group of potential heart transplant recipients. Given these findings, diabetes alone should not be a contraindication to heart transplantation. Well-selected diabetic patients achieve the same survival as non-diabetic patients. Conversely, patients with complicated diabetes have significantly worse survival. Therefore, in patients with uncontrolled diabetes treatment options other than heart

transplantation should be considered.

Alternative Treatment

Although selected patients with adequately controlled pre-transplant diabetes may have acceptable outcome after heart transplantation, other treatment options, in particular optimal medical management, combined with resynchronization therapy may offer a good alternative.

Medical Management

Diabetes has been demonstrated to increase mortality risk in patients with heart failure. Analysis of the prevention and treatment arms of the Studies of Left Ventricular Dysfunction (SOLVD) identified diabetes as an independent predictor of increased mortality in both symptomatic and asymptomatic heart failure (40). In the Rotterdam study, among a community cohort of patients found to have heart failure, diabetes was an independent predictor of mortality, along with renal insufficiency and atrial fibrillation (41). Similarly, in an analysis of a national cohort of 170,239 elderly patients newly hospitalized with heart failure in 1986 and followed up over the next 6 years, diabetes was an independent predictor of mortality (42). Thus, compared with patients with heart failure who do not have diabetes, patients with both diabetes and heart failure have a 1.5–2-fold higher risk of mortality (43).

Although patients with diabetes gain a substantial benefit from optimal medical management, underutilization of these therapies is especially prevalent in this population, primarily due to concerns about altered metabolism, altered elimination, and poor tolerability. Theoretical concerns regarding the use of these

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therapies vary from agent to agent. For beta-blockers, impaired insulin sensitivity and potentiation of insulin-induced hypoglycemia with delayed recovery of serum glucose levels are commonly expressed concerns. Beta-blocker therapy can mask hypoglycemic symptoms and worsen hyperlipidemia. With ACE inhibitors, ARBs, and aldosterone receptor antagonists, there are concerns about an increased risk of hyperkalemia in patients with declining renal function, which is commonly found in patients with diabetes. However, despite these concerns, every effort should be made to strictly apply these therapies to all patients with diabetes and heart failure, in the absence of contraindications or intolerance (44).

Mechanical Circulatory Support

Diabetes has been shown to be an independent predictor of worse peri-operative outcomes, such as stroke, respiratory insufficiency, delirium, long intensive care unit stay and in-hospital mortality after various cardiac surgery procedures (45). Experiments on animal models demonstrated that, despite impaired cardiac contractility and mechanical efficiency, cardiac output in diabetic heart can be maintained by favorable loading conditions (46). Thus ventricular unloading with LVAD may be particularly useful with this regard.

However, data on patients who underwent Novacor LVAD have shown an inferior survival of the diabetic cohort: 30, 180, and 365-day survival for diabetic versus nondiabetic patients was: 76.6%, 45.6%, and 30.4% for diabetics and 86.7%, 62.4%, and 47.1% for nondiabetics. No significant difference in survival was noted between insulin-dependent versus non-insulin-dependent diabetics (47). In a single center experience, diabetic patients undergoing Heartmate LVAD support, the post-LVAD survival was

similar, but post-transplant survival in diabetic patients was significantly lower compared to patients without diabetes with 1- and 5-year actuarial survival rates of 86.9%, and 56.5% for diabetics vs. 90.5% and 83.0% for non-diabetics (48).

Based on the current evidence, diabetic patients appear to have worse outcome after LVAD implantation when compared to the non-diabetic population. After cardiac surgery, diabetic patients treated with IV insulin in the intensive care unit (ICU) followed by SC insulin (outside ICU) have been shown to have similar rates of postoperative mortality, deep sternal wound infections, other infections, and pulmonary, cardiac, renal, and neurological complications compared with non-diabetic patients (49). It remains to be validated whether or not a similar treatment could also improve the outcome of diabetic patients undergoing LVAD support.

Cardiac Resynchronization Therapy

There are a few non-randomized studies reporting increased prevalence of cardiac conduction abnormalities, such as right bundle branch block (RBBB), bifascicular block and high degree atrioventricular (AV)-block but not left bundle branch block (LBBB), in patients with diabetes (50). This suggests that diabetes may significantly affect patterns of ventricular depolarization. Together with the effect of diabetes on myopathic mechanisms and on the progression of cardiac dysfunction this could influence the response of heart failure patients to CRT.

The analysis of CARE-HF does not suggest a differential response to cardiac resynchronization in diabetic versus nondiabetic patients. Diabetes, regardless of the therapy used to treat it and the presence of coronary artery disease, did not influence the beneficial effect of CRT on any end point (51).

Furthermore, in a study evaluating a population of patients with end-stage HF, there were no differences after 6 months of CRT in response and long-term survival in patients with and without diabetes (52).

Although CRT may prolong QTc interval and thereby potentially increase the arrhythmia risk (53), CRT, and CRT-D in particular could represent a good treatment option for diabetic patients with advanced heart failure.

Renal Dysfunction

In heart failure, a reduction of glomerular filtration rate and renal plasma flow occurs, although the filtration fraction increases. A reduction in effective circulating volume stimulates sympathetic activity and the renin-angiotensin-aldosterone system, and it is associated with increased concentrations of atrial natriuretic peptide, brain natriuretic peptide, and tumor necrosis factor alpha (54). Alternatively to renal function being a reflection of relevant aspects of the severity of heart failure, renal function impairment itself may induce unfavorable cardiovascular effects, such as disturbed calcium and phosphate homeostasis with possible adverse cardiovascular effects. Thus, it appears that chronic kidney disease can contribute to the development and exacerbation of heart failure, and progressive heart failure contributes to renal hypoperfusion and activation of inflammatory factors, which can lead to the development or worsening of kidney function (55).

Heart Transplantation

Renal function declines after heart transplantation and nearly 30% of transplant recipients demonstrate elevated serum creatinine levels already at 1 year after surgery (37). Use of nephrotoxic

calcineurin inhibitors is often implicated as the main cause for this renal dysfunction, but preexisting renal damage, altered hemodynamics causing relative hypoperfusion of kidneys, together with conditions such as hypertension, diabetes, and dyslipidemia may also play an important role.

It appears that the risk of developing chronic renal insufficiency during after heart transplantation could be predicted by peri-operative serum creatinine concentration (56): the group of patients who had pre-operative serum creatinine concentrations >1.5 mg/dl had a 3-times higher relative risk of chronic renal insufficiency when compared to the remaining cohort. Furthermore, pre-operative impairment of renal function (defined as a creatinine clearance <40 ml/min) was associated with higher early and late post-transplant mortality, as well as increased incidence of post-operative dialysis (57). Renal impairment is evident in about half of heart transplant recipients at 1 year post-transplant and represents an important risk factor for both all-cause and cardiac mortality long-term after transplantation (58).

Currently, the presence of pre-operative irreversible renal dysfunction (eGFR <40 ml/min) is considered a relative contraindication for heart transplantation (1). Since calcineurin inhibitors are associated with significant nephrotoxicity and chronic kidney damage, strategies to limit this effect include calcineurin inhibitor minimization, avoidance, and withdrawal, and could thus represent important tools in minimizing the decline in renal function in transplant recipients (59). Furthermore, with the development of novel surgical strategies, a combined heart/kidney transplantation could be considered in selected individuals (60). Best candidates for such therapy include patients with concurrent end-stage heart disease, fixed (nonreversible) renal disease, and the absence of other significant illness. The rate of cardiac

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rejection seems to be decreased in such patients relative to heart-only transplants. Because the incidence of simultaneous rejection of both organs seems low, surveillance of both organs is necessary. Despite the lack of HLA matching, short-term patient survival seems to be similar to that of heart-only transplants.

Alternative Treatment

Renal dysfunction is associated with worse outcome after heart transplantation. Clinical decision-making is further complicated by the fact that current measures of assessment for renal dysfunction reversibility appear to be inadequate to discriminate between those who will or will not recover renal function after transplant or LVAD implantation. Thus, in patients with renal insufficiency that precludes them from heart transplantation it may seem reasonable to undergo a trial of medical therapy and/or LVAD support in an effort to successfully bridge them to heart transplant candidacy.

Medical Management

Although renal dysfunction is present throughout the spectrum of patients with heart failure, it appears to be even more prevalent in patients with advanced heart failure of either ischemic or non-ischemic etiology (61). The results of a recent meta-analysis demonstrated that the majority of heart failure patients have some degree of renal impairment (creatinine >1 mg/dL), and these patients represent a high-risk group with an approximately 50% increased relative mortality risk compared with patients of normal renal function. Moreover, up to 29% of patients had moderate to severe renal impairment (creatinine >1.5 mg/dL), with more than 100% increased relative mortality risk and absolute mortality rate as high as 51% by five years of follow-up (62).

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Furthermore, worsening of renal function, defined as an increase in serum creatinine ≥ 0.2 mg/dL has been shown to predict substantially higher rates of mortality and hospitalization in patients with heart failure (63).

Definite evidence for therapeutic strategies to reduce mortality in heart failure patients with renal impairment is still lacking, because in most therapeutic trials patients with creatinine >2.5 have been systematically excluded, and thus optimal pharmacotherapy remains poorly defined, especially in patients with severe renal impairment (64). Compared to patients with heart failure with preserved renal function, patients with severely impaired renal function are far less likely to receive ACE inhibitor or ARB during hospitalization or at discharge. Although ACE inhibitors and ARB are not widely used in this population, data suggests their administration may be associated with an improved survival, both at 30 days and 1 year. The initiation of these agents at low dose with careful monitoring of renal function and serum electrolytes should be considered in all patients with heart failure, independent of renal function. However, the use of these agents in patients on hemodialysis warrants further investigation (65).

In a broad spectrum of heart failure patients from the CHARM study including those either receiving an ACE inhibitor or not receiving an ACE inhibitor due to intolerance, renal function was strongly and independently associated with prognosis (66). Therefore, in addition to medical therapy, other measures could be considered to further improve the outcome of patients with advanced heart failure and renal dysfunction.

Mechanical Circulatory Support

Patients undergoing cardiac surgery with non-dialysis-dependent renal dysfunction have significantly increased peri-operative

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morbidity and mortality. Mid-term survival is also significantly reduced at 5-years (67). On the other hand, both pulsatile and continuous-flow LVADs have been shown to maintain adequate long-term end-organ perfusion, which results in improvement of renal blood flow and thereby can improve renal dysfunction in patients with advanced heart failure (68). Thus, there are potentially countervailing influences on the interaction between pre-implant renal function and LVAD outcomes.

In a study evaluating the effects of pre-implant renal dysfunction on post-implant survival they reported higher peri-implant mortality for patients with the worst pre-implant creatinine clearance. However, in post-LVAD survivors renal function improves substantially within 1st post-implant week and was associated with improved outcomes (69). Renal insufficiency, as demonstrated by low creatinine clearance and high BUN was also predictive of worse outcome after LVAD implantation in the post-REMATCH era (11).

Therefore, it appears that significantly impaired renal function is linked to a relatively poor prognosis after LVAD implantation and should therefore be considered at least a relative contraindication to LVAD use. However, in selected patients with few other comorbidities, LVAD implantation may improve renal function and may thereby serve as a bridge-to candidacy for heart transplantation.

Cardiac Resynchronization Therapy

The duration of QRS complex is not a static ECG measurement but shows fluctuations, and it may change in the presence of oedematous states, such as heart failure or chronic kidney disease (70). Thereby, the presence of renal dysfunction could

potentially influence candidate selection and treatment response in patients undergoing CRT.

In a study on patients with moderate pre-implant renal dysfunction a successful LV reverse remodelling was associated with preservation of renal function. On the other hand, there was a rapid decline in renal function in those who did not respond to CRT. Moreover, changes in renal function at 3 months provided prognostic information in terms of long-term morbidity and mortality in patients receiving CRT (71).

Given the lack of other data and the relatively high non-responder rate after CRT implantation it appears that CRT may not lead to improved renal function in patients with advanced chronic heart failure and renal insufficiency and thus cannot be viewed as a successful bridge to heart transplantation candidacy.

Pulmonary Arterial Hypertension

Patients with chronic heart failure most commonly develop pulmonary hypertension due to elevated left ventricular end-diastolic pressure and, as a result, elevated left atrial pressure and pulmonary venous hypertension. This is considered to be a reactive form of pulmonary hypertension. However, pulmonary venous hypertension can lead to irreversible pulmonary arterial hypertension, as evidenced by fixed, elevated pulmonary vascular resistance. When static measures show elevation of the pulmonary vascular resistance, an attempt to unload the left heart and improve left ventricular performance to document reversibility is warranted. Of note, fixed pulmonary hypertension in advanced heart failure can also be a sign of underlying lung disease, obstructive sleep apnea or chronic pulmonary thromboembolic disease (72).

Heart Transplantation

Fixed pulmonary hypertension is one of the most prominent risk factors of early and late post-transplant mortality, and the risk of death increases in proportion to pulmonary vascular resistance (73). In many patients, however, severely elevated pulmonary pressures may be reversible with pharmacologic means, and therefore these patients are not necessarily excluded from transplantation. Reversible pulmonary hypertension (defined as pre-transplant pulmonary vascular resistance ≥ 3 Wood units, reversing to <3 Wood units either with sub-lingual or intravenous vasodilatory agents) was associated with similarly good post-transplant survival outcomes and morbidity, compared to patients without pulmonary hypertension (74).

The existence of a continuous positive relation between pulmonary vascular resistance and death after heart transplantation supports the notion that pulmonary vascular resistance should be considered a relative rather than an absolute contraindication to heart transplantation. To date, there is no reliable hemodynamic threshold beyond which right ventricular failure post-transplant is certain to occur, nor are there values below which right ventricular failure is always avoidable (75). Currently, a vasodilator challenge is recommended when the pulmonary artery systolic pressure is ≥ 50 mm Hg and either the transpulmonary gradient is ≥ 15 mmHg or the pulmonary vascular resistance (PVR) is >3 Wood units (1). Prolonged, continuous infusions of vasoactive agents, alone or in addition to inotropic agents, may be considered to optimize pulmonary vascular resistance in selected patients. If medical therapy over the subsequent days or weeks fails to lower pulmonary vascular resistance beyond 5 Wood units or transpulmonary gradient below 16 to 20 mmHg the patient should be considered to have a high

risk of post-transplant right ventricular failure.

Alternative Treatment

Irreversibly elevated pulmonary pressures and pulmonary vascular resistance are associated with higher post-transplant mortality. However, an intensive, possibly long-term trial with medical therapy and/or LVAD support is warranted in every patient before considering pulmonary hypertension irreversible. Patients with pulmonary hypertension that precludes them for heart transplantation listing may be good candidates for LVAD insertion, but not for CRT.

Medical Management

In patients with either ischemic or non-ischemic heart failure, a noninvasive assessment of pulmonary hypertension using continuous-wave Doppler of tricuspid regurgitation has been shown to predict morbidity and mortality (76). Using right heart catheterization, elevated pulmonary artery pressures (mean pulmonary artery pressure > 20mm Hg) have been shown to correlate with adverse outcome in patients with advanced chronic heart failure (77). Moreover, when pulmonary artery pressures remain high at rest despite optimized medical therapy, the prognosis of the patients has been shown to strongly relate to right ventricular performance.

In patients with advanced chronic heart failure and elevated pulmonary artery pressure, testing of potential reversibility of pulmonary hypertension carries useful information on the short-term prognosis. In this cohort, an improvement in right ventricular performance after vasodilation-induced decrease in afterload has been shown to significantly correlate with better outcome at 8 months (78). Treatment of right ventricular failure focuses on

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alleviating congestion, improving right ventricular contractility and right coronary artery perfusion and reducing right ventricular afterload. As part of the treatment, inhaled nitric oxide or prostacyclin effectively reduce afterload by vasodilating the pulmonary vasculature. Traditional positive inotropic drugs enhance contractility by increasing the intracellular calcium concentration and oxygen consumption of cardiac myocytes, while vasopressors such as norepinephrine increase arterial blood pressure, which improves cardiac perfusion but increases afterload (79). A new treatment, the calcium sensitiser, levosimendan, increases cardiac contractility without increasing myocardial oxygen demand, while preserving myocardial relaxation. Furthermore, it increases coronary perfusion and decreases afterload and as such may represent a preferable medical treatment for patients with right ventricular failure (80).

Mechanical Circulatory Support

Despite the clinical and physiologic benefits of LVADs, post-operative right heart failure occurs in approximately 15% to 20% of patients. The causes for right-side circulatory failure are multifactorial and are considered to be related to anatomic, intra-operative and perioperative factors (81). Patients with right heart failure have been shown to have higher early mortality rate, greater ICU length of stay, higher rates of re-operation for bleeding and renal failure, and lower bridge-to transplantation rates than patients without right heart failure (82). Although judicious application of inotropes and pulmonary vasodilators and timely RVAD insertion may partly improve the outcome of these patients the evaluation of pre- and intra-operative risk factors for the development of right heart failure is of paramount importance.

Pulmonary hypertension with elevated pulmonary vascular

resistance has traditionally been considered to be a contraindication for LVAD use because of the high risk for right ventricular failure (83). However, in more recent studies, it was low, not elevated pulmonary vascular pressures that were associated with right ventricular failure after LVAD implantation (84). These findings suggest that in some patients right ventricular contractility before LVAD insertion is not strong enough to elevate pulmonary artery pressures in the presence of high pulmonary vascular resistance.

In patients with pulmonary hypertension, a period of LVAD support has been shown to lead to a progressive decrease of pulmonary vascular resistance and normalization of pulmonary pressures, making these patients amenable for heart transplantation (85). Moreover, long-term post-transplant survival after reversing pulmonary hypertension using ventricular assist devices in cardiac transplant candidates with fixed pulmonary hypertension appears to be comparable to cardiac transplant recipients without pulmonary hypertension (86). Thus, LVAD implantation should be considered as a good treatment option in patients with pulmonary artery hypertension that is not reversible with conventional medical strategies and may represent a good 'bridge to candidacy' for heart transplantation.

Cardiac Resynchronization Therapy

There is limited clinical experience suggesting that the improvement in cardiac output seen with CRT can partially reverse the secondary pulmonary hypertension that develops in patients with heart failure (87). In general, the presence of high pulmonary artery systolic pressure at baseline has been shown to predict poor outcome after CRT despite improvement in left ventricular hemodynamics and the presence of favorable reverse

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remodeling (88). Therefore, it appears that CRT may not be able to reverse a possible fixed component of increased pulmonary vascular resistance secondary to longstanding left-sided elevated pressures and may not represent the preferable approach for lowering of pulmonary resistance in transplant candidates. Furthermore, since the mortality and morbidity with CRT in patients with systolic pulmonary artery pressures above 50 mmHg is almost twice higher compared to the remaining cohort, these patients might not be considered good candidates for this therapy.

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PART II:

**PATIENTS AFTER HEART
TRANSPLANTATION**

Chapter 1:

Determination of Outcome After Heart Transplantation

Based on the data from the ISHLT Twenty-fourth Official Adult Heart Transplant Report (1) the principal causes of death within the first post-transplant year included non-CMV infection (33% of deaths), followed by graft failure (primary and nonspecific, 18%) and acute rejection (12%). After 5 years, allograft vasculopathy (CAV) and late graft failure (likely due to allograft vasculopathy) together accounted for 30% of deaths, followed by malignancies (22%) and non-CMV infections (10%).

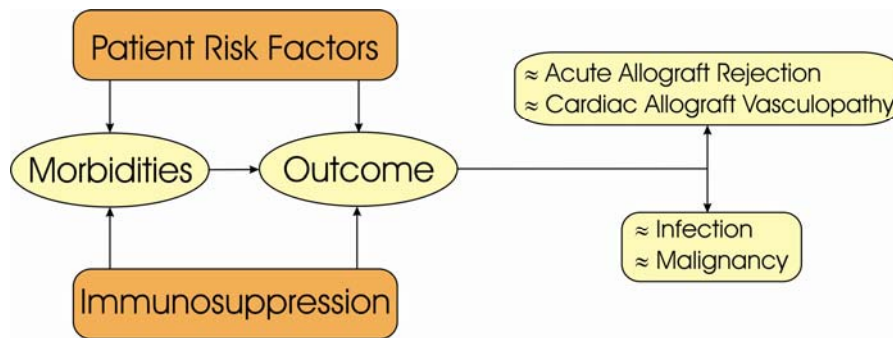
Immunosuppressive therapy aimed at the prevention of acute allograft rejection is the cornerstone of post-transplant management. In general, the principal causes of death after transplantation can be divided into the ones that reflect inadequate immunosuppression (cardiac allograft vasculopathy, acute rejection) and those resulting from excess immunosuppression (infection and malignancy) (Figure 4).

Part II: Determination of Outcome After Heart Transplantation

In addition to its direct effects, immunosuppressive therapy is also involved in the generation of a number of post-transplant morbidities that limit the long-term outcome of heart transplant recipients. In the ISHLT report (1), 98% of surviving recipients had hypertension, 14% had significant renal insufficiency (creatinine >2.5 mg/dl), 93% had hyperlipidemia, and 37% had diabetes by 10 years after transplantation.

Given these data it appears that the individual tailoring of immunosuppressive therapy is of paramount importance in determining the outcome of heart transplantation. To better define the potential for over- and under-immunosuppression, as well as the potential for development of post-transplant morbidities, a patient-specific risk assessment prior to the commencement of immunosuppressive therapy may be warranted.

Figure 4. Determinants of outcome after transplantation



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Chapter 2:

Inadequate Immunosuppression

The aim of immunosuppressive regimens after transplantation is to sufficiently suppress those aspects of the immune system, which when stimulated by donor HLA antigens, initiate the destruction of the transplanted organ. If the immune system is not sufficiently suppressed, acute allograft rejection results. Together with other risk factors, uncontrolled chronic allograft rejection may lead to development of cardiac allograft vasculopathy. The goal of this chapter is to identify a patient subgroup in which inadequate immunosuppression and its consequences are more likely to occur.

Acute Allograft Rejection

Although acute rejection seems to be less common with current immunosuppressive strategies it remains a major cause of morbidity and mortality following heart transplantation. Based on the recent data of the ISHLT Registry acute rejection accounts for 12% of deaths within the first post-transplant year (1). Although

the majority of rejection episodes can be biopsy-proven (acute cellular rejection), hemodynamic compromise can also occur without the evidence of cellular rejection and is generally felt to represent antibody-mediated rejection (2).

Acute Cellular Rejection

Acute cellular rejection is defined as a mononuclear inflammatory response, predominantly composed of lymphocytes, directed against the transplanted organ (3). Routine testing for rejection in the absence of symptoms is a standard procedure because clinical symptoms of rejection are often vague and relatively late in terms of immune cardiac myocyte injury. In the absence of a reliable noninvasive test, the endomyocardial biopsy remains the gold standard method for detecting acute rejection in transplanted hearts (4). Typically, patients are first biopsied weekly after transplantation for a month, then once every two weeks for the next eight weeks, once per month for the next three months, and every two months up to the first post-transplant year of the transplant. If rejection is detected, patients are treated and then re-biopsied after 10 to 14 days (5). The diagnosis of acute cellular rejection is based on histology of the biopsied samples using the ISHLT Standardized Cardiac Biopsy Grading (Table 6).

Acute rejection episodes (grades 2R or 3R) are not benign and should be treated even when the patient is asymptomatic. On the other hand, grade 1R have been shown to progress to high-grade rejection on the next biopsy in only 15% to 20% of cases and therefore are not considered a just reason for initiation of anti-rejection treatment regimen (4).

Table 6. Diagnosis of Acute Cellular Rejection: ISHLT Grading System

Grade 0	No rejection
Grade 1 R (mild)	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2 R (moderate)	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R (severe)	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis

Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Burke MM, Demetris AJ, Hammond E, Itescu S, Marboe CC, McManus B, Reed EF, Reinsmoen NL, Rodriguez ER, Rose AG, Rose M, Suci-Focia N, Zeevi A, Billingham ME. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant.* 2005 Nov;24(11):1710-20.

Antibody-Mediated Rejection

The presence of ‘biopsy negative’ rejection has also led to an appreciation of the role of antibody-mediated rejection, which is defined with the combination of clinical, histologic, and immunopathologic findings as well as demonstration of circulating donor specific antibodies (Table 7) (6). Antibody-mediated rejection is relatively frequent within the first post-transplant year with the incidence up to 15%, and the prevalence among biopsy specimens with concomitant cellular rejection is 23%. It has been shown to be associated with a significantly worse survival and to predispose patients to coronary vasculopathy (7).

Cardiac Allograft Vasculopathy

Based on histopathologic examinations, cardiac allograft vasculopathy is generally characterized by a diffuse, concentric intimal thickening of both epicardial and intramural arteries (8). The presence of angiographic cardiac allograft vasculopathy predicts a five times greater relative risk of cardiac events (9).

Table 7. Diagnosis of Antibody-Mediated Rejection

Clinical evidence of acute graft dysfunction	
+	
Histologic evidence of acute capillary injury	Capillary endothelial changes: swelling or denudation with congestion + macrophages in capillaries ± neutrophils in capillaries ± interstitial edema and/or hemorrhage
+	
Immunopathologic evidence for antibody mediated injury (in the absence of OKT 3)	Ig (G,M, or A) C3d, C4d or C1q demonstrated by immunofluorescence ± CD68 positivity for macrophages in capillaries and/or C4d staining of capillaries with 2–3+ intensity by paraffin immunohistochemistry ± fibrin in vessels
±	
Serologic evidence of anti-HLA class I and/or class II antibodies or other anti-donor antibody	

Reed EF, Demetris AJ, Hammond E, Itescu S, Kobashigawa JA, Reinsmoen NL, Rodriguez ER, Rose M, Stewart S, Suci-Foca N, Zeevi A, Fishbein MC; International Society for Heart and Lung Transplantation. Acute antibody-mediated rejection of cardiac transplants. *J Heart Lung Transplant.*;25(2):153-9.

Clinical manifestations include myocardial infarction, congestive heart failure, and sudden death. Survival is directly related to severity of the disease, with the poorest outcomes in patients with greater than a 70% stenosis of a primary or secondary coronary artery or three-vessel coronary artery disease (10).

Cardiac allograft vasculopathy has a multifactorial etiology. Although the exact pathogenesis remains to be established, there is growing evidence that allograft vasculopathy is a manifestation of both a chronic allogenic response to the transplanted organ and nonimmunologic factors that contribute to vascular injury (11). Endothelial damage and inflammatory processes contribute to

intimal thickening via cytokine-induced myofibroblast proliferation and fibrosis (12). Constrictive remodeling later in the disease process further contributes to the narrowing of vessels (13).

The majority of patients with allograft vasculopathy remain asymptomatic until they develop silent myocardial infarction, heart failure, arrhythmias, or sudden death. Since cardiac allograft vasculopathy progresses rapidly, identification of patients at high risk is important. The diagnosis of vasculopathy can be made with coronary angiography or intravascular ultrasound (IVUS). While cardiac angiography is routinely available, IVUS is more commonly used in investigational settings. However, since angiography tends to underestimate the disease process due to the diffuse narrowing characteristic of early vasculopathy, the more widespread use of IVUS may be warranted (14). Moreover, rapidly progressive vasculopathy by IVUS, defined as an increase of ≥ 0.5 mm in intimal thickness within the first year after transplantation, has been reported a powerful predictor of all-cause mortality, myocardial infarction, and angiographic abnormalities (15).

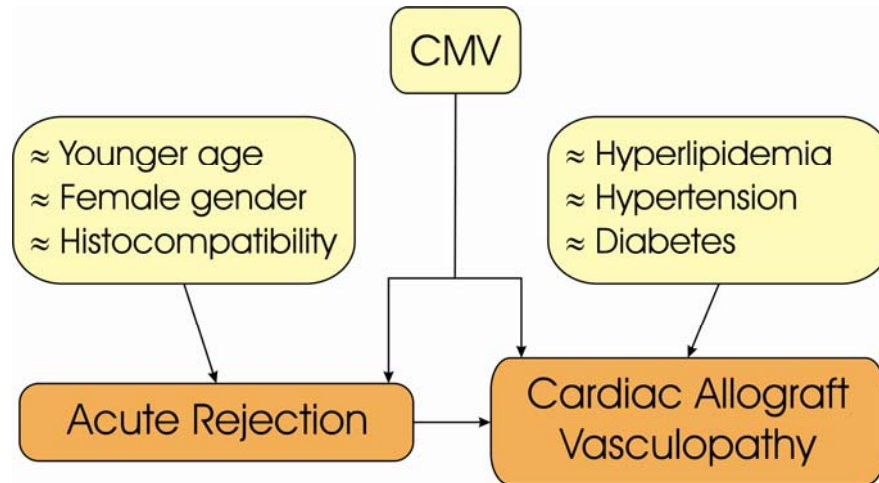
Risk Stratification

Assessment of risk factors for acute rejection may be a useful guide when choosing the adequate immunosuppressive regimen and can potentially be useful in individual tailoring of the frequency of heart biopsies. Similarly, screening for risk factors for development of cardiac allograft vasculopathy may prevent or delay its development (Figure 5).

Acute Allograft Rejection

Higher risk groups for increased frequency of rejection and shorter

Figure 5. Risk factors for acute rejection and cardiac allograft vasculopathy



time to first rejection include younger age, female gender, low histocompatibility, and positive cytomegalovirus (CMV) serology.

Younger recipient age is associated with increased risk of acute rejection (16). Therefore, as a general rule, older cardiac transplant patients should be treated with lower doses and fewer immunosuppressive drugs to avoid over-immunosuppression.

Women have a higher incidence of rejection and a poorer survival after transplantation (17). Although the underlying mechanisms for this phenomenon are not clear, one proposed reason is the greater frequency of autoimmune-mediated diseases in women. Because sequence homology exists between CMV and cardiac endothelium, an autoimmune mechanism whereby the body attacks itself may lead to a more vigorous reaction in women than in men (18). Alternatively, previous pregnancy, but not the recipient's sex, could be considered as a risk factor with this regard (19). Moreover, women are also at an increased risk for

developing antibody-mediated rejection following transplantation, which is more likely clinically significant and associated with severe allograft dysfunction, occasionally leading to death (20). Therefore, when compared to men, more intensive immunosuppressive strategies appear to be warranted when treating female heart transplant recipients.

Both HLA mismatches and higher panel of reactive antibodies (PRA) have been associated with higher incidence of allograft rejection. The probability of rejection-related death or re-transplantation by 2 years has been reported to be 0% with zero, one, or two HLA mismatches versus 5% for three to six mismatches (21). When evaluating the effects of PRA on rejection frequency they found that five-year actuarial freedom from death caused by all forms of rejection correlated with PRA values as follows: PRA 0% to 10%: 85%; PRA 11% to 25%: 68%; PRA greater than 25%: 57%. Additionally, there was a positive linear relationship between PRA and duration of acute rejection episodes in the first 3 months after transplantation (22). Recent data suggest that anti-HLA antibodies are also strongly correlated with the development of antibody-mediated rejection (20). Based on these findings, cardiac transplant recipients with a greater number of HLA donor/recipient mismatches and high PRA should be considered to have a higher risk of acute rejection and may require more intense immunosuppression modalities (23).

The most important pathogen affecting transplant recipients is CMV, which causes both direct effects, including tissue injury and clinical disease, and a variety of indirect effects. The relation between rejection and CMV appears to be bidirectional, with CMV causing rejection, and the inflammation caused by rejection increasing viral replication (24). A number of mechanisms have been proposed to explain increased acute allograft rejection

occurring as a consequence of subclinical CMV infection. These include viral up-regulation of adhesion molecules and of MHC class II molecules on multiple cell types in the graft, and enhanced expression of several cell surface molecules that are involved in the adhesion of leukocytes, such as ICAM-1, VCAM-1, VAP-1, and E-selectin. Given the importance of CMV infection in the pathogenesis of acute allograft rejection aggressive CMV prophylaxis may be warranted in all patients with subclinical CMV infection (25).

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy is initiated and propagated by both immunological and nonimmunologic factors. Immunological factors, such as acute cellular and antibody-mediated rejection are thought to play an important role in the vasculopathy initiation while nonimmunologic factors play a propagative role in its progression (14). The most important among nonimmunologic factors are hyperlipidemia, hypertension, CMV infection and diabetes.

Several studies uniformly demonstrated that hyperlipidemia is associated with higher incidence of allograft vasculopathy (26,27). The prevalence of lipid abnormalities in heart transplant recipients is high, ranging from 60 to 80% (28). Obesity, high cyclosporine levels, cumulative doses of prednisolone and insulin resistance all contribute to the development of hyperlipidemia in cardiac allograft recipients (29). Although the occurrence of post-transplant hyperlipidemia can be partly modified by dietary interventions and modification of immunosuppression, the post-transplant use of statins is of paramount importance. Besides their effects on cholesterol statins appear to possess immunomodulatory effects, including repressed induction of major histocompatibility complex class II by interferon-gamma, and

selective blocking of leukocyte function antigen 1 (30).

According to the ISHLT registry data hypertension affects more than 90% of cardiac transplant recipients within the first 7 years (1). The principal causes of post-transplant hypertension are prednisone and calcineurin inhibitor therapy (31). The calcium-channel blocker diltiazem started early after transplantation was associated with reduced incidence of allograft vasculopathy, and angiotensin- converting enzyme inhibitors may also be effective with this regard (32).

Cardiac allograft vasculopathy progression can be accelerated in the presence of CMV infection. CMV infection is associated with impaired coronary endothelial function, and CMV negative recipients of allografts from CMV-positive donors (D+/R-) are at a high risk for the development of CAV (33). Moreover, early angiographic appearance of CAV within 2 years after transplantation has been associated with a higher incidence of antecedent cytomegalovirus infection (34). Therefore, in high-risk patients, aggressive CMV prevention strategies may also lead to decreased incidence of allograft vasculopathy.

The development of diabetes after transplantation has been associated with reduced graft function and patient survival, and increased risk of graft loss (35). In a pre-clinical setting, diabetes has been shown to be an important parameter determining the progression of cardiac allograft vasculopathy (36). Furthermore, persistent glucose intolerance, as reflected by an increased plasma level of HbA1c, is significantly correlated with the occurrence of allograft vasculopathy, providing further evidence that glucose intolerance plays a role in the disease process (37). Therefore, strict control of blood glucose after transplantation levels may decrease the incidence of post-transplant coronary disease.

Part II: Inadequate Immunosuppression

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Chapter 3:

Excessive Immunosuppression

The intensive immunosuppressive regimens are associated with higher incidence of post-transplant infections and malignancy, both of which are important determinants of long-term post-transplant outcome. The goal of this chapter is to identify a patient subgroup which may be particularly susceptible to the excessive immunosuppressive effects.

Infection

Infections cause about 20% of deaths in the first year after transplantation and remain a common cause of morbidity and mortality after the first year (1). After heart transplantation there is a typical temporal pattern for the etiologies of different infectious disease syndromes with two important time landmarks being the 1st and the 6th post-transplantation month.

The predominant infections seen in the first month after transplantation are nosocomial bacterial and fungal infections

Part II: Excessive Immunosuppression

related to mechanical ventilation, catheters, and the surgical site, or the infections present within the donor organ. The most common cause of morbidity in this period is bacterial pneumonia, followed by the infection of the postoperative wound (2).

Between the 1st and the 6th month, the most important pathogens are immunomodulating viruses, particularly CMV. The direct effects of CMV infection, namely CMV disease, present either as CMV syndrome or as tissue-invasive disease. CMV syndrome is characterized by flu-like and mononucleosis-like symptoms, often with neutropenia. Tissue-invasive disease may present as pneumonitis, gastrointestinal disease, hepatitis or retinitis (3). The probability of developing CMV disease increases logarithmically with viral load. Patients suffering invasive CMV infection generally require prolonged courses of antiviral therapy and are more susceptible to additional episodes of viremia and to antiviral resistance (4). In addition to the direct effects of invasive infection, CMV is also associated with a number of indirect effects that are independent of level of CMV viremia, and that result in part from the influence of the virus on the host's immune response (5). Cytomegalovirus encodes many proteins that alter the immune environment of the host by modulating molecules involved in immune recognition and inflammation. As a result, CMV is associated with a general non-specific immunosuppressive syndrome, which leads to a higher risk of opportunistic infections without excessive environmental exposure (6). To prevent viral and opportunistic infections during after transplantation, prophylaxis against CMV, *Pneumocystis carinii*, herpes simplex virus, and oral candidiasis is routinely used. The prophylaxis against opportunistic infections is of particular importance in high risk patients, particularly in those with repeated exposure to high-dose immunosuppressant drugs and in those with poor allograft function (7).

Malignancy

Development of de novo malignancies is a well recognized complication in immunosuppressed transplant recipients and malignant neoplasms are a significant limiting factor for the long-term survival of heart transplant recipients. In particular, compared to the general population, cardiac transplant recipients have a markedly increased incidence of lymphoproliferative malignancy and carcinomas of the skin (8).

Lymphoproliferative disorders after heart transplantation mainly consist of B-lymphocytes and encompass a spectrum of B lymphoproliferative diseases ranging from reactive plasmacytic hyperplasia to monomorphic B cell lymphoma (9). Unlike lymphomas that occur in immunocompetent patients post-transplant lymphoproliferative disorders commonly present with extranodal involvement (10). The terms early and late are often used clinically and connote the lymphoproliferative disorders occurring before, and after the 1st post-transplant year, respectively. Clinical outcome of early versus late lymphoproliferative disorders in thoracic organ transplant patients is different for mortality (36% versus 70%), response to reduction immunotherapy (89% versus 0%) and clinical presentation with disseminated disease (23% versus 86%) (11).

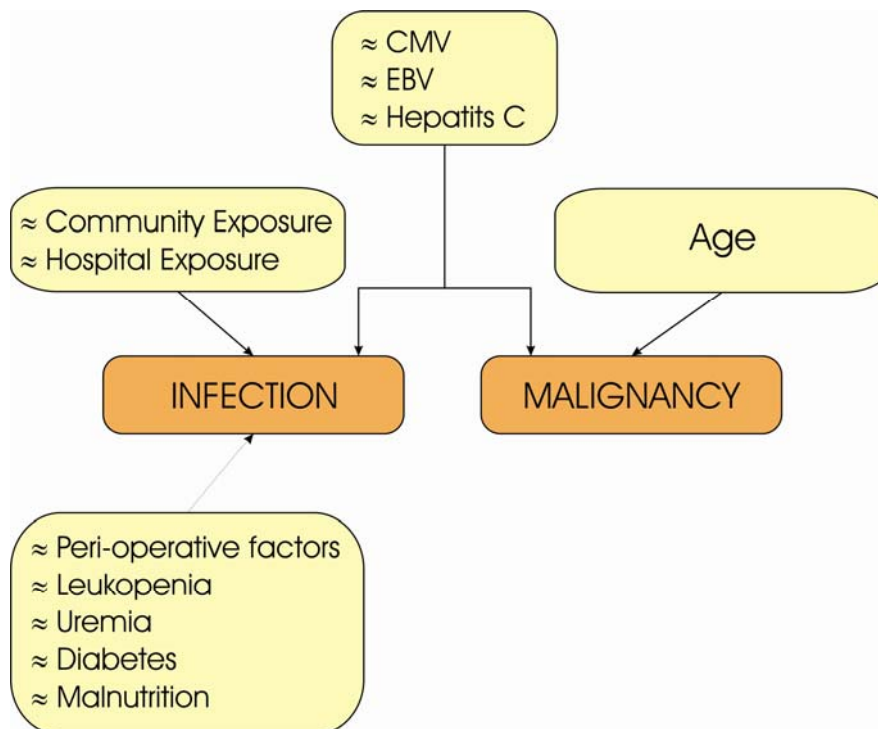
Heart transplant recipients are at increased risk of cutaneous malignancies and have a greater tendency to develop squamous cell carcinoma than basal cell carcinoma (12). The risk of skin cancer has been reported to increase after 3 years after transplantation, especially in older individuals (13). Moreover, squamous cell carcinoma is believed to be more aggressive, with a higher risk of metastasis (5–8%) in transplant recipients than in

the general population (14). The preferential location of skin cancers is on sun-exposed areas, which supports the experimental data suggesting that UV light may be a keratinocyte mutagen, acting like a tumor initiator and promoter (15).

Risk Stratification

Although the risk factors for infection and malignancy after heart transplantation may have a different background, it is important to consider their effects when tailoring immunosuppressive therapy and individual patient follow-up (Figure 6).

Figure 6. Risk factors for infection and malignancy



Infection

The risk of infection in the cardiac transplant recipient is determined largely by the interaction between the environmental exposures (community or hospital) and the state of immunosuppression.

In the community, patients may have recent or remote contact with potential pathogens including respiratory viruses and food-borne pathogens (salmonella, *Listeria monocytogenes*, *Campylobacter jejuni*). Community exposure also includes recent and remote exposure to such organisms as those causing the geographically restricted systemic mycoses (*Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*), *Mycobacterium tuberculosis*, and *Strongyloides stercoralis*. Within the hospital, excessive environmental exposure may be domiciliary or nondomiciliary. Domiciliary exposure occurs on the hospital unit where the patient is housed, and nondomiciliary exposure occurs within the hospital when the patient is exposed to contaminated air during travel to or from clinical procedures such as surgery or radiologic imaging (7).

The general state of immunosuppression depends on several parameters other than the post-transplant therapy. In the early post-operative period, the integrity of the mucocutaneous barrier (catheters, epithelial surfaces), and presence of devitalized tissue or fluid collections may increase the infection risk. In the later post-transplant period, neutropenia, lymphopenia, or certain metabolic conditions (uremia, malnutrition, diabetes, cirrhosis) may be of considerable importance. Furthermore, infection with immunomodulating viruses (CMV, Epstein–Barr virus, hepatitis B and C viruses, human immunodeficiency virus) is associated with a significantly increased risk of opportunistic infections (16).

Malignancy

Although all malignancies developing after transplantation may be dependent on the cumulative and specific immunosuppressive therapies, some specific risk factors that predispose a patient towards development of lymphoproliferative disorder and skin cancer can still be identified.

Patients with primary EBV infection, CMV mismatch or CMV disease and younger patients have higher risk for early post-transplant lymphoproliferative disorder, while older recipients appear to be at risk for late lymphoproliferative disease (17). The risk of lymphoid neoplasia after heart transplantation is raised by 10-fold raised in patients who were EBV seronegative before transplant. The risk appears to be further increased in young seronegative patients if the donor was older than the recipient (18). There are evidences suggesting that infection with CMV or other types of herpesviridae are also an important risk factor for the development of lymphoproliferative disease. An important synergy exists between the risk factors of pretransplant seronegativity for EBV, CMV mismatch and OKT3 treatment for rejection (19). Finally, in addition to EBV, hepatitis C virus has also been reported to be involved in the development of lymphoproliferative malignancies due to its lymphotropic properties (20).

Besides the cumulative exposure to immunosuppressant drugs, age at transplantation has been shown to be the most important risk factor for skin cancer of any type. Older patients (>50 years) not only had an increased risk but also showed a shorter mean interval between transplantation and development of the first skin cancer (15). Exposure to UV radiation and HPV infection may pose additional risk for this type of malignancy (21).

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Chapter 4:

Treatment Considerations

The goal of immunosuppressive therapy is to prevent rejection of the transplanted heart, while minimizing drug-related effects, such as infection, malignancy, diabetes, hypertension, and renal insufficiency. Preventing the occurrence or progression of cardiac allograft vasculopathy is another important consideration.

Induction Therapy

Induction therapy was originally conceived as a method for providing immunologic ablation with upstream antibody therapy as a prelude to inducing graft tolerance. Currently, a more relevant definition of induction therapy would probably be any intensive immunosuppressive therapy (other than steroids) used in a prophylactic manner before or early after transplantation that is not part of the chronic (maintenance) immunosuppressive regimen (1). Induction can be achieved either by lymphocytolytic

Part II: Treatment Considerations

agents (OKT3, anti-thymocyte globulins) or anti-interleukin-2 receptor antibodies (daclizumab, basiliximab).

Although induction therapy with lymphocytolytic agents has historically been shown to reduce the incidence of acute rejections (2), the survival benefit of induction therapy for patients at high risk for rejection death has progressively decreased over time, likely because of improvements in maintenance and possibly other adjunctive therapies (1). Furthermore, the use of OKT3 has been shown to be associated with poor patient tolerance, increased incidence of infections (particularly CMV), and increased incidence of lymphoproliferative disorders (2). This suggests that the use of OKT3 should largely be abandoned in favour of anti-thymocyte globulins or anti-interleukin-2 receptor antibodies.

Daclizumab and basiliximab appear to be well tolerated and exhibit a safety profile not statistically significantly different to placebo (3). Although both agents appear to be effective in preventing acute allograft rejection, daclizumab may be more potent with this regard (4,5). Basiliximab may be particularly useful in heart transplant recipients with impaired renal function. In these patients, basiliximab may allow delayed cyclosporine use while preventing cuter rejection and improving renal function, as measured by improvements in serum creatinine levels (6).

However, since the impact of induction therapy on all-cause mortality remains uncertain, as does the risk for increased infection, malignancy, and allograft vasculopathy, it should probably be used mainly in selective high-risk patients as a part of renal-sparing protocol (Table 8).

Table 8. Risks Associated with Induction Therapy

	Rejection	CAV	Infection	Malignancy
OKT3	Low	Intermediate	High	High
ATG	Low	Intermediate	Intermediate	Intermediate
Daclizumab	Low	Low	Low	Unknown
Basiliximab	Intermediate	Low	Low	Unknown

CAV, cardiac allograft vasculopathy; ATG, anti-thymocyte globulins

Steroids

Steroids produce immunosuppression by multiple mechanisms and result in a powerful and generalized anti-inflammatory response. Due to the many side effects (cataracts, osteoporosis, hypertension, hyperlipidemia and diabetes), there has been significant interest in early steroid withdrawal after heart transplantation. It appears that steroid withdrawal is possible in almost 60% of patients at 6 months after transplantation. Despite an increased frequency of acute rejection, early steroid withdrawal improves the freedom from malignancy and may decrease the frequency of infection and improve long-term survival in the cardiac transplant population without increasing the risk of posttransplant coronary artery disease (7) (Table 9).

Successful weaning from steroids likely involves a patient subgroup that is immunologically privileged, and the non-occurrence of steroid-induced toxicity and side effects promotes graft survival. In these patients close long-term surveillance seems warranted (8).

Table 9. Risks Associated with Steroid Therapy

	Rejection	CAV	Infection	Malignancy
Steroids	Low	Intermediate	High	Intermediate

CAV, cardiac allograft vasculopathy

Calcineurin Inhibitors

Calcineurin inhibitors, cyclosporine and tacrolimus are routinely used for immunosuppression following heart transplantation in conjunction with an antiproliferative agent with or without maintenance steroids. The advantage of these drugs over cytotoxic immunosuppressants is that they act specifically on the immune system, not affecting other rapidly proliferating cells (9).

In general, the two calcineurin inhibitors showed similar efficacies in preventing rejection and death within the first year after transplant, but tacrolimus appears to cause fewer cases of hypertension and hyperlipidemia than cyclosporine. On the other hand, tacrolimus appears to be associated with higher incidence of insulin-requiring diabetes mellitus (10). Thus, the choice between cyclosporine and tacrolimus seems currently dictated by their adverse effect profiles and by the results obtained for the individual patient (Table 10).

Table 10. Risks Associated with Calcineurin Inhibitor Therapy

	Rejection	CAV	Infection	Malignancy
Cyclosporine	Low	Intermediate	Intermediate	Intermediate
Tacrolimus	Low	Intermediate	Intermediate	Intermediate

CAV, cardiac allograft vasculopathy

Antiproliferative Agents

The antiproliferative agents used commonly after heart transplantation are azathioprine and mycophenolate mofetil (MMF). Azathioprine was the earlier agent used in this class and served as the mainstay of immunosuppression even prior to the routine use of cyclosporine. More recently, MMF replaced azathioprine as the first-line antiproliferative drug, with several randomized trials demonstrating superiority compared with azathioprine (11). MMF treatment was associated with a significant reduction in 1-year mortality and reduced rates of rejection (12). Furthermore, MMF also was associated with improvements in the intracoronary luminal area assessed by intravascular ultrasound suggesting that it may provide long-term benefits in reducing cardiac allograft vasculopathy (13). Data from the transplant registry of the International Society for Heart and Lung Transplantation demonstrated that the use of MMF in standard immunosuppressive regimens is associated with a significantly lower risk of developing malignancy (14). However, the risk of opportunistic infections appears to be higher in patients treated with MMF when compared with azathioprine (15).

Recently, an advanced formulation that delays the release of mycophenolic acid, has been investigated in a multicenter trial of de novo-heart transplant recipients (16). The 6- and 12-month results have shown that an enteric-coated mycophenolate sodium is therapeutically similar to MMF and has a comparable safety profile.

Based on these data it appears that MMF has substantial benefits over azathioprine, particularly with regards to prevention of vasculopathy and malignancy and should be therefore be

considered the antiproliferative agent of choice in heart transplantation (Table 11).

Table 11. Risks Associated with Anti-proliferative Therapy

	Rejection	CAV	Infection	Malignancy
Azathioprine	Intermediate	Intermediate	Low	Intermediate
MMF	Low	Low	Intermediate	Low

CAV, cardiac allograft vasculopathy; MMF, mycophenolate mofetil

Proliferation Signal Inhibitors

Proliferation signal or mammalian target-of-rapamycin inhibitors (PSI/mTOR inhibitors) include two drugs currently available for clinical use, sirolimus and everolimus. Because of their dual mode of action (immunosuppressive and antiproliferative) they represent attractive options for use in heart transplantation (17). Both agents have shown efficacy for reducing the incidence of acute rejection and cardiac allograft vasculopathy following heart transplantation; however, everolimus data are drawn from a larger double-blind study (18,19).

PSI/mTOR inhibitors work synergistically with calcineurin inhibitors and thus permit the minimization of calcineurin inhibitors without compromising efficacy. This approach is advantageous for the majority of heart transplant recipients and might provide particular benefit in specific cases, such as patients with cardiac allograft vasculopathy, malignancies and renal dysfunction, or in patients intolerant to other immunosuppressive agents (20)

Since proliferation signal inhibitors are potent immunosuppressive agents, infection is an expected adverse effect. Some studies have noted a trend towards an increased rate of bacterial infections in patients treated with PSIs when compared with azathioprine. In contrast, the incidence of cytomegalovirus syndrome is consistently lower in patients treated with PSIs versus MMF or azathioprine (21).

PSIs appear to inhibit growth of a wide variety of malignant cell lines. Data from large studies and registries in renal transplantation have documented that these cellular effects translate into a reduced incidence of malignancy in patients treated with PSIs compared with patients managed on a CNI-based regimen. Moreover, regression of Kaposi sarcoma after switching from CNI to sirolimus has been convincingly documented in both renal and heart transplant recipients (22).

Impaired wound healing associated with sirolimus and everolimus is common and may lead to major complications, especially when the drugs are used de novo after heart transplantation. Other common side effects that may necessitate dose reduction or discontinuation of PSIs include peripheral edema, pleural or pericardial effusions, mouth ulcers, acne, diarrhea, hyperlipidemia, and leucopenia. However, these side effects are often temporary and may respond to dose reduction (23).

Although their long-term efficacy remains to be defined, PSIs appear to offer a good treatment option after transplantation, particularly in patients with renal dysfunction, malignancy or cardiac allograft vasculopathy (Table 12).

Table 12. Risks Associated with Proliferation Signal Inhibitor Therapy

	Rejection	CAV	Infection	Malignancy
Sirolimus	Intermediate	Low	Intermediate	Low
Everolimus	Low	Low	Intermediate	Low

CAV, cardiac allograft vasculopathy

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