Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006

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1. EVALUATION OF LISTING CRITERIA FOR CARDIAC TRANSPLANTATION

Two of the previous International Society for Heart and Lung Transplantation (ISHLT) consensus conferences have addressed listing criteria for patients awaiting heart transplantation.[1,2] Guidelines from these two conferences were completed before the acceptance of β-blocker and device therapies in the clinical treatment of late-stage heart failure. Guidelines addressing the management of heart failure are now available from the European Society of Cardiology (ESC) as well as the American College of Cardiology (ACC), American Heart Association (AHA) and Heart Failure Society of America (HFSA) in the USA; however, these statements are not comprehensive regarding the criteria for listing patients for heart transplantation. Thus, the ISHLT has responded to this urgent need to re-evaluate the listing criteria to provide succinct and clear guidance to transplant centers. These recommendations can be used to update listing and management policies for potential heart transplant recipients.

1.1. Cardiopulmonary Stress Testing to Guide Transplant Listing

Recommendations for Cardiopulmonary Stress Testing to Guide Transplant Listing

Class I:

1. A maximal cardiopulmonary exercise (CPX) test is defined as one with a respiratory exchange ratio (RER) >1.05 and achievement of an anaerobic threshold on optimal pharmacologic therapy (*Level of Evidence: B*).
2. In patients intolerant of a β-blocker, a cutoff for peak Vo_2 of ≤14 ml/kg/min should be used to guide listing (*Level of Evidence: B*).
3. In the presence of a β-blocker, a cutoff for peak Vo_2 of ≤12 ml/kg/min should be used to guide listing (*Level of Evidence: B*).

Class IIa:

1. In young patients (<50 years) and women, it is reasonable to consider using alternate standards in conjunction with peak Vo_2 to guide listing, including percent of predicted (≤50%) peak Vo_2 (*Level of Evidence: B*).

Class IIb:

1. In the presence of a sub-maximal CPX test (RER <1.05), use of ventilation equivalent of carbon dioxide (Ve/Vco_2) slope of >35 as a determinant in listing for transplantation may be considered (*Level of Evidence: C*).
2. In obese (body mass index [BMI] >30 kg/m^2) patients, adjusting peak Vo_2 to lean body mass may be considered. A lean body mass–adjusted peak Vo_2 of <19 ml/kg/min can serve as an optimal threshold to guide prognosis (*Level of Evidence: B*).

Class III:

1. Listing patients based solely on the criterion of a peak oxygen consumption (Vo_2) measurement should not be performed (*Level of Evidence: C*).

1.1.1 Cardiopulmonary exercise testing. CPX testing is routinely used in the determination of candidacy for cardiac transplantation.[1–3] Mancini et al first demonstrated the prognostic utility of CPX testing.[4] Patients were divided into 3 groups: peak Vo_2 <14 ml/kg/min and eligible for transplantation; peak Vo_2 <14 ml/kg/min and ineligible for transplantation; and peak Vo_2 >14 ml/kg/min. Patients with a peak Vo_2 <14 ml/kg/min had a significant survival benefit with cardiac transplantation compared with the group ineligible for transplantation and who continued on their current medical regimen. However, the cutoff peak Vo_2 of 14

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ml/kg/min was arbitrary. Within the entire group, patients with peak Vo_2 <10 ml/kg/min had a lower survival rate than those with a peak Vo_2 of between 10 and 14 ml/kg/min. Based on this observation, the currently accepted indication for transplantation is patients with a peak Vo_2 <10 ml/kg/min who achieved anaerobic threshold.[1-3] Patients with a peak Vo_2 between 10 and 14 ml/kg/min who also have a major limitation to their activities of daily living (ADL) are categorized as having a probable indication for transplantation.

Since this initial study, advances in medical therapy and in the interpretation of CPX tests have occurred. β-blockers and implantable cardioverter defibrillators (ICDs) are now routinely prescribed for potential transplant patients. Many patients also have biventricular pacemakers implanted. These therapies improve survival for heart failure patients.[5-9] However, with the exception of biventricular pacemakers, they do not appreciably change exercise capacity.[10-13] Consideration should be given to revising the existing listing criteria because currently used therapies can improve survival but have a negligible effect on exercise performance. Zugck et al evaluated a group of 408 patients with an average peak Vo_2 of 14.4 ml/kg/min and found that the group taking a β-blocker had a significant reduction (34% vs 16%) in the combined end-point of hospital admission for worsening congestive heart failure (CHF) or death within 1 year.[14] This study was followed by 3 other studies, all of which showed improved survival in patients on β-blockers with an equivalent Vo_2.[15-17] Peterson et al demonstrated that, for patients on β-blockers, only those with a peak Vo_2 of <12 ml/kg/min had a survival advantage with cardiac transplantation at 1 year and 3 years.[16]

Normalizing peak Vo_2 for gender and age in terms of listing criteria may be particularly useful for young patients and women, for whom a threshold value of 14 ml/min/kg may be quite inappropriate.

In heart failure patients, the measurement of peak Vo_2 is limited by the difficulty in assessing whether a truly maximal test was performed. Heart failure patients rarely reach a true plateau of oxygen consumption with increasing workloads, the classic definition of a maximal test. Patients are often limited by deconditioning, lack of motivation, difficulty exercising with the measurement apparatus, or body composition. Because heart failure patients rarely reach a plateau of Vo_2 with increasing workloads, common determinants of a maximal exercise test have been RER >1.1 and reaching an anaerobic threshold.[1] However, a review of studies defining the criteria for Vo_2max showed that 6 of 14 studies used an RER cutoff of 1.0 or 1.05, so these criteria may be too stringent.[18] Decisions might also need to be made based on a sub-maximal test.

Investigators have recently shown the prognostic significance of the ventilation to carbon dioxide (V_E/Vco_2) slope.[19-25] The ventilatory response to exercise can be measured throughout the entire exercise duration and the V_E/Vco_2 slope has been shown to be steeper in patients with reduced cardiac output during exercise, increased pulmonary artery pressures and increased dead space/tidal volume ratio.[26,27] Many investigators have found that a V_E/Vco_2 slope of >35 is of greater prognostic value than a peak Vo_2 of <14 ml/kg/min.[19-25] The additional advantage of this measurement is that, if a patient does not reach a true peak Vo_2, one can still have a reliable V_E/Vco_2 slope because it is measured throughout exercise. However, similar to peak Vo_2, none of these data have been generated from patients receiving contemporary heart failure therapy including β-blockers.

In healthy individuals, peak Vo_2 varies by gender and age. In addition, because Vo_2 is normalized for body weight, heavier patients with a similar fitness level will have a lower peak Vo_2. Therefore, when considering an individual patient for transplant, one must consider the age, gender and weight of the patient. In a group of 181 patients evaluated for transplant, peak Vo_2 of <50% of predicted was the most significant predictor of cardiac death, even with peak Vo_2 in the model.[28] Similarly, Osman et al adjusted peak Vo_2 to lean body mass and found that a lean peak Vo_2 of <19 ml/kg/min was a better predictor of outcome than an unadjusted peak Vo_2 of <14 ml/kg/min.[29]

Most patients who undergo evaluation for transplantation perform a metabolic exercise test as part of that evaluation. However, once a patient is listed for transplantation, it is rare for repeat testing to be performed. Two studies have shown that patients who increase their peak Vo_2 on serial exercise tests have improved survival that may warrant removal from the transplant list.[30,31] These findings are in contrast to a third study in which changes in peak Vo_2 did not provide a prognostic benefit.[32] In addition, one of the studies demonstrating a benefit had an average peak Vo_2 of 18.2 ml/kg/min.[31]

1.2. Use of Heart Failure Prognosis Scores

Recommendations regarding the use of heart failure prognosis scores are as follows:

Class IIb:

1. In circumstances of ambiguity (e.g., peak Vo_2 >12 and <14 ml/kg/ml) a Heart Failure Survival Score (HFSS) may be considered, and it may add discriminatory value to determining prognosis and guide listing for transplantation for ambulatory patients (*Level of Evidence: C*).

1.2.1. Recommended prognostic factors for collection. Approximately 100 individual factors have been identified as having prognostic significance in heart failure, including: demographic and historical information; symptom severity, coronary artery disease (CAD) burden, co-morbidities, data derived from physical examination, routine serum biochemistry and hematology studies, neurohormones, cytokines, troponin, measures of collagen turnover, electrocardiography and chest radiology; measures of left and right ventricular (RV) systolic and diastolic function and mitral and tricuspid valve regurgitation; and sub-maximal and maximal exercise test data, including various measures derived from respiratory gas measurements. To be useful in the context of estimating prognosis for heart transplant candidates, these factors must be predictive in the patient population of interest (heart transplant candidates). One must consider not only whether a factor is prognostic, but also whether it adds incremental prognostic information in the context of other prognostic factors. The desire for accuracy must be balanced against practicality and cost. However, given the magnitude of the decision being made, the scale weighs heavily toward the side of accuracy.

Risk stratification of ambulatory transplant candidates with advanced heart failure has been studied extensively, yet for this group of patients the decision of whether to list an individual patient for transplantation remains challenging.

1.2.2. Risk stratification of ambulatory patients. In addition to peak Vo_2, the other component measures of the Heart Failure Survival Score (HFSS)—left ventricular ejection fraction (LVEF), serum sodium and mean blood pressure and heart rate at rest, ischemic heart failure etiology and QRS duration ≥120 milliseconds (left bundle branch block [LBBB], right bundle branch block [RBBB], non-specific intraventricular conduction delay [IVCD] or ventricularly paced rhythm)—have each been separately identified and validated as valid prognostic measures. Serum levels of uric acid and N-terminal pro–B-type natriuretic peptide (NT-pro-BNP) are each significantly correlated with HFSS and each is predictive of heart failure mortality, as are troponin levels. Additional studies are needed to confirm the validity of these latter measures, but they appear promising.

The HFSS is a predictive model calculated from 7 prognostic variables that are obtained commonly during the transplant evaluation process.[33] The HFSS was developed and validated in patients undergoing transplant evaluation and has been extensively re-validated by other investigators. Both calculation of the HFSS and grouping into HFSS risk strata are shown in Table 1. In the original validation sample, low-, medium- and high-risk HFSS strata were associated with 88 ± 4%, 60 ± 6% and 35 ± 10% 1-year transplant-free survival rates, respectively.

Table 1. Calculation of Heart Failure Survival Score

Clinical characteristic	Value (χ)	Coefficient (β)	Product
Ischemic cardiomyopathy	1	+0.6931	+0.6931
Resting heart rate	90	+0.0216	+1.9440
Left ventricular ejection fraction	17	−0.0464	−0.7888
Mean BP	80	−0.0255	−2.0400
IVCD	0	+0.6083	0
Peak Vo_2	16.2	−0.0546	−0.8845
Serum sodium	132	−0.0470	−6.2040

HFSS: low-risk strata, ≥8.10; medium-risk strata, 7.20 to 8.09; high-risk strata, <7.20.

The Heart Failure Survival Score (HFSS) is calculated by taking the absolute value of the sums of the products of each component variable's value and its model coefficient. For ischemic cardiomyopathy and intraventricular conduction delay (IVCD) (QRS ≥120 ms), use 0 if "no" or 1 if "yes." Mean blood pressure (BP) = diastolic BP + 1/3 (systolic BP − diastolic BP). *Example:* Patient with ischemic cardiomyopathy: Resting heart rate, 90 bpm; left ventricular ejection fraction (LVEF), 17%; BP, 100/70 mm Hg; peak oxygen consumption (Vo_2), 16.2 ml/min/kg; serum sodium, 132 mg/dl.

Although peak Vo_2 is a component measure of the HFSS, data provided by each may be complementary in some circumstances. The HFSS appears to be particularly useful in patients whose peak Vo_2 would put them at medium risk. Butler et al found that 55% of patients with peak Vo_2 of 10 to 14 ml/min/kg had a low-risk HFSS, with an 88% 1-year event-free survival.[34] In a study of mainly low- and medium-risk HFSS patients (85% of total), Lund et al also found a graded relationship between HFSS and peak Vo_2. They observed the best survival in patients with both low-risk HFSS and peak Vo_2 >14 ml/min/kg, the worst survival for those with high-risk scores for both HFSS and peak Vo_2, and intermediate outcomes for those with low-risk peak Vo_2 but medium-risk HFSS. However, patients with low-risk HFSS were at similar risk regardless of concomitant low-risk (>14 ml/min/kg) or medium-risk peak Vo_2 (10 to 14 ml/min/kg). One-year survival was 84% and 95% for patients with low- and medium-risk peak Vo_2, respectively.[17]

The HFSS was developed before the widespread use of biventricular pacemakers, implantable cardioverter defibrillators (ICDs), β-blockers and spironolactone, so its utility in the setting of these therapies cannot be determined. Only 10% and 11% of patients in the HFSS derivation and validation samples received a β-blocker. By lowering resting heart rate and raising blood pressure and LVEF, therapy with β-blockers would be expected to improve prognostic scores. Biventricular pacing should have concordant effects on the HFSS and survival because it improves LVEF, peak Vo_2 and blood pressure. The effect of spironolactone on the HFSS has

not been determined, but is likely to be modest. Likewise, an ICD would have no effect on HFSS, yet both significantly affect survival. In studies reflecting greater rates of β-blocker treatment, the predictive value of peak Vo_2 alone has been inconsistent, with a deterioration in performance in some studies[15,17] but continued excellent performance in others.[35,36]

A number of studies have evaluated the prognostic value of the HFSS in the present era. These studies have typically focused on the effects of β-blocker use, but they also reflect more contemporary use patterns for spironolactone and ICDs (although not biventricular pacing). These studies show that the HFSS continues to stratify risk; however, as survival has improved with the use of these agents, the risk associated with each level of HFSS (and for that matter, peak Vo_2) has decreased, as dictated by the Bayes theorem. Although the absolute risk associated with each stratum differs according to overall mortality in each study, patients in the low- and high-risk strata continue to have both good prognoses (i.e., no transplant needed) and poor prognoses (i.e., transplant listing warranted) with medical therapy alone. Patients in the medium-risk HFSS group on β-blockers now have a prognosis that is only slightly worse or may even approach post-transplant survival over the next 1 to 2 years. For these patients, additional clinical information (e.g., frequent hospitalizations for volume overload, angina or arrhythmias; a persistent rise in creatinine or pulmonary vascular resistance [PVR]; high levels of serum BNP or NT-pro-BNP, troponin or uric acid; or a lack of biventricular pacing and ICD) will argue for a relatively worse prognosis. Studies differ as to whether peak Vo_2 data may be used to further risk stratify the medium-risk HFSS group.[34,37]

The value of NT-pro-BNP and serum uric acid in the context of the HFSS has been investigated in several studies. NT-pro-BNP was as predictive as the HFSS in one study,[38] and in another study it was a stronger predictor of death.[39,40] The value of this marker as an adjunct to the HFSS in evaluation of heart transplant candidates requires further study.

Limited data on the prognostic value of uric acid in combination with the HFSS are also promising.[41] Serum uric acid was as predictive as the HFSS and, when dichotomized at 9.8 mg/dl (565 μmol/liter), it improved the accuracy of the HFSS at each HFSS risk level. Anker et al developed a 3-variable metabolic, functional and hemodynamic (MFH) model wherein 4 risk strata (0 to 3 points) are created by assigning 1 point for peak Vo_2 <14 ml/min/kg, LVEF $\leq 25\%$ and uric acid ≥ 9.8 mg/dl. Although no direct comparison with HFSS was given, this simple model performed quite well. The relatively low-risk HFSS scores (mean 8.56) were consistent with the relatively low mortality risk in this study (15% at 1 year vs 32% in the original HFSS validation sample), so applicability to more advanced ambulatory heart failure is uncertain.

Investigators at Heidelberg University compared the HFSS to a similar model, the HFSS-HD, containing 6 of the 7 variables in the HFSS plus a 6-minute-walk distance (6MW) in place of peak Vo_2. They also compared the HFSS to 2 simplified models containing only LVEF with peak Vo_2 and LVEF with 6MW in 208 heart transplant candidates (mean HFSS 8.61).[42] The areas under the receiver-operating-characteristic curve (AUCs) for the HFSS-HD and both 2-component models were all nearly identical and were significantly better than the HFSS. All of the predictive ability of the HFSS, HFSS-HD and the 2 component models in the Heidelberg sample was due to LVEF and the exercise variable (6MW or peak Vo_2)—none of the other 5 variables contributed significantly. The investigators speculated that the HFSS may not perform as well in this less ill patient cohort, consistent with the studies noted earlier. However, other studies suggested that the decreased performance of the HFSS in the Heidelberg study may have also resulted from peculiarities of the study sample. For example, the EPICAL (EPidémiologie de l'Insuffisance Cardiaque Avancée en Lorraine) investigators demonstrated good predictive ability for separate predictive models for ischemic and non-ischemic cardiomyopathy, both of which included serum sodium and heart rate.[43] The risk in ischemic patients was significantly worse than in non-ischemic patients, as has been shown in numerous other studies. Campana et al developed a model, including catheterization-derived variables, which limits its use in routine clinical practice.[44] Neither the EPICAL nor the Campana model has been validated in an independent patient sample. Other than the HFSS, no other model has been validated for use in patients receiving a β-blocker.

Finally, a notable model was developed by the German Transplant Society.[45] The model was developed from data on all new registrants on the German transplant list in 1997 and validated on new registrants the following year; the outcome measure was death while on the waiting list. The model contained 7 variables, including information about the urgency of transplantation (including location of home, ward or ICU; use of inotropes; mechanical circulatory support [MCS]; or dialysis) and left ventricular LV function (LVEF and cardiac index). Although the model performed quite well, its dependence on physician behavior as opposed to patient physiology greatly limits its prospective use, as the potential for manipulating the system would be large.

1.2.3. How frequently should prognosis be reassessed? Serial evaluation is essential both for patients placed on the transplant waiting list and for those for whom transplant listing can be safely deferred. Al-

though studies differ on the frequency of improvement in patient status while on the outpatient waiting list[46,47]—likely due to differences in patient presentation and the point of illness at which transplant evaluation is performed—all recognize that some patients will improve and others will deteriorate. The optimal frequency of evaluation has not been determined but a reasonable interval seems to be every 6 months. Until quite recently, no commonly used predictive measure had been validated for serial use. However, both peak Vo_2 and the HFSS have now been evaluated and have been shown to predict survival when used serially.[37,48] Patients who remain at low HFSS risk on serial evaluation have substantially better outcomes than those who deteriorate to medium or high HFSS risk. A low-risk HFSS on serially evaluated patients receiving a β-blocker continues to indicate good prognosis over the following year. Patients who improve to low-risk HFSS while receiving a β-blocker have an expected survival comparable to 1-year post-transplant survival, and can continue to have transplantation deferred.

1.2.4. Hospitalized patients. Two models have been developed recently to determine in-hospital, 30-day and 1-year mortality in patients hospitalized with acute decompensated heart failure (ADHF). Fonarow et al used the Acute Decompensated Heart Failure National Registry (ADHERE) to identify 3 variables at hospital admission (systolic blood pressure [SBP; stratified at 115 mm Hg], blood urea nitrogen [BUN; stratified at 43 mg/dl] and creatinine [stratified at 2.75 mg/dl]), with in-hospital mortality ranging from 2.1% to 21.9%. If confirmed in otherwise transplant-eligible patients, the presence of all 3 risk factors (the highest-risk group) could be appropriate justification for more aggressive therapy with inotropes or MCS so as to attempt rapid improvement in renal function and allow safe performance of heart transplantation. However, the threshold values of BUN and SBP may be too low for effective stratification of transplant candidates.[49]

Lee et al developed a model, the Heart Failure Risk Scoring System, to predict 30-day and 1-year mortality from community heart failure hospitalization in Ontario. The model was developed from data on >2,600 hospitalized patients and validated on >1,400 subsequently hospitalized patients, utilizing data available within hours of admission, including older age, lower systolic blood pressure, higher respiratory rate, higher urea nitrogen level, hyponatremia, and a number of co-morbid conditions (each of which would likely preclude transplant). The model was modestly improved by adding LVEF but still performed quite well without it (AUCs at 30 days and 1 year in the validation sample were 0.79 and 0.76, respectively, with improvements to 0.81 and 0.79 with inclusion of LVEF). The investigators provided a website for calculation of the risk score (http://www.ccort.ca/CHFriskmodel.asp).[50]

1.3. Role of Diagnostic Right Heart Catheterization

Recommendations for diagnostic right heart catheterization are as follows:

Class I:

1. Right heart catheterization (RHC) should be performed on all candidates in preparation for listing for cardiac transplantation and annually until transplantation (*Level of Evidence: C*).
2. RHC should be perfomed at 3- to 6-month intervals in listed patients, especially in the presence of reversible pulmonary hypertension or worsening of heart failure symptoms) (*Level of Evidence: C*).
3. A vasodilator challenge should be administered when the pulmonary artery systolic pressure is ≥50 mm Hg and either the transpulmonary gradient (TPG) is ≥15 or the pulmonary vascular resistance (PVR) is >3 Wood units while maintaining a systolic arterial blood pressure >85 mm Hg (*Level of Evidence: C*).
4. When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring should be performed, as often the PVR will decline after 24 to 48 hours of treatment consisting of diuretics, inotropes and vasoactive agents such as inhaled nitric oxide (*Level of Evidence: C*).

Class IIb:

1. If medical therapy fails to achieve acceptable hemodynamics and, if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or left ventricular assist device (LVAD), it is reasonable to conclude that the pulmonary hypertension is irreversible (*Level of Evidence: C*).

Right heart failure is a common occurrence and a cause of morbidity and mortality after cardiac transplantation. The recognition that the donor right ventricle would fail when post-reperfusion pulmonary artery systolic pressures exceeded 50 to 60 mm Hg led to early guidelines established by the Stanford program for the assessment of pulmonary hypertension and PVR in potential heart transplant candidates. Hence, the convention for the past 25 years has been to obtain invasive hemodynamics as an integral component of the assessment of heart transplant candidates. The premise is that elevated PVR is associated with right heart failure and mortality after cardiac transplantation. Contemporary registry data from the ISHLT indicate that approximately 20% of early deaths after cardiac transplantation are attributable to RV failure.[51] Although criteria have

Table 2. Important Hemodynamic Parameters to Assess Potential Cardiac Transplant Candidates

- Pulmonary artery hypertension and elevated PVR should be considered as a relative contraindication to cardiac transplantation when the PVR is >5 Wood units or the PVRI is >6 or the TPG exceeds 16 to 20 mm Hg
- If the PAS exceeds 60 mm Hg in conjunction with any 1 of the preceding 3 variables, the risk of right heart failure and early death is increased
- If the PVR can be reduced to <2.5 with a vasodilator but the systolic blood pressure falls <85 mm Hg, the patient remains at high risk of right heart failure and mortality after cardiac transplantation

Calculations: transpulmonary gradient (TPG [PAMP − PCWP]); pulmonary vascular resistance (PVR [TPG/CO Wood units]); pulmonary vascular resistance index (PVRI [TPG/CI]).

been proposed that contraindicate cardiac transplantation, increasingly it has been recognized that absolute cutoffs do not exist and large-cohort analyses have demonstrated that elevated PVR is an incremental risk factor from low to high values.[52] A variety of measures have been analyzed (Table 2) and correlated with outcomes, including both static measures of pulmonary artery resistance and provocative/dynamic measures after pharmacologic challenges.

Patients with chronic heart failure most commonly develop pulmonary hypertension due to elevated left ventricular end-diastolic pressure (LVEDP) and, as a result, elevated left atrial pressure and pulmonary venous hypertension. This is considered to be a reactive form of pulmonary hypertension. Usually, the pulmonary artery pressures fall rapidly when the left heart is "unloaded," either pharmacologically or mechanically. This is the basis of "vasodilator challenges," which most commonly, as in the case of nitroprusside, nitroglycerin and nesiritide, reduce pulmonary capillary wedge pressure (PCWP), and typically pulmonary artery pressures fall rapidly. However, pulmonary venous hypertension can lead to irreversible pulmonary arterial hypertension, as evidenced by fixed, elevated PVR.

When static measures show elevation of the PVR, clinicians attempt to unload the left heart and improve LV performance to document reversibility. Numerous studies have shown, however, that reversible pulmonary hypertension is associated with worse outcomes.[53] Patients with fixed, elevated PVR may have concomitant lung disease, obstructive sleep apnea or chronic pulmonary thromboembolic disease. Each of these potential causes should be considered and excluded. Listing criteria for cardiac transplantation published in 1998 concluded that the following variables are relative contraindications if they are present after an "aggressive challenge" with one or more vasodilators and/or inotropic agents while maintaining a systolic blood pressure of >90 mm Hg, PVR >5 Wood units, TPG >15 and pulmonary vascular resistance index (PVRI) >6 Woods units.[2] The 2004 ISHLT registry report demonstrated that, when comparing survival in patients with PVR of 1 to 3 Woods units vs PVR of >5 Woods units, outcomes were better in the low PVR group ($p = 0.02$; see www.ishlt.org).

Short-term studies are performed by administering a vasoactive agent (e.g., nitroprusside, nitroglycerin, nesiritide, prostacyclin or nitric oxide) and documenting an acute reduction in the PVR, usually in conjunction with a fall in pulmonary artery systolic (PAS) pressure and TPG. When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring may be considered, as often the PVR will decline after 24 to 48 hours of treatment consisting of diuretics, inotropes and vasoactive agents. Some patients may require prolonged therapy for weeks before an acceptable reduction in the PVR is obtained. Prolonged, continuous infusions of vasoactive agents, alone or in addition to inotropic agents, may be considered to optimize PVR while the patient awaits a suitable donor organ, hoping to normalize PVR and reduce the risk of post-transplantation right heart failure. If medical therapy over the subsequent days or weeks fails to reduce the PCWP to <25 mm Hg and the PAS to <60 mm Hg, the reversibility of the PVR cannot be determined. When the left ventricle cannot be effectively unloaded with medical therapy, mechanical adjuncts, including an IABP and/or LVAD, may be considered to indicate reversibility of the PVR.[54,55] Serial RHC should be performed more frequently in patients with marginal initial reductions in the PVR despite aggressive therapy (e.g., VAD and high-dose inotropes) to determine their ongoing acceptability for cardiac transplantation.

Pulmonary artery hypertension and elevated PVR should be considered as relative contraindications to cardiac transplantation when the PVR is >5 Woods units or the PVR index is >6 or the TPG exceeds 16 to 20 mm Hg. If the PAS exceeds 60 mm Hg in conjunction with any of the aforementioned 3 variables, the risk of right heart failure and early death is increased. If the PVR can be reduced to <2.5 with a vasodilator but the systolic blood pressure falls to <85 mm Hg, the patient remains at high risk of right heart failure and mortality after cardiac transplantation.[53,56]

1.4. Co-morbidities and Their Implications for Heart Transplantation Listing

1.4.1. Age, obesity and cancer. Recommendations with regard to age, obesity and cancer are as follows.

Class I:

1. Patients should be considered for cardiac transplantation if they are ≤70 years of age (*Level of Evidence: C*).
2. Pre-existing neoplasms are diverse and many are treatable with excision, radiotherapy or chemotherapy to induce cure or remission. In these patients needing cardiac transplantation, collaboration with oncology specialists should occur to stratify each patient as to their risk of tumor recurrence. Cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The specific amount of time to wait to transplant after neoplasm remission will depend on the aforementioned factors and no arbitrary time period for observation should be used (*Level of Evidence: C*).

Class IIa:

1. Overall, pre-transplant BMI >30 kg/m^2 or percent idea body weight (PIBW) >140% are associated with poor outcome after cardiac transplantation. For obese patients, it is reasonable to recommend weight loss to achieve a BMI of <30 kg/m^2 or percent BMI of <140% of target before listing for cardiac transplantation (*Level of Evidence: C*).

Class IIb:

1. Carefully selected patients >70 years of age may be considered for cardiac transplantation. For centers considering these patients, the use of an alternate-type program (i.e., use of older donors) may be pursued (*Level of Evidence: C*).

Selection criteria for transplantation attempt to ensure optimal allocation for a scarce resource.[57,58] This background revisits absolute and relative contraindications for heart transplantation with an emphasis on age, obesity, cancer, diabetes, renal dysfunction and peripheral vascular disease (PVD).

1.4.1.1. Select older patients should be considered for 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 survival in older age groups comparable to that of younger transplant patients.[59–63] A 10-year follow-up of cardiac transplant recipients >65 years of age (n = 66) demonstrated survival rates comparable to those of younger patients (<60 years: n = 679; 60 to 64 years: n = 137).[61] Ten-year survival was similar in all groups (<60 years: 53.7%; 60 to 64 years: 53.1%; >65 years: 60.2%; p = not statistically significant [NS]). Causes of death were similar among all patient groups. There were significantly fewer rejection episodes in the older patient group (freedom from rejection: 74.9 vs 83.5 vs 90.6, respectively; p = 0.03).

Patients >70 years of age have also been reported to have acceptable outcome.[60] In a study of 15 patients ≥70 years of age, the actuarial survival rates at 1 year and 4 years were not statistically different between older 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.[61,62,64] Therefore, an increasing tendency to perform transplantation in older patients has been observed in recent years. In 2002, 10% of patients undergoing cardiac transplantation were >65 years old. In contrast to those single-center reports, the ISHLT registry[65] and a few other single-center reports[66,67] indicated a progressive linear increase in post-transplant mortality with advancing age.

Allocation of donor hearts to older patients (>70 years) can be managed through the use of an alternate list or strategy where organs from donors (usually older donors) that would otherwise remain unused are allocated to older recipients. At first glance, this practice would appear destined to end in poor outcome, because both older donors and older recipients have been identified as risk factors for poor outcome in large registries. However, an older recipient on the alternate list[59] is theoretically in excellent physical condition (other than heart disease), and, according to the alternate list definition, not ill enough to merit a Status 1A listing. By using an alternate list for older patients, younger donor hearts are not allocated away from younger patients who are awaiting transplantation. It may be appropriate to allocate older donors only to older recipients. This practice has been done for younger patients. The current United Network for Organ Sharing (UNOS) policy for organ allocation specifies that all organs from donors <18 years of age be offered to recipients <18 years of age.[68]

Patients should be considered for cardiac transplantation if they are ≤70 years of age. Patients >70 years of age who meet specific criteria may be considered for cardiac transplantation. For these patients, the use of an alternate-type program (i.e., use of organs from older donors) should be pursued.

1.4.1.2. Caution should be exercised in considering obese patients for transplantation. Obese patients have a greater risk of morbidity and mortality after open-heart surgery.[69–71] This is manifested in poor wound healing, increased risk of infection, lower-extremity thrombosis and pulmonary complications. Sev-

eral methods may be used to measure obesity, including BMI, percent ideal body weight (PIBW) and direct measure of adiposity. BMI is measured as weight in kilograms divided by height in meters squared, and PIBW is weight expressed as a percentage of the mean ideal weight for a given height and gender. Both have been found to be associated with outcomes.

In cardiac transplantation, one study reported that 55 obese (BMI >30 kg/m^2) patients demonstrated nearly twice the 5-year mortality of 351 normal-weight or overweight recipients (53% vs 27%, respectively, $p = 0.001$).[72] In addition, these obese recipients had a shorter time to high-grade acute rejection ($p = 0.004$) as well as an increased annual high-grade rejection frequency when compared with normal-weight recipients ($p = 0.001$). By multivariate analysis, the incidence of transplant-related coronary artery disease (TCAD) was not increased in these obese patients.[72] Previous reports have demonstrated that obesity is a risk factor for the development of TCAD.[73] In a multicenter (Cardiac Transplant Research Database [CTRD]) study of 4,515 cardiac transplant patients,[74] pre-operative obesity (>140% of PIBW) was associated with increased 4-year mortality in males ($p < 0.001$) and a trend toward increased mortality in females ($p = 0.07$). These obese patients also had increased infections after cardiac transplantation. The increased infection rate was observed in both males and females <55 years of age, and in patients with ischemic heart disease. In this study, pre–heart transplant BMI and PIBW were not associated with acute rejection or cardiac allograft arteriopathy after transplant.

In contrast, the large ISHLT registry found that recipient weight is not a risk factor for 5-year survival.[75] However, weight alone may not be a reliable variable as compared with BMI or PIBW, both of which take height into account. A single-center study[76] evaluated 114 overweight and obese patients with BMI >27 kg/m^2. There was no effect of obesity on the incidence of acute rejection, infection or allograft arteriopathy. However, post-operative survival tended to be lower in these obese patients ($p = 0.084$).

Overall, it appears that pre-transplant BMI >30 kg/m^2 or PIBW >140% are associated with poor outcome after cardiac transplantation. Therefore, for severely obese patients, weight loss should be mandatory to achieve a BMI <30 kg/m^2 or PIBW <140% before listing for cardiac transplantation.

1.4.1.3. Pre-transplant cancer history requires individualization of treatment. Active neoplasm from origins other than skin has been an absolute contraindication to cardiac transplantation due to limited survival rates. Currently, heart failure patients with cancers that have been in remission for 5 years and cancers that are low grade, such as prostate, may be acceptable for transplant evaluation. The 5-year remission threshold to safely proceed with transplant appears somewhat arbitrary and depends on the type of pre-existing neoplasm. There is also concern that immunosuppression after transplant might reactivate the pre-existing neoplasm that went into remission. Nevertheless, there have been many reports of patients with pre-existing neoplasm (0 to 240 months before transplant) undergoing successful cardiac transplantation without recurrence of the primary tumor.[77–81] There are reports of patients being successfully transplanted with co-existing tumors, such as primary cardiac tumors and low-grade prostate cancer.[79]

Pre-existing neoplasms are diverse and many are treatable with chemotherapy to induce remission. In these patients needing cardiac transplantation, collaboration with oncology must occur to assess each patient as to their risk of tumor recurrence. When tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up, then cardiac transplantation may be considered. The specific amount of time to wait to transplant after neoplasm remission depends on the factors already discussed.

1.4.2. Diabetes, renal dysfunction and peripheral vascular disease. Recommendations for diabetes, renal dysfunction and peripheral vascular disease are as follows:

Class IIa:

1. Diabetes with end-organ damage other than non-proliferative retinopathy or poor glycemic control (glycosylated hemoglobin [HbA_{1C}] >7.5) despite optimal effort is a relative contraindication for transplant (*Level of Evidence: C*).
2. Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. Evidence of abnormal renal function should prompt further investigation, including renal ultrasonography, estimation for proteinuria, and evaluation for renal arterial disease, to exclude intrinsic renal disease. It is reasonable to consider the presence of irreversible renal dysfunction (eGFR <40 ml/min) as a relative contraindication for heart transplantation alone (*Level of Evidence: C*).

Class IIb:

1. Clinically severe symptomatic cerebrovascular disease, which is not amenable to re-vascularization, may be considered a contraindication to transplantation. Peripheral vascular disease may be considered as a relative contraindication for transplantation when its presence limits rehabilitation

and re-vascularization is not a viable option (*Level of Evidence: C*).

Diabetes, renal function and peripheral vascular disease (PVD) have been assessed sparingly in the proceedings from 3 previous conferences, including the 24th Bethesda Conference,[1] the ISHLT Consensus Conference on Candidate Selection for Heart Transplantation—1993[2] and the Consensus Manuscript of Working Thoracic Organ Transplantation of the German Society of Cardiology.[82]

1.4.2.1. Diabetes mellitus. In the proceedings from the 24th Bethesda Conference, insulin-dependent diabetes mellitus (IDDM) with end-organ damage was a secondary exclusion criterion for heart transplantation.[1] However, diabetic patients without severe secondary end-organ disease (retinopathy, neuropathy or nephropathy) have undergone transplantation successfully, with excellent intermediate results.[83,84] Because of these reasonable to very good results, diabetes mellitus (without end-organ damage) is not considered an absolute contraindication. In most U.S. centers (97%), diabetes mellitus is no longer considered a contraindication.[2] However, there are no clear data to guide assessment of the sub-group of patients with end-organ damage.

A study that investigated factors predicting 10-year survival after heart transplantation found a lower incidence of pre–heart transplantation diabetes (in addition to donor age, incidence of infection, and rejection within 2 years of heart transplantation) in those with better survival.[85] The ISHLT registry demonstrated an approximately 20% to 40% increase in 1- and 5-year mortality, even in carefully selected diabetes patients.[65,75] A specific area of grave concern is the presence of autonomic dysfunction due to diabetes and in those individuals with hypoglycemia unawareness. Anecdotal evidence suggests that these sub-groups represent an area of concern in heart transplant candidates and caution must be exercised in such individuals. About half of the centers consider IDDM with end-organ damage to be an absolute contraindication. Although background retinopathy alone is not considered a contraindication, proliferative retinopathy should raise caution.

It is important to be aware of each patient's diabetes status because corticosteroid therapy may worsen glucose intolerance or induce diabetes mellitus. In patients with IDDM, higher doses of insulin may be needed. Patients with diabetes mellitus who are treated with oral agents may require insulin after heart transplantation.[3] Therefore, an endocrinology assessment is recommended in diabetes patients being considered for transplantation and there should be tight control of blood sugar. In general, uncontrolled diabetes (HbA_{1C} >7.5), despite optimal education and expert consultation, should be considered a relative contraindication for transplantation.[86]

1.4.2.2. Renal function. Irreversible renal dysfunction with serum creatinine >2 mg/dl or creatinine clearance <50 ml/min was considered at the Bethesda Conference as a secondary exclusion criterion.[1] However, when serum creatinine was evaluated as a continuous variable, no specific level was identified beyond which the risk of heart transplant was unacceptable.[87] Two-thirds of U.S. centers have indicated that a serum creatinine of >3 mg/dl is an absolute contraindication for transplantation.[2] In 43% of German centers, irreversible renal dysfunction with a serum creatinine >5 mg/dl is considered an absolute contraindication for transplantation, whereas another 43% of centers consider this level a relative contraindication.[82]

Current surgical skills and immunosuppressive strategies now permit combined heart and kidney transplantation.[88–90] Such combined organ transplantations also challenge current indications and contraindications for heart transplantation. Evidence is accumulating that multi-organ transplantation should be carefully considered and used in the most appropriate individuals to maximize the supply of limited organ donors.

Although most centers use serum creatinine and creatinine clearance, we believe that eGFR should be evaluated.[3] In addition, in patients with a decreased eGFR, renal ultrasound (to assess renal size and chronicity), renal artery ultrasound (to assess for intrinsic renovascular disease) and urinalysis for proteinuria (to test for nephrotic syndrome) are recommended diagnostic tests.

1.4.2.3. Peripheral vascular disease. In 1996, 64% of German heart transplant centers considered a significant lesion of the cerebral or peripheral vasculature to be an absolute contraindication for transplantation. It was emphasized, however, that the clinical severity of symptoms (Fontan Stage $\geq$III) should be included in the assessment. It was noted that simultaneous vascular surgery might also be considered.[82] In contrast, only 30% of U.S. centers assessed asymptomatic PVD as an absolute contraindication, whereas 80% considered it a relative contraindication.[2]

Retrospective reviews suggested that the progression of peripheral vascular disease may be accelerated in heart transplant recipients. A study was undertaken to determine the incidence and to identify those risk factors associated with the development or progression of PVD in such individuals. Post-transplant peripheral vascular disease occurred in 10% of heart transplant recipients and was associated with pre-transplant ischemic cardiomyopathy and smoking. A previously unrec-

ognized sub-group of patients who have non-compressible vessels after surgery was described in one study.[91]

1.5. Tobacco Use, Substance Abuse and Psychosocial Evaluation in Candidates

1.5.1. Tobacco use. Recommendations for transplant candidates who use tobacco are as follows:

Class I:

1. Education on the importance of tobacco cessation and reduction in environmental or second-hand exposure should be performed before the transplant and continue throughout the pre- and post-transplant periods (*Level of Evidence: C*).

Class IIa:

1. It is reasonable to consider active tobacco smoking as a relative contraindication to transplantation. Active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation (*Level of Evidence: C*).

Tobacco exposure has become an increasingly important focus of health-care organizations, state legislatures and employers in the USA. Cigarette smoking is responsible for roughly 1 of every 5 deaths or 440,000 people each year, and it continues to be the foremost avoidable cause of death in the USA.[92,93]

An estimated 46 million Americans >18 years of age smoke cigarettes, with a higher prevalence seen in men as well as the younger age groups. In Italy, the estimated smoking frequency was found to be 27.6% (33.2% of men and 22.5% of women) based on a 2003 population-based survey of 3,535 individuals age ≥15 years.[94]

The health disadvantages of tobacco exposure are not limited to cardiovascular disorders, such CAD and stroke, but also include a myriad of cancers, including lung and prostate. A recent publication described a link between tobacco users and increased risk of high–normal urinary albumin excretion and microalbuminuria, when compared with non-smokers in the general population. Men who smoke tobacco have an elevated risk of reaching end-stage renal failure.[95]

A cardiac allograft is especially vulnerable to the effects of habitual tobacco use. Small case series of heart transplant recipients have demonstrated increased incidence of coronary allograft vasculopathy and malignancy, along with a decrease in survival in those patients who return to smoking after transplantation.[96]

Roughly 24% of heart transplant recipients return to tobacco abuse after transplantation, despite adhering to the imposed policy of cessation for 6 months to 1 year before surgery.[97,98] Many patients will not admit to smoking even though their urine nicotine and cotinine levels are in the range indicating that they are habitual smokers.

The most difficult undertaking will be convincing patients and caregivers of the risk associated with environmental or second-hand smoke exposure. Environmental tobacco exposure has been correlated with the development of CAD, chronic obstructive pulmonary disease and lung cancer; however, the general population has not accepted this causal relationship.[99,100] The use of surveillance measurements of nicotine and cotinine in patients with this type of exposure may facilitate education of caregivers and patients, because levels of nicotine and cotinine can be detected in individuals exposed to only second-hand smoke.

Smokeless tobacco is a method often used to help reduce nicotine cravings. However, there is a correlation between oral and gastric cancers and the use of smokeless tobacco. The cardiovascular risks associated with smokeless tobacco are less clear; nevertheless, patients should be warned against the use of such products.

The use of urinary measurements of nicotine and cotinine has been established in the literature as a valid measure of tobacco exposure. In urinary analyses for the estimation of nicotine and cotinine levels using gas chromatography–nitrogen phosphorus detection, a cotinine level of >50 ng/ml is considered to represent tobacco exposure.[97]

Tobacco abstinence should be ideally assessed a minimum of 6 months before transplantation and may need to be assessed frequently (every 1 to 3 months) in patients considered to be at elevated risk.

Tobacco is a readily available, highly addictive substance. Many patients attempting to refrain from tobacco use often relapse. Factors such as younger age at initiation of tobacco use, lower socioeconomic class, perceived stress and environmental tobacco exposure, have all been associated with tobacco relapse. Depression is an often underreported and underdiagnosed disorder associated with tobacco recrudescence.[101–103]

Many different methods have been studied to aid in the discontinuation of tobacco use. These include the use of nicotine replacement products, telephone support models, hypnosis, counseling and medications such as bupropion. A recurring theme discovered in most tobacco cessation studies is that there is a high failure rate, especially if only a single intervention for cessation is utilized. Therefore, the best chance for sustained tobacco abstinence is use of a combination approach.[104]

1.5.2. Substance abuse. Recommendations for transplant candidates who are substance abusers are as follows:

Class IIb:

1. A structured rehabilitative program may be considered for patients with a recent (24 months)

history of alcohol abuse if transplantation is being considered (*Level of Evidence: C*).

Class III:

1. Patients who remain active substance abusers (including alcohol) should not receive heart transplantation (*Level of Evidence: C*).

Chronic, excessive alcohol consumption may lead to cardiomyopathy. The onset of this disorder may be partially explained by genetic differences. The presence of an angiotensin-converting enzyme (ACE) DD genotype has demonstrated a genetic susceptibility to alcohol-induced myocardial damage.[105] Women also demonstrate greater susceptibility to alcohol-induced cardiac damage as a result of differences in alcohol metabolism.[106]

On the other hand, many studies have shown the use of moderate amounts of alcohol, particularly red wine, to be cardioprotective. The unanswered question among health-care professionals and patients is exactly how much alcohol is moderate and how much is excessive.

A position paper from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) on moderate alcohol consumption listed several factors that vary in patients, which may modify alcohol's influence on overall health. These include age, gender and genetic susceptibility to disease; metabolic rate; co-morbid conditions; lifestyle factors; and consumption patterns. The risk of alcohol abuse increases several-fold for men who have >4 drinks per occasion and for women who have >3 drinks per occasion.[107] A history of major depression or social anxiety disorders may augment alcohol dependence in patients.[108]

There are many long-term hazards to alcohol consumption, including interference with bone growth and replacement of bone tissue, which results in decreased bone density and increased risk of fracture; alcohol-related changes in the structure and function of the kidneys and impairment in their ability to regulate volume and composition of fluid and electrolytes in the body; and interference with the structure as well as function of gastrointestinal tract segments. Long-term excessive alcohol has also been linked to cancers, such cancer of the colon and esophagus.[109–111]

Binge drinking, defined as >5 drinks per event for men or >4 drinks per event for women, also conveys some notable perils. A study assessing the 10-year risk of binge drinking on college-age students found that this style of alcohol use poses significant risk factors for alcohol dependence.[112] The Coronary Artery Risk Development in Young Adults (CARDIA) study also showed a risk of alcohol dependence from binge drinking. In this study, adults 35 to 45 years of age, who reported at least one episode of binge drinking within the last month, had an increase in coronary calcium scores compared with individuals who did not binge drink.[113] Memory and psychomotor performance is impaired on the morning after binge drinking despite undetectable blood alcohol levels.[114]

The risk of recidivism to alcohol following transplantation is not fully known. In a study of 51 patients who underwent liver transplantation for alcoholic cirrhosis, the rate of alcohol relapse was 11% at 1 year and 30% at 2 years. Only abstinence for ≥6 months before liver transplantation significantly lowered the rate of relapse (23% vs 79%, $p = 0.0003$).[115]

1.5.3. Psychosocial evaluation. Recommendations for psychosocial evaluation are as follows:

Class I:

1. Psychosocial assessment should be performed before listing for transplantation. Evaluation should include an assessment of the patient's ability to give informed consent and comply with instruction including drug therapy, as well as assessment of the support systems in place at home or in the community (*Level of Evidence: C*).

Class IIa:

1. Mental retardation or dementia may be regarded as a relative contraindication to transplantation (*Level of Evidence: C*).

Class III:

1. Poor compliance with drug regimens is a risk factor for graft rejection and mortality. Patients who have demonstrated an inability to comply with drug therapy on multiple occasions should not receive transplantation (*Level of Evidence: C*).

There is general agreement, however, that heart transplantation should be reserved for those patients most likely to benefit both in terms of quality of life and survival. The major ethical argument for the use of psychosocial criteria is the same as for medical criteria, such as allocating scarce donor organs to those most likely to benefit. However, there are fewer data on the reliability and validity of psychosocial criteria and on the ability of such evaluations to predict outcome after transplantation. Care must be taken to ensure that psychosocial factors predictive of outcome are not confused with judgments of an individual's social worth.

Neurocognitive and social assessment concentrates on four areas: compliance; comprehension; quality of life; and social evaluation. Compliance, the capacity to adhere to a complex lifelong regime of drug therapy, lifestyle changes and regular follow-up, is a crucial element in attaining long-term success after transplan-

tation. Comprehension, the ability to understand explanations of relatively complex procedures and instructions about pre- and post-transplant care and ultimately to give informed consent is perhaps the most controversial area. Quality-of-life assessment focuses on the patient's perception of happiness and well-being and perhaps the desire for long-term survival. Social evaluation aims to identify whether the patient has family or friends who will provide support through what is obviously a difficult period and who are willing to make long-term commitments for the patient's welfare.

Transplant physicians routinely evaluate several of the aforementioned factors when assessing the suitability of transplantation for patients with heart failure. All programs do not insist on the involvement of a psychiatrist, psychologist or other mental health professional in the assessment of every patient. A survey of international practice in this field showed wide variation in the reasons for excluding patients from transplantation based on psychosocial grounds.[116–120]

1.6. Guidance for Screening Grids and Serial Pre-transplant Evaluation

Standard grids representing minimal screening criteria are useful to patients, transplant centers and third-party payers (Table 3). All patients should have a complete history and physical annually, as well as follow-up assessment at least every 3 months. The patient's weight should be obtained at each visit and BMI should be calculated.

Immunocompatibility testing should include ABO blood group typing, completed on two separate occasions. UNOS requires two separate test dates and requires a second person to verify the blood type as it is entered into the UNOS active waiting list. Although donor hearts are not selected on the basis of human leukocyte antigens (HLAs) because of time restrictions related to cardiac preservation, tissue type should be determined for retrospective analysis and may assist with determination of donor-specific antibodies. Screening for humoral sensitization is accomplished by means of panel-reactive antibody (PRA) testing to determine the presence of circulating anti-HLA antibodies. Sensitization, although usually caused by pregnancy, blood transfusion, prior transplantation or placement of a ventricular assist device (VAD), occasionally occurs without an obvious sensitizing event, representing cross-reactivity between bacterial or viral epitopes and HLA antigens. Using the cytotoxic test for PRA, sensitization is estimated by the percentage of a cell panel of random lymphocytes against which the patient's serum reacts. Flow cytometry is an immunofluorescence method for identifying cell surface antigens by detecting conjugated antibody. Cytometry is much more sensitive than cytotoxic methods for determining PRA and results from flow cytometry allow for better assessment regarding the risk of a positive crossmatch at the time of transplant. In turn, decisions can be made with more confidence regarding the need for a prospective vs retrospective crossmatch, as well as giving providers more insight into the likelihood of humoral rejection after transplantation.

A PRA of >10% is considered positive and a donor-specific prospective crossmatch is generally advised before transplant. If PRA is >10%, or if a ventricular assist device has been inserted, then PRA determination should be repeated every 1 to 2 months. If a blood transfusion is required, PRA testing should be repeated 2 weeks after transfusion and each month thereafter for 6 months. Desensitization strategies have been advocated in patients who are highly sensitized, but a discussion of the merits and demerits of such therapeutic avenues is beyond the scope of the present guidelines.

1.6.1. Heart failure stability. Assessment of heart failure stability should be undertaken utilizing CPX testing (see Section 2.1), echocardiogram and electrocardiogram. A right heart catheterization should be done to evaluate right heart and pulmonary pressures, utilizing vasodilator challenges whenever indicated to determine if pulmonary hypertension is fixed or reversible. Right heart catheterization should be repeated at least every 6 months and more often in the setting of borderline acceptable PVR as discussed in Section 2.3.

1.6.2. Multi-organ function. As part of an evaluation of multi-organ function, routine laboratory testing should be obtained at each follow-up appointment. If a patient is taking an anti-coagulant, prothrombin time/international normalized ratio (PT/INR) should be checked more frequently per protocol.

Renal function should be assessed at least every 6 months by estimation of GFR. The National Kidney Foundation recommends estimation of GFR by using prediction equations over traditional creatinine clearance because of problems associated with 24-hour creatinine clearance.[121] Levey et al concluded that the equation developed from the Modification of Diet in Renal Disease (MDRD) study provides a more accurate estimate of GFR than measured creatinine clearance or other commonly used equations in patients with chronic renal disease. The quadratic GFR equation:

$$\mathrm{GFR} = \exp\left(1.911 + \frac{5.249}{\mathrm{SCr}} - \frac{2.114}{\mathrm{SCr}^2} - 0.00686 \times \mathrm{Age} - 0.205\ (\text{if female})\right)$$

If SCr < 0.8 mg/dL, use 0.8 for SCr derived from the original MDRD equation, is the most highly recom-

Table 3. Recommended Schedule for Heart Transplant Evaluation

		Repeat			
Test	Baseline	3 months	6 months	9 months	12 months (and yearly)
Complete H & P	X				
Follow-up assessment		X	X	X	X
Weight/BMI	X	X	X	X	X
Immunocompatibility					
ABO	X				
Repeat ABO	X				
HLA tissue typing	Only at transplant				
PRA and flow cytometry	X				
• >10%	Every 1–2 months				
• VAD	Every 1–2 months				
• Transfusion	2 weeks after transfusion and then 9 month × 6 months				
Assessment of heart failure severity					
Cardiopulmonary exercise test with RER	X				X
Echocardiogram	X				X
Right heart catheter (vasodilator challenge as indicated)	X		X		X
ECG	X				X
Evaluation of multi-organ function					
Routine lab work (BMP, CBC, LFT)	X	X	X	X	X
PT/INR More frequent per protocol if on VAD or coumadin	X	X	X	X	X
Urinalysis	X	X	X	X	X
GFR (MDRD quadratic equation)	X	X	X	X	X
Unlimed urine sample for protein excretion	X	X	X	X	X
PFT with Arterial blood gasses	X				
CXR (PA and lateral)	X				X
Abdominal ultrasound	X				
Carotid Doppler (if indicated or >50 y)	X				
ABI (if indicated or >50 y)	X				
DEXA scan (if indicated or >50 y)	X				
Dental examination	X				X
Ophthalmologic examination (if diabetic)	X				X
Infectious serology and vaccination					
Hep B surface Ag	X				
Hep B surface Ab	X				
Hep B core Ab	X				
Hep C Ab	X				
HIV	X				
RPR	X				
HSV IgG	X				
CMV IgG	X				
Toxoplasmosis IgG	X				
EBV IgG	X				
Varicella IgG	X				
PPD	X				
Flu shot (q 1 year)	X				
Pneumovax (q 5 years)	X				
Hep B immunizations: 1_2_3_	X				
Hep B surface Ab (immunity)	6 weeks after third immunization				
Preventive and malignancy					
Stool for occult blood × 3	X				X
Colonoscopy (if indicated or >50 y)	X				
Mammography (if indicated or >40 y)	X				X
Gyn/Pap (if indicated ≥18 y sexually active)	X				X
PSA and digital rectal exam (men > 50 y)	X				X

Table 3. continued

Test	Repeat				
	Baseline	3 months	6 months	9 months	12 months (and yearly)
General consultations					
Social work	X				
Psychiatry	X				
Financial	X				
Neuro/psych (if applicable)	X				

mended because it is based on a combined sample of healthy patients and patients with chronic kidney disease.[122] Assessment of proteinuria using an untimed urine specimen has replaced protein excretion in a 24-hour collection as the preferred method of measurement.[123] Therefore, estimated GFR should be evaluated every 3 months using the MDRD quadratic equation and untimed urine samples for protein excretion. Serial assessments of proteinuria should also be considered in select patients, such those with diabetes.

A pulmonary function test and chest X-ray should be routinely obtained to test for ventilatory and thoracic abnormalities. Abdominal ultrasound should be obtained to screen for kidney size, gall bladder disease due to its association with high morbidity after transplantation, and any incidental abdominal findings. If there are any lesions or other suspicious findings on ultrasound or chest X-ray, an abdominal or chest computed tomography (CT) scan should be obtained.

Patients >50 years of age, or who have particular risk factors for cerebrovascular or peripheral vascular disease, should undergo carotid Doppler ultrasound and ankle brachial index (ABI) studies. Patients with signs or symptoms of intestinal angina should undergo mesenteric artery Doppler ultrasound to test for occlusive vascular disease. Potential recipients >50 years of age and those with other risk factors, such as those taking steroids or peri-menopausal women, should be considered for a dual-energy X-ray absorptiometry (DEXA) scan. If DEXA scanning shows severe osteoporosis, further work-up for osteoporosis should be obtained.

Dental examination and ophthalmologic examinations should be obtained on a yearly basis to test for potential problematic lesions or abscesses. Ophthalmologic consultation to determine the presence of retinopathy should be obtained at least annually in diabetic patients.

1.6.3. Infectious, serology and vaccinations. Infectious serology and vaccinations should be obtained at baseline and negative viral titers should be repeated at the time of transplantation to have a more accurate assessment of common viral exposures, particularly cytomegalovirus (CMV) and Epstein–Barr virus (EBV). Many centers recommend immunization against hepatitis A and B virus for patients who are hepatitis B antibody negative at the time of evaluation, or to allow consideration of a hepatitis B–positive donor offer. If any indication of infection is demonstrated on routine urinalysis, a urine culture should be obtained.

1.6.4. Prevention and malignancy. All patients should be screened for occult gastrointestinal bleeding. Based on American Cancer Society guidelines, patients >50 years of age should also undergo colonoscopy and annual prostate-specific antigen (PSA) testing. Women >40 years of age should have a yearly mammogram and clinical breast examination. Women who are sexually active or >18 years of age should obtain annual Papanicolaou (Pap) tests. Serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP) may be indicated if multiple myeloma is clinically suspected.[124]

1.6.5. General consultations. All patients should have the opportunity to meet with a social worker and financial counselor. Psychiatric consultations or neurocognitive testing may be obtained for patients with questionable psychologic or intellectual competence to adhere to a complex medical regimen or at the recommendation of the social worker.

Patients <50 years of age should not be required to undergo certain age-related screening tests, specifically carotid Doppler ultrasound, ankle-brachial index (ABI), DEXA scan, colonoscopy or PSA.

1.7. Dynamic Listing and New Donor Allocation Algorithms

Recommendations for donor algorithms are as follows:

Class I:

1. Listed patients who are in an outpatient ambulatory non–inotropic-therapy-dependent state should be continually evaluated for maximal pharmacologic and device therapy (including ICD or biventricular pacing, when appropriate). Such patients must be re-evaluated at 3- to 6-month intervals with cardiopulmonary exercise testing to assess their re-

sponse to therapy and, if they have improved significantly, they may be candidates for delisting (*Level of Evidence: C*).

2. Redesigned allocation algorithms should be considered that allow for the prioritization of higher-status patients within larger geographic areas (within accepted safe ischemic time limitations). This practice may reduce deaths on the waiting list by both providing more hearts in a timely fashion to the higher-acuity population (*Level of Evidence: C*).

Recent studies have pointed out that the majority of ambulatory heart transplant candidates who do not require inotropic support likely accrue little benefit from immediate transplantation.[125] Similarly, it has been demonstrated that those candidates initially considered too healthy for listing do well in the near term and are not subject to increased mortality.[126] It has therefore been suggested that the benefits of transplantation in patients requiring non-inotropic therapy should be tested in a randomized trial.[127] Other groups have suggested that the current donor allocation systems should be revised to preferentially steer donor hearts toward those patients in greatest need.[128] In this regard, UNOS has accepted a new allocation scheme to introduce zonal sharing. Under this system, donor hearts will be allocated to those in need of urgent or emergent transplants first within a radius of 500 miles before offering the heart to a local patient who is less sick. This model is predicted to reduce deaths on the waiting list and will likely decrease the number of listings for non–inotropic-dependent patients over time.

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