Cardiac transplantation: who to refer and when

For some patients with advanced heart failure, heart transplantation or mechanical circulatory support may be the only treatment left to improve quality life and survival. The timing of intervention is crucial, as patients should be referred before complications such as pulmonary hypertension, cardiorenal syndrome or liver failure develop.

Heart failure is a common condition affecting 1–2% of the population. The incidence rises with age in both men and women (Mehta and Cowie, 2006). The mean age at diagnosis is around 74 years of age (Cowie et al, 1997; Mehta and Cowie, 2006). Regardless of aetiology, heart failure is associated with a worse quality of life than many other common chronic illnesses such as chronic obstructive pulmonary disease, arthritis, depression and other cardiovascular disease (Hobbs et al, 2002). Survival and quality of life worsen as patients reach the advanced phase of heart failure (Hobbs et al, 2002).

The European Society of Cardiology defines advanced heart failure as a chronic condition in which patients are persistently restricted in performing their activities of daily living (New York Heart Association (NYHA) functional class III or IV) despite best medical therapy, with evidence of impaired cardiac function (left ventricular ejection fraction <30%) (Metra et al, 2007). Patients with advanced heart failure and reduced left ventricular ejection fraction should be treated with evidence-based therapy including angiotensin-converting enzyme inhibitors, beta-blockers and aldosterone antagonists together, when appropriate, with cardiac resynchronization therapy and an implantable defibrillator (McMurray et al, 2012).

Despite such treatment, in many patients heart failure is a progressive condition with worsening symptoms and deteriorating functional capacity. For a subgroup of such patients, heart transplantation or mechanical circulatory support may improve symptoms, quality life and survival. This article describes factors important in case selection for heart transplantation and emphasizes the importance of referral before serious complications have developed.

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Cardiac transplantation

The first UK heart transplant occurred in 1968 and the first UK heart transplant programme was established in 1979. Currently there are six adult heart transplant centres (Birmingham, Glasgow, Harefield, Manchester, Newcastle, and Papworth). The number of heart transplants reached a peak of approximately 300 transplants per year in the 1990s. Subsequently there has been a decline in activity with an average of 131 transplants per year between 2009 and 2012 (NHS Blood and Transplant, 2013). In contrast, the number of people on the heart transplant waiting list has increased from 92 in March 2009 to 194 in December 2012 (NHS Blood and Transplant, 2013). These trends have been attributed to a decreased availability of donor hearts suitable for transplantation. Currently approximately 31% (19 million) of the UK population are on the organ donor register (NHS Blood and Transplant, 2013). Limited donor availability means that the average time spent on the waiting list for a non-urgent heart transplant between 2007 and 2010 was 253 days (NHS Blood and Transplant, 2013).

Potential candidates for heart transplantation are assessed by a multidisciplinary team involving heart failure cardiologists, cardiac surgeons, specialist nurses, radiologists and psychologists with input from other specialties including palliative care. The decision to recommend transplantation is made by weighing the risks and benefits of surgery against those of ongoing medical treatment. The scarcity of donor hearts requires additional consideration of how to maximize the overall benefit from the hearts that are available for transplantation.

The timing of intervention is crucial. Late referral when patients have developed complications of advanced heart failure increases the risks of and may potentially contraindicate transplantation.

Although heart transplantation has never been subject to a clinical trial, statistical modeling has demonstrated that it improves survival in advanced heart failure (Banner et al, 2008; NHS Blood and Transplant, 2013), and improves quality of life and patients' ability to carry out activities of daily living (Almenar-Pertejo et al, 2006). In the UK post-transplant survival is 86.9% at 30 days, 80.8% at 1 year and 70.8% at 5 years (NHS Blood and Transplant, 2013).

Transplant recipients require lifelong pharmacological immunosuppression and need to undergo multiple invasive tests such as endomyocardial biopsies and coronary angiography, especially during the first year post-transplantation. Many go on to develop sequelae of chronic immunosuppression or chronic allograft rejection (cardiac allograft vasculopathy). Hypertension or hyperlipidaemia develops in approximately 90% of patients by 5 years. Cardiac allograft vasculopathy is prevalent in 20% at 3 years and 30% at 5 years. Diabetes, hypertension and the nephrotoxic effects of the immunosuppressant drugs largely explain the high incidence of chronic kidney disease in transplant recipients. Severe renal insufficiency (serum creatinine >191 μmol/litre, need for dialysis or kidney transplant) occurs in 11% at 1 year and 27% at 5 years. Diabetes mellitus is present in 28% of recipients at 1 year and in 40% at 5 years post-transplant (Stehlik et al, 2010).

Around 19% of patients can expect to develop a malignancy by 7 years post-transplantation. Non-melanoma skin cancer is the most frequent and occurs in 29% of heart transplant recipients by 15 years after transplantation. Non-dermatological malignancies are seen in 18%, and lymphoproliferative malignancies are seen in 6% of recipients by 15 years (Stehlik et al, 2010). Despite these complications over 60% of patients survive for more than a decade after transplantation and some individuals have survived for 30 years or more (Stehlik et al, 2010; Hamour et al, 2011).

Heart conditions that may indicate transplantation

The commonest indications for adult heart transplantation are left ventricular systolic dysfunction secondary to non-ischaemic dilated cardiomyopathy and ischaemic cardiomyopathy (Stehlik et al, 2010; Thekkudan et al, 2010). Other less common causes include valvular heart disease with poor ventricular function and infiltrative cardiomyopathy (such as amyloidosis, sarcoidosis or giant cell myocarditis). The decision to transplant such patients is made on a case by case basis. In addition to the usual considerations, infiltration of other organs must be assessed and the risk of disease recurrence in the transplanted heart considered.

Adult congenital heart disease is becoming more prevalent. Transplantation of adult congenital heart disease poses specific challenges (Irving et al, 2010). Surgery may be more complex because of the underlying anatomy and because of, often multiple, previous operations. Adult congenital heart disease patients are prone to HLA sensitization from previous surgery involving the use of homograft tissue and blood transfusions (Lamour et al, 2009; Burch, 2010; Irving et al, 2010).

Who to refer and when

Chronic heart failure caused by systolic left ventricular dysfunction is frequently a progressive condition and it is important for heart failure cardiologists to refer potential candidates at an appropriate stage in their disease. This requires an understanding of the transplant assessment process and an ability to provide patients and families with appropriate expectations.

Patients should be referred for transplantation before they develop serious complications of their heart failure such as secondary (World Health Organization group 2) pulmonary hypertension, cardiorenal syndrome or liver failure (Fang et al, 2012). These conditions all increase the risk of surgery and may potentially preclude transplantation (see below). Patients should be referred if they have advanced heart failure, fulfil the criteria listed in *Table 1* and are free of major contraindications (Banner et al, 2011). Features suggestive of a poor prognosis that might initiate referral for transplant assessment are shown in *Table 2* (Banner et al, 2011).

Evidence of prognosis may be derived from cardiopulmonary exercise testing, brain natriuretic peptide levels or using prognostic scoring systems (e.g. the Seattle Heart Failure Model).

Table 1. Conventional criteria for heart transplantation

Impaired left ventricular systolic function	
New York Heart Association class III (e.g. patient cannot climb one flight of stairs without symptoms) or class IV heart failure	
Receiving optimal medical treatment (including target or maximum tolerated doses of β-adrenergic antagonists, angiotensin-converting enzyme inhibitors and aldosterone antagonists)	
Cardiac resynchronization treatment, implantable cardioverter-defibrillator or cardiac resynchronization therapy–defibrillator device implanted (if indicated)	
Evidence of poor prognosis	Cardiopulmonary exercise testing (maximal oxygen consumption <12 ml/kg/min if on β-blockade, <14 ml/kg/min if not on β-blockade, ensuring respiratory quotient ≥1.05)
	Markedly elevated B-type natriuretic peptide (or N-terminal pro B-type natriuretic peptide) serum levels despite full medical treatment
	Established composite prognostic scoring system, such as the Heart Failure Survival Score or Seattle Heart Failure Model

From Banner et al (2011)

Cardiopulmonary exercise tests combine exercise testing with expired gas analysis (Wasserman et al, 2011). The patient's oxygen uptake is monitored continuously and the peak uptake is a strong predictor of survival provided the patient reaches his/her cardiovascular limit, indicated by exceeding the anaerobic threshold, and the peak respiratory exchange ratio exceeds 1.05. Patients with a peak oxygen uptake below 12–14 ml/kg/min have a poor prognosis and should be considered for transplantation (Francis et al, 2000).

The N-terminal prohormone of brain natriuretic peptide concentration in patients with advanced heart failure is an independent predictor of mortality or the need for urgent heart transplantation. Brain natriuretic peptide levels have also been shown to be good prognostic markers in a broader heart failure population (Gardner et al, 2003; Bettencourt et al, 2004).

The Seattle Heart Failure Model provides a validated estimate of predicted 1-year, 2-year and 5-year survival for patients with heart failure depending on their clinical, biochemical and treatment characteristics. Patients with a poor predicted survival according to the Seattle Heart Failure Model, despite maximum tolerated therapies, should be considered for transplantation (Levy et al, 2006).

Less common indications for transplantation are intractable angina or arrhythmia without heart failure but when symptoms are resistant to medical treatment and are not amenable to revascularization or electrophysiological intervention (Banner et al, 2011).

Some patients need to be referred for assessment as inpatients, usually because of dependence on intropes or an intra-aortic balloon pump. Such patients should be free of significant contraindications to transplantation.

Contraindications to transplantation

Absolute and relative contraindications to heart transplantation are shown in *Tables 3* and *4*. Many relative contraindications that, in isolation, may not preclude transplantation can become an absolute contraindication when present in combination (Banner et al, 2011).

Although age is not an absolute contraindication, increasing age is a risk factor (Stehlik et al, 2010). In practice very few patients have been transplanted over the age of 65 years in the UK and the average age of heart transplant recipients internationally is around 50 years (Stehlik et al, 2010), considerably younger than that in the unselected population of heart failure patients (Cowie et al, 1997).

Left ventricular assist devices as a bridge to transplantation

A left ventricular assist device is an electrically powered mechanical pump which is connected to the left ventricle

Table 2. Clinical indicators that should prompt consideration for referral

Two or more admissions for treatment of decompensated heart failure within the last 12 months
Persistent clinical evidence of overt heart failure after optimized medical treatment
Calculated Seattle Heart Failure Model score indicating a ≥20% 1-year mortality
Echocardiographic evidence of right ventricular dysfunction or increasing pulmonary artery pressure on optimal treatment (aim to refer before pulmonary artery systolic pressure exceeds 50 mmHg)
Anaemia, involuntary weight loss, liver dysfunction or hyponatraemia attributable to heart failure
Deteriorating renal function attributable to heart failure or inability to tolerate diuretic dosages sufficient to clear congestion without change in renal function (aim to refer before creatinine clearance falls below 50 ml/min or the estimated glomerular filtration rate falls below 40 ml/min/1.73m^2)
Significant episodes of ventricular arrhythmia despite full drug and electrophysiology or device treatment
Increasing plasma B-type natriuretic peptide or N-terminal pro B-type natriuretic peptide levels despite adequate heart failure treatment

From Banner et al (2011)

Table 3. Absolute contraindications to transplantation

Active malignancy other than localized non-melanoma skin cancer
Recent pulmonary embolism with pulmonary infarction
Irreversible pulmonary hypertension (pulmonary vascular resistance >5 woods units, transpulmonary gradient >15 mmHg, pulmonary artery systolic pressure >60 mmHg)
Sepsis and active infection
Inability to give informed consent

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Table 4. Relative contraindications to transplantation

Body mass index >32 kg/m^2
Diabetes mellitus with a glycosylated haemoglobin >7.5% or microvascular complications
Symptomatic peripheral or cerebrovascular disease
Multiple prior sternotomies
Age >65 years
Liver dysfunction
Irreversible renal failure (creatinine clearance <50 ml/min, estimated glomerular filtration rate <40 ml/min/1.73m^2)
Autoimmune disorders (e.g. systemic lupus erythematosus, rheumatoid arthritis and ulcerative colitis)
Substance abuse (including tobacco and excessive alcohol): abstinence from smoking is required for >6 months
Prior history of non-compliance to medication or treatment
Inadequate, unstable accommodation or social support

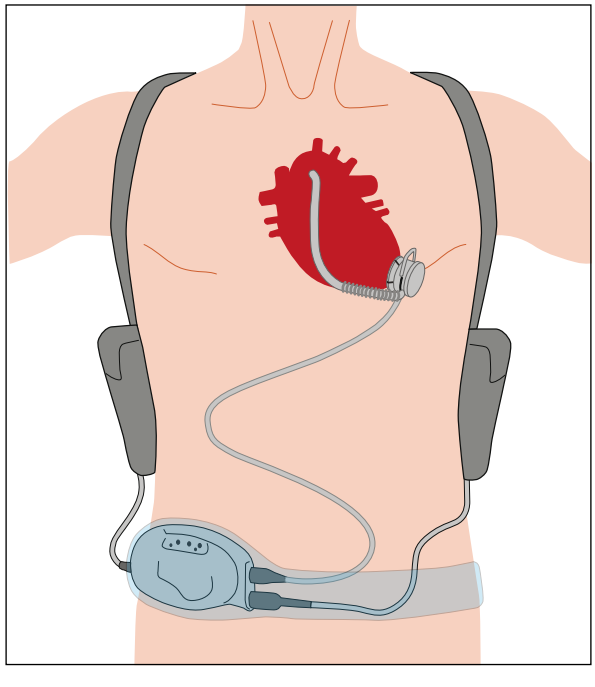
From Banner et al (2011)

and propels blood into the ascending aorta, thereby assisting the action of the left ventricle (*Figure 1*). A driveline is tunneled though the abdominal wall to supply electrical power from external batteries and transmit information bidirectionally between the pump and an external controller. The controller and batteries can be attached to a belt around the patient's waist, worn in a holster, or carried in a bag so allowing the patient to be ambulatory.

The first generation of implantable left ventricular assist devices were large devices that generated pulsatile flow, required extensive implant surgery and were prone to mechanical failure. Current devices provide continuous blood flow and are smaller and more durable. All continuous flow ventricular assist devices require the patient to be anticoagulated with warfarin and an antiplatelet agent. Bleeding and thrombosis can cause serious complications. Device-related infection is the other serious long-term complication (Slaughter et al, 2010). Medium-term survival has improved progressively, with up to 80% surviving 2 years post-implantation (Kirklin et al, 2012), but long-term survival is still below that achieved with heart transplantation.

Left ventricular assist device therapy alone has been shown to improve survival in selected patients with advanced heart failure (Rose et al, 2001; Slaughter et al, 2009) but currently the NHS only funds the implantation of left ventricular assist devices as a bridge to transplantation. The current service specification indicates that left ventricular assist devices should only be implanted in patients who are already on the heart transplant waiting list and who are deteriorating before a donor heart has become available, because long-term left ventricular assist device support without subsequent transplantation is not considered to be cost-effective by standard NHS criteria. Despite this, the scarcity of suitable donor hearts has led to a growing population of left ventricular assist device patients receiving long-term support while awaiting a transplant.

Figure 1. Schematic of a generic ventricular assist device attached to the heart with a driveline and controller.



In some patients with non-ischaemic dilated cardiomyopathy, left ventricular function can improve during left ventricular assist device support and concomitant heart failure drug therapy, thereby allowing explantation of the left ventricular assist device without transplantation and a return to long-term medical therapy (Birks et al, 2011).

Not all patients are suitable candidates for left ventricular assist device support, e.g. patients with predominant right ventricular failure, restrictive or hypertrophic cardiomyopathy, those who have undergone multiple previous cardiac operations or who have prosthetic heart valve replacements (particularly aortic). It is especially important that such patients are referred at a stage when they will be able to wait long enough to receive a transplant and before heart failure complications have developed which preclude transplantation.

Many of the factors that increase the risk of heart transplant surgery are also risk factors for left ventricular assist device implantation (e.g. sepsis, renal dysfunction, liver dysfunction, coagulopathy, respiratory failure and age over 65 years) (Wilson et al, 2009).

Problems caused by referral at the late stage of advanced heart failure

Patients referred in a very advanced stage of heart failure usually have complications that may prevent transplantation, particularly cardiorenal syndrome, group 2 pulmonary hypertension and hepatic dysfunction.

Renal failure is a risk factor for all forms of cardiac surgery (Nashef et al, 1999) including transplantation (Stehlik et al, 2010). It is also a risk factor for chronic kidney disease after transplantation (Stehlik et al, 2010). Investigations are required to look for intrinsic renal disease or systemic disease affecting the kidneys including diabetes with complications. When appropriate, the transplant centre will look for evidence that the renal dysfunction is at least partially reversible following a temporary withdrawal of angiotensin-converting enzyme inhibitors and treatment with inotropes to improve cardiac output. However, renal function that remains below acceptable limits may be a contraindication to transplant listing.

Similarly, increased pulmonary vascular resistance as a complication of prolonged pulmonary hypertension caused by left heart failure is a risk factor for heart transplantation because it may lead to failure of the donor right ventricle immediately after surgery. Patients who have elevated pulmonary vascular resistance need investigation to determine whether this can be reversed pharmacologically. Irreversible pulmonary hypertension is a contraindication to transplantation. Patients with revers-

ibility are usually suitable for transplantation but remain at a higher surgical risk than those without pulmonary hypertension (Chen et al, 1997).

Liver function and its response to short-term drug therapy is more difficult to assess. However, a raised bilirubin level and a prolonged prothrombin time are both surgical risk factors (Stehlik et al, 2010) and patients with liver dysfunction associated with right ventricular failure and tricuspid regurgitation leading to marked systemic venous hypertension are unsuitable for transplantation.

When the complications of advanced heart failure can be reversed, the patient may be able to be listed for transplantation on an urgent basis and, if a heart does not become available, could be eligible for a left ventricular assist device as a bridge to subsequent transplantation. However, late referral risks the possibility that the patient may not be eligible for listing or for a left ventricular assist device.

The heart transplant waiting list

The UK system for allocating donor hearts to those on the transplant waiting list is currently under review. Under the present system, patients who meet specific criteria including being dependent on inotropes, needing ongoing intra-aortic balloon pump support or short-term mechanical circulatory support may be placed on the national urgent waiting list. Other patients may be allocated a suitable heart from those not needed for urgent patients on the national list by their regional centre on the basis of biological matching criteria, clinical urgency and waiting time. Several factors influence heart allocation and are listed in *Table 5*.

Patients with certain characteristics are difficult to match to suitable donor hearts, especially when these are present in combination. For example large patients, blood type O (group O has the longest waiting list) and patients who are sensitized with a high reaction frequency against HLA antigens will have very long waiting times and some may never receive a transplant.

Table 5. Factors determining heart allocation

Biological matching	Blood group compatibility
	Appropriate size matching (accounting for recipient sex and pulmonary hypertension)
	Need to avoid specific donor HLA (human leucocyte antigen) antigens in sensitized recipients
Clinical need	Severity of heart failure
	Anticipated prognosis without transplantation
Logistic factors influencing operative cardiac ischaemic time	Distance of donor from recipient centre
	Prior surgery in the recipient (multiple sternotomies)
	Surgical complexity (e.g. prior ventricular assist device, adult congenital heart disease)
Fairness	Time on the waiting list

From Banner et al (2011)

KEY POINTS

- Despite optimal medical therapy, advanced chronic heart failure is usually a progressive disease and patients have a poor prognosis and quality of life.
- Heart transplantation is by far the most effective therapy for such patients, improving longevity and quality of life.
- It is important that patients who are potential candidates for transplantation should be referred before the complications of advanced heart failure such as pulmonary hypertension, cardiorenal syndrome or liver failure have developed and become a potential barrier to transplantation.

Conclusions

Despite optimal medical therapy, advanced chronic heart failure is usually a progressive disease and patients have a poor prognosis and quality of life. Heart transplantation is by far the most effective therapy for such patients, improving longevity and quality of life. It is important that patients who are potential candidates for transplantation should be referred before the complications of advanced heart failure become established as a potential barrier to transplantation. BJHM

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Conflict of interest: none.

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