
Medical Policy



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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Transplant-Heart

Description/Background

Solid Organ Transplantation

Solid organ transplantation offers a treatment option for individuals with different types of end-stage organ failure that can be lifesaving or provide significant improvements to an individual's quality of life.⁶ Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life, particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Individuals are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network and United Network for Organ Sharing (UNOS).⁷

Heart Transplant

In 2024, 21,921 heart transplants were performed in the United States procured from 21,921 deceased and living donors. Heart transplants were the third most common transplant procedure with 4,109 transplants performed. As of June 2024, there were 2,684 individuals on the waiting list for a heart transplant.³

*Historically, common accepted indications for **adult** heart transplantation include:*

1. Hemodynamic compromise due to heart failure demonstrated by any of the following 3 bulleted items, or
 - Maximal VO_2 (oxygen consumption) <10 mL/kg/min with achievement of anaerobic metabolism
 - Refractory cardiogenic shock
 - Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
2. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or

3. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities.

Probable indications for cardiac transplantation may include the following conditions:

1. Maximal $VO_2 < 14$ mL/kg/min and major limitation of the individual's activities, or
2. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or
3. Instability of fluid balance/renal function not due to individual noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

The following conditions are typically considered inadequate indications for transplantation unless other factors as listed above are present.

1. Ejection fraction $< 20\%$
2. History of functional class III or IV symptoms of heart failure
3. Previous ventricular arrhythmias
4. Maximal $VO_2 > 15$ mL/kg/min

For **pediatric** individuals, common accepted indications for heart transplant typically include:

1. Individuals with heart failure with persistent symptoms at rest who require one or more of the following:
 - Continuous infusion of intravenous inotropic agents, or
 - Mechanical ventilatory support, or
 - Mechanical circulatory support.
2. individuals with pediatric heart disease with symptoms of heart failure who do not meet the above criteria but who have:
 - Severe limitation of exercise and activity (if measurable, such individuals would have a peak maximum oxygen consumption $< 50\%$ predicted for age and sex); or
 - Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease; or
 - Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or
 - Restrictive cardiomyopathy with reactive pulmonary hypertension; or
 - Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or
 - Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
 - Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

Specific criteria for prioritizing donor thoracic organs for transplant are provided by the Organ Procurement and Transplantation Network (OPTN) and implemented through a contract with the United Network for Organ Sharing (UNOS). Donor thoracic organs are prioritized by UNOS on the basis of recipient medical urgency, distance from donor hospital, and pediatric status. Individuals who are most severely ill (Status IA) are given highest priority.

Transplant programs list adult heart transplant candidates according to six medical urgency statuses. Status 1 is the most urgent and Status 6 is the least urgent.⁵ This stratification reflects

the severity of the illness and prioritizes the individual with the greater chance of death (status 1) while awaiting transplant. Criteria from OPTN for listing status are as follows:¹

ADULT INDIVIDUALS (18 years of age or older)

Status 1

- Veno-arterial extracorporeal membrane oxygenation (VA ECMO)
- Non-dischargeable, surgically implanted, non-endovascular biventricular support device
- Mechanical circulatory support device (MCSD) with life-threatening ventricular arrhythmia

Status 2

- Non-dischargeable, surgically implanted, non-endovascular left ventricular assist device (LVAD)
- Total artificial heart (TAH), BiVAD, right ventricular assist device (RVAD), or ventricular assist device (VAD) for single ventricle individuals
- Mechanical circulatory support device (MCSD) with malfunction
- Percutaneous endovascular mechanical circulatory support device
- Intra-Aortic Balloon Pump (IABP)
- Ventricular Tachycardia (VT) or Ventricular Fibrillation (VF)

Status 3

- Dischargeable left ventricular assist device (LVAD) for discretionary 30 days
- Multiple inotropes or a single high-dose inotrope and hemodynamic monitoring
- Mechanical circulatory support device (MCSD) with hemolysis
- Mechanical circulatory support device (MCSD) with pump thrombosis
- Mechanical circulatory support device (MCSD) with right heart failure
- Mechanical circulatory support device (MCSD) with device infection
- Mechanical circulatory support device (MCSD) with mucosal bleeding
- Mechanical circulatory support device (MCSD) with aortic insufficiency (AI)
- Veno-arterial extracorporeal membrane oxygenation (VA ECMO) after 7 days
- Non-dischargeable, surgically implanted, non-endovascular left ventricular assist device (LVAD) after 14 days
- Percutaneous endovascular mechanical circulatory support device after 14 days
- Intra-aortic balloon pump (IABP) after 14 days
- Mechanical circulatory support device (MCSD) and has life threatening ventricular arrhythmia after 7 days

Status 4

- Dischargeable left ventricular assist device (LVAD) without discretionary 30 days
- Inotropes without hemodynamic monitoring
- Congenital heart disease
- Ischemic heart disease with intractable angina
- Amyloidosis, or hypertrophic or restrictive cardiomyopathy
- Re-transplant

Status 5

Registered on the heart waiting list, and is also registered on the waiting list for at least one other organ at the same hospital.

Status 6

The candidate is suitable for transplant.

PEDIATRIC INDIVIDUALS

A candidate registered on the waiting list before turning 18 years old remains eligible for pediatric status (pediatric criteria) until the candidate has been removed from the waiting list.

Status 1A

A candidate listed as Status 1A meets at least one of the following criteria:

1. Requires continuous mechanical ventilation and is admitted to the hospital that registered the candidate;
2. Requires assistance of an intra-aortic balloon pump and is admitted to the hospital that registered the candidate;
3. Has ductal dependent pulmonary or systemic circulation, with ductal patency maintained by stent or prostaglandin infusion, and is admitted to the transplant hospital that registered the candidate;
4. Has a hemodynamically significant congenital heart disease diagnosis, requires infusion of multiple intravenous inotropes or a high dose of a single intravenous inotrope, and is admitted to the transplant hospital that registered the candidate;
5. Requires assistance of a mechanical circulatory support device.

Status 1B

A candidate listed as Status 1B meets at least one of the following criteria:

1. Requires infusion of one or more inotropic agents but does not qualify for pediatric status 1A. The OPTN maintains a list of the OPTN-approved status 1B inotropic agents and doses.
2. Is less than one year old at the time of the candidate's initial registration and has a diagnosis of hypertrophic or restrictive cardiomyopathy.

Status 2

A candidate who does not meet the criteria for pediatric status 1A or 1B but is still suitable for transplant may be assigned pediatric status 2.

A candidate's pediatric status 2 does not require any recertification.

Inactive Adult and Pediatric Candidates

If an adult or pediatric candidate is temporarily unsuitable for transplant, then the candidate's transplant program may assign the candidate inactive status and the candidate will not receive any heart offers. Most heart transplant recipients are now hospitalized Status 1 individuals at the time of transplant. This shift has occurred due to the increasing demand on the scarce resource of donor organs resulting in an increased waiting time for donor organs. Individuals initially listed as a Status 2 candidates may deteriorate to a Status 1 candidate before a donor organ becomes available. At the same time, as medical and device therapy for advanced heart failure has improved, some individuals on the transplant list will recover enough function to become delisted.

Regulatory Status:

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration. The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

Medical Policy Statement

The safety and effectiveness of a heart transplant, both adult and pediatric, have been established. It may be considered an useful therapeutic option when indicated for patients meeting selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:

Human heart transplantation may be considered established for selected adults and children with end-stage heart failure when patient selection criteria, based on Organ Procurement and Transplantation Network (OPTN) guidelines, are met. The Status is determined by the information provided by the transplant facility.

Indications for cardiac transplantation include but are not limited to end-stage cardiac disease that is not amenable to any other form of therapy and is associated with a life expectancy of six to twelve months. The most common illnesses that may necessitate cardiac transplant include but are not limited to:

- Ischemic heart disease
- Cardiomyopathy of idiopathic, viral, post-partum or alcoholic origin
- Fulminant cardiac failure following an acute myocardial infarction
- Failure to wean from mechanical and/or inotropic support
- Refractory angina pectoris
- Life-threatening dysrhythmias uncontrolled by medical therapy or implantable defibrillator devices

Heart *re*-transplantation after a failed primary heart transplant may be considered established in individuals who meet criteria for heart transplantation.

Exclusions: Heart transplant-specific exclusions (contraindications):

- Pulmonary hypertension that is fixed as evidenced by pulmonary vascular resistance (PVR) greater than 5 Woods units, or trans-pulmonary gradient (TPG) greater than or equal to 16 mm/Hg*;
- Severe pulmonary disease despite optimal medical therapy, not expected to improve with heart transplantation alone*;
- Heart transplantation is considered investigational when medical criteria is not met.

Potential Contraindications for Transplant:

Note: Final patient eligibility for transplant is subject to the judgement and discretion of the requesting transplant center.

- Known current malignancy, including metastatic cancer;
- Recent malignancy with high risk of recurrence;
- History of cancer with a moderate risk of recurrence;
- Untreated systemic infection making immunosuppression unsafe, including chronic infection;
- Other irreversible end-stage disease not attributed to heart or lung disease;
- Stable systemic disease that could be exacerbated by immunosuppression;
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

All transplants must be prior authorized through the Human Organ Transplant Program.

* Some individuals may be candidates for combined heart and lung transplantation. Please refer to the Transplant-Heart and Lung (Combined) medical policy.

Note: Cardiac catheterization/evaluation for pulmonary hypertension is not routinely performed in infants/children and is therefore not required to determine heart transplant candidacy.

CPT/HCPCS Level II Codes (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)

Established codes:

33940 33944 33945

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Due to the nature of the population discussed herein, there are no RCTs comparing heart transplantation with alternatives, including ventricular assist devices. Systematic reviews are based on case series and registry data. RCTs have been published on related topics (e.g., comparing surgical technique, infection prophylaxis regimens, or immunosuppressive therapy) but are not germane to this evidence review.

INITIAL HEART TRANSPLANT

Clinical Context and Therapy Purpose

In the U.S., approximately 6 million people 20 years of age and older have heart failure and 1 in 8 deaths have heart failure mentioned on the death certificate.¹ The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion.

Heart failure may be due to a number of differing etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart disease (CHD). The leading indication for a heart transplant has shifted over time from ischemic to nonischemic cardiomyopathy. From 2009 to 2014, nonischemic cardiomyopathy was the dominant underlying primary diagnosis among patients 18 to 39 years (64%) and 40 to 59 years (51%) undergoing transplant operations.² Ischemic cardiomyopathy was the dominant underlying primary diagnosis among heart transplant recipients 60 to 69 years (50%) and 70 years and older (55%). Overall, ischemic cardiomyopathy is the underlying heart failure diagnosis in approximately 40% of men and 20% of women who receive a transplant. Approximately 3% of heart transplants during this time period were in adults with CHD.

The purpose of a heart transplant in patients who have end-stage heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are individuals who have end-stage heart failure.

Interventions

The therapy being considered is a heart transplant. Heart transplantation is provided in a hospital setting with specialized staff and equipment to perform the surgical procedure and provide postsurgical intensive care.

Comparators

The following therapies and practices are currently being used to make decisions about reducing the risk of end-stage heart failure: guideline-directed medical therapy; surgery including coronary bypass surgery, heart valve repair or replacement, and ventricular assist devices. Comparators are performed and managed by a physician in a clinical or hospital setting.

Outcomes

The general outcomes of interest are overall survival, treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for detailed discussion.

Follow-up of 1, 2, 5, and 10 years is of interest for heart transplant outcomes for overall survival, change in symptoms, morbid events, and treatment-related mortality and morbidity.

Review of Evidence

Retrospective Studies

A study by Jaramillo et al (2013) examined characteristics of patients who survived more than 20 years after heart transplantation at a single-center in Spain.²⁵ Thirty-nine heart transplant recipients who survived over 20 years posttransplant were compared with 98 patients who died between 1 and 20 years posttransplant. Independent factors associated with long-term survival were younger recipient age (i.e., <45 years vs ≥45 years; odds ratio [OR], 3.9; 95% CI, 1.6 to 9.7) and idiopathic cardiomyopathy (i.e., vs. other etiologies; OR, 3.3; 95% CI, 1.4 to 7.8).

Registry Studies

According to the Organ Procurement and Transplantation Network (OPTN), Kaplan-Meier survival rates for heart transplants performed during 2008-2015 based on available U.S. data as of June 3, 2022, were 90.5% (95% confidence interval [CI], 89.9% to 91.2%) and 91.1% (95% CI, 90.1% to 92.1%) for men and women, respectively.³ Three-year survival rates were 85.2% (95% CI, 84.3% to 86.0%) and 85.2% (95% CI, 83.8% to 86.4%) for men and women, respectively, and 5-year survival rates were 78.4% (95% CI, 77.3% to 79.3%) and 77.7% (95% CI, 76.0% to 79.2%), respectively. There was no major difference in 1-, 3- and 5-year survival rates between different age groups among adult recipients (see Table 1).

Table 1. Kaplan-Meier Patient Survival Rates for Heart Transplants Performed: 2008-2015

Recipient Age	Years Posttransplant						
	1 Year ^a No. Alive	Survival Rate(95% CI), %	3 Years ^a No. Alive	Survival Rate(95% CI), %	5 Years ^a No. Alive	Survival Rate(95% CI), %	
<1 year	407		87.6 (84.3 to90.3)	363	85.0 (81.3 to88.0)	317	77.2 (72.8 to80.9)
1-5 years	345		92.4 (89.2 to94.6)	282	87.1 (83.0 to90.2)	257	81.4 (76.8 to85.2)
6-10 years	223		92.3 (88.2 to95.0)	186	89.8 (84.9 to93.1)	166	89.3 (84.1 to92.9)
11-17 years	507		96.8 (94.9 to98.0)	459	92.3 (89.6 to94.3)	356	80.0 (76.1 to83.4)
18-34 years	845		91.8 (89.8 to93.4)	727	83.7 (81.1 to85.9)	600	75.0 (71.9 to77.8)
35-49 years	1590		90.9 (89.4 to92.1)	1402	85.4 (83.6 to87.0)	1243	79.1 (77.0 to81.0)
50-64 years	3900		90.7 (89.8 to91.6)	3382	85.3 (84.1 to86.3)	2982	78.5 (77.2 to79.8)

65+ years	1516	88.4 (86.7 to 89.8)	1196	82.2 (80.1 to 84.1)	NR	NR
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Source: Organ procurement and transplantation network, <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>.

CI: confidence interval

^a One-year survival based on 2012-2015 transplants, 3-year survival based on 2010-2013 transplants, 5-year survival based on 2008-2011 transplants.

Nguyen et al (2017) investigated the benefit of heart transplantation compared with waiting list while accounting for the estimated risk of a given donor-recipient match among 28,548 heart transplant candidates in the OPTN between July 2006 and December 2015.²⁶ Net benefit from heart transplantation was evident across all estimates of donor-recipient status 1A and 1B candidates: status 1A (lowest-risk quartile hazard ratio [HR], 0.37; 95% CI, 0.31 to 0.43; highest-risk quartile HR=0.52; 95% CI, 0.44 to 0.61) and status 1B candidates (lowest-risk quartile HR=0.41; 95% CI, 0.36 to 0.47; highest-risk quartile HR=0.66; 95% CI, 0.58 to 0.74). Status 2 candidates showed a benefit from heart transplantation; however, survival benefit was delayed. For the highest-risk donor-recipient matches, a net benefit of transplantation occurred immediately for status 1A candidates, after 12 months for status 1B candidates, and after 3 years for status 2 candidates.

Rana et al (2015) conducted a retrospective analysis of solid organ transplant recipients registered in the UNOS database from 1987 to 2012, including 54,746 patients who underwent a heart transplant.²⁷ Transplant recipients were compared with patients listed for transplant but who did not receive a transplant after propensity score matching based on a variety of clinical characteristics. After matching, the median survival was 9.5 years in transplant recipients compared with 2.1 years in waiting list patients.

Several studies have analyzed factors associated with survival in heart transplant patients. For example, Lund et al (2016) examined the risk factors associated with 10-year posttransplant mortality among patients undergoing heart transplantation between 2000 and 2005 using the International Society for Heart and Lung Transplantation (ISHLT) Registry.² Markers of pretransplant severity of illness, such as pretransplant ventilator use (HR=1.35; 95% CI, 1.17 to 1.56; n=338), dialysis use (HR=1.51; 95% CI, 1.28 to 1.78; n=332), underlying diagnoses of ischemic (HR=1.16; 95% CI, 1.10 to 1.23; n=7822), congenital (HR=1.21; 95% CI, 1.04 to 1.42; n=456) or restrictive (HR=1.33; 95% CI, 1.13 to 1.58; n=315) heart disease (vs. nonischemic cardiomyopathy), and retransplant (HR=1.18; 95% CI, 1.02 to 1.35; n=489) were associated with posttransplant mortality risk at 10 years.

A 2012 study by Kilic et al analyzed prospectively collected data from the UNOS registry.²⁸ The analysis included 9404 patients who had survived 10 years after heart transplant and 10,373 patients who had died before 10 years. Among individuals who had died, mean survival was 3.7 years posttransplant. In multivariate analysis, statistically significant predictors of surviving at least 10 years after heart transplant included age younger than 55 years (odds ratio [OR], 1.24; 95% confidence interval [CI], 1.10 to 1.38), younger donor age (OR=1.01; 95% CI, 1.01 to 1.02), shorter ischemic time (OR=1.11; 95% CI, 1.05 to 1.18), white race (OR=1.35; 95% CI, 1.17 to 1.56), and annual center volume of 9 or more heart transplants (OR=1.31; 95% CI, 1.17 to 1.47). Factors that significantly decreased the likelihood of 10-year survival in multivariate analysis included mechanical ventilation (OR=0.53; 95% CI, 0.36 to 0.78) and diabetes (OR=0.67; 95% CI, 0.57 to 0.78).

Pediatric Considerations

Retrospective Studies

In an analysis of data from the Pediatric Heart Transplant Study (2013), which includes data on all pediatric transplants at 35 participating institutions, suggest that 5-year survival for pediatric heart transplants has improved over time (76% for patients transplanted from 2000 to 2004 vs. 83% for patients transplanted from 2005 to 2009).²⁹

A retrospective review of pediatric cardiac transplantation patients was published by Auerbach et al in 2012.³⁰ A total of 191 patients who underwent primary heart transplantation at a single center in the United States were included; their mean age was 9.7 years (range, 0-23.6 years). Overall graft survival was 82% at 1 year and 68% at 5 years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall patient survival was 82% at 1 year and 72% at 5 years. In multivariate analysis, the authors found that congenital heart disease (HR=1.6; 95% CI, 1.02 to 2.64) and requiring mechanical ventilation at the time of transplantation (HR=1.6; 95% CI, 1.13 to 3.10) were both significantly independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small study group. Limitations of the study include that it was retrospective and conducted in only 1 center.

Registry Studies

The highest 1- and 3- year survival rate among pediatric patients undergoing heart transplant in the US, during 2008-2015, were 11-17 year old patients according to OPTN.³ Patients younger than 1-year-olds had the lowest 1-, 3-, and 5-year survival among pediatric patients (see Table1).

Rossano et al (2016) examined survival among pediatric heart transplant recipients using the ISHLT Registry.³¹ Among 12,091 pediatric patients undergoing heart transplantation during 1982-2014, the overall median survival was 20.7 years for infants (n=2994), 18.2 years for children ages 1 to 5 years (n=2720), 14.0 years for those ages 6 to 10 years (n=1743), and 12.7 years for those ages 11 to 17 years (n=4684). As the first year post transplant represents the greatest risk for mortality, survival conditional on survival to 1 year was longer.

Rossano et al conducted a multivariable analysis of pediatric patients undergoing heart transplant during 2003-2013 to identify the factors associated with 1-year mortality. Infection requiring intravenous drug therapy within 2 weeks of transplant (HR=1.36; 95% CI, 1.10 to 1.68; n=681), ventilator use (HR=1.41; 95% CI, 1.13 to 1.76; n=826), donor cause of death (cerebrovascular accident vs. head trauma) (HR=1.59; 95% CI, 1.20 to 2.09; n=396), diagnosis (congenital heart disease [CHD] vs. cardiomyopathy (HR=1.91; 95% CI, 1.46 to 2.52; n=1979), and retransplant vs. cardiomyopathy (HR=2.23; 95% CI, 1.53 to 3.25; n=304), recipient dialysis (HR=2.36; 95% CI, 1.57 to 3.57; n=146), ECMO with a diagnosis of CHD vs. no ECMO (HR=2.42; 95% CI, 1.74 to 3.35; n=145), ischemic time (p<0.001), donor weight (p<0.001), estimated glomerular filtration rate (eGFR; p=0.002), and pediatric center volume (p<0.001) were risk factors for 1-year mortality. Earlier era (1999-2000 vs. 2007-2009), CHD (vs. DCM), use of ECMO (vs. no device), and pediatric center volume were risk factors for 5-, 10-, and 15-year mortality. A panel-reactive antibody (PRA) greater than 10% was associated with worse 5- and 10-year survival and eGFR was associated with 5- and 10-year mortality.

A retrospective analysis of OPTN data focusing on the adolescent population was published by Savia et al in 2014.³² From 1987 to 2011, heart transplants were performed in 99 adolescents

(age 13-18 years) with myocarditis and 456 adolescents with coronary heart disease (CHD). Among adolescent transplant recipients with myocarditis, median graft survival was 6.9 years (95% CI, 5.6 to 9.6 years), which was significantly less than other age groups (i.e., 11.8 years and 12.0 years in younger and older adults, respectively). However, adolescents with CHD had a graft survival rate of 7.4 years (95% CI, 6.8 to 8.6 years), similar to that of other age groups.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond et al analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine if the pediatric heart allocation system, as revised in 1999, prioritizes patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices.³³ Of 3098 children (<18 years of age) listed between 1999 and 2006, a total of 1874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that Status 1A patients are a heterogeneous population with large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included extracorporeal membrane oxygenation support (hazard ratio [HR], 3.1), ventilator support (HR=1.9), listing status 1A (HR=2.2), congenital heart disease (HR=2.2), dialysis support (HR=1.9), and nonwhite race/ethnicity (HR=1.7). The authors concluded that the pediatric heart allocation system captures medical urgency poorly, specific high-risk subgroups can be identified, and further research is needed to better define the optimal organ allocation system for pediatric heart transplantation.

Section Summary: Initial Heart Transplant

The evidence supports a net benefit of heart transplantation compared with waitlist is evident for status 1A and 1B candidates. Status 2 candidates also show a benefit from heart transplantation; however, the survival benefit is delayed. Data from national and international registries have also found high patient survival rates after initial heart transplant among adult and pediatric patients (e.g., a 5-year survival rate, 78%).

HEART RETRANSPLANTATION

Clinical Context and Therapy Purpose

From 2008 to 2015, approximately 4% of heart transplants were repeated transplantations.³ Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. The UNOS does not have separate organ allocation criteria for repeat heart transplant recipients.

The purpose of heart retransplant in patients who have had a prior heart transplant complicated by graft failure or severe heart dysfunction is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals who have had a prior heart transplant complicated by graft failure or severe heart dysfunction.

Interventions

The therapy being considered is a heart retransplant. Heart retransplantation is provided in a hospital setting with specialized staff and equipment to perform the surgical procedure and provide postsurgical intensive care.

Comparators

The following therapies and practices are currently being used to make decisions about reducing the risk of end-stage heart failure: guideline-directed medical therapy; surgery including coronary bypass surgery, heart valve repair or replacement, and ventricular assist devices. Comparators are performed and managed by a physician in a clinical or hospital setting.

Outcomes

The general outcomes of interest are overall survival, treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for detailed discussion.

Follow-up of 1, 2, 5 and 10 years is of interest for heart transplant outcomes for overall survival, change in symptoms, morbid events, and treatment-related mortality and morbidity.

Review of Evidence

Systematic Reviews

A number of studies have reviewed clinical experience with heart retransplantation in adults. In 2008, Tjang et al published a systematic review of the literature on clinical experience with adult heart retransplantation that identified 22 studies.³⁴ The most common indications for retransplantation were cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). The early mortality rate in individual studies was 16% (range, 5%-38%). Some of the factors associated with poorer outcome after retransplantation were shorter transplant interval, refractory acute rejection, primary graft failure and an initial diagnosis of ischemic cardiomyopathy.

Retrospective Reviews

Zhu et al (2022) evaluated outcomes after heart retransplantation for 123 patients (112 adult and 11 pediatric patients) as compared to those who received a primary heart transplant at a single-center over a 50-year period (January 6, 1968 to June 2019).³⁶ The indications for retransplantation included cardiac allograft vasculopathy (80%), primary graft dysfunction (15%), and refractory acute rejection (5%). The mean time interval between the primary and retransplant was 6.4 years. Patients who underwent a retransplantation were significantly more likely to have hypertension (73.3% vs. 53.3%; $p=.0022$), hyperlipidemia (66.7% vs. 30.7%; $p<.0001$), and require dialysis (11.7% vs. 2.9%; $p=.0025$) as compared to those undergoing a primary heart transplant. After matching, postoperative outcomes and complications including hospital stay (mean 22.9 vs. 25.8 days; $p=.49$), intensive care unit stay (mean 12.2 vs. 9.9 days; $p=.48$), respiratory failure (41.7% vs. 20.6%; $p=.083$), dialysis (21.2% vs. 24.2%; $p=.82$), pneumonia (12.9% vs. 9.6%; $p=.48$), septicemia (1.6% vs. 9.4%; $p=.10$), and rejection within the first year after transplantation requiring hospitalization (21.5% vs. 26.2%; $p=.82$) were similar between the retransplant and primary transplant groups, respectively. Matched median survival after retransplantation was 4.6 years versus 6.5 years after primary heart transplantation ($p=.36$).

A representative study was published in 2013 by Saito et al.³⁶ This was a retrospective review of data on 593 heart transplants performed at their institution, 22 of which (4%) were retransplants. The mean interval between initial and repeat transplant was 5.1 years. The indications for a repeat transplant were acute rejection in 7 patients (32%), graft vascular disease in 10 patients (45%), and primary graft failure in 5 patients (23%). Thirty-day mortality after cardiac retransplantation was 32% (7/22 patients). Among patients who survived the first 30 days (n=15), 1-, 5-, and 10-year survival rates were 93.3%, 79% and 59%, respectively. Comparable survival rates for patients undergoing primary cardiac transplants at the same institution (n=448) were 93%, 82%, and 63%, respectively. An interval of 1 year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of 9 patients (33.3%) with less than 1 year between the primary and retransplantation survived to 30 days. In comparison 12 of 13 patients (92%) with at least 1 year between primary and retransplantation were alive at 30 days after surgery.

Registry Studies

An analysis of OPTN data from 2008 to 2015 reported that 724 retransplants were performed (of 18,676 heart transplants, 3.9% of all transplants). Kaplan-Meier patient survival rates at 1, 3, and 5 years were lower among the retransplant recipients compared with primary transplant recipients (see Table 2).

Table 2. Kaplan-Meier Patient Survival Rates for Primary and Repeat Heart Transplants Performed: 2008-2015

Years Posttransplant	Transplant Type						
	Primary Transplant			Repeat Transplant			
	No. Alive	Survival Rate, % ^a	95% CI, %	No. Alive	Survival Rate, % ^a	95% CI, %	
1 year	9013	90.9	90.9	90.3 to 91.4	320	87.0	83.1 to 90.0
3 years	7711	85.6	85.6	84.8 to 86.3	286	76.5	71.8 to 80.4
5 years	6572	78.6	78.6	77.7 to 79.4	237	69.7	64.6 to 74.2

CI: confidence interval.

^a One-year survival based on 2012-2015 transplants, 3-year survival based on 2010-2013 transplants, 5-year survival based on 2008-2011 transplants.

In a study analyzing UNOS data from January 1996 and November 2017, Miller et al (2019) reported that 349 (0.6%) early/acute retransplants (occurring ≤1 year after the previous transplant) and 2,202 (3.5%) late retransplants (occurring >1 year after the previous transplant) were performed from a sample of 62,112 heart transplants.³⁷ Compared with a matched group of patients undergoing initial transplantation, patients undergoing late retransplantation were not at an increased risk of death (HR, 1.08; p=0.084) or the combined outcome of death or retransplantation (HR, 1.07; p=0.114). Additionally, patients undergoing late retransplant had comparable rates of 1-year all-cause mortality when compared to patients undergoing initial transplant (13.8% vs 14.5%, respectively; p=0.517). Conversely, patients undergoing early/acute transplant had higher rates of 1-year all-cause mortality when compared to patients undergoing initial transplant (35% vs. 21.6%; p<0.001). Furthermore, early/acute retransplantation was associated with an increased risk of all-cause mortality (HR, 1.79; p<0.001) and the combined outcome of death or retransplantation (HR, 1.72; p<0.001).

Goldraich et al (2016) examined the survival in adult heart recipients with cardiac allograft vasculopathy who were retransplanted (n=65) or managed medically (n=4530).³⁸ During a median follow-up of 4 years, there were 24 deaths among those who underwent retransplantation and 1466 deaths among those who were medically managed. There was no significant difference in survival at 9 years (55% in retransplant recipients vs. 51% in medically managed patients, p=0.88). In subgroup analysis, overall the retransplant group (n=65) had better survival than medically managed group with systolic graft dysfunction at 1 year after development of CAV (n=124; p=0.02).

In an analysis of the OPTN data from 1995 to 2012, Belli et al (2014) reported that 987 (3.5%) retransplants were performed from a sample of 28,464 heart transplants.³⁹ Median survival among retransplant recipients was 8 years. The estimated survival rates at 1, 5, 10, and 15 years following retransplant were 80%, 64%, 47%, and 30%, respectively. Compared with primary transplant recipients, retransplant patients had a somewhat higher risk of death (relative risk, 1.27, 95% CI, 1.13 to 1.42).

In a study analyzing UNOS data, Friedland-Little et al (2014) reported no survival differences between third and second transplants (76% for third transplant vs. 80% for second transplant at 1 year; 62% for third transplant vs. 58% for second transplant at 5 years; 53% for third transplant vs. 34% for second transplant at 10 years, p=0.73).⁴⁰ However, study conclusions might have been limited because of the small number (n=25) of third heart transplants.

Pediatric Considerations

As with initial heart transplants, children awaiting heart retransplantation have high waitlist mortality. A 2014 study by Bock et al evaluated data on 632 pediatric patients who were listed for a heart retransplant at least 1 year (median, 7.3 years) after the primary transplant.⁴¹ Patients' median age was 4 years at the time of the primary transplant and 14 years when they were relisted. Median waiting time was 75.3 days and mortality was 25.2% (159/632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, p<0.01).

Conway et al (2014) analyzed the ISHLT Registry to describe the outcomes after retransplantation compared to primary transplantation among pediatric (<18 years of age) heart transplant recipients during 1998-2010.⁴² Of the 9882 heart transplant recipients with available clinical outcome data, 9248 (93.6%) were primary transplants, 602 (6.1%) were retransplants (second graft), and 32 (0.3%) were third or fourth grafts. The median age at primary transplant and retransplant was 7 (range, 0-14) and 14 (range, 1-26) years, respectively. The mean intertransplant interval was 6.8 years after primary transplant. The most common indications for retransplantation were coronary allograft vasculopathy (n=352 [59%]), nonspecific graft failure (n=52 [9%]) and acute rejection (n=49 [8%]). Retransplantation was associated with similar early survival but decreased long-term survival compared with initial transplantation. After primary transplantation, survival was 84% at 1 year, 72% at 5 years, 60% at 10 years, and 42% at 20 years, compared with 81% at 1 year, 63% at 5 years, 46% at 10 years, and 26% at 20 years after retransplantation. The median survival was longer in primary transplant recipients, reaching 15 years compared with 8.7 years after retransplantation. The most common causes of death after retransplantation were cardiovascular other than vasculopathy (28%), graft failure (10%), infection (9%), noncardiac organ failure (9%), coronary allograft vasculopathy (4%), and acute rejection (3%).

Section Summary: Heart Retransplantation

In both adult and pediatric studies, poorer survival after retransplantation than initial transplantation is not surprising given that patients undergoing retransplantation experienced additional clinical disease or adverse events.

Data from national and international registries have found high patient survival rates after heart retransplant among adult and pediatric patients (e.g., a 5-year survival rate, 69%). Cardiac allograft vasculopathy is the most common indication for heart retransplantation both among adult and pediatric patients. Considering the scarcity of donor heart and improving treatment options for cardiac allograft vasculopathy, studies need to be done to further examine the survival benefit of cardiac retransplantation over medical management among patients with cardiac allograft vasculopathy so that retransplantation could be limited to highly selected patients with cardiac allograft vasculopathy.

Potential Contraindications to Heart Transplant (Applies to All Indications)

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation e.g., imminently terminal cancer or other disease. Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy

Pretransplant malignancy is considered a relative contraindication for heart transplantation considering this has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer survival over the years and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population, Mistiaen et al (2015) conducted a systematic review to study the posttransplant outcome of pretransplant malignancy patients.⁴³ Most selected studies were small case series (median sample size, 17 patients; range, 7-1117). Mean patient age varied from 6 years to 52 years. Hematologic malignancy and breast cancer were the most common type of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy was mostly the common reason for transplantation in 4 case series, chemotherapy related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality varied between 0% and 33%, with small sample size potentially explaining the observed variation.

Yoosabai et al (2015) conducted a retrospective review among 23,171 heart transplant recipient in the OPTN/UNOS database to identify whether pretransplant malignancy increases the risk of post-transplant malignancy.⁴⁴ Post transplant malignancy was diagnosed in 2673 (11.5%) recipients during the study period. A history of any pretransplant malignancy was associated with increased risk of overall post-transplant malignancy (subhazard ratio [SHR], 1.51; $p < 0.01$), skin (SHR=1.55, $p < 0.01$), and solid organ malignancies (SHR=1.54, $p < 0.01$) on multivariate analysis.

One large series reported similar short-term and long-term post-transplant survival of chemotherapy related (N=232) and other nonischemic cardiomyopathy (N=8890) patients.⁴⁵

The 1-, 3-, and 5-year survival rates of were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients. Similar findings were observed for 1-year survival in smaller series. Two-, 5-, and 10-year survival rates among pretransplant malignancy patients were also comparable with other transplant patients. In addition to the nonmalignancy related factors such as cardiac, pulmonary, and renal dysfunction, 2 malignancy related factors were identified as independent predictors of 5-year survival. Malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with lower 5-year survival compared with a longer interval (<60% vs. >75%). Patients with prior hematologic malignancies had an increased post-transplant mortality in 3 small series. Recurrence of malignancy was more frequent among patients with a shorter disease-free interval, 63%, 26%, and 6% among patients with less than 1 year, 1 to 5 years, and more than 5 years of disease-free interval, respectively.⁴⁶

The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients for whom cancer is thought to be cured should not be excluded from consideration for transplant. ISHLT guidelines have recommended to stratify each patient with pretransplant malignancy as to their risk of tumor recurrence and that cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The guideline also recommended that the specific amount of time to wait to transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

Human Immunodeficiency Virus (HIV)

Solid organ transplant for patients who are HIV-positive (HIV+) was historically controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity and the impact of immunosuppression on HIV disease. Aguero et al (2016) reported a review on heart transplantation among HIV-infected patients.⁴⁷ Since 2001, 12 heart transplantations in HIV-infected patients has been reported and 3 patients acquired HIV after heart transplantation. Fourteen (93%) of these 15 patients were younger than 50 years of age, with CD4 counts greater than 200 cells/mm³, and all of them were taking antiretroviral therapy. Thirteen were alive with normal graft function at the end of follow-up. One patient had suboptimal adherence to ART and died of multiorgan failure. The cause of death in the other patient was not reported.⁴⁸ There are few data directly comparing outcomes for patients with and without HIV.

Current OPTN policy permits HIV-positive transplant candidates.⁴

The British HIV Association and the British Transplantation Society Standards Committee published guidelines (2017) for kidney transplantation in patients with HIV disease.⁴⁹ These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- CD4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis or lymphoma.

In 2021, Doberne et al compared survival outcomes of cardiac transplantation in HIV-positive recipients with HIV-negative recipients.⁵⁰ Utilizing UNOS data on first-time heart transplant recipients and their donors between January 2005 and June 2019, a total of 75 HIV-positive transplant recipients and 29,848 HIV-negative recipients were included in an analysis. Results revealed no difference in 30-day, 1-year, and 5-year survival of HIV-positive versus HIV-negative heart transplant recipients. However, HIV-positive recipients had significantly longer median lengths of hospital stays (18 vs. 15 days; $p=.006$), rate of acute rejection during initial hospitalization (38.7% vs. 17.7%; $p<.001$), and rate of anti-rejection treatment administration (26.7% vs. 10.4%; $p<.001$).

Age

The maximum acceptable age for heart transplantation is an issue for debate. While the maximum recipient age for heart transplantation was set at 55 years during the early years of heart transplantation, with increasing evidence of comparable survival among older population following heart transplantation, transplant centers have been accepting older recipients. However, the upper age limit for heart transplant candidates is still controversial and is generally defined by the transplant centers.

Jamil et al (2017) conducted a retrospective study of age as it relates to primary graft dysfunction after heart transplantation.⁵¹ Of the 255 heart transplants studied, 70 (27%) of recipients were 65 years and older and 185 were younger; there were no significant differences in posttransplant morbidity (all $p>0.12$) or at 1-year survival between groups ($p=0.88$). The incidence of moderate or severe primary graft dysfunction was lower among the older patients (6%) than in the younger (16%; $p=0.037$). Study limitations included the single-center design, lack of data on long-term survival, and the potential for selection bias in retrospective studies.

Cooper et al (2016) analyzed the UNOS database to examine the long-term outcomes of older recipients of orthotopic heart transplant in the United States during 1987-2014.⁵² During this period, 50,432 patients underwent orthotopic heart transplant; 71.8% ($n=36,190$) were 18 to 59 years old, 26.8% ($n=13,527$) were 60 to 69 years old, and 1.4% ($n=715$) were 70 years old or older. The 5-year mortality rate was 26.9% for recipients 18 to 59 years old, 29.3% for recipients 60 to 69 years old, and 30.8% for recipients 70 years of age and older. Survival between the oldest group and the 60- to 69-year-old group did not differ significantly ($p=0.48$).

Awad et al (2016) reported a single-center retrospective review of 704 adults who underwent heart transplantation from 1988 to 2012 to investigate the mortality and morbidity of heart transplantations among recipients 70 years of age and older ($n=45$) compared with recipients younger than 70 years ($n=659$).⁴⁹ The older and younger groups had similar 1-year ($93.0\pm 3.9\%$ vs. $92.1\pm 1.1\%$; $p=0.79$), 5-year ($84.2\pm 6.0\%$ vs. $73.4\pm 1.9\%$; $p=0.18$), and 10-year ($51.2\pm 10.7\%$ vs. $50.2\pm 2.5\%$; $p=0.43$) survival rates.

In 2012, Kilic and colleagues analyzed data from the UNOS on 5,330 patients age 60 and older (mean age 63.7 years) who underwent heart transplantation between 1995 and 2004.⁵³ A total of 3,492 individuals (65.5%) survived to 5 years. In multivariate analysis, statistically significant predictors of 5-year survival included younger age (OR: 0.97, 95% CI: 0.95 to 1.00), younger donor age (OR: 0.99, 95% CI: 0.99-1.00), white race (OR: 1.23, 95% CI: 1.02 to 1.49), shorter ischemic time (OR: 0.93, 95% CI: 0.87-0.99), and lower serum creatinine (OR: 0.92, 95% CI: 0.87 to 0.98). In addition, hypertension, diabetes, and mechanical ventilation each significantly

decreased the odds of surviving to 5 years. Patients with 2 or more of these factors had a 12% lower rate of 5-years survival than those with none of them.

Pulmonary Hypertension

Findings of several studies suggest that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant.⁵⁴⁻⁵⁸ For example, Tsukashita et al (2015) retrospectively compared the effect of continuous-flow left ventricular assist device support on pulmonary hypertension with post-transplantation outcomes among 227 potential OHT candidates with preexisting pulmonary hypertension.⁵⁹ Patients were divided into 2 groups based on preimplantation pulmonary vascular resistance (PVR): low (<5 Wood units) (n=182) and high (\geq 5 Wood units) (n=45). After left ventricular assist device (LVAD) implantation, PVR in the high PVR group decreased significantly (7.13 ± 2.09 Wood units to 2.82 ± 1.46 Wood units, $p < 0.001$) to a level similar that in the low PVR group (2.70 ± 1.20 Wood units, $p = 0.91$) and remained low after heart transplantation. The mean follow-up period after OHT was 3.5 ± 2.4 years (range, 1 month to 9.3 years). The in-hospital mortality rate after OHT was significantly higher in the high PVR group (20.7%) than in the low PVR group (5.8%; $p < 0.05$). The survival rates at 3 years post-OHT were 85.0% for the low PVR group and 79.0% for the high PVR group ($p = 0.45$).

De Santo et al (2012) reported on 31 consecutive patients who had been diagnosed with unresponsive pulmonary hypertension at baseline right heart catheterization.⁵⁵ After 12 weeks of treatment with oral sildenafil, right heart catheterization showed reversibility of pulmonary hypertension, allowing listing for heart transplant. Oral sildenafil treatment resumed following transplant. One patient died in the hospital. A right heart catheterization at 3 months post-transplant showed normalization of the pulmonary hemodynamic profile, thereby allowing weaning from sildenafil in the 30 patients who survived hospitalization. The reversal of pulmonary hypertension was confirmed at 1 year in the 29 surviving patients. Similarly, in a study by Perez-Villa et al, 22 patients considered high risk for heart transplant due to severe pulmonary hypertension were treated with bosentan.⁵⁶ After 4 months of treatment, mean pulmonary vascular resistance (PVR) decreased from 5.6 to 3.4 Wood units. In a similar group of 9 patients who refused participation in the study and served as controls, mean PVR during this time increased from 4.6 to 5.5 Wood units. After bosentan therapy, 14 patients underwent heart transplantation and the 1-year survival rate was 93%.

Renal Insufficiency

A retrospective report by Arshad et al (2019) compared renal outcomes and survival in patients who received an LVAD (n=45) or heart transplant (n=58).⁶⁰ The eGFR was similar between LVAD and transplant groups on day 30 after procedure ($75.1 \text{ mL/min/1.73 m}^2$ and $65.8 \text{ mL/min/1.73 m}^2$, respectively; $p = 0.057$), and significantly higher with LVAD versus transplant at 6 months ($68.3 \text{ mL/min/1.73 m}^2$ and $59.4 \text{ mL/min/1.73 m}^2$; $p = 0.046$) and 1 year ($68.3 \text{ mL/min/1.73 m}^2$ and $56.8 \text{ mL/min/1.73 m}^2$; $p = 0.15$). Survival rates were similar between LVAD and transplant groups at 1 year (84.4% and 81.0%, respectively; $p = 0.540$) and 2 years (78.3% and 78.8%, respectively; $p = 0.687$) after the procedure.

A retrospective report by Kolsrud et al (2018) investigated the association between post heart transplantation and measured glomerular filtration rate (GFR) as a risk factor for death and/or end-stage renal disease.⁶¹ During the first year after heart transplant, 416 adults showed a 12% mean drop in measured GFR compared with preoperative values and long-term survival was significantly worse in patients who experienced a 25% or greater decrease in measured GFR

during the first post transplantation year (HR=1.62; 95% CI, 1.04 to 2.53; p=0.03). Preoperative measured GFR was not predictive of mortality or end-stage renal disease, but older patients (HR=1.03; 95% CI, 1.02 to 1.04; p<0.001) or patients with ventricular assisted device (HR=2.23; 95% CI, 1.43 to 3.46; p<0.001) were predictors of death. The authors concluded that pretransplantation measured GFR was not predictive of mortality or end-stage renal disease after heart transplantation, but in this select patient population, simultaneous or late-stage concomitant kidney transplant was necessary. Patients who experienced a 25% or greater measured GFR decrease has the poorest prognosis. Study limitations included selection bias of patients, the retrospective study design, the exclusion of the sickest patients eligible undergoing post heart transplantation, changes in ventricular assisted device and concomitant kidney transplant methods over time, and the small sample size studied.

The 2016 ISHLT listing criteria for heart transplantation recommended irreversible renal dysfunction (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) as a relative contraindication for heart transplantation alone. The cutoff for eGFR in the previous recommendation was 35 mL/min/1.73 m². Hong et al (2016) conducted a study among 17,459 adult OHT recipients during 2001-2009 in the UNOS database to determine whether survival after OHT was associated with pretransplant eGFR and to define ranges of pretransplant eGFR associated with differences in post-transplant survival.⁶² Post transplant graft survival in the eGFR less than 34 mL/min/1.73 m² group was significantly worse than in the eGFR 35 to 49 mL/min/1.73 m² or eGFR greater than 49 mL/min/1.73 m² groups (p<0.001), with a median survival in the 3 groups at 8.2 years, 10.0 years, and 10.3 years, respectively. At 3 months, graft survival rates were 82.1%, 90.7%, and 94.0% in the eGFR less than 34 mL/min/1.73 m², eGFR 35 to 49 mL/min/1.73 m², and eGFR greater than 49 mL/min/1.73 m² groups, respectively. In multivariable logistic regression analysis, eGFR less than 34 mL/min/1.73 m² and eGFR 35 to 49 mL/min/1.73 m² were significant risk factors for death at 1 year (p<0.001). Rossano et al (2016) also reported eGFR to be an independent risk factor for 1-, 5- and 10-year post transplant mortality among pediatric population (described under pediatric considerations for survival after heart transplant).³⁰

Children With Intellectual Disability

Considering the shortage of available donor organs, heart transplantation in children with intellectual disability has been an issue of debate. In 2016, ISHLT removed explicit mention of 'mental retardation' as a relative contraindication to heart transplantation from its official guidelines. Multiple studies in recent years have examined if intellectual disability in children was associated with significantly lower survival following heart transplantation compared to children without intellectual disability.

Goel et al (2017) conducted a retrospective cohort study using UNOS database from 2008-2015 to describe the prevalence and outcomes of heart transplantation in this population.⁶³ Intellectual disability was assessed by using the cognitive development, academic progress, and academic level (5-point Likert scale scores for each of those) reported by transplant centers to UNOS. There were 565 pediatric (<19 years) patients with definite (n=131) or probable (n=434) intellectual disability who received first heart transplant, accounting for 22.4% of all first pediatric heart transplants (n=2524). Intellectual disability was associated with prolonged waitlist time (p<0.001). Patient survival rates at 1 and 3 years, respectively, were 88.9% and 86.0% for the definite intellectual disability group, 91.6% and 82.4% for probable intellectual disability group, and 91.8% and 86.2% for no intellectual disability group. Patient survival did not differ between groups at any time post-transplant (p=0.578). Intellectual

disability status at listing was not associated with graft mortality hazards in univariate and multivariate analysis.

Wightman et al (2017) performed a retrospective cohort analysis of all children receiving a first isolated heart transplant in the UNOS dataset during 2008 to 2013 for whom cognitive and educational data were available (n=1204).⁶⁴ Children identified as “definitely cognitive delay/impairment” by their transplant center using the Likert scales for cognitive development were categorized as with intellectual disability. All other recipients were classified as “No intellectual disability.” Kaplan-Meier curves and log-rank tests did not suggest a significant difference in graft survival during the first 4 years after transplantation (p=0.07), however, did suggest poorer patient survival among the intellectual disability group during the first 4 years following transplantation (p=0.05). In unadjusted Cox regression, intellectual disability was associated with poorer graft (HR=1.66; 95% CI, 1.01 to 2.72; p=0.05) and patient survival (HR=1.71; 95% CI, 0.99 to 2.94; p=0.05). After adjusting for covariates, however, there was no association between intellectual disability and graft (HR=0.95; 95% CI, 0.49 to 1.88; p=0.89) or patient survival (HR=0.80; 95% CI, 0.36 to 1.75; p=0.58).⁶⁵

Prendergast et al (2017) assessed the impact of cognitive delay on pediatric heart transplantation outcomes using academic progress as a surrogate for cognitive performance among pediatric heart transplant recipients (2004-2014) with reported academic progress in the OPTN database (n=2245).⁶⁶ Of the patients with complete academic progress data, 1707 (76%) were within 1 grade level of peers (WGL), 269 (12%) had delayed grade level (DGL), and 269 (12%) required special education (SE). There was no significant difference in post-transplant survival between patients WGL and those who required SE. However, patients with DGL demonstrated worse post-transplant survival compared to patients WGL and those who required SE (p<0.001). DGL remained as an independent predictor of post-transplant graft loss (adjusted HR=1.4; 95% CI, 1.02 to 1.79; p=0.03) in multivariate analysis. Authors conducted a secondary analysis substituting cognitive delay for academic progress, patients were divided into 2 groups based on whether any concern for cognitive delay (questionable, probable, or definite) was ever reported at the time of heart transplantation or in follow-up (1176 with cognitive delay, 1783 with no documented cognitive delay). There was no significant difference in post-transplant graft survival based on the presence of cognitive delay (p=0.57). Cognitive delay remained a statistically nonsignificant predictor in multivariate analysis (adjusted HR=1.01; 95% CI, 0.83 to 1.22; p=0.953).

Since all these studies were conducted among the patients who received transplants and children who were refused listing by a transplant center or never referred to transplant center were not assessed prevalence of intellectual disability among potential candidates of heart transplantation might have been underestimated. With low-risk intellectual disability patients receiving heart transplant and individuals with intellectual disability and other high-risk conditions being excluded might have resulted in a positive selection bias as well.

SUMMARY OF EVIDENCE

For individuals who have end-stage heart failure who receive heart transplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. Despite improvements in the prognosis for many patients with advanced heart disease, heart transplant remains a viable treatment for those with severe heart dysfunction despite appropriate medical management with medication, surgery, or medical devices. Given the exceedingly poor survival rates without

transplantation for these patients, evidence of post-transplant survival is sufficient to demonstrate that heart transplantation provides a survival benefit. Heart transplantation is contraindicated in patients for whom the procedure is expected to be futile due to comorbid disease or in whom post transplantation care is expected to significantly worsen comorbid conditions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a prior heart transplant complicated by graft failure or severe dysfunction of heart requiring heart retransplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. Despite improvements in the prognosis for many patients with graft failure, cardiac allograft vasculopathy, and severe dysfunction of transplanted heart, heart retransplant remains a viable treatment for those who have exhausted other medical or surgical remedies, yet are still with severe symptoms. Given the exceedingly poor survival rates without retransplantation for patients who have exhausted other treatments, evidence of post-transplant survival is sufficient to demonstrate that heart retransplantation provides a survival benefit in appropriately selected patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Cardiology Foundation et al

Heart failure guidelines from the American College of Cardiology Foundation, the American Heart Association and the Heart Failure society of American were updated in 2022. ⁶⁷

Recommendations for cardiac transplantation by the joint committee were as follows:

- "For selected patients with advanced HF [heart failure] despite GDMT [guideline-directed medical therapy], cardiac transplantation is indicated to improve survival and QOL [quality of life] (class of recommendation, 1; level of evidence, C-LD)
- In patients with stage D (advanced) HF despite GDMT, cardiac transplantation provides intermediate economic value(value statement: intermediate value)"

International Society for Heart and Lung Transplantation

In a 2004 statement, International Society for Heart and Lung Transplantation (ISHLT) recommended that children with the following conditions should be evaluated for heart transplantation.⁶⁸

- Diastolic dysfunction that is refractory to optimal medical/surgical management because they are at high risk of developing pulmonary hypertension and of sudden death (based on level of evidence B [a single randomized trial or multiple nonrandomized trials]).
- Advanced systemic right ventricular failure (Heart Failure Stage C described as patients with underlying structural or functional heart disease and past or current symptoms of heart failure) that is refractory to medical therapy (level of evidence C [primarily expert consensus opinion]).

In 2016, ISHLT published a 10-year update to its listing criteria for heart transplantation.⁶⁹ The guidelines recommended updates/changes to the 2006 guideline recommendations:

- Recommended use of heart failure prognosis scores (e.g., Seattle Heart Failure Model, Heart Failure Survival Score) along with cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients.
- Periodic right heart catheterization for routine surveillance was not recommended in children.
- Carefully selected patients >70 years of age may be considered for cardiac transplantation.
- Pre-existing neoplasm, body mass index of ≥ 35 kg/m², diabetes with “end-organ damage (other than non-proliferative retinopathy) or poor glycemic control ... despite optimal effort,” irreversible renal dysfunction, clinically severe symptomatic cerebrovascular disease, peripheral vascular disease, and frailty are considered relative contraindications to heart transplantation.
- Considering active smoking during the previous 6 months as a risk factor for poor outcomes after transplantation, active tobacco smoking is considered a relative contraindication for heart transplantation. Similarly, patients who remain active substance abusers (including alcohol) are not recommended to receive heart transplantation.

This same ISHLT 2016 guidelines update states the following regarding retransplantation indications:

“Retransplantation is indicated for those patients who develop significant CAV [(cardiac allograft vasculopathy)] with refractory cardiac allograft dysfunction, without evidence of ongoing acute rejection (Class IIa, Level of Evidence: C).”

The guidelines cite the published consensus by Johnson et al (2007) on indications for retransplantation.⁹ It states that, based on available data, appropriate indications for retransplantation include “the development of chronic severe CAV with symptoms of ischemia or heart failure, CAV without symptoms but with moderate to severe LV [(left ventricle)] dysfunction, or symptomatic graft dysfunction without evidence of active rejection. ”Retransplantation within the first 6 months after previous transplantation, especially with immunologic complications as a primary cause, was considered high risk.

As a note on heart transplantation in children, the 2016 guidelines update states, “although nearly half of all HTs [(heart transplants)] in children are done for CHD [(congenital heart disease)],... it should be noted that general considerations vary for more traditional indications, such as idiopathic dilated cardiomyopathy, for transplantation in the pediatric population..... Thus, as these guidelines are translated to the younger patient, such prudence will need to be exercised.”

The 2010 guidelines from ISHLT on the care of heart transplant recipients include the following recommendations on cardiac retransplantation⁷⁰:

- “Retransplantation is indicated in children with at least moderate systolic heart allograft dysfunction and/or severe diastolic dysfunction and at least moderate CAV (cardiac allograft vasculopathy).”
- “It is reasonable to consider listing for retransplantation those adult HT heart transplant recipients who develop severe CAV not amenable to medical or surgical therapy and symptoms of heart failure or ischemia.”
- “It is reasonable to consider listing for retransplantation those HT recipients with heart allograft dysfunction and symptomatic heart failure occurring in the absence of acute rejection.”

- “It is reasonable to consider retransplantation in children with normal heart allograft function and severe CAV.”

American Heart Association

The AHA Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group stated in 2007 that, based on level B (nonrandomized studies) or level C (consensus opinion of experts), heart transplantation is indicated for pediatric patients as therapy for the following indications:⁷¹

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previously repaired or palliated congenital heart disease,
- Stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributed to heart disease, pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension;
- The guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, in patients with pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m² and/or a transpulmonary pressure gradient >15 mm Hg if administration of inotropic support or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m² or the transpulmonary gradient to <15 mm Hg.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations

National:

National Coverage Determination (NCD) for Heart Transplants (260.9)⁷³

Effective Date of this Version 5/1/2008, Implementation Date 12/1/2008

Indications and Limitations of Coverage

A. General

Cardiac transplantation is covered under Medicare when performed in a facility which is approved by Medicare as meeting institutional coverage criteria. (See CMS Ruling 87-1.)

B. Exceptions

In certain limited cases, exceptions to the criteria may be warranted if there is justification and if the facility ensures our objectives of safety and efficacy. Under no circumstances will exceptions be made for facilities whose transplant programs have been in existence for less than 2 years, and applications from consortia will not be approved.

Although consortium arrangements will not be approved for payment of Medicare heart transplants, consideration will be given to applications from heart transplant facilities that consist of more than one hospital where all of the following conditions exist:

- The hospitals are under the common control or have a formal affiliation arrangement with each other under the auspices of an organization such as a university or a legally constituted medical research institute; and
- The hospitals share resources by routinely using the same personnel or services in their transplant programs. The sharing of resources must be supported by the submission of operative notes or other information that documents the routine use of the same personnel and services in all of the individual hospitals. At a minimum, shared resources means:
- The individual members of the transplant team, consisting of the cardiac transplant surgeons, cardiologists and pathologists, must practice in all the hospitals and it can be documented that they otherwise function as members of the transplant team; and
- The same organ procurement organization, immunology, and tissue-typing services must be used by all the hospitals;
- The hospitals submit, in the manner required (Kaplan-Meier method) their individual and pooled experience and survival data; and
- The hospitals otherwise meet the remaining Medicare criteria for heart transplant facilities; that is, the criteria regarding patient selection, patient management, program commitment, etc.

C. Pediatric Hospitals

Cardiac transplantation is covered for Medicare beneficiaries when performed in a pediatric hospital that performs pediatric heart transplants if the hospital submits an application which CMS approves as documenting that:

- The hospital's pediatric heart transplant program is operated jointly by the hospital and another facility that has been found by CMS to meet the institutional coverage criteria in CMS Ruling 87-1;
- The unified program shares the same transplant surgeons and quality assurance program (including oversight committee, patient protocol, and patient selection criteria); and
- The hospital is able to provide the specialized facilities, services, and personnel that are required by pediatric heart transplant patients.

D. Follow-Up Care

Follow-up care required as a result of a covered heart transplant is covered, provided such services are otherwise reasonable and necessary. Follow-up care is also covered for patients who have been discharged from a hospital after receiving a noncovered heart transplant. Coverage for follow-up care would be for items and services that are reasonable and necessary, as determined by Medicare guidelines. (See the Medicare Benefit Policy Manual, Chapter 16, "General Exclusions From Coverage," §180.)

E. Immunosuppressive Drugs

See the Medicare Claims Processing Manuals, Chapter 17, "Drugs and Biologicals," §§80.3.1 and, Chapter 8, "Outpatient ESRD Hospital, Independent Facility, and Physician/Supplier Claims," §120.1.

F. Artificial Hearts

Medicare covers ventricular assist devices (VAD) and artificial hearts when implanted under the coverage criteria stated in §20.9 of this manual (NCD Manual 100-03).

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Transplant-Heart-Lung (Combined)
 - Transplant-Heart-Kidney (Combined)
 - Transplant-Heart-Liver (Combined)
 - Immune Cell Function Assay
 - Laboratory Tests for Heart Transplant Rejection
 - Total Artificial Hearts and Implantable Ventricular Assist Devices
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
4/24/02	N/A	N/A	Joint policy established
12/5/03	12/5/03	1/16/04	Routine maintenance
2/2/05	2/2/05	2/2/05	Routine maintenance; criteria changed
9/1/06	7/10/06	7/5/06	Routine maintenance
9/1/07	7/3/07	7/21/07	Routine maintenance
9/1/08	7/28/08	7/3/08	Routine maintenance
9/1/09	6/16/09	6/16/09	Routine maintenance
9/1/12	6/12/12	6/19/12	Routine maintenance; policy reformatted to mirror BCBSA policy.
7/1/13	4/16/13	4/22/13	Policy reformatted; moved some guidelines to the description section, revised inclusionary/exclusionary guidelines, added references.
5/1/15	2/17/15	2/27/15	Routine maintenance - References and rationale updated. Added statement to the inclusions regarding retransplantation.
5/1/16	2/16/16	2/16/16	Policy updated with literature review; references added; OPTN guideline changes. No changes to policy status.
5/1/17	2/21/17	2/21/17	Routine policy maintenance.
5/1/18	2/20/18	2/20/18	Updated rationale added reference # 1-4, 20, 24, 31, 35-40, 43-45, 52-57, and 61. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance. Added references # 42, 51 and 56. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No added references. Inclusion/exclusion sections reorganized for consistency with other transplant policies. No change in policy status.

5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance, added reference #46, no change in policy status.
9/1/22	6/21/22		Added OPTN status definitions for status 2-7 to description section. Updated pediatric status description.
9/1/23	6/13/23		Rationale updated, added reference #5 and 36. No change in policy status. Vendor managed: N/A (ds)
9/1/24	6/18/24		Title change: Transplant-Heart. Additions made to inclusion/exclusion section. No changes in policy status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

**BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSPLANT-HEART**

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy guidelines apply Transportation, meals and lodging expenses related to the transplant are not covered unless specifically noted in the member's certificate/rider
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service. Transportation, meals and lodging expenses related to the transplant are not covered

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.