

# Heart Transplantation

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## Disclosures

- No relevant financial disclosures



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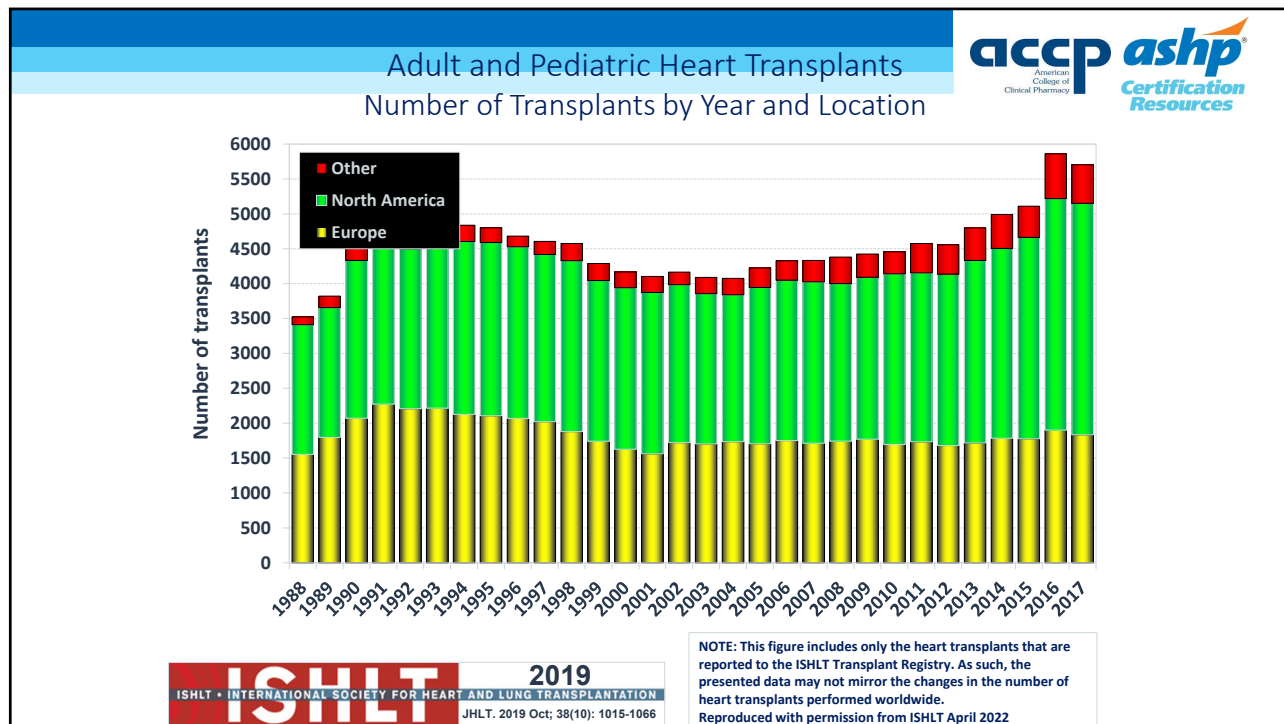
## Learning Objectives

- Describe common indications that may lead to heart transplantation.
- Identify pre-transplant risk factors that may impact outcomes after heart transplantation.
- Describe heart techniques for rejection surveillance.
- Understand heart specific pathologic findings.
- List and discuss heart specific post-transplant complications and strategies for management.

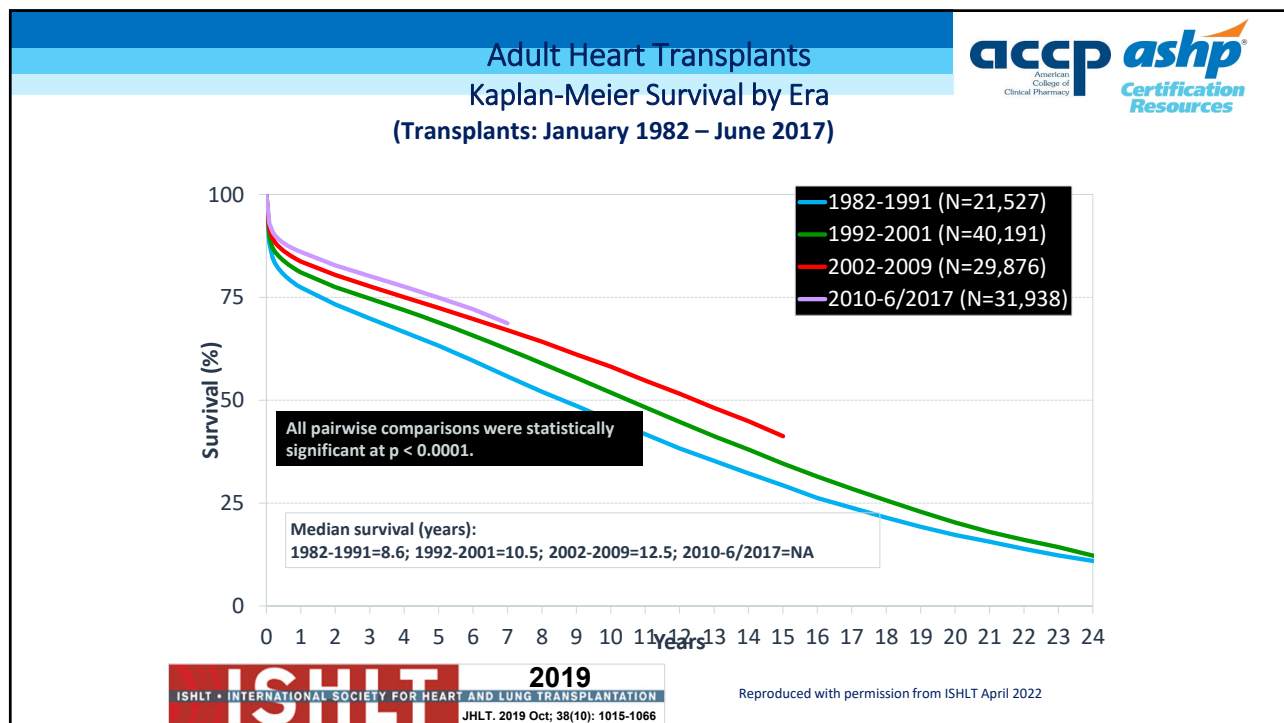
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## Background

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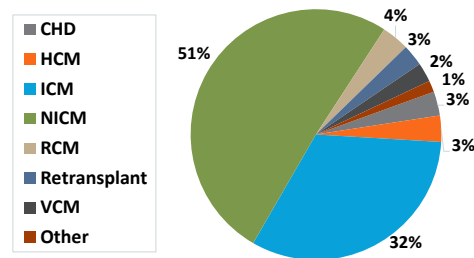
## Indication for Transplant

- Advanced heart failure
  - Refractory American Heart Association Stage D or NYHA class III-IV heart failure

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## Heart Transplantation

- Common Causes
  - Congenital Heart Disease
  - Hypertrophic Cardiomyopathy
  - Ischemic Cardiomyopathy
  - Non Ischemic Cardiomyopathy
  - Restrictive Cardiomyopathy
  - Retransplantation
  - Viral Cardiomyopathy
  - Other



1/2010 – 6/2018

JHLT. 2019 Oct; 38(10): 1015-1066

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## Question 1: Which of the following are indications for Heart Transplantation

- Arrhythmia
- Refractory American Heart Association Stage D or NYHA class III-IV heart failure
- Hypertrophic Cardiomyopathy
- Non Ischemic Cardiomyopathy

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## Question 1: Which of the following are indications for Heart Transplantation

- Arrhythmia
- Refractory American Heart Association Stage D or NYHA class III-IV heart failure
- Hypertrophic Cardiomyopathy
- Non Ischemic Cardiomyopathy

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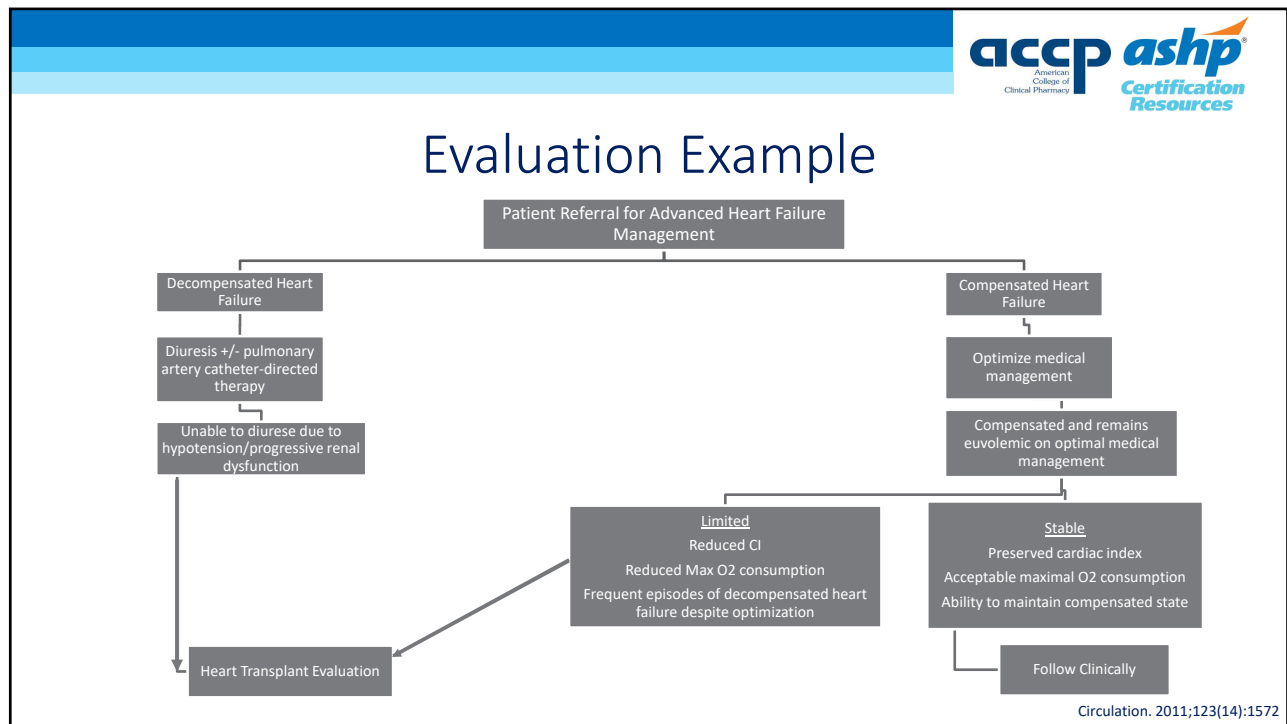
## Pre-Transplant

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## Patient Selection for Heart Transplantation

- The overriding principle is to select patients whose cardiac dysfunction substantially impairs their lifestyle and threatens their life span, but who do not have sufficient extracardiac comorbidities to importantly compromise post-transplant outcome
- Programs generally develop their own criteria

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## Example of Selection Criteria

- Candidates
  - Advanced heart failure with refractory New York Hospital Association class III and IV symptoms and markedly shortened life expectancy
  - Malignant ventricular arrhythmias unresponsive to standard therapies

Antman E. *Cardiovascular Therapeutics*. Philadelphia: Elsevier, 2013

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## Example of Selection Criteria

- Exclusion Criteria
  - Advanced age (>70)
  - Irreversible pulmonary hypertension (TPG >12 or 3 wood units)
  - Chronic noncardiac illness that compromises survival and functional recovery
  - Severe peripheral vascular disease
  - Morbid obesity
  - Active or recent malignancy
  - Active infection (excluding chronic drive line infections of mechanical circulatory support devices)
  - Human immunodeficiency virus seroconversion
  - Drug, tobacco, or alcohol abuse within the previous 6 months
  - Psychiatric or psychosocial instability

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## Common Contraindications

- |   |   |
|---|---|
| – Advanced Age  | – Active or recent malignancy             |
| – Irreversible Pulmonary Hypertension   | – Active Infection                        |
| – Non modifiable comorbid conditions which will compromise survival and functional recovery | – Ongoing substance abuse                 |
| – Severe peripheral vascular disease  | – Noncompliance                           |
| – Morbid obesity  | – Psychiatric or psychosocial instability |
| – Poor diabetic control   | – Poor diabetes control                   |
|   | – Cancer                                  |

Kobashigawa J. *Clinical Guide to Heart Transplantation*. Switzerland: Springer, 2017  
 Antman E. *Cardiovascular Therapeutics*. Philadelphia: Elsevier, 2013  
 JHLT. 2010;29:914-56

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## Cardiac Specific Testing for Evaluation

- Cardiopulmonary testing
  - Baseline and as indicated for ongoing care
- Diagnostic right heart catheterization
  - Baseline and at 3-6 month intervals
  - Vasodilator challenge in patients with PH
- Heart failure prognosis score
  - Considered in cases of ambiguity but not universally completed
- Special consideration testing
  - Infiltrative myopathies – RHC including biopsy
    - Amyloid- AL: Transthyretin related (TTR) may be considered
    - Autoimmune cardiomyopathy (giant cell, eosinophilic, etc)

J Heart Lung Transplant 2016;35(1):1-23

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## Question 2: Which of the following are common exclusion criteria for Heart Transplantation?

- Hepatitis B
- Gastric bypass
- Age >50
- Irreversible Pulmonary Hypertension

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- Hepatitis B
- Gastric bypass
- Age >50
- Irreversible Pulmonary Hypertension

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Heart Listing Status

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## Heart Listing Status

- UNOS implemented changes to the heart listing criteria in 2019
  - Expanded the number designations from 3 to 7
  - Status 1 is the most urgent
  - Status 6 is the least urgent
  - Status 7 is inactive
  - Adds specificity to patients current medical status
  - Better links status with acuity
  - Theoretically will increase organ utilization

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Previous wait list statuses

1A


1B

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### REVISED HEART WAITLIST STATUSES

<b>Status 1</b>	<ul style="list-style-type: none"> <li>• VA ECMO</li> <li>• Non-dischargeable, surgically implanted, non-endovascular biventricular support device</li> <li>• MCSO with life-threatening ventricular arrhythmia</li> </ul>
<b>Status 2</b>	<ul style="list-style-type: none"> <li>• Non-dischargeable, surgically implanted, non-endovascular LVAD</li> <li>• IABP</li> <li>• V-tach/V-fib, mechanical support not required</li> <li>• MCSO with device malfunction/mechanical failure</li> <li>• TAH, BVAD, RVAD, or VAD for single ventricle patients</li> <li>• Percutaneous endovascular MCSO</li> </ul>
<b>Status 3</b>	<ul style="list-style-type: none"> <li>• Dischargeable LVAD for discretionary 30 days</li> <li>• Multiple inotropes or single high-dose inotrope with continuous hemodynamic monitoring</li> <li>• VA ECMO after 7 days; percutaneous endovascular circulatory support device or IABP after 14 days</li> <li>• Non-dischargeable, surgically implanted, non-endovascular LVAD after 14 days</li> <li>• MCSO with one of the following:               <ul style="list-style-type: none"> <li>• Device infection</li> <li>• Hemolysis</li> <li>• Pump thrombosis</li> <li>• Right heart failure</li> <li>• Myocardial bleeding</li> <li>• Aortic insufficiency</li> </ul> </li> </ul>
<b>Status 4</b>	<ul style="list-style-type: none"> <li>• Dischargeable LVAD without discretionary 30 days</li> <li>• Inotropes without hemodynamic monitoring</li> <li>• Retransplant</li> <li>• Diagnosis of one of the following:               <ul style="list-style-type: none"> <li>• Congenital heart disease (CHD)</li> <li>• Ischemic heart disease with intractable angina</li> <li>• Hypertrophic cardiomyopathy</li> <li>• Restrictive cardiomyopathy</li> <li>• Amyloidosis</li> </ul> </li> </ul>
<b>Status 5</b>	<ul style="list-style-type: none"> <li>• On the waitlist for at least one other organ at the same hospital</li> </ul>
<b>Status 6</b>	<ul style="list-style-type: none"> <li>• All remaining active candidates</li> </ul>

Adult Heart Allocation Criteria for Medical Urgency Status: OPTN/UNOS 5/2018


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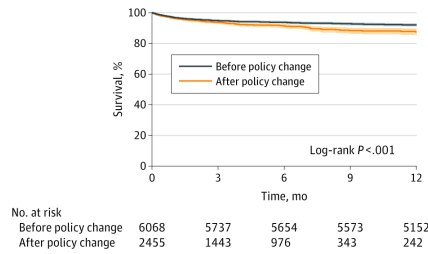
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## Impact of UNOS Allocation Policy Change

- Reduced time and mortality on waitlist
- Increased 1 year post transplant mortality (92.1% vs 87.5%)

Table 2. Comparison of Recipient, Donor, and Transplant-Related Characteristics at the Time of Transplant Before and After the Change in Heart Allocation Policy\*

Characteristic	Before change (n = 6078)	After change (n = 2801)	P value
Transplant Related			
Time on wait list, mean (SD), d	134.5 (162.6)	55.4 (83.0)	<.001
Donor hospital to transplant center distance, mean (SD), miles	157.3 (196.8)	279 (238.1)	<.001
Cold ischemic time, mean (SD), h	3.04 (1.05)	3.41 (1.00)	<.001
Status at transplant			
Old status			NA
1A	4159 (68.4)	NA	
1B	1746 (28.7)	NA	
2	173 (2.9)	NA	
New status			
1	NA	272 (9.7)	
2	NA	1446 (51.6)	
3	NA	544 (19.4)	
4	NA	430 (15.4)	
5	NA	0	
6	NA	108 (3.9)	



JAMA Cardiol 2021;6(2):159-167

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## Impact of UNOS Allocation Policy Change

- Patients with more urgent need (likely more ill) prioritized
  - Reduced number of patients transplanted off durable LVAD
  - Increased use of temporary mechanical support (ECMO, IABP, etc)
    - IABP: 5.1 vs 12.5%, p < 0.001
    - ECMO: 1.7 vs 2.8%, p < 0.001

JAMA Cardiol 2021;6(2):159-167

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## Risk Factors

### Donor risk

- Age
- Gender mismatch
- Size mismatch
- Left Ventricle thickness > 1.4 CM

J Heart Lung Transplant 2016;35(1):1-23  
J Heart Lung Transplant 2010 Aug;(29):914-56

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## Risk Factors

### Recipient risk

- Non-pharmacologic risk
  - » Age >70
  - » Comorbid conditions
    - HTN
    - Diabetes with end organ damage or HbA1c >7.5
    - Renal dysfunction
    - Obesity (BMI>35)
    - Vascular disease
    - Frailty

J Heart Lung Transplant 2010 Aug;(29):914-56

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## Additional Recipient Risk Factors

- Immunologic risk
  - Sensitization
    - Risk for AMR
    - Increased risk for coronary artery vasculopathy
- Pharmacologic risks
  - Anticoagulation
  - Tobacco
  - Drug interactions
  - Antiarrhythmic
    - Amiodarone

J Heart Lung Transplant 2010 Aug;(29):914-56

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## Amiodarone Use Pre-transplant

- Large Registry analysis
  - N=14955
  - Increased risk
    - 1 year mortality
    - Permanent pacemaker
    - Reoperation
  - No difference
    - Early graft failure
    - Retransplantation
    - Rehospitalization

J Heart Lung Transplant 2017 Feb;(36):202-210

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Question 3: Which of the following are risk factors that may impact post transplant outcomes?

- Ace Inhibitor use pre transplant
- Recipient age >50
- Reversible pulmonary hypertension
- Amiodarone use pre transplant

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Question 3: Which of the following are risk factors that may impact post transplant outcomes?

- Ace Inhibitor use pre transplant
- Recipient age >50
- Reversible pulmonary hypertension
- Amiodarone use pre transplant

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## Post-Transplant

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## Surgical Considerations

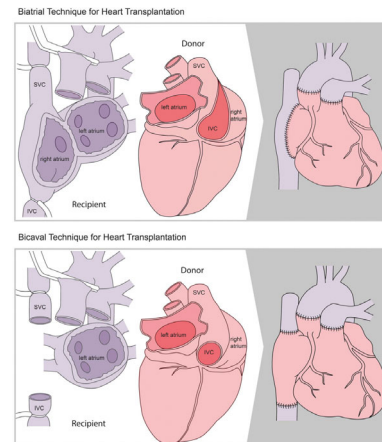
- Travel time
- Ischemic time
  - Ideal < 4 Hours with a maximum of 6 hours
- Organ Variables
  - Organ Size
    - Predicted heart mass
  - Gender match

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## Anastomosis type

- Two primary techniques
  - Biatrial vs Bicaval technique
    - Biatrial technique used more historically
    - Complications with biatrial anastomosis:
      - Mitral and aortic valve dysfunction
      - Arrhythmias/pacemaker need
      - Septal aneurysm
      - Thrombus formation
    - Bicaval technique results in improved atrial function; more routinely utilized in early-mid 2000's



Kobashigawa J. *Clinical Guide to Heart Transplantation*. Switzerland: Springer, 2017  
 Antman E. *Cardiovascular Therapeutics*. Philadelphia: Elsevier, 2013  
 Swiss Med Wkly. 2020;150:w20192

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## Point to Remember for Management

- Heart is now denervated
  - Dependent on circulating catecholamines to respond to stress
  - Slower response to exercise
  - Lower peak response to exercise
    - Due to some chronotropic incompetence; during exercise or if increased cardiac output is needed, stroke volume must increase to compensate
  - Atropine and digoxin do not have any effect on the denervated heart and should not be used to treat arrhythmias in heart transplant patients.
  - Beta blockers should be used cautiously because of risk for heart block

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## Organ Function

- Organ Function
  - Evaluation
    - Swan Ganz
      - » Cardiac Pressures
      - » CI/CO
      - » Heart Rate
      - » Central Venous Pressure
      - » Oxygen Saturation
    - ECHO
  - Management
    - Post Operative
      - » ICU--Chronotropic or Inotropic Support as required

J Heart Lung Transplant 2010 Aug;(29):914-56

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## ISHLT Recommendations for Post Operative Monitoring

- Post-operative 12 lead ECG
- Right atrial or central venous pressure monitoring
- Intermittent measures of cardiac output
- Intra-operative transesophageal echocardiogram
- Invasive arterial pressure monitoring
- Left atrial or pulmonary artery wedge pressure monitoring
- Arterial oxygen saturation monitoring
- Continuous assessment of urinary output

J Heart Lung Transplant 2010 Aug;(29):914-56

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## Vasoactive Post Operative Management

	Peripheral vasoconstriction	Cardiac contractility	Peripheral vasodilation	Chronotropic effect	Arrhythmia risk
Isoproterenol	0	++++	+++	++++	++++
Dobutamine	0	+++	++	+	+
Dopamine	++	+++	+	+	+
Epinephrine	+++	++++	+	++	+++
Milrinone	0	+++	+	++	++
Norepinephrine	++++	+++	0	+	+
Phenylephrine	++++	0	0	0	0
Vasopressin	++++	0	0	0	0

J Heart Lung Transplant 2010 Aug;(29):914-56

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## Common Post Operative Complications

- Early hemodynamic instability
  - Potential Causes
    - Primary graft dysfunction
    - Right ventricular dysfunction
    - Hyperacute rejection
    - Cardiac tamponade
    - Elevated pulmonary vascular resistance
- Bradycardia
  - Potential Cause
    - Sinus node dysfunction
    - Can utilize oral medications to mitigate (theophylline, terbutaline)
    - Rarely need for pacemaker

J Heart Lung Transplant 2010 Aug;(29):914-56  
 Kobashigawa J. *Clinical Guide to Heart Transplantation*. Switzerland: Springer, 2017

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## Common Post Operative Complications

- Tachyarrhythmias
  - Potential Cause
  - Rejection
- Renal Dysfunction
  - Potential cause
    - Preexisting cardiorenal syndrome
    - Hemodynamic instability
    - Nephrotoxic medications
    - Surgical complications

J Heart Lung Transplant 2010 Aug;(29):914-56  
 Kobashigawa J. *Clinical Guide to Heart Transplantation*. Switzerland: Springer, 2017

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Question 4: Which of the following is true regarding the transplant procedure and post transplant care?

- Ischemic time <8 hours is ideal
- Invasive atrial pressure monitoring is not required
- Surgical technique has no impact of post operative complications
- The heart is denervated

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## Question 4: Which of the following is true regarding the transplant procedure and post transplant care?

- Ischemic time <8 hours is ideal
- Invasive atrial pressure monitoring is not required
- Surgical technique has no impact of post operative complications
- **The heart is denervated**

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## Immunologic Risk

- Immunologic Risk
  - Acute Cellular rejection
    - Age
    - Race
    - Gender
  - Antibody Mediated Rejection
    - Donor specific antibodies
      - » Risk factor for coronary artery vasculopathy (CAV), rejection, and decreased allograft and patient survival
        - DSA prior to transplant
        - Development of denovo DSA
        - Patients with persistent denovo antibody appear to have the greatest risk of early mortality

Ann Thorac Surg. 2007;84(5):1556–62.  
 Hum Immunol. 2011;72(1):5–10.  
 JHLT.2016;35(1):87–91.  
 JHLT. 2015;34(10):1310–7.

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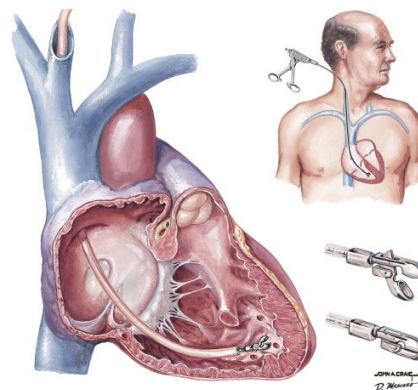
## Rejection Surveillance

- Rejection Surveillance
  - Endomyocardial Biopsy (EMB)
    - Pathology
      - » ACR
      - » AMR
  - Gene Expression Profiling (GEP)
  - Donor derived cell-free DNA (ddcfDNA)
  - Surveillance after treatment

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## Endomyocardial Biopsy (EMB)

- EMB
  - Transvenous endomyocardial biopsy
  - Usually 3-4 samples taken for staining
  - Gold standard to diagnose for ACR or AMR



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## ISHLT Adult Guidelines: Biopsies for rejection surveillance

Class IIa	Level of evidence
<b>First 6-12 months post-transplant</b>	
The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 post-operative months for surveillance of rejection.	<b>C</b>
<b>The 2<sup>nd</sup> to 5<sup>th</sup> post-operative year</b>	
Biopsies for surveillance for an extended period of time (eg, every 4–6 months) is recommended in HT recipients at higher risk for late acute rejection, to reduce the risk for rejection with hemodynamic compromise, and to reduce the risk of death in African-American recipients.	<b>C</b>
<b>Class IIb</b>	
<b>After the 5<sup>th</sup> post-operative year</b>	
Routine biopsies are optional, depending on clinical judgment and the risk for late allograft rejection.	<b>C</b>

J Heart Lung Transplant 2010 Aug;(29):914-56.

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## Pathology and Grading

ISHLT Acute Cellular Rejection Grading	
Grade 0 R	No rejection
Grade 1 R mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2 R moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R severe	Diffuse infiltrate with multifocal myocyte damage $\pm$ edema $\pm$ hemorrhage $\pm$ vasculitis

J Heart Lung Transplant 2005;24:1710-20

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## Pathology and Grading

**2013 ISHLT Pathology Grading of Antibody Mediated Rejection (AMR)**

Grade	Definition	Substrates
pAMR0	Neg for pathologic AMR	Histological and immunopathologic studies are both negative.
pAMR1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic are negative.
pAMR1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic are positive. (CD68+ and/or C4d+)
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with profound hemodynamic dysfunction and poor clinical outcomes.

J Heart Lung Transplant 2013;32:1147-62

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## Gene Expression Profiling

- Commercially available as AlloMap®
  - Panel of 20 gene assays, 11 informative and 9 used for normalization and/or quality control
  - Gene expression data used in the calculation of a test score
    - Integer ranging from 0 to 40
    - Compared with patients in the same post-transplant period, the lower the score, the lower the probability of acute cellular rejection at the time of testing
    - Common scores used as threshold for biopsy
      - 2-6 months post transplant: > 30
      - 6 months or more from transplant: ≥ 34
  - Can't use if:
    - Prednisone dose ≥ 20mg daily
    - Hematopoietic factors (filgrastim, epoetin) or blood transfusion in last 30 days

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## Gene Expression Profiling (GEP)

Study	Design	Primary Outcomes	Enrollment # patients	Timeframe Conducted
CARGO	Observational, Cohort, Prospective	Performance characteristics of GEP Test score correlated to centralized biopsy grades.	629	2001-2005
CARGO II	Observational, Cohort, Prospective	Performance characteristics of GEP Test score correlated to centralized biopsy grades and correlation of GEP score stability with clinical outcomes	741	2005-2009 2009-2012
IMAGE	Randomized, Prospective, Interventional	First occurrence of rejection with HDC, graft dysfunction due to other causes, death, or re-transplantation	602	2005-2009
EIMAGE	Randomized, Prospective, Interventional	First occurrence of rejection with HDC, graft dysfunction due to other causes, death, or re-transplantation and IVUS measurement	60	2009-2012

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## IMAGE Trial

### EMB compared to GEP for ACR

- Low risk patients only
- Primary endpoint
  - Rejection with hemodynamic compromise
  - Graft Dysfunction
  - Death or Re-transplantation
- Only useful for ACR surveillance
- Results
  - No difference in 2 year incidence of composite primary outcome
  - No difference in mortality

N Engl J Med 2010; 362:1890-1900

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## Non-Invasive Monitoring of Acute Heart Transplant Rejection

Class IIa	Level of evidence
<b>No Time Outlined</b>	
In centers with proven expertise in ventricular evoked potentials (VER) monitoring, intramyocardial electrograms recorded non-invasively with telemetric pacemakers can be used for rejection surveillance in patients at low risk for rejection.	<b>C</b>
<b>First 6 months -5 Years post-transplant</b>	
Gene Expression Profiling (Allomap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT.	<b>B</b>

J Heart Lung Transplant 2010 Aug;(29):914-56

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## Donor Derived Cell Free DNA (ddcfDNA)

- Multiple commercial products
  - Allosure® (CareDX)
  - Prospera® (Natera)
- Measure ddcfDNA in blood to determine potential myocyte damage

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## Donor Derived Cell Free DNA (ddcfDNA)

- D-OAR registry
  - Patients > 15 years old, > 55 days from transplant undergoing GEP surveillance
  - Paired with biopsy (841 samples)
    - Median level of ddcfDNA higher in patients with rejection
      - ACR 1R/OR = 0.08%; ACR 2R = 0.15%; ACR 3R = 0.3% (p=0.04)
      - AMR0 = 0.7%; AMR1 = 0.12%; AMR2 = 0.25% (p=0.249)
  - Negative predictive value 97.3%
  - Positive predictive value 8.1%

Am J Transplant 2019; 19:2889-2899

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## Donor Derived Cell Free DNA (ddcfDNA)

- GRAFT study
  - Prospective cohort study (n= 165) with paired plasma samples and EmBx
    - Approximately 8 EmBx performed per patient over 17.7 months
  - Median ddcfDNA after day 28 significantly higher in rejection/severe graft dysfunction

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**Table 2.** %ddcfDNA for Primary and Secondary End Points From Day 28 Onward

Clinical end point	Number of events	Subjects with events	Median %ddcfDNA	%ddcfDNA inter-quartile range (%)	P value
Controls (ACR 0, ACR 1, AMR 0)	1072	165	0.03	0.01–0.14	—
Acute rejection	49	31	0.38	0.31–0.83	<0.001*
ACR					
Grade 0	618	165	0.02	0.01–0.13	—
Grade 1	454	165	0.04	0.01–0.17	0.023†
Grade ≥2	28	21	0.34	0.28–0.72	<0.001†
AMR					
Grade 0	1072	165	0.03	0.01–0.14	—
Grade 1	14	9	0.63	0.34–0.77	<0.001‡
Grade ≥2	11	9	1.68	0.49–2.79	<0.001‡
Allograft dysfunction					
None	866	165	0.02	0.01–0.12	—
Mild	168	83	0.06	0.01–0.27	0.068§
Moderate	62	49	0.19	0.01–0.60	0.018§
Severe	38	28	0.32	0.05–0.47	<0.001§

**Table 3.** %ddcfDNA Test Characteristics to Detect Biopsy-Positive Acute Rejection: Eliminated Biopsies Before Day 28 After Transplantation

Variable	Sensitivity (%)			Specificity (%)			Area under the receiver operator characteristics curve
%ddcfDNA threshold	0.1	0.25	0.5	0.1	0.25	0.5	(95% CI)
Acute rejection diagnosis							
Acute rejection	95	81	41	68	85	92	0.92 (0.88–0.95)
Antibody-mediated rejection	100	88	65	68	85	92	0.95 (0.90–0.99)
Acute cellular rejection	89	79	21	68	85	92	0.89 (0.83–0.95)

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## Example Heart Transplant Rejection Surveillance Schedule

Time Post Transplant	Month 1	Month 2	Months 3–6	Months 7–12	Years 1–3	> 3 years
Biopsy or GEP/ddcfDNA testing	Weekly after POD7–10	Every 2 weeks	Every 4 Weeks	Every 2 Months	Every 4 Months	None unless clinically indicated

\*Surveillance post-rejection varies per center, but RHC/Bx usually done 1–3 weeks after treatment

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Question 5: Which of the following are true regarding rejection surveillance?

- Monthly Endomyocardial biopsy should be continued indefinitely
- Gene expression profiling is non inferior to endomyocardial biopsy when comparing death, hemodynamic rejection and graft dysfunction
- There are 4 acute cellular rejection pathology grades: 1-4R
- Antibody mediated rejection grading only includes histologic findings

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Question 5: Which of the following are true regarding rejection surveillance?

- Monthly Endomyocardial biopsy should be continued indefinitely
- Gene expression profiling is non inferior to endomyocardial biopsy when comparing death, hemodynamic rejection and graft dysfunction
- There are 4 acute cellular rejection pathology grades: 1-4R
- Antibody mediated rejection grading only includes histologic findings

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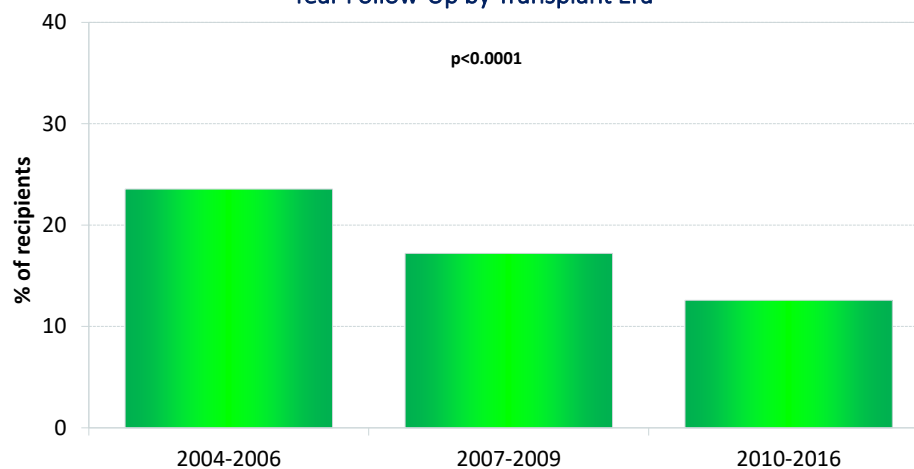
## Complications

- Complications
  - Immunologic
    - ACR
    - AMR
    - De novo* antibodies
    - Amnestic response

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### Adult Heart Transplants

% of Recipients Experiencing Treated Rejection Between Transplant Discharge and 1-Year Follow-Up by Transplant Era



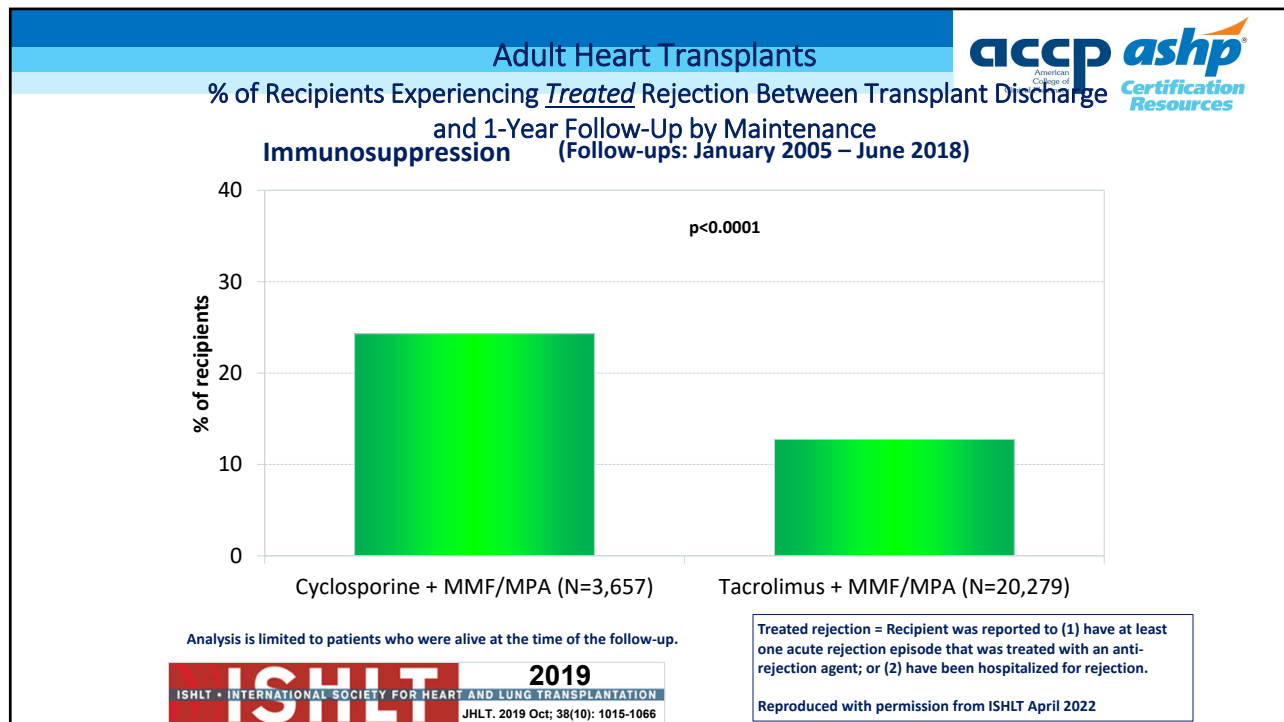
Analysis is limited to patients who were alive at the time of the follow-up.

**ISHLT** 2019  
 ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION  
 JHLT. 2019 Oct; 38(10): 1015-1066

Treated rejection = Recipient was reported to (1) have at least one acute rejection episode that was treated with an anti-rejection agent; or (2) have been hospitalized for rejection.

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## Complications

- Non- Immunologic
  - Coronary Artery Vasculopathy (CAV)
  - Renal dysfunction
  - Diabetes
  - Cancer
  - Lipids
  - HTN

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<div> <div>   </div> <div> <b>Adult Heart Transplants</b>            Cumulative Morbidity Rates in <u>Survivors</u> within 1, 5 and 10            Years Post Transplant (Transplants: January 1995 – June 2017)         </div> </div>						
Outcome	Within 1 Year	Total N with known response	Within 5 Years	Total N with known response	Within 10 Years	Total N with known response
Severe Renal Dysfunction <sup>1</sup>	6.7%	(N=39,544)	15.7%	(N=22,462)	22.3%	(N=9,195)
Creatinine > 2.5 mg/dl	5.1%		12.2%		14.3%	
Chronic Dialysis	1.5%		2.9%		6.0%	
Renal Transplant	0.1%		0.6%		2.0%	
Diabetes <sup>2</sup>	20.0%	(N=39,834)	33.8%	(N=22,720)	-	
Cardiac Allograft Vasculopathy	7.7%	(N=36,774)	29.0%	(N=17,392)	46.8%	(N=5,962)



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<sup>1</sup> Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 μmol/L), dialysis, or renal transplant  
<sup>2</sup> Data are not available 10 years post-transplant.  
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<div> <div>   </div> <div> <b>Coronary Artery Vasculopathy(CAV)</b> </div> </div>						
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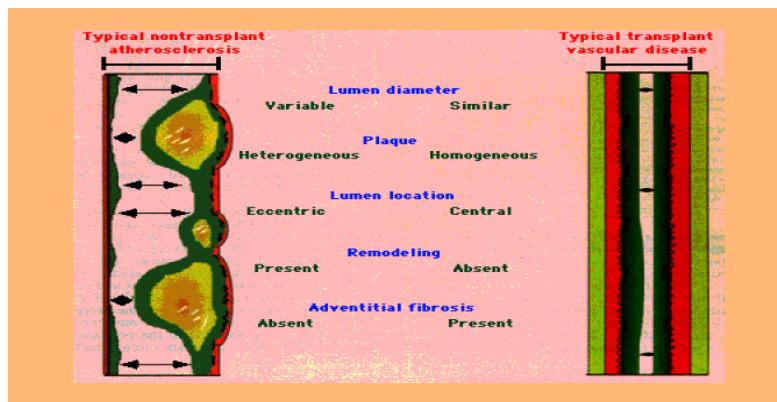


## CAV

- Significant impact on patient and graft survival
  - 29% develop within 5 years
  - 46% develop within 10 years
  - Multifactorial process including immunologic and non-immunologic mechanisms
- Risk factors include
- AMR
  - ACR
  - Presence of DSA
  - Advanced donor age
  - HTN
  - Hyperlipidemia
  - CMV infection
  - Diabetes

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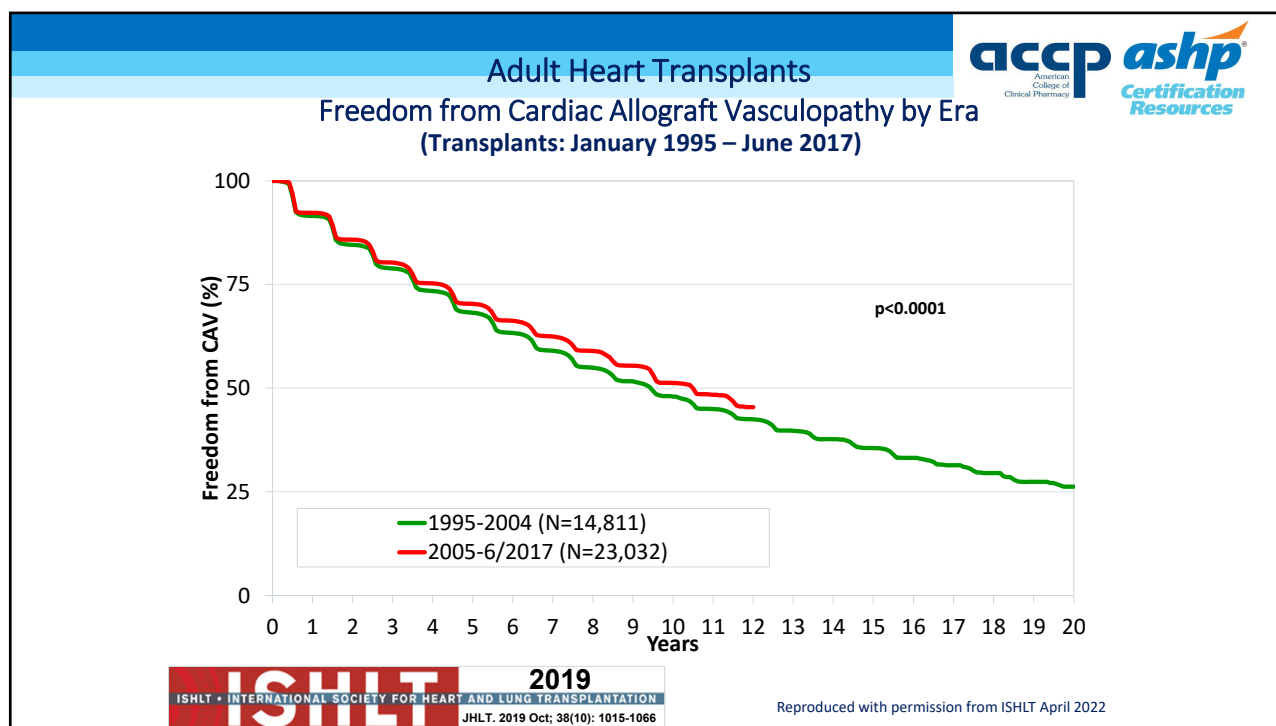
## CAV



### Natural atherosclerosis versus posttransplant vascular disease

Schematic representation of the anatomic differences between nontransplant atherosclerosis and posttransplant vascular disease. (Redrawn from Arbustini, E, Roberts, WC, Am J Cardiol 1996; 78:814.)

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**ISHLT CAV Nomenclature**

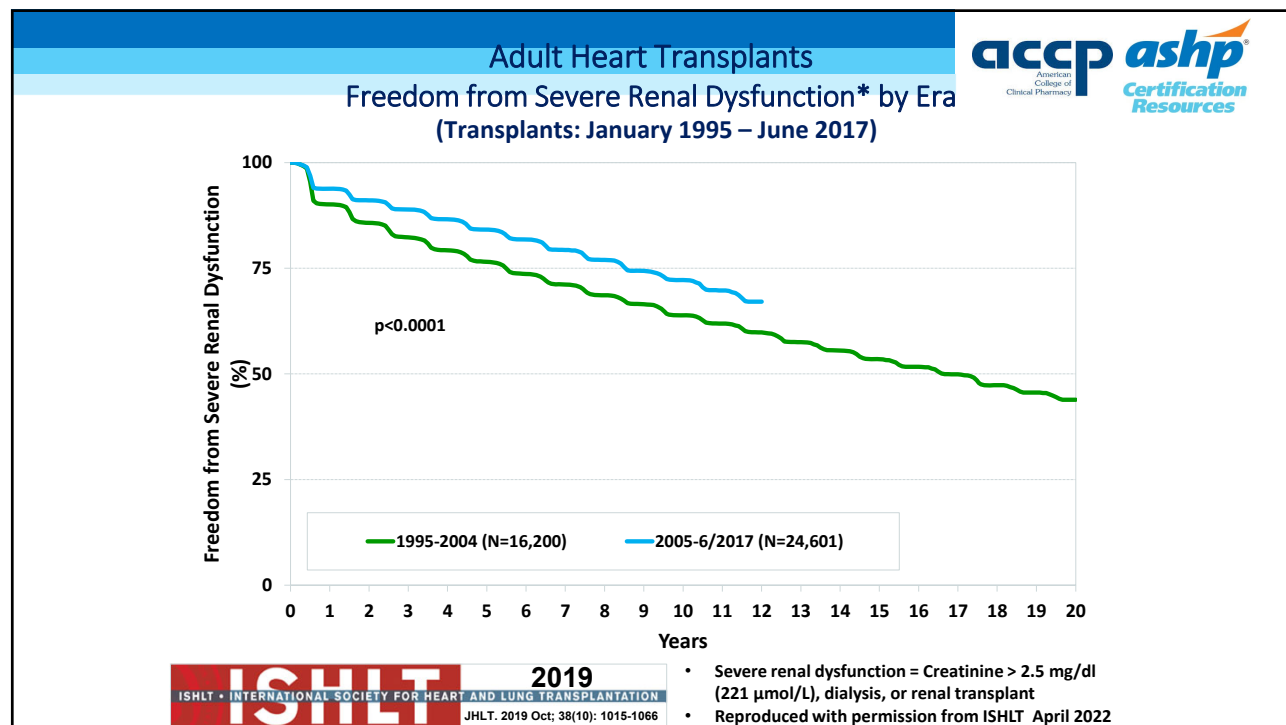
CAV	Description
ISHLT CAV0 (Not significant)	No detectable angiographic lesion
ISHLT CAV1 (Mild)	Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
ISHLT CAV2 (Moderate)	Angiographic LM ≤50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction
ISHLT CAV3 (Severe)	Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific;)

J Heart Lung Transplant 2010 Aug;(29):914-56

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## Renal Dysfunction

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## Cancer

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### Adult Heart Transplants

#### Post Transplant Malignancy (Transplants: January 1995 – June 2017)


##### Cumulative Morbidity Rates in Survivors



Malignancy/Type		1-Year Survivors	5-Year Survivors	10-Year Survivors
No Malignancy		38,866 (94.9%)	20,974 (84%)	8,466 (72.3%)
Malignancy (all types combined)		2,068 (5.1%)	3,997 (16%)	3,238 (27.7%)
<i>Malignancy Type*</i>	<i>Skin</i>	695 (1.7%)	2,395 (9.6%)	2,166 (18.5%)
	<i>Lymphoma</i>	190 (0.5%)	262 (1%)	200 (1.7%)
	<i>Other</i>	1,148 (2.8%)	1,562 (6.3%)	1,192 (10.2%)
	<i>Type Not Reported</i>	35 (0.1%)	28 (0.1%)	16 (0.1%)

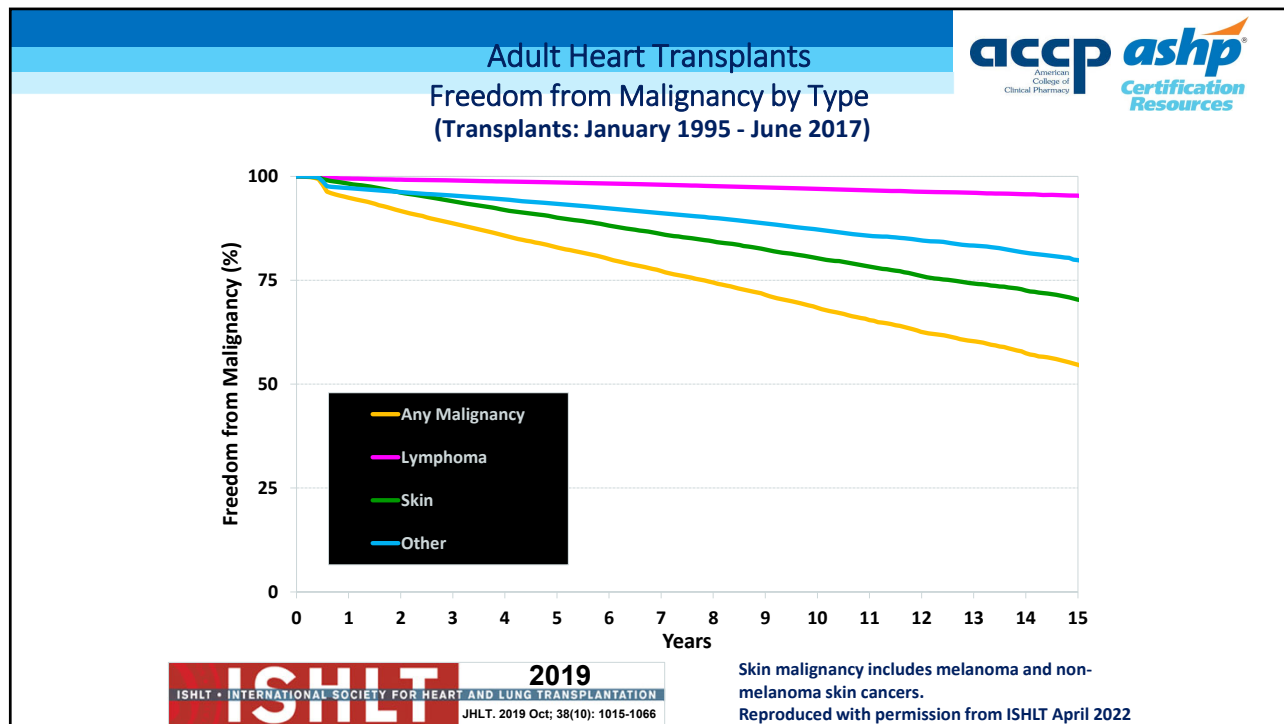
“Other” includes: prostate (8,18,9), adenocarcinoma (5, 2, 1), lung (6, 4, 1), bladder (2, 2, 0), Kaposi's sarcoma (0, 1, 0), breast (1, 3, 1), cervical (2, 3, 2), colon (0,3, 2), and renal (2, 4, 1). Numbers in parentheses are those reported within 1 year, 5 years and 10 years, respectively.

\* Recipients may have experienced more than one type of malignancy so the sum of individual malignancy types may be greater than the total number with malignancy.



Skin malignancy includes melanoma and non-melanoma skin cancers.  
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**Hyperlipidemia**

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## Hyperlipidemia

- Statins are a cornerstone of post transplant care
  - Prolong survival
  - Reduce incidence of CAV
  - Induce regression of existing atherosclerotic disease
- There is debate if this is exclusively related to statins pleotropic effects or LDL reduction
  - Current ISHLT guidelines do not provide LDL goals
  - Retrospective literature exists evaluating potential links of goal based LDL reduction to a decreased risk of CAV. Additional studies are required.

**Recommended Statin Doses in Heart Transplant Patients**

Drug	Dose (mg)	Risks
Pravastatin	20-25	Myositis (lower)
Simvastatin	5-20; >20mg not recommended	Myositis (higher)
Atorvastatin	10-20	Myositis (higher)
Fluvastatin	40-80	Myositis (lower)
Lovastatin	20	Myositis (higher)
Rosuvastatin	5-20	Myositis

J Heart Lung Transplant 2010;29:914-956  
 Clin tran. 2018. May;32(5):e13248  
 N Engl J Med 1995; 333: 621-27  
 Circulation 1997; 96:1398-1402.

Kobashigawa J. *Clinical Guide to Heart Transplantation*. Switzerland: Springer, 2017

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## Hypertension


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## Hypertension

- Heart transplant specific goals not established
  - Follow national guidelines based on comorbid conditions
- Medication choice important
  - Beta blockers are not contraindicated
  - Slow dose titration is necessary

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Adult Heart Transplants							
Cause of Death (Deaths: January 1995 – June 2018)							
Cause of Death	0-30 Days (N=6,871)	31 Days - 1 Year (N=5,980)	>1-3 Years (N=4,211)	>3-5 Years (N=3,630)	>5-10 Years (N=9,441)	>10-15 Years (N=7,108)	>15 Years (N=5,695)
Cardiac Allograft Vasculopathy	83 (1.2%)	190 (3.2%)	456 (10.8%)	449 (12.4%)	1,153 (12.2%)	859 (12.1%)	598 (10.5%)
Acute Rejection	268 (3.9%)	474 (7.9%)	412 (9.8%)	171 (4.7%)	176 (1.9%)	67 (0.9%)	29 (0.5%)
PTLD	2 (0.0%)	57 (1.0%)	94 (2.2%)	105 (2.9%)	305 (3.2%)	189 (2.7%)	121 (2.1%)
Malignancy (non-PTLD)	4 (0.1%)	137 (2.3%)	517 (12.3%)	712 (19.6%)	2,081 (22.0%)	1,525 (21.5%)	1,103 (19.4%)
CMV	3 (0.0%)	51 (0.9%)	19 (0.5%)	5 (0.1%)	8 (0.1%)	6 (0.1%)	2 (0.0%)
Infection, Non-CMV	958 (13.9%)	1,904 (31.8%)	561 (13.3%)	394 (10.9%)	1,023 (10.8%)	788 (11.1%)	702 (12.3%)
Graft Failure	2,716 (39.5%)	1,052 (17.6%)	1,112 (26.4%)	884 (24.4%)	1,838 (19.5%)	1,231 (17.3%)	944 (16.6%)
Technical	494 (7.2%)	94 (1.6%)	30 (0.7%)	28 (0.8%)	93 (1.0%)	85 (1.2%)	73 (1.3%)
Multiple Organ Failure	1,274 (18.5%)	1,006 (16.8%)	268 (6.4%)	209 (5.8%)	650 (6.9%)	599 (8.4%)	530 (9.3%)
Renal Failure	32 (0.5%)	53 (0.9%)	56 (1.3%)	113 (3.1%)	512 (5.4%)	569 (8.0%)	562 (9.9%)
Pulmonary	183 (2.7%)	235 (3.9%)	179 (4.3%)	163 (4.5%)	445 (4.7%)	336 (4.7%)	292 (5.1%)
Cerebrovascular	538 (7.8%)	332 (5.6%)	158 (3.8%)	119 (3.3%)	446 (4.7%)	387 (5.4%)	319 (5.6%)
Other	316 (4.6%)	395 (6.6%)	349 (8.3%)	278 (7.7%)	711 (7.5%)	467 (6.6%)	420 (7.4%)
Total Deaths (N)	7,759	6,912	5,223	4,607	12,586	10,268	8,531



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Percentages represent % of deaths in the respective time period.  
 Total number of deaths includes deaths with unknown causes.  
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Question 6: Which of the following are true regarding post transplant complications?

- The most common cause of death in patients whom live at least 5 years in CMV infection
- Statin therapy has been shown to increase survival and decrease the risk of CAV
- The use of beta blockers in contraindicated
- Immunologic factors have no effect on development of CAV

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Question 6: Which of the following are true regarding post transplant complications?

- The most common cause of death in patients whom live at lease 5 years in CMV infection
- Statin therapy has been shown to increase survival and decrease the risk of CAV
- The use of beta blockers in contraindicated
- Immunologic factors have no effect on development of CAV

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## Key Takeaways

- Primary indication is Refractory American Heart Association Stage D or NYHA class III-IV heart failure
- There are 7 status for heart listing. 1 (most urgent) - 7 (inactive)
- Risk factors include; advanced donor/recipient age, gender/size mismatch, CIT >4 hours, comorbid conditions and sensitization
- The transplanted heart is denervated
- Current rejection surveillance techniques includes both EMB and GEP
- Common causes of post transplant morbidity and mortality include, CAV, malignancy, renal dysfunction
- Statin therapy increases survival and decreased risk of CAV

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## Heart Transplantation

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