Forum on
U.S. Heart Allocation Policy

Friday, November 15th, 2013

Dallas Marriott City Center
Dallas, Texas

Conference Chair:
Jon Kobashigawa, MD

Conference Co-Chairs:
Maryl Johnson, MD
Joseph Rogers, MD
J. David Vega, MD

Conference Advisors:
Monica Colvin-Adams, MD
Leah Edwards
Dan Meyer, MD
Steven Webber, MD

CEDARS-SINAI Heart Institute

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

Forum on U.S. Heart Allocation Policy

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FORUM ON U.S. HEART ALLOCATION POLICY

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MORNING SESSION
Moderators: Maryl Johnson, MD and Jon Kobashigawa, MD

8:20 AM	History of Heart Allocation Policy in the United States and the Current U.S. Heart Allocation Algorithm - **Dan Meyer, MD**
8:40 AM	Heart Allocation Policy in Canada and Europe: Lessons Learned **Anne Dipchand, MD**
9:00 AM	Regional Differences in Wait Times, Deaths on the Waiting List, Numbers of Donors and MCS Use - **Donna Mancini, MD**
9:20 AM	Special Populations at Risk of Mortality on the Heart Transplant Waiting List: Reviewing the Data - **Monica Colvin-Adams, MD**
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MID-MORNING SESSION
Moderators: Joseph Rogers, MD and J. David Vega, MD

10:40 AM	Current Status of MCS Patients on the Heart Transplant Waiting List **Maryl Johnson, MD**
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LUNCH SESSION - CONCOMMITANT BREAKOUT GROUPS

12:45 PM - 2:30 PM	**Breakout Group 1** (Plaza Ballroom C) Moderators: Maryl Johnson, MD and Dan Meyer, MD
	Breakout Group 2 (Nice Meeting Room) Moderators: Joseph Rogers, MD and David Feldman, MD
	Breakout Group 3 (Normandy Meeting Room A) Moderators: J. David Vega, MD and Monica Colvin-Adams, MD
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2:30 PM - 3:00 PM	BREAK

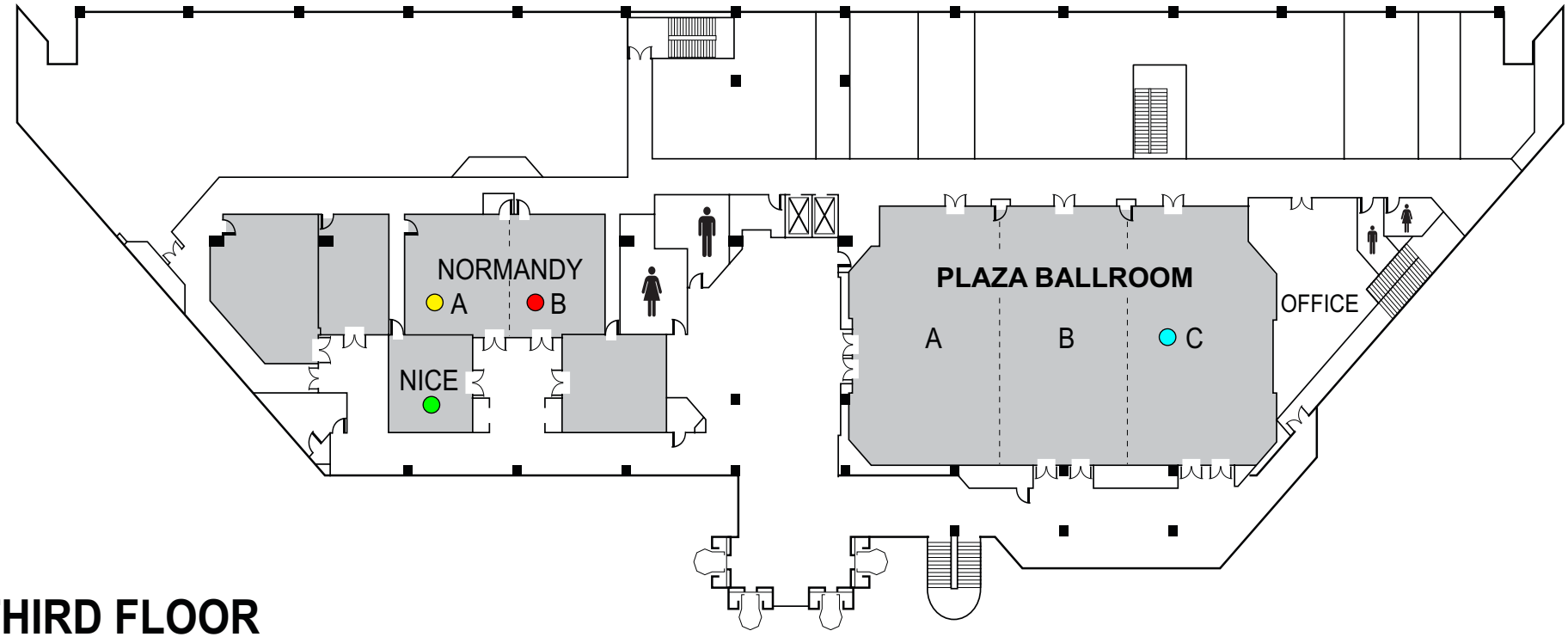
AFTERNOON SESSION
Moderator: Jon Kobashigawa, MD

3:00 PM	Discussion Forum (Full Session)
4:45 PM	Conference Summary
5:00 PM	Adjourn

Marriott
DALLAS CITY CENTER

Main Meeting Room: Plaza Ballroom "C"

Breakout Group #1: Plaza Ballroom "C"
Breakout Group #2: Nice Meeting Room
Breakout Group #3: Normandy "A" Meeting Room
Breakout Group #4: Normandy "B" Meeting Room



THIRD FLOOR

FORUM ON US. HEART ALLOCATION POLICY

BREAKOUT GROUP 1
(Plaza Ballroom "C")

Moderators:
Maryl Johnson/Dan Meyer

Luis Arroyo
Patricia Chang
Christian Bermudez
A. Michael Borkon
Todd Dardas
Shashank Desai
Anne Dipchand
Leah Edwards
Ranjit John
JoAnn Lindenfeld
Srinivas Murali
Pat Niles
JigneshPatel
Sean Pinney
Marc Semigran
Nicholas Smedira
Guillermo Torre-Amione
Jose Tallaj
Adrian Van Bakel

BREAKOUT GROUP 2
(Nice Meeting Room)

Moderators:
David Feldman/Joseph Rogers

Francisco Arabia
John Chin
Joseph Cleveland
David D'Allesandro
Eugene Depasquale
Mark Drazner
Howard Eisen
Jerry Estep
Dan Fishbein
Howard Gebel
Ray Hershberger
Jeffrey Hosenspud
Denise Kinder
Joren Madsen
Donna Mancini
Michael Pham
Mark Wigger
Mark Zucker

BREAKOUT GROUP 3
(Normandy Room "A")

Moderators:
Monica Colvin-Adams/J. David Vega

David Baran
Marco Caccamo
Teresa DeMarco
Fardad Esmailain
Gregory Ewald
Alain Heroux
Valluvan Jeevanandam
Andrew Kao
Abeel Mangi
David Nelson
Kevin O'Connor
Francis Pagani
John Ransom
Elaine Reed
Liset Stoletniy
Jeffrey Teuteberg
Sean VanSlyk
Hector Ventura
Mary Norine Walsh

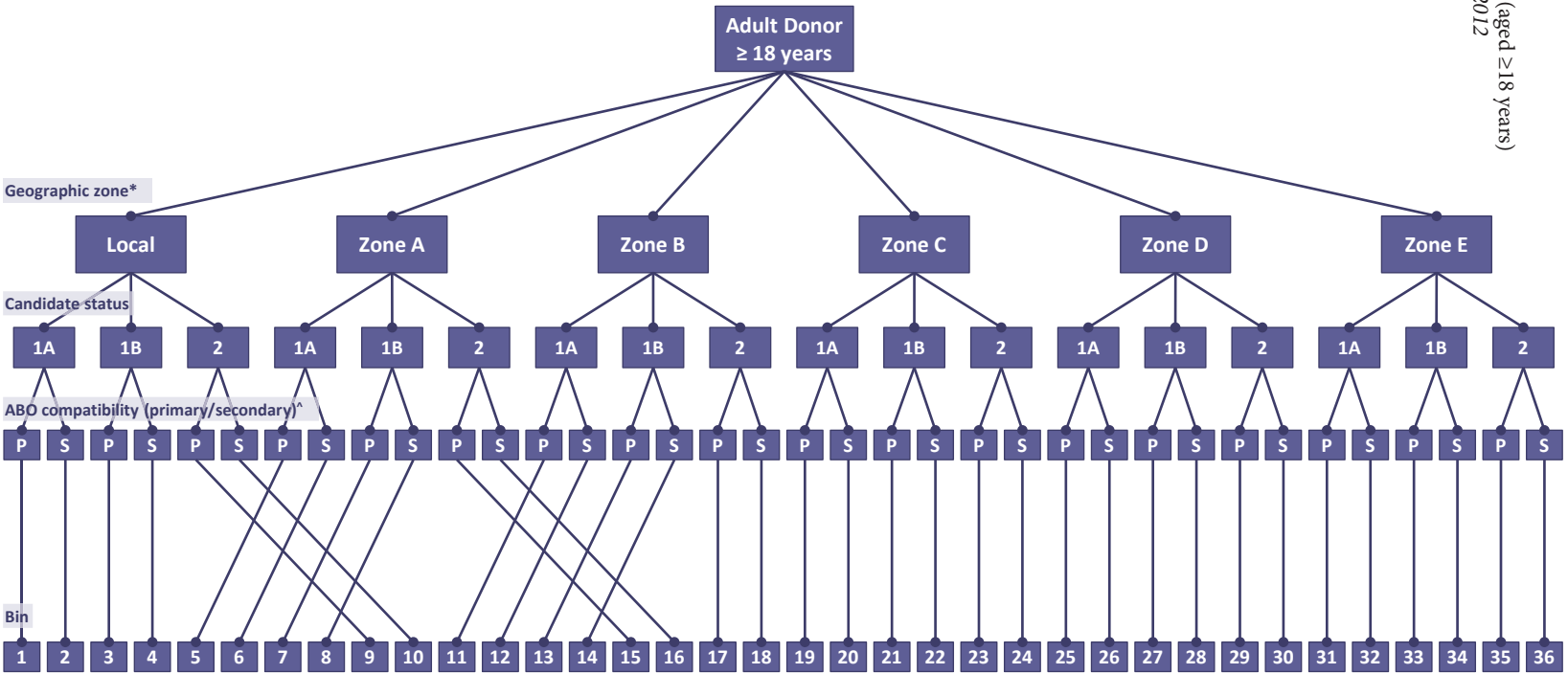
BREAKOUT GROUP 4
(Normandy Room "B")

Moderators:
Robert Kormos/Steven Webber

Allan Anderson
Jack Copeland
Richard Daly
Prasad Garimella
Alan Gass
Jason Gluck
Shelley Hall
Bertram Kasiske
A.G. Kfoury
James Kirklin
Les Miller
Myung Park
Tammie Peterson
Barbara Pisani
Nancy Reinsmoen
Liz Robbins
Andrew Smith
Lynne Stevenson
Dolly Tyan

CURRENT U.S. HEART ALLOCATION ALGORITHM

HEART
Adult donor (aged ≥18 years)
as of March 2012



Hearts will be allocated within priority bin to candidates with the longest active waiting time within current medical urgency status or higher status

* Geographic zones are defined by the distance between the donor hospital and transplant centers.
Local: same donor service area
Zone A: 0 – 500 miles
Zone B: > 500 – 1000 miles
Zone C: > 1000 – 1500 miles
Zone D: > 1500 – 2500 miles
Zone E: > 2500 miles

^ Primary includes all donor/candidate ABO pairs as shown in policy 3.7.8 (i)-(iv). All other compatible donor/candidate ABO pairs are secondary. Primary includes all 4 identical combinations and O donor/B candidate, A donor/AB candidate, and B donor/AB candidate. Secondary includes only O donor/A candidate and O donor/AB candidate.

Although unlikely, the match run for an adult donor heart can include ABO incompatible and in utero candidates. Although not shown above, these candidates would fall into bins 37- 62 according to the corresponding rules shown in the heart allocation flow chart for pediatric donors.

Table 4: Comparison of historical and current heart allocation policies[1]

Component	Policies		
	1989–1999	1999	Current
Medical urgency	2-tiered, Status 1 and 2	3-tiered, Status 1A, 1B and 2	Status 1A, 1B and 2
Geographic sequence	Local, zone A, zone B, zone C	Local, zone A, zone B, zone C	Adult donors: OPO Status 1A, 1B; zone A Status 1A, 1B; local Status 2 (Figure 5). Pediatric donors: combined OPO and zone A Status 1A pediatric; OPO Status 1A adult; OPO + zone A Status 1B pediatric; OPO Status 1B adult; zone A Status 1A, zone A Status 1B (Figure 6).
ABO blood type	Identical/compatible not differentiated for Status 1; differentiated for Status 2, identical prioritized for Status 2	Primary ABO prioritized before secondary ABO within each Status category	Primary ABO prioritized before secondary ABO within each status category; allocation to candidates eligible to receive a heart from any blood type donor after allocation to all compatible blood types
Time waiting	Status 1 time = Status 1 time; Status 2 time = Status 1 + Status 2 time	Status 1A time = Status 1A time; Status 1B time = Status 1A + 1B time; Status 2 time = Status 1A + 1B + 2 time	Status 1A time = Status 1A time; Status 1B time = Status 1A + 1B time; Status 2 time = Status 1A + 1B + 2 time
Heart–lung	Separate category, allocated after Status 1 heart	May be on both heart and lung lists; lungs go with heart or heart goes with lungs if no Status 1A heart candidate	May be on both heart and lung lists; lungs go with heart or heart goes with lungs if no Status 1A heart candidate
Pediatric considerations	Age < 6 months may be Status 1	Separate urgency criteria, preference to pediatric recipient for adolescent donor	Separate urgency criteria, preference to pediatric candidate for pediatric donor
Sensitized patients	Local agreement	Local agreement	Local agreement
Monitoring issues	Status 1 random audits of ICU location	Regional review boards for assignment of status; random audits of justification forms	Regional review boards for exceptions to Status 1A and 1B; random audits for Status 1A and Status 1B justification forms

OPO = organ procurement organization.
Status 1, candidates requiring total artificial heart, left or right ventricular assist device, intraaortic balloon pump, ventilator, or in intensive care unit requiring inotrope therapy; Status 2, all other actively listed candidates. Geographic zones: Local, donation service area; zone A, < 500 nautical mile radius of donor hospital; zone B, 500-< 1000 miles; zone C, 1000–1500 miles; zone D, 1501–2500 miles; zone E > 2500 miles. Pediatric heart donor is defined as age < 18 years; pediatric heart candidate is defined as age < 18 years at the time of listing. Primary ABO compatibility includes all four identical combinations (O donor/O candidate, A donor/A candidate, B donor/B candidate, AB donor/AB candidate) and O donor/B candidate, A donor/AB candidate, and B donor/AB candidate; secondary ABO compatibility includes O donor/A candidate and O donor/AB candidate; ABO identical includes O donor/O candidate, A donor/A candidate; B donor/B candidate, AB donor/AB candidate; ABO compatible includes O donor/A, B, or AB candidate and A donor/O candidate, B donor/O candidate.
[1]Adapted from Renlund et al. (20).

TITLE 42--Public Health
CHAPTER I--PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER K--HEALTH RESOURCES DEVELOPMENT
PART 121--ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK

§ 121.8 Allocation of organs.

(a) *Policy development.* The Board of Directors established under § 121.3 shall develop, in accordance with the policy development process described in § 121.4, policies for the equitable allocation of cadaveric organs among potential recipients. Such allocation policies:

(1) Shall be based on sound medical judgment;

(2) Shall seek to achieve the best use of donated organs;

(3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with § 121.7(b)(4)(d) and (e);

(4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate;

(5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;

(6) Shall be reviewed periodically and revised as appropriate;

(7) Shall include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program; and

(8) Shall not be based on the candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section.

(b) *Allocation performance goals.* Allocation policies shall be designed to achieve equitable allocation of organs among patients consistent with paragraph (a) of this section through the following performance goals:

(1) Standardizing the criteria for determining suitable transplant candidates through the use of minimum criteria (expressed, to the extent possible, through objective and measurable medical criteria) for adding individuals to, and removing candidates from, organ transplant waiting lists;

(2) Setting priority rankings expressed, to the extent possible, through objective and measurable medical criteria, for patients or categories of patients who are medically suitable candidates for transplantation to receive transplants. These rankings shall be ordered from most to least medically urgent (taking into account, in accordance with paragraph (a) of this section, and in particular in accordance with sound medical judgment, that life sustaining technology allows alternative approaches to setting priority ranking for patients). There shall be a sufficient number of categories (if categories are used) to avoid grouping together patients with substantially different medical urgency;

(3) Distributing organs over as broad a geographic area as feasible under paragraphs (a)(1)-(5) of this section, and in order of decreasing medical urgency; and

(4) Applying appropriate performance indicators to assess transplant program performance under paragraphs (c)(2)(i) and (c)(2)(ii) of this section and reducing the inter-transplant program variance to as small as can reasonably be achieved in any performance indicator under paragraph (c)(2)(iii) of this section as the Board determines appropriate, and under paragraph (c)(2)(iv) of this section. If the performance indicator “waiting time in status” is used for allocation purposes, the OPTN shall seek to reduce the inter-transplant program variance in this indicator, as well as in other selected performance indicators, to as small as can reasonably be achieved, unless to do so would result in transplanting less medically urgent patients or less medically urgent patients within a category of patients.

(c) *Allocation performance indicators.* (1) Each organ-specific allocation policy shall include performance indicators. These indicators must measure how well each policy is:

(i) Achieving the performance goals set out in paragraph (b) of this section; and

(ii) Giving patients, their families, their physicians, and others timely and accurate information to assess the performance of transplant programs.

(2) Performance indicators shall include:

(i) Baseline data on how closely the results of current allocation policies approach the performance goals established under paragraph (b) of this section;

(ii) With respect to any proposed change, the amount of projected improvement in approaching the performance goals established under paragraph (b) of this section;

(iii) Such other indicators as the Board may propose and the Secretary approves; and

(iv) Such other indicators as the Secretary may require.

(3) For each organ-specific allocation policy, the OPTN shall provide to the Secretary data to assist the Secretary in assessing organ procurement and allocation, access to transplantation, the effect of allocation policies on programs performing different volumes of transplants, and the performance of OPOs and the OPTN contractor. Such data shall be required on performance by organ and status category, including program-specific data, OPO-specific data, data by program size, and data aggregated by organ procurement area, OPTN region, the Nation as a whole, and such other geographic areas as the Secretary may designate. Such data shall include the following measures of inter-transplant program variation: risk-adjusted total life-years pre-and post-transplant, risk-adjusted patient and graft survival rates following transplantation, risk-adjusted waiting time and risk-adjusted transplantation rates, as well as data regarding patients whose status or medical urgency was misclassified and patients who were inappropriately kept off a waiting list or retained on a waiting list. Such data shall cover such intervals of time, and be presented using confidence intervals or other measures of variance, as may be required to avoid spurious results or erroneous interpretation due to small numbers of patients covered.

(d) *Transition patient protections*— (1) *General.* When the OPTN revises organ allocation policies under this section, it shall consider whether to adopt transition procedures that would treat people on the waiting list and awaiting transplantation prior to the adoption or effective date of the revised policies no less favorably than they would have been treated under the previous policies. The transition procedures shall be transmitted to the Secretary for review together with the revised allocation policies.

(2) *Special rule for initial revision of liver allocation policies.* When the OPTN transmits to the Secretary its initial revision of the liver allocation policies, as directed by paragraph (e)(1) of this section, it shall include transition procedures that, to the extent feasible, treat each individual on the waiting list and awaiting transplantation on October 20, 1999 no less favorably than he or she would have been treated

had the revised liver allocation policies not become effective. These transition procedures may be limited in duration or applied only to individuals with greater than average medical urgency if this would significantly improve administration of the list or if such limitations would be applied only after accommodating a substantial preponderance of those disadvantaged by the change in the policies.

(e) *Deadlines for initial reviews.* (1) The OPTN shall conduct an initial review of existing allocation policies and, except as provided in paragraph (e)(2) of this section, no later than November 16, 2000 shall transmit initial revised policies to meet the requirements of paragraphs (a) and (b) of this section, together with supporting documentation to the Secretary for review in accordance with § 121.4.

(2) No later than March 16, 2000 the OPTN shall transmit revised policies and supporting documentation for liver allocation to meet the requirements of paragraphs (a) and (b) of this section to the Secretary for review in accordance with § 121.4. The OPTN may transmit these materials without seeking further public comment under § 121.4(b).

(f) *Secretarial review of policies, performance indicators, and transition patient protections.* The OPTN's transmittal to the Secretary of proposed allocation policies and performance indicators shall include such supporting material, including the results of model-based computer simulations, as the Secretary may require to assess the likely effects of policy changes and as are necessary to demonstrate that the proposed policies comply with the performance indicators and transition procedures of paragraphs (c) and (d) of this section.

(g) *Variances.* The OPTN may develop, in accordance with § 121.4, experimental policies that test methods of improving allocation. All such experimental policies shall be accompanied by a research design and include data collection and analysis plans. Such variances shall be time limited. Entities or individuals objecting to variances may appeal to the Secretary under the procedures of § 121.4.

(h) *Directed donation.* Nothing in this section shall prohibit the allocation of an organ to a recipient named by those authorized to make the donation.

[64 FR 56659, Oct. 20, 1999, as amended at 64 FR 71626, Dec. 21, 1999]

3.7 ALLOCATION OF THORACIC ORGANS. This policy describes how thoracic organs (hearts, heart-lung combinations, single and double lungs) are to be allocated to candidates awaiting a thoracic organ transplant.

3.7.1 Exceptions. Unless otherwise approved according to Policy 3.4.8 (Variances), or specifically allowed by the exceptions described in this Policy 3.7.1, all thoracic organs must be allocated in accordance with Policy 3.7.

3.7.1.1 Exception for Sensitized Candidates. The transplant surgeon or physician for a candidate awaiting thoracic organ transplantation may determine that the candidate is "sensitized" such that the candidate's antibodies would react adversely to certain donor cell antigens. It is permissible not to use the allocation policies set forth in Policy 3.7 for allocation of a particular thoracic organ when all thoracic organ transplant centers within an OPO and the OPO agree to allocate the thoracic organ to a sensitized candidate because results of a crossmatch between the blood serum of that candidate and cells of the thoracic organ donor are negative (i.e., the candidate and thoracic organ donor are compatible). The level of sensitization at which a candidate may qualify for this exception is left to the discretion of the listing transplant center, and subject to agreement among all thoracic organ transplant centers within an OPO and the OPO. Sensitization is not a qualifying criterion for assigning a candidate to a heart status category as described in Policies 3.7.3 (Adult Candidate Status) and 3.7.4 (Pediatric Candidate Status).

3.7.2 Geographic Sequence of Thoracic Organ Allocation. Thoracic organs are to be allocated locally first, then within the following zones in the sequence described in Policy 3.7.10 and Policy 3.7.11. Five zones will be delineated by concentric circles of 500, 1,000, and 1,500 and 2,500 nautical mile radii with the donor hospital at the center. Zone A will extend to all transplant centers which are within 500 miles from the donor hospital but which are not in the local area of the donor hospital. Zone B will extend to all transplant centers that are at least 500 miles from the donor hospital but not more than 1,000 miles from the donor hospital. Zone C will extend to all transplant centers that are at least 1,000 miles from the donor hospital but not more than 1,500 miles from the donor hospital. Zone D will extend to all transplant centers that are located beyond 1,500 miles from the donor hospital, but not more than 2,500 miles from the donor hospital. Zone E will extend to all transplant centers that are located beyond 2,500 miles from the donor hospital.

3.7.3 Adult Candidate Status. Each candidate awaiting heart transplantation receives a status code corresponding to the candidate's medical urgency for transplant. A heart transplant candidate at least 18 years of age at the time of listing receives a status code as follows:

Status	Definition
Status 1A	A candidate listed as Status 1A is admitted to the listing transplant center hospital (with the exception for a 1A(b) candidate) and has at least one of the following devices or therapies in place: (a) Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following: (i) left and/or right ventricular assist device implanted Candidates listed under this criterion, may be listed for 30 days at any point after being implanted as Status 1A once the treating

physician determines that they are clinically stable. Admittance to the listing transplant center hospital is not required.

(ii) total artificial heart;

(iii) intra-aortic balloon pump; or

(iv) extracorporeal membrane oxygenator (ECMO).

Qualification for Status 1A under criterion 1A(a)(ii), (iii) or (iv) is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A to extend the Status 1A listing.

(b) Mechanical circulatory support with objective medical evidence of significant device-related complications such as thromboembolism, device infection, mechanical failure or life-threatening ventricular arrhythmias. A transplant center can report a complication not listed here. The report of an "other" complication will result in a review by the respective heart regional review board. (Candidate sensitization is not an appropriate device-related complication for qualification as Status 1A under this criterion. The applicability of sensitization to thoracic organ allocation is specified by Policy 3.7.1.1 (Exception for Sensitized Candidates).)

Admittance to the listing center transplant hospital is not required. Qualification for Status 1A under this criterion is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A to extend the Status 1A listing.

(c) Continuous Mechanical ventilation. Qualification for Status 1A under this criterion is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A to extend the Status 1A listing.

(d) Continuous infusion of a single high-dose intravenous inotrope or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of left ventricular filling pressures.

Qualification for Status 1A under this criterion is valid for 7 days and may be renewed for an additional 7 days for each occurrence of a Status 1A listing under this criterion for the same candidate. The OPTN contractor shall maintain in the heart status justification form in UNet℠ a list of the specific inotropes and doses approved by the Board of Directors to be compliant with this criterion.

Status 1A by Exception

A candidate who does not meet criterion (a), (b), (c), or (d) may nevertheless be Status 1A upon application by his or her transplant physician. The transplant physician must justify to the applicable Regional Review Board why the candidate is considered, using acceptable medical criteria, to have an

urgency and potential for benefit as other candidates in Status 1A. The justification must be for a candidate admitted to his or her listing transplant center hospital and must include a rationale for incorporating the exceptional case as part of Status 1A. ~~Timing of the review of these cases, whether prospective or retrospective, will be left to the discretion of each Regional Review Board.~~ Regional Review Boards will retrospectively review requests for Status 1A-exceptions.

A candidate's listing under this exceptional provision is valid for 14 days. Any further extension of the Status 1A listing by exception requires ~~prospective~~ retrospective review and approval by ~~a majority of~~ the Regional Review Board ~~Members~~. If Regional Review Board approval is not given, the candidate's transplant physician may override the Regional Review Board and list the candidate as Status 1A~~, subject to automatic referral to the Thoracic Organ Transplantation Committee~~. A report of the decision of the Regional Review Board and the basis for it ~~shall~~ may be forwarded for review by the Thoracic Organ Transplantation Committee. The Thoracic Organ Transplantation Committee may refer the case to the Membership and Professional Standards Committee.

Submission of Status 1A Justification Form
A completed Heart Status 1A Justification Form must be submitted in UNet^{SM} in order to list a candidate as Status 1A, or extend his or her listing as Status 1A in accordance with the criteria listed above. When a candidate's time at Status 1A expires, the candidate will automatically be classified as Status 1B. The attending physician must classify the candidate as Status 2 or 7 if the candidate's medical condition does not qualify for Status 1A or Status 1B.

Status 1B A candidate listed as Status 1B has at least one of the following devices or therapies in place:

(aa) left and/or right ventricular assist device implanted; or
(bb) continuous infusion of intravenous inotropes.

Status 1B by Exception
A candidate who does not meet the criteria for Status 1B may nevertheless be listed as Status 1B upon application by his or her transplant physician. The transplant physician must justify to the applicable Regional Review Board why the candidate is considered, using acceptable medical criteria, to have an urgency and potential for benefit as other Status 1B candidates. The justification must include a rationale for incorporating the exceptional case as part of Status 1B. Regional Review Boards will retrospectively review requests for Status 1B exceptions. A report of the decision of the Regional Review Board and the basis for it ~~shall~~ may be forwarded for review by the Thoracic Organ Transplantation Committee. The Thoracic Organ Transplantation Committee may refer the case to the Membership and Professional Standards Committee.

Submission of Status 1B Justification Form
A completed Heart Status 1B Justification Form must be submitted to UNet^{SM} in order to list a candidate as Status 1B.

Status 2 A candidate who does not meet the criteria for Status 1A or 1B

is listed as Status 2.

Status 7 A candidate listed as Status 7 is considered temporarily unsuitable to receive a thoracic organ transplant.

Change in Status 1A or 1B Criterion or Eligibility
If a change in the candidate's medical condition makes the criterion used to justify a candidate's Status 1A or 1B no longer accurate, the transplant program must report the accurate information in UNet℠ within 24 hours of the change in medical condition.

3.7.4 Pediatric Candidate Status. Each candidate awaiting heart transplantation receives a status code corresponding to the candidate's medical urgency for transplant. Pediatric heart transplant candidates who have not received a heart transplant before their 18th birthday shall continue to qualify for medical urgency status based on Policy 3.7.4. A heart transplant candidate who is less than 18 years of age at the time of listing receives a status code as follows:

Status Definition

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

(a) Requires assistance with a ventilator;

(b) Requires assistance with a mechanical assist device (e.g., ECMO);

(c) Requires assistance with a balloon pump;

(d) A candidate less than six months old with congenital or acquired heart disease exhibiting reactive pulmonary hypertension at greater than 50% of systemic level. Such a candidate may be treated with prostaglandin E (PGE) to maintain patency of the ductus arteriosus;

(e) Requires infusion of high dose or multiple inotropes (The OPTN contractor shall maintain in the heart status justification form in UNet℠ a list of the specific inotropes and doses approved by the Board of Directors to be compliant with this criterion.); or,

(f) A candidate who does not meet the criteria specified in (a), (b), (c), (d), or (e) may be listed as Status 1A if the candidate has a life expectancy without a heart transplant of less than 14 days, such as due to refractory arrhythmia. Qualification for Status 1A under this criterion is valid for 14 days and may be recertified by an attending physician for one additional 14-day period. Any further extension of the Status 1A listing under this criterion requires a retrospective conference with the applicable Regional Review Board. If Regional Review Board approval is not given, the candidate's transplant physician may list the candidate as Status 1A, subject to automatic referral to the Thoracic Organ Transplantation Committee. A report of the decision of the Regional Review Board and the basis for it shall be forwarded for review by the Thoracic Organ Transplantation Committee. The Thoracic Organ

Transplantation Committee may refer the case to the Membership and Professional Standards Committee.

Qualification for Status 1A under criteria (a) through (e) is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A to extend the Status 1A listing.

Submission of Status 1A Justification Form

A completed Heart Status 1A Justification Form must be submitted in UNet^{SM} in order to list a candidate as Status 1A, or extend his or her listing as Status 1A in accordance with the criteria listed above in Policy 3.7.4. When a candidate's time at Status 1A expires, the candidate will automatically be classified as Status 1B. The attending physician must classify the candidate as Status 2 or 7 if the candidate's medical condition does not qualify for Status 1A or Status 1B.

Status 1B

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

(a) Requires infusion of low dose single inotropes (The OPTN contractor shall maintain in the heart status justification form in UNet^{SM} a list of the specific inotropes and doses approved by the Board of Directors to be compliant with this criterion.);

(b) Less than six months old and does not meet the criteria for Status 1A; or

(c) Growth failure *i.e.,* less than 5th percentile for weight and/or height, or loss of 1.5 standard deviations of expected growth (height or weight) based on the National Center for Health Statistics for pediatric growth curves.

Note: This criterion defines growth failure as either < 5th percentile for weight and/or height, or loss of 1.5 standard deviation score of expected growth (height or weight). The first measure looks at relative growth as of a single point in time. The second alternative accounts for cases in which a substantial loss in growth occurs between two points in time. Assessment of growth failure using the standard deviation score decrease can be derived by, first, measuring (or using a measure of) the candidate's growth at two different times, second, calculating the candidate's growth velocity between these times, and, third, using the growth velocity to calculate the standard deviation score (*i.e.,* (candidate's growth rate - mean growth rate for age and sex) divided by standard deviation of growth rate for age and sex).

Status 1B by Exception
A candidate who does not meet the criteria for Status 1B may be listed as Status 1B upon application by his transplant physician to the applicable Regional Review Board. The transplant physician must justify why the candidate is considered, using acceptable medical criteria, to have an urgency and potential for benefit as other candidates listed as Status 1B. The justification must include a rationale for incorporating the exceptional case as part of Status 1B. A report of the decision of the Regional Review Board and the basis for it ~~shall~~ may be forwarded for review by the Thoracic Organ Transplantation Committee. The Thoracic Organ Transplantation Committee may refer the case to the Membership and Professional Standards Committee.

Submission of Status 1B Justification Form
A completed Heart Status 1B Justification Form must be submitted in UNet℠ to list a candidate as Status 1B.

Status 2 A candidate who does not meet the criteria for Status 1A or 1B is listed as Status 2.

Status 7 A candidate listed as Status 7 is considered temporarily unsuitable to receive a thoracic organ transplant.

Change in Status 1A or 1B Criterion or Eligibility
If a change in the candidate's medical condition makes the criterion used to justify a candidate's Status 1A or 1B no longer accurate, the transplant program must report the accurate information in UNet℠ within 24 hours of the change in medical condition.

3.7.5 Allocation of Pediatric Donor Hearts to Pediatric Heart Candidates. Within each heart status, a heart retrieved from a pediatric organ donor shall be allocated to a pediatric heart candidate (i.e., less than 18 years old at the time of listing) before the heart is allocated to an adult candidate. For the purpose of Policy 3.7, a pediatric organ donor is defined as an individual who is less than 18 years of age.

3.7.6 Lung Allocation. Candidates waiting for lung transplants receive priority for deceased donor lung offers based on Lung Allocation Score (LAS) if they are at least 12 years of age. Candidates less than 12 years of age receive deceased donor lung offers based on medical urgency priority.

3.7.6.1 Lung Allocation Score (LAS) System for Candidates at Least 12 Years of Age

Candidates who are at least 12 years of age receive offers for deceased donor lungs based on LAS, as well as geography and blood type. Candidates with higher LASs receive higher waiting list priority.

3.7.6.1.1 The LAS Calculation
The LAS calculation uses *all of* the following:

- Waitlist Urgency Measure, which is the expected number of days a candidate will live without a transplant during an additional year on the waiting list
- Post-transplant Survival Measure, which is the expected number of days a candidate will live during the first year post-transplant

Adult heart candidates and recipients: characteristics and outcomes

Listings and transplants 2010-2012

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Acknowledgment

This work was supported wholly or in part by HRSA contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of HHS, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government

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Data

- All tabulations are based on OPTN data as of October 18, 2013
- Data are subject to change based on future data submission or correction
- Waiting list tabulations were based on characteristics determined at the later of addition to the waiting list (if after 1/1/10) or 1/1/10 (if already listed)
- No exclusionary criteria were used

Methods and conventions

- **Waiting list outcomes**
  - Transplant rate = number of transplants performed/100 active patient-years
  - Rates of death or removal for too sick to transplant = number of removals for death or too sick to transplant/100 patient-years
  - As patients frequently inactivated shortly before removal for death, time spent as inactive is attributed to the preceding active status for death/too sick rate calculation.
  - Cohort includes adult heart candidates ever actively waiting between 1/10 and 12/12
  - Deaths reported to the OPTN were supplemented with the Social Security Death Master file. The public release of these data has been partially restricted as of November 2011.
  - Rates provided by strata, but not adjusted for other patient characteristics

- **Post-transplant survival rates**
  - Computed using the Kaplan-Meier method
  - Cohort includes adult heart transplant recipients transplanted between 1/10 and 6/12
  - Rates provided by strata, but not adjusted for other recipient characteristics
  - Rates provided only if at least 10 recipients still at risk at time point

Overview: waiting list

Between January 2010 and December 2012:

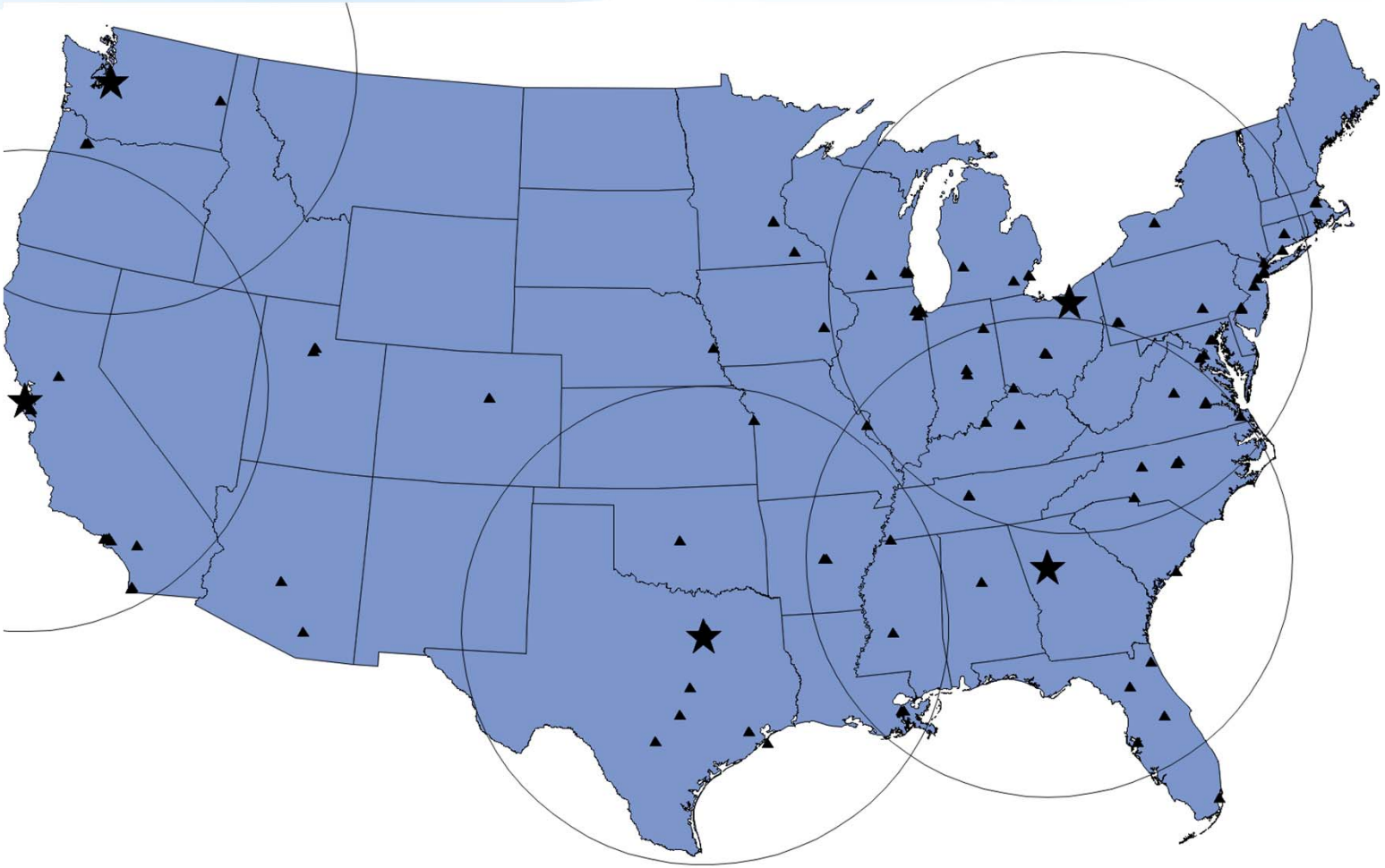
- 11,044 adult heart registrations were ever actively waiting at 127 programs
- Registrations per program
  - Range: 1 to 508 (median = 78)
  - Inter-quartile range (IQR): [31,131]
- 20% (N=2,169) of registrations were Status 1A at later of January 1, 2010, and listing
- Outcomes
  - The rates of removal for death/too sick per 100 patient-years were:
    - 54 for Status 1A; 16 for Status 1B; and 8 for Status 2
  - The transplant rates per 100 active patient-years were:
    - 532 for Status 1A; 82 for Status 1B; and 13 for Status 2.

Overview: transplant

Between January 2010 and December 2012:

- 5,931 adult heart transplants were performed at 120 programs
- Transplants per program
  - Range: 1 to 257 (median = 38)
  - Inter-quartile range: [22, 65].
- 57% of transplant recipients were Status 1A
- 1-year patient survival
  - Status 1A: 90%
  - Status 1B: 91%
  - Status 2: 93%

Centers within a 500 mile radius
For a sample of transplant programs



Depending on the geographic location of the center, the 500 mile radius for each program includes from 4 to 67 other transplant programs.

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Circles are centered about the sample of centers indicated by stars. All other transplant programs with adult candidates are shown as triangles.

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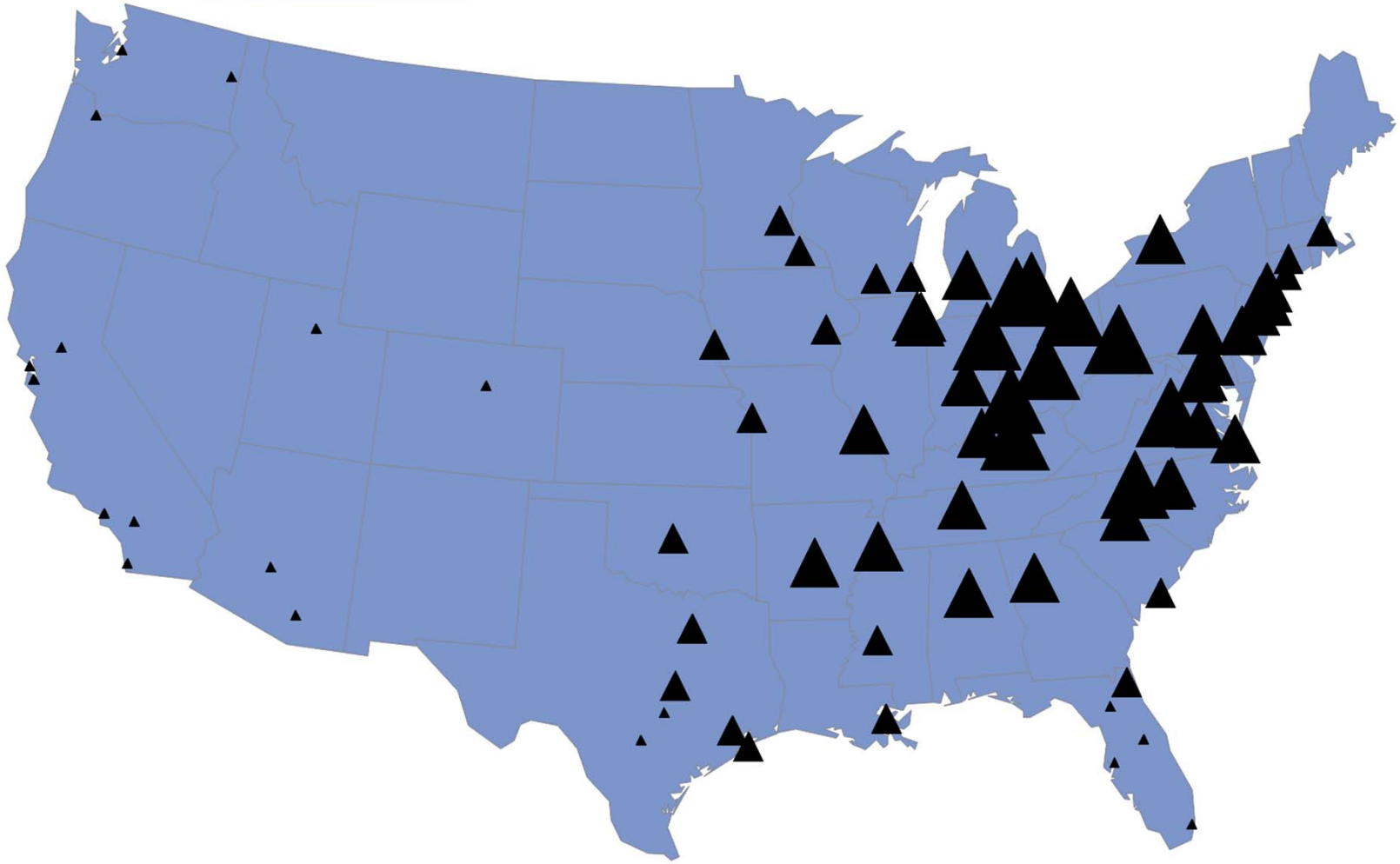
Number of centers within 500 miles



OPTN

NOTE: Each symbol represents one transplant center, with the size of the symbol proportional to the number of centers within 500 miles

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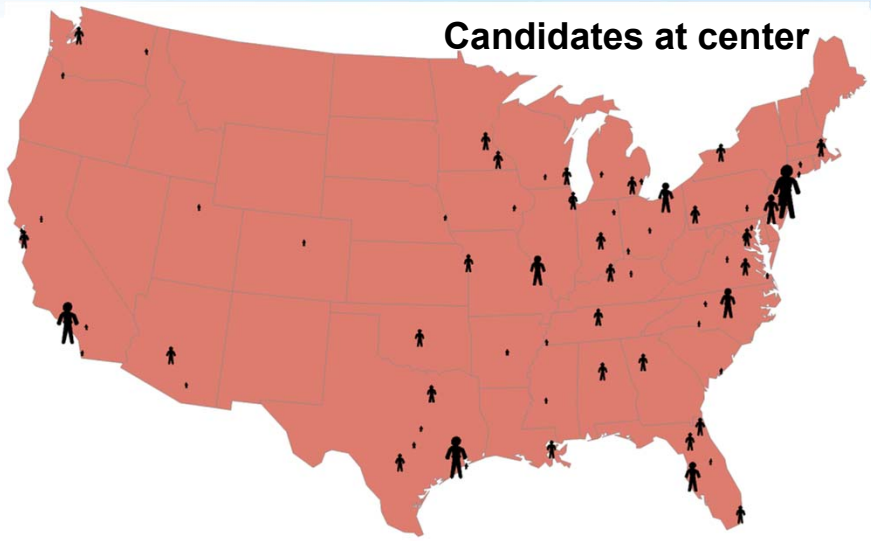
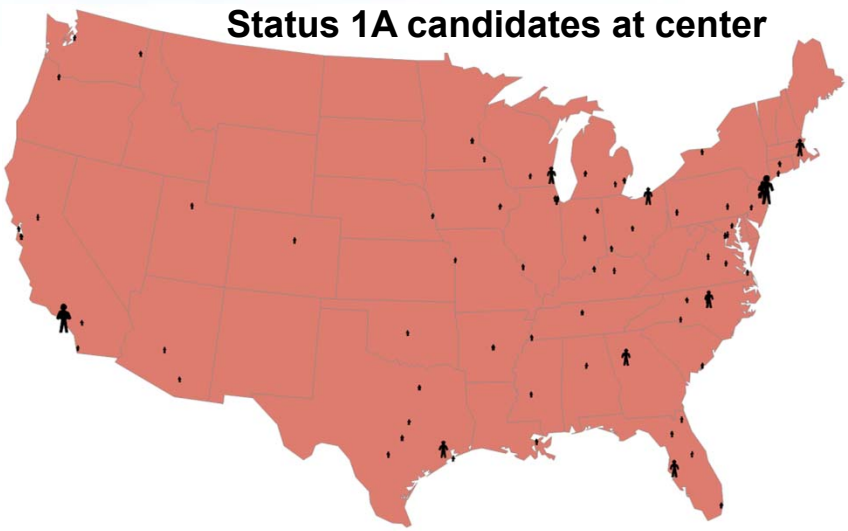
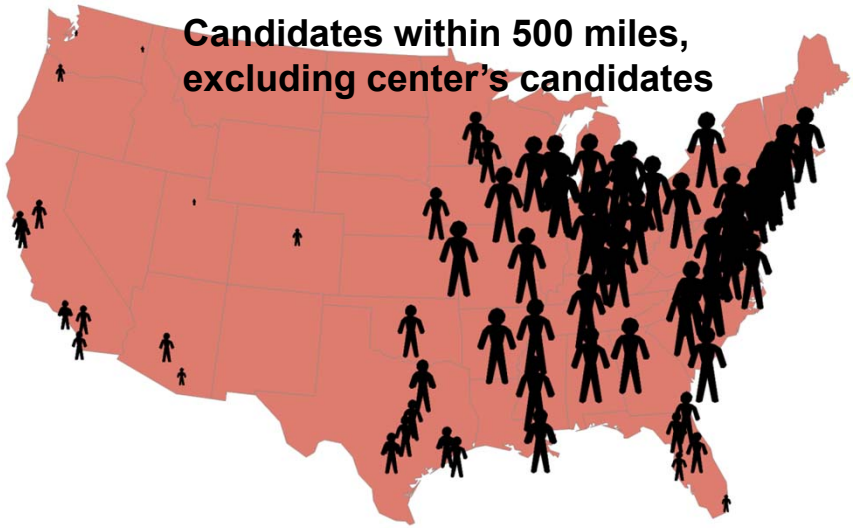
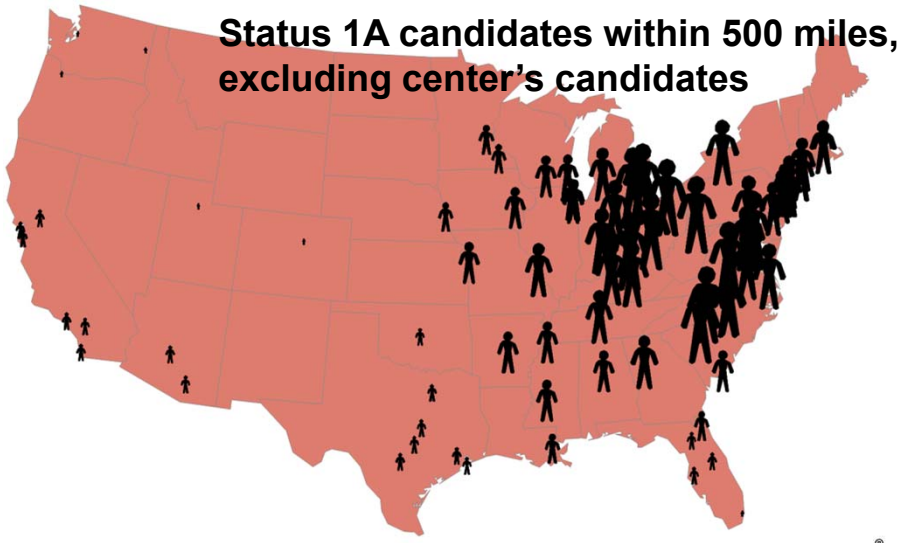
Number of candidates ever actively waiting (2010-2012)









OPTN

NOTE: Each symbol represents one transplant center, with the size of the symbol proportional to the number of candidates

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Waiting list: distribution and outcomes

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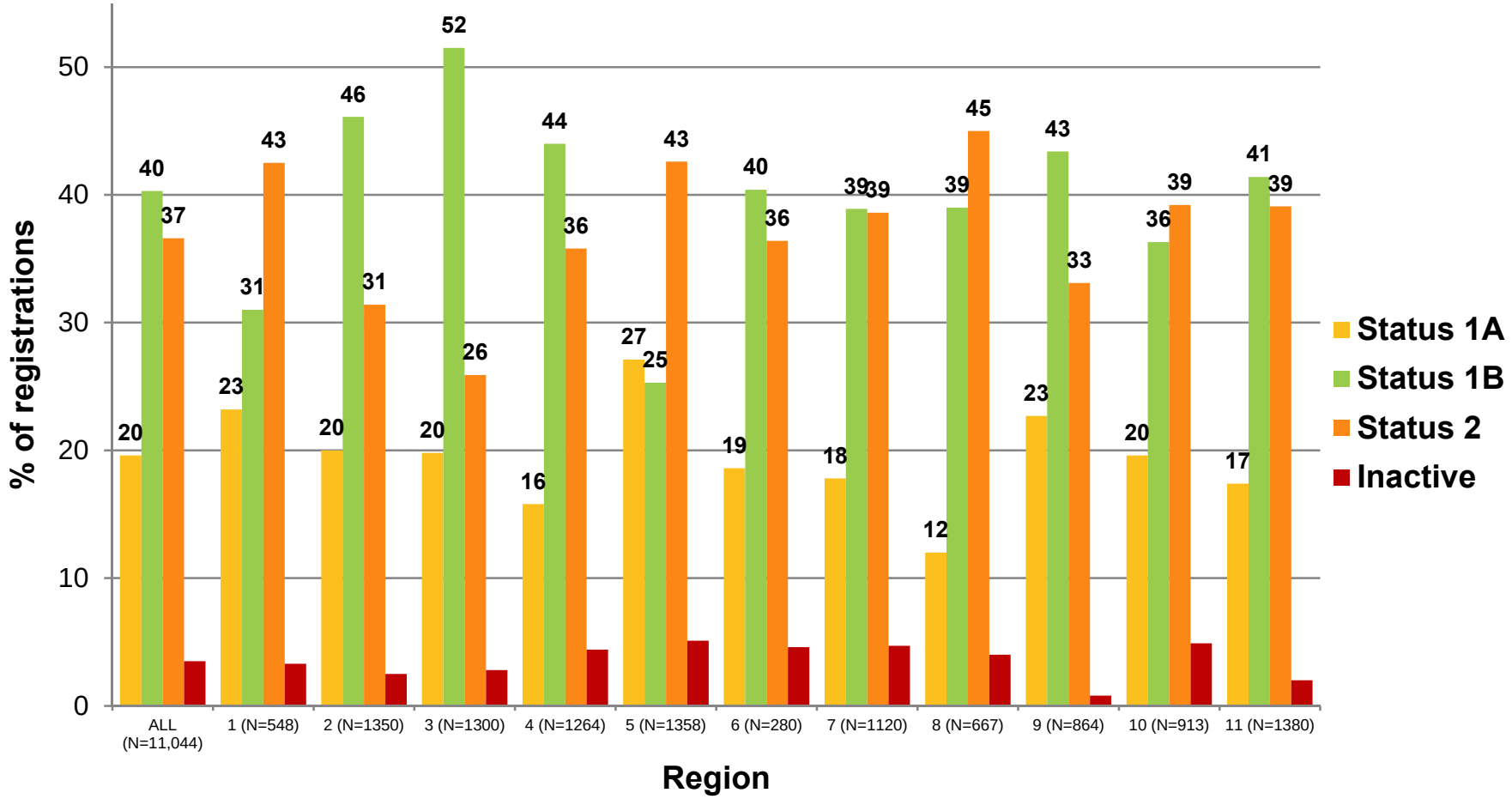
Adult heart registrations ever active 1/2010-12/2012
*Stratified by medical urgency status**



*Medical urgency status was determined at later of listing or 1/1/2010.

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Across regions:
- Status 1A percentage ranges from 12% to 27%
- Status 2 percentage ranges from 26% to 45%

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Waiting list outcomes for adult heart registrations ever active 1/2010-12/2012

Stratified by medical urgency status

Status	Patients ever waiting	Death/too sick			Transplant		
		Deaths/ removal for too sick	Patient-years (PY)	Deaths/ too sick per 100 PY	Transplants	Active Patient-years (APY)	Transplants /100 APY
Status 1A	5,737	474	873.3	54.3	3,328	626.1	531.6
Status 1B	7,060	512	3,243.3	15.8	2,199	2,666.4	82.5
Status 2	4,246	267	3,485.3	7.7	363	2,861.9	12.7

OPTN

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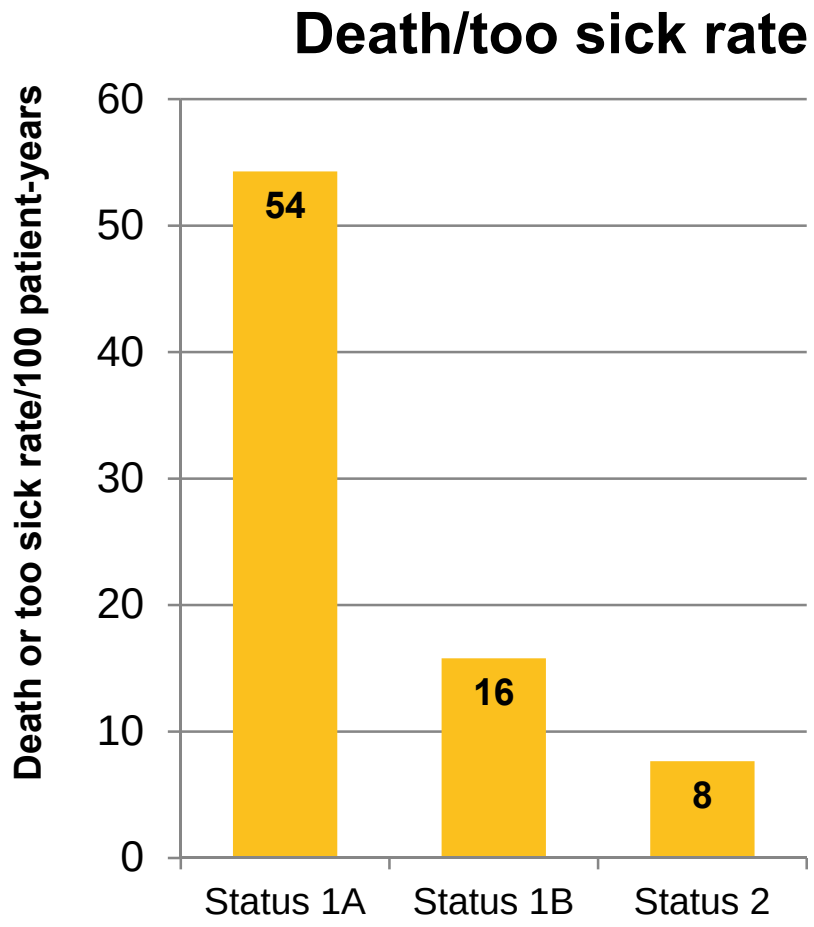
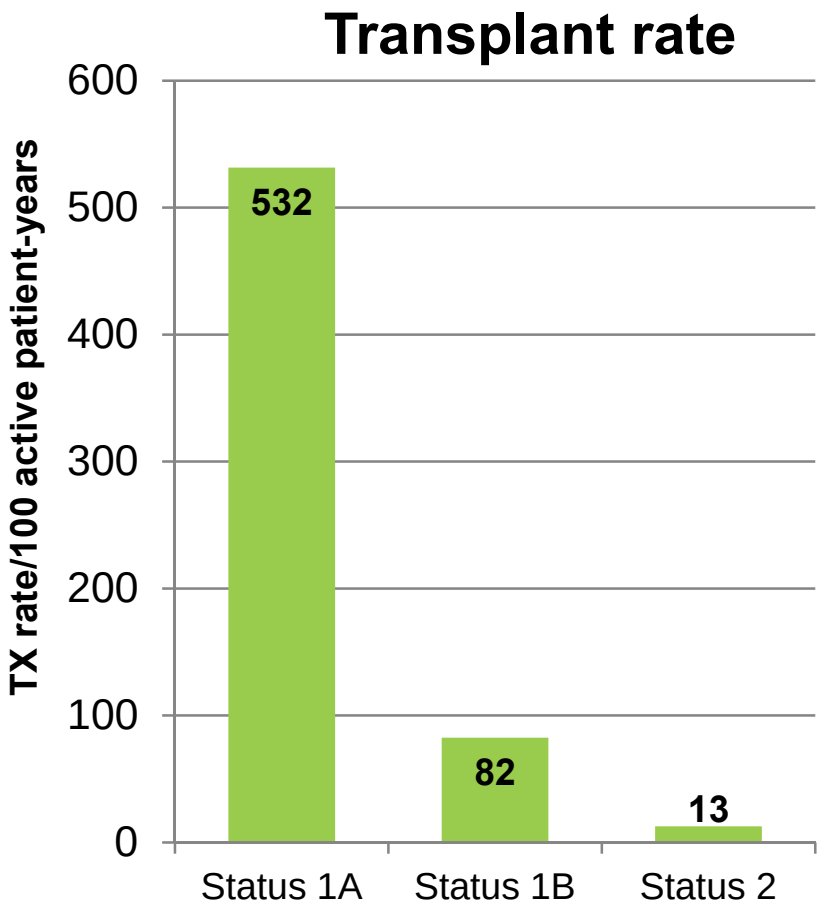
Waiting list outcomes for adult heart registrations ever active 1/2010-12/2012

Stratified by medical urgency status





OPTN

Note: Figures have different scales.

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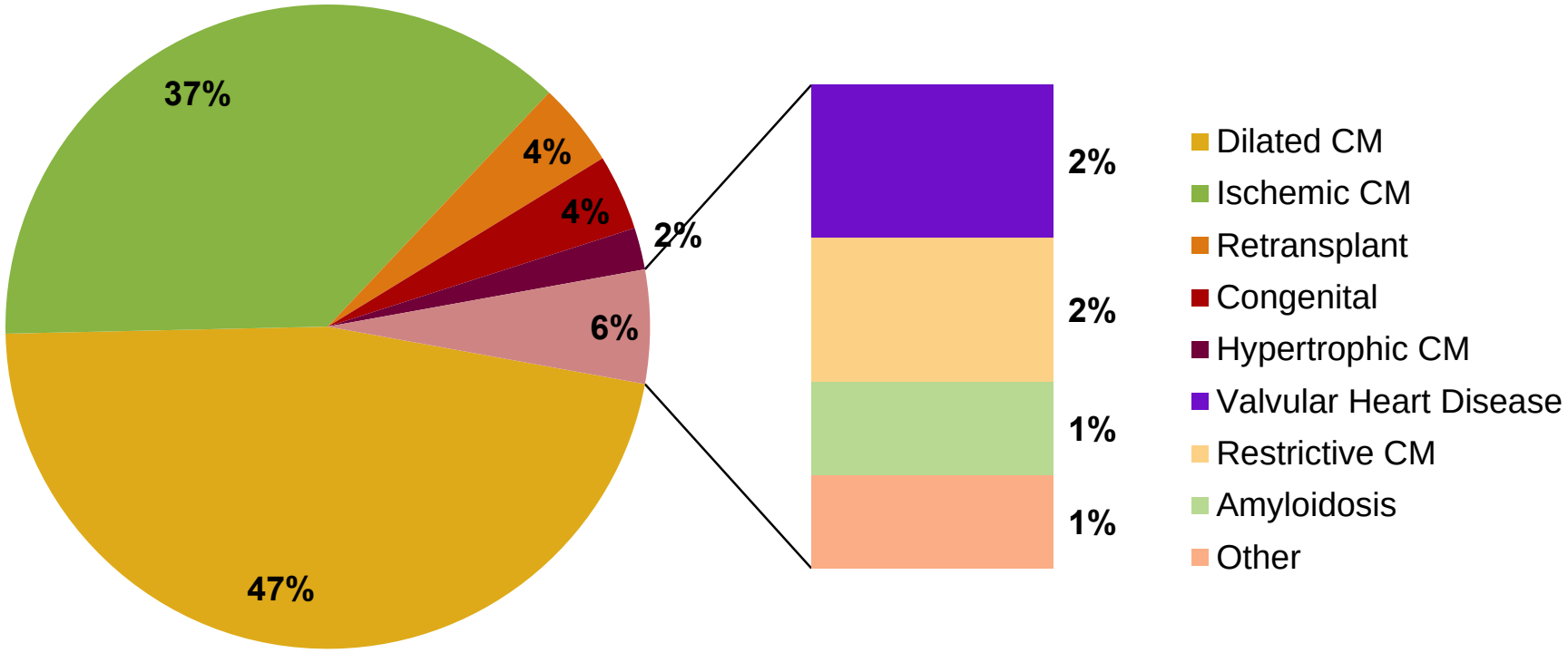
Adult heart registrations ever active 1/2010-12/2012
Stratified by diagnosis

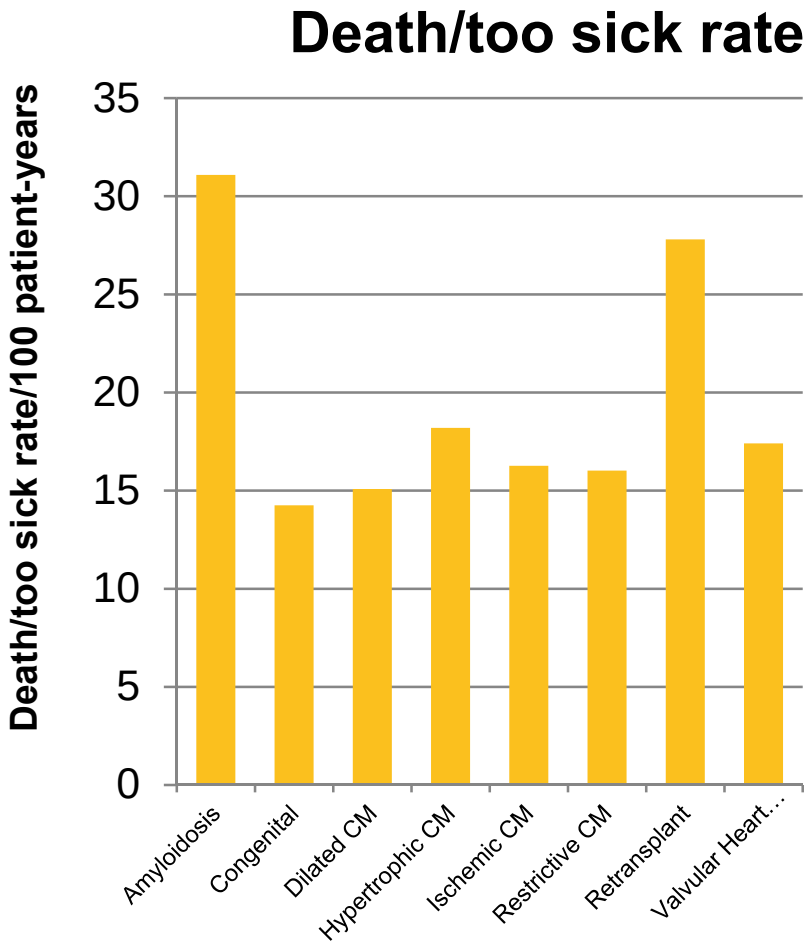


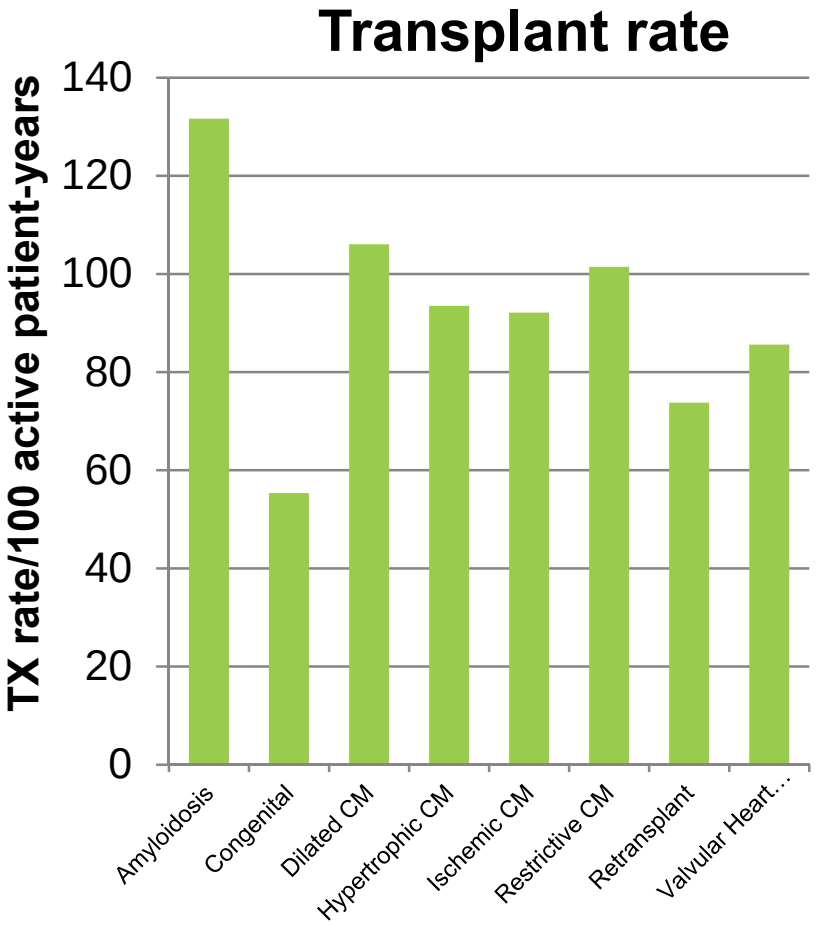
OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

Waiting list outcomes for adult heart registrations ever active 1/2010-12/2012

Stratified by diagnosis





OPTN

Note: Figures have different scales.

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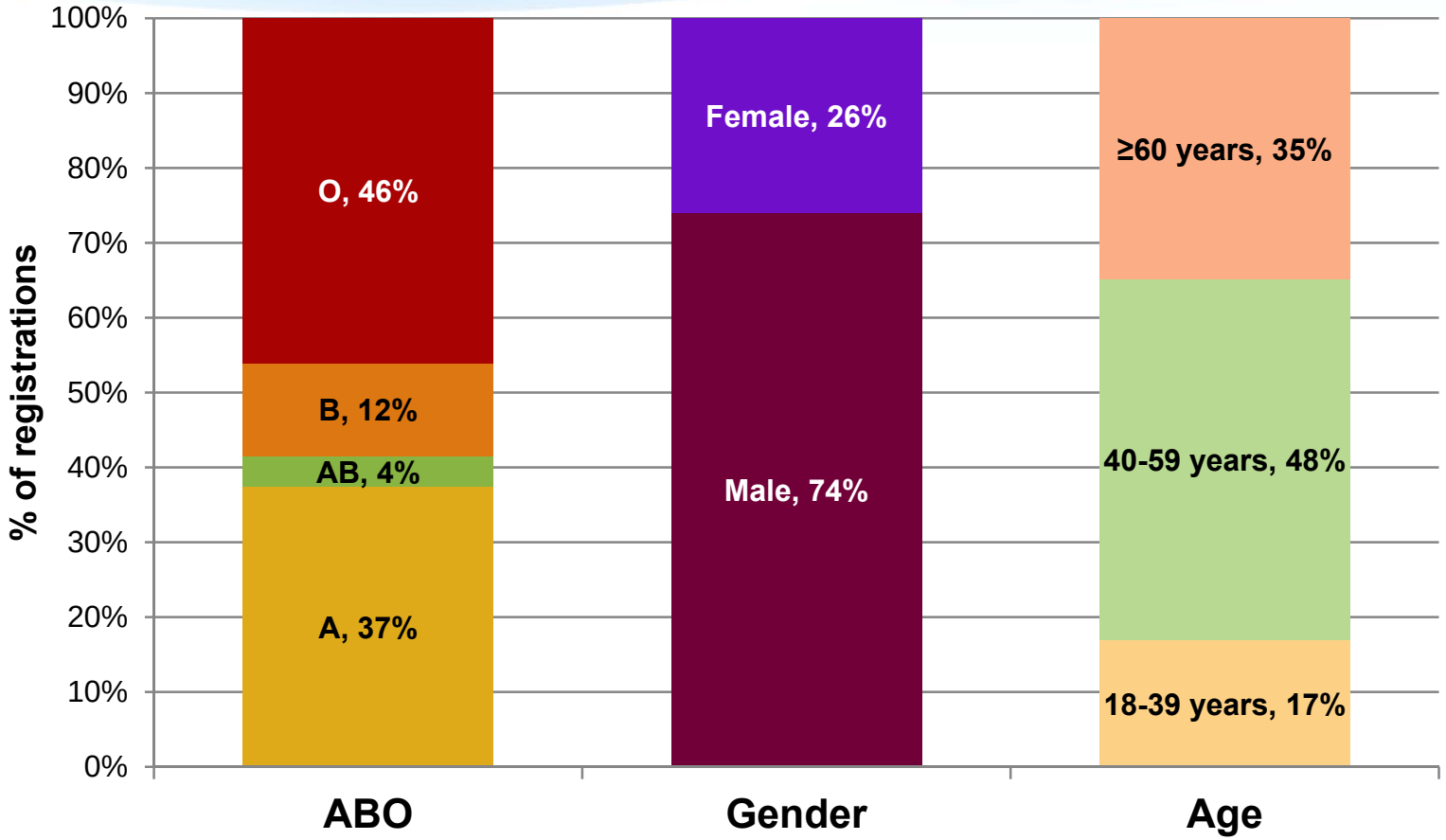
Adult heart registrations ever active 1/2010-12/2012
Stratified by demographics



OPTN

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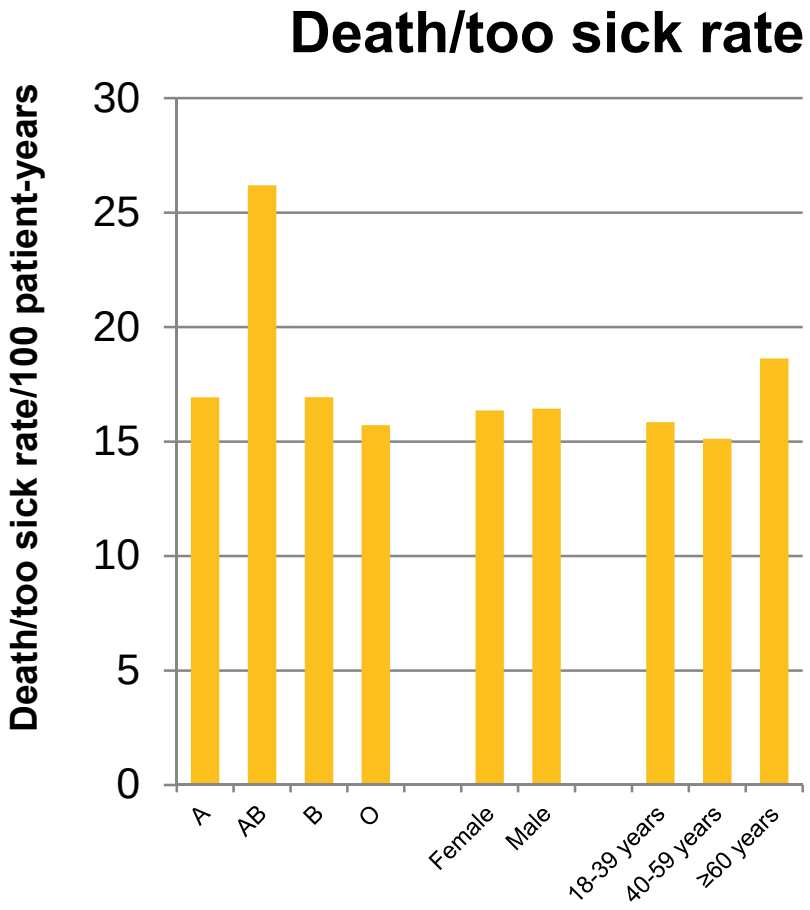
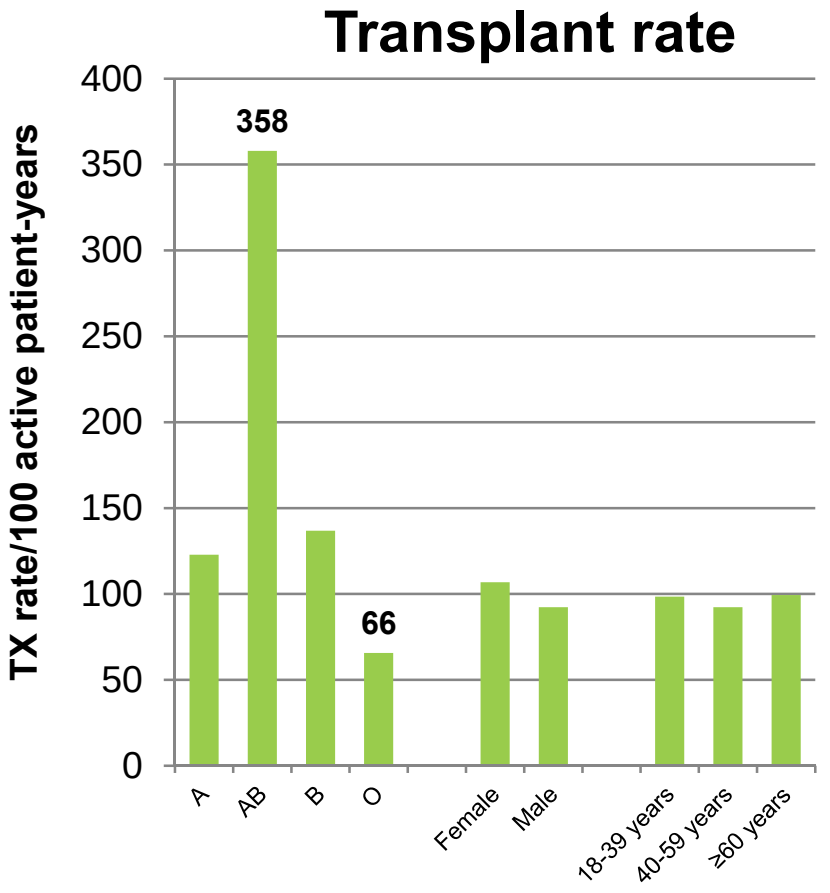
Waiting list outcomes for adult heart registrations ever active 1/2010-12/2012

Stratified by demographics





OPTN

Note: Figures have different scales.

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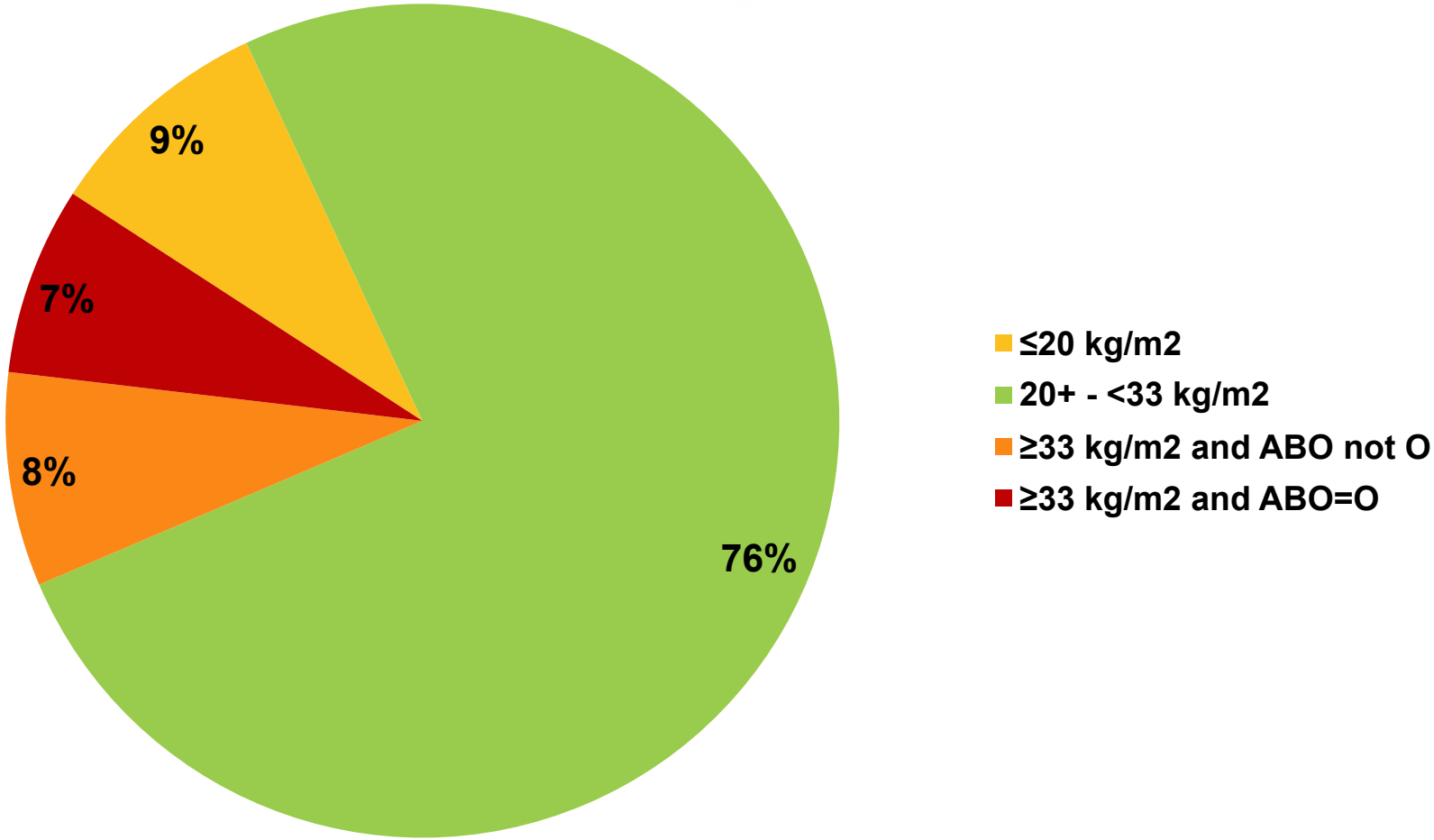
Adult heart registrations ever active 1/2010-12/2012
Stratified by BMI and ABO



OPTN

UNOS DONATE LIFE
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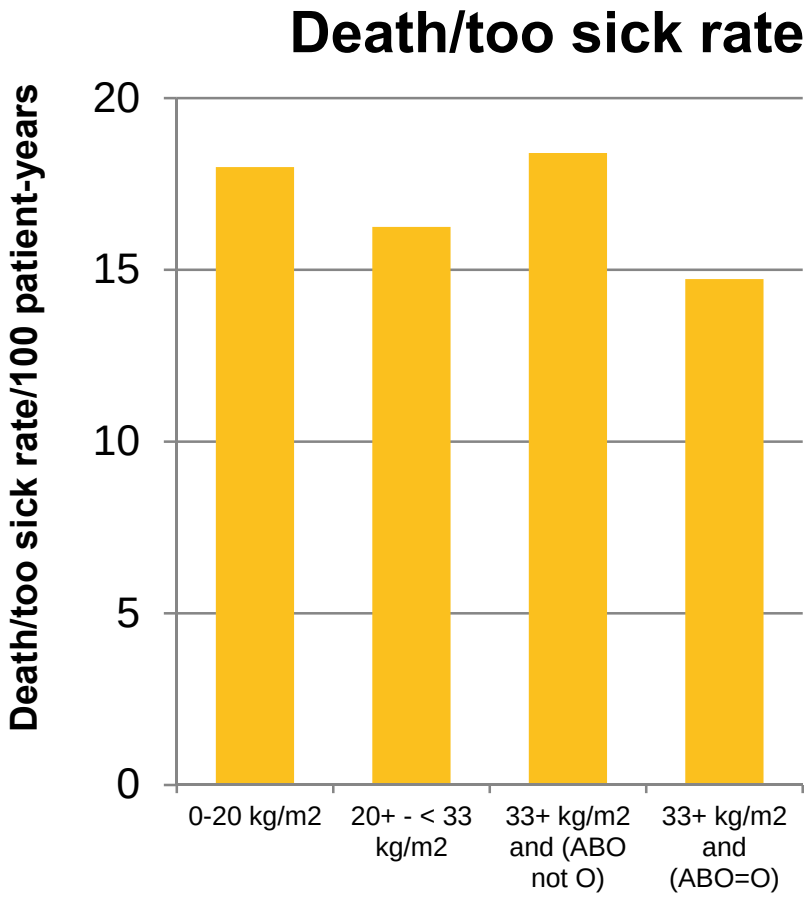
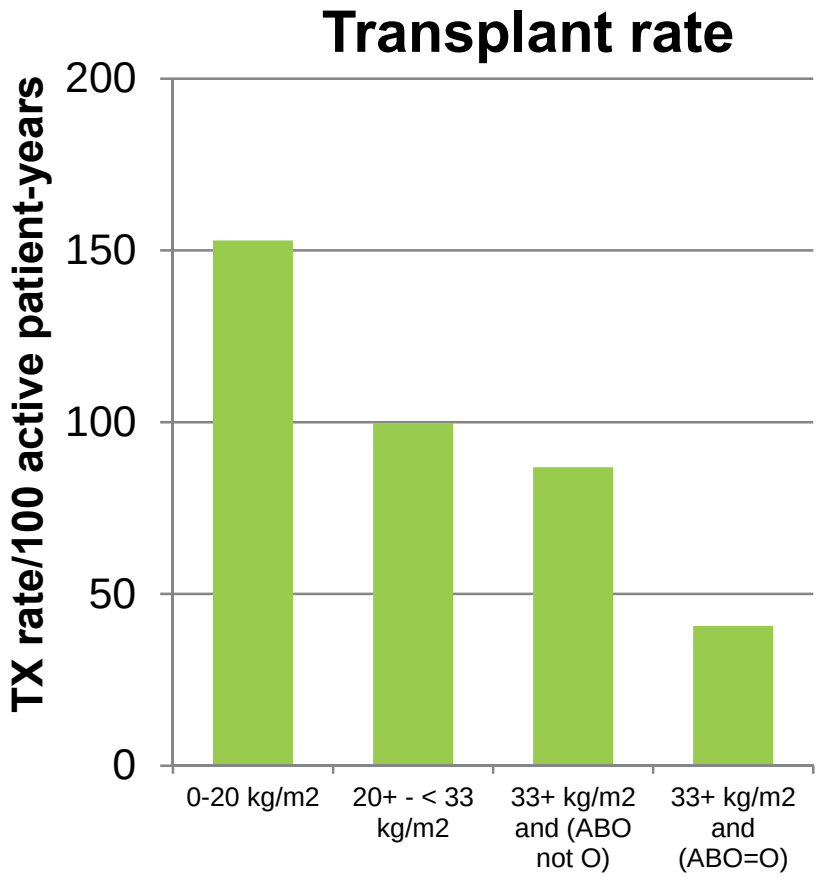
Waiting list outcomes for adult heart registrations ever active 1/2010-12/2012

Stratified by BMI and ABO





OPTN

Note: Figures have different scales.

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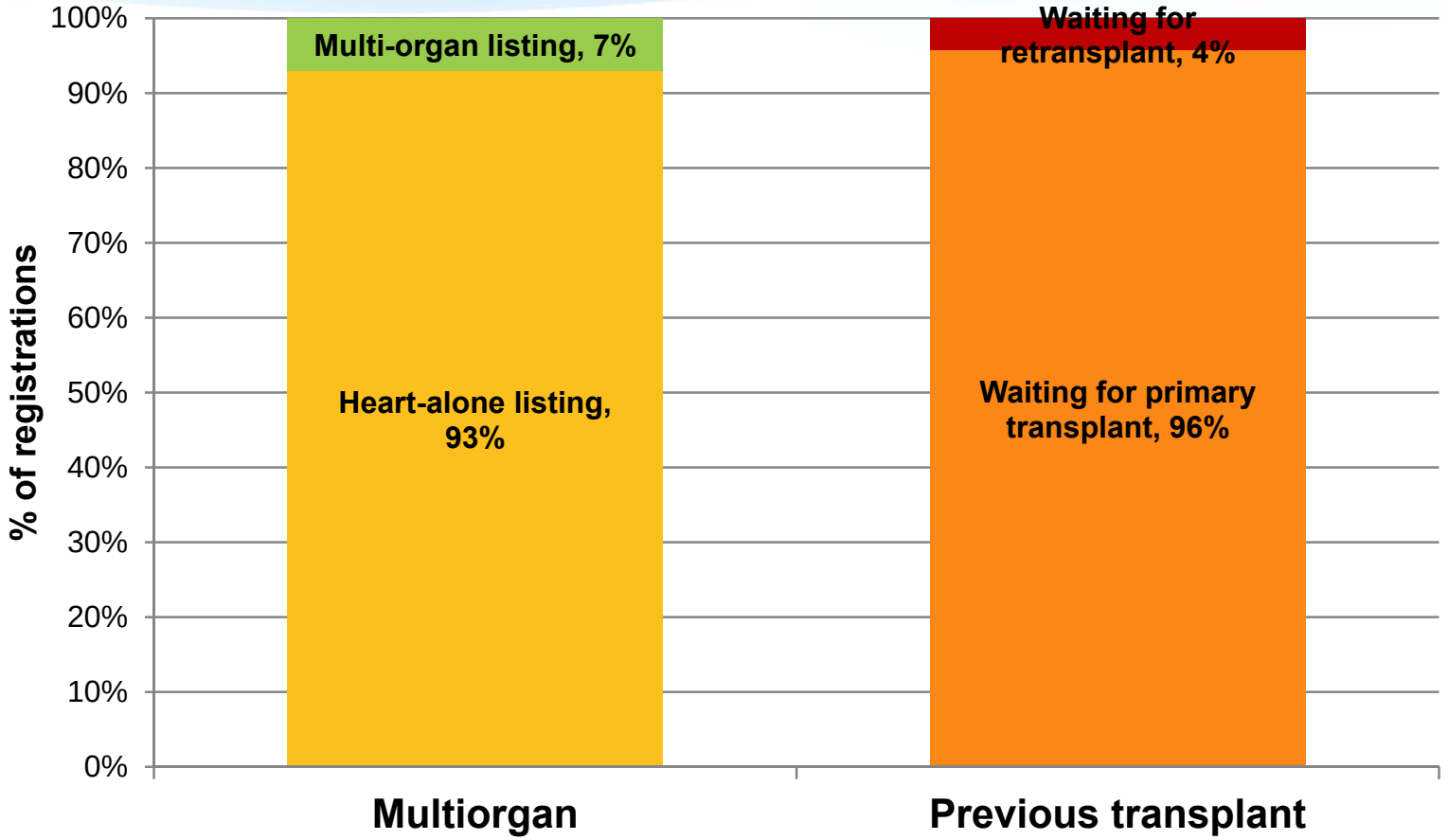
Adult heart registrations ever active 1/2010-12/2012
Stratified by procedure type



OPTN

UNOS DONATE LIFE
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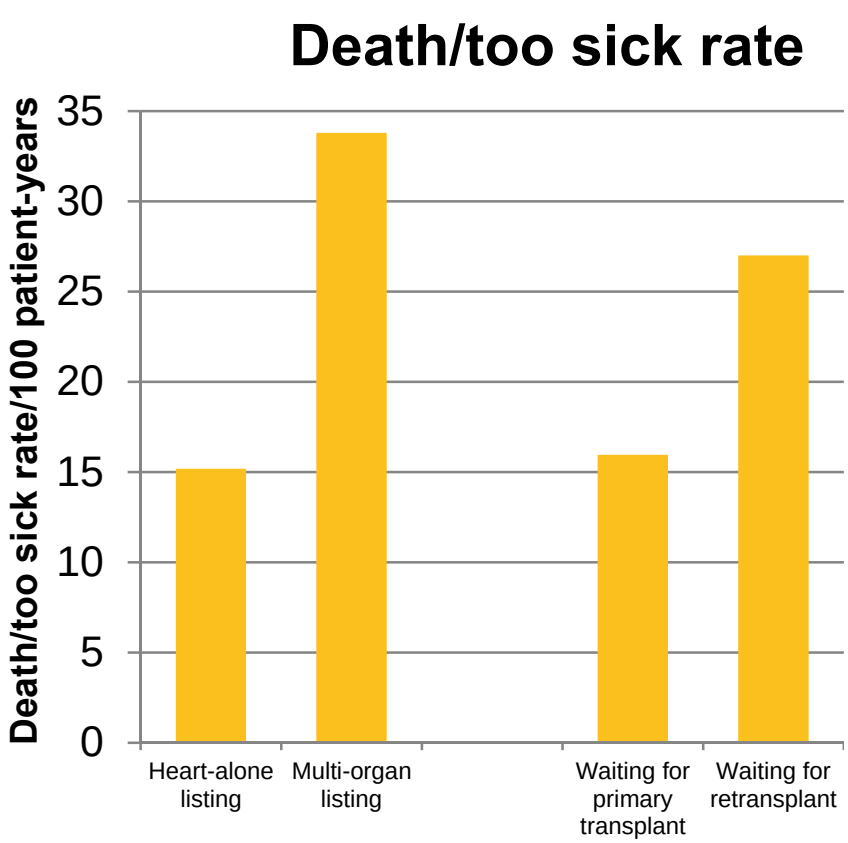
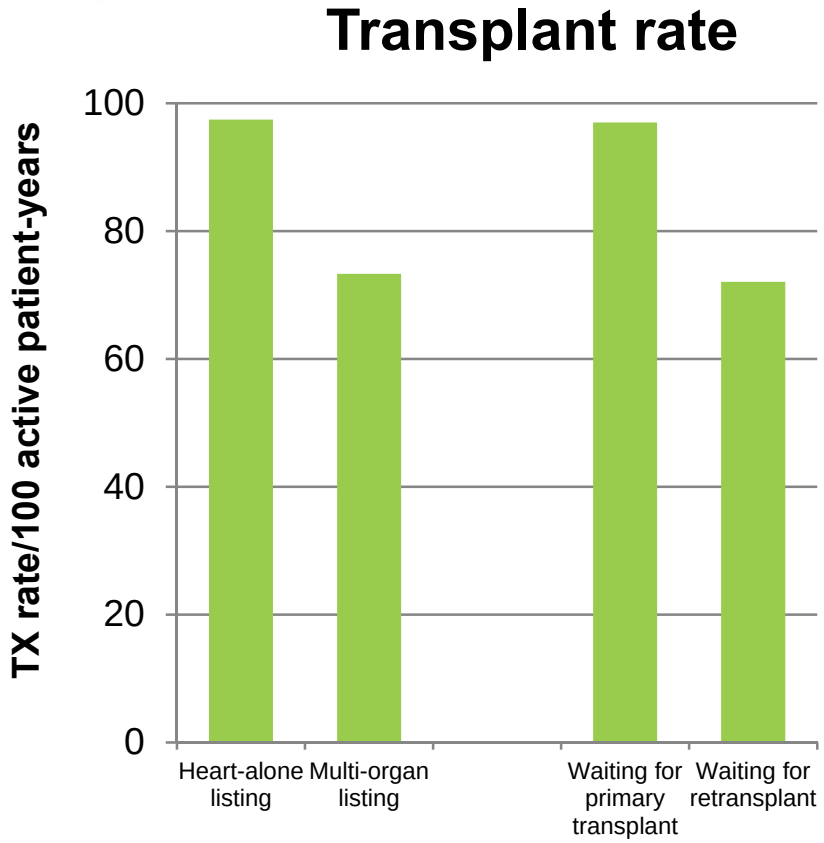
Waiting list outcomes for adult heart registrations ever active 1/2010-12/2012

Stratified by procedure type





OPTN

Note: Figures have different scales.

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Transplants: Distribution and outcomes

OPTN

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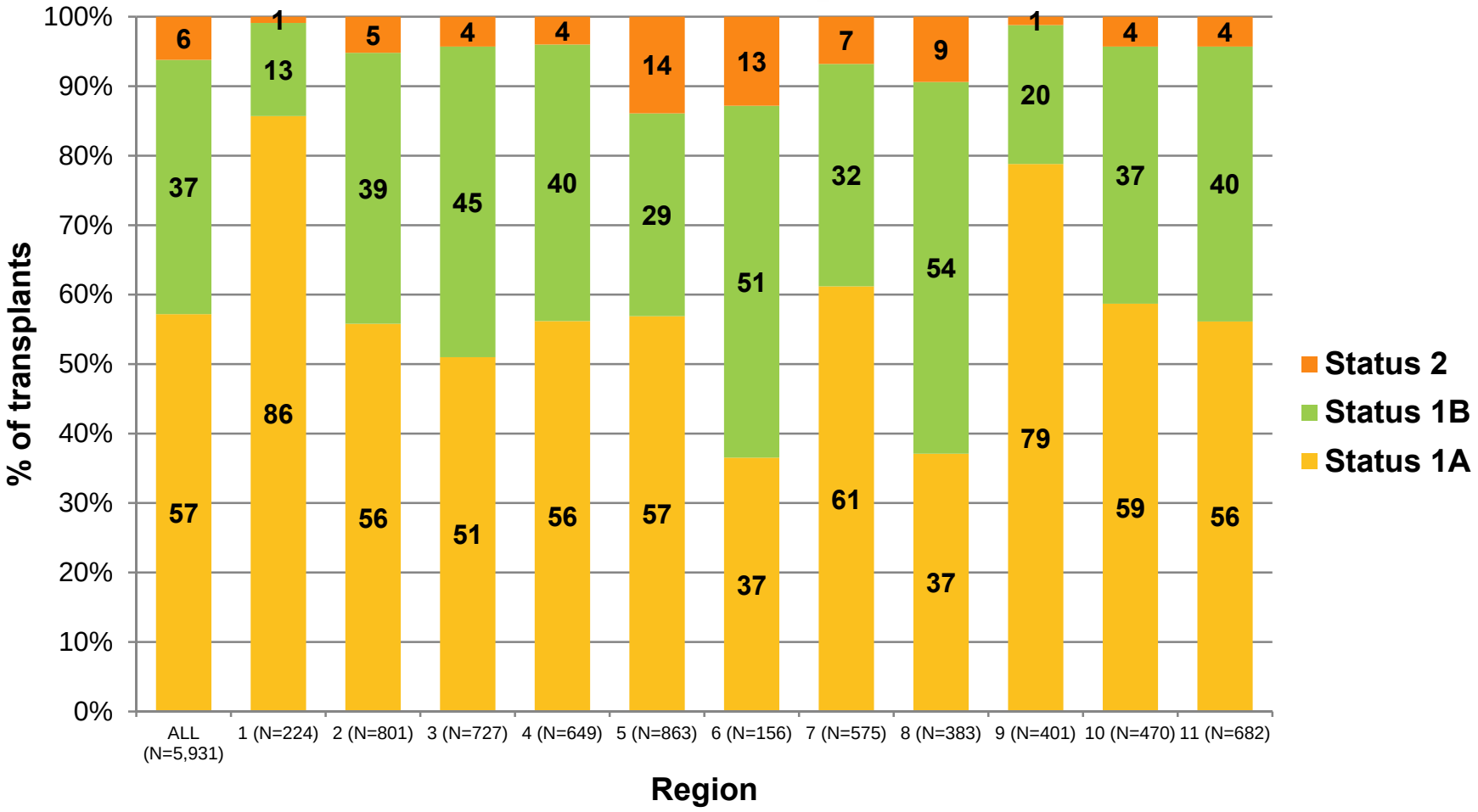
Adult heart recipients 1/2010-12/2012
Stratified by medical urgency status at transplant



OPTN

By region:
- Status 1A percentage ranges from 37% to 86%
- Status 2 percentage ranges from 1% to 14%

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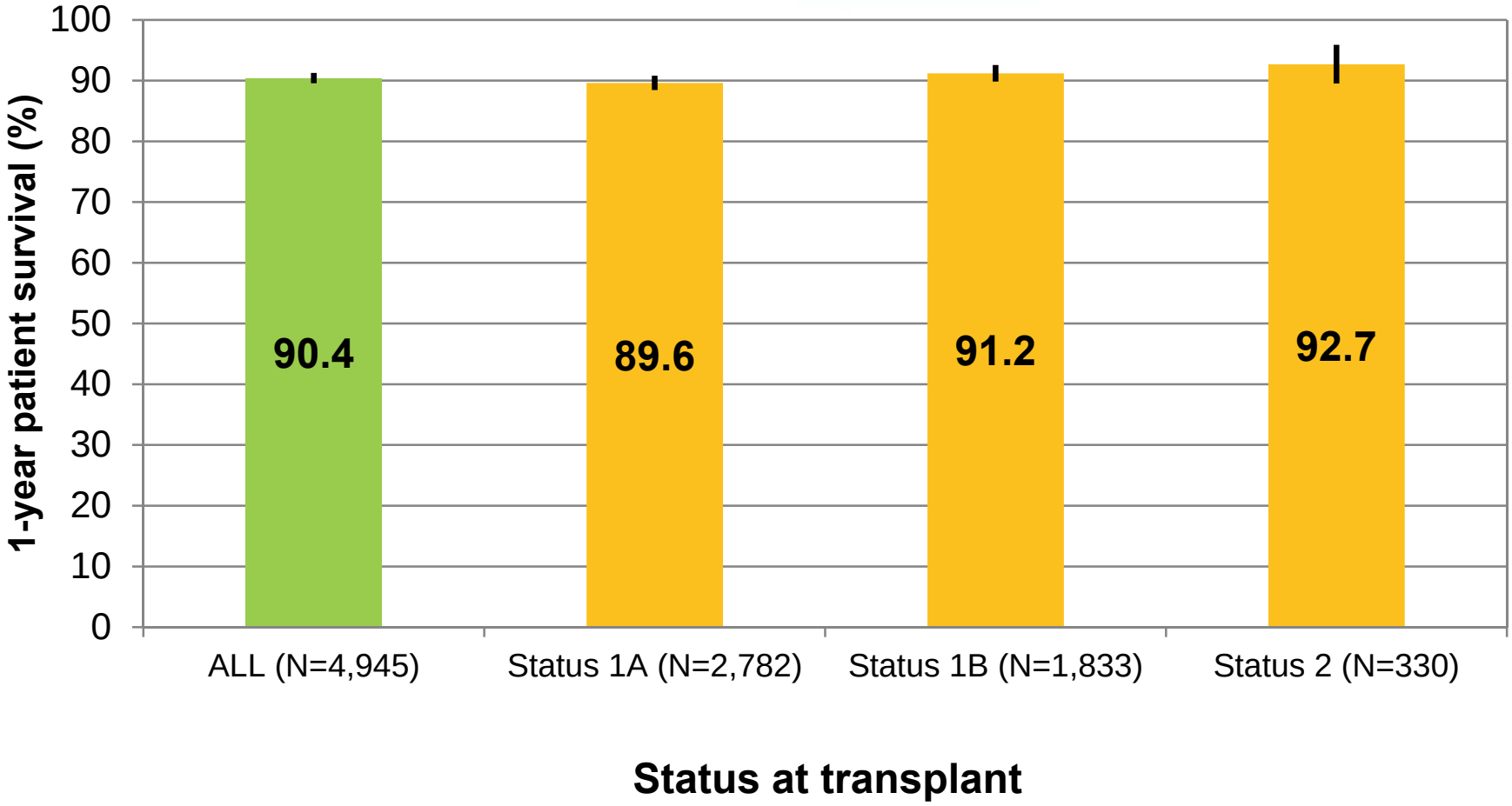
1-year survival in adult heart recipients 1/2010-6/2012
Stratified by medical urgency status at transplant



OPTN

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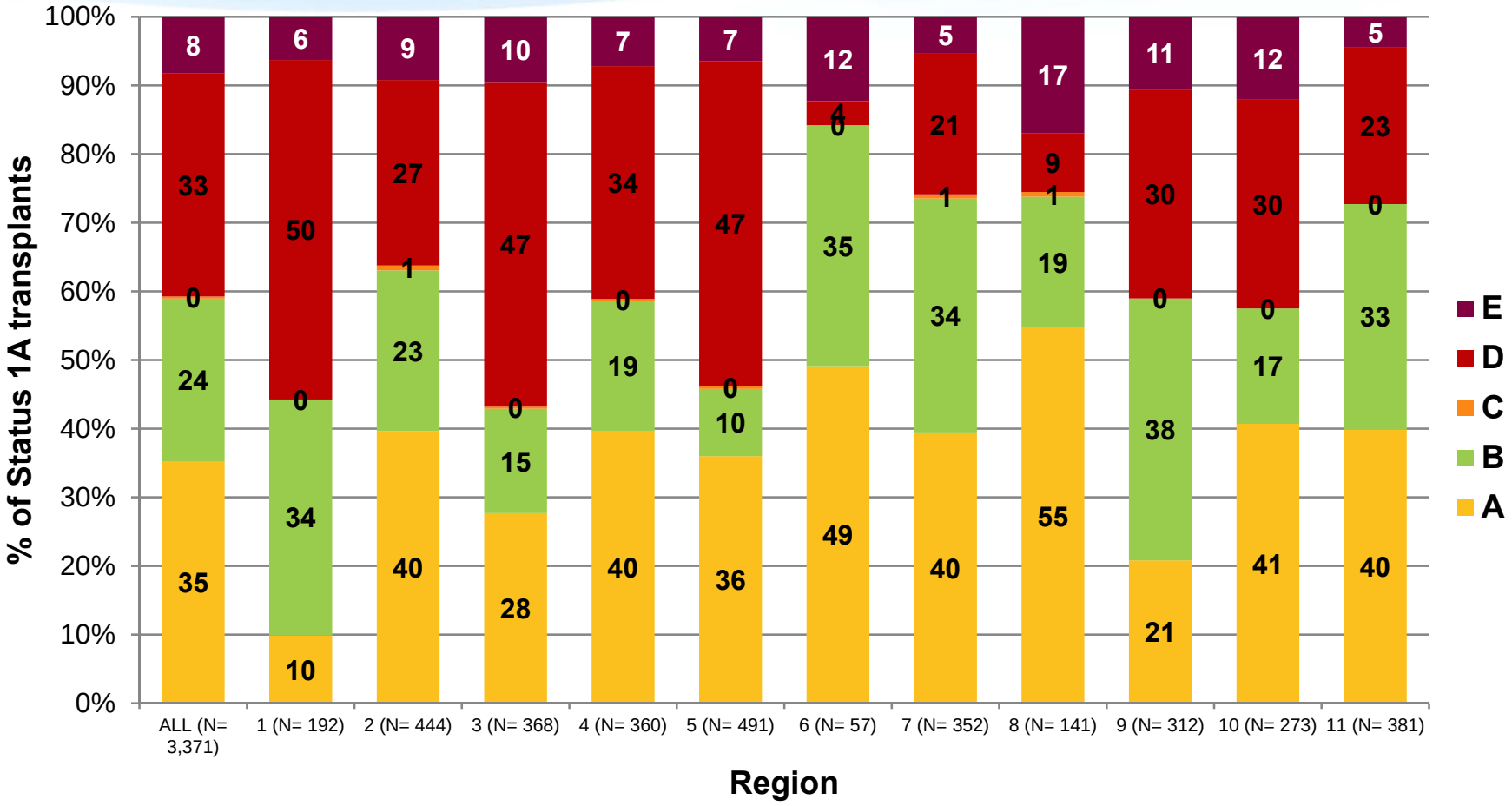
Adult heart recipients 1/2010-12/2012
Stratified by criteria for Status 1A at transplant



A = Mechanical circulatory support (i.e., VAD for 30 days, TAH, balloon pump, ECMO)
B = Mechanical circulatory support with device complications (i.e., thromboembolism, device infection/malfunction, ventricular arrhythmias)
C = Mechanical ventilation
D = Continuous infusion of single high dose or multiple inotropes and continuous monitoring of left ventricular pressures
E = Exception

OPTN

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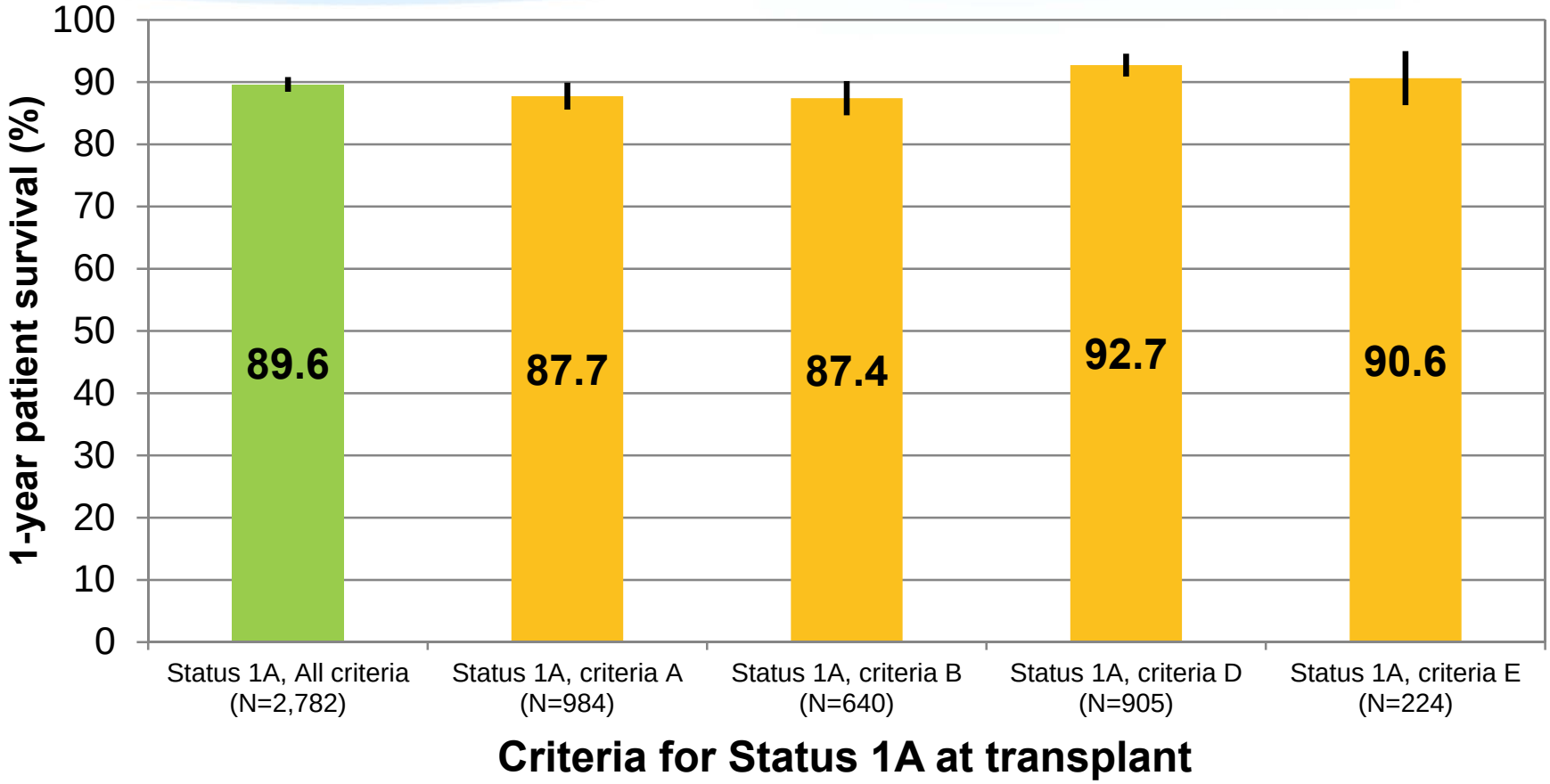
1-year survival in adult heart recipients 1/2010-6/2012
Stratified by criteria for Status 1A at transplant



A = Mechanical circulatory support (i.e., VAD for 30 days, TAH, balloon pump, ECMO)
B = Mechanical circulatory support with device complications (i.e., thromboembolism, device infection/malfunction, ventricular arrhythmias)
C = Mechanical ventilation
D = Continuous infusion of single high dose or multiple inotropes and continuous monitoring of left ventricular pressures
E = Exception

OPTN

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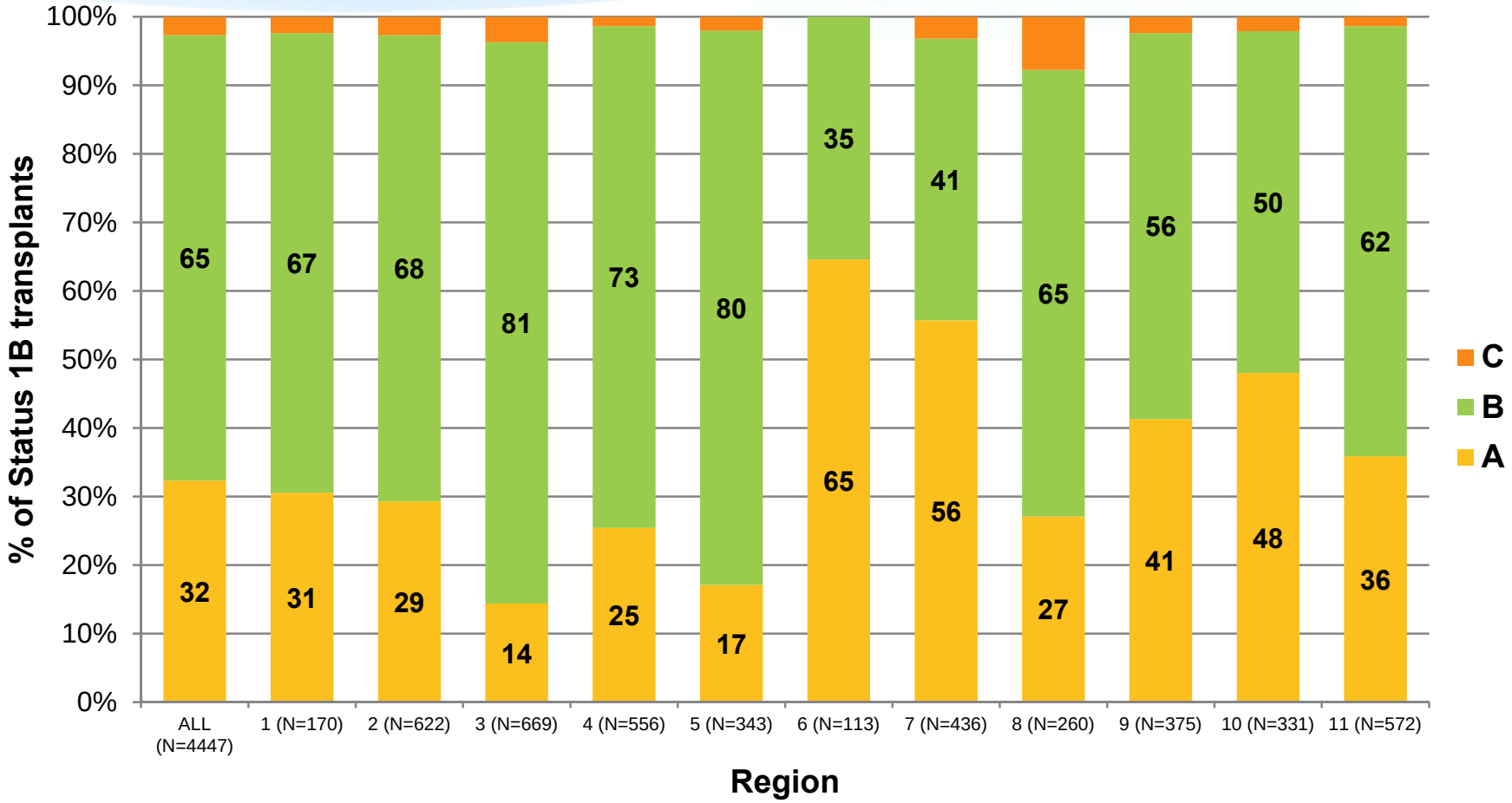
Adult heart recipients 1/2010-12/2012

Stratified by criteria for Status 1B at transplant



A = Left and/or right ventricular assist device implanted
B = Continuous infusion of intravenous inotropes
C = Exception

OPTN

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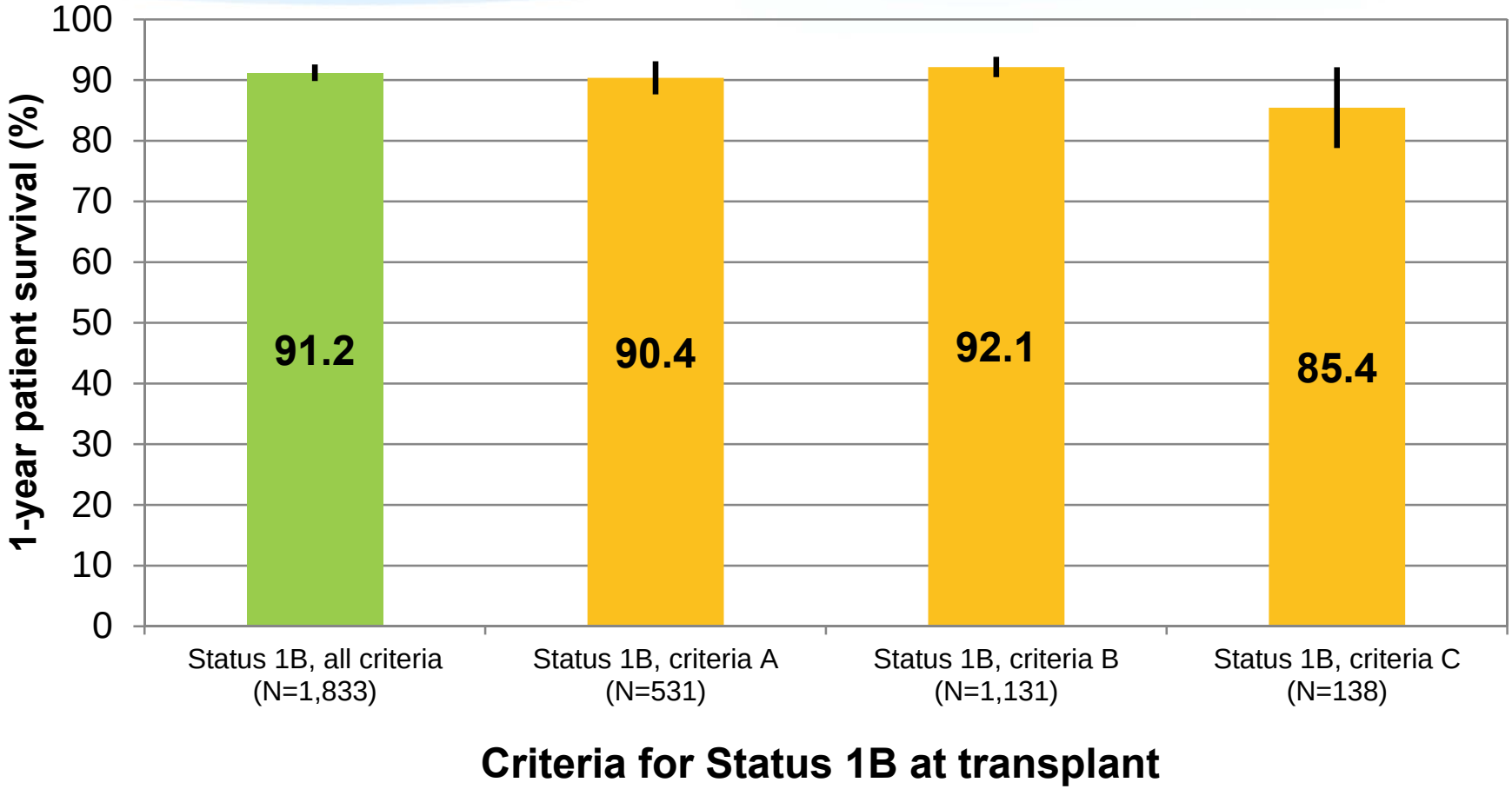
1-year survival in adult heart recipients 1/2010-6/2012
Stratified by criteria for Status 1B at transplant



A = Left and/or right ventricular assist device implanted
B = Continuous infusion of intravenous inotropes
C = Exception

OPTN

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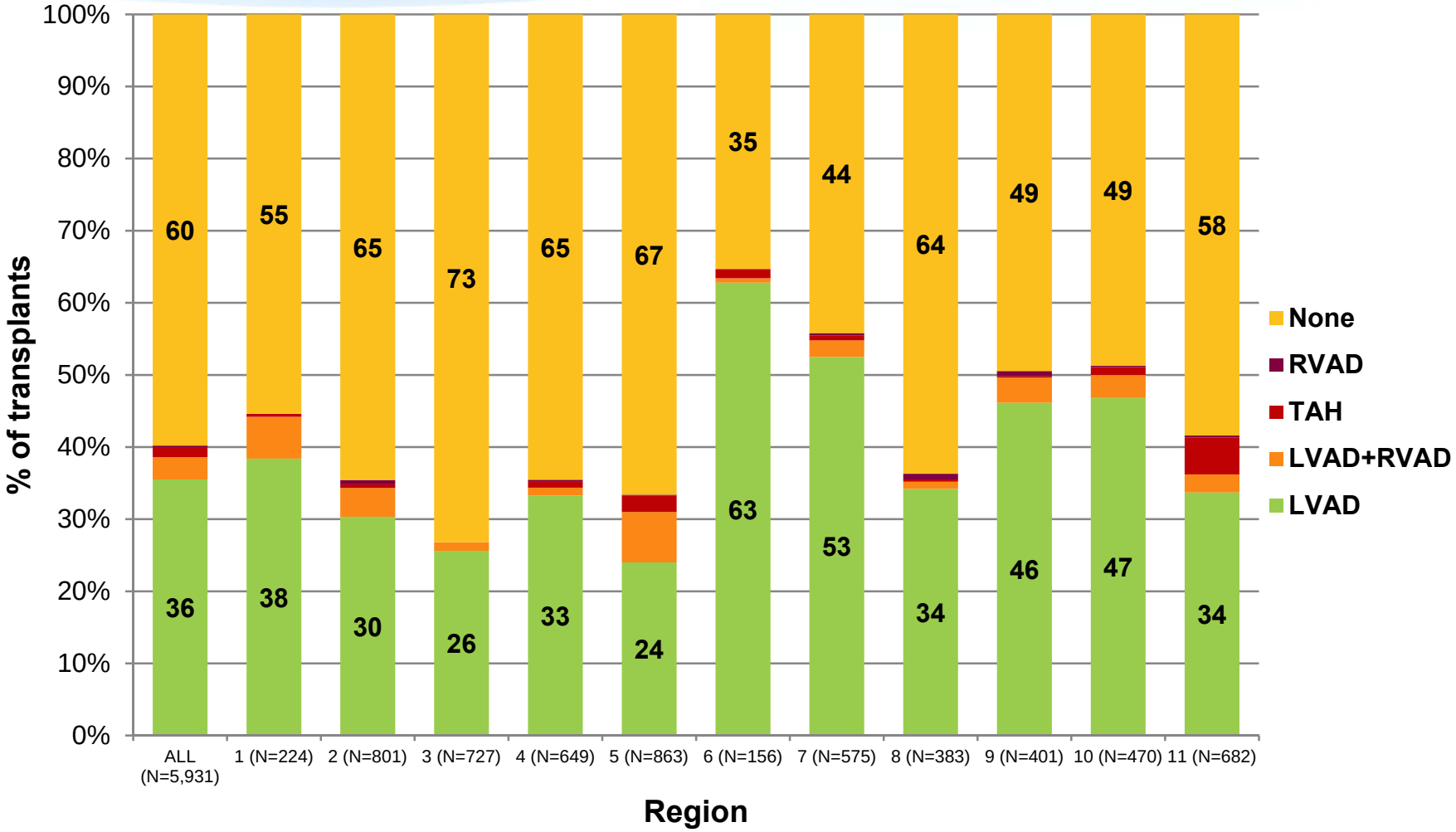
Adult heart recipients 1/2010-12/2012
Stratified by device use at transplant



OPTN

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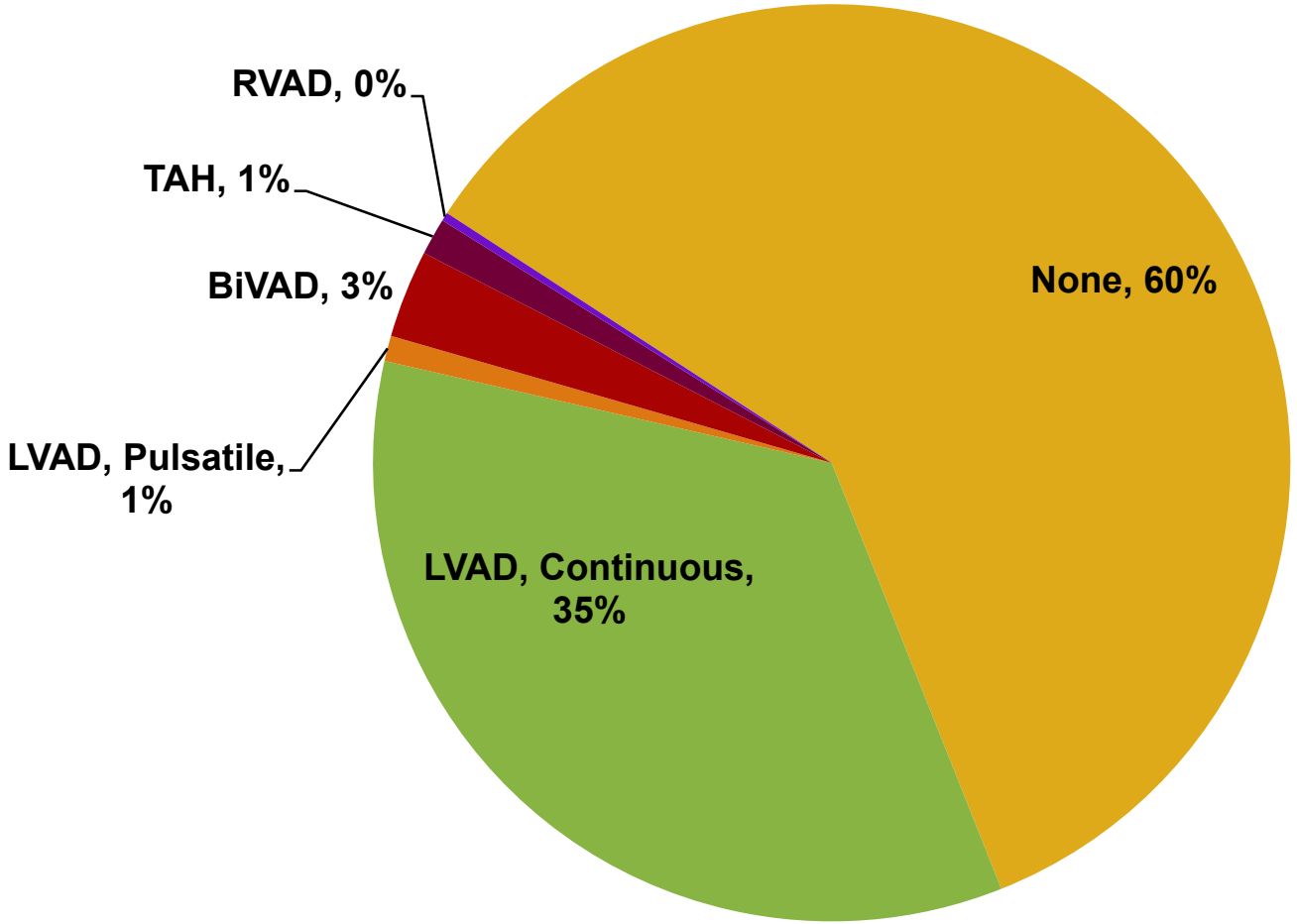
Adult heart recipients 1/2010-12/2012
Stratified by device use at transplant

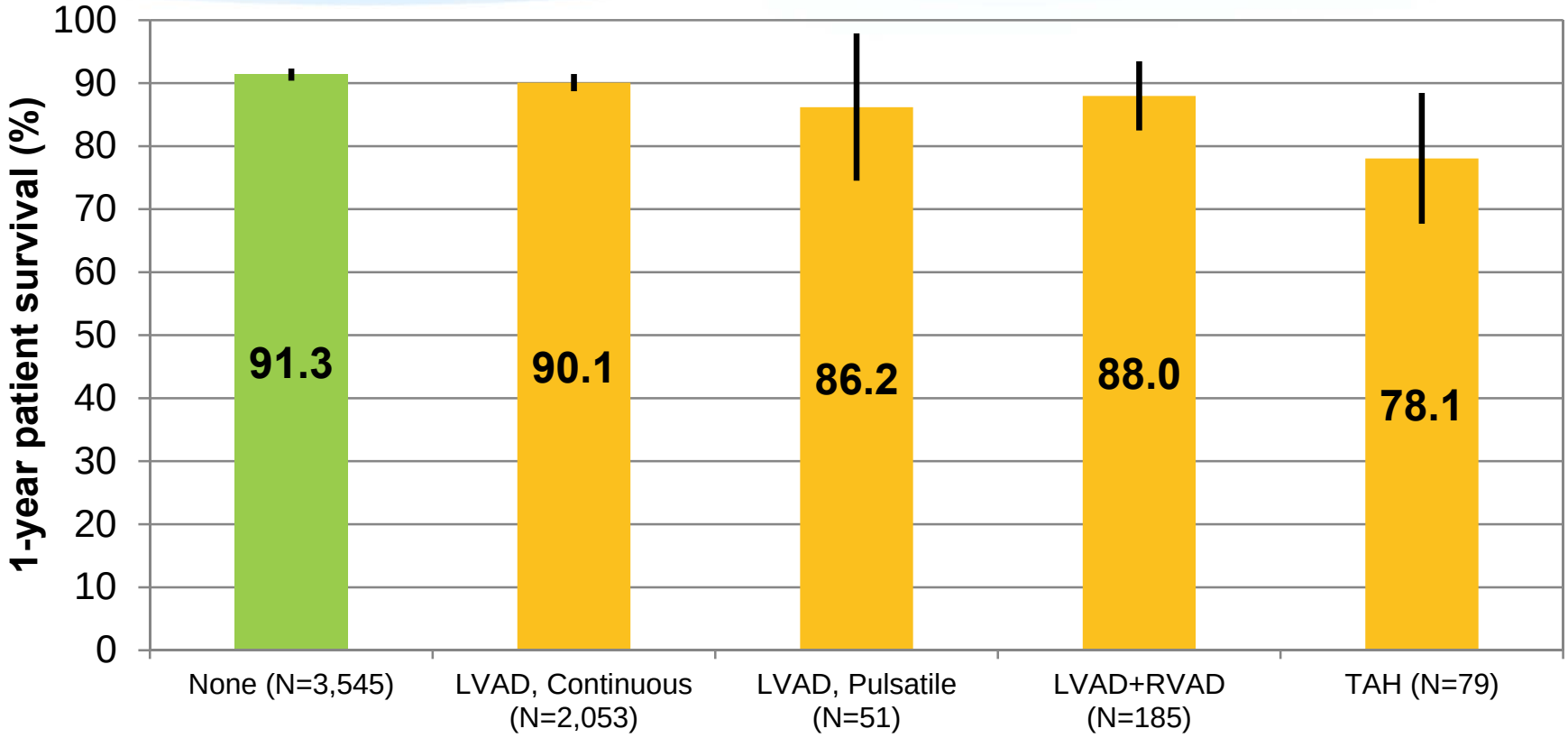


OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

1-year survival in adult heart recipients 1/2010-6/2012

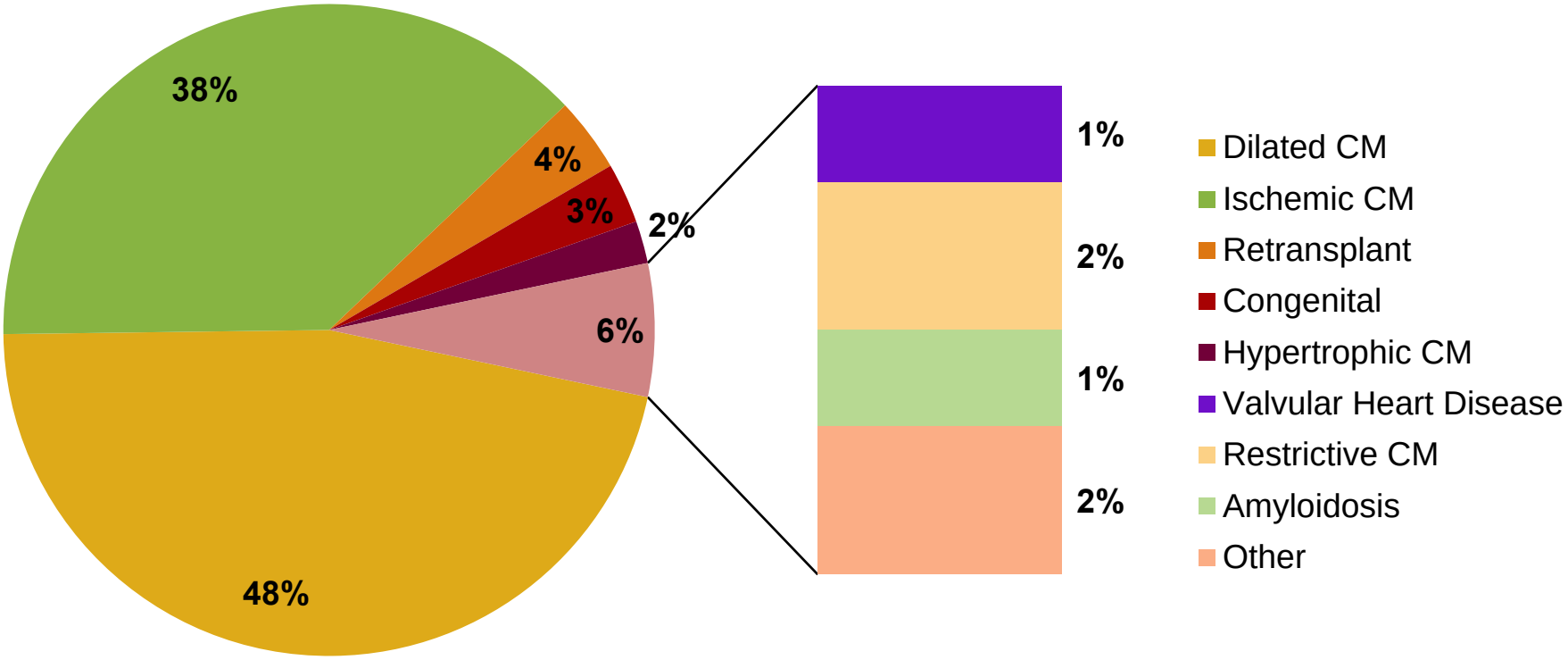
Stratified by device use at transplant



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

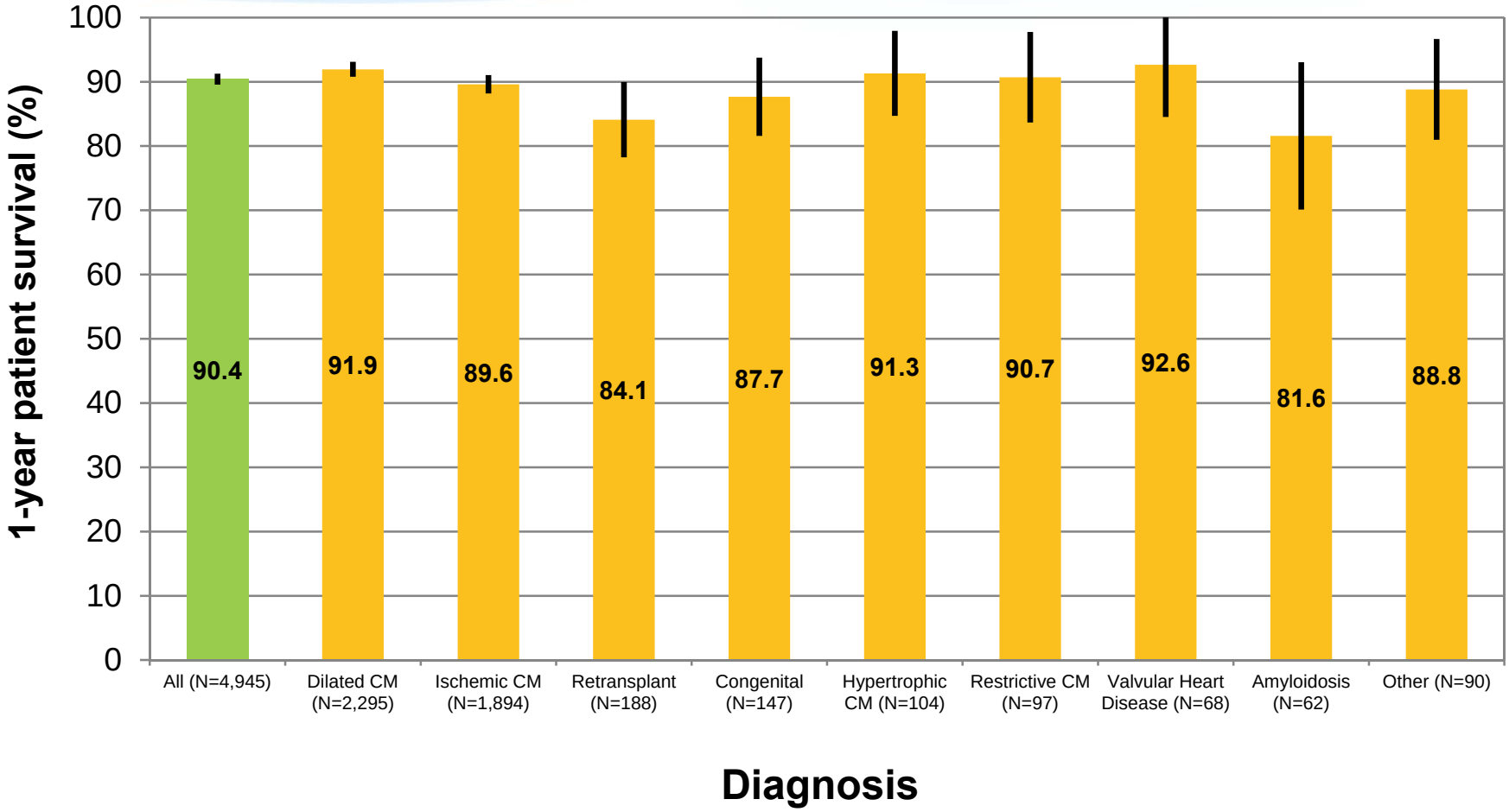
Adult heart recipients 1/2010-12/2012
Stratified by diagnosis



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

1-year survival in adult heart recipients 1/2010-6/2012
Stratified by diagnosis



OPTN

UNOS DONATE LIFE
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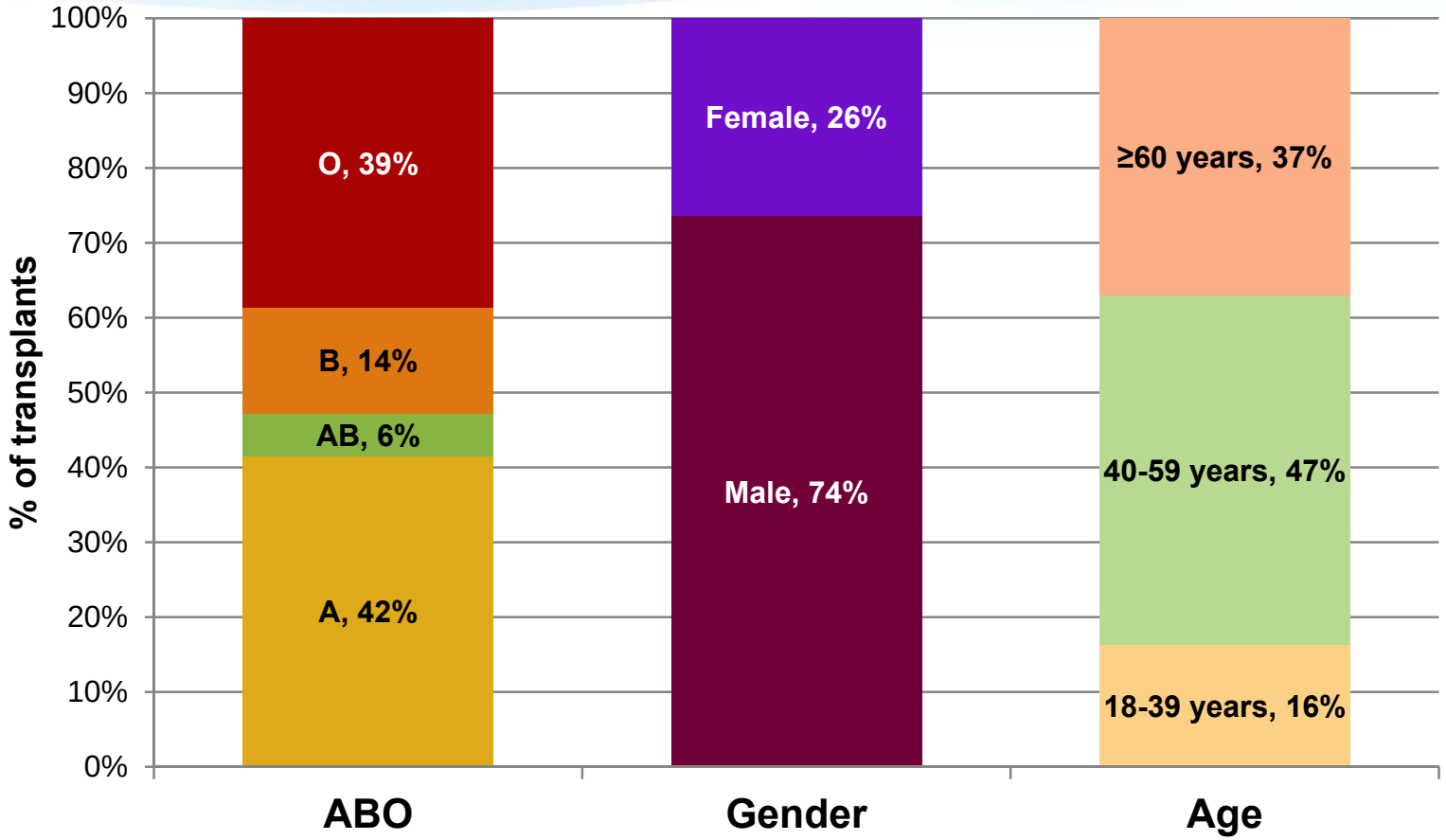
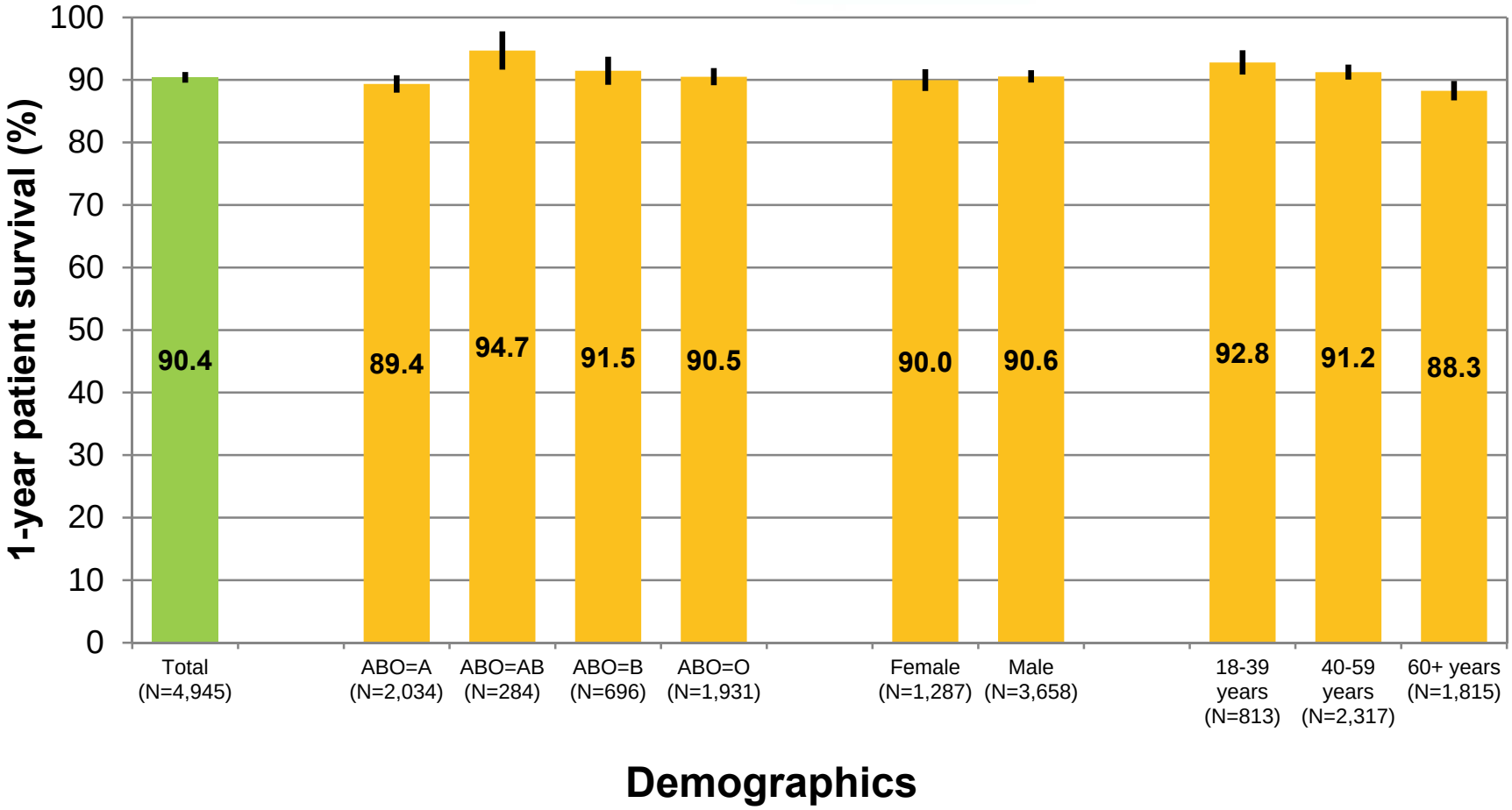
Adult heart recipients 1/2010-12/2012
Stratified by demographics



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

1-year survival in adult heart recipients 1/2010-6/2012
Stratified by demographics



OPTN

UNOS DONATE LIFE
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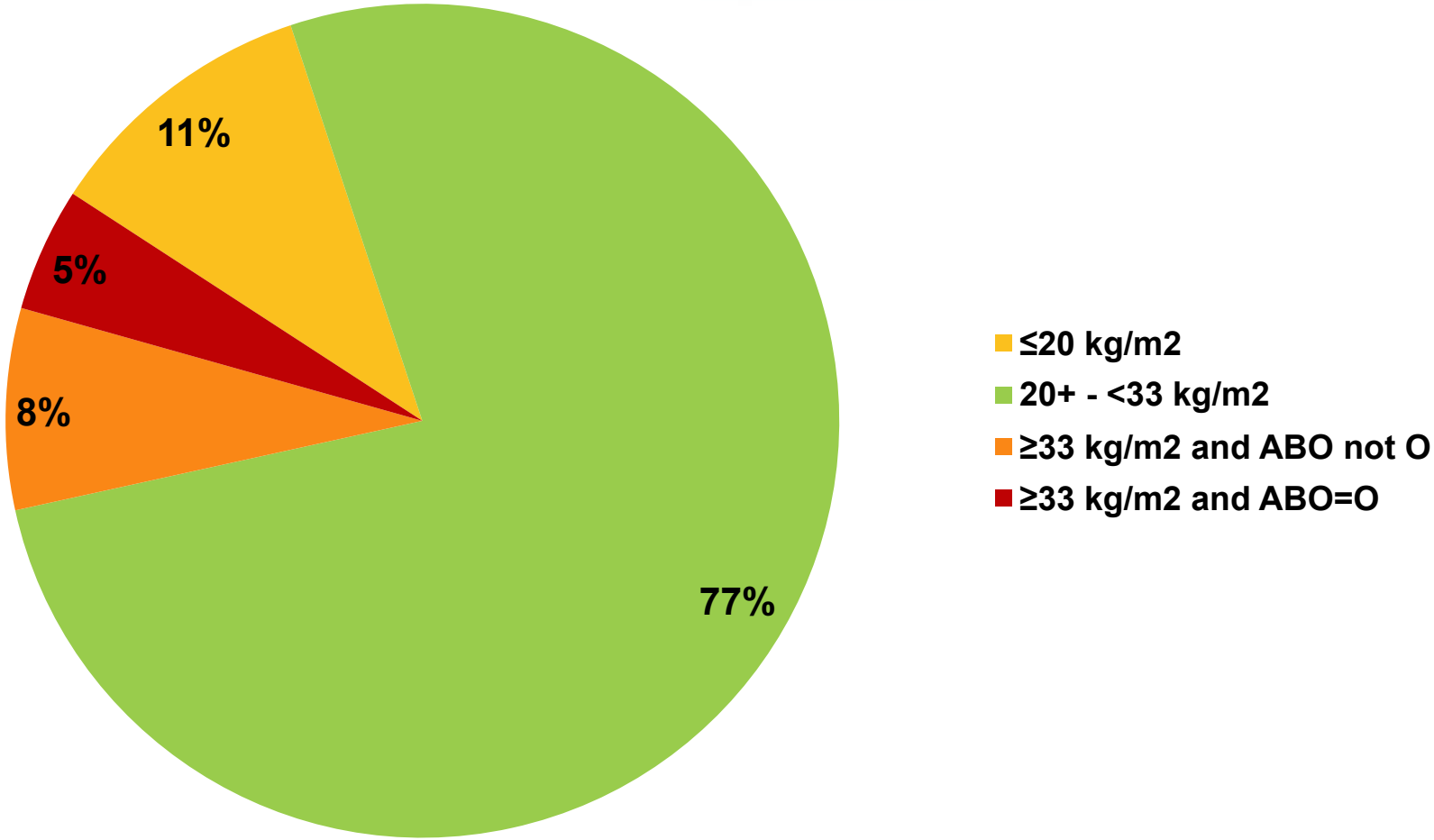
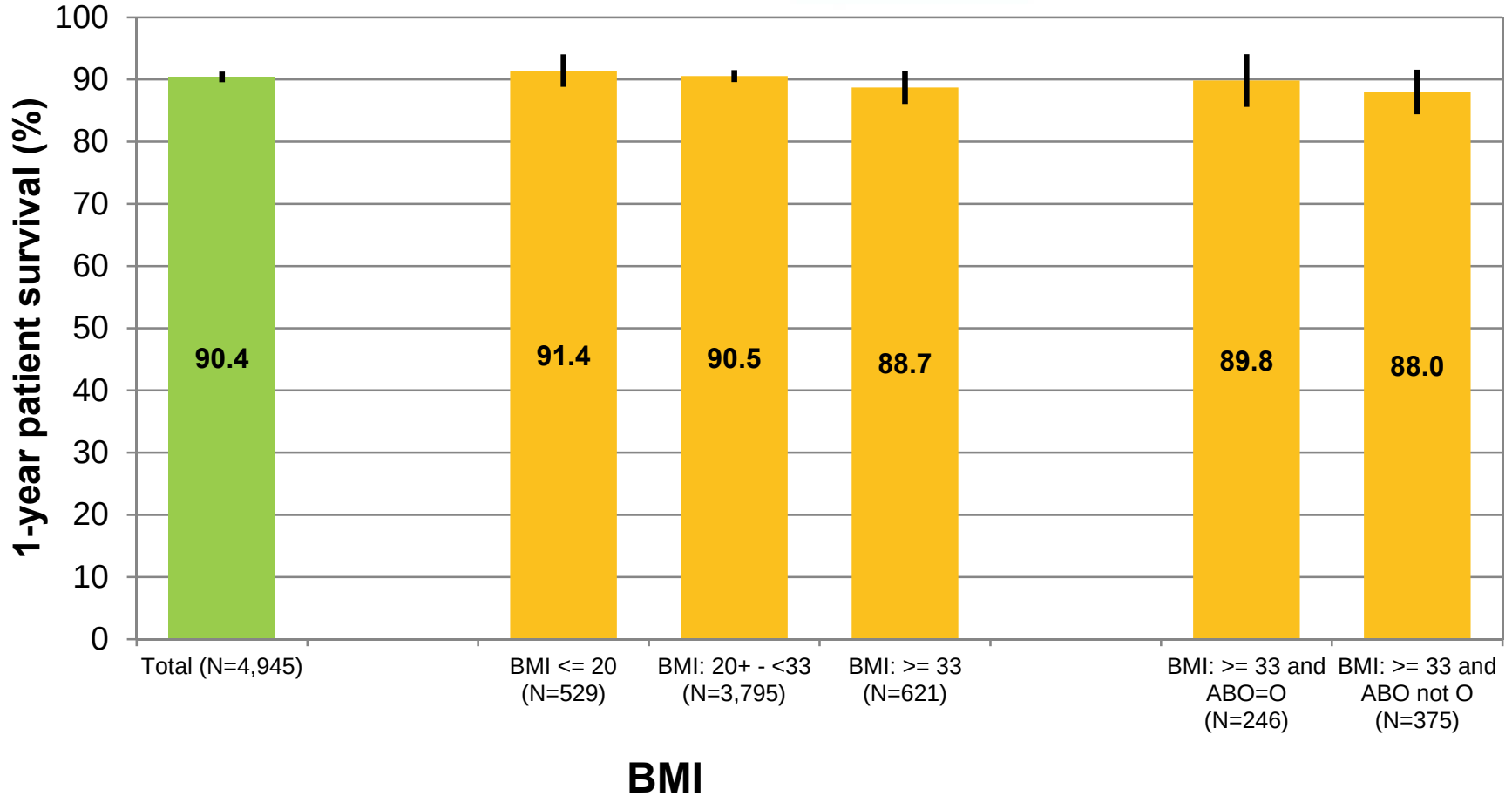
Adult heart recipients 1/2010-12/2012
Stratified by BMI and ABO



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

1-year survival in adult heart recipients 1/2010-6/2012
Stratified by BMI and ABO



OPTN

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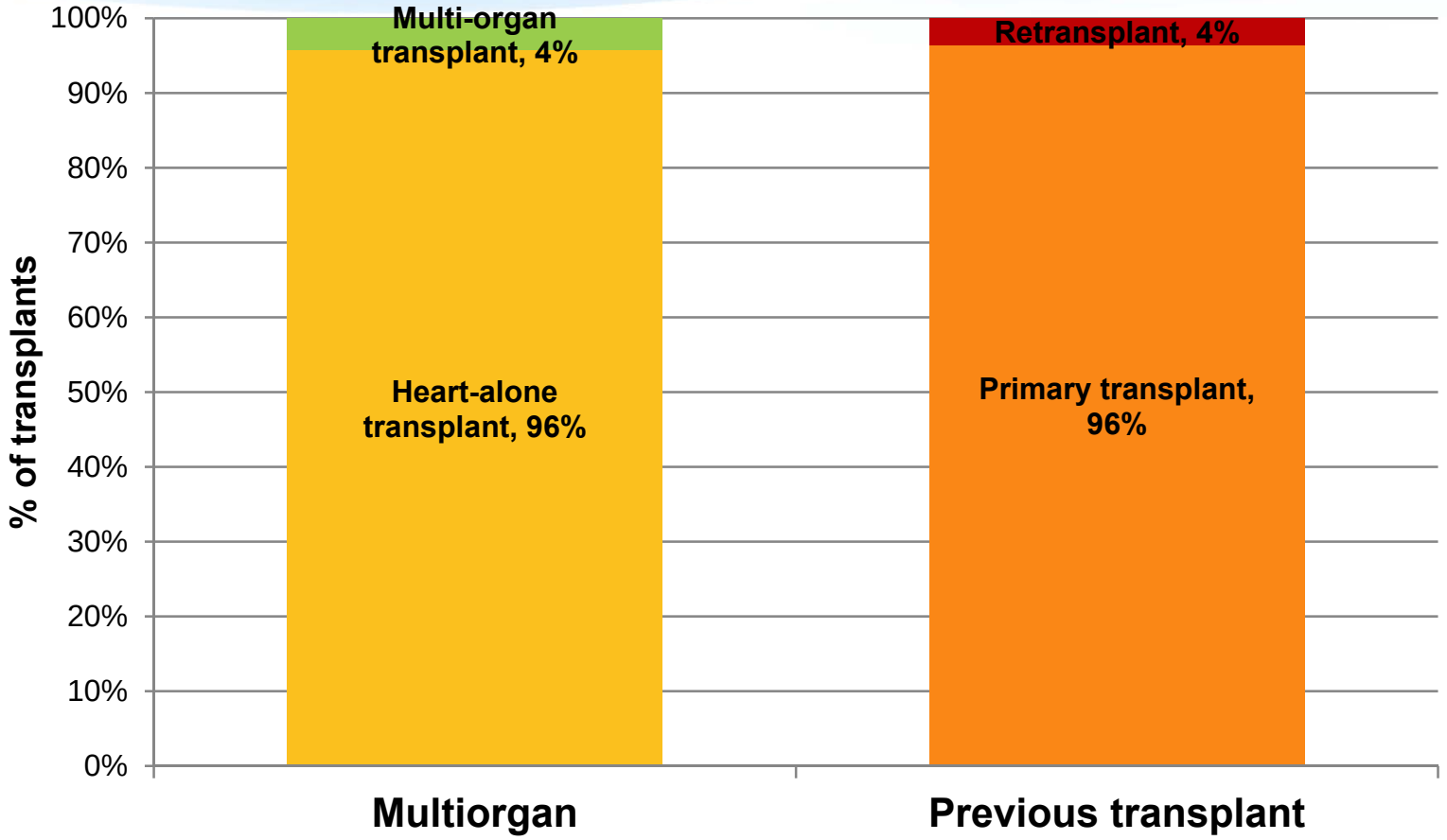
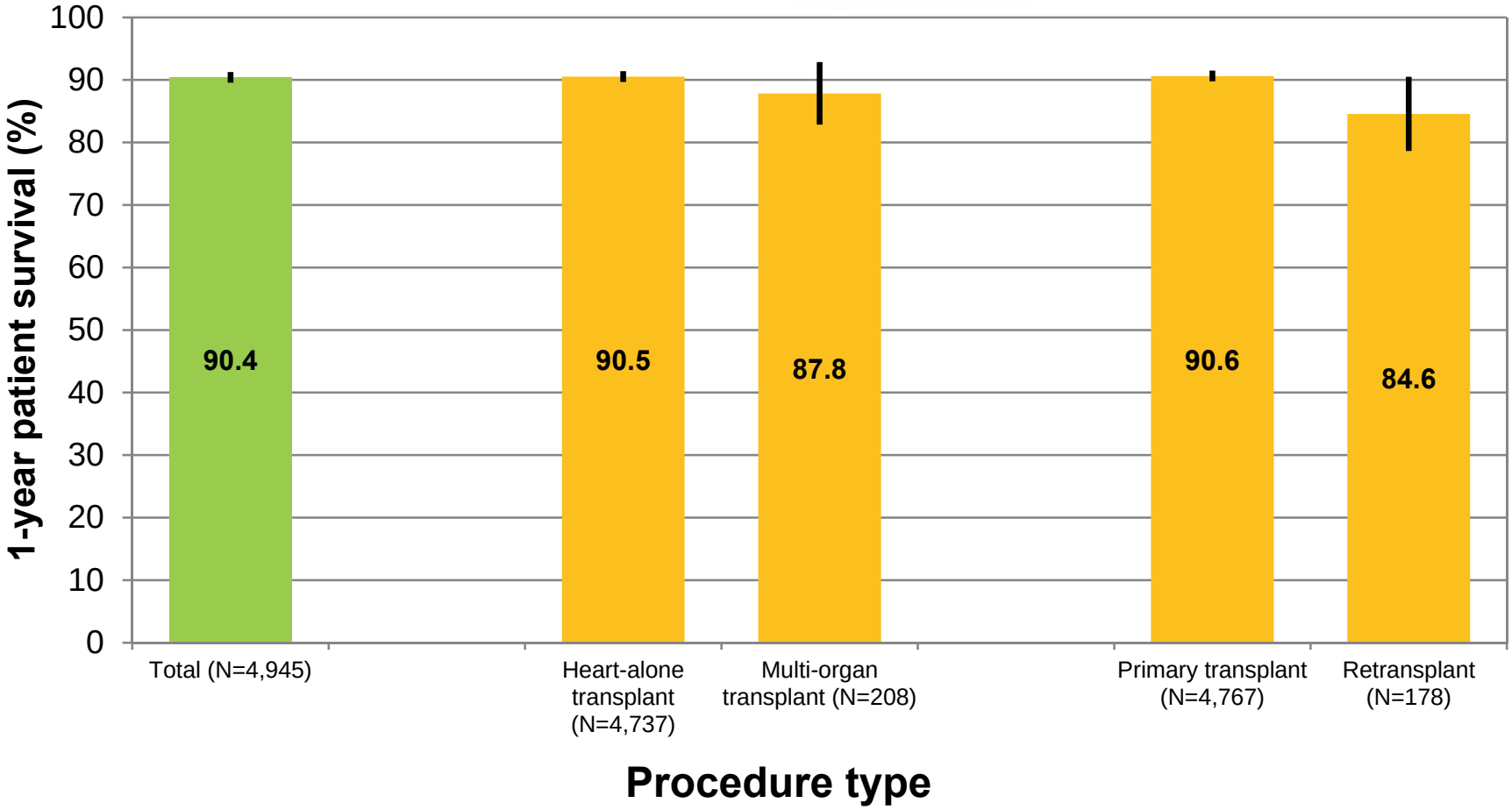
Adult heart transplants 1/2010-12/2012
Stratified by procedure type



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

1-year survival in adult heart recipients 1/2010-6/2012
Stratified by procedure type

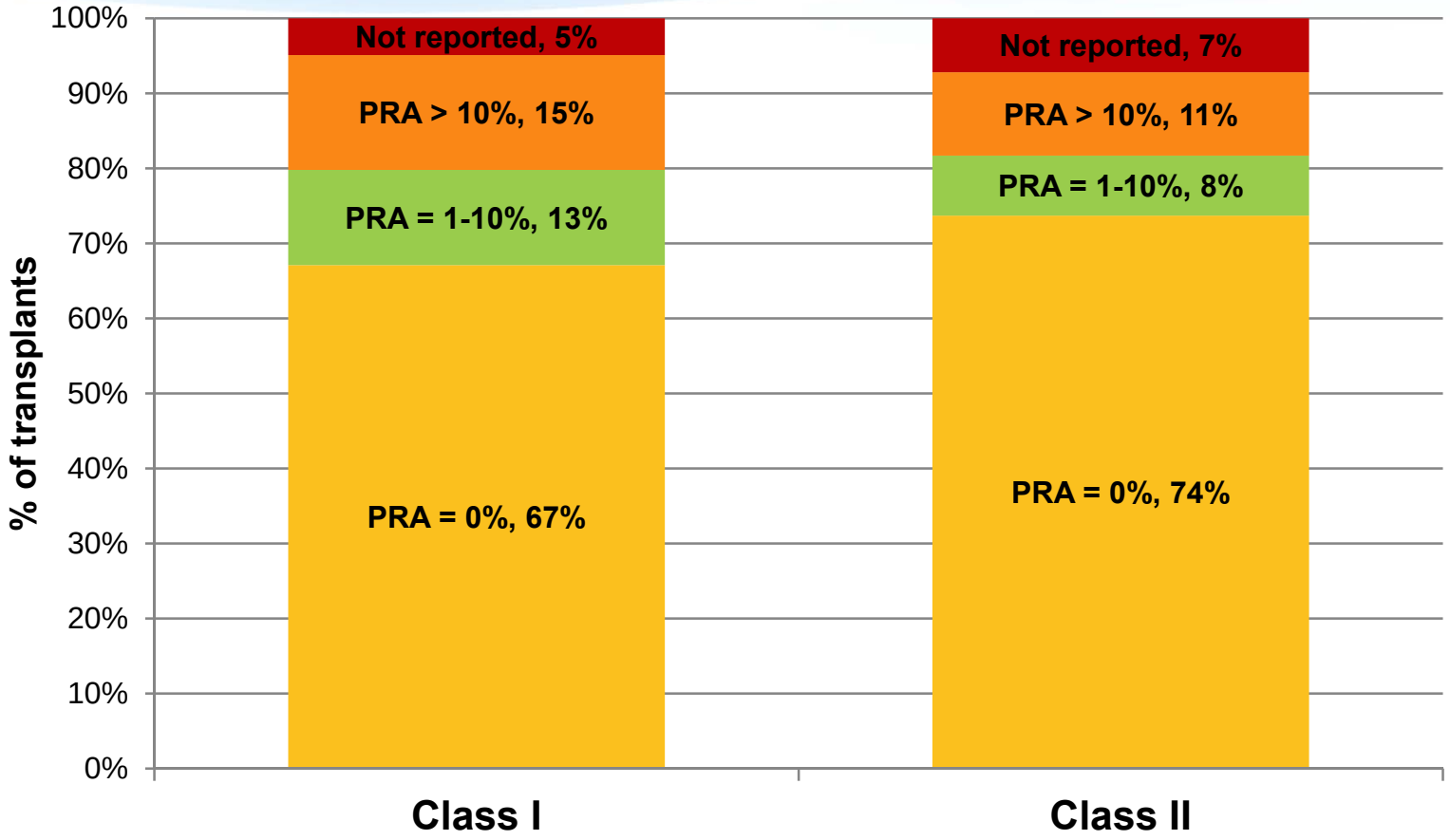


OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

Adult heart transplants 1/2010-12/2012

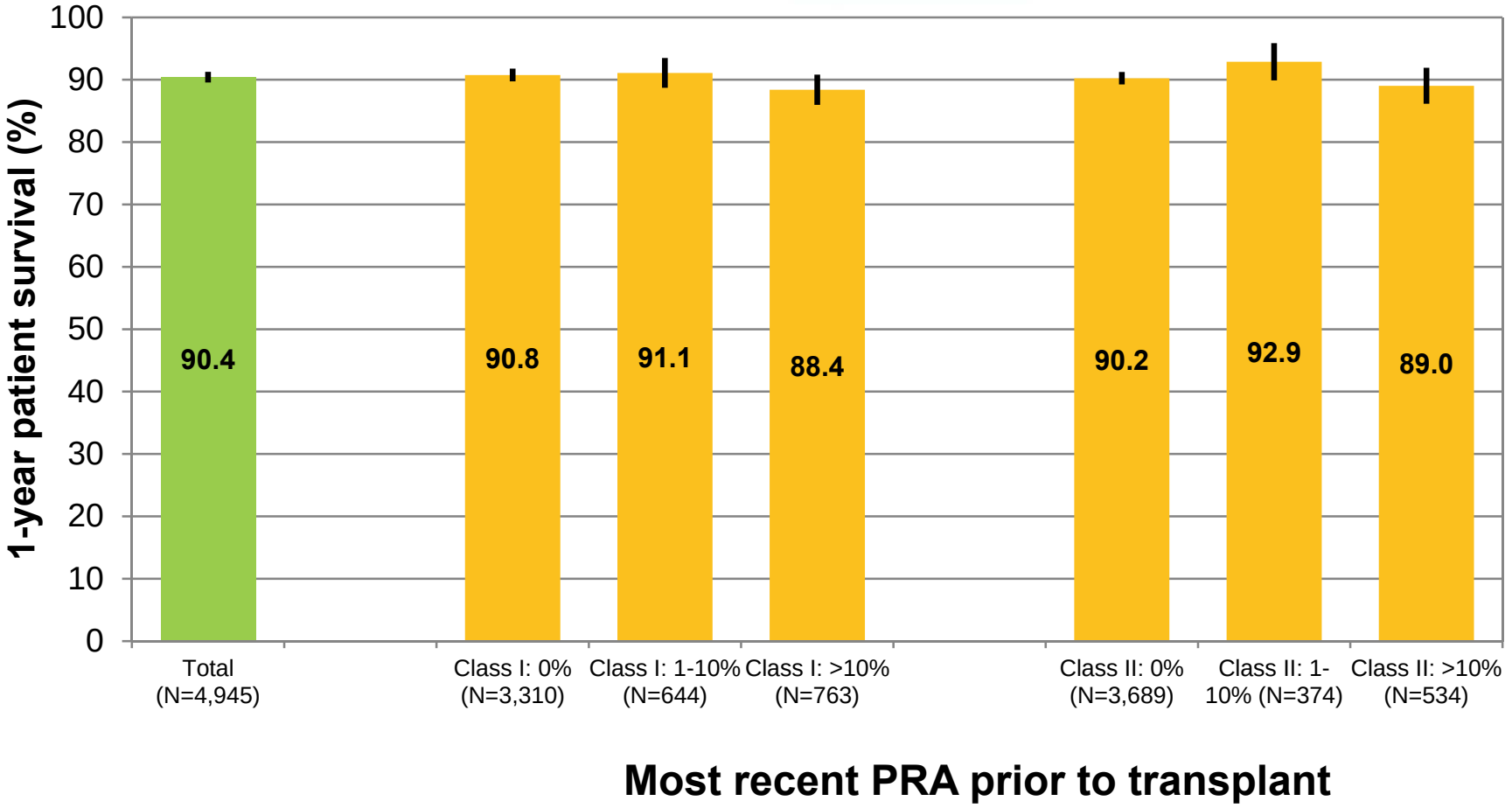
Stratified by most recent PRA prior to transplant



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

1-year survival in adult heart recipients 1/2010-6/2012
Stratified by most recent PRA prior to transplant



OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

FORUM ON U.S. HEART ALLOCATION POLICY

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Multiple listing for pediatric heart transplantation in the USA: Analysis of OPTN registry data from 1995 through 2009

Feingold B, Park SY, Comer DM, Webber SA, Bryce CL. Multiple listing for pediatric heart transplantation in the USA: Analysis of OPTN registry data from 1995 through 2009.

Abstract: Multiple listing is associated with shorter waitlist durations and increased likelihood of transplantation for renal candidates. Little is known about multiple listing in pediatric heart transplantation. We examined the prevalence and outcomes of multiple listing using OPTN data from 1995 through 2009. Characteristics and waitlist outcomes of propensity-score-matched single- and multiple-listed patients were compared. Multiple listing occurred in 23 of 6290 listings (0.4%). Median days between listings was 35 (0–1015) and median duration of multiple listings was 32 days (3–363). Among multiple-listed patients, there were trends toward less ECMO use (0% vs. 11%, p = 0.1) and more frequent requirement for a prospective cross-match (17% vs. 8%, p = 0.08). Multiple-listed patients more commonly had private insurance (78% vs. 56%; p = 0.03). Urgency status at listing was similar between groups (1/1A: 61% vs. 64%, 1B/2: 39 vs. 36%; p = 0.45) as were weight, age, diagnosis, ventilator/inotrope use, and median income (each p ≥ 0.17). There was a trend toward increased incidence of heart transplantation for multiple-listed patients at three, six, and 24 months (50%, 65%, 80%) vs. single-listed patients (40%, 54%, 64%; p = 0.11). Multiple listing for pediatric heart transplantation in the USA occurs infrequently and is more common in patients with private insurance.

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Key words: pediatric heart transplant – waitlist mortality – Organ Procurement and Transplantation Network – socioeconomic factors

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Multiple listing for transplantation is associated with shorter waitlist durations among renal and liver transplant candidates, as well as increases in the likelihood of transplantation and post-transplant survival for renal transplant candidates (1, 2). However, little is known about multiple listing for thoracic organ transplantation. While multiple listings account for 5–6% of renal and 3% of liver transplant listings, we could find only a single reference that indicated eight of 2749 patients (0.3%) listed for heart transplantation and nine of 1999 (0.5%) listed for lung transplantation in the USA as of January 31, 2009, were multiple listed (2). Because all solid organ transplant candidates face similar, chronic shortages in donor organ availability, factors like the severity of the candidate's clinical condition and knowledge about the possibility for multiple listing may drive the imbalance in multiple-listing practices across solid organs.

In this analysis, we sought to determine the prevalence and outcomes of multiple listing for pediatric heart transplantation in the USA. We also sought to explore patient, listing center, and UNOS region characteristics of multiple-listed patients. We hypothesized that multiple-listed candidates would have shorter waitlist durations and achieve transplantation more frequently than single-listed candidates and have similar post-transplant outcomes. We also hypothesized that second listings would more often occur in UNOS regions with shorter waitlist times to transplantation than the primary listing UNOS region.

Abbreviations: ECMO, extra-corporeal membrane oxygenation; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.

Patients and methods

Data source, study population, and definitions

This study used data from the OPTN. The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the USA, submitted by the members of the OPTN, and has been described elsewhere. The Health Resources and Services Administration, US Department of Health and Human Services Administration, provides oversight to the activities of the OPTN contractor. Analyses were performed on a cohort of 6290 children (age <18 yr) listed for isolated heart transplantation in the USA from April 1, 1995, to December 31, 2009, which we have previously described (3). We defined multiple listing as candidate registration at ≥2 centers simultaneously for ≥14 days, or <14 days if the candidate died or was transplanted in that time. Candidates with <14 days of simultaneous waiting time at ≥2 centers who did not meet these criteria were considered as transferring waiting time between these centers and were excluded. Waitlist outcomes were censored at a maximum of two yr after listing, on the last day of observation (March 4, 2011) or upon delisting for ≥14 days. Candidates who were delisted for reasons other than transplantation and then relisted at the same center within 14 days were considered to have a single listing comprised of waitlist time from both listings. Date of death was recorded as the earliest death date in the OPTN data fields or the social security data file death date included with the dataset. Median income was obtained from zip code-level median household income US Census data (4) according to each patient's home zip code at listing in the OPTN file. Distances were calculated from latitude and longitude coordinates determined from zip code (patient) or city and state (listing center) information (5).

Statistical analysis

Summary statistics are presented as mean ± standard deviation or number (percent). Baseline characteristics of all patients who were multiple listed were compared with patients who were single listed using Student's *t*-test, chi-square test, or Fisher's exact test, as appropriate. Because of the imbalances between the multiple- and single-listed groups in some baseline characteristics and to avoid possible selection bias when performing the waitlist outcome analysis of multiple- vs. single-listed patients, we then performed propensity score matching to identify single-listed patients for comparison with the multiple-listed group (6). For this analysis, a multivariable logistic regression model using 15 patient characteristics at listing (age, weight, sex, blood group, race/ethnicity, underlying cardiac diagnosis, preliminary cross-match requirement, year, use of ECMO, use of ventilator, use of inotropes, listing urgency status, UNOS region, median income, and primary payer) was used to generate a propensity score for each patient in the cohort. Single-listed patients were matched 20:1 to multiple-listed patients using optimal matching on the logit of the estimated propensity scores. We then excluded single-listed patients who did not have the same initial waitlist urgency status as their multiple-listed match and those with waitlist duration less than the duration from first to second listing for their multiple-listed match. We did this to ensure that any difference in favor of multiple-listed patients was not due to their time accrued/survival on the waiting list prior to becoming multiple listed. For each multiple-listed patient, we then selected the four matched single-listed patients with logit of the propensity score that was closest to their multiple-listed match and <7.5. Using this strategy, we were unable to match any single-listed patients to three multiple-listed patients (one for time and two for listing status), and these multiple-listed patients were excluded from the outcome analysis. Thus, we analyzed outcomes for 20 multiple-listed and 67 matched, single-listed patients.

To assess whether regional variations in time to transplantation may have influenced the choice of location of the multiple-listing center, we determined both national and UNOS region-specific median times to transplantation in our OPTN cohort by era. Three eras (listing dates 4/1/95-1/19/1999, 1/20/1999-6/30/2006, and 7/1/2006-12/31/2009) were chosen to coincide with major changes in OPTN heart allocation policy on urgency status (1 separated into 1A and 1B) or sequence of heart allocation (7–9). We then compared era-specific, regional median times to transplantation for the primary and secondary listing centers for each multiple-listed patient.

Waitlist outcomes (death, transplantation, delisting, and still awaiting transplant) were depicted as competing outcome plots and compared using Gray's test (10). Post-transplant survival was assessed by Kaplan–Meier plot with log-rank test. Nonparametric methodology was used to compare observed median times to transplantation of each era–region combination to the median time to transplantation of 1000 randomly drawn samples of the same size from (i) era-specific national data and (ii) other era-specific regions. All tests were two-sided with the significance level of 0.05. Data were analyzed with SAS v9.2 (SAS Institute Inc, Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). The study was conducted with the approval of the University of Pittsburgh Institutional Review Board and OPTN.

Results

Prevalence and distribution of multiple listings

Multiple listing occurred in 23 of 6290 (0.4%) listings for isolated pediatric heart transplantation in the USA between April 1995 and December 2009. No candidate was listed at >2 centers simultaneously. The distribution of multiple listings by UNOS region and listing center is shown in Fig. 1. All multiple listings were among 26 centers, and 78% of multiple listings occurred between unique pairings of transplant centers. Five UNOS regions (2, 3, 5, 7, and 8) accounted for 76% of all multiple listings.

The number of listings by year and era is shown in Fig. 2. Thirty-nine percent of multiple listings occurred between 1995 and 1997, and 91% of multiple listings occurred prior to June 30, 2006, when UNOS allocation policy was amended to expand regional organ sharing. When standardized for time, there were 1.9 ± 1.2 multiple listings per year from April 1995 through June 2006 and 0.6 ± 0.6/yr from July 2006 through December 2009 ($p = 0.057$).

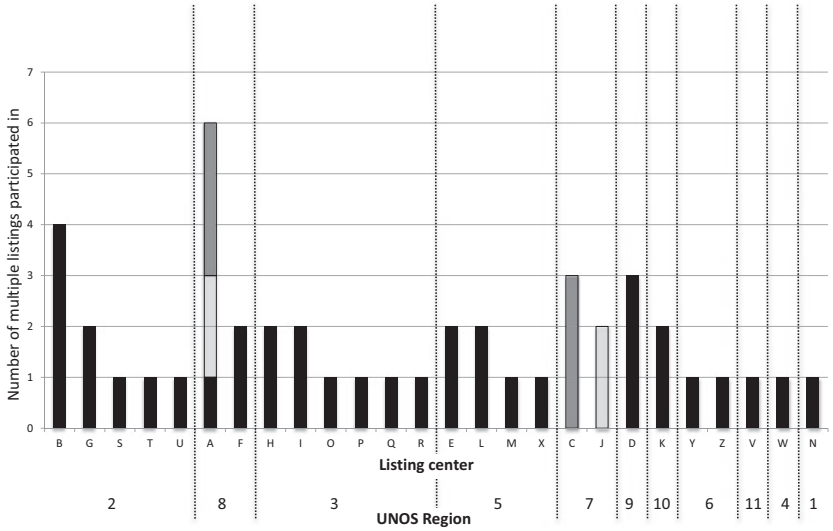

Fig. 1. Multiple listings for heart transplantation in USA by listing center and United Network for Organ Sharing (UNOS) region from April 1995 through December 2009. Centers are indicated by arbitrary letter assignment. Centers that shared repeated pairings for multiple listings are shown in light gray (A and J, n = 2) and dark gray (A and C, n = 3).

Multiple-listed patient characteristics

Characteristics of the single- and multiple-listed patients are shown in Table 1. Among multiple-listed patients, there was a greater proportion of males (78% vs. 56%; p = 0.03) and private insurance (78% vs. 56%; p = 0.03). Also, use of ECMO was less common (0% vs. 11%, p = 0.1), and prospective cross-match requirement was more common (17% vs. 8%, p = 0.08) for multiple-listed patients, although neither reached statistical significance. Prospective cross-match requirement was also not associated with multiple listing in different UNOS regions (1 of 4 with a prospective cross-match requirement was listed in a different region vs. 12 of 17 without a prospective cross-match requirement were listed in different UNOS regions; p = 0.9). A difference in urgency status between the groups was observed, with a greater proportion of multiple-listed patients listed status 1. However, when categorized into statuses 1/1A, 1B, and 2/7, there was no significant difference in listing status between the groups (p = 0.24).

The median number of days from first to second listing was 35 (range 0–1015), and the median duration of multiple listings was 32 days (3–363). The median distance between multiple-listing centers was 390.9 miles (0–905.0). One-quarter of the patients were multiple listed at centers that were ≤100 miles apart, and 78% were multiple listed at centers ≤500 miles apart. Ten of

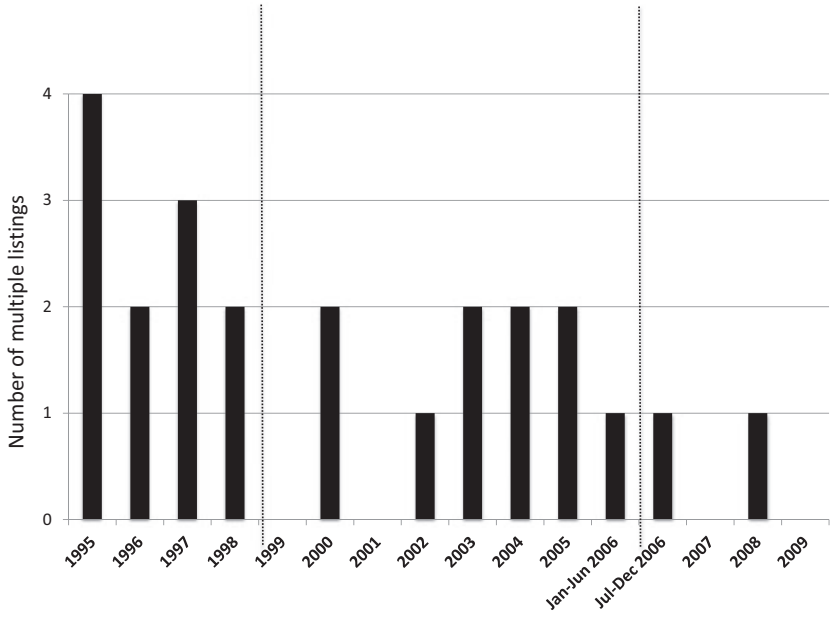

Fig. 2. Multiple listings for pediatric HTx in the USA from April 1995 through December 2009.

Table 1. Patient characteristics at listing

Variable	Single listed (n = 6267)	Multiple listed (n = 23)	p
Male	3523 (56%)	18 (78%)	0.03
Age	5.5 ± 6.1 2 (0–17)	6.1 ± 6.7 4 (0–17)	0.64**
Weight (kg)	23.4 ± 24.5 12 (1.4–187)	26.5 ± 28.7 14 (3.2–105)	0.55**
Listing year	2002 ± 4.3 2002 (1995–2009)	2000 ± 4.3 2000 (1995–2008)	0.022**
Blood group			
O	3058 (49%)	12 (52%)	0.97
A	2214 (35%)	7 (30%)	
B	761 (12%)	3 (13%)	
AB	234 (4%)	1 (4%)	
Race			
White	3676 (59%)	16 (70%)	0.76
Black	1235 (20%)	3 (13%)	
Hispanic	1045 (17%)	3 (13%)	
Other	311 (5%)	1 (4%)	
Cardiac diagnosis			
Dilated cardiomyopathy	2470 (39%)	7 (30%)	0.53
Hypertrophic cardiomyopathy	161 (3%)	0 (0%)	
Restrictive cardiomyopathy	302 (5%)	1 (4%)	
Previous transplant	175 (3%)	1 (4%)	
HLHS, unoperated	83 (1%)	0 (0%)	
CHD without prior surgery	176 (3%)	0 (0%)	
CHD with prior surgery	891 (14%)	2 (9%)	
CHD prior surgery unknown	1868 (30%)	12 (52%)	
Other	141 (2%)	0 (0%)	
UNOS status			
1	1076 (17%)	9 (39%)	0.025
1A	2909 (46%)	5 (22%)	
1B	603 (10%)	4 (17%)	
2	1639 (26%)	5 (22%)	
7	40 (1%)	0 (0%)	
Preliminary cross-match required	474 (8%)	4 (17%)	0.08
ECMO	667 (11%)	0 (0%)	0.1
Ventilator	1698 (27%)	5 (22%)	0.56
Inotropes	3073 (49%)	8 (35%)	0.17
Primary payer*			
Public/Gov't insurance	2700 (45%)	5 (22%)	0.03
Private Ins	3374 (55%)	18 (78%)	
Median income (USD)	43 272 ± 16 560	47 842 ± 19 337	0.19

CHD, congenital heart disease; ECMO, extra-corporeal membrane oxygenation; Gov't, government; HLHS, hypoplastic left heart syndrome; USD, US dollars.
*193 single-listed patients have a primary payer other than public/Gov't or Private (i.e., self, donation, free care, pending, foreign government, or missing) and are not included.
**Student's *t*-test. Statistical comparison of medians and ranges was not performed.

23 (44%) multiple-listed patients were transplanted at the primary listing center, and nine (39%) were transplanted at the secondary listing center.

Era–region analysis

Eight multiple listings were within the same UNOS region and 15 (65%) were in different UNOS regions. Among the 15 in different regions, five had their second listing in a region with a longer median time to transplantation than the region of their primary listing (56 vs. 32 days, p = 0.009; 48 vs. 36 days, p = 0.043; 53 vs. 33 days, p = 0.005; and for two patients 48 vs. 33 days, p = 0.002), while only one patient's second listing was in a region with a shorter time to transplantation (48 vs. 33 days; p = 0.005). There was no significant difference in regional median time to transplantation for the first and second listings for nine patients.

Outcomes for the propensity-score-matched cohorts

There were no significant differences in listing characteristics between the matched cohorts (Table 2). Fig. 3 shows the waitlist competing outcomes after multiple listing or equivalent amount of waitlist time accrued for matched, single-listed patients. There were no statistically significant advantages for patients who were multiple listed. Among the 17 multiple-listed and 44 single-listed patients who achieved transplantation, there was no statistically significant difference in post-transplant survival (p = 0.18; Fig. 4).

Discussion

In this analysis, we have shown that multiple listing for pediatric heart transplantation is rare, occurring in only 0.4% of listings between April 1995 and December 2009. Because of this low prevalence, we were limited in our ability to detect all but a large difference in outcomes. Thus, it is possible that the trend toward enhanced waitlist and post-transplant survival of multiple-listed patients observed here would be confirmed with a greater number of multiple-listed patients to analyze. This would be consistent with higher transplant rates observed in multiple-listed, adult renal and liver transplant candidates (1), which is the intended goal of multiple listing.

Males and those with private insurance were more common among multiple-listed candidates. This is interesting because it is consistent with the renal and liver experience on multiple listing despite the much lower prevalence of multiple listing in pediatric heart transplantation (0.4% vs. 3–6%) (1). One possible explanation is that the difference in insurance status signifies increased social and/or financial means of

Table 2. Patient characteristics at listing after propensity matching

Variable	Single listed (n = 67)	Multiple listed (n = 20)	p
Male	53 (79%)	16 (80%)	0.93
Age	6.9 ± 6.7 5 (0–17)	5.6 ± 6.5 2.5 (0–17)	0.42*
Weight (kg)	31.1 ± 32.5 17.7 (2.5–140)	26.3 ± 30.1 13.6 (3.2–105)	0.56*
Listing year	1999 ± 3.6 1998 (1995–2009)	1999 ± 4.3 1998 (1995–2008)	0.53*
Blood group			
O	38 (57%)	9 (45%)	0.73
A	16 (24%)	7 (35%)	
B	11 (16%)	3 (15%)	
AB	2 (3%)	1 (5%)	
Race			
White	48 (72%)	15 (75%)	0.29
Black	13 (19%)	1 (5%)	
Hispanic	4 (6%)	3 (15%)	
Other	2 (3%)	1 (5%)	
Cardiac diagnosis			
Dilated cardiomyopathy	27 (40%)	5 (25%)	0.27
Restrictive cardiomyopathy	2 (3%)	1 (5%)	
Previous transplant	4 (6)	1 (5%)	
CHD with prior surgery	1 (2%)	2 (10%)	
CHD prior surgery unknown	33 (40%)	11 (55%)	
UNOS status			
1	34 (51%)	9 (45%)	0.88
1A	11 (16%)	3 (15%)	
1B	6 (9%)	3 (15%)	
2	16 (24%)	5 (25%)	
7	0 (0%)	0 (0%)	
Preliminary cross-match required	12 (18%)	4 (20%)	0.83
ECMO	0 (0%)	0 (0%)	n/a
Ventilator	9 (13%)	5 (25%)	0.22
Inotropes	20 (30%)	6 (30%)	0.99
Primary payer			
Public/Gov't insurance	16 (24%)	4 (20%)	0.72
Private Ins	51 (76%)	16 (80%)	
Median income (USD)	45 448 ± 17 095	47 213 ± 16 937	0.69

CHD, congenital heart disease; ECMO, extra-corporeal membrane oxygenation; Gov't, government; USD, US dollars.
*Student's *t*-test. Statistical comparison of medians and ranges was not performed.

families of multiple-listed candidates. However, it is important to note that we did not observe a significantly greater median household income in multiple-listed candidates using zip code-based census data. We also observed a trend toward less ECMO support at listing among multiple-listed patients. This likely reflects severity of illness and thus an inability to be transported for evaluation (or transplantation) at another center. While our finding that multiple-listed patients more commonly had a requirement for a prospective cross-match might suggest that these patients sought to increase their chance of transplantation by having their serum available for a prospective cross-match at more than one center, we observed no difference in the proportions who listed within different UNOS regions among multiple-listed patients with and without a prospective cross-match requirement. We also found that a significant minority of patients (45%) were multiple listed in the same UNOS region and that regional differences in time to transplantation (adjusted for era) did not influence the selection of the second listing center.

While multiple listing was allowed early in the US solid organ transplant experience, UNOS sought to ban the practice in 1988 over concerns that patients who received organs while listed at more than one center did so at the expense of single-listed patients (2). Due to the lack of public support, the proposed ban was ultimately not enacted. For a period of time, there continued to be debate over the practice, but it is now well established and supported to the extent that OPTN policy stipulates that all candidates must be informed of the option of multiple listing (OPTN policy 3.2.3). One possible reason that multiple listing is more common among renal and liver transplant candidates is that nearly all await transplantation as outpatients. This more easily allows for travel to multiple centers for transplant evaluation than for patients who are awaiting transplantation as an inpatient. Once hospitalized to await transplantation, it is virtually impossible to remain multiple listed due to the impracticability of urgent medical transport with no advance notice should an organ becomes available to the candidate at the center where he/ she is not hospitalized. In our own center's recent experience, we found this to be a significant practical barrier to multiple listing. Although our status 1A candidate who was on "high-dose" inotropic support was multiple listed in Pittsburgh and at a center on the east coast, in practice, she would have been unable to travel to the other center had an organ come available to her there. Also because US heart allocation policy currently favors transplantation of higher-status candidates across regions over lower-status candidates within region (10), the advantages of multiple listing for outpatient, lower-status heart candidates are diminished relative to renal and liver candidates. This is consistent with our finding that multiple listing was less common following the 2006 change in heart allocation policy designed to reduce waitlist mortality through geographically broader organ sharing.

While our own experience suggests that multiple listing at geographically remote centers for inpatient status 1A candidates is impractical due

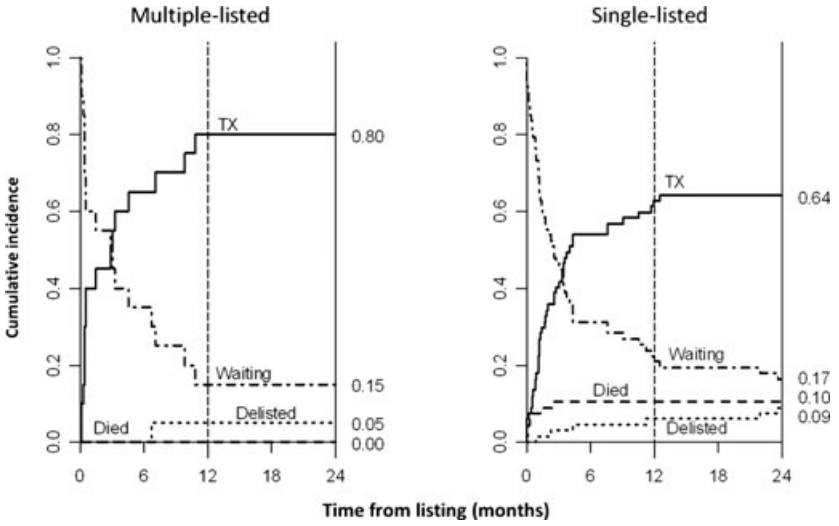

Fig. 3. Waitlist outcomes for the multiple- and single-listed matched cohorts.

to the time constraints upon receipt of donor organ offer, it is possible that multiple listing could be beneficial for outpatient status 1A candidates who are listed in different UNOS regions. Such candidates would theoretically be able to maximize access to a broader pool of donor organs (via multiple listing at remote centers) while maintaining priority to organ offers (based on current allocation policy) and be able to travel to either listing center via pre-arranged "on-call" air transportation.

Important limitations of our analysis are its use of registry data and the relative infrequency of the event of interest, which severely limited our power to detect smaller differences. We sought to overcome the low event frequency by propensity score matching of multiple-listed patients up to 4:1 with single-listed patients. Because we also thought it was vital to control for urgency status at listing and to match only to single-listed patients who had accrued at least as much waiting time as their multiple-listed match, we were only able to include 20 multiple-listed patients and 67 matched single-listed controls. Nonetheless, we found a trend consistent with renal and liver experience with regard to decreased time to transplantation for the multiple-listed pediatric heart cohort. Also our use of the OPTN dataset enabled us to study the entire US experience of multiple listing for pediatric heart transplantation. Finally, median income data were derived from zip code-level census data, the heterogeneity of which with respect to economic status (11) may have limited our ability

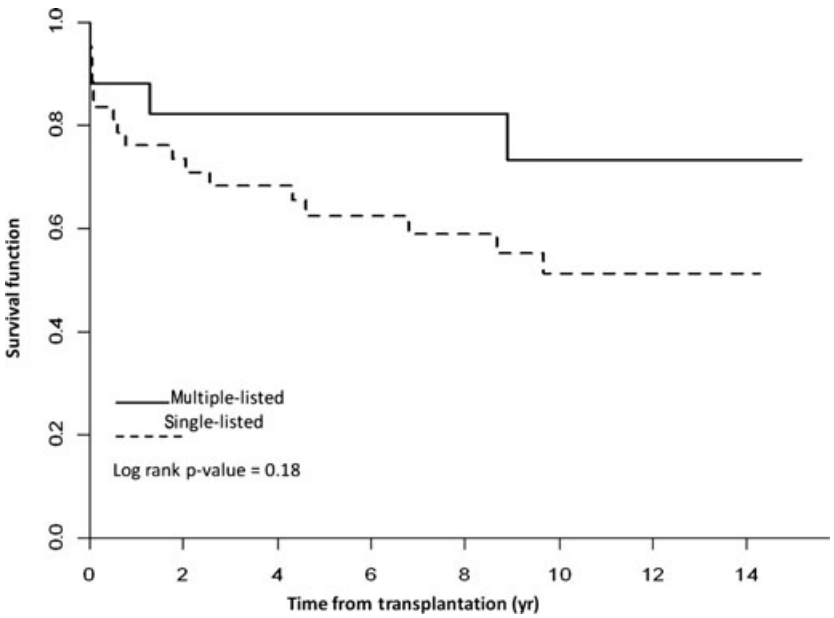

Fig. 4. Kaplan–Meier curve depicting survival after transplantation for the multiple- and single-listed matched cohorts.

to detect a true difference in income between the groups that could substantiate the difference in insurance status observed in this and other studies of multiple-listed candidates.

In summary, multiple listing for pediatric heart transplantation has occurred rarely in the USA since 1995, with a decrease in frequency since the 2006 change in allocation policy favoring regional sharing to the highest status candidates. Similar to renal and liver transplantation, multiple listing occurs more commonly in patients with private insurance. However, unlike renal and liver transplantation, we found only a trend toward improved waitlist survival and no statistically significant difference in post-transplant survival for multiple-listed patients. Because of the rarity of multiple listing, further registry analyses are unlikely to be informative, and alternative approaches, such as querying listing centers and candidates' families about perceived barriers to multiple listing, should be considered.

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Authors' contributions

Brian Feingold contributed to the concept/design, data analysis/interpretation, drafting of the article, critical revision of the article, and approval of the article. Seo Young Park was involved in statistics, data analysis, and approval of the article. Diane Comer contributed to statistics, data analysis, and approval of the article. Steven Webber was involved in data interpretation, critical revision of the article, and approval of the article. Cindy Bryce contributed to the design, data interpretation, critical revision of the article, and approval of the article.

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Editorial

Multiple listing for pediatric heart transplantation: Is one child's gain, another child's loss?

In the United States, the regulations from the United Network for Organ Sharing (UNOS) state that each candidate for organ transplantation be counseled regarding the opportunity for multiple listing (1). Multiple listing involves registering at two or more transplant centers. Some studies have suggested that multiple listing can shorten the average wait times of kidney transplants by several months (2). While the Organ Procurement and Transplant Network (OPTN) policy allows multiple listing, it is up to the individual transplant center to decide whether or not to accept a multiple listing patient. In general, this strategy of multiple listing has been considered more frequently in kidney and liver transplant candidates than in heart transplant candidates.

To date, almost nothing is known about the use of multiple listing in children being considered for heart transplantation. In the absence of any published data regarding multiple listing for pediatric heart transplant candidates, it has been quite difficult to counsel any families as to how they might benefit from such a strategy. In this intriguing paper by Feingold et al. (3), analysis of the OPTN data set provides the first insight into the use of multiple listing in children. The study found a trend toward a higher proportion of the multiply listed patients undergoing transplantation by three months in a competing risk analysis, suggesting that there may be a benefit to this approach. Interestingly, the authors also reported a non-significant trend toward a higher proportion of prospective cross-match listings in the multiple listing group. This subgroup of patients might represent the ideal group for multiple listing as prospective cross-match is difficult to achieve when the potential donor and recipient listing center are far apart. However, this theoretic benefit of multiple listing may be less relevant now as most pediatric centers utilize virtual cross-matching or forego prospective cross-matching altogether in sensitized patients (4, 5).

It is important to point out that the multiple listing strategy was used more commonly among patients who had private insurance. This association underlies one of the main ethical concerns about this strategy (6). Multiple listing often requires that families have the resources to visit multiple centers and to arrange for expeditious transport in the event that an organ becomes available at a center distant from where the child is residing. Some have suggested that this creates an unfair advantage to those higher income families. In addition, those children with governmental insurance such as Medicaid may find it more difficult to receive approval for transplant listing in a different state limiting this option for such patients. For this reason, a number of centers have been against the concept of multiple listing, being that it is not available to all of their patients. New York State banned the multiple listing process at one point due to these concerns (7).

Multiple listing for heart transplantation can be uniquely challenging. Those children most in need of an expeditious transplant, and hence a short wait-list time, are likely to be hospitalized. Such patients often would not be considered candidates for multiple listing. The benefit would most likely be accrued for those patients who are lower urgency such as UNOS status 1B or status 2. Patients who are typically at home while they await transplantation could arrange for transport to a more distant center and benefit from multiple listing. Because analysis of UNOS data has consistently demonstrated that those listed as status 1B and status 2 have lower risk of pretransplant mortality, it is doubtful that the strategy of multiple listing is benefitting those most in need.

Multiple listing for children awaiting transplantation is likely to remain controversial. Many transplant centers in the United States may choose not to offer multiple listing. Nonetheless, UNOS requirements clearly dictate that families need to be informed that multiple listing is permitted at many centers. This analysis by Feingold et al. can help inform these discussions. It is likely that a small proportion of families will explore the possibility of multiple listing. One hopes that our community continues to analyze this practice to ensure that those children most in need of transplant, rather than those with the most resources, have the highest priority for scarce donor organs.

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EDITORIAL COMMENTARIES

The urgent priority for transplantation is to trim the waiting list

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The recognized success of cardiac transplantation has encouraged increased referrals of patients with refractory heart failure to major transplant centers. Potential candidates join the long waiting list, only to suspend their lives as they deteriorate to win higher priority. This is true both in Europe and in the United States, where we list >3,000 adults each year while performing about 2,000 transplants (Figure 1). This system jeopardizes outcomes for both the patients and the transplanted hearts, and inflates costs. Smits and coauthors in the accompanying article have taken steps to reexamine and redesign priority in a thoughtful pilot study of 448 patients listed with urgent status during an 8-month period, 189 of whom underwent transplantation.[1]

General considerations in setting priority for transplantation

An allocation system for scarce donor hearts should maximize expected benefit, integrating risks with and without transplantation into a complex calculus. Optimally, the defined priority levels should support incentives to provide best care prior to transplantation, but they should at least not incentivize unnecessary interventions to escalate priority. The system should ensure that: (1) high-priority patients do have a high risk without transplantation; (2) transplantation will be performed with appropriately short waiting times for the highest priority patients; and (3) a reasonable proportion of patients can undergo transplantation at a lower priority level. No priority system can be effective or even evaluable except in the context of a waiting list length that is matched to the current donor heart supply.

Maximize benefit over risk

Risk scores

Of the multiple scores proposed for heart failure risk, the Seattle Heart Failure Survival Score is the most widely known, with serial remodeling of a risk equation derived primarily from outpatient medication trials in Class II or III heart failure.[2] A more recent Seattle model modified to include inotropic therapy and ventilator support surprisingly fared less well in this population of advanced heart failure. In the study, the survival outcomes separated between lowest 3 risk groups and the highest risk group, which had a 3-month mortality of 24%, but included only 7.5% of the 448 urgent patients. The Heart Failure Survival Score was validated previously from the potential transplant population,[3] which identified a high-risk group of 42% of the patients, with a 3-month mortality of 14%. This provides evidence of the deficiency of the current priority system to select patients at very high risk without transplant, as these mortality rates of <25% are the highest among a group of patients *who were all listed for urgent transplant.*

For post-transplant risk, the IMPACT (Index for Mortality Prediction After Cardiac Transplantation) score[4] was dominated by its highest risk group, which showed 3-month mortality of 70% in a group of only 7 patients, compared with another 182 patients, all with early mortality at <20%.

Benefit scores

Many of the factors predicting death on the waiting list also predict poor outcomes after transplant (or mechanical circulatory support), such as age, non-compliance and renal dysfunction. A key step taken by the Eurotransplant research group has been to move beyond the pre-transplant risk score to integrate the risk score for death after transplant as well. The resulting benefit score is based on estimation of the difference between survival time expected after transplant and survival time expected on the waiting list (analogous to the separate lung allocation scores

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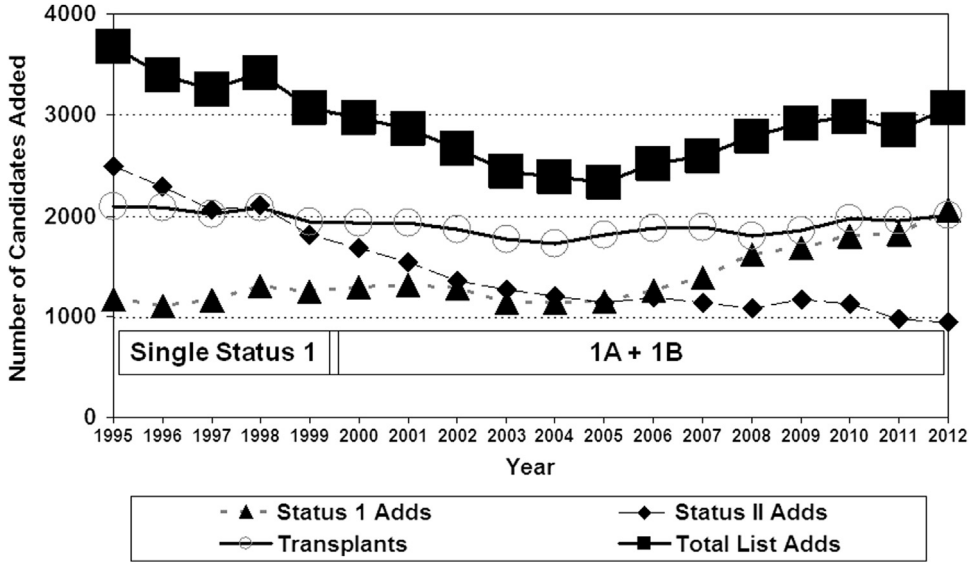

Figure 1 Trends in listing. Numbers of adult candidates (filled squares) added to the waiting list and number of adult transplants performed (open circles) each year since 1995, from national UNOS data.[10] Also shown are the annual number of candidates added as Status I (filled triangles). Note that, after 1999, Status I was divided into Status IA and IB, which are then added for the total number of Status I patients. The number of Status I patients has increased to equal the total number of patients transplanted in 2012. The number of candidates listed as Status II (filled diamonds) has declined during the same period.

in current use for different pulmonary diagnoses). Although their analysis focused on the 12-week data, it is the long-term outcomes after transplantation that will guide estimates of survival time. Patients at highest risk pre-transplant often have higher post-transplant risk early, which disappears during long-term follow-up. Previous Markov modeling of waiting list transitions and allocation has suggested that benefit is maximized when priority for donor hearts is awarded to patients most likely to die on the waiting list unless their post-transplant mortality approaches 50% in the first year.[5]

The authors described a key limitation of current scores in their pilot study. Neither the Seattle score nor the IMPACT score could predict outcomes for the patients on mechanical support. In the study, 26% of patients received implantable devices and 15% were on extracorporeal support at the time of listing. This proportion has continued to increase rapidly.

Range of uncertainty around survival time benefit

The margins of uncertainty around survival rates for populations stretch rapidly when applied to anticipate survival time for an individual patient. This is well-recognized in oncology, despite a more predictable pattern of decline than in heart failure. For cancer patients predicted to die at 180 days, half would instead live either <90 days or >1 year.[6] The daunting expanse of these confidence intervals is further extended when estimating *the difference* between survival with two different therapies, particularly when one involves the front-loaded risk of surgery, with different distributions of early and late hazards.

When comparing potential outcomes with and without transplantation, it is crucial to recognize that patients do not have an increase or decrease of risk, only survival or death. The functional and quality end-points offer higher relevance when sharing decisions with individual patients.[7] This provides strong rationale for retaining assessments that connote both survival and functional capacity, such as the peak VO_2 or Minnesota and Kansas City questionnaires, even when some of their predictive power can be replaced by integration of variables such as total lymphocyte count and diuretic doses that do not drive patient-reported outcomes.

Incentives driven by priority

Current definitions of priority levels have been based both on medical rationale and the attempt to protect the system from being "gamed." When the requirements for inotropic therapy for Status IB and pulmonary artery catheters for Status IA were adopted in the USA, it was with optimism that they would be used only when absolutely necessary to prevent imminent death, because continuous inotropic infusions and indwelling pulmonary artery catheters are inconvenient and costly and have been associated with serious complications. Although individual cases trigger heated controversy in regional committees, it is generally agreed that these therapies are being overused in patients awaiting transplantation.

If high priorities defined by therapies are the only route to access donor hearts, we face conflicted incentives as advocates for our patients. This is serious enough with incentives to inflate the description of severity of illness, but even more serious with incentive to impose interventions with complications, such as indwelling pulmonary artery catheters. One of the major conditions currently cited as justification for Status IA exceptions is vascular complications of indwelling catheters that preclude further catheterization. This complication on the list was virtually never seen before pulmonary artery catheters became an index of priority (although arrhythmia device leads have also added to the vascular complication rate).

The strength of inverse incentives in care of our waiting patients is indexed to the concern that they will die before a

transplant, or will develop unnecessary risk such as from cachexia before they finally enter into transplant. The priority status will more truly reflect patient illness when the listing physicians have reasonable confidence that patients will receive a heart in a timely manner, a confidence eroded by the lengthening waiting times, which in turn reflect the anasarca of the waiting list.

Broken priority systems

A well-functioning priority system as just described should be able to ensure that: (1) the high-priority patients do have high risk without transplantation; (2) transplantation will be performed with appropriately short waiting times for the highest priority patients; and (3) a reasonable proportion of patients can undergo transplantation at a lower priority level.

Diluting the urgency

The requirement that high-priority patients have appropriately high risk without transplantation is now challenged by their survival despite increasingly long waiting times. In this study, only 11% of urgently listed patients died, although only 42% had undergone transplant by the end of the study. In the USA system, the current high-priority status was originally defined with the expectation that patients would not survive more than a matter of days without transplant. For the high-priority Status IA exception as an example, the life expectancy is defined as <7 days. If this were an accurate reflection of the patients, the death rate on the list of highest priority patients would exceed 90%, as the average wait has doubled from <1 month in 2006 to almost 2 months in 2011. However, the waiting list mortality for patients listed as Status IA in the USA has declined from 92 to 35 per 100 waiting list years between 2006 and 2011.[8] Throughout the USA more than half of Status IA patients have been waiting <6 months. In Region 5 in the USA, 40% of patients waiting as Status IA have been waiting <1 month, compared with only 6% in Region 1 (Figure 2), although the proportions of patients listed as Status IA are comparable. (It should be noted that the amount of time patients spent in other statuses before Status I is not detailed in the current version of the publically available UNOS data.) Whatever the path, "urgency" has been seriously diluted. Is this the fault of how urgency is defined, or how the list has lengthened? When there is little confidence that even the highest status patients will soon receive a heart, the incentive is to list early and list high. The list is becoming the lottery.

Is there really a lower priority?

In many regions, there is currently little expectation of transplantation for patients in non-urgent priority. The introduction to the work by Smits et al addresses the situation in Germany, where heart donation has recently declined by 25%, which will soon lead to a doubling of the transplant list and distribution of 90% of all hearts to Status I patients. The problem was posed over 20 years ago in the USA, where the prediction was made based on modeling of listing in the early 1990s (before Status I split into Status IA and Status IB in 1999) that almost all hearts would soon go to patients with the high urgency status.[9] In 2012, 95% of the transplants indeed went to patients in Status I (60% of transplants in Status IA and 35% in Status IB). This is the first year that *the number of patients listed as Status I exceeded the total number of transplants performed* (Figure 1). In fact, although only 20% of patients were

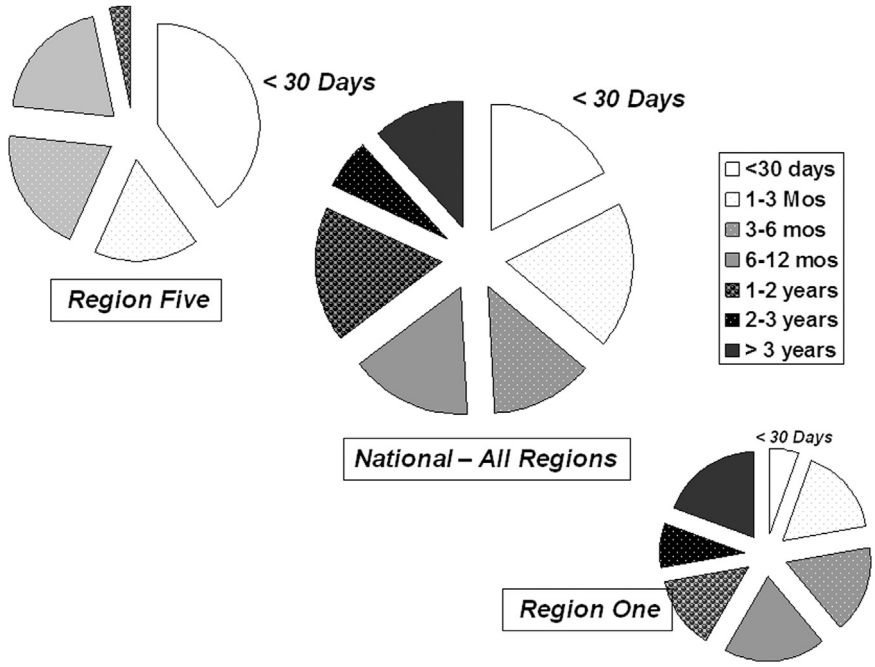

Figure 2 National and regional waiting times for candidates currently listed as Status IA. Center chart: waiting times in the USA. Upper left chart: waiting times in Region 5; lower right chart: waiting times in Region 1.[10]

listed as Status IA, patients in Status IA were receiving 70% of all transplants in the USA (Figure 3). By 2012, substantial disparity had grown between USA regions in the proportion of patients transplanted as Status IA, from 48% in in the California region (Region 5) to 85% of all transplants going to Status IA patients in the New England region.

Waiting list arithmetic

It is necessary to have a small excess of patients listed over the anticipated number of donor hearts to allow for matching, improvement and death on the list and other causes of mismatch between supply and demand. However, the wide disparity between patients listed and those transplanted has led to an unwieldy waiting list. The highest number of patients listed was in 1995, falling to a nadir in 2005 (Figure 1). This is the last period during which we may study the natural experiment of how the median waiting time decreases as the number of listed patients decreases (Figure 4). Between 1999 and 2004, the median waiting time for Status IA patients declined from 61 to 50 days, for Status IB from 87 to 78 days and for Status II from 503 to 309 days. Unfortunately, the number of listings soon rose again, with an increase in the size of the list carried over each year into the next. This increase is unsustainable with the current donor situation.

No system of priority, current or proposed, can allocate hearts equitably when there is such an excess of people listed compared with those transplanted. This is analogous to the oversold situation on airline flights. A large group of people moving no closer to their destination creates pandemonium whether waiting in the airport or on a transplant list.

Limitations of current estimates

The national UNOS data set provides an unparalleled resource both for longitudinal trends and for snapshots of different times and different regions.[10] The data presented here for the USA has been culled from publically available data, and these analyses for general estimates do not reflect expertise or review from the dedicated data analysts at UNOS. It is not possible from the national data set available to determine how often status has shifted for a given candidate, nor the subtleties of patients who are Status 7 or delisted. However, the definition of candidates rather than registrations within the data set is intended to minimize double counting. The data presented herein is for general illustration and thought experiments only.

We can trim the list

We cannot abdicate our responsibility to limit the number of patients we list. Of the alleged 150,000 patients who could benefit from heart transplantation, only about 3,000 are listed annually. We thus exercise severe restraint on listing every day, just not quite to the correct limit. We can regain control of the arithmetic, just as we balance household expenses to household income and the heart adjusts cardiac output to venous return. It is not clear how we decreased the number of patients newly listed yearly from almost 4,000 in 1995 to 3,000 in 2012, but it was probably not because there were fewer candidates or because they were less sick.

Details of strategic list reform depend on how much consensus can be achieved and how quickly we aim to restore meaning of listing and priority. Using recent data and trends, we can project the impact of an immediate reduction of 20% in the number of patients listed each year from 3,000 to 2,400. Based on current event rates on the list, this number is enough lower than the number of patients removed from the list during the year to initiate a steady reduction in the carry-over list size. The removal rate is of course primarily due to transplantation, but is also due to patients removed for listed reasons of death, which has been decreasing, or "too sick to transplant," which has been increasing (Figure 5A). This combined rate over the past 5 years has been approximately 8%.[11] There is an additional rate of approximately 6% of listed patients removed due to improvement, patient reluctance or other causes.[11] If the list

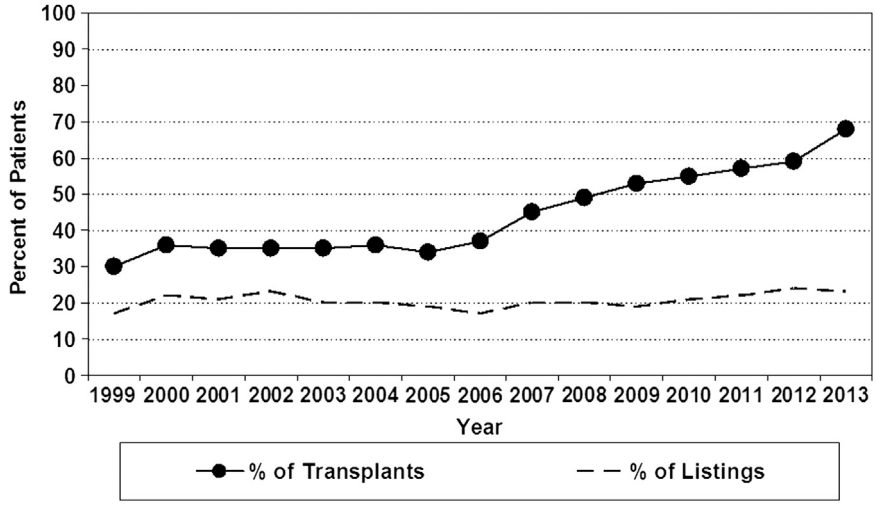

Figure 3 Status IA listing and transplant from 1999 to 2012 showing the proportion of adult patients listed as the highest status (IA) and the proportion of all adult patients undergoing heart transplantation who were Status IA at the time of transplant.

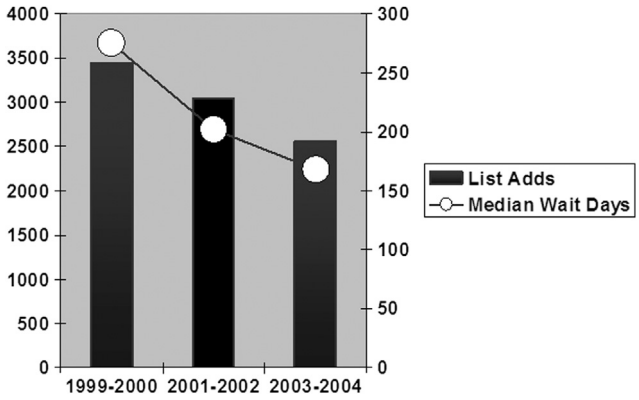

Figure 4 List length and time. The number of adult candidates added during each of three 2-year periods, and the median waiting time in days during the same periods, for candidates aged 50–64 years. For the recent past, the shortest waiting list length and the shortest waiting period were seen in 2004 (http://optn.transplant.hrsa.gov/latestData/step2.asp).[10]

additions were reduced soon to 2,400, the standing list would be decreased to <1,000 within 5 years (Figure 5B). Once the steady-state waiting list reaches <1,000, then the listing volume could increase slightly. The perennial mission to increase donor awareness and consent remains highly relevant, with any successful increase leading to an increase in the permitted number of annual candidate listings.

Where to trim?

Register instead of list? The Status II list is an obvious target for some trimming, as Status II listing in most regions of the USA is tantamount to placebo therapy, except with blood group AB. Recognition of their limited access to donor hearts has already reduced numbers of Status II patients listed for transplantation (Figure 1). Although sober predictions of long waiting times are delivered to patients and families, optimism usually prevails in the message received. Once "waiting for a heart", patients narrow their horizons and engagement in what may turn out to be a major chapter of their lives. However, referral to heart failure centers should not be delayed for patients with advanced heart failure, as it has long been recognized that function and outcomes on medical therapy benefit from ongoing heart failure management as offered at a transplant center.[12] Furthermore, the detailed evaluation necessary to determine eligibility for transplant is often incomplete or misleading in a patient in critical condition. For these reasons, the determination of "acceptability" for transplantation in a non-urgent candidate remains desirable. Perhaps the terminology could be updated to define such patients considered provisionally acceptable without contradictions as "registered for transplant" rather than "listed for transplant."

Benefit scores for listing rather than priority. There remains a set of ambulatory patients who have severely impaired function and high risk of poor outcomes, even as they can remain at home. Initial findings from the MedaMACS (Medical Arm of Mechanically Assisted Circulatory Support) pilot study suggests that patients at home on oral therapy with New York Heart Association (NYHA) Class IV symptoms with two or more recent hospitalizations have a mortality rate of >25% by 6 months, clearly with potential benefit from early transplantation or for ventricular assist devices (VADs) (Figure 6).[13] Ongoing studies, such as REVIVE-IT (Randomized Evaluation of VAD Intervention before Inotropic Therapy) and MedaMACS, will determine whether it is in these patients that scores of disease severity may have most utility. Perhaps scoring could be employed to determine *listing* rather than *priority after listing*. Those who do not pass the score for severity of disease to be listed could instead be registered for future listing, to preserve their access to close surveillance with optimal management of their advanced disease.

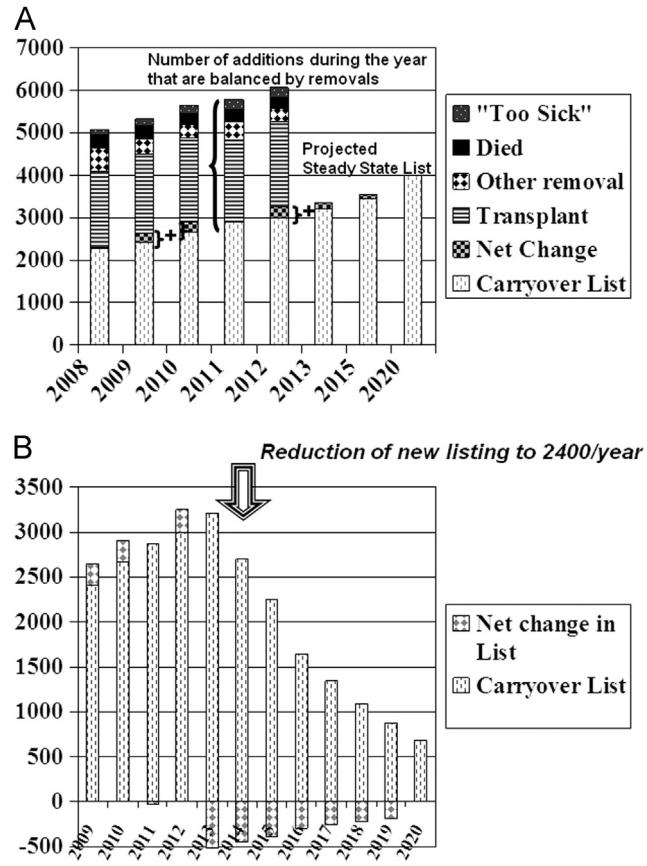

Figure 5 (A) Past and future arithmetic of the waiting list. For most recent years, the number of waiting list additions has been slightly greater than the number subtracted due to transplantation, improvement, death or other reasons. Thus, the "carry-over list" has gradually grown. As there has been a slight decrease in the number of patients withdrawn due to death, there has been a slight increase in the number withdrawn as "too sick to transplant." If the number of candidates added to the list were to be frozen at 3,000 per year, we will reach a steady state list of about 4,000 by 2020. (B) A progressive decline in the size of the waiting list if the number of listed candidates were reduced by 20% now and maintained at that level. Calculations based on data through 2012 as shown in (A). The projections assume that the proportional rate of death and removal on the list would remain the same, which is probably an overestimate as we approach the steady-state list of 700 by 2020.

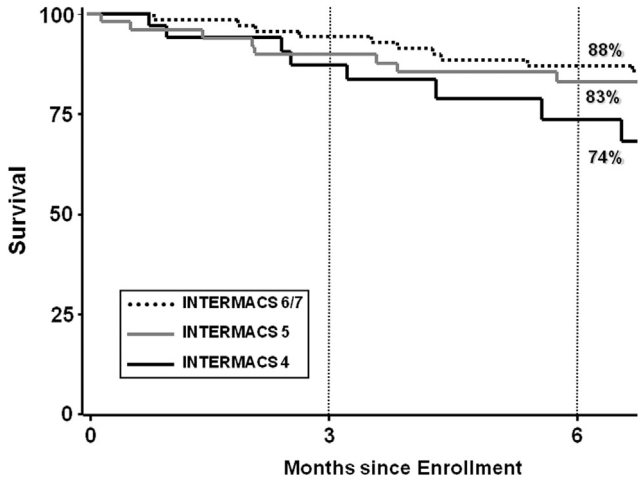

Figure 6 Kaplan–Meier survival curve for ambulatory outpatients with advanced heart failure, according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile. This screening pilot for MedaMACS followed 165 patients on optimal medical therapies without intravenous inotropic therapy at the time of enrollment at 10 VAD/transplant centers. Survival is depicted with censoring at time of transplant or mechanical circulatory support, showing 26% death by 6 months for the 37 patients enrolled with INTERMACS Profile 4 (resting symptoms of heart failure). If listed, these patients would be Status II and unlikely to undergo transplantation. Survival was better for the 53 patients in Profile 5 (housebound but comfortable at rest) and 75 patients in Profile 6 (walking wounded).[13]

Patients already listed would have to re-qualify at intervals of, for instance, 6 months. If they did not qualify while supported on inotropic therapy, it would need to be held to reassess. A strong case, based on the recent study by Kato et al, could be made for tightening the criteria on peak oxygen consumption to <10 ml/kg/min, as this describes not only the risk of mortality, but also a severe limitation in daily functional capacity that should improve dramatically after transplantation.[14] Furthermore, as emphasized by Rogers, this invokes the validity of intrinsic disease severity, rather than the therapies imposed.[15] Patients who become candidates only *after* VAD insertion would need to have their own score for listing, but there would be fewer patients who would need VADs solely as bridges if there were fewer people competing for transplants. (To cover the inevitable but uncommon cases such as truly refractory ventricular tachycardia, each center could perhaps include 1 patient outside usual indications for every 10 patients listed according to the accepted benefit score.)

Anyone who attends weekly transplant meetings is familiar with the evaluation that yields a heavy burden of relative contraindications. Without specifying when that burden becomes unsupportable, the list could be shortened and resources redirected by an infinitesimal shift toward palliative care in patients with multiple non-cardiac limitations that will not be lifted by transplantation.

A case for trimming by age? The percent of adult patients >65 years of age at the time of transplantation is 17% thus far in 2013, compared with 3.4% in 1990 (Figure 7). Some of us remember when the upper age was limited to 50 years. A modest restriction to age <65 years could bring us close to the 20% reduction needed. Furthermore, it would release almost as many hearts, as a higher proportion of the older patients receive hearts. Some of this reflects the use of alternative recipient lists, but good outcomes with donors labeled as "marginal" would generally support their use for the regular list instead.[16–18]

Although there has historically been strong opposition in the USA to rationing resource-intensive therapy, rationing is inevitable and is happening now, although its manifestation is irrational as each program endeavors to increase its transplant volume at the expense of others. The age distinction is at least one that can be applied without penalty to disadvantaged populations who currently have a decreased option to relocate to lower waiting list regions. Furthermore, the increasing

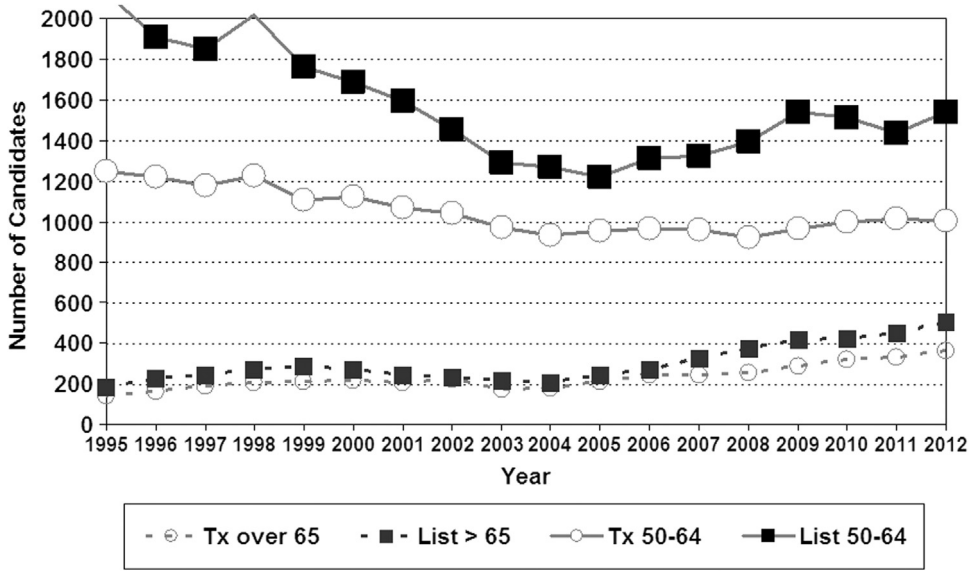

Figure 7 Waiting list candidates added to the list and patients undergoing transplantation in the two age groups: 50 to 64 and ≥65 years. The number of older patients transplanted is closer to the number of older patients listed, and both are increasing. The absolute number of patients transplanted at 50 to 64 years remains higher but is decreasing. Data taken from the UNOS website.[10]

burden of comorbidity contributes to slightly but consistently worse outcomes post-transplant for older transplant patients.[19] On the other hand, the age disparity in outcomes after mechanical circulatory support has diminished with the use of continuous-flow devices. As 2-year survival exceeds 75% in low-risk recipients, a compelling case has been made to emphasize the use of mechanical devices as lifetime therapy rather than as a bridge to transplantation for older candidates who are even older by the time transplantation occurs.[20]

A thought experiment

The debate over revised scores for priority will rapidly spiral into complexity. Before adding multiple factors, it may be illustrative to consider the simplest example. Working from a list appropriately trimmed to patients with high severity of illness, we could re-invoke the time-honored queue to determine transplant priority based solely on listing time. To be maintained until transplant, listed patients would receive inotropic therapy, intra-aortic balloon counterpulsation, mechanical ventilation, extracorporeal membrane oxygenation (ECMO) or implantable devices as necessary to survive rather than to shift priority. Think how few patients would warrant chronic indwelling pulmonary artery catheters for medical necessity. Knowing the position on the transplant list would guide decisions regarding the need for mechanical intervention, but there would be no priority awarded on the basis of therapies including VADs. One clock measures all time, and it starts at listing whether the patient is with or without a VAD. Consider the simplicity of the queue approach, the reduction of days spent captive in a hospital, the end of the argument about whether VAD patients should cut in line, and the re-alignment of incentives to provide exactly as much support as needed, and no more.

In conclusion, the Eurotransplant research consortium has shared their valuable experience and perspective on a dilemma that exists in every country offering cardiac transplantation. They have shown the paradox of patients with urgent priority for transplantation who often survive without it. They have emphasized the importance of integrating risk without transplant with the risk after transplant. However, no application of the calculus will solve the waiting list problem until we have answered the simple arithmetic required to trim the list to the proper size. This will be different for every country depending on their listing practices and donor supply. However, a consistent increase in candidate listing without an increase in donor supply is unsustainable for any country. When there is equilibrium between the patients entering and leaving the list, there will be greater tolerance for the uncertainty around any risk score, because there are likely to once again be enough hearts in time for those who need them.

Disclosure statement

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Impact of ABO compatibility on outcomes after heart transplantation in a national cohort during the past decade

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Background: Immunologic incompatibility has implications for primary graft failure, rejection, and survival in heart transplantation. To our knowledge, this is the first large cohort study investigating the impact of ABO-compatible versus identical blood type matching on post heart transplantation survival.

Methods: We used a nationwide sample (2000-2010) within the United Network for Organ Sharing database. Stratification was between ABO-identical and ABO-compatible heart transplantations for univariate and multivariate analyses. The primary end point was graft failure from all causes. Posttransplant survival was compared between groups using Cox proportional hazard and logistic regression models.

Results: A total of 17,951 patients met inclusion criteria, and 2684 (approximately 15%) underwent ABO-compatible heart transplantation. ABO-compatible recipients were generally sicker than ABO-identical recipients before transplant because more were status 1A, in the intensive care unit, and receiving mechanical ventilatory support ($P < .05$). Univariate analysis correlated ABO-compatible transplants with decreased posttransplant survival and a higher incidence of primary graft failure as cause of death ($P < .05$). There was no significant difference in acute graft rejection ($P = .53$). Multivariate analysis, however, did not demonstrate adverse outcomes in terms of decreased graft survival (hazard ratio, 0.99; $P = .87$). Blood type O donor grafts were associated with poorer outcomes compared with all other types ($P < .05$).

Conclusions: ABO-compatible transplantation does not result in adverse outcomes with respect to graft survival. Blood type O donor grafts, however, were associated with decreased survival. This has important implications for current graft allocation policies, particularly for type B recipients. (J Thorac Cardiovasc Surg 2013;■:1-8)

Cardiac transplantation is an accepted therapy for treating patients with end-stage heart failure. Although transplantation techniques and postoperative management strategies have continued to improve in the past several decades, of the approximately 2000 procedures performed in the United States annually, approximately 10% of patients do not survive the first year after transplant.[1] After 1 year, annual death rates approach 4% and approximately 50% of heart transplant recipients are alive at 10 years.[2] There are several risk factors known to be associated with premature death and other complications after cardiac transplantation, including donor cardiac function and preexisting disease, toxicity, systemic infection, ischemic time, and mismatches between donor and recipient heart size, sex, age, and antigenic phenotypes.[3]

Because basic immunologic incompatibility is a clear indication for posttransplant complications, it is common practice to avoid antigenic mismatch when pairing donor hearts with recipients. Human leukocyte antigen (HLA) matching is applied only to highly sensitized individuals listed for heart transplantation, although many centers are using a strategy of ''virtual'' cross matching. Organ donors and potential recipients are, however, paired based on ABO blood type matching. There are 3 categories of ABO matching: ABO identical, ABO compatible, and ABO incompatible. Although adult patients typically do not receive organs from ABO-incompatible donors, avoiding hyperacute graft rejection, recipients sometimes receive hearts from ABO-compatible donors. This is unlike transplant procedures for pediatric recipients, in whom ABO-incompatible grafts are sometimes acceptable because of a delay in the development of natural antibodies to ABO antigens.[4]

Morbidity and mortality associated with recent increases in donor shortages for all organ transplantation types have led to a renewed interest in ABO-incompatible matching. Although significant progress has been made on this front in the fields of kidney and pediatric heart transplantation, ABO compatibility is largely still a requirement for adult

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Abbreviations and Acronyms
ECMO = extracorporeal membrane oxygenation
HLA = human leukocyte antigen
ICU = intensive care unit
UNOS = United Network for Organ Sharing

heart transplantation.[4] Before ABO-incompatible adult heart transplantation can be considered, however, it is important to first solidify our understanding of ABO-identical and ABO-compatible heart transplantation. In the late 1980s and early 1990s, several anecdotal reports suggested unfavorable outcomes among ABO-compatible (nonidentical) adult heart transplants.[5,6] Since then, however, several small, hospital-based retrospective studies have been conducted, which have largely determined that there are no significant differences in outcomes of ABO-compatible versus ABO-identical cardiac transplants.[6-8] The 2012 International Society for Heart and Lung Transplantation Heart Transplant Report listed non–ABO-identical transplants as a borderline significant risk factor for 5-year mortality after transplant.[9] We believe that it would be clinically useful to compare the medium- with long-term outcomes of ABO-compatible and ABO-identical heart transplants in a large nationwide modern cohort study. Data gleaned from this study could have significant implications for the maximally efficient use of the limited donor pool.

METHODS

Data Source

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research files with deidentified donor and recipient transplant data from October 1987 to March 2012 and recipient follow-up data through December 2011. The database includes prospectively collected demographic, donor, operative, and postoperative information for all thoracic transplant recipients in the United States.

Study Design

We retrospectively reviewed the UNOS database from January 2000 to December 2009. The time points were chosen to identify a modern cohort of heart transplant patients with adequate time for follow-up. All adult (≥18 years) single-organ heart transplants were included. Transplants were primarily stratified by transplant donor-recipient ABO blood type matching (identical vs compatible). Transplants without available data on donor and/or recipient ABO types were excluded from the study (n = 1).

Outcome Measures

Demographic and clinical characteristics of all heart transplant donors and recipients were examined. The primary end point was all-cause graft failure during the study period. Secondary outcomes of interest included 30-day mortality, length of hospital stay, graft rejection, and recipient cause of death.

Statistical Analysis

Baseline demographic and clinical characteristics between the primary study cohorts were compared using the Student t test for continuous variables and the χ^2 test for categorical variables. For all Student t tests conducted, normality was assessed using skewness and kurtosis. Survival was modeled using the Kaplan-Meier method, with statistical differences between survival curves assessed using the log-rank (Mantel-Cox) test. Univariate and unadjusted 30-day and 1-, 3-, 5-, and 10-year graft survival analyses were also conducted using the χ^2 test. Multivariate analysis was conducted using both the Cox proportional hazards regression model and a logistic regression model. To adjust for potential confounders and accurately determine factors associated with decreased graft survival, variables describing baseline demographic and clinical characteristics that were significantly different ($P < .05$) between the 2 study cohorts on univariate analysis were included in the multivariate models. For the logistic regression analysis, variables were removed from the model in a stepwise manner until all included variables (except ABO compatibility and the variable of interest) were statistically significant ($P < .05$).

Statistical significance was established at $P < .05$ (2 tailed), and all hazard ratios are presented with 95% confidence intervals. All statistical analysis was generated using SAS software, version 9.3, of the SAS System for Windows (SAS Institute Inc, Cary, NC).

RESULTS

The UNOS database contained records of 15,267 ABO-identical transplants and 2684 ABO-compatible transplants during the study period from January 2000 to December 2009 that fit the study's inclusion criteria (Table 1). Of the transplant recipients with blood types A, B, and AB, the frequency of ABO-compatible transplants was 17.0%, 32.8%, and 61.8%, respectively. Blood type O recipients can only receive ABO-identical grafts.

The baseline demographic characteristics of both donors and recipients from these transplant surgical procedures are summarized in Tables 2 and 3, respectively. The allograft donors from both cohorts were well matched based on sex, age, mean left ventricular ejection fraction, cause of death, and a history of hypertension, diabetes, and cigarette use. There was a significant difference ($P < .05$) between the 2 groups in terms of donor ethnicity and history of cancer.

The baseline demographic and clinical characteristics of heart recipients in the ABO-identical and ABO-compatible cohorts differed ($P < .05$) with respect to sex, age, ethnicity, wait list status at transplant, status before transplant (in intensive care unit [ICU], in hospital, or not hospitalized), life support before transplant, and mean graft ischemic time and total bilirubin. More ABO-compatible transplant recipients were wait list status 1A (50.3%) than ABO-identical transplant recipients (28.3%, $P < .001$).

TABLE 1. ABO blood group distribution

	Donor blood type					
	A	AB	B	O	Total identical*	Total compatible*
Recipient blood type						
A	6340	0	0	1302	6340 (83.0)	1302 (17.0)
AB	274	342	189	90	342 (38.2)	553 (61.8)
B	0	0	1696	829	1696 (67.2)	829 (32.8)
O	0	0	0	6889	6889 (100)	0 (0)

*Total identical and total compatible measured as proportion of each recipient blood type.

TABLE 2. Donor characteristics stratified by ABO blood type matching

Variable	ABO identical (n = 15,267)*	ABO compatible (n = 2684)*	*P* value†
Female sex	4306 (28.2)	787 (29.3)	.24
Mean (SD) donor age, y	31.54 ± 12.35	31.40 ± 12.53	.58
Ethnicity			
White	10,687 (70.0)	1697 (63.3)	<.001
Black	1938 (12.7)	387 (14.4)	.01
Hispanic or Latino	2259 (14.8)	518 (19.3)	<.001
Asian	213 (1.4)	46 (1.7)	.20
History of hypertension	1829 (12.0)	336 (12.6)	.42
History of cancer	254 (1.7)	64 (2.4)	.01
History of diabetes	343 (2.3)	68 (2.5)	.35
History of cigarette use	3903 (25.8)	698 (26.2)	.67
Cause of death			
Anoxia	1562 (10.2)	288 (10.7)	.44
Cerebrovascular/stroke	3839 (25.2)	713 (26.6)	.12
Head trauma	9427 (61.8)	1615 (60.2)	.12
CNS tumor	158 (1.0)	25 (0.93)	.62
Mean (SD) LVEF	61.57 ± 7.83	61.62 ± 8.02	.74

CNS, Central nervous system; *LVEF*, left ventricular ejection fraction; *SD*, standard deviation. *Some patients were excluded from each analysis because of missing data fields or erroneously imputed data in the database. †*P* value based on Student *t* test for continuous variables and the χ^2 test for categorical variables ($P < .05$ is considered statistically significant).

TABLE 3. Recipient characteristics stratified by ABO blood type matching

Variable	ABO identical (N = 15,267)*	ABO compatible (N = 2684)*	*P* value†
Female sex	3584 (23.5)	708 (26.4)	.001
Mean (SD) recipient age, y	51.91 ± 12.26	51.12 ± 12.87	<.001
Ethnicity			
White	11,286 (73.9)	1882 (70.1)	<.001
Black	2399 (15.7)	498 (18.6)	<.001
Hispanic or Latino	1110 (7.3)	179 (6.7)	.27
Asian	311 (2.0)	102 (3.8)	<.001
Wait list status at transplant			
1A	5771 (37.8)	1350 (50.3)	<.001
1B	6040 (39.6)	928 (34.6)	<.001
2	3450 (22.6)	405 (15.1)	<.001
Status before transplant			
In ICU	4321 (28.3)	1083 (40.4)	<.001
In hospital (not ICU)	2853 (18.7)	545 (20.3)	.05
Not in hospital	8093 (53.0)	1056 (39.3)	<.001
Life support at transplant			
ECMO	67 (0.44)	25 (0.93)	.001
IABP	737 (4.8)	234 (8.7)	<.001
IV inotropes	6,786 (44.5)	1,330 (49.6)	<.001
Inhaled NO	36 (0.24)	7 (0.26)	.81
Ventilatory support	387 (2.5)	122 (4.5)	<.001
VAD	3609 (23.6)	608 (22.7)	.27
History of dialysis	368 (2.4)	76 (2.8)	.2
History of cardiac surgery	2918 (19.1)	543 (20.2)	.18
History of malignancy	739 (4.8)	137 (5.1)	.56
History of diabetes	3460 (22.7)	600 (22.4)	.73
History of cigarette use	3848 (25.2)	700 (26.1)	.34
Mean (SD) ischemic time, h	3.23 ± 1.05	3.11 ± 1.00	<.001
Mean (SD) serum creatinine at Tx, mg/dL	1.31 ± 0.56	1.33 ± 0.63	.14
Mean (SD) total bilirubin, mg/dL	1.23 ± 1.94	1.37 ± 2.01	<.001
CMV IgG positive	8675 (62.6)	1567 (63.7)	.32
CMV IgM positive	816 (8.8)	164 (9.6)	.24

ICU, Intensive care unit; *ECMO*, extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump; *IV*, intravenous; *NO*, nitric oxide; *VAD*, ventricular assist device; *Tx*, treatment; *CMV*, cytomegalovirus; *SD*, standard deviation; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M. *Some patients were excluded from each analysis because of missing data fields or erroneously imputed data in the database. †*P* value based on Student *t* test for continuous variables and the χ^2 test for categorical variables ($P < .05$ is considered statistically significant).

In addition, 40.4% of ABO-compatible recipients were in the ICU before transplant compared with only 28.3% of ABO-identical recipients ($P < .05$). When compared with ABO-identical transplant recipients, ABO-compatible transplant recipients were more frequently on life support before transplant ($P < .05$), including extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump, intravenous inotropes, and ventilator support. There was no statistical difference between the 2 groups in terms of ventricular assist device use ($P = .266$). Graft ischemic time and total bilirubin also differed between the 2 study cohorts ($P < .001$); ABO-identical transplant recipients had a longer mean ischemic time and lower total bilirubin (3.23 hours, 1.25 mg/dL) compared with ABO-compatible transplant recipients (3.11 hours, 1.48 mg/dL).

Table 4 shows unadjusted 30-day and 1-, 3-, 5-, and 10-year graft survival for ABO-identical and ABO-compatible heart transplant recipients. Recipients of ABO-identical grafts had increased graft survival ($P < .05$) compared with ABO-compatible recipients at 30 days (94.4% vs 93.3%), 1 year (87.0% vs 84.4%), 3 years (76.3% vs 73.4%), and 5 years (63.1% vs 60.0%) after transplant. There was no statistically significant difference in graft survival at 10 years after transplant ($P = .21$). In addition, there was no difference in the incidence of rejection between transplant and discharge ($P = .53$) and mean length of stay as well as length of stay between transplant and discharge ($P = .97$).

Transplant recipient cause of death was similar between ABO-identical and ABO-compatible recipients, except for mortality due to primary graft failure and malignancy (Table 5). More ABO-compatible heart recipients died from primary graft failure than ABO-identical recipients (8.7% vs 5.8%; $P = .003$). Interestingly, ABO-identical transplant recipients showed a greater incidence of death due to malignancy than the ABO-compatible cohort (9.8% vs 6.6%; $P = .007$).

When graft survival was compared between the 2 study cohorts using the Kaplan-Meier method (Figure 1), ABO-identical recipients showed a slightly higher degree of graft

TABLE 4. Outcomes stratified by ABO blood type matching

Variable	ABO identical (N = 15,267)	ABO compatible (N = 2684)	*P* value*
30-d Survival	14,396 (94.4)	2500 (93.3)	.02
1-y Survival	13,241 (87.0)	2258 (84.4)	<.001
3-y Survival	10,199 (76.3)	1720 (73.4)	.003
5-y Survival	6960 (63.1)	1140 (59.9)	.009
10-y Survival	1147 (17.8)	187 (16.3)	.21
Rejection between transplant and discharge	1319 (8.6)	222 (8.3)	.53
Mean (SD) length of stay, transplant to discharge, d	20.04 ± 25.86	20.05 ± 22.14	.97

Survival data based on graft survival time, after transplant; *SD*, standard deviation. **P* value based on Student *t* test for continuous variables and the χ^2 test for categorical variables ($P < .05$ is considered statistically significant).

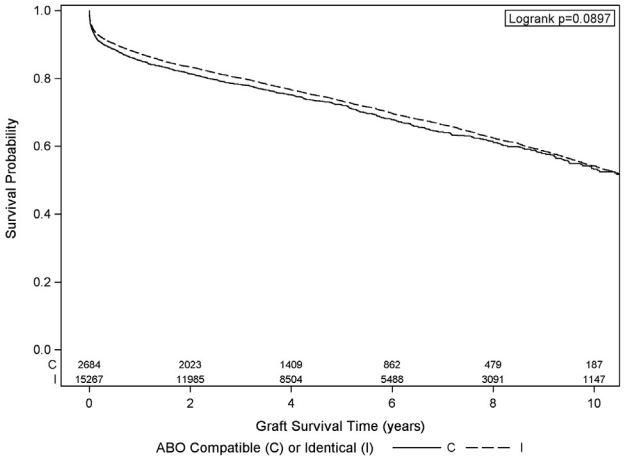

FIGURE 1. Kaplan-Meier graft survival analysis, ABO-compatible (*C*) versus ABO-identical (*I*) transplants. *Solid line*, ABO-compatible transplants; *dashed line*, ABO-identical transplants. A table is given with the number of patients at risk at each time point. The *P* value corresponds to Mantel-Cox log-rank test results.

survival, although the log-rank test showed that this difference was not statistically significant ($P = .09$).

The multivariate Cox proportional hazards regression model (Table 6) demonstrated 6 variables of significance ($P < .05$) for the outcome measure of graft failure: recipient ethnicity, ventilatory support at transplant, pretransplant ECMO use, graft ischemic time, total bilirubin, and patient status before transplant (in ICU, in hospital, or not hospitalized). Although univariate analysis showed ABO blood type matching (identical vs compatible) to have a significant impact on the incidence of graft failure, this effect was eliminated when controlling for potential confounders in the multivariate model (hazard ratio [ABO compatible], 0.991; $P = .865$).

In the multivariate logistic regression model showing risk factors for 30-day graft failure posttransplant, variables of significance ($P < .05$) were life support at transplant, including intravenous inotropes, ventilator support, and pretransplant ECMO use; ischemic time; wait list status at transplant; status before transplant (in ICU, in hospital, or not hospitalized); and total bilirubin (Table 7). Once again, when controlling for potential confounding variables, ABO matching (identical vs compatible) was not statistically significant ($P = .08$).

Posttransplant graft survival was also compared among different donor ABO blood groups using the Kaplan-Meier method (Figure 2). This analysis demonstrated decreased graft survival associated with type O donors and increased survival associated with type A donors ($P < .05$) when compared with all other blood types. Type B and AB donors were not associated with either increased or decreased graft survival when compared with the other ABO blood types ($P > .05$). When looking at posttransplant graft survival in blood type B recipients (Figure 3), blood type O donor hearts were associated with decreased graft survival when compared with type B grafts ($P < .05$).

TABLE 5. Recipient cause of death stratified by ABO blood type matching

Variable	ABO identical (N = 4000)	ABO compatible (N = 724)	*P* value*
Graft failure: all causes	709 (17.7)	149 (20.6)	.07
Primary failure	231 (5.8)	63 (8.7)	.003
Acute rejection	252 (6.3)	41 (5.7)	.51
Chronic rejection	108 (2.7)	25 (3.5)	.26
Infection	615 (15.4)	119 (16.4)	.47
Cardiovascular	773 (19.3)	144 (19.9)	.72
Pulmonary	259 (6.5)	45 (6.2)	.79
Cerebrovascular	180 (4.5)	23 (3.2)	.11
Hemorrhage	98 (2.5)	17 (2.4)	.87
Malignancy	392 (9.8)	48 (6.6)	.007
Renal failure	102 (2.6)	23 (3.2)	.33
Multiple-organ failure	417 (10.4)	78 (10.8)	.78

**P* value based on the χ^2 test for categorical variables ($P < .05$ is considered statistically significant).

DISCUSSION

Since the advent of cardiac transplantation in the 1960s, physicians have made considerable efforts to improve short- and long-term transplant outcomes by investigating the causes of graft rejection and generalized graft failure. Immunologically, as with other transplanted organs, this has involved minimizing antigenic mismatches between graft donors and recipients. Because of the high demand and comparatively low supply of available organs for transplant, emphasis has also been placed on generating graft allocation policies that are fair and effective. Because of the multifactorial nature of graft failure, these efforts have led to a debate about the impact of ABO blood type compatibility and the importance of HLA matching on adult heart transplant outcomes.

For HLA matching, Opelz and Wujciak[10] definitively showed a strong relationship between donor-recipient

TABLE 6. Multivariate Cox proportional hazards regression model

Variable	Hazard ratio (95% confidence limits)	*P* value*
ABO compatible†	0.99 (0.89-1.10)	.87
Sex (male vs female)	0.95 (0.88-1.03)	.24
Donor ethnicity‡		
Black	1.08 (0.98-1.20)	.14
Hispanic	1.00 (0.90-1.10)	.95
Asian	1.13 (0.87-1.47)	.37
Recipient ethnicity‡		
Black	1.42 (1.30-1.56)	<.001
Hispanic	1.09 (0.94-1.25)	.25
Asian	0.92 (0.70-1.19)	.52
Life support at transplant§		
All	1.07 (0.94-1.21)	.32
IABP	0.98 (0.81-1.20)	.85
IV inotropes	0.95 (0.85-1.06)	.34
Ventilatory support	1.88 (1.50-2.37)	<.001
ECMO	2.60 (1.72-3.83)	<.001
Ischemic time	1.09 (1.06-1.13)	<.001
Wait list status at transplant‖		
1B	1.00 (0.90-1.11)	.95
2	1.08 (0.94-1.23)	.29
Status before transplant¶		
In ICU	1.24 (1.10-1.39)	<.001
In hospital (not ICU)	1.13 (0.99-1.28)	.07
Total bilirubin	1.03 (1.02-1.04)	<.001

IABP, Intra-aortic balloon pump; *IV*, intravenous; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit. **P* value based on multivariate Cox proportional hazards regression model, using factors significant on univariate analysis ($P < .05$ is considered statistically significant). †Vs ABO incompatible. ‡Vs white ethnicity. §Vs no life support. ‖Vs UNOS wait list status 1A. ¶Vs not in hospital.

TABLE 7. Multivariable logistic regression model: 30-day graft failure

Variable	Odds ratio (95% confidence limits)	*P* value*
ABO compatible	1.23 (0.97-1.56)	.08
Life support at transplant†		
All	1.89 (1.40-2.54)	<.001
IV inotropes	0.58 (0.46-0.74)	<.001
Ventilatory support	2.78 (1.87-4.14)	<.001
ECMO	7.53 (4.18-13.55)	<.001
Ischemic time	1.24 (1.15-1.34)	<.001
Wait list status at transplant‡		
1B	1.23 (0.97-1.56)	.09
2	1.68 (1.19-2.36)	.003
Status before transplant§		
In ICU	1.60 (1.23-2.07)	<.001
In hospital (not ICU)	1.16 (0.86-1.56)	.34
Total bilirubin	1.08 (1.05-1.10)	<.001

IV, Intravenous; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit. **P* value based on logistic regression model ($P < .05$ is considered statistically significant). †Vs no life support. ‡Vs UNOS wait list status 1A. §Vs not in hospital.

HLA-A, HLA-B, and HLA-DR mismatches on posttransplant graft survival through the collaborative transplant study. More recent studies have demonstrated that the presence of circulating HLA-directed donor-specific alloantibodies are correlated with increased morbidity and mortality, cardiac allograft vasculopathy, and increased rates of graft rejection.[11,12]

Regarding ABO blood type matching, initial reports suggested that ABO-compatible transplants are less efficacious than ABO-identical ones.[5,6] More recently, investigators have disagreed with this conclusion.[7,8,13] A common problem of past studies has been a relatively small sample size precluding strong statistical power. In our analysis, we demonstrated that ABO-identical and ABO-compatible heart transplants have similar outcomes in terms of graft survival. By analyzing all adult cardiac transplants performed between 2000 and 2010, we were able to use a modern cohort of patients with a significantly larger sample size. Although our univariate analysis did show statistically significant differences in survival at 30 days and 1, 3, and 5 years posttransplant between the 2 study cohorts, these differences did not hold up after controlling for potential confounding variables in the multivariable models.

One of these possible confounding variables was Organ Procurement and Transplantation Network wait list status at transplant. Interestingly, according to our analysis, ABO-compatible heart recipients were more often status 1A at transplant when compared with ABO-identical recipients (50.3% vs 37.8%). In addition, ABO-compatible recipients were more likely to be in the ICU and receiving several different mechanisms of life support, including ECMO, intra-aortic balloon pump, parenteral inotropes, and ventilator support, than ABO-identical heart recipients. These data suggest that ABO-compatible recipients are generally sicker than ABO-identical recipients, contributing to a worse prognosis. This is further supported by

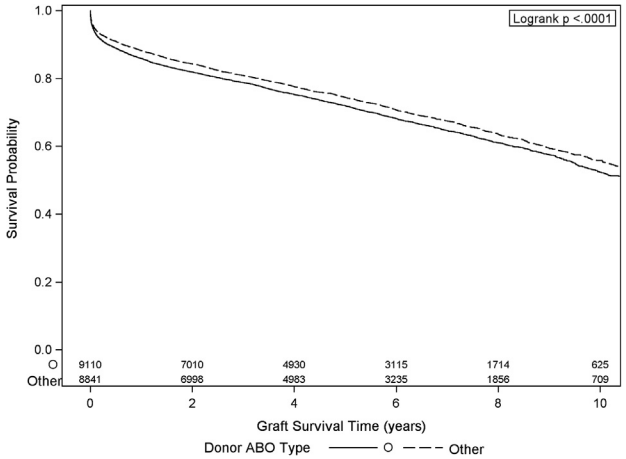

FIGURE 2. Kaplan-Meier graft survival analysis, donor type O versus all other heart transplants. *Solid line*, donor ABO type O; *dashed line*, all other donor types. A table is given with the number of patients at risk at each time point. The *P* value corresponds to Mantel-Cox log-rank test results.

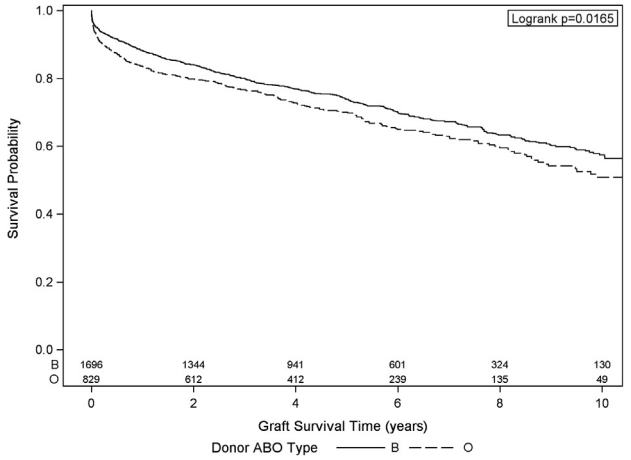

FIGURE 3. Kaplan-Meier graft survival analysis, donor type B versus donor type O heart transplants. *Solid line*, donor ABO type B; *dashed line*, donor ABO type O. A table is given with the number of patients at risk at each time point. The *P* value corresponds to Mantel-Cox log-rank test results.

the fact that ABO-compatible recipients had a higher pretransplant mean total bilirubin compared with ABO-identical recipients (1.48 vs 1.25 mg/dL), indicating a greater degree of heart failure.

On analysis of recipient cause of death by ABO blood type matching, ABO-compatible recipients died as a result of primary graft failure more frequently than recipients of ABO-identical hearts (8.7% vs 5.8%). Heart transplant recipient mortality due to primary graft failure is frequently associated with ''marginal'' donors or recipients.[14] This seems to suggest that ABO-compatible transplants involve more marginal recipients and/or donors than ABO-identical transplants.

In multivariate analysis, ABO blood type matching (identical vs compatible) was not a statistically significant predictor of decreased cumulative or 30-day graft survival. Instead, the Cox proportional hazards model indicated recipient ethnicity (specifically, African American), life support at transplant (ventilator support and ECMO), graft ischemic time, total bilirubin, and recipient status before transplant to be significant predictors of decreased graft survival after transplant. The multivariate logistic regression model indicated many of these variables (ie, life support at transplant, ischemic time, bilirubin, and status before transplant) and wait list status as statistically significant predictors of graft failure within 30 days of transplant. Other studies have demonstrated similar results regarding risk factors for decreased survival and increased graft failure after heart transplants.[15-17]

The observed discrepancies in the effect of ABO compatibility on cardiac transplant outcomes between our univariate and multivariate models can be explained by investigating the impact of individual donor ABO blood types on graft survival. We discovered, in both our univariate and multivariate analyses, that donor ABO blood type O is associated with decreased graft survival when compared with all other types. Because blood type O donor grafts are transplanted into recipients of all blood types (Table 1), the poorer outcomes associated with type O donor hearts could be skewing the results of our univariate analysis to misleadingly suggest that ABO-compatible transplants result in worse outcomes than ABO-identical ones. We confirmed this hypothesis by removing all type O donors from our univariate analysis, which demonstrated no statistically significant difference in graft survival at all time points after transplant between ABO-identical and ABO-compatible cohorts ($P > .05$).

The poor outcomes associated with type O donor grafts do have implications for organ allocation policies. According to the Organ Procurement and Transplantation Network policy 3.7.8.1 from February 2013, ''Blood type O donors shall only be allocated to blood type O or blood type B patients'' before being offered to blood type A or AB patients. Given the poor outcomes associated with blood type O grafts in type B recipients, this policy may need to be reviewed. Interestingly, previous studies have shown that blood type O individuals experience decreased rates of morbidity regarding conditions such as congestive heart failure.[18] Further research should be conducted to investigate possible explanations for the poor outcomes associated with blood type O donor hearts and the best organ allocation scheme for managing these grafts.

Limitations

Such as any other retrospective cohort study, this investigation was limited by the strength of the primary database in terms of completeness, accuracy, quality, and appropriateness of the predictor variables. Although the data set provided by UNOS was extremely comprehensive and included many important variables that described baseline donor and recipient information and postoperative outcomes, the study could have been strengthened if additional data were available to us. Furthermore, because it is a large national database compiled over many years, the accuracy of all the patient information coded in the UNOS database cannot be guaranteed. We are confident, however, that given the nature of our investigation, an analysis of a large national cohort of patients, any errors in patient data will not bias our results.

CONCLUSIONS

In the past decade, ABO-compatible donor hearts were preferentially given to sicker transplant recipients. As demonstrated in this study, transplantation using ABO-compatible adult hearts does not result in adverse outcomes with respect to graft survival and incidence of acute rejection compared with ABO-identical grafts. Therefore, ABO-compatible and ABO-identical heart transplant matches should be viewed equally in clinical decision

making and to maximize efficiency within the available donor pool. This will help optimize the use of donor organs, an extremely important, yet scarce, resource. In doing so, waiting times could be shortened and overall outcomes could be improved. In addition, because ABO blood type O donor grafts are associated with decreased survival after transplant, current organ allocation policies should be reviewed, particularly those pertaining to ABO blood type B heart transplant recipients.

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Discussion

Dr Nader Moazami *(Cleveland, Ohio)*. Well, let me start by congratulating you on your presentation. Many of us who were at your stage in our careers have not had the opportunity to present in such a prestigious forum, and I am hopeful that this bodes well for your future in academic surgery. I will start with a few general comments and then at the end ask my questions.

I think the topic and title of this talk are interesting. For many transplant clinicians, the issue of ABO-compatible transplantation seems to have been put to rest, particularly in the era of continued organ shortage. In fact, the current trend in the literature is largely focused on a completely opposite and different strategy, that is, ABO-incompatible transplantation. This strategy has been widely applied in the renal world and has led to an increase in the number of living-related kidney transplantations. A similar strategy has been successfully applied in the neonatal and pediatric heart transplant population for whom the availability of organs in a timely fashion is limited.

Now, most of us think of ABO as antigens expressed on the surface of red blood cells, but in fact they are widely expressed on endothelial cells, including those of the heart. The specter of antibody-mediated hyperacute rejection is what has made ABO-incompatible heart transplantation a hurdle in adults and, in the current era of LVADs, of much less interest. So the question is, where does ABO-compatible heart transplantation fit in our overall practice and how important is this in terms of graft and patient survival, a question that you have attempted to analyze in your presentation today.

I am going to draw 3 broad conclusions from your presentation and follow those with questions, and I will wait for your answer for each one.

As you know, graft failure is multifactorial and depends on many donor and recipient variables, some of which you have accounted for in your analysis, particularly those markers that identify sicker patients. I am not sure if in your analysis other well-known variables, such as pulmonary hypertension, recipient and donor age, and ischemic times, have been accounted for. Did you look at any of these factors for graft failure in your multivariable model?

Mr Jawitz. First of all, thank you, Dr Moazami, for your enthusiastic support and criticism. As a medical student planning to pursue a career in surgery, it really means a lot to me.

To answer your question, we were able to look at some of those variables in the database. Unfortunately, we were limited by the variables that were coded in the UNOS database, and in some instances there was a significant amount of data missing. In our multivariate analysis, however, we actually did show that total bilirubin time, ethnicity, and a number of other variables were actually independently associated with poorer outcomes. Pulmonary hypertension was included in our cause of death analysis, but not in our pretransplant univariate analysis of recipient baseline characteristics.

Dr Moazami. That brings me to the second conclusion that you drew, and that is that ABO-compatible heart transplantation is an acceptable strategy and unlikely to impact short- or long-term survival. In fact, the International Society of Heart and Lung Transplantation, which is a large registry of all transplant recipients, on an annual basis evaluates all transplant-related data. Interestingly, occasionally a small improved survival difference has been seen between ABO-identical and ABO-compatible donors. However, this generally has been negligible and largely accounted for by many other markers of immunogenicity, namely, the degree of HLA mismatching. This brings me to the next question for you.

In looking at short- and long-term results, the immunogenicity of MHC antigens and also presence of donor-specific antibodies play a large role in graft viability. In your analysis, were any of these factors, specifically HLA matching, panel-reactive antibody levels, or cross match results, available and accounted for?

Mr Jawitz. Thank you very much. That is an excellent question. Yes, it is true that HLA matching is extremely important in long-term graft outcomes. I believe, in the last 10 years, research conducted by Opelz and colleagues, the collaborative transplant study, showed that 2 HLA-A, HLA-B, or HLA-DR mismatches were actually associated with 25% increased graft failure compared to 0 or 1 mismatch within 3 years of transplant. In terms of our study, we really wanted to keep it simple and specifically focus on ABO blood types, namely, ABO-compatible versus ABO-identical matches. In addition, a recently published article specifically looking at renal transplantation showed no correlation between HLA matching and ABO blood type matching.

I do agree that HLA type would be interesting to look at and see, specifically, how differences in HLA blood type between donors and recipients have impacted these data.

Dr Moazami. Finally, I caution against one of your conclusions, which is regarding decreased survival of blood type O donors for, specifically, blood type B recipients. The UNOS organization mandate is based on 2 major premises: (1) the equity in organ allocation and (2) in maximizing the survival benefit for recipients that are at the highest risk of dying. The policy of allocating O donor hearts to type O recipients first and then type B is a reflection of this policy. Type O recipients can only receive organs from type O and, hence, typically have longer wait times on the list. Similarly, type B in the United States comprises only about 10% of the population and, hence, they are at a disadvantage compared to type A blood that comprises about 40% of the population.

So, with the Kaplan-Meier curve that you showed at the end in terms of the blood donor O to B recipients, were any of these risk adjusted, and is it possible that if we correct for some of the factors that I mentioned previously related to immunogenicity that these small differences in survival will disappear?

Mr Jawitz. Yes, that is a good question. We actually looked at primary graft failure as an outcome between donor type O hearts going to type B individuals and type B hearts going to type B recipients, and we actually found out that compatible matches, that is, type O hearts going to type B recipients, were actually associated with increased rates of primary graft failure.

As for the current OPTN policy and organ allocation scheme, you are right, the reason that blood type B recipients preferentially receive type O organs is because of the short supply of type B hearts in this country. When approaching a potential change in policy, it would be important to ensure that that any decrease in donor heart availability for type B recipients would be more than made up for by significantly improved posttransplant outcomes. More analysis is certainly needed before we would feel comfortable recommending such a policy.

Dr Moazami. Thank you.

Dr David McGiffin *(Birmingham, Ala)*. I just want to follow on from that point. You mentioned in your manuscript and in your talk about the poorer survival of blood O to B. You have demonstrated that there are no immunological consequences of that, but O to B is most likely a surrogate for sicker donors and sicker recipients. On that basis, though, how would you change the allocation system for what is probably an immutable problem?

Mr Jawitz. That is a good question. As Dr Moazami pointed out, the reason why blood type B recipients are receiving blood type O donor hearts is because of the comparative shortage of type B donor hearts in this country. To really change the current allocation scheme, we would have to take into account the potential of actually harming type B individuals by changing the policy. I do not think there is a really great answer to how to specifically change the policy at this point and I certainly believe that more research is warranted.

The senior author on this paper actually believes that changing the pretransplant management of type B patients, that is instead of rushing to transplant them with a type O donor heart, perhaps using an LVAD as a bridge to transplant as you wait for an identical type B donor graft, may be a method of mitigating this problem.

Dr Pieter Kappetein *(Rotterdam, The Netherlands)*. You showed that there is a significant difference between the different groups, especially for the blood type O patients. Of course, this is a large group of patients. For example, in the A-B group, you have few patients, and might that not be a type II error that maybe there might also be a difference there because you do not have enough patients that you do not see the difference?

Mr Jawitz. You are absolutely right. We were limited by the database that we had and in several instances due to incomplete data and a lack of certain variables, we were unable to answer all of our questions.

Dr Kappetein. And, of course, therefore, in a group where you have enough patients you can identify easier a difference and while in the groups that are smaller there might be a difference as well but it might be more difficult to identify.

Mr Jawitz. Yes, you are correct.

000 Impact of ABO compatibility on outcomes after heart transplantation in a national cohort during the past decade

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The United Network for Organ Sharing database was analyzed to determine the impact of ABO matching on post heart transplantation survival. It was demonstrated that ABO-compatible transplantation does not result in adverse outcomes with respect to graft survival, but type O donor grafts were associated with poorer outcomes.

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ORIGINAL CLINICAL SCIENCE

Organ allocation in adults with congenital heart disease listed for heart transplant: Impact of ventricular assist devices

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KEYWORDS:
heart defects;
congenital;
ventricular assist device;
heart failure;
heart transplantation;
transplant organ allocation

BACKGROUND: Adults with congenital heart disease (CHD) listed for heart transplantation are rarely supported by ventricular assist devices (VADs). This may be a disadvantage to their priority for organ allocation. We sought to determine the relationship between VAD implantation and successful transplantation among patients listed for heart transplant.

METHODS: Adults with CHD patients ($N = 1,250$) were identified from the United Network for Organ Sharing (UNOS) database from 1985 to 2010 and compared to patients without congenital etiology for heart failure ($N = 59,606$). VAD use at listing, listing status, status upgrades and reasons for upgrade prior to transplant were trended at 5-year intervals and appropriate statistical comparisons were made between groups.

RESULTS: Since 1985, VAD use prior to transplant has increased significantly in patients without CHD, but not in CHD patients (17% vs 3% in 2006 to 2010, $p < 0.0001$). CHD patients were more likely to be listed as Status 2, compared to those without (66% vs 40%, $p < 0.001$ for 2006 to 2010), and less likely to be upgraded to Status 1 after listing (43% vs 55%, $p = 0.03$). Among those upgraded to Status 1, CHD patients were less likely to have a VAD at transplant than those without (3% vs 18%, $p = 0.005$). VAD use was more likely to result in death in CHD patients.

CONCLUSIONS: VAD use is less common in CHD patients than in patients without CHD, both at the time of listing and transplantation. Reduced VAD use appears to contribute to lower listing status and organ allocation. These differences have grown more disparate over time. Separate criteria for organ allocation for CHD patients may be justified.

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Adult congenital heart disease (CHD) patients are growing more numerous because of improved survivorship through childhood. They remain vulnerable to myocardial dysfunction and clinical heart failure,[1] a major cause of death in these individuals.[2,3] Thus, adult CHD patients are increasingly referred for heart transplantation.[4] Despite the anatomic and physiologic challenges,[5] favorable long-term transplant outcomes have been reported.[6,7]

Use of ventricular assist devices (VADs) as a bridge to transplant has become more commonplace, particularly since the introduction of continuous-flow pumps.[8,9] Extension of this practice to CHD patients, however, has been slower. Data from the United Network for Organ Sharing (UNOS) standard transplant and research data set has demonstrated that, compared to those without CHD, listed CHD patients are less likely to have a VAD or other

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mechanical support, as well as longer wait times in Status 2.[10,11] Consequently, cardiovascular mortality on the heart transplant waiting list is higher in CHD patients.

In 2006, a universal policy change was made in U.S. organ allocation, such that Status 1 patients outside the local referral area were offered organs before local Status 2 patients. This change has decreased the number of overall transplants for Status 2 patients.[4,12,13] Because VAD implantation is a qualification for Status 1 listing, lower VAD implantation rates in listed patients with CHD may result in lower priority status and reduced organ allocation for these patients.[12] We sought to determine the impact of VAD utilization on listing and heart allocation for CHD heart transplant candidates by following trends over time.

Methods

Patient population

Patient-level data were obtained from UNOS, a U.S. registry of transplant listing, organ allocation, and outcomes maintained continuously since 1985. Our institutional review board approved use of these deidentified data, and the requirement for individual consent was waived. We excluded patients who were <18 years old at the time of listing, listed for double organ transplantation, or listed for re-transplantation. The remaining patients were classified as CHD or without CHD based on the stated etiology of their heart failure.

Variables obtained included age, gender, listing status, inotrope use and VAD implant at the time of listing. Patients who were Status 2 at listing, but Status 1 (1, 1A, or 1B) at the time of organ offering were considered to have had a status upgrade. Patients in whom inotropic support was provided at time of transplant but not at listing were considered upgraded on the basis of inotrope use. Similarly, patients in whom VAD was present at transplant but not at listing were considered upgraded on the basis of VAD placement. Both were expressed as a percentage of patients upgraded. These were not mutually exclusive, nor did they account for all upgrades. All VADs were included together regardless of designation as "right" or "left," given the potential incongruity of nomenclature for systemic vs sub-pulmonic ventricles. Missing values for VAD fields were assumed to indicate no VAD support was present.

Data were analyzed by 5-year incremental eras starting from 1985 and were based on the listing date. Groups were compared using SPSS (version 18) for Macintosh using chi-square testing for categorical variables, and Student's *t*-test for continuous variables. $p < 0.05$ was considered statistically significant.

Results

Of 78,470 individuals in the database, 40,785 were excluded (including 13,177 pediatric patients, 4,068 listed for multiple organs simultaneously, 2,389 listed for re-do transplant, not mutually exclusive), leaving a study population of 60,856. From these, we identified 1,250 CHD patients (36% female), and 59,606 without CHD (22% female). CHD patients were, in general, younger at listing (33.5 ± 12.5 years vs 51.4 ± 11.2 years, $p < 0.001$), as expected from previous studies.[10,11] Peak VO_2 was not significantly different (12.6 ± 3.2 vs 11.6 ± 3.5 ml/kg/min). The majority of CHD patients were classified as "CHD with unknown surgery" ($N = 828$), with 372 identified as "CHD with surgery" and 47 as "CHD without surgery."

Numbers of adults listed for transplantation for both groups are given by era (Table 1). The percentage of listed patients transplanted has declined over time, with a larger drop in CHD patients to 50% (95% CI 45% to 56%) vs 62% (95% CI 61% to 63%) of patients without CHD for the most recent era ($p < 0.001$).

The percentage of patients initially listed as Status 2 has not changed in the CHD group for the past 3 eras (Figure 1). However, this percentage has gradually dropped for those without CHD to 40% in the most recent era (95% CI 39% to 41%, $p < 0.001$ vs CHD). The number of patients transplanted after initial listing in Status 1 has not changed significantly over time for either group. Yet there has been a decline in transplantation from Status 2 since 2006 for both groups (Figure 2). Currently, the proportion of patients transplanted from Status 2 is 33% (95% CI 24% to 42%) for CHD, and 41% (95% CI 39% to 44%) for those without CHD ($p < 0.0001$ for both compared with prior era).

For patients without CHD, VAD use rose steadily to 17% (95% CI 16% to 17%) at listing and to 17% (95% CI 16.5% to 17.8%) at transplant over the study period ($p < 0.001$ for change from 1985 to 1990 for both listing and transplant; Figure 3). Strikingly, there has not been a significant change in VAD utilization in CHD patients over this same time period.

The frequency of status upgrades while listed is shown for both groups (Figure 4). A similar percentage of patients were upgraded from Status 2 at listing to Status 1 at transplant for both CHD vs those without CHD during all eras except 2006 to 2010, when there was a significantly higher percentage upgraded among patients without CHD (55%, 95% CI 53% to 56%) compared with the CHD group (43%, 95% CI 36% to 51%, $p = 0.003$ vs no CHD). Of

Table 1 Adults Listed for Heart Transplantation by Era

Era	CHD listed (*N*)	CHD transplanted (%)	95% CI	Without CHD listed (*N*)	Without CHD transplanted (%)	95% CI
1985–1990	69	100	(100–100)	6,712	85	(85–86)
1991–1995	204	77	(71–82)	14,004	70	(69–71)
1996–2000	293	57	(52–63)	15,414	61	(60–62)
2001–2005	366	67	(62–72)	11,825	67	(66–67)
2006–2010	318	50	(45–56)	11,651	62[a]	(61–63)

Number of adults listed for transplantation by era, together with percent transplanted (with 95% confidence interval), for adults with congenital heart patients (CHD) vs those without CHD.

[a] $p < 0.001$ for CHD vs no CHD.

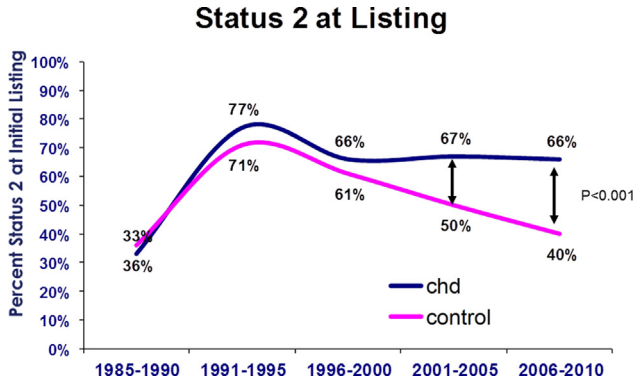

Figure 1 Percentage of patients from each group listed in Status 2 for both groups as a function of era. CHD, congenital heart disease. Controls are adult patients without CHD.

those upgraded, the percentage of patients upgraded with interval initiation of inotrope support did not differ between groups (Figure 5). This contrasts with the percentage of patients upgraded because of interval VAD implantation, which was significantly higher in those without CHD for each era from 1996 (Figure 6). For 2006 to 2010, 18% of patients without CHD upgraded had a VAD at the time of transplant (95% CI 16% to 20%) compared with only 3% in CHD patients (95% CI 0% to 6%, $p = 0.005$).

Outcomes for VAD patients at listing for the entire study period are shown in Table 2. For non-CHD patients, 68% (95% CI 67% to 70%) were transplanted, and 26% (95% CI 24% to 27%) died or were unstable. The remaining patients (6%) were removed for other reasons, including transfer out of area, refusal, clinical improvement or other. By comparison, for CHD patients, 48% (95% CI 33% to 63%) were eventually transplanted, 41% (95% CI 26% to 55%) had died or were too unstable for transplant, and 12% were removed from listing ($p = 0.015$ for CHD vs no CHD).

Discussion

Our analysis of the UNOS data demonstrates that CHD patients are: (1) less likely to have a status upgrade while listed; (2) less likely to receive a VAD after being listed;

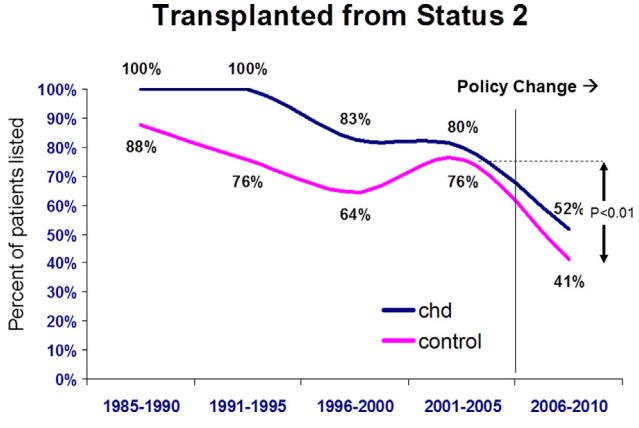

Figure 2 Percentage of patients from each group transplanted from Status 2 as a function of era. CHD, congenital heart disease. Controls are those without CHD. *p*-values are for comparison between eras for both patient groups.

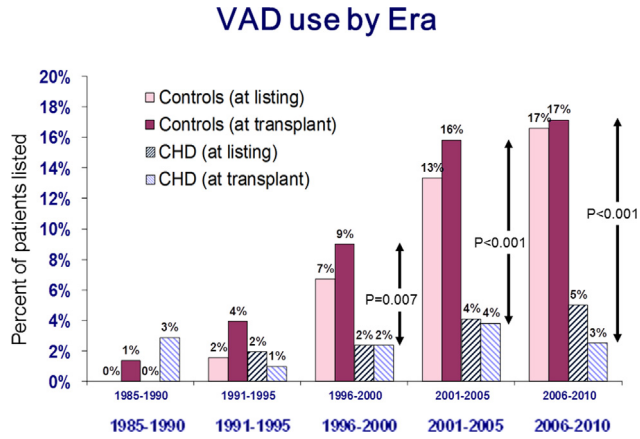

Figure 3 Percentage of patients with implanted ventricular assist devices at listing and transplant for both congenital heart disease (CHD) patients and those without CHD (controls), as shown by era. *p*-values are for comparison between patient groups for VAD use at transplant.

(3) less likely to receive an allograft while listed; and (4) more likely to die or become too unstable rather than be transplanted if a VAD is present. In addition, since 2006, there has been a considerable decline in transplantation from Status 2 among patients without CHD and especially with CHD, reflecting the allocation policy shift.

The observed low utilization of VAD among CHD patients can be interpreted in several ways. One possibility is that less severe heart failure is present in CHD patients listed for transplant. This seems unlikely given that CHD patients have similar exercise capacity and worse cardiovascular outcomes while listed.[11] A second more likely explanation is that increased anatomic complexity limits implantation. Based on single-center publications, the majority of congenital heart transplants are done in patients with transposition of the great arteries with a systemic right ventricle,[14–16] whereas most VADs are designed for implantation in a morphologic left ventricle. An alternative explanation is that CHD patients have severe circulatory failure, but not from ventricular systolic dysfunction. The patients most likely to fit this category are single-ventricle patients palliated with a Fontan procedure, who comprise a

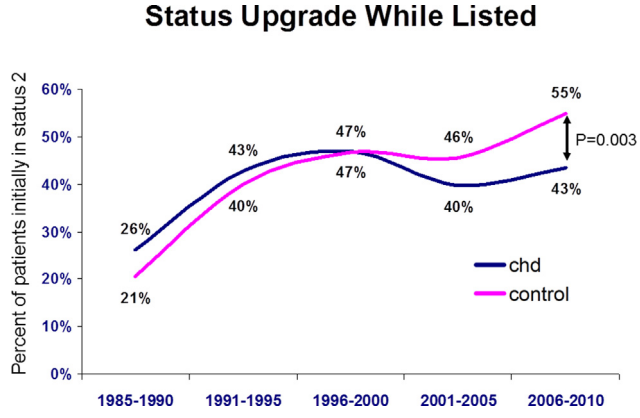

Figure 4 Percentage of patients from either group who were upgraded from Status 2 at listing to Status 1 at time of organ offering as a function of era. CHD, congenital heart disease.

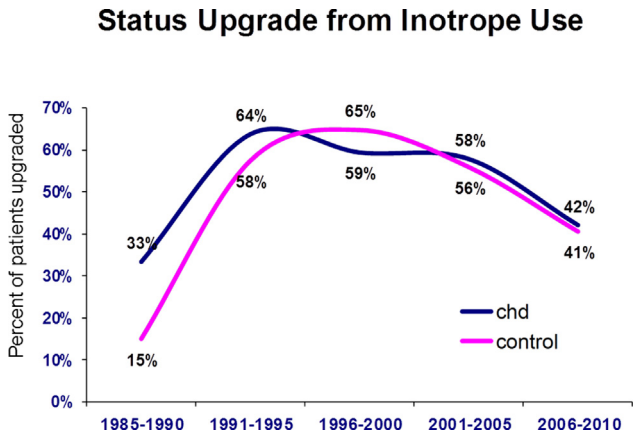

Figure 5 Percentage of patients upgraded from Status 2 with interval requirement of inotropic support. CHD, congenital heart disease.

considerable portion of transplanted CHD individuals.[14–16] Many single-ventricle patients develop significant morbidity from chronically elevated systemic venous pressure, including protein-losing enteropathy (PLE), malnutrition, ascites, coagulopathy, liver cirrhosis and desaturation through veno-venous collaterals. All of these occur in the context of normal systolic function of the systemic single ventricle. VAD use in the systemic circulation is therefore not a suitable solution for "Fontan failure."[17,18] To support the pulmonary circulation, VAD implantation requires complex cannulation,[19] and is currently reported only anecdotally,[20,21] often without successful outcome.[22] Novel pump designs have been proposed specifically for Fontan patients to address this problem,[19,23] with the expectation that successful utilization may favorably impact transplant candidacy and outcome.

Status upgrades in both groups were also attributable to inotropic support. However, dobutamine does not increase stroke volume in Fontan or systemic right ventricular (RV) patients.[24–28] Thus, inotropic support as a criterion for heart failure severity and heart allocation priority may also not be applicable to this population.

Given the scarcity of organs, should transplant priority be given to patients with lower risk of peri-operative

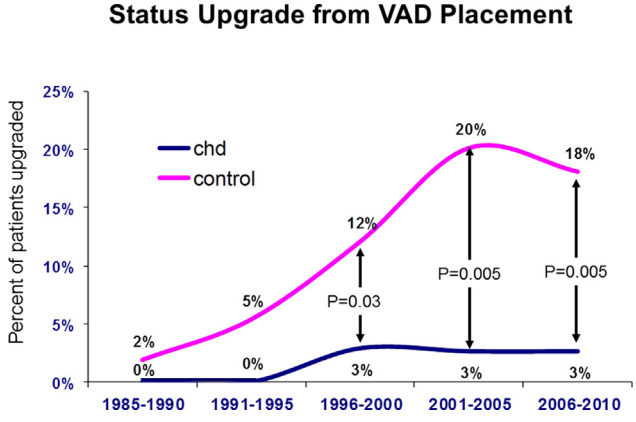

Figure 6 Percentage of patients upgraded from Status 2 with interval ventricular assist device implant (C). CHD, congenital heart disease.

Table 2 Outcome of All Patients With VADs at Time of Listing

	With CHD			Without CHD		
	N	%	95% CI	*N*	%	95% CI
Transplanted	20	48	(33–63)	3001	68	(67–70)
Died/unstable	17	40	(26–55)	1,128	26	(24–27)
Removed/other	5	12	(2–22)	255	6	(5–7)

Removed/other category includes those with clinical improvement, transfer away from the transplant center, refusal of transplant, or removed in error. CHD, congenital heart disease.

complications? CHD patients represent a dilemma; higher risk may be balanced by high potential benefits. Although early mortality in specific subsets is higher,[29] long-term survival is excellent and comparable to outcome in recipients without CHD. Despite these realistic concerns, in a contemporary cohort from a single center, there was no difference in post–heart transplant survival at 1 month, 1 year or 5 years between patients with CHD or without CHD.[30] As such, transplantation remains an important therapy for CHD patients. They are generally younger than patients without CHD and their transplant survival benefit may add years to their adulthood.[6,7] PLE, for example, contributes substantially to peri-operative mortality,[31] yet transplantation is curative.[18,32,33] Despite the favorable long-term outcomes, one could argue that VAD use stabilizes the patients prior to transplant, and that patients with higher peri-operative risk, such as single ventricle patients,[29] should not necessarily have priority. Yet CHD patients in whom a VAD is not an option may improve their peri-operative outcomes by earlier transplantation prior to progression of co-morbidities and concomitant risk.

Clinical relevance

The 2006 allocation policy change created a disadvantage for Status 2 patients, who now wait longer for an organ. Because VAD implant defines a Status 1A or 1B patient, there is a "cutting-in-line" effect for those with VADs who have a head start in allocation for this precious resource. VAD use offers recipients a period of potential stability, making them better suited for eventual transplant.[34] Non-VAD candidates do not have this safety net. In light of the disparity, we agree with others that for certain sub-populations, such as those with CHD, inapplicable or less effective therapies like VAD implantation or inotrope dependence should not be so heavily weighted in the determination of organ allocation.[10–12] It has been shown recently that the current status definitions that favor VAD patients are disproportionate to their actual mortality risk relative to those without VAD.[34] Collectively, the data support a reappraisal of allocation procedures to render the organ allocation process more equitable. Allocation priorities should balance the risks of mortality without transplant as well as peri-operative risks with the relative long-term benefits of transplantation in younger patients.

Limitations

Inherent limitations of this study include the retrospective design from a data set not necessarily tailored for CHD patients. There is no method to validate the reported CHD diagnosis within the registry. Our methods required assumption that missing data, particularly for VAD use, implied that therapy was not given. Although we cannot formally validate this assumption, we know from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data set on implanted devices, begun in 2005, that only 21 VADs were registered in CHD patients, which is comparable with the data reported in the present study. We did not differentiate right vs left VAD because of the lack of standardized nomenclature for congenital defects and uncertainty as to which circulation was being supported. We did not study children, in whom unique issues are often raised, although bridging to transplant with VAD has been done successfully.[21,35]

In conclusion, CHD poses new challenges to heart failure management and transplantation. Use of mechanical support as a bridge to transplantation in the CHD population is currently limited and highlights the need for VAD innovation and the development of surgical techniques for VAD implantation in anatomically complex CHD patients. Given the significant challenges of VAD use in this population, the feasibility of increasing VAD support in patients with CHD remains in question. Orthotopic heart transplant has been shown to be an effective therapy in these individuals. Given this, current allocation policies that favor patients without CHD may not be fair. Although the proportion of CHD patients undergoing transplant is small, national standards should account for their unique limitations and allow equitable organ allocation based on both risk and potential benefit.

Disclosure statement

The authors have no conflicts of interest to disclose.

The content of this study is the responsibility of the authors alone and does not necessarily reflect the views or policy of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizatiofns imply endorsement by the U.S. Government.

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ORIGINAL CLINICAL SCIENCE

Impact of long term left ventricular assist device therapy on donor allocation in cardiac transplantation

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KEY WORDS:
heart transplantation;
left ventricular assist device (LVAD);
organ allocation;
cardiac donor;
UNOS classification

BACKGROUND: Left Ventricular Assist Devices (LVAD) are increasingly used as a bridge to transplant (BTT) for patients with advanced congestive heart failure (CHF) and are assigned United Network for Organ Sharing (UNOS) high priority status (1B or 1A).

METHODS: The purpose of our study was asses the effect of organ allocation in the era of continuous flow pumps. A retrospective chart review was performed of all patients transplanted between 1/2001-1/2011 at Columbia University Medical Center.

RESULTS: Seven hundred twenty six adult heart transplantations were performed. Two hundred seventy four BTT patients were implanted with LVAD; of which 227 patients were transplanted. Sixty three patients were transplanted as UNOS-1B, while 164 were transplanted as UNOS-1A (72%). Of these 164 patients, 65 were transplanted during their 30-day 1A period (43%) and 96 after upgrading to UNOS-1A for device complication (56%). For 452 non-device patients 139 (31%) were transplanted as UNOS-1A, 233 as UNOS-1B (52%), and 80 as UNOS-2 (17%). The percentage of patients bridged with LVAD increased from 19% in 2001 to 64% in 2010 while the number transplanted during their 30 day 1A grace period declined from 57% in 2005 to 16% in 2011; i.e. 84% of BTT patients in 2011 needed more than 30 days 1A time to be transplanted. Most LVAD patients are now transplanted while suffering device complication. There was no difference in post transplant survival between LVAD patients transplanted as UNOS 1B, 1A grace period or for a device complication

CONCLUSIONS: As wait time for cardiac transplantation increased the percentage of patients being bridged to transplant with an LVAD has increased with the majority of them transplanted in the setting of device complication.

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Heart transplantation remains the treatment of choice for end-stage heart failure. With the scarcity of donor organs, the waiting time to transplant continues to lengthen.[1–3] As a result, left ventricular assist devices (LVADs) are increasingly being used as a bridge to transplant (BTT). Given the limited durability of earlier generation devices,[1–3] LVAD implantation automatically triggers a United Network for Organ Sharing (UNOS) status upgrade (1B) to increase the likelihood of cardiac transplantation as well as a 30-day period of upgrade of priority status to the highest level (1A) at the discretion of the transplant center.[4–6] This urgency status can also be upgraded in the event of device malfunction or device-associated complication.[6] Newer generation mechanical devices using axial continuous-flow pumps have

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been increasingly used as a BTT.[7] These smaller pumps have increased durability and reduced infection rates compared with earlier generation pumps, but other complications inherent to continuous-flow physiology are common, such as aortic insufficiency and recurrent bleeding due to von Willebrand factor deficiency.[8,9] The aim of this study was to evaluate the evolution of the transplant recipient in the era of increased use of LVADs and to assess the impact of the UNOS status listing policy on these candidates.

Methods

Study population

A retrospective chart review was performed from January 1, 2001 through January 1, 2011. All patients who underwent LVAD as BTT on the waiting list were identified and included in our study ($n = 274$). Patients with amyloidosis and those undergoing re-transplantation and/or double-organ transplants were excluded from analysis. Only long-term left ventricular devices were included in this analysis (HeartMate I and II, DuraHeart, DeBakey, Toyobo and VentrAssist devices) (Table 1), with all short-term and biventricular assist devices excluded. All patients were followed until death, orthotopic heart transplant (OHT), delisting from the UNOS registry, or in "still waiting" status on the UNOS registry on the day of the last observation, January 1, 2011. Patient data were obtained from electronic medical records and UNOS data were retrieved from the UNOS registry (beginning from initial listing and after each change, as well as reason for the status change) until the time of the ultimate disposition. The sub-categorization of Status 1A patients was as follows: (a) 30-day VAD time; (b) device complication; (c) on respirator; (d) in critical care unit (CCU) on inotropes; and (e) other (6). The sub-categorization at time of transplant was included in the analysis of device outcome post-transplant .

Outcome data of the BTT population were compared with all patients undergoing their first single-organ heart transplant at Columbia University in the same time period without mechanical support prior to OHT ($n = 452$).

Statistical analysis

Data were collected using EXCEL (2007) software (Microsoft Corp., Redmond, WA). All data were analyzed using STATA, version 11.0 (StataCorp, College Station, TX). Categorical variables were summarized by frequencies and percentages, and were analyzed using the chi-square test. Student's *t*-tests for independent samples were used to determine differences in normally distributed data. Wilcoxon's rank sum test was used to determine differences in non-normal distributions. Kaplan–Meier analysis was used to assess differences between survival functions.

Table 1 Distribution of Types of Left Ventricular Assist Device

Type of device	Number (total = 274)[a]
Debakey	9
DuraHeart	7
HeartMate I	128
HeartMate II	116
Jarvik 2000	1
Novacor	3
Toyobo	2
VentraAssist	8

[a]Patients with long-term LVAD support and short-term RVAD support.

Results

Study population

A total of 274 patients underwent long-term LVAD BTT implantation at the Columbia University Medical Center. Forty-five percent of the patients were supported by a HeartMate I (HM I) device as a bridge to transplant, 42% HM II, and the remaining 14% a combination of DuraHeart, DeBakey, VentrAssist or Toyobo devices. Forty patients died prior to transplant and one patient was delisted, leaving a study population of 234 patients (Figure 1). Six patients are still awaiting transplant. Clinical characteristics of the patients are shown in Table 2. Mean age was 53 ± 12 years. LVAD patients were mostly male (82%). Eighty-three percent ($n = 227$) were transplanted, 40 died, and 6 are still awaiting transplant. Four hundred fifty-two adult patients were transplanted during this period without the benefit of any type of mechanical support.

Bridge to transplant

The overall outcome of our BTT cohort is shown in Figure. 2. Eighty-five percent of the patients were alive on a device or transplanted after a mean follow-up time of 25 months; 83% were transplanted after a mean wait time of 288 ± 440 days. Only 15% of the patients were delisted or had died.

UNOS status at time of transplantation

UNOS status at the time of transplantation suggests increasing urgency as the vast majority had become UNOS Status 1A (Figure 3a). This can be partially explained by the increasing number of mechanical assist device patients being transplanted—of the 227 LVAD patients, the majority were UNOS 1A (72%) at time of transplant (Figure 1).

The proportion of bridged transplant candidates in priority Status 1A remained between 60% and 90% throughout the observation period at our center (Figure 3b); however, although UNOS 1A patients were traditionally those on inotropic support in the intensive care unit, most 1A patients at our institution qualified for status upgrade because of the LVAD grace period and/or LVAD-related complications: 65 patients were transplanted using sub-category (a) described earlier (i.e., 30-day wait time), and 1 patient was transplanted on mechanical ventilation. The high percentage of 1A exceptions in the years 2001 to 2004 reflects use of the 30-day grace period for devices, whereas most 1A listings in the current years were due to device complications (Figure 3c). Ninety-six of the 164 patients transplanted

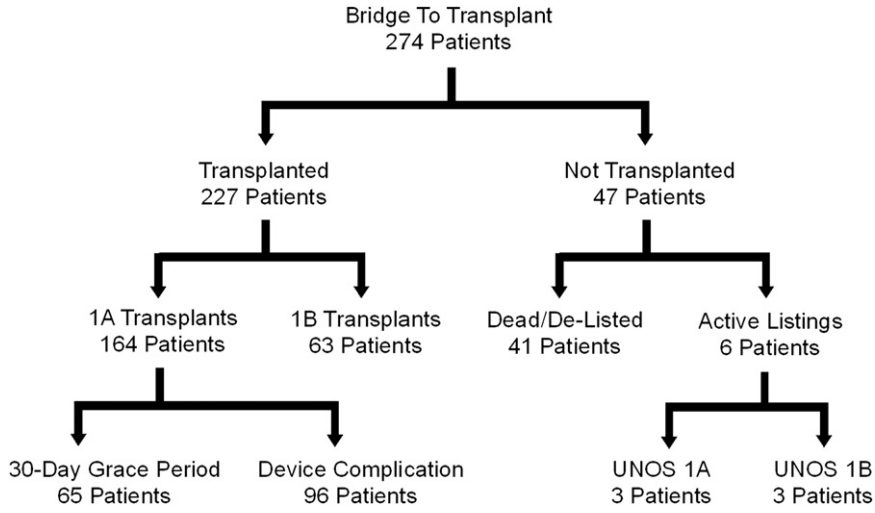

Figure 1 Outcomes of 274 bridge-to-transplant LVAD patients. Two hundred twenty-seven patients were successfully transplanted during the study period. Forty patients died prior to transplant and 1 patient was delisted.

as 1A during the observation period were upgraded to UNOS 1A due to device malfunction/complication, namely infection, refractory arrhythmia, thromboembolic events, bleeding or aortic insufficiency.

In our retrospective review we found the etiology of UNOS upgrade to 1A in 90 of 96 patients. Device-related infection was the most common cause (39 of 90), followed by device failure (25 of 90), heart failure need for inotropes/RVAD (12 of 90), recurrent bleeding (5 of 90), arrhythmia (5 of 90), aortic insufficiency (1 of 90) and others (3 of 90).

Thirty percent of patients with blood type O needed >30 days of 1A time (i.e., were not transplanted in the 30-day grace period), whereas this was true for only 10% of the patients with blood type B and 20% of patients with blood type A. In contrast, in transplant recipients without mechanical support, although the percentage of patients in the highest urgency category has increased in recent years, it remained less than that for mechanically supported patients (Figure 3d).

Table 2 Patients' Characteristics

	BTT (n = 274)	De novo Tx (n = 452)
Number transplanted	228	452
Time VAD to transplant (days)	208 ± 199	
Time list to transplant (days)	281 ± 440	272 ± 479
Dead without OHT	40	
Number of patients waiting	6	
Age (years)	53 ± 12	52 ± 12
UNOS status at List		
1a	62 (22.6%)	22 (4.9%)
1b	153 (55.8%)	186 (41.1%)
2	59 (21.5%)	205 (45.4%)
UNOS status at transplant		
1a	170 (64.4%)	139 (30.8%)
1b	94 (35.6%)	233 (51.5%)
2	0	80 (17.7%)
7	10 (3.8%)	
Gender		
Female	50 (18.9%)	120 (26.5%)
Male	224 (91.1%)	332 (73.5%)

Data expressed as number, mean ± SD or number (%). Tx, transplant.

Post–heart transplant survival

There was no difference in short- or long-term post-transplant survival in patients bridged with devices or medications (Figure 4). Similarly, survival post-transplant when categorized into priority groups was not significant for those transplanted with or without prior LVAD support (Figure 5a and b). When this was further broken down in the mechanically supported patients, there was no difference in survival between patients who were transplanted as UNOS 1A 30-day vs patients who were transplanted as UNOS 1A

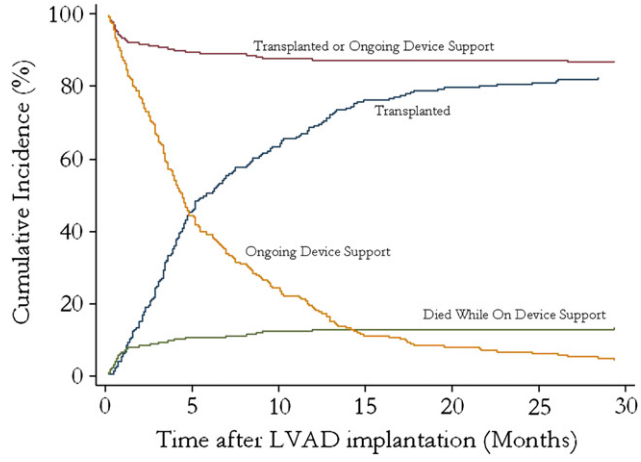

Figure 2 Competing risks analysis of BTT patients. The overall outcome data for bridging patients with LVAD to heart transplantation at our institution indicates that 85.4% of the listed patients are currently alive or transplanted after a mean follow-up time of 25 months.

Figure 3 (a) UNOS 1A at time of transplant proportion by year in all transplant patients. Status of current transplant recipients over the past decade demonstrates the increasing urgency such that now the vast majority of patients are in UNOS 1A. (b) UNOS 1A at time of transplant proportion by year in BTT patients. The proportion of BTT candidates in priority Status 1A remained between 60% and 90% throughout the observation period at our center. (c) Reasons for UNOS 1A at time of transplant by year in BTT patients. The high percentage of 1A exceptions in the years 2001 to 2004 reflects the use of the 30-day grace period for devices, whereas most 1A listings in the current years were due to device complications. (d) UNOS 1A at time of transplant proportion by year in transplant patients without a prior device. In transplant recipients without mechanical support, although the percentage of patients in the highest urgency category increased in recent years, it continued to be lower than for mechanically supported patients.

with device complications or UNOS 1B (1 year: 88% vs 83% vs 88%; 3 years: 81% vs 81% vs 86%; 5 years: 72% vs 72% vs 76% [$p = 0.57$]; Figure 6).

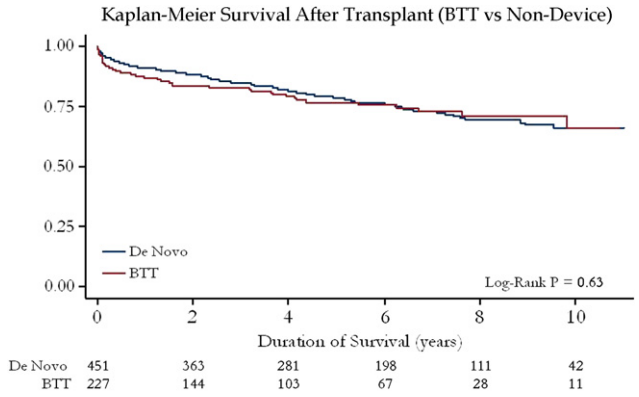

Figure 4 Survival post-transplant BTT vs patients without prior device. There were no differences in short- or long-term post-transplant survival in patients bridged with devices or medications.

Drive-line infection and its effect on heart transplant survival

The most common cause for upgrade from UNOS 1B to1A in the device patients was drive-line/device infection. Of the 227 transplanted patients, 56 had a history of drive-line infection, but only 22 had an ongoing drive-line infection at the time of transplant. Post-transplant survival of patients with device infection was not different from that in patients bridged with a device and without infection (Figure 7a) or UNOS 1A patients without prior LVAD (Figure 7b).

Discussion

We have examined UNOS status of patients at the time of heart transplantation at our institution between 2000 and 2010 and the effect of UNOS status policy conceived in the

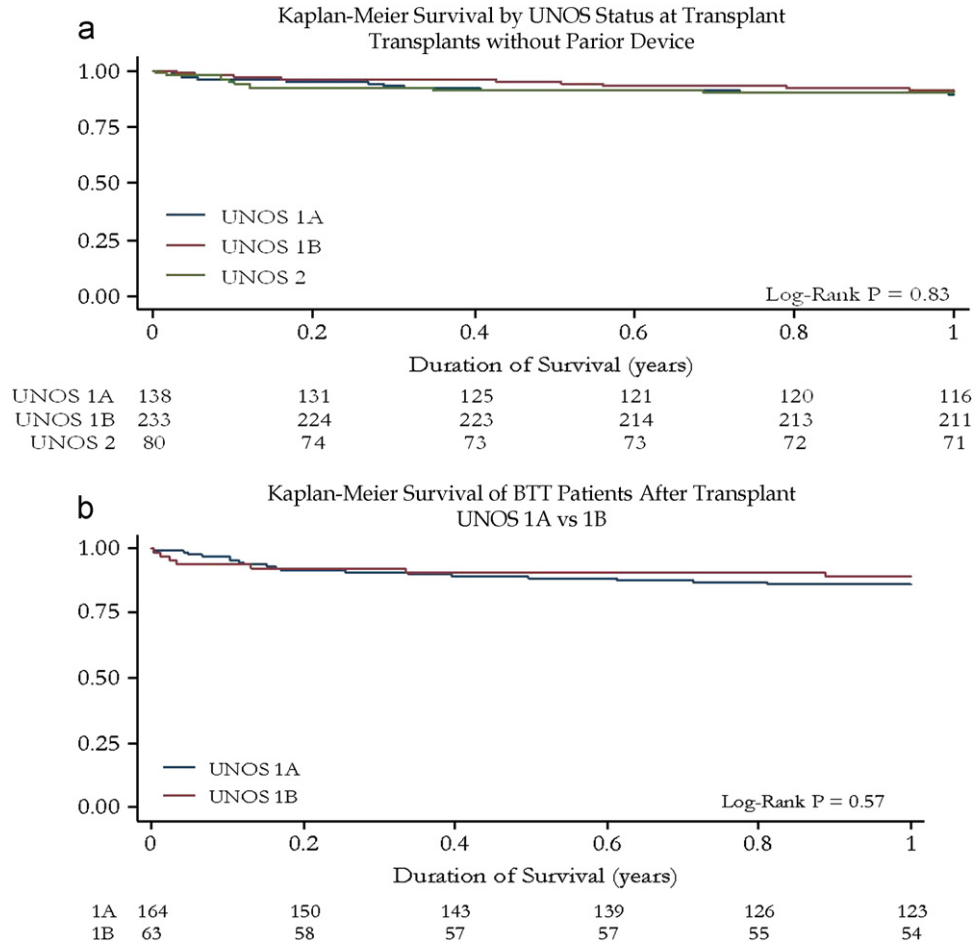

Figure 5 (a) Survival post-transplant by UNOS status of transplant patients without a prior device. Post-transplant survival for transplant patients without a prior device was not significantly different when categorized into priority groups. (b) Survival post-transplant by UNOS status of BTT patients. Post-transplant survival for the mechanically bridged patients was not significant different when categorized into priority groups.

early VAD era (before 2005) on organ allocation in the modern era. Our principal findings are as follows:

1. The percentage of patients receiving mechanical circulatory support as a bridge to transplant has increased dramatically, from 19% to 64%, over the past decade at our institution.
2. UNOS Status 1A, traditionally justified by parenteral inotropic use and invasive hemodynamic monitoring in the intensive care unit setting, in the current era is most often justified by the LVAD 30-day grace period and/or device complication.
3. There was no significant difference in post–heart transplant survival between patients who were bridged

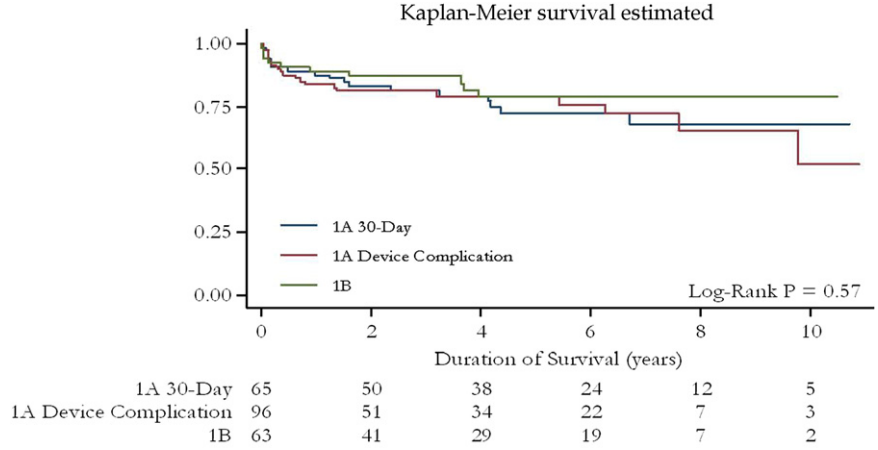

Figure 6 Survival post-transplant by UNOS 1A reason in BTT patients. No difference in survival between patients who were transplanted as UNOS 1A 30-day vs patients who were transplanted as UNOS 1A with device complication or UNOS 1B.

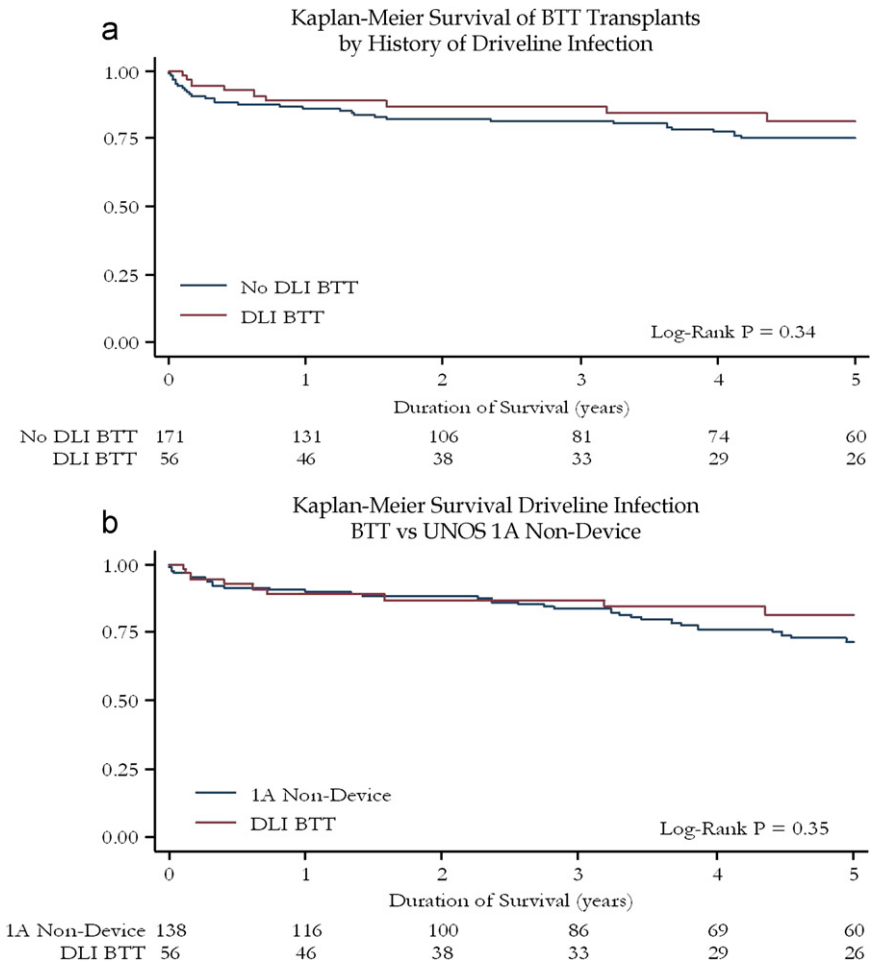

Figure 7 (a) Survival post-transplant for BTT patients by history of drive-line infection vs non–drive-line Infection. Post-transplant survival of patients with device infection was not different from that for patients bridged with a device and no infection. (b) Survival post-transplant for BTT patients with drive-line infection vs UNOS 1A transplant patients without prior device. Post-transplant survival of patients with device infection was not different from that for non-device 1A patients.

to transplant with an LVAD and those who were transplanted without LVAD support.

Heart transplant remains the "gold standard" for the treatment of end-stage heart failure. In the past decade, the number of heart transplantations in the USA has plateaued at 2,200/year, whereas the need for heart transplantation continues to grow. Due to the limited number of donor hearts, the waiting period has become longer. UNOS is contracted by the federal government to provide a system for equitable distribution of all organs available for transplantation in the USA. To achieve this objective in heart and lung transplantation, UNOS created the Thoracic Organ Committee, which includes a multidisciplinary group of professionals responsible for the design and monitoring of thoracic organ allocation algorithms. This algorithm has evolved over time. An allocation policy change in 1999 introduced Status 1A and 1B priority listings. Currently, organ allocation in heart transplantation is based on the severity of heart failure as defined by UNOS group (Status 1A, 1B or 2), duration of listing and geographic location. The most recent thoracic organ allocation policy change was implemented in 2006 and provides for regional sharing of organs for the most medically urgent adult cases.

Before 2006, donor hearts were offered first to local Status 1A patients, and then 1B and 2 in that order. If an appropriate recipient could not be located among those waiting locally, then the heart was offered out of the UNOS region. The new policy was designed to reduce waiting list mortality. Recent reports have differed as to the efficacy of this policy change.[10,11] What has been a consistent feature of the UNOS allocation policy has been the designation of LVAD recipients as 1B and assignment of a 30-day 1A period, as well as permanent upgrade to 1A in the setting of device-associated complications. The current heart allocation policy is based on prior experience with pulsatile pumps, primarily the HM I, as a long-term bridging device. The HM I was found to provide reliable support for only about 1 year, and its use was complicated by frequent and severe infections. Accordingly, the UNOS policy allowed "30-day 1A period in an effort to circumvent device complications. As device technology improved, with extended device durability and a lower rate of device infection, no change occurred in the allocation system. It is debatable whether successful LVAD candidates should be given automatic UNOS 1B status and/or a 30-day 1A grace period, particularly in light of near 90% 1-year survival in the current HM II BTT patients.

In Europe, stable heart failure patients on device support are not prioritized.

Given the persistent donor shortage and the growing list of prospective transplant candidates, with more requiring LVAD support, a revision of our allocation system needs to be addressed. This large, single-center experience in a region where the transplant rate is low per capita suggests that there will be an increasing shift to device use prior to transplant and that those bridged patients who will be transplanted are those with serious complications. The original intent of LVAD placement was to improve the patient's overall status and thus enhance post-transplant recovery. Although the 30-day grace period provides a welcome benefit to our device patients and was justified given the clinical results with earlier generation devices, it should not be overlooked that this policy has increased the wait time needed for all patients and, at least in our region, has practically deprived blood type O patients from receiving a transplant without LVAD bridging. The latter was clearly not the intent of the policy.

Post-transplant survival in patients with a device has been the subject of several reports, as a multivariate analysis of large registry data suggested that mechanical support is a predictive factor for poor transplant survival.[12] More recent reports, which focused exclusively on long-term left ventricular assist device use as BTT, has refuted these observations.[13,14] Nevertheless, if the trend continues that complicated LVAD patients comprise the majority of transplant candidates, it may only be a matter of time to when post-transplant survival will suffer. The task of sifting out which LVAD complications need to be prioritized is clearly at hand. Not all device complications and malfunctions are equal in severity and outcome. Currently, patients with drive-line infections, systemic infections related to device infection, severe aortic insufficiency or recurrent severe bleeding are all equally upgraded to UNOS 1A. However, our analysis suggests that patients transplanted with a device complication or malfunction after 2006 have a trend toward worse post-transplant survival. LVAD patients with device infection not localized to the pocket are at increased risk for septic and vasodilatory shock post-transplant in the setting of intense immunosuppression. Severe neurologic deficiency as a complication of a devastating stroke during LVAD support will preclude transplant; similarly, there may be infections that are too extensive or coagulopathies too profound to make transplantation tenable.

New organ allocation policy recommendation for LVAD patients

We believe that changes are needed in the organ allocation system to facilitate equitable use of organs with the best possible post-transplant outcomes. It should be considered whether LVAD implantation merits a separate category. The 30-day 1A grace period should be reconsidered, and probably removed, as outcomes and quality of life afforded by current generation LVADs do not seem to justify a "grace period." This is particularly true in light of the differences in waiting list time by UNOS regions. Upgrades for patients with LVADs should be stratified by the specific device complication; that is, systemic infection with bacteremia should have higher urgency than a superficial drive-line exit site infection.

Limitations

This study was a retrospective analysis and carries limitations inherent to this method. Specifically, patients reported as UNOS 1A with a 30-day grace period may actually have a coexistent device-related complication or malfunction. To overcome the aforementioned limitation our data were collected both from UNOS and electronic medical records.

In conclusion, the percentage of OHT patients requiring BTT LVADs is increasing. Most transplants are now performed in patients categorized as UNOS 1A and wait times have increased. More patients are categorized as UNOS 1A because of device-related complications and/or malfunction. With the dramatic improvement in device technology and substantial heterogeneity in device complications with a variable effect on prognosis, current allocation policies for cardiac transplantation with LVADs should be adjusted to reflect these changes.

Disclosure statement

The authors have no conflicts of interest to disclose.

The first two authors (N.U. and U.J.) contributed equally to this study.

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OPTN/SRTR 2011 Annual Data Report: heart

ABSTRACT Since 2005, the number of new active adult candidates on the heart transplant waiting list increased by 19.2%. The transplant rate peaked at 78.6 per 100 wait-list years in 2007, and declined to 67.8 in 2011. Wait-list mortality declined over the past decade, including among patients with a ventricular assist device at listing; in 2010 and 2011, the mortality rate for these patients was comparable to the rate for patients without a device. Median time to transplant was lowest for candidates listed in 2006-2007, and increased by 3.8 months for patients listed in 2010-2011. Graft survival has gradually improved over the past two decades, though acute rejection is common. Hospitalizations are frequent and increase in frequency over the life of the graft. In 2011, the rate of pediatric heart transplants was 124.6 per 100 patient-years on the waiting list; the highest rate was for patients aged less than 1 year. The pre-transplant mortality rate was also highest for patients aged less than 1 year. Short- and long-term graft survival has continued to improve. The effect on wait-list outcomes of a new pediatric heart allocation policy implemented in 2009 to reduce pediatric deaths on the waiting list cannot yet be determined.

KEY WORDS End-stage heart failure, heart transplant, transplant outcomes, ventricular assist device.

I want to do everything possible, because I don't want to waste any of the time I've been given. I am lucky, and I will do everything I can to make sure others get the same chance at life as I have been given. I tell everyone how important it is to be a donor. It really is about giving life.

Lacey, heart recipient

Introduction

Heart transplant has long been the best option for selected patients with end-stage heart failure. However, improvements in ventricular assist device (VAD) technology and increased experience with mechanical circulatory support have led to 1-year survival rates approaching those of heart transplant (1). The projected duration of current VADs is at least 5 years, and complications such as stroke and infection have declined substantially compared with complications related to older-generation devices. VADs bridge patients with end-stage heart failure safely to transplant and effectively treat heart failure. Thus, for many patients whose conditions are stable with a VAD, there is no urgency to proceed with listing for heart transplant. Durable devices have dramatically changed the way end-stage heart failure is managed and have resulted in shifts in post-transplant and wait-list trends.

Over the past decade, there have been minor fluctuations in the number of transplants performed per year, with a relatively consistent increase since 2004 (Figure 3.1). This increase in transplants has been mirrored by increases in donation rates, new listings, and transplant rates during the same period (Figures 1.1, 1.4, 2.1). This trend may be explained by policy changes that promote broader sharing. Substantial geographic variation in transplant rates still exists (Figure 3.4). Although geographic variations in donation rates may explain this trend, other factors may include regional donor use, access to the waiting list, geographic variations in listing practices, and death on the waiting list. Over the past decade, two major revisions to heart allocation policy have affected current trends: 1) in 2002, the policy regarding candidates with a VAD was changed to allow listing as status 1A for 30 days at any time after implant; 2) in 2006, the Organ Procurement and Transplantation Network (OPTN) implemented a broader sharing policy to preferentially allocate hearts to combined local and zone A status 1A and 1B candidates (2). In this report, when possible, we highlight trends that may have been influenced by these revisions.

Under the current allocation system, which was revised in 2002, all VAD patients, including those with complications as well as those who are stable, may accrue 30 days of status 1A time without a requirement for hospital admission. If patients with a VAD are not listed as status 1A, they can be listed indefinitely as status 1B. This revision, combined with the growing number of candidates with a VAD, has contributed to the increased proportion of status 1A and 1B registrations over the past decade and the decline in the proportion of status 2 registrations (Figures 1.2, 1.3, 1.12). Although candidates using intravenous inotropes can be listed as status 1A, the proportion of recipients receiving inotropes has declined over the past decade from 51% to 35%, presumably due to increased use of VADs in candidates who previously may have been prescribed inotropic therapy and the recognized survival benefit of VADs compared with inotropic therapy (3,4) (Figure 3.7). While these policies were developed during the early era of mechanical circulatory support, there have been substantial gains in VAD survival; thus the policies may need to be revised to reflect current clinical practice. Disease severity may vary widely among VAD patients. Variability in stability among VAD patients may contribute to differences in wait-list survival and possibly post-transplant survival. Currently, the OPTN Thoracic Organ Transplantation Committee is reassessing allocation policies in favor of a system that can better distinguish severity of illness among VAD patients. Furthermore, status 2 candidates are waiting longer due to changing trends in listing practices and the downstream effects of the broader sharing initiative. It remains to be seen whether longer waiting times will be detrimental to wait-list survival of status 2 candidates.

Adult Heart Transplant Waiting List Trends

New Listings, Wait-List Mortality, and Time to Transplant

Since 2004, the number of new active adult (aged 18 years or older at listing) candidates on the waiting list has increased by 19.2% (Figure 1.1). As expected, implementation of the broader geographic sharing policy and revision of the VAD policy have affected listing practices. Since 2006, the proportions of candidates who were first listed as status 1A and status 1B have increased by 5.4% and 7.3%, respectively, and the proportion initially listed as status 2 has declined by 11.7% (Figure 1.3).

The transplant rate peaked at 78.6 per 100 wait-list years in 2007 and has been declining since; in 2011, the rate was 67.8 per 100 wait-list years (Figure 1.4). Among candidates who were listed for transplant in 2008, 60.0% underwent transplant within 12 months of listing, 25.0% were still waiting at 12 months, and 9.5% had died. By 36 months, 69.7% had undergone transplant, 8.2% were still waiting, and 11.6% had died (Figure 1.6).

Wait-list mortality declined over the past decade, from 16.9 deaths per 100 wait-list years in 2001 to 11.6 per 100 wait-list years in 2011 (Figure 1.10). Trends were similar for men and women (data not shown), all age groups, all race categories, and all medical urgency status categories. In 2011, mortality by age was lowest for candidates aged 35 to 49 years; mortality was comparable for women and men (data not shown), and lowest for Asians. Wait-list mortality declined to approximately 10 deaths per 100 wait-list years for all diagnoses (Figure 1.10). Trends among candidates with a VAD at listing are notable. VAD survival has improved greatly. Historically, wait-list mortality has been substantially lower for candidates without a VAD than for candidates with a VAD; however, over the past decade, wait-list mortality improved dramatically among candidates with a VAD at listing, declining from 102.2 per 100 wait-list years in 2001 to 12.9 per 100 wait-list years in 2011. In 2010 and 2011, the mortality rate was comparable to the rate for candidates without a VAD at listing, a testament to improvements in VAD technology, experience, and application over the past 10 years (Figure 1.10). These data should be interpreted cautiously, however, as a marked proportion of candidates without a VAD received a VAD after listing; these candidates were included in the analysis as patients without a VAD at listing.

As expected with the broader sharing policy implemented in 2006, wait-list mortality declined substantially. Between 2006 and 2011, wait-list mortality for candidates listed as status 1A and 1B declined from 92.1 and 32.4 deaths per 100 wait-list years, respectively, to 36.9 and 11.0 deaths per 100 wait-list years. Wait-list mortality remains low for status 2 candidates, declining from 9.7 to 8.1 deaths per 100 wait-list years during this same time period (Figure 1.10). Mortality among candidates listed as inactive remained stable at 12.3 deaths per 100 wait-list years in 2011. Wait-list mortality remains highest for status 1A candidates compared with other medical urgency status categories.

Over the past decade, median time to transplant was lowest for candidates listed in 2006-2007, and has been increasing since. Overall, the duration of waiting time to transplant for candidates listed in 2010-2011 was 3.8 months longer than for the 2006-2007 cohort. In candidates listed as status 1A, median time to transplant increased from less than 1 month to 1.7 months. The trend was notable in candidates listed initially as status 1B and 2, for whom median waiting time increased by 3.5 months and 9.3 months, respectively (Figure 1.7). This trend does not, however, account for status upgrades or downgrades after listing. Median waiting time for candidates with a VAD at listing was 2.2 months less than for candidates without a VAD. Although waiting time also increased in recent years for candidates with a VAD, the magnitude was slightly less than for candidates without a VAD at listing, at 3.4 months compared with 4.4 months (Figure 1.7). As stated before, this analysis included candidates initially listed without a VAD who received a VAD after listing as candidates without a VAD at listing. The proportion of candidates listed in 2010 who underwent transplant within 1 year of listing varied widely by donation service area (DSA), from 27.1% to 81.0% (Figure 1.8). This variability may be due at least in part to differences among DSAs in listing practices and status changes after listing. Nationwide, the proportion of candidates undergoing transplant within 1 year of listing declined to 54.6% in recent years (Figure 1.9). Transplant within 1 year of listing was most likely for candidates with blood group AB and least likely for candidates with blood group O (Figure 1.9).

Candidate Characteristics

Since 2001, the proportion of candidates aged 18 to 34 years increased from 8.8% to 10.7%, and the proportion of those aged 65 years or older increased from 12.5% to 19.2%. While candidates aged 50 to 64 years compose the largest proportion

of heart transplant candidates, 49.5% in 2011, the size of this age group has declined in recent years (Figure 1.2). Over the past decade, the proportion of women increased by 4.2%. The proportions of ethnic minorities also increased; most notably, the proportion of black candidates increased substantially, from 13.8% to 21.2% between 2001 and 2011 (Figure 1.2). This increase may in part reflect the disproportionate and earlier occurrence of heart failure in black patients (5). The proportion of candidates with cardiomyopathy surpassed the proportion with coronary artery disease in 2003, and the proportion with congenital heart disease increased to 3.9% in 2011. In 2011, a smaller proportion of candidates (14.4%) waiting for heart transplant spent 3 or more years on the waiting list, compared with 2001 (23.2%). Listing practices, that is, centers electing to list candidates only when they qualify at a higher urgency status, may be partially responsible for shorter waits. Finally, the proportions of status 1A and 1B candidates on the waiting list have grown remarkably from 2001 to 2011, increasing from 9.6% to 14.1% for status 1A and from 17.2% to 35.0% for status 1B (Figure 1.2). These trends may be a consequence of increased use of VADs and of centers listing only candidates who qualify for higher urgency statuses. The increasing proportions of candidates awaiting heart transplant at a higher urgency status suggest increased morbidity among candidates, although the impact of VAD availability cannot be discounted. A comparison of candidates on the waiting list on December 31, 2001, and December 31, 2011, reveals similar trends (Figure 1.12).

Donation

The rate of heart donation among people aged less than 65 years has not changed substantially over the past decade; in 2010 this rate was 3.6 per 1,000 patient deaths. Donation rates since 2000 increased by approximately 20% in groups aged 0 to 14, 15 to 34, and 35 to 44 years, and declined by 23.0% and 40.0% in groups aged 45 to 54 and 55 to 64 years, respectively (Figure 2.1). Donation rates among blacks and Hispanics increased (Figure 2.1). Donors aged 18 to 34 years have consistently composed the greatest proportion of heart donors, and in 2011 represented 48.6% (Figure 2.7). The proportion of hearts recovered per organ donor declined from 0.37 in 2001 to 0.28 in 2004 and has since plateaued (Figure 2.3). The proportion of recovered hearts that are discarded has been declining over the past decade, and in 2011 ranged from 0.2% (1 heart) among heart donors aged 0 to 17 years to 1.8% (3 hearts) among heart donors aged 50 to 64 years (Figure 2.5). For the 17 recovered hearts discarded in 2011, the most common reason for discard was other (47.1%), followed by anatomical abnormalities (17.6%) (Figure 2.6). The most common cause of death among donors is head trauma (52.8%). For heart transplant donors, the prevalence of head trauma as a cause of death is slowly declining over time while the prevalence of anoxia is increasing (Figure 2.8).

Adult Heart Transplant

Trends in Transplant Rates

Overall, the number of adult heart transplants performed was stable between 2000 and 2011 (1,926 and 1,949, respectively). However, in 2004, this number reached a nadir of 1,724 (Figure 3.1). The transplant rate peaked in 2007 and has since declined for all status codes except status 1A (Figure 3.3). The anticipated effect of the broader sharing policy was more rapid transplants in status 1A and 1B candidates. Although the transplant rate for candidates listed at status 1A increased to 315 per 100 patient-years in 2011, the rate declined for status 1B candidates, from 267 to 103 transplants per 100 patient-years between 2007 and 2011. As expected, the transplant rate for status 2 candidates also declined, from 59 to 35 transplants per 100 patient-years. Among candidates with a VAD at the time of listing, the transplant rate decreased from 203 to 99 transplants per 100 patient-years between 2007 and 2011 (Figure 3.3). Despite this dramatic decline, candidates with a VAD continue to undergo transplant at higher rates than candidates without a VAD at listing, in part due to shorter waiting times. Candidates who received a VAD after listing are not accounted for in this analysis; these candidates were included in the analysis as patients without a VAD at listing; therefore, caution is warranted in interpretation.

Geographic trends in transplant rates are highly variable due to variations in center listing practices, donor availability

and perhaps DSA practices (Figure 3.4). Transplant rates varied from 0 to more than 200 transplants per 100 patient-years.

Trends in life support, including respiratory support and circulatory support, are also changing. Since 2001, the proportions of recipients who received intravenous inotropes immediately before transplant decreased from 51.1% to 35.1%. Since 2004, the proportion of recipients who received a left-VAD before transplant more than doubled, from 16.0% to 35.4% in 2011. Intra-aortic balloon pump use and ventilator use have been stable, as has right-VAD use (Figure 3.7).

Recipient Characteristics

The mean age of adult heart transplant recipients is 50.9 years and has not changed appreciably over the past decade (Figure 3.5); however, an increasing number of recipients are aged 65 years or older. Increasing proportions of recipients are female, are members of ethnic minorities, have cardiomyopathy, and have a VAD at the time of transplant (Figures 3.2, 3.9). Sensitization of heart transplant candidates remains a challenge and has increased since 2007. Increased use of VADs, evolving diagnostic methods to detect and quantify anti-HLA antibody, and increasing use of virtual cross-match, which may help increase access of sensitized candidates to heart transplant, have contributed to the growing number of sensitized candidates (Figure 4.1).

Transplant Outcomes

Aside from minor fluctuations, the overall adjusted probability of short-term graft failure (6 months and 1 year, adjusted for age, sex, and race) has been declining over the past decade, and in general is low, 0.07 at 6 months and 0.09 at 1 year for patients who underwent transplant in 2010. In addition, graft failure at 3, 5, and 10 years post-transplant has steadily declined (Figure 5.1). Early graft failure, within the first 6 weeks post-transplant, has declined, and occurred in only 4.9% of heart transplant recipients in 2011 (Figure 5.2). Overall, 5-year graft survival was 74.9%, and was similar among all status codes and disease groups (Figure 5.3). The greatest decline in graft survival occurred within the first 12 months post-transplant, when survival decreased by 12.7% (Figure 5.3). Graft survival has gradually improved over the past two decades. In recipients who underwent transplant in 2009 and had a functioning graft at 1 year, the predicted half-life, conditional on 1 year of survival, was 14.0 years (Figure 5.4). The number of heart transplant survivors is increasing; in 2011, 21,457 adult recipients were alive with a functioning graft, compared with 16,259 in 2001 (Figure 5.5). Among patients who underwent transplant between 2005 and 2006, 5-year survival was reduced in blacks compared with whites (68.2% vs. 77.9%); in recipients aged 18 to 34 years compared with those aged 35 to 49, 50 to 64, and 65 years or older (69.9%, 77.4%, 76.3%, and 73.9%, respectively); and in recipients with a non-durable VAD compared with those without a VAD and those with a durable VAD (54.9%, 76.6%, and 73.5%, respectively) (Figure 5.9). Only 51 recipients were included in the non-durable VAD category. Recipients with biventricular assist devices involving both durable and non-durable VADs were included in the durable category: 6 patients had a Heartmate XVE combined with a non-durable device. Among recipients in whom the cause of death post-transplant is known, cardiovascular disease remains the most common primary cause (Figure 5.10).

Post-Transplant Morbidity

Acute rejection during the first year post-transplant is common, occurring in 24.5% of recipients who underwent transplant 2005-2009. By 5 years post-transplant, 50.9% of recipients had at least one episode of rejection (Figure 5.6). Hospitalizations are frequent during the first year, occurring in 39.3% of recipients who underwent transplant 2006-2011, and continue to increase over the life of the graft; within 4 years post-transplant, 65.3% of recipients have been hospitalized (Figure 5.7). Post-transplant lymphoproliferative disorder (PTLD) is relatively infrequent in adults and is closely linked to Epstein-Barr virus (EBV) status (Figure 5.8).

Summary

This year's report highlights several successes, including notable improvements in wait-list survival and in patient and

graft survival. The broader sharing policy and increased VAD use have contributed to these successes but have introduced new challenges regarding allocation of donor hearts. Median time to transplant is increasing, particularly among status 2 candidates. Numbers of candidates listed as status 2 are declining; the appropriateness of performing transplants in status 2 candidates is even being questioned (6). Transplant rates are declining for status 1B and status 2 candidates. To continue allocating hearts to the highest urgency candidates, the allocation policy will need to further distinguish severity of illness between status 1A and status 1B candidates. Revisions to the heart allocation policy are currently being considered; these revisions are anticipated to further define VAD complications to ensure that criteria used for justification of medical urgency are more uniform. Finally, wide geographic variations persist in donation rates, transplant rates, and wait-list mortality. While these analyses are currently not adjusted for medical urgency, which may contribute to the perceived variations, the causes of these disparate trends warrant further investigation to assess equitable access to donor hearts around the country.

Pediatric Heart Transplant

Pediatric Waiting List Trends

Since 1998, the number of new pediatric candidates added to the heart transplant waiting list has increased slightly, and few candidates have been added as inactive. The number of prevalent wait-list candidates remained stable between 250 and just over 300 in the past decade. Historically, more candidates were listed as inactive than as active, but in a shift since 2008, 57.1% of candidates are now listed as active (Figure 7.1). The age distribution changed over the past 3 years; the percentage of wait-listed candidates aged 11 to 17 years increased, with a corresponding decrease in the percentage aged less than 1 year (Figure 7.2). Eight percent of candidates on the waiting list in 2010-2011 were waiting for a re-transplant. Among all candidates on the list, 2.3% of those aged 0 to 5 years were waiting for a re-transplant, as were 15.8% of those aged 6 to 10 years and 14.7% of those aged 11 to 17 years (Figure 7.3). Of candidates newly listed in 2008, 70.2% underwent transplant within 3 years; 14.7% died, 11.8% were removed from the list, and 3.3% were still waiting (Figure 7.5). Pre-transplant mortality decreased for all age groups. The pre-transplant mortality rate was highest for candidates aged less than 1 year, at 49 deaths per 100 wait-list years in 2010-2011 (Figure 7.7).

Pediatric Transplant

The number of pediatric heart transplants performed each year increased from 274 in 1998 to 375 in 2011 (Figure 7.8). In 2011, the rate of pediatric heart transplant was 124.6 per 100 patient-years on the waiting list; the highest rate was for recipients aged less than 1 year, at 271.3 transplants per 100 patient-years on the waiting list (Figure 7.9). Over the past decade, congenital defects remain the most common primary cause of disease, affecting 43.4% of recipients in 2009-2011 (Figure 7.10). The percentage of patients who underwent transplant as status 1A increased from 62.2% in 1999-2001 to 87.1% in 2009-2011. This increase may reflect the policy implemented in 2009 that prioritized pediatric candidates awaiting heart transplant as status 1A in the combined local DSA and zone A as the first unit of allocation. This policy also preferentially allocates all pediatric hearts to pediatric recipients, a change from the previous policy, which prioritized adolescent donor hearts for pediatric candidates. VAD use increased from only 7.6% of pediatric transplant recipients in 1999-2001 to 18.3% in 2009-2011. Development of the Berlin Heart, a VAD for pediatric patients; the HeartMate II, a left VAD smaller than its predecessor; and other newer-generation devices allowed expansion of durable and non-durable support to pediatric candidates.

Pediatric Immunosuppression and Outcomes

Substantial changes in maintenance immunosuppression have occurred. Tacrolimus use increased from 23.8% in 1998 to 83.2% in 2011. Mycophenolate mofetil use increased from 33.2% in 1998 to 90.0% in 2011. In 2010, mammalian target of rapamycin inhibitors were used in 1.4% of patients at the time of transplant and in 7.2% at 1 year post-transplant. Steroids were used in 75.2% of patients at the time of transplant in 2010,

and use decreased to 36.1% at 1 year (Figure 7.13). In 2011, no induction immunosuppression was used in 32.0% of recipients, T cell depleting agents were used in 48.0%, and interleukin-2 receptor antagonists were used in 25.7% (Figure 7.13).

Graft survival, both long-term and short-term, has continued to improve. Graft survival for heart transplants performed in 2005 was 87.5% at 6 months, 84.6% at 1 year, and 72.1% at 5 years (Figure 7.14). Graft survival for heart transplants performed in 2010 was 92.7% at 6 months and 91.2% at 1 year. The rate of late graft failure is traditionally measured by the graft half-life conditional on 1-year survival, defined as the time to when half of grafts surviving at least 1 year are still functioning. For heart transplants performed in 2009-2010, the 1-year conditional graft half-life was 17.4 years (Figure 7.15). Incidence of first acute rejection increased over time post-transplant; 24.4% of patients experienced rejection in the first 12 months and 38.2% by 24 months post-transplant (Figure 7.16). The highest risk for EBV infection and PTLD occurred in EBV-negative recipients. Incidence of PTLD was 8.4% at 5 years post-transplant among EBV-negative recipients and 2.7% among EBV-positive recipients (Figure 7.12).

Policy Updates

In 2009, a new pediatric heart allocation sequence was implemented that preferentially allocates pediatric hearts to status 1A pediatric candidates in a combined allocation unit composing the local DSA and zone A before local adult status 1A candidates and status 1B pediatric candidates; compared with the previous policy, which prioritized local status 1A pediatric candidates, the new policy prioritizes both local and zone A status 1A pediatric candidates. The ultimate goal of this policy is to reduce pediatric deaths on the waiting list and to expedite allocation of pediatric hearts to pediatric candidates at highest risk of wait-list mortality. Although it is too early to determine the effect of this policy on wait-list outcomes, during 2010-2011, wait-list mortality appeared to decline among pediatric candidates in all age categories compared with 2008-2009 (Figure 7.7). Future OPTN/SRTR data reports will focus on the impact of these allocation policy changes.

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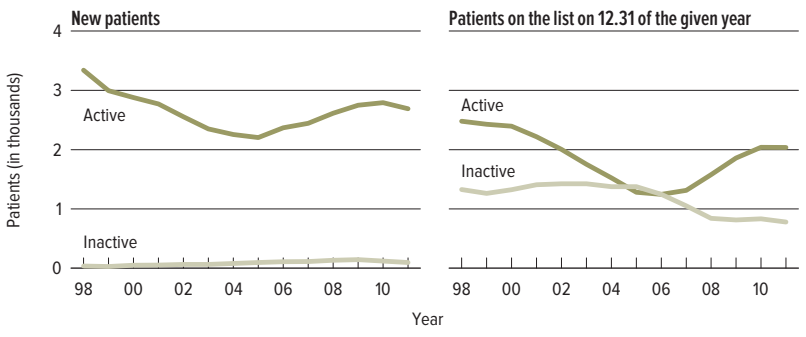
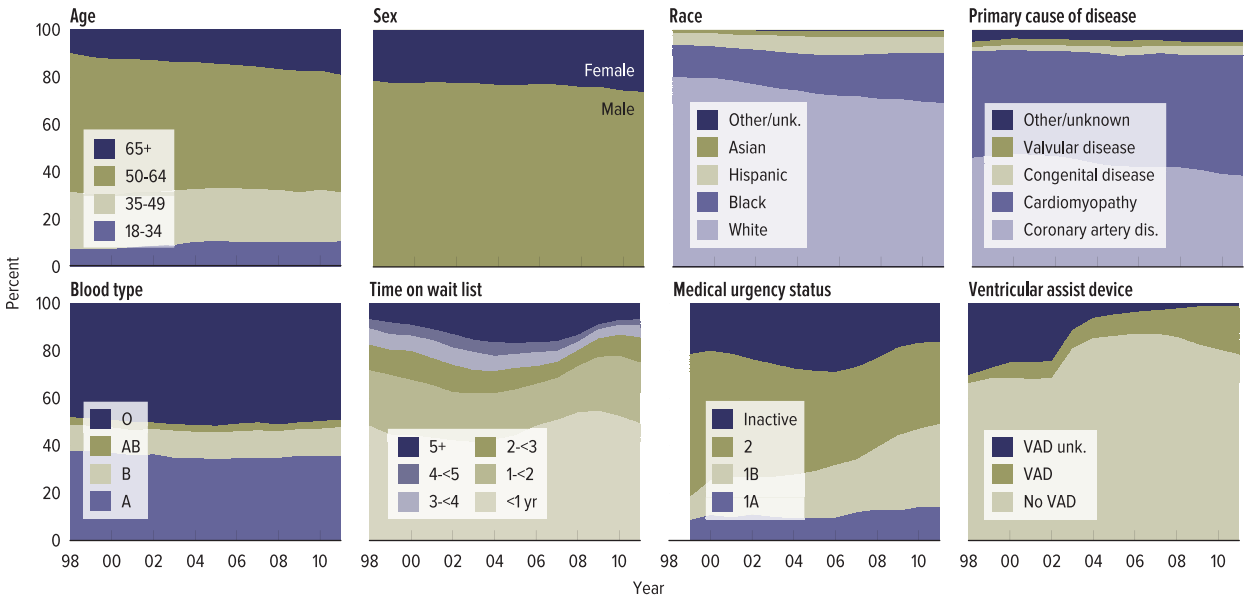
wait list



HR 1.1 Adult patients waiting for a heart transplant

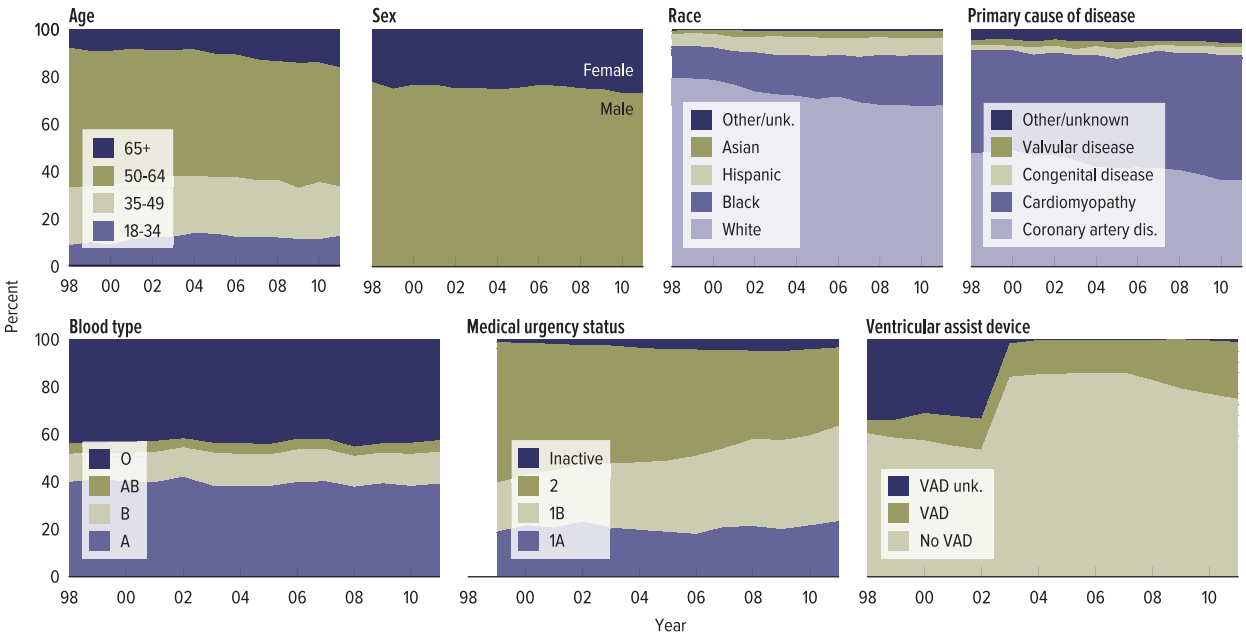
Patients waiting for a transplant. A "new patient" is one who first joins the list during the given year, without having listed in a previous year. However, if a patient has previously been on the list, has been removed for a transplant, and has relisted since that transplant, the patient is considered a "new patient." Patients concurrently listed at multiple centers are counted only once. Those with concurrent listings and active at any program are considered active; those inactive at all programs at which they are listed are considered inactive.



HR 1.2 Distribution of adult patients waiting for a heart transplant

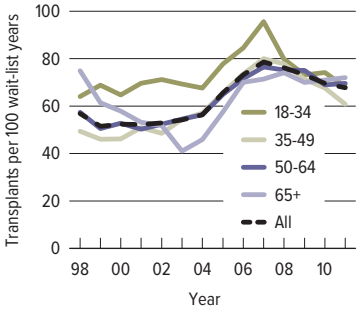
Patients waiting for a transplant any time in the given year. Age determined on the earliest of listing date or December 31 of the given year. Concurrently listed patients are counted once. Ventricular assist device information comes from the OPTN Transplant Candidate Registration form at the time of listing, and includes LVAD, RVAD, TAH, and LVAD + RVAD. Medical urgency status is the earliest available per year for each patient.

wait list



HR 1.3 Distribution of adult patients newly listed for a heart transplant

A newly listed patient is one who first joins the list during the given year, without having listed in a previous year. However, if a patient has previously been on the list, has been removed for a transplant, and has relisted since that transplant, the patient is considered a newly listed patient. Patients concurrently listed at multiple centers are counted only once. Ventricular assist device information comes from the OPTN Transplant Candidate Registration form at the time of listing, and includes LVAD, RVAD, TAH, and LVAD + RVAD.



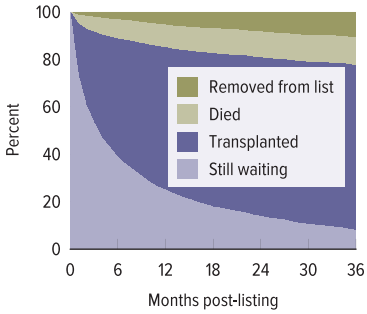
HR 1.4 Heart transplant rates among adult waiting list candidates, by age

Patients waiting for a transplant; age as of January 1 of the given year. Yearly period-prevalent rates computed as the number of deceased donor transplants per 100 patient years of waiting time in the given year. All waiting time per patient per listing is counted, and all listings that end in a transplant for the patient are considered transplant events.

	2009	2010	2011
Patients at start of year	2,409	2,668	2,867
Patients added during year	2,890	2,916	2,783
Patients removed during year	2,625	2,710	2,837
Patients at end of year	2,674	2,874	2,813
Removal reason			
Deceased donor transplant	1,840	1,965	1,931
Patient died	435	400	441
Patient refused transplant	14	12	18
Improved, tx not needed	193	164	166
Too sick to transplant	55	61	92
Other	88	108	189

HR 1.5 Heart transplant waiting list activity among adult patients

Patients with concurrent listings at more than one center are counted once, from the time of earliest listing to the time of latest removal. Patients listed, transplanted, and re-listed are counted more than once. Patients are not considered "on the list" on the day they are removed. Thus, patient counts on January 1 may be different from patient counts on December 31 of the prior year.

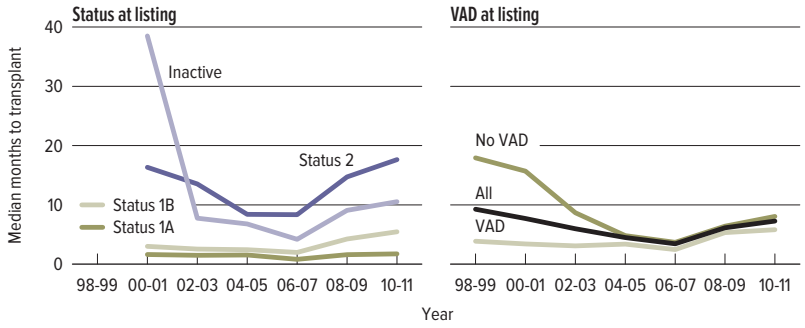


HR 1.6 Outcomes for adult patients waiting for a heart transplant among new listings in 2008

Patients waiting for a transplant and first listed in 2008. Patients with concurrent listings at more than one center are counted once, from the time of the earliest listing to the time of latest removal.

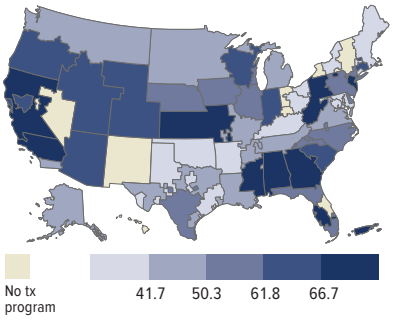
data behind the figures can be downloaded from our website, at www.srtr.org

wait list



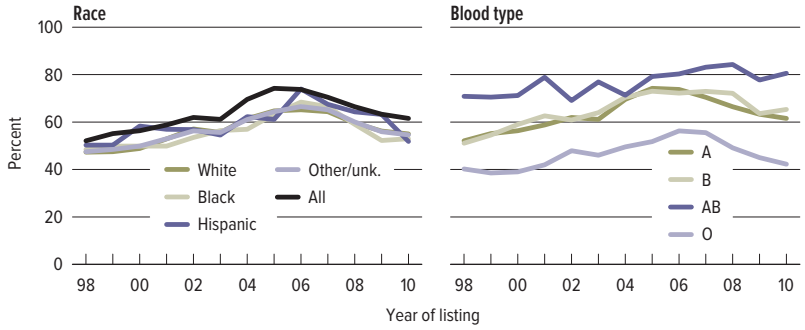
HR 1.7 Median months to heart transplant for wait-listed adult patients

Patients waiting for a transplant, with observations censored at December 31, 2011; Kaplan-Meier method used to estimate time to transplant. If an estimate is not plotted for a certain year, 50% of the cohort listed in that year had not been transplanted at the censoring date. Only the first transplant is counted.



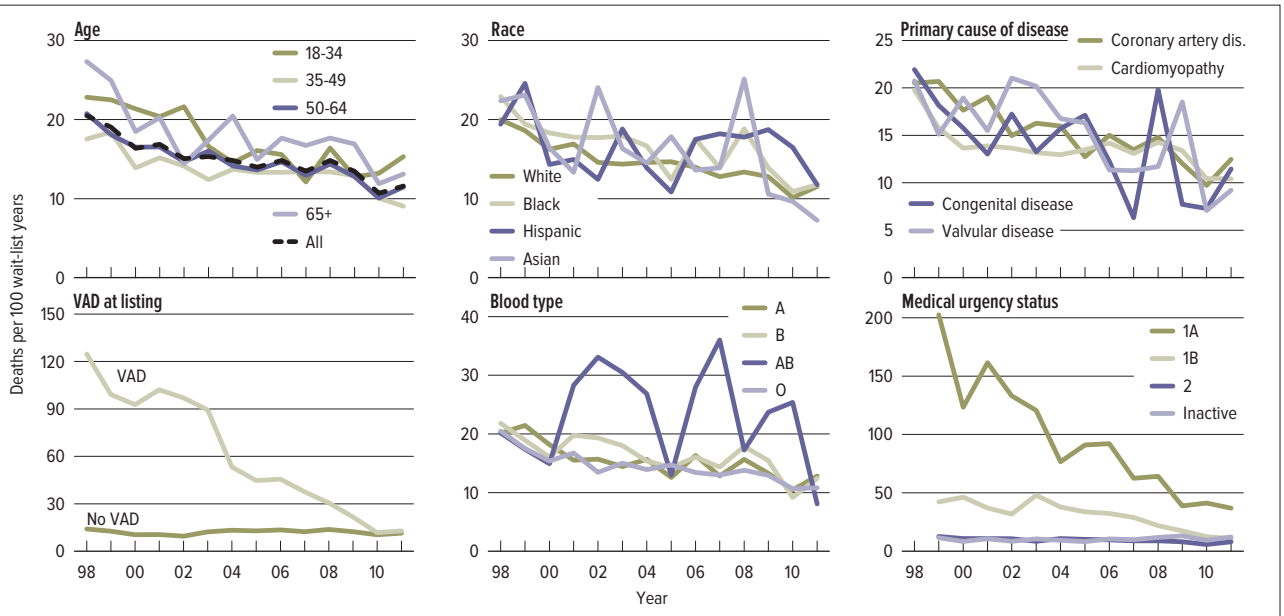
HR 1.8 Percent of adult wait-listed patients, 2010, who received a deceased donor heart transplant within one year, by DSA

Patients with concurrent listings in a single DSA are counted once in that DSA, and those listed in multiple DSAs are counted separately per DSA.



HR 1.9 Adult wait-listed patients who received a deceased donor heart transplant within one year

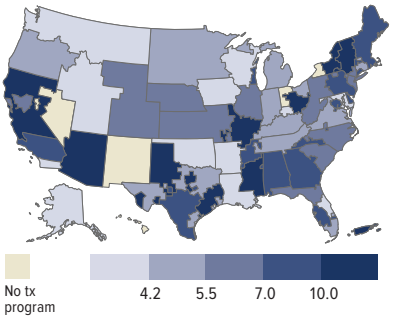
Patients with concurrent listings at more than one center are counted once, from the time of earliest listing to the time of latest removal. Patients listed, transplanted, and re-listed are counted more than once.



HR 1.10 Pre-transplant mortality rates among adult patients wait-listed for a heart transplant

Patients waiting for a transplant. Mortality rates are computed as the number of deaths per 100 patient-years of waiting time in the given year. For rates shown by different characteristics, waiting time is calculated as the total waiting time in the year for patients in that group. Only deaths that occur prior to removal from the waiting list are counted. Age is calculated on the latest of listing date or January 1 of the given year. Other patient characteristics come from the OPTN Transplant Candidate Registration form. Medical urgency status is the earliest known status in the given year.

wait list



HR 1.11 Mortality within 90 days of listing for heart transplant, by DSA, 2009–2010

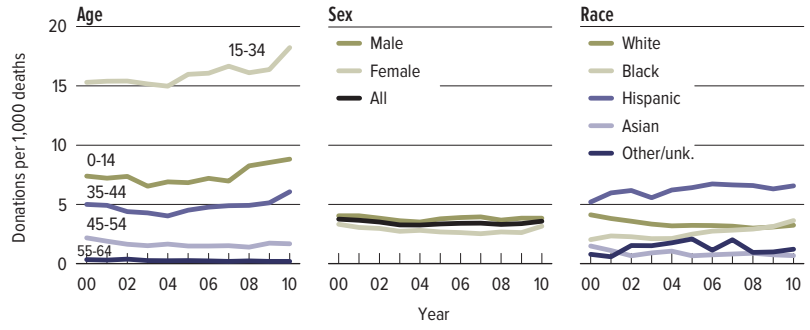
Patients with concurrent listings in a single DSA are counted once in that DSA, and those listed in multiple DSAs are counted separately per DSA. Deaths occuring within 90 days, but after transplant or removal from the waiting list, are included.

		2001		2011	
	Level	N	%	N	%
Age	18-34	270	7.4	305	10.8
	35-49	859	23.7	632	22.4
	50-64	2,081	57.3	1,401	49.7
	65+	421	11.6	481	17.1
Sex	Female	759	20.9	705	25.0
	Male	2,872	79.1	2,114	75.0
Race	White	2,863	78.9	1,952	69.2
	Black	489	13.5	602	21.4
	Hispanic	206	5.7	178	6.3
	Asian	60	1.7	61	2.2
	Other/unknown	13	0.4	26	0.9
Primary cause of disease	Cor. artery disease	1,680	46.3	1,079	38.3
	Cardiomyopathy	1,634	45.0	1,414	50.2
	Congenital disease	87	2.4	126	4.5
	Valvular disease	85	2.3	53	1.9
	Other/unknown	145	4.0	147	5.2
Transplant history	Listed/first transplant	3,532	97.3	2,706	96.0
	Listed/subseq. transplant	99	2.7	113	4.0
Blood type	A	1,164	32.1	906	32.1
	B	348	9.6	301	10.7
	AB	67	1.9	60	2.1
	O	2,052	56.5	1,552	55.1
Time on wait list	<1 year	1,282	35.3	1,387	49.2
	1-<2	722	19.9	626	22.2
	2-<3	457	12.6	323	11.5
	3-<4	356	9.8	166	5.9
	4-<5	237	6.5	71	2.5
	5+	577	15.9	246	8.7
Medical urgency status	1A	83	2.3	203	7.2
	1B	315	8.8	901	32.0
	2	1,759	49.4	936	33.2
	Inactive	1,405	39.4	779	27.6
Total		3,631	100.0	2,819	100.0

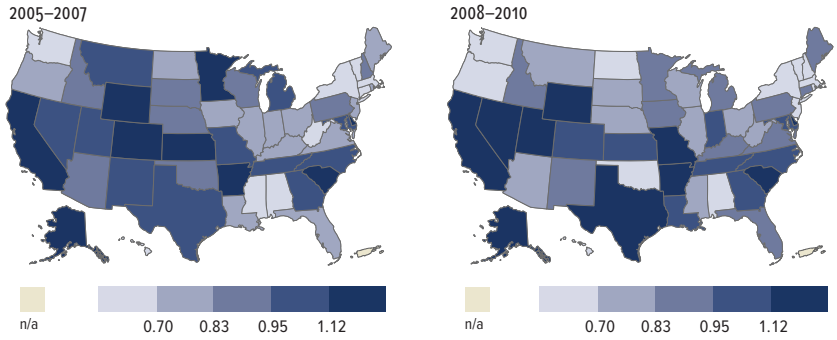
HR 1.12 Characteristics of adult patients on the heart transplant waiting list on December 31, 2001 & December 31, 2011

Patients waiting for a transplant on December 31, 2001 and December 31, 2011, regardless of first listing date; active/inactive status is on this date, and multiple listings are not counted.

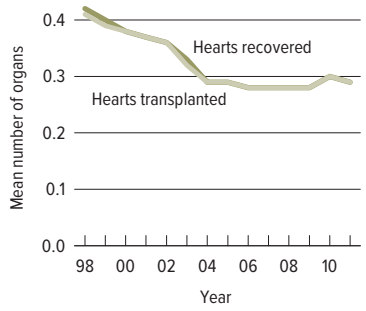
deceased donation



HR 2.1 Deceased donor heart donation rates
Numerator: Deceased donors age less than 65 whose organ(s) were recovered for transplant. Denominator: US deaths per year, age less than 65. (Death data available at http://www.cdc.gov/nchs/products/nvsr.htm.)

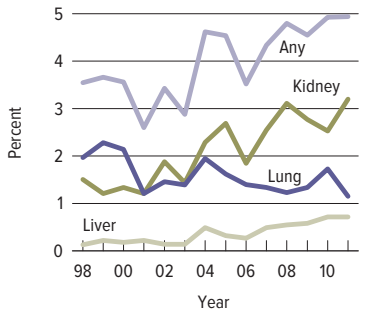


HR 2.2 Deceased donor heart donation rates (per 1,000 deaths), by state
Numerator: Deceased donors residing in the 50 states whose heart was recovered for transplant in the given year range. Denominator: US deaths by state during the given year range (death data available at http://www.cdc.gov/nchs/products/nvsr.htm). Rates are calculated within ranges of years for more stable estimates.



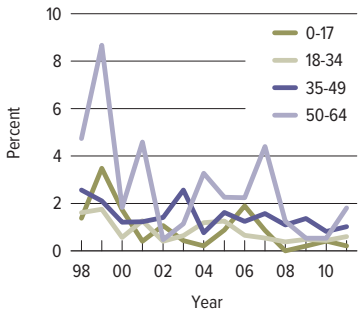
HR 2.3 Hearts recovered per donor & hearts transplanted per donor
Denominator: all deceased donors with at least one organ of any type recovered for transplant. Numerator for recovery rate: number of hearts recovered for transplant in the given year; hearts recovered for other purposes are not included. Numerator for transplant rate: all deceased donor hearts transplanted in given year.

deceased donation



HR 2.4 Deceased donor hearts transplanted with another organ

All patients receiving a deceased donor heart transplant. A transplant is considered multi-organ if any organ of a different type is transplanted at the same time. A multi-organ transplant may include more than two different organs in total; if so, each non-heart organ will be considered separately.



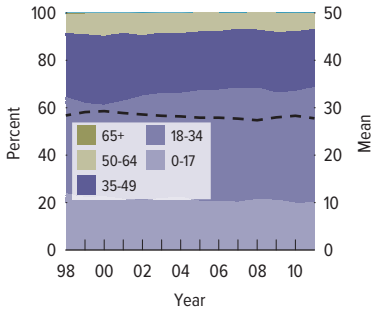
HR 2.5 Discard rates for hearts recovered for transplant, by age

Percent of hearts discarded out of all hearts recovered for transplant.

Reasons for discard	Percent	N
Other, specify	47.06	8
Anatomical abnormalities	17.65	3
Diseased organ	5.88	1
Donor medical history	5.88	1
Missing	5.88	1
Organ trauma	5.88	1
Poor organ function	5.88	1
Too old on ice	5.88	1

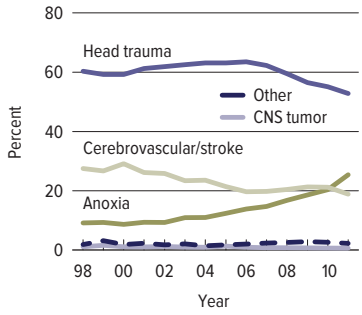
HR 2.6 Reasons for discards, 2011

Reasons for discard among hearts recovered for transplant but not transplanted in 2011.



HR 2.7 Heart donor age

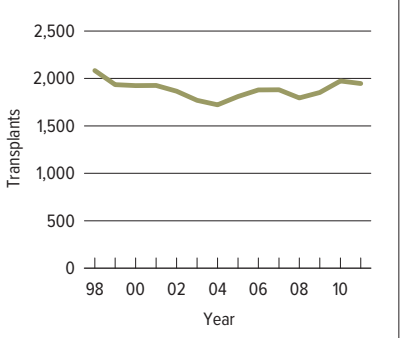
Transplanted hearts from US donors; age calculated at date of donation.



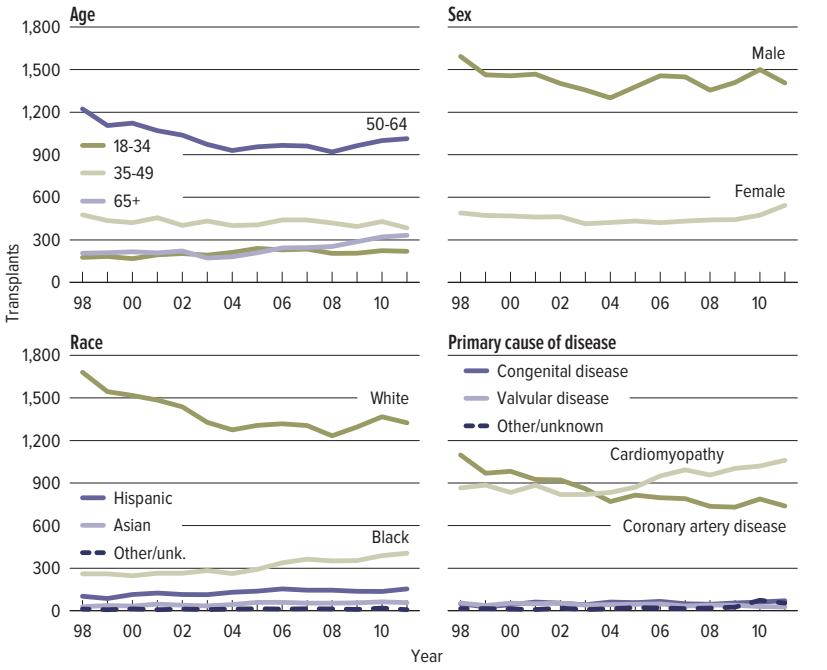
HR 2.8 Cause of death among deceased heart donors

Deceased donors whose heart was transplanted. CNS = central nervous system.

transplant

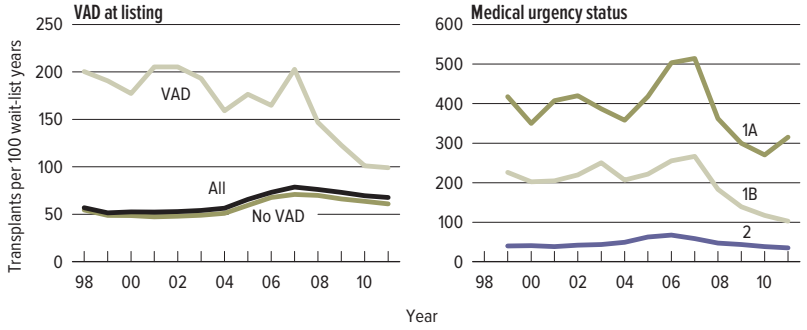


HR 3.1 Total adult heart transplants
Patients receiving a transplant. Retransplants are counted.



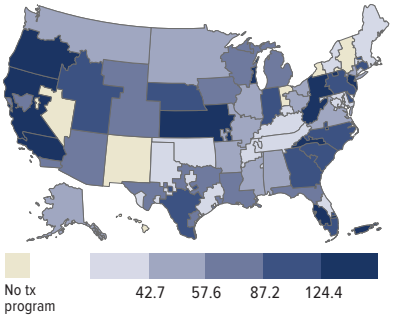
HR 3.2 Adult heart transplants
Patients receiving a transplant. Retransplants are counted.

transplant



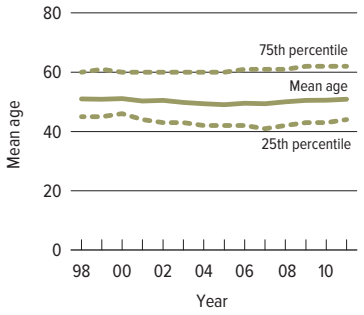
HR 3.3 Heart transplant rates in adult waiting list candidates

Patients waiting for a transplant. Transplant rates are computed as the number of transplants per 100 patient-years of waiting time in the given year. For rates by VAD and status, waiting time is calculated as the total waiting time in the given year for patients in each VAD/status group. All waiting time per patient per listing is counted, and all listings that end in a transplant for the patient are considered transplant events. Medical urgency status is updated each year, using the earliest known status in the given year.



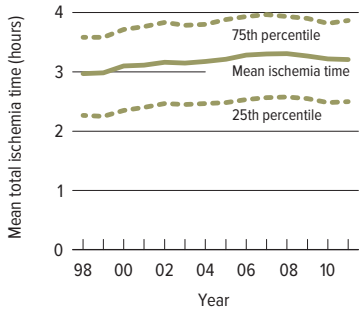
HR 3.4 Deceased donor heart transplant rates per 100 patient years on the waiting list among adult candidates, by DSA, 2010–2011

Transplant rates by DSA of the listing center, limited to those on the waiting list in 2010 and 2011; deceased donor transplants only. Maximum time per listing is two years.



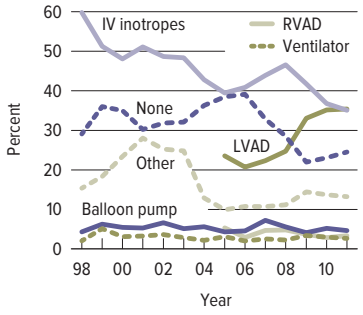
HR 3.5 Age at transplant for adult heart recipients

Patients receiving a transplant in the given year. Retransplants are included.



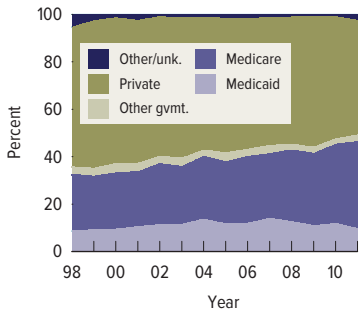
HR 3.6 Total ischemia time for adult heart transplants

Patients receiving a transplant in the given year. Retransplants are included. Total ischemia time includes cold, warm, and anastomotic time.



HR 3.7 Adult heart recipients on circulatory support prior to transplant

Patients may have more than one type of circulatory support. The "other" category includes types of circulatory support found in less than 2% of patients each year: total artificial heart, ECMO, inhaled NO, prostaglandins, and others.



HR 3.8 Insurance coverage among adult heart transplant recipients at time of transplant

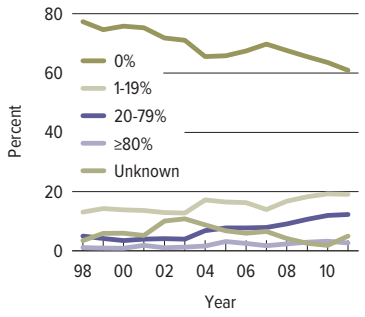
Patients receiving a transplant. Retransplants are counted.

	Level	2001 N	2001 %	2011 N	2011 %
Age	18-34	194	10.1	220	11.3
	35-49	457	23.7	384	19.7
	50-64	1,070	55.5	1,013	52.0
	65+	208	10.8	332	17.0
Sex	Female	461	23.9	544	27.9
	Male	1,468	76.1	1,405	72.1
Race	White	1,485	77.0	1,324	67.9
	Black	264	13.7	406	20.8
	Hispanic	125	6.5	154	7.9
	Asian	47	2.4	57	2.9
	Other/unk.	8	0.4	8	0.4
Primary cause of disease	Coronary artery dis.	925	48.0	738	37.9
	Cardiomyopathy	884	45.8	1,060	54.4
	Congenital disease	61	3.2	71	3.6
	Valvular disease	50	2.6	27	1.4
	Other/unknown	9	0.5	53	2.7
Transplant history	First	1,876	97.3	1,869	95.9
	Subsequent	53	2.7	80	4.1
Blood type	A	842	43.6	792	40.6
	B	261	13.5	276	14.2
	AB	118	6.1	105	5.4
	O	708	36.7	776	39.8
Primary payor	Private	1,160	60.1	941	48.3
	Medicaid	204	10.6	191	9.8
	Medicare	447	23.2	714	36.6
	Other government	70	3.6	55	2.8
	Other/unknown	48	2.5	48	2.5
Time on wait list	<30 days	485	25.1	531	27.2
	31-60 days	241	12.5	238	12.2
	61-90 days	195	10.1	199	10.2
	3-<6 months	325	16.8	304	15.6
	6-<12 months	299	15.5	323	16.6
	1-<2 years	228	11.8	232	11.9
	2-<3 years	82	4.3	73	3.7
	3+ years	74	3.8	49	2.5
Medical urgency status	1A	676	35.0	1,097	56.3
	1B	766	39.7	728	37.4
	2	486	25.2	124	6.4
	Other	1	0.1	0	0.0
Reported history of cigarette smoking at listing	No	.	.	1,044	53.6
	Yes	.	.	898	46.1
	Unknown	.	.	7	0.4
VAD status	No VAD	.	.	1,116	57.3
	VAD	513	27	819	42.0
	Unknown	.	.	14	0.7
Total		1,929	100.0	1,949	100.0

HR 3.9 Characteristics of adult heart transplant recipients, 2001 & 2011

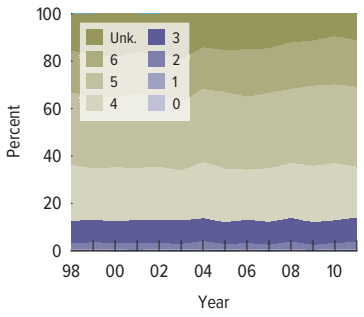
Patients receiving a transplant. Retransplants are counted. Ventricular assist device information comes from the OPTN Transplant Recipient Registration form and includes LVAD, RVAD, TAH, and LVAD + RVAD. Smoking history and VAD status were not collected on the TRR form in 2001.

donor-recipient matching



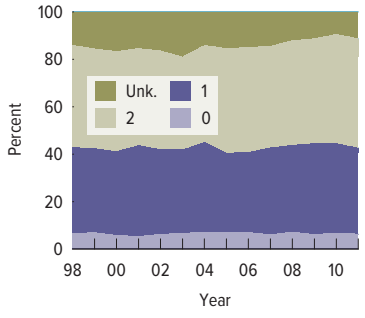
HR 4.1 PRA at time of heart transplant in adult recipients

PRA is the maximum of the most recent values recorded at the time of transplant. If "most recent PRA" is not provided, peak PRA is used.



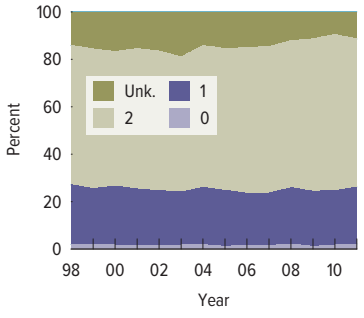
HR 4.2 Total HLA mismatches among adult heart transplant recipients

Donor and recipient antigen matching is based on the OPTN's antigen values and split equivalences policy as of 2011.



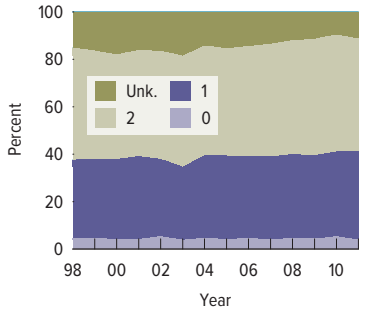
HR 4.3 HLA-A mismatches among adult heart transplant recipients

Donor and recipient antigen matching is based on the OPTN's antigen values and split equivalences policy as of 2011.



HR 4.4 HLA-B mismatches among adult heart transplant recipients

Donor and recipient antigen matching is based on the OPTN's antigen values and split equivalences policy as of 2011.



HR 4.5 HLA-DR mismatches among adult heart transplant recipients

Donor and recipient antigen matching is based on the OPTN's antigen values and split equivalences policy as of 2011.

donor-recipient matching

HR 4.6 Adult heart donor-recipient cytomegalovirus (CMV) serology matching, 2007–2011

Adult transplant cohort from 2007–2011. Donor serology is reported on the OPTN Donor Registration forms; recipient serology is reported on the OPTN Recipient Registration forms. Any evidence for a positive serology is taken to indicate that the person is positive for the given serology; if all fields are unknown, not done, or pending the person is considered to be "unknown" for that serology; otherwise, serology is assumed negative.

HR 4.7 Adult heart donor-recipient Epstein-Barr virus (EBV) serology matching, 2007–2011

Adult transplant cohort from 2007–2011. Donor serology is reported on the OPTN Donor Registration forms; recipient serology is reported on the OPTN Recipient Registration forms. Any evidence for a positive serology is taken to indicate that the person is positive for the given serology; if all fields are unknown, not done, or pending the person is considered to be "unknown" for that serology; otherwise, serology is assumed negative.

HR 4.8 Adult heart donor-recipient hepatitis B core antibody (HBcAb) serology matching, 2007–2011

Adult transplant cohort from 2007–2011. Donor serology is reported on the OPTN Donor Registration forms; recipient serology is reported on the OPTN Recipient Registration forms. Any evidence for a positive serology is taken to indicate that the person is positive for the given serology; if all fields are unknown, not done, or pending the person is considered to be "unknown" for that serology; otherwise, serology is assumed negative.

HR 4.9 Adult heart donor-recipient hepatitis B surface antigen (HBsAg) serology matching, 2007–2011

Adult transplant cohort from 2007–2011. Donor serology is reported on the OPTN Donor Registration forms; recipient serology is reported on the OPTN Recipient Registration forms. Any evidence for a positive serology is taken to indicate that the person is positive for the given serology; if all fields are unknown, not done, or pending the person is considered to be "unknown" for that serology; otherwise, serology is assumed negative.

HR 4.10 Adult heart donor-recipient hepatitis C serology matching, 2007–2011

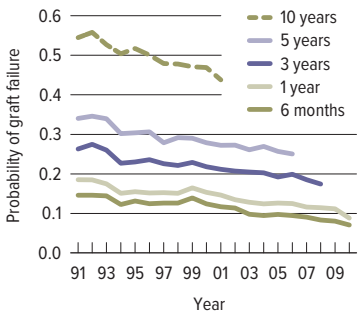
Adult transplant cohort from 2007–2011. Donor serology is reported on the OPTN Donor Registration forms; recipient serology is reported on the OPTN Recipient Registration forms. Any evidence for a positive serology is taken to indicate that the person is positive for the given serology; if all fields are unknown, not done, or pending the person is considered to be "unknown" for that serology; otherwise, serology is assumed negative.

	DONOR			
RECIPIENT	Negative	Positive	Unknown	Total
Negative	92.0	0.0	0.1	92.1
Positive	0.2	0.0	0.0	0.2
Unknown	7.7	0.0	0.0	7.7
Total	99.9	0.0	0.1	100

HR 4.11 Adult heart donor-recipient human immunodeficiency virus (HIV) serology matching, 2007–2011

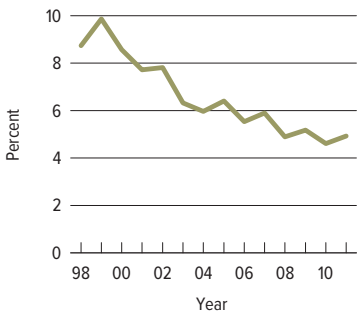
Adult transplant cohort from 2007–2011. Donor serology is reported on the OPTN Donor Registration forms; recipient serology is reported on the OPTN Recipient Registration forms. Any evidence for a positive serology is taken to indicate that the person is positive for the given serology; if all fields are unknown, not done, or pending the person is considered to be "unknown" for that serology; otherwise, serology is assumed negative.

outcomes



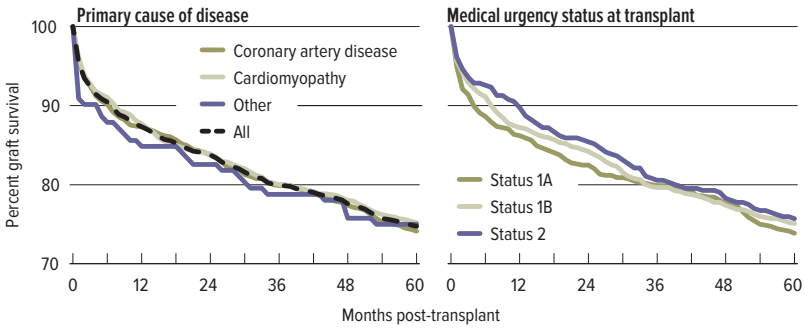
HR 5.1 Graft failure among adult heart transplant recipients

Cox proportional hazards models reporting probability, adjusting for age, sex, and race.



HR 5.2 Graft failure within the first 6 weeks after transplant among adult heart transplant recipients

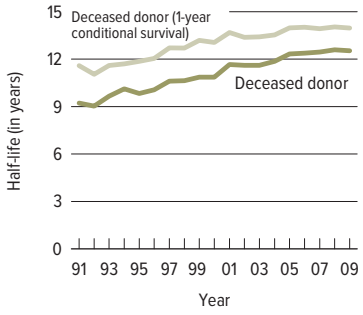
All-cause graft failure is identified from multiple data sources, including the OPTN Transplant Recipient Registration, OPTN Transplant Recipient Follow-up, as well as death dates from the Social Security Administration.



HR 5.3 Graft survival among adult heart transplant recipients transplanted in 2006

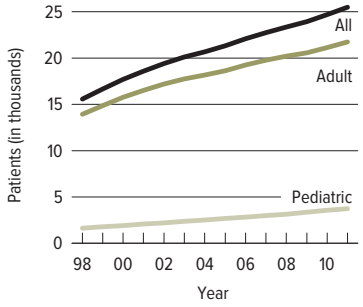
Graft survival estimated using unadjusted Kaplan-Meier methods.

outcomes



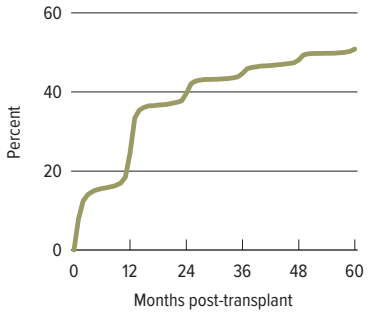
HR 5.4 Half-lives for adult heart transplant recipients

Estimated graft half-lives and conditional half-lives. Half-lives are interpreted as the estimated median survival of grafts from the time of transplant. Conditional half-lives are interpreted as the estimated median survival of grafts which survive the first year.



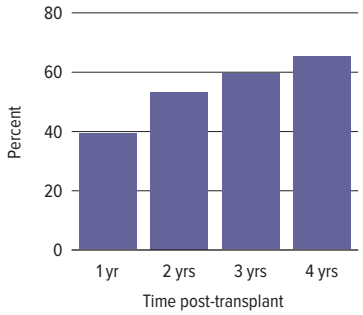
HR 5.5 Recipients alive & with a functioning heart transplant on June 30 of the year

Transplants before June 30 of the year that are still functioning. Patients are assumed alive with function unless a death or graft failure is recorded. A recipient can experience a graft failure and drop from the cohort, then be retransplanted and re-enter the cohort.



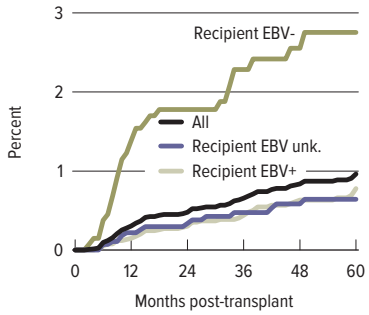
HR 5.6 Incidence of first acute rejection among adult patients receiving a heart transplant in 2005–2009

Acute rejection defined as a record of acute or hyperacute rejection, or a record of an anti-rejection drug being administered on either the Transplant Recipient Registration form or the Transplant Recipient Follow-up Form. Only the first rejection event is counted, and patients are followed for acute rejection only until graft failure, death, or loss to follow-up. Cumulative incidence, defined as the probability of graft failure at any time prior to the given time, is estimated using Kaplan-Meier methods.



HR 5.7 Reported cumulative incidence of rehospitalizations among adult patients receiving a heart transplant in 2006–2011

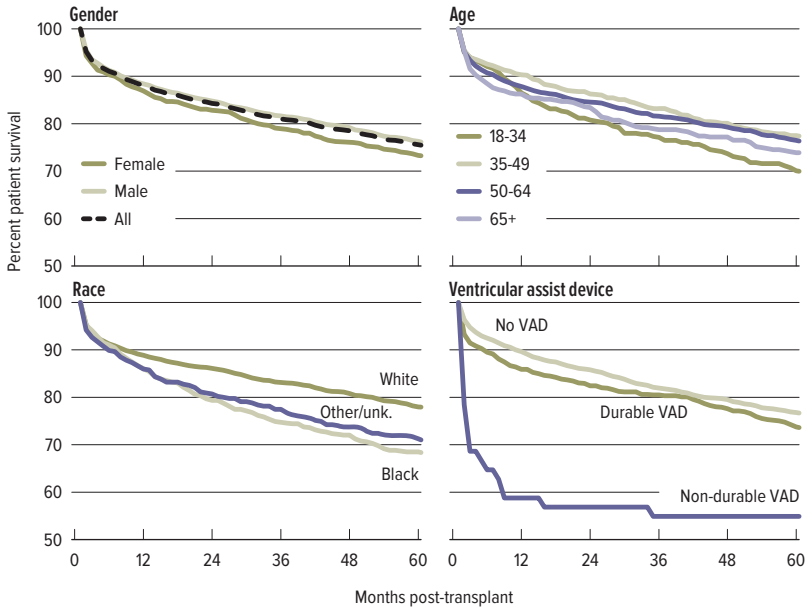
Cumulative incidence of rehosptalization post-transplant; hospitalization identified from the OPTN Transplant Recipient Follow-up form. Patients required to be alive with graft function at each time period, so denominators reduce over time.



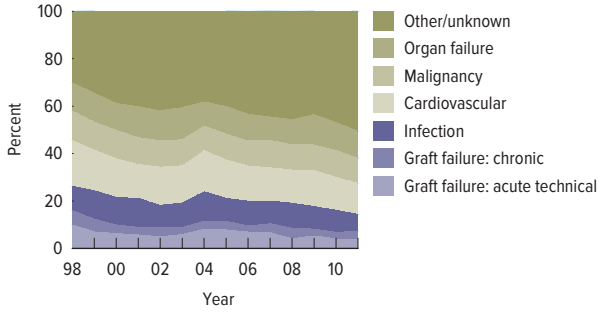
HR 5.8 Incidence of PTLD among adult patients receiving a heart transplant in 2005–2009, by recipient Epstein-Barr virus (EBV) status at transplant

The cumulative incidence, defined as the probability of post-transplant lymphoproliferative disorder (PTLD) being diagnosed between the time of transplant and the given time, is estimated using Kaplan-Meier methods. PTLD is identified as either a reported complication or cause of death on the Transplant Recipient Follow-up forms or on the Post-transplant Malignancy form as polymorphic PTLD, monomorphic PTLD, or Hodgkin's Disease. Only the earliest date of PTLD diagnosis is considered, and patients are followed for PTLD until graft failure, death, or loss to follow-up. Patients are censored at graft failure because malignancies are not reliably reported after graft failure.

outcomes

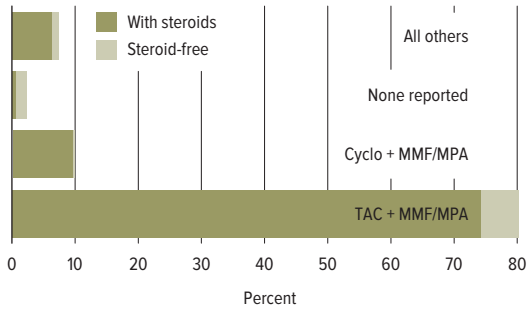


HR 5.9 Patient survival among adult heart transplant recipients, 2005–2006
Percent patient survival using unadjusted Kaplan-Meier methods. For patients with more than one transplant during the period, only their first transplant is considered. VAD status for each patient comes from time of transplant. Patients with both durable and non-durable VADs are included in the durable group.



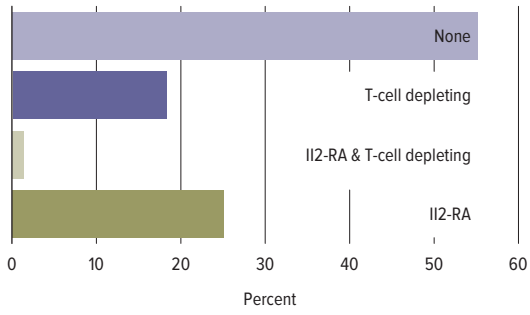
HR 5.10 Cause of death among adult heart transplant recipients
Patients who died in a given year are included regardless of when transplant was received. Primary cause of death is as reported by the OPTN from the Transplant Follow-up forms. Other causes of death include hemorrhage, trauma, non-compliance, unspecified other, unknown, etc.

immunosuppression



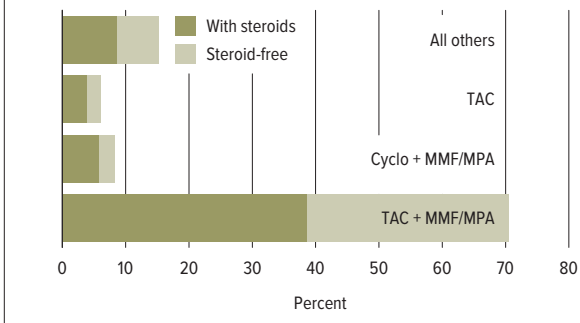
HR 6.1 Initial immunosuppression regimen in adult heart transplant recipients, 2011

Patients transplanted in 2011 and discharged with a functioning graft. Top three baseline immunosuppression regimens are given, plus the "all others" group. Regimens are defined by use of calcineurin inhibitors (TAC=Tacrolimus, Cyclo=Cyclosporine), anti-metabolites (AZA=Azathioprine, MMF/MPA=Mycophenolate), and mTOR inhibitors (mTOR). Data within each regimen are reported separately by steroid use.



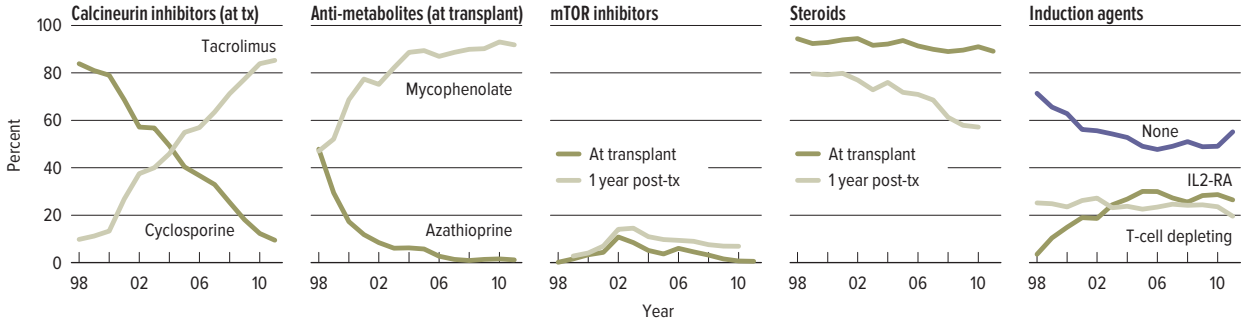
HR 6.2 Induction agents used at time of heart transplant, adult recipients, 2011

Patients transplanted in 2011 and discharged with a functioning graft.



HR 6.3 Immunosuppression at one year in adult heart transplant recipients, 2010

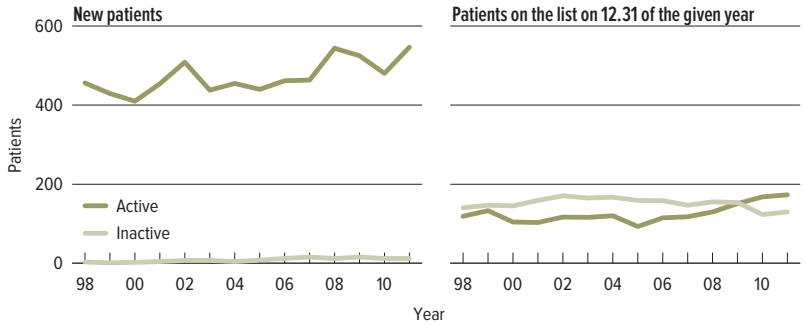
Patients transplanted in 2010 and remaining alive with graft function one year post-transplant. Top three one-year immunosuppression regimens are given, plus the "all others" group. Regimens are defined by use of calcineurin inhibitors (TAC=Tacrolimus, Cyclo=Cyclosporine), anti-metabolites (AZA=Azathioprine, MMF/MPA=Mycophenolate), and mTOR inhibitors (mTOR). Data within each regimen are reported separately by steroid use.



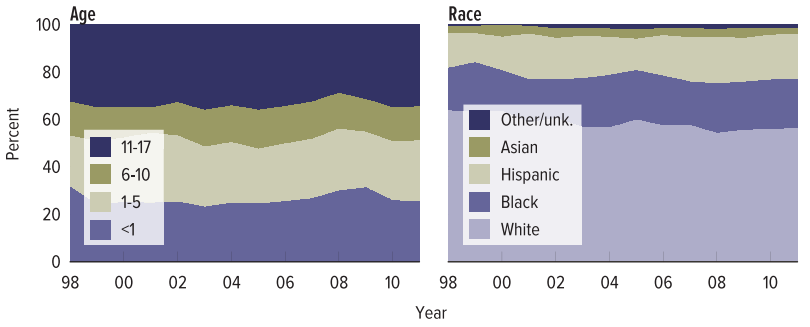
HR 6.4 Immunosuppression use in adult heart transplant recipients

One-year post-transplant data for mTOR inhibitors and steroids limited to patients alive with graft function one year post-transplant. One-year post-transplant data are not reported for 1998 transplant recipients, as follow-up data were very sparse.

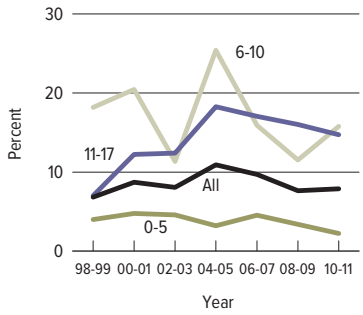
pediatric transplant



HR 7.1 Pediatric patients waiting for a heart transplant
Patients waiting for a transplant. A "new patient" is one who first joins the list during the given year, without having listed in a previous year. However, if a patient has previously been on the list, has been removed for a transplant, and has relisted since that transplant, the patient is considered a "new patient". Patients concurrently listed at multiple centers are counted only once. Those with concurrent listings and active at any program are considered active; those inactive at all programs at which they are listed are considered inactive.



HR 7.2 Distribution of pediatric patients waiting for a heart transplant
Patients waiting for a transplant any time in the given year. Age determined on the lastest of listing date or January 1 of the given year. Concurrently listed patients are counted once.



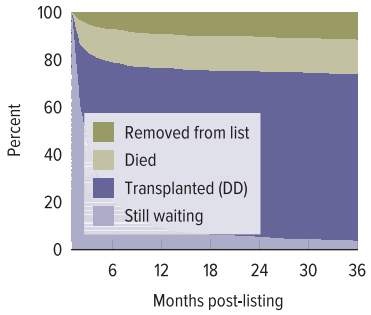
HR 7.3 Prior heart transplant in pediatric patients waiting for a heart transplant, by age
Prior transplant is obtained from the OPTN Transplant Candidate Registration form.

pediatric transplant

	2009	2010	2011
Patients at start of year	287	304	293
Patients added during year	537	487	544
Pts removed during year	518	497	536
Patients at end of year	306	294	301
Removal reason			
Received a transplant	365	364	384
Patient died	82	65	69
Patient refused transplant	1	1	0
Improved, tx not needed	47	43	47
Too sick to transplant	19	19	23
Other	4	5	13

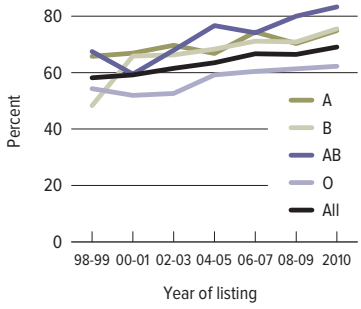
HR 7.4 Heart transplant waiting list activity among pediatric patients

Patients with concurrent listings at more than one center are counted once, from the time of earliest listing to the time of latest removal. Patients listed, transplanted, and re-listed are counted more than once. Patients are not considered "on the list" on the day they are removed. Thus, patient counts on January 1 may be different from patient counts on December 31 of the prior year.



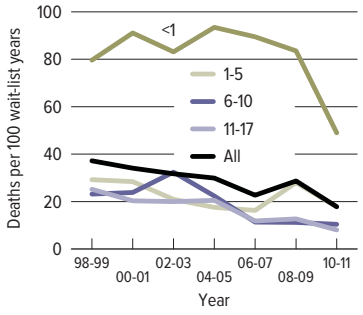
HR 7.5 Outcomes for pediatric patients waiting for a heart transplant among new listings in 2008

Patients waiting for a transplant and first listed in 2008. Patients with concurrent listings at more than one center are counted once, from the time of the earliest listing to the time of latest removal.



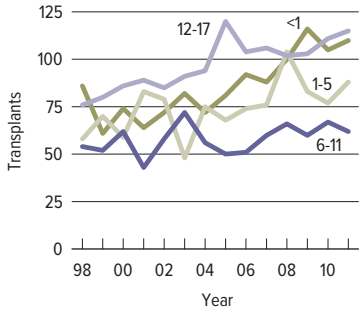
HR 7.6 Pediatric wait-listed patients who receive a deceased donor heart transplant within one year, by blood type

Patients with concurrent listings at more than one center are counted once, from the time of earliest listing to the time of latest removal. Patients listed, transplanted, and re-listed are counted more than once.



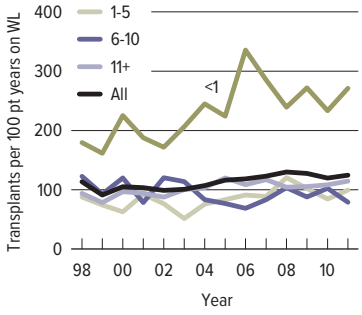
HR 7.7 Pre-transplant mortality rates among pediatric patients wait-listed for a heart transplant, by age

Patients waiting for a transplant. Mortality rates are computed as the number of deaths per 100 patient-years of waiting time in the given 2-year interval. Waiting time is calculated as the total waiting time per age group in the interval. Only deaths that occur prior to removal from the waiting list are counted. Age is calculated on the latest of listing date or January 1 of the given period.



HR 7.8 Pediatric heart transplants (including heart-lung), by age

Patients receiving a heart or heart-lung transplant.



HR 7.9 Heart transplant rates in pediatric waiting list candidates, by age

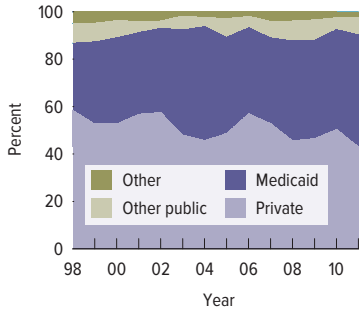
Patients waiting for transplant. Transplant rates are computed as the number of transplants per 100 patient-years of waiting time in the given year. Patients with concurrent listings at multiple centers are counted once.

pediatric transplant

		1999-2001		2009-2011	
	Level	N	%	N	%
Age	<1	197	24.7	331	30.3
	1-5	206	25.8	246	22.5
	6-10	111	13.9	147	13.5
	11-17	284	35.6	367	33.6
Sex	Female	349	43.7	511	46.8
	Male	449	56.3	580	53.2
Race	White	492	61.7	595	54.5
	Black	157	19.7	225	20.6
	Hispanic	111	13.9	195	17.9
	Asian	33	4.1	54	4.9
	Other/unk.	5	0.6	22	2.0
Primary cause of disease	Congenital defect	332	41.6	473	43.4
	Dilated myopathy: idiopathic	264	33.1	320	29.3
	Restrictive myopathy: idiopathic	42	5.3	47	4.3
	Dilated myopathy: myocarditis	15	1.9	49	4.5
	All others	145	18.2	202	18.5
Transplant history	First transplant	739	92.6	1018	93.3
	Subsequent	59	7.4	73	6.7
Blood type	A	310	38.8	403	36.9
	B	91	11.4	150	13.7
	AB	37	4.6	55	5.0
	O	360	45.1	483	44.3
Primary payer	Private	432	54.1	509	46.7
	Medicaid	280	35.1	476	43.6
	Other public	53	6.6	76	7.0
	Other	33	4.1	30	2.7
Time on wait list	<30 days	349	43.7	407	37.3
	31-60 days	144	18.0	228	20.9
	61-90 days	83	10.4	128	11.7
	3-<6 months	107	13.4	190	17.4
	6-<12 months	75	9.4	100	9.2
	1-<2 years	29	3.6	29	2.7
	2-<3 years	9	1.1	2	0.2
	3+ years	2	0.3	7	0.6
Status	1A	496	62.2	950	87.1
	1B	136	17.0	78	7.1
	2	155	19.4	63	5.8
	Unknown	11	1.4	0	0.0
Patient on VAD	No	30	3.8	889	81.5
	Yes	61	7.6	200	18.3
	Unknown	707	88.6	2	0.2
All patients		798	100.0	1091	100.0

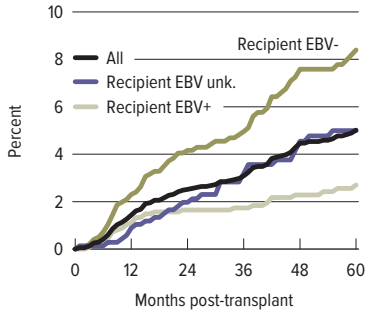
HR 7.10 Characteristics of pediatric heart transplant patients, 1999–2001 & 2009–2011

Patients receiving a transplant. Retransplants are counted.



HR 7.11 Insurance coverage among pediatric heart transplant recipients at time of transplant

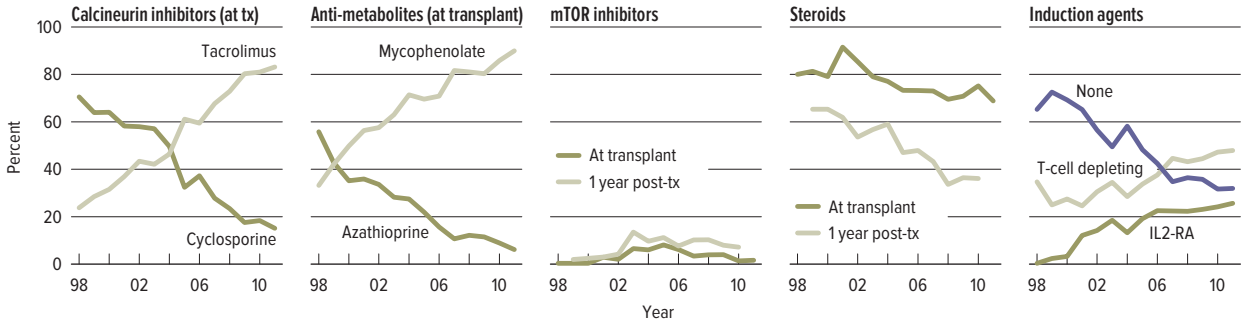
Patients receiving a transplant in given year; reported primary insurance payor at time of transplant. Retransplants are counted.



HR 7.12 Incidence of PTLD among pediatric patients receiving a heart transplant, 1999–2009, by recipient Epstein-Barr virus (EBV) status at transplant

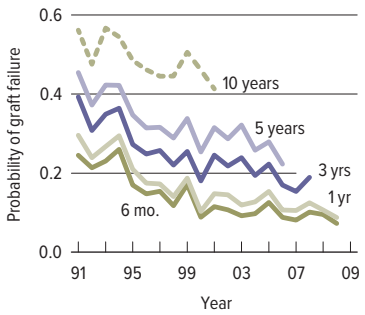
The cumulative incidence, defined as the probability of post-transplant lymphoproliferative disorder (PTLD) being diagnosed between the time of transplant and the given time, is estimated using Kaplan-Meier methods. PTLD is identified as either a reported complication or cause of death on the Transplant Recipient Follow-up forms or on the Post-transplant Malignancy form as polymorphic PTLD, monomorphic PTLD, or Hodgkin's Disease. Only the earliest date of PTLD diagnosis is considered, and patients are followed for PTLD until graft failure, death, or loss to follow-up. Patients are censored at graft failure because malignancies are not reliably reported after graft failure.

pediatric transplant



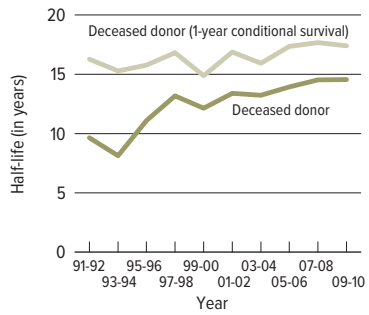
HR 7.13 Immunosuppression use among pediatric heart transplant recipients

One-year post-transplant data for mTOR inhibitors and steroids limited to patients alive with graft function one year post-transplant. One-year post-transplant data are not reported for 1998 transplant recipients, as follow-up data were very sparse.



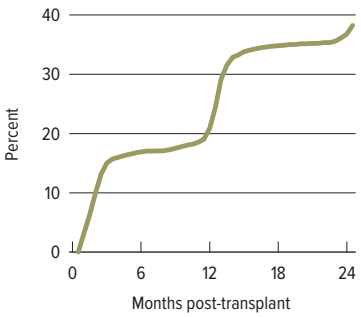
HR 7.14 Graft failure among pediatric heart transplant recipients

Cox proportional hazards model reporting probability, adjusting for age, sex, and race.



HR 7.15 Half-lives for pediatric heart transplant recipients

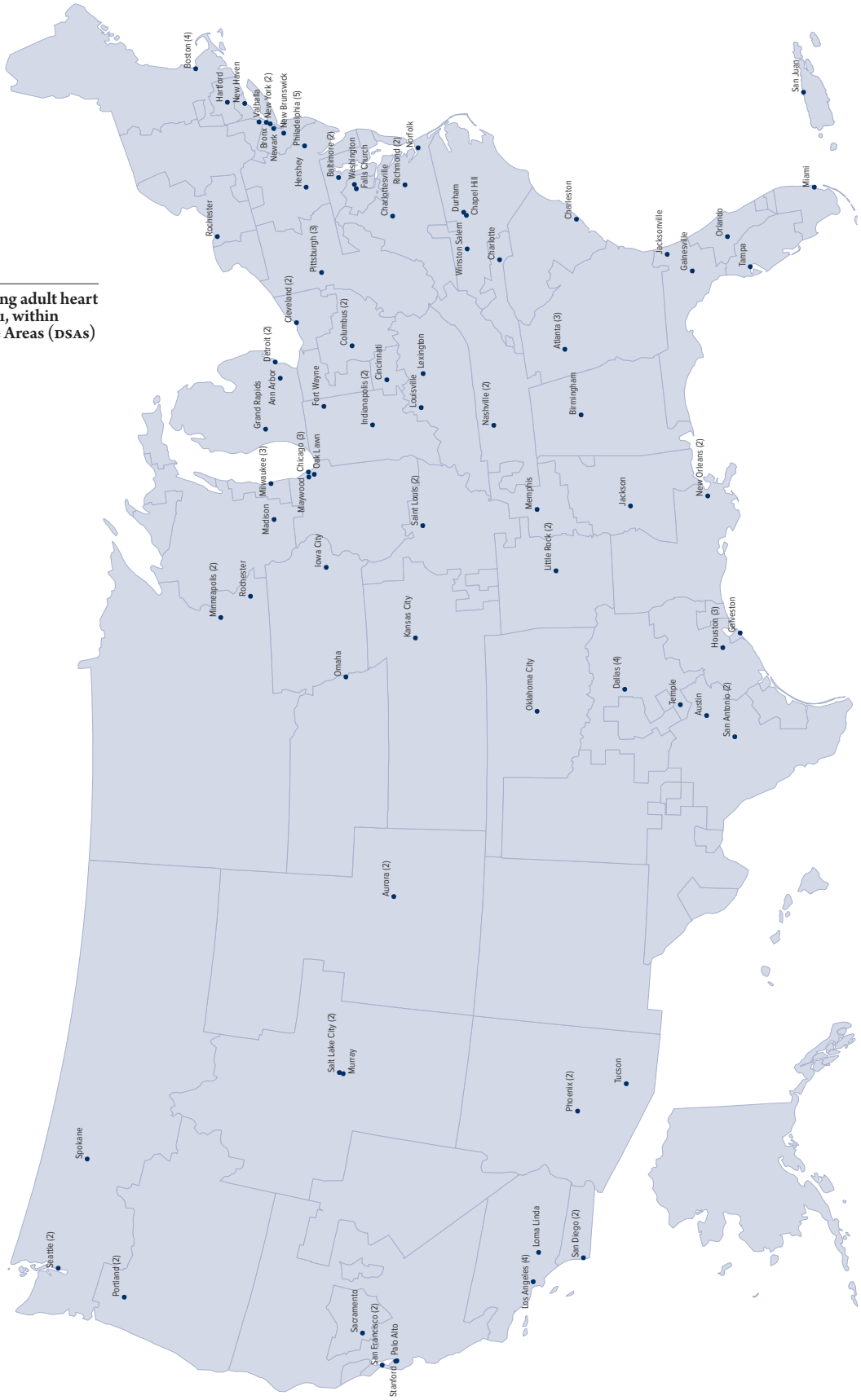
Estimated graft half-lives and conditional half-lives. Half-lives are interpreted as the estimated median survival of grafts from the time of transplant. Conditional half-lives are interpreted as the estimated median survival of grafts which survive the first year.



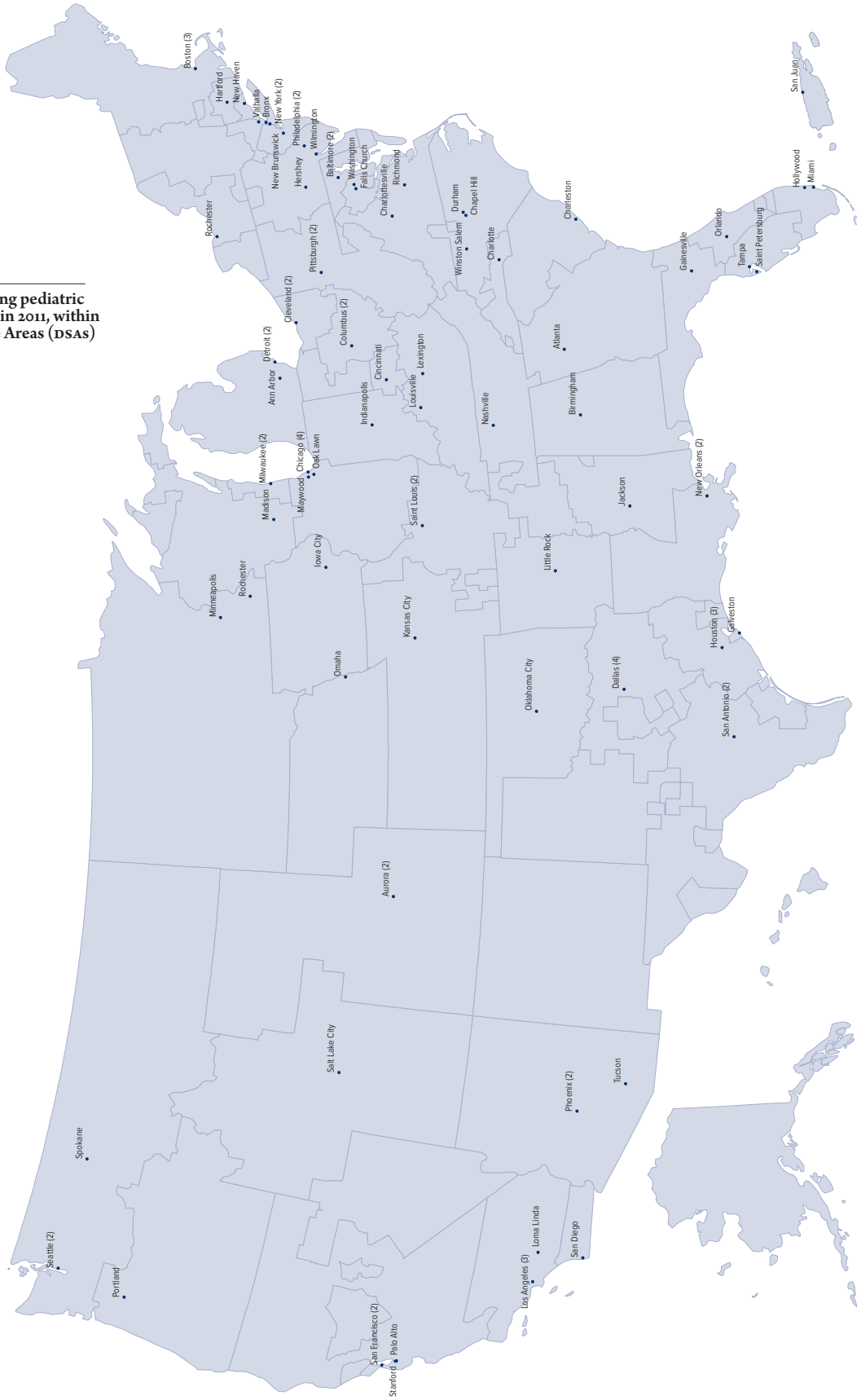
HR 7.16 Incidence of first acute rejection among pediatric patients receiving a heart transplant in 2005–2010

Acute rejection defined as a record of acute or hyperacute rejection, or a record of an anti-rejection drug being administered on either the Transplant Recipient Registration form or the Transplant Recipient Follow-up Form. Only the first rejection event is counted, and patients are followed for acute rejection only until graft failure, death, or loss to follow-up. Cumulative incidence, defined as the probability of graft failure at any time prior to the given time, is estimated using Kaplan-Meier methods.

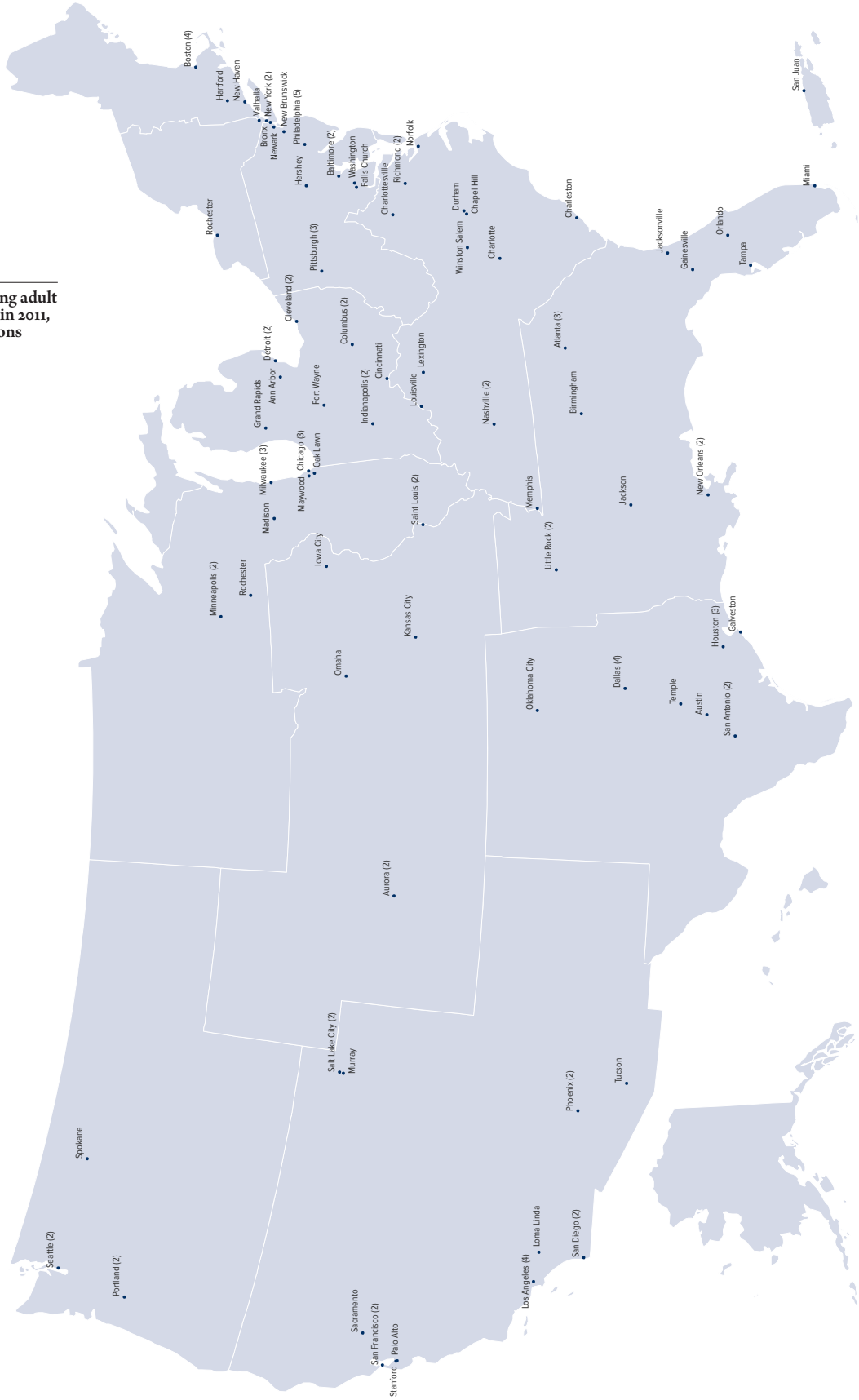
HR 8.1 Centers performing adult heart transplants in 2011, within Donation Service Areas (DSAs)



HR 8.2 **Centers performing pediatric heart transplants in 2011, within Donation Service Areas (DSAs)**



HR 8.3 Centers performing adult heart transplants in 2011, within OPTN regions



Morbidity and Mortality in Heart Transplant Candidates Supported With Mechanical Circulatory Support: Is Reappraisal of the Current United Network for Organ Sharing Thoracic Organ Allocation Policy Justified?

Omar Wever-Pinzon, Stavros G. Drakos, Abdallah G. Kfoury, Jose N. Nativi, Edward M. Gilbert, Melanie Everitt, Rami Alharethi, Kim Brunisholz, Feras M. Bader, Dean Y. Li, Craig H. Selzman and Josef Stehlik

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Morbidity and Mortality in Heart Transplant Candidates Supported With Mechanical Circulatory Support

Is Reappraisal of the Current United Network for Organ Sharing Thoracic Organ Allocation Policy Justified?

Omar Wever-Pinzon, MD; Stavros G. Drakos, MD, PhD; Abdallah G. Kfoury, MD; Jose N. Nativi, MD; Edward M. Gilbert, MD; Melanie Everitt, MD; Rami Alharethi, MD; Kim Brunisholz, MST; Feras M. Bader, MD, MS; Dean Y. Li, MD, PhD; Craig H. Selzman, MD; Josef Stehlik, MD, MPH

Background:—Survival of patients on left ventricular assist devices (LVADs) has improved. We examined the differences in risk of adverse outcomes between LVAD-supported and medically managed candidates on the heart transplant waiting list.

Methods and Results:—We analyzed mortality and morbidity in 33 073 heart transplant candidates registered on the United Network for Organ Sharing (UNOS) waiting list between 1999 and 2011. Five groups were selected: patients without LVADs in urgency status 1A, 1B, and 2; patients with pulsatile-flow LVADs; and patients with continuous-flow LVADs. Outcomes in patients requiring biventricular assist devices, total artificial heart, and temporary VADs were also analyzed. Two eras were defined on the basis of the approval date of the first continuous-flow LVAD for bridge to transplantation in the United States (2008). Mortality was lower in the current compared with the first era (2.1%/mo versus 2.9%/mo; $P<0.0001$). In the first era, mortality of pulsatile-flow LVAD patients was higher than in status 2 (hazard ratio [HR], 2.15; $P<0.0001$) and similar to that in status 1B patients (HR, 1.04; $P=0.61$). In the current era, patients with continuous-flow LVADs had mortality similar to that of status 2 (HR, 0.80; $P=0.12$) and lower mortality compared with status 1A and 1B patients (HR, 0.24 and 0.47; $P<0.0001$ for both comparisons). However, status upgrade for LVAD-related complications occurred frequently (28%) and increased the mortality risk (HR, 1.75; $P=0.001$). Mortality was highest in patients with biventricular assist devices (HR, 5.00; $P<0.0001$) and temporary VADs (HR, 7.72; $P<0.0001$).

Conclusions:—Mortality and morbidity on the heart transplant waiting list have decreased. Candidates supported with contemporary continuous-flow LVADs have favorable waiting list outcomes; however, they worsen significantly once a serious LVAD-related complication occurs. Transplant candidates requiring temporary and biventricular support have the highest risk of adverse outcomes. These results may help to guide optimal allocation of donor hearts. **(*Circulation*. 2013;127:452-462.)**

Key Words: heart-assist devices ■ mortality ■ outcome assessment ■ transplantation

Heart transplantation provides remarkable improvement of quality of life and survival in selected patients with advanced heart failure. However, the number of heart transplant procedures is limited by donor availability.[1] The Organ Procurement and Transplantation Network (OPTN), through a contract with the United Network for Organ Sharing (UNOS), has proposed, implemented, and updated policies that direct allocation of donor organs in the United States. UNOS has strived to create allocation policies based on algorithms that prioritize patients with the highest mortality risk in the period preceding transplantation.[2] Despite these policies and the multiple interventions aimed at increasing donor heart availability, mortality on the transplant waiting list remains considerable.[3–7]

Clinical Perspective on p 462

Left ventricular assist devices (LVADs) are increasingly used to improve hemodynamic status in patients with advanced

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heart failure awaiting heart transplantation.[8–11] The efficacy and risk profile of these devices have been further confirmed by postmarket approval data.[12–14] However, first-generation pulsatile-flow (PF) LVADs were associated with significant device-related complications, including device failure and suboptimal long-term outcomes.[8,9] Mortality risk was high during the first 3 weeks after PF-LVAD implantation (15%–30%),[2] and based on these data, a 1999 UNOS thoracic organ allocation policy revision allowed listing of LVAD patients in the high-urgency 1A status if the device had been in place for <30 days, with indefinite intermediate-urgency 1B status listing thereafter. Additional modification in 2002 allowed physicians to use 30 days of 1A status time at their discretion at any point after LVAD implantation.[2,15]

Advances in mechanical circulatory support (MCS) technology, specifically the introduction of the new-generation, smaller, and more durable continuous-flow (CF) LVADs, have further reduced the morbidity and mortality of advanced heart failure patients in need of LVAD bridging to transplantation.[11–13,16–18] These encouraging results, along with continued donor organ shortage and recent data suggesting that LVAD bridging is no longer associated with increased mortality after transplantation,[19] resulted in a substantial increase in the use of LVADs for bridging to transplantation.[1,7,14] In view of these results, it has been questioned whether the allocation advantage given to patients bridged with LVADs is still justified.[15] In this study, we sought to quantify the differences in risk of mortality and mortality or delisting as a result of worsening clinical status between LVAD-supported and medically managed candidates listed in the various urgency statuses of the heart transplant waiting list.

Methods

Data Source and Study Population

UNOS/OPTN provided deidentified patient-level data from the Waiting List Registry (data source No. 412012-2). These data included all heart transplant candidates registered on the waiting list between September 1985 and December 2011. There is 1 record per waiting list registration, and each record includes the most recent follow-up information, including patient survival, inactivation, and delisting reported to OPTN. Data entry by all US transplant centers has been mandatory since the passage of the National Transplantation Act of 1984.

We included adult candidates (age ≥18 years) registered for single-organ, primary heart transplantation between January 1999 and December 2011. The study cohort was divided on the basis of patient UNOS status at the time of last follow-up, transplantation, death, or delisting and the need for MCS with a durable LVAD (regardless of UNOS status) at the time of listing. The following 5 groups of patients were the focus of our analysis: medically managed candidates in (1) high-urgency UNOS status 1A, (2) intermediate-urgency UNOS status 1B, and (3) low-urgency UNOS status 2 and candidates requiring circulatory support with (4) PF-LVADs and (5) CF-LVADs. Durable LVADs are the most common type of assist device used for bridge to transplantation; therefore, among candidates requiring MCS, these patients were the main focus of our analyses. For completeness, patients who required support with biventricular assist devices (BIVADs), total artificial heart (TAH), and temporary extracorporeal VADs were also included in this analysis. For patients whose status on the waiting list changed, the cumulative time spent throughout the listed period in the status that was reported last was used for the analysis. Patients requiring implantation of an LVAD while on the waiting list were also included in the study but were assigned to their respective medically managed UNOS status groups. Patients without an LVAD who were listed for transplantation in an inactive status and remained inactive; patients with an unknown type of assist device and those registered after December 2, 2011 (to allow a minimum follow-up of 3 months) were excluded.

Two eras were defined within the study period. The first era included candidates registered between January 20, 1999, and April 20, 2008, and the current era included candidates registered between April 21, 2008, and December 2, 2011. The era boundaries were based on the following 2 events: The first era started on the day when a 3-tier allocation system (status 1 patients were subdivided into status 1A and 1B) went into effect, and the current era started on the day when the first CF-LVAD (HeartMate II) was approved by the Food and Drug Administration for clinical use in the bridge-to-transplant indication in the United States.

The primary outcome of our study was all-cause mortality on the waiting list. Some transplant candidates are removed from the waiting list when their clinical condition worsens and transplantation is no longer believed to be a good therapeutic option. Many of these patients die or are transitioned to hospice care soon after delisting. To ascertain that our results captured this clinical scenario, we designated as the secondary outcome of our study a composite end point of all-cause mortality or delisting as a result of worsening clinical status.

Statistical Analysis

Continuous variables were summarized as mean±SD and compared by means of ANOVA. Testing of normality and equal-variance assumptions was not performed before ANOVA because this test is known to be robust to both of these assumptions.[20,21] Categorical variables were summarized as frequencies and percentages and were compared by the Pearson χ^2 test or, when <5 outcomes were expected per cell, by the Fisher exact test. The *P* values for pairwise group comparisons were adjusted for multiplicity by use of the Holm multiple-comparison procedure. Cumulative survival rates were estimated with Kaplan-Meier survival analysis and compared between groups by means of the log-rank test.[22,23] The time to event was the amount of time spent in the listing status during which the patient was transplanted, delisted, or died. A death within 2 weeks of removal (resulting from any reason) from the waiting list, identified through Social Security Death Index data, was considered waiting list mortality and was included in the primary outcome. For the primary outcome of waiting list mortality, survival was censored at the time of delisting or transplant or at the last follow-up reported to UNOS for patients remaining on the waiting list. For the secondary outcome of death or delisting as a result of worsening clinical status, survival was censored at the time of transplantation or at the last follow-up reported to UNOS for patients remaining on the waiting list. Survival curves were constructed to illustrate multiple possible outcomes at any time after registration on the waiting list (competing outcomes) in the group of patients supported with durable LVADs: death, delisting as a result of worsening clinical status, delisting owing to clinical recovery, transplantation, and alive on waiting list.

The association of the different risk factors with hazard of the primary and secondary outcomes while on the waiting list was assessed separately by use of univariable Cox proportional hazards regression models.[24] The proportional hazards assumption of the Cox regression models was assessed graphically with log-log curves and was found to be adequately met. The models examined the effect of the following candidate characteristics present at registration on the heart transplant waiting list: age, sex, body mass index, ABO blood type, heart failure etiology, history of diabetes mellitus, tobacco use, serum creatinine, pulmonary artery pressures, pulmonary capillary wedge pressure, use of inotropes, dialysis, mechanical ventilation, TAH, BIVADs, temporary VADs, durable LVADs, and UNOS waiting list status. A multivariable Cox proportional hazards model was used to determine the independent effect of multiple risk factors on the hazard of the primary and secondary outcomes. Variables significant at the $P<0.10$ level in unadjusted analyses were considered for inclusion; only variables significant at the $P<0.05$ level on the basis of the likelihood ratio test were retained

in the final model. UNOS waiting list status groups were included in all multivariable analyses independently of their significance level in univariable analyses. The 7 comparisons to the status 2 reference group were adjusted for multiple comparisons by use of the Holm procedure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated for both univariable and multivariable analyses as measures of strength of association and precision, respectively. A 2-tailed value of $P<0.05$ was considered statistically significant. All analyses were performed with STATA software, version 12 (StataCorp LP, College Station, TX).

Results

There were 33 390 adult candidates registered for single-organ primary heart transplantation in the United States during the study period. We excluded transplant candidates who required MCS but the type of assist device was unknown (n=107) and registrations without an assist device that remained inactive on the list (n=210). In total, 33 073 patients met the inclusion criteria and comprised our study group. Of these, 23 217 candidates were registered in the first era and 9856 were registered in the current era.

Baseline Characteristics

Among the 23 217 heart transplant candidates registered in the first era, 5699 (24.5%) were status 1A, 7154 (30.8%) were status 1B, and 7585 (32.7%) were status 2. Circulatory support with durable LVADs was required in 2146 patients (9.2%), with most devices being PF-LVADs (84%). Other types of VADs were used less frequently and included TAH in 46 patients (0.2%), BIVADs in 295 patients (1.3%), and temporary VADs in 292 patients (1.3%). In the current era, the proportion of candidates registered as status 1A (28.3%) and 1B (31.8%) remained similar, whereas the percentage of status 2 patients decreased substantially (18.4%). The proportion of patients supported with durable LVADs doubled in the current era: 1763 patients or 17.9% were supported with mostly CF-LVADs (89%). The use of biventricular support with TAH (0.4%), BIVADs (2.4%), and temporary VADs (0.8%) remained infrequent. The distribution of VAD types and brands used in both eras is presented in the Table I of the online-only Data Supplement.

Baseline characteristics of the study groups, recorded at registration on the heart transplant waiting list, are summarized in Table 1. Although between-group comparisons for most baseline characteristics were statistically significant, the following were the most clinically relevant differences: Patients supported with LVADs were more likely to be male, had higher body mass index compared with status 1A and 1B listed patients, and were more likely to be of blood group O, particularly in the current era. Patients with restrictive and congenital heart disease were less likely to be supported with an LVAD compared with other groups. Patients on LVAD support in the first era were more likely to require support with mechanical ventilation and dialysis compared with the rest of the groups, and these differences were less pronounced in the current era. Patients on CF-LVAD support during the current era were less likely to be hospitalized or to require critical care and required inotropes or dialysis less frequently compared with other groups and LVAD patients from the first era.

Outcomes

First Era: January 1999 to April 2008

During this period, 3730 patients died while on the heart transplant waiting list, which represented a mortality rate of 2.9%/mo. Among patients without MCS, mortality of status 1A patients was the highest (21.8%/mo), mortality of status 1B patients was 4.6%/mo, and mortality of status 2 patients was the most favorable (1.2%/mo; Figure 1A). Waiting list mortality in patients with PF-LVADs was 4.5%/mo, which was similar to that of status 1B patients (4.6%/mo; $P=0.71$). Mortality of patients with PF-LVADs was significantly higher compared with that of status 2 patients (4.5%/mo versus 1.2%/mo; $P<0.0001$) and lower than mortality of status 1A patients (4.5% versus 21.8%; $P<0.0001$). CF-LVADs were used infrequently in the first era, and the waiting list mortality of this group was 2.5%/mo (Figure 1A). The overall incidence of the secondary outcome of death or delisting for worsening clinical status was 3.2%/mo, and the differences between the groups mirrored the primary outcome results (Figure 1B). The incidence of the composite end point was similar in patients with PF-LVADs and status 1B listed patients (5.0%/mo versus 5.2%/mo; $P=0.4$). Patients listed in status 1A had the highest event rate (23.2%/mo; $P<0.0001$ for comparison with all groups), whereas patients in status 2 had the lowest rate of the secondary outcome (1.5%/mo). The event rate in patients with CF-LVADs was 2.8%/mo. The results of the univariable analyses for both outcomes (Table II of the online-only Data Supplement) were confirmed in multivariable Cox regression analyses that included the variables detailed in the Methods section (Table 2).

Biventricular and Temporary Support

Patients with other forms of MCS—TAH, BIVADs, and temporary VADs—had a markedly (3- to 16-fold) increased risk of the primary and secondary outcomes compared with status 2 listed candidates (Table 2). Waiting list survival and survival free from death or delisting as a result of worsening clinical status in patients with the various forms of MCS are presented in Figure 2.

Current Era: April 2008 to December 2011

Waiting list mortality decreased significantly in the current era compared with the first era: 2.1%/mo versus 2.9%/mo ($P<0.0001$). In patients without MCS, the listing status still discriminated well the risk of waiting list mortality: 9.6%/mo in status 1A, 2.6%/mo in status 1B, and 1.0%/mo in status 2 patients ($P<0.0001$ for all comparisons; Figure 3A). CF-LVADs were the most commonly used devices for bridging to transplantation in this era. The waiting list mortality in the CF-LVAD group was 1.0%/mo, similar to the mortality rate of 1.0% in the low-urgency status 2 patients ($P=0.62$). Results of a univariable analysis of waiting list mortality are shown in the Table III of the online-only Data Supplement. After adjustment for variables detailed in the Methods section with a multivariable Cox regression analysis (Table 3), mortality risk in patients bridged to transplantation with CF-LVADs was no longer higher than in the low-urgency status 2 patients; in fact, there was a trend toward lower mortality risk in CF-LVAD–supported

Table 1. Baseline Characteristics of Heart Transplant Candidates on the Waiting List

Variable	UNOS status 1A	UNOS status 1B	UNOS status 2	PF-LVAD	CF-LVAD	*P*
First era						
n	5699	7154	7585	1808	338	
Age, y	51±12	52±12	52±12	50±12§‖	50±13§‖	<0.0001
Male sex, n (%)	4475 (78)	5403 (76)	5588 (74)	1468 (81)*	247 (73)‡#	<0.0001
BMI, kg/m^2	27±12	27±5	28±17	28±5§‡	28±5	<0.0001
ABO blood type, n (%)						<0.0001
A	2131 (37.4)	2875 (40.2)	3136 (41.3)	647 (35.8)§‖	128 (37.9)	
B	700 (12.3)	941 (13.2)	992 (13.1)	232 (12.8)	47 (13.9)	
AB	193 (3.4)	332 (4.6)	357 (4.7)	69 (3.8)	14 (4.1)	
O	2675 (46.9)	3006 (42.0)	3100 (40.9)	860 (47.6)§‖	149 (44.1)	
CMP type, n (%)						<0.0001
Nonischemic	2704 (47.5)	3280 (45.8)	3034 (40.0)	717 (39.6)‡§**	163 (48.2)‖#	
Ischemic	2451 (43.0)	3130 (43.8)	3709 (49.0)	998 (55.2)†	162 (47.9)	
VHD	138 (2.4)	197 (2.8)	208 (2.7)	41 (2.3)	3 (0.9)	
CHD	155 (2.7)	198 (2.8)	290 (3.8)	11 (0.6)†	4 (1.2)‖	
Restrictive	206 (3.6)	291 (4.0)	265 (3.5)	23 (1.3)†	3 (0.9)†	
Other	45 (0.8)	58 (0.8)	79 (1.0)	18 (1.0)	3 (0.9)	
Diabetes mellitus, n (%)	1432 (25)	1759 (25)	1784 (24)	460 (25)	93 (28)	0.10
Creatinine, mg/dL	1.4±0.8	1.4±0.8	1.3±0.9	1.4±0.8§‖	1.3±0.8#	<0.0001
Mean PAP, mm Hg	32±10	31±10	27±10	31±10‖	32±10‖	<0.0001
PCWP, mm Hg	22±8	21±8	18±8	22±8§‖	22±8‖	<0.0001
Required support, n (%)						
Hospitalized, ICU	3533 (62)	1574 (22)	194 (2.6)	506 (28)*	64 (19)‡‖#	<0.0001
Inotropic agents	3142 (55)	3574 (50)	540 (7)	724 (40)†	133 (39)†	<0.0001
Ventilator	358 (6.3)	86 (1.2)	52 (0.7)	378 (21)*	44 (13)*	<0.0001
Dialysis	237 (4.2)	133 (1.9)	125 (1.6)	129 (7.1)†	15 (4.4)§‖	<0.0001
Current Era						
n	2789	3131	1813	190	1573	
Age, y	52±13	52±12	54±12	50±13‖	52±12‖	<0.0001
Male sex, n (%)	2130 (76)	2274 (73)	1305 (72)	157 (83)§‖	1227 (78)†	<0.0001
BMI, kg/m^2	27±5	28±6	28±6	28±5‡	28±5‡§	<0.0001
ABO blood type, n (%)						0.007
A	1104 (39.6)	1175 (37.5)	701 (38.7)	64 (33.7)	552 (35.1)‡	
B	357 (12.8)	441 (14.1)	218 (12.0)	25 (13.1)	202 (12.8)	
AB	104 (3.7)	145 (4.6)	92 (5.1)	6 (3.2)	54 (3.4)	
O	1224 (43.9)	1370 (43.8)	802 (44.2)	95 (50.0)†	765 (48.6)†	
CMP type, n (%)						<0.0001
Nonischemic	1461 (52.4)	1570 (50.1)	710 (39.2)	90 (47.4)	853 (54.2)§‖	
Ischemic	977 (35.0)	1193 (38.1)	820 (45.2)	94 (49.5)‡§	675 (42.9)‡§	
VHD	59 (2.1)	53 (1.7)	46 (2.5)	1 (0.5)	13 (0.8)‡‖	
CHD	78 (2.8)	131 (4.2)	98 (5.4)	0 (0.0)†	6 (0.4)†	
Restrictive	184 (6.6)	154 (4.9)	110 (6.1)	3 (1.6)‡§	18 (1.1)†	
Other	30 (1.1)	30 (1.0)	29 (1.6)	2 (1.0)	8 (0.5)‖	
Diabetes mellitus, n (%)	760 (27)	941 (30)	531 (29)	61 (32)	492 (31)‡	0.04
Creatinine, mg/dL	1.3±0.6	1.3±0.8	1.4±1.0	1.3±0.6	1.2±0.7‖	0.001
Mean PAP, mm Hg	32±10	31±10	27±10	29±11‡§	30±11†	<0.0001
PCWP, mm Hg	22±8	21±8	18±8	19±8‡§	20±9†	<0.0001

(*Continued*)

Table 1. Continued

Variable	UNOS status 1A	UNOS status 1B	UNOS status 2	PF-LVAD	CF-LVAD	*P*
Required support, n (%)						
Hospitalized, ICU	1813 (65)	350 (11)	35 (2)	34 (18)*	132 (8)*	<0.0001
Inotropic agents	1320 (47)	1435 (46)	120 (7)	23 (12)†	191 (12)†	<0.0001
Ventilator	61 (2.2)	28 (0.9)	7 (0.4)	6 (3.2)§‖	77 (4.9)†	<0.0001
Dialysis	98 (3.5)	64 (2.0)	54 (3.0)	9 (4.7)	35 (2.2)	0.002

BMI indicates body mass index; CF-LVAD, continuous-flow left ventricular assist device; CHD, congenital heart disease; CMP, cardiomyopathy; ICU, intensive care unit; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PF-LVAD, pulsatile-flow left ventricular assist device; and VHD, valvular heart disease. Baseline characteristics were recorded at registration on the heart transplantation waiting list. First era: January 1999 to April 2008; current era: April 2008 to December 2011. Values are expressed as mean±SD when appropriate. Final column reflects overall group ANOVA, χ^2 test, or Fisher exact test as appropriate. For between-group comparisons in LVAD recipients: **P*<0.05 vs all the groups; †*P*<0.05 vs United Network for Organ Sharing (UNOS) status 1A, 1B, and 2; ‡*P*<0.05 vs UNOS status 1A; §*P*<0.05 vs UNOS status 1B; ‖*P*<0.05 vs UNOS status 2; #*P*<0.05 vs PF-LVAD; and ***P*<0.05 vs CF-LVAD. Multiple-group comparisons were adjusted by use of the Holm procedure.

patients (HR=0.80; *P*=0.12). The multivariable adjustment also confirmed that the high-urgency status 1A and the intermediate-urgency status 1B were independently associated with increased mortality risk compared with status 2 (*P*<0.0001 for both comparisons).

To ascertain that these results were not influenced by delisting of patients whose condition worsened while awaiting transplantation, we evaluated the composite outcome of waiting list mortality or delisting as a result of worsening clinical status. The composite outcome occurred with an incidence rate of 2.8%/mo. The incidence rate was 11.7%/mo in status 1A patients, 3.4%/mo in status 1B patients, and 1.4%/mo in status 2 patients (*P*<0.0001 for all comparisons). The incidence rate of the composite outcome in the CF-LVAD group most closely approximated status 2 patients (1.4%/mo versus 1.4%/mo; *P*=0.93; Figure 3B). Only a minority of patients were bridged with PF-LVADs in the current era, and the rate of mortality or delisting in this group was similar to that of status 1B patients (3.2%/mo versus 3.4%/mo; *P*=0.79). The results of a univariable (Table III of the online-only Data Supplement) and a multivariable Cox regression analysis for the composite outcome (Table 3) confirmed the favorable risk profile of CF-LVADs, and similarly to the primary outcome, candidates with CF-LVADs had a trend toward lower risk of the secondary outcome compared with status 2 candidates in the current era (HR=0.81; *P*=0.08).

Biventricular and Temporary Support

Heart transplant candidates requiring support with BIVADs (HR=5.00; *P*<0.0001) and temporary VADs (HR=7.72; *P*<0.0001) had the highest risk of death compared with status 2 and other candidates in the current era. Patients requiring TAH had a >2-fold increase in mortality risk, but this did not reach statistical significance (HR=2.36; *P*=0.14; Table 3 and Figure 4A). For the composite outcome, candidates requiring the use of BIVADs (HR=5.31; *P*<0.0001) and temporary VADs (HR=8.53; *P*<0.0001) had the highest risk of death or delisting as a result of worsening clinical status. Similar to the primary outcome, support with TAH resulted in a trend for an increased risk of death or delisting compared with status 2 candidates (HR=2.56; *P*=0.11; Table 3 and Figure 4B).

LVAD Listing, Status 1A and 1B Subgroups

LVAD-supported patients are afforded a 30-day period of 1A status listing and, if not transplanted, are then downgraded to 1B status. It would appear that the risk of an adverse event on the waiting list during status 1A and 1B time would be similar in these LVAD-supported patients; therefore, we approached

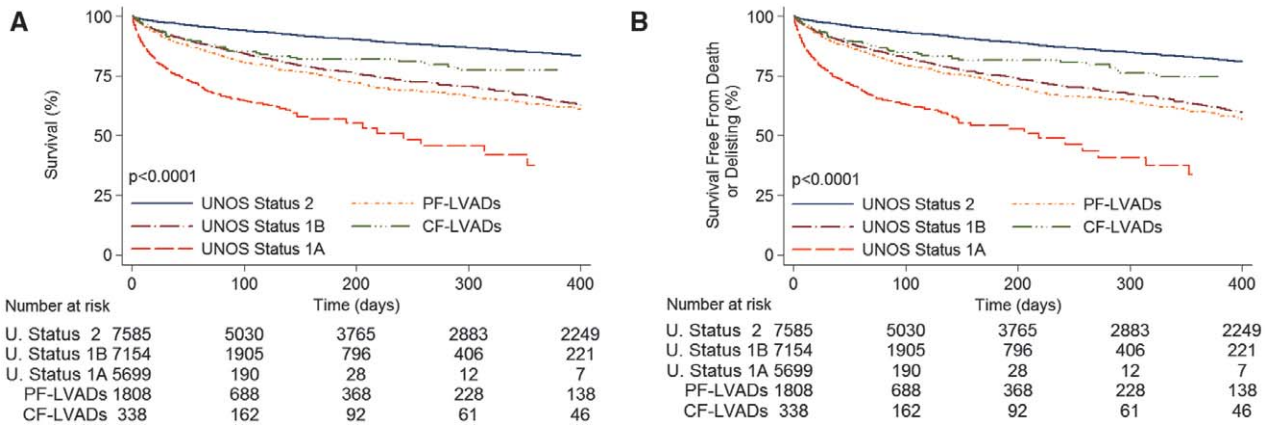

Figure 1. Outcomes for heart transplant candidates on the United Network for Organ Sharing (UNOS) waiting list in the first era. **A**, Unadjusted waiting list survival according to UNOS status and left ventricular assist device (LVAD) support type. **B**, Unadjusted waiting list survival free from death or delisting as a result of worsening clinical status according to UNOS status and LVAD support type. CF indicates continuous flow; and PF, pulsatile flow.

Table 2. Multivariable Hazard Ratio Estimates for the Risk of Death on the Waiting List and for the Risk of Death or Delisting Among Heart Transplant Candidates in the First Era (1999–2008)

	Mortality		Mortality or Delisting	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per year)	1.01 (1.01–1.02)	<0.0001	1.01 (1.01–1.02)	<0.0001
Restrictive vs nonischemic CMP	1.50 (1.25–1.81)	<0.0001	1.43 (1.20–1.72)	<0.0001
Valvular vs nonischemic CMP	…	…	1.22 (1.00–1.48)	0.049
Diabetes mellitus (yes vs no)	1.18 (1.08–1.27)	<0.0001	1.18 (1.10–1.28)	<0.0001
Serum creatinine (per 1 mg/dL)	1.21 (1.17–1.24)	<0.0001	1.21 (1.18–1.24)	<0.0001
Mean PAP (per 1 mm Hg)	…	…	1.01 (1.00–1.01)	0.046
PCWP (per 1 mm Hg)	1.01 (1.01–1.02)	<0.0001	1.01 (1.00–1.02)	0.003
Inotropic support (yes vs no)	1.24 (1.14–1.35)	<0.0001	1.24 (1.15–1.35)	<0.0001
Mechanical ventilation (yes vs no)	2.31 (2.02–2.65)	<0.0001	2.20 (1.92–2.51)	<0.0001
UNOS status 1A vs 2	5.56 (4.92–6.29)	<0.0001	5.40 (4.80–6.06)	<0.0001
UNOS status 1B vs 2	2.08 (1.86–2.31)	<0.0001	2.07 (1.87–2.29)	<0.0001
PF-LVAD vs status 2	2.15 (1.87–2.47)	<0.0001	2.11 (1.85–2.40)	<0.0001
CF-LVAD vs status 2	1.48 (1.13–1.93)	0.01	1.45 (1.12–1.87)	0.004
TAH vs status 2	3.58 (1.34–9.59)	0.01	4.05 (1.68–9.78)	0.004
BIVADs vs status 2	7.00 (4.89–10.03)	<0.0001	7.69 (5.52–10.70)	<0.0001
Temporary VAD vs status 2	16.18 (11.95–21.92)	<0.0001	16.45 (12.32–21.96)	<0.0001

BIVAD indicates biventricular assist device; CF-LVAD, continuous-flow left ventricular assist device; CI, confidence interval; CMP, cardiomyopathy; HR, hazard ratio; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PF-LVAD, pulsatile-flow left ventricular assist device; TAH, total artificial heart; and UNOS, United Network for Organ Sharing. HRs, 95% CIs, and *P* values were generated by use of a Cox proportional hazard analysis. Multiple-group comparisons were adjusted by use of the Holm procedure.

these patients as 1 group. To confirm that our assumption of risk was correct, we compared the risk of the primary and secondary outcomes in LVAD-supported patients during their status 1A and 1B time. There was no difference in survival free from the primary and secondary outcomes during LVAD patients' status 1A and 1B listings in the first era (Figure I of the online-only Data Supplement) or the current era (Figure II of the online-only Data Supplement). The risk remained similar after adjustment in a multivariable model.

Listing Status Upgrade Resulting From Device-Related Complications

For patients with MCS-related complications, the UNOS allocation algorithm allows status 1A (high-urgency) listing to expedite transplantation. Such complications are defined by the OPTN policy as objective medical evidence of significant device-related complications (thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias). Each such listing is reviewed by UNOS staff for appropriateness and has to be recertified by an attending physician every 14 days if extension of the status 1A listing is requested. Listing upgrade resulting from complications other than thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias results in a review by the UNOS Heart Regional Review Board, which votes to approve or disapprove the listing upgrade.[25]

We also evaluated the risk of the primary and secondary outcomes in the candidates whose status was upgraded to status 1A owing to LVAD-related complications. In the first era, the status of 616 LVAD-supported candidates (29%) was upgraded to 1A as a result of LVAD-related complications. Compared with LVAD-supported candidates without a complication, these patients had higher rates of death (7.4%/mo versus 5.8%/mo; *P*=0.04) and death or delisting (8.3%/mo versus 6.3%/mo; *P*=0.02; Figure 5). However, in multivariable analysis considering variables detailed in the Methods section, the risk of death (HR=0.89; 95% confidence interval, 0.69–1.14; *P*=0.36) and death or delisting (HR=0.96; 95% confidence interval, 0.76–1.22; *P*=0.75) was similar between candidates listed with and without LVAD-related complications. In the

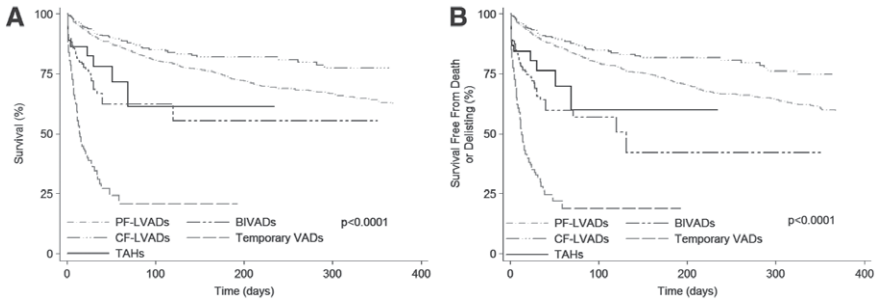

Figure 2. Outcomes for heart transplant candidates requiring mechanical circulatory support on the United Network for Organ Sharing (UNOS) waiting list in the first era. **A**, Unadjusted waiting list survival and **B**, unadjusted waiting list survival free from death or delisting as a result of worsening clinical status. BIVAD indicates biventricular assist device; CF, continuous flow; LVAD, left ventricular assist device; PF, pulsatile flow; and TAH, total artificial heart.

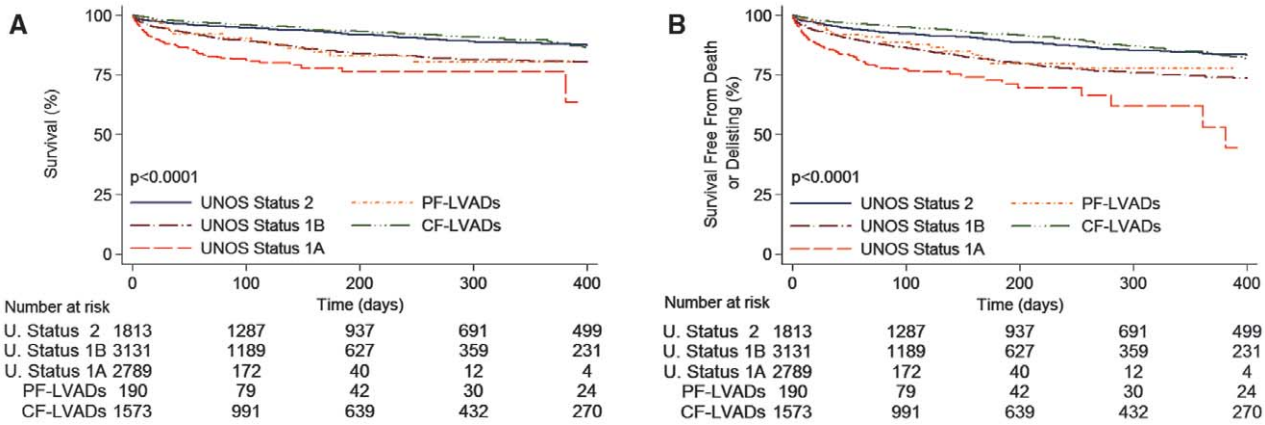

Figure 3. Outcomes for heart transplant candidates on the United Network for Organ Sharing (UNOS) waiting list in the current era. **A**, Unadjusted waiting list survival according to UNOS status and left ventricular (LVAD) support type. **B**, Unadjusted waiting list survival free from death or delisting as a result of worsening clinical status according to UNOS status and LVAD support type. CF indicates continuous flow; and PF, pulsatile flow.

current era, 491 candidates (28%) were upgraded to status 1A because of LVAD-related complications. Patients with complications had higher rates of death (2.3%/mo versus 1.2%/mo; $P<0.0001$) and death or delisting (2.7%/mo versus 1.3%/mo; $P=0.0008$) compared with patients without LVAD-related complications (Figure 6). These results were confirmed in multivariable analysis, in which candidates listed in status 1A as a result of an LVAD-related complication had a higher risk of death (HR=1.47; 95% confidence interval, 1.00–2.18; $P=0.05$) and death or delisting (HR=1.75; 95% confidence interval, 1.26–2.42; $P=0.001$) compared with candidates without an LVAD-related complication. In fact, their risk for both outcomes was now similar to that of status 1B listed candidates ($P>0.38$ for both comparisons; Figure 6). Survival free from listing status upgrade because of LVAD-related complications and the hazard function for such an upgrade in the current era are shown in Figure 7.

Competing Outcomes

To better illustrate the changing outcomes of LVAD-supported patients on the transplant waiting list, we display the different competing outcomes in Figure 8. In the first era, 83% of LVAD-supported patients at 180 days of listing and 80% of LVAD-supported patients at 365 days achieved a positive outcome of survival to transplantation, continued LVAD support, or delisting resulting from clinical recovery (Figure 8A). The outcomes were more favorable in the current era, in which 94% and 91% of the LVAD-supported patients were transplanted, continued on LVAD support, or delisted as a result of clinical recovery at 180 and 365 days (Figure 8B).

Table 3. Multivariable Hazard Ratio Estimates for the Risk of Death on the Waiting List and for the Risk of Death or Delisting Among Heart Transplant Candidates in the Current Era (2008–2011)

	Mortality		Mortality or Delisting	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per year)	…	…	1.01 (1.01–1.02)	<0.0001
Restrictive vs nonischemic CMP	1.47 (1.11–1.94)	0.007	1.50 (1.17–1.91)	0.001
Diabetes mellitus (yes vs no)	1.24 (1.08–1.41)	0.002	1.20 (1.07–1.36)	0.002
Serum creatinine (per 1 mg/dL)	1.23 (1.19–1.28)	<0.0001	1.21 (1.15–1.26)	<0.0001
Mean PAP (per 1 mm Hg)	1.02 (1.01–1.02)	<0.0001	1.01 (1.01–1.02)	0.001
Inotropic support (yes vs no)	1.20 (1.04–1.38)	0.01	…	…
Mechanical ventilation (yes vs no)	3.36 (2.58–4.38)	<0.0001	2.89 (2.25–3.71)	<0.0001
UNOS status 1A vs 2	3.26 (2.62–4.05)	<0.0001	3.14 (2.60–3.80)	<0.0001
UNOS status 1B vs 2	1.68 (1.38–2.04)	<0.0001	1.68 (1.42–1.98)	<0.0001
PF-LVAD vs status 2	2.04 (1.34–3.08)	0.003	1.97 (1.36–2.84)	<0.0001
CF-LVAD vs status 2	0.80 (0.63–1.01)	0.12	0.81 (0.66–0.99)	0.08
TAH vs status 2	2.36 (0.75–7.41)	0.14	2.56 (0.81–8.03)	0.11
BIVADs vs status 2	5.00 (3.34–7.49)	<0.0001	5.31 (3.60–7.82)	<0.0001
Temporary VAD vs status 2	7.72 (4.28–13.91)	<0.0001	8.53 (4.86–14.98)	<0.0001

BIVAD indicates biventricular assist device; CF-LVAD, continuous-flow left ventricular assist device; CI, confidence interval; CMP, cardiomyopathy; HR, hazard ratio; PAP, pulmonary artery pressure; PF-LVAD, pulsatile-flow left ventricular assist device; TAH, total artificial heart; and UNOS, United Network for Organ Sharing. HRs, 95% CIs, and *P* values were generated with a Cox proportional hazard analysis. Multiple-group comparisons were adjusted by use of the Holm procedure.

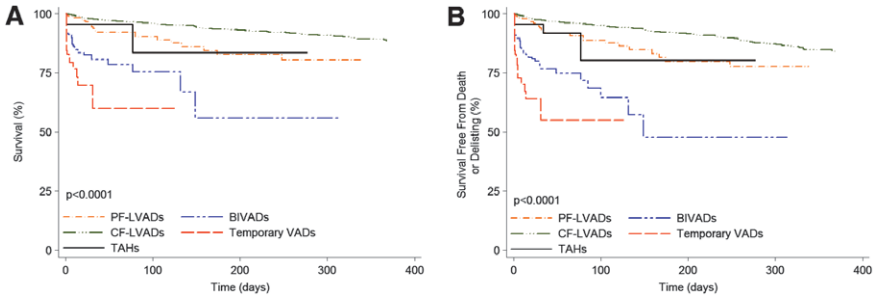

Figure 4. Outcomes for heart transplant candidates requiring mechanical circulatory support on the United Network for Organ Sharing (UNOS) waiting list in the current era. **A**, Unadjusted waiting list survival and (**B**) unadjusted waiting list survival free from death or delisting as a result of worsening clinical status. BIVAD indicates biventricular assist device; CF, continuous flow; LVAD, left ventricular assist device; PF, pulsatile flow; and TAH, total artificial heart.

The proportion of patients undergoing transplantation by 180 days in the current era was lower (46%) than in the first era (57%), and the number of patients who were not transplanted but remained alive on continued LVAD support at 180 days was higher in the current era (48% compared with 25% in the first era). The number of patients delisted as a result of worsening clinical status (1%) or clinical recovery (<1%) remained constant, whereas waiting list mortality of LVAD-bridged patients decreased by nearly 70% in the current era (16% versus 5%; $P<0.01$).

Discussion

This study evaluated the impact of MCS on heart transplant waiting list outcomes in an era of technological improvement and greater experience in the management of patients with VADs. The main finding of our study is the demonstration of markedly improved waiting list mortality and morbidity of heart transplant candidates bridged with durable LVADs in the current era. The mortality and morbidity risk in patients bridged with durable CF-LVADs is now similar to that in the status 2 listed patients (lowest priority). However, we also show that LVAD-supported transplant candidates whose status on the waiting list is upgraded as a result of an LVAD-related complication have a risk of mortality and mortality or delisting that is markedly higher compared with LVAD-supported candidates listed without complications and with status 2 listed patients. Interestingly, the proportion of patients who are listed in status 1A because of an LVAD-related complication is high and has remained without significant change between the 2 eras; 28% of LVAD-supported patients in the current era are listed in status 1A because of a device-related complication.

In the current era, the hazard of LVAD-related complications is highest early after listing for transplantation and nadirs at 80 days, after which it appears to again gradually increase (Figure 7). Patients requiring biventricular support and temporary VADs continue to have a very high risk of adverse outcomes on the waiting list.

Since its inception, OPTN/UNOS has strived to maintain a fair and balanced organ allocation system by prioritizing organ allocation to patients with the highest risk of death while waiting for a donor organ. Our analyses from the first era confirm the pertinence of the indefinite 1B status listing afforded to the LVAD-bridged candidates by the UNOS policies at the time. The use of the first-generation PF-LVADs was associated with reduced mortality in heart transplant candidates with a very high risk of death and allowed these patients to reach heart transplantation. The risk of death or delisting of these LVAD-supported candidates remained significant, however, and our study shows that this risk was similar to that of status 1B candidates without MCS. Assessment of more recent outcomes shows that waiting list mortality of patients bridged with CF-LVADs after 2008 has decreased significantly and is below the waiting list mortality of status 1B candidates not supported with LVADs. In fact, the waiting list mortality of CF-LVAD–supported patients without serious LVAD-related complications now is similar to the mortality of low-urgency status 2 transplant candidates. The impact of improving outcomes in LVAD-supported transplant candidates on reducing the wait-list mortality has been important. For illustration, the overall waiting list mortality has decreased in recent years, and much of this effect was attributed to the broader organ regional sharing implemented by UNOS in 2006.[26] It is likely, however, that LVAD use has also contributed significantly to this trend; our findings show that the reduction of waiting list mortality in LVAD-bridged patients in this time frame (4.1%/mo to 1.2%/mo, a 71% reduction) has been far larger than in patients without MCS (2.6%/mo to 2.3%/mo, a 12% reduction).

The improved waiting list survival of LVAD-supported candidates is a remarkable achievement that affords positive outcome to patients who would have been at a high risk of mortality in the past. Technological advances, expanding

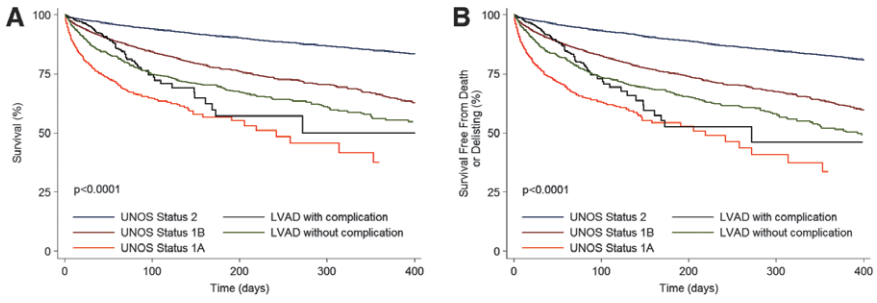

Figure 5. Waiting list outcomes in left ventricular assist device (LVAD) recipients with and without complications in relation to United Network for Organ Sharing (UNOS) status groups in the first era. **A**, Unadjusted waiting list survival. **B**, Unadjusted waiting list survival free from death or delisting as a result of worsening clinical status. Time 0 for LVAD recipients with complications is the time of status 1A upgrade resulting from an LVAD complication. Time 0 for LVAD recipients without complications is the time of listing for transplantation with an LVAD.

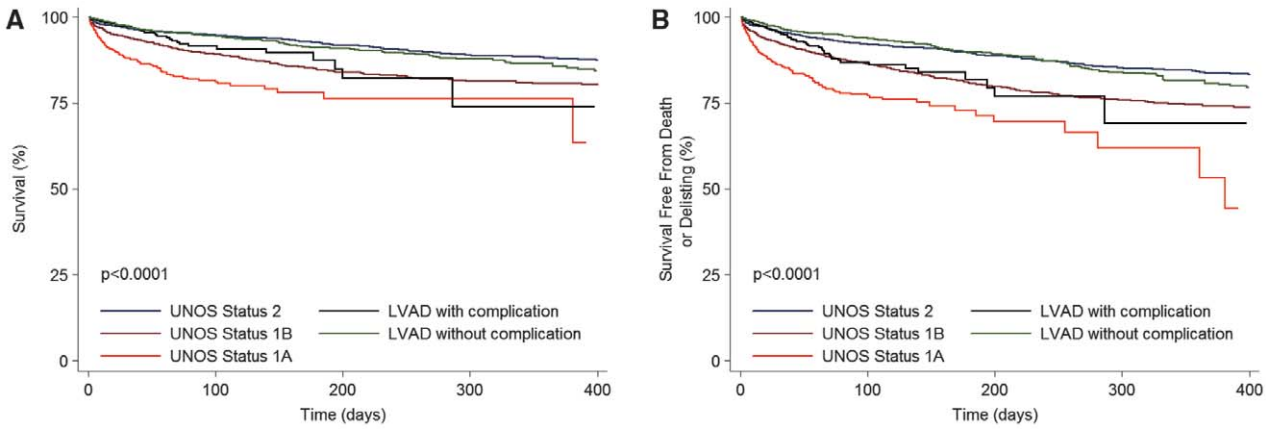

Figure 6. Waiting list outcomes in left ventricular assist device (LVAD) recipients with and without complications in relation to United Network for Organ Sharing (UNOS) status groups in the current era. **A**, Unadjusted waiting list survival. **B**, Unadjusted waiting list survival free from death or delisting as a result of worsening clinical status. Time 0 for LVAD recipients with complications is the time of status 1A upgrade resulting from an LVAD complication. Time 0 for LVAD recipients without complications is the time of listing for transplantation with an LVAD.

clinical experience with mechanical assist, and refined patient selection approaches have all contributed to the better outcomes and to the fact that more patients are now being considered for LVAD support.[1,27] However, with these uniformly positive developments, we are also faced with a question of whether the current UNOS heart allocation algorithm remains equitable.[15,28] Our data suggest that this question is multifaceted. For patients who require biventricular support and support with pulsatile or nondurable mechanical assist devices, the adverse outcomes on the waiting list remain high. Therefore, affording high-urgency status to these patients appears appropriate. The markedly improved wait-list mortality for patients bridged with CF-LVADs raises new considerations. Should the risk of mortality on the waiting list be the sole determinant of the allocation priority? If the answer is yes, then the current UNOS allocation system would appear to be outdated because patients with LVADs might have an advantage over patients at a higher risk of wait-list mortality, including those who may not be LVAD candidates. Along these lines, there have been suggestions to revise the UNOS allocation algorithm and possibly align it more closely with the Eurotransplant allocation system, which does not grant high-urgency status to LVAD-supported heart transplant candidates unless a device-related complication occurs.[15,29] In contrast, our data indicate that this approach might not necessarily improve outcomes on the UNOS waiting list. LVAD implantation often transforms a sick patient at very high risk of wait-list and posttransplant mortality into a good transplant candidate with improved organ function and nutritional and physical condition, so transplant in this favorable situation may be of the most benefit. Our data show that almost 30% of LVAD-supported transplant candidates develop a complication that justifies a higher-urgency status listing and that, once this occurs, the risk of death or delisting is markedly increased. Some of these complications (eg, stroke) may also have long-lasting effects on patient quality of life after transplantation. If, as a result of a change in the organ allocation algorithm, LVAD-supported patients were to remain on the waiting list for a longer period of time, the cumulative incidence of device-related complications would likely increase (Figure 7). Thus, the intent and the considerable expense that were dispensed to get an ill patient to transplant eligibility through the implantation of an LVAD could be negated, and the recent improvements in waiting list outcomes could be jeopardized.

Another consideration is that any organ allocation change is expected to result in changes in clinical decisions. It is conceivable that, if LVAD-supported patients were not given allocation priority, physicians and patients might opt to delay LVAD implantation for as long as possible in hopes of increasing the probability of receiving a heart transplant in high-urgency status on medical management. This, however, may expose the patients to higher risk of dying or becoming ineligible for transplantation (as our data for 1A and 1B status

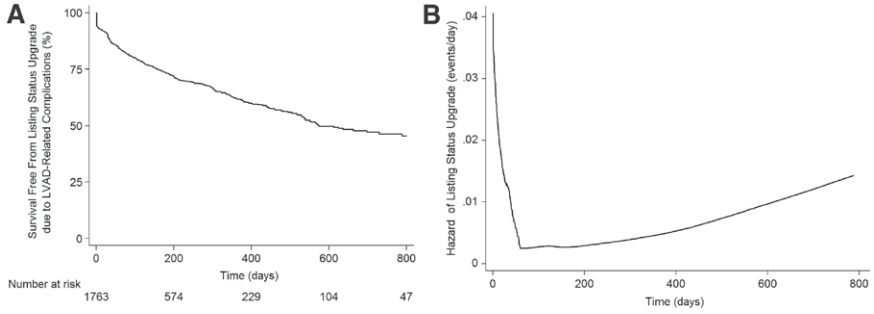

Figure 7. Listing status upgrade as a result of left ventricular assist device (LVAD)–related complications in the current era. **A**, Survival free from listing status upgrade resulting from LVAD-related complications. Patients were censored at the time of transplantation, death, or delisting. **B**, Hazard function for the risk of listing status upgrade owing to LVAD-related complications.

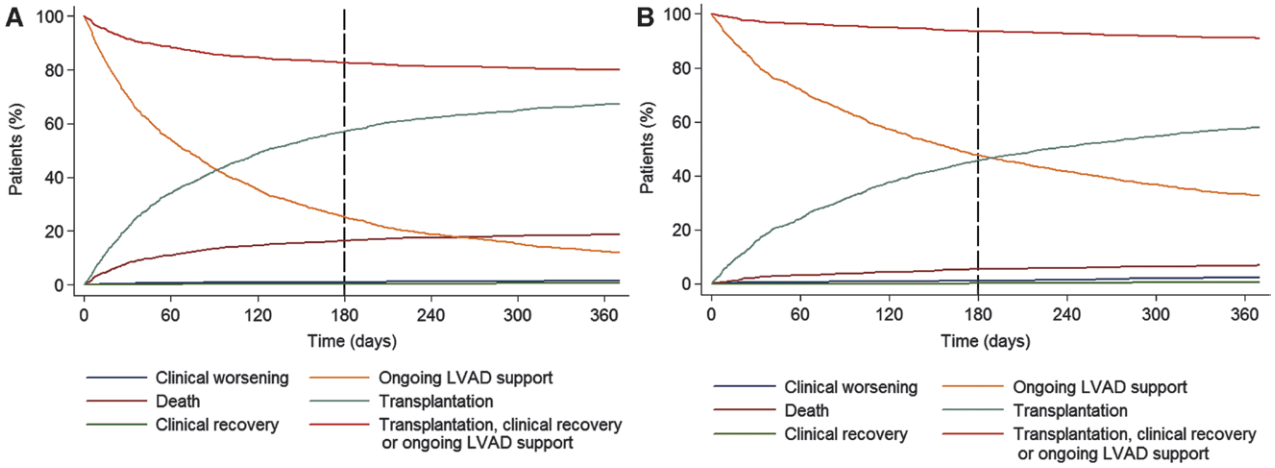

Figure 8. Competing outcomes for heart transplant candidates supported with left ventricular assist devices (LVADs) while on the United Network for Organ Sharing waiting list. **A**, In the first era, after 6 months of LVAD support, 83% of the patients were alive on ongoing LVAD support (25%), transplanted (57%), or delisted because of clinical recovery (0.3%). The remaining 17% of the patients had died (16%) or had been delisted as a result of worsening clinical status (1%). **B**, In the current era, after 6 months of LVAD support, 94% of the patients were alive on ongoing LVAD support (48%), transplanted (46%), or delisted because of clinical recovery (0.2%). The remaining 6% of the patients had died (5%) or had been delisted as a result of worsening clinical status (1%).

patients would suggest). In addition, those who decompensate on medical therapy may more likely require emergent LVAD implantation, increasing the risk profile of this group as well. These arguments would support continuation of the current allocation algorithm without change.

We recognize that there are limitations to our study. This was a retrospective analysis of a nationwide clinical registry. Although UNOS data collection is rigorous and undergoes periodic audits, some errors in data entry may be present. LVAD-specific morbidity outcomes and hospitalization data were not available and thus could not be contrasted with the morbidity outcomes and hospitalization rates of medically supported patients on the waiting list. Data on duration of LVAD support before registration on the waiting list were not available. Therefore, we were not able to accurately assess the effect of LVAD support duration on the risk of death. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile for the patients in our study was not available; therefore, we were unable to explore the effects of this characteristic on evaluated outcomes. Some patients who were already active on the waiting list later received mechanical assist devices. We assigned these patients to the medical therapy group because that was the original intent at the time of listing. Patients who underwent VAD implantation but died or had significant complications precluding their relisting contributed to the primary and secondary outcomes of the medical treatment groups. Patients who were relisted for transplantation with an LVAD in the current era had an exceptionally good outcome: waiting list mortality rate of 0.74%/mo and mortality or delisting rate of 1.0%/mo. For completeness, we performed ancillary analyses with the group of patients requiring LVAD placement while already on the waiting list. We determined that this study group assignment did not change the results of the study (data not shown). Finally, the prevalence of conditions that would preclude LVAD implantation such as significant right ventricular dysfunction or certain forms of congenital heart disease could not be determined from this registry. We are aware that not all the questions raised can be answered by our study. Nevertheless, as an allocation change is being considered, we believe our analysis provides important insights that can help inform policy.

Conclusions

Mortality and morbidity have decreased in patients awaiting heart transplant in the current era. Although the current allocation system accurately reflects the risk of mortality in medically managed patients awaiting heart transplantation, the issue of the most appropriate allocation priority in MCS-supported patients remains complex. Contemporary heart transplant candidates supported with CF-LVADs have the lowest risk of adverse outcomes while on the waiting list. However, serious LVAD-related complications occur frequently and are associated with an increased risk of death or delisting in these patients. Furthermore, transplant candidates requiring temporary and biventricular support represent a group at the highest risk of adverse outcomes on the waiting list. These results provide important information that can be helpful in guiding future allocation changes involving the complex and urgent topic of transplant prioritization.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart transplant candidates supported with left ventricular assist devices (LVADs) are granted 30 days in high-urgency status 1A and indefinite time in intermediate-urgency status 1B. Improvement in outcomes observed with the new continuous-flow LVADs has brought into question whether current allocation policy, implemented in the pulsatile-flow LVAD era, is still justified. The United Network for Organ Sharing (UNOS) registry was used to analyze the risk of death or delisting while on the heart transplant waiting list in 33 073 candidates listed from 1999 to 2011. Study groups were selected on the basis of the need for an LVAD and UNOS listing status. Two eras were defined on the basis of the approval date of the first continuous-flow LVAD for bridge to transplantation in the United States. Waiting list mortality decreased in the current compared with the first era. In the current era, patients with continuous-flow LVADs had a mortality risk that was similar to that of status 2 patients (lowest priority) and lower than for status 1B and 1A listed candidates. This was a significant change compared with the first era, in which the mortality of pulsatile-flow LVAD–supported patients was higher than that of status 2 patients and similar to that of status 1B patients. However, status upgrade for LVAD-related complications occurred frequently in both eras and significantly increased the risk of adverse outcomes. The risk of mortality and morbidity was highest in patients with biventricular assist devices and temporary VADs. These results may help to guide optimal allocation of donor hearts.

Supplemental Material

Supplemental Tables

Supplemental Table 1. Types and Brands of Ventricular Assist Devices. Distribution by Era

Device type/brand	First Era (N=2,779)	Current Era (N=2,123)
PF-LVAD	**1,808**	**190**
HeartMate IP, VE, XVE	1,196	121
Novacor PC, PCq	120	1
Thoratec	481	64
Toyobo	10	4
HeartSaver	1	-
CF-LVAD	**338**	**1,573**
HeartMate II	262	1,458
HeartWare	-	61
Jarvik 2000	33	22
Micromed DeBakey	29	-
VentrAssist	14	24
Others	-	8
TAH	**46**	**44**
BIVADs	**295**	**233**
Temporary VADs	**292**	**83**

First Era: January 1999 to April 2008; Current Era: April 2008 to December 2011. BIVADs=biventricular assist device; CF-LVAD=continuous-flow left ventricular assist device; PF-LVAD=pulsatile-flow left ventricular assist device; TAH=total artificial heart. Values are expressed as frequencies.

Supplemental Table 2. Univariable Hazard Ratio Estimates for the Risk of Death on the Waiting List and for the Risk of Death or Delisting Among Heart Transplant Candidates in the First Era (1999-2008)

	Mortality		Mortality or Delisting	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year)	1.01 (1.00-1.01)	<0.0001	1.01 (1.00-1.01)	<0.0001
Body mass index (per kg/m^2)	0.99 (0.99-1.00)	0.06	0.99 (0.98-0.99)	0.02
Ischemic vs. Nonischemic CMP	1.09 (1.02-1.17)	0.01	1.13 (1.06-1.21)	<0.0001
Restrictive vs. Nonischemic CMP	1.36 (1.15-1.61)	<0.0001	1.30 (1.10-1.53)	0.002
Valvular vs. Nonischemic CMP	-	-	1.24 (1.03-1.48)	0.02
Diabetes mellitus (yes vs. no)	1.27 (1.18-1.36)	<0.0001	1.29 (1.21-1.38)	<0.0001
Tobacco use (yes vs. no)	1.06 (0.99-1.15)	0.09	1.10 (1.02-1.17)	0.009
Blood type O vs. type A	1.13 (1.06-1.22)	0.001	1.12 (1.04-1.19)	0.002
Serum creatinine (per mg/dl)	1.16 (1.14-1.18)	<0.0001	1.16 (1.14-1.18)	<0.0001
Mean PAP (per mm Hg)	1.02 (1.02-1.03)	<0.0001	1.02 (1.02-1.03)	<0.0001
PCWP (per mm Hg)	1.03 (1.03-1.04)	<0.0001	1.03 (1.03-1.04)	<0.0001
Inotropic support (yes vs. no)	2.22 (2.08-2.38)	<0.0001	2.19 (2.05-2.33)	<0.0001
Need for dialysis (yes vs. no)	1.64 (1.39-1.92)	<0.0001	1.60 (1.37-1.87)	<0.0001
Mechanical ventilation (yes vs. no)	4.08 (3.69-4.51)	<0.0001	3.88 (3.52-4.28)	<0.0001
UNOS status 1A vs. Status 2	7.43 (6.71-8.24)	<0.0001	7.02 (6.36-7.74)	<0.0001
UNOS status 1B vs. Status 2	2.52 (2.30-2.76)	<0.0001	2.48 (2.28-2.71)	<0.0001
PF-LVAD vs. Status 2	2.89 (2.57-3.26)	<0.0001	2.75 (2.46-3.07)	<0.0001
CF-LVAD vs. Status 2	1.78 (1.37-2.30)	<0.0001	1.72 (1.35-2.20)	<0.0001
TAH vs. Status 2	7.31 (3.91-13.65)	<0.0001	7.12 (3.92-12.91)	<0.0001
BIVADs vs. Status 2	10.49 (8.15-13.51)	<0.0001	10.69 (8.44-13.53)	<0.0001
Temporary VAD vs. Status 2	30.72 (25.32-37.28)	<0.0001	30.25 (25.18-36.33)	<0.0001

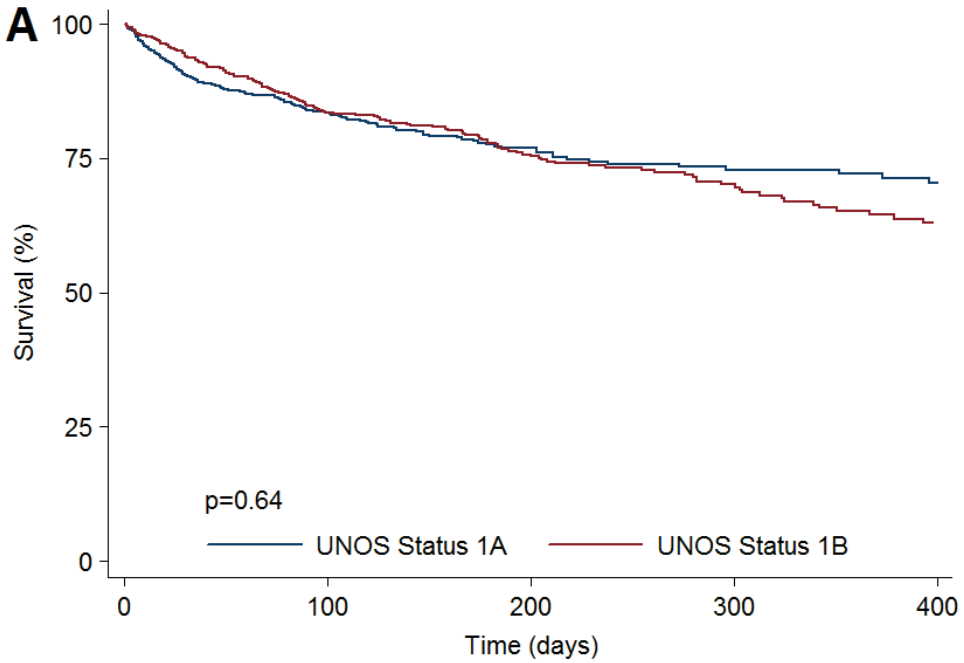
BIVADs=biventricular assist devices; CF-LVAD= continuous-flow LVAD; CI= confidence interval; CMP=cardiomyopathy; PAP=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure; PF-LVAD=pulsatile-flow LVAD; TAH=total artificial heart; UNOS=United Network for Organ Sharing. Hazard ratios, 95% CI and p values were generated using a Cox proportional hazard analysis. Multiple group comparisons were adjusted using the Holm procedure.

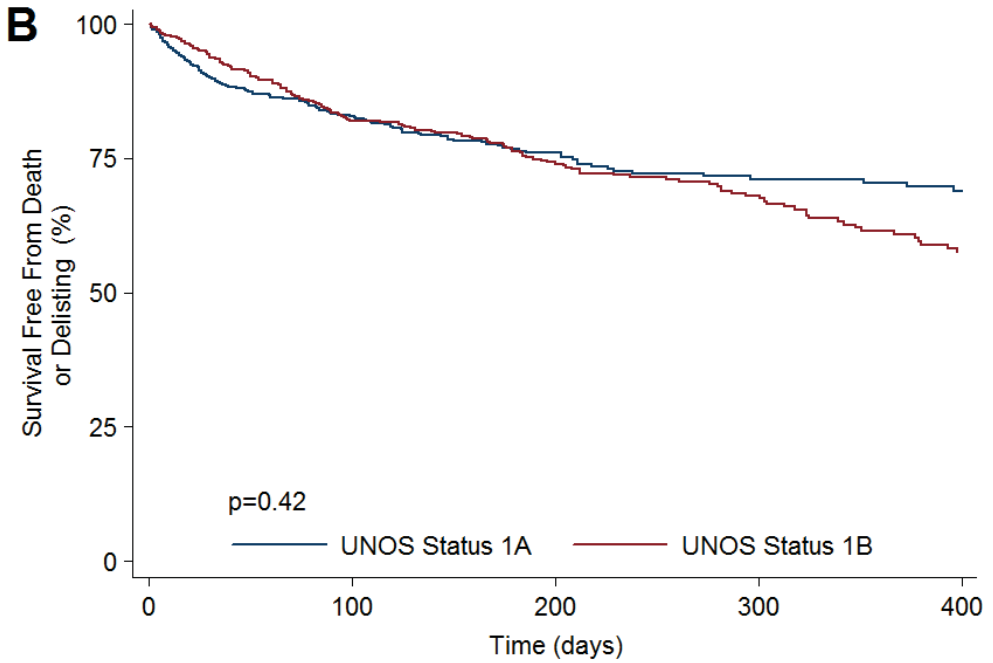
Supplemental Table 3. Univariable Hazard Ratio Estimates for the Risk of Death on the Waiting List and for the Risk of Death or Delisting Among Heart Transplant Candidates in the Current Era (2008-2011)

	Mortality		Mortality or Delisting	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year)	1.01 (1.00-1.01)	0.04	1.01 (1.00-1.01)	<0.0001
Ischemic vs. Nonischemic CMP	-	-	1.12 (0.99-1.26)	0.06
Restrictive vs. Nonischemic CMP	1.42 (1.08-1.87)	0.01	1.47 (1.16-1.87)	0.002
Diabetes mellitus (yes vs. no)	1.27 (1.11-1.44)	<0.0001	1.30 (1.16-1.46)	<0.0001
Serum creatinine (per mg/dl)	1.22 (1.18-1.27)	<0.0001	1.23 (1.19-1.26)	<0.0001
Mean PAP (per mm Hg)	1.02 (1.02-1.03)	<0.0001	1.02 (1.02-1.03)	<0.0001
PCWP (per mm Hg)	1.03 (1.02-1.04)	<0.0001	1.03 (1.02-1.03)	<0.0001
Inotropic support (yes vs. no)	1.75 (1.54-1.99)	<0.0001	1.64 (1.46-1.84)	<0.0001
Need for dialysis (yes vs. no)	2.72 (2.12-3.48)	<0.0001	2.75 (2.21-3.41)	<0.0001
Mechanical ventilation (yes vs. no)	3.87 (3.07-4.87)	<0.0001	3.30 (2.66-4.10)	<0.0001
UNOS status 1A vs. Status 2	3.76 (3.06-4.61)	<0.0001	3.47 (2.90-4.15)	<0.0001
UNOS status 1B vs. Status 2	1.92 (1.59-2.31)	<0.0001	1.85 (1.58-2.17)	<0.0001
PF-LVAD vs. Status 2	2.11 (1.40-3.19)	<0.0001	1.94 (1.35-2.79)	<0.0001
CF-LVAD vs. Status 2	0.95 (0.75-1.19)	0.64	0.91 (0.75-1.11)	0.37
TAH vs. Status 2	1.83 (0.58-5.73)	0.60	1.83 (0.68-4.92)	0.46
BIVADs vs. Status 2	6.64 (4.68-9.42)	<0.0001	6.03 (4.40-8.26)	<0.0001
Temporary VAD vs. Status 2	15.34 (9.56-24.63)	<0.0001	14.22 (9.26-21.83)	<0.0001

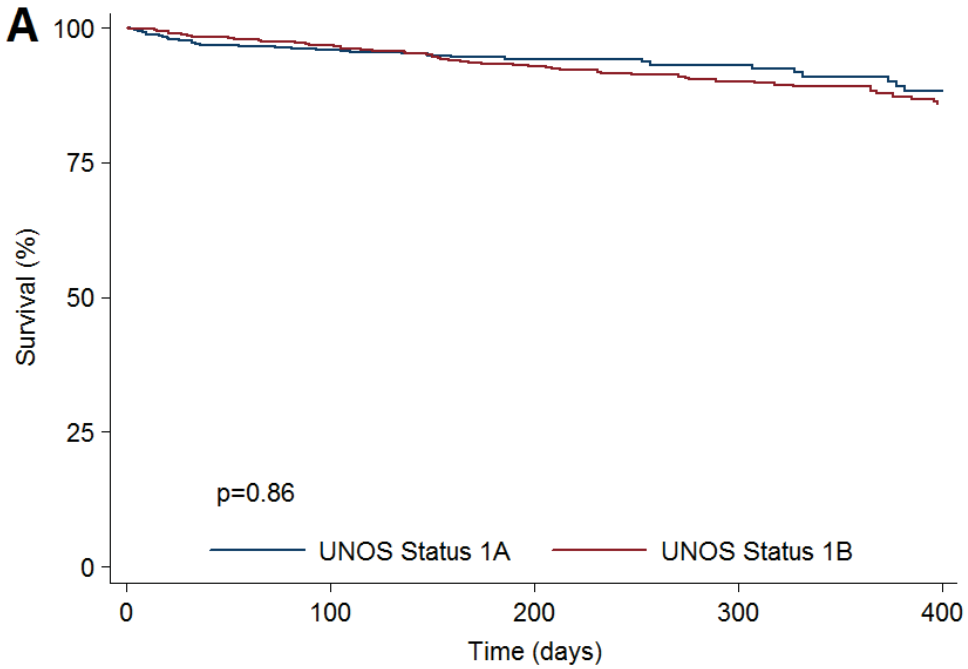
BIVADs=biventricular assist devices; CF-LVAD= continuous-flow LVAD; CI= confidence interval; CMP=cardiomyopathy; PAP=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure; PF-LVAD=pulsatile-flow LVAD; TAH=total artificial heart; UNOS=United Network for Organ Sharing. Hazard ratios, 95% CI and p values were generated using a Cox proportional hazard analysis. Multiple group comparisons were adjusted using the Holm procedure.

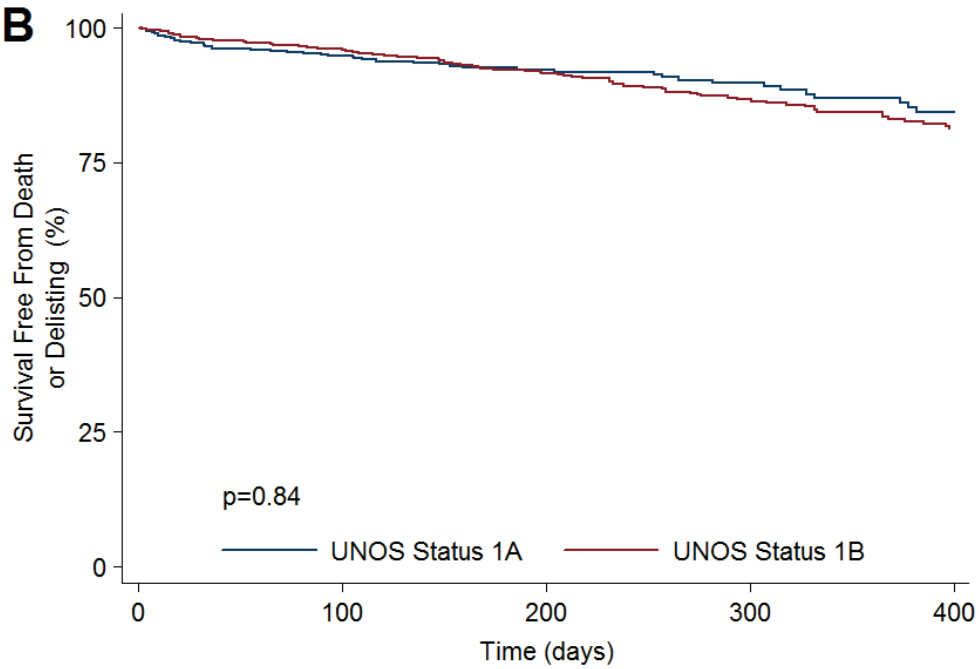
Supplemental Figure 1





Supplemental Figure 2





Supplemental Figure Legends

Supplemental Figure 1. Outcomes for heart transplant candidates requiring LVAD support on the UNOS waiting list stratified by their listing status as UNOS Status 1A or 1B in the first era. (A) Unadjusted waiting list survival and (B) unadjusted waiting list survival free from death or delisting due to worsening clinical status.

Supplemental Figure 2. Outcomes for heart transplant candidates requiring LVAD support on the UNOS waiting list stratified by their listing status as UNOS Status 1A or 1B in the current era. (A) Unadjusted waiting list survival and (B) unadjusted waiting list survival free from death or delisting due to worsening clinical status.

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Special Article

Lung and Heart Allocation in the United States

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Lung and heart allocation in the United States has evolved over the past 20–30 years to better serve transplant candidates and improve organ utilization. The current lung allocation policy, based on the Lung Allocation Score, attempts to take into account risk of death on the waiting list and chance of survival posttransplant. This policy is flexible and can be adjusted to improve the predictive ability of the score. Similarly, in response to the changing clinical phenotype of heart transplant candidates, heart allocation policies have evolved to a multitiered algorithm that attempts to prioritize organs to the most infirm, a designation that fluctuates with trends in therapy. The Organ Procurement and Transplantation Network and its committees have been responsive, as demonstrated by recent modifications to pediatric heart allocation and mechanical circulatory support policies and by ongoing efforts to ensure that heart allocation policies are equitable and current. Here we examine the development of US lung and heart allocation policy, evaluate the application of the current policy on clinical practice and explore future directions for lung and heart allocation.

Key words: Heart allograft, lung allograft, organ allocation, transplant waiting list, transplantation

Abbreviations: DSA, donation service area; ECMO, extracorporeal membrane oxygenation; HHS, Health and Human Services; HRSA, Health Resources and Services Administration; IABP, intraaortic balloon pump; ICU, intensive care unit; iPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; LAS, lung allocation score; LVAD, left-ventricular assist device; MCS, mechanical circulatory support; NOTA, National Organ Transplant Act; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; RRB, regional review board; RVAD, right-ventricular assist device; SRTR, Scientific Registry of Transplant Recipients; TAH, total artificial heart; UNOS, United Network for Organ Sharing; VAD, ventricular assist device.

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Introduction

The allocation of hearts and lungs for transplant in the United States involves distribution of a limited resource to a select few of the transplant candidates in need. The goals of lung allocation policies have evolved over the past three decades; the primary challenge now is to find methods that will allow equitable access to organs while maximizing the net benefit of transplant. Today, the Lung Allocation Score (LAS) is the primary determinant of candidate priority on the waiting list. Similarly, heart allocation has evolved over time. Since the first heart transplant was performed in 1967, the medical and surgical management of heart failure has changed dramatically, increasing survival among patients with heart failure and reducing morbidity and mortality among patients on the transplant waiting list. Concurrently, improved clinical management of heart transplant candidates has improved survival posttransplant. This overview does not discuss historical or current variances, but reviews the generally applied Organ Procurement and Transplantation Network (OPTN) national lung, then heart allocation policies.

Lung Allocation

History of lung allocation

The first lung transplant was performed by J.D. Hardy at the University of Mississippi in 1963; however, it would take 20 years before lung transplant was established as a treatment option for patients with end-stage pulmonary diseases (1). After the first transplant, refinement of the procedure proceeded slowly until the advent of cyclosporine in 1982; the emergence of this immunosuppressant

moved lung transplant beyond experimental medicine into mainstream therapy (2,3). After 1982, heart–lung and lung transplants were used to treat a growing number of pulmonary diseases and achieved substantially increased survival rates (4–6).

In 1984, Congress passed the National Organ Transplant Act (NOTA), which mandated creation of a national organ transplant organization to act as a registry and organ matching entity to monitor allocation across the United States. This Act led to creation of the OPTN to organize allocation policies and, later, the Scientific Registry of Transplant Recipients (SRTR) to monitor outcomes (7). The OPTN contract for day-to-day organ donation and waiting list management operations is carried by the United Network for Organ Sharing (UNOS) (8).

After the passage of NOTA, OPTN began tracking solid organ transplants, but lung transplants were included with the thoracic organs and were not separately monitored. In 1990, OPTN amended the thoracic organ policies to monitor lung allocation. Until 1995, lungs were allocated to candidates purely on the basis of time spent on the waiting list, blood type and geographic proximity of the donor to the candidate (9). Because mortality rates vary for different pulmonary conditions, the waiting-time-only allocation policy tacitly discriminated against candidates who were most likely to die while waiting for an organ. In 1995, to remedy this discrepancy, OPTN amended the allocation process to include a special dispensation for patients with idiopathic pulmonary fibrosis (IPF). This change gave candidates with IPF credit for an extra 90 days on the waiting list, in hopes that the extra time credit would expedite their access to organs. Despite this modification, overall waiting times continued to increase (10). Before long, more than half the candidates for transplant waited more than 2 years after listing to gain access to lungs. The dramatically increased waiting times meant that many candidates died while on the waiting list, and a disproportionate number of lungs were allocated to candidates with more stable diagnoses.

In 1999, 599 of the 4868 candidates on the waiting list died; this is a wait-list mortality rate of 190 deaths per 1000 patient-years at risk. The wait-list mortality rate was highest for diseases such as IPF (with a rate 70% higher than average at 323 deaths per 1000 patient-years) and lowest for diseases such as emphysema (114 deaths per 1000 patient-years at risk) (10). In part to address high wait-list mortality across all organs, the US Department of Health and Human Services (HHS) issued the Final Rule, effective March 16, 2000, to mandate development of organ allocation policies based on medical necessity rather than waiting time (11). As a result of this rule, OPTN created the Lung Allocation Subcommittee and charged it with developing an allocation process that would decrease the wait-list mortality rate and give access to organs to candidates most in need (12).

In 2005, OPTN approved the implementation of the LAS for lung allocation (13). The revised allocation policies removed the emphasis on waiting time and replaced it with a combination of geographic priority and the LAS, a calculation of illness severity and projected posttransplant survival that was intended to place the sickest candidates with the best chance of survival at the top of the waiting list. This was the first time "utility" of the transplant was included as part of an organ allocation policy (14; OPTN Policy 3.7.6.1). Adoption of the LAS decreased the size of the waiting list by reducing the incentive for early listing, and improved access to lungs for candidates at greatest risk of dying while on the waiting list.

The LAS-based allocation policy had a dramatic effect on lung transplantation trends in the United States. By 2006, the size of the waiting list had decreased from 2163 to 1031 candidates. The LAS also affected which candidates were gaining access to transplants. Patients with IPF underwent 23% of lung transplants performed each year before the LAS and more than 33% after the LAS (10). From its inception, the LAS was designed to be an evolving calculation, changing in response to altered cohort composition, improved therapies and identified gaps in the process.

Current lung allocation policies

In addition to the LAS, national lung allocation policy is based on geography, age and blood type (ABO) compatibility; other criteria, such as thoracic cavity size match, are considered at the local level. The LAS is calculated for all candidates aged 12 years or older. Geographic distribution remains a central consideration in organ allocation as a means of minimizing ischemic times. With a limited exception, lungs are first offered locally and then to candidates outside the local area, in defined zones extending from the donor hospital. Local is defined as within the organ procurement organization's (OPO) donation service area (DSA). OPTN/UNOS defines the zones as: A (within 0–500 miles, nonlocal), B (within 501–1000 miles), C (within 1001–1500 miles), D (within 1501–2500 miles) and E (>2500 miles) (14; OPTN Policy 3.7.2.). The predefined borders of DSAs may allow organs to initially be offered to candidates hundreds of miles from the transplant center, well beyond the extent of zone A. For example, lungs available in Minneapolis are first offered to candidates in the local DSA including Minnesota, North Dakota and South Dakota, but will not be offered to candidates across the Wisconsin border until zone A offers are made. This remains true despite the fact that a candidate in Wisconsin may be hundreds of miles closer to the organ than a candidate in western North Dakota (Figure 1).

Allocation of adult donor lungs

Lung allocation is first determined based on the age of the lung donor; adult donors are defined as aged 18 years or older. An organ from an adult donor is first offered to local wait-list candidates (Figure 2). Within the local area,

Figure 1: Lung transplant programs within each donor service area.

candidates aged 12 years and older have priority over children (aged 0–11 years), primarily because of thoracic size considerations. Of the local candidates aged 12 years or older, those who are ABO identical with the donor (Figure 2, bin 1) have priority over those who are nonidentical but ABO compatible (bin 2). The LAS is considered at this point, determining which of the local ABO identical candidates aged 12 years or older will be offered the lungs first. If none of those candidates accept the organ, it is offered to local ABO compatible candidates aged 12 years or older. If none of those candidates accept the organ, it is allocated to child candidates. Children are designated priority 1 or priority 2, based on severity of illness. Offers of adult lungs to children are made to priority 1 candidates first, then to priority 2 candidates. Offers are made to priority 1 local ABO identical children (bin 3), then to priority 1 local ABO compatible children (bin 4), priority 2 local ABO identical children (bin 5), and priority 2 local ABO compatible children (bin 6). If all offers within the local zone are turned down, the organ is offered in the same order to candidates in zone A, then sequentially to candidates in zones B, C, D and E. If the lungs are offered to a candidate who needs only one lung, the remaining lung is matched to another single-lung candidate (14; OPTN Policy 3.7.11).

Transplant centers are responsible for evaluating any determining factors not indicated or proscribed by the allocation policy. For example, considerations such as thoracic size, organ quality, and other factors are left up to the individual transplant center, surgeon and patient (14; OPTN Policy 3.7.1.1).

To ensure that LAS and illness severity are accurately assessed, lung transplant candidates must be up to date on all critical measures for predicting wait-list and posttransplant survival (Table 1). All noninvasive criteria are updated once in every 6-month interval following listing (14; OPTN Policies 3.7.6.3 and 3.7.6.3.2). If a measure that does not require clinical testing, such as functional status, is not updated during an interval, the candidate's LAS score reverts to zero until the measure is updated. Candidates with LAS of zero are screened from the organ matching process. Noninvasive clinical measures must also be updated during every 6-month interval or the measure will be replaced with the least beneficial value and the candidate's LAS will be recalculated using the substituted data. Ties between candidates are broken using accumulated active waiting time (14; OPTN Policy 3.7.9).

Allocation of adolescent donor lungs

Adolescent donors are defined as aged 12–17 years. Although the LAS is used to allocate organs to adolescent candidates much like adults, adolescent organs are

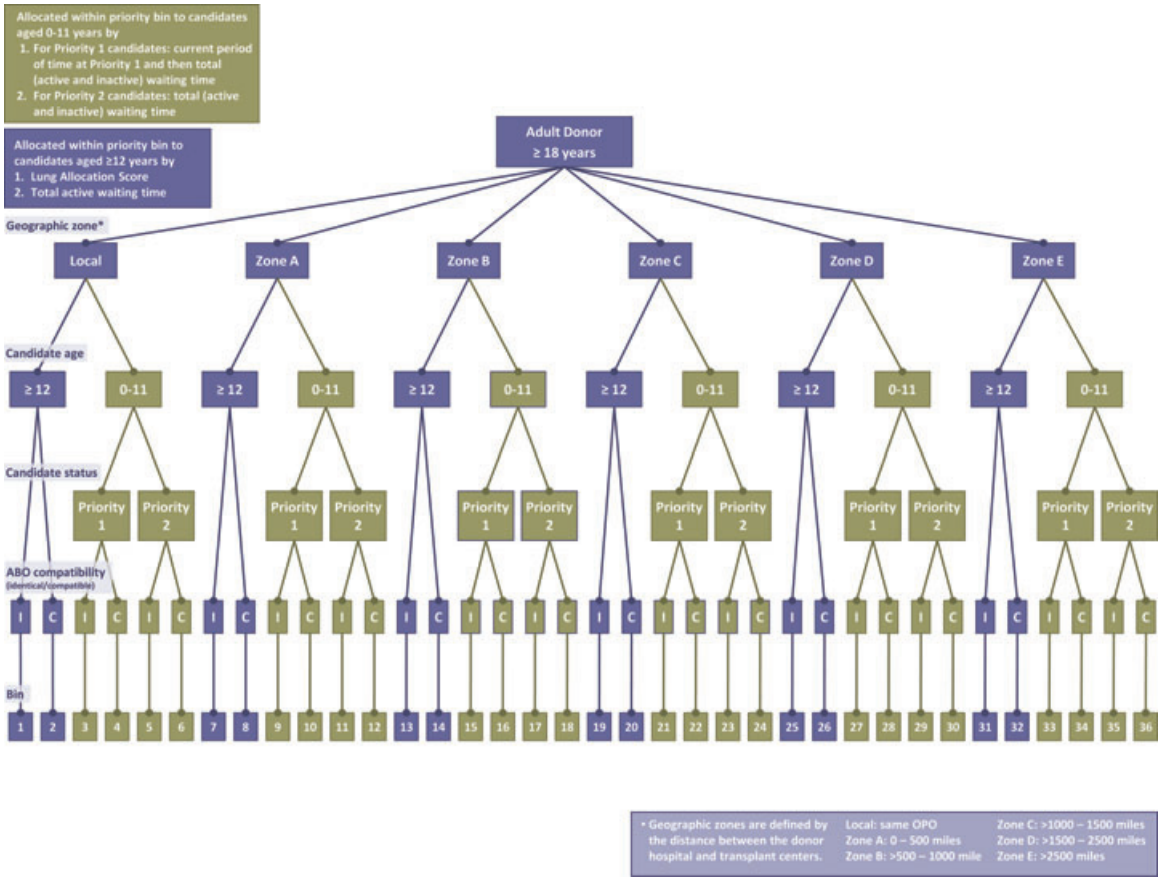

Figure 2: Allocation of adult donor lungs. This figure can be downloaded in color from www.srtr.org.

Table 1: Measures used to calculate the lung allocation score

Factors used to predict waiting list survival
Forced vital capacity (FVC)
Pulmonary artery systolic pressure (PA) for groups A, C and D[1]
O_2 required at rest for groups A, C and D
Age
Body mass index (BMI)
Diabetes
Functional status
6-min walk distance
Continuous mechanical ventilation
Diagnosis
PCO_2
Factors used to predict posttransplant survival
Forced vital capacity (FVC) for groups B and D
Pulmonary capillary wedge (PCW) pressure $\geq$ 20 for group D
Continuous mechanical ventilation
Age
Serum creatinine
Functional status
Diagnosis

[1] Group A, obstructive lung disease; Group B, pulmonary vascular disease; Group C, cystic fibrosis and immunodeficiency disorders; Group D, restrictive lung disease.

preferentially offered to adolescent candidates (Figure 3). When adolescent lungs become available, they are first offered to local candidates. The offer is first made to local ABO identical adolescent candidates, then to local ABO compatible adolescent candidates. If there are no suitable adolescent candidates in the local DSA, local child candidates are next in line. The lungs are offered to local adult candidates only if they have been turned down by all adolescent and child candidates in the local area. After the local candidate population has been exhausted, the lungs are offered in the same order to candidates in zones A, B, C, D and E (14; OPTN Policy 3.7.11.1).

Allocation of child donor lungs

For allocation purposes, child donors are defined as children aged 0–11 years. When the LAS-based allocation policy was implemented in 2005, children were excluded from the policy due to differences in diagnoses that made the LAS calculation inappropriate as a measure of medical urgency. Child candidates are ranked as priority 1 if they fulfill certain set criteria, or as priority 2 (Table 2; 14; OPTN Policy 3.7.6.2). Candidates who do not meet priority 1 criteria and are not inactive are designated priority 2. Qualified priority 1 candidates within a specific geographic zone are always

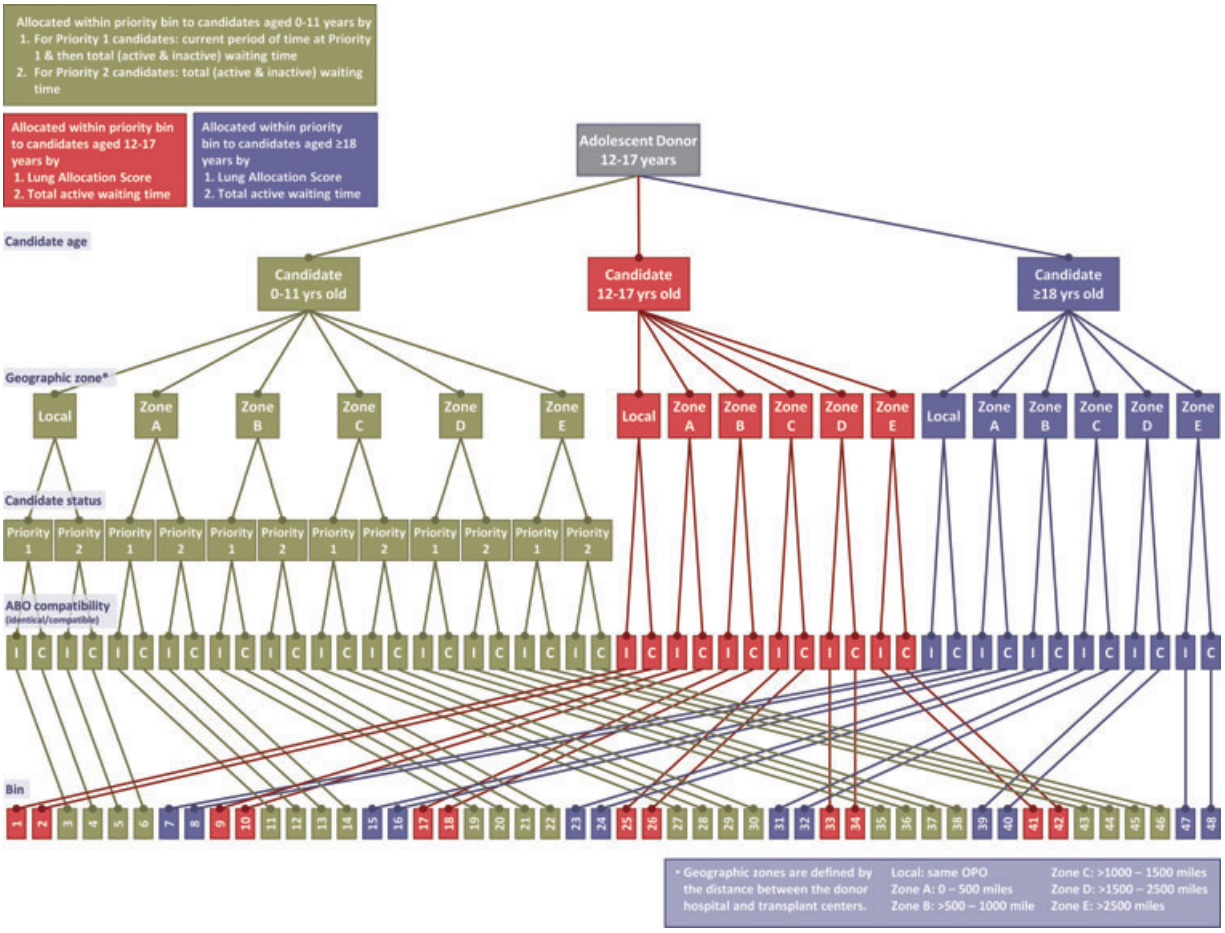

Figure 3: Allocation of adolescent donor lungs. This figure can be downloaded in color from www.srtr.org.

Table 2: Criteria for determining Priority 1 child candidates

Candidates must have one or more of the following:
Respiratory failure
Requiring continuous mechanical ventilation; OR
Requiring supplemental oxygen delivered by any means to achieve $FiO_2 > 50\%$ to maintain oxygen saturation levels > 90%; OR
Having an arterial or capillary $PCO_2 > 50$ mmHg or a venous $PCO_2 > 56$ mmHg
Pulmonary hypertension
Pulmonary vein stenosis involving three or more vessels; OR
Exhibiting any of the following, in spite of medical therapy:
Suprasystemic pulmonary artery pressure on cardiac catheterization or by echocardiogram estimate
Cardiac index < 2 L/min/m^2
Syncope or hemoptysis

ranked above priority 2 candidates. Within the priority rankings, candidates are ordered by ABO compatibility, then by waiting time. Waiting time for priority 1 candidates is defined as the time spent waiting as a priority 1 candidate since the most recent listing at priority 1. Priority 1 candidates cannot sum the total of all time spent waiting if they have multiple priority 1 periods. Total waiting time, defined as the sum of priority 1, priority 2 and inactive time, is used to break ties between priority 1 candidates (14; OPTN Policy 3.7.9.3). Priority 2 candidates are ranked by total waiting time. As always, the transplant center considers thoracic size, organ quality and other indicators when deciding if the organ is appropriate for transplant.

Just as with adult candidates, clinical data must be updated at least once in every 6-month interval (14; OPTN Policies 3.7.6.2 and 3.7.6.3). Failure to keep clinical data up to date will reduce a candidate's status from priority 1 to priority 2. Candidates remain at priority 2 as long as they are in need of an organ, unless they are removed from the list by the transplant center. The process of child donor lung allocation is illustrated in Figure 4.

When lungs become available from a child donor, they are preferentially offered to child candidates (ages 0–11 years). Due to the difficulty in finding a size match, this priority is

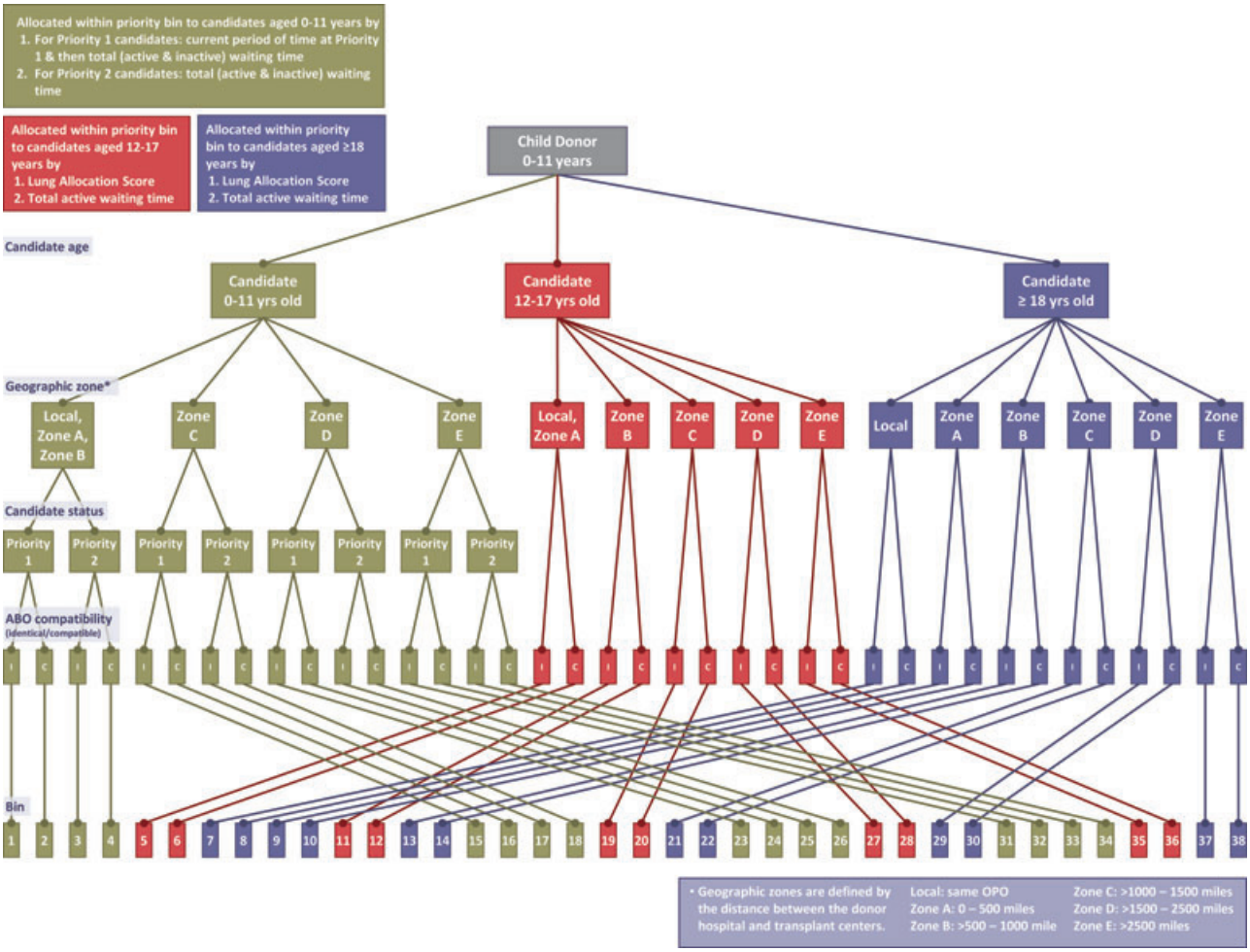

Figure 4: Allocation of child donor lungs. This figure can be downloaded in color from www.srtr.org.

critical to children on the waiting list. First, offers are made to child candidates from the local DSA, zone A, and zone B combined. Within that expanded geographic area, the first offer is made to a priority 1 ABO identical candidate (Figure 4, bin 1). If that offer is declined or there is no suitable candidate at that level, the next offer is made to a priority 1 ABO compatible candidate from the local area, zone A, or zone B (bin 2). Priority 2 candidates are offered the lungs if there are no suitable priority 1 candidates (bins 3 and 4). Successive offers are made to the following candidates in order: adolescent ABO identical candidates from the local area and zone A combined (bin 5), adolescent ABO compatible candidates from the local area and zone A (bin 6), adult ABO identical candidates from the local area (bin 7), adult ABO compatible candidates from the local area (bin 8), adult ABO identical candidates from zone A (bin 9) and adult ABO compatible candidates from zone A (bin 10). If there are no suitable candidates, the lungs are offered to adolescents in zone B (bins 11 and 12) and adults in zone B (bins 13 and 14) before being offered to child candidates in zone C (bins 15–18). If there are no acceptable child candidates in zone C, the organs will be offered to adolescents in zone C (bins 19 and 20), then to adults in zone C (bins 21 and 22). If no suitable candidates are identified, the order of offers in zone C is followed for zones D and E (bins 23–38) (14; OPTN Policy 3.7.11.1).

Allocation exceptions

The current allocation policy allows for special review of exceptional cases when the treating transplant team believes that the assigned LAS or priority level does not appropriately reflect the severity of the case, or when essential clinical values must be estimated to assign a score (14; OPTN Policy 3.7.6.4). Requests for exceptions to the standard scoring criteria are sent to the Lung Review Board through OPTN/UNOS. The Lung Review Board, a seven-member board selected from separate lung transplant centers, reviews all exception requests nationwide (15). The Board has 7 days to reach a decision about each case. If the exception is granted, the requested score or value applies for 6 months. If the candidate remains on the waiting list

6 months after being granted an exception, the request for exception must be renewed or the candidate's score will be recalculated according to the standard formulae (14; OPTN Policies 3.7.6.4, 3.7.6.1 and 3.7.6.3).

If the Lung Review Board denies the request for exception, the transplant center may appeal the decision. If the request is denied a second time, the transplant center has the option of overriding the decision of the Board. If the transplant center chooses to override the decision, the action will be reviewed by the OPTN/UNOS Thoracic Organ Transplantation Committee to determine if the center abused the override provision. If abuse is determined, the action may be referred to the Membership and Professional Standards Committee of OPTN/UNOS for evaluation (14; OPTN Policy 3.7.6.4).

The evolution of the LAS and future directions

The current LAS calculation was designed to be re-evaluated and refined as frequently as every 6 months. The first change to the LAS formula occurred in late 2008, when PCO_2 level was added to the LAS calculation (14,16; OPTN Policy 3.7.6.1 (b)). This parameter was added after analysis indicated that including PCO_2 values would increase the accuracy of the LAS in predicting wait-list mortality and posttransplant survival.

In 2008, OPTN approved the addition of bilirubin to the LAS calculation, although determining how bilirubin could be most effectively integrated into the calculation has taken some time (14,17; OPTN Policy 3.7.6.1 (c)). The proposed methodology for including bilirubin is expected to be factored in to LAS calculations sometime in 2012–2013. Although the bilirubin modification to the LAS will have little effect on most current transplant candidates, it will make a substantial difference for some candidates with idiopathic pulmonary arterial hypertension (iPAH), whose scores currently understate risk of death while on the waiting list.

The Lung Subcommittee of the OPTN/UNOS Thoracic Committee is in the process of developing and approving a revision to the LAS to improve the score's overall ability to predict wait-list mortality and posttransplant survival. This modification will include the already approved and developed bilirubin addition, and more comprehensive adjustments to the formula (18). The approval process to implement the fully revised LAS model has not been completed and the full effects of the final adjustments are not known. Modifications to the LAS calculation will continue as additional measures and criteria are determined to be predictors of waiting list and posttransplant outcomes. The required reviews of the formula have imparted flexibility that will allow the calculation to change with new criteria and changing candidate populations. Though the LAS assigned to an individual candidate may change based on evolving models, the mandate to decrease wait-list mortality and increase posttransplant survival will ensure that the candidates most in need will continue be prioritized on the waiting list.

Heart Allocation

History of heart allocation

We provide an overview of heart allocation policy evolution (Table 3) in response to changing trends in treatment and outcomes (including use of mechanical circulatory support [MCS] to stabilize critically ill patients awaiting transplant), historically, at present, and into the future. In the 1980s, OPTN assembled a policy review committee of heart surgeons and cardiologists, which became the Heart Transplant Committee. The Heart Transplant Committee expanded to include all thoracic organs in 1988, and in 1991 it became known as the Thoracic Organ Transplantation Committee. This committee primarily develops and monitors heart and lung organ allocation policies and reviews issues related to procurement and transplant, including the scientific, medical and ethical aspects. The committee is composed of regional representatives including physicians, surgeons or transplant coordinators; transplant hospital and OPO representatives; and at least one public or patient representative (e.g. a transplant candidate or recipient or a family member). Additional monitoring oversight is provided by the regional review boards (RRBs), which evaluate regional requests to list candidates as Status 1A or 1B by exception. Generally composed of transplant surgeons, physicians and coordinators, RRBs evaluate the appropriateness of exceptions on the basis of clinical information and compliance with OPTN policies.

To initially list a heart transplant candidate as Status 1A or 1B or to extend Status 1A time, the transplant center must submit a heart Status 1A or 1B justification form. OPTN is responsible for "the development, monitoring, enforcement and modification of the policies that govern the allocation, procurement and the transportation of deceased organs" (19). Policies under OPTN jurisdiction are outlined in detail in the Code of Federal Regulations (Final Rule) Part 42, section 121.4, and in the OPTN bylaws (20). Policy development is a collaborative process between OPTN, the transplant community, and the public. Any interested party may forward proposals for policies directly to the Committee Chair or via other representatives. Although time-limited variances may be established for experimental policies that test methods of improving allocation, most policy changes undergo lengthy evaluation and comment before implementation (20). When heart allocation policy changes are required or requested, the Thoracic Committee develops a proposal using data provided by UNOS and/or SRTR. Performance indicators and additional analyses may also be requested to measure the effect of the proposed changes. Required analyses may include the effect on various transplant programs due to transplant volume, risk-adjusted total life-years pre- and posttransplant, risk-adjusted waiting time and OPO performance. If the

Table 3: Summary of major changes to heart allocation policy

Date	Policy change
1988	Approved primary allocation criteria for hearts: medical urgency status; waiting time; distance of donor to recipient hospital and identical blood groups unless medical urgency dictated otherwise.
	Approved 2 medical urgency categories: Status 1 (candidates implanted with MCS device or admitted to ICU and requiring inotropic support) and Status 2 (all other candidates).
	Approved geographic zones A, B and C, comprising concentric circles with the donor hospital at the center (zone A, within 500 miles of the donor hospital; zone B within 1000 miles; zone C beyond 1000 miles).
	Permitted local OPOs to allocate hearts to potential recipients at local transplant programs on the basis of the primary allocation criteria.
	Permitted the Heart Transplant Committee, Organ Procurement and Distribution Committee, and Board of Directors to resolve local-level inequities or conflicts regarding donor heart distribution arising from prevailing OPO boundaries or policies.
	Established essential and desirable data needed for each heart offer.
1989	Required OPOs to apply to the Heart Transplant Committee to establish a variance.
	Prohibited inter-OPO sharing of hearts.
	Included allocation of lungs in the existing heart allocation criteria.
	Prohibited heart or heart–lung candidates from accruing waiting time while inactive on the waiting list.
1990	Enabled candidates aged $<$ 6 months to be categorized Status I.
	Changed "heart" to "thoracic organ" in the policy dictating the minimum data requirements for thoracic organ offers.
	Removed requirement to confirm blood typing of thoracic organs in the policy dictating the minimum data requirements for thoracic organ offers because rerunning the test is redundant.
1991	Required that heart and lung be recovered from a deceased donor if these organs could be transplanted.
	Made the host OPO responsible for appropriate donor management to assure recovery of multiple thoracic organs when possible.
1992	Permitted registration of *in utero* candidates on the waiting list.
1993	Permitted candidates to receive the waiting time accrued for 1 thoracic organ when listed for a second thoracic organ.
	Permitted a candidate to transfer waiting time for multiple thoracic organ transplant to a single thoracic organ.
	Required transplant programs to list candidates needing heart and liver transplants as two separate waiting list registrations.
	Created a joint heart–liver allocation policy that: (1) required the OPO to offer a heart and liver from a deceased donor to a joint heart–liver candidate if the donor and candidate were in the same local area and (2) recommended that OPOs voluntarily share the second required organ (heart or liver) if the candidate and the deceased donor were not in the same local area.
	Restricted accrual of Status 1 time to the period when the candidate was listed as Status 1.
	Allowed a candidate to carry over time accrued at Status 1 to Status 2.
1994	Required reporting of hepatitis B and C data for all thoracic organs offered.
	Stratified heart–lung match runs by acceptable donor height instead of donor weight.
	Required reporting of echocardiogram data, if the donor hospital has the facility to perform it, for all thoracic organs offered.
	Required all thoracic organ transplant centers within an OPO and the OPO to agree to prioritize a sensitized thoracic candidate for an organ offer.
1999	Prioritized pediatric candidates for receiving adolescent deceased donor heart offers.
	Prohibited use of an adult or pediatric candidate's level of sensitization as a reason for listing that candidate as Status 1A by exception.
	Permitted an adult or pediatric candidate's transplant center to determine the candidate's sensitization level.
	Implemented heart medical urgency Statuses 1A, 1B and 2 for adult and pediatric candidates.
	Assigned Status 1A to candidates with uncomplicated VADs for $\leq$ 30 days and admitted to the listing transplant center.
	Assigned Status 1A to candidates with complicated MCS for $>$ 30 days.
	Required submission of a heart Status 1A justification form to the OPTN contractor within 24 h of listing or recertification as Status 1A.
	Created the primary blood group matching system still in use.
	Allocated deceased donor hearts to local Status 1A, 1B and 2 candidates before offering them to Status 1A and 1B candidates in zones A and B (Status 2 candidates in zones A and B received deceased donor heart offers after Status 1A and 1B candidates in zones A and B).
	Dissolved variances that existed until this time, but participants in the dissolved variances could reapply in cases of need for alternative local allocation systems.
	Allowed adult and pediatric candidates to be listed as Status 1B by exception.
	Enabled adult and pediatric candidates in need of both a heart and lung to appear on lung match runs.
	Allowed for allocation of domino donor hearts.
2000	Required that RRBs approve extensions of Status 1A by exception listings, beyond an extra 7 days for adult and an extra 14 days for pediatric candidates.

Continued

Table 3: Continued

Date	Policy change
2001	Allowed submission of heart status justification forms via UNet.
	Lowered status to 1B automatically upon conclusion of a candidate's permitted time at a Status 1A criterion, unless the candidate's physician recertified Status 1A listing.
2002	Allowed candidates implanted with VADs to receive 30 days of time at Status 1A, regardless of admission to the listing center.
	Classified as blood type "Z" candidates listed *in utero* or able to accept an ABO-incompatible deceased donor heart offer.
	Allowed candidates aged < 1 year to receive ABO-incompatible deceased donor heart offers but only after these hearts were offered to ABO-compatible candidates.
	Allowed candidates *in utero* to receive deceased donor hearts after all born candidates.
2003	Created the geographic zone D for thoracic organ allocation.
2005	Removed inpatient requirement for adult candidates listed as Status 1A by criterion (b).
2006	Modified the heart allocation sequence so adult local and zone A Status 1A and 1B candidates receive heart offers from deceased donors aged 0–11 years and adult deceased donors before local Status 2 candidates; zone B Status 1A and 1B candidates receive these heart offers before zone A and B Status 2 candidates.
	Dissolved all programmed heart variances.
2007	Defined zone D as the geographic area 1500–2500 miles, inclusive, from the donor hospital.
	Created the geographic zone E, > 2500 miles from the donor hospital.
2009	Prioritized pediatric candidates to receive pediatric (ages 0–17 years, inclusive) deceased donor hearts.
	Combined local and zone A geographical areas for broader geographic sharing of pediatric donor hearts.
2010	Increased the maximum age for listing pediatric candidates for ABO-incompatible hearts from 1 to 2 years.
	Required isohemagglutinin titer data entry for all born candidates eligible to receive an ABO-incompatible heart offer, and set isohemagglutinin titer and treatment-based eligibility restrictions for ABO-incompatible transplants.
	Created an interim policy for adult, outpatient candidates implanted with TAHs allowing these candidates to be listed as Status 1A for 30 days.
2011	Required OPOs to provide human leukocyte typing of thoracic organs offered if requested to do so by the transplant programs receiving the organs offered.
	Codified the process whereby RRBs examine and approve requests to list candidates as Status 1A for device-related infection or complications not detailed in policy.
	Dissolved the Status 1 listing verification policy, as it was no longer current.
	Extended for 1 year the interim policy for outpatient candidates implanted with TAHs.
	Removed identification of specific inotropic agents from the adult heart policy, because the OPTN contractor maintains an updated list of these medicines in UNet.

ICU = intensive care unit; MCS = mechanical circulatory support; OPO = organ procurement organization; OPTN = Organ Procurement and Transplantation Network; RRB = Regional Review Board; TAH = total artificial heart; VAD = ventricular assist device.

proposal involves a substantive change in policy, the Committee distributes the proposal for public comment for a maximum of 45 days. Policy proposals that require immediate action due to patient health and safety concerns, that clarify or correct existing policy rather than substantively change it, or are administrative in nature do not require public comment (19). When the public comment period ends, the Committee submits a briefing document, including its responses to public comments and its final recommendations, to the Board of Directors, which then votes on the policy. Policies approved by the Board and recommended for enforcement as mandatory are forwarded to the Secretary of HHS for review and comment a minimum of 60 days before implementation, in accordance with OPTN Final Rule Section 121.4(b) (19). Mandatory policies cannot be enforced without the Secretary's approval. The Secretary may solicit guidance from the Advisory Committee on Organ Transplantation and elect to publish proposed policies in the Federal Register for public comment before approval (20). OPTN provides the Secretary and the membership with copies of its policies as they are adopted and publishes current and pending policies on the Internet for public access. OPTN heart allocation policies are re-evaluated periodically by the Thoracic Committee to determine whether they achieve their stated objectives and remain relevant in light of scientific and technological advances (19).

The overarching goal of heart allocation policy is to prioritize organ allocation to the most critically ill heart transplant candidates, as evidenced by the current urgency-based algorithm and ongoing policy deliberations. Over the past two decades, as the clinical profile of end-stage heart failure patients has evolved, heart allocation policies have similarly evolved. The original heart allocation system approved in 1988 was a two-tiered policy using medical urgency codes that applied to adult and pediatric candidates. Regional variances were allowed but required approval by the Heart Transplant Committee (Report of the Heart Transplant Committee to the Board of Directors, February 28, 1989). Hearts were allocated based on medical urgency code and time, first within the DSA, then within the OPO region and subsequently to the rest of the United States (20).

In 1989, the Heart Transplant Committee implemented the new allocation algorithm using only two tiers for medical urgency, Status 1 and Status 2. This policy, in effect until 1999, applied to adult and to pediatric candidates. Status I defined patients who required MCS, including total artificial heart (TAH), ventricular assist device (VAD), intraaortic balloon pump (IABP) or ventilator support; candidates in an intensive care unit (ICU) and requiring inotropes; and, in the one pediatric-specific consideration, candidates aged <6 months. All other actively listed heart transplant candidates were designated Status 2. Although this policy was an improvement over the prior system, it did not include in the highest urgency category other critically ill adult patients, such as those with untreatable, life-threatening arrhythmias or those in whom MCS or inotropes were contraindicated (20).

In 1999, OPTN implemented a major policy change that assigned higher priority to sicker Status I patients whose short-term survival was compromised. Medical urgency was expanded to three tiers (Status 1A, 1B, and 2). The highest urgency category (1A) required that candidates be admitted to the transplant center. Candidates whose life expectancy was <7 days could be listed and recertified as Status 1A after review by the RRB and Thoracic Organ Transplantation Committee. Candidates with VADs (and no VAD complications) for more than 30 days and candidates on continuous inotropes qualified for Status 1B. This new allocation scheme decreased median waiting times for Status 1A and 1B patients compared with prepolicy Status I patients, and decreased wait-list mortality (21).

The 1999 heart allocation policy change also established criteria for pediatric candidates (aged 0–17 years at the time of listing) and mandated that within each status category, adolescent donor hearts (ages 11–17 years) would be offered preferentially to pediatric candidates in an effort to improve wait-list survival (14,20,22). The preferential allocation to pediatric candidates resulted in more adolescent donor hearts being transplanted into pediatric recipients (23). Young donor hearts (ages 0–10 years), however, continued to be allocated according to the algorithm for adult donor hearts. As part of the broader geographic sharing initiative, the pediatric policy was revised in 2008 and implemented in 2009. This revision preferentially allocated *all* pediatric donor hearts (ages 0–17 years) to pediatric candidates and used the pediatric distribution sequence for all pediatric donor hearts rather than the adult distribution scheme for younger hearts as in the previous policy.

Monitoring oversight of Status 1A listings increased with the establishment of RRBs in 1999 and the requirement that Status 1A justification forms be completed by the transplanting center to justify a candidate's listing as 1A, which replaced random ICU audits under the previous policy. Increased oversight improved compliance with Status 1A listing policies (23). Table 4 lists the major adult and pediatric heart allocation policy changes, 1988 through 2011.

Adult candidates implanted with VADs

Early MCS devices improved survival over medical therapy, but were associated with significant device- and procedure-related complications and lacked durability (24). Newer devices have substantially fewer complications and improved durability compared with their predecessors. Heart allocation policies have kept pace with changes in VAD development and have been adjusted accordingly.

Under the 1989 policies, transplant candidates with VADs were categorized as Status I due to lack of durability of the devices and high complication rates. Beginning in 1999, candidates with VADs could be listed as Status 1A only if the device had been implanted for ≤30 days or for >30 days if a device-related complication occurred, such as thromboembolism, infection or mechanical failure. Candidates with TAH, IABP, extracorporeal membrane oxygenator (ECMO), mechanical ventilation or high dose inotropes also qualified for Status 1A. To minimize VAD-associated complications, candidates with left and/or right VADs (LVAD/RVAD) were upgraded to Status 1A for 30 days immediately after implantation regardless of medical stability or appropriateness for a second surgery.

In June 2002, OPTN discontinued the policy requiring Status 1A time to be accrued immediately after VAD implantation. As a result, candidates with VADs can be listed as Status 1A for 30 days any time after VAD implantation. The 2002 policy did not require that VAD patients be hospitalized to be listed as Status 1A, allowing VAD patients to stabilize before listing to minimize perioperative and post-transplant complications.

Pediatric candidates implanted with VADs

The 1999 changes to the pediatric heart allocation policy allowed pediatric candidates implanted with VADs or other MCS devices, including ECMO, to qualify for listing as Status 1A. Admission to the listing transplant center was not and is not required. No major policy change has occurred in this category since 1999.

Geographic sequence for organ distribution

Under early policies, heart allocation first occurred locally within the DSA or an approved alternative local unit. DSAs are geographic units served by an OPO. If no local recipient was identified, the donor heart was allocated to one of three zones defined by concentric circles of 500 nautical miles with the donor hospital at the center; zone A is within 500 miles of the donor hospital, zone B > 500–1000 miles, and zone C > 1000 miles. The zones were established to facilitate coordination and to minimize ischemic time.

The sequence of allocation has undergone revision to prioritize organs to the most critically ill heart transplant candidates (Table 5). In the 1999 revision, organs were offered to local Status 1A, 1B and 2 candidates before being offered to candidates in zones A, B or C. A consequence

Table 4: Comparison of historical and current heart allocation policies[1]

Component	Policies		
	1989–1999	1999	Current
Medical urgency	2-tiered, Status 1 and 2	3-tiered, Status 1A, 1B and 2	Status 1A, 1B and 2
Geographic sequence	Local, zone A, zone B, zone C	Local, zone A, zone B, zone C	Adult donors: OPO Status 1A, 1B; zone A Status 1A, 1B; local Status 2 (Figure 5). Pediatric donors: combined OPO and zone A Status 1A pediatric; OPO Status 1A adult; OPO + zone A Status 1B pediatric; OPO Status 1B adult; zone A Status 1A, zone A Status 1B (Figure 6).
ABO blood type	Identical/compatible not differentiated for Status 1; differentiated for Status 2, identical prioritized for Status 2	Primary ABO prioritized before secondary ABO within each Status category	Primary ABO prioritized before secondary ABO within each status category; allocation to candidates eligible to receive a heart from any blood type donor after allocation to all compatible blood types
Time waiting	Status 1 time = Status 1 time; Status 2 time = Status 1 + Status 2 time	Status 1A time = Status 1A time; Status 1B time = Status 1A + 1B time; Status 2 time = Status 1A + 1B + 2 time	Status 1A time = Status 1A time; Status 1B time = Status 1A + 1B time; Status 2 time = Status 1A + 1B + 2 time
Heart–lung	Separate category, allocated after Status 1 heart	May be on both heart and lung lists; lungs go with heart or heart goes with lungs if no Status 1A heart candidate	May be on both heart and lung lists; lungs go with heart or heart goes with lungs if no Status 1A heart candidate
Pediatric considerations	Age < 6 months may be Status 1	Separate urgency criteria, preference to pediatric recipient for adolescent donor	Separate urgency criteria, preference to pediatric candidate for pediatric donor
Sensitized patients	Local agreement	Local agreement	Local agreement
Monitoring issues	Status 1 random audits of ICU location	Regional review boards for assignment of status; random audits of justification forms	Regional review boards for exceptions to Status 1A and 1B; random audits for Status 1A and Status 1B justification forms

OPO = organ procurement organization.
Status 1, candidates requiring total artificial heart, left or right ventricular assist device, intraaortic balloon pump, ventilator, or in intensive care unit requiring inotrope therapy; Status 2, all other actively listed candidates. Geographic zones: Local, donation service area; zone A, < 500 nautical mile radius of donor hospital; zone B, 500-< 1000 miles; zone C, 1000–1500 miles; zone D, 1501–2500 miles; zone E > 2500 miles. Pediatric heart donor is defined as age < 18 years; pediatric heart candidate is defined as age < 18 years at the time of listing. Primary ABO compatibility includes all four identical combinations (O donor/O candidate, A donor/A candidate, B donor/B candidate, AB donor/AB candidate) and O donor/B candidate, A donor/AB candidate, and B donor/AB candidate; secondary ABO compatibility includes O donor/A candidate and O donor/AB candidate; ABO identical includes O donor/O candidate, A donor/A candidate; B donor/B candidate, AB donor/AB candidate; ABO compatible includes O donor/A, B, or AB candidate and A donor/O candidate, B donor/O candidate.
[1]Adapted from Renlund et al. (20).

of this allocation sequence was that local Status 2 candidates would be offered a compatible donor heart ahead of Status 1A or 1B candidates in zone A or B. The sequence was revised in 2006; under the new policy, hearts could be offered to Status 1A and 1B candidates in zone A before being offered to Status 2 local candidates. This policy change affected adult and young pediatric (ages 0–10 years) donor hearts.

In 2008, the Pediatric Transplantation Committee proposed a new allocation sequence to reduce wait-list mortality in younger patients and to expedite allocation of young donor hearts (ages 0–10 years) to pediatric patients. The new sequence, implemented in 2009, mandated that all pediatric donor offers be allocated first to combined local and zone A pediatric Status 1A candidates, then to local adult Status 1A candidates, then to combined local and zone A pediatric Status 1B candidates, before being offered to adult and pediatric candidates according to the prior algorithm (Table 5).

Blood group considerations

In the 1989 system, ABO identical and ABO compatible were considered equal for Status 1 patients. A Status 1 candidate whose blood group was identical to a donor's received the same consideration as a candidate whose blood group was compatible. For Status 2 candidates within a specified geographic zone, ABO identical received priority over ABO compatible. Consequently, waiting times for blood group O candidates increased substantially

Table 5: Evolution of the heart allocation sequence

January 1999–June 2006	Current Adult Heart Sequence[1]	Current Pediatric Heart Sequence
	1. OPO Status 1A ABO primary candidates	1. Combined OPO and zone A Status 1A ABO primary pediatric candidates for pediatric donor
1. Local Status 1A	2. OPO Status 1A ABO secondary candidates	2. Combined OPO and zone A Status 1A ABO secondary pediatric candidates for pediatric donor
2. Local Status 1B	3. OPO Status 1B ABO primary candidates	3. OPO Status 1A ABO primary candidates
3. Local Status 2	4. OPO Status 1B ABO secondary candidates	4. OPO Status 1A ABO secondary candidates
		5. OPO + zone A Status 1B ABO primary pediatric candidates for pediatric donor
	5. Zone A Status 1A ABO primary candidates	6. OPO + zone A Status 1B ABO secondary pediatric candidates for pediatric donor
	6. Zone A Status 1A ABO secondary candidates	7. OPO Status 1B ABO primary candidates
4. Zone A Status 1A	7. Zone A Status 1B ABO primary candidates	8. OPO Status 1B ABO secondary candidates
5. Zone A Status 1B	8. Zone A Status 1B ABO secondary candidates	9. Zone A Status 1A ABO primary candidates
	9. OPO Status 2 ABO primary candidates	10. Zone A Status 1A ABO secondary candidates
6. Zone B Status 1A	10. OPO Status 2 ABO secondary candidates	11. Zone A Status 1B ABO primary candidates
7. Zone B Status 1B	11. Zone B Status 1A ABO primary candidates	12. Zone A Status 1B ABO secondary candidates
	12. Zone B Status 1A ABO secondary candidates	13. OPO Status 2 ABO primary pediatric candidates for pediatric donor
8. Zone A Status 2	13. Zone B Status 1B ABO primary candidates	14. OPO Status 2 ABO secondary pediatric candidates for pediatric donor
	14. Zone B Status 1B ABO secondary candidates	15. OPO Status 2 ABO primary candidates
	15. Zone A Status 2 ABO primary candidates	16. OPO Status 2 ABO secondary candidates
	16. Zone A Status 2 ABO secondary candidates	17. Zone B Status 1A ABO primary pediatric candidates for pediatric donor
	17. Zone B Status 2 ABO primary candidates	18. Zone B Status 1A ABO secondary pediatric candidates for pediatric donor
9. Zone B Status 2	18. Zone B Status 2 ABO secondary candidates	19. Zone B Status 1A ABO primary candidates
	19. Zone C Status 1A ABO primary candidates	20. Zone B Status 1A ABO secondary candidates
	20. Zone C Status 1A ABO secondary candidates	21. Zone B Status 1B ABO primary pediatric candidates for pediatric donor
10. Zone C Status 1A	21. Zone C Status 1B ABO primary candidates	22. Zone B Status 1B ABO secondary pediatric candidates for pediatric donor
11. Zone C Status 1B	22. Zone C Status 1B ABO secondary candidates	23. Zone B Status 1B ABO primary candidates
12. Zone C Status 2	23. Zone C Status 2 ABO primary candidates	24. Zone B Status 1B ABO secondary candidates
	24. Zone C Status 2 ABO secondary candidates	25. Zone A Status 2 ABO primary pediatric candidates for pediatric donor
		26. Zone A Status 2 ABO secondary pediatric candidates for pediatric donor
		27. Zone A Status 2 ABO primary candidates
		28. Zone A Status 2 ABO secondary candidates
		29. Zone B Status 2 ABO primary pediatric candidates for pediatric donor
		30. Zone B Status 2 ABO secondary pediatric candidates for pediatric donor
		31. Zone B Status 2 ABO primary candidates
		32. Zone B Status 2 ABO secondary candidates
		33. Zone C Status 1A ABO primary pediatric candidates for pediatric donor
		34. Zone C Status 1A ABO secondary pediatric candidates for pediatric donor
		35. Zone C Status 1A ABO primary candidates
		36. Zone C Status 1A ABO secondary candidates
		37. Zone C Status 1B ABO primary pediatric candidates for pediatric donor
		38. Zone C Status 1B ABO secondary pediatric candidates for pediatric donor
		39. Zone C Status 1B ABO primary candidates
		40. Zone C Status 1B ABO secondary candidates
		41. Zone C Status 2 ABO primary pediatric candidates for pediatric donor
		42. Zone C Status 2 ABO secondary pediatric candidates for pediatric donor
		43. Zone C Status 2 ABO primary candidates
		44. Zone C Status 2 ABO secondary candidates

OPO = organ procurement organization.
Zone D was added in 2003 and zone E in 2007.
[1]At implementation, this policy applied to adult donors and young pediatric donors but not to adolescent donors. In May 2009, when the pediatric donor policy was modified, this policy applied only to adult donors.

between 1988 and 1995 (20). The 1999 revisions attempted to rectify this by prioritizing blood group O hearts first to blood group O or B recipients (primary ABO matching), irrespective of waiting time for other potentially compatible blood groups. Other primary ABO matching categories included the following: blood type A donors were prioritized to blood type A or AB recipients; blood type B donors to type B or AB recipients and blood type AB donors to type AB recipients. Other compatible pairs, O donor/A candidate or O donor/AB candidate, were considered secondary ABO matching pairs. This prioritization scheme applied to each urgency category and geographic zone. Policy for ABO-incompatible (ABO-I) heart transplant was established by OPTN in 2001 (25,26); hearts were allocated to infants aged <1 year listed for ABO-I heart transplant only if no ABO compatible candidate nationwide accepted the donor heart.

Current heart allocation policies

Current heart allocation policy reflects an effort to prioritize hearts to the sickest heart transplant candidates on the waiting list, while taking into account technological advances that have changed the clinical profile and prognosis. This is supported by recent revisions to the policy and ongoing proceedings attempting to provide more granularity to the current medical urgency criteria. US heart allocation policy is based on medical urgency, waiting time, blood group compatibility and geography. The most important recent revision to heart allocation policy occurred in 2006, when the geographic sequence was modified, prioritizing the most critically ill patients while taking into account optimal maximal ischemia time. Changing VAD technology and effective heart failure therapies have introduced a new level of medical and ethical complexity to the discussion of allocation policies, and the current policy is being reviewed and revisions considered that would reflect emerging technology and changing wait-list survival and posttransplant outcomes.

Medical urgency status (OPTN Policies 3.7.3 and 3.7.4)

Adult criteria: Adult heart transplant candidates qualify for a status code corresponding to medical urgency. Status 1A, the highest medical urgency code, has 4 subcategories (Table 6). Status 1A candidates must be admitted to the listing transplant center, except for LVAD/RVAD candidates, who qualify for 30 days as Status 1A (subcategory a (i)), and candidates with device complications (subcategory b). Status 1A candidates must meet one of the four criteria outlined in Table 6 (Policy 3.7.3).

Qualification for Status 1A under subcategories a–c (with the exception of a (i)) is valid for 14 days and must be recertified every 14 days from the time of initial listing. Qualification for Status 1A under subcategory d is valid for 7 days and must be recertified every 7 days. Centers are notified of the need for recertification and unless the criteria are recertified, candidates are automatically reclassified to Status 1B (9).

LVAD/RVAD candidates and candidates on continuous intravenous inotrope infusion who do not meet Status 1A criteria qualify for Status 1B. These candidates are not required to be admitted to the transplant center or to be using high-dose inotrope infusion. Candidates who do not meet criteria for Status 1A or 1B may be listed as Status 2. Those who are temporarily unsuitable for receiving an organ are listed as Status 7 (inactive) and will not receive organ offers.

Pediatric criteria: Pediatric candidates (aged <18 years) qualify for listing as Status 1A for 14 days under five criteria (Table 7). After 14 days from the initial listing, the candidate is automatically downgraded to Status 1B, unless the attending physician recertifies the 1A listing. A heart Status 1A justification form must be submitted to UNet^{SM} for new Status 1A candidates, and for extension of current Status 1A candidates. The pediatric policy is similar to the adult policy but provides two additional criteria: 1A (d) addresses candidates who qualify for Status 1A if they are infants aged <6 months with acquired or congenital heart disease and reactive pulmonary hypertension (>50% of systemic level); 1A (f) addresses candidates who qualify for Status 1A if the life expectancy is <14 days without heart transplant (e.g. refractory arrhythmia) and do not meet criteria for Status 1A (a), (b), (c), (d) or (e). Pediatric candidates who are receiving a single inotrope (dopamine or dobutamine) in low dosage, are aged <6 months and do not fulfill the criteria of Status 1A, or have growth failure (defined as <1.5 standard deviations of expected growth or greater than fifth percentile for height and/or weight) qualify as Status 1B. Candidates who do not meet criteria for Status 1A or 1B are listed as Status 2, and candidates who are temporarily unsuitable to receive a thoracic organ transplant are listed as Status 7. Pediatric heart transplant candidates who remain on the waiting list at the time of their eighteenth birthdays without having undergone heart transplant continue to qualify for medical urgency status based on the pediatric criteria. There is no policy requirement that pediatric candidates be hospitalized or receiving hemodynamic monitoring to qualify for Status 1A.

Status exceptions (OPTN Policy 3.7.3)

Candidates who do not meet criteria for Status 1A or 1B but have documented need for urgent listing may qualify for an exception. Transplant physicians must submit a status justification form to the RRB describing the rationale for the exception. Candidates may be listed as Status 1A or 1B by exception whereas the RRB reviews the status justification. If the RRB does not approve the exception, the physician may list the candidate as Status 1A or 1B while awaiting an appeal to the Thoracic Organ Transplantation Committee. Adult candidates considered for Status 1A

Table 6: Adult candidate status 1A and 1B (OPTN Policy 3.7.3)

Status	Subcategory	Qualifications	Comments
1A		Candidate should be admitted to the hospital where the heart transplant is to be performed and should be managed with one of the following therapies or devices:	
	(a)	MCS for acute hemodynamic decompensation and at least one of:	
		(i) LVAD/RVAD	Candidates may be listed for 30 days as 1A at any point, hospitalization not required.
		(ii) TAH	
		(iii) IABP	
		(iv) ECMO	Qualification under criterion 1A(a)(ii), (iii) or (iv) is valid for 14 days and must be recertified to extend 1A Status.
	(b)	MCS with objective medical evidence of significant device-related complications (infection, thromboembolism, ventricular arrhythmias, mechanical failure, other related complications) approved by heart RRB.	Admission to listing center not required.
	(c)	Continuous mechanical ventilation.	Qualification under criterion 1A(b) or (c) is valid for 14 days and must be recertified every 14 days to extend 1A Status.
	(d)	Continuous infusion of single or multiple inotropes in addition to hemodynamic monitoring.	Qualification under 1A(d) is valid for 7 days and must be recertified every 7 days to extend 1A Status.
1A exception		Candidates who do not meet the above criteria	Initial listing requires approval by the RRB and is valid for 14 days. Further extension requires review and approval by the RRB.
1B		At least one of the following devices or therapies:	
	(aa)	LVAD/RVAD	
	(bb)	Continuous infusion of intravenous inotropes	
1B exception		Does not meet the above criteria for 1B	Requires provision of justification and review by the RRB.

ECMO = extracorporeal membrane oxygenation; IABP = intraaortic balloon pump; LVAD/RVAD = left or right ventricular assist device; MCS = mechanical circulatory support; OPTN = Organ Procurement and Transplantation Network; RRB = Regional Review Board; TAH = total artificial heart.

exception must be admitted to the listing transplant hospital. The pediatric allocation policy incorporates language for exceptions to Status 1A under criterion (f). Listing under this criterion is valid for 14 days and does not require admission to the listing transplant center hospital. Further extension requires a conference with the RRB. If a pediatric candidate does not meet Status 1B criteria but is considered a 1B candidate, the transplant physicians can apply for and justify Status 1B listing to the RRB.

Waiting time (OPTN Policy 3.7.9)

Within each status category, allocation is based on waiting time. Waiting time is accrued while the candidate is listed as Status 1A, 1B and 2; however, time accrued at a lower status does not accrue toward time at a higher status. Specifically, all accrued time is applied while awaiting heart transplant as Status 2, but time accrued as Status 1A is applied only to 1A time, and time accrued as Status 1B is combined with 1A time for total 1B time. Therefore, a candidate on the waiting list for 3 weeks as Status 1A and never listed as Status 2 receives priority over a candidate who has waited for 2 weeks as Status 1A and has combined Status 1A and Status 2 time of 3 months. When applicable, time accrued on the waiting list for a single thoracic organ (heart or single lung) may also accrue for a second thoracic organ when the candidate requires a multiple thoracic organ transplant (heart–lung or double lung). Alternatively, time accrued for a multiple thoracic organ transplant (heart–lung) may be transferred to time for a single thoracic organ (heart only) (14).

Mechanical circulatory support

Adult candidates with MCS devices: Ventricular assist devices

Current OPTN thoracic organ allocation policy allows LVAD and/or RVAD patients to be listed as Status 1A for 30 days at any point after implantation once they are deemed clinically stable by the treating physician, without being admitted to the transplant facility (14; Policy 3.7.3). Candidates with objective evidence of MCS device-related complications can be listed as Status 1A, subcategory (b), without being admitted to the hospital. Centers may request exceptions for other complications (except sensitization) not described in the policy statement as justification for listing

Table 7: Pediatrics candidate status 1A and 1B (OPTN Policy 3.7.4)

Status	Subcategory	Qualification	Comments
1A		Candidates aged < 18 years at the time of listing qualify for Status 1A if one of the following criteria is met:	
	(a)	Ventilator	
	(b)	Mechanical assist device	
	(c)	IABP	
	(d)	Infant aged < 6 months with acquired or congenital heart disease and reactive pulmonary hypertension > 50% of systemic level	May be treated with prostaglandin E.
	(e)	High dose inotropes (e.g. dobutamine ≥ 7.5 mcg/kg/mn or milrinone ≥ 0.5 mcg/kg/mn) or multiple inotropes (e.g. addition of dopamine ≥ 5 mcg/kg/mn).	Qualification for 1A(a), (b), (c), (d) and (e) is valid for 14 days and requires recertification.
	(f) Exception	Does not meet above criteria but has a life expectancy without heart transplant of < 14 days (e.g. refractory arrhythmias)	Qualification for 1A(f) is valid for 14 days and may be recertified for one additional 14-day period; extensions beyond this require conference with the RRB.
1B		Candidate must meet at least one of the following criteria:	
	(a)	Infusion of low dose single inotropes	
	(b)	Aged < 6 months and does not meet criteria for Status 1A	Growth failure is defined as defined as loss of 1.5 standard deviations of expected growth (height or weight) or < 5th percentile for height and/or weight.
	(c)	Growth failure	
1B exception		Does not meet above criteria for Status 1B	Requires provision of justification and review by the RRB.

IABP = intra-aortic balloon pump; OPTN = Organ Procurement and Transplantation Network; RRB = regional review board.

as Status 1A. These requests are subject to review by the respective RRB (14; Policy 3.7.3).

Total artificial heart. The policy implemented in 1999 classified inpatient heart transplant candidates with TAHs as Status 1A. Once discharged, however, these candidates no longer qualified as Status 1A but could be listed as Status 1B. This policy did not address outpatient TAH candidates, as this patient population did not exist until recently. The Thoracic Organ Transplantation Committee thus proposed an interim policy that allows for the accrual of 30 days of Status 1A time at any point after discharge for a TAH candidate, similar to the VAD policy. This policy was approved by the OPTN Board of Directors and implemented in November 2010. Candidates with TAHs can qualify for an unlimited amount of Status 1A time, a provision that remains contentious because the total Status 1A time that can be accrued by an LVAD and/or RVAD candidate without complications is 30 days. As of this writing, the current revision to the TAH policy will expire in December 2012 (14).

Pediatric candidates with MCS devices: Pediatric candidates with MCS, including ECMO, VADs and TAHs, are eligible to be listed as Status 1A indefinitely with recertification every 14 days under criteria (b) (Table 7). Because all pediatric candidates with MCS are eligible under this criteria, the pediatric heart policy does not specifically address VAD-related complications or infections.

Geographic Sequence (OPTN Policy 3.7.2)

Adult donors: In 2006, OPTN began prioritizing zone A Status 1A and 1B candidates ahead of local Status 2 candidates (Table 5). This revision was intended to reduce the death rate on the waiting list. Despite an increase in wait-list mortality between 2007 and 2008, wait-list mortality decreased overall from 199 deaths per 100 patient-years at risk in 1999 to 170 in 2008 (27). Thus, the policy change appeared, in part, to have favorably influenced wait-list mortality.

The policy change also resulted in a higher proportion of candidates undergoing transplant as Status 1A and 1B. The wider geographic sharing promoted by this policy raised concerns regarding decreased posttransplant survival, due to potentially longer ischemia times and more procedures in more urgent recipients; however, 1-year survival after this policy was implemented was not adversely affected, based on OPTN/SRTR data as of October 2010.

Heart allocation accounts for medical urgency while optimizing geographic distribution to reduce ischemia time. Allocation begins within the DSA and expands according

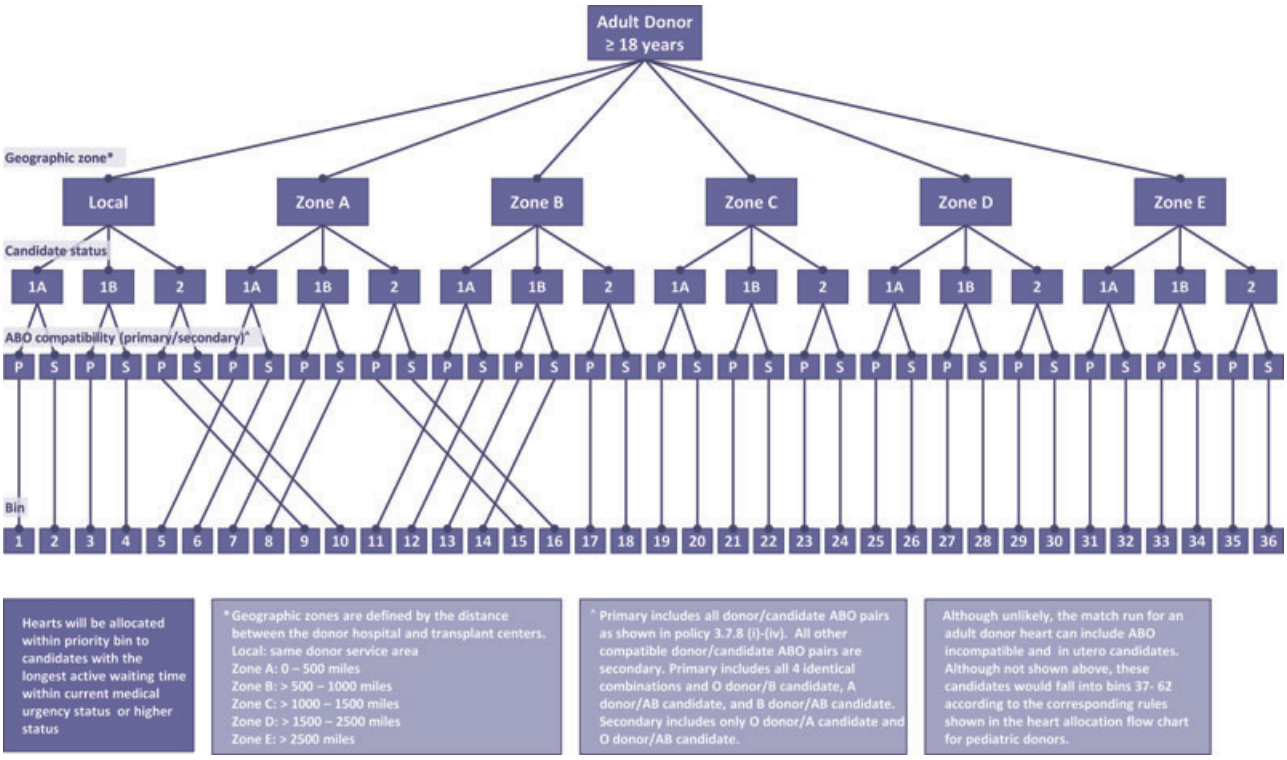

Figure 5: Allocation of hearts from adult (ages ≥ 18 years) donors. This figure can be downloaded in color from www.srtr.org.

to geographic zones defined by concentric circles of 500 nautical mile radii from the donor recovery hospital as follows: zone A, 0–500 miles; zone B, >500–1000 miles; zone C, >1000–1500 miles; zone D, >1500–2500 miles; zone E, >2500 miles. A donor heart is first offered locally to Status 1A (Figure 5, bins 1 and 2) or 1B (bins 3 and 4) candidates. Within each status category, hearts are allocated first to candidates with primary ABO matches and subsequently to secondary blood types. If the organ is not accepted for a compatible recipient, it is offered to zone A Status 1A (bins 5 and 6) or 1B (bins 7 and 8) candidates. If there is no zone A recipient, the offer reverts to the DSA for local Status 2 candidates (bins 9 and 10). If there is no compatible recipient, the organ is offered to zone B Status 1A (bins 11 and 12) or 1B (bins 13 and 14) candidates. If there is no compatible recipient, the organ is offered to zone A Status 2 (bins 15 and 16) candidates. If there is no compatible recipient, allocation proceeds as follows: zone B, Status 2 (bins 17 and 18); zone C, Status 1A, 1B or 2 (bins 19–24); zone D, Status 1A, 1B or 2 (bins 25–30); zone E, Status 1A, 1B or 2 (bins 31–36). Thus, in this sequence, Status 1A or 1B candidates in the subsequent region precede Status 2 candidates in the preceding region up to zone B (OPTN Policy 3.7.8; Figure 5).

Pediatric donors: Current pediatric heart allocation policy preferentially allocates pediatric donor hearts to pediatric candidates. Consistent with the broader sharing policy, offers for pediatric donor hearts are initially made to pediatric candidates within the combined local DSA and zone A region for Status 1A candidates with preference for primary ABO matching (Figure 6A, bins 1 and 2). If the heart is not accepted for a pediatric candidate, it is offered to local Status 1A adults (bins 3 and 4). If there is no compatible Status 1A recipient, the organ is offered to Status 1B pediatric candidates within the combined DSA and zone A region (bins 5 and 6), and subsequently to Status 1B adults within the OPO (bins 7 and 8). If there is no compatible recipient, the heart is offered to Status 1A and 1B adult candidates within zone A (bins 9–12). Allocation then proceeds to candidates as follows: OPO Status 2 pediatric and adult (bins 13–16), zone B Status 1A pediatric then adult (bins 17–20), zone B Status 1B pediatric then adult (bins 21–24); zone A Status 2 pediatric then adult (bins 25–28); zone B Status 2 pediatric then adult (bins 29–32). Allocation to candidates in zones C–E proceeds in order of medical urgency with pediatric candidates first within each Status category and preference to primary ABO compatibility (bins 33–68).

ABO considerations (Policy 3.7.8)

Very young pediatric candidates (aged ≤14 months) are unique in their potential to accept an ABO-I donor heart because isohemagglutinins (anti-A and anti-B antibodies) develop late in infancy (28,29). In 2006, OPTN approved

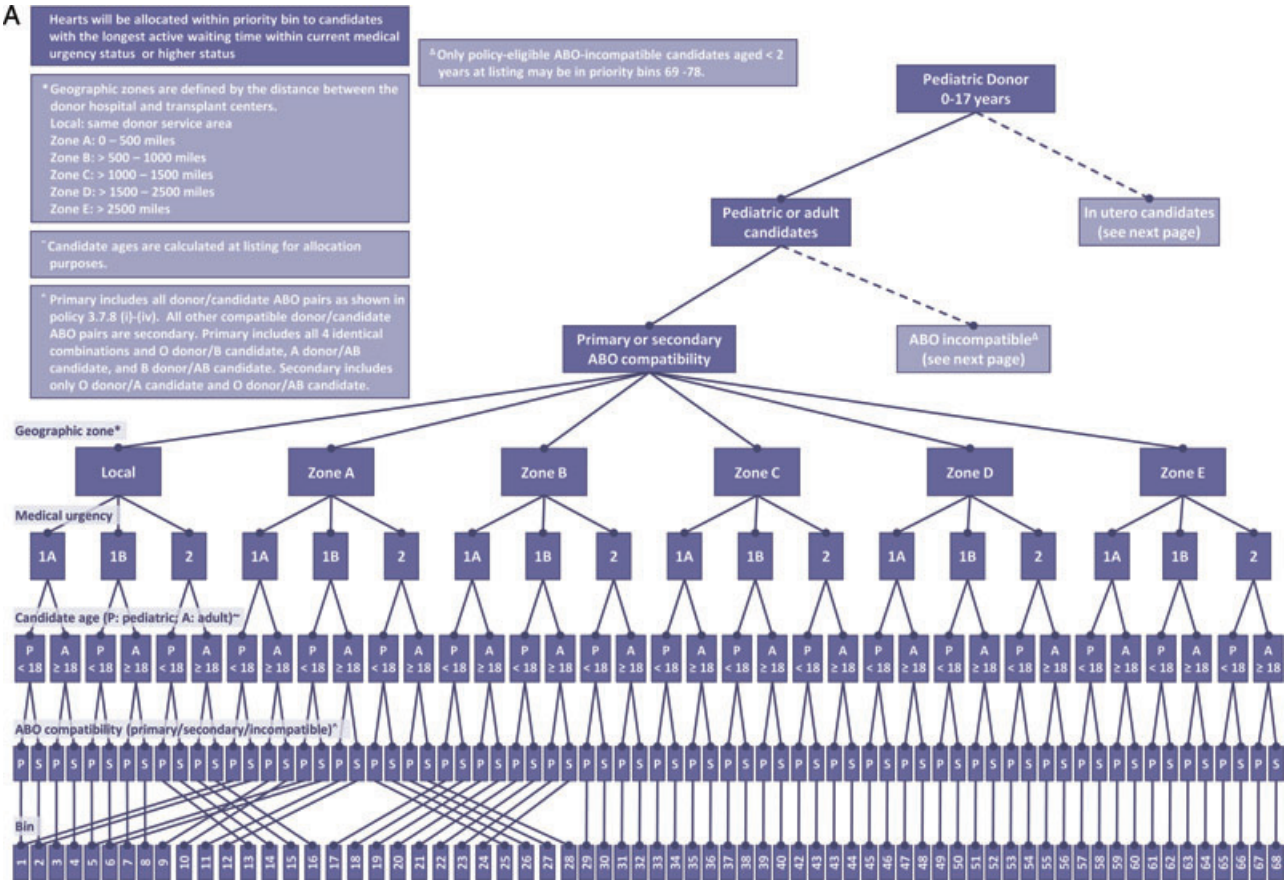

Figure 6: Allocation of hearts from pediatric (ages 0–17 years) donors, (A) bins 1–68 and (B) bins 69–93. This figure can be downloaded in color from www.srtr.org.

ABO-I heart transplant in children added to the waiting list before their second birthdays and meeting certain conditions (30). This policy was implemented in 2010. As a result, in 2007 the proportion of eligible infants aged <6 months listed for ABO-I heart transplant was 53% (31). Before a donor heart is allocated to an ABO-I candidate, the list of born (postnatal) ABO-compatible recipients must be exhausted (Figure 6A, bins 1–69). The donor heart is allocated first to Status 1A and 1B ABO-I pediatric candidates in the combined OPO and zone A region (Figure 6B, bins 69 and 70), then to local Status 2 pediatric ABO-I candidates (bin 71), then to Status 1A and 1B pediatric ABO-I candidates in zones B–E (bin 72–79). If no compatible candidates are eligible for ABO-I transplant, the heart is allocated to *in utero* candidates. Under current policies, to qualify for an ABO-I donor heart, a candidate must be (1) *in utero*; (2) aged <1 year and listed as Status 1A or 1B or (3) aged ≥1 year but listed before age 2 years and currently listed as Status 1A or 1B. For candidates aged ≥1 year, current isohemagglutinin titer must be ≤1:4 for A or B blood type antigens and the candidate must not have received treatments within the prior 30 days that may have reduced titer values to ≤1:4 (Policy 3.7.8).

Heart–lung allocation (Policy 3.7.7)

Between 2000 and 2011, 399 simultaneous heart–lung transplants were performed. In January 2011, the Thoracic Organ Transplantation Committee encouraged thoracic transplant programs to list candidates who require simultaneous heart–lung transplant for both organs according to listing policies governing each organ individually, and to list them on the heart–lung waiting list. Priority for a heart–lung transplant candidate on the lung transplant waiting list is determined by the LAS (for candidates aged ≥12 years), and on the heart waiting list by medical urgency status code as described earlier. When a donor heart becomes available to an eligible candidate, the lung is allocated from the same donor. When the candidate is eligible to receive a lung, the heart is allocated from the same donor only if no suitable Status 1A isolated heart candidates are eligible to receive the heart.

ABO matching requirements are determined by which organ match run the candidate is included in; ABO matching policy for heart allocation is used if the candidate is included in the heart match run, and for lung allocation if in the lung match run.

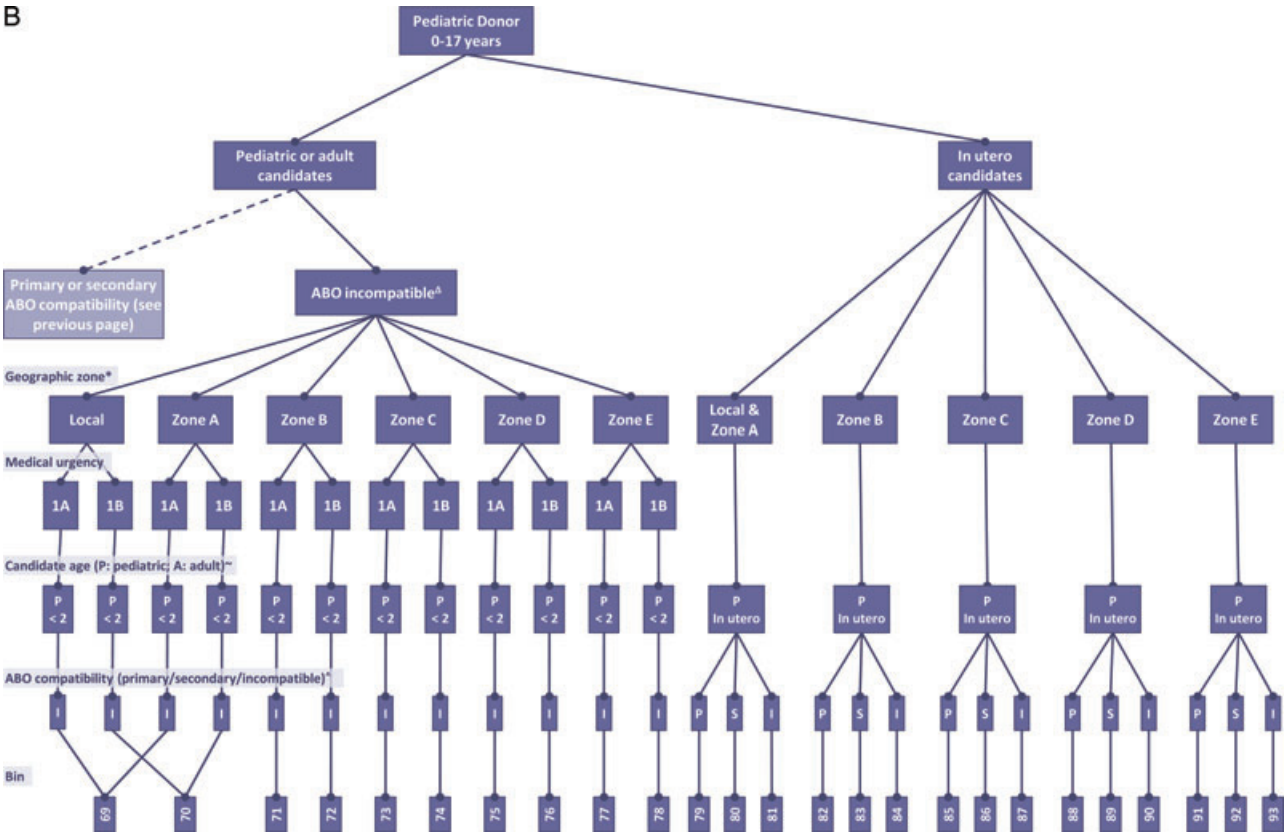

Figure 6: Continued.

Allocation of domino donor hearts (Policy 3.7.15)

Domino heart transplant refers to procurement and transplant of the native heart of a combined heart–lung transplant recipient. When a domino heart is available, it is first offered to candidates at the transplant center from which the native heart was procured. If the program does not use the heart, it is allocated based on the general heart policy or an approved variance. Only one domino heart transplant procedure has been performed in the United States since 1997.

Comparison to international heart allocation policies

Most heart allocation policies throughout the international transplant community are based on medical urgency with waiting time being a secondary feature (Table 8). Similar to the US allocation policies, algorithms are based on geography, which in some countries may extend to neighboring countries. For instance, if no country within the Scandiatransplant community has a suitable donor, a donor heart may be allocated to a recipient in another European country through an international exchange program. In general, heart transplant candidates appear to be grouped into urgent and nonurgent categories in several international allocation schemes. Similar to trends in the United States, a growing proportion of candidates are listed in the high-urgency category, similar to UNOS Status 1A, following revision of the Eurotransplant allocation policy in 2000 and 2005, which provided for a high urgency category in addition to an urgent category (32–34). Furthermore, candidates who receive VADs (excluding nondurable mechanical support such as ECMO or IABP) are removed from the urgent category unless they develop VAD-related complications, a policy similar to that in the United Kingdom and countries in the Scandiatransplant program (35,36). Scandiatransplant policy will consider candidates aged less than 16 years and with an LVAD for more than 1 year as high-urgent status (Priority 0) (37). The Canadian Cardiac Transplant Network allocation system promotes nationwide allocation. The allocation algorithm has six categories, with Status 4 being the highest urgency category. (Table 8) Hearts are allocated using a nationwide list, although priority is given to the region where the donor heart becomes available. When there are competing potential recipients, the recipient with the longest current listing as Status 4 is given priority. Similar to other international policies, candidates with VADs are listed in the highest urgency category when complications occur. Otherwise, candidates with VADs are listed as Status 3 (38). These international allocation policies could help inform discussions about future heart allocation policy in the United States.

Table 8: Examples of international heart allocation policies

Country	Policies
Canadian Cardiac Transplant Network (38)	Status 4: (1) Mechanically ventilated patient on high-dose single or multiple inotropes ± mechanical support (e.g. IABP, ECMO, abiomed BVS5000 or biomedicus), excluding VAD. (2) Patient with VAD malfunction or complication, such as thromboembolism, systemic device-related infection, mechanical failure or life-threatening arrhythmia. (3) Patient should be reconfirmed every 7 days as a Status 4 by a qualified physician if still medically appropriate. Status 4S: (1) High PRA (> 80%), or PRA > 20% with three prior positive crossmatches (in the setting of negative virtual or actual donor/recipient-specific crossmatch and appropriate size and blood type of the prospective donor). Status 3.5: (1) High-dose or multiple inotropes in hospital, and patients not candidates for VAD therapy or no VAD available. (2) Acute refractory ventricular arrhythmias. Status 3: (1) VAD not meeting Status 4 criteria. (2) Patients on inotropes in hospital, not meeting above criteria. (3) Heart/lung recipient candidates. (4) Cyanotic congenital heart disease with resting saturation < 65%. (5) Congenital heart disease, arterial-shunt dependent. (6) Adult-sized complex congenital heart disease with increasing dysrhythmic or systemic ventricular decline. Status 2: (1) In-hospital patient, or patient on outpatient inotropic therapy not meeting the above criteria. (2) Adult with cyanotic CHD: resting 02 saturation 65%-75% or prolonged desaturation to <60% with modest activity (i.e. walking). (3) Adult with Fontan palliation with protein-losing enteropathy or plastic bronchitis. (4) Patients listed for multiple organ transplantation (other than heart–lung). Status 1: All other out-of-hospital patients
Eurotransplant community[1] (32–34)	Each EU country has a unique algorithm. Heart allocation policy generally based on medical urgency. Major difference from US policy is that candidates with VAD are not automatically considered candidates for urgent heart transplant. Once a VAD is implanted, patient loses urgent status. If a patient with a VAD (irrespective of medical urgency for heart transplant) develops VAD-related complications, status for heart allocation is changed to urgent. Criteria for urgency status include: 1. Continuous IV inotropic therapy. 2. Assist device complications. 3. Documented intractable recurrent ventricular rhythm disorders. 4. End-stage transplant vasculopathy. 5. Persisting angina pectoris.
Scandiatransplant[2] (37) countries	Donor hearts used locally among patients labeled priority 0 (high urgent). If a member country lacks a priority (0/1) patient, a donor heart is provided to a patient labeled priority 2 in the region. If all member countries lack a suitable recipient, the donor heart is provided to other European countries through European organ-exchange organizations. Priority classifications: 0: ECMO, centrifugal pumps, blood pumps (implantable) with uncontrollable infection or device failure; patients aged < 16 years on LVADs for more than 1 year or on inotropes. Patient status renewed weekly. 1: This classification not used for heart transplant. 2: Patients who are transplantable. 3: Patients who are not transplantable.
United Kingdom Transplant Services Authority (36)[3]	Heart-allocation policies in the United Kingdom and Ireland are based on principles of biological matching, clinical priority, logistical factors such as ischemia time, prior sternotomies, adult congenital heart disease (ACHD), prior VADs etc. and fairness (time on waiting list) (19). Uses urgent heart allocation scheme. Candidates on the nonurgent waiting list are allocated hearts when there are no suitable candidates on the urgent list. Urgent status includes use of high-dose continuous inotropes, IABPs (with or without inotropes), short-term MCS (e.g. venoarterial ECMO), long-term VADs and device-related complications.

CHD = coronary heart disease; ECMO = extracorporeal membrane oxygenation; IABP = intraaortic balloon pump; LVAD = left-ventricular assist device; MCS = mechanical circulatory support; PRA = panel reactive antibody; VAD = ventricular assist device.
[1]Netherlands, Germany, Austria, Belgium, Croatia, Germany, Slovenia.
[2]Denmark, Finland, Norway, Sweden.
[3]United Kingdom and Ireland.

Future directions

Adult heart allocation policy: Current heart allocation policy attempts to prioritize allocation to the sickest candidates. As evidenced by recent revisions to the TAH policy, the policy is dynamic, allowing for adaptation in response to the latest technological and medical innovations, and the changing transplant candidate population. There is controversy over whether candidates with VADs, who are now stabilized, should continue to receive 30 days of Status 1A time and a potential listing advantage over sicker patients (39). Compared with older VADs, newer-generation VADS produce fewer complications and can effectively treat heart failure for extended periods; thus this policy may no longer be necessary. In its effort to revise the adult heart Status 1A policy, the OPTN/UNOS Thoracic Organ Transplantation Committee is considering changing the length of time a VAD candidate would receive Status 1A time. Thirty days is arbitrary, and how long a VAD candidate should receive Status 1A time may depend on factors such as the type of VAD. These data are being evaluated and will inform planned future policy change. The OPTN/UNOS Thoracic Organ Transplantation Committee is revising criterion (b), which allows clinicians to classify adult heart transplant candidates experiencing MCS device complications as Status 1A. The goal of this revision is to more clearly define what constitutes VAD complications to prioritize the sickest VAD patients.

Policy revisions may also consider candidates who are disadvantaged by the current listing process due to cardiomyopathies for which VADs or inotropes are contraindicated. As VAD survival improves, it may be prudent to consider prioritizing patients who are unable to benefit from VADs. Finally, many heart transplant professionals question the continued appropriateness of the Status 2 category. One-year survival of Status 2 candidates approaches that of heart transplant recipients, suggesting that early listing of adults may no longer be justified (27). Furthermore, waiting times for Status 2 candidates have risen dramatically in recent years. The median time to transplant for a Status 2 candidate on the waiting list in 2010–2011 was 17.6 months, compared with 1.7 months for Status 1A and 5.5 months for Status 1B (based on SRTR data as of March 15, 2012). In some regions, wait-list survival of Status 2 candidates may exceed the projected survival benefit of heart transplant (40).

A new allocation scheme predicated on evidence-based markers of disease severity and outcomes is being considered. The Heart Subcommittee of the OPTN Thoracic Organ Transplantation Committee is currently considering revising the entire policy (Policy 3.7.3) to better address medical urgency and disease severity in candidates with MCS devices. These revisions are expected to specify definitions of MCS-related infections and complications to provide more guidance and consistency in assigning medical urgency subcategories.

In January 2011, OPTN began collecting data on MCS devices at the time a candidate is removed from the waiting list. These and other analyses are being reviewed to more accurately address the clinical heterogeneity among candidates with MCS devices. The revised allocation system may account for posttransplant survival and wait-list mortality as indicators of disease severity (41).

Pediatric heart allocation policy

The Heart Subcommittee, the Thoracic Working Group of the Pediatric Committee and investigators from the Pediatric Heart Transplant Study, an international registry of pediatric heart transplant candidates and recipients, have evaluated revisions to current heart allocation policies that will address medical urgency categories, *in utero* listings, and ABO-I transplant. *In utero* listings are rare, and at its April 2011 meeting the Pediatric Transplantation Committee voted unanimously to submit for public comment a proposal to eliminate all policies allowing *in utero* listings (42). Also, in light of data demonstrating that ABO-I transplants may be performed safely at isohemagglutinin titers higher than 1:4, proposals for a new titer threshold for ABO-I transplant are being considered. Finally, a proposal for revising medical urgency categories for pediatric candidates is in development, with a goal of reducing wait-list mortality in the highest risk groups. Under the current system, most pediatric heart candidates, particularly infants, are listed as Status 1A at the time of transplant, in effect changing the allocation process to one based on time rather than medical urgency. Current policy may disadvantage certain patients, such as infants with restrictive cardiomyopathy and hypertrophic cardiomyopathy. A revised pediatric heart policy is anticipated for public comment distribution in 2012. Proposed revisions will specifically address listing criteria for candidates with congenital heart disease (41).

Heart–lung policy

The current heart–lung allocation policy does not address the potential occurrence of a tie, in which 2 heart–lung candidates are eligible to receive the same heart–lung bloc in the same geographic area. Further, the current policy does not address geography, Status 1B candidates, or sick lung transplant candidates also in need of heart transplants. The Policy Oversight Committee is currently developing principles for multiorgan allocation that will be considered by the Thoracic Organ Transplantation Committee in the development of modifications for this policy.

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The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*: By virtue of employment at or affiliation with a transplant program or an organization with an interest in transplant program performance, any author of this manuscript could be perceived to have a conflict of interest. Beyond that, no author has any conflict of interest to disclose as described by the *American Journal of Transplantation*.

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EDITORIAL COMMENT

Timing Isn't Everything: Donor Heart Allocation in the Present LVAD Era*

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Trust in an organ allocation system is predicated on fairness, a belief that organs will be directed to the most deserving patients first. To this end, the Organ Procurement and Transplantation Network contractor, the United Network for Organ Sharing (UNOS), created a system that prioritizes the allocation of hearts to patients with the highest likelihood of dying while waiting for a donor organ. Revised in 2006 to incorporate broader regional sharing, this allocation system has succeeded in directing hearts to a greater proportion of high-urgency patients (UNOS 1A) and in so doing reduced waiting list mortality without compromising post-transplant outcomes (1).

See pages 36 and 44

This new allocation system left in place a provision for the elective use of 30 days of high-urgency status, commonly referred to as 1A time, for recipients of implantable left ventricular assist devices (LVAD). The rationale for granting this specialized status stemmed from an earlier experience with pulsatile, implantable LVADs in which the mortality in the first 3 weeks after LVAD surgery was 5% to 10% per week (2). These LVAD recipients were granted 30 days of 1A status from the date of LVAD implant, but some experienced inferior outcomes by proceeding with transplant surgery so soon thereafter. Recognizing that LVAD-supported patients remained at risk of device failure over time, a provision was made to allow them to carry forward these 30 prioritized days to be used at any time at the listing center's discretion. This prioritization has remained even after the emergence of continuous flow LVADs, which are less likely to fail and have produced higher survival rates (3). This has created a perception of stable patients being able to "jump the list" ahead of other, more critically ill patients and has cast doubt as to whether the UNOS donor heart allocation system in its present configuration is indeed fair (4).

To be considered fair and balanced, an organ allocation system must be guided by 2 ethical principles, maximizing utility and distributing resources justly. These 2 ideals are occasionally at odds with one another whereby prioritizing one compromises the other. If one wanted simply to maximize the utility of a transplanted heart by focusing on the number of years of life gained, older recipients or those with certain comorbidities would be passed over in favor of younger, more robust recipients with a greater life expectancy after transplant. Conversely, in prioritizing justice, one would choose to ensure equal access to lifesaving organs, usually in the face of greatest need, regardless of the outcome.

Heart transplant programs must also be guided by these principles when deciding the appropriateness of transplant for an individual candidate and when considering how best to manage deserving patients while awaiting transplantation. Such decisions boil down to answering 4 practical questions: First, what are the expected outcomes with and without a transplant? Second, what are the expected outcomes while waiting for a donor heart? Third, what are the expected outcomes after LVAD surgery? Finally, what is the expected survival after transplant, whether bridged with medical therapy or with an LVAD?

In this issue of the *Journal*, we are provided some insight into 2 of these questions. In the first paper, Teuteberg et al. (5) evaluated the discriminatory value of the Destination Therapy Risk Score (DTRS) in patients receiving a continuous flow LVAD, the HeartMate II (Thoratec Corporation, Pleasanton, California). They retrospectively analyzed prospectively collected data from 2 mechanical circulatory support trials including >1000 patients. They discovered that the DTRS was a poor mortality risk discriminator for bridge to transplant recipients and a modest discriminator for destination therapy patients. Furthermore, the score failed to characterize a population in whom mechanical support would be futile. The authors are to be congratulated for providing us with a cautionary tale about prematurely adopting risk predictor models into clinical decision making. Even though this DTRS has been widely applied and almost universally accepted, this score was never sufficiently prospectively validated. Not only did the DTRS fail to risk-stratify recipients of a continuous flow pump, but it failed to effectively risk-stratify destination therapy recipients of a HeartMate XVE, a population similar to the derivation cohort. This is an important and timely observation for those working in the field of mechanical support, a field that depends on accurate and effective risk predictor models to advise patients and inform clinical decision making.

In an adjoining paper, Dardas et al. (6) examined the outcomes for wait-listed registrants to examine whether disparities in risk exist within and between UNOS status

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designations. They reviewed data on >15,000 patients collected by the Scientific Registry of Transplant Recipients from 2005 to 2010, a period of time characterized by the transition from first-generation pulsatile LVADs to smaller continuous flow devices. They report that the chance of experiencing an adverse event (death or wait-list removal for ineligibility) varied significantly within status 1A indications. Those with the lowest risk were LVAD patients using elective 30-day 1A time (1% cumulative hazard) followed by those on medical therapy (6%), LVAD complication (6%), and 1A paracorporeal ventricular assist devices (15%). Over this time period, candidates listed status 1A with an implanted LVAD without complication increased from 11% to 26%, while those on medical support decreased from 44% to 39%. There were no significant differences in survival after status 1A transplantation except for those patients who were previously ventilator dependent.

Should clinically stable LVAD patients continue to receive prioritization for donor hearts? Dardas et al. (6) contend that they should not because doing so violates the justice principle. First, they cite the higher risk for adverse events in medically supported or mechanically ventilated patients and suggest that these patients may be disenfranchised by preferentially allocating hearts to stable LVAD patients who have the lowest risk of wait-list mortality. Second, they argue that there is no utilitarian reason to prioritize stable LVAD recipients because transplant outcomes are not superior in this group compared with other 1A or 1B subgroups. Third, they suggest that in an ideal system there should be no disparity and that all 1A patients should be at equal risk.

These are compelling arguments but not persuasive. Consider the following in rebuttal. First, there is no direct evidence that prioritizing stable LVAD patients has prevented other 1A patients from receiving timely transplants. In fact, wait-list mortality has actually gone down (1). It is likely that centers are exercising good judgment by timing these upgrades to avoid competition with other 1A patients, thereby preserving their exposure to donor hearts. Second, before concluding that in the absence of a utilitarian reason there is no rationale to justify 1A prioritization one should be reminded of the German experience (7). In the Eurotransplant system, there is no prioritization for stable LVAD patients, which effectively eliminates the likelihood of their receiving a transplant in the absence of developing a device complication. Choosing to remain in urgent status on medical therapy instead of accepting an LVAD may increase the odds of receiving a transplant but does so at the risk of dying or becoming ineligible while waiting. Patients who opt for watchful waiting but end up requiring bailout LVAD placement have inferior survival while on the waiting list and, among the few who receive a heart, after transplant. Finally, even if one were to craft an entirely new allocation system, disparities in risk would still exist. Consider the authors' own data. Patients supported with paracorporeal ventricular assist devices or mechanical ventilation had risk profiles exceeding those of the other 1A categories, including those who are medically supported or have an LVAD complication.

Despite these differences in opinion, there is agreement that the current allocation system needs further refinement. The widespread adoption of smaller, continuous flow LVADs has begun to deliver on the promise of minimizing the risk of mechanical support and maximizing its beneficial outcomes. They are also improving the short- and mid-term survival of transplant-eligible recipients. How UNOS adjusts to this changing landscape is not yet clear. The adoption of a heart allocation score, similar in principle to the model for end-stage liver disease or the lung allocation score, is one possibility. Another is to expand the number of prioritization categories matching individual risk profiles. Regardless of which system emerges, facilitating this change will require robust data collection and analysis similar to the ones published today to achieve a fair and balanced system for our patients.

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Heart Allocation in the United States: Intended and Unintended Consequences

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Heart Allocation in the United States
Intended and Unintended Consequences

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The consequences of our actions are so complicated, so diverse, that predicting the future is a very difficult business indeed.

—J.K. Rowling, British Novelist (1965–present)

Nearly 20 years ago, clinical leaders in the field of heart transplantation met in Bethesda, Maryland, to address the growing disconnect between the numbers of patients with end-stage heart failure who were listed for cardiac transplant and those who actually received transplants.[1] As stated by Dr Norman Shumway in his keynote address to the conference, "The principle issue that stands before us is the donor problem." The severity of the crisis at the time was reflected in the fact that more patients were listed on any given date than underwent transplantation in the previous year. In an effort to ease the supply-demand mismatch, conference leaders developed objective criteria for candidate listing and prioritization, suggested new strategies to improve survival on the waiting list, and broadened donor selection. Despite these initiatives as well as the intensification of efforts toward public education, the actual number of transplants leveled off and has remained flat for more than a decade.[2] Prioritization on the waiting list, however, has continued to evolve. In 1989, a simplified algorithm was implemented with 2 categories for medical urgency, and in 1999, a 3-tiered system (status 1A, 1B, and 2) was approved to address perceptions of unfairness in heart allocation. Most recently, the US allocation system was modified in 2006 to allow broader regional sharing of donor hearts to status 1A and 1B patients before allocating organs to local status 2 patients (Table).[3] The primary objective of this algorithm change was to decrease wait-list mortality without effecting a change in posttransplant mortality.

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National Trends and the Intended Consequences of Allocation Change

Over the past decade, there has been a slow, but steady increase in the percentage of patients listed as status 1A and 1B and a decline in status 2 patients (Figure 1A).[2] There are 2 major reasons given for these trends, including the increased use of mechanical circulatory support as a bridge to transplant[4] and the tendency of programs to wait until patients deteriorate clinically before listing. This latter practice may be based on recent data showing similar long-term survival between patients receiving transplants as status 2 and those with advanced heart failure receiving optimal medical management.[5] Furthermore, with the evolution of mechanical circulatory support, there has been increased attention focused on the posttransplant outcomes of bridged patients. In an initial report using Organ Procurement and Transplantation Network (OPTN) data collected between 1995 and 2004, intracorporeal ventricular assist devices (VADs) were associated with an increased hazard of both early (within 6 months) and late (beyond 5 years) mortality.[6] However, these data were based primarily on first-generation, pulsatile-flow VADs. More recent data from both national[7] and international[8] registries show similar posttransplant outcomes between patients on continuous-flow VADs and patients not on VADs.

Against this background, Singh et al,[9] in this issue of *Circulation: Heart Failure*, hypothesized that the risk of death while on the waiting list has decreased following the 2006 algorithm change. Using adult OPTN data from 2004 to 2009 (excluding retransplants and multiorgan transplants), they compared the overall and risk-adjusted wait-list mortality and early posttransplant mortality before and after implementation of the new allocation system. The analysis included 4503 patients in era 1 (2004–2006) compared to 7361 patients in era 2 (2006–2009). Importantly, complete data were available on age, sex, race/ethnicity, cardiac diagnosis, blood type, hemodynamic support, and United Network of Organ Sharing (UNOS) listing status as well as on dates of listing, transplant, death, and removal from the waiting list.

Following the algorithm change, listed patients were slightly older and heavier and more likely to be black and have type 2 diabetes and an implantable cardioverter-defibrillator (ICD). As anticipated, a greater proportion of patients in era 2 were listed as status 1A or 1B (57% versus 50%) and bridged with mechanical circulatory support, especially continuous-flow VADs. Despite this higher-risk profile, the wait-list mortality for status 1A and 1B patients decreased significantly by 17%, and in multivariable analyses, the use of continuous-flow VADs and ICDs predicted lower wait-list mortality. In a sensitivity analysis, decreased risk of wait-list mortality was also observed

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Table. Initial Sequence of Adult Heart Allocation

1999–2006	2006–Present
Local	Local
1. Status 1A candidates	1. Status 1A candidates
2. Status 1B candidates	2. Status 1B candidates
3. Status 2 candidates	Zone A
Zone A	3. Status 1A candidates
4. Status 1A candidates	4. Status 1B candidates
5. Status 1B candidates	Local
	5. Status 2 candidates

Adapted from Nativi et al.[3] Zone A refers to all transplant centers within 500 nautical miles of the donor hospital but that are not in the local area of the donor hospital.

in patients not on VADs (hazard ratio, 0.77). Importantly, the 2006 algorithm change was associated with no change in hospital length of stay or mortality or 1-year posttransplant mortality, despite longer median waiting times (63 versus 55 days), decreased use of local donors (52% versus 62%), greater transport distance (125 versus 89 miles), and increased ischemic times.

The data by Singh et al[9] are remarkable in their clarity and consistency, but what do they really tell us about the effect of the new allocation policy? As noted here, important trends toward increased wait-list status and decline in wait-list mortality have been observed for >10 years now (Figure 1).[2] These data would suggest that the improved wait-list survival rates observed by Singh et al are coincidental with the 2006 change in heart allocation and due to other factors. Advances in the care of patients with end-stage heart disease, evolution of mechanical circulatory support, and more-careful attention to delisting marginal patients have all likely contributed to improved wait-list outcomes despite a sicker cohort. However, these advantages may not be generalized to all patients. In the current analysis, decline in wait-list mortality was observed only in white candidates ($P=0.04$ for interaction of white versus nonwhite) (Figure 3 in Singh et al). We have also observed that longer-term survival posttransplant has improved in white recipients but not in black or Hispanic recipients, resulting in a more marked disparity in outcomes in the current era.[10] Risk factors not adjusted for in our prior analysis include differences in access to care, severity of illness at presentation, and rate of disease progression. Potential mechanisms responsible for worse outcomes in black patients include differences in biological factors (more hypertension, higher likelihood of human leukocyte antigen mismatch)[11] and socioeconomic factors (lower socioeconomic status, less formal education).[12] Black race has also been associated with worse outcomes following renal and liver transplant and attributed to a combination of biological and nonbiological factors.[13,14] Going forward, specialized care, including individualized immunosuppression and quality improvement initiatives, may be critical to achieving similar outcomes and reducing healthcare disparities in organ transplantation.

Unintended Consequences of Allocation Change

One of the unique aspects of transplant care in the United States is significant variability in listing strategies and waiting times among UNOS regions.[15] Although the data of Singh et al[9] suggest national progress toward improving wait-list outcomes, other published data have raised concerns about unintended regional consequences of allocation change. In an initial effort to look at the early effects of the 2006 algorithm, Nativi et al[3] analyzed data from 4 Utah centers in UNOS region 5 and noted some concerning trends. As in the current report, there were significant increases in the percentage of status 1A and 1B patients receiving transplants (76% versus 44%) and bridged to transplant with VADs (31% versus 17%) after 2006. However, these investigators observed no change in wait-list or posttransplant mortality and increases in median waiting time, graft ischemic time, and donor procurement costs, the latter because of the increased number of imports and longer travel distances.

Even within a region, wait-list times, use of imports, and outcomes may vary. In a 6-month snapshot of UNOS region 1 data, we observed significant differences between

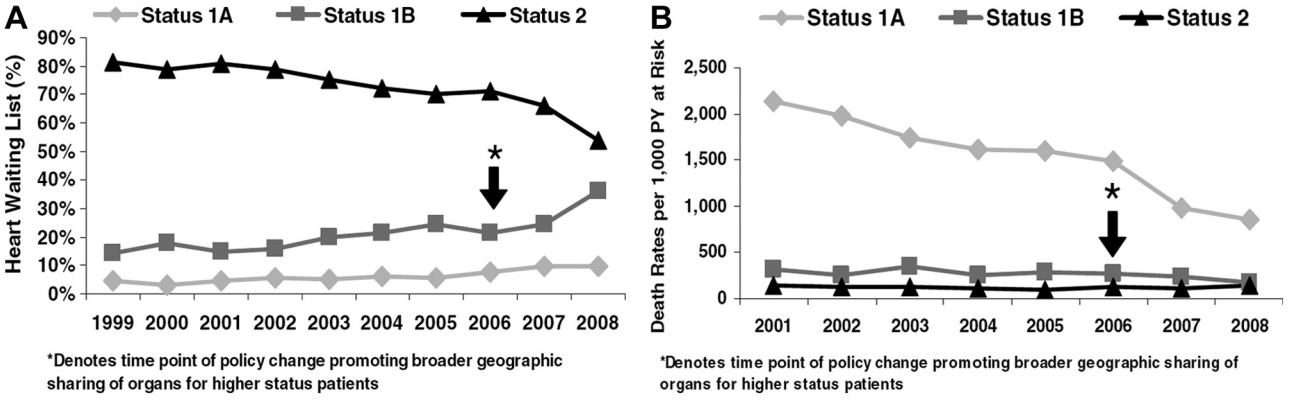

Figure 1. A, Status of heart transplant waiting list candidates, 1999 to 2008. Source: 2009 OPTN/SRTR Annual Report, Table 11.1a. **B**, Annual death rates per 1000 patient-years on the heart transplant waiting list by status, 2001 to 2008. Source: 2009 OPTN/SRTR Annual Report, Table 11.3. Reprinted with permission from Johnson et al.[2]

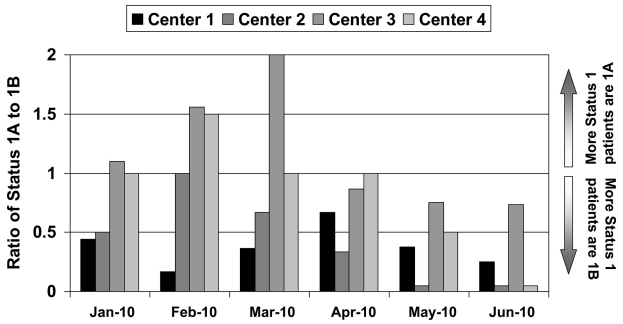

Figure 2. Status 1 listing practices at 4 adult heart transplant centers in the same United Network of Organ Sharing region during a 6-month period in 2010. As shown, there is significant variability in the ratio of status 1A to 1B patients between centers and between time points.

centers and between time points in the ratio of status 1A to 1B listings (Figure 2). These differences likely exist across the United States and are not fully explained by patient characteristics and severity of illness alone. Rather, they may be due to variable application of listing criteria and increasing use of exceptions for VAD complications and need for continuous hemodynamic monitoring. Appropriate behavior of individual physicians is to act as advocates for their patients to maximize the likelihood that they will receive a transplant after clinical deterioration. Furthermore, although continuous-flow VADs have excellent durability and reduced rates of long-term complications compared with first-generation devices,[16] life-threatening thromboembolism, gastrointestinal bleeding, and infection can lead to candidate delisting and transition to destination therapy. The decreased wait-list times observed by Singh et al[9] may have been biased by OPTN data that do not accurately reflect permanent wait-list removals for noncardiac reasons or temporary inactivation for complications related to indwelling catheters or mechanical support. Quarterly comparisons of center and Scientific Registry of Transplant Recipient data by UNOS, along with recent concerns about falling transplant volumes, have heightened center awareness of their wait-list and transplant outcomes.

Emerging Issues and Future Prospects

On balance, advance heart disease physicians and healthcare extenders should be cautiously optimistic. Perioperative care and overall survival of heart transplant patients continue to improve.[2] Although additional analyses are needed to demonstrate no detrimental effect of allocation change on longer-term outcomes, the evolution in VAD technology and emerging understanding of myocardial recovery and stem cell biology may obviate the need (or least the urgency) for heart transplant. The REVIVE-IT (Randomized Evaluation of VAD Intervention before Inotropic Therapy) trial will determine the role of continuous-flow VADs in patients with stable moderate heart failure, whereas a small, but growing number of patients will be living at home on total artificial hearts.[17] Additionally, novel organ preservation techniques may allow significant increase in travel distances without compromising donor heart function.[18] Within this framework, the UNOS Thoracic Organ Committee will be challenged to rethink the allocation algorithm and should consider the use of severity of illness scores (eg, the lung allocation or model for end-stage liver disease scores) for better risk stratification. This will likely be more complex, however, as the indexes of disease severity in heart failure are more amenable to the effects of therapy, which can then be modified to achieve shorter waiting times. In addition, heart allocation simulation models[19] should be redesigned to account for changing demographics, indications for transplant, and comorbidities (eg, obesity, diabetes) as well as the stability of physician and patient preferences in the face of life-threatening illness.[20]

As suggested by J.K. Rowling, predicting the consequences of policy change is a difficult business, indeed. Heart transplant leaders who gathered in Bethesda in 1992 understood the importance of forward thinking and outlined broad principles for improving both wait-list and posttransplant outcomes. As the field evolved, policymakers tried to redirect the donor algorithm to benefit sicker patients. Despite these efforts, the current system is flawed by perpetuating regional and center differences that threaten the principles of fairness and equity in donor allocation. Furthermore, racial and ethnic disparities in transplant care persist. It is the responsibility of current and future advanced heart disease leaders to maximize the intended, and limit the unintended, consequences of allocation policy.

Disclosures

None.

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Restricted mean models for transplant benefit and urgency

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The US lung allocation policy estimates each individual's urgency and transplant benefit in defining a lung allocation score (LAS). Transplant benefit, as defined by the Organ Procurement and Transplantation Network Thoracic Committee, is the days of life gained over the following year if transplanted versus not transplanted. Urgency is measured by days of life during the next year without transplant. In both definitions, accurate estimation of wait list days lived, or a wait list restricted mean lifetime, is required. Risk factors are available to estimate patient urgency when listed, with more urgent patients removed from the wait list upon death or transplant. As a patient progresses, priority for transplant (censoring) changes accordingly. Therefore, it is crucial to adjust for dependent censoring in modeling days of life. We develop a model for the restricted mean as a function of covariates, by using pseudo-observations that account for dependent censoring linked to a series of longitudinal measures (LAS). Simulation results show that our method performs well in situations comparable with the LAS setting. Applying wait list and post-transplant model results that account for dependent censoring to wait list patients, we obtain estimates of transplant benefit that are larger for many of the more urgent patients in need of transplant. The difference in LAS for an individual, when properly accounting for dependent censoring, has high impact on the priority and timing of an organ offer for these patients. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: dependent censoring; pseudo-observation; restricted mean life; survival; transplant benefit

1. Introduction

For the statistical aspects of lung transplant candidate data to be appreciated, some background is required. To get a lung transplant in the USA, candidates register with the Organ Procurement and Transplantation Network (OPTN) to obtain placement on a lung waiting list. When these transplants were infrequent, a first come, first served policy seemed equitable to those waiting for transplant. But as the demand increased, so did the average waiting time to transplant, and an increasing number of end-stage lung disease patients died while waiting for an organ offer. Published in 1998 and enacted in 2000, a Final Rule, crafted by the Health Resources and Services Administration of the US Department of Health and Human Services, dictated, among other things, that a more equitable organ allocation algorithm needed to be created and maintained based on objective medical data [1].

In the case of patients waiting for a lung transplant, a statistical algorithm (lung allocation score or LAS) for ranking patients was implemented on May 4, 2005 [2]. The LAS includes measures of the net benefit of the transplant to the candidate as well as the candidate's clinical urgency over the upcoming year. The measure for net transplant benefit is calculated by subtracting the patient's estimated number of days lived on the waiting list without a transplant over the next year (i.e., transplant urgency) from the estimated number of days lived during the first year following transplantation (i.e., post-transplant survival measure). This is an individual measure of transplant benefit rather than a collective measure of transplant benefit that is sometimes obtained through the use of a time-dependent covariate for transplant, as in analyses carried out for the original Stanford Heart Transplant study [3].

Figure 1 shows the estimated patient-specific urgency by anticipated transplant benefit for a group of lung candidates actively listed between September 1, 2006 and September 30, 2008. It was recognized

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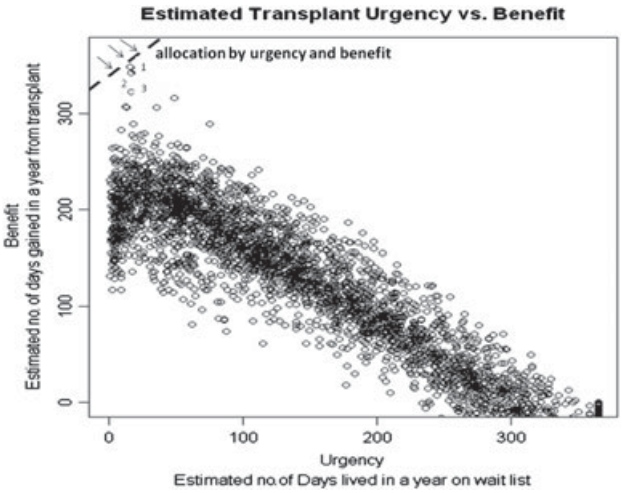


Figure 1. Scatterplots of estimated days lived in a year on the waiting list versus estimated 1-year transplant benefit (transplant benefit = estimated post-transplant days lived in next year minus estimated waiting list days lived in a year without transplant) at the time of listing for $n = 3701$ patients. Allocation follows according to the movement of the diagonal line from the top left to the bottom right. Patients marked as 1, 2, and 3 are the first patients to be offered a lung transplant.

that ordering patients based on urgency alone, that is, from left to right in Figure 1, might prioritize patients with little or no transplant benefit, whereas ordering patients solely based on higher benefit, that is, from top to bottom of Figure 1, would likely result in many deaths of urgent patients who would not live until an organ offer. In the end, a compromise was reached so that both benefit and urgency were taken into consideration, that is, allocation according to the diagonal line moving from top left to bottom right of Figure 1. The LAS takes the difference between the net transplant benefit and the transplant urgency, with the final score normalized to produce a range from 0 to 100.

Estimates for both urgency and benefit depend on accurate estimation of wait list days lived during the year following listing. Patients' risk factors measured at listing include diagnosis, age, body mass index (BMI), diabetes, assistance with activities of daily living (ADL), 6-min walk distance (6MWD), forced vital capacity (FVC), oxygen (O_2) requirement at rest, pulmonary artery (PA) systolic pressure, partial pressure of carbon dioxide in the blood (PCO_2), continuous mechanical ventilation, creatinine, and cardiac index. For estimating days lived in the year following transplant, risk factors used in the LAS include diagnosis, age, assistance with ADL, 6MWD, FVC, continuous mechanical ventilation, cardiac index, O_2 requirement at rest, and creatinine. More details on statistical methodology will be given shortly.

The LAS has been largely successful since its implementation. The number of deaths on the waiting list and the waiting time for transplant have decreased. As opposed to 512 wait list deaths in 2004, there were only 266 deaths in 2008, in spite of more urgent patients being listed in 2008 [4]. Listing behavior of end-stage lung patients has changed dramatically since the implementation of LAS. With no advantage to accruing waiting time in the new allocation score, the number of patients actively listed for transplant decreased from 2163 candidates at the end of 2004 to 1089 patients at the end of 2008 [4]. That is, patients not yet ready to accept an organ offer began to remove themselves from the active candidate pool and delay entering the pool until further progression of disease. As a consequence, the median waiting time has dropped from 792 days in 2004 to 200 days or less after the LAS was used [4]. As successful as the LAS has been, national policy dictates that the algorithm must be continually updated to reflect more recent cohorts of patients, and this is occurring right now in a post-LAS implementation cohort.

The estimated number of days lived during a year in the calculation of LAS is sometimes called the restricted mean life. When estimated nonparametrically, under independent censoring, it is typically defined using the area under a Kaplan–Meier (KM) survival curve [5] for the period of interest (0 to 1 year). In the original development of the LAS, a Cox proportional hazards (PH) model [6] was used to estimate each individual's survival curve, and the area under the first year of the survival curve was used to estimate the restricted mean life. We feel that a more appropriate model would target the restricted

mean more directly, rather than modeling the hazard ratio. Not only would regression parameters be more directly linked to the restricted mean of interest, but also increased transparency of how scores for the LAS are produced would be welcomed by patients and physicians following allocation scores.

Andersen *et al.* [7] introduced one modeling strategy for the restricted mean. First, they generated pseudo-observations (POs) that have the same conditional mean of interest for regression modeling as the original individual level data. The advantage of creating POs in the first modeling step is that they can be modeled using traditional uncensored linear models. Pseudo-observations for mean restricted life, as defined by Andersen, Hansen, and Klein, are created using marginal estimates of restricted mean life; that is, $\hat{\alpha}_0 = \hat{E}[\min(\tau, T)] = \int_0^\tau \hat{P}(T > t)\mathrm{d}t$, where T denotes the failure time, τ is the upper limit of a time window of interest, and $\hat{P}(T > t)$ is the KM estimate. Then, the pseudo-observation (PO) for each individual, also known from jackknife methodology, is calculated as

$$n\hat{\alpha}_0 - (n-1)\hat{\alpha}_0^{-i}, \tag{1}$$

where $\hat{\alpha}_0^{-i} = \int_0^\tau \hat{P}^{-i}(T > t)\mathrm{d}t$ with $\hat{P}^{-i}(T > t)$, the KM estimate based on data leaving out patient i.

The intuition behind POs given in (1) is that any nonparametric estimator of $\alpha_0 = E[\min(\tau, T)]$ is also implicitly an estimator of

$$E_Z[E[\min(\tau, T)|Z]], \tag{2}$$

where the inner expectation is of interest in regression modeling. In the case where the outermost expectation is viewed with respect to the empirical distribution of Z, with $\tilde{\alpha}_0 = \frac{1}{n}\sum_{i=1}^n E[\min(\tau, T)|Z_i]$, POs take the form $n\tilde{\alpha}_0 - (n-1)\tilde{\alpha}_0^{-i} = n[\frac{1}{n}\sum_{i=1}^n E[\min(\tau, T)|Z_i]] - (n-1)[\frac{1}{n-1}\sum_{j=1, j\neq i}^n E[\min(\tau, T)|Z_j]] = E[\min(\tau, T)|Z_i]$, the quantity of interest in regression modeling. Andersen, Hansen, and Klein make the case that $\hat{\alpha}_0$ and $\tilde{\alpha}_0$ are both consistent for α_0; hence, POs based on (1), which are estimable from censored data, can be used to estimate regression parameters predicting $E[\min(\tau, T)|Z_i]$ by using readily available linear models. That is, models based on individual specific POs in (1), $i = 1, \ldots, n$ will have regression parameters similar to a model fit to $\min(\tau, T)$ values, $i = 1, \ldots, n$, if these values were available (uncensored). Graw *et al.* [8] formalize this argument and verify appropriate asymptotics of parametric estimates.

Any modeling strategy for estimating restricted means requires taking into account an especially interesting dependent censoring issue when updating the LAS to a more current cohort of patients. By removing more urgent patients from the waiting list to get transplanted (via the LAS), our resulting analysis data set is dependently censored in direct relationship to daily changing LAS of individual patients. In considering a restricted mean model approach, KM estimates used in creating POs are especially subject to dependent censoring bias. Inverse probability of censoring weighted (IPCW) methods, such as those discussed by Robins and Finkelstein [9], Robins [10], Robins and Rotnitzky [11], Satten *et al.* [12], and Scharfstein *et al.* [13] among others, have been successful in counteracting this type of bias and can be used to consistently estimate $S_T(t) = P(T > t)$, cumulative hazard functions, and other quantities of interest.

In this paper, we propose to estimate transplant urgency and benefit by using a PO approach to estimate 1-year restricted mean life separately in wait list and post-transplant cohorts. Our approach will modify each wait list restricted mean PO by including IPCW-based survival estimates in place of KM estimates to account for dependent censoring linked to time-dependent LAS of patients. We will estimate a 1-year transplant benefit for each patient by using a restricted mean model estimate of days lived in a year following transplant minus a separate restricted mean model estimate of days lived in a year following listing without transplant.

We structure the rest of the manuscript as follows. In Section 2, we formally describe the mean structure for restricted life given covariates, an appropriate PO approach to fit this mean structure, and the IPCW implementation of POs required to account for censoring via time-dependent LAS. Section 3 briefly shows simulation studies that ensure that our overall analysis approach in the presence of dependent censoring is sound in finite sample populations. In Section 4, we present a restricted mean model for lung wait list candidates and separately for post-transplant recipients to be used in constructing an LAS for each patient. We provide results on estimated days of life without transplant in a 1-year period (urgency) as well as estimated days gained from transplant over the following 1-year period (benefit). We also display estimated LAS for lung transplant candidates by using the new methodology and also

provide results by using estimates of restricted means for lung candidates based on integrating both traditional and IPCW-adjusted Cox PH model survival curves. Discussion follows in Section 5.

2. Estimating restricted mean life by using inverse probability of censoring weighted pseudo-observation

2.1. Mean structure for restricted mean life

The mean structure for the restricted mean life is

$$E[\log\{\min(\tau, T)\}] = \beta^T Z, \tag{3}$$

where τ is fixed and is within the range of the observed data. When there is no censoring, uncensored data applied to model (3) becomes a standard linear model on $\log\{\min(\tau, T)\}$. However when censoring is present and informative, the use of observed data will lead to biased results.

Andersen *et al.* [7] formulated POs by using (1) and then fitted model (3) to the resulting POs by using standard linear models. An equally appropriate approach would be to fit the model of the restricted mean by using a log link. We have found that the intercept estimator is somewhat improved upon creating POs based on the transformed random variable $\log\{\min(\tau, T)\}$. That is, instead of creating POs based on $\hat{\alpha}_0 = \hat{E}[\min(\tau, T)] = \int_0^\tau \hat{S}(t)\mathrm{d}t$ and log transforming the pseudo-values, we will create POs based on marginal estimates of $\hat{\delta}_0 = \hat{E}[\log\{\min(\tau, T)\}]$. Let $Y = \log\{\min(\tau, T)\}$, ranging from $-\infty$ to $\log\tau$. Assume for the moment the simplest form of model (3), where $E[Y] = \delta_0$, that is, the marginal mean of $\log\{\min(\tau, T)\}$ that does not depend on any covariates. We may derive the mean of Y as follows:

$$\begin{aligned} E(Y) = \delta_0 = E[\log\{\min(\tau, T)\}] &= \int_0^\infty \log[\min(\tau, T)]\mathrm{d}F_T(t) \\ &= \int_0^\tau \log t \ \mathrm{d}F_T(t) + \int_\tau^\infty \log\tau \ \mathrm{d}F_T(t) \\ &= \int_0^\tau \log t \ \mathrm{d}(1 - S_T(t)) + \log\tau(1 - F_T(\tau)) \\ &= -\int_0^\tau \log t \ \mathrm{d}S_T(t) + \log\tau \cdot S_T(\tau). \end{aligned} \tag{4}$$

2.2. Pseudo-observation approach

From Equation (4) in Section 2.1, the marginal mean of $\log\{\min(\tau, T)\}$ can be estimated via

$$\hat{\delta}_0 = \hat{E}(Y) = -\int_0^\tau \log t \ \mathrm{d}\hat{P}(T > t) + \log\tau \cdot \hat{P}(T > \tau) \tag{5}$$

where $\hat{P}(T > t)$ is some marginal survival estimate on the original time scale. In the context of dependent censoring, we will describe a consistent estimate for $S_T(t)$ in Section 2.3, $\hat{S}_T^W(t)$, that uses an inverse weight approach and show that its use in (5) gives a consistent estimate of δ_0.

Arguments justifying the use of POs in fitting (3) proceed similarly to the original justification made for the PO approach. That is, any estimator of δ_0 is implicitly an estimator of $E_Z[E[\log\{\min(\tau, T)\}|Z]]$. When the outermost expectation is viewed with respect to the empirical distribution of Z with $\tilde{\delta}_0 = \frac{1}{n}\sum_{j=1}^n E[\log\{\min(\tau, T)\}|Z_j]$ and $\tilde{\delta}_0^{-i} = \frac{1}{n-1}\sum_{j=1, j\neq i}^n E[\log\{\min(\tau, T)\}|Z_j]$, POs, $n\tilde{\delta}_0 - (n-1)\tilde{\delta}_0^{-i}$, reduce to $E[\log\{\min(\tau, T)\}|Z_i]$, which matches in expectation the quantity that we wish to model. Although both $\tilde{\delta}_0$ and $\hat{\delta}_0$ are consistent for δ_0, the latter gives the most useful form for estimating δ_0 based on censored survival data. So, similar to the strategy employed on the scale of α_0, we base our inference on POs, $n\hat{\delta}_0 - (n-1)\hat{\delta}_0^{-i}$, where $\hat{\delta}_0^{-i}$ is estimated from (5) leaving out individual i.

Once POs, $\mathcal{PO} = (\mathcal{PO}_1, \mathcal{PO}_2, \ldots, \mathcal{PO}_n)$ are obtained, the regression model (3) can be estimated using $\mathcal{PO}$ as the response. Our parameter estimates become $\hat{\beta} = (Z^T Z)^{-1} Z^T \mathcal{PO}$ with estimated covariance matrix $\hat{V}(\hat{\beta}) = \hat{\sigma}^2 (Z^T Z)^{-1}$, where $\hat{\sigma}^2$ is computed in the usual way as $(\mathcal{PO} - \mathbf{Z}\beta)^T(\mathcal{PO} - \mathbf{Z}\beta)/(n-p)$ for p parameters in the model. These results can be estimated from nearly any statistical software package once $\mathcal{PO}_i, i = 1, \ldots, n$ are obtained.

2.3. *Inverse probability of censoring weighted estimates of survival probability*

In the case of dependent censoring, care needs to be taken in estimating $S_T(t)$. Of all the potential methods for consistently modeling marginal survival in the presence of dependent censoring, methods based on inverse probability censoring weights used by Robins and his coauthors are perhaps the easiest to apply when there are many time-dependent measures over time, so we selected that approach for estimating $S(t)$ for the lung allocation data.

First, one estimates the censoring survival function at any fixed time t, denoted by $\hat{K}_i^{\mathbf{V}}(t) = P(C_i > t|\bar{\mathbf{V}}_i(t))$, where C_i is the censoring time for patient i and $\bar{\mathbf{V}}_i(t) = \{\mathbf{V}_i(u); 0 \leqslant u \leqslant t\}$ is the patient's recorded history up to time t of a vector of possibly time-dependent covariates, $\mathbf{V}_i$, that predict the censoring time C_i. In the case of the lung allocation data, C_i is the time a patient is removed from the lung wait list for transplant, and $\bar{\mathbf{V}}_i(t)$ consists of patient LAS used to rank patients for transplant from time 0 (listing time) to time t as well as a few additional predictors including race, gender, blood type, height, and active waiting status. In calculating the contribution of a subject at risk at time t, the subject is given a weight inversely proportional to his or her estimated probability of remaining uncensored until time t with a history of $\bar{V}_i(t)$, that is,

$$\hat{W}_i(t) = 1/\hat{K}_i^{\mathbf{V}}(t).$$

The Cox model for censoring survival is often used in inverse weighting approaches because of its flexibility in modeling time-dependent covariates. Because time-dependent LAS is an issue in our case, this is the approach that we adopt as well. A Cox model for the censoring hazard is given by

$$\lambda_Q\{t|\bar{\mathbf{V}}(t)\} = \lambda_{Q0}(t)\exp\{\gamma'\mathbf{V}(t)\}. \tag{6}$$

In the case of the lung wait list data, $\gamma'\mathbf{V}(t)$ becomes γ_1 LAS$(t) + \gamma_2$ race $+ \gamma_3$ gender $+ \gamma_4$ blood type $+$ γ_5 height $+ \gamma_6\, I$ (active waiting status). Then, a consistent estimate of the probability that subject i gets censored after time t, $K_i^V(t)$, becomes

$$\hat{K}_i^V(t) = \exp\{-\sum_{k=1}^{n}\int_0^t \frac{e^{\hat{\gamma}'\mathbf{V}_i(u)}\mathrm{d}N_{Q_k}(u)}{\sum_{j=1}^n Y_j(u)e^{\hat{\gamma}'\mathbf{V}_j(u)}}\},$$

where $N_{Q_i} = I(X_i \leqslant u, \delta_i = 0)$ is the observable counting process for censoring (transplant), with X_i as the observed event time and δ_i as the censoring indicator, and $Y_i(u) = I(X_i \geqslant u)$ is the risk indicator for subject i at time u. The subject-specific weight then becomes

$$\hat{W}_i(t) = 1/\hat{K}_i^V(t) = \exp\{\sum_{k=1}^{n}\int_0^t \frac{e^{\hat{\gamma}'\mathbf{V}_i(u)}\mathrm{d}N_{Q_k}(u)}{\sum_{j=1}^n Y_j(u)e^{\hat{\gamma}'\mathbf{V}_j(u)}}\}.$$

An IPCW version of Nelson–Aalen estimator for $\Lambda(t)$ is calculated using

$$\hat{\Lambda}^W(t) = \sum_{i=1}^{n}\int_0^t \frac{\mathrm{d}N_{T_i}(u)\cdot\hat{W}_i(u)}{\sum_{j=1}^n Y_j(u)\cdot\hat{W}_j(u)},$$

where $N_{T_i}(u) = I(X_i \leqslant u, \delta_i = 1)$ is the observable counting process for death. Then, the survival probability is estimated with $\hat{S}^W(t) = \exp\{-\hat{\Lambda}^W(t)\}$. The adjusted POs described in Section 2.2 use $\hat{P}(T > t) = \hat{S}^W(t)$ in Equation (5). Product-integral versions of inverse weighted survival functions such as those described by Satten and Datta [14] would also be appropriate for use as an alternative to $\hat{S}^W(t)$.

Proof of consistency of $\hat{S}_T^W(t) = \exp(-\hat{\Lambda}^W(t))$ for $S_T(t)$ proceeds from consistency of $\hat{\Lambda}^W(t)$ for $\Lambda(t)$, a property that was studied extensively by Robins [10] and Robins and Finkelstein [9]. Conditions required for this consistency to hold are that (i) $\lambda_Q(t|\bar{V}(t))$ follows the form given in Equation (6) and (ii) $\lambda_Q(t|\bar{V}(t), T, T > t) = \lambda_Q(t|\bar{V}(t), T > t)$. Consistency of $\hat{E}(Y)$, used in creating POs in this manuscript, follows from noting that $\int_0^\tau \log t\ \mathrm{d}\hat{S}_T^W(t)$ in (5) can be written as

$$\lim_{m\to\infty}\sum_{j=1}^{m}\log t_j\ \triangle\ \hat{S}_T^W(t_j) \xrightarrow{p} \lim_{m\to\infty}\sum_{j=1}^{m}\log t_j\ \triangle\ S_T(t_j) = \int_0^\tau \log t\ \mathrm{d}S_T(t).$$

3. Simulation study

To validate the method used in analyzing the lung candidate wait list data subjected to dependent censoring, we conduct a simulation study comparing parameter estimates of model (3) by using linear regression when (i) $\log[\min(\tau, T)]$ is uncensored, (ii) $\log[\min(\tau, T)]$ is subject to censoring and is replaced by log-transformed POs defined by (1), and (iii) $\log[\min(\tau, T)]$ is subject to censoring and is replaced by IPCW-adjusted POs.

In each simulation, we perform the following procedures.

Step 1: We simulate Z_0 from a Bernoulli(0.5) distribution, Z_1 from Bernoulli(0.5), and Z_2 from Uniform(0,1), where Z_0 is a binary covariate measured at time 0, Z_1 is the time-dependent covariate measured at time $t_1 = 0.2$, and Z_2 is a continuous time-independent covariate.

Step 2: We simulate failure times, T_i, from piecewise exponential distributions; that is, $T_i \sim \exp(\lambda_{z_0})$ before time t_1, and $T_i \sim \exp(\lambda_{z_0 z_1})$, after time t_1, where $\lambda_0 = 0.3$ and $\lambda_1 = 0.2$ are fixed and $\lambda_{00}, \lambda_{01}, \lambda_{10}$, and λ_{11} are solved so that the mean structure $E[\log\{\min(\tau, T)\}] = \beta_0 + \beta_1 Z_0 + \beta_2 Z_2$ is satisfied for a pre-specified $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)$. That is, although T_i is influenced by the time-dependent covariate, Z_1, the restricted mean of interest is captured by baseline predictors Z_0 and Z_2. We provide more details for these calculations in Appendix A.

Step 3: We also generate dependent censoring times C_i from piecewise exponential distributions and obtain hazard rates based on the Cox model $\lambda^C(t|\bar{\mathbf{Z}}(\mathbf{t})) = \lambda_0^C(t)\exp\{\gamma_0 Z_0 + \gamma_1 I[Z_0 = 0, Z_1 = 1, t > t_1] + \gamma_2 I[Z_0 = 1, Z_1 = 0, t > t_1] + \gamma_3 I[Z_0 = 1, Z_1 = 1, t > t_1] + \gamma_4 Z_2\}$, where $\lambda_0^C(t) = 0.15$ for $t \leqslant t_1$ and $\lambda_0^C(t) = 0.4$ for $t > t_1$, $\gamma_0 = 0.3, \gamma_1 = -1.4, \gamma_2 = 0.5, \gamma_3 = -1.5$, and $\gamma_4 = 1$. So, Z_0, Z_2, and time-dependent Z_1 influence censoring.

For each scenario of $\boldsymbol{\beta}$, we run 1000 simulations with $\tau = 5$ years and either $n = 150$ or $n = 300$ patients. Results for the scenario with $\beta_0 = 0.8, \beta_1 = \beta_2 = 0$ are located in part (1) of Table I. In this

Table I. Comparison of estimates from model (3) by using uncensored observations (uncensored), the traditional pseudo-observation (PO) approach, and the inverse probability of censoring weighted (IPCW) PO approach under two scenarios, 1000 iterations.

Parameter	Uncensored	PO	IPCW PO	Uncensored SE*	PO SE	IPCW PO SE	Uncensored ESD†	PO ESD	IPCW ESD
(1) Covariate effects are zero, sample size = 150									
$\beta_0 = 0.8$	0.808	0.105	0.702	0.210	0.425	0.243	0.220	0.576	0.235
$\beta_1 = 0$	0.012	−0.266	0.059	0.187	0.380	0.217	0.195	0.400	0.215
$\beta_2 = 0$	−0.013	0.154	−0.022	0.325	0.658	0.377	0.328	0.705	0.372
Covariate effects are zero, sample size = 300									
$\beta_0 = 0.8$	0.798	0.137	0.697	0.148	0.294	0.172	0.153	0.460	0.163
$\beta_1 = 0$	0.001	−0.296	0.049	0.132	0.263	0.154	0.134	0.281	0.155
$\beta_2 = 0$	0.008	0.170	0.000	0.230	0.456	0.267	0.234	0.472	0.262
(2) Covariate effects are nonzero, sample size = 150									
$\beta_0 = 1$	0.998	0.759	0.891	0.202	0.309	0.239	0.205	0.324	0.220
$\beta_1 = -0.8$	−0.799	−1.025	−0.796	0.181	0.276	0.214	0.180	0.326	0.194
$\beta_2 = -0.5$	−0.497	−0.443	−0.426	0.314	0.479	0.372	0.315	0.496	0.351
Covariate effects are nonzero, sample size = 300									
$\beta_0 = 1$	0.992	0.772	0.883	0.142	0.206	0.170	0.146	0.220	0.158
$\beta_1 = -0.8$	−0.799	−0.971	−0.792	0.128	0.184	0.152	0.127	0.225	0.138
$\beta_2 = -0.5$	−0.486	−0.413	−0.417	0.221	0.319	0.263	0.224	0.325	0.247

*SE is the average of estimated standard errors across 1000 iterations.
†ESD is the empirical standard deviation of 1000 parameter estimates.

case, the true baseline covariate effects on survival are zero, but dependent censoring is being driven by the time-dependent covariate. The unadjusted PO method gives more biased estimates for all the parameters, especially for β_0 and β_1. The IPCW-adjusted PO method reduces bias substantially and also has smaller standard error after adjusting for dependent censoring. When both baseline covariates are equal to 0.5, the PO method underestimates the time lived during the 5-year period by 14 months on average whereas the IPCW PO method is off by only 2 months over the 5-year period. Empirical standard deviations were comparable with standard errors averaged across simulations, with the exception of the intercept term for the traditional PO method. Coverage for the traditional PO intercept was 66.7%, in spite of its much wider confidence interval width, because of the increased bias and underestimated variability for that term.

Simulation results for the scenario with $\beta_0 = 1$, $\beta_1 = -0.8$, and $\beta_2 = -0.5$, that is, nonzero baseline covariate effects, are located in part (2) of Table I. Again, bias is higher for β_0 and β_1 by using the traditional PO, but in this case, the value for β_2 is largely unaffected by the dependent censoring. The adjusted PO method has both smaller bias and smaller standard error for β_0 and β_1. The overall degree of bias for estimating the time lived during the 5-year period was smaller in this scenario, with the traditional PO method off by approximately 4–5 months of life lived and the IPCW PO method off by 1 month over the 5-year period for a patient with $z_0 = z_2 = 0.5$.

Parameter estimates were similar for cases with $n = 150$ and $n = 300$. We were unable to explore larger sample sizes because of limitations in computing speed, so it is not clear at what sample size remaining bias with the IPCW PO method vanishes. Across a grid of possible covariate values for these two scenarios, the bias for the IPCW PO method did not exceed 3.6 months over the 5 years of follow-up. But bias as high as 16 months was seen using the unadjusted PO method.

4. Example

We organize this section into three components. Section 4.1 summarizes analyses for the lung wait list candidates, Section 4.2 summarizes analyses for the post-transplant cohort, and Section 4.3 interprets these analyses in terms of urgency, benefit, and LAS calculated for the wait list patient cohort. Results are typically reported by the four defined diagnosis groups A, B, C, and D. Diagnosis group A is obstructive lung disease, primarily chronic obstructive pulmonary disease. Group B consists of pulmonary vascular diseases, primarily idiopathic pulmonary arterial hypertension. Group C consists of cystic fibrosis, as well as immunodeficiency disorders. Group D is restrictive lung disease, primarily interstitial pulmonary fibrosis. The OPTN Thoracic Committee classifies all lung wait list patients into one of these four diagnosis groups for the purpose of estimating diagnosis group influence on urgency and benefit, and modeling interactions across diagnosis groups. A few diagnoses, such as bronchiectasis, are given a parameter to distinguish their estimated days of life from that of their overall diagnosis group. These parameters have historically not been significantly different from those of their overall diagnosis group, and yet patient advocates have actively pursued the ability to estimate urgency and benefit more specifically for their patients to the extent that enough data are available to do so.

4.1. Lung candidate analysis

The wait list candidate data contain 3701 lung candidates aged 12 years and above who were newly listed in the lung wait list during September 1, 2006 and September 30, 2008. Censoring within 1 year of listing only occurs when a candidate is transplanted, which was the case with 2698 (73%) of the candidates. By diagnosis group, 923 (70%) of 1317 group A candidates, 67 (58%) of 116 group B candidates, 294 (69%) of 428 group C candidates, and 1414 (77%) of 1840 group D candidates were transplanted. Historically, of the four groups, diagnosis group D has had the poorest wait list survival, and with the LAS based in part on urgency, this group also currently experiences the shortest time to transplant. The median time to transplant for group D is only 71 days, as opposed to 170 days for group A, 221 days for group B, and 126 days for group C. We show baseline characteristics by primary diagnosis group in Table II. At listing, group D patients typically have very high severity and poor physiologic reserve. In contrast, group A patients have historically had much lower urgency for transplant as measured by survival. These patients are often seeking a transplant based on improving quality of life as opposed to lengthening life.

Table II. Baseline characteristics by diagnosis group for 3701 lung wait list patients.

Characteristics	Group A (primarily COPD) $n = 1317$	Group B (primarily iPAH) $n = 116$	Group C (primarily CF) $n = 428$	Group D (primarily IPF) $n = 1840$
Physiologic reserve				
Age (years)	57.6 ± 8.1*	45.9 ± 15.1	27.9 ± 10.3	55.9 ± 11.6
BMI (kg/m^2)	24.6 ± 4.3	24.8 ± 4.3	19.1 ± 2.9	26.7 ± 4.6
Diabetes	11.0%†	10.3%	48.4%	22.9%
No assistance with ADL	10.4%	9.4%	20.9%	9.6%
6-min walk distance (feet)	770.5 ± 356.0	733.3 ± 480.8	902.2 ± 508.0	755.8 ± 482.0
Severity				
FVC (% predicted)	52.4 ± 17.2	69.3 ± 23.1	38.1 ± 11.1	47.0 ± 16.7
O_2 requirement at rest (l/min)	3.1 ± 2.5	4.6 ± 5.1	3.4 ± 4.1	4.6 ± 4.7
PA systolic (mmHg)	38.0 ± 10.8	78.5 ± 24.0	38.8 ± 10.6	42.9 ± 17.0
PCO_2 (mmHg)	50.3 ± 11.7	43.5 ± 7.0	56.2 ± 20.0	45.9 ± 11.6
Continuous mechanical ventilation	1.1%	2.6%	7.5%	6.1%
Serum creatinine (mg/dl)	0.82 ± 0.2	0.94 ± 0.3	0.67 ± 0.2	0.91 ± 0.3
Cardiac index< 2.0 (l/min/min^2)	5.5%	35.6%	1.6%	7.8%

*For continuous variables, the numbers shown are mean $\pm$ standard deviation.
†For binary variables, the numbers shown are proportions.
ADL, activities of daily living; BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; iPAH, idiopathic pulmonary arterial hypertension; IPF, interstitial pulmonary fibrosis; PA, pulmonary artery; PCO_2, partial pressure of carbon dioxide.

Table III. Proportional hazards censoring model (3701 candidates).

Parameter	HR	95% CI	p-value
Characteristic at listing			
Female (versus male)	0.72	(0.63, 0.82)	<.0001
Race: Black (versus White)	0.81	(0.68, 0.95)	0.0116
Race: Other (versus White)	0.91	(0.77, 1.08)	0.3016
Height: $<5'3''$ (versus $>5'9''$)	0.54	(0.45, 0.65)	<.0001
Height: $5'3''$ to $5'6''$ (versus $>5'9''$)	0.73	(0.62, 0.86)	0.0001
Height: $5'6''$ to $5'9''$ (versus $>5'9''$)	0.80	(0.71, 0.90)	0.0001
Blood type: B (versus A)	1.06	(0.91, 1.23)	0.4801
Blood type: O (versus A)	0.92	(0.84, 1.02)	0.1118
Blood type: AB (versus A)	1.07	(0.85, 1.33)	0.5669
Time-dependent patient condition and listing status			
LAS $= 0$ (versus LAS > 0)	0.16	(0.02, 1.18)	0.0728
LAS: linear spline for 30+	1.12*	(1.06, 1.19)	<.0001
LAS: linear spline for 35+	0.98†	(0.91, 1.06)	0.6779
LAS: linear spline for 40+	0.95‡	(0.91, 0.99)	0.0070
LAS: linear spline for 60+	0.97§	(0.95, 0.98)	<.0001
Inactive status (versus active)	0.00	(0, >1000)	0.8780
Off the wait list (versus active)	0.00	(0, >1000)	0.9410

Inverse weights based on this model are capped at 20.
*Hazard ratio (HR) corresponding to one unit increase for lung allocation score (LAS) 30+ relative to those with $0 <$ LAS < 30.
†HR corresponding to spline term for LAS 35+, giving HR due to one unit increase in LAS in the range $35 \leqslant$ LAS < 40 of $1.12 * 0.98 = 1.10$ relative to $0 <$ LAS < 30.
‡HR corresponding to spline term for LAS 40+, giving HR due to one unit increase in LAS in the range $40 \leqslant$ LAS < 60 of $1.12 * 0.98 * 0.95 = 1.04$ relative to $0 <$ LAS < 30.
§HR corresponding to spline term for LAS 60+, giving HR due to one unit increase in LAS in the range LAS $\geqslant 60$ of $1.12 * 0.98 * 0.95 * 0.97 = 1.01$ relative to $0 <$ LAS < 30.

We use the P(censoring occurs after time t|candidate's history up to and including t) to calculate an inverse weight used in consistent estimation of survival curves and adjusted POs as described in Sections 2.2 and 2.3. In particular, we use a time-dependent Cox model for time to censoring, which

includes patients' daily updated LAS, gender, race, blood type, status (active, inactive, offlist), and height, as given in Equation (6). We summarize parameter estimates from the Cox model on the censoring hazard in Table III. Probability of transplant is strongly influenced by current LAS values. Although one might expect the probability of transplant to increase monotonically as current LAS increases, in fact, the higher transplant priority is tempered by a lower chance of surviving until an organ becomes available for those with the highest LAS values. This feature is reflected in the parameter estimates shown.

To estimate lung candidate urgency, we fit model (3) by using both IPCW-adjusted POs and traditional POs. For comparison, we estimate restricted means for lung candidates by integrating traditional and IPCW-adjusted survival curves based on Cox model [6]. Predictors included in all lung candidate models are the same as those proposed by the OPTN Thoracic Committee in modeling wait list survival for this cohort [15]. The Thoracic Committee has vetted extensively all predictors as being worthy of inclusion in the algorithm based on statistical and/or clinical validity based on either the current or

Table IV. Lung wait list results for model (3) by using IPCW PO and traditional PO methods for 3701 lung candidates.

	IPCW PO			Traditional PO		
	$e^{\hat{\beta}}$*	95% CI	p-value	$e^{\hat{\beta}}$	95% CI	p-value
(Intercept)	102.15	(15.96, 653.55)	<0.0001	301.71	(162.16, 561.37)	<0.0001
Diagnosis group (ref = group A, primarily COPD)						
Group B (primarily iPAH)	0.19	(0.05, 0.73)	0.0158	0.25	(0.16, 0.39)	<0.0001
Group C (primarily CF)	0.57	(0.17, 1.90)	0.3627	0.56	(0.38, 0.84)	0.0047
Group D (primarily IPF)	0.11	(0.03, 0.38)	0.0004	0.40	(0.27, 0.60)	<0.0001
Diagnosis†						
Bronchiectasis	0.76	(0.21, 2.72)	0.6694	0.98	(0.64, 1.50)	0.9230
Lymphangioleiomyomatosis	1.25	(0.10, 16.41)	0.8639	0.93	(0.39, 2.20)	0.8711
Obliterativebronchiolitis	0.25	(0.03, 1.86)	0.1744	1.61	(0.82, 3.17)	0.1667
Pulmonary fibrosis other	0.77	(0.37, 1.59)	0.4741	1.04	(0.82, 1.33)	0.7445
Sarcoidosis and PA mean >30 mmHg	0.46	(0.16, 1.37)	0.1641	1.37	(0.95, 1.97)	0.0910
Sarcoidosis and PA mean ⩽30 mmHg	0.84	(0.22, 3.13)	0.7893	0.64	(0.41, 1.00)	0.0480
Physiologic reserve						
Age (years)	1.00	(0.98, 1.02)	0.9919	1.00	(1.00, 1.01)	0.8456
BMI (kg/m^2)	1.07	(1.03, 1.11)	0.0011	1.03	(1.01, 1.04)	0.0001
Diabetes	0.49	(0.33, 0.73)	0.0005	0.92	(0.80, 1.05)	0.2131
No assistance with ADL (ref = some/total assistance with ADL)	1.08	(0.65, 1.80)	0.7609	1.00	(0.85, 1.19)	0.9642
6-min walk (per 100 ft)	1.07	(1.03, 1.12)	0.0012	1.04	(1.02, 1.05)	<0.0001
Severity						
FVC for group D (per 10% predicted)	1.25	(1.08, 1.43)	0.0019	1.06	(1.01, 1.11)	0.0243
O_2 requirement for groups A, C, and D (l/min)	0.87	(0.83, 0.91)	<0.0001	0.92	(0.90, 0.93)	<0.0001
PA systolic (per 10 mmHg) for group A	0.91	(0.71, 1.16)	0.4331	0.94	(0.87, 1.02)	0.1613
PCO_2 increase of ⩾15%	1.03	(0.41, 2.59)	0.9449	1.00	(0.73, 1.36)	0.9889
PCO_2 (mmHg)	1.00	(0.99, 1.02)	0.6560	0.99	(0.99, 1.00)	0.0068
Continuous mechanical ventilation	0.07	(0.03, 0.20)	<0.0001	0.13	(0.10, 0.18)	<0.0001
Creatinine (mg/dl)	0.60	(0.32, 1.12)	0.1111	0.91	(0.74, 1.13)	0.3999
Cardiac index <2.0 (l/min/min^2)	0.48	(0.25, 0.94)	0.0315	0.62	(0.50, 0.77)	<0.0001

*For risk factors, $e^{\hat{\beta}}$ acts multiplicatively on the number of days lived in a year.

†The OPTN Thoracic Committee grouped these diagnoses into larger diagnosis groups (A, B, C, and D) for the purpose of modeling risk factors that may vary by diagnosis group. Bronchiectasis, lymphangioleiomyomatosis, and sarcoidosid and PA mean ⩽30 mmHg share risk factor parameters with diagnosis group A; Eisenmenger with group B; and obliterativebronchiolitis, pulmonary fibrosis other, and sarcoidosis and PA mean >30 mmHg with group D.

ADL, activities of daily living; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; iPAH, idiopathic pulmonary arterial hypertension; IPCW PO, inverse probability of censoring weighted pseudo-observation; IPF, interstitial pulmonary fibrosis; PA, pulmonary artery; PCO_2, partial pressure of carbon dioxide.

a prior wait list cohort studied. In some cases, statistically insignificant parameters are maintained as placeholders with the expectation that statistical significance will re-assert itself in future cohorts; age, assistance with ADL, PA systolic, PCO_2, and creatinine fall into this category. With many fewer wait list deaths available for modeling purposes after LAS implementation, loss of statistical power has also been cited as an argument for maintaining a predictor in the LAS that has previously been shown to be statistically significant.

We show parameter estimates for fitting model (3) to patients awaiting transplant in Table IV. For risk factors, $e^{\hat{\beta}}$ acts multiplicatively on the number of days lived in a year. For instance, the estimated number of days lived is $102.15\times0.11\times1.07^{25}\times0.49\times1.07^{3}\times1.25^{5.5}\times0.87^{2}\times0.60^{0.8}=63$ days based on IPCW PO and $301.71\times0.40\times1.03^{25}\times0.92\times1.04^{3}\times1.06^{5.5}\times0.92^{2}\times0.91^{0.8}=283$ days based on traditional PO for a 55-year-old diagnosis group D patient who has a BMI of 25, has diabetes, requires assistance with ADL, walks 300 ft in 6 min, has 55% predicted FVC, requires 2 l/min of O_2 at rest, is not on a ventilator, has a stable creatinine of 0.8 mg/dl, has no partial pressure of CO_2 in their blood, and has a cardiac index >2 l/min/min^2. So, the unadjusted PO overestimates the number of days lived in the next year without transplant by 220 days for this very urgent group D patient. We show estimated KM and IPCW survival curves used in PO calculations in Figure 2; overestimation of days lived using the traditional PO model stems from the overestimation of survival by the KM method.

We show traditional and IPCW-adjusted Cox model hazard ratios estimated from the lung candidate data in Table V. The difference in area under the baseline survival curves over a year for the two methods was 11 days, with a more favorable survival profile without adjustment. Integrating a survival curve estimated from a traditional Cox PH model for this patient yields an estimated number of days lived of 330, which exceeds the estimate based on the unadjusted PO model. The IPCW-adjusted Cox model estimates a restricted mean of 301 for the same patient. Because bias due to dependent censoring has been accounted for in both IPCW PO method and IPCW Cox method, different modeling restrictions account for the observed differences in estimation. We provide additional information on urgency estimates based on different modeling paradigms in Section 4.3.

4.2. Lung recipient analysis

The post-transplant data contain 4784 patients aged 12 years and above who received a lung transplant between May 4, 2005 and September 3, 2008. One-year event rates from the time of transplant are perfectly known, that is, no censoring, with 816 (17%) deaths within the first year. We show results from fitting model (3) in the uncensored case in Table VI. For the same group D wait list patient described in Section 4.1, the estimated days lived in the first year following transplant is 254 days based on the model in Table VI. Recall that the estimated days gained in the first year following transplant is calculated using the estimated days lived 1 year post-transplant as in Section 4.2 minus the estimated days lived

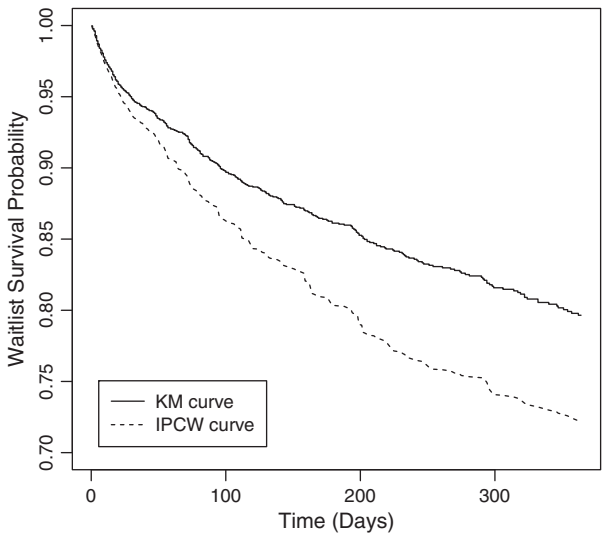


Figure 2. Wait list survival probabilities estimated using KM and IPCW.

Table V. Lung wait list survival model by using IPCW Cox and traditional Cox methods for 3701 lung candidates.

	Hazard ratio	IPCW Cox 95% CI	*p*-value	Hazard ratio	Traditional Cox 95% CI	*p*-value
Diagnosis group (ref = group A, primarily COPD)						
Group B (primarily iPAH)	2.75	(1.70, 4.45)	<.0001	2.47	(1.78, 3.44)	<.0001
Group C (primarily CF)	1.65	(1.05, 2.59)	0.0299	1.46	(1.09, 1.95)	0.0105
Group D (primarily IPF)	2.58	(1.56, 4.27)	0.0002	2.39	(1.75, 3.25)	<.0001
Diagnosis*						
Bronchiectasis	1.27	(0.78, 2.10)	0.3381	1.19	(0.86, 1.65)	0.3027
Lymphangioleiomyomatosis	1.10	(0.40, 2.98)	0.8529	0.93	(0.44, 1.93)	0.8358
Obliterativebronchiolitis	0.61	(0.19, 1.90)	0.3917	1.39	(0.89, 2.16)	0.1429
Pulmonary fibrosis other	1.07	(0.78, 1.49)	0.6673	0.80	(0.67, 0.96)	0.0180
Sarcoidosis and PA mean >30 mmHg	0.72	(0.49, 1.07)	0.1063	0.89	(0.73, 1.10)	0.2803
Sarcoidosis and PA mean ⩽30 mmHg	1.25	(0.80, 1.96)	0.3292	1.03	(0.76, 1.39)	0.8513
Physiologic reserve						
Age (years)	1.00	(1.00, 1.01)	0.6546	1.00	(1.00, 1.01)	0.4194
BMI (kg/m^2)	0.98	(0.97, 1.00)	0.0428	0.97	(0.96, 0.98)	<.0001
Diabetes	1.23	(1.04, 1.44)	0.0144	1.38	(1.25, 1.52)	<.0001
No assistance with ADL (ref = some/total assistance with ADL)	1.00	(0.82, 1.21)	0.9987	1.00	(0.88, 1.14)	0.9882
6-min walk (per 100 ft)	0.97	(0.95, 0.98)	0.0001	0.97	(0.96, 0.98)	<.0001
Severity						
FVC for group D (per 10% predicted)	0.93	(0.87, 0.99)	0.0161	0.94	(0.90, 0.97)	0.0005
O_2 requirement for groups A, C, and D (l/min)	1.11	(1.09, 1.13)	<.0001	1.10	(1.09, 1.11)	<.0001
PA systolic (per 10 mmHg) for group A	1.04	(0.94, 1.14)	0.4304	1.05	(0.99, 1.12)	0.0924
PCO_2 increase of ⩾15%	1.13	(0.79, 1.62)	0.5023	1.38	(1.08, 1.75)	0.0095
PCO_2 (mmHg)	1.01	(1.01, 1.02)	<.0001	1.01	(1.01, 1.01)	<.0001
Continuous mechanical ventilation	5.59	(4.08, 7.66)	<.0001	4.29	(3.49, 5.28)	<.0001
Creatinine (mg/dl)	1.57	(1.23, 2.01)	0.0003	1.68	(1.43, 1.98)	<.0001
Cardiac index <2.0 (l/min/min^2)	1.36	(1.07, 1.73)	0.0128	1.30	(1.11, 1.52)	0.0010

*The OPTN Thoracic Committee grouped these diagnoses into larger diagnosis groups (A, B, C, and D) for the purpose of modeling risk factors that may vary by diagnosis group. Bronchiectasis, lymphangioleiomyomatosis, and sarcoidosid and PA mean ⩽30 mmHg share risk factor parameters with diagnosis group A; Eisenmenger with group B; and obliterativebronchiolitis, pulmonary fibrosis other, and sarcoidosis and PA mean >30 mmHg with group D.
ADL, activities of daily living; BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; iPAH, idiopathic pulmonary arterial hypertension; IPCW PO, inverse probability of censoring weighted pseudo-observation; IPF, interstitial pulmonary fibrosis; PA, pulmonary artery; PCO_2, partial pressure of carbon dioxide.

1 year without transplant as in Section 4.1. So, the IPCW PO method estimates $254 - 63 = 191$ days gained during the first year after a transplant for this patient. All other methods indicate days of life lost if transplanted. The IPCW Cox method, the traditional PO method, and the unadjusted Cox method give $254 - 301 = -47$ days, $254 - 283 = -29$ days, and $254 - 330 = -76$ days, respectively.

4.3. Urgency, benefit, and lung allocation scores

Figure 3 shows boxplots of estimated transplant urgency for the 3701 wait listed patients by diagnosis group, using the two PO modeling paradigms laid out in Table IV and the two Cox modeling paradigms in Table V. By adjusting for dependent censoring, POs based on IPCW survival curves estimated a higher urgency in group D patients, which better matches group D survival experience seen before organ allocation took urgency into account (i.e., before LAS-induced dependent censoring was introduced). The integrated IPCW Cox survival curves also show more urgency than the integrated Cox survival curves that do not take into account dependent censoring. The interquartile range for urgency estimates based on integrated Cox PH survival curves is decidedly more narrow than the range of estimated restricted means based on model 3 for either the PO or the IPCW PO methods. In addition, the Cox modeling approaches tend to estimate many more days lived without transplant compared with the PO methods.

Table VI. Lung post-transplant results for model (3) for 4784 transplant recipients (no censored data).

	$e^{\hat{\beta}}$*	95% CI	p-value
(Intercept)	344.42	(303.36, 391.03)	<0.0001
Diagnosis group (ref = group A, primarily COPD)			
Group B (primarily iPAH)	0.65	(0.52, 0.81)	0.0002
Group C (primarily CF)	0.92	(0.82, 1.04)	0.1713
Group D (primarily IPF)	0.84	(0.73, 0.96)	0.0107
Diagnosis†			
Bronchiectasis	0.96	(0.78, 1.17)	0.6796
Eisenmenger	0.32	(0.11, 0.91)	0.0331
Lymphangioleiomyomatosis	1.24	(0.89, 1.74)	0.2060
Obliterativebronchiolitis	1.25	(0.93, 1.69)	0.1437
Pulmonary Fibrosis other	1.01	(0.89, 1.15)	0.8734
Sarcoidosis and PA mean >30 mmHg	0.90	(0.74, 1.08)	0.2561
Sarcoidosis and PA mean ⩽30 mmHg	1.00	(0.79, 1.26)	0.9927
Physiologic reserve			
Age > 45 spline‡ (years)	0.99	(0.99, 1.00)	0.0139
No assistance with ADL	1.02	(0.94, 1.11)	0.6648
6-min walk (per 100 ft)	1.01	(1.01, 1.02)	0.0002
Severity			
Creatinine at transplant (mg/dl)	0.89	(0.83, 0.96)	0.0017
FVC for dgn groups B and D (per 10% predicted)	1.01	(0.99, 1.03)	0.4567
Continuous mechanical ventilation at transplant	0.72	(0.63, 0.83)	<0.0001
Cardiac index <2.0 (l/min/min^2)	0.86	(0.74, 1.00)	0.0496
O_2 at rest for dgn group A (l/min)	0.97	(0.96, 0.99)	0.0063
O_2 at rest for dgn groups B, C, and D (l/min)	0.99	(0.98, 1.00)	0.2129
Change in creatinine ⩾150%	0.78	(0.65, 0.95)	0.0132

*For risk factors, $e^{\hat{\beta}}$ acts multiplicatively on the number of days lived in a year.
†The OPTN Thoracic Committee grouped these diagnoses into larger diagnosis groups (A, B, C, and D) for the purpose of modeling risk factors that may vary by diagnosis group. Bronchiectasis, lymphangioleiomyomatosis, and sarcoidosid and PA mean ⩽30 mmHg share risk factor parameters with diagnosis group A; Eisenmenger with group B; and obliterativebronchiolitis, pulmonary fibrosis other, and sarcoidosis and PA mean >30 mmHg with group D.
‡Age >45 spline: the maximum of 0 and age −45.
ADL, activities of daily living; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; iPAH, idiopathic pulmonary arterial hypertension; IPF, interstitial pulmonary fibrosis; PA, pulmonary artery; PCO_2, partial pressure of carbon dioxide.

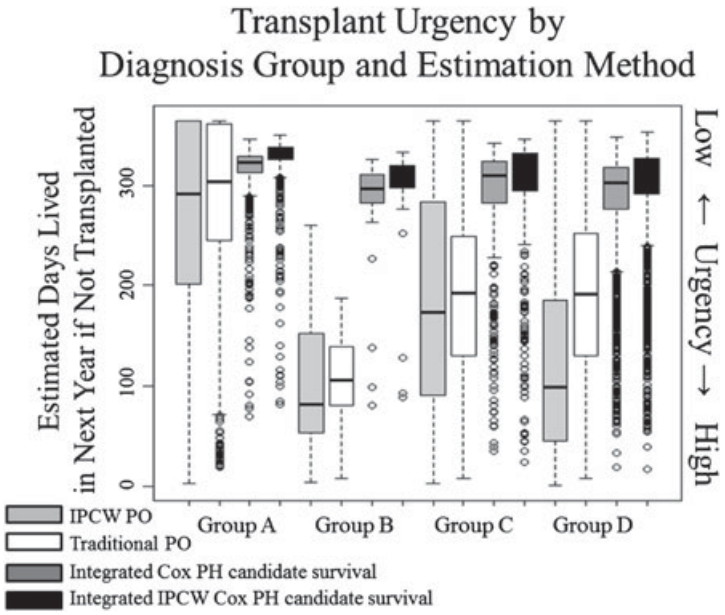


Figure 3. Urgency by diagnosis group.

Transplant benefit calculations similar to those carried out for the hypothetical group D wait list patient described in Sections 4.1 and 4.2 were performed for all 3701 patients in our wait list cohort. Figure 4 shows boxplots of estimated transplant benefit by diagnosis group by using IPCW PO, traditional PO, integrated IPCW Cox PH survival, and integrated Cox PH survival for this cohort. In each case, the lung recipient model used model (3) applied to the original (perfectly observed) data for this setting. Patient transplant benefit calculations incorporating the IPCW PO model for urgency identified more benefit in group D patients than when using any other modeling paradigm. The use of integrated IPCW Cox survival curves also exhibit more estimated benefits than the use of integrated Cox survival curves not adjusting for dependent censoring. However, benefit estimates remain low, with tight interquartile ranges, when compared with either of the PO methods.

Figure 5(a) shows scatter plots of LAS calculated using IPCW PO versus traditional PO by diagnosis group, with a 45° line superimposed on the plot. For each diagnosis group, the LAS changes substantially when taking into account dependent censoring. When looking at the top 100 ranked patients based on their IPCW PO derived LAS, their scores estimated using traditional PO methods dropped by approximately 16 points on average (0.8 standard deviations of the estimated LAS distribution) when not adjusting for dependent censoring. Similarly, scores dropped by approximately 36 points on average using the traditional Cox model integrated wait list survival curves. Model paradigm selection and adjustment for dependent censoring have a serious impact on time to transplant for those top priority candidates identified using IPCW PO methodology. Figure 5(b) shows a scatter plot of LAS values when calculated using the IPCW PO method versus using integrated IPCW Cox survival curves for wait list urgency. Circled values represent patients who would move from having a low allocation priority by using PH assumptions to a very high allocation priority by using model (3). We rank only 30 patients in the top 100 scores regardless of the IPCW method used, IPCW PO or IPCW Cox integrated survival curves.

5. Discussion

We present new methodology for estimating restricted means in the presence of dependent censoring captured by longitudinal covariates. Upon estimation of $S_T(t)$ by using inverse weight methodology, remaining inference becomes very straight forward using our suggested approach. In particular, it is not necessary to program complicated variances of inverse weighted estimates, because the PO approach

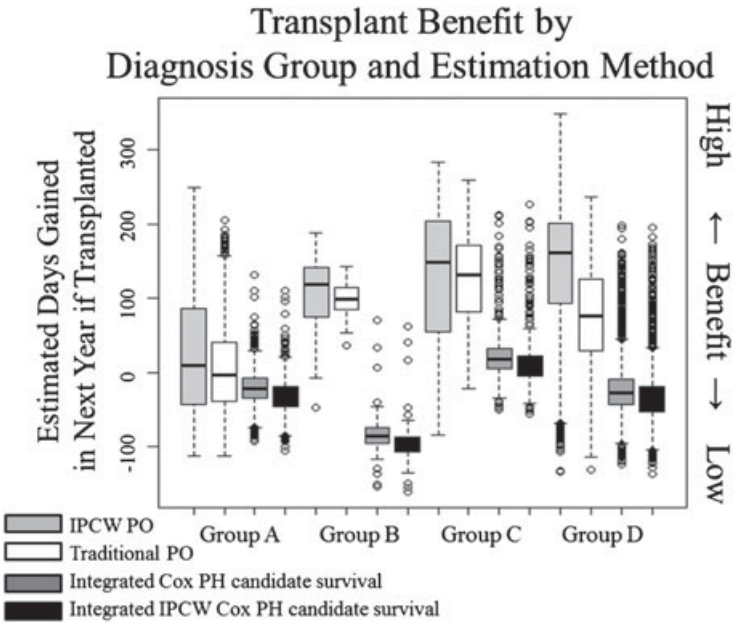
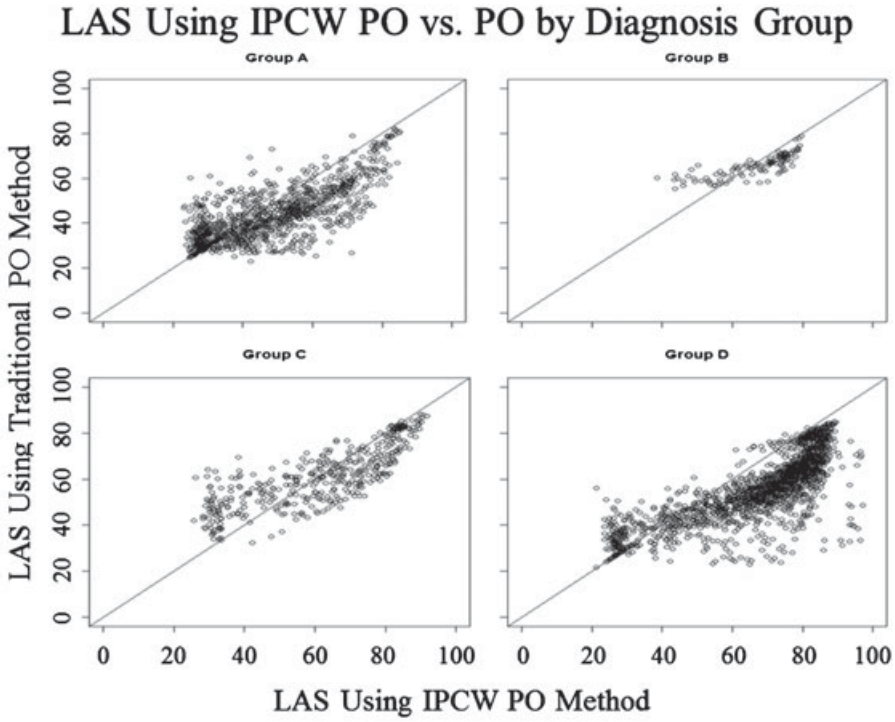
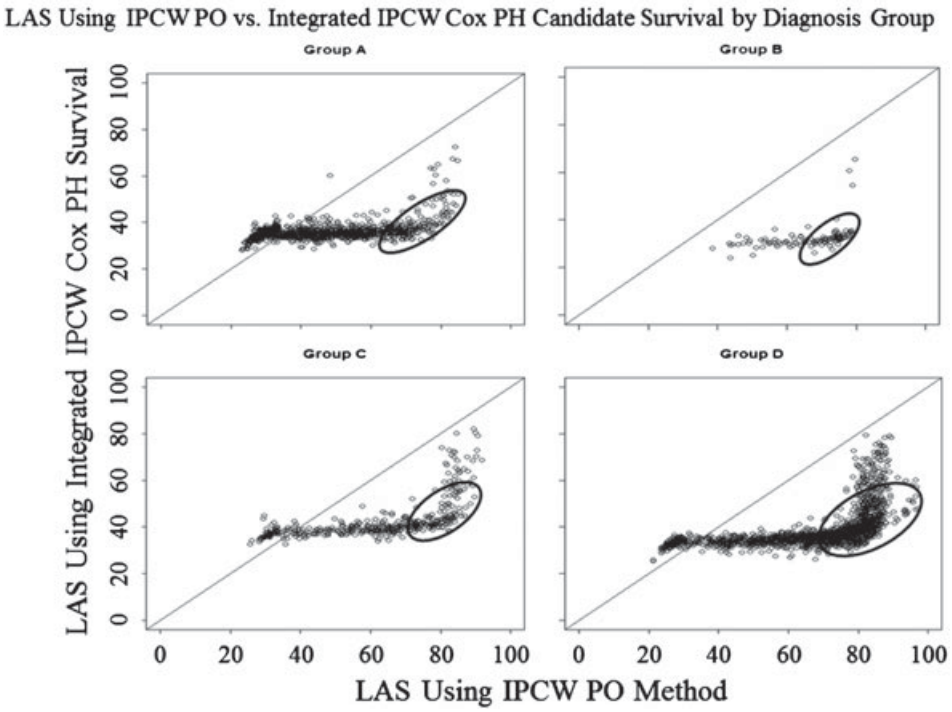


Figure 4. Estimated transplant benefit at time of listing by diagnosis group and estimation method for 3701 lung transplant candidates.



(a) IPCW PO vs. PO



(b) IPCW PO vs. IPCW Cox

Figure 5. LAS at listing calculated using IPCW PO, PO, and Cox PH model by diagnosis group for 3701 lung candidates.

merges nicely into use of more standard software package for regression in evaluating parameter estimates. Hence, this approach can realistically be implemented by statistical practitioners.

Statistical input into properly modeling components of the LAS in the USA has high impact on perhaps 1000 patients at any given time, as the rate of new listings and wait list removals seems to balance at that level. The success of devising and maintaining an intelligent and practical allocation system

for urgent patients introduces a uniquely interesting set of statistical issues. Defining 1-year transplant urgency and benefit at the individual level can be achieved successfully using our described methodology, even when subjected to dependent censoring by transplant for more urgent patients. Hence, the LAS can be updated now and in the future using the most recent cohort of patients with minimal bias.

When applied to the lung candidate data, the IPCW PO method gives a broader range of urgency estimates than when estimating urgency based on integrated IPCW Cox model survival curves. This in turn leads to a broader range of LAS values with which to prioritize the candidates. Our feeling is that parameterization on the scale of the restricted mean leads to more appropriate urgency estimates than parameterization based on constant hazard ratios over time, particularly after viewing the range of scores from using different modeling paradigms in Figure 5(b).

Availability of this methodology also opens up the important possibility of adding new predictors to the LAS, as these are identified as relevant by the transplant community and collected on OPTN lung transplant candidates. The LAS is the first organ allocation system to explicitly order patients by both estimated urgency and transplant benefit, although liver allocation introduced an urgency score in prioritizing patients around the same time the LAS was developed. No OPTN organ allocation committees have yet updated their algorithms with adjustment for dependent censoring in more recent cohorts of patients. Hence, this type of analysis could be applied to other allocation settings with similar dependent censoring issues as well.

APPENDIX A.

In Section 3, we simulate settings when dependent censoring affects estimation of (3) unless adjustments are made via the IPCW PO method. The survival function for piecewise exponential failure times used in Section 3 is

$$S_T(t) = \begin{cases} e^{-\lambda_{Z_0} t} & 0 \leqslant t \leqslant t_1 \\ e^{-\lambda_{Z_0} t_1} e^{-\lambda_{Z_0 Z_1}(t-t_1)} & t > t_1 \end{cases},$$

with pdf

$$f_T(t) = \begin{cases} \lambda_{Z_0} \cdot e^{-\lambda_{Z_0} t} & 0 \leqslant t \leqslant t_1 \\ \lambda_{Z_0 Z_1} \cdot e^{-(\lambda_{Z_0} - \lambda_{Z_0 Z_1}) t_1} \cdot e^{-\lambda_{Z_0 Z_1} t} & t > t_1 \end{cases}.$$

In step 2 of Section 3, parameters $\lambda_0 = 0.3$, $\lambda_1 = 0.2$, $\lambda_{01} = 0.1$, and $\lambda_{11} = 0.5$ are fixed. The remaining parameters λ_{00} and λ_{10} are chosen to satisfy (3) as described in the succeeding equation. Recall that Z_1 is measured at time $t_1 = 0.2$ and that $\tau = 5$. Also, Z_0 and Z_1 are generated from independent Bernoulli(0.5).

$$\begin{aligned} & E[\log\{\min(\tau, T)\}] \\ =& E\big[E[\log\{\min(\tau, T)\}|Z_1]\big] \\ =& \sum_{z_1} P(Z_1 = z_1) E[\log\{\min(\tau, T)\}|Z_1 = z_1] \\ =& 0.5E[\log\{\min(\tau, T)\}|Z_1 = 0] + 0.5E[\log\{\min(\tau, T)\}|Z_1 = 1] \end{aligned}$$

When $Z_0 = 0$, we have

$$\begin{aligned} & E[\log\{\min(\tau, T)\}] \\ =& 0.5\left(\int_0^{t_1} \log t \cdot \lambda_0 e^{-\lambda_0 t} \mathrm{d}t + \int_{t_1}^{\tau} \log t \cdot \lambda_{00} \cdot e^{-(\lambda_0 - \lambda_{00}) t_1} \cdot e^{-\lambda_{00} t} \mathrm{d}t + \log \tau \cdot e^{-\lambda_0 t_1} \cdot e^{-\lambda_{00}(\tau - t_1)}\right) \\ & + 0.5\left(\int_0^{t_1} \log t \cdot \lambda_0 e^{-\lambda_0 t} \mathrm{d}t + \int_{t_1}^{\tau} \log t \cdot \lambda_{01} \cdot e^{-(\lambda_0 - \lambda_{01}) t_1} \cdot e^{-\lambda_{01} t} \mathrm{d}t + \log \tau \cdot e^{-\lambda_0 t_1} \cdot e^{-\lambda_{01}(\tau - t_1)}\right) \\ =& \beta_0 + \beta_2 Z_2 \end{aligned}$$

We solve the aforementioned equation for λ_{00}. Similarly, when $Z_0 = 1$, we solve the following equation for λ_{10}:

$$
\begin{aligned}
&E[\log\{\min(\tau, T)\}] \\
&= 0.5\left(\int_0^{t_1} \log t \cdot \lambda_1 e^{-\lambda_1 t}\mathrm{d}t + \int_{t_1}^{\tau} \log t \cdot \lambda_{10} \cdot e^{-(\lambda_1-\lambda_{10})t_1} \cdot e^{-\lambda_{10} t}\mathrm{d}t + \log\tau \cdot e^{-\lambda_1 t_1} \cdot e^{-\lambda_{10}(\tau - t_1)}\right) \\
&\quad + 0.5\left(\int_0^{t_1} \log t \cdot \lambda_1 e^{-\lambda_1 t}\mathrm{d}t + \int_{t_1}^{\tau} \log t \cdot \lambda_{11} \cdot e^{-(\lambda_1-\lambda_{11})t_1} \cdot e^{-\lambda_{11} t}\mathrm{d}t + \log\tau \cdot e^{-\lambda_1 t_1} \cdot e^{-\lambda_{11}(\tau - t_1)}\right) \\
&= \beta_0 + \beta_1 + \beta_2 Z_2
\end{aligned}
$$

The resulting parameters λ_{00} and λ_{10} vary according to the values of Z_2 for patient i, $i = 1, \ldots, n$.

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ORIGINAL CLINICAL SCIENCE

Development of a quantitative donor risk index to predict short-term mortality in orthotopic heart transplantation

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KEYWORDS:
orthotopic heart transplantation;
outcomes;
database analysis;
UNOS;
organ donor;
risk analysis

BACKGROUND: No standard index based on donor factors exists for predicting mortality after orthotopic heart transplantation (OHT). We utilized United Network for Organ Sharing (UNOS) data to develop a quantitative donor risk score for OHT.

METHODS: We examined a prospectively collected open cohort of 22,252 patients who underwent primary OHT (1996 to 2007). Of the 284 donor-specific variables, those associated with 1-year (year) mortality (exploratory p-value < 0.2) were incorporated into a multivariate (MV) logistic regression model. The final model contained donor factors that improved the explanatory power (by pseudo-R2, area under the curve and likelihood ratio test). A quantitative donor risk score was created using odds ratios (ORs) from the final model. For external validity, a cross-validation strategy was employed whereby the score was generated using a randomly generated subset of cases ($n = 17{,}788$) and then independently validated on the remaining patients ($n = 4{,}464$).

RESULTS: A 15-point scoring system incorporated 4 variables: ischemic time; donor age; race mismatching; and blood urea nitrogen (BUN)/creatinine ratio. Derivation and validation cohort scores ranged from 1 to 15 and 1 to 12, respectively (mean 4.0 ± 2.1 for each). Each increase of 1 point increased the risk of 1-year death by 9% (OR = 0.09 [1.07 to 0.12]) in the derivation cohort and 13% (OR = 0.13 [1.08 to 0.18]) in the validation cohort (each $p < 0.001$). The odds of 1-year mortality by increments of 3 points were: 0 to 2 points (reference); 3 to 5 points (OR = 0.25 [1.12 to 0.40], $p < 0.001$); 6 to 8 pts (OR = 0.77 [1.56 to 2.02], $p < 0.001$); and 9 to 15 points (OR = 1.92 [1.54 to 2.39], $p < 0.001$). Donor risk score was predictive for 30-day mortality (OR = 0.11 [1.08 to 0.14], $p < 0.001$) and 5-year cumulative mortality (OR = 0.11 [1.09 to 0.13], $p < 0.001$).

CONCLUSIONS: We present a novel donor risk index for OHT predicting short- and long-term mortality. This donor risk score may prove valuable for donor heart allocation and prognosis after OHT.

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Identifying factors that impact survival after adult orthotopic heart transplantation (OHT) could ultimately improve outcomes by allowing for more optimal organ allocation. Although multiple studies have examined the impact of recipient characteristics on survival after OHT, emerging data suggest that donor data are also a major factor in post-transplant outcomes. For instance, data from the International Society for Heart and Lung Transplantation (ISHLT) demonstrate that donor age, ischemic time and donor body mass index (BMI) are predictors of early death in risk-adjusted models.[1,2] In renal transplantation, there has been substantial work done on donor risk indices for prediction of graft function after transplantation.[3–8] Donor risk scores can aid in organ selection, have policy implications

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regarding allocation, assist in recipient prognosis, and serve as tools for future research. Currently, no such donor-specific scoring system exists for OHT.

Our purpose was to use United Network for Organ Sharing (UNOS) data to create and validate a risk score based solely on heart transplant donor factors. The primary goals were to generate a score that combined accuracy, predictive accuracy and simplicity to aid the busy practitioner in identifying high-risk donors. We hypothesize that donor-specific factors are identifiable, which can accurately predict short-term mortality in OHT.

Methods

Data source

UNOS provided Standard Transplant Analysis and Research (STAR) files with donor-specific data from December 1987 to May 2008. The data set comprises a prospectively collected sample of all thoracic transplantation patients in the USA. No patient or center identifiers were included in this analysis and the study was granted institutional review board exemption at our institution.

Study design

We examined all primary, adult (>17 years) OHT patients from January 1996 to December 2007. The interval was designed to identify a modern cohort of OHT recipients. For cross-validation, the cohort was randomly divided into two sub-cohorts. The "training set," or derivation cohort, comprised 80% of the total sample and the "test set," or validation cohort, comprised the remaining 20%. All score derivation was performed on the training set and then independently validated in the test set.

As the primary intention was to develop a donor-specific risk score, we focused on those variables specific to the donor (i.e., donor age, donor BMI, mechanism of death) or variables that involved both the donor and recipient (i.e., HLA match level or gender and race mismatch). For score generation, we excluded all variables related solely to the recipient. The primary end-point was mortality within 1 year of transplantation.

Analysis

The UNOS dataset utilized contained 284 donor-specific variables. All variables with plausibility for predicting 1-year mortality were tested using univariate logistic regression. Those associated with 1-year mortality on exploratory analysis ($p \leq 0.2$) were incorporated into a multivariate logistic regression model. As models were constructed via case-wise deletion, covariates with >15% missing data in the registry were excluded. Assessment of the functional form of continuous covariates on the outcome was evaluated using Lowess smoothing. Spline terms were utilized when appropriate. In addition, potential interactions between significant covariates were thoroughly tested. The final model contained significant donor factors that improved the explanatory power as assessed by use of Akaike's information criterion (AIC), the likelihood ratio test and the area under the receiver operating curve.

From the final model a 15-point donor risk score was created approximating the magnitude of relative odds of 1-year cumulative mortality revealed from the model. The score was applied to all members of both the training set and test set and effects on 1-year

Table 1 Baseline Characteristics Among the Derivation and Validation Cohorts

Characteristic	Derivation cohort (n = 17,788)	Validation cohort (n = 4,464)	p-value[a]
Demographics			
Age (mean ± SD)	52.0 (± 11.8)	52.1 (± 11.8)	0.69
Female	4,174 of 17,788 (23.5%)	1,044 of 4,464 (23.4%)	0.91
Caucasian	13,647 of 17,055 (77.0%)	3,408 of 4,444 (76.7%)	0.68
BMI	26.3 (± 4.8)	26.2 (± 4.9)	0.59
Diagnosis			
Idiopathic	7,301 of 17,788 (41.1%)	1,810 of 4,464 (40.6%)	0.54
Ischemic	8,592 of 17,788 (48.3%)	2,143 of 4,464 (48.0%)	0.72
Congenital	399 of 17,788 (2.2%)	112 of 4,464 (2.2%)	0.29
Other	1,495 of 17,788 (8.4%)	399 of 4,464 (8.9%)	0.25
Acuity			
UNOS Status I	4,561 of 17,779 (74.4%)	3,283 of 4,463 (73.5%)	0.27
HTN	6,250 of 16,047 (39.0%)	1,502 of 4,004 (37.5%)	0.09
Diabetes mellitus	3,599 of 17,316 (20.8%)	909 of 4,344 (20.9%)	0.84
Creatinine	1.38 (± 1.12)	1.38 (± 1.17)	0.84
ICU at time of OHT	6,764 of 17,713 (37.2%)	1,689 of 4,447 (38.0%)	0.80
Mechanical ventilation at time of OHT	474 of 17,788 (2.7%)	119 of 4,464 (2.7%)	0.99
Ischemic time	3.11 (± 1.04)	3.09 (± 1.03)	0.28
Hemodynamics			
Cardiac index	2.18 (± 0.69)	2.16 (± 0.69)	0.90
Mean PAP	30.7 (± 10.5)	30.9 (± 10.6)	0.49
TPG	9.70 (± 6.19)	9.58 (± 6.14)	0.32

BMI, body mass index; HTN, hypertension; ICU, intensive care unit; OHT, orthotopic heart transplantation; PAP, pulmonary artery pressure; TPG, transpulmonary gradient; UNOS, United Network for Organ Sharing.

[a]Based on results of Student's t-test (continuous variables) or chi-square test (categorical variables).

Table 2 Univariate and Multivariate Logistic Regression for Variables Used to Generate Donor Risk Score

Covariates used	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis OR (95% CI)	*p*-value
Ischemic time				
<2 hours	Reference	Reference		
2–3.9 hours	1.23 (1.06–1.44)	**0.006**	1.22 (1.05–1.42)	**0.01**
4–5.9 hours	1.86 (1.57–2.2)	**<0.001**	1.82 (1.53–2.17)	**<0.001**
6–7.9 hours	2.72 (1.76–4.22)	**<0.001**	2.93 (1.88–4.57)	**<0.001**
≥8 hours	3.55 (1.22–10.31)	**0.02**	3.93 (1.33–11.65)	**0.01**
Donor age				
<40 years	Reference	Reference		
40–49 years	1.34 (1.20–1.49)	**<0.001**	1.29 (1.14–1.45)	**<0.001**
≥50 years	1.60 (1.40–1.83)	**<0.001**	1.57 (1.35–1.81)	**<0.001**
Race mismatch	1.14 (1.04–1.25)	**0.004**	1.13 (1.02–1.24)	**0.02**
BUN/creatinine ratio ≥30	1.35 (1.10–1.60)	**0.003**	1.33 (1.07–1.67)	**0.01**
Ejection fraction ≤25%	5.71 (1.84–17.73)	**<0.001**	–	–
Female donor for male recipient	1.17 (1.08–1.28	**<0.001**	–	–
Donor cigarette use	1.18 (1.09–1.28)	**<0.001**	–	–
History of donor HTN	1.34 (1.20–1.50)	**<0.001**	–	–
History of donor-treated infection	1.10 (1.01–1.21)	**0.02**	–	–
Donor CMV-positive	1.09 (1.01–1.18)	**0.03**	–	–

Boldface indicates factors utilized in final model.

mortality were assessed by examining the score in a continuous fashion as well as by stratified disjoint categories of donor risk score.

Cumulative survival stratified by donor risk score was estimated using the Kaplan–Meier method focused on time intervals with adequate follow-up. Censoring occurred for those individuals lost to follow-up and those alive at the end of the study period (administratively censored).

All means are presented with standard deviations, medians with interquartile ranges and odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analyses were performed using STATA software, version 9.2 SE (StataCorp LP, College Station, TX).

Results

Cohort statistics

A total of 22,252 patients comprised the sample. The mean age was 52.0 ± 11.8 years, with 23.5% (n = 5,218) being women. Patients averaged 217.6 ± 350.3 days on the waitlist, with 50.9 ± 40.9 months of follow-up time. During the study period, 6,637 patients died (incidence rate 7.13 deaths per 100 person-years). The Kaplan–Meier cumulative incidence of 1-year mortality was 13.9% (n = 2,944 deaths within the first year).

Random stratification of the entire cohort yielded a derivation cohort (n = 17,788, 80% of total sample) and a validation cohort (n = 4,464, 20% of total sample). The derivation set and validation cohort did not differ significantly by key recipient pre-operative variables (Table 1). There were no differences in pre-operative acuity or key hemodynamic variables among the recipient groups, indicating that the validation cohort was appropriate for testing the generated score.

Variables examined in the derivation cohort

Exploratory logistic regression of donor variables in the derivation cohort identified 9 variables that significantly increased the risk of 1-year mortality: ischemic time; donor age; blood urea nitrogen (BUN)/creatinine ratio; donor–recipient gender mismatch (for males only); donor cigarette use; history of donor hypertension; and cytomegalovirus (CMV)-positive donor. Only 4 of these variables were strongly associated with risk of 1-year mortality when combined in a multivariate model. All 4 variables showed improvement in the AIC and significant likelihood ratio test results ($p < 0.001$ for the addition of each covariate) (Table 2). It should be noted that, for males in the derivation cohort (n = 13,614), female donor gender persisted as significant in a multivariate model examining males only (OR = 1.32 [1.12 to 1.53], $p < 0.001$), but this was not included in score generation due to its isolated effect for males. Similarly, although ejection fraction ≤25% persisted as significant in multivariate analysis (OR = 5.75 [1.74 to 19.0], $p = 0.004$), it was not included in the risk index given that so few

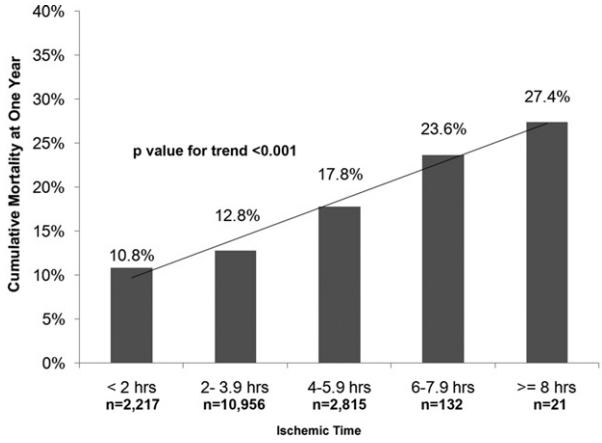

Figure 1 Cumulative incidence of recipient mortality at 1-year post-OHT by categories of ischemic time.

patients had this risk factor (0.2%, $n = 21$), and therefore its clinical utility would be extremely limited.

Examining the associated variables, we observed a strong correlation between ischemic time and 1-year mortality (Figure 1). Among those patients transplanted with ≥8 hours of ischemic time, Kaplan–Meier cumulative 1-year mortality was 27.4%. This was 16.6% higher than the mortality risk observed with those patients receiving organs with ≤2 hours of ischemic time. The mean ischemic time in the derivation cohort was 3.11 ± 1.04 hours and the vast majority of recipients (67.9%, or 10,956 of 16,141) received organs with ischemic times of 2 to 3.9 hours. Only 0.95% of the sample received organs with ≥6 hours of ischemic time ($n = 153$). A similar trend was observed with donor age in the derivation cohort. Mean donor age was 31.3 ± 12.6 years. Age was strongly associated with 1-year mortality, as donors >50 years of age had a 6.3% higher incidence of cumulative mortality than those <40 years of age ($p < 0.001$; Figure 2). Of the donors, 4.3% had BUN/creatinine ratios >30, and their 1-year mortality was significantly higher than those with a ratio <30 (18.7% vs 14.6%, $p = 0.001$). In addition, recipient–donor race-mismatched patients had a cumulative 1-year mortality of 15.8% as compared with 14.1% for matched patients ($p = 0.004$).

Score generation

Using regression coefficients from the multivariate analysis (Table 2), we assigned points to generate a donor risk score with a maximum of 15 points (Table 3). In the derivation cohort, donor scores were minimally positively skewed in distribution, ranging from 1 to 15, with the mean score 4.0 ± 2.1 (Figure 3).

The score was confirmed to be associated with risk of 1-year mortality in the derivation cohort when examined on both univariate and multivariate analysis adjusted for recipient variables known to be associated with mortality.[1] Each 1-point increase roughly correlated with an 11% increase in the odds of one 1-year mortality on unadjusted analysis (OR = 1.11 [1.09 to 1.13], $p < 0.001$). In addition, examining scores in 1-point increments demonstrated a gradual increase in the risk of 1-year cumulative mortality with each 1-point increase (Table 4).

Score validation

In the validation cohort ($n = 4,464$), scores similarly centered around a mean of 4.0 ± 2.1, but ranged from 1 to 12 (Figure 3). The score showed good predictive accuracy. Specifically, as a continuous variable, each 1-point increase predicted a 13% increase in the odds of 1-year mortality on both univariate analysis (OR = 1.13 [1.09 to 1.18], $p <$ 0.001) and after adjustment for recipient confounders (OR = 1.13 [1.08 to 1.18], $p < 0001$) (Table 4). Although ORs increased with increasing point totals, the relationship was less clear in the validation cohort when 1-point increments were examined.

Effect of primary diagnosis

To determine whether the generated score was valid across a range of recipient disease types, recipients were stratified by primary diagnosis in a pooled analysis. When the entire cohort was pooled in this fashion, donor risk score strongly correlated with mortality for those patients with ischemic, idiopathic and other forms of cardiomyopathy, but not for those adults with congenital cardiomyopathies (Table 4).

Long-term survival

When examining 5-year Kaplan–Meier survival, donor risk score (stratified by 3-point increments) again showed accuracy in the derivation cohort and predictive accuracy in the validation cohort, as lower risk scores correlated with improved survival. Specifically, in the derivation cohort, those patients receiving donor hearts with scores of ≥9 had a 9% lower 5-year cumulative survival than those in the 0- to 2-point range ($p < 0.001$) (Figure 4). Similarly, the validation cohort showed a 13% lower 5-year cumulative survival for patients with high donor risk indices ($p < 0.001$) (Figure 5).

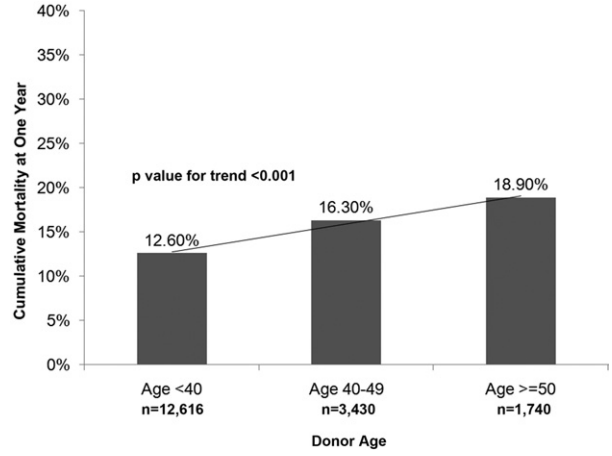

Figure 2 Cumulative incidence of recipient mortality at 1-year post-OHT by categories of donor age.

Table 3 Score Calculation

Variable	Points assigned
Ischemic time	
<2 hours	1
2–3.9 hours	2
4–5.9 hours	3
6–7.9 hours	4
≥8 hours	5
Donor age	
<40 years	0
40–49 years	3
≥50 years	5
Race mismatch	2
BUN/creatinine ratio ≥30	3
Total points possible	15

Discussion

Although OHT continues to be the "gold standard" therapy for end-stage heart failure, its utilization continues to be limited by the shortage of available donor organs. Although incorporating marginal organs into the donor pool could help to augment the number of transplants performed, this would likely come at the expense of poorer outcomes. Therefore, creating a risk score for survival post-transplant based solely on donor factors could help in distinguishing suitable organs from those that would be too high risk to transplant. Accordingly, in this study we utilized UNOS data to design a simple and easily calculable donor risk index for use in OHT. We both derived and validated the risk score using independent subsets of the UNOS database.

It was encouraging that 4 donor-specific variables were present that could accurately predict risk of 1-year mortality in OHT. The combination of these 4 variables into the donor risk index not only predicted 1-year mortality in the derivation cohort (as expected), but also accurately predicted 1-year mortality in the 4,464-patient validation cohort. Specifically, each point increment in risk score was associated with a 9% and 13% increase in the odds of 1-year mortality in the derivation and validation cohort, respectively. It was of interest to note that risk index (in 3-point increments) also predicted 5-year cumulative mortality in both derivation and validation cohorts. Donor indices of ≥9 consistently demonstrated the lowest 5-year survival.

To create an index that was easy to apply, we chose not to apportion points exactly according to regression coefficients, but rather to roughly approximate the relative magnitude of the coefficients. This strategy provides a practical index that the clinician can rapidly apply when evaluating a potential donor.

Although only 1 patient in either cohort reached the 15-point maximum score, there was robust score distribution in both cohorts (1 to 15 in the derivation cohort and 1 to 12 in the validation cohort).

The 4 variables used in the index each strongly predict recipient 1-year mortality in univariate analysis and in multivariate analysis adjusting for recipient factors. In addition, all variables substantially improved the predictive power of the model. We expected age and ischemic time to contribute to risk of death. We chose to use BUN/creatinine ratio after donor creatinine and BUN individually did not significantly impact mortality. We were surprised to find that the BUN/creatinine ratio predicted mortality in this sample. Although the reasons for this are not clear from this data set, it is possible that this ratio reflects the perfusion state of the donor prior to organ harvest. Investigations examining BUN/creatinine ratios in patients with heart failure have shown this ratio to be a better predictor of cardiac performance and ultimate outcomes as compared with BUN or creatinine alone.[9,10] Although the relative importance of race matching in transplantation is controversial, we have previously shown lower rates of survival in race-mismatched recipients. We speculated that this may not be directly related to mismatch but rather to an overall increase in black recipients in race-mismatched trans-

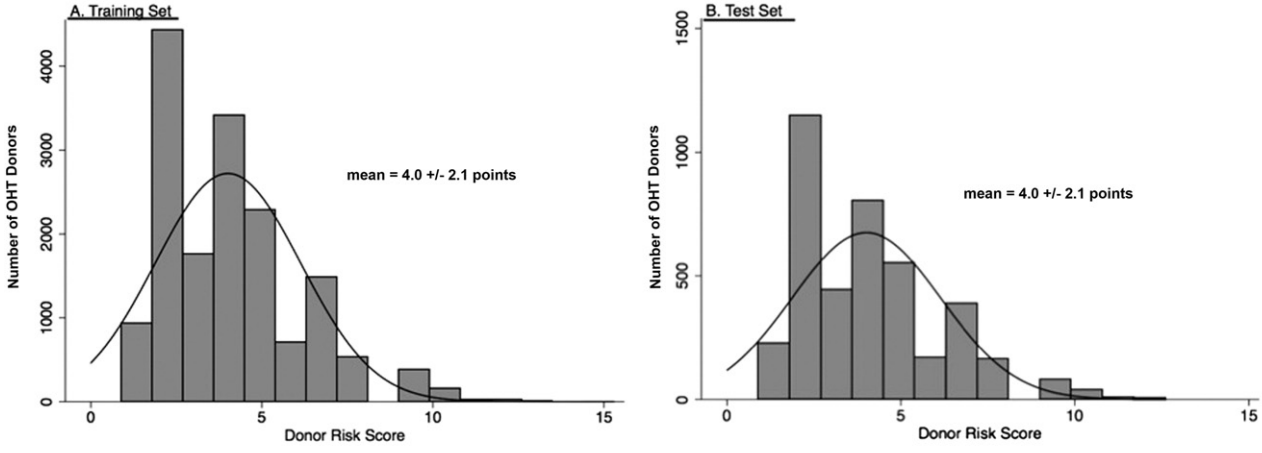

Figure 3 Distribution of donor risk index in derivation and validation cohorts.

Table 4 Multivariate Logistic Regression Analysis Examining Odds of 1-Year Mortality in Training Cohort, Validation Cohort and in Total Sample Stratified by Recipient Primary Diagnosis

	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis OR (95% CI)	*p*-value[a]
Training cohort (n = 17,788)				
Risk score (continuous)	1.11 (1.09–1.13)	**<0.001**	1.09 (1.07–1.12)	**<0.001**
Risk score (categorical)				
1	Reference		Reference	
2	1.24 (0.97–1.58)	0.09	1.14 (0.89–1.48)	0.30
3	1.77 (1.36–2.30)	**<0.001**	1.55 (1.18–2.04)	**0.002**
4	1.43 (1.12–1.84)	**0.005**	1.26 (0.97–1.64)	0.08
5	1.66 (1.28–2.15)	**<0.001**	1.51 (1.15–1.97)	**0.003**
6	2.13 (1.58–2.89)	**<0.001**	1.89 (1.37–2.59)	**<0.001**
7	2.09 (1.61–2.73)	**<0.001**	1.77 (1.34–2.34)	**<0.001**
8	2.80 (2.06–3.82)	**<0.001**	2.38 (1.71–3.29)	**<0.001**
9	2.16 (1.52–3.08)	**<0.001**	1.74 (1.20–2.53)	**0.004**
10^{+}	2.29 (1.77–2.95)	**<0.001**	2.01 (1.53–2.64)	**<0.001**
Validation cohort (n = 4,464)				
Risk score (continuous)	1.13 (1.09–1.18)	**<0.001**	1.13 (1.08–1.18)	**<0.001**
Risk score (stratified)				
1			Reference	
2	0.86 (0.54–1.37)	0.53	0.79 (0.48–1.28)	0.34
3	1.19 (0.72–1.98)	0.49	1.12 (0.66–1.91)	0.68
4	0.91 (0.56–1.46)	0.69	0.83 (0.50–1.38)	0.48
5	1.22 (0.75–1.99)	0.42	1.16 (0.69–1.94)	0.57
6	1.69 (0.95–3.01)	0.08	1.52 (0.81–2.84)	0.19
7	1.93 (1.18–3.16)	**0.01**	1.66 (0.98–2.80)	0.06
8	1.56 (0.86–2.85)	0.15	1.59 (0.85–3.00)	0.15
9	2.58 (1.32–5.03)	**0.006**	2.41 (1.18–4.94)	**0.02**
10^{+}	1.87 (1.16–3.01)	**0.01**	1.80 (1.07–3.03)	**0.03**
Recipient primary diagnosis in total cohort (training and validation)				
Dilated cardiomyopathy (n = 9,112)	1.09 (1.06–1.13)	**<0.001**	1.07 (1.04–1.11)	**<0.001**
Ischemic cardiomyopathy (n = 10,735)	1.12 (1.09–1.15)	**<0.001**	1.11 (1.08–1.14)	**<0.001**
Adult congenital (n = 511)	1.09 (0.96–1.23)	0.17	1.05 (0.92–1.19)	0.49
Other (n = 1,894)	1.16 (1.10–1.24)	**<0.001**	1.14 (1.07–1.22)	**<0.001**

[a]Multivariate logistic regression model adjusted for the following recipient covariates: age; creatinine; diabetes mellitus; hypertension; mechanical ventilation; race; gender; and UNOS Status 1 listing. Boldface indicates statistical significance ($p < 0.05$).

plantation owing to a lack of minority donors.[11] The relative contribution of race mismatch to donor and recipient race is difficult to address with this data set.

A notable finding is that the donor index applied to all etiologies of heart failure except congenital. In a recent review of adult transplant recipients for congenital disease, congenital patients tended to have longer ischemic times and higher pulmonary vascular resistance than other recipients.[12] Although survival did not differ significantly in our study, it appears that the congenital patient population is intrinsically different from other OHT recipients. Hence, it is not surprising that the derived donor risk index does not apply to this group, and therefore, should not be applied to patients with congenital causes of heart failure. It is important to note, however, that they only comprised 2.3% of our sample, thus representing a paucity of OHT recipients.

Scoring systems in cadaveric renal transplantation

Although scoring systems are pervasive in the medical literature, they have not been routinely employed in solid-organ transplantation. Use of donor scoring systems have found greatest utility in cadaveric renal transplantation.[5–8,13] Nyberg and colleagues developed a quantitative risk index in 2001 (later revised in 2003), which was ultimately composed of 39 points from 5 donor variables (age, history of hypertension, creatinine clearance, cause of death, HLA mismatch).[5,6] The score accurately predicted both 12-month renal function and cumulative graft survival. Of these factors, our risk index employs only donor age. HLA match level was not a predictor of mortality in this analysis. If HLA match had been significant, however, its use would be irrelevant, due to the lack of HLA typing information available before OHT. In our study, it is noteworthy that the

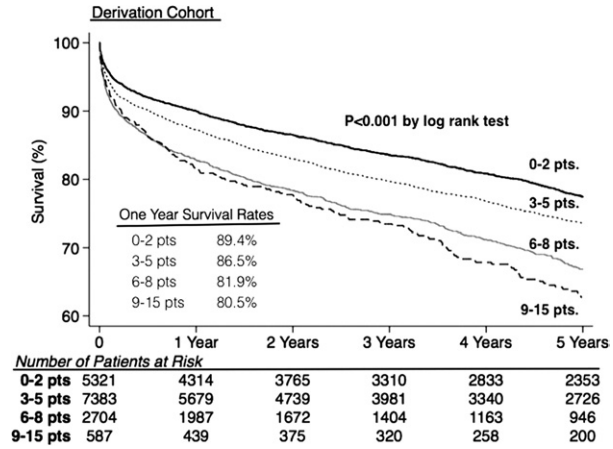

Figure 4 Kaplan–Meier cumulative survival of recipients in the derivation cohort as stratified by 3-point increments of donor risk score (based on OPTN data, May 2009).

mechanism of donor death was not associated with recipient mortality and therefore not included in the risk index.

Despite their use for cadaveric renal transplantation, risk indices have not found popularity in OHT practice. Our literature review identified one published abstract by Segovia and colleagues in which 6 variables were utilized to generate a clinical score predicting primary graft failure.[14] In that 621-patient study, only donor age and ischemic time were utilized, along with 4 recipient variables. There was no comment on validation. Russo and colleagues recently examined marginal donors for high-risk recipients.[15] In their study, marginal donors were defined as those with age >55 years, diabetes mellitus, hepatitis C positivity, human immunodeficiency virus (HIV) positivity, ejection fraction <45% and donor:recipient weight ratio <0.7. The focus of their investigation, however, was not to create a donor risk score but rather to determine whether high-risk recipients derive benefit from receiving marginal hearts. Although our criteria have similarities to those in the study by Russo et al, we did not find that hepatitis C infection, HIV infection, diabetes or weight ratio increased the predictive power of our generated index. Hence, this calls into question whether these factors truly render a donor "high risk."

It is of interest that, of all potential variables analyzed in this study, only 4 factors influenced outcomes. This finding highlights that it is truly recipient factors as well as processes of care that drive outcomes for OHT patients and it also quantifies the meaning of "high-risk donors," compared with the non-standard approach often currently employed.

Utility of donor risk index in OHT

Given the lack of predictive indices in OHT, it is important to ask whether use of a donor-specific index has a place in clinical heart transplantation. It may be that renal transplantation is better suited to use of a scoring system because of the allowance of prolonged storage times prior to decisions regarding allocation. This is unfortunately not possible with OHT. In addition, patients awaiting renal transplantation can be sustained using dialysis, whereas no such universal back-up exists in OHT. However, it must also be noted that, because of these reasons, the consequences of utilizing a bad heart are more severe. With evidence that OHT is still valuable for high-risk recipients, it may be beneficial to identify high-risk donors in a quantitative manner.[15] Furthermore, as we move into an era of increased bridging with mechanical circulatory support, it is reasonable to expect that donor factors will be heavily scrutinized.

Limitations

Our study is subject to the limitations of large retrospective studies from administrative data sets. Specifically, we had limited follow-up and a lack of control of variables available. Furthermore, there may be specific confounders not accounted for in the data set.

Accurate validation is an important component of creation of any clinical scoring system. In this study, we utilized cross-validation, whereby the index was derived from a random subset of donor–recipient pairs and then validated in the remainder of the sample. We chose 80% of the sample for derivation in order to have a robust amount of data for score generation. Although we believe our methodology did not introduce bias into the validation, we acknowledge that our donor index will benefit from external validation in an independent sample in the future.

A potential bias inherent in our approach is that poor organs may have been allocated to poor candidates. Therefore, the increased mortality observed with organs having a high risk score may be more related to the recipient than the donor. Although we cannot eliminate this possibility, we attempted to control for this factor by examining the score's predictive capacity in a multivariate model adjusted for key recipient factors (including UNOS status). The fact that each point increment increase in score was associated with a 9% and 13% increase in the odds of 1-year mortality after this adjustment is an indication that donor factors are also

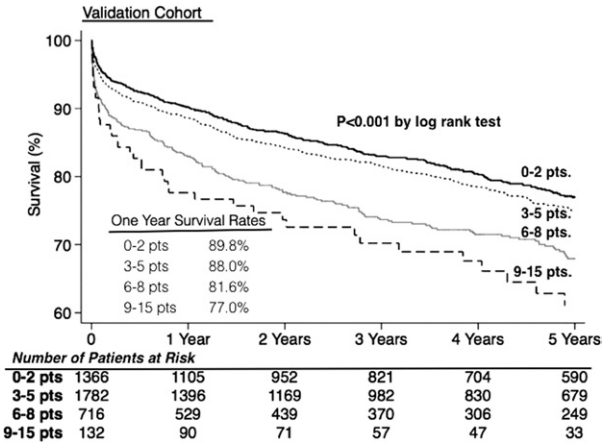

Figure 5 Kaplan–Meier cumulative survival of recipients in the validation cohort as stratified by 3-point increments of donor risk score (based on OPTN data, May 2009).

important. In future investigations, it may be prudent to combine recipient and donor risk indices to determine whether a combined model would improve the predictive power of either model alone.

Additional limitations include that this study represents data from transplantations performed in the USA only. Therefore, this risk score may not be applicable to patients outside the USA, although this is unknown and would be of interest to evaluate. Finally, we excluded covariates with >15% missing data, and these may potentially have important implications in overall donor risk. Unfortunately, missing data is an inherent limitation of registries such as UNOS.

We have analyzed over 22,000 OHT recipients, and their donors, to design a simple, easily calculable, donor risk index for use in OHT. It was designed specifically to predict 1-year post-transplant mortality, based solely on donor factors, and proved accurate in the derivation sample with predictive accuracy in the validation sample. The risk index can serve to drive clinical decisions regarding allocation of marginal organs and may prove especially useful in an era of increased use of ventricular assist devices. It further offers predictive capabilities for recipients and may aid in future epidemiologic investigations.

Disclosure statement

The content of this study is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the U.S. Government. The authors have no further conflicts of interest to disclose. This work was supported in part by the Health Resources and Services Administration (231-00-0115) and by a Ruth L. Kirschstein National Research Service Award (NIH 2T32DK007713-12 to E.S.W.). These findings were presented at the 29th annual meeting and scientific sessions of the International Society for Heart and Lung Transplantation, April 2011, Paris, France.

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Decline in Heart Transplant Wait List Mortality in the United States Following Broader Regional Sharing of Donor Hearts

Tajinder P. Singh, Christopher S. Almond, David O. Taylor and Dionne A. Graham

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Decline in Heart Transplant Wait List Mortality in the United States Following Broader Regional Sharing of Donor Hearts

Tajinder P. Singh, MD, MSc; Christopher S. Almond, MD, MPH; David O. Taylor, MD; Dionne A. Graham, PhD

Background—A change in allocation algorithm in July 2006 allowed broader regional sharing of donor hearts in the United States (US). We assessed if the allocation change has been associated with a decline in wait list mortality in the US.

Methods and Results—We compared baseline characteristics and outcomes in patients ≥18 years old listed for a primary heart transplant in the US before (July 1, 2004–July 11, 2006, Era1) and after (July 12, 2006–June 30, 2009, Era 2) the change in allocation algorithm. Of 11 864 patients in the study, 4503 were listed during Era 1 and 7361 during Era 2. Patients listed during Era 2 were more likely to be listed status 1A, have an implantable cardioverter-defibrillator, and supported on a continuous flow assist device ($P<0.001$ for distribution. Patients listed in Era 2 were at a 17% lower risk of dying on the wait list or becoming too sick to transplant (adjusted hazard ratio, 0.83, 95% CI 0.75, 0.93). Transplant recipients in Era 2 were more likely to be transplanted as status 1A (37% versus 48%, respectively, $P<0.001$). Post-transplant in-hospital mortality (6.3% versus 5.4%; adjusted odds ratio, 0.86 for Era 2, 95% CI 0.79, 1.06) and 1-year survival were similar.

Conclusions—The risk of death on the wait list or becoming too sick to transplant has decreased by 17% in the US since the allocation algorithm allowing broader regional sharing was implemented in 2006. The shift in hearts to sicker candidates has not resulted in higher in-hospital or first year post-transplant mortality. **(*Circ Heart Fail*. 2012;5:249-258.)**

Key Words: transplantation ■ risk factors ■ outcomes ■ heart failure

Because the demand for donor hearts as a life-saving therapy has continued to exceed their supply, the United Network for Organ Sharing (UNOS) has periodically modified the allocation algorithm to improve outcomes among wait listed candidates in the United States (US).[1,2] A change in allocation algorithm implemented on July 12, 2006 allowed broader regional sharing of available hearts to those in more immediate need (Status 1A and 1B candidates) prior to their allocation to local, less sick candidates.[3–5] A fundamental goal of the new algorithm is to decrease national wait list mortality among heart transplant (HT) candidates without a concurrent increase in post-transplant mortality.[2] The latter consideration arises from the observation that sicker patients, on average, are also at a higher risk of surgical mortality.[6,7] Although early analyses after the change in allocation suggested that the trends in wait list outcomes were consistent with intended outcomes,[4,8] a regional analysis has questioned the merits of the new allocation algorithm.[5]

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We hypothesized that the risk of wait list mortality among HT candidates in the US has decreased since the implementation of the new allocation algorithm. The specific objectives of this study were (1) to compare overall and risk-adjusted wait list mortality before and after implementation of the new allocation algorithm, (2) to determine if wait list outcomes in subgroups of listed patients have been affected differently by the change in allocation algorithm, and (3) to compare overall (unadjusted) and risk-adjusted early post-transplant mortality before and after the change in allocation algorithm.

Methods

Study Population

We identified all patients ≥18 years of age in the Organ Procurement and Transplantation Network (OPTN) database who were listed for their first HT in the US between July 1, 2004 and June 30, 2009. The OPTN database includes information at the time of listing for all wait

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Table 1. Baseline Characteristics of Patients Listed for a Heart Transplant Before (Era 1) and After (Era 2) the Change in Allocation Algorithm

Variable	Era 1 (N=4503)	Era 2 (N=7361)	Total (N=11 864)	*P* Value
Age (y)	54 (44, 60)	54 (45, 61)	54 (45, 61)	0.002
Age categories (y)				<0.001
18–39	795 (18%)	1261 (17%)	2056 (17%)	
40–59	2462 (55%)	3771 (51%)	6233 (53%)	
60–69	1176 (26%)	2182 (30%)	3358 (28%)	
70+	70 (1.6%)	147 (2.0%)	217 (1.8%)	
Sex, male	3444 (76%)	5547 (75%)	8991 (76%)	0.16
Blood type				0.53
A	1752 (39%)	2874 (39%)	4626 (39%)	
B	609 (13%)	947 (13%)	1556 (13%)	
0	1948 (43%)	3248 (44%)	5196 (44%)	
AB	194 (4.3%)	292 (4.0%)	486 (4.1%)	
BMI (N=11 853)	26.3 (23, 30)	26.5 (23, 30)	26.5 (23, 30)	0.09
BMI categories				0.01
<25	1660 (37%)	2512 (34%)	4172 (35%)	
25–29	1602 (36%)	2691 (37%)	4293 (36%)	
30–34	934 (21%)	1591 (22%)	2525 (21%)	
35+	302 (6.7%)	561 (7.6%)	863 (7.3%)	
Race/ethnicity				<0.001
White	3241 (72%)	5066 (69%)	8307 (70%)	
Black	759 (17%)	1500 (20%)	2259 (19.0%)	
Hispanic	344 (7.6%)	546 (7.4%)	890 (7.5%)	
Other	159 (3.5%)	249 (3.4%)	408 (3.4%)	
Diabetes (N=11 524)				<0.001
Type I	196 (4%)	267 (4%)	463 (4%)	
Type II	823 (19%)	1632 (23%)	2455 (21%)	
Listing status				<0.001
1A	832 (18%)	1464 (20%)	2296 (19%)	
1B	1446 (32%)	2758 (37%)	4204 (35%)	
2	2225 (49%)	3139 (43%)	5364 (45%)	
Diagnosis				<0.001
Dilated CMP	1965 (44%)	3453 (47%)	5418 (46%)	
Ischemic CMP	1787 (40%)	2713 (37%)	4500 (38%)	
Congenital Heart disease	162 (3.6%)	214 (2.9%)	376 (3.2%)	
Hypertrophic	94 (2.1%)	131 (1.8%)	225 (1.9%)	
Restrictive	74 (1.6%)	172 (2.3%)	246 (2.1%)	
Valvular	114 (2.5%)	155 (2.1%)	269 (2.3%)	
Other	307 (6.8%)	523 (7.1%)	830 (7.0%)	
ICD (N=11 696)	2980 (68%)	5549 (76%)	8529 (73%)	<0.001
Mean PAP (N=10 756)	30 (23, 37)	30 (23, 37)	30 (23, 37)	0.01
Mean PAP >30 mm Hg	1919 (47%)	3290 (49%)	5209 (48%)	0.05
PCWP (N=10 436)	20 (14, 26)	20 (15, 27)	20 (15, 26)	0.04
PCWP >20 mm Hg	1892 (48%)	3197 (49%)	5089 (49%)	0.09
Ventilation	171 (3.8%)	222 (3.0%)	393 (3.3%)	0.02

(*Continued*)

Table 1. Continued

Variable	Era 1 (N=4503)	Era 2 (N=7361)	Total (N=11 864)	*P* Value
Mechanical support				<0.001
ECMO	19 (0.4%)	39 (0.5%)	58 (0.5%)	
Total artificial heart	1 (0.0%)	21 (0.3%)	22 (0.2%)	
BIVAD	114 (2.5%)	184 (2.5%)	298 (2.5%)	
Pulsatile LVAD	382 (8.5%)	401 (5.4%)	783 (6.6%)	
Continuous flow LVAD	75 (1.7%)	432 (5.9%)	507 (4.3%)	
None	3912 (87%)	6284 (85%)	10196 (86%)	
IV inotropes	1526 (34%)	2408 (33%)	3934 (33%)	0.19
Dialysis at listing	80 (1.8%)	123 (1.7%)	203 (1.7%)	0.67
Creatinine >1.5 (N=11 594)	1298 (30%)	2076 (28%)	3374 (29%)	0.06
GFR (N=11 601)				0.15
<30*	240 (5.6%)	348 (4.8%)	588 (5.1%)	
30–59	1540 (36%)	2651 (36%)	4191 (36%)	
≥60	2523 (59%)	4299 (59%)	6822 (59%)	
Medicaid insurance	646 (14%)	1049 (14%)	1695 (14%)	0.89

Data presented as median (25th, 75th percentile) or N (percent).

BMI indicates body mass index; CMP, cardiomyopathy; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; ECMO, extra-corporeal membrane oxygenation; BIVAD, bi-ventricular assist device; LVAD, left ventricular assist device; IV, intravenous; GFR, glomerular filtration rate.

*Includes patients on dialysis.

listed candidates and at the time of transplant for all transplant recipients in the US submitted by their transplant centers. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN contractor, UNOS.

Patients who were listed for a heart retransplantation or multiorgan transplantation were excluded. For analysis of wait list outcomes, all candidates were followed from the time of listing until death, HT, removal from the wait list, or the day of last observation on November 20, 2009. Patients who received a HT were followed until hospital discharge, death, or the day of last observation.

Study Design and Definitions

The primary study hypothesis was that the risk of death on the wait list has decreased in the US since the implementation of the new allocation algorithm on July 12, 2006. We compared baseline characteristics and outcomes between patients listed for a primary HT during July 1, 2004 to July 11, 2006 (Era 1), and those listed during July 12, 2006 to June 30, 2009 (Era 2). The primary end point was a composite of death on the wait list or becoming too sick to transplant (removal from the wait list due to clinical deterioration). Patients who received a HT or those who were removed from the list due to recovery or other reasons were censored. Clinical variables were defined at the time of listing for analysis of wait list outcomes. Secondary end points included (1) post-transplant in-hospital mortality, (2) 1-year survival among those who received a HT and, (3) post-transplant length of stay in recipients who survived to hospital discharge. Post-transplant mortality was compared between groups defined by the date of listing (Era 1 versus Era 2, as defined above), rather than between groups defined by the date of HT (intention to treat principle). Post-transplant mortality was analyzed using clinical variables at the time of transplant.

Patient race/ethnicity was recorded as reported by the transplant center and analyzed as white, black, Hispanic, or Other. Renal function was analyzed as a categorical variable (plasma creatinine >1.5 mg/dL) and as estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula.[9,10]

None of the subjects had any missing data for the variables of age, gender, race/ethnicity, cardiac diagnosis, blood type, hemodynamic support (intra-aortic balloon pump, inotrope support, ventilator, mechanical support), medical insurance (Medicaid), UNOS listing status, dialysis and the dates of listing, transplant, death, or removal from the wait list. For patients with missing data on other variables, we created indicator variables "variable not reported" for each such variable to allow these subjects to contribute their available risk factors in multivariable models.

Statistical Analysis

Summary data are presented as median (25th, 75th percentile) or number (percent). Baseline characteristics between patients in the 2 eras were compared using the χ^2 test for categorical and the Kruskal-Wallis test for continuous variables. Overall wait list mortality before and after the change in allocation algorithm was assessed using the Kaplan-Meier method and using competing outcomes analysis.[11,12] A multivariable Cox proportional hazards model was developed using a forward selection procedure retaining variables significant at the 0.10 level based on a likelihood ratio test; all variables in Table 1 were considered. Interactions of patient risk factors with era were assessed to ascertain if the effect of allocation change on the primary end point has been significantly different in patient subgroups. A multivariable logistic regression model was developed to evaluate era effect for post-transplant in-hospital mortality among transplant recipients adjusted for baseline risk factors. A Cox regression model was used to evaluate era effect for 1-year survival. Post-transplant length of stay among those who survived to hospital discharge was compared during the 2 eras using an unpaired *t* test.

Data were analyzed using SAS statistical software version 9.1 (SAS Institute Inc.). All statistical tests were 2-sided, and a probability value of less than 0.05 was used to define statistical significance. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Study Population

During the 5-year study period, 11 864 patients ≥18 years of age were listed in the US for their primary HT and formed the study cohort. Of these, 4503 (38%) were listed before the

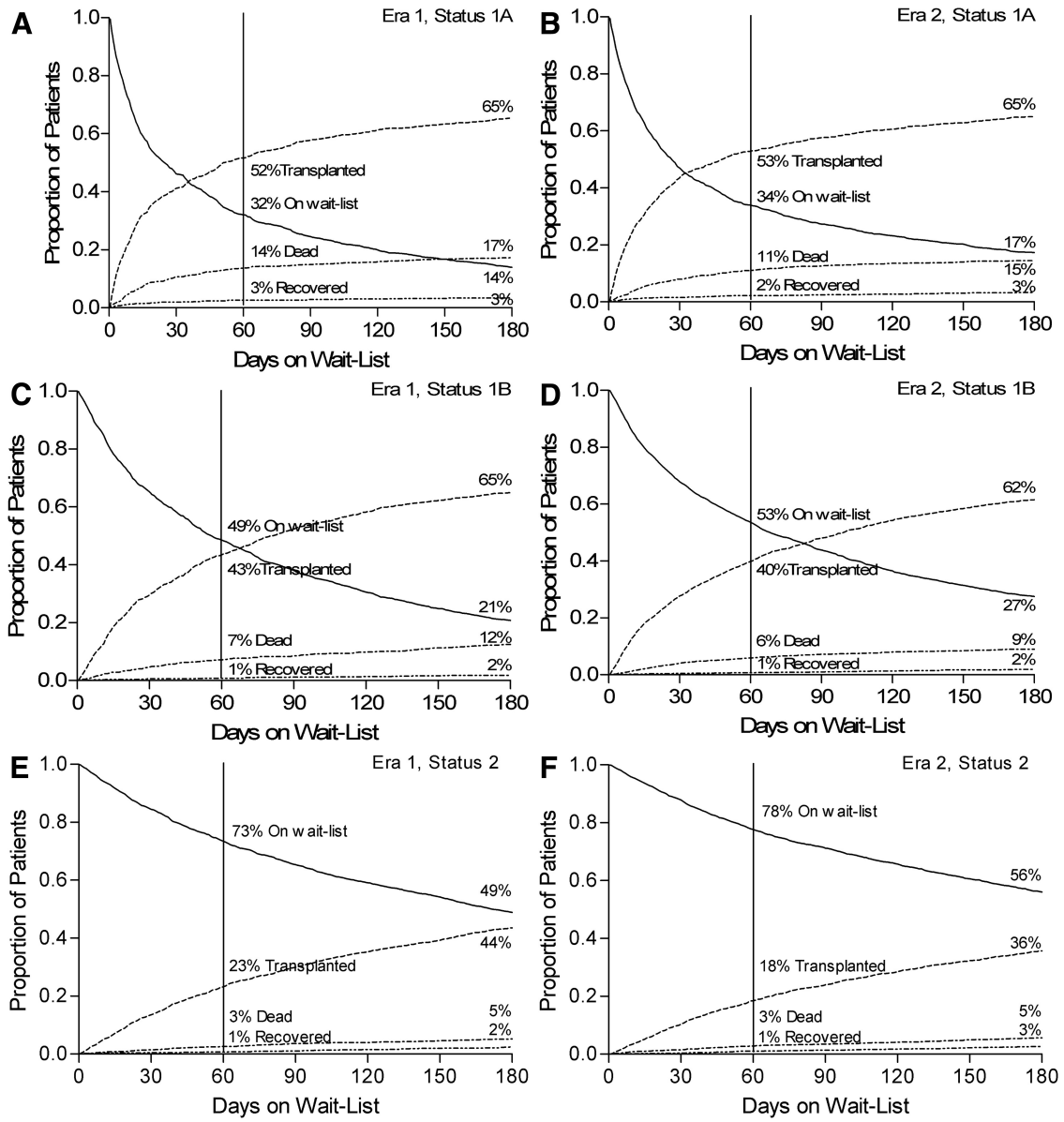

Figure 1. Competing outcomes for patients listed as status 1A during Era 1 (1A) and Era 2 (1B), status 1B during Era 1 (1C) and Era 2 (1D), and status 2 during Era 1 (1E) and Era 2 (1F). Patients shown as having died include those who were removed from the list due to deterioration.

allocation change (Era 1) and 7361 (62%) after the allocation change (Era 2). Table 1 summarizes baseline characteristics of patients listed for HT during the 2 eras. Patients listed during Era 2 were older and were more likely to be black, have type 2 diabetes, listed status 1A or 1B, have dilated or restrictive cardiomyopathy, and have an implantable cardioverter-defibrillator (ICD; ($P<0.001$ for distribution of age, race, diabetes, listing status, diagnosis, or ICD). The

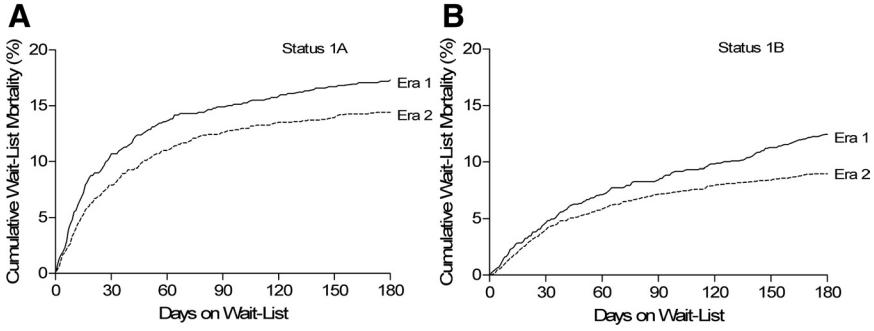

Figure 2. Cumulative wait list mortality (includes removal from the wait list due to deterioration) before (Era 1) and after (Era 2) the change in allocation algorithm in patients listed as status 1A (2A) and status 1B (2B).

percentage of patients listed on a mechanical support was higher in Era 2 (13.1% versus 14.6%, $P=0.02$). A higher percentage of patients were supported on a continuous-flow left ventricular assist device (LVAD) or total artificial heart at listing during Era 2 compared with patients listed during Era 1 ($P<0.001$ for distribution of type of mechanical support between the groups).

Wait List Mortality

Overall, 1557 (13.1%) patients reached the primary end point (1092 died on the wait list, 465 became too sick to transplant), 7896 (66.6%) received a HT, 955 (8.0%) were removed from the list due to recovery or other reasons, and 1456 (12.3%) were still listed for HT on the last day of the study. Figure 1 illustrates competing outcomes for patients listed as status 1A (Panels A and B), those listed as status 1B (Panel C and D), and patients listed as status 2 (Panel E and F) before and after the change in allocation algorithm. The incidence rate of wait list mortality (including patients removed due to deterioration) decreased from 80/100 patient-years in Era 1 to 63/100 patient-years in Era 2 in patients listed as status 1A ($P=0.02$), and from 41/100 patient-years in Era 1 to 31/100 patient-years in Era 2 in patients listed as status 1B ($P=0.01$). It was unchanged in patients listed as status 2 in the 2 eras (12 versus 13/100 patient-years, $P=0.56$). Figure 2 illustrates cumulative wait list mortality during the 6-month period after listing during the 2 eras among patients listed status 1A (Panel A) and those listed status 1B (Panel B).

Overall, patients listed in Era 2 were at lower risk of wait list mortality or becoming too sick to transplant compared with those listed in Era 1 (hazard ratio [HR] 0.86 in unadjusted analysis, 95% CI 0.78, 0.96, $P=0.005$). Compared with patients listed during July 2004 to June 2005, the risk of dying on the wait list or becoming too sick to transplant was similar for patients listed during July 2005 to June 2006 (HR 1.0, CI 0.86, 1.16), but was 14% lower for patients listed during July 2006 to June 2007 (HR 0.86, CI 0.73, 1.00), 13% lower for patients listed during July 2007 to June 2008 (HR 0.87, CI 0.74, 1.01), and 13% lower for those listed during July 2008 to June 2009 (HR 0.87, CI 0.74, 1.02). The decline in risk for patients listed during Era 2 remained significant in adjusted analysis (HR 0.83, CI 0.75, 0.93, Table 2). Furthermore, in an analysis adjusted for all risk factors in Table 2 (except era) with patients listed during July 2004 to June 2005 as the reference group, those listed during July 2005 to June 2006 were at similar risk of dying or becoming too sick to transplant (HR 1.0, CI 0.86, 1.17). However, the risk was 13% lower for patients listed during July 2006 to June 2007 (HR 0.87, CI 0.74, 1.02), 17% lower for patients listed during July 2007 to June 2008 (HR 0.83, CI 0.70, 0.97), and 17% for those listed during July 2008 to June 2009 (HR 0.83, CI 0.70, 0.97). Other multivariable predictors of death on the wait list or becoming too sick to transplant were older age, restrictive cardiomyopathy, pulmonary capillary wedge pressure >20 mm Hg, listing status 1A or 1B, intravenous inotropes, mechanical ventilation, extracorporeal membrane oxygenation support, Hispanic ethnicity, diabetes, and renal dysfunction (Table 2). Patients on a continuous-flow LVAD and those with an ICD were at lower risk of wait list mortality.

Table 2. Multivariable Predictors of Wait List Mortality or Becoming Too Sick to Transplant

Predictor	HR (95% CI)	*P* Value
Age at listing (ref: 18–39 y)		<0.001
40–59 y	1.28 (1.09, 1.50)	
60–69 y	1.55 (1.29, 1.86)	
≥70 y	2.52 (1.78, 3.57)	
BMI (ref: <25)		0.05
25–29	0.87 (0.77, 0.99)	
30–34	0.81 (0.70, 0.93)	
≥35	0.93 (0.77, 1.12)	
Diagnosis (ref: dilated CMP)		<0.001
Congenital heart disease	1.11 (0.81, 1.53)	
Hypertrophic CMP	1.27 (0.84, 1.91)	
Ischemic CMP	1.09 (0.97, 1.23)	
Other	1.05 (0.86, 1.29)	
Restrictive CMP	2.31 (1.70, 3.15)	
Valvular	1.08 (0.77, 1.50)	
PCWP >20 mm Hg	1.27 (1.13, 1.42)	<0.001
Listing status (ref: status 2)		<0.0.001
1A	3.38 (2.88, 3.97)	
1B	2.06 (1.79, 2.38)	
Intravenous inotropes	1.17 (1.03, 1.33)	0.01
Ventilation	1.87 (1.52, 2.30)	<0.001
Mechanical support (ref: none)		<0.001
Continuous flow LVAD	0.56 (0.43, 0.75)	.
Pulsatile LVAD	1.06 (0.87, 1.28)	
BIVAD	1.14 (0.84, 1.53)	
Total artificial heart	0.88 (0.28, 2.75)	
ECMO	3.13 (1.99, 4.93)	
Race/ethnicity (ref: white)		0.04
Black	1.12 (0.98, 1.28)	
Hispanic	1.29 (1.07, 1.56)	
Other	1.13 (0.84, 1.51)	
Diabetes (ref: non-diabetic)		0.006
Type I	1.31 (1.04, 1.66)	
Type II	1.12 (0.99, 1.27)	
GFR (ref: ≥60 mL/min/1.73 m^2)		<0.001
30–59	1.58 (1.41, 1.77)	
<30 or dialysis	3.21 (2.72, 3.77)	
ICD	0.87 (0.78, 0.98)	0.01
Era 2 (ref: Era 1)	0.83 (0.75, 0.93)	0.001

HR indicates hazard ratio; BMI, body mass index; CMP, cardiomyopathy; PCWP, pulmonary capillary wedge pressure; LVAD, left ventricular assist device; BIVAD, bi-ventricular assist device; ECMO, extra-corporeal membrane oxygenation; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator.

Subgroup Analysis

Figure 3 demonstrates the risk of death on the wait list or becoming too sick to transplant in Era 2 compared with Era 1 in subgroups of patients controlling for risk factors identified in Table 2. The improvement in wait list mortality was consistent across most subgroups, particularly those with

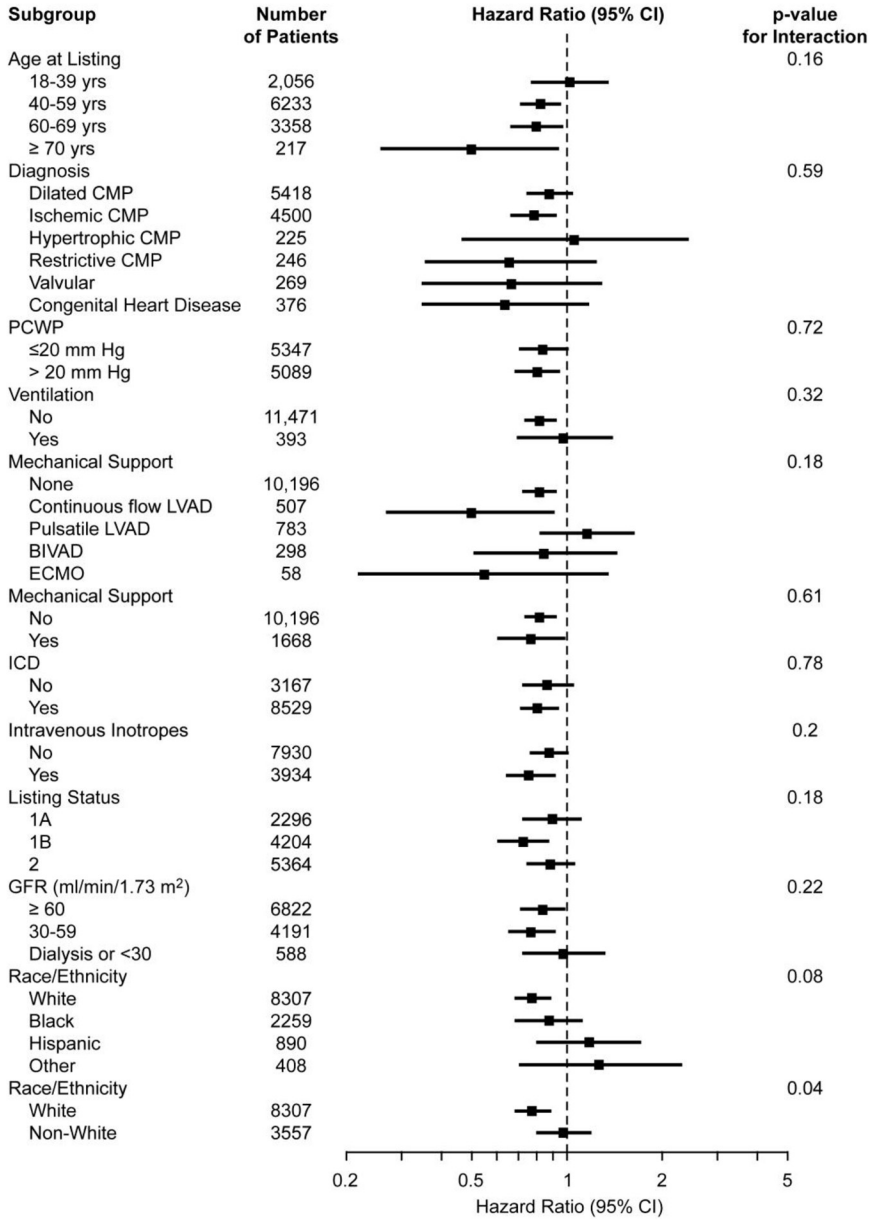

Figure 3. Risk of wait list mortality or becoming too sick to transplant after the change in allocation algorithm (Era 2) compared with Era 1 in subgroups of listed patients adjusted for other risk factors of wait list mortality in Table 2.

adequate sample size. There was no interaction of era with listing status. Furthermore, there was no interaction of era with mechanical support; the improvement in wait list outcomes appeared to be similar among patients listed on or without mechanical support. In subgroup analysis, the risk of dying on the wait list or becoming too sick to transplant decreased among candidates listed while on mechanical support (n=1668; HR 0.77 for Era 2, CI 0.61, 0.98), as well as among those listed while not on any mechanical support (n=10 196; HR 0.82 for Era 2, CI 0.74, 0.92), adjusting for other risk factors. Of note, in adjusted analysis stratified by era, the risk of wait list mortality in patients on continuous-flow LVAD was similar to those not on any mechanical support during Era 1 (HR 0.83; CI 0.50, 1.41), but was significantly lower in such patients during Era 2 compared with those not on any mechanical support (HR 0.51; CI 0.37, 0.70). The risk of wait list mortality associated with extracorporeal membrane oxygenation (ECMO) also was lower in Era 2 (HR 2.70; CI 1.53, 4.79) compared with Era 1 (HR 4.07, CI 1.99, 8.32). The race-era interaction was borderline significant ($P=0.08$ assessed as individual groups, $P=0.04$ assessed as white/nonwhite), and showed a decrease in wait list mortality associated with change in allocation only in white candidates.

Because the increased ventricular assist device (VAD) use in Era 2 may have contributed to the improved wait list outcomes, we performed a subgroup analysis on patients that were not VAD supported at either listing or transplant (n=9348). The competing outcomes and cumulative wait list mortality in Era 1 and Era 2 in non-VAD patients listed 1A/1B is illustrated in Figure 4. In an adjusted model (adjusted for all variables in Table 2), non-VAD patients listed in Era 2 were at 23% lower risk of dying on the wait list or becoming too sick to transplant (HR 0.77, 95% CI 0.69, 0.87).

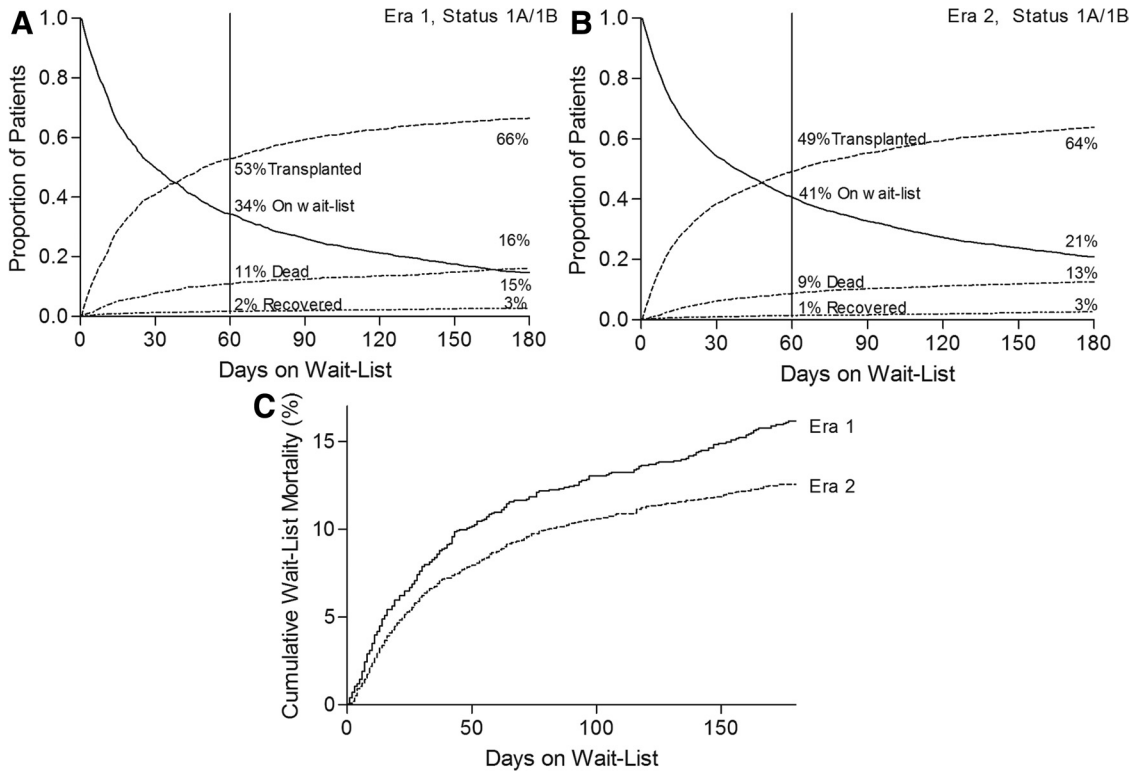

Figure 4. Competing outcomes for patients listed as status 1A/1B during Era 1 (4A) and Era 2 (4B) not supported on a ventricular assist device at either listing or transplant. A comparison of cumulative wait list mortality in 1A/1B patients in Era 1 and Era 2 is depicted in 4C.

Post-Transplant Mortality

The median waiting time for HT was 63 days (interquartile range 19–170 days) for patients listed during Era 1 and 55 days (interquartile range 17–146 days) for patients listed during Era 2 ($P<0.0001$). Although the median waiting times for HT in patients listed status 1A (20 versus 21 days) and those listed status 1B (48 versus 49 days) were similar in the 2 eras, a higher percentage of patients were transplanted as status 1A among those listed in Era 2 (37% in Era 1 versus 48% in Era 2, $P<0.0001$). The percentage of HT surgeries performed using hearts from local donors declined from 62% in Era 1 to 52% in Era 2 ($P<0.001$). As a result, the median distance between the recipient and the donor hospital increased in Era 2 (89 miles in Era 1 versus 125 miles in Era 2, $P<0.001$). Donor ischemic time for HT recipients was somewhat higher during Era 2 (3.2 ± 1.0 hours versus 3.3 ± 1.0 hours, $P=0.02$). The proportion of patients whose level of support increased between listing and transplant (no mechanical support to any mechanical support *or* LVAD to bi-ventricular assist device/total artificial heart/ECMO) was similar among patients listed during the 2 eras.

Among 7747 patients who received a HT and whose discharge status was known (3191 listed in Era 1, 4556 listed in Era 2), 7298 (94.2%) patients were discharged from the hospital by the last day of the study and 449 (5.8%) died prior to hospital discharge (Table S1 for clinical variables at transplant; see online-only supplement). Post-transplant in-hospital mortality was 6.3% for HT recipients listed before and 5.4% for HT recipients after the allocation change. Table 3 lists risk factors for post-transplant in-hospital mortality in the study cohort. Listing after allocation change was not associated with a change in early post-transplant mortality (risk-adjusted odds ratio, 0.85 for Era 2 versus Era 1, 95% CI 0.69, 1.04, $P=0.11$) or in 1 year survival (risk-adjusted HR 0.98 for Era 2 versus Era 1, 95% CI 0.85, 1.12, $P=0.73$). Post-transplant length of stay (mean$\pm$standard deviation) among those who survived to discharge was similar during the 2 eras (20 ± 25 days during Era 1 versus 19 ± 18 days during Era 2, $P=0.09$).

Discussion

In this study, we sought to assess whether the implementation of the new allocation algorithm in 2006 allowing broader regional sharing of donor hearts for sicker heart failure patients (those listed 1A and 1B) has been associated with a change in national wait list and early post-transplant mortality in the US. We found that the risk of dying on the HT wait list or becoming too sick to transplant has declined since the implementation of the new algorithm, as has the median waiting time among HT recipients. As expected, implementation of the new allocation algorithm has led to a higher percentage of HT surgeries being performed in patients listed status 1A. However, this redirection of donor hearts to sicker heart failure patients has not resulted in higher early post-transplant mortality. Although a higher VAD use in Era 2 probably has contributed to improved wait list outcomes, an important role of allocation change is suggested by (1) the improvement in wait list outcomes in patients not on VAD at either listing or at transplant, (2) unchanged wait list time in

Table 3. Multivariable Predictors of Post-Transplant In-Hospital Mortality

Predictor	OR (95% CI)	*P* Value
Age at transplant (ref: 18–39 y)		0.006
40–59 y	1.03 (0.75, 1.41)	
60–69 y	1.43 (1, 2.04)	
≥70 y	2.2 (1.15, 4.2)	
Race/ethnicity (ref: white)		0.02
Black	1.47 (1.13, 1.91)	
Hispanic	0.87 (0.57, 1.32)	
Other	0.91 (0.53, 1.59)	
Diagnosis (ref: dilated CMP)		<0.0001
Congenital heart disease	5.24 (3.25, 8.45)	
Hypertrophic CMP	1.42 (0.67, 3.0)	
Ischemic CMP	1.25 (0.98, 1.59)	
Other	1.59 (1.08, 2.34)	
Restrictive CMP	2.04 (1.08, 3.84)	
Valvular	1.78 (0.99, 3.21)	
Ventilation at transplant	2.49 (1.6, 3.85)	<0.0001
Mechanical support (ref: none)		<0.0001
Continuous flow LVAD	1.28 (0.85, 1.93)	
Pulsatile LVAD	1.47 (1.05, 2.07)	
BIVAD	2.03 (1.32, 3.11)	
Total artificial heart	2.92 (1.25, 6.79)	
ECMO	6.16 (3.09, 12.27)	
Increased mechanical support*	1.61 (1.15, 2.25)	0.005
GFR (ref: ≥60 mL/min/1.73 m^2)		<0.0001
30–59	1.8 (1.44, 2.25)	
Dialysis or <30	3.61 (2.6, 5.01)	
Bilirubin (ref: <1.5)		<0.0001
1.5–2.5	1.29 (1.03, 1.62)	
>2.5	2.23 (1.63, 3.05)	
Donor age 40–69 vs 18–39	1.76 (1.43, 2.16)	<0.0001
Ischemic time >4 h	1.57 (1.25, 1.98)	<0.0001
Era 2 (ref: Era 1)	0.85 (0.69, 1.04)	0.11

OR indicates odds ratio; CMP, cardiomyopathy; LVAD, left ventricular assist device; BIVAD, bi-ventricular assist device; ECMO, extra-corporeal membrane oxygenation; GFR, glomerular filtration rate.

*No mechanical support at listing to any mechanical support at transplant *or* LVAD at listing to BIVAD/total artificial heart/ECMO at transplant.

patients listed as status 1A, despite a higher percentage of patients listed and transplanted as status 1A, and (3) the decline in risk in the year following the allocation change. These findings suggest that the potential problems anticipated from change in allocation algorithm have not materialized, and the new allocation algorithm appears to be achieving its intended goal.

Since the early days of transplantation, UNOS has considered use/benefit and justice/fairness as the 2 fundamental ethical principles in allocating solid organs, giving equal weight to both.[13] Following the publication of the Final Rule by the Department of Health and Human services,[14] there were major changes in allocation of hearts, livers, and lungs, so that medical urgency became the predominant determinant of the new algorithms in the US.[15–19] Thus, patients listed for a HT have been considered in a new 3-tier system (versus a prior 2-tier system) of medical urgency since 1999.[1] It is important to note that allowing a broader sharing of donor hearts for 1A and 1B heart candidates is well within the scope of the First Rule (medical urgency first followed by first-come first-served among those with equal medical urgency). It assumes, however, that sharing hearts with candidates located up to 500 miles of the donor hospital will lead to better overall wait list outcomes and will not result in decline in overall transplant benefit due to worse post-transplant outcomes or futile transplants.[14]

The findings of our analysis support and expand on previous observations in the Scientific Registry of Transplant Recipients (SRTR) reports, which showed fewer deaths/patient-years of wait list time early after the change in allocation algorithm.[4] Although the improvement in wait list outcomes was not confirmed in a subsequent regional analysis limited to Utah candidates,[5] regional heterogeneity in benefits of allocation change are to be expected, first because of the variations in recipient characteristics and donor pool in different regions, and second due to a relatively small number of subjects in each region.[20] Thus, an analytic approach similar to that employed in the current study for subjects of a single region may demonstrate lack of benefit due simply to a small sample size (type II error). The new algorithm does not explicitly consider the potential for worse prognosis in sicker patients. However, similar post-transplant survival in the 2 eras noted in the current analysis suggests that while subjects who received a HT in Era 2 were sicker, appropriate patient selection by transplant centers ensured that their risk profile for post-transplant outcomes was acceptable.

An examination of wait list mortality among patients listed for a HT in the US in SRTR reports (deaths/patient-years of wait list time) suggests a progressive decline in wait list mortality even before the new allocation algorithm was implemented.[4] This decline appeared to be particularly noticeable during the years 2001 to 2004, before appearing to plateau during 2004 to 2006, and may be explained by advances in HT candidate selection and in medical management of listed patients. Although the decline in wait list mortality observed in our study occurred coincident with the change in allocation, the relative contributions of the new allocation algorithm and the concurrent advances in care of heart failure patients to the decline in wait list mortality cannot be assessed because of the absence of a contra-factual cohort. An important role of the new allocation algorithm is suggested by a rather abrupt decline in overall and risk-adjusted wait list mortality in the year following the allocation change, which then was maintained at that level in subsequent years.

The finding that the decrease in wait list mortality associated with the change in allocation algorithm was limited to white candidates was surprising, in particular because the interaction was observed after adjusting for all other risk factors (Figure 3). A previous OPTN analysis for patients listed for a HT during 1990 to 2005 found white candidates to be at higher risk of death within 60 days of listing.[21] Potential

explanations for lack of benefit from allocation change in minority candidates may include racial differences in the distributions of cardiac diagnoses, blood type, listing status, access to care, timing of presentation, and progression of heart failure. Further work is needed to determine if there are significant racial differences in wait list outcomes in the current era, and if so whether they are caused by biological differences among racial groups or represent racial disparities.

Because the results of wait list outcomes were predicted by a simulation that preceded the implementation of the new algorithm, they highlight the value of such simulations prior to changes in allocation algorithm.[2,22] Future simulations could consider not only the effect of allowing longer distance between the donor and the recipient hospitals for those in immediate need of a transplant, but also other factors associated with worse wait list outcomes, such as the cardiac diagnosis. Almost half of all wait list deaths with the current allocation algorithm occur within 60 days of listing, suggesting the potential for such simulations to unearth further opportunities for improving wait list outcomes.

This study has a few limitations. First, being a retrospective analysis of a national database, the quality control of submitted data may not be as rigorous as in prospective, controlled trials. However, because these data are used by UNOS for real-time organ allocation and for subsequent evaluation of center performance, and are subject to periodic audit, reasonable safeguards to data quality may be expected. Second, patients who were waiting for a HT at the time of implementation of allocation change were affected by the new allocation and may have affected the results of the current analysis. Assuming a net benefit based on this analysis, however, this would bias the results of our analysis toward null and may suggest an underestimation of the magnitude of benefit associated with the change in allocation. Third, allocation change may not be the only explanation for improved wait list outcomes, despite our analysis adjusting for all available risk factors. Advances in heart failure management, particularly in management of patients on mechanical support, have occurred rapidly and may have contributed to the improved outcomes over and above that captured by multivariable analysis. However, the consistency of improvement in outcomes across subgroups, in particular those not on mechanical support at listing, suggests an important role of allocation change. Finally, these national outcomes may not be applicable to all US regions because individual regions represent nonrandom samples of the US population, with outcomes affected by differences in recipient characteristics and by local practice patterns and donation rates.

Conclusions

In conclusion, the risk of dying on the HT wait list or becoming too sick to transplant has declined in the US since the allocation algorithm allowing broader regional sharing was implemented in 2006. The shift in hearts to sicker HT candidates has not resulted in higher early post-transplant mortality.

Sources of Funding

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Disclosures

None.

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CLINICAL PERSPECTIVE

The sequence of donor heart allocation in the United States (US) was changed in July 2006 to promote a broader regional sharing of available donor hearts for sicker patients on the wait list before hearts are allocated to less sick, local candidates. Using the United Network for Organ Sharing database, the authors compared wait list outcomes in adults listed for heart transplant in the US before (2004–2006, Era 1) and after (2006–2009, Era 2) the change in allocation algorithm. There were 11 864 patients in the study, 4503 listed during Era 1 and 7361 during Era 2. Patients listed during Era 2 were sicker (more listed status 1A) and more likely to be supported on a continuous flow assist device ($P<0.001$ for distribution). Patients listed in Era 2 were at 17% lower risk of dying on the wait list or becoming too sick to transplant in multivariable analysis. The findings were similar when analysis was limited to patients who were not supported by a ventricular assist device at either listing or at transplant. Transplant recipients in Era 2 were more likely to be transplanted as status 1A (37% versus 48%), but this shift in hearts to sicker patients did not result in higher hospital mortality or worse 1-year survival among transplant recipients in Era 2. The authors conclude that although increased use of ventricular assist devices in patients waiting for a heart has contributed to improved outcomes after 2006, the change in allocation of hearts has been accompanied by a decreased risk of wait list death in the US.

SUPPLEMENTAL MATERIAL

Supplemental Table 1: Clinical Characteristics at Transplant in Heart Transplant Recipients Grouped by Era of Listing (Before and After the Change in Allocation)

Variable	Era 1 N =3191	Era 2 N=4556	Total N =7747	P-value
Age (Yrs)				0.02
18-39	546 (17%)	745 (16%)	1291 (17%)	
40-59	1689 (53%)	2309 (51%)	3998 (52%)	
60-69	906 (28%)	1404 (31%)	2310 (30%)	
≥ 70	50 (1.6%)	98 (2.2%)	148 (1.9%)	
Blood Type				0.52
A	1347 (42%)	1967 (43%)	3314 (43%)	
B	468 (15%)	664 (15%)	1132 (15%)	
O	1221 (38%)	1681 (37%)	2902 (37%)	
AB	155 (4.9%)	244 (5.4%)	399 (5.2%)	
Sex, Male	2453 (77%)	3428 (75%)	5881 (76%)	0.10
BMI (N=7745)				0.17
<25	1266 (40%)	1766 (39%)	3032 (39%)	
25-29	1206 (38%)	1668 (37%)	2874 (37%)	
30-34	553 (17%)	879 (19%)	1432 (18%)	
35+	165 (5%)	242 (5%)	407 (5%)	
Diagnosis				<0.001
Dilated CMP	1415 (44%)	2222 (49%)	3637 (47%)	
Ischemic	1265 (40%)	1650 (36%)	2915 (38%)	
CHD	99 (3.1%)	96 (2.1%)	195 (2.5%)	
Hypertrophic CMP	75 (2.4%)	89 (2.0%)	164 (2.1%)	
Restrictive CMP	46 (1.4%)	99 (2.2%)	145 (1.9%)	
Valvular CMP	75 (2.4%)	105 (2.3%)	180 (2.3%)	
Other	216 (6.8%)	295 (6.5%)	511 (6.6%)	
Diabetes (N=7530)				<0.001

Type I	126 (3.9%)	169 (3.7%)	295 (3.8%)	
Type II	568 (18%)	950 (21%)	1518 (20%)	
PAP >30 mmHg (N=6720)	1060 (39%)	1773 (44%)	2833 (42%)	<0.001
PCWP>20 mmHg (N=6496)	1059 (40%)	1733 (45%)	2792 (43%)	<0.001
Ventilation	79 (2.5%)	118 (2.6%)	197 (2.5%)	0.75
Inotropes	1322 (41%)	1941 (43%)	3263 (42%)	0.30
ICD	2306 (72%)	3578 (79%)	5884 (76%)	<0.001
Mechanical Support				<.0001
ECMO	19 (0.6%)	31 (0.7%)	50 (0.6%)	
Total Artificial Heart	9 (0.3%)	37 (0.8%)	46 (0.6%)	
BIVAD	130 (4.1%)	180 (4.0%)	310 (4.0%)	
Pulsatile LVAD	429 (13%)	381 (8.4%)	810 (10%)	
Continuous-flow LVAD	178 (5.6%)	549 (12%)	727 (9.4%)	
None	2426 (76%)	3378 (74%)	5804 (75%)	
Listing Status				<0.001
1A	1169 (37%)	2195 (48%)	3364 (43%)	
1B	1284 (40%)	1876 (41%)	3160 (41%)	
2	738 (23%)	485 (11%)	1223 (16%)	
Dialysis	90 (2.8%)	94 (2.1%)	184 (2.4%)	0.03
Creatinine >1.5 (N=7742)	883 (28%)	1205 (26%)	2088 (27%)	0.23
GFR (N=7674)				0.43
*< 30	171 (5.4%)	226 (5.0%)	397 (5.2%)	
30-59	1110 (35%)	1537 (34%)	2647 (34%)	
>=60	1883 (59%)	2747 (61%)	4630 (60%)	
Race/Ethnicity				<0.001
White	2306 (72%)	3118 (68%)	5424 (70%)	
Black	522 (16%)	914 (20%)	1436 (18%)	
Hispanic	248 (7.8%)	357 (7.8%)	605 (7.8%)	
Other	115 (3.6%)	167 (3.7%)	282 (3.6%)	
Medicaid Insurance	464 (14%)	720 (16%)	1184 (15%)	0.13
Increased Mechanical Support#	444 (14%)	657 (14%)	1101 (14%)	0.53

Bilirubin (N=7438)				0.18
<1.5	1667 (52%)	2464 (54%)	4131 (53%)	
1.5-2.5	1112 (35%)	1550 (34%)	2662 (34%)	
>2.5	269 (8.4%)	376 (8.3%)	645 (8.3%)	
PRA Class 1>10% (N=7184)	343 (12%)	575 (14%)	918 (13%)	0.02
PRA Class 2>10% (N=6274)	195 (8.3%)	303 (7.7%)	498 (7.9%)	0.46
PRA Class 1 or 2>10% (N=7201)	433 (15%)	696 (16%)	1129(16%)	0.07
Ischemic time >4hrs (N=7398)	621 (20%)	976 (22%)	1597 (22%)	0.07
Donor Cause of Death				<0.001
Anoxia	324 (10%)	626 (14%)	950 (12%)	
Stroke	719 (22%)	1028 (23%)	1747 (23%)	
Head Trauma	2061 (65%)	2753 (60%)	4814 (62%)	
CNS Tumor	43 (1.3%)	35 (0.8%)	78 (1.0%)	
Other	44 (1.4%)	114 (2.5%)	158 (2.0%)	
Donor age				0.69
18-39	2319 (73%)	3292 (72%)	5611 (72%)	
40-69	872 (27%)	1264 (28%)	2136 (28%)	
Gender Mismatch	871 (27%)	1183 (26%)	2054 (26%)	0.19
Donor/Recipient Weight Ratio<0.8	408 (13%)	539 (12%)	947 (12%)	0.20
Donor/Recipient BMI Ratio<0.8	488 (15%)	689 (15%)	1177 (15%)	0.83

Data are presented as median (25^{th}, 75^{th} percentile) or number (percent). yr (year), CMP (cardiomyopathy), BMI (body mass index), PAP (pulmonary artery pressure), PCWP (pulmonary capillary wedge pressure), ECMO (extra-corporeal membrane oxygenation), ICD (implantable cardioverter-defibrillator), VAD (ventricular assist device), IV (intravenous), CHD (congenital heart disease), GFR (glomerular filtration rate), *Includes patients on dialysis, #No mechanical support at listing to any mechanical support at transplant *or* LVAD at listing to BIVAD/total artificial heart/ECMO at transplant.

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The effectiveness of United Network of Organ Sharing status 2 transplantation in the modern era

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KEYWORDS:
heart transplant;
transplant list;
survival analysis;
risk stratification;
heart failure

BACKGROUND: The continued benefit of United Network of Organ Sharing (UNOS) status 2 transplantation in the modern era has been questioned.

METHODS: We measured deterioration to higher status designations, improvement allowing delisting, and risk of death or delisting as too ill, regardless of subsequent status, from the Scientific Registry of Transplant Recipients database. Extended Cox models were used to assess the relative hazard of status 2 transplantation vs waiting after status 2 listing. The likelihood of transplantation was measured with logistic regression.

RESULTS: We analyzed 14,153 candidates listed from 2003 to 2008. Within 1 year of initial listing, deterioration to status 1B occurred frequently (63%), while delisting as too well occurred rarely (2%–7%). Death or delisting as too ill occurred among 27% at 2 years after initial status 2 listing. Mortality at 2 years after status 2 transplantation was 13%. The hazard ratio (HR) after 180 days of status 2 transplantation vs waiting during or after initial status 2 listing was 0.41 (95% confidence interval, 0.31–0.55). The likelihood of transplantation was markedly diminished for women (odds ratio, 0.71; $p < 0.001$) and congenital heart disease (odds ratio, 0.24; $p < 0.001$). Death or delisting as too ill for women (HR, 1.7; $p < 0.001$) and congenital heart disease (HR, 3.2; $p < 0.001$) were substantially higher than in other groups.

CONCLUSIONS: Escalation of UNOS status is common and delisting as too well is uncommon after initial status 2 listing. Despite the decreasing number of transplants provided to status 2 registrants, sub-groups of patients may be at high risk of waiting at status 1A, justifying the continued use of the status 2 designation.

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The survival, expectancy of deterioration, and expectancy of benefit from transplantation are of great interest among status 2 registrants because they represent most of the registrants listed at any given time. Aggregate data reported by the Scientific Registry of Transplant Recipients (SRTR) demonstrates a decrease in mortality rates from 2000 to 2008 among those listed as status 1A, 1B and 2; and recent reports question the benefit of transplantation in status 2 registrants.[1–3] If there is no net benefit in transplantation for stable registrants, organ allocation to low-risk registrants may not be warranted.

Transplant registrants experience many diverse pathways once listed, however, including list removal as the result of clinical improvement, temporary periods of transplant ineligibility, or sudden death. Many patients will deteriorate to status 1B or 1A, and sub-groups of registrants may have increased mortality while waiting in status 1B or 1A. This situation may favor early status 2 listing vs a strategy of delayed status 1B or 1A listing.

In this study we used a contemporary population of transplant registrants and recipients to demonstrate that transplantation from status 2 offers a survival benefit for the average status 2 registrant and that selected sub-groups of registrants may be better served by status 2 listing because

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they experience increased risk while waiting at higher United Network of Organ Sharing (UNOS) status designations.

Methods

The University of Michigan Institutional Review Board (HUM00033840) and the SRTR approved this study. All transplant registrants listed for heart transplantation in the United States at any status (including status 7 or temporarily inactive status) from January 1, 2003, to August 1, 2008, were included. Status designations at the time of an outcome required persistence in that status for at least 2 days. For status persistence of ≤2 days at the time of an outcome, the proximate listing status was used without regard to the duration of that status. This strategy is the standard method of status adjudication by the SRTR. Dates of death were reported by the local Organ Provision Organization (OPO) or Social Security Death Index records. Registrants were censored alive if they remained listed on the administrative censoring date, August 1, 2008.

The SRTR data tables were used to analyze listing and transplant trends.[2] Cochrane-Armitage tests of trend, Poisson regression, and goodness-of-fit chi-square methods were used to analyze the temporal listing and transplant trends.

Using Kaplan-Meier analysis, we were able to assess whether the time to death for those actively listed is the same for those who were delisted as too ill for transplantation (Wilcoxon log-rank test, $p = 0.22$). Because the risk of death was not significantly different, we used a composite end point of death on the waiting list or delisting as too ill.

A Cox model based on initial status designation and aggregate time in any subsequent status was used to estimate the risk of death or delisting as too ill regardless of UNOS status after initial listing. We used a similar Cox model to assess the risk of death or delisting as too ill after a registrant was placed in hold status immediately after an active status 2 listing to assess the likelihood of death or delisting as too ill once delisted from status 2. Post-transplant mortality rates were similarly estimated using UNOS status at the time of transplant to measure transplant mortality specific to the status from which transplantation occurred.

We used extended Cox models to compare the relative benefit of transplantation from any status with the risk of waiting after initially being listed in a given status.[4] For those initially listed status 2, this model gives the hazard ratio (HR) of transplantation directly from status 2 relative to waiting. By including all times after initial listing, without regard to subsequent status, and using transplantation by status designation as the variable of interest, we avoid underestimating the risk of death or delisting as too ill for stable status 2 patients, while still assessing the effect of a status 2 transplantation vs probable deterioration in the future. Patients were censored if transplantation occurred from a status other than the status of interest (ie, for the model of status 2 transplant, censoring occurred at the time of 1A or 1B transplantation), removal from the list for reasons other than the primary outcome (ie, declined transplant, removed in error), or the administrative censoring date (August 1, 2008). The Cox model of transplantation vs waiting had no interaction with transplant status ($p = 0.099$). We report the model results in a piecewise fashion before and after 180 days, because the HR approaches $p = 0.05$ and the hazards of transplantation vs waiting are not proportional graphically.

We used univariate logistic regression models limited to each active transplant status to assess the odds of transplantation according to age, sex, weight, ABO blood type, and type of cardiomyopathy to better evaluate the relative likelihood of transplant. We used Cox models to assess the risk of death or delisting as too ill within demographic sub-groups. These 2 measures describe the likelihood of transplant and adverse outcomes for important subgroups of registrants that may have different likelihoods of transplant provision or adverse outcomes when waiting at higher status designations.

The counting process of estimation was used to account for UNOS status changes, transplantation, and list removal.[4] Reporting of the cumulative mortality (hazard) was used instead of cumulative survival, because the interpretation of cumulative survival in the presence of competing outcomes could lead to an overestimate of mortality.[4–6] The number needed to treat (NNT) was calculated as: 1/(waiting mortality in any status after initial listing – transplant mortality from the same initial status) and can be interpreted as the number of patients who would need to undergo transplantation from a given status to prevent 1 death on the waiting list among those who continued to wait after initial listing in the selected status (status 2 transplant mortality vs all events during and after initial status 2 listing). SAS 9.2 software (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Sample characteristics

The sample included 14,153 adult candidates with complete status, outcomes, and dates. All candidates were initially listed between January 2003 and August 2008. Baseline demographics and initial listing characteristics are reported in Table 1.

Trends in heart transplant listing

During the period of observation with complete data (2003–2007), the proportion of first-time registrants initially listed as status 2 declined from 55.3% to 42.0% ($p < 0.0001$ for trend over time), those initially listed as status 1B increased from 26.4% to 36.4% ($p < 0.0001$ for trend over time), and those initially listed as 1A remained stable ($p = 0.16$ for trend over time).

The number of status 2 registrants on the list at year's end between 2003 and 2007 decreased by 9.7% per year ($p < 0.0001$ for trend over years). The number of status 1B registrants listed during the same time increased by 2.5% per year ($p = 0.15$ for trend), whereas the number of 1A registrants increased by 9.7% per year ($p = 0.004$ for trend).

Of all transplants performed from 2003 to 2007, the proportion of status 2 transplants decreased from 24.7% to 16.3% ($p < 0.000$ for trend). The proportion of status 1B transplants increased from 35.5% to 41.8% ($p < 0.0001$ for trend), and the proportion of 1A transplants increased from 39.8% to 41.8% ($p = 0.072$ for trend).

A ventricular assist device was placed in 1,493 patients, and was followed by transplantation in 65% of candidates who received a device; however, the intended strategy at the

Table 1 Demographics at the Time of Initial Listing[a]

	Status 1A	Status 1B	Status 2
Initial status	2,791 (20)	4,428 (31)	6,344 (45)
Number, No. (%)	Median (IQR)	Median (IQR)	Median (IQR)
Age (years)	53 (42–60)	53 (43–60)	54 (45–60)
Body mass index, kg/m^2	26 (23–30)	26 (23–30)	27 (24–31)
Albumin, g/dl	3.3 (2.8–3.7)	3.6 (3.2–4.0)	4.0 (3.6–4.3)
Creatinine, μmol/liter	106 (88–141)	106 (88–141)	106 (88–137)
Peak VO_2, ml/kg/min	10 (8–13)	11 (9–13)	12 (10–14)
Cardiac output, liter/min	3.9 (3.1–5)	4.0 (3.1–5.0)	4.3 (3.5–5.1)
Wedge pressure, mm Hg	22 (16–28)	22 (16–28)	18 (13–24)
Women, %	26.5	26.4	24.6

[a]Registrants inactive at the time of initial listing are not reported.

time of ventricular assist device implantation was not available for analysis.

Death after initial listing

For a registrant who was initially listed as status 2, death or delisting as too ill occurred among 14% at 1 year (95% confidence interval [CI] 13%–16%) and 27% at 2 years (95% CI, 25%–30%, Figure 1). Registrants delisted from status 2 to an inactive status had a risk of death or delisting as too ill of 7% ± 1% at 1 year, 14% ± 1% at 2 years, and 25% ± 2% at 3 years. For a registrant who was initially listed status 1B, death or delisting as too ill occurred among 47% (95% CI, 42%–54%) at 1 year and 92% (95% CI, 77% to >99%) at 2 years. For a registrant who was initially listed status 1A, death or delisting as too ill occurred among 52% (95% CI, 46%–59%) at 180 days and in 86% (95% CI, 74% to >99%) at 1 year. Each of these models allows for deterioration after initial listing.

Frequency of transitions

After 2 years from initial listing, 388 of 6,217 individuals (6%) initially listed as status 2 remained at status 2. The likelihood of at least 1 transition from status 2 directly to status 1B within 1 year was 63% (95% CI, 60%–67%), to status 1A was 16% (95% CI, 14%–18%), and to an inactive status was 56% (95% CI, 60%–63%). The cumulative risk of status 1B or 1A upgrade reached 50% at 160 days after initial status 2 listing (Figure 2). Of registrants initially listed status 2, 2% were delisted from status 2 as too well, no need for transplant, and 7% of registrants were delisted as too well, no need for transplant, if all patients initially listed status 2 and any final status designation at the time of delisting are included.

Risk of waiting among selected sub-groups

Sub-groups of patients have a differential likelihood of receiving an allograft and of adverse outcomes when waiting at the same UNOS designation. Compared with men, women have a higher risk of death or delisting as too ill (HR, 1.7; $p = 0.0002$) and a lower likelihood of transplant (OR, 0.71; $p < 0.0001$) when listed status 1A (Table 2). Women also have a higher risk of death or delisting as too ill when listed as status 1B (HR, 1.3; $p = 0.02$). However, women have a higher likelihood of transplantation (OR, 1.5; $p < 0.0001$) and a decrease in the likelihood of death or delisting as too ill (HR. 0.7; $p = 0.03$) relative to men waiting in status 2, suggesting that early status 2 listing may be a better option for women.

Compared to those with ischemic cardiomyopathy, registrants with congenital heart disease have a very low likelihood of transplantation (OR, 0.24; $p < 0.0001$) and a high risk of death or delisting as too ill (HR, 3.2; $p = 0.0004$) while listed status 1A. While listed status 1B, those with a congenital etiology had no difference in the likelihood of transplant provision (OR, 0.82; $p = 0.29$) or adverse outcomes (HR, 0.82; $p = 0.62$) compared with those with ischemic cardiomyopathy. While listed status 2, those with congenital etiology had a lower likelihood of transplant provision (OR, 0.82; $p = 0.023$) and no increase in adverse outcomes (HR, 0.92; $p = 0.77$) compared with those with ischemic cardiomyopathy. These data suggest that those with congenital heart disease have no advantage while waiting status 1B or status 2, but a distinct disadvantage waiting

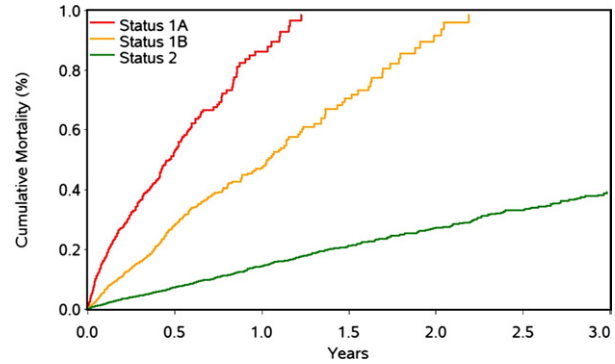

Figure 1 Primary outcome by status at the time of initial listing. Registrants may transition to other status designations after initial listing.

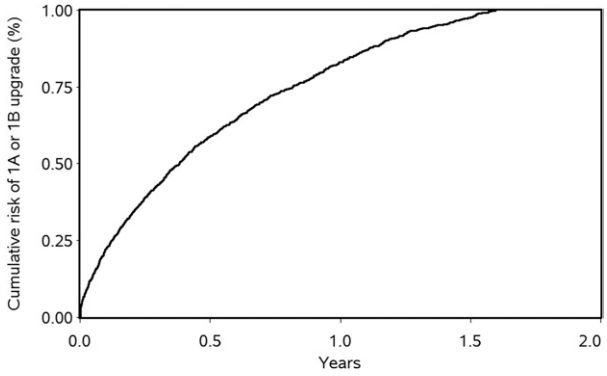

Figure 2 Cumulative risk of deterioration from status 2 directly to status 1B or 1A.

at status 1A, suggesting that early status 2 or status 1B listing may be advantageous for this sub-group of patients.

Weight increased the likelihood of transplantation in status 1A (OR for 10-kg increase in weight, 1.2; $p < 0.0001$), but decreased the likelihood of transplantation in status 1B (OR for 10-kg weight increase, 0.90; $p < 0.0002$) and status 2 (OR for a 10-kg weight increase, 0.82; $p < 0.0001$). Regardless of transplant status, type O registrants had a decreased likelihood of transplantation across status designations 1A (OR, 0.63), status 1B (OR, 0.46), and status 2 (OR, 0.26; all $p < 0.0001$) compared with blood type A registrants.

Benefit of transplantation among status 2 registrants

The unadjusted cumulative mortality rates after status 2 transplantation were 9% (95% CI, 8%–10%) at 1 year and 13% (95% CI, 11%–15%) at 2 years. The cumulative probability of the primary end point for those waiting after initial status 2 listing and post-transplant mortality after status 2 transplantation are shown in Figure 3. The HR of transplantation (death) from status 2 vs continued waiting in any status after initial status 2 listing (death or delisted as too ill) was 1.2 (95% CI, 0.90–1.6) within 30 days and HR 0.41 (95% CI, 0.31–0.55) after 180 days (Figure 2).

The number of status 2 transplants needed to prevent one death (NNT) was 6.7 at 2 years and 4.8 at 3 years (Table 3). The NNT was 1.3 at 2 years for status 1B transplants and 1.3 at 1 year for status 1A transplants. The HR of mortality after transplantation from status 1B vs status 2 was 1.02 (95% CI, 0.9–1.2), and status 1A transplantation vs status 2 transplantation was 1.2 (95% CI, 1.1–1.4).

Discussion

This analysis addresses the effectiveness of UNOS status 2 transplantation in an era of improved medical and device therapies and improved post-transplant survival. The main findings of this study are that the average status 2 registrant receives a survival benefit when transplantation occurs from status 2 compared with continued waiting on the transplant list, and certain sub-groups of patients are well served by the status 2 designation. Although status 2 transplantation has become increasingly rare, status 2 remains a safe and effective method for early listing of selected sub-groups of transplant candidates.

Table 2 Odds Ratio of Transplantation and Hazard Ratio of the Composite End Point for Selected Demographics by United Network of Organ Sharing Transplant Status[a]

	Status 1A		Status 1B		Status 2	
	Transplant	Composite end point	Transplant	Composite end point	Transplant	Composite end point
Variable	OR	HR	OR	HR	OR	HR
Female gender	0.71[b]	1.7[b]	0.89	1.32[b]	1.5[b]	0.7[b]
Non-white race	0.79[b]	1.1	0.95	0.99	1.1	1.1
Blood type						
A	Ref	Ref	Ref	Ref	Ref	Ref
B	0.79	1.2	0.96[b]	0.9	1.2	1.2
AB	1.1	1.0	1.7	1.6	3.4[b]	1.3
O	0.63[b]	1.0	0.46[b]	0.93	0.26[b]	1.0
Weight, 1 kg	1.02[b]	0.99	0.994[b]	0.99[b]	0.98[b]	0.99[b]
Diagnosis						
Ischemic	Ref	Ref	Ref	Ref	Ref	Ref
Congenital	0.24[b]	3.2[b]	0.86	0.82	0.82[b]	0.92
Hypertrophic	1.0	0.48	1.2	0.76	1.4	0.93
Non-ischemic	1.1[b]	0.64[b]	1.2[b]	0.71[b]	1.2	1.1
Other	0.63	1.3	0.83[b]	1.1	0.93	0.97

HR, hazard ratio; OR, odds ratio.

[a]Transplant: OR of transplantation vs any other mode of delisting. Composite end point: HR of death or delisting as too ill for transplantation.

[b]$p \leq 0.05$.

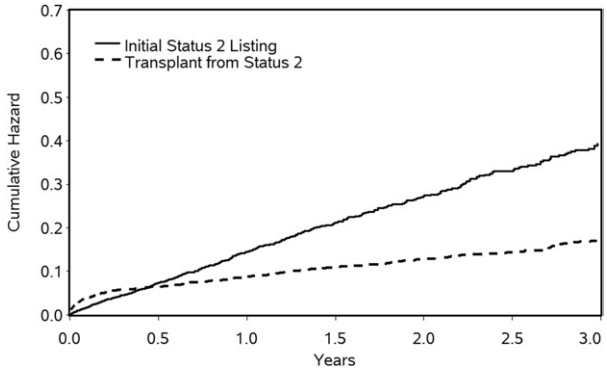

Figure 3 Primary outcome for registrants waiting after status 2 listing and status 2 transplant recipients. For those waiting, events are defined as death on the list or delisting as too ill for transplant.

Should eligible transplant candidates be listed status 2?

Several reports have questioned whether stable registrants should undergo transplantation and if further risk stratification would increase the efficacy of status 2 transplantation.[1,7–10] Krakauer et al[8] concluded that the likelihood of transplantation does not increase proportionately to the likelihood of death. Jimenez et al[9] reported that there was no benefit of status 2 transplantation among those who were stable in status 2. Mokadam et al[7] used data from 2001 to 2003 to confirm that benefit from status 2 transplantation was only evident among those who deteriorated. Lietz et al[1] demonstrated that survival among status 2 registrants improved by era (1990–2005) and that the magnitude of benefit for transplanting status 2 patients has declined. In aggregate, these studies reflect the growing concern that transplantation should be provided to those most likely to receive a benefit and that medical therapy has improved substantially, perhaps diminishing the need for the status 2 designation.

In the present study, we demonstrate that status 2 registrants rarely leave the list as the result of clinical improvement (2%–7% in our sample). Transplantation of these stable patients while listed would not result in a meaningful survival benefit. The risk of death or delisting as too ill is 14% at 2 years among those in a hold status after being listed status 2, whereas the status 2 transplant mortality rate is 13% at 2 years. Our analysis suggests that escalation of status designation within 1 year to status 1B (63%) or 1A (16%) is a much more common event than downgrade of status. Patients listed status 2 cannot be considered a stable group of patients based on these measures.

Although a strategy of waiting to initiate transplant listing until a patient reaches status 1A or 1B criteria may not expose the average registrant to excessive risk, selected sub-groups of patients may be disadvantaged by this approach, because their likelihood of transplantation diminishes and their likelihood of adverse outcomes increases at higher status designations. The status 2 designation allows the possibility of organ allocation to registrants who are difficult to transplant and who have differential survival compared with other registrants waiting in the same status. Careful consideration of the role of the status 2 designation may be necessary, because women and those with congenital heart disease and other sub-groups we did not analyze may be well served by the status 2 designation. Those with congenital heart disease are a particularly difficult group of patients to transplant.[11] Our analysis suggests that even though the number of status 2 registrants and transplant recipients continues to decrease, status 2 transplantation remains a safe and effective method of listing among selected sub-groups of patients and should remain an option for listing.

Measuring waiting list mortality

Our analysis evaluates mortality after initial status 2 listing and accounts for deterioration while listed. We allow for deterioration, because any adverse event that occurs from the day of initial status 2 listing until the day of removal from the transplant list could have potentially been prevented by transplantation while listed status 2. Allowing for upgrades in status is also reasonable given the high risk of deterioration (63% chance of an upgrade to status 1B by 1 year among those initially status 2). The absence of a long-term survivor effect among those initially listed status 2 would suggest that, in general, removal of chronic heart failure patients from the transplant list after prolonged periods of status 2 listing should only occur if the treating physician believes that transplantation is no longer a suitable option and not because that registrant would be expected to appreciate extended survival after proving long-term stability in status 2. We demonstrate that very few patients, only 6%, remain status 2 after 1 year from initial listing, most likely due to deterioration, as described above.

Limitations

Our analysis includes patients listed for transplant. Therefore, we cannot make direct inferences about the survival of status 2-like patients who were not listed. Our survival estimates are based on observation in a transplant program, which may increase survival in the presence of the close observation common among transplant registrants. The risk of adverse outcomes among patients delisted as too well from status 2 is likely lower than our measurement of patients placed in temporary hold status. Our analysis does

Table 3 Number Needed to Transplant From a Given United Network of Organ Sharing Status vs Waiting After Initial Listing in that Status

	Year[a]		
Status	1	2	3
Status 2, No.	20	6.7	4.8
Status 1B, No.	2.6	1.3	1.1
Status 1A, No.	1.3	1.0	1.0

[a]Indicates the waiting time since initial status listing or status-specific transplantation. Waiting time includes status transitions.

not include an assessment of the effects of status 2 listing at the OPO level. We do not have sufficient data to evaluate the quality of organ allocation to status 2 recipients. Women, specific racial minorities, and congenital registrants may have high levels of allosensitization that we cannot analyze given the available data.

Conclusions

Our analysis shows that registrants initially listed status 2 have a high probability of transition to higher status designations and high risk of death or delisting as too ill after initial listing. Selected sub-groups of registrants may have a distinct advantage when listed early as status 2 candidates rather than waiting until their clinical condition has deteriorated. Although the highest relative benefit of organ allocation is provided to registrants listed 1A or 1B, selected sub-groups of UNOS status 2 candidates should continue to be allocated organs according to the current urgency system on the basis of effectiveness and the risk of waiting at higher status designations.

Disclosure statement

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PERSPECTIVE

Stable patients on left ventricular assist device support have a disproportionate advantage: Time to re-evaluate the current UNOS policy

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LVAD;
Staus 1A;
heart transplantation urgency;
UNOS policy

Over the years, policies adopted by United Network of Organ Sharing (UNOS) have directed allocation of donor hearts in the USA. These policies have been based on algorithms that allocate a higher priority status to those patients who are the most infirm, and would thereby benefit patients in the most dire of circumstances. Over the last 2 decades, the increased use of LVADs as a bridge to transplantation has had a major impact on lowering the mortality among those on the heart transplant waiting list. Given the constant risk of potential complications related to these devices, early UNOS policies were implemented to specifically allocate higher priority status to patients on LVADs. However, recent advances in LVAD technology coupled with refinements in patient selection and management have dramatically improved patient survival and led to a reduction in complications. It is inevitable that favorable experiences with the current generation of LVADs coupled with continued improvements in technology will lead to increased use of these devices as a bridge to transplantation or to candidacy. J Heart Lung Transplant 2011;30:971–4

The current UNOS policy, which grants 30 days of Status 1A time to patients on LVADs, lags behind clinical results obtained with the current generation of LVADs. The increasing number of patients on LVAD support, coupled with a flat trend in donor heart availability, reduces the chances of receiving a donor heart for patients listed using a non-device strategy. These trends may be even more pronounced in geographic areas where there is a general shortage of organs. With the survival rate on LVADs now approaching 90% at 12 months, an important issue needs to be addressed: Is it time to question the validity and justification of giving 30 days of Status 1A time to these patients? As many patients on LVADs are completely stable, most are transplanted "electively" as Status 1A while waiting at home. In all transplant centers, a subgroup of patients continue to exist in whom LVADs are not an appropriate option, and may be at the highest risk for death without timely transplantation. The objective of this study is to highlight the recent outcomes achieved with the current generation of LVADs and to focus attention on whether the time has come to reassess the current allocation policies.

Heart allocation in the USA

The United States Congress passed the Uniform Anatomical Gift Act in 1968 in an effort to have a national organ transplantation policy. By 1980, every state had adopted some form of this legislation. In 1984, Congress passed the National Organ Transplant Act (NOTA) to streamline the organ distribution process. One of the primary purposes of NOTA was to establish the Organ Procurement and Transplantation Network (OPTN), a system that both maintains the names of individuals who need transplants and, when organs become available, matches organs with the appropriate patients.

In 1986, the Health Resources and Services Administration, a division of the Department of Health and Human

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Services (DHHS), contracted with UNOS, a private, not-for-profit corporation, to maintain the OPTN. Initially, a point-based algorithm for heart allocation was developed largely based on the renal allograft distribution model. In this model, which was in effect between 1989 and 1999, heart allocation was based on a 2-tiered system. Individuals were considered Status 1 upon meeting any of the following criteria: in the ICU on inotropic therapy; on mechanical circulatory support on an intra-aortic balloon pump; or on a ventilator.

With broader input from the heart transplant community, including surgeons, allied health professionals and cardiologists, the original 2-tiered system was revised in 1999 to further refine the details of priority status, with the goal to direct organs to those with the highest medical urgency. Based on the 1999 revision, patients on LVADs could be listed as Status 1A if the device had been in for <30 days. This rationale was based on the assumption that these LVAD patients had 5% to 10% mortality per week. In addition, patients with an LVAD implanted for >30 days could be listed as Status 1A if a device-related complication had occurred such as infection, thromboembolism, mechanical failure or life-threatening arrhythmia.

A further revision was made in the Thoracic Organ Allocation Policy in June 2002. Under this latest revision, UNOS Policy 3.7.3 states that a patient with an implanted left and/or right ventricular assist device "may be listed for 30 days at any point after being implanted as Status 1A, once the treating physician determines that they are clinically stable." Notably, this newest provision did not require the patient to be hospitalized. As before, this grace period for Status 1A time was designed to minimize the occurrence of complications, while the patient was on LVAD support and maximized the benefit obtained from heart transplantation by allowing an interval of time for patient recovery after the LVAD implant. In contrast, the Eurotransplant organization (which has responsibilities similar to those of UNOS) has aimed to implement policies for allocating hearts to the sickest patients by creating a high-urgency status that neither prioritizes nor lists stable VAD recipients as critically ill and in need of urgent heart transplantation.[1,2]

Trends in heart transplantation

Despite improvements in medical and device therapy for heart failure, heart transplantation remains the best option for patients with end-stage heart failure who are deemed appropriate candidates. Although the incidence and prevalence of heart failure are increasing, the number of heart transplants performed in the USA has plateaued, if not decreased slightly. Recent trends suggest that the number of heart transplants performed in the USA has varied by 10% over the past decade, from a low of 2,015 in 2004 to a high of 2,209 in 2007. It is likely that the imbalance between supply and demand for hearts will continue in the foreseeable future.

It is logical that with the slowed growth in heart transplantation and the concordant increase in the number of end-stage heart disease patients, there will be an increasing trend in the number of patients receiving VADs. In July 2006, UNOS added a further modification for heart distribution. Hearts were now to be offered locally to Status 1A and 1B patients first and subsequently to any Status 1A or 1B listed patient within 500 nautical miles of the donor hospital (Zone A). The impact of this policy has clearly produced the desired effect of increasing the availability of hearts for Status 1A and 1B patients. These categories, encompassing all LVAD patients, have concomitantly resulted in a marked decline in transplantation of Status 2 patients. In fact, many transplant centers have decreased "routine listing" of patients as Status 2 unless their clinical status is expected to deteriorate to Status 1A or 1B imminently.[3] The annual reports from the OPTN indicate that, in 1999, patients transplanted as Status 1A, 1B and 2 accounted for 34%, 36% and 26% of transplants, respectively. In 2008, the proportions for Status 1A, 1B, and 2 were 54%, 37% and 9%, respectively.[3]

A review of the data from 2000 to 2008 demonstrates that the number of patients undergoing heart transplantation after LVAD implantation had remained steady at approximately 20%.[4] However, a more recent review of the UNOS database shows that, in 2009, 26% had received LVADs prior to transplant and, as of October of 2010, the number of implants prior to transplant reached almost 30%. This increasing trend of LVAD utilization is, in part, coincident with the HeartMate II being approved by the United States Food and Drug Administration (FDA) in April 2008. Not surprisingly, the 2009 statistics *also* showed that an increasing proportion of transplants occurred in patients who arrived from home, suggesting that less *sick* patients in Status 1A were getting 48% of the available hearts.

Recent data on LVADs

The new generation of continuous-flow pumps has revolutionized the field of mechanical circulatory support. With the improvement in device technology, miniaturization of pumps and improved patient selection, the morbidity and mortality associated with LVADs has continued to decline. The field is now reaching an inflection point, as mechanical circulatory support (MCS) is no longer considered only appropriate for those in extremis, but rather it has emerged as an important tool in the armamentarium of physicians who manage patients with advanced, end-stage heart failure. In the future, we are likely to see an increase in elective implantation of these devices in stable heart failure patients (INTERMACS Levels 3 to 7). These trends are a reflection of the data that continue to accrue on the survival and long-term outcomes with these pumps based on well-designed, prospective, multicenter trials. The initial bridge-to-transplant (BTT) trial with the HeartMate II demonstrated a survival rate of 75% at 6 months and 68% at 12 months.[5] As this was an early experience with a continuous-flow pump in the USA, it is not surprising that the subsequent continuous-flow data from this device, as well as the recent HeartWare device, all show continued improvements in survival.

The most recent data suggest that, in select centers, 6-month survival is now approaching 90%. In parallel to the trajectory of improved survival, the morbidity of MCS has markedly decreased relative to the previous generation of pulsatile pumps. In particular, adverse events related to infections, neurologic events and both renal and hepatic dysfunction have all decreased (described as events per 100 patient-months) to 11.8, 1.93, 2.18 and 0.68 events, respectively.[6] The most recent BTT trial involving the HeartWare device showed similar results, with 92% of patients transplanted or alive at 6 months.[7] These data are likely a reflection, in part, of the attributes of the device itself but may importantly reflect the increased experience with the devices and refinement of patient care in selected centers. These survival data have also been corroborated in European centers where actuarial survival after 6 months was 91%, and 86% at 1-year follow-up.[8]

To date, with >6,000 HeartMate II implants worldwide, no cases of mechanical failure have been reported. However, device replacement for percutaneous lead damage has been reported in 4.9% of all patients with total support duration of 1,155 patient-years. With continued improvements made in lead design, as well as better patient education and management, the incidence of lead failure has also steadily declined.[9]

Stage D disadvantaged patients for whom mechanical support is not the best option

Our current system emphasizes systolic heart failure, whereas the most recent data set would suggest that >50% of all heart failure (HF) patients have diastolic heart failure.[10] A certain cohort of these patients will develop severe restrictive physiology and New York Heart Association (NYHA) Class IV, Stage D symptoms, many of whom are women. These patients frequently do not have an attenuated ejection fraction; however, many have markedly decreased cardiac indexes, elevated vital capacity/VO_2 levels, pulmonary hypertension, poor organ perfusion and lethal arrhythmias. Many other groups of patients are also disadvantaged by our current system, including those with isolated or predominately right-sided heart failure, hypertrophic cardiomyopathies, some valvular cardiomyopathies, some congenital/familial heart patients, and possibly those who are highly sensitized. These patients no longer represent an insignificant epidemiologic phenomenon. Such changes are in part due to management improvements and partly due to more heightened recognition. For example, between 1999 and 2008, the proportion of candidates with congenital heart disease has increased (4% to 9%).[3] All of these patients generally do less well, or even poorly, with VADs. In addition, many of these patients do poorly with conventional inotropic or intra-aortic balloon pumps and have limited bailout strategies, placing them at greater risk of dying than those with VADs waiting at home. In addition, some patients (many of whom are women) will also be disadvantaged by their size (body mass index or height) or eligibility for enrollment in clinical trails, based on the aforementioned comorbidities. In short, smaller non-traditional patients have fewer options.

In 1998, DHHS Secretary Donna Shalala issued the original Final Rule designed to distribute organs more equitably by replacing the local allocation system with a national one. On March 16, 2000, DHHS announced an amended Final Rule that reflected public input by including clarifications of many of the criticized provisions of the original regulation. The amended Final Rule, still in effect today, directs the OPTN to create policies based on sound medical judgment and to avoid futile transplantations.[11] Specifically, the amended Final Rule provides that organs should be distributed as broadly as possible over the largest geographic area with consideration of the urgency of a recipient patient's need for a heart transplant.

Recent improvements in LVAD design have resulted in improved short- and long-term outcomes. The time has now come to reconsider the current UNOS policy for assigning a 30-day period of Status 1A time to patients on LVADs who have no complications and perhaps refocusing on *major* VAD complications as the criteria for Status 1A listing. It is also important to understand that a shift in policy may lead to heart transplantation as a bailout procedure for patients with LVAD complications, which could result in higher transplant mortality for these patients. A recent analysis of the UNOS database for patients transplanted as Status 1A under the criteria of LVAD complication suggested that 1-year mortality risk post-transplant only increased in patients with device infections.[12] In that review, other device-related or non–device-related complications, such as malignant arrhythmias, thromboembolism and device malfunction, did not have an impact on 1- and 10-year survival. One possible explanation for this may be that there is a self-selection process where near-fatal complications automatically remove patients from transplant consideration, whereas others, such as intractable arrhythmias, may not necessarily impact post-transplant survival. Nevertheless, most clinicians and scientists in this field no longer believe that heart transplantation is an urgent matter in patients on LVADs. In a recent analysis of the HeartMate II patients who were transplanted, the investigators found no relationship between duration of LVAD support and transplantation outcomes.[13] At the same time, the current policy is diverting organs to this stable population of patients at the expense of a subgroup of patients with complex pathophysiology, who are not suitable candidates for MCS.

In conclusion, our system inappropriately offers advantages to some and discriminates against other patients. The time has come to re-evaluate the urgency status of uncomplicated LVAD patients. As we continue to accumulate data longitudinally, our societal views on this subject are likely to change again, but maintaining the current state of organ allocation is a disservice to many patients and is counterintuitive to the innovative nature of this field.

Disclosure statement

The authors have no conflicts of interest to disclose.

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19th Annual THI Summit

UNOS Status of Heart Transplant Patients Supported with a Left Ventricular Assist Device

Is It Time to Reconsider the Status Criteria?

Mark S. Slaughter, MD

The recent introduction of the continuous-flow left ventricular assist device (LVAD) has had an important impact on outcomes for those receiving bridge-to-transplantation (BTT) therapy. Because of the demonstrated survival and quality-of-life benefit with LVAD support and the broader availability of these devices after their commercialization, the number of supported patients waiting for heart transplantation is increasing. Progress in LVAD technology, better patient selection, and refined postoperative management all contribute to improved operative outcomes and long-term survival. Patients can now be safely supported by LVADs for many years. As demand for the limited number of available donor organs increases, policies regarding the status of transplant candidates may need to be revised for optimal management of this scarce resource.

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Heart Transplant Waiting-List Status

The United Network for Organ Sharing (UNOS) status code 1A is designated for candidates on the waiting list who have the highest priority on the basis of medical urgency. Patients may be listed as Status 1A for 30 days at any time after LVAD implantation when they are clinically stable. Patients who are experiencing LVAD-related complications, such as infection, thromboembolism, or device malfunction, may also be listed as Status 1A (Table I). Patients who are supported by an LVAD but who do not meet the aforementioned criteria are listed as Status 1B. Status 2 does not apply to patients with LVADs.

Changes in LVAD Technology

The criteria for the UNOS listing status were established when the previous generation of pulsatile LVADs was being used for BTT therapy. The chief drawbacks of the pulsatile LVAD were related to its large size and poor durability. The device had to be placed in an abdominal pocket that remained susceptible to serious infection throughout support. Durability was limited due to bearing wear and the development of valve incompetence in the device. Therefore, reliable LVAD operation was limited to approximately 18 months, which greatly increased the chances of morbidity and death from either the cessation of LVAD support or the need to replace the device.

In comparison with the pulsatile LVAD, the continuous-flow LVAD is considerably smaller and more durable. The surgery required for LVAD implantation is less extensive, which helps to reduce complications related to bleeding and infection. The lack of device failure has nearly eliminated the need for replacement surgery, which further reduces the incidence of serious complications. In the only randomized clinical trial comparing the 2 types of LVADs, complications—including pump replacement, infection, bleeding, right-sided heart failure, arrhythmia, respiratory failure, renal failure, and hospitalization—were all significantly less for the continuous-flow LVAD group.[1] The survival rate was also significantly higher (P <0.001) with the continuous-flow device.

The current survival rate for BTT therapy with a continuous-flow LVAD is 85%, and the device is associated with greatly improved functional capacity and quality of

TABLE I. UNOS Definition of Status 1A for Candidates on Waiting List*

A candidate listed as Status 1A is admitted to the listing transplantation center hospital (with the exception for 1A[b] candidates) and has at least one of the following devices or therapies in place:

a) Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:

i) left and/or right ventricular assist device-implanted candidates listed under this criterion may be listed for 30 days at any point after implantation as Status 1A once the treating physician determines that they are clinically stable. Admittance to the listing transplantation center hospital is not required.

ii) total artificial heart;

iii) intra-aortic balloon pump; or

iv) extracorporeal membrane oxygenator (ECMO).

Qualification for Status 1A under criterion 1A(a)(ii), (iii) or (iv) is valid for 14 days and must be recertified by an attending physician every 14 days from the date of the candidate's initial listing as Status 1A in order to extend the Status 1A listing.

b) Mechanical circulatory support with objective medical evidence of significant device-related complications such as thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias.

*Adapted from the United Network for Organ Sharing's Organ Procurement & Transplantation Network policies: 3.7 Organ Distribution; Allocation of Thoracic Organs

life.[2,3] The risk of serious complications is low, which may result in less urgency to perform heart transplantation in clinically stable outpatients. In the early BTT experience with continuous-flow LVADs (2005–2008), 48% of patients had undergone transplantation at 1 year, compared with 39% in the later experience (2008–2010). This shows increasing confidence that LVADs can support patients longer.[4] Also, some patients have chosen to forgo transplantation in favor of continued LVAD support.

Although the clinical experience with continuous-flow LVADs has been largely positive, some problems persist and new ones have emerged. Rarely, patients may need to be readmitted to the hospital because the LVAD percutaneous driveline becomes infected; in some cases, this complication increases the urgency for transplantation.[5] Surgical bleeding has been reduced but not been eliminated. Late gastrointestinal bleeding associated with continuous-flow LVADs is controllable in most cases; however, it can be persistent or severe and require multiple transfusions. Patients who are supported for longer periods of time might develop recurrent right-sided heart failure, which can limit pump performance and worsen quality of life. Similarly, with longer durations of support, new valve gradients and stress on the native aortic valve will cause some patients to develop substantial aortic insufficiency.

Reevaluating UNOS Status

The criteria for UNOS status codes were developed at a time when device-related infections were prevalent and when life-threatening LVAD failure or pump malfunction was due to failure of the device's bearings or incompetence of its valves. However, outcomes of BTT therapy have dramatically improved over the past decade, while unanticipated device-related complications have emerged. Currently, driveline infection is a common reason for upgrading a patient to Status 1A, but in the absence of sepsis or a true device-pocket infection, the driveline infection rarely threatens a patient's life or alters the device. In addition, impending pump failure or a device-related complication, such as bearing wear, was once easy to recognize and attribute to the device; however, this has changed with the new technology. Complications such as gastrointestinal bleeding and aortic insufficiency are probably related to the pump, whereas hemolysis is perhaps the new indicator of impending pump failure.

These new complications are not clearly considered in the current UNOS guidelines. Also, given the increasing number of outpatients who are on LVAD support, it is very difficult to perform heart transplantation in a Status 1B patient who is receiving continuous inotropic agents without invasive monitoring. Today, a patient who is at home with long-term LVAD support is more like the traditional Status 2 patient with respect to the risk of serious complications or death. According to the current UNOS status criteria, all medically stable BTT patients can be given 1A status for 30 days. This 30-day 1A listing window for BTT patients does not reflect true urgency on the basis of medical need. Many of these patients undergo transplantation when they are doing well at home with an excellent functional status and without device complications.

Overall, the UNOS criteria for listing patients for heart transplantation and for determining their status for priority has resulted in the best use of a limited resource. However, the evolving LVAD technology has led to significant shifts in patient outcomes and device-related complications. Technological improvements and

the increasing clinical use of LVADs have resulted in a new generation of patients waiting for heart transplantation. It might be time to revisit the clinical indications for establishing the priority and status categories for patients who are eligible to receive a donor offer for heart transplantation.

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FEATURE ARTICLE

Effects of the 2006 U.S. thoracic organ allocation change: Analysis of local impact on organ procurement and heart transplantation

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KEYWORDS:
organ procurement;
organ donation;
heart transplantation;
transplant waiting list;
waiting list mortality

BACKGROUND: The United Network for Organ Sharing (UNOS) implemented a thoracic organ allocation policy change (APC) in July 2006 that aimed to reduce death on the waiting list by expanding regional organ sharing. As such, organs would be allocated to the sickest recipients with highest listing status across the region. Our aim was to determine the impact of the new policy on the procurement and transplant process within our program.

METHODS: We analyzed data supplied by UNOS as the contractor for the Organ Procurement and Transplantation Network and from the local organ procurement organization for 2 years before and 2 years after implementation of the APC.

RESULTS: The APC resulted in an increase in the proportion of Status 1A patients transplanted (24% to 43%, $p = 0.015$) and a decrease in the proportion of Status 2 patients transplanted (56% to 24%, $p = 0.001$). Significant increases were observed in mean graft ischemic time (196 minutes to 223 minutes, $p = 0.022$), number of patients transplanted with ventricular assist devices (17% to 31%, $p = 0.036$), and procurement costs. There was no significant difference in waiting-list mortality (6% to 5%, $p = 0.75$) and short-term post-transplant survival.

CONCLUSIONS: The 2006 change in UNOS organ allocation policy resulted in an increase in Status 1A transplants, graft ischemic time and procurement costs, and a decrease in Status 2 transplants, but no effect on mortality on the waiting list within our center. To assess the full effect of the APC on outcomes, the long-term impact of the increased graft ischemic time on survival should be quantified.
J Heart Lung Transplant 2010;29:235–9

The United Network for Organ Sharing (UNOS) is contracted by the federal government to provide a system for equitable distribution of all organs available for transplantation in the USA.[1,2] To achieve this objective in heart and lung transplantation, UNOS created the Thoracic Organ

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Table 1 Sequence of Adult Heart Allocation[a]

Before July 2006	After July 2006
Local	Local
1. Status 1A candidates	1. Status 1A candidates
2. Status 1B candidates	2. Status 1B candidates
3. Status 2 candidates	Zone A
Zone A	3. Status 1A candidates
4. Status 1A candidates	4. Status 1B candidates
5. Status 1B candidates	Local
Zone B	5. Status 2 candidates
6. Status 1A candidates	Zone B
7. Status 1B candidates	6. Status 1A candidates
Zone A	7. Status 1B candidates
8. Status 2 candidates	Zone A
Zone B	8. Status 2 candidates
9. Status 2 candidates	Zone B
Zone C	9. Status 2 candidates
10. Status 1A candidates	Zone C
11. Status 1B candidates	10. Status 1A candidates
12. Status 2 candidates	11. Status 1B candidates
	12. Status 2 candidates

Zones are determined by the distance from donor hospital to transplant hospital: Zone A, ≤500 nautical miles; Zone B, 500–1,000 nautical miles; Zone C, >1,000 nautical miles.

[a]Adapted from UNOS Policy 3.7.10.

Committee, which embraces a multidisciplinary group of professionals responsible for the design and monitoring of thoracic organ allocation algorithms. The first algorithm for the allocation of donor hearts was a 7-tiered medical urgency category system, similar to kidney allocation models. In 1989, the algorithm was simplified and included only two medical urgency categories, Status 1 and Status 2. The major limitation of this system was the inability to allocate organs preferentially to the most critically ill patients. To overcome this limitation, an allocation policy change in 1999 introduced Status 1A and Status 1B.[3]

On July 1, 2006, the most recent thoracic organ allocation policy change (APC) was implemented. It provides for regional sharing of organs for the most medically urgent patients.[4] Under the new policy, hearts are offered to candidates in Status 1A and Status 1B locally and then regionally (up to a distance of 500 miles from the donor hospital), and subsequently to local candidates in Status 2. Statistical modeling of the waiting list had shown that the most medically urgent patients, those in Status 1A and 1B, benefit the most from heart transplantation.[5–7] The new policy is predicted to reduce waiting-list mortality.[8] Before 2006, donor hearts were offered first to local Status 1A patients, then 1B and 2 sequentially. If an appropriate recipient could not be located among those waiting locally, then the heart was offered regionally. Table 1 compares the old and the new allocation algorithms.

The Utah Transplant Affiliated Hospitals (U.T.A.H.) Cardiac Transplant Program includes four transplant centers: Intermountain Medical Center (previously LDS Hospital); Primary Children's Medical Center; University of Utah Health Sciences Center; and the George E. Wahlen Veterans Affairs Medical Center. This program is a member of the UNOS Geographic Region 5 and has followed the new allocation system since July 2006. After 2 years of implementation, the full effects of the new APC are unknown. Our aim was to determine the impact the new allocation policy had on the procurement process, procurement cost, waiting-list mortality, and recipient outcomes.

Methods

Patients

The study included all patients who underwent heart transplantation in the U.T.A.H. Cardiac Transplant Program. Two eras were selected for comparison, the 2-year era immediately before the APC (from July 1, 2004, to June 30, 2006) and the 2-year era immediately after the APC (from July 1, 2006, to June 30, 2008). Clinical information was supplied by UNOS as the contractor for the Organ Procurement and Transplantation Network (OPTN) and the procurement and cost information was obtained from Intermountain Donor Services, the local organ procurement organization (OPO). The study was approved by the institutional review board.

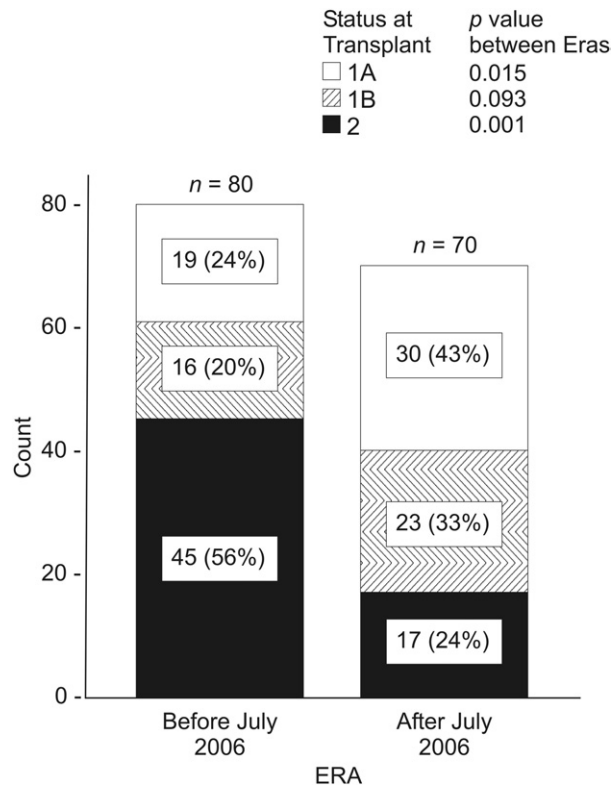

Figure 1 UNOS status at transplantation before and after thoracic organ allocation policy change (based on Organ Procurement and Transplantation Network data).

Statistical analysis

Comparisons between the two eras were made using the Fisher's exact test or the Mann–Whitney *U*-test as appropriate. Survival analyses were performed using the Kaplan–Meier method, and survival curves were compared with the log-rank test. A 2-tailed $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS software (version 17.0).

Results

Eighty patients were transplanted in the pre-APC era. Their mean age was 43 ± 19 years, 22 (27%) were female, and 12 (15%) were <18 years of age. Seventy patients were transplanted in the post-APC era. The mean age was 46 ± 18 years, 12 (17%) were female, and 7 (10%) were <18 years of age. A comparison of the UNOS status at transplantation between eras is shown in Figure 1. After the APC, there was an increase in the number of patients transplanted in Status 1A (24% to 43%, $p = 0.015$) and Status 1B (20% to 33%, $p = 0.093$). There was a significant decrease in the number of Status 2 patients undergoing heart transplantation in the post-APC era (56% to 24%, $p = 0.001$).

Since the APC we have seen a significant increase in the mean waiting time for Status 1A patients (5 days to 11 days, $p = 0.002$), in the mean graft ischemic time (196 minutes to 223 minutes, $p = 0.022$), in the proportion of patients with graft ischemic time >4 hours (36% to 51%, $p = 0.044$), and in the proportion of patients on ventricular assist devices (VADs) at the time of transplantation (17% to 31%, $p = 0.036$) (Table 2). Although the difference did not reach statistical significance, after the APC there was an absolute increase in the number of donor hearts imported from outside of our local procurement area (54% to 66%) and in the median procurement travel distance (306 to 355 miles). A cost analysis comparing the two eras shows that the transportation cost as well as the total procurement cost per imported donor organ both increased significantly after July 2006 (Figure 2).

The waiting-list mortality did not change significantly between the two eras ($p = 0.75$; Figure 3). In the pre-APC era, a total of 94 patients were on the cardiac transplant

Table 2 Recipient, Donor, and Procurement Characteristics in the U.T.A.H. Cardiac Transplant Program Before and After the Change in Thoracic Organ Allocation Policy

	Before July 2006 ($n = 80$)	After July 2006 ($n = 70$)	*p*-value[a]
1. Waiting time in last status, mean days (range)			
UNOS Status 1A	5 (0–16)	11 (1–29)	0.002
UNOS Status 1B	24 (0–64)	46 (1–604)	NS
UNOS Status 2	166 (6–684)	210 (5–896)	NS
2. Graft ischemic time, mean minutes (range)	196 (60–450)	223 (54–420)	0.022
3. Patients with graft ischemic time more than 4 hours, *n* (percentage)	29 (36)	36 (51)	0.044
4. Patients with ventricular assist devices, *n* (percentage)	14 (17)	22 (31)	0.036
5. Length of hospital stay, median days (range)	10 (0–98)	11 (2–172)	NS
6. Imported donor hearts, *n* (percentage)	43 (54)	46 (66)	NS
7. Procurement travel distance, median miles (range)	306 (0–799)	355 (0–799)	NS

Based on the Organ Procurement and Transplantation Network data and Intermountain Donor Services data. U.T.A.H., Utah Transplant Affiliated Hospitals; UNOS, United Network for Organ Sharing.

[a]$p < 0.05$ considered statistically significant (NS, not statistically significant).

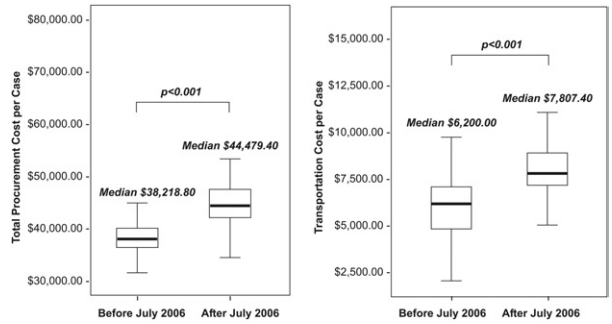

Figure 2 Total procurement and transportation cost per imported donor organ before and after July 2006 (based on Intermountain Donor Services data).

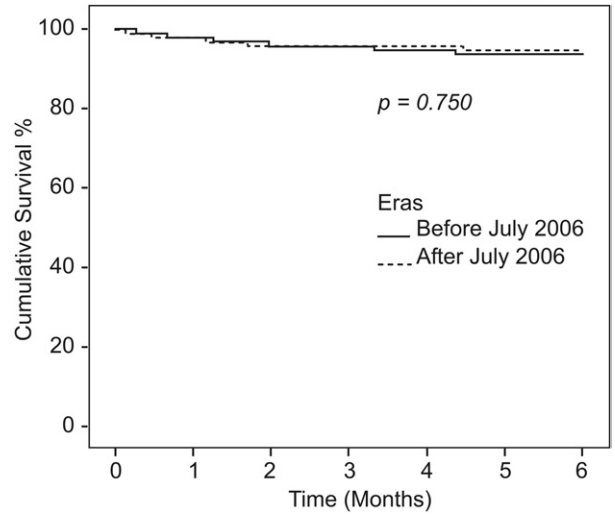

Figure 3 Survival on heart transplant waiting list before and after thoracic organ allocation change (based on Organ Procurement and Transplantation Network data).

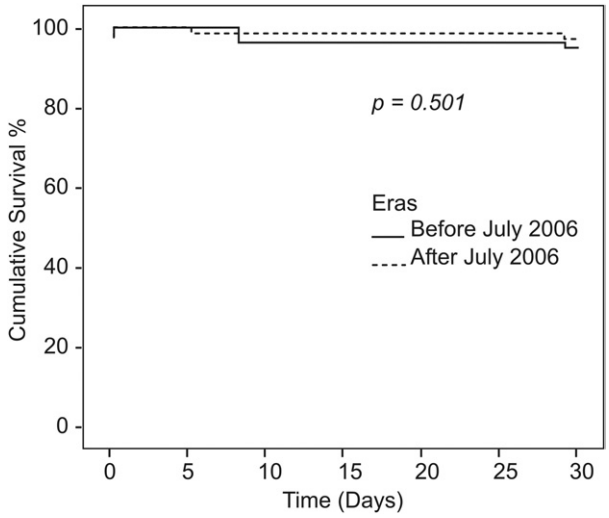

Figure 4 Thirty-day survival after heart transplant, before and after the thoracic organ allocation policy change (based on Organ Procurement and Transplantation Network data).

waiting list and 6 of them died within 6 months of listing. In the post-APC era, 95 patients were on the waiting list and 5 of them died within 6 months of listing. Short-term post-transplant survival has also not changed significantly. Four patients died within 30 days of transplant in the pre-APC era as compared with 2 patients in the post-APC era ($p = 0.5$; Figure 4).

Discussion

The intent of the new thoracic organ allocation policy was to decrease mortality on the cardiac waiting list by expanding regional sharing of organs for the sickest patients. Although the statistical modeling that led to the change was meticulous, the real-life results of any such change are always awaited with some degree of apprehension. The waiting list is not static and it is therefore possible that, with time, the impact of an allocation intervention can change. In addition, the allocation modeling was done on national data, but significant regional differences exist in both the distribution of patients with different urgency status on the waiting list, as well as in the proportion of patients transplanted in the different categories of urgency status in the different regions.[9] Therefore, it can be expected that the changes to be seen at different transplant centers and OPOs may vary as well. Our analysis focused on assessment of the impact of the APC on a 4-hospital transplant program and a local OPO. We have not seen a change in mortality on the waiting list. There was a significant increase in the number of heart transplant candidates transplanted in a higher urgency Status 1A and a noticeable decrease in the number of organs allocated to the more stable candidates in the Status 2 category. These changes were accompanied by a significant increase in average graft ischemic time, and procurement cost.

What are the implications of these findings? Our study was not powered to demonstrate changes in waiting-list mortality and this will have to be addressed by analyses of the national OPTN data. We have seen, however, significant changes that did affect the processes of care of patients awaiting heart transplantation. The change resulted in greater allocation of hearts to patients with higher urgency status. This trend observed after the APC is consistent with the national data from the OPTN/Scientific Registry of Transplant Recipients, which showed an increase in patients transplanted in Status 1A (40% in 2005, 42% in 2006, 50% in 2007) and a decrease in patients transplanted in Status 2 (25% in 2005, 20% in 2006, 14% in 2007).[10,11] This tendency clearly appears to be a positive development as statistical models by Stevenson et al[5] and Krakauer et al[6] demonstrated that the highest survival benefit of heart transplantation is realized by transplanting patients in the higher urgency status. Lietz et al showed that 1-year mortality of candidates in Status 1 who did not undergo transplantation approached 60%, as compared with 10% in Status 2 candidates.[12] In fact, it has been questioned whether all Status 2 patients benefit from transplantation or whether it would be of benefit to define sub-groups of Status 2 patients more likely to derive benefit.[13–17] Although some Status 2 patients remain on the waiting list in relatively stable condition for prolonged periods of time, a significant proportion of these patients will decompensate and be upgraded to Status 1A or 1B.[18]

The increase in the proportion of patients transplanted in Status 1A was, however, associated with additional changes that may be of concern. The median waiting time to transplant in a Status 1A patient has increased significantly. In our clinical practice, we can no longer plan on receiving a suitable organ for a patient upgraded to Status 1A within a few days. We believe this is one of the reasons we have also seen a significant increase in the number of patients being bridged to transplantation with ventricular assist devices. Arguably, compared with transplantation alone, this approach results in excess morbidity, mortality, and markedly higher cost.[19] In addition, we have observed a significant increase in the mean graft ischemic time; in half of our patients, graft ischemic time surpassed 4 hours after the APC was implemented. Although we have not seen a change in short-term mortality, the longer graft ischemic time could still impact long-term survival of the patients. Further, the fact that an increased number of grafts are now being transported over longer distances by air brings two additional considerations. One is the increase in transportation and overall procurement cost that we have documented. A second relates more to logistics. These changes are happening at a time when corporate travel is in rapid decline and, with that, a decrease in the number of corporate jets available for hire for organ procurement. In our experience, it has been more difficult to secure predictable, continuous availability of aircraft for organ procurement. At times, we have had to request air service from other regions, resulting in time delays and further increases in cost.

To what degree the experience of other regions will mirror ours remains to be seen. It will also be important to examine whether the effect of the new allocation algorithm

remains constant, or whether it may be altered by the very consequences of its implementation.

Limitations

This study was conducted in only one procurement area and the transplant centers located within. The number of patients was relatively low. Although adequate to demonstrate the impact of the APC on certain clinical outcomes and processes of care, the mortality events and length of follow-up are not sufficient to show changes in survival. It is uncertain whether the APC was the sole cause of some of the changes seen.

Conclusion

In conclusion, in a single-area study, the 2006 change in UNOS thoracic allocation policy has resulted in an increased proportion of patients transplanted in Status 1A. In addition, there has been an increase in the time to transplant for Status 1A patients and an increase in mean graft ischemic time and in procurement costs. We did not observe a change in mortality of patients on the waiting list. The long-term impact of the allocation change on heart transplant recipient survival should be evaluated carefully.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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EDITORIAL COMMENTARY

The change in heart allocation policy in the United States: Is it working as designed?

See companion article on page 235.

The most recent change in heart allocation policy in the United States became effective on July 12, 2006. The intent of the change in policy was to direct donor hearts to the most critically ill patients and thereby reduce the waitlist mortality. Nativi et al[1] report on the effect of the change in allocation policy on the Utah Transplant Affiliated Hospitals (UTAH) Cardiac Transplant Program in Salt Lake City, Utah, in the first 2 years after the change took effect.

The impact nationally is markedly different. In contrast to the results at UTAH, adult waitlist mortality nationally has decreased significantly for status 1A and 1B patients. The waitlist mortality for status 1A patients in the 2 years preceding the change in allocation policy was 115.6 deaths per 100 patient-life years; in the 2 years after the change, the waitlist mortality had decreased to 75.8 deaths per 100 patient life-years, a 34% reduction in waitlist mortality. Similar results were found for status 1B patients, who experienced a 27% reduction in waitlist mortality, with a decrease from 34.8 deaths per 100 patient-years before the change in allocation to 25.3 deaths per 100 patient-years after the change. There was no subsequent increase in waitlist mortality for status 2 patients during the same period (6.1 to 6.2 deaths per 100 patient-years). The percentage of transplants occurring in status 1A and 1B adult recipients has increased from 74% to 90%, whereas the percentage occurring in status 2 patients has decreased from 26% to 10%. Despite an increase in the number of donor hearts allocated to more critically ill patients, the predicted increase in post-transplant mortality has not occurred.

The authors also report a significant increase in median waiting time to transplant for status 1A patients and a subsequent increase in the use of ventricular assist devices (VAD) as a bridge to transplant. Nationally during that same period, the median waiting time to transplant actually decreased for status 1A patients from 55 to 39 days.

Many factors influence time on the waiting list that the authors have not commented on. These factors include, but are not limited to, blood type, body size, degree of sensitization, and donor availability. The timing of implant of VADs as a bridge to transplant varies greatly from center to center, and United Network of Organ Sharing (UNOS) does not currently have the data available to ascertain whether there has been an increase in the use of VADs for bridge to transplant. Perhaps Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) will be able to provide objective data on this issue in the near future.

The authors observed a significant increase in median graft ischemic time and procurement costs associated with the change in allocation policy. Nationally, there has not been a significant increase in graft ischemic time. The median graft ischemic time was 192 minutes in the year before the change in allocation and 197 minutes in the most recent cohort examined. Additional surgical strategies can be used to decrease the ischemic time for distant procurements, such as performing the left atrial anastomosis, followed by the aortic anastomosis and then releasing the cross-clamp to reperfuse the transplanted heart. The subsequent pulmonary artery and right atrial or bicaval anastomoses can be performed with the heart perfused and beating, thereby significantly reducing the ischemic time.

Organ procurement costs, as do all health care costs, vary greatly across the United States. Standard organ acquisition charges increase nearly every year as the organ procurement organizations (donor service areas) realize increased costs related to their activities. The authors do not mention in their article whether their local standard acquisition charges have increased during the 4-year period of their study.

In the 2 years before the change in allocation, 56% of the heart transplants at U.T.A.H. occurred in status 2 patients. As the authors note, several investigators have questioned the benefit of heart transplantation in status 2 patients. The risk of death on the waiting list for status 2 patients is significantly lower than the risk for status 1A and 1B patients. Nonetheless, some sub-groups of status 2 patients do not meet "traditional criteria" for 1A and 1B listing and deserve special consider-

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ation. Their increased risk of waitlist mortality may not be adequately accounted for in the current allocation system. These sub-groups would include patients with restrictive cardiomyopathy, hypertrophic obstructive cardiomyopathy, adults with congenital heart disease, and those that need retransplant. There have not yet been sufficient numbers of these types of patients on the waitlist to provide for meaningful analysis. Despite the inability to meet "traditional criteria" for 1A and 1B listing, these patients can still be listed as a 1A or 1B under the (e) criterion for exceptional circumstances.

The changes in heart allocation that have occurred during the past 25 years have been made to decrease waitlist mortality and improve post-transplant survival. Are we finished? Of course not. As we gather and analyze new data, the allocation system will have to be further refined to meet societal needs and objectives. The system needs to be fair, equitable, and transparent, without regard to provincial interests. It is only in this manner that the public will trust the system that allocates this precious resource.

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Enemies or Allies? The Organ Transplant Medical Community, the Federal Government, and the Public in the United States, 1967–2000

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Abstract. The transplant medical community in the United States has frequently been divided over the appropriate role of the federal government and of the public in matters related to organ transplantation. Using public statements in government hearings, newspapers, and press releases, this article traces the thinking of the transplant medical community in particular during three especially politicized periods: the heart transplant and brain death controversies in the late 1960s, consideration of the National Organ Transplant Act and other legislation during the mid-1980s, and the controversy over organ allocation regulations issued by the Department of Health and Human Services in the late 1990s. Even while sometimes denouncing "politicization," over time surgeons, physicians, representatives of the United Network for Organ Sharing, and other leaders in the field became increasingly politically active and more accustomed to the notion that because of the unique nature of organ transplantation, both the public and the federal government have a legitimate and potentially beneficial oversight role. ***Keywords:*** organ transplantation policy, organ transplant community, United Network for Organ Sharing, U.S. Department of Health and Human Services, National Organ Transplant Act.

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Liver surgeon Anthony D'Alessandro wrote an impassioned opinion piece in the *Washington Times* on 16 March 2000, a day he said organ transplant patients and their doctors in the United States had been trying to stave off for almost two years. On that date, regulations issued by the U.S. Department of Health and Human Services (HHS) would go into effect. D'Alessandro characterized the regulations as a "hostile takeover of America's transplant system," which had been run since the 1980s by the United Network for Organ Sharing (UNOS), a nonprofit organization contracting with the government. He held Donna Shalala, Secretary of the Health and Human Services, responsible for this disaster: "Miss Shalala is determined to anoint herself federal organ transplant czar." As a result, "political appointees" would make the final decisions about who lives and who dies that previously had been reached by consensus among transplant doctors. "Instead, we have Donna Shalala and her cynical, sound-bite political meddling," asserted D'Alessandro. "The doctor is out and Miss Shalala will decide what is good for us. We do not know, of course, exactly what policies she will choose to impose, or how often or on what whims they will be changed."[1] Not surprisingly, Donna Shalala characterized HHS actions and the regulations quite differently—as responsible guidelines to insure fairness and consistency for all transplant patients, which still left specific decisions about how to allocate organs in the hands of medical experts in UNOS.

D'Alessandro's letter effectively captures the intensity of a controversy in the mid- and late 1990s. The heart of the battle over HHS regulations was about how to allocate the nation's scarce organs for transplantation, but an important subtheme was the role of the federal government in that process. D'Alessandro did not mention that other surgeons and patients had urged the U.S. Department of Health and Human Services to step in and issue regulations and that they agreed with the substance of the regulations. Clearly the transplant community[2] in the United States was divided, and this ambivalence about

1. Anthony M. D'Alessandro, "Hostile Organ Takeover; Donna Shalala, Organ Donor Czar," *Washington Times*, 16 March 2000, A21.

2. In this article, the term "transplant medical community," refers especially to surgeons who transplanted various solid organs, who were the leaders and most vocal members of this community, but also includes transplant physicians, coordinators (who are often nurses), and various other medical personnel involved in the surgery and treatment of

the role of the government dated back to discussion about early heart transplants and brain death in 1968, when some surgeons welcomed and others feared the involvement of the government and outsiders. The interest of national politicians and the accompanying ambivalence from the transplant medical community surfaced again in the mid-1980s when organ transplantation enjoyed a resurgence and again captured the public eye. The third and most heated period of national government involvement was in the late 1990s. By then, both sides in the organ allocation dispute criticized the "politicization" of the debate, but at the same time both sides were using shrewd political tactics and looking to officials in the federal government to take their side. The federal government has been involved in organ transplantation to a degree that is unusual in American medicine, but in retrospect, neither the politicization nor the role of the federal government are surprising given the special needs and characteristics of this unique medical procedure.

In December 1967, South African Christiaan Barnard's first transplant of a human heart captivated the world.[3] Newspapers and television reported every positive detail of the "miracle in Cape Town" and Barnard became an international celebrity. Reporters deemed him "a young revolutionary who had changed the whole nature of cardiac medicine" and the "greatest physician of the age."[4] Only a handful of surgeons had already been doing extensive research and animal experimentation on heart transplantation; hoping to replicate Barnard's feat and gain the same notoriety for themselves or their countries, scores of others around the world suddenly seemed to "jump on the bandwagon." In 1968 alone, 101 heart transplants were performed by sixty different medical teams in twenty-two nations, some of which did not have much experimental or other relevant background.[5] Many did just one or two

transplant patients and the procurement of organs, and UNOS staff. The more general term "transplant community" includes the medical practitioners as well as patients and their loved ones, donors and donor families, and other interested parties like ethicists, lawyers, etc.

3. Donald McRae, *Every Second Counts* (New York: G. P. Putnam's Sons, 2006), 146–154, 166, 208.

4. Jürgen Thorwald, *The Patients* (New York: Harcourt Brace Jovanovich, 1972), 269, 287–8.

5. Anon., "Saving New Hearts," *Newsweek*, 7 January 1980, 39.

transplants, but Denton Cooley in Houston performed seventeen in 1968. Adrian Kantrowitz, a heart specialist at New York's Maimonides Medical Center with years of transplant experimentation behind him, performed the first human heart transplant in the United States. He was shocked by the "frenzied interest" of over two hundred insistent journalists who appeared in the middle of the night when someone leaked news of his surgery. Patients with heart disease, not realizing the experimental status of the procedure, soon crammed the hallways of some U.S. hospitals, hoping that star surgeons might perform miracles on them.

The positive glow soon wore off, however. The results of the early heart transplants could not match the media hype. Although Barnard's second recipient lived over nineteen months, even the well-prepared teams of Adrian Kantrowitz and Norman Shumway at Stanford had bad outcomes. Kantrowitz's first patient, a seventeen-day-old infant, lived for only a few hours. His second survived just eight hours. Shumway's first patient lived fifteen days, but struggled with internal hemorrhaging and underwent two additional surgeries in those two weeks. Only three of Denton Cooley's seventeen patients lived more than six months. Indeed, only forty-seven of the first 140 heart recipients lived more than three months after the surgery, and there was a dismal 22 percent one-year survival rate. For the typical recipient who lived a few months, the quality of life left much to be desired.[6] At the same time, other physicians criticized the "circus atmosphere" surrounding the procedures and the rise of "surgical show biz."[7] They feared that surgeons lured by "the glamour that surrounds them" were losing sight of the well being of their patients.[8] A number of prominent cardiologists called for a moratorium on heart transplantation, emphasizing that the odds of success were slim because although surgical techniques were advanced, there was not sufficient immunological understanding to prevent rejection of transplanted

6. Anon., "The Hasty Hearts?" *Newsweek*, 22 January 1968, 60; Anon., "Transplants: Guarded Outlook," *Newsweek*, 21 July 1969, 109; Anon., "Heart-Transplant Revival," *Newsweek*, 1 November 1976, 12, Thorwald, *The Patients*, 284, 287, 320; Tony Stark, *Knife to the Heart* (London: Macmillan, 1996), 93.

7. Anon., "Surgical Show Biz," *The Nation*, 22 January 1968, 100.

8. Edwin Diamond, "Are We Ready to Leave Our Bodies to the Next Generation?" *New York Times*, 21 April 1968, SM 26; Anon., "The State of Many Arts," *Science News*, 2 March 1968, 233.

hearts.[9] "Surgeons love to show they can do things," observed an administrator from the National Institutes of Health, "but there is a morality gap in doing those things before there is good enough scientific base." The media picked up on the criticism. Newspapers printed "box scores" on the outcomes of all the heart transplants, illustrating their high mortality rates. "Were Transplants Premature?" asked *Time* magazine. "Hasty Hearts?" asked *Newsweek*.[10]

The heart transplants were on Senator Walter Mondale's mind when in February 1968 he proposed a one-year National Commission on Health Science and Society to investigate the legal, social, and ethical implications of medical research. Mondale noted that unprecedented developments like heart transplants, artificial hearts, and greater understanding of the human genetic code held "great promise for the present and future of mankind," but at the same time raised "profound and complex questions of ethics, law, and public policy."[11] Philosophers and religious leaders were discussing the implications of organ transplantation, and physicians themselves were grappling with issues such as when it was justifiable to undertake a heart transplant. There were many legal issues to be worked out, Mondale noted, including how people could consent to donation, whether organs could be bought and sold, and the responsibilities and culpabilities of physicians and medical examiners. Commission recommendations could help American society deal with the implications of scientific advancements "in as rational and public a fashion as possible." Anticipating there might be

9. Anon., "A Plea for a Transplant Moratorium," *Science News*, 16 March 1968, 256. This "quasimoratorium" continued until the early 1980s, when cyclosporine was approved as an immunosuppressive drug. Renée C. Fox and Judith P. Swazey, *The Courage to Fail: A Social View of Organ Transplants and Dialysis* (Chicago: University of Chicago Press, 1974), 123–148; Renée C. Fox and Judith Swazey, *Spare Parts: Organ Replacement in American Society* (New York: Oxford University Press, 1992), 7.

10. Anon., "Reassessing Transplants," *Newsweek*, 1 September 1969, 73; Anon., "Heart Surgery: Were Transplants Premature?" *Time*, 15 March 1968, 66; Anon., "Transplant Slump," *Newsweek*, 17 May 1971, 69; Anon., "Hasty Hearts?"; Fox and Swazey, *The Courage to Fail*, 140, 146.

11. Walter Mondale, Introduction of Joint Resolution to Establish a Commission on Health Science and Society, *Congressional Record*, 8 February 1968, included as an appendix in *National Commission on Health Science and Society*, Hearings before the Subcommittee on Government Research of the Committee on Government Operations, United States Senate, 90th Congress, 2nd session, on S. J. Res. 145, 7, 8, 21, 22, 27, 28 March and 2 April 1968, 445–451. Mondale quotation on p. 445.

resistance to the idea, Mondale said, "I think the medical professional has a right to ask us to give him the resources and the elbow room he needs to fulfill his function. But I think that same professional must understand that society has a stake in what he is doing, and that society must know not only what he is doing, but the implications of his efforts." Mondale hoped to persuade the medical profession "that they have far more to gain than lose in the responsible pursuit of this subject."[12]

Mondale's call for a commission fit into a trend in the 1960s in which medical authority was being more closely examined. The 1960s was a period in which all sorts of traditional authority (with regard to race relations, foreign policy, male dominance, politicians, police, parents, etc.) was questioned, and scientists and physicians were not exempt. News of a number of examples of unethical medical research on human subjects helped spur new procedures to ensure informed consent and more checks on research methods. Simultaneously, practitioners of the new field of bioethics argued that outsiders like philosophers, theologians, and even the general public could contribute helpful insights to the biomedical field. In addition, patients came to expect more information, rights, and participation in their health care, and sometimes these changed expectations contributed to pressures for government intervention.[13] Not everyone in the medical field welcomed the perspective of outsiders, however, whether they were the public, ethicists, or politicians.

Hearings on Senator Mondale's proposed commission illustrated differences among transplant medical personnel about the federal government's role that would persist for three decades. A few prominent heart surgeons welcomed a government commission. Adrian Kantrowitz did so because his field faced some significant issues, including the scientific, philosophical and legal question: "What is death? At what point do we pronounce the donor dead

12. Comments by Walter Mondale, *National Commission on Health Science and Society*, 6.

13. Albert R. Jonsen, *The Birth of Bioethics* (New York: Oxford University Press, 1998), 140–4; Fox and Swazey, *Spare Parts*, 23–4; Paul Starr, *The Social Transformation of American Medicine* (New York: Basic Books, 1982), 389–93; Anita Guerrini, *Experimenting with Humans and Animals: From Galen to Animal Rights* (Baltimore, MD: Johns Hopkins University Press, 2003), 137–141; Jonathan B. Imber, *Trusting Doctors: The Decline of Moral Authority in American Medicine* (Princeton, NJ: Princeton University Press, 2008), 107–9.

and remove the heart?" He suggested that it would be helpful if local statutes were amended to redefine death in terms of irreversible brain damage. He also predicted that once transplantation techniques were perfected, there would be a shortage of organs, leaving another extremely difficult question: which of several dying patients should get the available organ and the chance to live? "I hardly need observe that we are not now organized to make such decisions," Kantrowitz said. "Government leadership will be needed."[14] Stanford's Norm Shumway also welcomed governmental involvement. Indeed, he credited federal funding for the progress made in heart transplantation. Shumway thought a national commission would be beneficial, even if it included nonmedical people, since it would serve to educate members of Congress and the public. Shumway was angry that prominent cardiologists, who were ignorant of the results of experimental work, had denounced heart transplantation. He said their statement demonstrated that physicians, too, needed to be educated. In order to realize the full potential of a wondrous new era in medicine, Shumway said doctors would need help, and "much of the assistance will come from sources outside the medical profession." Once people learned more of the facts about transplantation, he felt certain they would be more likely to support the field. "Transplantation of the heart," observed the far-sighted Shumway, "fortunately or unfortunately, cannot be done without public notice and public support."[15]

Others were less supportive, however. Christiaan Barnard, who had studied in the United States, found the very concept of a commission insulting. The only possible reasons to propose such a commission, he told a Congressional subcommittee, were if one perceived problems with the procedures or if there were new issues posed by transplantation. He vigorously defended his heart transplants and denied there were any such new issues. Asked about potentially difficult ethical decisions about who should receive scarce organs, he said doctors should decide. Asked if society should consider a new definition of death, he said doctors did not need

14. Adrian Kantrowitz testimony, *National Commission on Health Science and Society*, 30–38, 30.

15. Norman Shumway testimony, *National Commission on Health Science and Society*, 146–9, 149.

the help of a commission to tell them when a potential donor died. When one Senator noted that the public paid for the costs of transplantation and research, Barnard said it did not matter. Comparing surgery to a war, a combative Barnard declared that the public might pay the costs, but only "the general is qualified to make the decision."[16] Minnesota's Owen Wangensteen told the subcommittee that the medical community already monitored itself through peer review committees. All innovative new procedures were subject to careful scrutiny, and there was no need for legislation or the input of theologians, lawyers, philosophers, or others. "I cannot see how they can help," said Wangensteen. He cited specific historical examples of government commissions that had opposed promising new medical procedures (like smallpox inoculations and anesthesia), and asserted that doctors should be trusted and medical innovators should not be "second-guessed by self-appointed arbiters more versed in the art of criticism than the subject under scrutiny."[17] More than simply the government, then, it was the scrutiny of the public and "outsiders" that some in the medical community worried about. Even Henry Beecher, a Harvard anesthesiologist who supported a commission, observed, "[V]ery properly, the medical professional is fearful of outside control."[18] Near the end of the hearings, Senator Mondale lamented "the strange gap that exists in communications between the medical profession and the community at large, and in some parts of the medical profession an almost inexplicable paranoia about opening up communications."[19]

Mondale did not get his wish for a commission in 1968, but as he predicted, legal and social problems arose, especially related to the status of organ donors. The Uniform Anatomical Gift Act (UAGA), crafted in 1968 by the National Conference of Commissioners of Uniform State Laws, solved some of the immediate issues. It recognized the right of an individual to donate his or her organs for use after death, spelled out who else (e.g.

16. Christiaan Barnard testimony, *National Commission on Health Science and Society*, 77–86, 82.

17. Owen Wangensteen testimony, *National Commission on Health Science and Society*, 89–102, 100, and 98.

18. Henry Beecher testimony, *National Commission on Health Science and Society*, 117.

19. Comments by Walter Mondale, *National Commission on Health Science and Society*, 326.

immediate family) might make the decision to donate, and designated to whom (e.g. transplant hospitals) organs could be given. To facilitate donation, soon many states had adopted a method by which anyone getting a driver's license could indicate the desire to be an organ donor in case of unexpected death. All fifty states eventually passed a fairly similar version of the UAGA by 1972.[20]

There could be no transplantation without good donors, and surgeons knew that the ideal ones were otherwise healthy individuals who had suffered traumatic irreversible head injury and were maintained on artificial support. By the 1960s, respirators regularly were keeping the lungs breathing and hearts beating in many patients whose brains were fatally damaged even after there was no chance of existence off of the respirator. However, because common law and common sense decreed that a person had died when he or she stopped breathing and the heart stopped beating, it would require a major change in perspective to recognize that these fatally brain-injured patients actually were deceased.[21] In 1968 in an article in the *Journal of the American Medical Association* (*JAMA*), a prestigious Harvard committee recommended adopting a new "brain death" standard for determining the moment of death. The Harvard committee stated that the characteristics of a permanently nonfunctioning brain included unreceptivity and unresponsiveness, no movements or spontaneous breathing, and no reflexes. It suggested that tests for these criteria should be repeated over the course of twenty-four hours, and said that a flat EEG would be of great confirmatory value.[22] The Harvard committee declared that speedy acceptance of this standard would help the families of brain-dead patients understand what was happening, assist hospitals and patients who

20. Sam Crowe and Eric Cohen, "Organ Transplantation Policies and Policy Reforms," staff discussion paper, President's Council on Bioethics, http://www.bioethics.gov/background/organ_donation.html, accessed 29 October 2008; R. Randal Bollinger, "The Role of UNOS in Thoracic Organ Transplantation," in *Thoracic Transplantation*, ed. Sara J. Shumway and Norman Shumway (Cambridge, MA: Blackwell Science, 1995), 141–48; Jeffrey Prottas, *The Most Useful Gift: Altruism and the Public Policy of Organ Transplants* (San Francisco, CA: Jossey-Bass, 1994), 12.

21. Prottas, *The Most Useful Gift*, 235; Anon., "Heart Operation Key Issue in Trial," *New York Times*, 29 October 1973, 5.

22. Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, "A Definition of Irreversible Coma," *J. Am. Med. Assoc.*, 1968, *205*, 337–340; Robert Reinhold, "Harvard Panel Asks Definition of Death Be Based on Brain," *New York Times*, 5 August 1968, 1.

needed intensive care beds currently occupied by brain dead patients, and insure that there would be no controversy in obtaining organs for transplantation.[23] Relieved, the transplant medical community quickly moved forward to using brain dead donors.

Despite compelling reasons unrelated to organ transplantation for seeking clarity on the issue, however, some ethicists and members of the public were concerned that the very meaning of death was being altered partly because of a desire for organs.[24] "I have a horrible vision of ghouls hovering over an accident victim with long knives unsheathed, waiting to take out his organs as soon as he is pronounced dead," said one man.[25] Popular culture suggested that some mistrusted the motives of transplant surgeons, who were viewed as "vultures, waiting for a convenient death to bring life to their patients."[26] Indeed, Robin Cook's best-selling 1977 novel *Coma*, which was later made into a popular movie, portrayed a corrupt underground where physicians caused brain death in patients in order to sell their organs. The director of a pediatric lung transplant program declared, "*Coma* probably set transplantation back five years!"[27]

23. Margaret Lock, *Twice Dead: Organ Transplants and the Reinvention of Death* (Berkeley: University of California Press, 2002), 89; Robert M. Veatch, *Transplantation Ethics* (Washington, DC: Georgetown University Press, 2000), 58; Reinhold, "Harvard Panel."

24. The procedures for stating death has occurred, said ethicist Paul Ramsey, should not be "distorted by any reference to someone else's need for organs." Quoted in Jonsen, *The Birth of Bioethics*, 242. Reasons unrelated to organ transplantation were cited in President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Defining Death: A Report on the Medical, Legal and Ethical Issues in the Determination of Death* (Washington, DC: The Commission, 1981), 10, 18–20, 24.

25. Quoted in Lock, *Twice Dead*, 96–97.

26. Quoted in Craig McInnes, "The Beat Goes on," *The Globe and Mail*, 28 November 1987, D1. Others mentioned that the evocative labels "vulture" and "vampire" were used to describe transplant surgeons. Roy Calne, *A Gift of Life* (New York: Basic Books, 1970), 78; McRae, *Every Second Counts*, 209. Some transplant surgeons seemed callous regarding donor rights. See Raymond Hoffenberg, "Christiaan Barnard: His First Transplants and Their Impact on Concepts of Death," *Brit. Med. J.*, 2001, *323*, 1478–80, and Lock, *Twice Dead*, 87–88. Others, though, were very concerned about absolute certainty that donors were dead and the need for public understanding. See, for example, discussion at a Ciba-sponsored international conference in 1966, and the Second International Congress of the Transplant Society where it was clear that even transplant surgeons had to get used to the concept and evidence for "brain death." Gordon Wolstenholme and Maeve O'Connor, eds., *Law and Ethics of Transplantation: A Ciba Foundation Blueprint* (London: J and A Churchill, Ltd., 1968), 67, 72–73; Harold M. Schmeck, "Symposium Hears Transplant Plea," *New York Times*, 9 September 1968, 23.

27. Walter Robinson quoted in Eman Quotah, "Organ Donation: The Feds, Film, and Family," *Harvard Public Health Review*; Winter 2002, http://www.hsph.harvard.edu/review/review_winter_02/alumorgan.html, accessed 5 August 2008; Robin Cook, *Coma* (Boston: Little, Brown and Company, 1977).

If the Harvard Commission's pronouncement did not assuage public concerns regarding brain death, neither did it take care of legal issues. In a prominent court case, transplant surgeons at the Medical College of Virginia were sued for the wrongful death of a brain dead man whose heart and kidneys were donated after doctors had turned the ventilator off. Surgeon Richard Lower was acquitted, but the outcome had been far from certain, and in the years while the case languished in the legal system, he was unable to perform organ transplants.[28] In California, heart surgeon Norman Shumway clashed with his county coroner over use of cadaver organs for transplant, and uncertainty about the legal definition of death had "scared hell out of doctors" who feared lawsuits.[29] Some states passed a law recognizing brain death, but others did not, and even the versions they passed differed, resulting in the bizarre circumstance that a person could be considered dead in one state but not another. Confusion reigned for over a decade.[30] It required a national Presidential Commission formed in 1980 to bring together medical and other experts to recommend the use of brain death criteria and craft a uniform law that was quickly adopted by the American Medical Association, American Bar Association, and the states.[31] It's clear that both implementation and acceptance of brain death criteria took longer than the eager transplant community

28. R. Converse, "But *When* Did He Die? Tucker v. Lower and the Brain-death Concept," *San Diego Law Review,* 1975, *12*, 424–435; Anon., "Controversy on Coast," *New York Times*, 25 August 1968, 50; Anon., "Heart Operation Key Issue in Trial," *New York Times*, 29 October 1973, 5; Anon., "How to Define Death Is the Issue in Murder Trial," *New York Times*, 20 May 1974, 23; Anon., "Shooting That Led to an Implant Produces Manslaughter Verdict," *New York Times*, 24 May 1974, 20; Harold A. Schmeck, "Brain Death: When Does Life Cease?" *New York Times*, 4 June 1972, E7; Veatch, *Transplantation Ethics*, 43–52.

29. Alexander M. Capron, "To Decide What Dead Means," *New York Times*, 24 February 1974, 168.

30. Jonsen, *Birth of Bioethics*, 242. Sociologists Fox and Swazey referred to "conceptual confusion and emotional unease" about brain death, *Spare Parts*, 59–63.

31. The model statute read: "An individual who has sustained either (1) irreversible cessation of circulation and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made with accepted medical standards." President's Commission, *Defining Death*, 1–12, 24–30, 73. Thirty-seven states had passed the Uniform Determination of Death Act by December 1983. Frank J. Veith, "Define Brain Death," *New York Times*, 17 December 1983, 23. There has never been absolute consensus on the whole brain standard in the United States, with some arguing for a less stringent "higher brain" standard and a few maintaining we should return to solely the cardiopulmonary standard. See for example, Veatch, *Transplantation Ethics*, 53–83, and Lock, *Twice Dead*, 125.

wanted, and the involvement of the federal government facilitated the cause.

With the introduction of cyclosporine as an immunosuppressant drug, organ transplantation took off in the early 1980s, and politicization soon followed. When the media and President Ronald Reagan aired pleas for organ donation to benefit some desperate children waiting for transplants, it called attention to problems in the nation's procedures. In a very fragmented system, not enough organs were procured, and at the same time many organs were being wasted. People worried that those with money or connections had a better chance at getting a transplant, and a physician had even started a business to broker kidneys. In response to these concerns, Congressional Representative Al Gore proposed path-breaking new legislation in which the federal government would support and contract with a nonprofit organization to coordinate an efficient national transplantation network.[32] Besides wanting to ban commercialism, Gore hoped legislation could "insure equitable and timely access" to the lifesaving procedures. Gore noted that before the federal government had gotten involved in kidney dialysis and transplantation, the recipients had been predominantly young, white, college-educated males, and afterwards, they were far more representative of those who had kidney disease. Gore said the federal government, which was already paying for most of the nation's organ procurement through its End Stage Renal Disease Program, should act. "I believe only the Federal Government can best provide the glue and the conscience from which a national system can be formed."[33]

At first there was some uncertainty among the transplant medical community over the proposed National Organ Transplant Act (NOTA). For example, surgeon Thomas Starzl initially felt

32. Al Gore testimony, *National Organ Transplant Act*; Hearing before Subcommittee on Health of Ways and Means Committee, House of Representatives, 98th Congress, 2nd session, on H.R. 4080, February 9, 1984, 19.

33. Al Gore testimony, *Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce*, House of Representatives, 98th Congress, first session, on H.R. 4080, 29 July and 17 and 31 October 1983, 8–9, 111, 123–5. Quotation on p. 9. See also Gene A. Pierce, "Legislative Perspectives on the Development of the End–Stage Renal Disease Network and the National Organ Procurement and Transplantation Network," in *Principles of Organ Transplantation*, ed. M. Wayne Flye (Philadelphia: W.B. Saunders, 1989), 652–63; Steven J. Peitzman, *Dropsy, Dialysis, Transplant* (Baltimore, MD: Johns Hopkins University Press, 2007), 114–6.

skeptical, since he'd been displeased with federal bureaucrats who had decreed liver transplants "experimental" and ineligible for Medicare coverage. "I don't for a moment want to leave the impression that I trust the Government," he declared to a House subcommittee.[34] Ironically, though, the heaviest opposition to NOTA came from within the Reagan administration, which in general favored smaller federal government. Reagan's Surgeon General and his appointees in the Department of Health and Human Services (HHS) argued that control over organ transplantation should remain solely in the private sector.[35] The Surgeon General quickly helped start a private organization, the American Council on Transplantation (ACT), which was a consortium of individuals and organizations that he hoped could handle the issues and thereby avoid government involvement. However, even the surgeon who was interim president of ACT said there should be some kind of "strong federal statement" regarding organ transplantation and "a well-defined and visible focus within the Federal Government, presumably within DHHS, to interface with groups such as ACT, to share concerns and more importantly, solutions."[36] The divided membership of the hastily assembled ACT decided not to take a formal position on the proposed legislation.

Eventually most of the transplant community, including organizations representing surgeons, physicians, coordinators, and patients, came to advocate for the National Organ Transplant Act. Even the initially skeptical Starzl concluded, "[I]t is a very fine bill and I hope it passes. I think it would do wonderful things for health care in this country." Starzl decided it would make multi-organ procurement easier. "The procurement agencies cannot be little cottage industries devoted only to the kidney transplant programs," he asserted. "There is only one set of donors for all the needed organs and the organs are a resource of the entire United States. This concept has to be built into the system." The national network, agreed a kidney surgeon,

34. Thomas Starzl testimony, *Hearings before the Subcommittee on Health and the Environment*, 1983, 109.

35. Edward Brandt testimony, *Hearings before the Subcommittee on Health and the Environment*, 1983, 146; and Brandt testimony, *National Organ Transplant Act Hearing*, 1984, 41.

36. Gary Friedlander testimony, *Hearings before the Subcommittee on Health and the Environment*, 1983, 259.

was "an outstanding idea and one whose time has finally come."[37] Others wanted the government to outlaw the sale of organs and oversee the collection of transplant data. At Congressional hearings in 1984, Representative Henson Moore pointed out to a panel of surgeons that the bill empowered federal bureaucrats. "If you are giving them power," he warned, "you are giving yourself problems."[38] But Starzl and his colleagues replied that they were not worried, because the government *already* subsidized and influenced almost all the nation's organ procurement and transplantation without interfering in a problematic way.[39] They were swayed by the many benefits the government seemed to be offering, including the possibility of recognition that heart and liver transplants were no longer "experimental," Medicare coverage for some immunosuppressant drugs, better computers and public and professional education, and support for national coordination. They hoped that since the government would contract with a private nonprofit organization to run the network, they as surgeons would continue to make decisions about allocation policies. Oscar Salvatierra, president of the American Society of Transplant Surgeons (and also a member of ACT), said "[t]he issues facing transplantation today are of a more critical nature and require more urgent action than this type of loose federation [in ACT] could ever conceivably give. . . . [T]hese latter problems would best be solved by congressional action like H.R. 4080 proposes." Salvatierra concluded the legislation could result in a "more effective public/private partnership."[40]

The National Organ Transplant Act passed easily with bipartisan support in 1984.[41] It outlawed profit from the purchase of solid

37. Thomas Starzl testimony, *Hearings before the Subcommittee on Health and the Environment*, 1983, 228, and *National Organ Transplant Act Hearing*, 1984, 104; Robert Mendez testimony, *Hearings before the Subcommittee on Health and the Environment*, 1983, 317.

38. Comments by Henson Moore, *National Organ Transplant Act Hearing*, 1984, 109.

39. See Thomas Starzl testimony, *National Organ Transplant Act Hearing*s, 1984, 108–10; see also testimony of Oscar Salvatierra, President of the American Society of Transplant Surgeons, and others, *Hearings before the Subcommittee on Health and the Environment*, 1983, 29–41, 187–97, 228–9, 301–4, 329–30.

40. Oscar Salvatierra testimony, *Hearings before the Subcommittee on Health and the Environment*, 1983, 330. See also Salvatierra testimony, *National Organ Transplant Act Hearing*, 1984, 92.

41. The House of Representatives voted 396 to 6 in favor of the law. *National Organ Transplantation Act, Hearing before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce*, House of Representatives, 101st Congress, 2nd session,

organs, insuring that organ transplantation would continue to rely on voluntary donation of the public and not become a commercial venture within the United States. It also decreed that the Secretary of Health and Human Services should contract with a nonprofit Organ Procurement and Transplantation Network (OPTN) that would, among other things, establish a national system to list individuals who needed transplants and match them with available organs. It established an administrative unit within the federal bureaucracy to submit annual reports to Congress about the effectiveness of the system. In addition, it created a national task force to consider medical, legal, ethical, economic, and social issues related to organ transplantation.[42]

The resulting twenty-five-member national task force greatly influenced the subsequent direction of organ transplantation in the United States. The secretary of HHS appointed Olga Jonasson, professor of surgery at the University of Illinois, to chair the committee, which was composed of nine physicians or scientists in specialties related to transplantation; three nonphysicians in fields of procurement; four nonphysicians with expertise in law, theology, ethics, or health care financing; three members of the general public; two health insurance representatives; and four ex-officio members from NIH, FDA, HCFA, and the Surgeon General's office. The task force commissioned studies, did literature reviews, and held public hearings. In the fall of 1985 the committee submitted its report.[43]

The committee's key recommendation was for a single national system for organ sharing with mandatory and uniform policies and standards. In addition to medical professionals, governance of that system should include groups representing patient, community, and ethical perspectives. The task force said the public deserved input not only because decisions about how to allocate organs were difficult, but because of the "special nature" of organ transplantation. Transplantation was unlike most medical procedures because

on H.R. 3968, a bill to amend the Organ Transplant Amendments Act of 1988 to Change effective date, April 20, 1990, 1.

42. Public Law 98–507, 98th Congress. 98 Stat. 2339. 19 October 1984.

43. Task Force on Organ Transplantation, *Organ Transplantation: Issues and Recommendations; Report of the Task Force on Organ Transplantation* (Washington, DC: U.S. Department of Health and Human Services, 1986).

it relied on a very scarce resource: an organ voluntarily donated by another human being. Other medical resources (such as drugs or expensive technology) might be scarce, but usually more money could obtain them. Organs were different in the U.S. system; money could not and should not obtain more of them. The only way to increase the supply was through persuading the public that their generosity was for a worthwhile cause. And "[c]ontinued public support for organ transplantation," it stated, "depends on public confidence that organs are distributed equitably to those who need them."[44] Selection of patients for transplant should not be subject to favoritism or discrimination on the basis of nonmedical factors, such as race or sex, or ability to pay.

The task force asserted, just as Thomas Starzl had, that "each donated organ [should] be considered a national resource to be used for the public good." The corollary, though, was that "the public must participate in the decisions of how this resource can be used to best serve the public interest."[45] While the public was to serve as trustee of donated organs, the task force recommended important duties for the federal government in implementing that role, including that HHS establish minimum criteria for and certify organ procurement organizations and transplant centers, and that Congress spur collection of transplant data and make transplants available to all by funding coverage of them and the necessary immunosuppressant drugs. It also recommended various strategies for increasing organ donation, including a law requiring hospitals to provide the opportunity for organ donation to suitable families. Over the next few years, Congress enacted many of the national commission's recommendations, giving (in somewhat vague terms) oversight responsibility to the Department of Health and Human Services.[46]

44. Task Force on Organ Transplantation, *Organ Transplantation*, 24, 87–89.

45. Ibid., 85–89. See also Jed Adam Gross, "Playing with Matches without Getting Burned; Public Confidence in Organ Allocation," in *A Death Retold: Jesica Sanitllan, the Bungled Transplant, and Paradoxes of Medical Citizenship*, ed. Keith Wailoo, Julie Livingston, and Peter Guarnaccia (Chapel Hill: University of North Carolina Press, 2006), 180–204.

46. The Omnibus Budget Reconciliation Acts in 1986 and 1987 gave HHS responsibility for monitoring each OPO's performance and declared that hospitals meet certain criteria about organ transplantation or lose Medicare reimbursement money. HHS also was given authority to review UNOS membership requirements and policies. "HRSA Contracts Unify Organ donor and Transplant Information Networks," *Pub. Health Rep.*, 1987, *102*, 452; Prottas, *The Most Useful Gift*; 14–19, 44–45; Margaret Engel, "Organ Network Dies in Reagan Plan," *The Washington Post*, 11 January 1987, A11; *National*

The United Network for Organ Sharing (UNOS) was chosen by HHS to serve as the nation's organ procurement and transplantation network, and UNOS accepted responsibility for establishing criteria for the listing of patients for transplantation, maintaining the waiting list, and operating an equitable system for matching and allocating donated organs. Hospitals that performed transplants, organ procurement agencies, and tissue typing labs were required to be members of UNOS; some institutions like nonprofit professional and health organizations were members as well.[47] All UNOS policies had to be approved by the board of directors after consideration by committees. The makeup of this board was contested. At first, HHS declined to award UNOS the contract because its board was not as representative as the national task force had recommended—suggesting some lingering reluctance to allow people other than surgeons a voice in organ transplantation—but UNOS resubmitted a more acceptable proposal.[48] Over time, the membership of the board of directors has evolved so that it now includes approximately 50 percent transplant surgeons and physicians; at least 25 percent transplant candidates, recipients, donors, or their families; and the rest representatives of other interested groups, including coordinators, organ procurement operations, labs, nonprofit health groups, and the general public.[49]

After awarding the contract for the national network, the government's executive branch was not very active. In the first few years of its existence, UNOS developed an increasingly responsive and efficient system.[50] Its policies for the allocation of organs, however,

Organ Transplants, Hearing before the Subcommittee on the Health and the Environment of the Committee on Energy and Commerce, House of Representatives, 100th Congress, 1st session, 2 April 1987; 1–2; 20–23.

47. Some interested and involved private individuals could also be members.

48. Prottas, *The Most Useful Gift*, 138–9. UNOS received the federal contract on 30 September 1986. Its board was restructured to meet the requirements of the national task force. Statement of John C. McDonald, president, UNOS, *National Organ Transplants Hearing*, 1987, 43–50.

49. The OPTN's current membership, board of directors, and purpose can be found on UNOS website at http://www.optn.org/policiesAndBylaws/charterAndBylaws.asp, accessed 12 February 2009.

50. By 1987, UNOS had a twenty-four-hour, voice-activated computer to assist organ matching and was handling over 150 calls each day. Its recommended procedures had improved procurement, increasing the number of multi-organ donors and decreasing the number of kidneys that were discarded or exported outside the United States. Anon.,

were contested and sometimes resisted by its member transplant centers and surgeons who were accustomed to making their own decisions about how best to distribute organs retrieved locally. These life and death decisions were not easy, especially given loyalty to one's own patients. How would it be determined which hospital in an area received an organ that became available? Should the procuring hospital get priority? Or was it fairer for hospitals in the same region to take turns? How big should a "region" be? And what about individual patients? Doctors agreed on some basic medical criteria for matching patient and donor organ size and blood type, but after those were met, should the patients who had waited longest get first priority for organs? The ones closest to death? The youngest? The most "worthy" in some way? Despite Congress' desire for consistency in the policies, many transplant centers insisted on being allowed to develop their own policies, which UNOS permitted. "At the outset, the exceptions were invited to swallow up the rule," observed analyst Jeffrey Prottas.[51] All of UNOS' policies were voluntary, and would not have the power of law until HHS issued formal regulations. Because the Reagan administration wanted the federal government to stay out of transplantation, it never issued regulations and consistently undermined Congressional intent regarding transplantation, which infuriated the National Organ Transplant Act's early sponsors. Representative John Dingell denounced the "insurmountable inertia in HHS" and the fact that organ procurement organizations were "not accountable to anyone."[52]

By 1993, many in the transplant community wanted the government to issue regulations, and let the new Clinton Administration know it. At hearings on reauthorization of

"Organ Match Gets High-tech Help," *The Advertiser*, 19 September 1987, http://www.lexisnexis.com/us/lnacademic.

51. Prottas, *The Most Useful Gift*, 141–2.

52. Comments by John Dingell, *Organ Transplant and Bone Marrow Donor Reauthorization*, Hearings before the subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, 103rd Congress, 1st session, 22 April and 19 May 1993, 3. See also Engel, "Organ Network Dies," A11; Don Colburn, "Transplants: Who Lives? Who Decides? Doctors Can Make Them Work—But Can Society Make Them Fair?" *Washington Post*, 20 January 1987, Z1; "Backers of Organ Gifts Criticize Reagan Cuts," *The New York Times*, 13 January 1987, C9; Comments of Henry Waxman and Al Gore in *National Organ Transplants*, 1–4.

legislation, patient advocacy groups complained in Congressional hearings about the variances from one region of the country to another. A Pittsburgh surgeon criticized UNOS for changing its liver allocation rules in a way that had "enormous and devastating impact" without any appreciable public comment or HHS approval.[53] While Randal Bollinger, the president of UNOS, worried about whether federal rule-making could adjust to the rapid changes in transplantation, he too lamented the fact that in the absence of HHS action UNOS did not have the ability to enforce its policies. He acknowledged HHS' "ultimate authority," but hoped the federal government would mandate some broad parameters of principles and let UNOS handle the details of procurement and allocation.[54]

Like its predecessors, the Clinton Administration moved slowly, until transplantation politics heated up in 1996. Complaints about recent changes in UNOS' liver allocation policies prompted HHS to hold three days of hearings to make sense of serious disagreements within the transplant community. Surgeons contended that some of their colleagues stretched the truth to push their patients up the waiting list. Some accused UNOS of ignoring up-to-date data, discriminating against people with chronic liver disease, and putting the needs of inefficient transplant centers above those of patients. Counter accusations implied that those transplant centers who did not benefit from UNOS policies were sore losers who appealed to the federal government to overturn the policies.[55]

53. Testimony of John C. Dingell, Charles Fiske, Craig Irwin, and Andreas Tazakis, *Organ Transplant and Bone Marrow Donor Reauthorization*, 3–6, 67–71, 51–64, 109–23. Quotation from Pittsburgh surgeon Tazakis on p. 121.

54. Randal Bollinger testimony, *Organ Transplant and Bone Marrow Donor Reauthorization* Hearings, 80–88, 126. Quotation on p. 81.

55. The arguments made at the 1996 hearings echoed some made at the 1993 hearings and anticipated those made after the final rule was released in 1998. UNOS announced that 95 percent of its members supported its policies but also seemed shocked at the number of complaints it received. "Patient Advocacy Group Condemns UNOS Interference with Government Hearings," National Transplant Action Committee press release, PR Newswire, 9 December 1996, http://www.lexisnexis.com/us/lnacademic; "Transplant Community Overwhelmingly Supports UNOS," UNOS press release, PR Newswire, 6 December 1996, http://www.lexisnexis.com/us/lnacademic; Paul Recer, "Patients Say Transplants Should Go First to the Sickest," Associated Press Online, 10 December 1996, http://www.lexisnexis.com/us/lnacademic; Rick Weiss, "A Searing Debate over a Life-and-Death Policy," *Philadelphia Inquirer*, 15 December 1996, E3; "Some Patients Object to Rule Change on Who Gets Scarce Livers," *New York Times*, 18

All contended that more people would die under their opponents' policies. UNOS tried to prevent HHS from holdings hearings at all.[56]

After years of study and consideration of hundreds of comments, in March 1998 the Department of Health and Human Services finally issued regulations. HHS Secretary Donna Shalala said the "final rule," as such federal regulations are called, was intended to remedy inequities in the current system. One inequity was that patients in one part of the country were waiting as much as five times as long for an organ as those in others, a disparity apparently caused by the practice in which organs were first offered to all patients in a narrowly defined local area before being shared more widely with those who needed them more desperately. Accidents of geography should not determine whether a patient lived or died, said Secretary Shalala. Nor should the wealthy be able to travel somewhere with a shorter list. "Instead, patients everywhere in the country should have an equal chance to receive an organ, based on their medical condition."[57] While not specifying a particular method of organ allocation, the final rule required that the nation's network (UNOS) develop a policy using medical urgency, not geography, as the main criterion for allocating organs. The regulations also asserted that every transplant center should use the same medical criteria for placing patients on the list. "There is a central purpose to the performance goals," stated Shalala, "which is to ensure, to the maximum possible extent, that all patients, regardless of where they live, are treated the same."[58] The final rule included

November 1996, A15; Ann Mongoven, "Federal Hearings on Liver Transplant Allocation and Donation," *BioLaw*, 1997, *II*, S373–89.

56. *Putting Patients First: Resolving Allocation of Transplant Organs*, Joint Hearing before the Subcommittee on Health and Environment of the Committee on Commerce, House of Representatives, and the Committee on Labor and Human Resources, U.S. Senate, 105th Congress, 2nd session, 18 June 1998, 98–106.

57. The wait could vary even within the same state, as in Kentucky where the median waiting time for livers was 38 and 226 days at different centers. Donna Shahala is quoted in "HHS Rule Calls for Organ Allocation Based on Medical Criteria, Not Geography," Health Resources and Services Administration (HRSA) Press Release, 26 March 1998, archived at http://www.hhs.gov/news/press/1998pres/980326a.html, accessed 12 November 2008.

58. Donna Shalala testimony, *Putting Patients First*, 1998, 69–86; quotation on p. 77. See also Weiss, "New Rules for Organ Waiting Lists," *Washington Post*, 27 March 1998, A1.

a sixty-day comment period, and was scheduled to take effect after ninety days.

The regulations alarmed some in the transplant community. The influential transplant center in Pittsburgh, however, which had been pushing UNOS for a liver allocation policy that gave priority to the most urgent patients all over the country, applauded the final rule. Joining its doctors were other transplant centers and a number of patient advocacy groups. But other patients, surgeons, and hospitals had reservations.[59] Some interpreted the final rule as saying that organs had to go to the very sickest patients first, which, since the very sickest might not survive a transplant as well, would not be the wisest use of resources.[60] Some worried HHS was mandating a single nation-wide waiting list, and like the patient testifying who said she feared "organs flying and patients dying," believed it was impractical to transport organs all over the country.[61] Some asserted that it was unfair (and unwise) for communities that were good at soliciting organ donation to lose the organs donated locally. "We urge you not to punish States for their successes and to reward others for their failures," said a letter to Shalala, and consequently some states considered laws to prevent organs from leaving their state.[62] The biggest concern for some opponents, though, was that the new regulations might put smaller transplant centers out of business, since they would be forced to share organs with urban areas with more needy patients. Economics mattered. "This is about the financial life and death of transplant centers around the country," asserted Representative Thomas Barrett.[63] While smaller centers accused larger ones of trying to prevent competition that

59. See for example, the Joint Statement on the Organ Allocation Provisions in the OPTN Rule, *Putting Patients First*, 17–26. "Campaign for Transplant Patient Fairness Weighs in on UNOS Plan, Calls on HHS to Protect Patient Interests, U.S. Newswire, 13 March 2000, http://www.lexisnexis.com/us/lnacademic.

60. Apparently President Clinton had used the phrase "sickest first" when the regulations were first released, leading to understandable confusion about whether HHS recognized the very sickest might not always be the best candidates. *Putting Patients First*, 90.

61. Tom Meredith testimony, *Putting Patients First*, 33.

62. Besides saying they were losing their fair share, some argued that if more organs left the community in which they were donated, local people would be upset and stop donating. Letter from Congressional Representatives to Donna Shahala, 3 June 1998, included in *Putting Patients First*, 65–66, 66; Anon., "Fighting over Organs: The War over Transplants: States v. Washington," *The Economist*, 2 May 1998, 26–31.

63. Thomas Barrett testimony, *Putting Patients First*, 59.

cut into their market share, larger ones accused smaller ones of inefficiency and the hoarding of organs.[64]

Shalala tried to reassure the regulation's opponents. "We know that transplanting the sickest patient is not always the best course," Shalala explained. "We believe that transplants should be performed on the basis of medical urgency, the definition of which includes viability and chances of survival. Further, it is up to UNOS to develop policies on medical urgency." HHS also clarified that it was not requiring a single national waiting list. The best system might prove to be national or regional lists, but again, HHS left it up to the medical experts in UNOS to develop a system that promoted more sharing and equity in a practical manner. "The rule calls for fairness. How fairness is achieved in terms of allocation policy is primarily up to UNOS. . . . Any policy that is sensible, is based on sound medical judgment, and reduces geographic inequity, will be taken seriously by the Department." Though Shalala did not see how the regulation might force some transplant centers to close, she was willing to add something to the regulation to monitor its impact on different-sized centers. She recognized that there were concerns that organs would leave areas that had worked hard to get organs, but said the entire transplant community needed to come together to address the organ shortage. Citing the AMA's code of medical ethics, she noted, "Organs should be considered a national, rather than a local or regional resource."[65]

UNOS opted to fight the regulations and HHS with no holds barred. The organization paid a firm over $1 million to conduct a public relations campaign and lobby Congress to block the regulations. UNOS warned its members about the worst possible outcomes of the new rules and said unqualified bureaucrats in HHS were wresting control over medical decisions from the appropriate medical professionals. UNOS created a "legislative kit" for members that included sample form letters to Congress. It was certainly unusual for a federal contractor to publicly lobby against the

64. Sheryl Gay Stolberg, "Patients' Lives on the Line in Battle over Transplants," *New York Times*, 25 March 1998, A1; Weiss, "A Searing Debate," E3; University of Pittsburgh Medical Center, "Liver Allocation Policies Should Serve Public's Interest Not Transplant Centers" PR Newswire, 10 December 1996, http://www.lexisnexis.com/us/lnacademic.

65. Donna Shalala testimony, *Putting Patients First*, 69–86, 76, and 77.

federal agency charged with overseeing it. The staff at HHS, an agency that had oversight over many health areas and other federal contractors, could not believe how difficult UNOS was to work with. On one occasion, UNOS defied HHS by denying its request for data—data which HHS thought would have further bolstered its position.[66] HHS staffers were dismayed. "To have UNOS do such a blanket smear campaign just has been extremely frustrating," said HHS' Claude Earl Fox. Secretary Shalala agreed, telling Congress, "I have been very critical of UNOS. I have never dealt with a contractor quite in this way. I want this relationship to move into a collegial stage. We need to do that for the American people."[67]

Yet according to observers, the conflict was "adversarial," "polarized," "fierce," and "nasty."[68] Opponents of the regulation said HHS was simply "not qualified" and suggested its policies were crafted in response to improper influence from a longtime friend of Bill Clinton. "Where does all this [government interest] come from?" asked UNOS' Walter Graham. "The only answer I can come up with is that it came as a result of political influence."[69] They characterized HHS as making a dictatorial federal power grab.[70] As mentioned earlier, liver surgeon Anthony D'Alessandro complained that "Miss Shalala is determined to anoint herself federal organ transplant czar," and "political appointees" would make the final decisions about who lived and who died that previously had been reached by consensus among transplant

66. "Spending Bill Will Delay Organ Transplant Policy Rules," Reuters Health Medical newswire, 19 October 1998, http://www.lexisnexis.com/us/lnacademic; Walter K. Graham, "The Organ-Transplant Controversy," *The Washington Post*, 6 August 1997, A18. See also Donna Shalala and Lawrence Hunsicker testimony, *Putting Patients First*, 93–97, 180, 84.

67. Claude Earl Fox quoted in Laura Meckler, "Transplant World in Nasty Fight over New Rules," Associated Press Online, 30 May 1998, http://www.lexisnexis.com/us/lnacademic; Donna Shalala quotation in *Putting Patients First*, 97.

68. Meckler, "Transplant world in nasty fight"; Anon., "Patient Advocates Reject Transplant Network's Proposal to Revise Pending Federal Regulations," U.S. Newswire, 15 September 1999, http://www.lexisnexis.com/us/lnacademic; James Childress, a member of the original national task force on organ transplantation, said he was discouraged by the adversarial nature of the discussions about allocation. Childress testimony, *Putting Patients First*, 200.

69. Walter Graham, quoted in Stolberg, "Patients' Lives on the Line."

70. In 1996 UNOS had already portrayed the possibility of regulations as an "unprecedented federal takeover." Quoted in Rich Weiss, "Who Should Get Liver Transplants? As Demand Far Outpaces Donors, Federal Officials May Revamp Rules," *Washington Post*, December 9, 1996, A1.

doctors.[71] Both sides accused the other of putting self-interest above patient care and of having "politicized" the disagreement in an unseemly manner.[72] Supporters of the regulations fought back by questioning whether UNOS' policy-making processes were fair and the organization representative. "Where's the public accountability?" asked patient advocate Charles Fiske. "It's a private little club."[73] Congressman John Dingell went further, characterizing UNOS as "a shoddy, shabby contractor who seeks an absolute monopoly over the handling of organs in this nation" and which perpetuated "deceit, misrepresentation and falsehood."[74] In an unusual turn of events, the battle lines in Congress were not drawn over political ideology; indeed, some conservative Republicans and liberal Democrats found themselves on the same side.[75] Nor was it the transplant community against the government. The transplant community itself was deeply divided—along the lines of urban versus rural centers, larger centers versus small, or advocates for the acutely ill versus the chronically ill. The disagreements that they fought over inside UNOS and inside their professional organizations had simply been transferred to the political realm. Senator Bill Frist, who had been a transplant surgeon before being elected to national office, reported, "When you go into board meetings at UNOS and the regional meetings, there are more politics there than there are here [in Congress]."[76]

71. D'Alessandro, "Hostile organ takeover."

72. See, for example, the exchange of comment letters between two surgeons. Dr. John J. Fung, "We Need an Equitable, National System of Organ Distribution," *Washington Times*, 14 January 1998, A16; John Rabkin, "Patient Care vs. Market Share," *Washington Times*, 27 December 1997, C1. In 1996 when HHS was holding hearings on the liver allocation policy, UNOS president James Burdick was quoted as lamenting "this unfortunate politicization." Quoted in *Putting Patients First*, 100.

73. Charles Fiske quoted in anon., "UNOS: Some Call for More Public Accountability," American Health Line news wire, 10 April 2000, http://www.lexisnexis.com/us/lnacademic; Brigid McMenamin, "The Organ King," *Forbes*, 1999, *164*, 164–7.

74. John Dingell quoted in Juliet Eilperin, "House Acts to Reject Rules on Transplants; Voting 275–147, Lawmakers Side With Private Network in Dispute with HHS," *Washington Post*, 5 April 2000, A2.

75. Allies in the Senate included two of the most liberal Senators, Charles Schumer of New York and Richard Durbin of Illinois, and two of the most conservative, Peter Fitzgerald of Illinois and Rick Santorum of Pennsylvania. Anon., "Senators Introduce Organ Transplant Bill," Reuters Health Medical News, 12 April 2000, http://www.lexisnexis.com/us/lnacademic.

76. Comments of Bill Frist, *Putting Patients First*, 93.

While the battle focused mainly on the implications of the regulations with regard to organ allocation, a crucial subtheme was the appropriate role of the federal government. Whether because of legitimate differences over policy, defensiveness over criticism of their work, or fear of losing the independence the organization had enjoyed during previous presidential administrations, UNOS leaders wanted little to do with HHS. "UNOS is not an agent of the government," asserted executive director Walter Graham, and on a number of occasions, some UNOS presidents had suggested HHS had no authority to shape policy on allocation.[77] When questioned before Congress, UNOS President Larry Hunsicker was more moderate, claiming UNOS "certainly [did] not object to the Federal Government's appropriate oversight role."[78] Still, he interpreted the fact that the National Organ Transplant Act made the nation's organ network a private organization to mean that the government "should be shielded from direct involvement in sensitive medical and ethical issues." When asked how he envisioned the appropriate relationship with HHS, Hunsicker said it should be a partnership, "with the lead being taken in terms of developing policies by the community that is being governed by them." Interestingly, this was quite similar to what was being proposed by HHS in the final rule. Yet in the next breath Hunsicker also said that the relationship UNOS had had with HHS for the previous twelve years (during which HHS rarely intervened) was "an appropriate way to do things."[79] To UNOS leaders, "appropriate oversight" appeared to mean no oversight. Of course not everyone in the transplant community shared the official position of UNOS; after all, it had been some patient groups and disaffected transplant centers who had appealed to HHS in the first place to arbitrate, and many testified at hearings in 1998 and wrote comments in support of the regulations.

77. Walter Graham, quoted in Meckler, "Transplant World in Nasty Fight over New Rules"; Dave Davis and Joan Mazzolini, "Organ Centers Oppose Oversight; Allocation Rules May Change," *The Times Picayune*, 24 November 1996, inserted into the record in *Putting Patients First*, 102. See also Walter K. Graham, "The Organ-Transplant Controversy," *The Washington Post*, 6 August 1997, A18 and *Putting Patients First*, 34.

78. Lawrence Hunsicker testimony, *Putting Patients First*, 136.

79. Lawrence Hunsicker testimony, *Putting Patients First*, 178 and 181; Davis and Mazzolini, "Organ Centers Oppose Oversight."

Although Shalala met with many groups and modified aspects of the regulations, she and her HHS colleagues would not budge from their main direction nor cede authority. She asserted that the National Organ Transplant Act gave HHS the responsibility to oversee the network—and had done so precisely because there had been inconsistency, inefficiency, and abuses in the nation's transplant system. Subsequent laws reinforced the requirement that transplants paid for by the government had to comply with criteria issued by HHS, and the federal government paid for well over half the transplants in the country. "To say we have no basis to issue regulations when our authority is clear," she asserted, "is a disservice to Congress, which created the network, and to the patients, whose transplant bills are paid by taxpayers."[80] HHS' Claude Fox pointed out that UNOS received many benefits from the government, including the right to operate as a monopoly, and as a result had to accept controls. "We answer to Congress," he said bluntly, "and they answer to us."[81] Shalala seemed especially frustrated because her staff had specifically allowed UNOS to retain primary responsibility over the particulars of the allocation rules. HHS had intentionally not crafted detailed, heavy-handed regulations as it had done for other issues. "We are trying to strike a balance here," she stated, "a balance between the responsibility that we have for oversight of a very sensitive issue and the very important role of the medical professionals in providing for the system."[82]

Characterized by shrewd maneuvers and counter-moves, the regulation controversy continued for two years. Opponents of the regulations won an early round by bypassing HHS and taking their case to Congress. In October 1998, Congress passed a measure that delayed the regulations for a year, required UNOS to provide certain data, and commissioned a study by the more neutral Institute of Medicine.[83] HHS won a round when the Institute's report largely endorsed the direction of the regulations, concluding

80. Donna Shalala testimony, *Putting Patients First*, 78.

81. Claude Fox, quoted in Meckler, "Transplant World in Nasty Fight over New Rules."

82. Donna Shalala testimony, *Putting Patients First*, 110.

83. "Spending Bill Will Delay Organ Transplant Policy Rules," Reuters Health Medical newswire, 19 October 1998, http://www.lexisnexis.com/us/lnacademic; Mary Jacoby, "Organ Transplants May Go Nationwide," *St. Petersburg Times*, 26 November 1999, 1A.

the system was "not functioning as well as it could" and recommending that HHS "exercise the legitimate oversight responsibilities assigned to it."[84] As the end of the year approached, regulation opponents successfully added a rider with another ninety-day delay to an unrelated bill that was approved by Congress.[85] Meanwhile, they introduced a new bill that would have created a long-term solution, nullifying the final rule, lessening HHS power, and effectively giving UNOS a permanent position as the nation's organ transplant network.[86] The House of Representatives passed this bill. Supporters of the regulations called the bill "outrageous," threatened a presidential veto, and worked with Senator Bill Frist on an alternative. Frist crafted a middle-of-the-road bill with the goal of having "medical decisions made by the transplant community, with strong oversight and strong accountability." Reaching a compromise on the different Senate and House bills was difficult; according to Senator Ted Kennedy, it was like trying to "cross a Chihuahua with a Great Dane."[87] When compromise proved impossible, the final result was that Congress passed no new transplant legislation. This

84. Committee on Organ Procurement and Transplantation Policy, Institute of Medicine, *Organ Procurement and Transplantation; Assessing Current Policies and the Potential Impact of the DHHS Final Rule* (Washington, DC: National Academy Press, 2000), http://books.nap.edu/catalog/9628.html, accessed 10 November 2008, 1–14, 14.

85. Anon., "NTAC Condemns House Commerce Committee Chairman Bliley for Latest Attempt," U.S. Newswire, 17 November 1999, http://www.lexisnexis.com/us/lnacademic; Anon., "UNOS Statement on HR 1180," PR Newswire, 17 December 1999, http://www.lexisnexis.com/us/lnacademic; Anon., "Shalala, Congress Agree on Organ Transplant Plan," Reuters Health eLine News, 12 November 1999, http://www.lexisnexis.com/us/lnacademic; Jacoby, "Organ Transplants"; Anon., "HHS Amends Organ Transplant Rules," Reuters Health eLine News, 18 October 1999, http://www.lexisnexis.com/us/lnacademic; Anon., "HHS Amends Donor Rules in Face of Criticism," *Washington Post*, 19 October 1999, A7; Anon., "Organs: Online UNOS Database Provides Limited Info," American Health Line, 9 September 1999, http://www.lexisnexis.com/us/lnacademic.

86. *Organ Procurement and Transplantation Network Amendments of 1999*, Hearing before the Subcommittee on Health and Environment of the Committee on Commerce, 106th Congress, 1st session, on H.R. 2148, 22 September 1999; Anon., "Organ Donation: Comt. Blocks White House Revisions," American Health Line, 14 October 1999, http://www.lexisnexis.com/us/lnacademic.

87. Ted Kennedy quoted in Anon., "Organ Allocation: Senate Committee Passes Compromise," American Health Line, 13 April 2000, http://www.lexisnexis.com/us/lnacademic. See also Laura Meckler, "Transplant Fight Shifts to Senate," Associated Press Online, 5 April 2000, http://www.lexisnexis.com/us/lnacademic; Eilperin, "House Acts to Reject Rules on Transplants"; "Organ Transplant: House and Senate Negotiations Fail," American Health Line, 19 October 2000, http://www.lexisnexis.com/us/lnacademic.

meant that the HHS regulations took effect on 16 March 2000. HHS solidified its victory by putting compliance with the regulations in the new UNOS contract.[88]

Though the bruising battle over HHS regulations took a toll, it resulted in positive outcomes. UNOS suffered blows to its reputation, and more significantly, the intense dispute over the regulations had exposed divisions and irritated wounds in the transplant community.[89] However, issuance of the federal regulations gave UNOS the authority it wanted and needed to make its policies mandatory rather than voluntary, which *all parties* had agreed was necessary. The regulations declared that the criteria for listing and prioritizing patients on the waiting list must be consistent everywhere in the nation and based on medical factors. As required, UNOS then developed policies that were far more complex and objective. Based on algorithms related to medical urgency and likelihood of survival on the waiting list, the new policies decreased the number of patients who died while waiting for transplant while still maintaining a very high level of success. UNOS leaders agreed it was an improvement.[90] More effective and more just (by eliminating the wiggle room in the old system), the new policies increased trust

88. Laura Meckler, "New Contract for Transplant Network May Settle Fight," Associated Press newswire, 29 September 2000, http://www.lexisnexis.com/us/lnacademic; Walter Graham, "Statement of Walter Graham, UNOS Executive Director, On HHS Selection of an Alternative Scientific Registry Contractor," PR Newswire, 28 September 2000, http://www.lexisnexis.com/us/lnacademic; Karen Pallarito, "UNOS Retains Control of Transplant Network with New Multimillion-dollar Contract," Reuters Health Medical News, 29 September 2000, http://www.lexisnexis.com/us/lnacademic; Anon., "Organ Transplant: House and Senate Negotiations Fail," American Health Line, 19 October 2000, http://www.lexisnexis.com/us/lnacademic.

89. UNOS lost one of the contracts it had with the government, the one which gave it responsibility as the scientific registry that analyzed all of the nation's data on all transplant recipients. Laura Meckler, "New Contract for Transplant Network May Settle Fight." The Institute of Medicine declared, "The polemical nature of the debate has increased public skepticism about the integrity and fairness of the system." Quoted in *Organ Procurement and Transplantation*, 2.

90. Walter Graham, "The 'Yin and Yang' of UNOS," *UNOS Update*, July–August 2008, 8. UNOS, "Liver Allocation Policy Refinements Approved by OPTN/UNOS Board," UNOS press release, PR Newswire, 15 November 2001, http://www.lexisnexis.com/us/lnacademic; Anon., "Organ Transplants: UNOS OKs Need-Based Distribution Plan," American Health Line, 16 November 2001, http://www.lexisnexis.com/us/lnacademic; "Patient Advocates Urge Transplant Network to Comply with Federal Rule Requiring Fair Organ Allocation Policy," U.S. Newswire, 15 November 2001, http://www.lexisnexis.com/us/lnacademic. In response to the regulations, UNOS also dramatically revised its lung allocation system, the initial results of which seem equally positive. Benjamin Kozower, et al., "The Impact of the Lung

in the system. "Blood tests don't lie," noted one surgeon.[91] Outside pressure from HHS, then, forced UNOS to transcend the competing claims and squabbles that had hampered the organization. Moreover, HHS managed to spur these positive changes while still leaving development of the specific allocation policies in the hands of the medical professionals (along with representatives of patients and donors) in UNOS. Thus the fears expressed by D'Alessandro did not come to fruition. HHS merely set parameters to insure greater fairness and achieved that without "taking over" organ transplantation. Ironically, despite the complaints, the federal government's interference ultimately led to more consistency, legitimacy, and strength for UNOS.

Looking back, it is clear that in the three key periods of politicization of organ transplants in 1968, the mid-1980s, and the late 1990s, some in the U.S. transplant medical community had resisted while others had welcomed the involvement of the federal government. It is natural for any profession to want to develop and enforce its own ethics and standards, so not surprisingly, some surgeons in particular fiercely defended their area of expertise. Others simply saw no need for outside assistance or opposed the specific HHS regulations. In contrast, others eagerly embraced the benefits that accrued from government assistance, such as legal clarification of donor status, grants to subsidize organ procurement, Medicare/Medicaid coverage of transplant surgeries and immunosuppressant drugs, standards for organ procurement agencies, and establishment of a national organ transplant network. In the 1990s, others simply agreed with the content of HHS regulations. Some pondered the transplant community's partnership with the government and thought it made sense. Despite warnings from the Reagan administration and questioning from Congress, however, not everyone who supported the laws of the mid-1980s appreciated the wider implications of government support. They did not always consider that oversight accompanied the benefits or what "oversight" might involve. "Miss Shalala's department has oversight responsibility for

Allocation Score on Short-term Transplantation Outcomes," *J. Thorac. Cardiovas. Surg.*, 2008, *135*, 166–171.

91. Anon., "Organs: UNOS Approves New Liver Distribution Plan," American Health Line newswire, November 17, 2000, http://www.lexisnexis.com/us/lnacademic.

this process," acknowledged surgeon D'Alessandro, "but no one ever dreamed that HHS would ever seek to exercise direct policy-making authority."[92]

Despite disagreement over it, the federal government's involvement in organ transplantation made sense. Unlike most medical treatments, public support and outside help were crucial. There could be no transplantation without the gift of scarce organs by the general public, and history proved that public support was not automatic. The early heart surgeries suggested that if the profession did not monitor itself, there could be fallout. Years after the heart transplant craze in 1967–68, surgeons admitted that too many of them had performed heart transplants and done so for the wrong reasons. "People were performing transplants who had no idea what they were doing," declared Norm Shumway. "It wrecked the field for a good five years."[93] Indeed, kidney transplant pioneer Joseph E. Murray referred to the period from 1968 to 1970 as "transplantation's darkest hour."[94] Public scrutiny, though, caused heart transplant leaders to take a hard look at their practices, set strict criteria for future transplants, and communicate more clearly with the public, which was best for all concerned.[95] The issue of brain death also illustrated the necessity of achieving public understanding as well as a legal infrastructure for the procurement of donor organs. On issues like recognition of brain death criteria and the outlawing of profit from organs, it made sense for there to be national policies rather than state-by-state variations. In addition, because organ transplantation relies upon quick matching and transportation of organs to the appropriate people, it is crucial for there to be

92. D'Alessandro, "Hostile organ takeover."

93. Adrian Kantrowitz admitted, "The world's outstanding cardiovascular surgeons underestimated the problems to be solved before the procedure could become routine." Kantrowitz, "America's First Human Heart Transplantation: The Concept, the Planning, and the Furor," *ASAIO Journal*, 1998, *44*, 251. See also, Anon., "Saving New Hearts," *Newsweek*, 7 January 1980, 39, and McRae, *Every Second Counts*, 272. Shumway is quoted in the *Newsweek* article.

94. Joseph E. Murray, "Human Organ Transplantation: Background and Consequences," *Science*, 1992, *256*, 1414.

95. Statement of the Board of Medicine of the National Academy of Science, *Science News*, 9 March 1968, 233; Statement of the Judicial Council of the AMA, quoted in George W. Miller, *Moral and Ethical Implications of Human Organ Transplants* (Springfield, Illinois: Thomas, 1971), 93–94; Herrman L. Blumgart, "The Medical Framework for Viewing the Problem of Human Experimentation," *Daedalus, Proceedings of the American Academy of Arts and Sciences*, 1969, *98*, 248–74.

cooperation, communication, and sharing between hospitals and across state lines. A fragmented and competitive system did not serve patients well, and in the mid-1980s it became clear that national coordination was essential to achieving both efficiency and fairness. Again the government seemed to be the logical party to spur such coordination, which it did in the National Organ Transplant Act. Transplant surgeons recognized that Congress had not only improved public awareness of and access to transplantation, but its legislation had served as an "extremely important catalyst in bringing together the relevant interests to move transplantation forward."[96]

Not surprisingly, the allocation of organs had become especially politicized. Different plans necessarily benefit different patients, such as the chronically ill, the most acutely ill, those with particular diseases, or those in different locations. Reasonable, caring, and dedicated people could differ over how to resolve the medical and ethical dilemmas caused by the organ shortage, and the stakes were high. "A lot of things we do involve peoples' lives," said an HHS official, "but changing the system of distributing organs alters who lives and who dies, or how long you live and when you die."[97] "[R]eally the wisdom of Solomon is called for here," agreed one Congressman.[98] Achieving the elusive goal of equity required not just quality data and medical expertise, but vision, commitment to a fair process, the desire to build consensus, civility, and a special sensitivity, all of which disappeared at times during the battle. Surgeons and transplant centers fought hard to save their patients, as they should have, but also displayed concern for their self-interest, power, or profits. Even worries about losing their "fair share" of organs suggested a sense of ownership and an assumption that organs belonged to a certain group of people or a particular locale. In the face of established interests, UNOS had difficulty building consensus on allocation policies.[99] In appeasing the forces who

96. They cited the House subcommittee on Health and Welfare, in particular, for stimulating "greater communication and cooperation among the professionals involved in organ transplantation." Statement of the American Society of Transplant Surgeons, Robert J. Corry, president, *National Organ Transplants*, 38–40, 38.

97. Stolberg, "Patients' Lives on the Line."

98. Bob Inglis testimony, *Putting Patients First*, 67.

99. Mongoven, "Federal Hearings on Liver Transplant Allocation and Donation."

wanted to keep allocation decisions local, UNOS lost sight of the sentiment expressed in the national task force's report that organs are a *national resource* to be carefully nurtured. HHS appropriately stepped in and provided the national perspective that had been missing, and acted—with moderation—to insure fairness for patients all over the country.

The federal government, subject as it is to political pressures, cannot necessarily be counted on to be an efficient overseer or an objective arbiter; neither, however, should it be assumed to be a dangerous or dictatorial intruder. So far in the case of organ transplantation it has tended to be a helpful trustee. It helped provide a legal basis for obtaining organs from brain-dead donors and has taken other actions supporting organ donation. By funding organ procurement and transplants, it provided legitimacy for new procedures that influenced private insurers and made it possible for thousands of patients to receive a second chance at life. It pushed the field to become nationally coordinated faster than it could have without external assistance, which meant more efficiency and the saving of more lives. It pushed UNOS, transplant centers, and organ procurement organizations to be more accountable, share data that empowers patients, be more self-conscious about the medical and ethical bases for its decisions, and listen to voices other than those of surgeons.[100] HHS regulations resulted in greater equity and increased trust in the allocation system, and did so while still insuring that the medical experts and affected parties crafted the specific rules by which they must abide. The transplant medical community now assumes that the public has a legitimate and important role in organ transplantation.[101]

From the failed early heart transplants, the establishment of brain death criteria, benefits from legislation in the mid-1980s, and controversy over organ allocation, the transplant medical community appears to have learned that the federal government has the potential to be a helpful partner. After the nasty battle of the late 1990s firmly established the government's oversight, transplanters seem to have moved on and are working toward a productive relationship. Indeed, recently leaders in the American Society of Transplant

100. *Putting Patients First*, 94.
101. *Putting Patients First*, 138; Prottas, *The Most Useful Gift*, 153.

Surgeons said they had "played a major role" in guiding the development of new federal regulations for transplant centers being considered in 2008. Though still not entirely pleased with those regulations, they characterized their work with the federal bureaucracy as "fruitful dialogue" and said the government, transplant caregivers, and patients were "all on the same page." UNOS' website declares that before policy proposals are submitted to HHS for review, "public input . . . is an essential part of the policy development process."[102] Long gone are the days when transplant surgeons could arrogantly assert their expertise and expect the public would not question them. Today's transplant practitioners would probably agree that Norm Shumway was right when he said, "[F]ortunately or unfortunately, [transplantation] cannot be done without public notice and public support," and that Senator Mondale was prescient when he said in 1968, "Those who really believe in advancing medical knowledge have far more to gain from public understanding than public ignorance."[103]

102. M.M. Abecassis, et al., "Transplant Center Regulations—A Mixed Blessing? An ASTS Council Viewpoint," *Am J. Transplant*, 2008, *8*, 2496–502; The Organ Procurement and Transplantation Network, Policies, http://www.optn.org/policiesAndBylaws/publicComment/, accessed 15 December 2008.

103. Comments by Walter Mondale, *National Commission on Health Science and Society*, 13; Norman Shumway quoted in *National Commission on Health Science and Society*, 149.

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