OPEN

Optimal and Equitable Allocation of Donor Hearts: Which Principles Are We Translating Into Practices?

Maria Frigerio, MD[1]

Selection of heart transplantation (HTx) candidates should take into account the need and the probability of success of transplantation. The output of a process that is focused on the careful evaluation of individuals, per international experts' recommendations,[1] is by the end, the building of a group, because each patient that is deemed eligible and deserving of an HTx is added to the others on a transplant waitlist. Conversely, organ allocation criteria are defined within each country, considering ethical principles and societal values besides strictly medical considerations.[2,3] The output of this process is the assignment of single hearts to single patients. Balancing the best interests of individual with a community's interests may be a difficult task when the gap between demand and supply is wide, as in the case with HTx. Local heart allocation per the "first come, first serve" rule has been progressively abandoned in favor of broader organ sharing and urgency-based prioritization to reduce inequalities and meet the patient needs (Table 1). The increasing proportion of patients undergoing HTx in critical conditions could limit posttransplant survival without reducing the waitlist mortality, ultimately worsening overall patient outcomes.[4]

In this issue, Cantrelle et al[5] analyzed 1-year mortality in patients listed for HTx in France from 2010 to 2013, with the aim to distinguish patient-related predictors and the influence of allocation policy. Of the 2053 candidates, two thirds underwent HTx within 1 year, and a quarter died while waiting for transplantation, with half of them passing away in the first year. Independent predictors for death or delisting due to worsening conditions within 1 year were as follows: age, >55 years, New York Heart Association class IV, being hospitalized and/or on inotropes, high levels of natriuretic peptides, pulmonary hypertension, and renal and/or liver dysfunction. These parameters were consistent with those included in a multivariable score obtained by the same authors from 2010 to 2014 candidates, but not identical.[6] Zero blood type and body mass index greater than 30 were associated with lower access to HTx because donors with these characteristics were used for other candidates in high-urgency status. Considering HTx as a competing event, zero blood type and obesity also emerged as risk factors for dying on the waitlist. Conversely, prioritization of candidates requiring inotropes or temporary mechanical circulatory support (MCS) resulted in similar or even lower than average 1-year waitlist mortality. Lower access to transplantation did not impact 1-year survival of candidates with long-term MCS (mostly left ventricular assist devices [LVAD]), whose proper priority level beyond 1 year was not analyzed. In the authors' opinion, prioritization rules miss the declared scope of minimizing mortality on the waitlist. Moreover, they modify natural risk of death, but do not correct all risk factors in the right proportion to favor equitable access to HTx and may contribute to creating disparities.

The article by Cantrelle et al analyzes a country-specific condition, offering important warnings and a methodological approach rather than ready-made solutions to the ongoing debate about heart allocation.[2,4-9] Where do we go from there? The main questions can be summarized as follows:

(1) Should imminent death remain the driver for prioritization?
(2) Should expected posttransplant outcome be factored into allocation algorithm?
(3) Would an allocation score work better?

Various scores have been published in the recent years to estimate the risk of death on the waitlist and/or the early probability of survival and life expectancy after transplantation, either excluding or including donor-related parameters.[8,10-12] The set of variables and endpoints were chosen and analyzed per the intended scope that is to verify and improve the performance of allocation algorithms based on the urgency of need and/or evaluate the accuracy of new models based on the estimate of the net transplant benefit.

Received 23 May 2017. Revision requested 21 June 2017.

Accepted 21 June 2017.

[1] 2nd Section of Cardiology—Heart Failure and Transplantation, De Gasperis CardioCenter, Niguarda Hospital, Milan, Italy.

The author declares no funding or conflicts of interest.

Correspondence: Maria Frigerio, MD, De Gasperis CardioCenter, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy. (maria.frigerio@ospedaleniguarda.it).

ISSN: 2373-8731

Transplantation Direct 2017;3: e197; doi: 10.1097/TXD.0000000000000712. Published online 18 July, 2017.

TABLE 1.

Conditions commonly considered for organ allocation and/or prioritization of heart transplant candidates

Categories	Conditions	Details
Blood type	Compatible	Allowed in high urgency/urgency conditions, with or without limitations, with or without priority over other consideration
Therapy	IV inotropes	–Excluding outpatients
		–Excluding low-dose dopamine
		–Multiple (vs single)
		–High (vs low) dosage
		–May require also hemodynamic monitoring
		–Not valid for high-urgency everywhere
	Ventilator	–Excluding noninvasive ventilation
	Temporary MCS	–IABP (not accepted everywhere as single criteria)
		–ECMO
		–Impella
		–Other
	LVAD	–High-urgency only if complicated
		–High-urgency in the absence of major complications for a limited period of time per year
	Other long-term MCS (TAH, BVAD)	–Always or only if complicated
Time	–On urgent/high-urgent status	–For priority when level of urgency is equal
	–Limitations	–Priority for urgency/high-urgency status may be limited to days/week, and may allow or not resubmission
Placement	Hospital (vs home)	–ICU (vs other)
	Distance from donor's hospital	–Different criteria for matching distance and recipient urgency among countries
Other	Pediatric age	–vs adult candidates when competing for the same donor (not valid everywhere)
	Refractory arrhythmias	–Requiring hospitalization
	Sensitization	–With hemodynamic compromise
		–May allow priority for compatible donors
		–Not valid everywhere
Exceptions	Other conditions at high-risk per Htx Center	–May require validation by independent experts/board of experts

Although sharing many criteria, final allocation models may be very different.

BVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenator; IABP, intraaortic balloon pump; ICU, intensive care unit; NIV, noninvasive ventilation; TAH, total artificial heart.

Whatever their accuracy in cohorts, multiparametric scores may not be the proper tool for supporting critical decisions in individuals, being influenced by the case-mix and unable to intercept high-risk but rare conditions or different clusters of risk factors.[13] The US Committee for heart allocation expressed concerns regarding the capability of any score to fit the heterogeneity of HTx candidates and to adapt to changes in risk profile that may derive from innovations, for example, in device therapy. Thus, the committee opted for reviewing the waitlist mortality and posttransplant survival in categories qualifying for high priority and in presumably disadvantaged subgroups (eg, restrictive cardiomyopathies or congenital heart disease, in which available therapies, including MCS, are less useful), to redesign the sequence of allocation per contemporary risk profiles.[9,14] With the new system, effective in the United States since April, 2017, the areas for organ sharing are wider than with the previous system, and the levels of priority have been detailed and reclassified.[15] The system remains essentially based on the urgency of need, which remains defined qualitatively by ongoing therapies, with possibly unnecessary escalation of supports to reach higher priority status.[4,16]

In France and in Italy, after a substantial increase in the proportion of urgency or high-urgency transplantations, 1-year post-HTx survival went below 80%.[17,18] The same did not happen in the United States, possibly due to lower donor age, differences in defining urgency (eg, patients with uncomplicated LVAD), and higher donor availability, implying better odds to get HTx before dying or deteriorating with significant increase of transplant-related risk. In 2015, the number of HTx per million people (pmp) was 8.8 in the United States, 7.4 in France, and 4.1 in Italy.[19] The perceived relevance of estimated posttransplant survival for allocation may differ per local HTx numbers. Not surprisingly, there is much interest in the Eurotransplant area, where high-urgency HTx exceeded 50% (>80% in Germany), and average number of HTx pmp was 4.5 (3.5 in Germany) in 2015.[19,20]

The declared goal of HTx is to maximize patient survival gain, or transplant benefit, that is, the difference between survival with and without transplantation. When looking at cohorts with a wide range of estimated survival without transplantation, the differences in expected transplant benefit depend mostly on the risk of dying and the imminence of death on the waitlist. Conversely, expected transplant benefit differs depending mostly on estimated posttransplant survival among patients whose life expectancy, without HTx, is invariably and uniformly—even if not equally—very short (Table 2). Nevertheless, there will be reluctance in denying priority to a patient with the shortest life expectancy (eg, on extracorporeal membrane oxygenator) in favor of a less critical candidate, despite their higher estimated transplant benefit. We need to improve the accuracy of prediction of

TABLE 2.

Urgent heart transplant candidates: 3 scenarios

	Patient 1	Patient 2	Patient 3
Sex, age (y)	Male, 38	Male, 16	Male, 63
Body surface area (m^2)	1.9	1.7	1.65
Blood type	Zero	A	A
Social status	Manager of a small shop; living with his wife and 2 kids	Student; living with his parents (teachers) and 2 siblings	Retired, formerly metal worker; living with his wife
Adherence to therapy	Excellent	Good	Unknown
Heart failure etiology	Cardiomyopathy	Cardiomyopathy	Ischemic
CV risk factors	None	None	Smoking, diabetes
Comorbidities	None	Becker dystrophy	Type 2 diabetes
Medical history	Severe to refractory HF, LVAD (Intermacs 3 + PH, normalized)	Severe to refractory HF, low-output state	Acute STEMI, delayed access to hospital, shock, failed rescue PCI, IABP + ventilator
Place and status	Hospital ward—fully mobilized—deep LVAD-related infection, mild renal dysfunction	Hospital ward—mostly in bed, continuous IV milrinone, dopamine, furosemide—fluctuating liver function	ICU ➔ ECMO, ventilator, vasopressors, SNP, furosemide—moderate renal dysfunction, mild liver dysfunction
Time on the WL	4 y (on LVAD)	2 months	0 (just listed)
Reason for urgency	LVAD, complicated	Inotrope-dependent	Short-term MCS
Urgency status[a]	Emergency (national priority—mandatory)	Urgency (priority on agreement)	Emergency (national priority—mandatory)
Life expectancy	Weeks	Weeks to months	Days
Alternative/bridge procedures	None	Short-term MCS (no LVAD for RV dysfunction)	None (no LVAD for small LV, wall thinning, mural thrombus)
Probability of early post-HTx success	Average/less than average	Average	Less than average
– Same, 4 wk later[b]	Less than average	Average	N/A
Risk factors for early post-HTx complications	LVAD, infection: infection; bleeding	Dystrophy: delayed weaning from ventilator, slow functional recovery	Age, diabetes, smoking, ventilator, renal dysfunction: infection, MOF, other
Probability of long-term post-HTx survival	Average	Average/less than average	Less than average
Risk factors for late complications	None	Adolescent, dystrophy: inadequate adherence, reduced functional recovery	Age, diabetes, smoking, renal dysfunction: cancer, renal failure, CAV

[a] In Italy, inotropes do not qualify for high-urgency (=emergency) status, but only for anticipated allocation as per agreement between Centers.

[b] In the absence of new complications.

CV, cardiovascular; CAV, cardiac allograft vasculopathy; HF, heart failure; LV, Left ventricular; MCS, mechanical circulatory support; MOF, multi organ failure; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; RV, right ventricular; STEMI, ST-elevation myocardial Infarction; VAC, vacuum assisted; WL, waitlist.

posttransplant survival to be confident in making it part of the allocation process. Given the growing proportion of patients awaiting and getting HTx in critical conditions, it is important to discriminate high-risk, but "reasonable," from "futile" transplantations. To do so, the type and level of therapies should not be entered in the model, although they could be useful to define specific subgroups with distinct prognostic factors.[5,10,11]

We must realize that no choice could satisfy all the principles we value.[3,7] For example, in the clinical scenarios summarized in Table 2, we could choose to save the patient that is going to die first (patient 3). Or we may maximize transplant benefit, early by choosing patient 2, or in the long term by choosing patient 1. Or we may decide to follow the "children first" rule (patient 2), as human beings generally feel to do when people needing rescue exceed the number of those that ultimately would be saved.

REFERENCES

1. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35:1–23.
2. Stehlik J, Stevenson LW, Edwards LB, et al. Organ allocation around the world: insights from the ISHLT International Registry for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2014;33:975–984.
3. Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. *Lancet*. 2009;373:423–431.
4. Smits JM, Samuel U, Laufer G. Bridging the gap in heart transplantation. *Curr Opin Organ Transplant*. 2017;22:221–224.
5. Cantrelle C, Legeai C, Latouche A, et al. Access to heart transplantation: a proper analysis of the competing risks of death and transplantation is required to optimize graft allocation. 2017. *Transplantation Direct* 2017; 3:e198; doi: 10.1097/TXD.0000000000000711.
6. Jasseron C, Legeai C, Jacquelinet C, et al. Prediction of waitlist mortality in adult heart transplant candidates: the candidate risk score. *Transplantation*. 2017.
7. Stevenson LW. Crisis awaiting heart transplantation: sinking the lifeboat. *JAMA Intern Med*. 2015;175:1406–1409.
8. Dorent R, Epailly E, Sebbag L. The effect of graft allocation system on outcomes in heart transplantation in France: has the time come to take calculated survival benefit into account? *J Heart Lung Transplant*. 2011;30:1299–1300.
9. Meyer DM, Rogers JG, Edwards LB, et al. The future direction of the adult heart allocation system in the United States. *Am J Transplant*. 2015;15:44–54.
10. Weiss ES, Allen JG, Arnaoutakis GJ, et al. Creation of a quantitative recipient risk index for mortality prediction after cardiac transplantation (IMPACT). *Ann Thorac Surg*. 2011;92:914–921.
11. Smits JM, de Vries E, De Pauw M, et al. Is it time for a cardiac allocation score? First results from the Eurotransplant pilot study on a survival benefit-based heart allocation. *J Heart Lung Transplant*. 2013;32:873–880.

12. Nilsson J, Ohlsson M, Höglund P, et al. The international heart transplant survival algorithm (IHTSA): a new model to improve organ sharing and survival. *PLoS One*. 2015;10:e0118644.
13. Stevenson LW, Davis RB. Model building as an educational hobby. *Circ Heart Fail*. 2016;9.
14. Kobashigawa JA, Johnson M, Rogers J, et al. Meeting report: report from a Forum on US Heart Allocation Policy. *Am J Transplant*. 2015; 15:55–63.
15. OPTN- Organ Procurement and Transplantation Network. Policy 6: allocation of hearts and heart-lungs. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_06. Updated June 1, 2017. Accessed May 20, 2017.
16. Stevenson LW, Kormos RL, Young JB, et al. Major advantages and critical challenge for the proposed United States heart allocation system. *J Heart Lung Transplant*. 2016;35:547–549.
17. Le rapport médical et scientifique de l'Agence de la biomédecine 2015. Le rapport médical et scientifique du prélèvement et de la greffe en France. Greffe cardiaque. https://www.agence-biomedecine.fr/annexes/bilan2015/donnees/organes/03-coeur/pdf/coeur.pdf. Accessed May 20, 2017.
18. Italian Ministry of Health, Centro Nazionale Trapianti. Valutazione di qualità dell'attività del trapianto dicuore 2000–2014. http://www.trapianti.salute.gov.it/imgs/C_17_pubblicazioni_2595_allegato.pdf. Published November 10, 2017. Accessed May 20, 2017.
19. European Directorate for the Quality of Medicines. Newsletter Transplant: international figures on donation and transplantation 2015. https://www.edqm.eu/sites/default/files/newsletter_transplant_volume_21_september_2016.pdf. Published 2016. Accessed May 18, 2017.
20. Nashan B, Hugo C, Strassburg CP, et al. Transplantation in Germany. *Transplantation*. 2017;101:213–218.