

How to obtain and maintain favorable results after heart transplantation: keys to success?

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We compared survival in our heart recipients with survival rates reported by the International Society of Heart and Lung Transplantation (ISHLT) Registry. As recipient and donor characteristics are changing over time, we studied four different eras. In order to differentiate between short- and long-term survival, we analyzed both overall survival and survival at one year. Obviously, this exercise is only relevant when baseline donor and recipient characteristics are comparable, as these differences may affect the outcome in opposite directions. To overcome this potential bias as much as possible, we calculated the Index for Mortality Prediction After Cardiac Transplantation (IMPACT)-scores and the Donor Risk Index (DRI). Looking to our results, we found that our DRIs in the different eras are almost equal to those obtained from the United Network for Organ Sharing database in the very same eras. Our IMPACT-scores, on the other hand, seem higher than those reported by ISHLT. Survival after transplantation and conditional on 1-year survival was higher than the outcome reported by the ISHLT Registry. As our operation technique and post-transplant immunosuppressive schedule did not differ from most centers, we speculated on potential factors that might contribute to our positive results. Patient selection and a relatively short waiting time are important contributors to the overall survival benefit. Our centralized follow-up may also have played an important role. Finally, the indefinite compulsory health insurance coverage in our country and easy access to different screening programs might also have influenced our outcome in a positive way. We are well aware that with challenges like donor organ shortage, more and more patients on mechanical circulatory support (MCS) will affect outcomes in the future.

Keywords: Heart transplantation; predictors; survival



Submitted Sep 11, 2017. Accepted for publication Nov 25, 2017.

doi: 10.21037/acs.2017.12.03

View this article at: <http://dx.doi.org/10.21037/acs.2017.12.03>

Introduction

Comparing the results of hip surgery performed by one surgeon with the results of his colleague working in the hospital next door, is asking for trouble. Comparing results of one heart transplant center with those of another or, even more challenging, those of a registry, is at least as daunting.

Nevertheless, it is worthwhile to critically review one's results and compare them with those of peers. In case they differ manifestly, one has to speculate on why this is the case considering the importance our society currently attributes to cost effectiveness and transparency. Of course, this exercise only makes sense when you are comparing

apples with apples. You should first examine that you are transplanting the same types of patients and that you are using the same types of donors.

We compared our short- and long-term survival data with those of the ISHLT registry. To do so, we also compared our recipient and donor risk profiles with those of the UNOS database. Finally, we speculated on contributing factors that affected our outcome.

Patients and methods

We compared baseline characteristics of heart recipients

transplanted in the University hospital of Leuven (Leuven) between September 1987 and December 2015, with those of recipients reported to the International Society of Heart and Lung Transplantation (ISHLT) and transplanted in the same period. As baseline characteristics changed over time, we analyzed four different eras: 1987–1991, 1992–2001, 2002–2008 and 2009–2015. Data were derived from our own database and from the 2009 (1992–2001 and 2002–2008) and 2016 (2009–2015) ISHLT Registries (1,2). In the Leuven cohort, ANOVA was used to compare differences between groups. Tests for trend over time were performed with the actual year of transplantation, using a Spearman correlation for continuous variables, a Kruskal Wallis test for categorical data and a Cochran-Armitage trend test for ordinal or binary variables. Baseline characteristics of the Leuven cohort and the ISHLT Registries were compared with a two-sided z-test or a Chi-Square test as appropriate. As we had no access to sufficient ISHLT data for the era between 1987 and 1991, comparisons are only made for the 3 last eras.

To estimate the risk profile of our donors, we calculated the average Donor Risk Index (DRI) for transplantations performed between 1-2-1996 and 01-08-2010 and compared them with the DRI derived from the independently validated United Network for Organ Sharing (UNOS) database of donors (3). The DRI incorporates 4 donor and procedure variables (donor age and blood urea nitrogen ratio, race mismatch and ischemic time) and predicts 30-day, 1- and 5-year post-transplant mortality (3). For the recipient risk profile, we measured the individual Index for Mortality Prediction After Cardiac Transplantation (IMPACT)-scores in corresponding eras. This allowed us to match these data with two published cohorts namely one derived from a UNOS database from which the IMPACT-score was originally derived and validated and one from an ISHLT database that validated the United-States derived IMPACT-score using international data (4,5). The IMPACT score relies on pre-operative recipient characteristics and predicts short- and long-term survival after heart transplantation (4).

As we only had access to individual data from our own database, a 2-sided Z-test was used to compare our DRI and IMPACT-scores with those of the registries. The individual characteristics used to calculate the DRI and the IMPACT-score, were compared between the Leuven and the other cohorts with a 2-sided Z-test and a Chi-Square test, when available in the original publications.

In the survival analyses, recipients were censored when

re-transplanted. We compared the Leuven and ISHLT results for the total cohort and for recipients transplanted in the 4 different eras. To better distinguish between early and late differences in survival, we repeated the analyses for survival at one year. A Log-rank test was used to compare differences in survival between the different era's in the Leuven group.

Differences in survival between the Leuven and ISHLT cohorts were compared with a Chi-Square test for each individual postoperative year. Statistical analyses are performed with SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

The Leuven heart transplant program started in September 1987. Until the end of 2015, 648 transplantations were performed in 615 patients, resulting in an average annual transplantation rate of 23 (range, 15–33). Thirty recipients received a second donor heart and one patient was transplanted three times. Ten patients were re-transplanted for primary graft failure within the first post-operative week. The other re-transplantations were performed because of acute (n=7) or chronic (n=14) late graft failure after 9 (range, 0.5–22) years on average. Three recipients underwent a combined heart-liver and 23 a heart-kidney transplantation. No patient was lost to follow-up.

The average recipient age at transplantation was 49 ± 14 (range, 3–70) years and 126 (19%) were women. The most frequent indications for transplantation were ischemic heart disease (42%), cardiomyopathy (40%, mainly dilated cardiomyopathy), valvular (5%) and congenital (5%) heart disease.

Patients were transplanted after 123 ± 115 days (range, 0–566 days) on the waiting list. Eleven percent were transplanted from the high urgency (HU) list and had to wait 11 ± 20 (range, 1–117) days.

The mean donor age was 34 ± 13 (range, 1–66) years and 70% of the donors were men.

Treatment and follow-up

Initially all transplantations were performed using the Shumway bi-atrial technique. Since 2009 this technique was converted to a bi-caval anastomosis. All recipients receive induction therapy with anti-thymocyte globulin (rATG). Maintenance immunosuppression changed over

time. Initially, patients were treated with cyclosporine A, azathioprine and steroids. Since 2000 tacrolimus became the standard calcineurin inhibitor (CNI), mycophenolate mofetil replaced azathioprine and most patients went off steroids after the first year. Everolimus is occasionally used in combination with a reduced dose of tacrolimus in patients with graft vasculopathy or with renal failure.

All recipients receive prophylaxis against pneumocystis jiroveci pneumonia for 6 months and CMV-negative recipients with a CMV-positive donor are treated with ganciclovir and anti-CMV globulins for 3 months. Statins are given unless contra-indicated. Antiplatelet agents are only initiated in case of new atherothrombotic events.

All follow-up is centralized to one center. Around 15 per protocol endomyocardial biopsies are performed in the first postoperative year or on indication, thereafter.

CNI through levels are checked monthly. Every 3 months, recipients have an out-patient visit and are seen by a specialized transplant nurse and a transplant cardiologist. At follow-up, they have a more extensive blood test, an electrocardiogram, an X-ray of the chest and a cardiac ultrasound. Every year there is a comprehensive check-up including a right heart catheterization. After 1, 2, 3, 5 years and every 5 years thereafter, or on clinical indication, a coronary angiography is performed. In case of medical problems, a 24/7 helpline is available. All major non-cardiac health problems are preferentially referred to treatment in our hospital.

Comparability of donors and recipients

Recipient and donor characteristics of the Leuven transplant program that affected short- and long-term post-transplant survival in different studies and registries are summarized in *Table 1*. Comparable data for heart recipients reported to the ISHLT are shown in the Supplementary (*Table S1*).

Over time similar changes are seen in the Leuven and ISHLT cohorts. For the recipients, there is a decrease in male preponderance and in patients with ischemic heart disease, and fewer recipients are hospitalized at the moment of transplantation. In both groups, the percentage of patients on mechanical circulatory support (MCS) increases rapidly. As for the donors, we see an increasing donor age and longer ischemic times (*Figure 1*). In the Leuven group, there is also an increase in waiting time (*Figure 1*).

Despite resemblances in trends, important differences remain between the Leuven and the ISHLT cohorts that might result in different transplant risks. Due to insufficient

data for the era between 1987 and 1991, comparisons are only made for the 3 last eras (*Table S1*).

Some factors might disproportionately increase the risk of the ISHLT group, for example, the higher proportion of hospitalized patients and patients on inotropes, or the use of an intra-aortic balloon pump (all eras). Furthermore, ISHLT recipients were older and had twice as much diabetes (2 most recent eras). The risk of our recipients increased due to older donor age (2 most recent eras) and longer ischemic times (second and third era). On top of that, we had more patients that underwent previous cardiac surgery, more re-transplantations and more patients with congenital heart disease (all eras) or valvular heart disease (second and third era). All these factors might negatively impact our results.

Obviously, these numbers only provide an indication of the expected risk and can by no means lead to the conclusion that we transplant higher risk recipients with higher risk donors. In order to better quantify our donor and recipient risk, we calculated our DRI and IMPACT-scores.

As shown in *Table 2*, the DRI of our group is almost numerically identical to the DRIs in the derivation and validation cohorts from the UNOS database. Most probably a slightly shorter ischemic time neutralized our manifestly higher donor age. As for the IMPACT-scores, no difference was found with those obtained from the UNOS database (*Table 3*). The IMPACT-score in the ISHLT publication was significantly lower, suggesting a lower risk profile of their recipients (*Table 4*). Behind the composite scores, we see again significant differences in contributing factors. The protective effect of our younger recipients with less diabetes might be leveled out by the fact that we have fewer patients with an idiopathic cardiomyopathy, more with congenital heart disease and more on mechanical ventilation, temporary circulatory support and late VAD's.

Survival

Survival of our recipients is compared with survival of all patients reported to the ISHLT registry for the entire cohort (*Figure 2A*) and for the recipients transplanted in 4 different eras (*Figure 2B*). Except for the follow-up beyond 14 years of recipients transplanted in the first era, our results are above the average of the Registry (*Tables S2-S7*). In *Figure 3A,B*, survival curves are shown conditional on survival to 1 year. The fact that the differences in

Table 1 Baseline characteristics: recipients and donors (Leuven)

Era	1997-1991 (n=100)	1992-2001 (n=222)	2002-2007 (n=141)	2009-2014 (n=179)	P value	P value (trend)
Rec. age (years)	51±12	51±13	47±16	47±16	NS	NS
Rec. male (%)	25 [25]	123 [20]	112 [79]	132 [74]	NS	0.05
Rec. weight (kg)	62±12	70±13	71±16	74±17	0.01	0.001
Rec. height (cm)	171±9	171±9	172±12	172±14	NS	NS
Rec. creatinine (mg/dL)	1.4±0.4	1.5±0.6	1.4±0.6	1.3±0.6	0.01	0.01
Rec. diabetes (%)	9 [9]	22 [10]	14 [10]	17 [10]	NS	NS
Rec. cardiac surgery (%)	31 [31]	96 [42]	76 [54]	119 [66]	0.001	0.0001
Rec. diagnosis (%)					0.01	0.0001
Ischemic CMP	52 [52]	104 [46]	53 [32]	61 [34]		
Idiopathic CMP	34 [34]	79 [39]	57 [41]	77 [44]		
Valvular CMP	7 [7]	13 [6]	9 [6]	3 [2]		
Re-transplantation	3 [3]	11 [5]	7 [5]	12 [7]		
Congenital	2 [2]	7 [4]	10 [7]	13 [7]		
Other	2 [2]	3 [1]	4 [3]	12 [7]		
Hospitalized (%)	36 [36]	61 [27]	39 [22]	40 [22]	NS	0.05
iv inotropes (%)	9 [9]	6 [3]	12 [9]	7 [4]	0.05	NS
Ventilator (%)	1 [1]	6 [3]	2 [1]	0 [0]	NS	NS
iABP (%)	1 [1]	0 [0]	0 [0]	0 [0]	NS	NS
ECMO/hemopump (%)	1 [1]	0 [0]	1 [1]	3 [2]	NS	0.05
LVAD (%)	2 [1]	15 [7]	33 [23]	71 [40]	0.001	0.0001
RVAD (%)	3 [3]	11 [5]	4 [3]	5 [3]	NS	NS
TA (%)	0	0	0	0		
Don. age (years)	27±9	33±12	36±14	39±14	0.001	0.0001
Don. weight (kg)	71±12	72±12	73±14	76±17	0.01	0.01
Don. height (cm)	176±10	174±10	174±12	174±15	NS	NS
Don. male (%)	76 [76]	157 [69]	96 [62]	121 [62]	NS	NS
Waiting time (days)	60±60	97±95	115±93	197±139	0.001	0.0001
Waiting time U (days)	NA	4±4	13±21	12±21	NS	NS
Ischemic time (hours)	2.2±0.7	2.6±0.7	3.0±0.7	3.2±0.7	0.001	0.0001
U LA mismatches (%)					0.05	NS
0-2	9 [9]	10 [4]	6 [4]	6 [3]		
3-4	46 [46]	71 [31]	49 [35]	60 [34]		
5-6	45 [45]	147 [65]	76 [61]	113 [63]		
Don. cause of death (%)					0.001	0.0001
Head trauma	73 [73]	135 [59]	71 [52]	77 [43]		
Stroke	23 [23]	67 [30]	42 [30]	73 [41]		
Other	4 [4]	25 [11]	17 [13]	29 [16]		
Male rec./fem. don. (%)	19 [19]	49 [21]	27 [19]	22 [12]	NS	NS
Fem. rec./male don. (%)	10 [10]	23 [10]	10 [7]	10 [6]	NS	NS

Continuous variables are shown as mean ± standard deviation and categorical variables as numbers and percentages. Rec., recipient; CMP, cardiomyopathy; iv, intravenous; iABP, intra-aortic balloon pump; U, high urgency (comparable to UNOS 1A); ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TA, total artificial heart; don., donor; U LA, human leukocyte antigen; fem., female; NS not significant.

survival remain significant in this analysis suggests that our better long-term survival is not merely due to a lower 1-year mortality (Table S3). Seemingly, we also succeeded in making a difference during the late follow-up.

Mortality

Two hundred and forty-four (40%) recipients died during follow-up until the end of 2016 (Table 5). Not surprisingly both cardiovascular causes and malignancies account for more than 1/3 of deaths. Malignancies, especially lung carcinomas, play an important role. Concerning cardiovascular causes of death, many recipients die suddenly. As graft vasculopathy had been demonstrated in many recipients before their sudden death, we believe that most of the sudden deaths were due to coronary artery disease. However late acute rejection cannot be excluded.

Limitations

Our study has several limitations. The most important being that it is impossible to prove that our baseline predicted risk doesn't differ from ISHLT. A case-control study matching for baseline characteristics was not feasible as we did not

have access to the individual recipient and donor data from the ISHLT Registry. For the same reason, we could not perform a Cox proportional hazard regression analysis, using center as an independent variable. Potentially, important risk factors such as waiting time could not be imputed as they were not available in the Registries, nor in the seminal papers on the DRI and IMPACT-scores. Finally, we used data from the voluntary ISHLT Registry and the mandatory UNOS-database. Both depend on center reporting accuracy and completeness.

Discussion

We showed that both our short- and long-term survival are above the average reported by ISHLT. Despite the many differences in baseline recipient and donor characteristics between our group and the ISHLT cohorts, the remarkable similarities between our IMPACT-score and DRI and those reported in the literature strengthen our assumption that the difference in survival is not merely due to a lower risk profile of our donors or recipients. As we use standard operative techniques and immunosuppressive schedules, other factors have to be involved. In the absence of randomized clinical trials, we can only speculate which might play a role.

We focus on four different time intervals: the pre-transplant period, the transplantation, the first year after transplantation and the long-term follow-up.

We are convinced that the importance of patient selection cannot be overestimated. The first hurdle in this process is to translate the indications and contra-indications, described in the guidelines, to the individual patient (6,7). As confidence may grow with experience and as several absolute contra-indications of the original guidelines have metamorphosed into relative contra-indications, there is an inherent risk of progressively raising the bar, finally transplanting recipients with an unacceptably

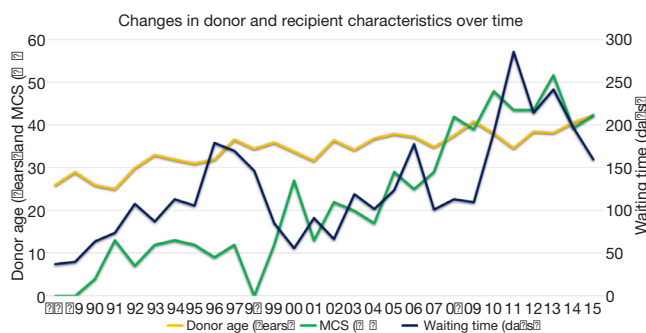


Figure 1 Changes in recipient and donor characteristics over time (Leuven).

Cohort	UNOS		Leuven (n=316)	P value	
	Derivation (n=17,722)	Validation (n=4,464)		Leuven vs. derivation	Leuven vs. validation
DRI-score	4.0±2.1	4.0±2.1	4.0±2.3	NS	NS
Donor age (years)	31.3±12.6	NA	36.0±13.7	0.0001	0
Ischemic time (min)	3.1±1.0	3.0±1.0	2.9±0.7	0.0001	0.0001

Continuous variables are shown as mean ± standard deviation and compared using a 2-sided t-test. NA, not available; NS, not significant.

Table 3 IMPACT-score: comparison between Leuven and UNOS databases (1-1997 to 12-2008)

Cohort	UNOS		Leuven (n=254)	P value	
	Derivation (n=17,079)	Validation (n=4,299)		Leuven vs. derivation	Leuven vs. validation
IMPACT-score	6.1±3.7	6.1±3.7	6.2±5.2	NS	NS
Recipient age (years)	52.1±11.9	51.7±12.1	49.7±14.9	0.05	0.05
Female sex (%)	4,04 (23.7)	1,019 (23.7)	55 (21.7)	NS	NS
HF etiologies					
Ischemic CMP	2,112 (47.1)	2,024 (47.1)	102 (42.5)	NS	NS
Idiopathic CMP	7,050 (42.1)	1,209 (42.1)	22 (34.7)	0.05	0.05
Congenital	400 (2.3)	106 (2.5)	13 (5.1)	0.005	0.01
Other	1,511 (2.2)	360 (2.4)	45 (17.7)	0.0001	0.0001
Diabetes mellitus (%)	3,612* (21.6)	257** (20.4)	25 (10.0)	0.0001	0.0001
Clearance (mL/min, Cockcroft)	66.3±25.2	66.0±25.6	64.1±27.1	NS	NS
Bilirubin (mg/dL)	1.24±2.11	1.31±2.27	1.06±1.67	NS	0.05
Mechanical ventilation (%)	456 (2.7)	102 (2.5)	21 (2.2)	0.0001	0.0001
temp. circulatory support (%)	240 (1.4)	46 (1.1)	23 (9.1)	0.0001	0.0001
iABP (%)	927 (5.4)	220 (5.1)	2 (3.1)	NS	NS
Ventricular assist devices (VAD)					
Early VAD (%)	2,292 (13.5)	526 (13.6)	11 (4.3)	0.0001	0.0001
Late VAD (M II included, %) (%)	374 (2.2)	27 (2.0)	12 (7.1)	0.0001	0.0001

Continuous variables are shown as mean ± standard deviation and compared using a 2-sided t-test; categorical variables are shown as numbers and percentages and compared using a Chi Squared Test; data available on *16,712; **4,200 recipients. HF, heart failure; CMP, cardiomyopathy; iABP, intra-aortic balloon pump; VAD, ventricular assist device; M II, HeartMate II[®]; NS, not significant.

high risk. For several of these patients, transplantation might indeed be the better option, but wasting an organ in an era of scarcity will automatically affect survival of other candidates on the waiting list. As the final decision to list can be cumbersome in particular patients, we always discuss high risk candidates on a formal monthly meeting (ad hoc, in case of urgency) with all transplant cardiologists, at least one cardiac surgeon and other (para-)medical specialists when applicable (psychologist, pediatrician, oncologist, pulmonologist, nephrologist, ...). Even when we realize that transplantation might be the better option for an individual patient, we will not list him, when the risk is considered unacceptably high. Using this strategy of consensus, a motivated and well-communicated negative advice is rarely questioned by the patient, his family or the referring physician.

When the patient is considered a potential candidate

by the transplant team, a second crucial step is to obtain informed consent. Explaining the operative risk and the first-year results is not sufficient. Time should be taken to describe the long-term results, including the limitations and potential complications, in order to protect the candidate recipient against unrealistic expectations. Although often sobering, we believe that the median survival should be mentioned. It is a simple figure that helps the patient and his family to realize that even a successful transplantation is no guarantee for a normal lifespan. Only after understanding the complex consequences of a heart transplantation, the candidate can make a motivated choice.

In an era where many patients are referred for screening, after they received a long-term MCS in critical circumstances, it becomes more challenging to maintain this conservative policy and many patients that would

Table 4 IMPACT-score: comparison between Leuven and ISHLT databases (1-2001 to 7-2010)

Cohort	ISHLT (n=29,242)	Leuven (n=205)	P value
IMPACT-score	5.1±3.6	6.1±4.2	0.005
Recipient age (years)	51.1±12.3	47.7±15.1	0.05
Female sex (%)	6,600 (22.6%)	47 (23.4%)	NS
HF etiologies			
Ischemic CMP	11,463 (39.2%)	75 (41.5%)	NS
Idiopathic CMP	12,709 (43.5%)	74 (36.1%)	0.05
Congenital	771 (2.7%)	11 (5.4%)	0.05
Other	4,279 (14.7%)	35 (17.7%)	NS
Diabetes mellitus (%)	4,163* (22.3%)	20 (10.0%)	0.0001
Clearance (mL/min, Cockcroft)	71.3±22.5	67.2±30.0	NS
Bilirubin (mg/dL)	1.34±2.56	1.05±1.77	NS
Mechanical ventilation (%)	491** (2.2%)	11 (5.4%)	0.05
temp. circulatory support (%)	225 (1.7%)	19 (9.3%)	0.0001
iABP (%)	1,091 (7.6%)	9 (4.3%)	NS
Ventricular assist devices (VADs)			
Early VAD	1,461 (10.9%)	12 (5.9%)	0.05
Late VAD	147 (1.0%)	1 (0.2%)	0.0001
M II	1,041 (6.9%)	11 (5.4%)	NS

Continuous variables are shown as mean ± standard deviation and compared using a 2-sided t-test; categorical variables are shown as numbers (percentages) and compared using a Chi Square test; data available on *17,700; **17,539; †13,443; ‡17,709; §15,137 recipients. HF, heart failure; CMP, cardiomyopathy; iABP, intra-aortic balloon pump; VAD, ventricular assist device; M II, heartMate II[®]; NS, not significant.

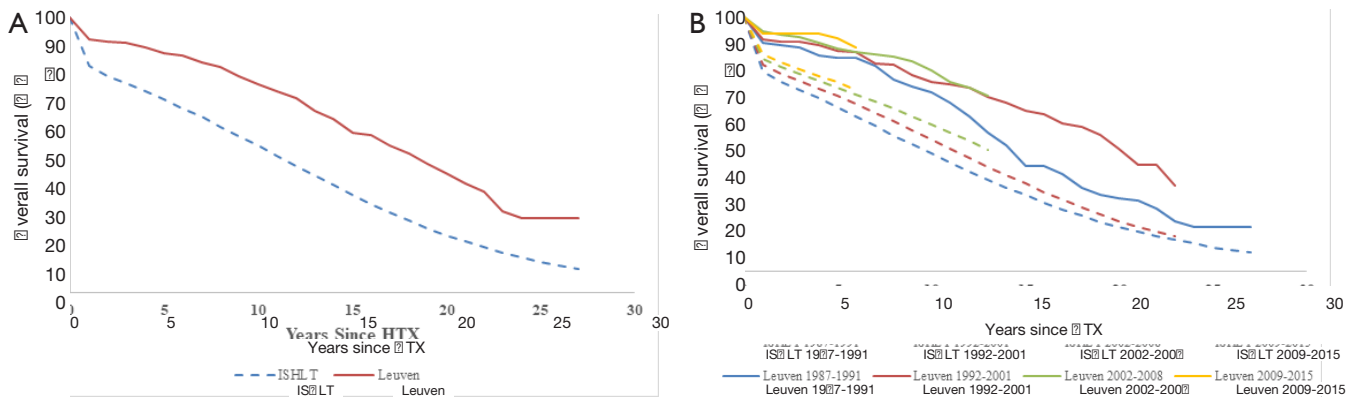


Figure 2 Survival of heart transplant recipients reported to ISHLT (from 1-1-1987 to 6-30-2015) and recipients transplanted in Leuven (from 9-1-1987 to 31-12-2015). (A) All recipients. Leuven (n=648) versus ISHLT (n=109,423) P<0.0001 up to 27 years; (B) recipients by era: 1987–1991 (n=100) and (n=17,173) P<0.05 up to 22 years; 1992–2001 (n=228) and (n=40,019) P<0.01 up to 23 years; 2002–2008 (n=141) and (n=26,044) P<0.001 up to 13 years; 2009–2015 (n=179) and (n=26,187) P<0.001 up to 6 years. Chi Squared tests for differences in survival between Leuven and ISHLT per year. Log-rank test for survival in different eras in Leuven P<0.01.

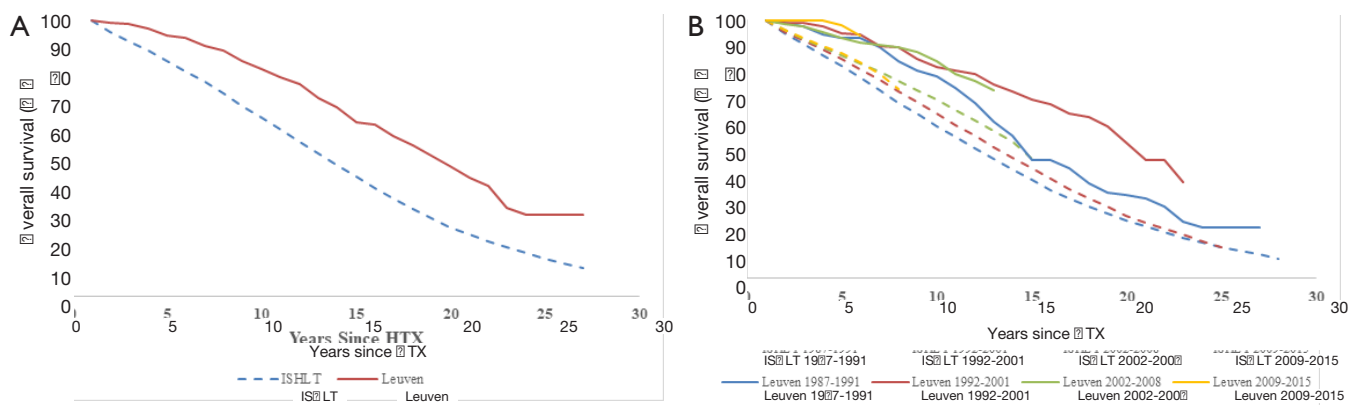


Figure 3 Conditional 1-year survival of heart recipients reported to ISHLT and recipients transplanted in Leuven. (A) All recipients. Leuven (n=584) versus ISHLT (n=86,551) Chi Squared test $P < 0.001$ up to 27 years; (B) recipients by era: 1987–1991 (n=87) and (n=13,149) $P < 0.05$ up to 14 years; 1992–2001 (n=201) and (n=31,493) $P < 0.01$ up to 23 years; 2002–2008 (n=132) and (n=21,130) $P < 0.05$ up to 13 years; 2009–2015 (n=164) and (n=20,779) $P < 0.05$ up to 6 years. Chi Squared tests for differences in survival between ISHLT and Leuven per year. Log-rank test for survival in different eras in Leuven $P < 0.01$. HTX, heart transplant; ISHLT, International Society for Heart and Lung Transplantation.

probably never have been listed without their MCS, now become candidates. As they were once considered suitable candidates for implanting a MCS, the threshold to list them for transplantation reduces. Unless the results of long-term MCS improve and destination therapy can truly compete with transplantation, this evolution might negatively impact survival in the next decades.

Although impossible to prove, we strongly believe that the rigorous selection procedure we aimed for played an important role in our results.

Having an opt-out law, the number of donors per million inhabitants in Belgium is among the highest in the world (8–10). This results in shorter waiting times, for patients on the regular and the HU waitlist. A (very) short time on the HU waiting list was the only key to survival in the era before long-term MCS. Even nowadays it can be lifesaving for patient that is not a candidate for an MCS, such as those with hypertrophic cardiomyopathy or some complex forms of congenital heart disease and those needing a re-transplantation. As has been shown in several countries dealing with growing waitlists, a prolonged waiting time negatively impacts post-transplant survival (11). Many patients that were good candidates at the moment of listing, may turn out poor recipients 2 years later. Delisting patients that spanned their window of opportunity is extremely difficult. Pushed by increasing waiting times, we recently started discussing this possibility, at the moment of listing, especially when

long waiting times are anticipated. The prolonged waiting time has another deleterious effect: it shifts patients from the regular to the HU waitlist, once their condition deteriorates. This is not a problem as long as the waiting time on the HU list is short. A long time on the HU list, however, is a recipe for bad results. The future transplant cardiologist will have the difficult task to be the gate keeper of his waitlist. When he or she allows too many patients on board, the boat might sink. As for our program, we are convinced that short waiting times, especially in the first 15 years of our program, have significantly contributed to our good survival results.

In contrast with the process of selecting a recipient, accepting or rejecting a donor is a fast-forward procedure. Initially, only young donors without vasopressors were accepted. Confronted with the growing number of patients on the waiting list and the decreasing number of donors (especially in Europe), most centers, including ours, progressively started accepting more marginal donor hearts (12–14). Nowadays, an ideal donor has become an exception and donors aged 60 years are no longer rejected automatically. Although the increase in donor age did not decrease our short-term survival, long-term survival might be negatively impacted. Time will tell.

Needless to say, the expertise and dedication of our surgeons played an important role in our survival results. This is indirectly suggested by the low rate of primary graft failure and the high 30-day survival. As the explantation

Table 5 Causes of death: Leuven (follow-up until 12-31-2016)

Causes	N/244	Type [number]
Cardiovascular	93 [32]	Sudden cardiac death [35] Primary graft failure [16] Acute rejection [7] Late graft failure (FrEF) [6] [Non-STEMI] [4] Post-PCI/CABG [3] Technical problems during Tx [3] Stroke/intracranial bleeding [12] Aortic rupture [4] Intestinal ischemia [3]
Malignancy	7 [32]	Lung [35] GI tract [10] PTLD [9] Kidney-bladder [6] Pancreas [4] Blood [4] Prostate [3] Skin [3] Primary tumor unknown [3] Brain [1]
Infection	43 [12]	Pneumonia [22] Sepsis [15] [ther] [6]
[ther]	27 [11]	[Id age] [2] Dementia [5] Suicide [4] Therapy withdrawal [3] Trauma [3] Respiratory failure [1] Bleeding [1] ALS [1] Euthanasia [1]
Unknown	3 [1]	[?]

[FrEF, heart failure with reduced ejection fraction; STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; Tx, heart transplantation; GI, gastro-intestinal; PTLD, post-transplant lymphoproliferative disease; ALS, amyotrophic lateral sclerosis.

of the donor heart is performed by our own surgeons, the direct communication between the procurement and the implanting team might help to significantly reduce ischemic times (15-18). Also, most donors come from Belgian hospitals which results in short transportation times. Short transportation times may result in shorter ischemic intervals. In our analysis we, however, did not observe shorter ischemic times compared to ISHLT data.

Patients with complex congenital abnormalities and children are exclusively transplanted by surgeons that are used to performing congenital heart surgery. This can be considered to be a potential advantage.

In small countries such as Belgium it is not difficult to centralize follow-up. Obviously in the first postoperative year, when the risk of life threatening complications such as rejection and infection is highest, we think that presence of experienced transplant physicians can minimize the delay between the initiation of symptoms and the time of diagnosis and starting adequate treatment. It is difficult to prove that this system outperforms a more lenient follow-up, but we are convinced it does. Obviously, the advantage of a centralized follow-up stands or falls with the stability of the medical and paramedical teams involved. Even during long-term follow-up, when transplant recipients start to resemble general internal medicine patients, we think that having pathologists, microbiologists, hematologists, oncologists and other specialists with a large experience in transplant patients still implies an added benefit.

The effect of a well deployed social security system with a compulsory health insurance coverage, providing full reimbursement of immunosuppressive and other drugs, has not been studied extensively in heart recipients (19-22). It seems logical that these facilities, present in our country, decrease the risk of non-adherence and postponing medical help. They also might have contributed to our results, as was recently indirectly suggested in a large study comparing long-term graft kidney survival in Europe and the United States (22).

Patient education and medication adherence are two other important factors that might impact survival after transplantation. Since the beginning of our transplant program we have actively invested in these topics (23-27). This has not only resulted in scientific output, but has also likely lowered the threshold for patients to contact the transplant nurses and physicians in case of questions or problems. It may have also assisted in creating a culture where patients and their families form a team together with

paramedics and physicians. The “Transplantoux”-project, a bi-annual biking and walking event organized for transplant recipients near the French Mont Ventoux, is a testament to this supportive cultural development (28). If nothing else, it temporarily stimulates a healthy lifestyle among the participants.

Finally, we pay a lot of attention to cardiovascular prevention and screening for malignancies. The significant and consistent decreases in age-adjusted cardiovascular mortality shown in European and US registries was attributed to better prevention and better treatment of cardiac disease (29). Although never investigated in heart recipients, we suppose that a healthy lifestyle and a low threshold for statin therapy and treatment of hypertension and diabetes will improve long-term survival after transplantation (30-32). The fact that a large number of our recipients had ischemic heart disease before the transplantation and the high percentage of recipients dying of cardiovascular causes enforces our belief. Considering the high prevalence of post-transplant smoking (more than 25% of heart recipients in a recent meta-analysis), patients' smoking status is systematically assessed at the out-patient visits and motivated recipients are referred to smoking cessation services (33).

Malignancies, particularly respiratory tumors, are a frequent cause of death (34,35). Until recently, screening consisted of three monthly chest X-rays. Hoping to detect more cancers at a treatable stage, we shifted to an annual low-dose CT scan (36).

Conclusions

The relatively small number of heart transplantations performed worldwide and the impracticality of long-term follow-up studies explains the absence of large clinical trials trying to answer the question of how to obtain and maintain favorable results after heart transplantation. Even if these studies would have been performed, continuing changes in recipient and donor characteristics would reduce their relevance and hinder their translation into guidelines. Therefore, we can only speculate on factors that might explain our short- and long-term survival results. We focused on selection of potential candidates, obtaining informed consent, waiting time, ischemic time, centralized follow-up, health insurance coverage, patient education, medication adherence, cardiovascular prevention and screening for malignancies. Unfortunately, there is not such a thing as one master key to success. Many small keys

however can contribute to a successful heart transplant program.

Acknowledgements

We sincerely thank Josef Stehlik (Chair ISHLT International Thoracic Transplant Registry Steering Committee) as well as Heather Neil, Aparna Sadavarte and Wida Cherikh from the UNOS Research Department (ISHLT Registry) for kindly providing us the ISHLT survival data and Ann Belmans for her statistical support. Special gratitude goes to Johan Vanhaecke and Wim Daenen, who founded the Leuven heart transplant program. Johan Vanhaecke initiated and personally maintained the database up to 2016. Finally, we thank the whole team, all recipients and their families and all donors and their families. Without their efforts and willingness, the exciting journey of heart transplantation would never have been possible.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Van Cleemput JJ, Verbelen TO, Van Aelst LN, Rega FR. How to obtain and maintain favorable results after heart transplantation: keys to success? *Ann Cardiothorac Surg* 2018;7(1):106-117. doi: 10.21037/acs.2017.12.03

Supplementary

Table S1 Baseline characteristics of recipients and donors: ISHLT

Eras	1992-2001 (n=36,452) P value	2002-2007 (n=17,797) P value	2009-2014* (n=19,770) P value
Rec. age (years)	51.4±11.0 NS	51.1±12.4 0.05	54 [25-66] 0.0001
Rec. male (%)	70.0 NS	77.3 NS	74.9 NS
Rec. weight (kg)	76.0±14.5 0.0001	72.3±15.5 0.0001	79.7 (53.5-110.7) 0.0001
Rec. height (cm)	172.7±8.7 0.001	172.9±8.9 NS	175 [157-192] 0.001
Rec. BMI	25.3±4.1 0.0001	26.0±4.3 0.0001	24.6 (19.2-34.4) NS
Rec. creatinine (mg/dL)	1.3±0.5 0.0001	1.3±0.5 NS	1.2 (0.7-2.3) 0.05
Rec. diabetes (%)	13.1 NS	22.0 0.001	25.9 0.0001
Rec. cardiac surgery	NA NA	40.0± 0.001	49.6 0.0001
Rec. diagnosis			
Ischemic CMP (%)	45.2 NS	39.5 NS	35.1 NS
Idiopathic CMP (%)	45.9 0.05	49.5 0.05	55.6 0.005
Valvular CMP (%)	3.2 0.05	2.4 0.005	2.2 NS
Re-transplant (%)	1.9 0.005	2.3 0.05	2.2 0.001
Congenital (%)	1.2 NS	2.4 0.001	3.3 0.005
Other (%)	1.9 NS	3.2 NS	0.6 0.0001
Hospitalized	52.6 0.0001	46.5 0.0001	43.2 0.0001
iv inotropes	42.9 0.0001	44.2 0.0001	39.9 0.0001
Ventilator	3.1 NS	2.9 NS	2.3 0.05
iABP	6.2 0.001	6.9 0.005	6.2 0.001
ECM	0.3 NS	0.7 NS	1.2 NS
LVAD	4.1 NS	19.0 NS	36.6 NS
RVAD	0.1 0.0001	2.9 NS	3.2 NS
TA	0.4 NS	0.4 NS	1.4 NS
Donor age (years)	32.3±12.2 NS	33.6±13.0 0.05	35 [17-57] 0.0001
Donor male (%)	67.2 NS	69.5 NS	62.2 NS
Ischemic time (hours)	2.5±1.4 0.05	2.2±1.5 0.001	3.3 (1.6-5.1) NS
HLA mismatches (%)			
0-2	4.2 0.01	4.3 NS	3.2 NS
3-4	41.5	40.5	32.4
5-6	53.7	55.2	57.2
Donor cause of death (%)			
Head trauma	45.2 0.0001	52.1 NS	42.9 NS
Stroke	27.4	29.6	23.2
Other	26.5	17.3	33.9
Male rec./female donor (%)	20.7± NS	17.3± NS	16.6 NS
Female rec./male donor (%)	9.2± NS	10.1± NS	9.2± NS

See ISHLT reports 2009 (1992-2001 and 2002-2007) and 2015 [2009-2014] (1992-2003 (n=42,061) and 2004-2007 (n=17,366). Continuous variables are expressed as mean ± standard deviation or *median and 5th to 95th percentile and compared with Leuven data from same eras using a 2-sided t-test; categorical variables are shown as percentages and compared with Leuven data from same eras using a Chi Square Test. Rec., recipient; BMI, body mass index; HF, heart failure; CMP, cardiomyopathy; iv, intravenous; iABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TA, total artificial heart; HLA, human leucocyte antigen; NS, not significant.

Table S2 Overall survival: Leuven versus ISHLT			
Year	Leuven (n=64)	ISHLT (n=109,426)	P value
0	100.0	100.0	
1	91.9	92.1	0.0001
2	91.1	72.6	0.0001
3	90.7	75.2	0.0001
4	89.0	72.9	0.0001
5	87.0	70.0	0.0001
6	86.1	66.9	0.0001
7	83.3	63.6	0.0001
8	81.7	60.1	0.0001
9	78.3	56.6	0.0001
10	75.5	53.2	0.0001
11	73.1	49.5	0.0001
12	70.5	45.9	0.0001
13	66.0	42.4	0.0001
14	62.2	39.0	0.0001
15	57.0	35.4	0.0001
16	56.9	31.9	0.0001
17	53.5	27.2	0.0001
18	50.2	25.9	0.0001
19	46.7	23.1	0.0001
20	43.2	20.5	0.0001
21	39.3	17.3	0.0001
22	36.7	16.2	0.0001
23	29.4	14.4	0.0001
24	26.9	12.6	0.001
25	26.9	11.0	0.0001
26	26.9	9.6	0.0001
27	26.9	7.4	0.0001
28		6.9	
29		5.4	

Data are expressed as percentages ± standard error.

Table S3 Conditional survival: Leuven versus ISHLT			
Year	Leuven (n=524)	ISHLT (n=26,551)	P value
1	100.0	100.0	
2	99.1	95.2	0.0001
3	97.7	92.3	0.0001
4	96.2	87.9	0.0001
5	94.6	85.3	0.0001
6	93.7	81.5	0.0001
7	90.6	77.5	0.0001
8	87.2	73.3	0.0001
9	85.2	69.0	0.0001
10	82.1	64.2	0.0001
11	79.5	60.3	0.0001
12	76.7	56.0	0.0001
13	71.2	51.6	0.0001
14	67.3	47.5	0.0001
15	63.1	43.1	0.0001
16	61.9	37.9	0.0001
17	57.1	35.1	0.0001
18	54.6	31.6	0.0001
19	50.2	27.2	0.0001
20	47.0	25.0	0.0001
21	42.7	22.3	0.0001
22	39.9	19.2	0.0001
23	32.0	17.6	0.001
24	29.2	15.4	0.001
25	29.2	13.4	0.0001
26	29.2	11.7	0.0001
27	29.2	10.3	0.0001
28		7.4	
29		6.5	

Data are expressed as percentages ± standard error.

Year	Leuven (n=100)	ISHLT (n=17,173)	P value
0	100.0	100.0	
1	99.7	77.2	0.0002
2	97.7	74.2	0.0001
3	97.6	71.0	0.0001
4	94.5	67.7	0.0001
5	93.5	64.4	0.0001
6	93.5	60.7	0.0001
7	90.4	57.0	0.0001
8	75.3	53.2	0.0001
9	72.2	49.7	0.0001
10	70.1	46.2	0.0001
11	66.0	42.7	0.0001
12	60.7	39.3	0.0001
13	54.6	36.1	0.0001
14	49.5	33.0	0.01
15	41.2	30.0	0.05
16	41.2	26.7	0.01
17	37.1	24.3	0.01
18	33.0	21.7	0.05
19	29.9	19.5	0.05
20	27.9	17.5	0.05
21	27.7	15.7	0.01
22	24.7	14.0	0.05
23	19.6	12.4	NS
24	17.5	11.0	NS
25	17.5	9.6	0.05
26	17.5	7.4	0.05
27	17.5	7.4	0.01
28	7	6.0	?
29	?	4.7	?

Data are expressed as percentages ± standard error.

Year	Leuven (n=222)	ISHLT (n=36,45)	P value
0	100.0	100.0	
1	90.7	90.9	0.0001
2	89.9	77.3	0.0001
3	89.9	74.5	0.0001
4	87.5	71.7	0.0001
5	86.2	67.7	0.0001
6	85.7	65.6	0.0001
7	81.6	62.2	0.0001
8	81.1	57.7	0.0001
9	77.0	55.2	0.0001
10	74.2	51.7	0.0001
11	73.3	47.1	0.0001
12	71.9	44.6	0.0001
13	67.2	41.1	0.0001
14	65.9	37.7	0.0001
15	63.0	34.4	0.0001
16	61.4	31.2	0.0001
17	57.1	27.1	0.0001
18	56.6	25.2	0.0001
19	53.3	22.4	0.0001
20	47.9	19.7	0.0001
21	41.6	17.5	0.0001
22	41.6	15.6	0.0001
23	33.9	13.9	0.05
24	?	11.6	?
25	?	9.7	?

Data are expressed as percentages ± standard error.

Table S6 Survival era 2002–2008: Leuven versus ISHLT

Year	Leuven (n=141)	ISHLT (n=17,79)	P value
0	100.0±0.00	100.0±0.0	
1	94.0±2.1	83.4±0.2	0.0001
2	92.5±2.3	80.2±0.3	0.0001
3	91.7±2.4	77.5±0.3	0.0001
4	89.6±2.6	74.7±0.3	0.0001
5	87.3±2.9	72.1±0.3	0.0001
6	85.7±3.0	69.4±0.3	0.0001
7	85.1±3.1	66.7±0.3	0.0001
8	84.3±3.1	63.7±0.3	0.0001
9	82.4±3.4	60.7±0.3	0.0001
10	78.9±3.7	57.6±0.3	0.0001
11	74.3±4.4	54.2±0.4	0.0001
12	72.0±4.7	51.1±0.4	0.0001
13	67.6±5.7	47.5±0.4	0.001
14	?	44.1±0.5	?
15	?	38.7±0.9	?

Data are expressed as percentages ± standard error.

Table S7 Survival era 2009–2015: Leuven versus ISHLT

Year	Leuven (n=179)	ISHLT (n=19,770)	P value
0	100.0±0.00	100.0±0.0	
1	93.2±2.0	85.0±0.2	0.0001
2	93.2±2.0	81.9±0.2	0.0001
3	93.2±2.0	79.2±0.3	0.0001
4	93.2±2.0	76.6±0.3	0.0001
5	91.3±2.7	74.0±0.3	0.0001
6	87.6±4.4	71.1±0.4	0.001
7	?	67.5±0.5	?
8	?	62.3±0.7	?

Data are expressed as percentages ± standard error.