ORIGINAL ARTICLE

Heart re-transplantation in Eurotransplant

Jacqueline M. Smits[1], Michel De Pauw[2], Uwe Schulz[3], Johan Van Cleemput[4], Philip Raake[5], Ivan Knezevic[6], Kadir Caliskan[7], Zeljko Sutlic[8], Christoph Knosalla[9], Felix Schoenrath[9], Zoltan Szabolcs[10], Jens Gottlieb[11], Christian Hagl[12], Andreas Doesch[5], Davor Baric[8], Igor Rudez[8], Agita Strelniece[1], Erwin De Vries[1], Dave Green[1], Undine Samuel[1], Davor Milicic[13], Istvan Hartyanszky[10], Michael Berchtold-Herz[14], P. Christian Schulze[15], Friedrich Mohr[16], Bruno Meiser[12], Axel Haverich[17], Hermann Reichenspurner[18], Jan Gummert[3], Guenter Laufer[19] & Andreas Zuckermann[19]

1 Eurotransplant International Foundation, Leiden, The Netherlands
2 Department of Cardiology, University Hospital Ghent, Ghent, Belgium
3 Department of Thoracic and Cardiavascular Surgery, University Hospital of the Ruhr-University of Bochum, Bad Oeynhausen, Germany
4 Department of Cardiology, University Hospital Gasthuisberg, Leuven, Belgium
5 Department of Cardiology, University Hospital Heidelberg, Heidelberg, Germany
6 Department of Cardiothoracic Surgery, University Medical Centre Ljubljana, Ljubljana, Slovenia
7 Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands
8 Department of Cardiac Surgery, University Hospital, Zagreb, Croatia
9 Department of Cardiothoracic and Vascular Surgery, German Heart Institute Berlin, German Center for Cardiovascular Research, Berlin, Germany
10 Department of Cardiovascular Surgery, Semmelweis University, Budapest, Hungary
11 Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany
12 Department of Cardiac Surgery, Transplant Center Munich, Munich, Germany

SUMMARY

Internationally 3% of the donor hearts are distributed to re-transplant patients. In Eurotransplant, only patients with a primary graft dysfunction (PGD) within 1 week after heart transplantation (HTX) are indicated for high urgency listing. The aim of this study is to provide evidence for the discussion on whether these patients should still be allocated with priority. All consecutive HTX performed in the period 1981–2015 were included. Multivariate Cox' model was built including: donor and recipient age and gender, ischaemia time, recipient diagnose, urgency status and era. The study population included 18 490 HTX, of these 463 (2.6%) were repeat transplants. The major indications for re-HTX were cardiac allograft vasculopathy (CAV) (50%), PGD (26%) and acute rejection (21%). In a multivariate model, compared with first HTX hazards ratio and 95% confidence interval for repeat HTX were 2.27 (1.83–2.82) for PGD, 2.24 (1.76–2.85) for acute rejection and 1.22 (1.00–1.48) for CAV ($P < 0.0001$). Outcome after cardiac re-HTX strongly depends on the indication for re-HTX with acceptable outcomes for CAV. In contrast, just 47.5% of all hearts transplanted in patients who were re-transplanted for PGD still functioned at 1-month post-transplant. Alternative options like VA-ECMO should be first offered before opting for acute re-transplantation.

Transplant International 2018; 31: 1223–1232

Key words
complications, heart clinical, outcome, rejection

Received: 25 February 2018; Revision requested: 23 April 2018; Accepted: 5 June 2018; Published online: 16 July 2018

Correspondence
Jacqueline M. Smits MD, MSc, PhD, Eurotransplant International Foundation, PO Box 2304, 2301 CH Leiden, The Netherlands.
Tel.: 31715795700;
fax: 31715790057;
e-mail jsmits@eurotransplant.org

doi:10.1111/tri.13289

13 Department of Cardiovascular Diseases, University Hospital Centre Zagreb, Zagreb, Croatia
14 Department of Cardiovascular Surgery, University Heart Center Freiburg-Bad Krozingen, Freiburg, Germany
15 Division of Cardiology, Department of Internal Medicine, University Hospital Jena, Jena, Germany
16 Department of Cardiothoracic Surgery, Leipzig Heart Center, Leipzig, Germany
17 Department of Cardiovascular Surgery, Hannover Medical School, Hannover, Germany
18 Department of Cardiovascular Surgery, University Hospital Eppendorf, Hamburg, Germany
19 Department of Cardiac Surgery, University Hospital Vienna, Vienna, Austria

Introduction

Attributable to surgical and medical advances, heart transplantation has become the preferred treatment option in selected patients with end-stage heart failure. Over the last three decades graft survival rates have significantly improved, but many patients who underwent heart transplantation will eventually have complications resulting in allograft failure [1,2].

Three percent of the available donor hearts are currently distributed to re-transplant patients [1]. In Eurotransplant (ET) the indications for high urgent listing of patients needing a cardiac re-transplantation have sharpened over the years (Table 1), but those in need of a re-transplantation have, in contrast with the situation in the US, always received priority in organ allocation [3].

As an integral part of the development of a new allocation scheme based on benefit instead of urgency, special recipient groups who cannot be judged by a score were defined; one of these groups consists of re-transplant candidates. The working group on the Cardiac Allocation Score convened in Leiden, the Netherlands on October 6, 2015 to discuss outcomes following re-transplantation [4]. Until the cardiac allocation score (CAS) system will be implemented, the urgency tier system will still determine the allocation policy. In its current form, patients suffering a primary graft dysfunction within 1 week after heart transplantation are indicated for high urgency (HU) listing.

There are three major ethical issues affecting allocation policy for repeat transplantation [5]. These three ethical considerations are the following: (i) the obligation a transplant team has to continue to offer the best possible care to a patient they previously transplanted, (ii) the fairness of assigning a second allograft while others die awaiting their first, and (iii) the difference in utility between primary and re-transplantation. Arguments to deny a heart re-transplant are usually based on this latter point, namely futility of the intervention, where medically futility is interpreted as an unacceptable likelihood of achieving life prolongation or a therapeutic benefit [6].

In Eurotransplant one of five patients listed for a first heart transplantation dies on the waiting list within 3 years [7]. International data show that re-transplantation yields worse results compared with primary transplants, where the indication for the repeat transplant strongly determines the prognosis [8–10].

The aim of this study is to examine the outcome after cardiac re-transplantation in the Eurotransplant cohort of 35 years in order to provide evidence for the discussion, whether patients suffering from primary graft dysfunction (PGD) within 1 week after heart transplantation should still be allocated heart allografts with high priority.

Materials and methods

Study design

Retrospective study including all consecutive heart transplantations performed in the Eurotransplant area.

Study population

All consecutive heart transplantations performed between January 1981 and December 2015 were included.

Statistical analysis

Survival rates were examined with time-to-event analysis in which the event was defined as graft failure, with censoring for death with functioning graft. For re-transplants, survival was computed from the date of the re-transplant.

Multivariate analysis included the following factors: donor and recipient age, donor and recipient gender, ischaemia time, recipient diagnose, urgency status and era of the transplant.

Continuous variables were analysed using Wilcoxon-Mann-Whitney test, while Chi-square statistics were used to compare categorical variables. Survival analyses were performed by Kaplan–Meier method. Survival rates were compared using the log-rank test. All analyses were

Table 1. Overview of heart allocation policies for re-transplantation.

HU status for all acute re-transplantation <3 days (before August 23, 2000)
No audit
Same rule for children (<16 years)
No international priority
HU status for all acute re-transplantation <3 days (August 23, 2000–August 31, 2005)
International audit
Same rule for children (<16 years), but no audit if <45 kg
International priority
HU status for PGD <1 week (September 1, 2005–present)
International audit
Same rule for children (<16 years), but no audit if <45 kg
International priority
Only if VAD implant is not possible or has limited chances for success
HU status for all children (April 21, 2011–present)
No audit
International priority
Pediatric status*

*A transplant candidate with a paediatric status is a patient, who at time of organ offer for heart transplantation is under the age of 16 years or older but proven to be in maturation. This proof has to be delivered by the transplant centre by a report from a competent radiologist or paediatric endocrinologist on an X-ray of the left hand, not older than 3 months.

performed using SAS STATISTICAL program version 9.1 (SAS Institute, Cary, NC, USA). A *P*-value below 0.05 was considered statistically significant.

Results

Demographics

The study population included 18 490 heart transplants, of these 463 (2.6%) were repeat transplants with 447 second transplants, 15 third transplants and one patient received four heart transplants. The major indications for cardiac re-transplantation were cardiac allograft vasculopathy (50%), primary graft dysfunction (26%) and acute rejection (21%). Median time between the first and the re-transplants was 2 years and 10 months and ranged between 0 days and 27 years and 11 months. Donor, recipient and transplant characteristics are shown in Table 2. Re-transplant rates over time have been stable around 2.5% (Fig. 1), but indications for re-transplantation have shifted in this 35 year period (Fig. 2). In the early years a majority of patients were re-transplanted following acute rejection and PGD, while in the latter decade the major indication for heart re-transplantation was cardiac allograft vasculopathy.

Survival rates – Univariate analysis

Graft survival rates for cardiac re-transplants in the Eurotransplant cohort have improved over time with 1-month, 1- and 5-year rates of 63.2%, 43.5%, 37.9% and 67.9%, 59.3%, 48.6% and 87.5%, 73.5%, 62.1% and 86.7%,75.8%, 66.7% for patients re-transplanted in the period: 1981–1991 and 1992–2001 and 2002–2005 and 2006–2015, respectively ($P < 0.0001$) (Fig. 3).

Outcome after cardiac re-transplantation is compared with other diagnoses significantly worse ($P < 0.0001$) (Fig. 4). The 1-month, 1- and 5-year graft survival rates by indication were for coronary artery disease: 86.8%, 76.0% and 64.8%; for cardiomyopathy: 89.1%, 79.8%, and 70.5%; for congenital: 83.0%, 76.2% and 69.3%; for valvular diseases: 83.6%, 72.2% and 65.7%, for other: 85.9%, 75.2% and 66.1% and for re-transplantation: 74.4%, 62.3% and 53.1%.

Figure 5 shows the graft survival by indication for re-transplants and the outcome of first transplants. Compared with first transplant, patient re-transplanted after cardiac allograft vasculopathy (CAV) fared equally well with 1-month, 1- and 5-year rates of 89.5%, 79.3% and 67.8% for patient re-grafted after CAV and 87.9%, 78.0%, 68.3% for first HTX ($P = 0.54$). The graft survival for patients re-transplanted after PGD or rejection fared worse compared with first transplants with 1-month, 1- and 5-year rates of 47.5%, 39.7% and 35.1% for PGD and 70.9%, 51.9% and 40.6% for rejection ($P < 0.0001$).

The interval between transplants is significantly associated with graft survival ($P < 0.0001$) (Fig. 6). Early or acute re-transplants (<31 days) yielded 1-month, 1- and 5-year graft survival rates of 49.6%, 40.9% and 34.8%. If the interval was between 31 and 364 days the 1-month, 1- and 5-year graft survival rates were at 69.8%, 46.7% and 38.7%, and if the interval was 365 days or longer the 1-month, 1- and 5-year graft survival rates were: 88.3%, 76.8% and 64.7%.

Factors associated with overall graft survival – multivariate analysis

Donor and recipient age, recipient gender, cold ischaemia time, era of transplant and the indication for re-transplantation were found to be significantly associated with graft outcome (Table 3). The multivariate model showed that all three major indications

Table 2. Patient characteristics of all patients transplanted in ET in period 1983 until 2015 (*N* = 18 490).

	Primary HTX [*N* = 18 027]	Repeat heart transplantation				
		All repeat [*N* = 463]	CAV [*N* = 233]	PGD [*N* = 119]	Rejection [*N* = 98]	Other [*N* = 13]
Recipient age (years)	53 (43–59)	49 (36–57)	48 (34–57)	52 (38–59)	50 (40–55)	45 (33–56)
Recipient gender						
Male	14 402	373	182	91	91	9
Female	3625	90	51	28	7	4
Donor age (years)	36 (23–47)	34 (22–45)	37 (22–48)	32 (23–42)	30 (21–42)	41 (23–50)
Donor gender						
Male	11 179	299	138	80	73	8
Female	6848	164	95	39	25	5
Ischemic time (hours)	2.9 (2.3–3.6)	3.3 (2.7–3.8)	3.3 (2.7–3.8)	3.2 (2.8–3.9)	3.5 (2.8–3.8)	3.3 (2.7–4.0)
HU status	4705	240	93	101	37	9
Combined organ TX						
With kidney	252	38	36	–	2	–
With liver	21	–	–	–	–	–
Diagnosis for TX						
CAD	4951					
CMP	10 385					
Congenital	449					
Other	1847					
ReHTX		463				
Valvular	395					
Time span between first and retx						
≤ 31 days		141	–	119	17	5
1 month <1 year		52	–	–	44	8
>1 year		270	233	–	37	–
30 day survival	87.9	74.4	89.5	47.5	70.9	81.8
1 year survival	78.0	62.3	79.3	39.7	51.9	36.4

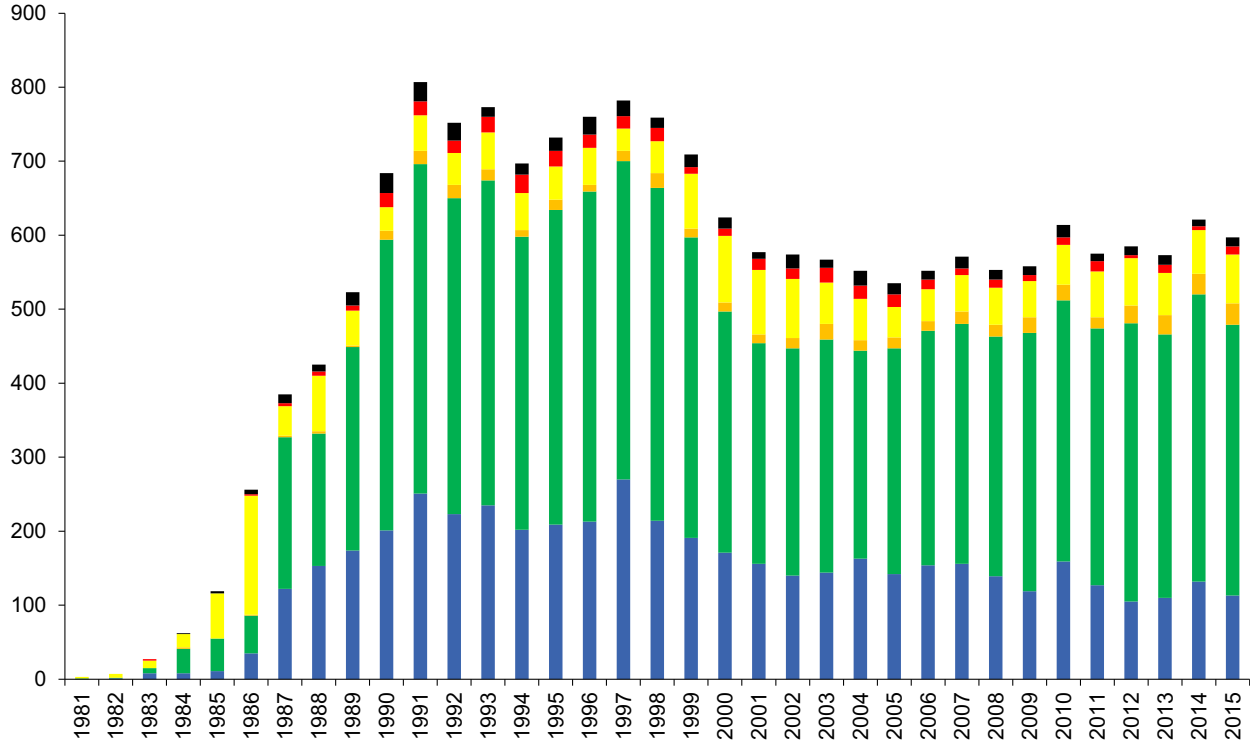

Figure 1 Number of transplants by indication in the Eurotransplant cohort. Coronary artery disease (blue bar), cardiomyopathy (green bar), congenital (orange bar), re-transplantation (black bar), valvular (red bar), other (yellow bar).

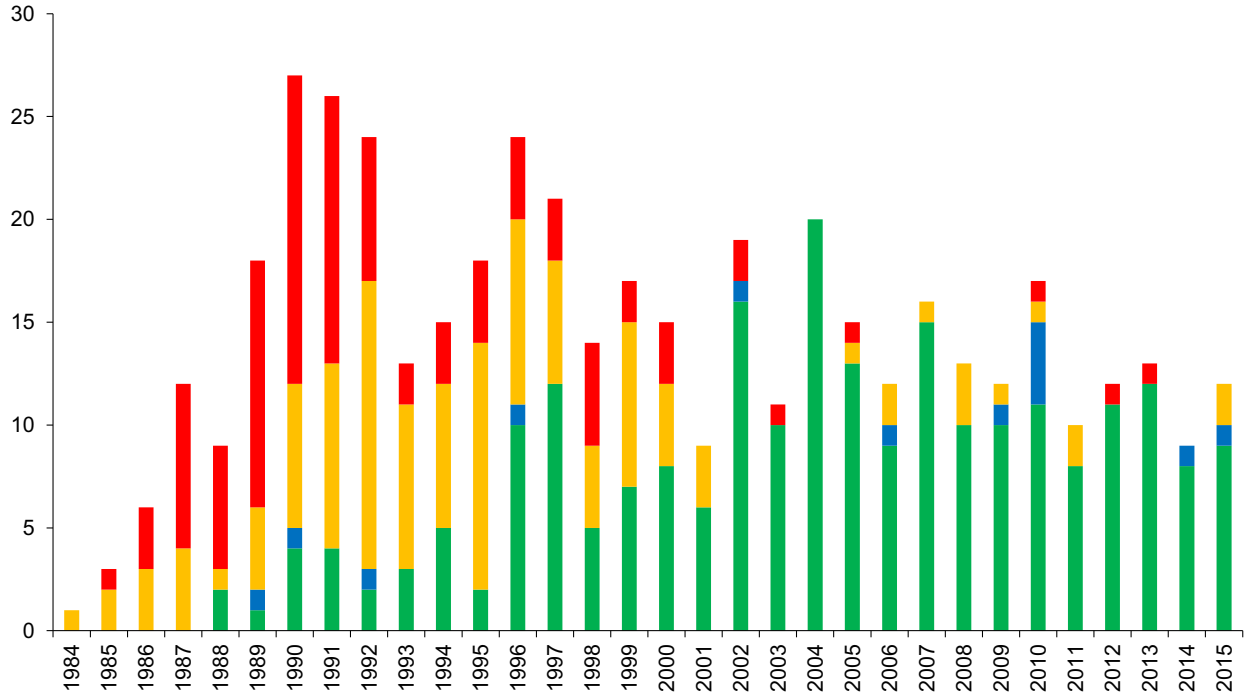

Figure 2 Number of heart re-transplantations by indication. Cardiac allograft vasculopathy (geen bar), primary graft dysfunction (orange bar), rejection (red bar), other causes (blue bar).

of repeat HTX have a significantly worse outcome compared with first HTX with hazards ratio (HR) and 95% confidence interval (CI) of 2.27 (1.83–2.82), 2.24 (1.76–2.85), 1.22 (1.00–1.48) and 1.96 (0.98–3.93) for repeat Htx for PGD, rejection, CAV and other, respectively ($P < 0.0001$).

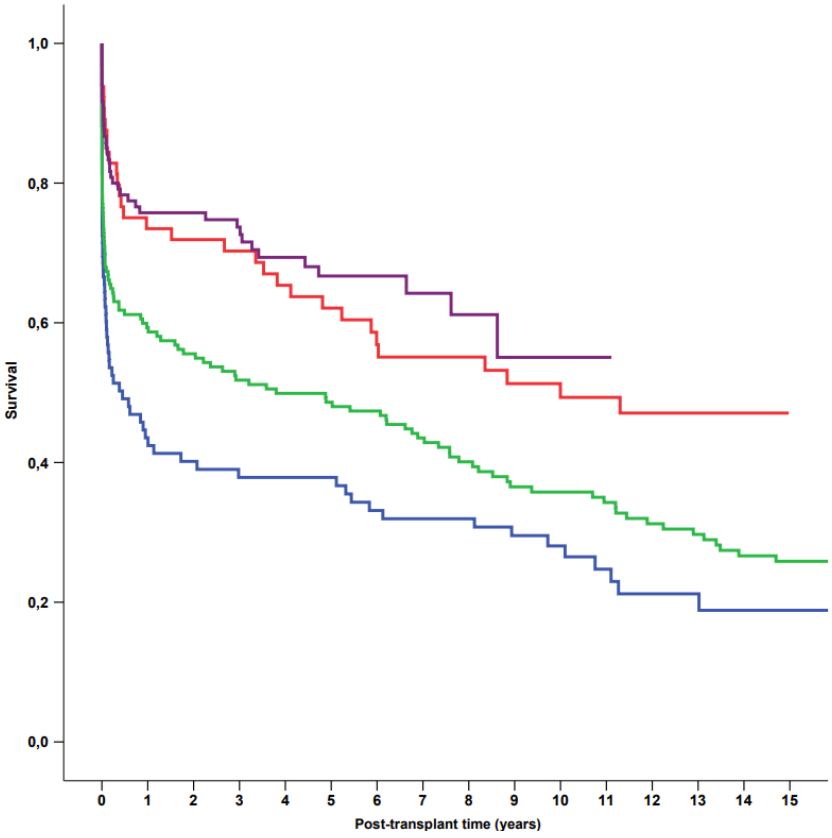

Figure 3 Graft survival of all consecutive heart re-transplants performed in Eurotransplant in the period 1981–2015 by period. Period: 1981–1991 [*N* = 102] (blue line), 1992–2001 [*N* = 170] (green line), 2002–2005 [*N* = 65] (red line), 2006–2015 [*N* = 126] (purple line).

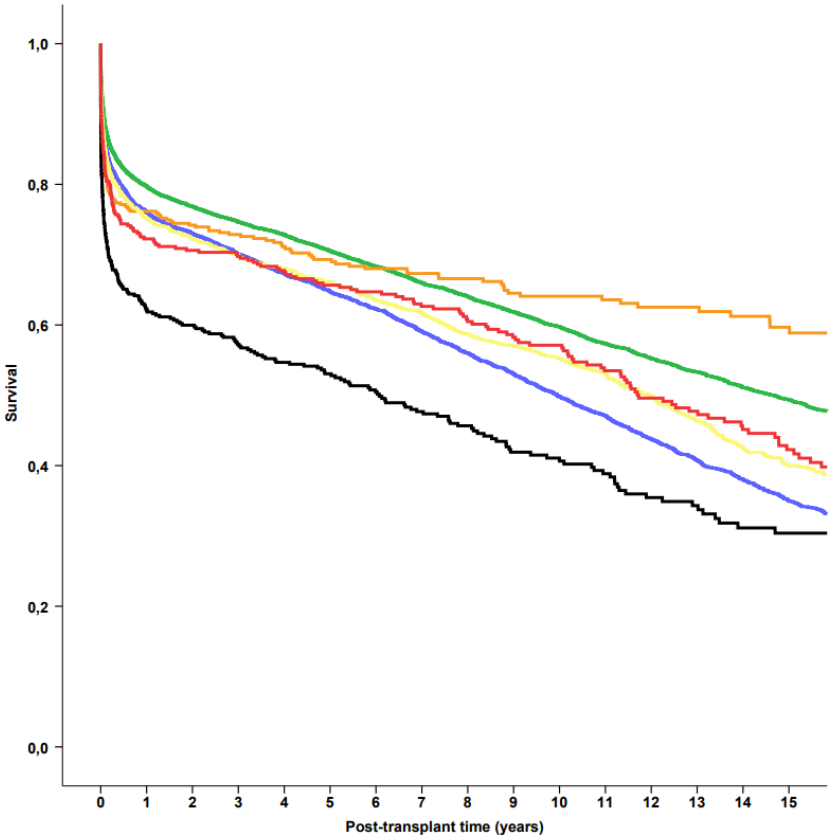

Figure 4 Graft survival of all consecutive heart transplants performed in Eurotransplant in the period 1981–2015 by indication. Coronary artery disease [*N* = 4951] (blue line), cardiomyopathy [*N* = 10 385] (green line), congenital [*N* = 449] (orange line), re-transplantation [*N* = 463] (black line), valvular [*N* = 395] (red line), other [*N* = 1847] (yellow line).

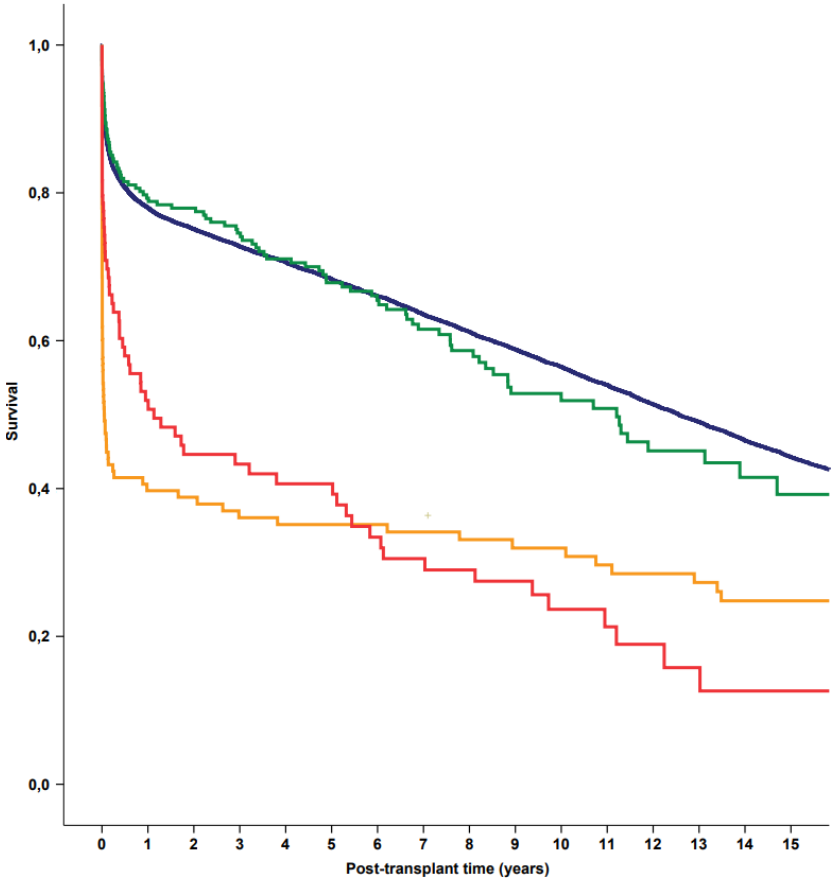

Figure 5 Graft survival of all consecutive heart transplants performed in Eurotransplant in the period 1981–2015 by indication for Re-transplants versus first transplants. First transplant [*N* = 18 027] (blue line), cardiac allograft vasculopathy [*N* = 233] (green line), primary graft dysfunction [*N* = 119] (orange line), rejection [*N* = 98] (red line). Note the group other [*N* = 13] is not shown.

Discussion

In Eurotransplant 2–3% of the available hearts are currently distributed to re-transplant patients where every year between 10 and 15 patients receive a second heart transplant.

Our data show that cardiac re-transplantation outcome has improved over the decades, but is still inferior to primary transplantation. Outcome after cardiac re-transplantation depends on the indication for re-transplantation, and a shift in indication favouring the patients re-transplanted for cardiac allograft vasculopathy in the most recent years, is partly accountable for this improvement. In this 35 years Eurotransplant cohort, when compared with outcome after primary transplantation, graft survival for patients re-transplanted following primary graft dysfunction and rejection was significant worse with hazards ratios of 2.27 and 2.24 respectively, while the risk of graft loss for patients re-transplanted for cardiac allograft vasculopathy was 1.22.

Allocation rules are conceived and decided upon by clinicians – collaborating in the international organ advisory committee – but whose first job is to care for transplant candidates and recipients. As a consequence, since the early days acute re-transplantation has always been a standard indication for listing on the high urgency waiting list as this rule facilitates and supports the transplant teams that consider their patient eligible for acute re-transplantation [7]. However, with growing organ shortage, the role of the policy makers has changed towards being also the guardian of a shared scarce commodity where the fairness of assigning a second graft while other die awaiting their first, is a substantial ethical issue.

The graft survival rates for patients re-transplanted in Eurotransplanted after PGD at 1-month, 1- and 5-years were 47.5%, 39.7% and 35.1%, respectively. Given these jeopardized results, the Eurotransplant Thoracic Advisory Committee is currently discussing whether the allocation priority currently assigned to patients with PGD

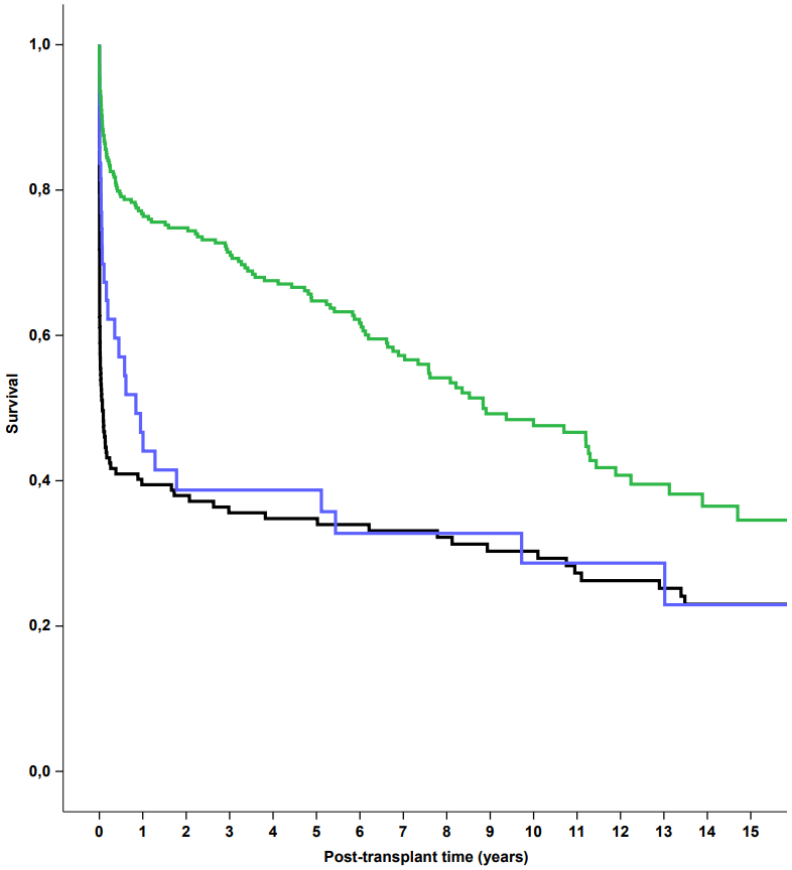

Figure 6 Graft survival of all consecutive heart re-transplants performed in Eurotransplant in the period 1981–2015 by interval between the transplants. Interval between first and re-transplant ≤31 days [*N* = 141] (black line), between 32 and 364 days [*N* = 50] (blue line), ≥365 days [*N* = 270] (green line).

can be sustained. Until recently the only therapeutic option for PGD was a re-HTX. During the latest consensus conference on PGD after cardiac transplantation and confirmed by single centre experiences temporary ventricular assist devices and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can now be seen as established effective treatment options for severe PGD whose intervention can preclude emergency salvage re-transplantation [11,12]. In the majority of cases (75–87%), donor hearts recovered and patients could be weaned from ECMO support with acceptable survival (55–70%) [13]. In the absence of randomized clinical trials, extracorporeal life support (ECLS) as bridge to recovery for severe PGD after heart transplant continues to be the first line of support with some recent evidence of improved outcomes as compared with short-term VAD use [14]. Based on the acceptable success rate of ECMO bridge to recovery and the better survival rates compared with those after acute re-transplantation we would consider a patient eligible for re-transplantation because of PGD only if he cannot be weaned from mechanical support, if he has good end-organ function (besides donor heart, kidney, liver, lung) and if he has a normal neurological condition.

Center volume and patient survival are consistently shown to be positively related in the ISHLT database [1]. As a result of its international composition in Eurotransplant this association is not so obvious as a large program in one country might be considered small in another country [15]. However the centre's expertise is instrumental in dealing with complicated cases and protocols for PGD treatment should be available and regularly be audited.

Acute rejection accounted for 21% of all cardiac re-transplants in our total study cohort. Compared with first transplants, patient re-transplanted after rejection fared worse with 1-month, 1- and 5-year rates of 70.9%, 51.9% and 40.6%, respectively. However, during the last decade acute rejection as indication for re-transplantation has become an infrequent event. This is related to the fact that refractory acute rejection is rarely seen because of improvements with diagnosis allowing identification of high risk patients, early detection of events and because of improved treatment options like extracorporeal

Table 3. Multivariate model for risk factors for graft failure.

Variable	Hazard ratio	95% Confidence interval	*P*-value
Type HTX			
First HTX	1		
Repeat for PGD	2.27	1.83–2.82	<0.0001
Repeat for rejection	2.24	1.76–2.85	<0.0001
Repeat for CAV	1.22	1.00–1.48	0.049
Repeat for other	1.96	0.98–3.93	0.057
Era			
2006–2015	1		
2002–2005	1.05	0.97–1.15	0.23
1992–2001	1.32	1.23–1.42	<0.0001
1981–1991	1.74	1.59–1.89	<0.0001
Recipient age	1.01	1.01–1.02	<0.0001
Donor age	1.01	1.0–1.01	<0.0001
Recipient gender			
Female	1		
Male	1.06	1.00–1.13	0.045
Donor gender			
Female	1		
Male	0.97	0.93–1.02	0.25
Cold ischaemic time	1.06	1.03–1.09	<0.0001
HU status			
Elective	1		
HU	1.02	0.95–1.10	0.57

pheresis, the availability of new antibodies and better maintenance immunosuppression [16]. Monitoring immunosuppressive drug intake compliance should be rigidly undertaken; many of the patients with refractory severe rejection had adherence problems with medication and are therefore ineligible for re-transplantation [17].

Current graft surveillance protocols for acute rejection entail invasive endo-myocardial biopsy, further research should focus on refining molecular analysis as a diagnostic tool [18]. This will be achieved by refining reference sets through accurate phenotyping of biopsy samples. Non-invasive biomarkers can then be refined according to the true pathological picture by using molecular analysis as a benchmark rather than subjective histology readings [19,20].

Our data show that outcome for patients re-transplanted after suffering CAV is excellent with 1-month, 1- and 5-year rates of 89.5%, 79.3% and 67.8%, respectively. However, with the availability of good long-term viable alternatives based on pharmacological management and percutaneous coronary intervention strategies, re-transplantation should be restricted to selected patients with CAV [21,22]. Again, prevention is key and surveillance strategies by invasive angiography and intravascular ultrasound should be set up and executed [23].

The limitations of this study are inherent to using registry data obtained from different transplant centres on a voluntary basis and where standardization of the definition of clinical events is difficult. Sabatino *et al.* [24] have recently shown that it is crucial not only to determine the aetiology of the graft dysfunction but most importantly it is to know the severity of the PGD as this will determine the clinical management strategy and the patient outcome. However, as the standard definitions and the grading system for PGD in heart transplantation only appeared in 2014, our data contain events using different definitions for PGD [11].

In conclusion, our data show that cardiac re-transplantation outcome has improved over the decades, but is still inferior to primary transplantation. Outcome after cardiac re-transplantation depends on the indication and hence on the time span between the first and the re-transplantation. Only 47.5% of all hearts transplanted in patients who were re-transplanted for primary graft dysfunction still functioned at 1-month post-transplant. Alternative therapeutic options like VA-ECMO should be first offered before opting for an acute

re-transplantation, since a sequential mode of treatment lowers the individual risk of the transplant patient.

Authorship

JMS: designed study. JMS, AS, DG: analysed data. EDV: collected data. JMS: wrote the paper. All contributed to the discussion of this paper.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

REFERENCES

1. http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry. Accessed February 11, 2018
2. Tsao L, Uriel N, Leitz K, Naka Y, Mancini D. Higher rate of comorbidities after cardiac retransplantation contributes to decreased survival. *J Heart Lung Transplant* 2009; **28**: 1072.
3. 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.
4. 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.
5. Ubel PA, Arnold RM, Caplan AL. Rationing failure. The ethical lessons of the re-transplantation of scarce vital organs. *JAMA* 1993; **270**: 2469.
6. Jecker NS, Schneiderman LJ. Futility and rationing. *Am J Med* 1992; **92**: 189.
7. www.eurotransplant.org.
8. Magee JC, Barr ML, Basadonna GP, *et al.* Repeat organ transplantation in the United States, 1996–2005. *Am J Transplant* 2007; **7**(5 Pt 2): 1424.
9. Radovancevic B, McGiffin DC, Kobashigawa JA, *et al.* Re-transplantation in 7,290 primary transplant patients: a 10-year multi-institutional study. *J Heart Lung Transplant* 2003; **22**: 862.
10. Tjang YS, Tenderich G, Hornik L, Wlost S, Bairaktaris A, Körfer R. Long-term experiences on cardiac re-transplantation in adults. *Eur J Cardiothorac Surg* 2007; **32**: 923.
11. Kobashigawa J, Zuckermann A, Macdonald P, *et al.* Consensus conference participants. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant* 2014; **33**: 327.
12. Loforte A, Murana G, Cefarelli M, *et al.* Role of intra-aortic balloon pump and extracorporeal membrane oxygenation in early graft failure after cardiac transplantation. *Artif Organs* 2016; **40**: E136.
13. Bermudez CA, McMullan DM. Extracorporeal life support in preoperative and postoperative heart transplant management. *Ann Transl Med* 2017; **5**: 398.
14. Takeda K, Li B, Garan AR, *et al.* Improved outcomes from extracorporeal membrane oxygenation versus ventricular assist device temporary support of primary graft dysfunction in heart transplant. *J Heart Lung Transplant* 2017; **36**: 650.
15. Smits JM, De Meester J, Deng MC, *et al.* Eurotransplant heart transplant programs. Mortality rates after heart transplantation: how to compare center-specific outcome data? *Transplantation* 2003; **75**: 90.
16. Patel J, Klapper E, Shafi H, Kobashigawa JA. Extracorporeal photopheresis in heart transplant rejection. *Transfus Apher Sci* 2015; **52**: 167.
17. Brocks Y, Zittermann A, Grisse D, *et al.* Adherence of heart transplant recipients to prescribed medication and recommended lifestyle habits. *Prog Transplant* 2017; **27**: 160.
18. Hasan R, Ela AA, Goldstein D. Innovations in cardiac transplantation. *Curr Opin Cardiol* 2017; **32**: 336.
19. Loupy A, Duong Van Huyen JP, Hidalgo L, *et al.* Gene expression profiling for the identification and classification of antibody-mediated heart rejection. *Circulation* 2017; **135**: 917.
20. Kobashigawa JA. The search for a gold standard to detect rejection in heart transplant patients. *Circulation* 2017; **135**: 936.
21. Goldraich LA, Stehlik J, Kucheryavaya AY, Edwards LB, Ross HJ. Re-transplant and medical therapy for cardiac allograft vasculopathy: international society for heart and lung transplantation registry analysis. *Am J Transplant* 2016; **16**: 301.
22. Cheng R, Vanichsarn C, Patel JK, *et al.* Long-term clinical and angiographic outcomes of percutaneous coronary intervention with everolimus-eluting stents for the treatment of cardiac allograft vasculopathy. *Catheter Cardiovasc Interv* 2017; **90**: 48.
23. Chih S, Chong AY, Mielniczuk LM, Bhatt DL, Beanlands RS. Allograft vasculopathy: the Achilles' heel of heart transplantation. *J Am Coll Cardiol* 2016; **68**: 80.
24. Sabatino M, Vitale G, Manfredini V, *et al.* Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: epidemiology, risk factors, and outcomes. *J Heart Lung Transplant* 2017; **36**: 1217.