

Changes in patient characteristics following cardiac transplantation: the Montreal Heart Institute experience

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Background: Heart transplantation is no longer considered an experimental operation, but rather a standard treatment; nevertheless the context has changed substantially in recent years owing to donor shortage. The aim of this study was to review the heart transplant experience focusing on very long-term survival (≥ 20 years) and to compare the initial results with the current era.

Methods: From April 1983 through April 1995, 156 consecutive patients underwent heart transplantation. Patients who survived 20 years or longer (group 1) were compared with patients who died within 20 years after surgery (group 2). To compare patient characteristics with the current era, we evaluated our recent 5-year experience (group 3; patients who underwent transplantation between 2010 and 2015), focusing on differences in terms of donor and recipient characteristics.

Results: Group 1 ($n = 46$, 30%) included younger patients (38 ± 11 v. 48 ± 8 yr, $p = 0.001$), a higher proportion of female recipients (28% v. 8%, $p = 0.001$) and a lower prevalence of ischemic heart disease (42% v. 65%, $p = 0.001$) than group 2 ($n = 110$, 70%). Patients in group 3 ($n = 54$) were older (52 ± 12 v. 38 ± 11 yr, $p = 0.001$), sicker (rate of hospital admission at transplantation 48% v. 20%, $p = 0.001$) and transplanted with organs from older donors (42 ± 15 v. 29 ± 11 yr, $p = 0.001$) than those in group 1.

Conclusion: Very long-term survival (≥ 20 yr) was observed in 30% of patients transplanted during the first decade of our experience. This outcome will be difficult to duplicate in the current era considering our present population of older and sicker patients transplanted with organs from older donors.

Contexte : De nos jours, la transplantation cardiaque n'est plus considérée comme une intervention expérimentale, mais bien comme une opération standard; mais le contexte a substantiellement changé ces dernières années en raison d'une pénurie de donneurs. Cette étude avait pour but de faire le point sur la situation de la greffe cardiaque, et plus particulièrement sur la survie à très long terme (≥ 20 ans), et de la comparer aux résultats initiaux.

Méthodes : Entre avril 1983 et avril 1995, 156 patients consécutifs ont subi une greffe cardiaque. Les patients qui ont survécu 20 ans ou plus (groupe 1) ont été comparés aux patients décédés moins de 20 ans après l'intervention (groupe 2). Pour comparer les caractéristiques des premiers patients à celles des cas plus récents, nous avons fait un bilan des 5 années allant de 2010 à 2015 (groupe 3), en portant attention aux différences quant aux caractéristiques des donneurs et des receveurs.

Résultats : Le groupe 1 ($n = 46$, 30 %) incluait des patients plus jeunes (38 ± 11 ans c. 48 ± 8 ans, $p = 0,001$), une proportion plus élevée de femmes (28 % c. 8 %, $p = 0,001$) et la prévalence de maladie cardiaque ischémique y était moindre (42 % c. 65 %, $p = 0,001$) comparativement au groupe 2 ($n = 110$, 70 %). Les patients du groupe 3 ($n = 54$) étaient plus âgés (52 ± 12 ans c. 38 ± 11 ans, $p = 0,001$), plus malades (taux d'hospitalisation au moment de la transplantation 48 % c. 20 %, $p = 0,001$) et ont reçu le cœur de donneurs plus âgés (42 ± 15 ans c. 29 ± 11 ans, $p = 0,001$) que ceux du groupe 1.

Conclusion : Une survie à très long terme (≥ 20 ans) a été observée chez 30 % des patients ayant reçu leur greffe au cours de la première décennie de notre expérience. Ce résultat sera difficile à reproduire de nos jours étant donné que notre population actuelle est constituée de receveurs plus âgés et plus malades, qui reçoivent le cœur de donneurs plus âgés.

Cardiac transplantation is the gold standard for patients with ischemic and nonischemic end-stage heart failure and is associated with a median survival exceeding 10 years.¹⁻³ This remarkable achievement of modern medicine was made possible with substantial improvements in the field of immunosuppression, infection prophylaxis and surgical techniques.^{1,4-11} Today, heart transplantation is no longer considered an experimental operation, but rather a standard treatment; nevertheless the context has changed substantially in recent years owing to donor shortage.

With these concerns in mind, we decided to review the heart transplantation experience at the Montreal Heart Institute, focusing on patients who have experienced very long-term survival (≥ 20 yr).¹²⁻¹⁵ Our first objective was to determine the prevalence and characteristics of patients who achieved prolonged survival. The second objective was to compare these patients with those who had shorter survival in terms of recipient and donor characteristics. Finally, the third objective was to compare patient demographics in the first era with patients in our current practice, aiming to identify differences in terms of donor and recipient characteristics.

METHODS

Study population and study design

From April 1983 through April 2015, 425 consecutive patients underwent heart transplantation at the Montreal Heart Institute. We first analyzed patients who experienced very long-term survival (≥ 20 yr). For this reason, only patients transplanted before April 1995 were considered. Consequently, the study population for the present analysis is the group of patients who received transplants between April 1983 and April 1995 (156 consecutive patients). Patients who underwent a second heart transplantation were included in the analysis. To compare the transplant results of our initial experience with our current practice, we evaluated our recent 5-year experience (2010–2015), focusing on differences in terms of donor and recipient characteristics.

We conducted a retrospective cohort study. Patients' clinical charts were reviewed, and pre-, intra- and postoperative data were prospectively recorded in an electronic database. We considered the following relevant clinical information for analysis: demographic characteristics of both donors and recipients (age, sex, race), cause of heart failure (HF; idiopathic, ischemic, miscellaneous), ischemic time of the transplanted heart, clinical preoperative status (active working or studying, at home stable, admitted to hospital with pharmacological support, admitted with mechanical support), time on the waiting list, long-term complications and causes of death. Patient follow-up involved regular visits at the specialized transplant clinic,

with echocardiographic and/or hemodynamic controls and planned biopsies and coronary angiographies. All patients provided informed consent, and the Montreal Heart Institute Research Centre Ethics Committee approved the study protocol.

Statistical analysis

Statistical analyses were performed using analyses of variance and Fisher least significant difference (LSD) tests for continuous variables among the 3 groups and with χ^2 tests for categorical variables. Rates of survival, freedom from acute rejection, infection, chronic rejection characterized by any coronary lesions documented at angiographies and cancer were calculated according to actuarial analyses using the NCSS (2012) statistical system. We used the log-rank test to study differences among the groups. Continuous variables are presented as means \pm standard deviations, and categorical variables are reported as frequencies (percentages). We developed a Cox regression model to study donor and recipient variables associated with late survival. We considered results to be significant at $p < 0.05$.

RESULTS

Patients surviving 20 years after transplantation (1983–1995)

Preoperative characteristics of patients who underwent cardiac transplantation between 1983 and 1995 ($n = 156$) are shown in Table 1. Patients who survived 20 years or longer were included in group 1 ($n = 46$), whereas patients who died within 20 years of transplantation were included in group 2 ($n = 110$). Overall, 30% of patients transplanted during the first decade of our experience survived 20 years or more. The cumulative mean survival of the whole population was $35\% \pm 4\%$ 20 years after transplantation, and the median survival was 15 years (Fig. 1).

All patients who underwent mechanical support in this era of our experience with left ventricular assist devices (LVAD) or total artificial hearts (TAH) waited in the hospital in status 4 (the most urgent status). Immunosuppression varied according to study periods, although the basic treatment was based on triple drug therapy including cyclosporine, azathioprine and prednisone in groups 1 and 2, and tacrolimus, mycophenolate mofetil (MMF) and prednisone in group 3. The treatment was individualized to allow prednisone tapering and cessation if it was possible in a case by case approach (Table 1).

Causes of death for patients in group 2 were cancer ($n = 21$); myocardial infarction, chronic rejection or graft vasculopathy ($n = 18$); graft failure ($n = 15$); acute rejection ($n = 5$); renal failure ($n = 6$); bleeding ($n = 6$); pancreatitis ($n = 6$); sepsis ($n = 5$); stroke ($n = 3$); cardiac failure ($n = 4$); respiratory infection ($n = 2$); arrhythmias ($n = 1$); other

Table 1. Demographic and clinical characteristics of the study sample

Characteristic	Group; mean \pm SD or no. (%)			p value
	Group 1, \geq 20 yr survival (n = 46)	Group 2, < 20 yr survival, (n = 110)	Group 3, 2010–2015, (n = 54)	
Recipient age, yr	38 \pm 11	48 \pm 8	52 \pm 12	0.001
Recipients, female sex	13 (28)	9 (8)	11 (20)	0.004
Donor age, yr	29 \pm 11	27 \pm 10	42 \pm 15	0.001
Donors, female sex	20 (43)	28 (25)	13 (24)	0.05
Ischemic time, min	141 \pm 43	136 \pm 47	137 \pm 54	0.86
Waiting time, d	119 \pm 179	101 \pm 110	99 \pm 140	0.73
Diagnosis pretransplant				0.001
Idiopathic	14 (30)	21 (19)	22 (41)	
Ischemic	19 (42)	71 (65)	10 (18)	
Other	13 (28)	18 (16)	22 (41)	
Status pretransplant				0.001
Work/home	37 (80)	99 (90)	28 (52)	
Hospital, IV drugs, VAD or TAH	9 (20)	11 (10)	26 (48)	
LVAD and TAH before transplantation	7 (15)	12 (11)	12 (22)	
No. of HLA-DR mismatches				0.86
0	1	1		
1	13	28		
2	25	54		
Immunosuppression	Cyclosporine-based	Cyclosporine-based	Tacrolimus-based	
HLA-DR = Human Leukocyte Antigen - antigen D Related; IV = intravenous; SD = standard deviation; TAH = total artificial heart; VAD = ventricular assist device.				

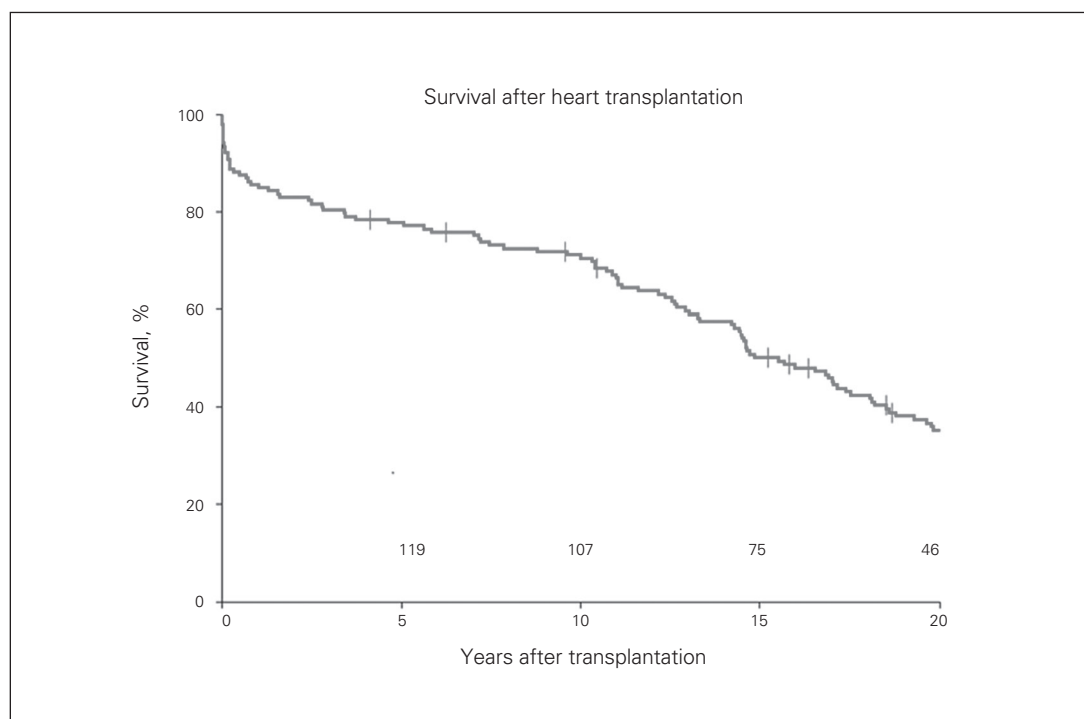


Fig. 1. Kaplan–Meier curve for survival after cardiac transplantation for patients operated between 1984 and 1995. Patient survival at 1, 5, 10, 15 and 20 years averaged 84% \pm 3%, 76% \pm 3%, 69% \pm 4%, 49% \pm 4% and 35% \pm 4%, respectively. The number of patients at risk is shown at the bottom of the graph.

infections ($n = 1$); hepatic failure ($n = 1$); and sudden death ($n = 1$). In 15 patients, the cause of death was unknown.

As shown in Table 1, group 1 included younger patients (mean age 38 ± 11 v. 48 ± 8 yr, $p = 0.001$), a greater proportion of women (28% v. 8%, $p = 0.001$) and a lower prevalence of ischemic heart disease (42% v. 65%, $p = 0.001$) than group 2. Of interest, the number of Human Leukocyte Antigen - antigen D Related (HLA-DR) mismatches was similar in the 2 groups. Four patients in group 1 underwent a second heart transplant for chronic rejection or transplant vasculopathy 14 \pm 4 years after their initial graft.

Freedom rates from cancer and chronic rejection, the 2 main causes of adverse long-term outcome, are shown in Figure 2 and Figure 3, respectively. Although patients in group 1 showed a significantly lower incidence of cancer than patients in group 2 ($p = 0.005$), the rate of allograft vasculopathy was similar in both groups ($p = 0.96$).

The current era (2010–2015)

Table 1 also shows the preoperative characteristics of patients transplanted between 2010 and 2015 (group 3), who represent our current population of candidates. Patients in group 3 were older (mean age 52 ± 12 v. $38 \pm$

11 yr, $p = 0.001$), sicker (rate of hospital admission at transplantation 48% v. 20%, $p = 0.001$) and transplanted with organs from older donors (mean age 42 ± 15 v. 29 ± 11 yr, $p = 0.001$) than patients in group 1. It is important to recognize that 12 patients (22%) in group 3 were on mechanical support with LVAD or TAH before undergoing transplantation. Eight patients waited in hospital in status 4, and 4 patients waited at home in status 3 (urgent, but the patient can wait at home) before transplantation. Actuarial survival 5 years after transplantation averaged $71\% \pm 2\%$ in group 3 and $76\% \pm 3\%$ in groups 1 and 2. The freedom rate from acute rejection 1 year after transplantation averaged $37\% \pm 7\%$ in group 1, $41\% \pm 5\%$ in group 2 and $85\% \pm 5\%$ in group 3 ($p = 0.001$).

A Cox regression multivariate analysis including all 11 variables reported in Table 1 showed that younger age of recipients (relative risk 1.04, $p < 0.001$) was the only characteristic associated with late survival.

DISCUSSION

Results from the present study show that one-third of the patients who underwent cardiac transplantation during the first decade of our experience achieved a long-term survival of 20 years or more. Patients with shorter survival

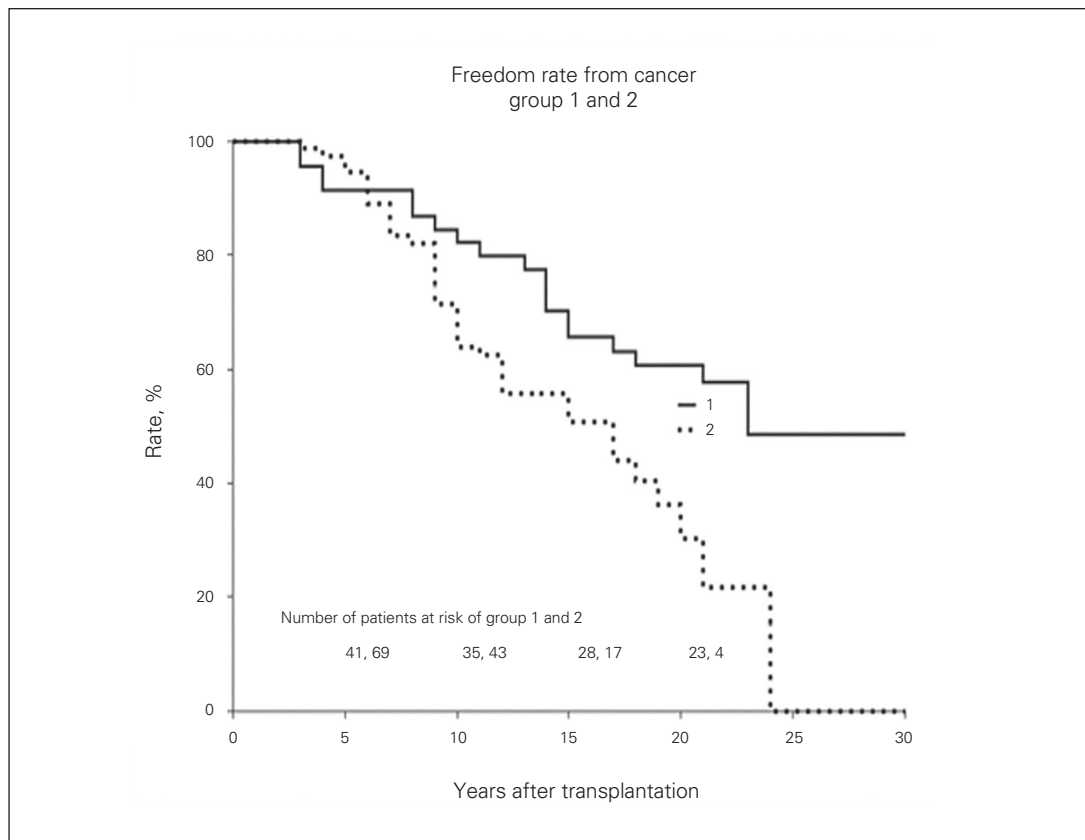


Fig. 2. Freedom from cancer after cardiac transplantation. The freedom rate from cancer averaged $82\% \pm 6\%$ and $61\% \pm 7\%$, respectively, 10 and 20 years after transplantation in group 1 patients compared with $64\% \pm 6\%$ and $30\% \pm 9\%$, respectively, in group 2. The difference was significant using the log-rank test ($p = 0.005$).

after transplantation were older at the time of surgery and were more likely to have ischemic heart disease before transplantation.

Furthermore, in the current era, patients and organs transplanted were both significantly older than in our initial group of long-term survivors. Heart transplantation has made substantial progress in the last 50 years, with dramatic improvements in different fields, such as immunosuppression^{8,9} and prevention of infectious complications.^{10,11} As reported by the International Society for Heart and Lung Transplantation (ISHLT) in 2013, the median survival after cardiac transplantation in adults has increased from 8.4 years between 1982 and 1991 to 10.7 years between 1992 and 2011 and has remained at 11 years in 2012.¹ Several experienced centres have reported remarkable long-term outcomes after heart transplantation, with survival rates up to 56% at 15 years.¹²⁻¹⁵ In this regard, our long-term results compare favourably with the published literature and with other Canadian centres,^{16,17} with a 35% survival rate at 20 years. Moreover, acute rejection episodes were significantly reduced in group 3 patients, who were administered long-term tacrolimus and MMF immunosuppression.

Patients who experienced better long-term survival were younger (< 40 yr), were more likely to be women,

were less frequently affected by ischemic heart disease and, in most cases, were in stable clinical condition at the time of transplantation. Although, the incidence of cardiac allograft vasculopathy was similar in both groups, cancer was a significant cause of death in patients who experienced a shorter survival after transplantation (Fig. 2 and Fig. 3). The Stanford group¹⁵ reported similar results, with long-term survivors being significantly younger at the time of transplantation (35.0 ± 10.5 yr) and with a lower prevalence of coronary artery disease than shorter-term survivors. Others have also reported excellent long-term survival after cardiac transplantation in cohorts of patients who were younger at the time of transplantation and who had a greater prevalence of nonischemic cardiomyopathy.^{13,14} The causes of death among patients with longer survival after transplantation, in our experience, were similar to those reported in the literature, with chronic rejection or coronary allograft vasculopathy and cancer being the 2 major causes of death.¹

The 2002 report of the ISHLT showed that age distribution of heart transplant recipients has changed between the periods 1985-1996 and 1997-2001, with an increase in the proportion of patients between 50 and 64 years old.² Moreover, as stated in the 2013 report of the ISHLT, the current median age of a

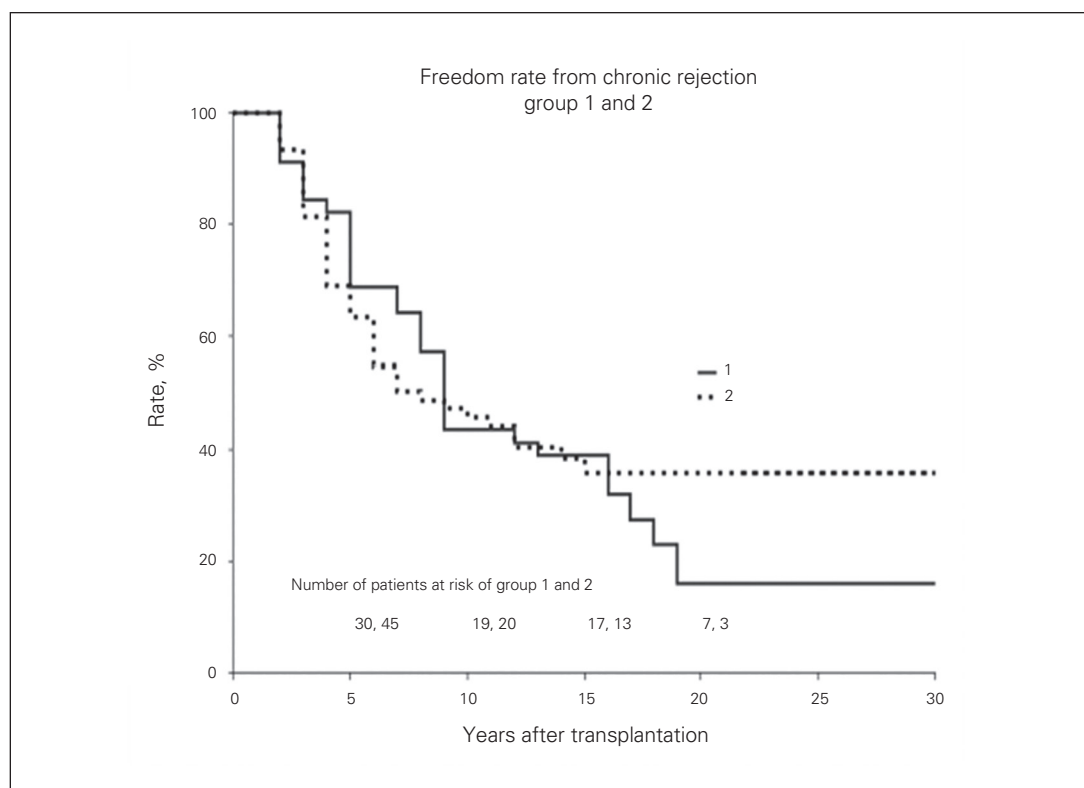


Fig. 3. Freedom from development of graft vasculopathy. The freedom rate from allograft vasculopathy (also called chronic rejection), defined by any coronary artery lesions at planned and unplanned coronary angiography, averaged $44\% \pm 7\%$ and $39\% \pm 7\%$, respectively, 10 and 15 years after transplantation in patients of group 1 compared with $46\% \pm 6\%$ and $36\% \pm 6\%$, respectively, in group 2 patients. The difference was not significant ($p = 0.96$).

cardiac transplant recipient was 54 years.¹ In addition to being older, a substantial proportion of patients currently awaiting transplant are in unstable clinical conditions, with a preoperative hospitalization rate of 44% and a need for intravenous drugs in 42%, and they are supported by different types of mechanical circulatory devices (intra-aortic balloon 6%, LVAD 29%, right ventricular assist device 4%, extracorporeal membrane oxygenation 1%).¹ This new reality and the increasing use of ventricular assist devices is a reflection of the extreme shortage of donor organs, which greatly limits the number of patients who can receive a heart transplant. For this reason, we compared the characteristics of our long-term survivors (group 1) with our cohort of patients transplanted during the most recent 5-year period (group 3). This latter group reflects more accurately the present population of patients on the waiting list. These patients are older and more often hospitalized and on inotropes, short-term mechanical support or with device-related complications. In addition to having a higher risk profile, they undergo transplantation with organs from older donors (so-called marginal), which is associated with an increased risk of death and allograft failure.¹⁸⁻²⁰ Furthermore, the shortage of donor organs is also associated with longer waiting time and the possibility of further clinical deterioration while on the waiting list.

CONCLUSION

Very long-term survival (≥ 20 yr) has been achieved in almost one-third of patients who received transplants during the first decade of our experience. This outcome will be difficult to match in the current era, considering our present population of older and sicker patients receiving organs from older donors. In the near future, a greater use of increasingly refined ventricular assist devices used as destination therapy may provide the ideal solution for many patients with advanced heart failure. Nevertheless, cardiac transplantation will certainly remain, for a long time, the best available treatment option of advanced heart failure for select patients.

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Competing interests: None declared.

Contributors: All authors designed the study, acquired and analyzed the data, wrote and reviewed the article, and approved the final version for publication.

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