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Heart transplantation and mechanical circulatory support: From established treatment to current trends in management of end-stage heart failure

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Summary

In patients with end-stage heart failure refractory to medical and cardiac resynchronisation therapy, heart transplantation is recognised as the treatment of choice. As compared to medical therapy, heart transplantation is considered to be associated with a survival benefit, to enhance functional capacity and improve quality of life, provided that patients are properly selected in accordance with guidelines. However, a powerful trial to compare heart transplantation with conventional management is still lacking and is unlikely to be performed. Individually tailored anti-rejection regimens, based on the currently used immunosuppressive agents, have produced an excellent survival rate following heart transplantation. Unlike the increase in survival in the early phase after transplantation, the attrition rate over the long term has remained similar in recent decades, largely because of associated complications such as chronic allograft vasculopathy and malignancy, the incidence of which could not be markedly reduced. Since the number of heart transplantations is limited due to the shortage of donor organs, and since, in parallel, the number of patients with end-stage heart failure is constantly increasing, mechanical circulatory support is gaining in importance. The pulsatile devices originally used were associated with a high frequency of adverse events such as bleeding and thromboembolic events, noisiness and patient discomfort, which prevented widespread application. The introduction of continuous-flow pumps which are silent and comfortable, and cause fewer side effects, has revolutionised mechanical circulatory support. Since survival on such devices has significantly improved as compared to the previous era, implant rates have dramatically increased, particularly as an alternative to transplantation. In carefully selected patients the outcome of destination therapy approaches survival rates close to those after heart transplantation.

Introduction

Heart failure is a major cause of morbidity and mortality in the population of the western world, with significant societal implications. The direct and indirect cost of heart failure in the US for the year 2010 was estimated at $ 39.2 billion [1, 2]. According to AHA statistics for 2010 the prevalence of heart failure in the US is 5,800,000, nearly half of these patients (48%) presenting reduced left ventricular function (LVEF <40%). 30% of patients are in NYHA functional class III or higher (class III 25%, class IV 5%) [2]. In the United States the incidence of heart failure approaches 10 per 1,000 people after the age of 65. The 1-year mortality for heart failure in this population is as high as 20%. At age 40 the lifetime risk of developing heart failure is 1 in 5 [1]. Since life expectancy is steadily increasing, the heart failure population will grow further. Medical management of heart failure has substantially improved in recent decades. By introducing angiotensin-converting enzyme inhibitors and angiotensin-receptor antagonists, beta-blockers, aldosterone receptor inhibitors and hydralazine/isosorbide dinitrate as main pillars of drug therapy, mortality in patients with heart failure and reduced left ventricular function has been significantly lowered. The concept of implanting ICDs in this patient population was similarly important in this context (for references see Fonarow et al. [2]). In

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addition, cardiac resynchronisation therapy has been shown to be beneficial in selected patients with advanced as well as mild-to-moderate heart failure [3, 4]. In severely advanced heart failure heart transplantation is still believed to be the gold standard of treatment, although controlled trials have never been performed [5, 6]. The concept of mechanical circulatory support was initially introduced to bridge to heart transplantation in the most severely ill patients who would otherwise not survive the time on the waiting list. Due to increasing mismatch between the number of patients in need of heart transplantation and the pool of suitable donors, mechanical circulatory support increasingly emerges as an alternative to heart transplantation, particularly since technical progress has made the devices more durable, reliable and comfortable. Against this background the indications and results of heart transplantation and mechanical circulatory support will be highlighted.

Heart transplantation

In patients with severely advanced heart failure, heart transplantation is generally considered to increase survival and improve quality of life as compared to conventional medical treatment, given that the patients are properly selected [7]. In 2006, the International Society for Heart and Lung Transplantation (ISHLT) issued distinct listing criteria to provide clear guidance to transplant centres for assessment of cardiac function and comorbidities in potentially transplant-eligible patients [6]. Adequate selection of transplant candidates is particularly important, since heart transplantation may be associated with a survival benefit only in patients with a predicted high risk of dying on the waiting list, whereas patients with a predicted low or medium risk have no reduction in mortality risk associated with transplantation, as was shown in a prospective observational study in Germany in 1997 (COCPIT) [8]. However, a randomised multicentre study to compare outcome following heart transplantation versus optimal medical management in patients with end-stage heart failure has not as yet been performed.

Introduction of cyclosporine: the success story of heart transplantation begins

Survival following heart transplantation has continuously improved in recent decades. This is mainly due to a reduction in early mortality within the first year after transplantation. Currently, the 1-year post-transplant survival of all patients reported to the registry of the International Society for Heart and Lung Transplantation (ISHLT) is approx. 84% [9]. Improvement of peri-operative management and, in particular, advances in immunosuppressive therapy have contributed to this success. After the introduction of cyclo-sporine had triggered the breakthrough of heart transplantation in the 1980s, the development of tacrolimus, another calcineurin inhibitor (CNI), opened up the possibility of further refining immunosuppression. Administration of tacrolimus could be shown to reduce the frequency of acute rejection episodes and the incidence of chronic allograft vasculopathy [10]. Also, chronic renal disease developed less frequently under immunosuppression based on tacrolimus as compared to cyclosporine [11]. As a result, tacrolimus is currently more widely used as part of maintenance immunosuppression. Within the last decade the percentage of all patients reported to the ISHLT registry who receive tacrolimus at one year after heart transplantation increased from 23% in 2000 to 73% in 2010, while the number of patients receiving cyclosporine fell from 75% to 18% in the same period [9].

The second component of immunosuppressive therapy: from azathioprine to mycophenolate mofetil and mTOR inhibitors

Whereas in the early period of heart transplantation azathioprine (AZA) served as the second pillar of the immunosuppressive regimen, it has been replaced in most centres by mycophenolate mofetil (MMF), which was introduced in 1991 [9]. Mycophenolate mofetil has been shown to improve survival after heart transplantation as compared to AZA, and to be superior to AZA in preventing acute rejection episodes and the development of chronic allograft vasculopathy and malignancies [12–14]. However, MMF seems to be associated with a higher rate of viral infections [12, 13]. More recently, mammalian target of rapamycin (mTOR) inhibitors, also called proliferation signal inhibitors (PSI), such as sirolimus and everolimus, have aroused the interest of transplant physicians for use as an immunosuppressive agent. They show synergy with the CNIs in their anti-rejection potential and, therefore, allow reduction of CNI drug doses without compromising efficacy, thus lowering nephrotoxicity associated with the administration of both drugs [15, 16]. In combination with cyclosporine or tacrolimus, mTOR inhibitors achieve rejection rates which are equivalent or superior to those seen in mycophenolate mofetil combinations [15]. However, their profile of adverse effects has prevented them from being widely used in transplantation. Currently they are a component of maintenance immunosuppression in only 8% of patients at one year after heart transplantation [9]. Side effects include hyperlipidaemia, wound healing complications, proteinuria and the increase in CNI-induced nephrotoxicity, although they do not present inherent nephrotoxicity. However, due to their antiproliferative effects they may bestow particular benefit on heart transplant recipients with chronic allograft vasculopathy and malignancies, or those at high risk for malignancies [15–17].

Steroids – the first immunosuppressive drug: are they still necessary?

Steroids have been a fundamental element in immunosuppression since the beginning of transplantation. Because of their numerous side effects, attempts have been made in recent years to withdraw steroids from the immunosuppressive protocol after varying time intervals following heart transplantation, most frequently 6–12 months after transplantation. As yet there is no clear evidence in the literature concerning the potential risks and benefits of steroid withdrawal. In a meta-analysis some positive effects on cardiovascular risk factors were identified, whereas a trend towards an increased risk of acute rejection was seen although with no measurable effect on graft or patient survival. The lack of robust evidence requires larger scale randomised controlled trials to fully ascertain the risk/benefit ratio of steroid withdrawal [18]. Currently some 80% of heart transplant recipients remain on steroids at one year and some 50% at five years following transplantation [9].

Figure 1
Survival after heart transplantation: Worldwide and Zurich.
Zurich = Survival of patients transplanted from 1985 to 2011;
ISHLT (International Society for Heart and Lung Transplantation) =
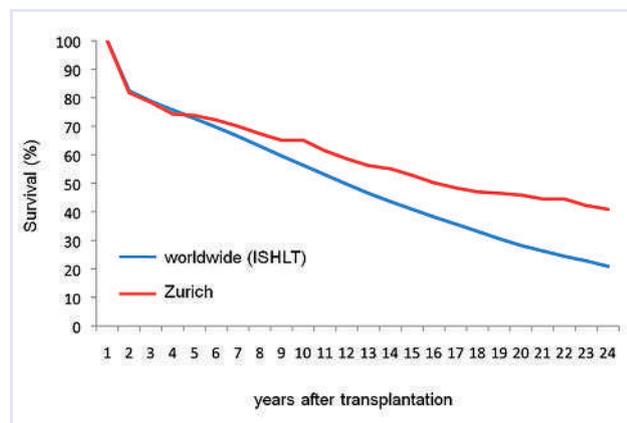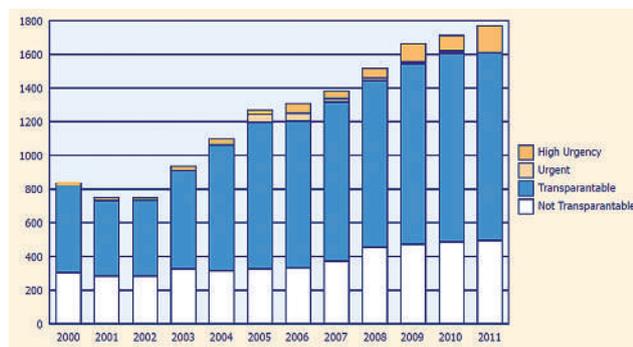Survival of patients transplanted from 1982 to 2010 [9].

Induction therapy – to do it or not to do it?

Induction therapy has always been controversial in heart transplantation. The rationale for its use is prevention of early acute rejection. This may allow reduction of maintenance immunosuppression and have a beneficial effect on the development of chronic allograft vasculopathy. It is used in 52% of heart transplant patients worldwide and is more popular in Europe (76% of patients) than in the US (51% of patients) [9]. Originally, polyclonal anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG) were used for induction therapy. With the introduction of monoclonal interleukin-2 receptor (IL-2R) antagonists, the use of ALG and ATG has declined to 20% of patients, while the use of IL-2R antagonists has increased to 30% of patients. OKT3, a murine monoclonal antibody against the CD3 antigen on T-cells, has lost its relevance in induction therapy, and alemtuzumab, a new, humanised monoclonal antibody against the CD52 antigen on mature lymphocytes, currently accounts for induction therapy in some 3% of patients [9]. However, current data do not allow a firm conclusion on the benefit of induction therapy. The advantage over an immunosuppressive protocol without induction is not clear [9, 19]. Data from the 2011 ISHLT registry show no survival benefit in patients who received induction therapy as compared to those without induction [9]. Randomised trials with induction therapy are lacking [19]. No recent randomised trials comparing ATG with no induction exist. Trials comparing IL-2R antagonists with no induction have shown contradictory results [19, 20]. Alemtuzumab was analysed against no induction in a large retrospective study showing a significant reduction in rejection episodes. However, survival was lower in the alemtuzumab group [21]. Some patient groups may particularly benefit from induction therapy. These are patients sensitised with circulating preformed antibodies who are at high risk for acute rejection episodes, and patients with severe preoperative and perioperative renal dysfunction in whom induction therapy al-

Figure 2
Heart transplant waiting list and heart transplants in the Eurotransplant region (source: Eurotransplant Foundation, Leiden, NL [22]).
A   Heart waiting list, number of patients at year end, by urgency.
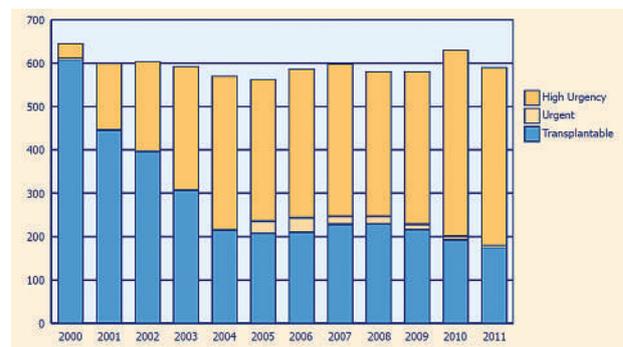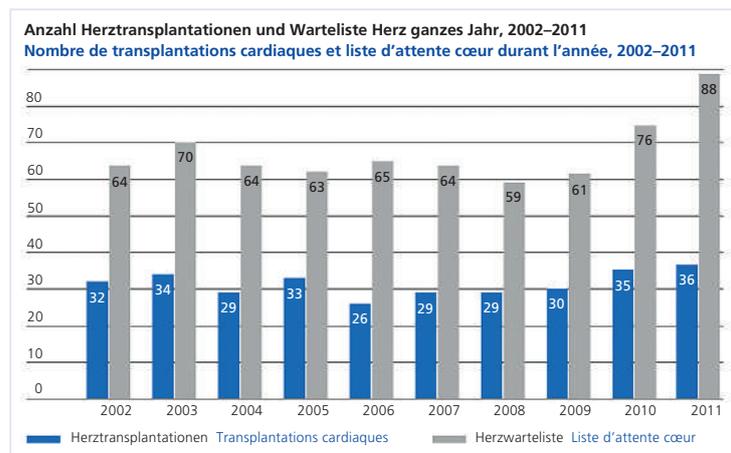B   Number of heart transplants, by recipient urgency at transplant.

A

B

Figure 3

Heart transplant waiting list and heart transplants in Switzerland (source: Swiss-transplant, Bern, CH [23]).

Anzahl Herztransplantationen und Warteliste Herz ganzes Jahr, 2002–2011
Nombre de transplantations cardiaques et liste d'attente cœur durant l'année, 2002–2011

Herztransplantationen / Transplantations cardiaques
Herzwarteliste / Liste d'attente cœur

lows a delay in onset of treatment with nephrotoxic CNI without running a higher risk of acute rejection [19].

Excellent long-term results contrast with unsolved late complications

Long-term results following heart transplantation are excellent, particularly if they are compared with medical management of end-stage heart failure. According to the international registry, ca. 53% of patients are still alive ten years after transplantation, and ca. 26% after 20 years [9]. At Zurich University Hopital 10-year survival compares favourably with the ISHLT registry data with 65% 10-year survival and 50% survival at 20 years (fig. 1). In contrast to the improvement in early survival after heart transplantation, the attrition rate in the long term has remained similar over the years. Independently of the era, some 3–4% of patients die per year [9]. This might be attributable to the long-term complications following heart transplantation, such as chronic allograft vasculopathy and malignancy, which account for ca. 35% of all deaths 10 to 15 years following heart transplantation [9]. Despite improvement in posttransplant management, over the last two decades, it has only been possible to reduce the incidence of chronic allograft vasculopathy and malignancy at 8 years after transplantation from 47% to 45% and from 28% to 23%, respectively.

The problem: not enough donor hearts for the increasing number of transplant candidates

While the number of patients in need of a heart transplant is steadily increasing, the number of suitable donors cannot keep up with this demand. The total count of heart transplantations worldwide has remained more or less unchanged since 2002 at some 3,700 per year [9]. In the Eurotransplant (ET) region, the number of patients on the waiting list has doubled from 2003 to 2011, but the number of heart transplantations

performed within the same period stayed the same (fig. 2) [22]. The same trend is seen in Switzerland (fig. 3) [23]. As a consequence, the number of highly urgent transplantations in ET has increased from 50% to 70% of all transplantations in the same time interval [22]. Patients who are listed electively on the waiting list have a lesser chance of receiving a donor heart. In some countries this has already led to the paradoxical situation that outcomes after transplantation deteriorate due to negative (high risk) patient selection. Because of the gap between demand and supply of donor hearts, the number of patients who have to be bridged to transplantation with a ventricular assist device (VAD) has increased from 18% in the year 2000 to 32% in 2009 [9]. With the advent of newer-generation devices, so-called continuous-flow devices, which are significantly reduced in size as compared to first generation pulsatile devices, survival of patients bridged to transplantation has markedly improved and reaches post-transplant survival rates similar to patients who are transplanted without the need for mechanical support [9]. Technical advances in the field of ventricular assist devices and the resultant success of mechanical circulatory support has led to a dramatic increase in VAD implantations over the last five years [24]. Since heart transplantation cannot cover the demand for end-stage heart failure therapy, and its associated long-term complications are still not controlled, mechanical circulatory support is increasingly considered as an alternative to heart transplantation.

Mechanical circulatory support – an alternative to transplantation?

Introduction of continuous-flow devices: the success story of mechanical circulatory support begins

Mechanical circulatory support was originally implemented to bridge patients to heart transplantation who would otherwise not survive the time on the waiting list. In the mid-1980s, when VADs found their way into clinical use, they consisted of a large pulsatile pump weighing ca. 1 kg which was implanted intracorporeally into the abdominal wall, such as the Novacor N100 (originally Baxter, later World Heart Inc., Ottawa, Canada) and HeartMate® I (originally Thermo Cardiosystems, Inc., Woburn, MA, USA; currently: Thoratec Inc., Pleasanton, CA, USA) [25, 26]. Alternatively, the pumps were located paracorporeally outside the body, like the Thoratec VAD (Thoratec Inc., Pleasanton, CA, USA) and the Berlin Heart Excor (Berlin Heart GmbH, Berlin, Germany) [27, 28]. Although, with increasing experience, survival on the device reached rates of approximately 60–70%, adverse events including thrombosis and embolism, bleeding, infection, and mechanical failure, as well as patient discomfort due to the size and noisiness of the pumps, precluded more ex-

tensive use other than in the most severely ill patients with end-stage heart failure. The introduction of continuous-flow pumps in 1998 revolutionised mechanical circulatory support. Due to the new principle of rotating pumps, the size of the housing could be markedly reduced. Implantation became much easier, and patient comfort increased significantly. However, experience with the first such pump, the axial-flow MicroMed DeBakey VAD (MicroMed Cardiovascular, Inc., Houston, TX, USA), did not live up to expectations. The survival rate on the pump of ca. 55% could not compare with that on pulsatile devices [29]. Pump thrombus formation turned out to be a major problem, causing thromboembolism and irreversible pump stop which certainly contributed to the disappointing results. With further advances in axial-flow technology, second generation pumps such as the Jarvik 2000 (Jarvik Heart, Inc., New York, NY, USA), the Berlin Heart Incor (Berlin Heart GmbH, Berlin, Germany) and the HeartMate® II (Thoratec Inc., Pleasanton, CA, USA) became available. Survival on the pump or to transplantation improved, and adverse effects were reduced [30–32]. The introduction of centrifugal pumps as the third generation of assist devices may further improve outcomes (fig. 4) [33].

Improved results with continuous-flow devices pave the way for destination therapy

Due to the persistent shortage of donor hearts and the increasing number of patients with advanced heart failure, mechanical circulatory support is under increasing consideration as an alternative treatment rather than a bridge to heart transplantation, particularly in the light of the significant technical improvements in the devices. A first attempt to compare VAD therapy with conservative medical treatment in end-stage heart failure patients was made at the turn of the millennium. In the revolutionary REMATCH trial, patients in NYHA IV heart failure not eligible for heart transplantation were randomised to left ventricular assist device (LVAD) therapy versus optimal medical management (OMM) [34]. Patients on mechanical support had a significant survival benefit over medically treated patients. After one year, 52% of patients in the LVAD group were alive, as opposed to 25% in the OMM group ($p = 0.002$). At two years, survival was still higher in the device group (23%) than in the OMM group (8%), but did not reach statistical significance ($p = 0.09$). Adverse events such as bleeding, neurological dysfunction and infection were significantly more frequent in the device group, whereas quality of life was better in the device group than in the medical group. In the REMATCH trial the HeartMate® I was used for LVAD therapy. As outlined above, this was a first generation device of large size and associated with clinically significant adverse events including pocket and driveline infection and limited mechanical reliability and durability [35]. Since the introduction of continuous-flow devices, pumps have become available which are smaller, quieter and more durable than pulsatile devices, making them potentially more suitable for long-term support. This prompted investigators to compare the performance and adverse events of first generation pulsatile devices with second generation continuous-flow pumps. In a landmark trial, patients with end-stage heart failure NYHA class III b or IV, who were ineligible for transplantation, were randomised to undergo implantation of a continuous-flow pump (HeartMate® II) or pulsatile-flow device (HeartMate® I) [36]. Actuarial survival was significantly better for patients with a continuous-flow device as compared to those with a pulsatile-flow pump. After one and two years, 68% and 58% of patients respectively with a continuous-flow pump were alive, but only 55% and 24% of patients, respectively, with a pulsatile pump. In addition, adverse events such as device-related and non-related infections as well as right heart, respiratory and renal failure were less frequent in pa-

Figure 4

The third-generation centrifugal pump HeartWare® (by courtesy of HeartWare International, Inc., Framingham, MA, USA).

A   The HeartWare® LVAD in situ.

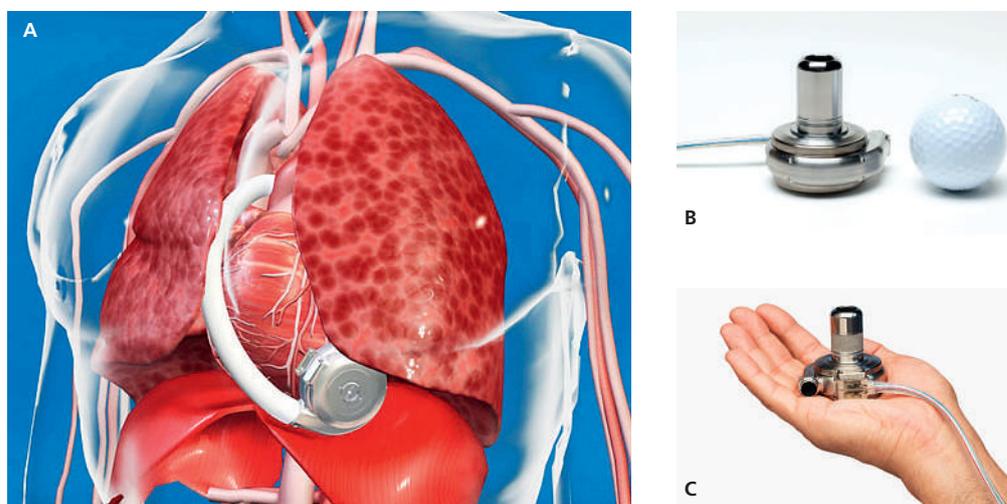B, C   The size of the HeartWare® in comparison with a golf ball and an adult hand.

Figure 5

Survival rates in two trials of LVADs as destination therapy (REMATCH trial 2001, HeartMate® II destination therapy trial 2009). (From [37]: Fang JC. Rise of the machines – left ventricular assist devices as permanent therapy for advanced heart failure. N Engl J Med. 2009;361:2282–5. Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from the Massachusetts Medical Society.)
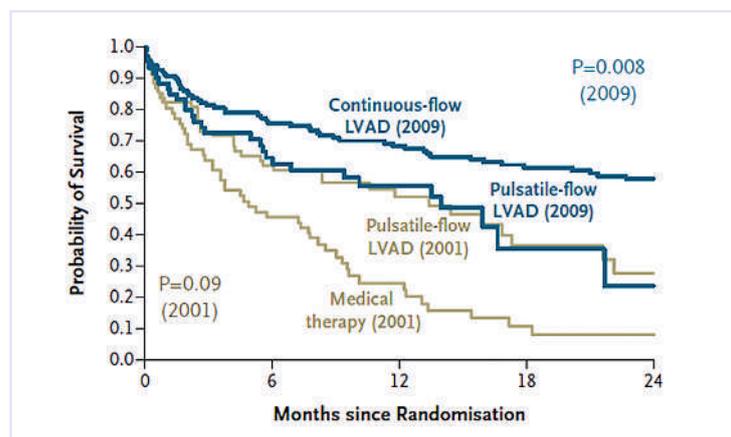

tients with the continuous-flow device. Also, there was a significant reduction in the rate of rehospitalisation and a significant improvement in device durability in the continuous-flow pump group. Quality of life and functional capacity improved in both groups. Interestingly, survival of patients on pulsatile pumps in this study was similar to the survival of the device patients in the REMATCH trial, showing that in the time period of eight years since then there has been no potential for improvement with pulsatile pumps (fig. 5) [37].

The increasing use of ventricular assist devices and the continuously improving survival of patients with such therapy is reflected in the recently published fourth INTERMACS Annual Report [24]. The Inter-

Figure 6

Actuarial survival following ventricular assist device implantation, stratified by era. (Reprinted from [24]: Kirklin JK, Naftel DC, Kormos RL, et al. The Fourth INTERMACS Annual Report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31:117–26. Copyright © 2012 Elsevier, Oxford, UK, reprinted with permission.)
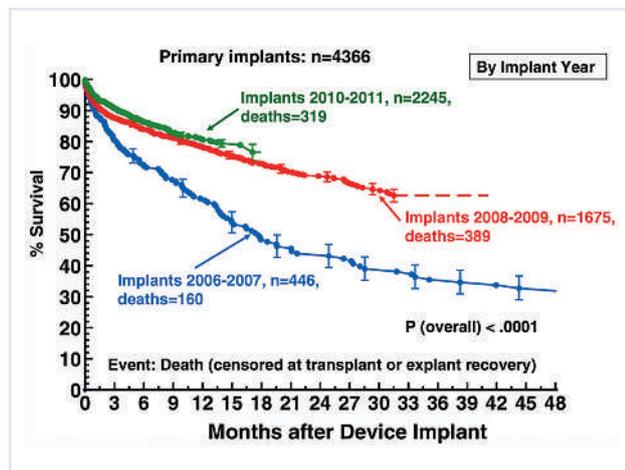

agency Registry For Mechanically Assisted Circulatory Support (INTERMACS) analyses FDA-approved durable mechanical circulatory support device implants in the United States. Since its launch in June 2006 more than 4,500 patients with a primary device implant have been entered into the database. The actuarial survival among all implants amounts to 78% at one year and 68% at two years. The need for BVAD support is associated with a marked reduction in survival. In the recent period from 2008–2011, overall survival for all implants has significantly improved as compared to the previous years and currently exceeds 80% (fig. 6). This may be explained for the most part by the shift in device type away from pulsatile-flow technology to continuous-flow devices over the last four years. Currently more than 99% of all LVAD implants are continuous-flow pumps (fig. 7). The rise of such pumps is related to their excellent success rate. Survival at one and two years after implantation is significantly higher with continuous-flow devices (82% and 74%, respectively) than with pulsatile pumps (61% and 43%, respectively) (fig. 8). If outcome on continuous-flow pumps is analysed by the initial intention-to-treat, the one-year survival of patients on destination therapy (78%) comes close to that of patients who are bridged to transplant (89%) (fig. 9). In the light of such dramatic improvement in survival of patients on modern devices, the European Society of Cardiology has upgraded its recommendation for LVAD implantation in patients with end-stage heart failure who are not eligible for heart transplantation but expected to survive more than one year, from a class IIb to a class IIa recommendation, meaning that in those patients LVAD implantation should be considered [7].

Identification of risk factors helps in selecting patients suitable for destination therapy

To further improve the results of VAD therapy, the influence of preoperative risk factors needs to be investigated. Thus, the fourth INTERMACS Annual Report presented an analysis of risk factors concerning the entire patient population of primary device implants [24]. In the first three months after implant, cardiogenic shock corresponding with INTERMACS level 1, the need for BVAD support, older age, larger BSA, history of cardiac surgery (CABG or valve), higher bilirubin and higher creatinine were identified as risk factors for death in all patients. In the "chronic" phase, between one and three years following implantation, the presence of a pulsatile-flow VAD was the most prominent risk factor. Further detailed risk analyses are certainly required which examine risk factors in the different subgroups of device type (LVAD, BVAD), pump type (continuous-flow, pulsatile-flow) and device strategy (bridge to transplant, destination therapy). Most recent data indicate that in selected patients without the most prominent risk factors, one-year survival on des-

Figure 7

Number of LVAD implantations, stratified by device type and implant year. (Reprinted from [24]: Kirklin JK, Naftel DC, Kormos RL, et al. The Fourth INTERMACS Annual Report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31:117–26. Copyright © 2012 Elsevier, Oxford, UK, reprinted with permission.)

Technical advances in devices will further increase the number of implants
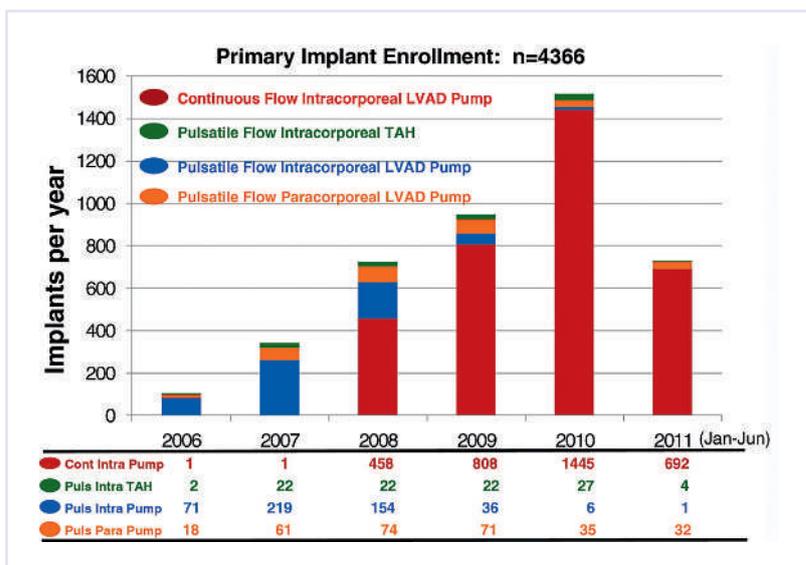
tination therapy can compete with one-year survival following heart transplantation (approx. 85%) [38].

Future trends in this rapidly evolving field focus on several different aspects. Miniaturisation of internal and external components will allow minimally invasive implantation with less surgical trauma, avoidance of cardiopulmonary bypass and reduced hospital stay. With advances in technology adverse events may be reduced, device durability and reliability enhanced, and quality of life improved. When transcutaneous energy transfer is available devices will be fully implantable,

with no need for external components and drivelines penetrating the skin, hereby reducing device-related infection. Some of these developments are already on the horizon. They will further revolutionise mechanical circulatory support and lead to even wider application of mechanical devices.

Conclusion

Heart transplantation has been the gold standard for treatment of patients with end-stage heart failure in recent decades. Refinement of immunosuppressive therapy and posttransplant management have improved its results. However, long-term complications

Figure 8

Actuarial survival following implantation of continuous-flow (CFP) versus pulsatile-flow pumps (PFP). (Reprinted from [24]: Kirklin JK, Naftel DC, Kormos RL, et al. The Fourth INTERMACS Annual Report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31:117–26. Copyright © 2012 Elsevier, Oxford, UK, reprinted with permission.)

Figure 9

Actuarial survival for primary continuous-flow implants, depending on the initial device strategy ("intention-to-treat"). (Reprinted from [24]: Kirklin JK, Naftel DC, Kormos RL, et al. The Fourth INTERMACS Annual Report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31:117–26. Copyright © 2012 Elsevier, Oxford, UK, reprinted with permission.)
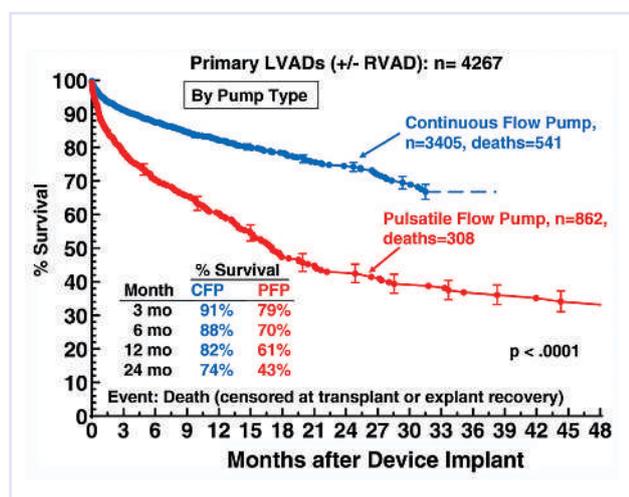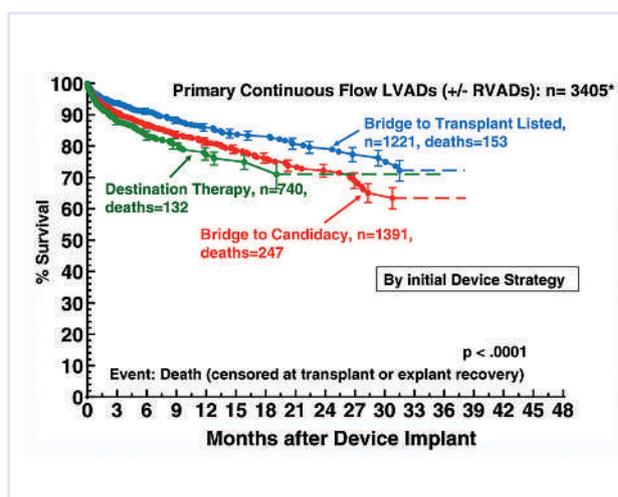
following heart transplantation are still an unsolved problem. Due to the continuing shortage of donor hearts and the increasing number of patients with end-stage heart failure who are not eligible for transplantation, the need for mechanical circulatory support has grown. The availability of modern continuous-flow pumps has dramatically improved the outcome of this therapy. This has led to rapid growth of device implantations in recent years. With future advances in technology it is foreseeable that mechanical circulatory support will further increase its success and may become competitive with heart transplantation.

References

1 Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics – 2010 update: A report from the American Heart Association. Circulation. 2010;121:e46–e215.

2 Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J. 2011;161;1024–1030.e3.

3 Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140–50.

4 Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010:363:2385–95.

5 Banner NR, Bonser RS, Clark AL, et al. UK guidelines for referral and assessment of adults for heart transplantation. Heart. 2011;97:1520–7.

6 Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates – 2006. J Heart Lung Transplant. 2006;25:1024–42.

7 McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Heart Journal, first published online May 19, 2012, doi:10.1093/eurheartj/ehs104

8 Deng MC, De Meester JM, Smits JM, Heinecke J, Scheld HH. Effect of receiving a heart transplant: analysis of a national cohort entered on to a waiting list, stratified by heart failure severity. Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study Group. BMJ. 2000;321:540–5.

9 Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report – 2011. J Heart Lung Transplant. 2011; 30:1078–94.

10 Kofler S, Bigdeli AK, Kaczmarek I, et al. Long-term outcomes after 1000 heart transplantations in six different eras of innovation in a single center. Transpl In. 2009;22:1140–50.

11 Delgado JF, Crespo-Leiro MG, Gómez-Sánchez MA, et al. Risk factors associated with moderate-to-severe renal dysfunction among heart transplant patients: results from the CAPRI study. Clin Transplant. 2010;24:E194–200.

12 Dandel M, Jasaityte R, Lehmkuhl H, Knosalla C, Hetzer R. Maintenance immunosuppression with mycophenolate mofetil: long-term efficacy and safety after heart transplantation. Transplant Proc. 2009:41: 2585–8.

13 Eisen HJ, Kobashigawa J, Keogh A, et al. Three-year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. J Heart Lung Transplant. 2005;24:517–25.

14 O'Neill JO, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: Analysis of the Transplant Registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25:1186–91.

15 Macdonald AS. Use of mTOR inhibitors in human organ transplantation. Expert Rev Clin Immunol. 2007;3:423–36.

16 Zuckermann A, Manito N, Epailly E, et al. Multidisciplinary insights on clinical guidance for the use of proliferation signal inhibitors in heart transplantation. J Heart Lung Transplant. 2008;27:141–9.

17 Epailly E, Albanell J, Andreassen A, et al. Proliferation signal inhibitors and post-transplant malignancies in heart transplantation: practical clinical management questions. Clin Transplant. 2011;25:E475–86.

18 Knight SR, Morris PJ. Steroid sparing protocols following nonrenal transplants; the evidence is not there. A systematic review and meta-analysis. Transpl Int. 2011;24:1198–207.

19 Aliabadi A, Grömmer M, Zuckermann A. Is induction therapy still needed in heart transplantation? Curr Opin Organ Transplant. 2011;16: 536–42.

20 Campara M, Tzvetanov IG, Oberholzer J. Interleukin-2 receptor blockade with humanized monoclonal antibody for solid organ transplantation. Expert Opin Biol Ther. 2010;10:959–69.

21 Teuteberg JJ, Shullo MA, Zomak R, et al. Alemtuzumab induction prior to cardiac transplantation with lower intensity maintenance immunosuppression: one-year outcomes. Am J Transplant. 2010;10:382–8.

22 Oosterlee A, Rahmel A. Eurotransplant International Foundation – Annual report 2011. www.eurotransplant.org

23 Swisstransplant Jahresbericht 2011. www.swisstransplant.org

24 Kirklin JK, Naftel DC, Kormos RL, et al. The Fourth INTERMACS Annual Report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31:117–26.

25 El-Banayosy A, Deng M, Loisance DY, et al. The European experience of Novacor left ventricular assist (LVAS) therapy as a bridge to transplant: a retrospective multi-centre study. Eur J Cardiothorac Surg. 1999;15:835–41.

26 Frazier OH, Rose EA, Oz MC, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. J Thorac Cardiovasc Surg. 2001;122: 1186–95.

27 Farrar DJ, Hill JD. Univentricular and biventricular Thoratec VAD support as a bridge to transplantation. Ann Thorac Surg. 1993;55: 276–82.

28 Schmid C, Tjan T, Etc C, et al. The excor device – revival of an old system with excellent results. Thorac Cardiovasc Surg. 2006;54:393–9.

29 Goldstein DJ. Worldwide experience with the MicroMed DeBakey Ventricular Assist Device as a bridge to transplantation. Circulation. 2003; 108(suppl1):II272–7.

30 Frazier OH, Myers TJ, Gregoric ID, et al. Initial clinical experience with the Jarvik 2000 implantable axial-flow left ventricular assist system. Circulation. 2002;105:2855–60.

31 Schmid C, Tjan TD, Etz C, et al. First clinical experience with the Incor left ventricular assist device. J Heart Lung Transplant. 2005;24: 1188–94.

32 Strüber M, Sander K, Lahpor J, et al. HeartMate II left ventricular assist device; early European experience. Eur J Cardiothorac Surg. 2008; 34:289–94.

33 Strüber M, O'Driscoll G, Jansz P, et al. Multicenter evaluation of an intrapericardial left ventricular assist system. J Am Coll Cardiol. 2011;57: 1375–82.

34 Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001; 345:1435–43.

35 El-Banayosy A, Arusoglu L, Kizner L, et al. Novacor left ventricular assist system versus Heartmate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. J Thorac Cardiovasc Surg. 2000;119:581–7.

36 Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241–51.

37 Fang JC. Rise of the machines – Left ventricular assist devices as permanent therapy for advanced heart failure. N Engl J Med. 2009;361: 2282–5.

38 Kirklin JK. AATS 2012.