REVIEW

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New role of ventricular assist devices as bridge to transplantation: European perspective

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Purpose of review
Progress of ventricular assist devices (VAD) technology led to improved survival and apparently low morbidity. However, from the European perspective, updated analysis of EUROMACS reveals a somewhat less impressive picture with respect to mortality and morbidity.

Recent findings
We describe the great demand of cardiac allografts versus the lack of donors, which is larger in Europe than in the United States. Technical progress of VADs made it possible to work out a modern algorithm of bridge-to-transplant, which is tailored to the need of the particular patient. We analyze the burden of patients undergoing bridge-to-transplant therapy. They are condemned to an intermediate step, coupled with additional major surgery and potential adverse events during heart transplantation.

Summary
Based on current registry data, we do have to question the increasingly popular opinion, that the concept of heart transplantation is futureless, which seems to be for someone who treats and compares both patients (VAD and heart transplantation) in daily practice, questionable. Up to now, left ventricular assist device therapy remains a bridge to a better future, which means a bridge to technical innovations or to overcome the dramatic lack of donors in Europe.

Keywords
bridge-to-transplantation, heart transplantation, ventricular assist device

INTRODUCTION

Mechanical circulatory support (MCS) has become a pre-dominant factor in the treatment of end-stage heart failure. Especially technical advances in the field of left ventricular assist devices (LVADs) offer solutions that are not only about survival but offer quality of life at the cost of acceptable morbidity on the waiting list in times of donor scarcity. We will focus on the new role of bridging a patient to transplant and try to highlight differences in approaches between Europe and the United States. We will discuss the burdens of such a therapy, not only on the patients but also on relatives. Whether LVADs will replace organ heart transplantation (HTx) in the future is uncertain. Today, HTx is the only reasonable option for transplantable patients.

GREAT DEMAND OF ORGANS VERSUS LACK OF DONORS

Two main factors are responsible for organ scarcity in transplantation medicine. There is a growing lack of donors especially in the European countries because of scepticism towards the organ allocation system, e.g. scandals in Germany due to irregularities, and an ever-growing demand of organs because of patients benefiting from improving medical systems (Fig. 1). This is especially true in cardiovascular medicine. While in the last 30 years coronary death was halved by medical progress, heart failure has almost tripled with more patients reaching end-stage heart failure and requiring transplantation [1,2].

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KEY POINTS

- Progress of VAD technology is promising, however, from the European perspective, less impressive with respect to mortality and morbidity.
- Gap between demand of cardiac allografts and the lack of donors is larger in Europe than in US.
- A modern algorithm of BTT is tailored to particular needs of patients.
- There is a significant burden for patients undergoing BTT therapy for an additional intermediate step of major surgery and potential adverse events during HTx.

Although orthotopic HTx is up to date, the only curative option in the treatment of end-stage heart failure, the great imbalance between donors and patients listed for HTx consequently results in patients being increasingly treated with mechanical support devices for bridge to transplant (BTT) [3].

MODERN CONCEPT OF BRIDGE TO TRANSPLANT

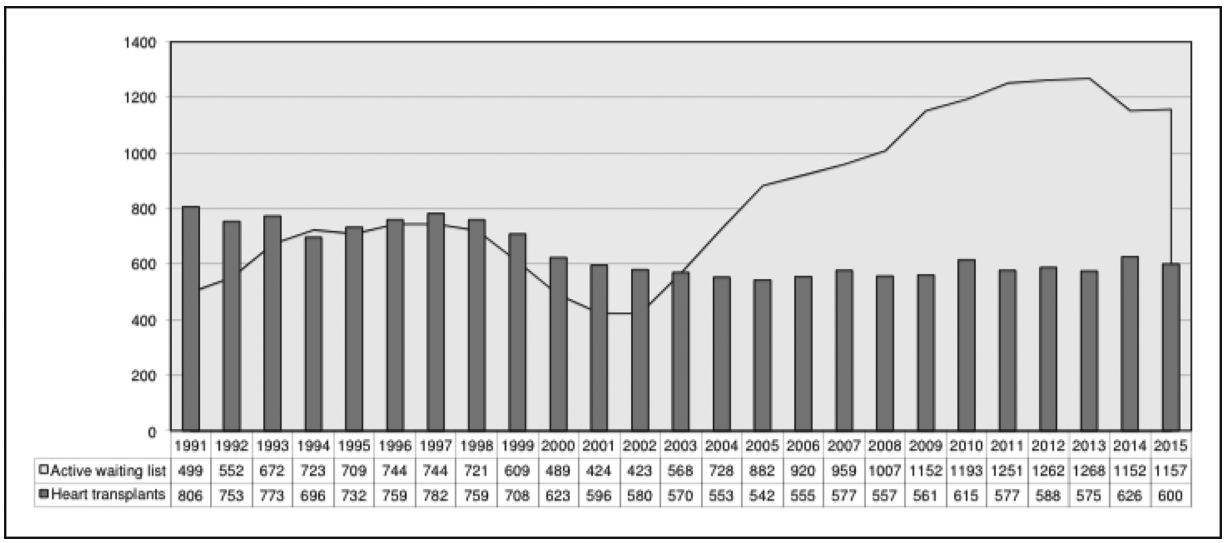
The concept of bridging a patient to transplant has changed in the last years from simply preventing a patient dying on the waiting list to making him/her eligible for receiving an organ [bridge to candidacy (BTC)]. The possibility to offer patients these options can mostly be put back to the technical advances moving from first-generation pulsatile flow LVADs to second- and third-generation continuous flow (CF) devices.

TECHNICAL PROGRESS

The change from pulsatile to CF devices has opened the door to very differentiated treatment concepts. Miniaturized third-generation 'hydrodynamic' (HVAD HeartWare/Medtronic) and fully 'magnetically' (SJM/Thoratec, HeartMate 3) levitated flow technology has enabled minimal invasive implants placed intrapericardially and via left anterior thoracotomy protecting the right ventricle and making reoperations easier [4].

Newest third-generation devices such as SJM's HeartMate 3 combine CF and an artificial pulse assisting with pump washing in order to reduce thrombus related adverse events. This concept of a 'programmed pulsatility' might in the long-term reduce gastric bleeding, aortic valve insufficiency and peripheral vasoplegia. These factors seem to be closely related to a pulseless life and increase morbidity especially in long-term LVAD support [5▪].

Second and third-generation devices dominate the market since 2008 with superior outcomes to their predecessors with survival of 90, 84 and 79% at 6, 12 and 24 months respectively [6]. Well-designed studies monitor long-term efficacy of two key devices. ENDURANCE (HVAD) and MOMENTUM 3 (HeartMate 3) will hopefully be able to give a sound ideas of state of the art device therapy and further improve their quality adjusted life year values [7▪▪,8▪▪].



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Active waiting list	499	552	672	723	709	744	744	721	609	489	424	423	568	728	882	920	959	1007	1152	1193	1251	1262	1268	1152	1157
Heart transplants	806	753	773	696	732	759	782	759	708	623	596	580	570	553	542	555	577	557	561	615	577	588	575	626	600

FIGURE 1. Imbalance of demand and supply: waiting list is increasingly larger than the number of heart transplants. Reused with permission from eurotransplant.org —Heart waiting list and transplants, by year-chart. Source: http://statistics.eurotransplant.org/index.php?search_type=transplants&search_organ=&search_region=& search_period=by+year+chart&search_characteristic=&search_text=.

TAILOR MADE APPROACHES

Because of these incredible advances in device manufacturing, today bridging a patient to transplantation is about offering tailor made solutions for defined situations. To preserve end-organ function, LVADs may even be implanted electively when a long wait is foreseeable, especially in patients with blood type 0 [9▪]. The same goes for patients who are stable, will need an organ at some stage, but are not yet eligible for transplant. A good example for this strategy is cardiorenal syndrome, pulmonary hypertension (PH) or a recently treated malignoma.

Transplantation in patients with presumably 'fixed' PH is contraindicated because of the high rate of right heart failure post-transplantation. It was demonstrated, that LVAD therapy is able to decrease elevated transpulmonary gradients or pulmonary vascular resistance and successfully overcome this contraindication for cardiac transplantation. Zimpfer *et al.* were able to show a relevant decrease in PH during a six-week period of support. In view of the high risk of donor heart failure in patients with 'fixed' PH, the alternative of prior LVAD support and subsequent orthotropic HTx has proven to be a good concept [10].

This concept is theoretically also applicable to tumour illnesses in the form of bridge to tumour-free status. For patients with chemotherapy-induced DCM technical advances allow device placement and achievement of tumour-free intervals over a two to five-year interval prior to HTx [11,12].

BRIDGE TO TRANSPLANT IN EUROPE AND THE UNITED STATES

Because of differences in donor availability and allocation process the relationship and approach towards implanting VADs as BTT is different in the United States and Europe. Although 1-year survival has considerably improved, current UNOS policy is still based on the experience with first-generation assist devices, which in general were able to only provide reliable support for 1 year. LVAD patients are automatically given 1B status and are allowed a 30-day 1A period to avoid device complications. This is of course questionable in light of near 90% survival in the current BTT patients [13]. In Europe, on the other hand, stable heart failure patients on device support are not prioritized.

This has led to a diametric development in the lives of BTT patients on both continents. While the concept of BTT has more than halved the rate of patients dying on the waiting list in Europe and America [14] the fate of these patients is completely different. As reported in the 7th INTERMACS annual report, in America about 60% of donor hearts now go to patients with LVADs on the waiting list due to early automatic prioritization [15▪▪]. This is not the case in Europe. In 2015, Germany transplanted 82% of the patients in high urgency category. As only device complications are prioritized in Germany, waiting lists of patients on LVAD support are on the increase [16]. So in reality, in Germany, the decision to implant an LVAD very nearly equals the concept of destination therapy (DT).

FATE OF BRIDGE TO TRANSPLANT PATIENTS

Although VAD patients have a substantial improvement in activities and quality of life, they do not reach levels generally achieved after HTx. Despite of LVAD support, 12% of patients die on the waiting list. After 2 years, 30% have become ineligible for an HTx because of disabling stroke from embolic or intracranial bleeding events, sepsis, progressive kidney or liver dysfunction. Once any of these conditions become severe enough to compromise outcome of HTx, these patients find themself on an unidentified pathway they did not consent to [9▪,17].

While at first glance abbreviations like BTT or DT seem to have a semantic character, the endorsement to one of those acronyms has in reality forced clinicians into the practice of stating their intention of therapy and strategy at the time of implant. In order to avoid these polarizing decisions a 'no clear intent' strategy in the form of a 'BTC' has become a third option.

Implant strategies change all the time or as Fang *et al.* nicely pointed out in an editorial on an article on VAD strategies 'that an inherent limitation of such an approach is the attempt to predict the future'. In his study, Teuteberg *et al.* focus on the practice of formulating intent strategy at the time of LVAD implant. They show that intended strategies change over time, limiting the usefulness of these plans. In this study, among 2816 primary LVAD patients, 1060 patients were designated BTT candidates. At 2 years, 43.5% where no longer listed for transplant [17,18]. More realistic triage to VAD as lifetime (destination) therapy, rather than to a long transplant waiting list would encourage patients and families to more fully embrace and adapt their lives to enjoy maximal benefit from MCS [9▪].

BURDEN OF BRIDGE TO TRANSPLANT THERAPY

Psychological issues and the effect on surrounding relatives

Compared to palliative treatment strategies [19,20], MCS is an alternative, but expensive treatment

option for end-stage heart disease. The incidence of pre-morbid and post-surgical psychiatric disorders, the use of psychotropic drugs, as well as neurologic events must be taken into account when evaluating the indication for an LVAD [21,22] as psychiatric burden influences compliance and overall outcome. After discharge of a VAD patient, caregivers are additionally placed under significant pressure, which changes over the span of the VAD experience. Different coping mechanisms are used to deal with the initial shock and significant burden [23]. However, partner support seems to be one of the most significant psychosocial variables that can influence clinical success after HTx [24]. Since most of the LVAD patients are waiting for a HTx, the following psychological predictors [24] might also be applied for VAD candidates: empathy, partner support (affective involvement), few demands for emotional communication (affective expression), self-control, stress resistance, emotional stability, high frustration tolerance, low aggression level and younger age. Interestingly, BTT strategy does not lead to post-traumatic stress disorder in patients but may do in their spouses in the long run [25,26].

Redo operation

Several reports have focused on post-transplant survival in patients who were previously treated with a device. Multi-variate analysis of registry data suggested that mechanical support is a predictive factor for poor transplant survival [27]. More recent reports focusing exclusively on long-term LVAD use as BTT has refuted these observations [28,29].

For a centre having great experience with all kinds of redo-surgery including transplantation after LVAD, it is not understandable why results should not suffer from a redo situation. Increased bleeding with post-operative mass transfusions surely influence the acute function of the right ventricle and may influence the immune system with possible rejections in the future. Current research shows that open-heart surgery for the placement of VADs in heart failure patients may be associated with the development of a systemic inflammatory response syndrome because of increased oxidative stress leading to clinical complications and organ dysfunction. VADs are thought to induce high levels of inflammation as a result of exposure to non-physiological flow conditions or artificial surfaces. In daily life we witness that capillary leak syndromes after VAD-transplantations prolong hemodynamic stabilization and post-operative course [30,31▪,32▪]. Should complicated LVAD patients comprise the majority of transplant patients in the future, it will only be a matter of time, when post-transplant survival will suffer.

Neurologic dysfunction

Recently reported event rates vary between 9.8 and 40% (0.21 thromboembolic strikes per year and 0.19 haemorrhagic strokes per year). The ReVOLVE trial revealed neurological dysfunction accounting for death in 4.3% of patients after a mean time of 145 days within a range of 1–730 days. Stroke of any kind occurred in 8% of patients during the same period. The 7th INTERMACS report reported 1.17 neurologic events per 100 patient months for patients implanted between 2008 and 2011, and 1.71 events for patients implanted between 2012 and 2014. INTERMACS levels did not influence neurological events significantly.

Comparing third- and second-generation devices in view of neurologic outcomes, complication rates were reported as 19% for 0.44 median years (HeartWare) and 16% for 0.95 median years (HeartMate II) of follow-up [13,15▪▪,32▪,33–36].

Gastrointestinal bleeding

Gastrointestinal bleeding (GIB) is the most common reason for readmission after implantation of MCS. Although direct comparison in literature is difficult because of differences in definitions and reporting, similar rates of GIB are documented throughout current literature. ReVOLVE and Slaughter *et al.* report comparable event rates per patient year of 14.8, 12.7 and 26%. These results are also in line with the 7th INTERMACS report. A recent meta-analysis by Draper *et al.* which included 17 studies and 1697 patients reported a pooled incidence rate of GIB in patients on LVAD of 23%. The prevalence of GIB was increased in LVAD patients, primarily because of proximal GI angiodysplastic lesions. Risk factors included older age and elevated creatinine [13,36–38].

Infections

Infections are a frequent complication. They can occur because of exposure to invasive therapies, prolonged hospitalizations and of course, because of the percutaneous lead. Causes for readmission are mainly VAD specific complications in the form of driveline or even hardware infections. Antibiotic and antifungal therapy in addition to surgical source control is crucial. Every effort must be made to clear the infection prior to HTx with its immunosuppressive therapy.

In the ADVANCE BTT trial, which was aimed at the approval of the HVAD HeartWare as BTT,

driveline infections and sepsis, occurred in 12 and 11% of patients, respectively. This is numerically lower than in second-generation device pivotal trials. In a pooled multi-centre analysis of Stulak *et al.* 734 patients with an LVAD where reviewed for their adverse events. Cumulative risk of percutaneous driveline infection at 1, 3 and 5 years was 7, 20 and 29% respectively. Cumulative risk of any infection for the entire cohort was 17, 33 and 45%, at 1, 3 and 5 years [39,40▪▪].

Pump thrombosis

Despite an overall reduction of adverse events over the last years, the INTERMACS database reported a six-fold increase in the rates of pump thrombosis in Heart Mate II patients between 2011 and 2012. HeartWare investigators also noticed a higher incidence of thrombosis in their device (0.063–0.08 events/patient year). An investigation found that most pump thromboses occurred because of sub-therapeutic warfarin anticoagulation and taking low-dose aspirin (i.e., 81 mg) or no antiplatelet therapy at all. After additional technical modifications in the region of the inflow cannula and stricter management of anticoagulation, device exchange because of pump thrombosis fell by greater than 50%. Stulak *et al.* reported a cumulative risk of pump thrombus for his entire cohort of 14, 24 and 25%, at 1, 3 and 5 years. In accordance with the above cited data, pre-2011 data showed a high overall incidence of thrombosis of 30% and a much lower rate of 7.6% after change of strategy [13,41▪▪,42▪▪].

EUROMACS VERSUS INTERMACS

The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) was founded in 2009 to focus on European data. EUROMACS is the only existing European-based mechanical support registry for all devices implanted in children and adults. Other registries like the American counterpart INTERMACS (Interagency registry on mechanically assisted circulatory support) only register Food and Drug Administration (FDA)–approved devices and no paediatric patients. When the first annual EUROMACS report was presented at the Annual Meeting of the European Association of Cardio-Thoracic Surgery authors emphasized that no big differences could be seen between the continents. In our view, there are noteworthy differences to mention. While in EUROMACS only 16% patients are categorized as destination patients it is nearly half of all implants in INTERMACS. What strikes the attentive reader of both reports is also the outcome. While the actuarial survival rate of CF LVADs in the INTERMACS cohort after 12 and 24 months is 80 and 70%, survival in EUROMACS is considerably lower with 72.5% after one year and 62.8 at 2 years. Equally interesting is the comparison of causes of death. While in EUROMACS, the main cause of death is infection, sepsis and multi-organ failure, in INTERMACS its neurologic events. Of course this is in some way like comparing apples and pears but once reporting mechanisms in both registries are fully deciphered it will be interesting to see whether existing differences influence implantation strategies in both Europe and America [13,43▪▪]. These differences should also be taken into account in amalgamated data, such as the IMACS registry (ISHLT mechanically assisted circulatory support registry) [44].

CONCLUSION

The VAD technology improved from generation to generation remarkably leading to improved survival and seemingly low morbidity, at the same time. However, from the European point of view, updated analysis of EUROMACS retrieves a different picture with respect to mortality and morbidity. In fact, we do have to accept in daily life the burden of serious adverse events of about 65% during the first year of bridging, which reinforces the incredible value of HTx. We are sometimes faced by the statement that the concept of HTx is futureless, which seems to be for someone who treats and compares both patients in daily practice questionable. Up to now, LVAD therapy remains a bridge to a better future, which means a bridge to technical innovations or to overcome the dramatic lack of donors in Europe.

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Conflicts of interest

P.J.M. received honoraria and travel grants from Medtronic (HeartWare). He is also founding member and currently vice-chairman of EUROMACS.

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