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A contemporary review of mechanical circulatory support

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Mechanical circulatory support has seen numerous advances in the recent years, with important observations made to guide patient selection for the therapy, indications for use, and management of devices after implantation. There is rapid growth in the use of left ventricular assist device therapy (LVAD) for advanced heart failure, with a movement to pursue device intervention earlier in the disease spectrum before comorbidities escalate. With this increase in LVAD use have come new challenges, including unanticipated adverse events and high readmission rates. Simultaneously, complications encountered during LVAD support and an increased number of patients supported with a goal for transplant have had an important effect on the allocation of cardiac allografts. Still, the field continues to evolve and address these challenges in systematic fashion to provide novel solutions and meet the needs of a growing population with advanced heart failure. This has led to an extensive body of literature, ranging from case reports to multicenter clinical trials, which will enhance the future of LVAD technology and patient outcomes. This review summarizes important publications in mechanical circulatory support during the past 24 months.
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Mechanical circulatory support (MCS) continues to evolve in device technology, patient selection, and long-term management of patients undergoing implantation of durable MCS systems. A larger number of patients worldwide are being considered for these therapies due to the growing experience with these devices and larger acceptance of implantation under the destination therapy (DT) indication. Commensurate with this expansion, societal organizations have developed and published guidelines regarding patient selection and device management. Many of these recommendations are based on findings from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), which continues to provide data on our collective experience to date with MCS. In addition to these important publications, many other reports in 2012 to 2013 have highlighted the ongoing development of MCS as an important therapy in advanced heart failure. In this contemporary review, we summarize some of the most important articles published in the last 24 months.

Expansion of MCS therapy, changing indications, and effect on cardiac transplantation

The fifth INTERMACS annual report provided data on nearly 7,000 patients receiving durable MCS devices in the United States (U.S.).[1] The number of implanting centers in the U.S. has continued to rise, demonstrating the staggering expansion of MCS as a therapeutic option for end-stage heart failure. The number of implanting centers in the U.S. increased from approximately 109 in January 2011 to 147 by January 2012, and 131 of these centers have approval for DT implants.

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Simultaneously, the INTERMACS report demonstrated a changing pattern in MCS intent, with an increasing number of patients (> 40% in the last report) now receiving an MCS implant under the DT indication. There are likely multiple reasons for this trend change, ranging from a fixed and limited donor pool for bridge to transplant (BTT) recipients, improved patient selection for left ventricular assist device (LVAD) therapy, an increase in the number of VAD implant centers, greater clinician and patient comfort with the concept of DT, and increased accessibility after regulatory approval for DT in many countries.

Although device intent (BTT vs DT) is often assigned before durable LVAD implant, Tueteberg et al[2] highlighted the dynamic nature of transplant candidacy during VAD support. In an analysis of 2,816 patients enrolled in INTERMACS, they showed that 43.5% of patients who were initially implanted with the BTT intent were no longer listed for cardiac transplantation at 2 years after implant. In contrast, nearly 15% of patients implanted as DT were being considered for transplant at the same time point. Not surprisingly, the most common pre-implant strategy (which remains unapproved by U.S. regulatory bodies) was bridge to candidacy (BTC).

Implant strategy also forecasts patient outcome. The 2-year survivals of patients supported for BTT, BTC, and DT were 78% 70%, and 61%, respectively. Rapid changes in patient nutritional status, functional status, end-organ function, and adherence after LVAD can affect transplant candidacy and post-transplant survival, and the Tueteberg et al[2] study highlights the need for continued efforts to reevaluate the dichotomous implant indications (BTT vs DT) we use in the current era. It also raises questions for VAD programs that specialize only in DT care, without an option for cardiac transplantation, and strategies of care in DT patients who may transition to transplant eligibility.

Although the percentage of total LVAD implants defined a priori with BTT intent has decreased, MCS is playing a larger role in patients ultimately undergoing cardiac transplantation. The latest International Society for Heart and Lung Transplantation (ISHLT) Heart Report, which includes more than 3,529 adult transplants reported worldwide, indicates that nearly 30% of heart transplants were performed in adult patients supported by MCS, and the number continues to rise.[3] Post-transplant outcomes in BTT patients overall are improving with growing experience, particularly with long-term durable LVAD therapy.[2] As such, studies show that MCS is having a larger effect on cardiac transplantation and the allocation process of organs in many U.S. centers and abroad. An analysis of the Scientific Registry of Transplant Recipients database found survival at 12 months in United Network of Organ Sharing (UNOS) status 1A listed patients was 75% in those with and 71% in those without VAD support and that transplants are now occurring more frequently in U.S. patients bridged with VAD support.[4]

Columbia University Medical Center, one of the largest U.S. cardiac transplant centers, reported its experience with patients supported with long-term MCS and the effect of MCS on donor allocation.[5] Of the 726 adult heart transplants, 227 were bridged with MCS, and 164 (72%) received a transplant as UNOS 1A status. During a 6-year period, fewer patients received a transplant during their 1A grace period, and the number of BTT patients who received a transplant due to urgent 1A status for VAD complications increased from 43% to 86%.[5] Although multiple potential factors contribute to such trends, the increase in urgency statuses due to VAD complications is especially important in the context of data from the UNOS database that shows a 75% increase in mortality on the waiting list in patients whose status was upgraded because of LVAD-related complications.[6,7]

Opportunities in MCS as a BTT

Many advanced heart failure patients are reaping a survival benefit with the increased use of LVAD support, but important studies in 2013 highlighted sub-groups of heart failure patients with less success. Patients with biventricular failure demonstrate increased mortality after LVAD implant[1] and have reduced BTT[6] and post-transplant survival.[5] Although rates of VAD use as BTT has significantly increased in those without congenital lesions, patients with congenital heart disease (CHD) have not enjoyed significant gains from MCS support. An analysis of UNOS data compared outcomes in 1,250 CHD patients listed for cardiac transplant vs outcomes in 59,606 listed patients without congenital lesions.[8] Whereas 18% of non-CHD adults in UNOS were listed on VAD support, this number represented only 3% of listed CHD patients. Further, mortality on the transplant list in VAD-supported patients was 26% in those without CHD compared with 41% in those with CHD.[8]

The problem of allosensitization continues to be a challenge for listed patients supported with MCS technologies, and the problem is further confounded by improved technology to detect anti-human leukocyte antigen antibodies. Higher detection to date has not resulted in a clear signal toward increased rejection rates or allograft failure.[9]

Improving outcomes and risk stratification for durable MCS

Multicenter studies have demonstrated a continued improvement in outcomes with durable MCS. The greatest survival gains are reported in patients implanted under the DT indication with a HeartMate II axial-flow device (Thoratec Corp, Pleasanton, CA),[10] mainly because of the inferior survival in the early DT experience. The BTT HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) study compared outcomes in 140 BTT patients undergoing a HeartWare HVAD (HeartWare International Inc, Framingham, MA) implant with 499 patients in a contemporaneous control group from INTERMACS[11] who were largely supported with the HeartMate II. Survival rates at 1 year were 90.7% in the HVAD group and 90.1% in control group, leading to U.S. Food and Drug Administration approval of the

HeartWare HVAD for BTT candidates and an expansion of HVAD indications beyond European borders. The results of the ENDURANCE study, which compared outcomes in DT patients supported with the HeartWare vs the present industry DT leader—the HeartMate II LVAD—are eagerly awaited and are expected to be available in 2014.

Despite improving outcomes, efforts to refine patient risk assessment and selection for MCS continue to be a theme of MCS research. There was renewed interest in use of echocardiographic parameters to assess risk for right ventricular (RV) failure after durable LVAD therapy. Investigators at Cleveland Clinic used quantitative measures of RV function to assess risk of RV failure by echocardiography. Patients requiring an RVAD or prolonged inotropic support (> 14 days) were more likely to have reduced RV free wall strain by echocardiographic vector velocity imaging. A peak strain cutoff of –9.6% was associated with the highest sensitivity and specificity to predict RV failure. Moreover, incorporating RV strain was incremental to the previously reported scores for RV failure.[12] A complementary study examining the comparative size of the RV and LV in 109 patients showed that an RV-to-LV diameter ratio > 0.75 was predictive of RV failure after LVAD implantation.[13] This variable also added incremental value to other scores, including those that included hemodynamic variables.

Global risk scores also remain of interest with the expansion of therapy, especially in older individuals. Using the HeartMate II clinical trials database of 1,122 patients, Cowger et al[14] developed the most comprehensive global risk score to date for patients being considered for continuous-flow technology. Components of the Heart Mate II multivariable risk score (HMRS) included age (decade), serum albumin (mg/dl), serum creatinine (mg/dl), international normalized ratio (INR), and implanting center volume (increasing risk with annual center volume < 15).[14] An application for mobile devices is available for score calculation (https://itunes.apple.com/us/app/lvad-calc/id773254190?ls=1&mt=8). The score can be used to estimate patient mortality after VAD implant and may be an important patient tool for the informed consent process.

Older risk scores were also tested in an era with modern surgical techniques, improved patient selection, and continuous-flow devices. The Lietz-Miller Destination Therapy Risk Score (DTRS), derived from a HeartMate XVE cohort, was analyzed in more than 1,000 patients supported with the HeartMate II device and only had modest discriminatory value for DT patients treated with continuous-flow LVADs.[15] Finally, scores developed to assess non-cardiac organ function were also applied to the MCS field to assess post-implant outcomes. The model of end-stage liver disease (MELD) was shown to be a predictor of adverse events in INTERMACS,[16] and findings were validated by Yang et al[17] in a study of 200 patients. The MELD score and Heart Mate II risk score have similar score components and neither was superior in direct comparison.[14] Nevertheless, both risk models emphasize the need (as in other global scores) for a careful evaluation of extracardiac function in the pre-operative setting.

Short-term MCS

The study of short-term MCS in the past year provided important insight into the heterogenous nature of cardiogenic shock and the need for carefully designed future studies in this realm. The intraaortic balloon pump (IABP) SHOCK-II trial examined the use of an IABP in cardiogenic shock complicating acute myocardial infarction. This prospective study randomized 600 patients to IABP therapy or usual care at the time of anticipated revascularization. Surprisingly, IABP therapy was not associated with reduced 30-day mortality.[18] Given the moderate-risk nature of the randomized cohort, O'Connor and Rogers[19] suggested these results should lead to a reevaluation of our understanding and subsequent therapeutic strategies in cardiogenic shock, with a need to readdress our current indications for device support. Use of this decades-old technology has subsequently been explored in a slightly different population: chronic heart failure progressing to cardiogenic shock.[19] Estep et al[20] described an experience of extended IABP support (median support time, 18 days; range, 4–152 days) from a percutaneous axillary approach in 50 patients as a BTT. Not only did this expand the use of this device, which has been in clinical practice for many years, but this study also reported a novel insertion method that would allow ambulation in the end-stage heart failure patient.

MCS and myocardial recovery

Although myocardial recovery with a variety of long-term and short-term MCS devices has been reported, overall rates of myocardial recovery with long term MCS devices remain very low.[1] There have been some interesting insights into this low rate, including the assessment of myocardial samples after prolonged MCS and the use of plasma biomarkers. Not all patients treated with durable LVAD have a decrease in markers of extracellular matrix proteins, such as the matrix metalloproteinases, and persistent elevation in these markers may result in RV failure.[21] Similarly, galectin-3, a novel heart failure biomarker that is associated with myocardial fibrosis, was examined in peripheral blood samples with concomitant measurement of myocardial messenger RNA in patients undergoing MCS. Galectin-3 levels remained elevated after MCS and predicted worse outcomes with higher levels.[22] Collectively, these data suggest there may be novel targets for therapies beyond neurohormonal antagonists to treat heart failure as an adjunct to MCS support.

In addition to fully understanding the recovery process, studies have challenged the methods and frequency with which we assess for improved myocardial function. Investigators from the Utah Cardiac Recovery Program assessed myocardial recovery by using a protocol-driven echocardiographic assessment in ischemic and non-ischemic cardiomyopathy and showed evidence of recovery as early as 30 days after LVAD implantation, with the greatest effect seen at 6 months.[23] The greatest improvement was in younger patients with the shortest duration of heart failure, and these finding were consistent with other studies.[24]

However, the results suggest that some recovery is possible in a larger proportion of patients with mechanical unloading and that further investigation will be required to see how much recovery is adequate for LVAD explant.

Beyond survival in MCS: Focus on adverse events and readmissions

The growing population of patients supported by durable MCS devices has had an important effect on the infrastructure required to manage patients outside of the implanting hospital and on costs to the health care system. Single-center studies have reported readmission rates after LVAD implantation between 1.5 and 2.5 per patient-year of support, with an increased rate in the first 6 months after implant.[25–27] The leading cause for readmission was bleeding (primarily gastrointestinal), followed by heart failure/arrhythmia and then infection.[25] Gastrointestinal bleeding due to development of arteriovenous malformations remains common after implantation of continuous-flow devices and is believed to be due to reduced pulse pressure. For the first time, the survival effect of this most common adverse event was reported by the group at Henry Ford Hospital, who demonstrated that although gastrointestinal bleeding is a common morbidity associated with LVAD therapy, survival was not negatively affected.[28] In an effort to reduce events, investigators also showed that increased pulsatility is associated with reduced bleeding events, setting the stage for a possible prospective study examining different unloading strategies during continuous-flow device support.[29]

On the opposing side of the bleeding-thrombosis paradigm, there was emerging interest in understanding the risk of thrombosis and associated phenomena such as hemolysis. A multicenter study of 837 patients undergoing HeartMate II implant between 2004 and 2013 documented 72 device thromboses in 66 patients.[30] Importantly, the authors showed a time-related increase in LVAD thrombosis. The occurrence of confirmed device thrombosis within 3 months of device implant increased from 2.2% (95% confidence interval [CI], 1.5%–3.4%) in patients implanted in March 2011 to 8.4% (95% CI, 5.0%–13.9%) in those implanted in January 2013. Further, median times to device thrombosis from implant decreased from 18.6 months (95% CI, 0.5–53 months) for HeartMate II implants before March 2011 to 2.7 months for implants thereafter.

Several studies have identified better means of detecting device thrombosis and risk factors for thrombosis development. Cowger et al,[31] with the University of Michigan group, showed that the current INTERMACS definition for hemolysis and thrombosis using a serum free hemoglobin $>$ 40 mg/dl lacks sensitivity and, potentially, the lead time necessary to reduce patient morbidity by device intervention. Compared with the INTERMACS serum free hemoglobin threshold, lactate dehydrogenase (LDH) values $>$ 600 IU/liter (representing 2.5 times the laboratory upper limit of normal) provided an earlier (by ~4 months) and more accurate detection of patients on HeartMate II LVAD support who subsequently required device exchange for confirmed thrombosis.[31] This group also showed that 1-year event-free survival after the onset of LDH defined hemolysis (a single LDH $>$600 IU/liter) was 32% $\pm$ 7.2% compared with 89% $\pm$ 3.2% in those with persistent LDH values $<$ 600 IU/liter (hazard ratio, 8.0; 95% CI, 4.4–14; area under the curve, 0.87 $\pm$ 0.04; $p < 0.001$) and patients with an elevated LDH had a 4-fold higher risk of stroke.[32] The University of Michigan group also showed that device type affects hemolysis marker detection thresholds. In patients supported with the HeartWare HVAD, LDH was again superior, but thresholds for detecting device thrombosis were lower at LDH values $>$ 400 IU/liter.[33]

In addition to hemolysis marker elevation and era of device implant, other risks for LVAD thrombosis are beginning to be elucidated. Ravichandran et al[34] compared 18 patients with confirmed HeartMate II thrombosis with 82 patients without and found that, in addition to elevated hemolysis markers, younger age and lower INRs were risk factors for hemolysis. In a multicenter study of 389 patients with continuous-flow LVAD support, thromboembolic and hemolysis events occurred 7.4 [4.9–11] times more frequently in patients with prior gastrointestinal bleeding,[35] possibly also due to alterations in anti-coagulant management during bleeding events.

Although mortality on VAD support continues to decrease, morbidity due to device thrombosis is becoming more apparent. Suspected or confirmed thrombosis was one of the most common indications for device exchange in an analysis of 1,128 patients of whom 72 underwent replacement between 2005 and 2010.[36] The primary indication was percutaneous lead damage (3%), followed by thrombosis and then infection (0.6%). Operative mortality at 30 days was 6.5%, and 65% were alive at 2 years after exchange, suggesting pump replacement for most confers low mortality.[36] Studies are needed to better determine the timing of pump exchange for patients with asymptomatic hemolysis, operative procedure of choice (subcostal vs sternotomy approach), and if alterations in anti-coagulation (higher INR goals) and/or anti-platelet management improve outcomes in patients at risk for hemolysis or those with hemolysis.

LVAD exchange and patient readmission because of these complications appears to impart a significant effect on the costs of long-term MCS therapy over the lifetime of support. With the growing number of patients treated with LVAD therapy, there was an interest in understanding the current cost-effectiveness of LVAD therapy as a bridging therapy and as permanent support.[37,38] Rogers et al,[38] from Duke University, described a significant decrease in costs associated with LVAD therapy in the transition from pulsatile-flow to continuous-flow devices, although the current costs of the therapy do not meet U.S. benchmarks for cost-effectiveness. Further, the significant additional costs associated with adverse events highlight the need for future research to focus on outcomes other than survival.[38,39]

MCS physiology

The physiologic interaction between MCS, the native heart, and other organs has also been intensely examined.

Augmentation of cardiac output with MCS appears to result in improvements in total-body insulin resistance and improvement in myocardial catabolism, which was identified using paired myocardial samples.[40] There have been further reports of worsening aortic insufficiency after implantation of continuous-flow LVADs,[41] novel minimally invasive methods to correct this common problem,[42,43] and more data suggest tricuspid repair at the time of LVAD implantation may reduce right heart failure and length of stay during the index hospitalization.[44]

A recent report from Segura et al[45] highlighted the potentially unanticipated changes in the aortic wall after continuous-flow LVAD support. In an elegant study of aortic wall samples before and after continuous flow LVAD implantation, investigators showed important histologic changes in the aortic wall, with smooth muscle degeneration and elastic fiber degeneration.[45] The implications of these changes in patients on long-term support have yet to be determined.

Ventricular arrhythmias have been more extensively studied as an ongoing manifestation of heart failure after MCS, with a greater appreciation for the degree of pre-implant arrhythmia burden as a risk factor for recurrent ventricular tachycardia.[46,47] Strategies to manage these episodes were also carefully considered,[48] and in a provocative article, Uriel et al[47] challenged the need for ongoing defibrillator therapy in patients treated with durable MCS who have not had pre-operative ventricular arrhythmic events. In patients without pre-implant ventricular arrhythmias, the incidence of post-implant arrhythmia was very low compared with those with any electrical instability (4% vs 45.5%, $p < 0.001$) in the pre-operative setting. Further, no patients discharged post-implant without implantable cardioverter defibrillator therapy died in follow-up.[47]

Expanding horizons and special populations in MCS

With the continued miniaturization and technological maturation of devices, progress was made in the use of MCS in the pediatric population. The Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany) pediatric VAD was evaluated in a multicenter trial, with results published in 2011, but reports did not capture the results of patients who were excluded and received treatment with the device under a compassionate use protocol. A study that combined the

Table 1 Recently Completed and Future Studies in Mechanical Circulatory Support

Study	Study design	Study population	Study information	Status
ADVANCE	Prospective non-randomized, 2 arms	NYHA class IV and transplant listing eligible	HeartWare[a] vs INTERMACS control	Completed
ROADMAP	Prospective observational two arm study	NYHA class IIIb and class IV INTERMACS 4 DT- transplant ineligible	HeartMate II[b] vs continued medical therapy	Completed enrollment
REVIVE-IT	Randomized controlled study	NYHA class III patients INTERMACS 4–7 DT-transplant ineligible	HeartMate II vs continued medical therapy	Enrolling
ENDURANCE	Randomized controlled trial	NYHA class IIIb/IV INTERMACS 1–3 DT	HeartWare HVAD vs commercially available device	Completed enrollment
IMPELLA-RP	Non-randomized, single arm	RV failure after myocardial infarction or cardiac surgery	Impella-RP[c] for RV failure refractory to pharmacologic support	Enrolling
MedaMACS	Prospective registry	NYHA class IIIb and class IV with high risk features	Prospective registry for patients not being considered for LVAD therapy	Enrolling
MVAdvantage	Nonrandomized, single arm	NYHA class IIIb/IV INTERMACS 1–3	HeartWare MVAD	Not yet enrolling
Jarvik DT trial	Randomized open label	NYHA class IIIb/IB INTERMACS 1–3 DT	Jarvik[d] 2000 vs HeartMate II	Enrolling

ADVANCE, HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure; DT, destination therapy; ENDURANCE, A clinical trial to evaluate the HeartWare ventricular assist system for destination therapy of advanced heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MedaMACS, medical arm for mechanically assisted circulatory support; MVAD, miniaturized ventricular assist device; NYHA, New York Heart Association; REVIVE-IT, Randomized Evaluation of VAD Intervention before Inotropic Therapy; ROADMAP, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device (LVAD) and Medical Management; RV, right ventricle.

[a]HeartWare International, Inc. Framingham, Massachusetts.
[b]Thoratec, Pleasanton, California.
[c]Abiomed, Danvers, Massachusetts.
[d]Jarvik Heart Inc, New York, New York.

original investigational device exemption (IDE) protocol and this expanded protocol ($n = 204$ patients) found the EXCOR VAD provided successful BTT, recovery, or continued support for nearly 75% of the cohort.[49] Neurologic events remained high, with an incidence of ~30%, and contributed significantly to those who died on support.[49,50] Post-transplant outcomes of these patients remained improved compared with those bridged with extracorporeal membrane oxygenation until a suitable organ was available.[50] Cassidy et al[51] presented data on 102 pediatric patients implanted with the Berlin Heart during a 7-year period (5,247 days of total support) in the United Kingdom.[51] They also showed promising results, with 84% survival to transplant or device explant. Of the 16 deaths, 7 patients died of multisystem organ failure, and 6 had catastrophic strokes. A small analysis from INTERMACS by Cabrera et al[52] compared outcomes in 28 pediatric patients (aged 11–18 years) and in 359 young adults (aged 19–39 years) in the U.S. Survival was > 95% in both groups at 6 months of support, with the major complication being bleeding (0.5–0.6 events per year of support).

These results are timely given the growing population of young adults with CHD and interest in expanding the use of MCS, including total artificial heart (TAH) systems to patients with single-ventricle physiology and failing cavopulmonary circuits.[53] Indeed, TAH technology continues to be evaluated extensively as a BTT for patients with severe biventricular failure as a BTT. The U.S. experience with > 100 TAH implants (Syncardia Systems Inc, Tucson, AZ) was reported by Copeland et al,[54] with 68.3% survival (87-day median follow-up) in extremely sick patients who were not candidates for isolated LV support. Other special populations were also considered for this technology, including patients with allograft failure.[55] Continuous-flow technology has also been considered a suitable mechanism for long-term biventricular support, with reports of successful placement of currently available LVADs in a biventricular configuration and even after cardiectomy.[56,57] These advances again bring into the question the absolute need for pulsatile flow in the human circulation and the technologic advances awaiting us moving forward with MCS.

Conclusions and future direction

MCS continues to be one of the most dynamic therapies in medicine and, as reported in this review, is being studied extensively across the globe to ensure optimal outcomes. Durable devices are under the most intense investigation (Table 1), with a shift in focus from survival to a reduction in adverse events and minimizing negative patient–device interactions. At the forefront of this will be a further study into the growing problem of LVAD thrombosis, which was highlighted in a special edition of the *Journal of Heart and Lung Transplantation* and a high-profile study by leading U.S. centers.[30] Factors studied as part of this process will include patient, device, and practice variables but will also require careful assessment of current and future regulatory oversight in MCS therapy.

Future discussion will revolve around reevaluation of current indications for implantation of durable devices, with a continued shift away from the BTT and DT designation. This will require a commitment to innovative clinical trial design incorporating active controls and registry data, as well as carefully selected end points that incorporate functional status and adverse events. Improvements in device technology will certainly play an important role in this effort, with continued partnering between investigators, industry, and international regulatory agencies. Indeed, some leaders in the field have asked how European and Asian regulatory processes can be used to develop market standards in the U.S. and standardized clinical standards for future trials.[58] These trials will include not only durable devices for adults but also short-term devices for acute cardiogenic shock and for pediatric patients.

Disclosure statement

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References

1. Kirklin JK, Naftel DC, Kormos RL, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141-56.
2. Teuteberg JJ, Stewart GC, Jessup M, et al. Implant strategies change over time and impact outcomes: insights from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). JCHF 2013;1:369-78.
3. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth official adult heart transplant report–2013; focus theme: age. J Heart Lung Transplant 2013;32:951-64.
4. Colvin-Adams M, Smith JM, Heubner BM, et al. OPTN/SRTR 2011 Annual Data Report: heart. Am J Transplant 2013;13(Suppl 1):119-48.
5. Uriel N, Jorde UP, Woo Pak S, et al. Impact of long term left ventricular assist device therapy on donor allocation in cardiac transplantation. J Heart Lung Transplant 2013;32:188-95.
6. Wever-Pinzon O, Drakos SG, Kfoury AG, et al. Morbidity and mortality in heart transplant candidates supported with mechanical circulatory support: is reappraisal of the current United network for organ sharing thoracic organ allocation policy justified? Circulation 2013;127:452-62.
7. Healy AH, Baird BC, Drakos SG, Stehlik J, Selzman CH. Impact of ventricular assist device complications on posttransplant survival: an analysis of the United Network of Organ Sharing database. Ann Thorac Surg 2013;95:870-5.
8. Gelow JM, Song HK, Weiss JB, Mudd JO, Broberg CS. Organ allocation in adults with congenital heart disease listed for heart transplant: impact of ventricular assist devices. J Heart Lung Transplant 2013;32:1059-64.
9. Shankar N, Daly R, Geske J, et al. LVAD implant as a bridge to heart transplantation is associated with allosensitization as measured by single antigen bead assay. Transplantation 2013;96:324-30.
10. Park SJ, Milano CA, Tatooles AJ, et al. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circ Heart Fail 2012;5:241-8.
11. Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191-200.

12. Grant ADM, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. J Am Coll Cardiol 2012;60:521-8.
13. Vivo RP, Cordero-Reyes AM, Qamar U, et al. Increased right-to-left ventricle diameter ratio is a strong predictor of right ventricular failure after left ventricular assist device. J Heart Lung Transplant 2013;32:792-9.
14. Cowger J, Sundareswaran K, Rogers JG, et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. J Am Coll Cardiol 2013;61:313-21.
15. Teuteberg JJ, Ewald GA, Adamson RM, et al. Risk assessment for continuous flow left ventricular assist devices: does the destination therapy risk score work? An analysis of over 1,000 patients. J Am Coll Cardiol 2012;60:44-51.
16. Matthews JC, Pagani FD, Haft JW, Koelling TM, Naftel DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. Circulation 2010;121:214-20.
17. Yang JA, Kato TS, Shulman BP, et al. Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: use of the Model of End-stage Liver Disease (MELD) and MELD eXcluding INR (MELD-XI) scoring system. J Heart Lung Transplant 2012;31:601-10.
18. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
19. O'Connor CM, Rogers JG. Evidence for overturning the guidelines in cardiogenic shock. N Engl J Med 2012;367:1349-50.
20. Estep JD, Cordero-Reyes AM, Bhimaraj A, et al. Percutaneous placement of an intra-aortic balloon pump in the left axillary/subclavian position provides safe, ambulatory long-term support as bridge to heart transplant. JCHF 2013;1:382-8.
21. Kato TS, Chokshi A, Singh P, et al. Markers of extracellular matrix turnover and the development of right ventricular failure after ventricular assist device implantation in patients with advanced heart failure. J Heart Lung Transplant 2012;31:37-45.
22. Erkilet G, Ozpeker C, Bothig D, et al. The biomarker plasma galectin-3 in advanced heart failure and survival with mechanical circulatory support devices. J Heart Lung Transplant 2013;32:221-30.
23. Drakos SG, Wever-Pinzon O, Selzman CH, et al. Magnitude and time course of changes induced by continuous-flow left ventricular assist device unloading in chronic heart failure: insights into cardiac recovery. J Am Coll Cardiol 2013;61:1985-94.
24. Goldstein DJ, Maybaum S, MacGillivray TE, et al. Young patients with nonischemic cardiomyopathy have higher likelihood of left ventricular recovery during left ventricular assist device support. J Card Fail 2012;18:392-5.
25. Hasin T, Marmor Y, Kremers W, et al. Readmissions after implantation of axial flow left ventricular assist device. J Am Coll Cardiol 2013;61:153-63.
26. Forest SJ, Bello R, Friedmann P, et al. Readmissions after ventricular assist device: etiologies, patterns, and days out of hospital. Ann Thorac Surg 2013;95:1276-81.
27. Smedira NG, Hoercher KJ, Lima B, et al. Unplanned hospital readmissions after HeartMate II implantationfrequency, risk factors, and impact on resource use and survival. JCHF 2013;1:31-9.
28. Morgan JA, Paone G, Nemeh HW, et al. Gastrointestinal bleeding with the HeartMate II left ventricular assist device. J Heart Lung Transplant 2012;31:715-8.
29. Wever-Pinzon O, Selzman CH, Drakos SG, et al. Pulsatility and the risk of nonsurgical bleeding in patients supported with the continuous-flow left ventricular assist device HeartMate II. Circ Heart Fail 2013;6:517-26.
30. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med 2014;370:33-40.
31. Shah P, Mehta VM, Cowger JA, et al. Lactate dehydrogenase is superior to serum free hemoglobin as a marker of pump thrombosis in left ventricular assist devices. J Heart Lung Transplant 2013;32:S37.
32. Cowger JA, Romano MA, Shah P, et al. Hemolysis: A harbinger of adverse outcome after left ventricular assist device implant. J Heart Lung Transplant 2014;33:35-43.
33. Shah P, Mehta VM, Cowger JA, Aaronson KD, Pagani FD. Diagnosis of hemolysis and device thrombosis with lactate dehydrogenase during left ventricular assist device support. J Heart Lung Transplant 2014;33:102-4.
34. Ravichandran AK, Parker J, Novak E, et al. Hemolysis in left ventricular assist device: A retrospective analysis of outcomes. J Heart Lung Transplant 2014;33:44-50.
35. Stulak JM, Lee D, Haft JW, et al. Gastrointestinal bleeding and subsequent risk of thromboembolic events during support with a left ventricular assist device. J Heart Lung Transplant 2014;33:60-4.
36. Moazami N, Milano CA, John R, et al. Pump replacement for left ventricular assist device failure can be done safely and is associated with low mortality. Ann Thorac Surg 2013;95:500-5.
37. Moreno SG, Novielli N, Cooper NJ. Cost-effectiveness of the implantable HeartMate II left ventricular assist device for patients awaiting heart transplantation. J Heart Lung Transplant 2012;31:450-8.
38. Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circ Heart Fail 2012;5:10-6.
39. Slaughter MS, Rogers JG. Editorial Commentary: Determining the cost-effectiveness of mechanical circulatory support. J Heart Lung Transplant 2012;31:448-9.
40. Chokshi A, Drosatos K, Cheema FH, et al. Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance, and normalizes cardiac metabolism in patients with advanced heart failure. Circulation 2012;125:2844-53.
41. Rajagopal K, Daneshmand MA, Patel CB, et al. Natural history and clinical effect of aortic valve regurgitation after left ventricular assist device implantation. J Thorac Cardiovasc Surg 2013;145:1373-9.
42. D'Ancona G, Pasic M, Buz S, et al. TAVI for pure aortic valve insufficiency in a patient with a left ventricular assist device. Ann Thorac Surg 2012;93:e89-91.
43. Parikh KS, Mehrotra AK, Russo MJ, et al. Percutaneous transcatheter aortic valve closure successfully treats left ventricular assist device–associated aortic insufficiency and improves cardiac hemodynamics. JACC: Cardiovasc Interv 2013;6:84-9.
44. Piacentino V 3rd, Ganapathi AM, Stafford-Smith M, et al. Utility of concomitant tricuspid valve procedures for patients undergoing implantation of a continuous-flow left ventricular device. J Thorac Cardiovasc Surg 2012;144:1217-21.
45. Segura AM, Gregoric I, Radovancevic R, Demirozu ZT, Buja LM, Frazier OH. Morphologic changes in the aortic wall media after support with a continuous-flow left ventricular assist device. J Heart Lung Transplant 2013;32:1096-100.
46. Raasch H, Jensen BC, Chang PP, et al. Epidemiology, management, and outcomes of sustained ventricular arrhythmias after continuous-flow left ventricular assist device implantation. Am Heart J 2012;164:373-8.
47. Garan AR, Yuzefpolskaya M, Colombo PC, et al. Ventricular arrhythmias and implantable cardioverter-defibrillator therapy in patients with continuous-flow left ventricular assist devices. Need for primary prevention? J Am Coll Cardiol 2013;61:2542-50.
48. Nakahara S, Chien C, Gelow J, et al. Ventricular arrhythmias after left ventricular assist device. Circ Arrhythm Electrophysiol 2013;6:648-54.
49. Almond CS, Morales DL, Blackstone EH, et al. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation 2013;127:1702-11.
50. Eghtesady P, Almond CS, Tjossem C, et al. Post-transplant outcomes of children bridged to transplant with the Berlin Heart EXCOR Pediatric ventricular assist device. Circulation 2013;128:S24-31.
51. Cassidy J, Dominguez T, Haynes S, et al. A longer waiting game: bridging children to heart transplant with the Berlin Heart EXCOR device–the United Kingdom experience. J Heart Lung Transplant 2013;32:1101-6.
52. Cabrera AG, Sundareswaran KS, Samayoa AX, et al. Outcomes of pediatric patients supported by the HeartMate II left ventricular assist device in the United States. J Heart Lung Transplant 2013;32:1107-13.

53. Rossano JW, Woods RK, Berger S, et al. Mechanical support as failure intervention in patients with cavopulmonary shunts (MFICS): rationale and aims of a new registry of mechanical circulatory support in single ventricle patients. Congenit Heart Dis 2013;8:182-6.
54. Copeland JG, Copeland H, Gustafson M, et al. Experience with more than 100 total artificial heart implants. J Thorac Cardiovasc Surg 2012;143:727-34.
55. Quader MA, Tang D, Katlaps G, Shah KB, Kasirajan V. Total artificial heart for patients with allograft failure. J Thorac Cardiovasc Surg 2013;145:e21-3.
56. Strueber M, Schmitto JD, Kutschka I, Haverich A. Placement of 2 implantable centrifugal pumps to serve as a total artificial heart after cardiectomy. J Thorac Cardiovasc Surg 2012;143:507-9.
57. Frazier OH, Cohn WE. Continuous-flow total heart replacement device implanted in a 55-year-old man with end-stage heart failure and severe amyloidosis. Tex Heart Inst J 2012;39:542-6.
58. Acker MA, Pagani FD, Stough WG, et al. Statement regarding the pre and post market assessment of durable, implantable ventricular assist devices in the United States. J Heart Lung Transplant 2012;31:1241-52.