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IN DEPTH

Left Ventricular Assist Devices

Synergistic Model Between Technology and Medicine

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ABSTRACT: Ventricular assist device has rapidly emerged as a durable and safe therapy for end-stage heart failure patients with >22 000 implantations to date. Though originally conceived for bridge-to-transplant indication, significant advancements in medical management as well as technology with arrivals of newer generation devices have improved patient outcomes, leading to increasing use as destination therapy. Despite such improvement, however, the burden of adverse events remains significant and defines the most pressing issue in the current state of ventricular assist device therapy. Eventual use of ventricular assist device technology as a comparable alternative to heart transplantation will ultimately rely on our ability to mitigate these risks. Therefore, this review article provides the narrative surrounding the rapid integration of this technology into the heart failure paradigm, specifically in the context of the most recent data on its outcomes and adverse event profiles. It describes ongoing investigations and general trends that may have significant implications for future improvements in device-related outcomes, as the field continues to grow as the epitome of synergy between advancements in engineering and clinical medicine.

Mechanical circulatory support (MCS) with ventricular assist device (VAD) is a safe and efficacious treatment strategy for patients with end-stage heart failure (HF) that is refractory to medical therapy,[1–3] with >22 000 devices implanted to date in America and >2500 new implants occurring annually.[4] Although these patients appreciate 81% and 70% survival at 1 year and 2 years, respectively,[4] they still experience high rates of VAD-related adverse events (AEs), which require our keen attention and understanding. This manuscript aims to provide a necessary overview regarding the current use of VADs in the treatment of end-stage HF, with a specific focus on AEs.

INDICATIONS AND DEVICE TYPE

The concept of MCS developed concomitantly with the field of heart transplantation (HT), as VADs were originally conceived as temporary, bridge-to-transplant (BTT) platforms. Initially, BTT was an effective strategy to rescue patients whose severity of HF precluded survival on medical therapy alone until a donor organ became available. However, it was recognized early on that utilizing VAD solely as BTT was inadequate in addressing the growing prevalence of end-stage HF. With

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List of Definitions

- Suck-Down Event: A significant decrease in ventricular assist device (VAD) output from contact between the VAD inflow cannula and the ventricular cavity or septum. It is multifactorial (eg, inflow cannula position, high speed, low ventricular volume), and may trigger ventricular tachyarrhythmia.
- Park Stitch: A central coaptation stitch for the aortic valve, which aims to eliminate aortic insufficiency at the time of VAD implantation.
- HMIII Artificial Pulsatility: A programmed setting on the Heartmate III device, which results in rhythmic deceleration and acceleration of the rotor by 2000 rpm every 2 seconds from the user set speed. The design intent was to wash out the device and eliminate areas of stasis.
- Hemocompatability: A term that encapsulates the overall measure of the device's compatibility with the native circulatory system based on the incidence and the severity of hematologic adverse events.
- Quality-Adjusted Life Years: A measure of disease burden, which takes into account quality of life as well as quantity of years
- Incremental Cost-Effectiveness Ratio: A commonly used measure of cost-effectiveness, which is calculated as the difference in cost between 2 possible interventions divided by the difference in their impact

the annual volume of HT in the U.S. stagnating around 3000, implanting VADs as BTT without addressing this bottleneck only increased the size of the BTT population vying for HT. The proportion of those who received HT as BTT increased from 19.1% in 2000 to 41.0% in 2012.[5] This epidemiological challenge inspired the utilization of VADs as destination therapy (DT)— potentially a durable, lifelong alternative to HT.[1,6] Today, as the number of patients who are supported by VADs continues to grow, those indicated as DT constitute ≈50%, whereas BTT constitutes 26%.[4] For the remaining 24%, the other indications include bridge-to-candidacy and bridge-to-decision, which suggest the possibility of transplant evaluation after VAD implantation, and bridge-to-recovery, which offers temporary MCS for the duration of the acute insult.

Successful industry partnerships continue to challenge the boundaries of device design. The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial in 2001 by Rose et al[1] first demonstrated the potential of using VADs as a durable DT platform with superior survival outcomes compared with conventional medical therapy alone. The trial was initially received with equal parts excitement for the immense potential of this platform and legitimate trepidation over its alarmingly high rates of complications. Since then, the field has undergone several paradigm shifts with commensurate improvements in AE profiles. The early-generation devices were pneumatically driven and pulsatile-flow, which contributed to significant morbidity profiles, including high incidence of device failure and poor survival. Recognizing these limitations, subsequent clinical investigations began to focus on a new design in MCS that would come to actualize its potential as mainstream therapy for HF—continuous-flow (CF) devices. Smaller and more durable, their early results demonstrated significantly improved survival and complication profiles, both for BTT and DT patients.[2,7,8]

As the field transitioned toward CF-VADs, 2 distinct subclassification of CF design also emerged: axial and centrifugal mechanisms. Axial flow is generated by a propeller in a pipe, whereas centrifugal flow is generated by a bladed disk spinning in a cavity. During this era, 2 devices in particular, the axial-flow Heartmate II device (Abbott Laboratories, Abbott Park, IL) and the centrifugal-flow HeartWare HVAD device (Medtronic, Minneapolis, MN) constituted the majority of devices implanted worldwide. The HeartMate II has a cylindrical body that sits in the upper abdominal pocket, whereas the HVAD is a smaller device that is circular and entirely intrapericardial. Both designed to directly unload the LV and to augment cardiac output into the ascending aorta, they can provide full cardiac output, nearing 10 L per minute. Both devices are connected to an external power source via a driveline that is tunneled subcutaneously and exits at the level of the abdomen.

Several key engineering differences between the 2 devices are that the HeartMate II rotor spins on blood-immersed ruby bearings, whereas the HVAD has a magnetically levitated, frictionless rotor. The HVAD's smaller size is theoretically more conducive to biventricular or minimally invasive placement via thoracotomy. The results from the LATERAL trial, which prospectively compared outcomes of HVAD placement using traditional sternotomy versus thoracotomy approaches, will soon be published. Some of the engineering differences between centrifugal and axial flow devices carry important physiological and management implications.[9] Although the effects of different flow-profiles are clinically harder to distinguish than in a laboratory, they point to important considerations for patient management. For instance, centrifugal output is exquisitely sensitive to loading conditions, producing high pump-flow pulsatility in accordance with native ventricular activity. On the contrary, axial output is relatively inelastic across varied pressure gradients, which during low LV volume states, can potentially lead to a higher incidence of suck-down events[9] (Table 1).

The most recent addition to the field of MCS is a new-generation centrifugal-flow device, the HeartMate III (Abbott Laboratories), which has a fully magnetically levitated rotor, wider blood-flow paths and artificial pulsatility. By programming the device to rhythmically

Table 1. Device Types Currently Approved by the US Food and Drug Administration and Their Mechanical Properties

Device Type	HeartWare HVAD System	HeartMate II	HeartMate III
Speed range, rotations per minute	2400–3200	6000–15,000	3000–9000
Rotor design	Centrifugal	Axial	Centrifugal
Pump position	Intrapericardial	Pump pocket	Intrapericardial
Blood flow gaps, mm	≈0.05	≈0.08	≈0.12
Food and Drug Administration–approved indication	Bridge to transplant (2012) Destination therapy (2017)	Bridge to transplant (2008) Destination therapy (2010)	Bridge to transplant (2017) Destination therapy (2017)
Magnetic levitation	*		*
Artificial pulsatility			*
High inlet suction		*	

*Notes the presence of the characteristic.

decelerate and accelerate, the Heartmate III aimed to partially mimic and restore native pulsatility with the hypothesis that it would reduce bleeding and thromboembolic AE rates. In the recently published MOMENTUM trial (The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3), the third-generation device demonstrated superiority over the HeartMate II in its composite outcome of survival without disabling stroke and reoperation because of malfunctioning device at 2 years (79.5% versus 60.2%). This difference was primarily driven by the dramatic reduction in the incidence of pump thrombosis (PT) requiring device exchange (1.6% versus 17.0%).[10] Of note, this manuscript did not aim to directly compare the results between most recent clinical trials using HVAD and Heartmate III devices given the unavailability of primary data for analysis. Nonetheless, the excellent outcomes noted in both trials are emblematic of the exciting engineering potential and ongoing innovation that define this field.

PATIENT SELECTION AND RISK STRATIFICATION

According to the most recent HF guidelines published by the American College of Cardiology and American Heart Association in 2013, VAD implantation is indicated for patients who have Stage D HF with reduced ejection fraction, which is estimated to include 100 000 to 250 000 patients.[11,12] However, although the demand is alarmingly high, VAD remains a highly invasive intervention that requires a careful, multidisciplinary evaluation of patients' candidacy before implantation. Numerous studies have reported patient characteristics associated with high risks of AEs and ultimately poor outcome, leading to a general agreement regarding contraindications to therapy (Table 2).[13] These broadly include factors which limit life expectancy at the onset, such as ongoing malignancy or irreversible end-organ failure, those which may precipitate AEs postimplantation such as significant pulmonary hypertension or right ventricular (RV) dysfunction, and those which preclude adequate follow-up care such as psychosocial limitations. These boundaries are continually being redrawn as technological progress continues to improve patient outcomes and to diminish the burdens of AE.

Various attempts to stratify risk prior to implantation have been proposed. The most longitudinal and widescale effort to-date has been the use of INTERMACS scale (Interagency Registry for Mechanically Assisted Circulatory Support), which divides advanced HF (New York Heart Association [NYHA] score III–IV) into 7 different risk levels (Table 3). INTERMACS class 1, the so-called "Crash and Burn" status, comprising approximately 15% of all implantations, signifies highest degree of acuity with critical cardiogenic shock, whereas a score of 7 denotes hemodynamically stable HF with minimal symptoms. Majority of patients receiving VADs are INTERMACS classes 2 (36.4%) or 3 (29.9%). As evidenced by INTERMACS class 1 patients having reduced survival at 1-year compared with class 2 and 3 (74% versus 82%), preimplantation acuity has lasting significant prognostic implications. At the other end of the spectrum, growing evidence suggests that pre-emptively implanting VADs in ambulatory HF patients (INTERMACS classes 4–7), which comprise a shrinking minority (19.4%), have excellent outcomes, approaching 80% to 95% survival at 1-year.[14–16] Other risk stratification strategies have been proposed, such as the HeartMate Risk Score and recently, the Penn-Columbia Risk Score, utilizing clinical, laboratory, and echocardiographic parameters.[17,18] In one study, the HeartMate Risk Score was shown to validly risk-stratify patient survival more accurately than INTERMACS class, indicating the potential of increasingly more sophisticated patient selection methods in the future.[17]

SURVIVAL AND OTHER PARAMETERS

As aforementioned, survival among all CF-VAD patients is currently 81% and 70% at 1 and 2 years postimplanta-

Table 2. Indications and Contraindications Regarding Ventricular Assist Device Implantation

Indications	Contraindications					
New York Heart Association Class IV congestive heart failure refractory to maximal medical therapy and conventional surgery	Limited life expectancy	Age >80 y	Active malignancy			
Ejection fraction <25%	Severe comorbidities precluding meaningful outcome	End-stage renal disease (glomerular filtration rate < 30 or creatinine clearance < 30)	Severe liver disease (bilirubin < 2.5 or international normalized ratio > 2.0 with cirrhosis or portal hypertension)	Severe lung disease (obstructive or restrictive, home O2); pulmonary infarction within the past 6 wk	Severe vascular disease; severe arthritis	Unconfirmed neurological status, unresolved stroke, or severe neuromuscular disorder
Reduced functional capacity as measured by a maximal oxygen consumption VO2 <14 mg/kg/min	Hematologic	Active severe bleeding; chronic thrombocytopenia	Active infection	Refusal of blood transfusions	Confirmed heparin induced thrombocytopenia	Intolerance to anticoagulation
Exceptions for select patients may include clinical trial protocol requirements	Anatomic	Congenital heart disease	Hypertrophic cardiomyopathy	Large ventricular septal defect	Body mass index precluding implantation or rehabilitation	
	Hemodynamic	Severe independent right heart failure	Pulmonary vascular resistance >6 or transpulmonary gradient >15 on testing with inhaled nitric oxide, flolan, or intravenous nitroprusside	Existing significant aortic insufficiency unable to be corrected		
	Psychosocial	Evidence of ongoing alcohol, smoking or drug use or dependency	Inability to provide informed consent	Inability to adhere to medical regimen	Inability to maintain device (drive line, console)	Active mental illness or psychosocial instability

tion, respectively. Outcomes are currently more favorable in the BTT than in the DT cohort, with 30% receiving HT at 1-year and 77% surviving to 2 years. Nonetheless, even in the DT population, which inherently possess greater comorbidities that contraindicate them for HT, long-term outcomes are still excellent with 68% overall survival at 2 years.[19] These figures are consistent across the Heartware HVAD and HMII trials; 46% to 59% of them were able to reach the primary composite outcome of survival without disabling stroke or reoperation at 2 years.[12,14,20,21] The Heartmate III cohort recently achieved a 79.5% rate of the same composite outcome, owing to significantly reduced stroke and PT burden.[22] These figures, compared with the trial in 2009 by Slaughter et al,[23] where only 11% of the pulsatile-flow VAD patients were able to reach the composite outcome, convey a narrative of remarkable progress. Although long-term VAD outcomes with 30% survival at 5 years are still inferior to HT, VAD therapy is on the right trajectory to become an equivalent alternative in the future.[19]

Table 3. INTERMACS Class Definitions, Prevalence, and Outcomes

New York Heart Association Class	IV						III
INTERMACS	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Clinical status	Critical cardiogenic shock	Progressive decline	Stable but inotrope dependent	Resting symptoms	Exertion intolerant	Exertion limited	Advanced class III
	Inotropy			Ambulatory			
Possible modifiers	Arrhythmia or temporary circulatory support			Arrhythmia or frequent flier			Arrhythmia
Implantation, %	14.3	36.4	29.9	18.4			1.0
1-year survival, %	74	82		84			
6-month readmission, %	57	42		61 to 80			

Statistics were derived from the 8th annual INTERMACS report. INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support; and NYHA, New York Heart Association.

FUNCTIONAL STATUS AND QUALITY OF LIFE

Therapeutic benefits of VAD implantation also extend to functional capacity and quality of life. Randomized clinical trial data regarding the use of Heartmate II, Heartmate III, and HVAD have consistently demonstrated that ≈80% of patients belong to NYHA functional class I or II symptoms at 24 months postimplantation.[2,10,24] Their 6-minute walk test distances also doubled from baseline and were sustained at 24 months. Quality of life postimplantation was also evaluated using the Minnesota Living with Heart Failure, Kansas City Cardiomyopathy, and EQ-5D questionnaires.[2,10,24] Across all trials, patients experienced immediate and sustained improvements in their quality of life parameters by a significant margin. As VAD use, especially for DT, continues to grow more prevalent, these measures help ensure meaningful survival, in addition to extension of life.

ADVERSE EVENTS

If the previous decade of MCS can be characterized by incremental progress in survival and durability, the overarching challenge of the next will be to neutralize the still high burden of AEs. Despite marked improvements in device design and clinical management, AEs still occur frequently at all time points, with 31% of the patients who survive the index operation being readmitted within 30 days.[19] According to the 8th annual INTERMACS report, 60% of the patients are rehospitalized at least once by 6 months postimplantation.[4] At 1 year, rate of rehospitalization has been estimated to be as high as 65% to 80%, a figure which has remained relatively stagnant for both axial and centrifugal-flow devices.[25,26] All AEs are major harbingers of morbidities. Stroke and multi-system organ failure have been identified as major causes of early death. Additionally, the rate of rehospitalization has not only profound clinical, but also economic and ethical implications.[27,28] All of these domains warrant critical investigation going forward. Being in a state of cardiogenic shock (INTERMACS 1) at time of implantation has been correlated with higher risks of AEs, as would be expected. However, even among healthier patients who are not dependent on IV inotropic support at the time of implant (INTERMACS 4–7), the ROADMAP trial demonstrated unacceptably high morbidity at 1-year follow-up with 80% readmission rate.[19] Though VAD therapy may improve functional capacity and quality of life in this cohort, the concomitantly elevated burden of AEs ought to be an important consideration in the extension of MCS to a wider, ambulatory HF patient population.[22]

Preexisting severity of illness, organ dysfunction, a hybrid physiology rendered complex by the need for anticoagulation predispose VAD patients to high rates of AEs. These include bleeding, infection, sepsis, right-heart failure (RHF), PT, stroke, and aortic insufficiency (AI; Table 4). Notably, concomitant risks of PT, bleeding, and stroke represent the complex hematologic challenges inherent in MCS, simultaneously manifesting as increased bleeding risks and hypercoagulability.

RIGHT HEART FAILURE

The vexing combination of existing RV dysfunction, pulmonary hypertension, and acute hemodynamic shifts often precipitates RHF early on post-VAD implantation in ≈15% to 25% of the patients with 4% requiring RVAD implantation within 2 weeks.[4,29,30] Though its exact mechanism is unclear, it is believed to be driven by sudden increases in LV unloading and RV preload, which distorts RV geometry and unmasks underlying dysfunc-

Table 4. Various Adverse Events, Their Incidence, Timeline, Mechanism, and Proposed Therapies

Adverse Event	Incidence Range, %	Timeline	Risk Factors	Diagnostic Modality	Treatment
Right heart failure	15 to 25	Bimodal (acute or delayed onset)	Pulmonary hypertension, existing right ventricular dysfunction	Clinical; echocardiography	Inotropy; right ventricular assist device
Pump thrombosis	1.1 to 12.2	Varied	Inadequate anticoagulation; mechanical; low-flow	Hemolysis; echocardiography; intraoperative	Thrombolytics; device exchange
Gastrointestinal bleeding	15 to 30	Varied; recurrent	Low pulsatility; acquired von Willebrand factor deficiency; arteriovenous malformation; anticoagulation	Endoscopy	Proton pump inhibitor; cauterization
Driveline infection	15 to 24	Varied	Driveline; poor hygiene; hematoma;	Clinical; visual inspection	Antibiotic therapy; device exchange if systemic
Stroke	13 to 30	Varied; possible hemorrhagic conversion	Hypertension; anticoagulation;	Computed tomography scan or magnetic resonance imaging	Multifactorial
Aortic insufficiency (moderate or severe)	30% at 2 yr	Chronic	Chronic nonopening of aortic valve	Echocardiography	Surgical or transcatheter valve repair or closure

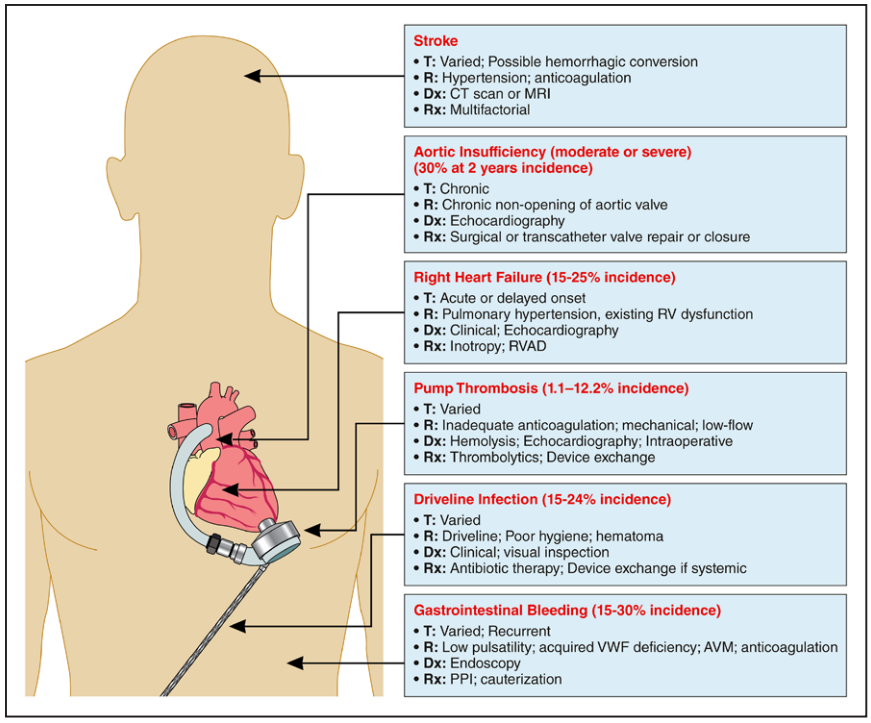

Figure. Descriptions of various complications related to ventricular assist device therapy.
Dx indicates diagnostic method; R, risk factors; Rx, treatment; and T, timeline.

tion. To date, various measures have been correlated with increased likelihood of RHF, including signs of existing RV dysfunction on echocardiography and right-heart catheterization (increased pulmonary vascular resistance, pulmonary capillary wedge pressure to central venous pressure ratio, etc.), higher acuity in INTERMACS class, and other measures of end-organ dysfunction, such as blood-urea nitrogen levels or ventilator-dependence.[25,31] Although most cases of RV dysfunction improve with inotropic support, early RVAD utilization is associated with better prognosis in refractory cases.[32] Planned bi-VAD implantation in patients with high-risk of RHF may help mitigate the described hemodynamic challenges in the early postoperative period, though it remains to be studied prospectively. Impella RP (Abiomed, Danvers, MA) is a percutaneous, partial-support device that was approved by the Food and Drug Administration (FDA) in 2017, which may permit earlier and less invasive utilization in this setting and reduce the number of patients who ultimately require RVAD.[31] Studies regarding its safety and efficacy are ongoing. Recent studies analyzing the timeline of RHF have also identified late-onset RHF as a separate entity, occurring in 10% of patients months to years after VAD implantation.[33] As its onset portends dismal prognosis with 38% survival at 1-year, future studies regarding its cause, precipitating factors, and preventive measures are warranted.

PUMP THROMBOSIS

PT is a multifactorial phenomenon which can result in rapid clinical deterioration and even demand emergent pump exchange.[34] Its occurrence negatively influences survival. Its proposed mechanism involves factors leading to decreased or turbulent flow in the VAD as well as suboptimal anticoagulation. Diagnosis relies on abnormal pump parameters, such as power spikes, elevated hemolytic markers, and evidence of reduced ventricular unloading.[35] Though in the original trials it was relatively infrequent, an unexplained and abrupt increase in its incidence was observed in the early 2010s, showing a drastic rise from 2.2% in 2011 to 8.4% in 2013.[2,3,21] Most recent clinical trial data suggest that 10.7% to 12.2% of HeartMate II patients and 4.2% to 6.4% of Heartware HVAD patients experience PT requiring device exchange in 2 years.[8,10,36,37] A recent prospective trial demonstrated that strictly adhering to surgical implantation techniques, anticoagulation regimen, and pump speed (1.9% versus 8.9%) further protect against the risk of PT, though the role of device geometry in relation to the heart remains to be further elucidated.[23,38] Combined with the results from the MOMENTUM 3 trial, which showed almost no suspected or confirmed PT events at 6 months and at 2 years (1.1%) in the HeartMate III cohort,[10] these results indicate the tantalizing possibility of nearly eliminating PT in the future of MCS.

BLEEDING

Bleeding is the most common complication and cause of readmission after VAD implantation.[23] Of these, gastrointestinal bleeding (GIB) is the most common, occurring in 15% to 30% of patients across all device-types, especially among older patients with previous history.[24,39,40]

Various mechanisms, such as low-pulsatility, shear-stress leading to acquired von Willebrand deficiency, angiodysplasia (arteriovenous malformation) and anticoagulation have been proposed, with endoscopic or laboratory correlations.[41] Management options, including resuscitation, use of proton pump inhibitors, endoscopic cauterization, and temporary discontinuation of anticoagulation, have demonstrated modest benefit in reducing the overall burden of GIB in this patient population with the recurrence rate estimated around 9%.[42] Of note, these interventions are not risk-free. GIB may require multiple transfusions, which may sensitize BTT patients' panel reactive antibody status against potential donors and ultimately increase waiting time and risk of rejection. Cessation of anticoagulation may increase risks of thromboembolic risk.[24] Although engineering-based approach to reducing GIB have been tried, most recently by introducing intrinsic pulsatility to the HeartMate III, the results did not show improved rates of GIB.[10]

STROKE

More common among women, stroke is arguably the most debilitating AEs while on VAD, occurring in 13% to 30% of VAD patients.[4,31,36,43] Its occurrence is significantly associated with mortality.[43,44] The concomitantly elevated risks of ischemic and hemorrhagic strokes represent the vexing hematologic challenges in their management, with ischemic etiology (5.5% annual incidence) being more common than hemorrhagic (3.1%).[44] Mechanism behind ischemic stroke is believed to include embolic sources, such as thrombus deposition at the pump, the aortic valve (AV), inflow, or outflow grafts.[45] Both endovascular and systemic thrombolytic therapy should be considered carefully because of high risk of hemorrhagic conversion in this population. Hemorrhagic stroke is believed to occur secondary to hypertension, endocarditis, and hemorrhagic conversion of ischemic infarcts. Its correlation with coagulopathy is generally inconsistent.[45] Recently, the early results from the ENDURANCE II trial (The HeartWare Ventricular Assist System as Destination Therapy of Advanced Heart Failure) demonstrated equivalent stroke rates between the centrifugal HVAD and the axial HeartMate II as long as hypertension is well controlled.[8,46] The MOMENTUM trial demonstrated a lower incidence of stroke with the HeartMate III device compared WITH the HeartMate II (10.1% versus 19.2%) at 2 years.[10]

AORTIC INSUFFICIENCY

Progressive, de novo AI post-VAD implantation is a significant barrier to long-term support, with >30% of the patients reaching moderate or worse AI after 2 years.[47,48] AI, which is believed to be caused by the device-generated pressure gradient across the AV leading to AV closure and eventual commissural fusion, results in blood volume recirculation, increased pump work, and HF exacerbation. Speed optimization or maintenance of pulsatility, whether it be native or device-generated, to ensure AV opening also appears to be protective by preserving the integrity of AV structure and function. As the Heartmate III device is capable of artificial pulsatility, the degree to which this feature protects against de novo AI remains to be explored. Surgical options for AI, such as AV closure using Park stitch or replacement, are available but appears to increase risk of mortality, whether it is performed concomitantly at the time of VAD implantation or on development of hemodynamically significant de novo AI with VAD.[49] Off-label use of transcatheter aortic valve replacement technology for this indication has been noted in isolated case reports, but remains to be further studied.[50]

DRIVELINE INFECTION

Infection is a common VAD-related AE and an independent predictor of mortality.[4] Though it may occur at any aspect of the VAD apparatus ranging from local to systemic, driveline infection in the soft tissues surrounding the outlet is the most common, occurring in 15.4% TO 23.8% in recent CF-VAD cohorts.[8,10] Compared with the 41% originally reported in the REMATCH trial, this marks a remarkable improvement. Colonization with local flora, which begins locally during or after implant, may progress to a systemic infection without adequate recognition and treatment, conferring significant morbidity. Gram-positive cocci, particularly Staphylococcus epidermidis and aureus, are the most commonly identified pathogens, although Gram-negative rods, such as Pseudomonas and Klebsiella, fungi, and mycobacterium are also associated.[51] Those with abilities to form bio-films are particularly virulent. In addition to usual risk factors for infection, several mechanical and patient-specific factors render VAD patients particularly conducive to driveline infection. The percutaneous driveline can be an ideal gateway for pathogens, especially in this patient population that is often critically ill, immune-compromised, or malnourished. As the mechanism of infection is direct, excellent hygiene is imperative in addition to preoperative antibiotic therapy and avoidance of hematomas, which can be a nidus for infection. Early recognition and aggressive treatment are essential in preventing rapid dissemination of pathogen, which may ultimately require device exchange.

FUTURE DIRECTIONS

As we have observed multiple meaningful paradigm shifts in MCS over the past decade, the following de-

cade has the potential to significantly further advance the field of MCS. Here we describe a few foreseeable trends.

Continued Innovation in Device Engineering

While the Heartmate II, III and HVAD devices are the only commercially FDA-approved adult options in North America and constitute the largest percentage of devices implanted to date, the field of MCS is a global phenomenon undergoing constant innovation with varying approvals for clinical use in other continents such as Europe or Asia. In addition to INTERMACS, international research efforts based on high-volume experiences, such as those captured in the EUROMACS (European Registry for Patients with Mechanical Circulatory Support), have led to significant contributions to the field. In this era of robust innovation and collaboration, numerous devices with respective engineering advantages are competing to create the most effective and safest interface including the INCOR (approved in EU; Berlin Heart, Berlin, Germany), Jarvik 2000 (approved in EU; ongoing DT trial in U.S.; Jarvik Heart Inc, New York, NY), EVAHEART LVAS (ongoing BTT trial in U.S.; EVAHEART, Houston, TX), and more. The total artificial heart (TAH; SynCardia, Tucson, AZ) is the only FDA-approved device in its class allowing native heart explantation. Utilized in select patients with biventricular HF, these have been implanted in <2% of the MCS population to-date and currently portend <60% survival at 1 year.[52] Similar devices such as the CARMAT bioprosthetic artificial heart (CARMAT, Velizy Villacoublay), which is a hydraulic, pulsatile device comprising 2 ventricles and 4 bioprosthetic valves, and BiVACOR TAH (BiVACOR Inc, Houston, TX), which is a rotary pump with 2 centrifugal impellers, are currently in the pipeline undergoing clinical investigation and may immensely expand the potential of artificial heart technology.

Although investigational and commercial uses of devices significantly vary and are constantly evolving, the general trajectory of the industry follows several key biomedical principles that are essential to the future of MCS. These broadly include increased durability, biocompatibility, and less invasiveness, both in terms of device profiles and implantation strategies. These advances have the potential to not only improve survival but also to significantly reduce AEs. These concepts are described in detail in the following sections.

Over the ensuing decade, as MCS utilization continues to increase with new generations of devices and engineering concepts, the clinical trial environment must commensurately grow more robust. Despite tremendous opportunities for research in MCS, an estimated <1% of VAD patients currently enter into clinical trials. Thus, the responsibilities of the academic community to advocate for, to design, and to engage patients in clinical trials where there is equipoise will only continue to grow, with an increasingly multidisciplinary approach. In addition to simply studying new devices, other topics of interest to the community include their medical management, such as determining the appropriate heart failure medication or anticoagulation regimen that is tailored to patient profiles.

Miniature, Minimally Invasive

In a remarkably brief time span, the scientific community has observed the rapid miniaturization of machines. Just as the gargantuan computers of the 20th century have become smartphones that fit inside our pockets, so too have the original extracorporeal VADs become today's implantable, intrapericardial devices. Over the following decades, this trend will only continue to quicken. An ongoing clinical trial is investigating the efficacy of the HeartWare miniaturized ventricular assist device system (MVAD), which is an axial-flow device that can generate full cardiac output despite being a third of the size of the HVAD device. Miniaturization also lends itself to more minimally invasive operative techniques. Numerous studies have described thoracotomy-based approaches for device implant and exchange with less perioperative morbidity. The LATERAL trial has finished enrollment and is awaiting publication on the safety and efficacy of HVAD implantation via thoracotomy instead of median sternotomy. The Impella device can be installed percutaneously, though in its current state it comes at the cost of reduced durability, stability, and strength. Be that as it may, these exciting trends foreshadow a not-too-distant future where miniature, minimally invasive VADs will become the standard of care, rendering it widely available to patients at considerably lower risks.

Interplay Between Innovative Engineering and Medical Management

Ultimately, success in long-term utilization of VAD as an alternative to HT will be predicated on our ability to minimize AEs, gleaning insights from interplay between design innovation and improvements in clinical management. The HeartMate III device and its improved hemocompatibility profile is a timely example. As novel engineering features in the HeartMate III have led to significant reductions in the incidence of PT, it opens up an array of potential ways to fine-tune and to study innovative anticoagulation or device-management strategies.[20] These changes may improve on the device's intrinsic hemocompatibility even further, promoting synergy between medical providers and the industry.

Similarly, imminent technological breakthroughs may have significant implications for infection rates. As

devices become totally implantable with transcutaneous recharging capabilities, rates of driveline infection will by design be eliminated. Several device companies, through strategic partnerships, are currently working to develop a wireless VAD power delivery system, using technologies such as magnetic resonance coupling. Battery capabilities are also improving rapidly enabling greater efficiency even at more compact scales. Although it is not clear when VADs will become fully wireless, once released, their impact on patient care will be immediate.

Evolving biventricular support paradigms, including the Total Artificial Heart (TAH), may reduce or prevent RHF altogether and potentially offer MCS therapy to patients with anatomic contraindications to VAD placement such as diastolic HF, noncompaction HF, or other congenital abnormalities. In a cohort of predominantly INTERMACS class I (91%) patients, TAH successfully bridged 68% to HT with reasonable long-term outcomes post-HT (41% at 10 years).[52] Based on the remarkable trajectory of VAD technology over the past several decades, highlighted by incremental advancements in and synergy between engineering and medical management, the future potential of these newly emerging, innovative solutions is bright and limitless.

Cost

Cost of care is a major global future challenge. This issue is particularly salient in the field of MCS given its rapidly increasing usage worldwide and the inherently high cost of device implantation and management. The original REMATCH trial data reported an incremental cost-effectiveness ratio of $802 700 per quality-adjusted life-year. The acquisition cost per Heartmate II was estimated to be nearly $150 000,[53] which led to >$479 million in VAD-related healthcare spending in 2009.[54] Simulated projections comparing the cost-effectiveness of HF treatment strategies using incremental cost-effectiveness ratio have highlighted significantly increased costs attributable to VADs, requiring as much as $200 000 quality-adjusted life-years gained in some studies, which far exceeds those of orthotopic heart transplantation ($97 000) or medical therapy ($54 000).[55,56] Although VAD technology has undoubtedly been recognized as life-saving therapy, these figures as they currently remain may be prohibitively high to sustain the rapid expansion of its usage. Continued progress in device innovation and medical management will be essential to curbing the cost of this rapidly burgeoning therapy. The cost-effectiveness of VADs is projected to improve as survival and quality of life continue to improve with reduced rates of AEs and readmissions. In the aforementioned study, being able to eliminate these costs led to an estimated reduction in the overall incremental cost-effectiveness ratio of VAD therapy by ≈40%,[55] which highlights the magnitude of potential future savings.

CONCLUSIONS

In a remarkably short span of time, MCS using VAD has become a mainstream treatment option for end-stage HF, with a growing proportion of patients successfully undergoing VAD implantation as DT. Survival outcomes have and will continue to improve with the emergence of newer generations of CF-VADs. Although risks of various AEs are still significant, posing a predominant challenge for the coming decade, altogether, the synergy between medical management and engineering innovations will continue to actualize the unlimited potential of MCS, marking one of the most exciting eras in the treatment of HF.

ARTICLE INFORMATION

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Disclosures

Dr Acker is a consultant for Thoratec Corp. Dr Atluri is a principal investigator for the ENDURANCE, MOMENTUM III, and LATERAL clinical trials. Dr Han reports no conflicts.

REFERENCES

1. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345:1435–1443. doi: 10.1056/NEJMoa012175
2. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361:2241–2251. doi: 10.1056/NEJMoa0909938
3. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med*. 2007;357:885–896. doi: 10.1056/NEJMoa067758
4. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB, Naftel DC. Eighth annual intermacs report: special focus on framing the impact of adverse events. *J Heart Lung Transplant*. 2017;36:1080–1086. doi: 10.1016/j.healun.2017.07.005
5. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, Hertz MI; International Society of Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart trans-

plant report–2012. *J Heart Lung Transplant*. 2012;31:1052–1064. doi: 10.1016/j.healun.2012.08.002
6. Sun BC, Catanese KA, Spanier TB, Flannery MR, Gardocki MT, Marcus LS, Levin HR, Rose EA, Oz MC. 100 long-term implantable left ventricular assist devices: the Columbia Presbyterian interim experience. *Ann Thorac Surg*. 1999;68:688–694. doi: 10.1016/S0003-4975(99)00539-1
7. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, Jessup ML, Gregoric ID, Loyalka P, Frazier OH, Jeevanandam V, Anderson AS, Kormos RL, Teuteberg JJ, Levy WC, Naftel DC, Bittman RM, Pagani FD, Hathaway DR, Boyce SW; HeartWare Ventricular Assist Device (HVAD) Bridge to Transplant ADVANCE Trial Investigators. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation*. 2012;125:3191–3200. doi: 10.1161/CIRCULATIONAHA.111.058412
8. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V, Anderson AS, Gregoric ID, Mallidi H, Leadley K, Aaronson KD, Frazier OH, Milano CA. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med*. 2017;376:451–460. doi: 10.1056/NEJMoa1602954
9. Moazami N, Fukamachi K, Kobayashi M, Smedira NG, Hoercher KJ, Massiello A, Lee S, Horvath DJ, Starling RC. Axial and centrifugal continuous-flow rotary pumps: a translation from pump mechanics to clinical practice. *J Heart Lung Transplant*. 2013;32:1–11. doi: 10.1016/j.healun.2012.10.001
10. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC Jr, Yuzefpolskaya M, Salerno C, Walsh MN, Milano CA, Patel CB, Ewald GA, Itoh A, Dean D, Krishnamoorthy A, Cotts WG, Tatooles AJ, Jorde UP, Bruckner BA, Estep JD, Jeevanandam V, Sayer G, Horstmanshof D, Long JW, Gulati S, Skipper ER, O'Connell JB, Heatley G, Sood P, Naka Y; MOMENTUM 3 Investigators. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med*. 2018;378:1386–1395. doi: 10.1056/NEJMoa1800866
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807
12. Roger VL. Epidemiology of heart failure. *Circ Res*. 2013;113:646–659. doi: 10.1161/CIRCRESAHA.113.300268
13. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J; International Society for Heart and Lung Transplantation. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant*. 2013;32:157–187. doi: 10.1016/j.healun.2012.09.013
14. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, Horstmanshof DA, Kormos RL, Teuteberg JJ, Slaughter MS, Birks EJ, Farrar DJ, Park SJ; HeartMate II Clinical Investigators. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol*. 2014;63:1751–1757. doi: 10.1016/j.jacc.2014.01.053
15. Boyle AJ, Ascheim DD, Russo MJ, Kormos RL, John R, Naka Y, Gelijns AC, Hong KN, Teuteberg JJ. Clinical outcomes for continuous-flow left ventricular assist device patients stratified by pre-operative INTERMACS classification. *J Heart Lung Transplant*. 2011;30:402–407. doi: 10.1016/j.healun.2010.10.016
16. Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB, Bruckner BA, Lee S, Long JW, Selzman CH, Kasirajan V, Haas DC, Boyle AJ, Chuang J, Farrar DJ, Rogers JG; ROADMAP Study Investigators. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP Study 2-year results. *JACC Heart Fail*. 2017;5:518–527. doi: 10.1016/j.jchf.2017.02.016
17. Adamo L, Tang Y, Nassif ME, Novak E, Jones PG, LaRue S, Spertus JA, Mann DL. The HeartMate risk score identifies patients with similar mortality risk across all INTERMACS profiles in a large multicenter analysis. *JACC Heart Fail*. 2016;4:950–958. doi: 10.1016/j.jchf.2016.07.014
18. Birati EY, Hanff TC, Maldonado D, Grandin EW, Kennel PJ, Mazurek JA, Vorovich E, Seigerman M, Howard JLL, Acker MA, Naka Y, Wald J, Goldberg LR, Jessup M, Atluri P, Margulies KB, Schulze PC, Rame JE. Predicting long term outcome in patients treated with continuous flow left ventricular assist device: the Penn-Columbia risk score. *Journal of the American Heart Association*. 2018;7:e006408.
19. Agrawal S, Garg L, Shah M, Agarwal M, Patel B, Singh A, Garg A, Jorde UP, Kapur NK. Thirty-day readmissions after left ventricular assist device implantation in the United States: insights from the nationwide readmissions database. *Circ Heart Fail*. 2018;11:e004628. doi: 10.1161/CIRCHEARTFAILURE.117.004628
20. Uriel N, Colombo PC, Cleveland JC, Long JW, Salerno C, Goldstein DJ, Patel CB, Ewald GA, Tatooles AJ, Silvestry SC, John R, Caldeira C, Jeevanandam V, Boyle AJ, Sundareswaran KS, Sood P, Mehra MR. Hemocompatibility-related outcomes in the MOMENTUM 3 trial at 6 months: a randomized controlled study of a fully magnetically levitated pump in advanced heart failure. *Circulation*. 2017;135:2003–2012. doi: 10.1161/CIRCULATIONAHA.117.028303
21. Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, Rame JE, Acker MA, Blackstone EH, Ehrlinger J, Thuita L, Mountis MM, Soltesz EG, Lytle BW, Smedira NG. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med*. 2014;370:33–40. doi: 10.1056/NEJMoa1313385
22. Shah KB, Starling RC, Rogers JG, Horstmanshof DA, Long JW, Kasirajan V, Stehlik J, Chuang J, Farrar DJ, Estep JD; ROADMAP Investigators. Left ventricular assist devices versus medical management in ambulatory heart failure patients: an analysis of INTERMACS Profiles 4 and 5 to 7 from the ROADMAP study. *J Heart Lung Transplant*. 2018;37:706–714. doi: 10.1016/j.healun.2017.12.003
23. Maltais S, Kilic A, Nathan S, Keebler M, Emani S, Ransom J, Katz JN, Sheridan B, Brieke A, Egnaczyk G, Entwistle JW 3rd, Adamson R, Stulak J, Uriel N, O'Connell JB, Farrar DJ, Sundareswaran KS, Gregoric I; PREVENT Study Investigators. PREVENtion of HeartMate II pump thrombosis through clinical management: the PREVENT multi-center study. *J Heart Lung Transplant*. 2017;36:1–12. doi: 10.1016/j.healun.2016.10.001
24. Stulak JM, Lee D, Haft JW, Romano MA, Cowger JA, Park SJ, Aaronson KD, Pagani FD. Gastrointestinal bleeding and subsequent risk of thromboembolic events during support with a left ventricular assist device. *J Heart Lung Transplant*. 2014;33:60–64. doi: 10.1016/j.healun.2013.07.020
25. Khazanie P, Hammill BG, Patel CB, Eapen ZJ, Peterson ED, Rogers JG, Milano CA, Curtis LH, Hernandez AF. Trends in the use and outcomes of ventricular assist devices among Medicare beneficiaries, 2006 through 2011. *Journal of the American College of Cardiology*. 2014;63:1395–1404.
26. Hasin T, Marmor Y, Kremers W, Topilsky Y, Severson CJ, Schirger JA, Boilson BA, Clavell AL, Rodeheffer RJ, Frantz RP, Edwards BS, Pereira NL, Stulak JM, Joyce L, Daly R, Park SJ, Kushwaha SS. Readmissions after implantation of axial flow left ventricular assist device. *J Am Coll Cardiol*. 2013;61:153–163. doi: 10.1016/j.jacc.2012.09.041
27. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, Owens DK, Hlatky MA. Cost-effectiveness of left ventricular assist devices in ambulatory patients with advanced heart failure. *JACC Heart Fail*. 2017;5:110–119. doi: 10.1016/j.jchf.2016.09.008
28. Entwistle JWC 3rd. The American Association for Thoracic Surgery 2016 Ethics Forum: cost-effectiveness and the ethics of left ventricular assist device therapy. *J Thorac Cardiovasc Surg*. 2017;154:1315–1318. doi: 10.1016/j.jtcvs.2017.03.121
29. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, Massey T, Milano CA, Moazami N, Sundareswaran KS, Farrar DJ; HeartMate II Clinical Investigators. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. *J Thorac Cardiovasc Surg*. 2010;139:1316–1324. doi: 10.1016/j.jtcvs.2009.11.020
30. Kapur NK, Esposito ML, Bader Y, Morine KJ, Kiernan MS, Pham DT, Burkhoff D. Mechanical circulatory support devices for acute right ventricular failure. *Circulation*. 2017;136:314–326. doi: 10.1161/CIRCULATIONAHA.116.025290
31. Anderson MB, Goldstein J, Milano C, Morris LD, Kormos RL, Bhama J, Kapur NK, Bansal A, Garcia J, Baker JN, Silvestry S, Holman WL, Douglas PS, O'Neill W. Benefits of a novel percutaneous ventricular assist device for right heart failure: The prospective RECOVER RIGHT study of the Impella RP device. *J Heart Lung Transplant*. 2015;34:1549–1560. doi: 10.1016/j.healun.2015.08.018
32. Kiernan MS, Grandin EW, Brinkley M, Jr., Kapur NK, Pham DT, Ruthazer R, Rame JE, Atluri P, Birati EY, Oliveira GH, Pagani FD, Kirklin JK, Naftel D, Ko-

rmos RL, Teuteberg JJ, DeNofrio D. Early right ventricular assist device use in patients undergoing continuous-flow left ventricular assist device implantation: incidence and risk factors from the interagency registry for mechanically assisted circulatory support. *Circ Heart Fail*. 2017;10:e003863. doi: 10.1161/CIRCHEARTFAILURE.117.003863
33. Rich JD, Gosev I, Patel CB, Joseph S, Katz JN, Eckman PM, Lee S, Sundareswaran K, Kilic A, Bethea B, Soleimani B, Lima B, Uriel N, Kiernan M; Evolving Mechanical Support Research Group (EMERG) Investigators. The incidence, risk factors, and outcomes associated with late right-sided heart failure in patients supported with an axial-flow left ventricular assist device. *J Heart Lung Transplant*. 2017;36:50–58. doi: 10.1016/j.healun.2016.08.010
34. Uriel N, Han J, Morrison KA, Nahumi N, Yuzefpolskaya M, Garan AR, Duong J, Colombo PC, Takayama H, Thomas S, Naka Y, Jorde UP. Device thrombosis in HeartMate II continuous-flow left ventricular assist devices: a multifactorial phenomenon. *J Heart Lung Transplant*. 2014;33:51–59. doi: 10.1016/j.healun.2013.10.005
35. Uriel N, Morrison KA, Garan AR, Kato TS, Yuzefpolskaya M, Latif F, Restaino SW, Mancini DM, Flannery M, Takayama H, John R, Colombo PC, Naka Y, Jorde UP. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. *J Am Coll Cardiol*. 2012;60:1764–1775. doi: 10.1016/j.jacc.2012.07.052
36. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Myers S, Acker MA, Rogers J, Slaughter MS, Stevenson LW. Pump thrombosis in the Thoratec HeartMate II device: an update analysis of the INTERMACS Registry. *J Heart Lung Transplant*. 2015;34:1515–1526. doi: 10.1016/j.healun.2015.10.024
37. Najjar SS, Slaughter MS, Pagani FD, Starling RC, McGee EC, Eckman P, Tatooles AJ, Moazami N, Kormos RL, Hathaway DR, Najarian KB, Bhat G, Aaronson KD, Boyce SW; HVAD Bridge to Transplant ADVANCE Trial Investigators. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. *J Heart Lung Transplant*. 2014;33:23–34. doi: 10.1016/j.healun.2013.12.001
38. Han JJ, Gaffey AC, Sooppan R, Hung G, Venkataraman C, Phillips E, Howard J, McLean R, Acker MA, Atluri P. HeartMate II left ventricular assist device geometry on chest radiograph does not correlate with risk of pump thrombosis. *ASAIO J*. 2016;62:128–132. doi: 10.1097/MAT.0000000000000326
39. Goldstein DJ, Aaronson KD, Tatooles AJ, Silvestry SC, Jeevanandam V, Gordon R, Hathaway DR, Najarian KB, Slaughter MS; ADVANCE Investigators. Gastrointestinal bleeding in recipients of the HeartWare Ventricular Assist System. *JACC Heart Fail*. 2015;3:303–313. doi: 10.1016/j.jchf.2014.11.008
40. Joy PS, Kumar G, Guddati AK, Bhama JK, Cadaret LM. Risk factors and outcomes of gastrointestinal bleeding in left ventricular assist device recipients. *Am J Cardiol*. 2016;117:240–244. doi: 10.1016/j.amjcard.2015.10.041
41. Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, Bogaev RC, Frazier OH. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant*. 2011;30:849–853. doi: 10.1016/j.healun.2011.03.008
42. Draper KV, Huang RJ, Gerson LB. GI bleeding in patients with continuous-flow left ventricular assist devices: a systematic review and meta-analysis. *Gastrointest Endosc*. 2014;80:435–446.e1. doi: 10.1016/j.gie.2014.03.040
43. Willey JZ, Gavalas MV, Trinh PN, Yuzefpolskaya M, Reshad Garan A, Levin AP, Takeda K, Takayama H, Fried J, Naka Y, Topkara VK, Colombo PC. Outcomes after stroke complicating left ventricular assist device. *J Heart Lung Transplant*. 2016;35:1003–1009. doi: 10.1016/j.healun.2016.03.014
44. Parikh NS, Cool J, Karas MG, Boehme AK, Kamel H. Stroke risk and mortality in patients with ventricular assist devices. *Stroke*. 2016;47:2702–2706. doi: 10.1161/STROKEAHA.116.014049
45. Willey JZ, Demmer RT, Takayama H, Colombo PC, Lazar RM. Cerebrovascular disease in the era of left ventricular assist devices with continuous flow: risk factors, diagnosis, and treatment. *J Heart Lung Transplant*. 2014;33:878–887. doi: 10.1016/j.healun.2014.05.005
46. Milano CA, Rogers JG, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Mokadam NA, Mahr C, Miller JS, Jeevanandam V, Leadley K, Aaronson KD, Pagani FD. The treatment of patients with advanced heart failure ineligible for cardiac transplantation with the heartware ventricular assist device: Results of the endurance supplement trial. *J Heart Lung Transplant*. 2017, 36:S10.
47. Cowger J, Rao V, Massey T, Sun B, May-Newman K, Jorde U, Estep JD. Comprehensive review and suggested strategies for the detection and management of aortic insufficiency in patients with a continuous-flow left ventricular assist device. *J Heart Lung Transplant*. 2015;34:149–157. doi: 10.1016/j.healun.2014.09.045
48. Jorde UP, Uriel N, Nahumi N, Bejar D, Gonzalez-Costello J, Thomas SS, Han J, Morrison KA, Jones S, Kodali S, Hahn RT, Shames S, Yuzefpolskaya M, Colombo P, Takayama H, Naka Y. Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. *Circ Heart Fail*. 2014;7:310–319. doi: 10.1161/CIRCHEARTFAILURE.113.000878
49. Robertson JO, Naftel DC, Myers SL, Prasad S, Mertz GD, Itoh A, Pagani FD, Kirklin JK, Silvestry SC. Concomitant aortic valve procedures in patients undergoing implantation of continuous-flow left ventricular assist devices: an INTERMACS database analysis. *J Heart Lung Transplant*. 2015;34:797–805. doi: 10.1016/j.healun.2014.11.008
50. Phan K, Haswell JM, Xu J, Assem Y, Mick SL, Kapadia SR, Cheung A, Ling FS, Yan TD, Tchantchaleishvili V. Percutaneous transcatheter interventions for aortic insufficiency in continuous-flow left ventricular assist device patients: a systematic review and meta-analysis. *ASAIO J*. 2017;63:117–122. doi: 10.1097/MAT.0000000000000447
51. Martin SI. Infectious complications of mechanical circulatory support (MCS) devices. *Current infectious disease reports*. 2013;15:336–339. doi: 10.1007/s11908-013-0366-9
52. Copeland JG, Copeland H, Gustafson M, Mineburg N, Covington D, Smith RG, Friedman M. Experience with more than 100 total artificial heart implants. *J Thorac Cardiovasc Surg*. 2012;143:727–734. doi: 10.1016/j.jtcvs.2011.12.002
53. 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;31:450–458. doi: 10.1016/j.healun.2011.10.017
54. Mulloy DP, Bhamidipati CM, Stone ML, Ailawadi G, Kron IL, Kern JA. Orthotopic heart transplant versus left ventricular assist device: a national comparison of cost and survival. *J Thorac Cardiovasc Surg*. 2013;145:566–73; discussion 573. doi: 10.1016/j.jtcvs.2012.10.034
55. Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. *Circ Heart Fail*. 2014;7:470–478. doi: 10.1161/CIRCHEARTFAILURE.113.000807
56. 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;5:10–16. doi: 10.1161/CIRCHEARTFAILURE.111.962951