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Invited Review

What Did We Learn about VADs in 2018?

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Introduction

This is our 5th annual literature review on mechanical circulatory support (MCS) devices.
All of our previous reports were well received by the readers. The full text of the reviews for
2014 (https://uknowledge.uky.edu/vad/vol1/iss1/9/),
2015 (https://uknowledge.uky.edu/vad/vol2/iss1/2/),
2016 (https://uknowledge.uky.edu/vad/vol3/iss1/1/),
and 2017 ((https://uknowledge.uky.edu/vad/vol4/iss1/4/) (1-4)
were downloaded 758, 770, 558, and 513 times, respectively.

In this paper, we summarized the most interesting and important, from our standpoint, publications from 2018. There may be some slight overlapping with the end of 2017 because some papers were published online first.
For the second time this year, we added a section on extracorporeal membrane oxygenation (ECMO) which primarily addresses new developments in veno-arterial (VA) ECMO.

Readers who wish to supplement this review, to argue with the author's statements or to express their opinions are encouraged to do so by sending letters to the editor or posting on our Facebook page at https://www.facebook.com/TheVADJournal.

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LVADs and new organ allocation system

In October 2018, a newly designed organ allocation system for donor hearts went into effect. While the consequences for the volumes of transplantations nationwide, in the regions and for individual programs remain to be seen, it is important to acknowledge that the priority of patients with left ventricular assist devices (LVADs) on the waiting list has shifted.
Below (Table 1) is a summarization of the old and new allocation of patients on MCS and on the transplantation waiting list (5).

Table 1. Mechanical circulatory support in old and new transplant listing

	Old status	New status
ECMO	1A	1
IABP	1A	2
Inpatient total artificial heart	1A	2
Non-dischargeable BiVAD or RVAD	1A	1
Acute percutaneous endovascular circulatory support device	1A	2
Mechanical circulatory support with device malfunction/mechanical failure	1A	2
Dischargeable BiVAD or RVAD	1B	2
Uncomplicated LVAD or BiVAD for 30 days with arbitrary timing	1A	3
Mechanical circulatory support with significant device-related complications (thromboembolism, device infection, pump thrombosis, bleeding)	1A	3
MCS with life-threatening ventricular arrhythmias	1A	1
Uncomplicated LVAD or BiVAD, outside of 30 days	1B	4
Outpatient total artificial heart	1B	2

BiVAD- biventricular assist device
ECMO - extracorporeal membrane oxygenation
IABP- intraaortic balloon pump
LVAD – left ventricular assist device
MCS – mechanical circulatory support
RVAD- right ventricular assist device

It is evident that many categories of patients on MCS are classified in a lower status compared to that of the previous allocation. Importantly, the largest group of patients on the waiting list (high dose inotropes with pulmonary arterial catheter in 1A status and ambulatory inotrope-dependent patients in 1B status) are now downgraded to status 3 and 4, respectively. Without the advantage of getting priority access to local donors (since all organs are now distributed within a 500 miles radius), it is going to be all but impossible to transplant them.

We anticipate two major consequences:

1. The field will move away from cardiac transplantation and towards a higher proportion of LVAD implantations as a vast majority of patients on the waiting list will never receive high enough listing status to be transplanted. Although stable on inotropes for substantial amount of time, they will not be stable long enough to wait for the heart. They will be getting LVADs.

2. The overall LVAD population will increase because it will be exceedingly difficult to transplant both stable and unstable patients on LVAD support.

In fact, the "bridge to transplant" category, which was historically a dominant indication for LVAD, may dwindle to nearly obsolete.

Outcomes

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) released their 8th annual report in 2017. According to the report, overall survival on LVAD remains 81% at one year and 70% at 2 years (6).
In 2018, we had some insights into worldwide outcomes. The second annual report from the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS) registry, which includes data on over 14, 000 patients from 35 countries, has an overall survival of LVAD recipients at 79% and 70%, respectively. The 3-year survival is approximately 60%.

The overwhelming majority of patients (97%) in this report received continuous flow LVADs. Unlike in the USA, where an increasing proportion of implantations are performed in the lower risk profile 3 (stable inotrope-dependent patients) which currently account for 38% of new implants, only 16% of LVAD recipients in the IMACS were ambulatory patients with heart failure (HF). A much higher proportion (51%) of implanted patients were in cardiogenic shock or rapidly declining (INTERMACS profile 1 and 2). Similarly to the INTERMACS data, the most frequent primary causes of death were multiorgan failure (21% of mortality), right heart failure (20%), and stroke (19%).

The two most dominant risk factors for early mortality were a diagnosis of congenital heart disease (hazard ratio [HR] 5.2) and the need for biventricular support (HR3.4). The adverse effect of congenital heart disease was only evident during the first 2 months after the implant, after which the survival was no different from the rest. Renal dysfunction, older age, peripheral vascular disease and low albumin were other factors associated with long term poor outcomes (7).
The volume of LVAD implants continues to grow. According to the analysis from the National Inpatient Sample covering the period of 2009 to 2014, LVAD implants increased significantly, with average annual change of +12.6% ($p < 0.001$). Rates of in-hospital mortality decreased by average annual rate of -5.3% ($p = 0.02$). The rates of major complications including ischemic stroke, major bleeding, and cardiac tamponade did not change significantly over the study period.

Interestingly, LVADs are gradually getting cheaper. Although the length of stay did not change over time, there was a significant decrease in cost of hospitalization from the median $218,170 in 2009 to $203,405 in 2014 (p = 0.001) (8).

Another analysis from National Readmission Database (2010-2014) compared outcomes in recipients of heart transplantation (45%) and LVADs (55%). Overall, patients receiving a LVAD had an increased duration of stay (36.3 days versus 35.2 days, p< 0.001). Inpatient mortality in patients receiving an LVAD nearly doubled that of heart transplant patients (10% versus 5.2%, p <0.001). Patients receiving an LVAD also had slightly increased costs of index hospitalization ($213,667 vs $177,128, p = 0.05). Readmissions were more frequent in patients with LVADs (62% versus 46%, p <0.001 at 6 months). Cost of readmissions was also increased for LVADs ($34,878 versus $20,144, p = 0.0106 at 6 months) (9).

Although total artificial heart is not an LVAD, the outcomes with this device are of interest to everyone who is involved in MCS. Arabia et al. examined the outcomes of 450 patients with a total artificial heart (SynCardia Systems, LLC, Tucson, AZ) from the INTERMACS. Overall 3-, 6-, and 12-month actuarial survival rates were 73%, 62%, and 53%, respectively. Besides older age, dialysis, higher creatinine and lower albumin, implantation at a low volume center with fewer than 10 total artificial heart implantations per year was a potent risk factor for death. In high volume centers, 71% of patients were alive on device support or had undergone transplantation at 12 months versus 57% in low-volume centers (p = 0.003) (10).

Also, the outcomes in patients undergoing implantation of an LVAD directly after extracorporeal life support were reported. In a single center study, there were 100 such patients, 33 of which also required a temporary RV mechanical support after the surgery. In this very sick population, LVAD was a life-saving treatment and possibly the only means to survival. Their 30-day, 1-year and 2-year survival after LVAD was 62.0%, 43.0%, and 37.1%, respectively (11).

Although many centers empirically preferred Heartware to HM2 in patients with small ventricles, there was no clear-cut evidence to support such practice. In 2018, HM2 and Heartware were compared in patients with LV end diastolic dimension ≤5.5 cm. For HM2, a 2 year survival was 66.8% for the non-small LV patients and 56.1% for the small LV patients (p = 0.17), and non-small LV patients had significantly better overall survival (p = 0.02). For the Heartware recipients, the 2-year survival was 71.3% for normal and large LVs and 70.8% for small LVs (p = 0.96). Apparently, Heartware is indeed better for small ventricles (12).

Outcomes of VA ECMO as a bridge to heart transplantation are a very timely topic as this patient population is given priority for cardiac transplantation in the new organ allocation system. Using the United Network of Organ Sharing data, these patients were compared with those who were bridged with long-term LVAD. The post-transplant survival was 73.1% versus 93.1% at 90 days (p <0 .001) and

67.4% versus 82.4% at 3 years (p < 0.001) in ECMO and continuous-flow LVAD groups, respectively (13).

Pumps

HeartMate III

In November 2018, HeartMate III (Abbott, Abbott Park, IL) (HM3) received the Food and Drug Administration (FDA) approval for destination therapy (approval for bridging to transplant was received in 2017). This decision was made after recent data from the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), a randomized trial comparing HM3 and HM2. The newer pump provided a 2 year survival of 82.8%, while survival on HeartMate2 was 76.2% (14).
Last year, the findings from the short term cohort showed that a composite of survival free of disabling stroke or pump replacement at 6 months was better in HM3 (86.2%) than in HM2 recipients (76.8%), with p<0.001 for non-inferiority and p=0.04 for superiority (15). In the long-term cohort, the primary end point occurred in 151 patients (79.5%) in the HM3 arm versus 106 (60.2%) in the HM2 arm (p<0.001 for both non-inferiority and for superiority). Reoperation for pump malfunction was less frequent in HM3 than in HM2 (1.6% vs. 17.0%) (14). Difference in the primary end point was driven by the freedom of pump exchange. In the same trial, only 1.1% of patients on HM3 had pump thrombosis over 2 years, and neither required pump exchange while in the HM2 arm 15.7% had pump thrombosis with the majority of the patients requiring pump exchange (14). Although disabling stroke occurred at a similar rate in both cohorts (6.9% and 5.2%, respectively), overall rate of cerebrovascular accidents (CVAs) occurred in 10.1% on HM3 vs 19.2% on HM2 (p=0.02), including hemorrhagic in 4.2% vs 9.3% (p=0.06) and ischemic in 6.3% vs 13.4% (p=0.03) (14).

A comprehensive analysis of stroke events in the MOMENTUM 3 trial showed no difference in stroke rate between HM2 and HM3 up to 180 days of follow-up. However, stroke incidence in the long-term period (181-730 days after the implantation) was 3.3 times lower for the HM3 group (HM3: 0.04 versus HM2: 0.13 events per patient-year; odds ratio, 0.23; 95% CI, 0.08-0.63; p=0.01). Treatment with the HM3 pump was the only independent predictor of lower stroke events. There was no direct association of blood pressure or antithrombotic regimens with observed stroke rates (16).

Because of fewer readmissions for pump thrombosis/exchange and stroke, HM3 had more of an overall cost effectiveness compared to HM2. The HM3 patients experienced fewer total hospitalizations per patient-year (2.1±0.2 versus 2.7±0.2; p=0.015) and 8.3 fewer hospital days per patient-year (17.1 days versus 25.5 days; p=0.003). Post discharge HM3 –associated costs were 51% lower than with the HM2 (HM3: $37 685±4251 versus HM2: $76 599±11 889, p<0.001) (17).

European experience with HM3 was consistent with a 2 year survival of 74 ±6%, with no pump thrombosis or malfunction, with good functional status and with almost half of the patients in New York Hear Association I-II (18).

The lack of pump thrombosis encouraged several center to test less rigorous use of anti-thrombotics and anticoagulants in HM3. In a single-center experience, 15 patients were managed without aspirin for over a year and reported no pump thrombosis or thromboembolism (19). In the Minimal AnticoaGulation EvaluatioN To aUgment heMocompatibility (MAGENTUM 1), a prospective single-arm study, 15 patients were treated with warfarin (international normalization ratio[INR] 2-3) for the first 6 weeks after the implant and then transitioned to a lower INR target range of 1.5 to 1.9. In 6 months thereafter, there were no thrombotic events (20). Larger randomized studies are warranted, but it hopefully HM3 will require less anticoagulation than other pumps resulting in subsequent reduction in bleeding complications.

On the other hand, some complications, such as twisting of the outflow graft, seem to be specific to HM3 (21). Potapov et al. suggested a surgical technique which prevents this from happening (22).

The response of the heart to the LVAD speed change differs between devices. Measuring both ventricles in the ramp study, Uriel et al. demonstrated that as the LV is getting smaller, the right ventricle (RV) is getting a little bigger and septum shifts leftwards at higher speeds of the HM3. The LV volume decreases by 24 mL per 100 revolutions per minute (rpms). Importantly, ejection fraction of both ventricles remains grossly unaffected (23).

Like HeartWare (Medtronic, Minneapolis, MN), HM3 was tried for biventricular support. In 2018, the first experience with 14 patients supported with HM3 in both ventricles was published. Nine of the 14 were alive, with one transplanted and eight still on support at the mean of 266 days (24).

HeartWare

HeartWare (Medtronic, Minneapolis, MN) is another pump currently approved for both destination therapy and as bridge to transplant. Last year, the Evaluate the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure (ENDURANCE) proved a non-inferiority of HeartWare to HM2 in safety and effectiveness. Briefly, survival free from disabling stroke or need for device replacement at 2 years was 55.0% for HeartWare and 57.4% for HM2 (not significant). The rates of complications were similar except for stroke which was more prevalent in HeartWare (29.7% vs. 12.1%, $p<0.001$) (25). Post hoc analysis identified increased mean arterial blood pressure (>90 mmHg) as a significant independent risk factor for stroke. Congruently, mean arterial blood pressure of ≤90 mm Hg was associated with a lower frequency of strokes, particularly hemorrhagic ones. The ENDURANCE Supplemental Trial tested the enhanced blood pressure protocol and showed that it significantly reduced both blood pressure and the incidence of ischemic stroke (26).

Recently, the Lavare cycle was added to this device. This cycle represents a periodic speed modulation designed to alter flow patterns within the LV and reduce areas of potential blood stasis. Patients with active Lavare cycle had significantly fewer rates of stroke (0.06 vs 0.20 events per patient-year, p = 0.0008), sepsis, and right heart failure with no decrease in the transplant or recovery rates among the two cohorts. (27).

Recovery

The topic of myocardial recovery continues to generate a lot of interest. Several great reviews were published in 2018, each focusing on a certain angle of the problem. Dandel and Hetzer (28) summarized pathophysiological and clinical data, Jaiswal et al (29) reviewed patients baseline characteristics and candidate selection as a key to understanding discrepant results of recovery, and Uriel et al. (30) presented all aspects of mechanical unloading of the heart from molecular biology to clinical data.

A retrospective analysis from the German Heart Center Berlin group presented their approach to the problem, along with the protocol and results. The protocol is presented on Figure 1.

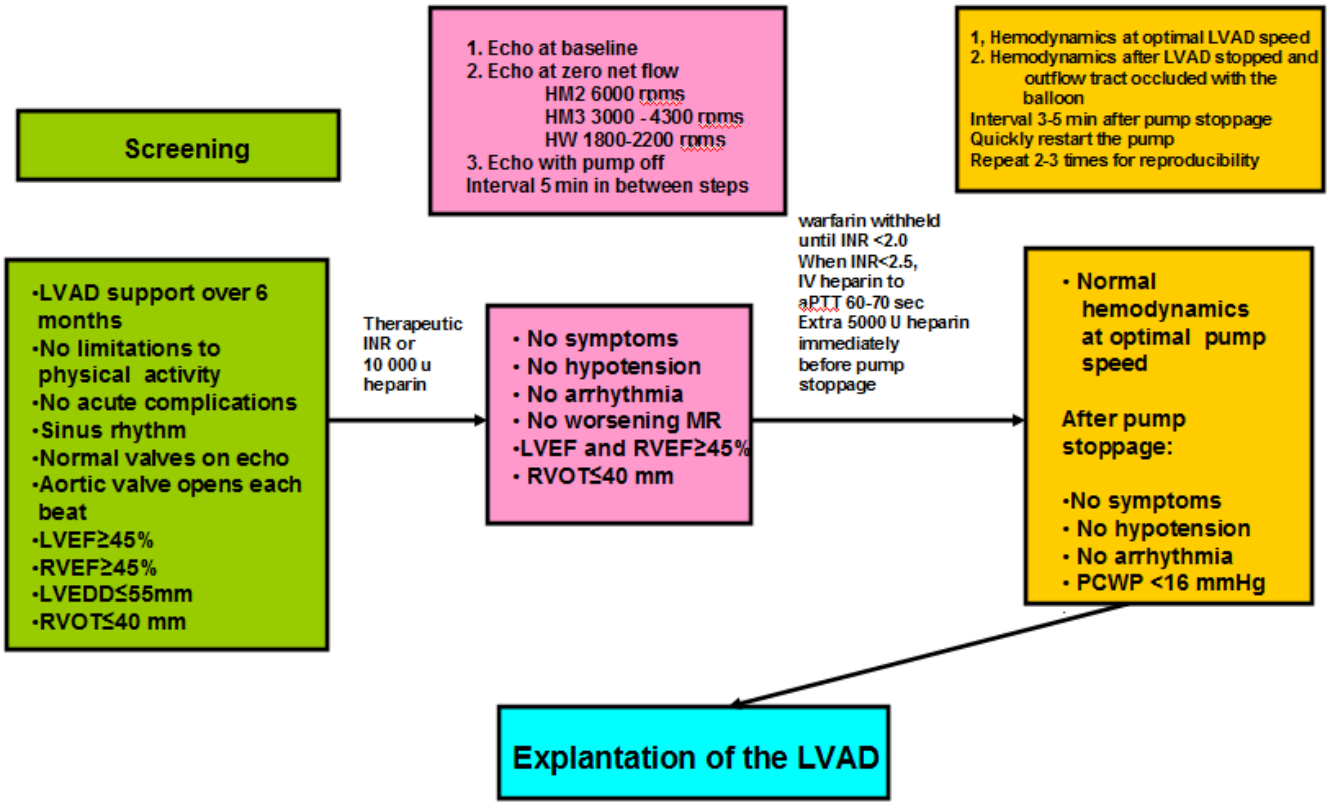

Figure 1. Cardiac recovery protocol (31)

Out of a total of 424 patients, 33 met the screening criteria and entered the second step (echocardiography testing) with 20 patients proceeding to the final step of evaluation (in the catheterization laboratory). In 14 patients all criteria for recovery were met and 13 of those patient's underwent LVAD explantation. One year later, there were no signs of HF recurrence. Therefore, the true recovery rate was 3% (31).

Once the recovery is achieved the LVAD can be either explanted or decommissioned. In a meta-analysis of published studies, explantation was done in 80% of cases and decommissioning in 20%. In a year, there were no significant differences in the incidence of cerebrovascular accidents and survival. Both approaches seem to be acceptable (32).

Also, based on our experience, we made an argument that true recovery is rare as all three patients who underwent LVAD explantation at our institution had a recurrence of HF within a year (33).

Management of patients on LVAD support

Hemodynamics

In the past reviews, we stressed the need of hemodynamic optimization of LVADs. It appeared that patients with optimal hemodynamic parameters (defined as central venous pressure < 12 mmHg, pulmonary artery wedge pressure < 18 mmHg and cardiac index > 2.2 L/min/m^2) have fewer adverse events which are seemingly unrelated to hemodynamic status. Their one-year survival free of non-surgical bleeding, thromboembolic event, pump thrombosis, or neurological event was 75%, versus only 44% of the hemodynamically non-optimized group (hazard ratio 0.36, 95% confidence interval 0.18-0.73, P = 0.003) (34).

Also, there is new evidence that HF medications should be resumed and continued while on LVAD support. Patients on angiotensin converting enzyme inhibitors/angiotensin receptor blockers had lower pro-B-type natriuretic peptide at 6 and 12 months, lower right atrial pressures (9 vs 12 mmHg, p=0.03) and significantly lower mortality than patients not on these medications (35).

Several cases of cardiopulmonary resuscitation in LVAD patients were published in the VAD Journal in 2018 (36) as well as our detailed analysis of the approach to unresponsive LVAD patients. This included the analysis and comparison of all published algorithms (37).

Last year, we wrote about use of Cardiomems (Abbott, Abbott Park, IL) in patients with LVADs. Below is the illustration of a dramatic decrease of pulmonary arterial pressure after the LVAD implantation (Figure 2).

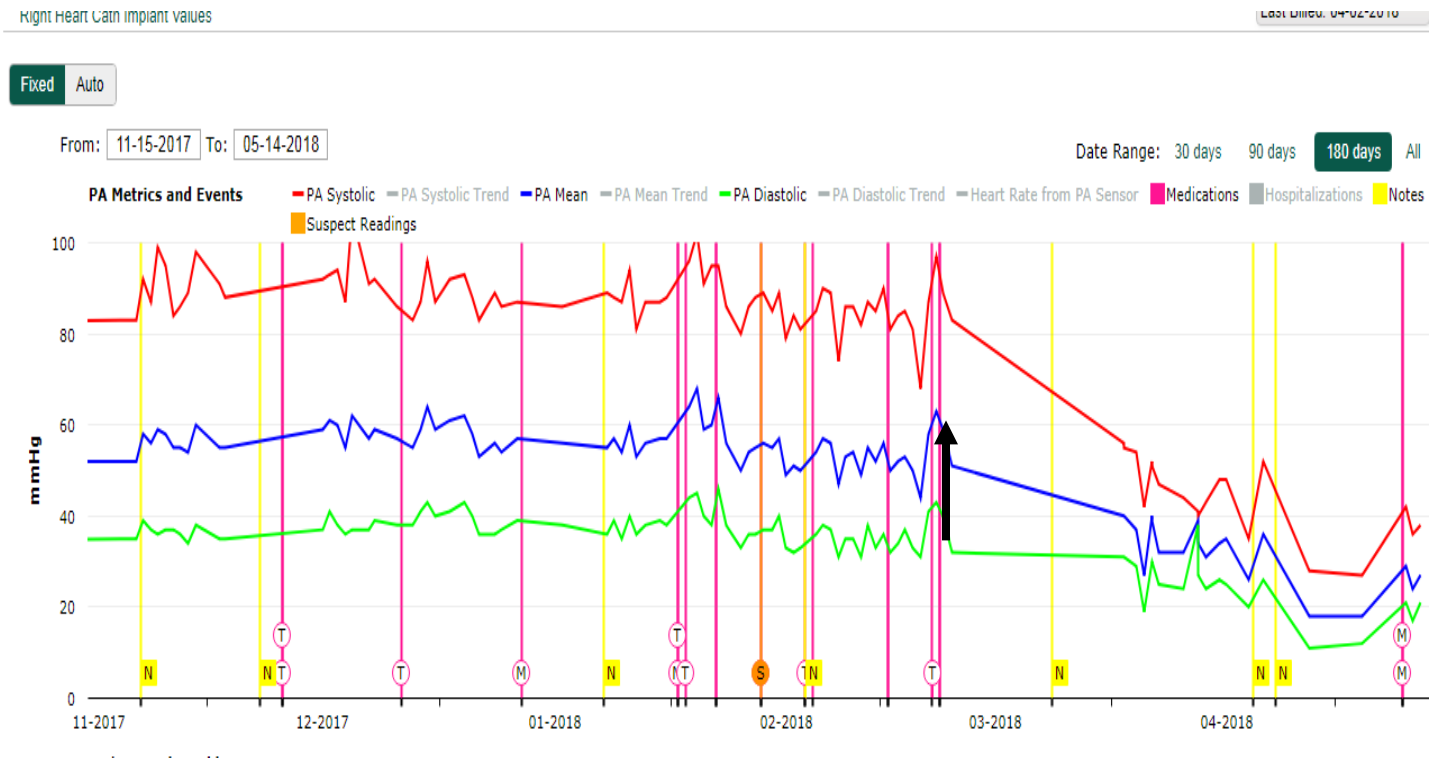

Figure 2. A Cardiomems tracing showing a dramatic decrease of pulmonary arterial pressure after the LVAD implantation (arrow) after failure of multiple adjustments of the medications

Arrhythmias

Arrhythmias in patients on LVAD support remains a common problem. In 517 patients with LVAD implantation, ventricular tachycardia (VT) or ventricular fibrillation lasting over 30 seconds was recorded in 47% of patients within first month after surgery. The early VT was associated with a significant reduction in survival (hazard ratio: 1.83; 95% confidence interval: 1.28 to 2.61; p = 0.001) compared with patients with late VT or no VT. Prior cardiac surgery and prior VT storm were major predictors of early VT (38).

Atrial arrhythmias are also common. Atrial fibrillation (AF) was documented in 32% of patients following LVAD placement. The presence of AF was not associated with increased risk of death or stroke (39).

In patients with VT on chronic LVAD support, ablation is becoming a standard practice. Ablation of VT in 21 patients with LVADs resulted in termination of a clinical VT in 62% of cases. However, only 29% of patients were completely non-inducible after the ablation. In 38% of those with successful ablation VT recurred within a year. In the whole cohort, mortality was 47% at 1 year. Interestingly,

mortality was higher among patients with VT recurrence after ablation than in those without recurrence (71% vs 33%, p=0.049) (40).

Subcutaneous defibrillators are being considered in patients with LVAD. The benefits include absence of intracardiac leads and presumed reduced risk of infection (41). On the other hand, there are more possibilities for device interaction with the LVAD. Different retrospective studies showed significant variation in sensing, lead impedance, pacing threshold and device–device communication, with 13% of patients requiring lead revisions and 20% requiring implantable Cardioverter-defibrillator (ICD) testing. There is also a concern that electrical artifacts created by LVAD activity could cause an inappropriate shock delivery in up to 18% of patients. Also, while this device can deliver shocks, it does not provide anti-tachycardia pacing. Given relatively good tolerability of VT/VF post LVAD, many cardiologists program ICDs to minimize shocks and maximize antitachycardia pacing (42).

The effects of cardiac resynchronization therapy (CRT) in LVADs were studied again. On right heart catheterization, there was no difference in hemodynamic parameters including right atrial pressure, pulmonary arterial pressures, pulmonary capillary wedge pressure, cardiac index or any LVAD parameter regardless of whether LV lead was activated or not (43). With biventricular pacing, RV pacing only, or no pacing at all, Tehrani et al.(44) saw no difference in echocardiographic or hemodynamic characteristics at different LVAD speeds. In terms of long-term effects, a meta-analysis of the literature failed to find any effects of CRT on mortality, re-hospitalization, ventricular arrhythmia incidence and ICD therapies (45).

These results are very intuitive. Clearly, if the patients with CRT had to be placed on LVAD support, it means that CRT produced no response.

LVAD and Valves

Mitral valve

The need to repair mitral valve with greater than mild regurgitation during the LVAD implantation is still debated.

A meta-analysis published by Choi et al. (46) showed than only 25.4% of patients with moderate to severe mitral regurgitation had concomitant mitral valve surgery. There were no significant differences in cardiopulmonary bypass time (154 min vs. 119 min) or hospital length of stay (21 days vs. 18 days). On follow-up, none of the patients post mitral valve surgery had greater than moderate mitral regurgitation vs 26% in patients without such surgery. Survival was also comparable at 6-months (77% vs. 81%), 1-year (72% vs. 80%), and 2-years of follow-up (65% vs. 70%, p = 0.56) (46). According to these results, the benefit of concomitant mitral valve surgery is questionable.

On the other hand, patients with moderate to severe mitral regurgitation from the INTERMACS database (n = 4,930) who underwent concomitant mitral valve repair, replacement or neither, had similar two-year survival (76%, 57%, and 71%, respectively), but those who had mitral valve surgery had fewer readmissions on LVAD support (47).

Percutaneous repair of mitral valve with MitraClip (Abbott, Abbott Park, IL) resulting in hemodynamic and clinical improvement was also reported (48).

Aortic valve

Aortic regurgitation is seen in about 30% of patients on LVAD support in the first year after the implantation, and the prevalence increases thereafter. A detailed review on all aspects of aortic insufficiency in LVADs was published this year (49).

Percutaneous replacement of leaking aortic valve remained in the focus of attention (50). In another case report, transcatheter aortic valve replacement resulted in reversal of pulmonary hypertension caused by aortic regurgitation (51).

A meta-analysis summarizing the experience of 29 patients who underwent percutaneous interventions on aortic valve was published by Phan et al. Two modalities of the interventions were transcatherer aortic valve replacement (27.6%) and occlusion devices (72.4%). Interventionists performing the procedures used all kinds of the approaches, including transfemoral, apical approach, brachial, subclavian and mini-sternotomy. Severe (grade 4) aortic regurgitation reduced to 0 post procedure and remained at grade 1 long term. Both modalities were equally effective. In terms of complications, two devices migrated in each group (52).

LVAD and Lifestyle

Driving patterns of patients after LVAD implantation were studied by a worldwide multicenter survey. It appeared that 72% resumed driving after LVAD implantation. Reasons for discontinuation were capability (24%), insecurity (17%), and disapproval by family members (9%) or doctors (5%). Ninety percent of the patients describe their ability to drive as perfect or adequate. The majority of patients (94%) have not been involved in car accidents. Authors concluded that driving with an LVAD is safe for stable patients and driving can be resumed 3 months after LVAD implantation (53). Per previously published study, similar proportion of 70% of patients returned to driving after LVAD (54).

Specific recommendations on exercise training in patients with LVAD were presented in the position paper from the Committee on Exercise Physiology and Training and the Committee of Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology(55).

Surgery

Effects of pump position on outcomes were studied in patients with Heartware. Being an intrapericardial pump, Heartware does not migrate over time, so correct positioning of the device during the surgery is critically important.
Lower cannula coronal angle was associated with better LV unloading (as measured by smaller LV diastolic dimension and lower pulmonary capillary wedge pressure). Cannula coronal angle ≤65° was associated with reduced HF readmissions HR 10.33; p = 0.007 by log-rank test). (56).

Also, in one third of the cases, the left atrial appendage gets isolated during the surgery. It appeared that patients who had this procedure are at a lower risk of thromboembolic events during the next year (HR 0.27 (0.08-0.95), p=0.04(57).

Complications of the VADs

Pump thrombosis

The relationship between surgical positioning of the pump and the risk of pump thrombosis was further explored. Virtual surgery with computational modeling to study flows through the pump for different inflow cannula angulations showed that optimal flow is achieved when the inflow angulation is within 7° of the left ventricular apical axis (58).

In the PREVENtion of HeartMate II pump thrombosis through clinical management (PREVENT) study, patients with extreme pump position had a significantly higher risk of hemolysis, elevated lactate dehydrogenase (LDH) and pump thrombosis with HR 3.6; 95% CI 1.5-8.9; p = 0.006 (59).

Curiously, sildenafil may not only improve hemodynamics but prevent pump thrombosis. In one single center retrospective study, patients with HM2 who had low level hemolysis (400 < LDH ≤ 700 U/L) differed in their risk for thromboembolic event (pump thrombosis and ischemic stroke) depending on whether or not they were taking sildenafil (for other indications). In those who were not on sildenafil, the risk of thromboembolism was higher (HR 14.4, 95%-CI: 1.8-117.1, P = 0.001). As expected, mean pulmonary artery pressure and pulmonary vascular resistance decreased significantly on sildenafil (p < 0.0001) while cardiac index increased (p < 0.0001) (60).

LVAD Outflow graft obstruction

Special attention should be taken not to confuse pump thrombosis with other kinds of pump obstruction, especially at the outflow graft level, which is a distinctly different complication. Causes of outflow graft obstruction include compression by mediastinal tissue, twisting or kinking of the outflow graft, anastomosis stenosis and accumulation of gelatinous protein matrix/hematoma between the bend relief and the outflow graft (61).

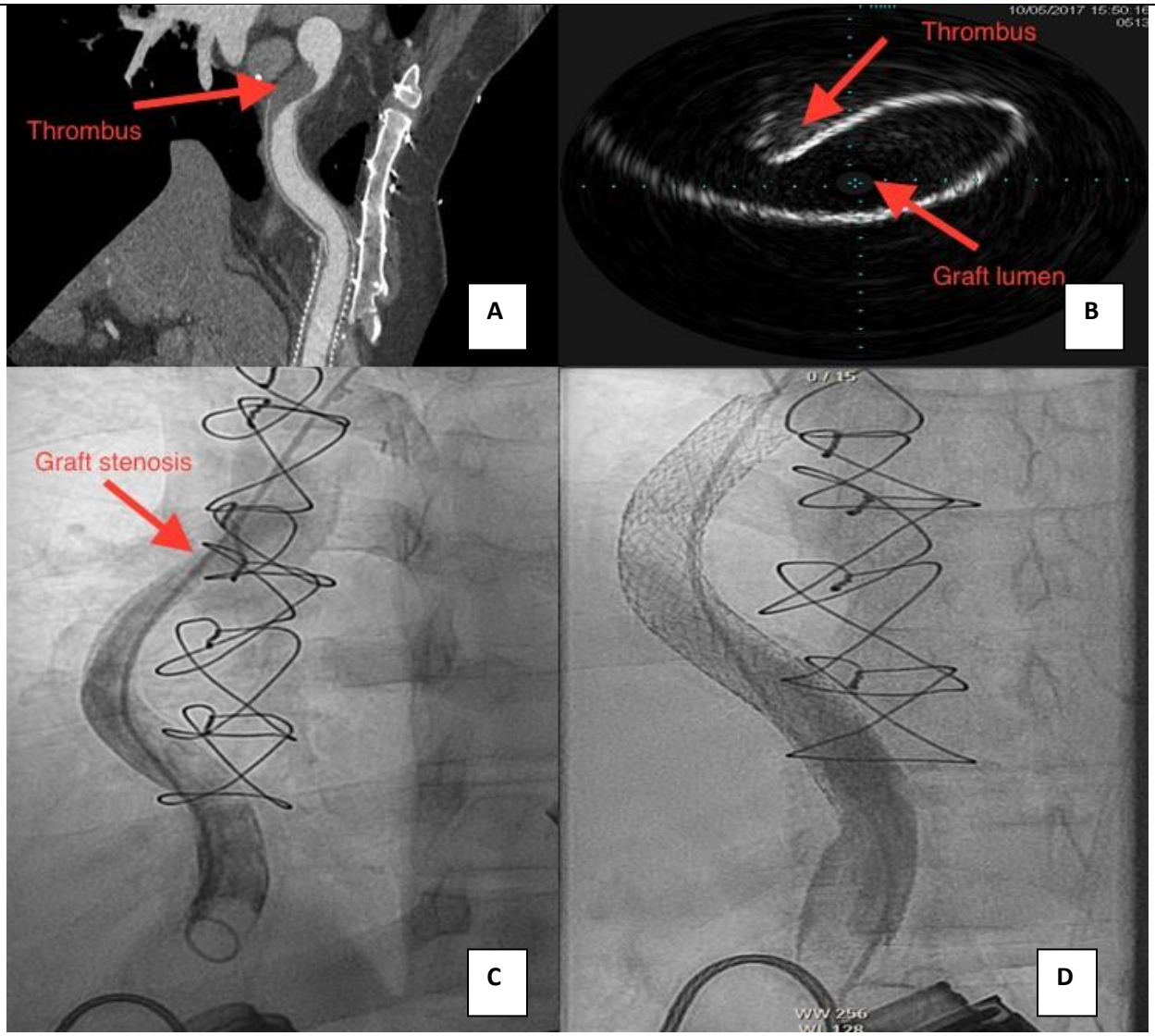

Figure 3. LVAD outflow graft stenosis due to thrombus between the LVAD outflow cannula and the Gore-tex cover
A. Computer tomography angiography demonstrating compression of the LVAD outflow cannula by external thrombus
B. Intravascular ultrasound showing extensive external compression of the outflow graft confirming a thrombus between the outflow graft and the Gor-Tex graft
C. Angiography demonstrating stenosis in the outflow graft (red arrow)
D. Stent in the LVAD outflow graft

Outflow graft obstruction by thrombotic masses accumulating between the Gore-tex (Gore Medical, AZ) polytetrafluoroethylene cover of the outflow graft and the outflow graft itself is a recently recognized complication. This was first reported by Bhamidipati et al. (62) in 2017. They recognized and described this phenomenon

in three patients, all with HM2, on LVAD support from 33 to 57 months, all successfully treated by stenting of the outflow graft. The phenomenon is not specific to the type of LVAD but rather to the surgical technique. Gore-tex is placed around the outflow graft to minimize development of adhesions and to make it easier to re-operate in the event the patient undergoes heart transplantation or pump exchange at a later time. The fabric of the outflow graft is porous and allows leakage of intravascular contents, while the outer gore-tex in impenetrable. Slow leakage over months and years may create thrombus, which grows gradually resulting in progressing obstruction of the outflow graft.

On Figure 3, we show different imaging modalities demonstrating LVAD outflow cannula external compression by a thrombus between the outflow graft and Gore-tex.

In the table below (Table 2), we collected the cases reports of this complication. It occurs in all three types of currently used long term LVADs. The key features for recognition of the outflow graft obstruction are:

- Surgical technique: gore-tex aroung the outflow tract
- Timing: months to years after the implantation
- Symptoms: HF, low flows, with or without low flow alarm, and decreased pulsatility index
- No hemolysis
- Diagnosis: computer tomography angiography (CTA)
- Treatment: stenting
- Prevention: discontinuation of wrapping the outflow tract with the gore-tex

Table 2. LVAD outflow tract obstruction caused by thrombus/debris between Gore-tex cover and the outflow cannula

			Patient (age, sex)	Mechanism	Time after implant, months	Diagnostic modality	Hemo-lysis	Symptoms	Treat-ment
1	**HM2**	Pham (63)	64M	Stenosis, kink, or obstruction, no further discussion	12	CTA, ventriculogr am	No	HF, low flow	Stent
2		Jackson(64)	68F	Collection of thrombotic material between outflow graft and gore-tex	26	CTA, direct inspection	Not repor-ted	HF, low flow	Surgery
3		Jackson(64)	29M	Collection of thrombotic material between outflow graft and gore-tex	42	CTA, direct inspection	Not repor-ted	HF, ventricular tachy-cardia, cardiogenic shock	Surgery

4		Alnabelsi(65).	56 M	Collection of thrombotic material between outflow graft and gore-tex	23	CTA	No	Fatigue. low flow, low pulsatility index	Stent
5		Trankle (66)	62F	External compression in the gore-tex covered portion	60	CTA	Not repor-ted	Syncope, low flow	Stent
6	**HM3**	Duergo Posada (67)	41M	Collection of thrombotic material between outflow graft and bend relief	6	CTA, pathology after Heart transplant	Not repor-ted	Low flow	Heart transplant
7		Duergo Posada (67)	65M	Collection of thrombotic material between outflow graft and gore-tex	12	Pathology after heart transplant	No	HF, Low flow	Heart transplant
8	**HW**	Pieri (68)	29M	None suggested	60	Fluoro-scopy with IV contrast injected into proximal part of the outflow graft	No	HF, low flow	Stent
9		Alnabelsi(65).	54 M	Collection of thrombotic material between outflow graft and gore-tex	41	CTA, direct inspection	No	Dizziness and blurred vision. low-flow alarms, low pulsatility index	Pump replace-ment
10		Alnabelsi(65).	57F	Collection of thrombotic material between outflow graft and gore-tex	29	CTA	No	Low flow	Stent
11		Jackson(64)	46M	Collection of thrombotic material between outflow graft and gore-tex	54	CTA, direct inspection	Not repor-ted	HF, low flow	Surgery

CTA – computer tomography angiography
F- female
HF – heart failure
HM2- HeartMate II
HM3- HeartMateIII
HW - Hearware
M- male

Gastrointestinal Bleeding

In 2018, there were some advances towards better understanding of the nature of gastrointestinal bleeding (GIB) in patients with LVAD. It is well established that shear stress causes degradation of large multimers of von Willebrand factor (vWF) altering the process of coagulation and causing coagulopathy. In concert with chronic anticoagulation with warfarin, this increases propensity to bleeding. This does not, however, explain the genesis of atriovenous malformations in the small bowel.

In an in vitro experiment, fragments of vWF were shown to alter angiogenesis and facilitate angiodysplasia. The same investigators found an abnormally high content of vWF fragments in the blood of patients with a LVAD, but only in those whose source of bleeding was angiodysplasia (69). Also, it was found that magnitude of the vWF degradation is modulated by the pulsatility level, and that pulsatility triggers the endothelial release of vWF in a dose-dependent manner and increases the levels of multimers in the circulation (70).

Per this observation, increased pulsatility may result in clinically significant reduction in GIB. And indeed, 92% of patients with pulse pressure ≥35 mmHg were free from GIB at 6 months, compared with 76% with pulse pressure <35 mmHg. Interestingly, higher right atrial pressure was also associated with more GIB (71).
Also, the University of Chicago group demonstrated that preoperative central venous pressure≥ 18 mmHg (HR 3.56; 95% CI 1.16-10.9; p = 0.026), mean pulmonary artery pressure ≥ 36 mmHg (HR 4.14; 95% CI 1.35-12.7; p = 0.013), and the presence of moderate/severe tricuspid regurgitation (HR 1.01; 95% CI 1.01-3.86; p = 0.046) were associated with the risk of GIB (72). In summary, higher pulsatile arterial pressure and lower central venous pressure are protective from GIB. This correlates well with the previously referenced paper stating that hemodynamically optimized LVAD produces fewer complications in general (34).

Clinicians continue to experiment with off-label medications for treatment of GIB. Schettle et al., who previously reported the use of danazol 200-400 mg a day for GIB in LVADs, conducted a study with this drug in 19 patients with one or more episodes of GIB. Danazol was given for the mean duration of 12.5 ± 10.5 months. They categorized 58% of patients as responders to danazol (their requirements for blood transfusions decreased by 50% or more). The source of bleeding was small bowel angiodysplasia in 79% of patients.

The average number of GIB-related hospitalizations per month was significantly reduced from 0.4 ± 0.6 before treatment with danazol to 0.1 ± 0.1 after treatment ($p < 0.0001$). The average requirement for blood transfusions per month reduced from 1.3 ± 2.4 to 0.2 ± 0.3 units ($p = 0.0002$). one possible mechanism is the known ability of danazol to increase the level of factor VIII which is essential for activity of vWF (73).

The efficacy of octreotide was again reported this year, with a decrease in GIB from 3.4 ± 3.1 to 0.7 ± 1.3 events/year; p <0.001 (74).

Interestingly, a retrospective chart review from Montefiore found that overall frequency of GIB was lower in patients receiving digoxin compared with the patients not receiving it (16% versus 33%, P=0.01). Multivariable-adjusted Cox regression analysis confirmed that digoxin use was independently associated with a reduced risk for overall GIB (hazard ratio, 0.49; 95% CI, 0.24-0.98; p=0.045). Digoxin appeared to be especially protective if the source of bleeding was atriovenous malformations (75).

RV failure

An excellent review on temporary mechanical circulatory support for failing RV was published by Dandel and Hetzer (76).

The main points are:

- Failing RV is more likely to recover than failing LV
- Only temporary support may be required
- Up to 60% of end-stage RV failure cases can be reversible with short-term MCS
- Primary RV failure originates from an underlying pathological process affecting only RV or both LV and RV
- Secondary RV failure originates from overload from pulmonary hypertension, pre-or post-capillary
- LVAD improves loading conditions of the RV and may facilitate the RV recovery if there is no primary RV failure
- The major causes of death during temporary RVAD support are multi-organ failure, sepsis, and bleeding
- Early implantation of MCS devices for RV support is critical for good outcome (concomitantly with LVAD implantation is the best)
- Two dimensional echo and right heart catheterization are the cornerstones of the RV evaluation
- On right heart catheterization, high central venous pressure (CVP), high CVP/PCWP ratio, low cardiac index, and low pulmonary arterial pressure predict post-LVAD RV failure
- Combination of high CVP and low pulmonary arterial pressure is particularly risky
- CentriMag (Abbott, Abbott Park, IL) system allows 30 days of support with up to 10L/min flow but needs to be surgically implanted
- Percutaneous cannulation may be used with several devices such as TandemHeart-RVAD (CardiacAssist, Inc., Pittsburgh, PA) allowing 30 days of support with up to 4L/min flow, with ambulation possible
- Percutaneous Impella-RP (Abiomed, Danvers, MA) allows ≤ 30 days of support and up to 4L/min flow
- VA ECMO can provide biventricular support for 7 days with up to 6L/min flow

- Weaning from RVAD is done by gradual reduction of flow to 2 L/min at 0.5L/day increments under echocardiography guidance
- Phosphodiesterase-5 inhibitors can be useful for RV recovery
- Freedom from RV failure recurrence after removal of temporary RVAD can reach 90%

Leading indications for temporary MCS for RV failure are postcardiotomy cardiogenic shock (16%), post cardiac transplant (31%), and post LVAD (53%). MCS was successfully weaned in 46% of postcardiotomy shock cases, 84% of post-transplant cases and in 83% of post-LVAD cases. Survival up to 3 months was better for patients who received immediate versus delayed support (79% vs 46%, p =0.003) (77).

In another report, Impella RP was used in 60 patients with severe RV failure either post LVAD or as a result of medical condition such as post-cardiotomy, heart transplant or myocardial infarction. Patients were supported with the Impella RP for 4.0 ± 1.5 (0.5 to 14) days. Hemodynamics improved immediately after initiation of device support, with an increase in cardiac index from 1.9 ± 0.1 to 3.1 ± 0.2 liters/min/m^2 ($p < 0.001$) and a decrease in central venous pressure from 19.0 ± 1 to 13 ± 1 mm Hg ($p < 0.001$). The overall survival at 30 days (or discharge) was 72% (78).

In terms of long term support for RV, an analysis from the INTEMACS identified 38 adult patients on two centrifugal pumps for biventricular support. The RVAD was implanted in the RV in 59% and in the right atrium in 41%. Survival was below the outcomes usually reported for LV support only: 68% at 6 months and 62% at 12 months. Also, the complication rate was high with infection in 50%, bleeding in 44%, respiratory failure in 31.6%, malfunction in 26.3% and neurologic dysfunction in 26.3% of patients (79). Nevertheless, considering the dismal prognosis in RV failure, this still appears to be a viable option.

The Berlin group reported their experience in 39 patients with two continuous-flow VADs in a biventricular assist device configuration. They used both Heartware and HM3, and modified both devices for biventricular use. In Heartware, they banded the outflow graft and reduced the intracaval length of the inflow cannula. In HM3, they increased the extraventricular part of the inflow cannula. The 30-day survival for the group was 72.7% and the 1-year survival was 45.0% (80).

What is new in VA ECMO World?

Left ventricular decompression

This year, several good reviews were published on LV distension and LV venting (81-84).
Also, there were several single center studies on Impella for LV venting. Terms suggested for this combination were Ecmella (85) and Ecpella (86). In the largest published series of 106 patients, a combination of VA ECMO and Impella resulted in a 30-day mortality of 35.8%, which was higher than predicted by risk scores.

There was a marked decrease of pulmonary capillary wedge pressure after addition of Impella (87).

Another study had similar findings where 30-day mortality was significantly lower in the VA ECMO + Impella cohort (57% vs. 78%; hazard ratio [HR] 0.51 [0.28-0.94], log rank p = 0.02) (86).

Also, there were new reports on a concomitant use of VA ECMO and intra-aortic balloon pump (IABP). A meta-analysis of 22 observational studies showed no significant mortality difference in VA ECMO only (57.8%) and VA ECMO +IABP (42.1%). However, the combination appeared to deliver better outcomes in patients with cardiogenic shock due to acute myocardial infarction (88).

In a single center study on patients with postcardiotomy cardiogenic shock, concurrent implantation of IABP with ECMO (OR=0.177, P=0.015, 95% CI: 0.044-0.718) was an independent predictor of survival to discharge (89).

Anticoagulation

Heparin induced thrombocytopenia

Because of low platelets in patients on ECMO, heparin induced thrombocytopenia is commonly suspected and tested for.

Meanwhile, it appeared to be extremely rare. Out of almost 6,000 patients, heparin induced thrombocytopenia was confirmed in only 0.36%. In confirmed cases, mortality was no different than in patients without this condition (90).

Bivalirudin in ECMO

Many programs actively explore direct thrombin inhibitors as an alternative to heparin on VA ECMO.

Bivalirudin is a semisynthetic thrombin inhibitor with a short half-life of 25 minutes. It is mainly cleared by blood proteases, but about 20% of clearance occurs in kidneys. It is also removed by hemodialysis. Unlike heparin it does not affect platelets and provides more predictable anticoagulation effect which is highly desirable in patients on ECMO support.

Bivalirudin dosing requirements increase by 75-125% when renal replacement therapy is in use (91).

In practice, it is unclear whether bivalirudin has advantages over heparin. In comparison with patients anticoagulated with heparin while on ECMO, patients receiving bivalirudin show similar rates of thrombotic events during the initial 96 hours of anticoagulation, over the course of their entire ECMO run, and at any time during the admission (17.9% vs. 9.1%; p = 0.47, 21.4% vs. 11.4%; p = 0.41, and

25% vs. 22.7%; p = 1.00, respectively). In-hospital (32.1% vs. 36.4%; p = 0.91) and 30-day mortality (32.1% vs. 36.4%; p = 0.91) were no different. Similarly, no differences were observed in percent time within therapeutic range, neurological events, vascular complications or bleeding (92).

As a pump with continuous flow, VA ECMO is accompanied by acquired von Willebrand syndrome. After initiation of ECMO, all patients developed this syndrome within hours. After explantation, vWF recovered within 3 hours in 60%, within 6 hours in 86%, and in all patients within 1 day (93).

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