Editorial Review

What Did We Learn about VADs in 2023?

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Abstract

This is our 10th annual literature review on mechanical circulatory support (MCS) devices. All of our previous reports were well received by the readers.[1-9]

In this paper, we summarized the most interesting and important, from our standpoint, publications from 2023. There may be some slight overlap with the end of 2022, because some papers were published online first, and the year of publication changed when they became available in print.

For the seventh time this year, we wrote a section on extracorporeal membrane oxygenation (ECMO), which primarily addresses new developments in veno-arterial ECMO.

Readers who wish to supplement this review, argue with the author's statements, or express their opinions are encouraged to do so by sending letters to the editor at mguglin@gmail.com.
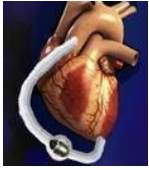
Outcomes

According to the 14th Annual Report from the Interagency Registry for Mechanically Assisted Circulatory Support, 99.8% of left ventricular assist devices (LVADs) implanted in 2022 were Heartmate 3 (HM3) pumps (Abbott; Chicago, IL).[10] Patients supported by HM3 had a 1-year survival of 86% and a 5-year survival of 64%. For comparison, patients in the contemporary (2013-2022) cohort with other pumps had a 1-year survival of 79% and a 5-year survival of 44%, and in a historical (2013-2017) cohort, the survival was 81% and 44%, respectively. All differences in survival with HM3 were highly significant with $P < .0001$. These improvements in survival were consistent for all ages, including patients over 70.[10]

Freedom from gastrointestinal bleeding (72% vs 60%, $P < .0001$), stroke (87% vs 67%, $P < .0001$), and device malfunction/pump thrombus (83% vs 54%, $P < .0001$), but not device-related infection (61% vs 64%, $P = .93$), was higher with HM3 than with other pumps during the contemporary era.[10] In the same three cohorts, freedom from device malfunction or pump thrombus over 5 years was the highest in patients with HM3 at 83%, compared with 54% in those with other devices in the current era and 45% in the historical era. Freedom from stroke at one-year (93%) and 5-years (87%) was also greater in patients with HM3 than in patients with other pumps in the contemporary (1 year: 83%, 5 years: 67%; $P < .0001$) and historical (1 year: 85%, 5 years: 65%; $P < .0001$) periods. Hospitalizations remained very common, with only 11% of patients with HM3 without readmissions at 5 years.[10]

The real-life outcomes in patients supported by HM3 continued to be consistent with the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) trial. The European Evaluating HeartMate 3 with Fully Magnetically Levitated Technology in a Post-Market Approval Setting (ELEVATE) registry started after CE Mark approval of HM3 in Europe and collected data on 540 patients implanted at 26 centers. The overall survival rate for primary implants was 63.3% at two years.[11]

In the past, a similar two-year survival with HM3 and cardiac transplantation appeared to be a breakthrough; however, the three-year survival may not be that different either. A retrospective analysis from Columbia demonstrated equivalent three-year survival on HM3 and transplant (83.7% for HM3 vs 87.0% for heart transplant; $P = .91$).[12] In the subgroup of recipients older than 50, survival with HM3 was somewhat inferior to cardiac transplantation, although it did not reach statistical significance (75.0% vs 83.9%; $P = .60$). The mean number of readmissions was higher in the HM3 group than in the transplant recipients (3.89 vs 2.05; $P < .001$).[12]

The outcomes remain dependent on the experience of the program. Sagheer et al.[13] analyzed the Nationwide Readmission Database for 2019 for new LVAD implantations. They stratified the hospitals by the volume of LVAD implants per year into low-volume (1-5 implants/year), medium-volume (6-16 implants/year), and high-volume (more than 17 implants/year). The inpatient mortality rate was lower in the high-volume centers than in the low-volume centers (9.04% vs 18.49%; adjusted odds ratio [OR] 0.41; confidence intervals [CI] 0.21-0.80; $P = .009$). The difference from medium-volume centers was insignificant. The complications and length of stay rates were similar in all hospital types.[13]

Management of Patients with LVADs

In 2023, a significant breakthrough was made in the area of antithrombotic drugs in LVAD management. Initially, a single-center, retrospective study found no difference in bleeding or thromboembolic events in HM3 recipients receiving warfarin alone or with aspirin.[14]

Later, a randomized, double-blind controlled trial, Antiplatelet Removal and Hemocompatibility Events With the HeartMate 3 Pump (ARIES-HM3) tested the hypothesis that patients with HM3 can be managed without aspirin.[15] A total of 628 patients implanted with HM3 were randomized to receive 100 mg of aspirin a day or placebo while on routine anticoagulation with warfarin (314 in the placebo group and 314 in the aspirin group). The survival free of a major nonsurgical (> 14 days after implantation) hemocompatibility-related adverse event (including stroke, pump thrombosis, major bleeding, or arterial peripheral thromboembolism) at 12 months was observed in 74% of patients on placebo versus 68% of patients on aspirin. Aspirin avoidance was associated with reduced nonsurgical bleeding events (relative risk, 0.66 [95% confidence limit, 0.51-0.85]; $P = .002$), with no increase in stroke or other thromboembolic events.[15]

Another avenue of exploration was alternative anticoagulation. Using direct anticoagulants in place of warfarin is very attractive for patients and clinicians. In a single-center study, 35 patients underwent HM3 implantation and took 325 mg of aspirin daily.[16] Each patient was given a choice of warfarin or apixaban; 43% took apixaban, and 57% chose warfarin. At 6 months, thrombotic complications and death were similar between the groups, but the apixaban group had lower rates of bleeding (5% vs 30%).[16]

Several smaller reports support this finding, which has the potential to become a justification for a new management strategy. The first case report of successfully managing a patient with a Heartmate II (HMII; Abbott; Chicago, IL) on apixaban was published by Pollari et al.[17] Later, Parikh et al. collected data on seven patients treated with apixaban/rivaroxaban for an average of 1459 days; there was no difference between this group and patients on warfarin in the rates of strokes (0.20 vs 0), other embolisms (0.54 vs 0), pump thrombosis (0.27 vs 0), major gastrointestinal bleeding (0.20 vs 0.50), or intracranial hemorrhage (0.13 vs 0).[18] Finally, Kluis et al. published data on four patients, who were on apixaban because of individual contraindications to warfarin. After a median duration of 242 days on apixaban, there were no thrombotic complications, although three of the four patients were not taking aspirin.[19] Kobayashi et al. reported the use of apixaban in children and young adults with congenital heart disease and a VAD. Two patients were over 18, and neither had any adverse events.[20]

Conversely, Horn et al.[21] described seven patients receiving apixaban who did not have good outcomes. They were switched from warfarin because of uncontrolled international normalized ratios; three of them developed bleeding while on apixaban, and two developed suspected or confirmed pump thrombosis, although one of the two had a prior thrombosis on warfarin. After a median of 248 days (IQR, 70.5-323 days) on apixaban treatment, 6 patients died, and the last one was lost to follow-up. Most patients were supported with HMII or Heartware (Medtronic; Minneapolis, MN), and only one out of seven had an HM3.[21]

Maintenance on LVAD

Although rare, pregnancy does occur in women on LVAD support. Oren et al.[22] identified 10 such cases, 8 of which ended with a successful delivery. In one case, both mother and fetus died, and another case resulted in spontaneous abortion. There are several key points from this review:

- Successful pregnancy is possible with no or low pulsatility of blood flow

- Predominant mode of delivery was C-section (seven out of eight cases)

- Pump speed was left unchanged or minimally increased

- LVAD was deactivated because of pump thrombosis in two cases (HMII and Heartware)

In a single-center study, high rates of erectile dysfunction in male patients on LVAD support were reported.[23] Patients were assessed via a questionnaire; they were clinically stable and at least three months after LVAD implantation. Erectile dysfunction was identified in 80% of participants.[23]

Another topic of interest in 2023 was vitamin D deficiency. Several years ago, Zittermann et al.[24] addressed this issue in LVAD recipients. They reported an association between low levels of vitamin D and cerebrovascular accidents. The prevalence of vitamin D deficiency in their study was very high at 92.2%; a mixture of HMII and Heartware devices supported these patients. The multivariable-adjusted hazard ratio (HR) of stroke was 2.44 (95% CI: 1.09-5.45; P = .03) for the subgroup of low 25-hydroxyvitamin D levels (< 25 nmol/L); the group with normal levels was used as a reference. The 1-year mortality had a HR of 2.78 (95% CI: 1.52-5.09; P = .001).[24] Last year, the same authors reported that vitamin D deficiency was associated with driveline infection.[25]

Different Devices

Aortix

Aortix (Procyrion; Houston, TX) is a novel, catheter-deployed, 6-mm intra-aortic entrainment pump. It was tested in 18 patients in a multicenter, nonrandomized, single-arm safety and feasibility study.[26] This device is placed in the descending aorta and augments pressure and flow in the aorta. Aortix provides partial circulatory support with a flow of 3.5 L/min and increases the pressure in the renal artery by 35%, leading to the hypothesis that Aortix may benefit patients with cardiorenal syndrome. In a reported study, the time on this pump averaged 4.6 ± 1.6 days. As a result of this therapy, net fluid loss was 10.7 ± 6.5 L, with significant reductions in central venous pressure, pulmonary capillary wedge pressure, and serum creatinine. However, at 30 days, there were 37 serious adverse events, including 18 events related to the device or procedure. The most serious of these were five bleeding events, one case of hemolysis, and two occurrences of vascular injury.[26] A case of successful use of the device was also reported.[27]

Intra-aortic Balloon Pump

The longitudinal changes of hemodynamic parameters on intra-aortic balloon pump (IABP) support were studied by investigators from Montefiore Medical Center. The mean cardiac index (CI) before IABP insertion was 1.9 ± 0.6 L/min/m^2, and the mean arterial pressure (MAP) was 86 ± 15 mm Hg. In the first hours on IABP support, CI increased on average by 0.44 ± 0.82 L/min/m^2,
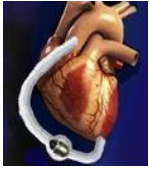
while MAP decreased by 3.4 ± 19.4 mm Hg.[28] In patients with shock, CI increased by 0.65 ± 0.74 L/min/m^2, while MAP decreased by 3.8 ± 19.9 mm Hg.[28] Interestingly, CI continued to increase until days seven to eight, after which it stabilized and then started declining.[28]

Impella

In our previous annual review,[9] we commented on a growing interest in Impella 5.5 (Abiomed; Danvers, MA). This pump successfully bridged patients to transplant with a mean support duration of 70 days (maximum 83 days).[29] Haddad et al. also reported a high success rate with this device; all 16 patients in the study survived to cardiac transplantation after a median support of 19 days (range 3-31 days).[30] While on Impella, their renal function improved, with the median creatinine decreasing from 1.55 mg/dL to 1.25 (P = .007) and pulmonary artery pulsatility index increasing from 2.56 (0.86-10) to 4.2 (1.3-10) (P = .048).[30]

At Cedars-Sinai, Impella 5.0 or 5.5 was used more often than an IABP to treat patients with severe cardiogenic shock. Patients with Impella support had a higher in-hospital mortality (19.4% vs 3.4%, P = .018).[31]

A retrospective study compared Impella 5.5 to Impella 5.0 using data from an FDA-mandated database.[32] The Impella 5.5 was associated with higher survival in acute myocardial infarction-related cardiogenic shock (70.5% vs 56.8%; P = .005), cardiomyopathy (88.1% vs 76.9%; P = .001), and postcardiotomy cardiogenic shock (76.1% vs 55.7%; P = .003). Duration of support was significantly longer for Impella 5.5 patients with acute myocardial infarction-related cardiogenic shock (9.2 vs 6.1 days; P = .008) and cardiomyopathy (10.7 vs 8.1 days; P < .001).[32] In the Cedars-Sinai experience, Impella 5.5 also had lower rates of device exchange than Impella 5.0 (4.0%, n = 3 vs 13.3%, n = 10; P = .04).[33]

The first experience with Impella 5.0/5.5 for high-risk ablation of scar-mediated ventricular tachycardia was reported last year by the Cleveland Clinic.[34] There was a higher number of induced episodes of ventricular tachycardia (2.73 vs 1.45; P = .032), mapped ventricular tachycardia circuits (2 vs 1; P < .001), and ventricular tachycardias terminated with ablation (1 vs 0; P < .001) in patients supported with an Impella than in patients who did not receive MCS. At the same time, there were more procedure-related complications on Impella support (12 [29.3%] vs 1 [2.4%]; P = .002), including access-site hematomas, infected deep vein thrombosis, and pulseless electric activity arrest during Impella placement. Three of the complications in the Impella group resulted in death. The net effect was neutral: a composite of all-cause death, permanent LVAD, and heart transplantation was similar in the patients supported or unsupported by Impella. Recurrent ventricular tachycardia or ventricular fibrillation during follow-up was also similar between groups.[34]

Another novel application of Impella 5.5 is the treatment of primary graft dysfunction after cardiac transplantation in patients who already had an Impella 5.5 as a bridge to transplant.[35] The Impella 5.5 device was left in place in the donor heart if the cardiac output was less than 2.5 L/min, adequate perfusion was not achieved at a P4 level, or two or more high-dose inotropes/vasopressors were required. The device was removed when the hemodynamics stabilized, with an average postoperative support duration of 3.8 days.[35]

What is New in the V-A ECMO World?

In 2023, the results of several randomized trials on V-A ECMO were published. They can be grouped by clinical indications for V-A ECMO.

1. Acute Myocardial Infarction (AMI)-related Cardiogenic Shock

The ECLS-SHOCK trial tested the hypothesis that early initiation of V-A ECMO in AMI-related cardiogenic shock could be beneficial.[36] A total of 420 patients were randomized into V-A ECMO or medical management groups. The initiation of ECMO typically took place in the catheterization laboratory before the intervention or stenting.[36]

The investigators included adult patients with AMI and the following features of cardiogenic shock:

- Systolic blood pressure of less than 90 mm Hg for more than 30 minutes or the initiation of catecholamines to maintain this level of blood pressure

- Arterial lactate > 3 mmol/L

- Signs of impaired organ perfusion, such as altered mental status, cold or clammy skin and limbs, or urine output < 30 ml/hour

The primary outcome of death from any cause at 30 days occurred in similar proportions for both groups: 47.8% of the patients in the V-A ECMO group and 49.0% in the medical management group (relative risk, 0.98; 95% CI, 0.80 to 1.19; P = .81). Complications were more prevalent in the ECMO group, especially bleeding and limb ischemia.[36]

2. Mixed AMI- and Heart Failure-related Cardiogenic Shock

In the ECMO-CS trial, 122 patients with cardiogenic shock were randomly assigned to immediate V-A ECMO or delayed V-A ECMO support; cardiogenic shock etiology was mixed, AMI, and heart failure (HF).[37] The primary endpoint was the composite of death, cardiac arrest, or the addition of another MCS device within 30 days. The inclusion criteria were described as either rapidly deteriorating or severe cardiogenic shock.[37] The specific requirements for inclusion were as follows:

- CI < 2.2 L/min/m^2 + norepinephrine dose > 0.1 μg/kg/min + dobutamine dose > 5 μg/kg/min

  or

- Systolic blood pressure < 100 mm Hg + norepinephrine dose > 0.2 μg/kg/min + dobutamine dose > 5 μg/kg/min + (left ventricular ejection fraction < 35% or left ventricular ejection fraction 35-55% + severe mitral regurgitation or aortic stenosis)

- Arterial lactate > 3 mmol/L on 2 occasions at least 30 minutes apart

- SvO$_2$ < 50% on 2 occasions at least 30 minutes apart

The primary endpoint occurred in 63.8% of patients in the V-A ECMO group and 71.2% of patients in the conservative group (hazard ratio, 0.72; 95% CI, 0.46 to 1.12; P = .21). There was no significant difference in outcomes by the shock etiology (AMI versus HF), and the rate of complications was similar between the ECMO and no ECMO arms.[37]

3. Cardiac Arrest

The Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac arrest (INCEPTION) trial randomized 160 patients into extracorporeal cardiopulmonary resuscitation (CPR) or conventional CPR after out-of-hospital cardiac arrest.[38]

The investigators included adult patients with out-of-hospital cardiac arrest if they met the following criteria:

- Bystander CPR

- Ventricular arrhythmia

- No return of spontaneous circulation within 15 min

The primary outcome was survival with favorable neurologic status 30 days after the arrest. Logistically, they initiated transportation to the hospital if the standard resuscitation failed for 15 minutes. The median interval between hospital admission and cannulation was 16 minutes, and the median interval between the start of cannulation and the start of ECMO flow was 20 minutes. Thus, the earliest initiation of ECMO support was 51 minutes, assuming that transportation to the hospital took no time, which is impossible.[38]

When analyzed by intention to treat, the primary outcome of survival with good neurologic function occurred in 20% of patients in the extracorporeal-CPR group and 16% in the conventional-CPR group (OR, 1.4; 95% CI, 0.5 to 3.5; P = .52). The number of serious adverse events was similar between groups.[38]

A separately published per-protocol analysis also failed to show a significant advantage of ECMO-assisted CPR.[39]

Left Ventricular Venting

There is an ongoing discussion about the need for left ventricular (LV) venting for patients on V-A ECMO. Yet another randomized clinical trial was published in 2023: The Early Venting versus cOnventional treatment for Left Ventricular distention during venoarterial ExtraCorporeal Membrane Oxygenation support (EVOLVE-ECMO) trial.[40]

Patients enrolled in this trial demonstrated some evidence of LV distension:

- Significant pulmonary edema on chest radiography

- Frothy, blood-tinged secretions from the endotracheal tube

- Intermittent opening or complete closure of the aortic valve

Patients randomized to the intervention group received a trans-septal left atrial drainage, and those randomized to the control group were treated medically with inotropes, diuretics, and renal replacement therapies. If attempts to remove the fluid without venting failed, patients underwent a similar procedure with trans-septal venting of the left atrium. The primary endpoint was the weaning rate from V-A ECMO during the index admission.[40]

As a result, 29 (96.7%) patients in the early venting arm were started on the venting drain after a median ECMO support of 2.4 hours. A total of 23 (76.7%) patients in the conventional arm were started on the drainage after a median ECMO support of 48.4 hours.[40]

The weaning from ECMO was achieved in 70.0% of patients in the early LV unloading group and 76.7% in the conventional group during follow-up (relative risk [RR], 0.91; 95% CI, 0.67–1.24; P = .386). In addition, survival to discharge did not differ between the groups (53.3% in the early LV venting group vs 50.0% in the conventional group). Pulmonary congestion improved more on the LV vent than without it.[40]

As the investigators noted in their conclusions, "our sample size was too small and underpowered to investigate the efficacy and safety of early LV unloading, for which a further large randomized controlled trial will be essential."[40]

A larger randomized trial was also published last year by Kim et al.[41] The EARLY-UNLOAD trial enrolled 116 patients with cardiogenic shock diagnosed by clinical rather than hemodynamic criteria. The patients were randomly assigned to have LV unloading early (within 12 hours of ECMO support) versus rescue only LV unloading if the signs of LV distension develop. The trans-septal atrial cannulation was used for LV venting. The primary outcome was all-cause mortality within 30 days.[41]

In the early venting arm, 46.6% of patients died versus 44.8% in the conventional arm (HR, 1.02; 95% CI, 0.59-1.74; P = .942). Crossover to rescue trans-septal left atrial cannulation occurred in 50% of patients in the conventional group, according to a clear indication. As in the prior study, pulmonary congestion resolved faster in the early venting arm.[41]

Analyzing the international registry data, Schrage et al.[42] found that early (up to 2 hours after cannulation) LV venting was associated with lower mortality at 30 days (HR, 0.64; 95% CI: 0.46-0.88) and greater weaning off ECMO rate (OR, 2.17; 95% CI: 1.19-3.93), without an increase in complications. An Impella device was used for unloading.[42]

Interestingly, Kang et al.[43] reported that LV unloading did not reduce 90-day mortality in AMI-related cardiogenic shock but significantly reduced 90-day mortality in HF-related cardiogenic shock (adjusted HR, 0.37; 95% CI, 0.14-0.96; P = .041; P for interaction = .029). They predominantly used an IABP for venting. Potential explanations include:

- The larger ventricle of an HF patient has a greater stroke volume; therefore, augmentation of cardiac output by an intra-aortic balloon pump may be greater
- AMI-related cardiogenic shock may be more severe, and unloading with an IABP may be insufficient[43]

Mortality was similar in a meta-analysis of seven observational studies comparing concomitant use of Impella versus IABP for LV venting on V-A ECMO; however, Impella use was associated with a higher rate of bleeding and hemolysis.[44]

Indications

ECMO indication may be one of the factors influencing the decision to vent. In the Montefiore experience, when transplant recipients are placed on V-A ECMO support for primary graft dysfunction, they almost always recover without LV venting. Successful decannulation with full graft function recovery occurred in 22 out of 24 (92%) patients cannulated peripherally.[45]

While cardiogenic shock is a clear-cut indication for V-A ECMO support, septic shock is questionable. A combination of cardiogenic and septic shock is often encountered in cardiac intensive care units. In a single center study, Kim et al. compared cardiogenic, septic, and mixed shock outcomes.[41] They found that both 30-day- and 1-year-mortality was the worst in patients with septic shock at 69.0% and 81.0%, respectively.[41] Cardiogenic shock carried the lowest mortality at 43.3% and 53.2%, and mixed shock was in between at 50.4% and 67.5%, respectively.[41]

Pasrija et al. reported a case series of ischemic spinal cord injury during prolonged V-A ECMO support.[46] The median support time was 7 days and ranged from 6 to 17 days. The location of the injury was from the lower thoracic spine, starting at the T7 level to the cauda equina. They observed this complication in 5.3% of patients. Although the authors considered several mechanisms, including hypercoagulable state/thromboembolism, regional hypoxia/hypocarbia, hyperperfusion and spinal cord edema, and mechanical coverage of spinal arteries, the pathophysiology remains uncertain. The authors favored hyperperfusion and spinal cord edema as the most likely pathophysiology. The median total flow, including V-A ECMO plus the intrinsic cardiac output, was 8.5 L/min.[46]

In terms of LV venting, various novel approaches have been reported. They include percutaneous pigtail catheter placement into the LV through the radial artery under transesophageal echocardiogram guidance.[47]

Inglis et al. studied different strategies of LV venting and compared the outcomes of left atrial venoarterial cannulation or pulmonary artery venoarterial venting versus Impella or IABP.[48] The difference was insignificant.[48]

Conclusions

In summary, the most impactful contribution of 2023, from our standpoint, was the ARIES-HM3 trial, indicating that patients on HM3 can be successfully managed without aspirin.[15] We expect that multiple programs around the globe will modify their protocols to adopt this practice, which will likely result in further decrease in bleeding complications in patients on LVAD support.

Acknowledgments

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