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The ever-changing field of mechanical circulatory support: new challenges at the advent of the ‘single device era’

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In the past few decades, the treatment options for patients with advanced heart failure (HF) have changed dramatically.¹ Since the introduction of (long-term) mechanical circulatory support (MCS), the prognosis and quality of life of these patients have improved significantly. Technological improvements have changed the landscape of left ventricular assist devices (LVADs): the first-generation pulsatile pumps were large devices that were implanted in the abdomen and the second-generation pumps (axial-flow pumps) were smaller devices implanted within the thorax, more suitable for long-term support. In the most recent decade the third-generation centrifugal continuous-flow LVADs have dominated the field of durable MCS: the HeartWare VAD (HVAD, Medtronic, Minneapolis, MN, USA) with hydro-magnetic (hybrid) levitation and the HeartMate 3 (HM3, Abbott Labs, Chicago, IL, USA) with full magnetic levitation. In large studies, these devices have demonstrated superior survival free from disabling stroke or reoperation to replace a malfunctioning device, compared with second-generation pumps.^{2–4}

Both HVAD and HM3 have been approved for long-term support in advanced HF patients as a bridge to transplantation option and for those patients ineligible to transplantation as ‘destination therapy’. However, in the past few years, the amount of *de novo* HM3 implants have outnumbered the HVAD implants.⁵ Recently, two observational studies from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the European Registry for Patients on Mechanical Circulatory Support (EUROMACS) have described worse outcomes for HVAD vs. HM3 implanted patients.^{6,7} In addition, in 2020 Medtronic issued a Safety Notice regarding the HVAD related to a delayed or even failure to restart the LVAD after controller exchange. These factors may have led to the decision of Medtronic to stop the global production and distribution of the HVAD on 3 June 2021.⁸

In this viewpoint, we would like to shed light on the outcome data that preceded this decision and address the consequences and challenges it poses to our patients and their health care providers.

INTERMACS and EUROMACS analyses

Two recent reports from INTERMACS⁶ and EUROMACS⁷ have assessed various outcomes of patients implanted with an HVAD vs. HM3. In these reports, these large international registries provided real-world data on the characteristics and outcomes of almost 6000 LVAD supported patients worldwide. From the unmatched cohorts in both registries, it becomes apparent that the HVAD has been on average implanted in smaller patients with more comorbidities, and more frequently in females (*Table 1*). Importantly, the HVAD implanted patients have a worse preoperative clinical status (lower INTERMACS profile) and worse preoperative right ventricular function. In both studies, cardiopulmonary bypass time in the HVAD cohort was shorter, and in the INTERMACS study, more frequently a (less invasive) left thoracotomy approach was chosen in the HVAD cohort.

In addition, both studies provided data on propensity matched cohorts (*Table 1*). Although there are differences in the exact parameters that were selected in both registries, the cohorts were matched regarding demographics and parameters representing disease severity (e.g. INTERMACS profile) and organ function (e.g. renal dysfunction). Of note, in the INTERMACS registry, 30.5% of the HVAD patients and 42.6% of the HM3 patients of the original cohort were excluded for this analysis. Although the 2-year survival of the HVAD patients as compared to the HM3 patients in the matched cohorts of the EUROMACS registry did not reach statistical significance [HVAD 61% (95% confidence interval 56–67%) vs. HM3 68% (95% confidence interval 63–73%)], in the INTERMACS registry that difference in survival was significant (70% and 84% for HVAD and HM3, respectively; $P < 0.05$).^{6,7} Moreover, HVAD patients experienced more device malfunction, pump thrombosis and neurological dysfunction.⁷

These studies comprise the largest propensity matched cohorts of the two LVADs to date. Although sound statistical methods were

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Table 1 INTERMACS and EUROMACS analysis of HVAD vs. HM3: patient characteristics and outcome

	INTERMACS				EUROMACS			
	Unmatched cohort		Matched cohort		Unmatched cohort		Matched cohort	
	HVAD	HM3	HVAD	HM3	HVAD	HM3	HVAD	HM3
Patient characteristics								
No. of patients	2012	2436	1400	1400	612	923	361	361
Percentage of original cohort			69.5%	57.4%			58.9%	39.1%
Age (years), mean \pm SD	56.6 \pm 13.2	56.7 \pm 12.7	56.7 \pm 12.9	56.7 \pm 12.7	54.3 \pm 12.3	55.5 \pm 11.9	55.5 \pm 11.6	56.1 \pm 11.6
Male sex, n (%)	1471 (73.1)	1940 (79.6)*	1075 (76.8)	1071 (76.5)	515 (84.2)	805 (87.2)	311 (86.1)	309 (85.6)
BMI (kg/m ²), mean \pm SD	28.1 \pm 7.7	29.3 \pm 7.3*	28.5 \pm 7.1	28.6 \pm 7.2	26.1 \pm 5.1	27.1 \pm 4.9	26.6 \pm 5.5	26.9 \pm 4.9
INTERMACS profile, n (%)								
1	398 (19.8)	361 (14.8)*	246 (17.6)	234 (16.7)	131 (21.6)	101 (11.2)	50 (13.9)	55 (15.2)
2	702 (34.9)	787 (32.3)	467 (33.4)	472 (33.7)	171 (28.2)	282 (31.2)	115 (31.9)	93 (25.8)
IABP, n (%)	360 (17.9)	332 (13.6)*	232 (16.6)	224 (16.0)	56 (9.2)	55 (6.0)	24 (6.6)	22 (6.1)
Dialysis, n (%)	23 (1.1)	24 (1.0)	13 (0.9)	13 (0.9)	16 (2.6)	18 (2.0)	36 (10.0) ^a	38 (10.5) ^a
Severe RV dysfunction, n (%)	309 (18.2)	253 (12.5)*	181 (15.4)	171 (14.8)	N/A	N/A	N/A	N/A
RV function: TAPSE (mm), mean \pm SD	N/A	N/A	N/A	N/A	14.7 \pm 4.6	15.1 \pm 4.4	N/A	N/A
Previous cardiac surgery, n (%)	573 (28.5)	609 (25.0)*	372 (26.6)	366 (26.1)	81 (13.2)	82 (8.9)	34 (9.4)	38 (10.5)
Operative details								
Surgical approach, n (%)								
Sternotomy	1657 (82.5)	2185 (90.0)*	1197 (85.6)	1202 (86.2)	N/A	N/A	N/A	N/A
Thoracotomy	351 (17.5)	244 (10.0)*	202 (14.4)	193 (13.8)	N/A	N/A	N/A	N/A
CPB time (min), mean \pm SD or median (IQR)	89.1 \pm 47.0	100.1 \pm 104.6*	91.8 \pm 49.1	93.2 \pm 42.4	79 (52–117)	85 (62–117)	76 (52–113)	85 (60–116)
Outcome								
Follow-up duration, median (IQR)	12.9 months (6.3–19.0)	10.3 months (7.3–14.2)	N/A	N/A	N/A	N/A	396 days (112–771)	376 days (100–816)
1-year survival ^b	79%	88%*	80%	87%*	N/A	N/A	71%	73%
2-year survival ^b	70%	85%*	70%	84%*	N/A	N/A	61%	68%

BMI, body mass index; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; IQR, interquartile range; N/A, not available; RV, right ventricular; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

^aIncluding ultrafiltration.

^bIn INTERMACS and EUROMACS outcome was assessed with Kaplan–Meier analysis.

* $P < 0.05$.

used, differences in patient selection and management, surgeons' individual preferences and local protocols for the different devices may still have influenced the results. The question whether the observed differences in outcome are truly related to pump-specific factors will never be answered since a randomized trial comparing the two devices cannot be performed anymore. With the results of these registries and the consequent withdrawal of the HVAD, patients supported with this device face an uncertain future and the HF health care providers, both cardiologists and surgeons, a dramatically changed MCS landscape and the need to confront new and unexpected challenges.

Challenges for the mechanical circulatory support field in the single device era

Emerging challenges exist in the areas of patient selection, patient management and device innovation, and all will require direct attention from patients, physicians, health care systems and industry. At present, as reported by Medtronic in its dramatic announcement, there are about 4000 patients worldwide supported with an HVAD system. A substantial proportion of these patients is supported with the 'destination therapy' indication, requiring long-term support (sometimes for many years). Since it is not recommended

to routinely exchange the HVAD for the HM3, clinicians and researchers should continue their search for the optimization of care and reduction of adverse events in these patients. Despite exiting the market, Medtronic has declared the establishment of a support programme dedicated for the continuing care of all 4000 implanted patients.

For advanced HF patients, being potential candidates for LVAD therapy, a timely referral to an advanced care hospital has become even more crucial. Early recognition of the transition to advanced HF is essential. For this, the 'I Need Help' mnemonic has been proposed to help physicians in identification of advanced HF patients and timely referral for advanced HF treatment options.¹ The absence of randomized studies comparing the efficacy and safety of the two centrifugal continuous-flow LVADs allowed different centres to prefer the use of either one of the two devices (HVAD or HM3) or use them both. Due to its mildly smaller size and slightly shorter implantation time, some centres preferred the HVAD over HM3 for smaller patients and for those with preoperative right ventricular dysfunction. Although the HM3 is now also implanted in paediatric patients⁹ and the results of the MOMENTUM 3 Continuous Access Protocol study demonstrate favourable outcomes also in HM3 patients with worse clinical profiles as compared with the pivotal trial,¹⁰ there yet remains a clear need for smaller devices that can be implanted in selected patient groups, such as smaller candidates, mainly females, paediatric patients and those

with congenital heart disease with failure of systemic right ventricles, a group whose number is expected to increase.¹¹ Often, these patients have had several surgical interventions and have complex anatomy and present surgical challenges at the time of ventricular assist device implantation. In the 'single device era', the inability to tailor the most appropriate device for the certain patient may result in a revival of left behind older technologies such as the extracorporeal pulsatile devices (Berlin Heart).¹² For the selected group of patients, innovations are needed with the intent of developing smaller and easier-to-implant pumps.

Although the HM3 is associated with fewer thrombotic events compared to the HVAD,⁶ there is still an urgent need to reduce haemocompatibility-related adverse events. At present, LVAD patients are advised to combine oral anticoagulation with anti-platelet therapy for preventing thrombotic events. However, this, together with the acquired von Willebrand disease attributed to the continuous-flow LVAD physiology, results in an increased risk of bleeding.¹³ The Antiplatelet Removal and Hemocompatibility Events with the HeartMate 3 Pump (ARIES HM3) trial will randomize HM3 supported patients to two groups: traditional and less aggressive anticoagulation regimens.¹⁴ The results of this trial will be of great value for patient management as would have been the results of other future studies held by researchers and industry in their search for elimination of haemocompatibility-related and other adverse events in LVAD patients. Health care providers and researchers can only hope that a reduced interest to invest in future clinical studies and device innovation will not result from the effective industrial monopoly of one company producing one device. We call for increased efforts at innovation and research not less at this difficult time.

The MCS field has eagerly awaited innovations regarding driveline elimination and remote monitoring. Recently, the first experience with a fully implantable LVAD, the FIVAD system, was reported,¹⁵ with obvious potential advantages in patient quality of life and obviating the risk of driveline infections. In addition, as has become clearer during the COVID-19 pandemic, remote monitoring can reduce routine hospital visits, thereby improving quality of life of LVAD patients.^{16,17} Innovation is also needed for more dedicated remote monitoring capabilities of LVAD systems, while respecting patient privacy safety, to improve early detection of pump malfunction and other patient-device related adverse events.

Conclusions

With the withdrawal of the HVAD system from the market, the landscape of MCS has changed significantly, posing new challenges to patients, physicians and industry alike. The multidisciplinary LVAD teams and the industry should continue their search on optimizing care for living HVAD patients and in general for all LVAD supported patients. Health care providers and researchers should partner with industry to introduce novel technologies such as fully implantable LVADs and dedicated remote monitoring capabilities.

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