

The dominant left ventricular assist device: lessons from an era

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Abstract

The production and distribution of the HeartWare ventricular assist device has come to an abrupt end, but with this end comes the opportunity to reflect upon lessons learned from its lifespan. Running counter to the standard of evidence-based practice, the era of the HeartWare ventricular assist device was marred with fragmented data in relation to its primary counterpart, the HeartMate III. This created an incomplete understanding of devices, limited individualized patient care, and effectively positioned providers to make inferences regarding device superiority. We briefly review pertinent literature on this topic among the most commonly implanted durable devices from the era, detail the inherent limitations of this data, and argue the necessity of randomized clinical trials among novel devices towards the optimization of patient care.

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Heart failure remains a substantial source of global morbidity and mortality for which durable left ventricular assist devices (LVADs) offer an opportunity to improve survival among patients who fail to respond to optimal therapy. The HeartWare ventricular assist device (HVAD), HeartMate II (HM2), and HeartMate III (HM3) have been the most commonly implanted LVADs worldwide in recent years prior to the cessation of HVAD manufacturing; however, the data guiding clinical decision-making regarding superiority among these devices were fragmented at best. We briefly review pertinent literature on this topic, detail the inherent limitations of this data, and discuss the lessons learned from this era in advocacy of the need for randomized clinical trials.

The ENDURANCE trial demonstrated the HVAD was non-inferior to the HM2 with respect to survival free from disabling stroke or device removal for failure or malfunction.¹ A final report of the MOMENTUM 3 trial demonstrated superiority of the HM3 over the HM2 with regards to survival free of disabling stroke or reoperation for device malfunction.² An inference was therefore often made that the HM3 was superior to HVAD despite a lack of prospective randomized trials comparing the HVAD and HM3 LVADs. Further complicating this inference were advancements made from 2010

to 2012, the enrolment period of the ENDURANCE trial. It has been demonstrated that following the introduction of sintered titanium microspheres on the HVAD inflow cannula in 2011, together with proper anticoagulation and blood pressure management, has led to a reduction in HVAD thrombosis and need for HVAD exchanges.³ Poorly controlled blood pressure was the strongest predictor of haemorrhagic CVA in original trials leading to the FDA approval for the HVAD as a bridge-to-transplant,⁴ and this has been further demonstrated in the post-hoc analysis of the ENDURANCE trial,¹ which noted a 34% reduction in CVA risk among HVAD patients with a mean arterial pressure less than 90 mmHg compared with those with mean arterial pressure greater than 90 mmHg. This draws into question whether these technical and medical advancements, had they been available throughout enrolment periods, would have contributed to alternative conclusions drawn from these device trials.

Further complicating the body of evidence among LVADs is the ENDURANCE supplemental trial that employed intensive blood pressure management protocols yet still failed to demonstrate non-inferiority of HVAD to HM2 for the primary end point of incident transient ischemic attack over 12 months or stroke with residual deficit 24 weeks

post-event.⁵ However, the same trial demonstrated that HVAD was superior to HM2 for secondary outcomes of the composite endpoint of survival free from disabling stroke and need for device exchange, urgent transplantation, or death.⁵ Mahr *et al.* demonstrated that after a cross-trial analysis of HVAD patients from the ENDURANCE supplemental and ADVANCE Bridge to Transplant Continued Access Protocol when compared with clinically similar HM3 patients from the MOMENTUM 3 trial, HM3 patients failed to show any significant difference of overall neurological events occurring at 6 months or 2 years.⁶ Additionally, in a retrospective analysis after a propensity score matching of 79 patients in each arm of HVAD and HM3 cohorts, comparable survival at 30 months and freedom from CVA were noted.⁷ More recently, observational data of 2964 centrifugal LVADs from the Intermacs registry demonstrated higher survival and freedom from major adverse events including gastrointestinal bleeding, stroke, and infection among fully magnetically levitated centrifugal devices as compared with hybrid-levitated centrifugal devices.⁸

The primary literature evaluating safety and outcomes among the most commonly implanted LVADs in recent years is effectively a mosaic of piecemealed data, which led to a lack of consensus regarding LVAD superiority. This was due to a multitude of factors, including heterogeneous patient populations in primary trials, inconsistent adverse event definitions, and irregular event reporting metrics among trials.

Variability of these factors alone has been demonstrated to show inconsistent neurologic outcomes within the same device.⁹ Additionally, a lack of long-term follow-up data given a relatively nascent and continually evolving field and the necessity of open label study designs further contribute to sub-optimal comparisons between devices; however, perhaps the primary limitation is the lack of a well-designed randomized clinical trial. We therefore utilize this moment to reflect upon the era and specifically what knowledge could have been gained from a randomized trial between centrifugal devices. History has taught us that such a prospective randomized trial between two different devices is feasible as demonstrated in the landmark ENDURANCE trial.¹ A similar trial design between the HVAD and the HM3 is highlighted in *Figure 1*, and details with regards to patient characteristics, management protocols, and definitions according to INTERMACS of each adverse event category are summarized in *Table 1*. We reflect upon this hypothetical trial to highlight the level of detail in design and control necessary to derive meaningful data to drive evidence-based patient care. It highlights that any single device may not reign supreme in all potential adverse events post-implantation and a clear understanding of outcomes in every category must therefore be sought to individualize patient care and optimize outcomes.

The state of data among LVADs in the HVAD era was fragmented at best. This positioned providers to effectively make inferences regarding device superiority, and the

Figure 1 HVAD vs. HM3 trial design. BTT, bridge to transplant; DT, destination therapy; HM3, HeartMate3; HVAD, HeartWare ventricular assist device; LVAD, Left ventricular assist device.

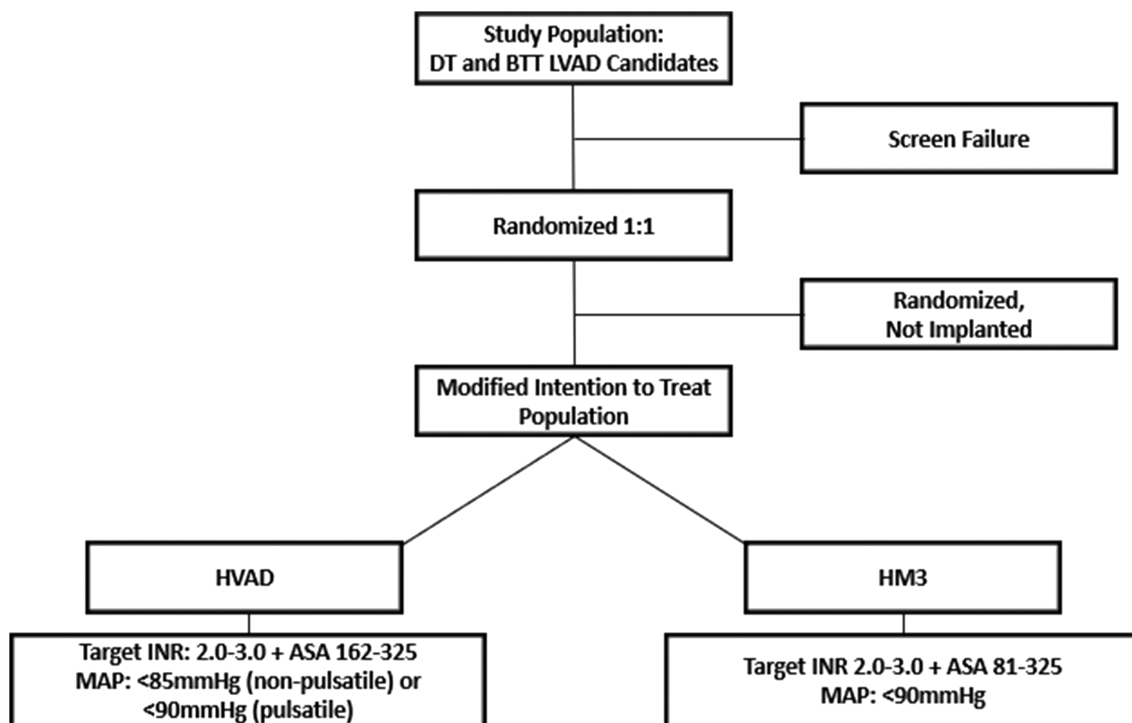


Table 1 Trial eligibility criteria, interventions, and outcome measures

Patient selection	
Inclusion criteria	Destination therapy and bridge to transplant
Exclusion criteria	eGFR < 30 Active malignancy within 5 years Expected lifespan < 1 year Cirrhosis History of known coagulopathy History mechanical mitral valve History of haemophilia or unspecified bleeding diathesis requiring alteration of target INR
Standardization protocol	
Hemocompatibility	
Anti-coagulative therapy	HVAD: target INR 2.0–3.0 with aspirin 162–325 HM3: target INR 2.0–3.0 with aspirin 81–325 Per implanting surgeon
Surgical technique	
Right ventricular failure	
Medical therapy	Optimized per guidelines
Ramp study	Performed post-implant prior to discharge of index hospitalization
Sheer stress	
Aortic valve	At discretion of care team
Lavare cycle	At discretion of care team
Aortic pressure (obtained with Doppler)	HVAD: SBP < 130, DBP < 85 in pulsatile patients, MAP < 80 in non-pulsatile HM3: SBP < 130, DBP < 85 in pulsatile patients, MAP < 80 in non-pulsatile
Short and long term outcomes	
Primary outcomes	Composite of death, disabling stroke, and reoperation to replace or remove malfunctioning device
Secondary outcomes	Ischemic stroke Haemorrhagic stroke Disabling stroke: modified Rankin > 3 Replacement or explantation of malfunctioning device Death Right sided heart failure Renal failure ICU length of stay Gastrointestinal bleeding Non-gastrointestinal bleeding Sepsis Driveline exit site infection Cardiac arrhythmias Readmission Kansas City Cardiomyopathy Questionnaire Other serious adverse event not otherwise specified

DBP, diastolic blood pressure; HM3, Heartmate III; HVAD, HeartWare ventricular assist device; INR, international normalized ratio; MAP, mean arterial blood pressure; SBP, systolic blood pressure.

Blood pressure goals in pulsatile and non-pulsatile patients based upon 2013 International Society for Heart and Lung Transplantation consensus guidelines.¹¹

potential implications were vast. Given lifetime estimated costs for an LVAD implanted patient of over \$500 000,¹⁰ and post-implant complications impacting patient quality of life, survival, and quality adjusted life years, we must strive to fully understand the devices we choose for patients. We recognize the intrinsic challenges such a trial represents to compare devices, particularly with regards to the continuous evolution of technology in a growing field; however, we argue the necessity of such a trial given the magnitude of potential

implications in its continued absence. The HM3 and HVAD will surely not be the last durable circulatory support devices on the market as the investigative device Eavaheart, for instance, is on the horizon. As we reflect upon the end of the HVAD era, we must not settle for inference-based medicine, and rather strive to fully understand the devices we choose for patients. This is a level of understanding that can only come by way of detailed and well-designed clinical trials among durable circulatory support devices.

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