

EDITORIAL

Pump thrombosis redux



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"You can observe a lot by just watching"

Lawrence Peter "Yogi" Berra (1925-2015)

U.S. Professional Baseball Player and Manager

Left ventricular assist devices (LVADs) are now a durable mainstay of therapy for medically refractory advanced heart failure (HF).¹ Continuous-flow LVADs demonstrated increased longevity and enhanced quality of life in a series of landmark trials, ushering in an era where more LVADs are now implanted annually than hearts transplanted.^{2,3} Less than 50% of current LVAD recipients are listed for heart transplantation at the time of implant, and many stand-alone VAD programs, outside of transplant centers, are well established. Enthusiasm grew in the early part of this decade to investigate expanded indications for LVADs in ambulatory patients before transition to inotrope dependence.^{4,5} Even as adoption of this technology accelerated, concerns about a rise in pump malfunction due to device thrombosis were reported in the most widely implanted LVAD platform worldwide, the HeartMate (HM) II (Thoratec Inc, Pleasanton, CA).

Two separate reports in 2013 documented a spike in HM II pump thrombosis rates beginning in 2011, several years after U.S. Food and Drug Administration approval of the device.^{6,7} These reports estimated the risk of thrombosis at 6 months to be between 6% and 12%, at least 3-fold higher than noted in the registration trials. Another report suggested that this problem was not confined to the HM II device but was also observed with the HeartWare HVAD (HeartWare International Inc, Framingham, MA) pump.⁸ Fueling more uneasiness, thrombosis rates appeared to be increasing with each subsequent year, threatening the viability of mechanical support in expanded indications. Although rising thrombosis rates were not initially linked to a decline in overall post-LVAD survival, the diagnosis of pump thrombosis conferred substantial morbidity, need for pump exchange, and increased cost of care.

Awareness of the effect of pump thrombosis on patient outcomes prompted the United Network of Organ Sharing in 2013 to allow emergency priority listing for patients with impending or manifest pump thrombosis, whereas no

bailout option was available to lifetime ("destination") therapy patients who were not eligible for transplant.⁹ The increase in thrombosis risk also led directly to the indefinite suspension of the National Heart, Lung, and Blood Institute (NHLBI) sponsored Randomized Evaluation of VAD Intervention before Inotropic Therapy (REVIVE-IT) trial of LVAD therapy with the HM II pump in earlier-stage, non-inotrope-dependent patients after equipoise was lost to randomize New York Heart Association Functional Classification III patients to the HM II device.

A vigorous debate ensued as multiple explanations for increased LVAD thrombosis rates were posited.¹⁰ A mechanical defect in the device could not be confirmed, and prevailing theories centered around the device-patient interface, including unfavorable angulation of the inflow cannula relative to the septum and a constellation of alterations in clinical management. These included a relaxation of anti-coagulation targets in the face of gastrointestinal bleeding and acquired von Willebrand factor deficiency, a reduced emphasis on post-operative bridging anti-coagulation, and the lowering of pump speeds to facilitate aortic valve opening to reduce the risk of aortic insufficiency and maintain transaortic pulsatile flow. After the initial reports on the pump thrombosis problem, most centers rapidly adopted risk-mitigation strategies to emphasize bridging anti-coagulation, vigilant monitoring for intravascular hemolysis as a harbinger of pump thrombosis, and early aggressive treatment of suspected thrombosis with augmented anti-coagulation and pump exchange.¹¹

In early 2015, the NHLBI commissioned 2 separate analyses of the most current HM II data to explore the evolving effect of pump thrombosis on patient care. These updated analyses, which are highlighted in this issue of the *Journal*, used data on HM II devices implanted between April 2008 and June 2014 at 146 centers participating in the Interagency Registry of Mechanically Assisted Circulation Support (INTERMACS). Kirklin et al¹² analyzed 9,808 primary HM II implants and confirmed an increasing risk of thrombosis from 2009 through 2013, followed by an observed decrease in risk in the first half of 2014. By

2014, the freedom from thrombosis at 6 months (95%) was approaching 2011 levels, although no long-term follow-up was available for the most recent implants.¹²

Using different analytic methods on the same data set, Smedira et al¹³ analyzed all HM II devices (n = 11,123) registered in INTERMACS, not just primary implants. Their unique analysis, using machine learning techniques, concluded that early risk for thrombosis plateaued in 2013 and early 2014 but remained approximately 10% at 1 year even in the latest cohort implanted.¹³ What is clear from both analyses is that a plateau has occurred in observed pump thrombosis rates, if not a modest decrease, although rates have not returned to pre-2011 levels¹⁴ (Table 1).

These reports present sobering data on the consequences of pump thrombosis and suggest several important clinical directions. First, the probability of recurrent thrombosis is progressively higher after each pump exchange, and the thrombosis event confers an increased risk of morbidity and death. Because the pump is the location of the thrombus leading to device malfunction, isolated pump exchanges do not adequately address cannula position or the intrinsic abnormal rheology of an individual, which may explain residual risk.

Both analyses confirm that the greatest hazard for thrombosis in HM II is early, within the first 3 to 6 months after implant. Factors related to the surgery itself and the early post-operative period may sow the seeds for thrombus. Both reports also identified younger age and higher body mass index as risk factors for thrombosis. It is not known whether obesity represents a hypercoagulable state in HF or whether the intra-abdominal positioning of the HM II pump makes its inflow cannula angulation particularly vulnerable to mechanical shifts over time.

Non-adherence was also found to be a risk factor for thrombosis, with sub-therapeutic anti-coagulation or inadequate laboratory monitoring presumed to be causative links. Finally, there is considerable institutional variability in the thrombosis rate, reinforcing that patient selection, surgical

technique, and post-implant management protocols mediate this observed pump thrombosis risk.

This series of manuscripts is an important referendum on the INTERMACS registry, now entering its second decade, and confirm the vital role for collecting real-world data in cardiac device therapy. A post-marketing registry, such as INTERMACS, has unique nationwide coverage and standard definitions to facilitate surveillance of evolving adverse events that directly affect patient care. INTERMACS is also in a unique position to compare adverse event rates among different pumps and manufacturers. However, INTERMACS does not collect granular data on surgical technique or details of individual patient management from which conclusions might be drawn about differing strategies to reduce thrombosis risk. As evidenced by the initial report by Starling et al,⁶ there will always be a vital complementary role for smaller, collaborative studies in high-volume centers to raise awareness about evolving adverse events, drill down on patient-level factors that contribute to device complications, and evaluate the effect of risk-mitigation strategies.

We do not yet have a clear explanation why thrombosis rates leveled off. The widespread attention to the problem in late 2013 might have led to a Hawthorne effect—a change in behavior as a response to observation and assessment—whereby increased vigilance to maintaining higher pump speeds, appropriate anti-coagulation targets, and lactate dehydrogenase monitoring contributed to a reduced event rate. The recently completed, industry-sponsored, multi-center Prevention of HeartMate II Pump Thrombosis (PREVENT) study will further evaluate the risk of early HM II pump thrombosis in 300 patients who received standardized implantation technique, anti-coagulation, pump speed adjustment, and blood pressure control.¹⁷

Pump thrombosis is an adverse event by no means confined to the HM II LVAD. In this issue of the *Journal*, Stulak et al¹⁶ explore this device complication in 175 patients implanted with the HeartWare HVAD between

Table 1 Estimates of Left Ventricular Assist Device Pump Thrombosis Incidence

Device	Source	Setting	No.	Implant year	6 months (%)	12 months (%)	24 months (%)			
HeartMate II	Kirklin et al ¹²	INTERMACS registry	9,808	2008–2014	Overall: 5	Overall: 7	Overall: 11			
					2012: 7	2012: 10	2012: N/A			
						2013: 8	2013: 11	2013: N/A		
						2014: 5	2014: N/A	2014: N/A		
						2012: 7	2012: 10	2012: 13		
HVAD	Smedira et al ¹³	INTERMACS registry	11,123	2008–2014	2013: 8	2013: 11	2013: 14			
					2014: 9	2014: 12	2014: 14			
	Starling et al ⁶	Multicenter study	837	2004–2013	7	11	18			
	Pagani et al ¹⁵	ENDURANCE trial	149	2010–2012	N/A	N/A	13			
	Estep et al ⁴	ROADMAP study	94	2011–2013	N/A	6	N/A			
	Slaughter et al ²	ADVANCE trial and CAP	332	2008–2011	N/A	5	N/A			
					Pagani et al ¹⁵	ENDURANCE trial	200	2011–2012	N/A	n/a
Stulak et al ¹⁶					Multicenter study	175	2009–2014	8	13	24

ADVANCE, HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure; CAP, continued access protocol; ENDURANCE, A Clinical Trial to Evaluate the HeartWare® Ventricular Assist System; HVAD, HeartWare ventricular assist device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; N/A, not available; ROADMAP, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients.

2009 and 2014. These data from 3 centers span the period before and after important changes to inflow cannula sintering were made, which led to reduced thrombosis risk. Even so, nearly 8% of patients experienced thrombosis after sintered pumps were produced, with a median time to thrombosis of 6 months. In this series, patients often presented catastrophically and without the antecedent rise in lactate dehydrogenase often seen with HM II thrombosis. Attempts to treat HVAD thrombosis medically with anticoagulation or thrombolytic therapy were not often successful (48%) and carried an unacceptably high risk of hemorrhagic stroke and death. By contrast, surgical therapy was uniformly successful without significant complication. Once thrombosis is associated with device malfunction in the HM II or HVAD, pump exchange remains the only proven treatment option, albeit with a high residual risk of recurrent thrombosis.

In August 2015, the U.S. Food and Drug Administration issued a safety communication on adverse events in LVADs to warn health care providers, patients, and caregivers of the risk of thrombosis in the HM II, stroke in the HVAD, and bleeding in both devices.^{15,18} Understandably, potential LVAD recipients, their caregivers, and the wider medical community may be increasingly skeptical of mechanical support technology in light of these reports.

What should we tell patients and their caregivers about LVAD therapy? First, we must reaffirm that LVADs can be a life-saving and life-sustaining therapy for appropriately selected patients with advanced HF in INTERMACS Profiles 1 to 4. Extending implants into a less sick advanced HF population (Profiles 5–7) will require both a better understanding of the natural history of ambulatory advanced HF and better devices with lower complication rates.

Next, informed consent and pre-implant education must be transparent about the risk of pump thrombosis requiring device exchange (1 in 10 with the HM II; 1 in 13 with the HVAD) as well as the risk of recurrent thrombosis. Just as thrombosis is a complication of all current LVADs, so are bleeding, disabling stroke, and infection. Stroke risk appears to be significantly higher in HVAD than in the HM II, although more conclusive data comparing the devices will need to await the publication of the Evaluation of the HeartWare Ventricular Assist System in Patients Ineligible for Cardiac Transplantation (ENDURANCE) trial or until INTERMACS compares these outcomes directly between the 2 pumps.¹⁵ Patients selected for device therapy and their caregivers must be motivated to adhere to vigilant anticoagulation and close follow-up with the multidisciplinary VAD team.¹⁹

Given the complexity of these decisions and the stakes involved, the mechanical support community urgently needs to understand better how to communicate both risk and benefit of LVAD support to patients and families, while placing these factors in the context of a given individual's quality of life, disability, and imminent risk of death.^{20,21} Strategies for improving communication and enhancing patient-centered decisions are being actively explored in the ongoing Decision Support Intervention for Patients and Caregivers Offered Destination Therapy Heart Assist Device (DECIDE-LVAD) trial.²²

Is there a glimmer of hope in reducing risk of pump thrombosis with newer devices? Promising preliminary data have emerged about the next-generation magnetically levitated centrifugal-flow HeartMate 3 from its Conformité Européenne Mark Trial. In the first 50 HeartMate 3 recipients who received the device in 10 centers across 6 countries, there were no reported adverse events of pump malfunction, pump thrombosis, or significant intravascular hemolysis through 6 months of support, although a 12% incidence of stroke was observed.²³ It must be emphasized that these observational data are in a small series limited to select centers. Nevertheless, they provide some reassurance and encouragement to patients and their providers considering randomization into the Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3 (MOMENTUM 3) pivotal trial of the HeartMate 3 in the United States and in other upcoming trials of next-generation blood pump technology.²⁴

Engineering progress, along with a better understanding of hemocompatibility, will undoubtedly help to reduce the problem of pump thrombosis and will allow the expansion of mechanical circulatory support into broader groups of patients. Until then, we must redouble our efforts to ensure that today's patients live longer and better with approved pump technology even as we look with hope to the future.

Disclosure statement

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