

# Treatment of device thrombus in the HeartWare HVAD: Success and outcomes depend significantly on the initial treatment strategy



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## KEYWORDS:

ventricular assist device;  
thrombus;  
pump thrombosis;  
device exchange;  
lytic therapy;  
anti-coagulation;  
HeartWare

**BACKGROUND:** Pump thrombosis is a major adverse event in patients supported with a left ventricular assist device (LVAD). Treatment approaches include device exchange, lytic therapy, or augmentation of anticoagulation or antiplatelet therapy. The optimal strategy in the HeartWare HVAD Ventricular Assist System (HeartWare, Framingham, MA) is uncertain, and because few large studies have examined differing treatment outcomes, we have reviewed findings from the Mechanical Circulatory Support Research Network registry.

**METHODS:** Between March 2009 and August 2014, 175 patients (133 male) underwent implantation of the HeartWare HVAD at institutions that comprise the Mechanical Circulatory Support Research Network. Median age at implant was 59 years (range, 18–76 years). Follow-up was available in all patients for a median of 6 months (maximum, 61 months) and for a total of 163 patient-years of support. There were 36 pump thromboses (using Interagency Registry for Mechanically Assisted Circulatory Support criteria) in 21 patients for a total event rate of 0.22 events/patient-year of support; 13 patients had 1 event, 4 had 2, 2 had 3, 1 had 4, and 1 had 5. The median time to the first thrombosis was 6.4 months, and to each subsequent thrombosis was 4, 3, 2, and 2 months, respectively. Primary treatment success was defined as the patient remaining alive and within the first 30 days of the initial treatment be free from stroke, recurrence of pump thrombosis, device exchange, or urgent transplantation (United Network of Organ Sharing Status 1A). Medical treatment was defined as tissue plasminogen activator, heparin plus glycoprotein IIb/IIIa inhibitor, or heparin alone, not followed by surgical treatment within 72 hours.

**RESULTS:** Initial medical treatment was used in 29 episodes (tissue plasminogen activator in 24, heparin alone in 4, and heparin plus glycoprotein IIb/IIIa in 1) and surgical (device exchange) in 7. Medical treatment was successful in 14 of 29 episodes (48%). Complications of medical treatment included hemorrhagic stroke in 6 patients (21%), need for urgent device exchange/transplant in 6 (21%), and death in 3 (10%). Surgical treatment was successful in all 7 patients (100%). No significant early complications or early deaths occurred after device exchange.

**CONCLUSIONS:** In this large multicenter analysis, we observed that medical therapy, as the initial treatment strategy for HeartWare HVAD thrombosis, is associated with low success (48%) and a significant risk of hemorrhagic stroke (21%) and death (10%). However, initial treatment with device

exchange was uniformly successful and not associated with significant early morbidity or death. Although the optimal treatment approach for HeartWare HVAD pump thrombosis remains undecided, these data do not support the routine use of medical therapy as an initial treatment strategy.

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Despite an overall trend toward a decrease in adverse events associated with left ventricular assist device (LVAD) therapy, a detailed analysis of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database reported a 6-fold increase in the rates of pump thrombosis of the HeartMate II (Thoratec Corp, Pleasanton, CA) LVAD beginning in 2011 to 2012, and the 6-month actuarial freedom from device exchange or death due to pump thrombosis significantly fell from 99% in 2008 to 2009 to 95% in 2011 and to 94% in 2012.<sup>1</sup>

The HeartWare Investigators also noted high incidence (0.063–0.08 events/patient-year) of thrombosis in the HeartWare HVAD Ventricular Assist System (HeartWare Inc, Framingham, MA) which subsequently prompted a detailed analysis.<sup>2,3</sup> Interestingly, investigators found that most pump thromboses occurred in patients with sub-therapeutic warfarin anti-coagulation and taking low-dose aspirin (i.e., 81 mg) or no anti-platelet therapy. After modifications were made to the inflow cannula design (sintering) and recommendations were made for strict patient management to adhere to an international normalized ratio (INR) of 2 to 3 and high-dose aspirin (i.e., 325 mg), the rate of device exchange due to pump thrombosis fell by greater than 50%, and the incident rate of stroke fell significantly.<sup>2–4</sup> Analysis of the available reports to date stresses not only the complexity of the phenomenon of LVAD thrombosis but also highlights the challenges associated with treatment, especially because no standardized approach exists.

Because very few large analyses exist specifically analyzing success and failure of medical and surgical therapy for HeartWare HVAD pump thrombosis, we sought to analyze all patients who underwent HVAD implantation

in the Mechanical Circulatory Support Research Network registry. After identifying those undergoing treatment for pump thrombosis according to pre-defined criteria, we aimed to define and document the primary treatment strategy and analyze success according to more pre-defined criteria. Outcomes, log file analyses, and predictors of pump thrombosis were then analyzed.

## Methods

### Study population

The data collection process and analysis were performed after informed patient consent and approved by the Institutional Review Board at each center that comprises the Mechanical Circulatory Support Research Network (Mayo Clinic College of Medicine, Vanderbilt Heart and Vascular Institute, and University of Michigan). Between May 2004 and August 2014, 734 patients underwent primary continuous-flow LVAD implantation at our centers. Of these, 175 patients (24%) received a HeartWare HVAD and represent the contemporary cohort for this analysis. The HeartWare HVAD was implanted in 30 patients before August 2011 and in 145 after August 2011.

Demographic and other patient-related data were obtained from the University of Michigan, Mayo Clinic College of Medicine, and Vanderbilt Heart and Vascular Institute medical records and our prospectively collected clinical databases. Follow-up information was obtained from subsequent clinic visits and written correspondence from local physicians. There were 133 men (76%), and the median age at implant was 59 years (range, 18–76 years). Pre-operative clinical characteristics of the overall cohort and stratified by thrombus and no thrombus are presented in [Table 1](#).

**Table 1** Preoperative Clinical Characteristics in Patients With and Without Pump Thrombus

Clinical characteristic <sup>a</sup>	Thrombus (n = 21)	No thrombus (n = 154)	Total (N = 175)	p-value
Age at implant, year	54 (18-82)	59 (19-76)	59 (18-76)	0.56
Male sex	13 (62)	120 (78)	133 (76)	0.11
Ischemic etiology	11 (52)	81 (53)	92 (53)	0.99
Bridge to transplant	15 (71)	126 (82)	141 (81)	0.26
INTERMACS 1, 2	6 (29)	39 (25)	45 (26)	0.75
Atrial fibrillation	4 (19)	71 (46)	75 (43)	0.65
Hypertension	11 (52)	85 (55)	96 (55)	0.91
Diabetes mellitus	6 (29)	29 (19)	35 (20)	0.94
Creatinine, mg/dl	1.2 ± 0.6	1.3 ± 0.7	1.3 ± 0.7	0.54
Hemoglobin, g/dl	11.5 ± 1.3	11.5 ± 1.4	11.5 ± 1.4	0.32
Total bilirubin, mg/dl	0.9 ± 0.6	1.2 ± 0.9	1.2 ± 0.9	0.03
> Moderate RV dysfunction	2 (10)	28 (18)	30 (17)	0.28
> Moderate TVR	4 (19)	37 (24)	41 (23)	0.48

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RV, right ventricular; TR, tricuspid valve regurgitation.

<sup>a</sup>Continuous data are presented as the median (range) or the mean ± standard error of the mean and categorical data as number (%).

All institutions generally monitor lactate dehydrogenase (LDH) weekly for the first month, monthly thereafter until 6 months, and then every 6 months. INR values are closely monitored by institutional anti-coagulation programs, and patients are routinely bridged with unfractionated intravenous heparin if the INR is below 2.0. All patients with HeartWare HVAD were maintained on 325 mg of aspirin.

## Definitions

Primary treatment therapy was at the discretion of the multi-disciplinary LVAD team at each respective institution. Medical therapy was defined as tissue plasminogen activator (tPA), intravenous unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor, or heparin alone not accompanied by device exchange or urgent transplantation for pump thrombus within 72 hours of initiation of treatment. Surgical treatment was defined as device exchange. Primary treatment success was defined as the patient remaining alive and within the first 30 days of initial treatment be free from (1) stroke, (2) recurrence of pump thrombosis, (3) device exchange, or (4) urgent transplantation (United Network of Organ Sharing Status 1A).

The INTERMACS Executive Committee publishes adverse event (AE) definitions that centers use to ensure standardization in reporting of AEs. The most recent version of the AE definitions was approved on May 15, 2013. Pump thrombus is considered a specific case of a major device malfunction and is classified as suspected or confirmed pump thrombus. With suspected pump thrombus, clinical patient condition or pump parameters suggest thrombus on any of the blood-contacting surfaces of the pump (inflow cannula, pump itself, or outflow graft). Criteria (at least 2 present) should include presence of hemolysis, presence of heart failure not explained by structural disease, or abnormal pump parameters. Confirmed pump thrombus can be observed by visual inspection (at the time of device exchange, transplantation, or autopsy), irrefutable radiographic evidence, or absence of Doppler inflow or outflow signals.

Although these are the current definitions, this study spans a wide time interval during which differing definitions were used according to the era in which the patient was implanted. The definitions may have changed throughout the study period but were in accordance with the accepted INTERMACS definition at the time of occurrence.

Log file analysis definitions include percentage expected power and growth rate. Percentage expected power equals the absolute percentage above the power baseline the patient exhibited in the 24 hours before pump thrombus onset. This value can be calculated by dividing the maximum power value by the baseline power and then multiplying this value by 100. Growth rate is calculated by dividing the difference of the maximum and baseline powers by the length of time elapsed to arrive at maximal power.

## Statistical analysis

Data are expressed as mean  $\pm$  standard error of the mean for normally distributed data or as the median with the range for non-normally distributed data. Data between 2 groups were compared using the chi-square test for continuous and dichotomous variables, respectively. A backward stepwise Cox regression analysis was used to identify peri-operative variables independently affecting outcomes. Kaplan-Meier survival analysis was used to evaluate time-related outcomes and produce plots, which were subsequently compared by the log-rank test. Association of pump thrombus

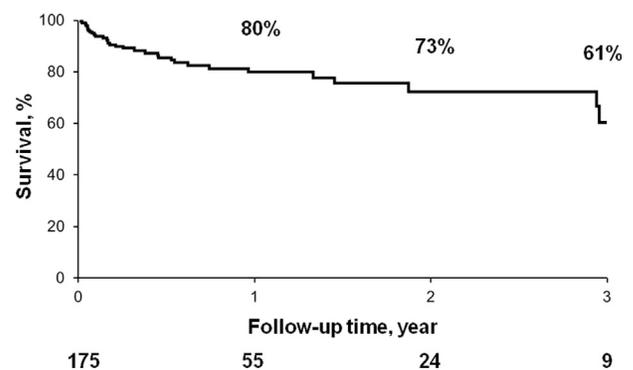
during follow-up and subsequent risk of death was analyzed using a time-dependent covariate. Statistical significance was considered at  $p < 0.05$ . Early operative mortality was defined as death occurring within 30 days of the operation or at any time during the index hospitalization. Log files were analyzed for calculation of growth rate (rise in power per unit time) and percentage expected power.

## Results

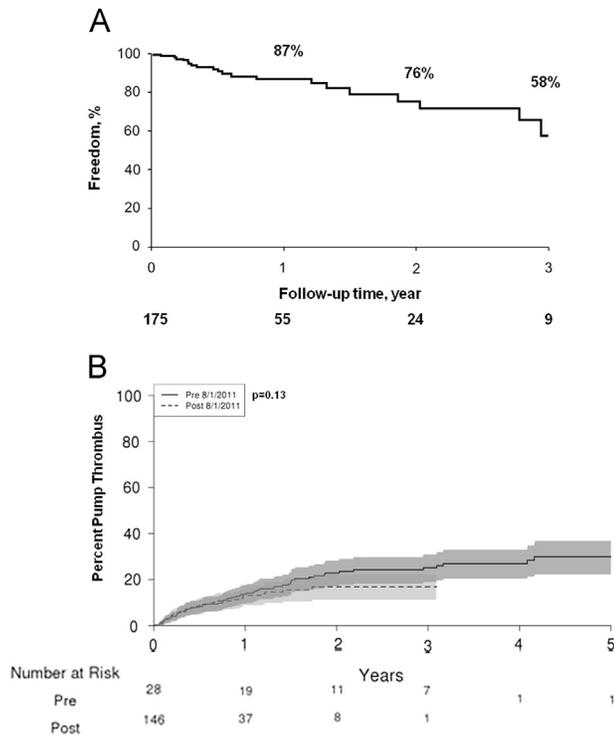
All patients underwent primary implantation of the HeartWare HVAD. There were 7 early deaths (4%). Follow-up was available in the 168 early survivors for a median of 6 months (maximum, 61 months). A total of 163 patient-years of support were available for analysis. Overall survival was 80% at 1 year, 73% at 2 years, and 61% at 3 years (Figure 1). When analyzed as a time-dependent covariate, no significant association was found between pump thrombus and late survival (hazard ratio, 1.7 [95% confidence limit 0.46, 6.2],  $p = 0.433$ ).

Overall freedom from pump thrombosis for the entire cohort was 87% at 1 year, 76% at 2 years, and 58% at 3 years (Figure 2A). Overall freedom from pump thrombosis stratified according to date of implant before and after August 1, 2011, is demonstrated in Figure 2B. No statistically significant difference was found in the time-related cumulative risk of pump thrombosis between eras. However, when the true incidence was analyzed, pump thrombosis occurred in 10 of 30 patients (30%) who received a device before August 2011 and in 11 of 145 patients (7.6%) who underwent implantation after August 2011 ( $p < 0.012$ ).

In the study cohort, 36 pump thromboses occurred in 21 patients for a total event rate of 0.22 events/patient-year of support: 13 patients had 1 event, 4 had 2, 2 had 3, 1 had 4, and 1 had 5. The median time to the first thrombosis was 6.4 months and to each subsequent thrombosis was 4, 3, 2, and 2 months, respectively. Univariable analysis testing association of pre-operative clinical characteristics and the development of pump thrombosis is presented in Table 2. No pre-operative variables were significantly predictive of pump thrombosis. Medical treatment was the primary therapy in 29 instances of pump thrombosis, with thrombolytic therapy used in 24, heparin alone in 4, and heparin plus a glycoprotein IIb/IIIa inhibitor in 1. Of the 29 patients with primary medical treatment, treatment success



**Figure 1** Overall late survival is shown for all patients in the study cohort.



**Figure 2** Overall freedom from pump thrombosis is shown (A) for all patients in the study cohort and (B) stratified by date of implant before and after August 1, 2011. The shaded areas represent confidence intervals.

was obtained in 14 (48%), hemorrhagic stroke occurred in 6 (21%), urgent device exchange was required in 6 (21%), and death occurred in 3 (10%). For the 14 patients in whom a treatment success was initially obtained, 6 (45%) went on to have no further recurrence (21% overall), whereas 8 (57%) had a recurrence. In the 8 patients with recurrence, 7 (88%) were treated with further medical therapy, and 1 (12%) underwent surgical therapy.

Surgical treatment was the primary therapy in 7 patients, with all patients undergoing device exchange. Treatment

**Table 2** Univariable Analysis Testing the Association of Pre-operative Factors With Development of Pump Thrombosis

Variable	HR	95% CL	p-value
Age at implant	0.99	0.96, 1.02	0.55
Female	1.66	0.68, 4.04	0.54
Ischemic etiology	1.23	0.52, 2.9	0.64
Destination therapy	0.77	0.27, 2.2	0.63
INTERMACS 1, 2	1.2	0.71, 1.91	0.54
Atrial fibrillation	0.44	0.15, 1.32	0.14
Hypertension	0.91	0.38, 2.14	0.82
> Moderate RV dysfunction	0.6	0.13, 2.77	0.52
> Moderate TVR	1.2	0.39, 3.54	0.78
Hemoglobin	0.97	0.76, 1.24	0.81
Creatinine	0.84	0.29, 2.4	0.75
Diabetes	0.82	0.29, 2.34	0.71
Total bilirubin	0.52	0.21, 1.3	0.16

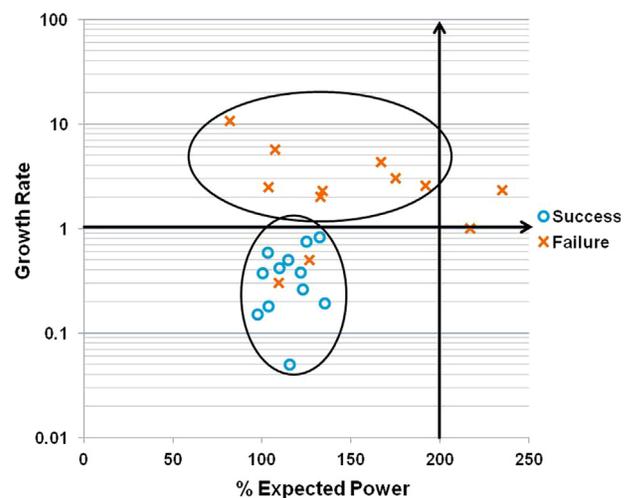
CL, confidence limits; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RV, right ventricular; TR, tricuspid valve regurgitation.

success was obtained in all 7 (100%), with no hemorrhagic strokes or deaths and no major early non-fatal morbidity.

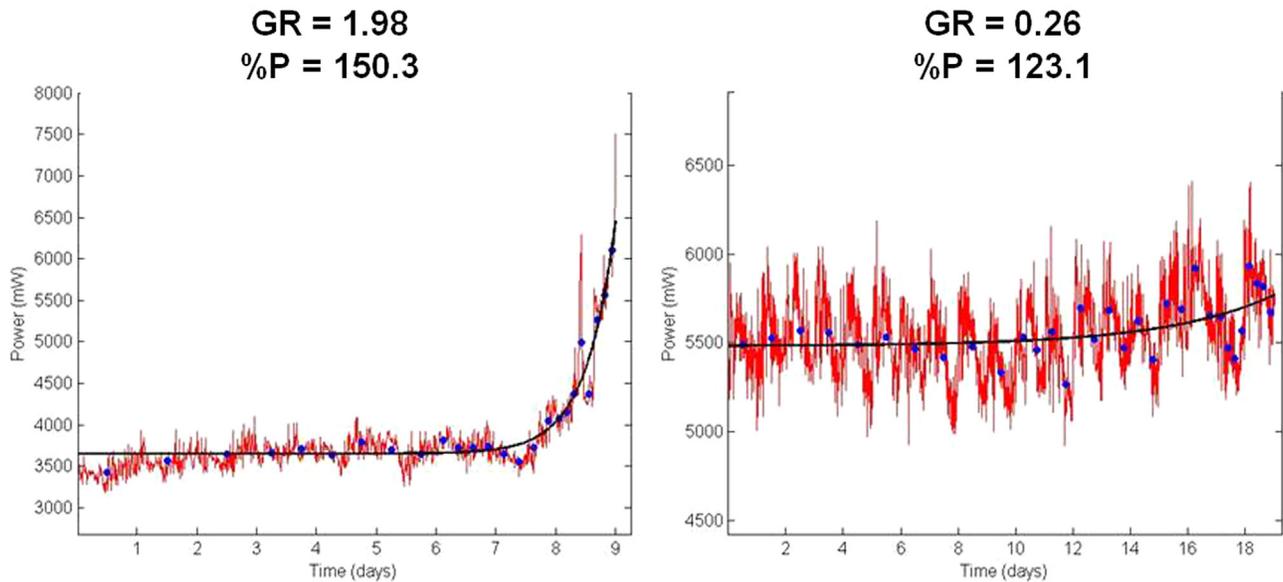
Log file analysis showed the percentage expected power was significantly lower in the setting of treatment success compared with treatment failure ( $115.25 \pm 3.5$  vs  $148 \pm 7$ ,  $p = 0.03$ ), as was growth rate ( $0.4 \pm 0.24$  vs  $3.1 \pm 1.7$ ,  $p = 0.003$ ). Most of the treatment successes occurred with a growth rate of less than 1 and a percentage expected power of less than 200, whereas most failures occurred with a growth rate of greater than 1 and a percentage expected power of less than 200 (Figure 3). Examples of log file analysis demonstrating patients with a high and low percentage expected power and growth rate are shown in Figure 4.

## Discussion

In this large multiinstitutional analysis of treatment approach to pump thrombosis of the HeartWare HVAD, we observed low treatment success of 48% (14 of 29) associated with medical therapy along with a significant rate of hemorrhagic stroke (21%), urgent device exchange after failed treatment (21%), and death (10%). Failure was associated with a significantly higher power growth rate and percentage expected power. Furthermore, an analysis of 14 patients who had initial success with medical therapy showed only 6 had no further recurrence, placing the overall success without recurrence to only 21% of medically treated patients. Surgical therapy was used in 7 patients, and was uniformly successful, with no early deaths or major nonfatal morbidity. There were 2 recurrences after the initial device exchange, which were treated successfully with thrombolytics. These data greatly facilitate our ability to counsel patients about the risks and benefits of a certain treatment approach and also enlighten practitioners about the potential adverse outcomes that accompany either intervention.



**Figure 3** Scatter-plot shows the percentage expected power and growth rate for patients who had a treatment success (○) and treatment failure (×). As shown, most of the treatment successes occurred with a growth rate of less than 1 and a percentage expected power of less than 200, whereas most of the failures occurred with a growth rate greater than 1 and a percentage expected power of less than 200.



**Figure 4** Examples of a patient with a (Left) a high growth rate (GR) and percentage expected power (P) and (Right) a patient with a low growth rate and percentage expected power.

Our observed outcomes are similar to those reported by the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) Trial Investigators, who documented a 50% success rate for medical therapy, with a 16% occurrence of hemorrhagic stroke for all patients undergoing treatment for pump thrombus and 17% mortality after failed medical therapy.<sup>3</sup> Also similar to the current series, no decrement in survival was observed for patients who had a thrombus event compared with those who did not. Importantly, our incidence rate of pump thrombus was higher in this series compared with prior series,<sup>2-4</sup> which may reflect a very high pre-2011 pump thrombus rate of 30% because the more contemporary implants have demonstrated a lower rate of 7.6%, which is more consistent with the aforementioned published reports.

Patients may present in several fashions in the setting of HVAD pump thrombus, including acute occlusion, which would manifest as a sudden drop in flow and power and a gradual rise in flow and power with high power alarms. This clearly depends on the clot severity and rapidity of formation, but nonetheless, an analysis of the log files may prove very helpful in anticipating patients who may have an enhanced success with medical management. We observed in the current series that most of the medical treatment failures were associated with a significantly higher power growth rate and percentage expected power. Specifically, we observed that all medical treatment successes were associated with a power growth rate of  $<1$  and that all but 3 failures were in the setting of a power growth rate of  $>1$ . Furthermore, all medical treatment successes were with a percentage expected power of  $<150\%$ , whereas treatment failures were less consistent, ranging from 75% to  $>250\%$  expected power.

Our log file analysis associations with treatment outcomes are similar to a recent analysis of clinical records of pump thrombus events and medical therapy treatment for patients from the ADVANCE Bridge to Transplant (BTT) and

Continued Access Protocol (CAP) trial.<sup>5</sup> Our general cutoffs for success differed slightly from the ADVANCE BTT/CAP cohort, in which a threshold of 1.25 for growth rate and 200% for percentage expected power were “determined” (personal communication, HeartWare Inc). Our lower observed percentage expected power may reflect our collective experience, which has possibly led to faster recognition of thrombus and earlier treatment before excessive power growth.

Analysis of the available reports to date stresses the complexity of the phenomenon of LVAD pump thrombosis and that causes can be differentiated into non-mechanical and mechanical. In relation to the former, most prominently, there exists a fine balance between anti-coagulation and bleeding complications. In parallel to the relationship of maintenance anti-coagulation and anti-platelet therapy, some have demonstrated a subsequent increased risk of thromboembolic events after gastrointestinal bleeding and the resultant alteration in anti-coagulation.<sup>6</sup> Aside from anti-coagulation, one must recall that the HeartWare HVAD is sensitive to afterload to a greater degree than axial-flow pumps. Flow through the pump itself is lower in the presence of a high afterload, and some have observed an association between high blood pressure and pump thrombosis.<sup>3</sup>

The HeartWare HVAD has undergone some mechanical design modifications aimed at lowering pump thrombosis.<sup>3</sup> Originally, tissue in-growth around the inflow cannula was observed that could pre-dispose to clot ingestion and pump thrombus. After these observations, the inflow cannula was sintered to prevent tissue in-growth, and the coring tool was increased in diameter and provided a more homogeneous surface into which the inflow cannula is inserted. Tissue in-growth around the inflow cannula is a chronic condition that is less likely to respond to medical therapy. We certainly observed a decrease in the incidence of pump thrombosis after August 2011 when sintering of the inflow was available, with a 30% pump thrombosis rate before sintering and 7.6% after sintering.

Although there is growing understanding of HVAD thrombosis, including etiologies, patient presentation, and clinical manifestations, most of the current literature on therapeutic approach is on the HeartMate II.<sup>7</sup> Cowger et al,<sup>8</sup> have demonstrated that serum hemolysis marker elevations are associated with increased events in LVAD patients. Furthermore, patients who met their definition of hemolysis according to the LDH definition had longer times from hemolysis to the onset of AEs and a larger risk for embolism and need for device exchange compared with hemolysis defined by serum free hemoglobin. However, chronic elevation in LDH as a marker of hemolysis does not often occur in the HVAD. Thrombus events in the HVAD tend to be more acute, and thrombus events in the HeartMate II are more commonly chronic. Clinically, it is not likely that an HVAD patient will be observed to have chronic elevation of LDH. Although much clinical experience has been gained in the HeartMate II, the approach and clinical management may not be applicable to the HVAD.

The optimal treatment and primary approach for the patient with pump thrombosis of the HeartMate II or HeartWare HVAD has not been fully established. In hemodynamically stable patients, medical therapy is often used initially, which most commonly includes high-dose unfractionated heparin, fluid resuscitation, with or without the addition of glycoprotein IIb/IIIa inhibitors, and thrombolytics. A collection of small and large series have documented outcomes with either pump.<sup>9–15</sup> Although small series demonstrate a high success rate with low morbidity, an analysis of larger series demonstrate success rates ranging from 23% to 50%, stroke from 10% to 15%, bleeding complications at 65%, and mortality rates from 17% to 52%.<sup>9–11,13,14</sup> It is very clear that even in the face of “successful medical therapy,” there is an accompanied high morbidity rate. These series reporting outcomes with medical therapy for LVAD pump thrombosis also include a significant number of patients who failed medical therapy and progressed to undergo surgical therapy. Thus, in a sub-set of stable patients, a role for attempted medical therapy may not preclude further consideration of surgical therapy.

Several series have documented outcomes after LVAD device exchange, and although initially considered a highly morbid procedure, improvement of peri-procedural care, surgical approach, and post-operative support in the current era has resulted in very low early mortality and low complication rates with LVAD device exchange.<sup>9,16–18</sup> Surgical therapy is most often undertaken as the primary approach in patients who present with pump malfunction or stoppage with associated hemodynamic instability. Alternate approaches are now more commonly used, which have lowered morbidity and mortality after device exchange.<sup>16,19</sup>

The HeartWare HVAD is an intrapericardial pump that requires full dissection, exposure, and elevation of the left ventricular apex into the wound to facilitate device exchange, especially in the absence of an articulating wrench for loosening and tightening the apical connector. An HVAD that was implanted through a left anterior thoracotomy could be exchanged during this approach.

## Limitations

This study has the limitations inherent in its study design and retrospective nature. This study includes data from 3 institutions and also contains the limitations in data drawn from a registry in terms of missing data fields and potential inconsistency of data entry. Approaches in the post-operative period differ across the institutions in the Network in the setting of pump thrombosis. Patients in this series were selected for the executed treatment plan according to multiple factors, as discussed. The approach to pump thrombosis in the 3 centers is not standardized and neither is the dosage and approach to thrombolytics. The analysis of predictive factors pre-disposing to pump thrombosis was limited to pre-operative clinical characteristics, and critical measurements, such as anti-coagulation and blood pressure, were not included in this analysis.

## Conclusions and perspective

The choice of initial therapy for the patient with LVAD pump thrombosis, whether HVAD or HeartMate II, depends on several factors, including patient presentation, surgical candidacy, and to a large degree, institutional philosophy. There is growing appreciation of the high morbidity associated with thrombolytics when balanced with a modest success rate, especially if the onset of thrombosis is greater than 24 to 48 hours. The utility of thrombolytics decreases significantly in this sub-set of patients with a delayed presentation. In these patients, surgical device exchange is arguably the more effective approach. However, the ideal approach remains elusive and will always depend heavily on a combination of patient-related and device-related factors and the weighing of risks of benefits of each approach.

## Disclosure statement

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