An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial

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KEYWORDS:
HeartWare HVAD;
bridge to transplant;
left ventricular assist
device;
thrombus;
heart failure

BACKGROUND: The HeartWare left ventricular assist device (HVAD, HeartWare Inc, Framingham, MA) is the first implantable centrifugal continuous-flow pump approved for use as a bridge to transplantation. An infrequent but serious adverse event of LVAD support is thrombus ingestion or formation in the pump. In this study, we analyze the incidence of pump thrombus, evaluate the comparative effectiveness of various treatment strategies, and examine factors pre-disposing to the development of pump thrombus.
METHODS: The analysis included 382 patients who underwent implantation of the HVAD as part of the HeartWare Bridge to Transplant (BTT) and subsequent Continued Access Protocol (CAP) trial. Descriptive statistics and group comparisons were generated to analyze baseline characteristics, incidence of pump thrombus, and treatment outcomes. A multivariate analysis was performed to assess significant risk factors for developing pump thrombus.
RESULTS: There were 34 pump thrombus events observed in 31 patients (8.1% of the cohort) for a rate of 0.08 events per patient-year. The incidence of pump thrombus did not differ between BTT and CAP. Medical management of pump thrombus was attempted in 30 cases, and was successful in 15 (50%). A total of 16 patients underwent pump exchange, and 2 underwent urgent transplantation. Five patients with a pump thrombus died after medical therapy failed, 4 of whom also underwent a pump exchange. Survival at 1 year in patients with and without a pump thrombus was 69.4% and 85.5%, respectively ($p = 0.21$). A multivariable analysis revealed that significant risk factors for pump thrombus included a mean arterial pressure > 90 mm Hg, aspirin dose ≤ 81 mg, international normalized ratio ≤ 2, and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile level of ≥ 3 at implant.

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CONCLUSIONS: Pump thrombus is a clinically important adverse event in patients receiving an HVAD, occurring at a rate of 0.08 events per patient-year. Significant risk factors for pump thrombosis include elevated blood pressure and sub-optimal anti-coagulation and anti-platelet therapies. This suggests that pump thrombus event rates could be reduced through careful adherence to patient management guidelines.
J Heart Lung Transplant 2014;33:23–34

Mechanical circulatory support is an effective therapy for advanced heart failure. Technologic advances have enabled the development of implantable, continuous-flow left ventricular assist devices (LVADs) that have been shown to improve survival, functional capacity, and quality of life in patients with advanced heart failure who are refractory to medical therapy.[1–5] The HeartWare Ventricular Assist System (HVAD; HeartWare Inc, Framingham, MA) is the first continuous-flow pump with centrifugal design to receive Conformité Européene Mark and United States (U.S.) Food and Drug Administration (FDA) approval for bridge to transplantation (BTT).

The occurrence of pump thrombus events that can obstruct blood ingress or egress or interfere with pump action by impinging on the internal impeller is a serious complication for all continuous-flow VADs. In most cases, thrombus events appear to be due to ingestion of material external to the pump itself. Thrombus may originate from post-surgical ventricular debris, emboli arising from the left atrial appendage, or possibly, from the endocardial surface of the LV. In addition, malposition of the inflow cannula resulting in partial inflow cannula obstruction and inadequate anti-coagulation or anti-platelet therapy during the long-term use of the device may precipitate a thrombus event.

In the original design of the HVAD, the external and internal surfaces of the inflow cannula consisted of a highly polished titanium alloy. However, inspection of explanted hearts at transplantation showed tissue ingrowth encircling the external surface of the inflow cannula, which introduced the possibility that this encircling tissue might be a source of emboli that could compromise HVAD function (personal communication, David R. Hathaway, HeartWare Inc). Therefore, the exterior surface of the inflow cannula was modified to include sintered titanium microspheres that covered approximately half of the length of the inflow cannula, extending from the base to
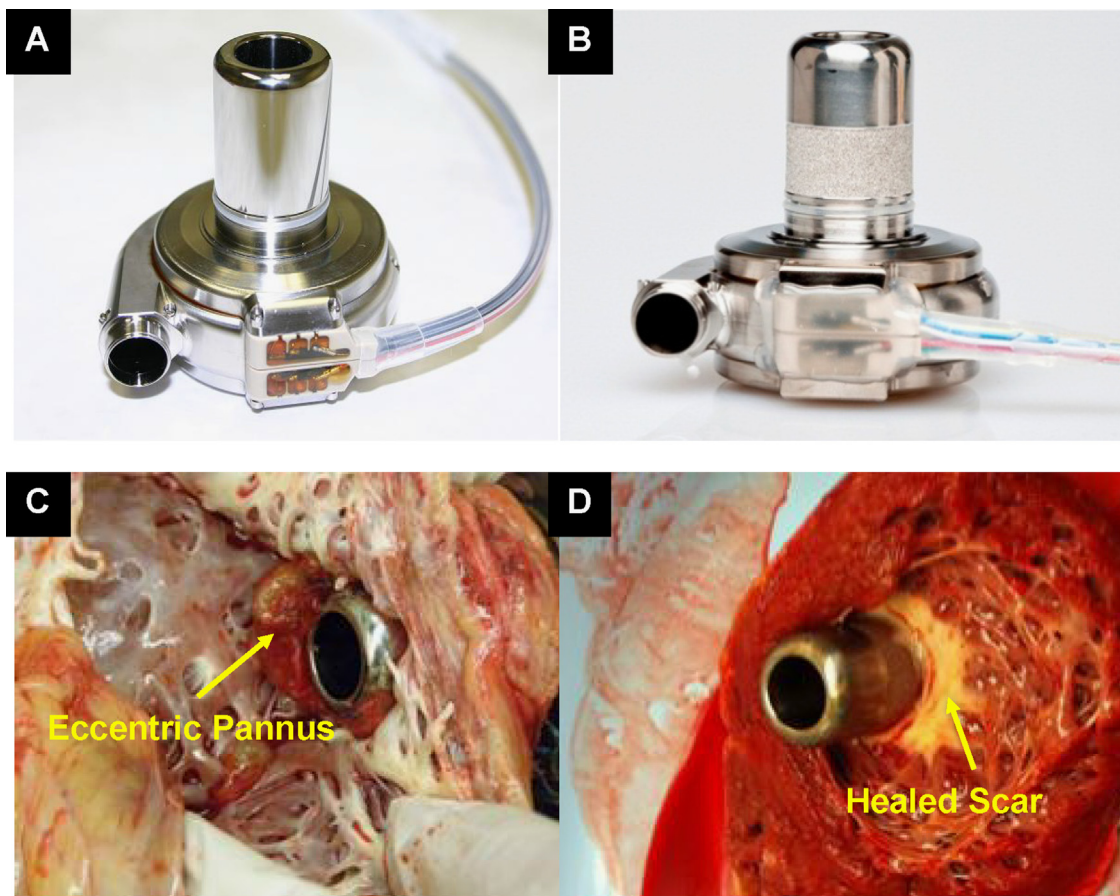

Figure 1   (A) Non-sintered vs (B) sintered HVAD (HeartWare, Framingham, MA) pumps. (C) Tissue growth on the inflow cannula of a non-sintered pump extends across the length of the cannula, (D) whereas tissue growth on the inflow cannula of a sintered pump does not extend beyond the sintered area.

the midsection circumferentially (Figure 1). This technology has been successfully incorporated in other LVAD platforms.[6–8] The goal was to prevent tissue growth progression beyond the sintered area of the cannula. The sintered cannula was introduced beginning in May 2011. Concurrently with the introduction of the sintered pump, a coring tool was introduced that increased the coring diameter from 16 to 19 mm, which provided cleaner cuts along the edges of the myocardium into which the inflow cannula is inserted.

In this analysis, we evaluate the incidence of pump thrombus in patients who received the HVAD, review the therapies used to manage pump thrombus, analyze the effect of sintering, and perform a multivariable risk model assessment to identify significant risk factors for these events.

Methods

The study cohort included 382 patients who underwent implantation of the HVAD as a BTT and were enrolled in the HeartWare BTT clinical trial or its Continued Access Protocol (CAP). The design of the BTT trial has previously been described.[4] This HeartWare-sponsored study was conducted at 30 centers in the U.S. and enrolled patients between August 2008 and February 2010, with the primary end point completed in August 2010. The study enrolled 140 adults with refractory advanced heart failure who were eligible for heart transplantation and who were in need of mechanical circulatory support. After accrual was completed, the FDA granted additional patient cohorts to be enrolled at 30 U.S. centers under a CAP between April 2010 and November 2012, resulting in enrollment of an additional 242 patients. This analysis includes all patients who received a HVAD under the BTT and CAP protocol.[5]

All adverse events, including those meeting the Interagency Registry for Mechanically Assisted Circulatory Support (INTER-MACS) definitions at the time of the study (www.uab.edu/medicine/intermacs/appendices/appendix-a), were evaluated. A pump thrombus was defined in the clinical trial as an event that occurred > 72 hours after LVAD implantation, manifesting:

1. alterations in pump parameters, defined as unexpected power increases with higher than expected flow estimation ("pseudo-flow") or a precipitous drop in flow and power;
2. an associated increase in biochemical markers of hemolysis, including lactate dehydrogenase (LDH) > 2.0 times the upper limit of normal, or plasma free hemoglobin (pfHgb) > 40 mg/dl or hemoglobinuria; and/or
3. visualization of organized fibrin in the pump housing after exchange of the LVAD; and/or
4. abnormal pump sounds identified by auscultation.

These findings were supplemented with reviews of patient safety narrative reports and controller log files, evaluating signal dissociation between power and flow. All events were censored at the time of pump exchange, pump explantation for recovery, or transplantation.

Successful medical therapy of a suspected pump thrombus was defined as clinical resolution of pump thrombus, improvement in biochemical markers of hemolysis, and return to normal pump parameters, without recurrence or need for exchange, urgent United Network of Organ Sharing (UNOS) status 1A transplant, or death within 1 month of thrombus resolution. Time in therapeutic range (TTR) for international normalized ratio (INR) was calculated using the method described by Rosendaal et al.[9]

The cohort was stratified into 2 groups: those who experienced a pump thrombus event and those who did not. The baseline clinical and demographic characteristics of the 2 groups were compared using a 2-sample t-test for continuous variables and Fisher's exact test for categoric variables. Thrombus events and other adverse events are reported as the percentage of patients affected and as rate of events per patient-year (EPPY) of support. These variables were compared between the 2 groups with Fisher's exact test and a Poisson regression methodology, respectively. Survival estimates and time-to-event curves were generated using Kaplan-Meier analysis.

A multivariable analysis was conducted to identify major risk factors for pump thrombus, and 38 dichotomous covariates were considered as critical risk factors. Each covariate was assessed independently as a predictor by univariable analysis, and covariate influence was measured with odds ratios and accompanying p-values using the Cochran–Mantel-Haenszel test. Covariate reduction was performed based on the univariable analysis results, using a p-value limit of < 0.15 as well as the impact of potential multicolinearity. The remaining covariate terms were modeled using a logistic regression analysis. SAS 9.2 software (SAS Institute, Cary, NC) was used for the statistical analyses.

Results

Baseline characteristics

The BTT+CAP trial enrolled 382 patients. Of those, 272 (71.2%) received a non-sintered HVAD, and 110 (28.8%) received an HVAD with a sintered inflow cannula. During the study, 34 pump thrombus events occurred in 31 patients. Baseline clinical and demographic characteristics of patients with and without pump thrombus are reported in Table 1. Age, sex, race, body surface area, LV ejection fraction, systemic blood pressure, and cardiac index at the time of device implant did not significantly differ between the 2 groups. Patients with a pump thrombus had a lower baseline creatinine (1.1 vs 1.3 mg/dl, respectively; p = 0.02). The median time on LVAD support did not significantly differ between patients without a pump thrombus and those with a thrombus event (271 [range, 1–1,506] days vs 289 [range, 18–1,293] days, respectively; p = 0.85). During support, the average LVAD speed, power, and flow did not significantly differ between patients without a thrombus event and those with a thrombus event (parameters averaged to within a week of an event; Table 2).

Pump thrombus events

Signs of pump thrombus included unexpected power increases, flow estimation beyond that predicted from power consumption, hemoglobinuria, log file analysis demonstrating signals of flow and power dissociation, and elevated levels of LDH and pfHgb. Patients with pump thrombus exhibited a mean LDH value of 863 U/liter (range, 129–8,233 U/liter) and a mean pfHgb of 92.4 mg/dl (range, 1.0–538 mg/dl) at the time of pump thrombus presentation.

Fibrin or clot material on the surface of the impeller may cause an increase in power consumption resulting in a decrease in pump efficiency. Thrombus events exhibited different patterns of presentation (Figure 2), including (1) acute occlusion associated with suction events (total occlusion); (2) a precipitous drop in flow and power (subtotal occlusion); and (3) a gradual rise in flow and power associated with high power alarms over days leading up to the thrombus event. The latter pattern of presentation was the most

Table 1 Baseline Demographic and Clinical Characteristics[a]

Baseline Characteristic	No Thrombus (n = 351)	Thrombus (n = 31)	p-value[b]
Age, years	53.4 ± 11.7	50.3 ± 11.3	0.16
Male sex,%	71.2	58.1	0.10
Race,%			0.16
Caucasian	68.1	67.7	
Black/African American	26.8	22.6	
Asian	1.7	0.0	
Other	3.4	9.7	
Body mass index, kg/m^2	28.0 ± 5.9	29.9 ± 7.3	0.10
Body surface area, m^2	2.0 ± 0.3	2.0 ± 0.3	0.80
Ischemic cause of heart failure, %	38.0	32.3	0.57
Left ventricular ejection fraction, %	17.2 ± 7	17.5 ± 6	0.84
Blood pressure, mm Hg			
Arterial	103 ± 15	106 ± 17	0.47
Systolic	64 ± 10	62 ± 12	0.30
Diastolic	78 ± 11	76 ± 11	0.60
Cardiac index, liters/min/m^2	2.2 ± 0.6	2.1 ± 0.7	0.56
Pulmonary artery pressure, mm Hg			
Systolic	49 ± 15	51 ± 13	0.53
Diastolic	24 ± 8	27 ± 9	0.07
NYHA Functional Class, %			
I	0.0	0.0	0.70
II	0.6	0.0	
III	3.7	0.0	
IV	95.4	100	
Not available	0.3	0.0	
INTERMACS Profile Level, %			0.69
1	6	3	
2	36	26	
3	39	55	
4–7	19	16	
Medical history, %			
Smoker	52	45	0.46
Diabetic	35	32	0.85
Arrhythmia	73	58	0.09
Stroke/transient ischemic attack	10	16	0.35
Cancer	5	6	0.68
Significant alcohol use	6	0	0.40
Illicit drug use	3	6	0.28
Hypertension (requiring medication)	61	48	0.19
Valve repair or replacement	3	0	1.00
Blood urea nitrogen, mmol/liter	9 ± 5	8 ± 4	0.22
Lactate dehydrogenase, U/liter	318 ± 190	317 ± 175	0.96
Creatinine, mg/dl	1.3 ± 0.49	1.1 ± 0.36	0.02

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

[a]Data are stratified according to the occurrence of a pump thrombus event. Continuous data are presented as mean ± standard deviation and categoric data as the percentage.

[b]Significance testing performed using Fisher's exact test for categoric data and a two-sample t-test for quantitative data.

frequent. Depending on the severity and formation characteristics of the thrombus, an increasing trend and/or rapid rise in LVAD power consumption is observed. Figure 2C is a log file with thrombus resolution after successful treatment with tissue plasminogen activator (tPA).

The pump thrombus events occurred at an average of 353 ± 329 days after LVAD implantation, with a median time to thrombus event of 245 days (range, 14–1,293 days). The overall rate of pump thrombus in the entire cohort was 8.1%, or 0.08 EPPY. Pump thrombus requiring exchange occurred in 4.2%

patients or 0.04 EPPY. At 3, 6, and 12 months, the freedom from any pump thrombus event was 98%, 96%, and 92%, respectively, whereas the freedom from pump exchange for pump thrombus was 99%, 98%, and 95%, respectively (Figure 3).

There was no statistically significant difference in the mean TTR of INR in patients with thrombus compared with those without an event (40.5% ± 22.4 [median, 40.0%] vs 42.1% ± 26.2 [median, 44.0%], respectively). There was a trend (p = 0.09) toward a lower mean INR in patients at the time of a thrombus event (1.9; range, 0.9–3.4) compared with the overall mean INR

Table 2   Various HVAD Parameters[a]

Variable	No thrombus (n = 350)	Thrombus (n = 31)	p-value
Power, Watts			0.42
Mean ± SD	4.3 ± 0.9	4.2 ± 0.8	
Median (min–max)	4.2 (2.5–7.7)	4.3 (3.0–5.7)	
Flow, liters/min			0.89
Mean ± SD	5.1 ± 0.9	5.0 ± 0.8	
Median (min–max)	5.0 (2.8–8.7)	5.0 (4.0–7.7)	
Speed, rpm			0.24
Mean ± SD	2,744 ± 177	2,705 ± 189	
Median (min–max)	2,754 (2,240–3,322)	2,724 (2,300–3,100)	

SD, standard deviation.

[a]Parameters were averaged over the time on original device support in patients without thrombus events or up to 1 week before an event in those with thrombus.
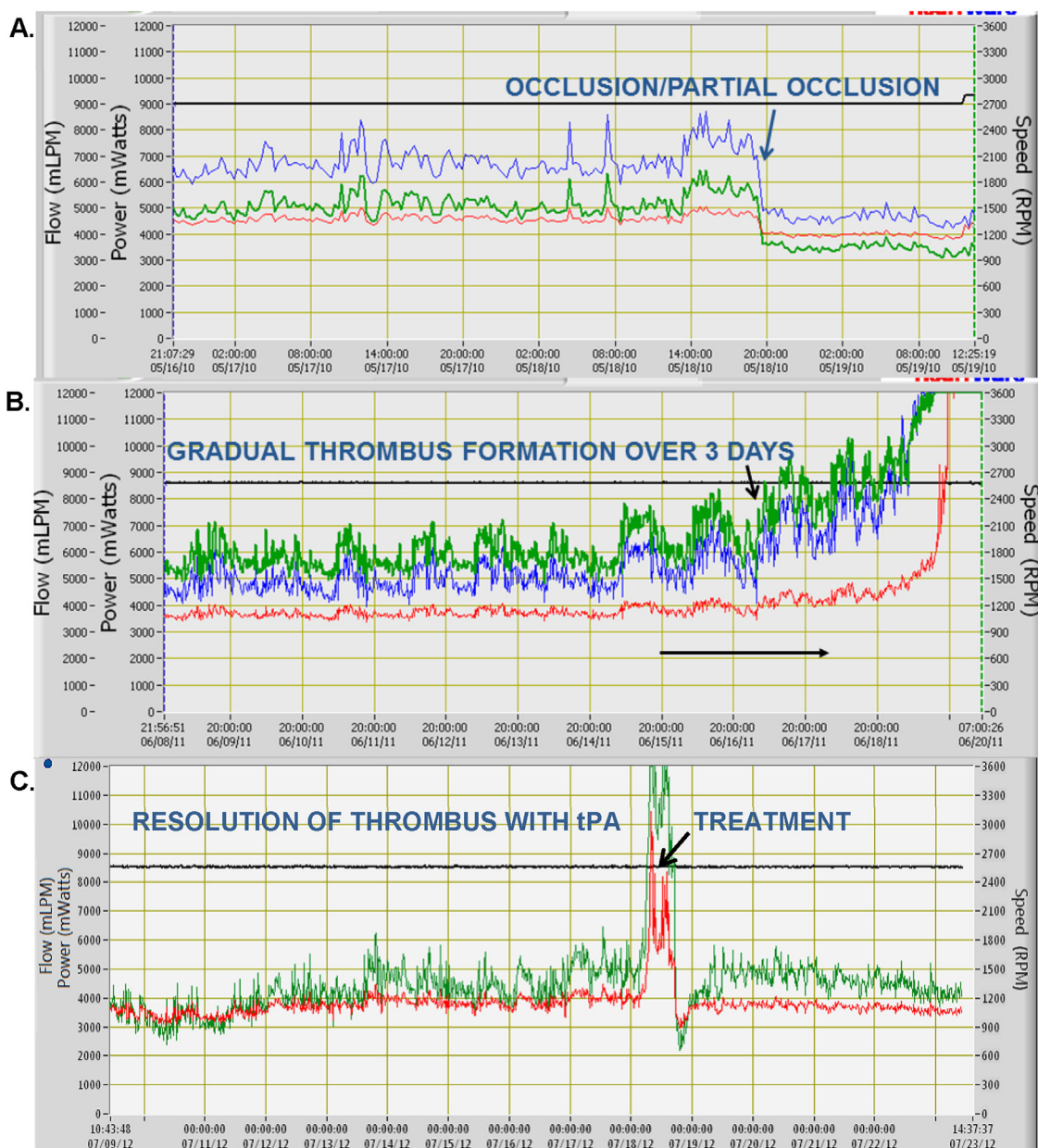
Figure 2   Log file analysis of pump thrombus. Representative log file tracings of power (red line), speed (black line), average controller flow (green line), and estimated flow at constant viscosity (blue line) as seen in (A) a partial or total acute occlusion, (B) the appearance or formation of thrombus over several days, and (C) a thrombus treated with thrombolytic therapy, showing resolution of the clot.
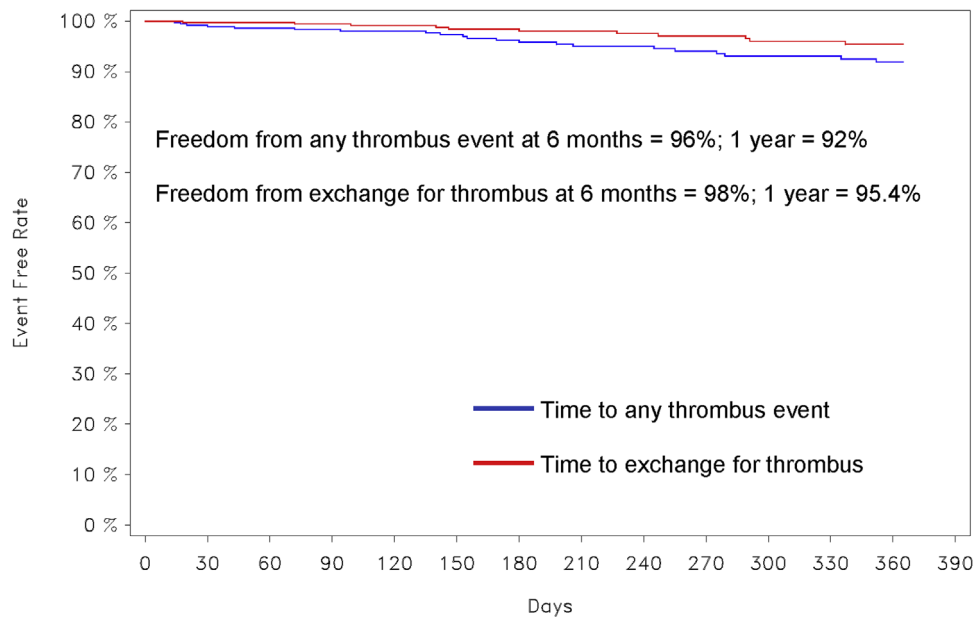
Figure 3   Kaplan-Meier analysis shows time to any thrombus event and time to left ventricular assist device exchange for pump thrombus.

for patients without a pump thrombus event (2.2; range, 0.9–4.2). Also, 58% of patients without thrombus were taking 325 mg aspirin at the time of discharge from the index hospitalization, compared with 52% of patients with a pump thrombus event (p = 0.57). In addition, ~3% of patients without a thrombus were not taking aspirin at discharge, whereas 13% of patients with a pump thrombus were not taking aspirin (p = 0.02).

Pump thrombus events by era

The baseline characteristics of the patients enrolled in the BTT cohort (August 2008–February 2010) did not significantly differ from those enrolled in the CAP cohort (April 2010–November 2012). Median time on HVAD support was similar in BTT (249 days; range, 6–1506 days) and CAP (275 days; range, 1–1043 days; p = 0.67); but as would be expected, median follow-up time was longer in BTT (1,107 days; range, 11–1,569 days) than CAP (491 days; range, 12–1,051 days; p < 0.0001). The incidence or prevalence of pump thrombus did not differ significantly between the 2 cohorts: pump thrombus occurred in 10% (14 of 140) of BTT patients and in 7% (17 of 242) of CAP patients (p = 0.33). The event rate was 0.08 EPPY in BTT and 0.08 EPPY in CAP (p = 0.98). However, pump exchange for thrombus differed between the 2 cohorts. This was performed in 7% (10 of 140) of BTT patients and in 2% (5 of 242) of CAP patients (p = 0.02). The corresponding event rate was 0.07 EPPY in BTT and 0.02 EPPY in CAP (p = 0.02).

Sintered pumps were introduced during the CAP trial in Spring 2011. Thus, the 110 patients with sintered pumps had a shorter median follow-up time than the 272 patients with non-sintered pumps, at 309 days (range, 12–679 days) vs 790 days (range 11–1569 days), respectively (p < 0.0001). The pump thrombus event rate was similar (0.08 EPPY) in these 2 groups. Given their shorter duration of follow-up, patients with sintered pumps had a numerically lower prevalence of pump thrombus (5.5%) than those with a non-sintered pump (9.2%), but this was not statistically significant (p = 0.30). Only one patient with a sintered

pump required a pump exchange for thrombus. This was performed in 0.9% of patients with sintered pumps and in 5.5% of patients with non-sintered pumps (p = 0.048). The corresponding event rate was 0.01 EPPY in sintered pumps and 0.05 EPPY in non-sintered pumps (p = 0.20).

Treatment and outcome of pump thrombus events

The management of pump thrombus is summarized in Figure 4 and Table 3. Most events (30 of 34) were treated with medical therapy first, which was successful in resolving the pump thrombus in 15 cases. Medical therapy failed in 15 patients, of whom 12 required pump exchange, 2 went on to emergent transplant, and 1 patient died. In all, 16 events required a pump exchange, for an incidence of 4.2% in the entire cohort, or 0.04 EPPY. Medical therapy consisted of heparin, glycoprotein (GP) 2b/3a antagonists (e.g., eptifibatide), and tPA, used individually or in combination. The tPA was infused at doses that varied according to site (total dose range, 15–100 mg) and was administered peripherally or centrally in the LV cavity. The tPA was successful in resolving the pump thrombus in 6 of 8 patients when administered peripherally and in 4 of 7 when administered centrally. However, the route of administration of tPA was not available in 4 patients, 2 of whom were successfully treated.

Five of the patients who received medical therapy for a pump thrombus died, 4 after a device exchange, and 1 after developing a hemorrhagic cerebrovascular accident (CVA) after treatment with triple therapy, consisting of tPA, heparin, and eptifibatide. Of the 8 patients who received triple therapy, 1 died, therapy failed in 4 and they required pump exchange, and the thrombus event successfully resolved in 3. When tPA was used alone or combined with heparin or eptifibatide (dual therapy), it successfully resolved the pump thrombus in 9 of 11 patients (82%). Eptifibatide alone or combined with heparin succeeded in 50% (3 of 6), whereas heparin alone was never successful (0 of 5), always requiring an exchange or a heart transplant. Among the 30 thrombus events that were
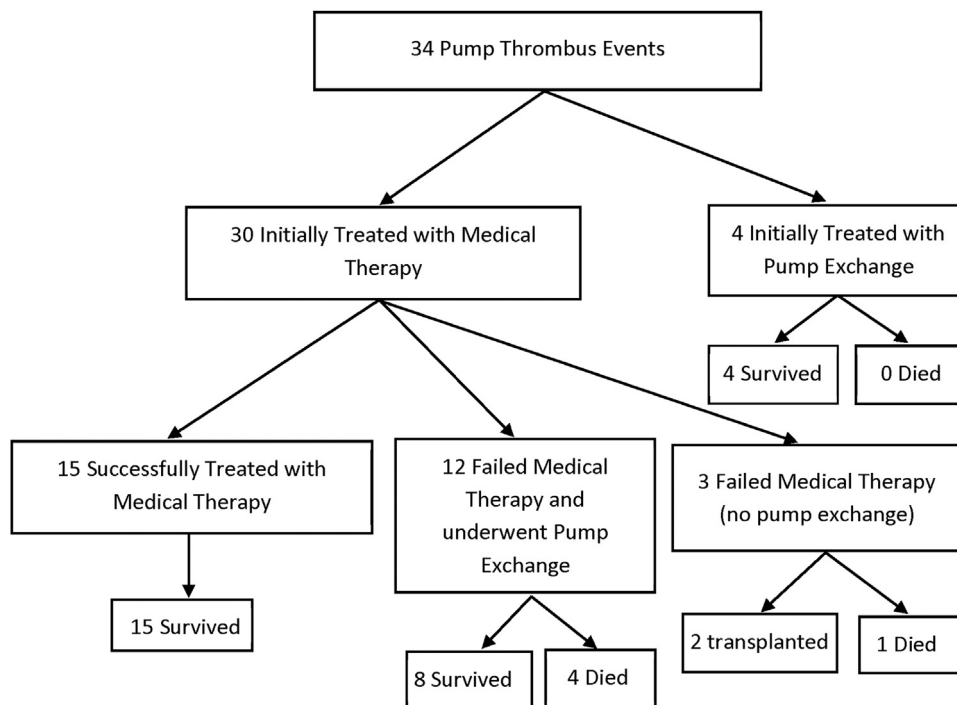
Figure 4 Flow diagram shows the outcome of the therapies used for the management of pump thrombosis. Outcomes are evaluated up to 1 month after administration of the therapy.

managed medically, there were 5 bleeding events, comprising 2 hemorrhagic CVAs, 2 gastrointestinal hemorrhages, and 1 implantable cardioverter defibrillator pocket bleed.

Three patients had a recurrent pump thrombus event after completing a course of medical therapy. One occurred in a 61-year-old Caucasian man who had a sintered pump and a history of a lower extremity thrombotic event. After the first pump thrombus, he was found to have lupus anti-coagulant and was maintained on aspirin and clopidogrel in addition to warfarin. He had a recurrent pump thrombus 6 months later and underwent a second course of medical therapy. He died of multisystem organ failure 2.5 months later.

Another recurrent pump thrombosis occurred in a 32-year-old Caucasian man who had a non-sintered pump. The second event occurred 37 days after the initial pump thrombus, while receiving 325 mg aspirin and with an INR of 2.4. The patient received a second course of medical therapy and has remained free of clinical pump thrombus for > 1 year.

The third case occurred in a 59-year-old Caucasian man who had a non-sintered pump. The recurrent pump thrombus occurred

just over 2 months after the initial event, while the patient was taking 81 mg aspirin and had an INR of 1.1. The patient underwent a successful pump exchange, but developed a hemorrhagic CVA 2 months later and died after 1 week.

Adverse events and survival in patients with pump thrombus

As summarized in Table 4, the incidence of bleeding, renal dysfunction, infections, right heart failure, or stroke did not significantly differ between the patients with and those without a pump thrombus. However, patients with a pump thrombus event more frequently experienced cardiac tamponade, ventricular arrhythmias, and arterial thromboembolism. These events mostly occurred before the thrombus event, with the following exceptions: 1 patient had a tamponade event that occurred > 30 days after the thrombus, 4 patients experienced ventricular arrhythmias ≤ 30 days after a pump thrombus, and 3 patients had 4 arterial thrombus

Table 3 Pump Thrombus Event Management and Disposition[a]

Treatment	Events No. (% total)	Success No. (% treated)	Exchange No. (% treated)	Transplant No. (% treated)
tPA	19 (56)[b]	12 (63)	6 (32)	0 (0)
GP 2b/3a inhibitor	6 (18)	3 (50)	2 (33)	1 (17)
Heparin	5 (15)	0 (0)	4 (80)	1 (20)
None	4 (12)	0 (0)	4 (100)	0 (0)
Total	34	15 (44)	16 (47)	2 (6)

GP 2b/3a, glycoprotein 2b/3a antagonist; tPA, tissue plasminogen activator.
[a]The number of events treated with the various therapeutic strategies and their clinical outcome. Data are presented hierarchically—higher-level treatment could have been alone or in combination with a lower level treatment.
[b]One patient treated medically died during the course of treatment.

Table 4   Major Adverse Events in Patients With Versus Those Without Thrombus Events (N = 382)[a]

Event	No thrombus (n = 351) (PY = 371.5)			With thrombus (n = 31) (PY = 35.1)			p-value comparison	
	Patients affected No. (%)	Events No.	Event rate PPY	Patients affected No. (%)	Events No.	Event rate PPY	Proportion of patients	Event rate
Bleeding								
Requiring reoperation	50 (14.2)	55	0.15	7 (22.6)	9	0.26	0.20	0.15
Requiring transfusion[b]	50 (14.2)	52	0.14	4 (12.9)	7	0.2	1.0	0.40
Gastrointestinal	55 (15.7)	99	0.27	4 (12.9)	9	0.26	1.0	0.92
Cardiac tamponade	14 (4.0)	14	0.04	5 (16.1)	5	0.14	0.01	0.02
Infections								
Driveline exit site	70 (19.9)	94	0.25	5 (16.1)	8	0.23	0.81	0.77
Sepsis	65 (18.5)	84	0.23	7 (22.6)	8	0.23	0.63	0.98
Arrhythmia								
Ventricular	65 (18.5)	87	0.23	12 (38.7)	14	0.40	0.02	0.08
Supraventricular	75 (21.4)	94	0.25	10 (32.3)	12	0.34	0.18	0.38
Renal dysfunction	36 (10.3)	42	0.11	3 (9.7)	4	0.11	1.0	0.99
Acute	36 (10.3)	42	0.11	2 (6.5)	3	0.09	0.75	0.63
Hepatic dysfunction	18 (5.1)	18	0.05	2 (6.5)	2	0.06	0.67	0.83
Respiratory dysfunction	79 (22.5)	102	0.27	9 (29.0)	14	0.40	0.38	0.25
Hemolysis	9 (2.6)	11	0.03	12 (38.7)	13	0.37	<0.0001	<0.0001
Neurologic events[c]								
Ischemic CVA	17 (4.8)	20	0.05	3 (9.7)	4	0.11	0.21	0.21
Hemorrhagic CVA	27 (7.7)	29	0.08	5 (16.1)	5	0.14	0.16	0.25
TIA (<24 hours)	21 (6.0)	25	0.07	2 (6.5)	4	0.11	1.0	0.36
Right heart failure	121 (34.5)	139	0.37	8 (25.8)	10	0.28	0.43	0.45
Inotropic therapy	108 (30.8)	122	0.33	6 (19.4)	7	0.20	0.22	0.20
RVAD	13 (3.7)	13	0.03	2 (6.5)	2	0.06	0.35	0.55
Thromboembolism								
Venous	17 (4.8)	17	0.05	4 (12.9)	4	0.11	0.08	0.14
Arterial[d]	6 (1.7)	7	0.02	3 (9.7)	4	0.11	0.03	0.01

CVA, cerebrovascular accident; RVAD, right ventricular assist device; TIA, transient ischemic attack.

[a]All adverse events were adjudicated by the Clinical Events Committee and include events censored at the time of transplant, explant for recovery, or device exchange. Fisher's exact test was used for proportions and Poisson regression for event rate.
[b]Include those requiring > 4 U within 7 days.
[c]Procedural ischemic CVAs occurring within 2 days after implant have been excluded.
[d]Defined by Interagency Registry for Mechanically Assisted Circulatory Support as an acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following: (1) standard clinical and laboratory testing, (2) operative findings, (3) autopsy findings.

events, of which 50% occurred ≤ 30 days after a thrombus event. Hemolysis occurred with more frequency in patients who experienced a pump thrombus event. Patients with pump thrombus did not have more VAD-related infection events.

Kaplan-Meier analyses showed no statistically significant difference in survival at 1 year between the 351 patients without pump thrombus events vs the 31 patients with thrombus events (85.4% vs 69.4%, p = 0.21; Figure 5A). However, the number of events was low, making valid statistical comparisons difficult. Among patients with pump thrombus, there was no statistically significant difference in survival at 6 months between those who were treated with medical therapy alone vs those who underwent a pump exchange for a pump thrombus (91.7% vs 68.8%, p = 0.27; Figure 5B).

Pathology

Most hearts explanted for transplantation were inspected by an independent pathologist. Tissue growth was observed along the entire length of the inflow cannula in patients with non-sintered pumps (Figure 1C) but did not extend beyond the area of sintering in patients with sintered pumps (Figure 1D), supporting the beneficial effect of sintering.

Multivariable analysis for predictors of pump thrombus events

Multivariable analysis included all baseline demographic data and clinically significant adverse events. The analysis identified 4 independent risk factors for pump thrombosis, all with an odds ratio > 2: mean arterial blood pressure (MAP) > 90 mm Hg, antiplatelet regimen with ≤ 81 mg aspirin, INR ≤ 2.0, and a baseline INTERMACS Patient Profile level ≥ 3 at implant (Figure 6). The measured significant covariates (MAP, aspirin, and INR) involve averages for patients without thrombus and event-specific values for those with thrombus. Borderline covariates that did not achieve statistical significance included non-sintered pumps, overall average speed < 2,750 rpm, arterial thromboembolism ≤ 7 days, and prior history of stroke.

Patients in INTERMACS class ≥ 3 had a similar blood pressure and a similar mean INR and TTR to those in INTERMACS class
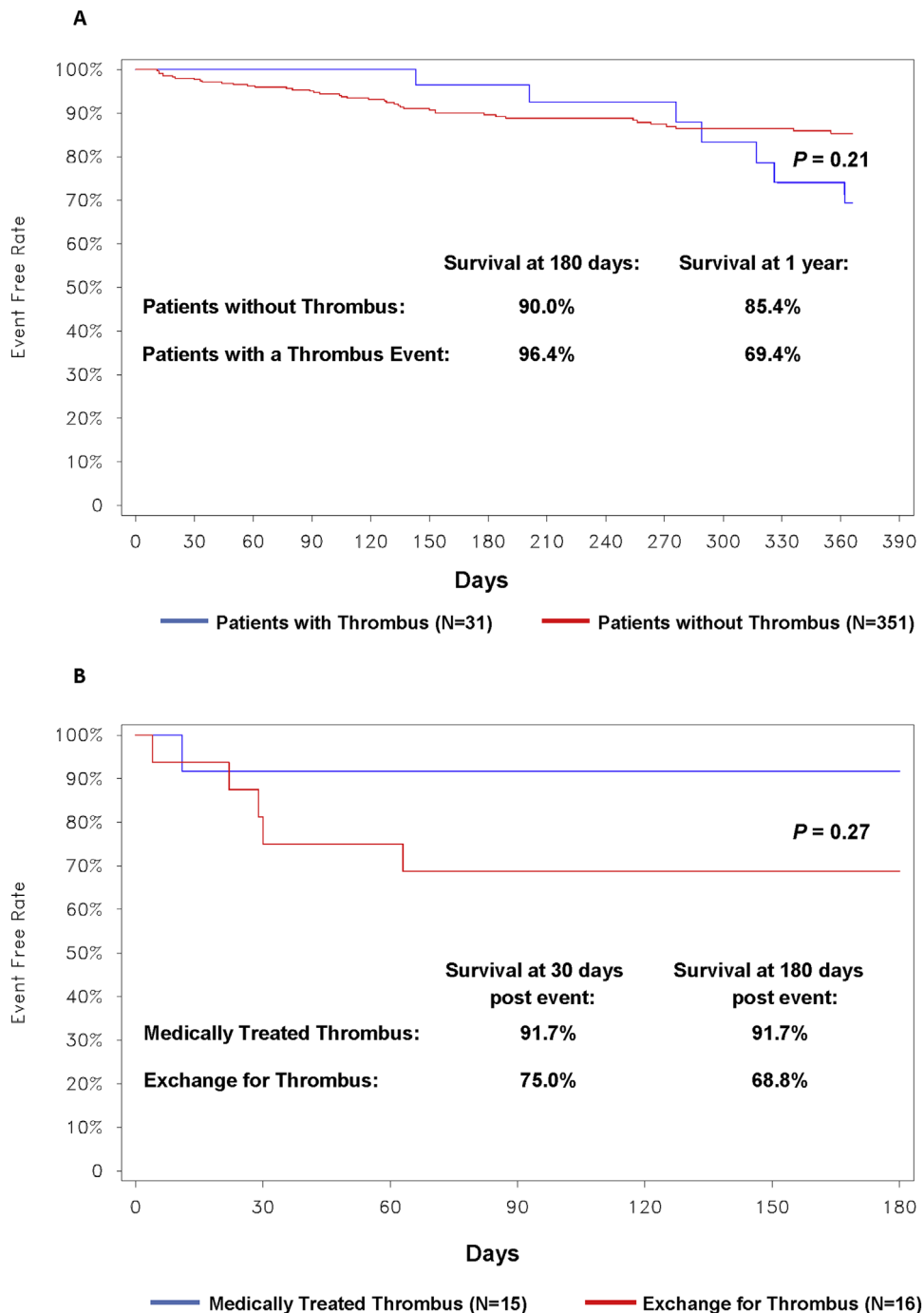
A

B

Figure 5 (A) Kaplan-Meier curve shows survival for patients with and without thrombus (censored at exchange, transplant, or recovery). A log-rank test was performed for significance. (B) Kaplan-Meier curve shows time to death after treatment for a pump thrombus event comparing medical therapy alone vs pump exchange. Time 0 was at a thrombus event. Patients were censored at transplant. A log-rank test was performed for significance.

1 to 2. However, they had less usage of aspirin at a dose of 325 mg (53% vs 65%, $p = 0.02$). The time on LVAD support did not significantly differ ($p = 0.14$) between those with INTERMACS class ≥ 3 (median, 308 days; range, 6–1,506 days) vs INTERMACS class 1 and 2 (median, 250 days; range, 1–1,506 days).

Discussion

The use of LVADs in patients with advanced heart failure is rapidly increasing. The occurrence of a pump thrombus is a feared complication due to the morbidity associated with its treatment and

the attendant costs. Understanding the predisposing risk factors for a pump thrombosis is critical to devising preventive strategies.

In this study, we examined the HVAD pump thrombus events that were observed in the BTT and CAP clinical trial. A pump thrombus event for this analysis was defined as any event occurring ≥ 72 hours after implant, exhibiting high power and flow (pseudo-flow; flow that is outside the expected coupling of power to flow) with rising LDH (>2.0 times the upper limit of normal) or pfHgb > 40 mg/dl, or visualization of organized fibrin in the pump housing or inflow. Over the course of the study period, pump thrombus requiring exchange occurred in 4% of patients at a rate of
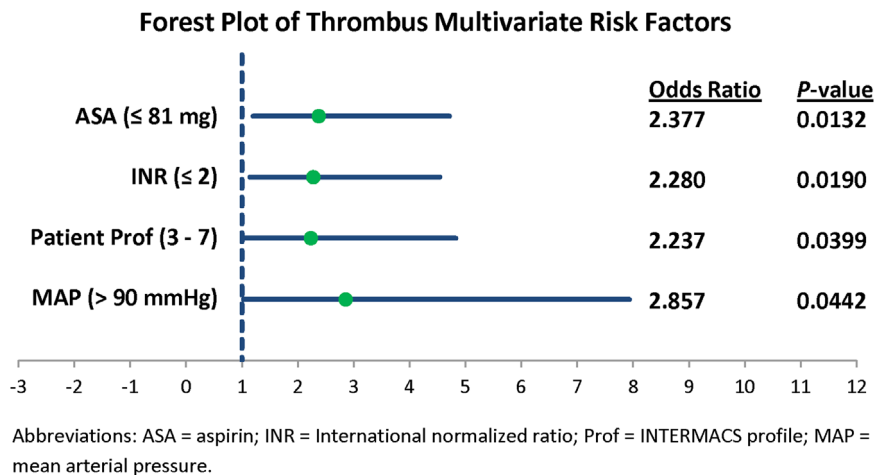
Forest Plot of Thrombus Multivariate Risk Factors

Figure 6   Multivariate predictors of pump thrombus. A Forest plot illustrates the odds ratios and relative influence of the top risk factors emerging from the multivariate analysis. The odds ratio is indicated by the dot, and the lines represent 95% confidence intervals. All thrombus events are included in this analysis. ASA, acetylsalicylic acid; INR, international normalized ratio; MAP, mean arterial pressure; Patient Prof, Interagency Registry for Mechanically Assisted Circulatory Support profile.

0.04 EPPY, and the overall incidence and prevalence of suspected pump thrombus were 0.08 EPPY and 8.1%, respectively. Previous studies with axial-flow LVADs evaluating pump thrombosis focused on pump thrombus requiring surgical exchange and reported exchange rates of 0.014 to 0.04.[3,10–13]

Recently, Kirklin et al[14] analyzed the incidence of pump thrombosis in the HeartMate II LVAD (Thoratec, Pleasanton, CA) in the INTERMCAS database. They found 382 cases of device exchange or death due to probable or definite pump thrombosis among 6,910 patients, yielding an overall prevalence of 5.5%. Survival free of this event was 97% at 6 months, 95% at 1 year, and 92% at 2 years.

Starling et al[15] recently reported the experience of pump thrombosis in the HeartMate II LVAD among 3 high-volume centers. They found 108 cases of confirmed (n = 72) or suspected (n = 36) pump thromboses among 895 LVADs (overall prevalence of 12%) implanted in 837 patients, with an estimated occurrence of 7.1% at 6 months, 11.3% at 12 months, and 18.3% at 24 months. Similar to our study, Starling et al[15] did not restrict their analyses only to patients who underwent pump exchange but also included patients who were treated medically for a suspected pump thrombus. Importantly, unlike Starling et al,[15] we did not observe any change in the incidence of pump thrombosis during the trial. The event rate remained constant at 0.08 EPPY in the BTT and in the CAP cohorts and at 0.08 EPPY in patients with non-sintered and those with sintered pumps.

However, there are important differences between axial-flow and centrifugal-flow pumps and the software algorithms that monitor and depict pump performance. Shah et al[16] recently identified differences in LDH levels in patients with suspected pump thrombus with centrifugal-flow vs axial-flow pumps.[16] Also, with the HVAD, large visible clots within the housing are very rare on pump inspection (internal HeartWare data on file).

Of the 31 patients who experienced 34 pump thrombus events, 5 patients died ≤ 1 month of presentation. The 1-year survival for these patients (Figure 5A) was nominally lower than those who did not have a thrombus event (69.4% vs 85.4%). This difference did not achieve statistical significance; however, this may be partly related to the sample size and the low number of events in this study. Thus, the difference in survival may still be clinically relevant. Indeed, recent studies with the HeartMate II device showed that pump thrombosis was associated with lower survival.[14,15] Additional analyses in a larger cohort of patients who were implanted with an HVAD are needed to better characterize the effect of pump thrombus on survival in these patients.

The treatment of LVAD thrombus has traditionally involved surgically exchanging the pump.[11,17] A growing number of mostly single-center studies have described medical management of pump thrombosis.[15,18–20] The management of pump thrombosis in the BTT+CAP trial was left up to the discretion of the individual centers. Interestingly, the rate of pump exchange for pump thrombus was significantly lower in the CAP cohort than in the BTT cohort. Because the overall pump thrombus event rate was similar between the 2 groups, we infer that the lower rate of pump exchange reflects a change in practice pattern involving a greater acceptance of medical therapy as the first line of intervention for pump thrombosis.

In 34 patients with thrombus, 4 underwent pump exchange immediately, whereas medical therapy was attempted first in 30 patients. Medical therapy alone was successful in resolving the pump thrombus in 15 (50%), but when it failed, patients required a pump exchange or urgent transplantation. Medical therapy used for the management of pump thrombosis was not standardized and consisted of varying combinations of tPA, GP 2b/3a antagonist, and heparin. tPA was successful in treating the pump thrombus in 12 of 19 patients (63%), whereas heparin when used alone failed to resolve the thrombus in the 5 patients in whom it was attempted.

The small number of events and the heterogeneity of therapies used do not allow us to make strong inferences about preferred strategies for the management of pump thrombosis. Nonetheless, our findings provide further support for a role of medical therapy in managing pump thrombosis. Additional studies are needed (1) to better characterize the patients with pump thrombus who would benefit from a trial of medical therapy first vs those who should undergo primary pump exchange and (2) to identify the preferred regimen, dosage, and duration of medications that provide the optimal balance between efficacy and safety.

In this study, we compared sintered vs non-sintered surfaces using the same device in the same patient population. Sintering is the process by which small titanium beads are mechanically affixed to the titanium surface of the inflow cannula. These beads create a matrix into which tissue can be incorporated. The incorporation of connective tissue into this matrix is preferred over the alternative of pannus tissue that surrounds but does not adhere to the pump surface and may continue to grow upwards to the orifice of the inflow cannula. The addition of sintering to the inflow cannula of the HVAD appears to have succeeded in limiting the growth of tissue along the shaft of the cannula so it does not extend beyond the sintered area (Figure 1) and is more firmly adherent to it.

The observed pump thrombus event rate did not differ significantly between the patients who received a sintered HVAD and those who received the original non-sintered pump. However, it is worth noting that the former group had a significantly shorter total exposure time (76.6 vs. 330.1 patient-years) and that there was a possible trend for sintering to achieve protection from pump thrombus ($p = 0.11$ by univariate analysis). Thus, it is possible that a longer observation period is required to better evaluate the effect of sintering on the occurrence of late pump thrombus events.

Serum creatinine was modestly lower in those with vs. those without a pump thrombus. We suspect that this is a spurious association due to the large number of baseline comparisons made without adjustment for multiple testing.

The multivariable analysis identified several variables that are independent predictors of pump thrombosis. Importantly, 3 of these risk factors are modifiable, namely, aspirin dose of ≤ 81 mg, INR ≤ 2, and a mean arterial pressure of > 90 mm Hg. Current guidelines for the management of HVAD recommend that aspirin be used in doses ≥ 162 mg daily, warfarin be administered with a target INR between 2.0 and 3.0, and blood pressure be maintained at < 90 mm Hg. Whereas the relationship between pump thrombosis and anti-platelet or anti-coagulant therapy is intuitive, the association of pump thrombosis with blood pressure control is intriguing. Further studies are needed to elucidate the pathophysiology that underlies this association. However, careful blood pressure management is included in the recent International Society for Heart and Lung Transplantation recommendations for all patients with advanced heart failure on mechanical circulatory support.[21]

The identification of the variable of INTERMACS class 3 to 7 as having a higher risk for pump thrombus is also surprising. It is possible that this may be related to aspirin therapy, because a lower proportion of patients who were INTERMACS class 3 to 7 were discharged from the hospital on 325 mg aspirin compared with those who were INTERMACS 1 and 2 (53% vs. 65%).

The major limitation of this study is the post hoc nature of the analysis, because the clinical trial was not powered to evaluate pump thrombus events. The small number of patients with thrombus events makes interpretation of statistical comparisons difficult. Also, the follow-up time of the sintered group was shorter due to the later introduction of this technology. A longer observation period and more patient exposure time are needed to better evaluate the effects of sintering on pump thrombosis. Fortunately, this information will be forthcoming because a post-approval study is currently being implemented at all sites that enrolled patients in the ADVANCE and CAP trial.

Although the BTT clinical trial protocol collected LDH values at pre-specified time points, it did not mandate the measurement of LDH at time of presentation with pump thrombosis or the serial measurements of LDH during therapy for pump thrombosis. Thus, 11 patients with pump thrombosis did not have LDH values near the time of the event.

These analyses excluded events occurring in the first 72 hours after pump implantation. Because these early perioperative events are so strongly associated with technical surgical issues, their inclusion in these analyses would have limited our ability to identify risk factors for subsequent events.

In conclusion, pump thrombus with the HVAD occurred at a rate of 0.08 EPPY, and exchange for pump thrombus occurred at a rate of 0.04 EPPY. Patients were successfully managed medically in 50% of pump thrombus cases, with good outcomes. Significant risk factors for pump thrombosis include sub-optimal anti-coagulation and anti-platelet therapy as well as elevated blood pressure. This suggests that pump thrombus event rates could be reduced through careful adherence to patient management guidelines.

Disclosure statement

Supplementary material

Supplementary material is available online at jhltonline.org.

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