ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

FEATURED PAPERS

Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump—the MAGENTUM 1 study

Ivan Netuka, MD, PhD,[a] Peter Ivák, MD, PhD,[a,b] Zuzana Tučanová, MD,[a] Stanislav Gregor, PharmD,[c] Ondrej Szárszoi, MD, PhD,[a] Poornima Sood, MD,[d] Daniel Crandall, PhD,[d] Jessica Rimsans, PharmD, BCPS,[e] Jean Marie Connors, MD,[f] and Mandeep R. Mehra, MD[g]

From the [a]Department of Cardiovascular Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [b]Third Faculty of Medicine, Charles University, Prague, Czech Republic; [c]Department of Pharmacy, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [d]Global Clinical, Heart Failure, Abbott, Burlington, Massachusetts, USA; [e]Department of Pharmacy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [f]Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; and the [g]Heart and Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

KEYWORDS:
HeartMate 3;
INR management;
left ventricular assist device;
LVAD;
reduced intensity anti-coagulation;
Rosendaal method;
TTR;
time in therapeutic range

BACKGROUND: The HeartMate 3 left ventricular assist system is engineered to avoid pump thrombosis, yet bleeding complications persist. We investigated the safety of low-intensity anti-coagulation in patients with the HeartMate 3.

METHODS: The Minimal AnticoaGulation EvaluatioN To aUgment heMocompatibility (MAGENTUM 1) pilot study is a prospective, single-arm study of low-intensity warfarin anti-coagulation in patients implanted with the HeartMate 3 pump. After standard warfarin anti-coagulation (international normalized ratio [INR] 2.0 to 3.0) and aspirin for 6 weeks post-implant, patients were transitioned to a lower INR target range of 1.5 to 1.9. The primary end-point was a composite of survival free of pump thrombosis, disabling stroke (modified Rankin score [MRS] >3), or major bleeding (excluding peri-operative bleeding) with at least 6-month post-implant follow-up. Time in therapeutic range (TTR) was measured to assess anti-coagulation target efficacy using the Rosendaal method. A safety algorithm to monitor for signs of pump thrombosis was developed and implemented.

RESULTS: We enrolled 15 patients (mean age 57.3 $\pm$ 13.3 years), 13 men with advanced heart failure (67% with INTERMACS Profiles 2 or 3), irrespective of therapeutic goal of bridge-to-transplant or destination therapy. The primary end-point was met in 14 of 15 (93 $\pm$ 6%) patients; 1 patient developed recurrent gastrointestinal bleeding. The TTR during the reduced anti-coagulation phase (6 weeks to 6 months) was 75.3 $\pm$ 8.6%. No thrombotic events occurred.

CONCLUSIONS: This pilot study suggests low-intensity anti-coagulation targeting an INR between 1.5 and 1.9 is achievable and safe with the HeartMate 3 cardiac pump in the short-term phase, 6-months post-implant. A large-scale trial is now warranted.

Funded by Abbott and the Ministry of Health, Czech Republic (ClinicalTrials.gov NCT03078374).

Reprint requests: Ivan Netuka, MD, PhD, Department of Cardiovascular Surgery, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, Prague 4, Czech Republic. Telephone: +420-261365015. Fax: +420-261365015.

E-mail address: ivan.netuka@ikem.cz

See Related Editorial, page 568

https://doi.org/10.1016/j.healun.2018.03.002

J Heart Lung Transplant 2018;37:579–586

The use of anti-platelet and anti-thrombotic therapy is a mainstay in left ventricular assist systems (LVAS) to mitigate complications such as pump thrombosis or systemic thromboembolism.[1–3] Typically, an anti-platelet agent, such as acetylsalicylic acid, and a vitamin K antagonist are used in therapeutic doses with the international normalized ratio (INR) targeted to 2.0 to 3.0. This approach, although effective, tilts the adverse effect profile toward surgical and non-surgical bleeding-related complications. As elderly patients are implanted with such devices for destination therapy with increasing frequency, bleeding complications have risen, largely due to coexisting morbidity.[4] Any attempt at reduction in anti-coagulation intensity is usually met with clinical concern for an increased risk of pump thrombosis and stroke with current devices, although this has not been systematically investigated.

The HeartMate 3 (HM3) LVAS (Abbott, Chicago, IL) is a continuous centrifugal–flow device with a fully magnetically levitated rotor, engineered with wide blood-flow paths and intrinsic pulsatility facilitated by speed changes of the rotor at fixed programmed intervals. In a series of experiences from Europe and the United States, this LVAS has shown absence of pump thrombosis (de novo; occurring within the pump) in the short term at 6 months.[2,3] However, these benefits have been observed in the setting of therapeutic use of aspirin and standard vitamin K antagonist anti-coagulation targeting an INR of 2.0 to 3.0. Encouraged by this early experience, we hypothesized that a lower intensity anti-coagulation range than that used currently may be employed with the HM3 LVAS, and this may reduce bleeding-related adverse events, without increasing thromboembolic complications. Thus, the Minimal Anti-coaGulation EvaluatioN To aUgment heMocompatibility (MAGENTUM 1) study was designed as a pilot trial to study feasibility and safety of a strategy to reduce anti-coagulation goals (INR 1.5 to 1.9) in stable patients supported with the HM3 LVAS, with closely monitored clinical surveillance and a structured anti-coagulation management protocol.

Methods

Study design

MAGENTUM 1 is a prospective, single-center, single-arm trial to evaluate safety and feasibility of a low-intensity anti-coagulation regimen in patients implanted with the HM3 LVAS. Low-intensity anti-coagulation was defined as a target INR of 1.5 to 1.9 (reduced from the standard target of 2.0 to 3.0 for HM3) starting at 6 weeks post-implant. The primary end-point of the study was survival free of pump thrombosis, disabling stroke (modified Rankin score [MRS] >3), and major bleeding with at least 6 months of post-implant follow-up, measured during the low-intensity anti-coagulation phase. All adverse events, principally those in the hemocompatibility (thrombosis and bleeding) domain, were collected as secondary end-points. Adequacy of anti-coagulation during the low-intensity phase was ascertained by calculating the time in therapeutic range (TTR) using the Rosendaal method. The trial is registered on ClinicalTrials.gov number NCT03078374.

Patients receiving the HM3 LVAS, irrespective of intended goal of therapy (either bridge to transplantation or destination therapy), were enrolled. The institutional ethics committee approved the protocol for a 6-month follow-up. Once patients reached the 6-month pre-specified goal of follow-up, the steering committee extended the follow-up to 12 months, with a conditional extension within the cohort for the entire duration of support on the HM3 (institutional ethics committee approval was also obtained). This strategy facilitated a safety measure in case futility of the approach was demonstrated during the initial phase of low-intensity anti-coagulation.

The trial was conducted at the Institute for Clinical and Experimental Medicine (IKEM), Prague, after design input from collaborators at Brigham and Women's Hospital/Harvard Medical School and Abbott. All adverse events were reviewed by the steering committee (IKEM and Brigham and Women's Hospital/Harvard Medical School) of the trial during weekly review of the trial. Data were collected and maintained by the study team at IKEM; the Brigham and Women's team reviewed and analyzed the data to calculate anti-coagulation efficacy, per protocol. The authors had access to the data and vouch for the completeness and accuracy of the data and the analyses.

Study conduct

Consecutive patients surgically implanted with the HM3 were managed based on institutional standard-of-care procedures and screened for study enrollment. Individuals who met study criteria and provided informed consent were enrolled. The reduced anti-coagulation regimen was commenced 6 weeks post-implant (on post-operative day [POD] 43). For details see the CONSORT diagram (Figure 1).

Study enrollment

The observation period of 6-week post-HM3 implantation was chosen to ensure clinical stability with anticipated discharge to the ambulatory setting. In addition, anti-coagulation management compliance was evaluated to ensure that patients could adhere to the rigorous follow-up, as judged by the principal investigator.

Exclusion criteria were a pre-implant history of major thrombotic event (e.g., deep vein thrombosis, pulmonary embolism); presence of any artificial valve prosthesis, except biological aortic valve; persistent atrial fibrillation or atrial flutter not amenable to left atrial appendage resection/exclusion; and hemodynamically significant or symptomatic carotid artery stenosis. All patients were tested before enrollment for such major hypercoagulable disorders by assessing Factor V Leiden, Prothrombin G20210A, anti-phospholipid syndrome, and lupus anti-

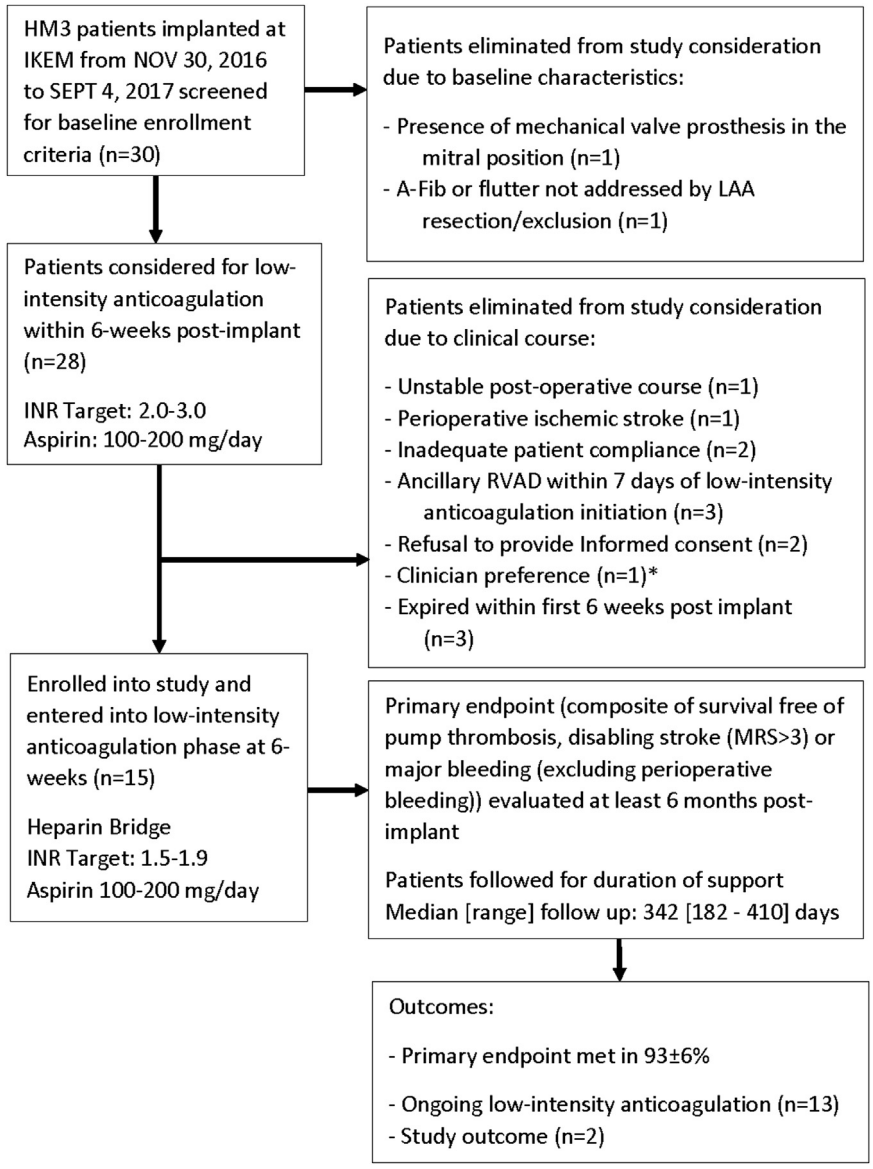

Figure 1 Study CONSORT diagram. *One BTT not enrolled due to clinician preference.

coagulant. Of note, presence of known hypercoagulable disorder did not affect enrollment nor the therapeutic strategy (unless a previous thromboembolic event history was identified).

Anti-coagulation management

Post-implant, all patients were bridged with unfractionated heparin until target anti-coagulation with warfarin was reached. Based on the standard anti-thrombotic regimen, all patients were maintained with a target INR of 2.0 to 3.0 for the first 6 weeks. Each patient received anti-platelet therapy (acetylsalicylic acid 100 to 200 mg) beginning on POD 3. If INR dropped below the therapeutic range, low-molecular-weight heparin was used until therapeutic range was restored.

Standardized warfarin management was based on a protocol established at Brigham and Women's Hospital/Harvard Medical School (refer to sections S1 to S3 in Supplementary Material available online at www.jhltonline.org). A dedicated inter-institu tional expert team, which included the study site's clinical pharmacist responsible for anti-coagulant dosing, was established to provide protocol-based INR management. The TTR was calculated using the Rosendaal method[5] as a measure of the efficacy of this anti-coagulation management strategy. INR testing was performed using venipuncture samples in a certified laboratory facility at least once per week throughout follow-up. Home INR point-of-care testing was not allowed in this study.

Safety measures

A safety algorithm to detect and manage pump thrombosis based on the patient's individual lactate dehydrogenase (LDH) profile and device log files analysis was developed and implemented as depicted in section S4 (refer to Supplementary Material online).

Adverse event definitions

Standard Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions (version 3.0, www.intermacs.org) for adverse events were utilized. Pump thrombosis and stroke events were subject to immediate reporting and adjudication by the steering committee to determine safety of continuation of the study.

Statistical analysis

Categorical data are presented as both number and percent (%), whereas continuous variables are presented as mean ± standard deviation (SD). Time in therapeutic range was calculated using the Rosendaal interpolation method, presented as a percentage of days within range for each patient and as mean ± standard deviation (SD) for individual patients. The center TTR was calculated as the TTR for all values. TTR was calculated in the early 6-week post-implant phase for the target range 2.0 to 3.0, and then during the low-intensity anti-coagulation period. We excluded INRs from the TTR calculation during initial heparin bridging and during transition to the lower INR target per convention to allow clear distinction and separation of the switch in target INR ranges.[6]

The second INR measurement that was within the INR range after discontinuing heparin and after transitioning to the lower target range were used as the starting point for TTR calculations for the different INR target ranges. No other INR values were excluded from the individual or center TTR calculations, including INR values when patients required outpatient low-molecular-weight heparin (LMWH) bridging for sub-therapeutic INR. Uncensored TTR results are also calculated and reported in Table S5 (refer to Supplementary Material online). Actuarial analysis was conducted using the Kaplan–Meier plot estimate method to evaluate clinical outcomes after reduction in anti-coagulation. All outcomes and adverse events were evaluated through at least 6 months post-implant or last available follow-up.

Results

Patients' characteristics

Fifteen (n = 15) patients were implanted between November 30, 2016 and September 4, 2017, which included 13 men, all Caucasian, with a mean age of 57.3 ± 13.3 (range 18 to 72) years. Patients were distributed equally among bridge to transplantation, bridge to candidacy, and destination therapy (5 patients each); had INTERMACS Profiles of 2 or 3 (67%); and a mean cardiac index 1.6 ± 0.4 liters/min/m^2. Heterozygous Factor V Leiden mutation was found in 1 patient without a history of thromboembolic events. Patients were implanted via the sternotomy approach in 12 of 15 (80%) cases and via left thoracotomy in 3 of 15 (20%) cases. Left atrial appendage exclusion was performed in 5 patients (33%) using the Atriclip device (Atricure, Mason, OH). Detailed baseline characteristics and pre-operative risk factors are summarized in Table 1. All patients provided informed consent and completed a minimum of 6 months of post-implant follow-up.

Table 1 Demographics and Baseline Characteristics

Age [median (range)], years	61 (18 to 72)
Male sex	13 (87)
BMI (kg/m^2)	26.6 ± 2.7
Ischemic etiology	8 (53)
Indication	
Bridge to transplant	5 (33)
Bridge to candidacy	5 (33)
Destination therapy	5 (33)
INTERMACS profile	
Profile 2	3 (20)
Profile 3	7 (47)
Profile 4	3 (20)
Profile 5	2 (13)
Cardiac index (liters/min/m^2)	1.6 ± 0.4
LVEF (%)	22 ± 4
Atrial fibrillation	5 (33)
TIA or stroke	2 (13)
Pre-existing aortic bioprosthesis	1 (7)
Prior sternotomy	3 (20)

Values expressed as number (%) or mean ± standard deviation, unless otherwise stated. BMI, body mass index; INTERMACS, Inter-agency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular assist device; TIA, transient ischemic attack.

Trial experience

The median primary hospitalization was 29 (range 11 to 62) days. Rehospitalizations, for any reason, occurred in 7 of the 15 (47%) patients for a median of 20 (range 6 to 54) days within the first 6 months of follow-up. The median follow-up duration for all patients was 342 (range 182 to 410) days. Patients spent a median of 133 (range 83 to 162) days out of the hospital within the first 6 months post-implant. For additional details see Table S6 (refer to Supplementary Material online).

Bridging for a sub-therapeutic INR was performed on 14 of 15 (93%) patients within the low-intensity anti-coagulation phase of the trial. Further details regarding LMWH bridging are presented in Table 2. Supra-therapeutic INR readings were found in all patients and accounted for 130 of the 930 (14%) INR readings.

Two patients had high baseline LDH: 1 patient (M1-04), with a baseline LDH 707 U/liter, had a partially dehisced mitral valvuloplasty ring resulting in hemolysis, and the second patient (M1-08), with an LDH 701 U/liter, had a confirmed history of Danon disease, which results in elevated LDH. LDH profiles excluding these 2 outliers are shown in Figure S7 (refer to Supplementary Material online).

The primary end-point of survival free of pump thrombosis, disabling stroke, and major bleeding was reached in 93 ± 6% of the patients (Figure 2A). No patients died, underwent transplant, or were explanted due to myocardial recovery within 6 months of implant. No (0%) neurologic complications (transient ischemic attack, seizure, or disabling stroke) were observed within 6 months of implant. Both hemocompatibility-related[7] and overall adverse events are presented in Table 3.

Hemocompatibility-related adverse events

No (0%) episodes of clinically relevant hemolysis were noted. In 1 patient (M1-09), an episode of suspected gastrointestinal bleeding with a drop in hemoglobin was encountered on POD 119 with a recurrent event on POD 210. In the first event, the patient presented with anemia (hemoglobin 4.9 g/dl) and an elevated INR of 3.34. The patient was transfused with 3 units of packed red blood

Table 2 Details of Anticoagulation Management: TTR and Bridging for Low INR

				INR Range: 1.5 – 1.9		
				6 weeks - 6 months		Bridging with LMWH for Low INR
Magentum ID	Sex	Age	Indication	TTR	% Time Above 1.8	Instances of Bridging (total days)
M1-01	M	60	BTC	56.4%	58.7%	2 (11)
M1-02	M	60	BTT	80.5%	18.5%	3 (4)
M1-03	M	50	BTT	80.6%	8.8%	4 (15)
M1-04	M	61	BTC	86.5%	26.9%	1 (2)
M1-05	F	51	BTT	67.2%	30.8%	3 (5)
M1-06	M	69	DT	81.9%	19.0%	1 (3)
M1-07	M	67	DT	77.2%	20.7%	3 (11)
M1-08	M	18	BTT	76.4%	23.1%	1 (3)
M1-09	M	64	BTT	65.4%	42.3%	2 (10)
M1-10	F	41	BTC	74.2%	22.2%	1 (4)
M1-11	M	64	DT	74.0%	21.6%	1 (5)
M1-12	M	72	DT	80.1%	12.1%	2 (14)
M1-13	M	50	BTC	77.8%	8.0%	3 (15)
M1-14	M	65	BTC	88.4%	20.3%	0 (0)
M1-15	M	67	DT	62.0%	45.6%	2 (8)
Mean				75.3%	25.2%	

cells, aspirin therapy was reduced from 200 to 100 mg/day, and the INR target reduced to a target close to 1.5. No source of active bleeding was found on gastroscopy, colonoscopy, or capsule enteroscopy, although internal hemorrhoids were observed. Upon re-admission for recurrent bleeding, the patient was treated with further reduction in anti-coagulation and use of octreotide, and subsequently underwent a successful transplant (refer to section S8 in the Supplementary Material online).

Anti-coagulation management

The center TTR in the reduced anti-coagulation phase from 6 weeks post-implant through Month 6 was 75.3 ± 9.0% (56.4% to 88.4%); individual patient TTR results are shown in Figure 2B and Table 2. Ability to achieve and maintain the INR target range of 1.5 to 1.9 throughout the full follow-up is depicted in Figure 3. Over 67% of all INR values in the low-intensity INR range fell between 1.5 and 1.9 for full patients follow-up. The uncensored center TTR value and uncensored individual TTR results are presented in Table S5 in the Supplementary Material online.

Safety monitoring—pump thrombosis and LDH algorithm

The safety algorithm was activated a total of 3 times in 2 patients, both presenting with elevated baseline LDH within the first 6 months. Beyond 6 months, safety monitoring was performed in 2 patients (once each). The first patient (M1-08) was among the 2 patients with elevated baseline LDH. The second patient (M1-02) presented at

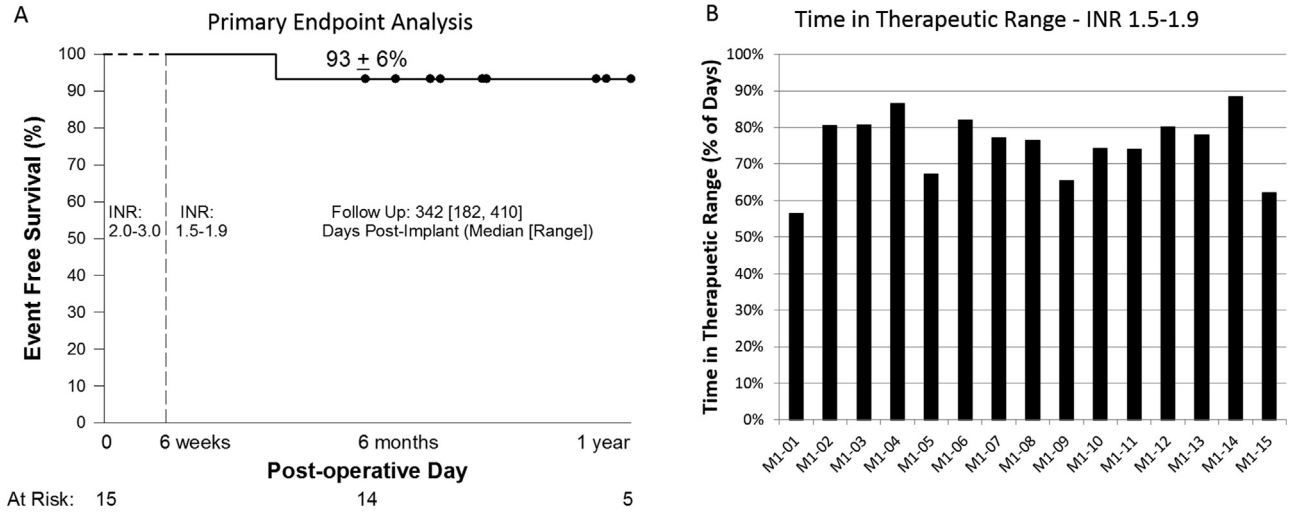

Figure 2 Primary end-point: event-free survival and patient TTRs.

Table 3 Adverse Events

Patient	Sex	Age	Indication	Hemocompatibility Related Adverse Events	All Other Adverse Events
1	M	60	BTC	none	none
2	M	60	BTT	none	Ventricular Arrhythmia (66, 283 POD)
3	M	50	BTT	none	Driveline Infection (28, 126 POD)
4	M	61	BTC	none	Urinary Tract Infection (49 POD)
5	F	51	BTT	none	none
6	M	69	DT	none	Hematoma in Urinary Bladder (17 POD)
7	M	67	DT	none	Revision for Cardiac Tamponade (13 POD) Infection – Sternotomy (102, 147, 239, 341 POD)
8	M	18	BTT	none	none
9	M	64	BTT	Suspected GI Bleeding (119, 210 POD)	none
10	F	41	BTC	none	none
11	M	64	DT	none	Ventricular Tachycardia, Cardioversion (2 POD)
12	M	72	DT	none	Respiratory Failure (8 POD) Urinary Tract Infection (29, 106 POD)
13	M	50	BTC	none	none
14	M	65	BTC	none	Urinary Tract Infection (3 POD) Gout (37 POD) Enlarged prostate resulting in TURP (49 POD)
15	M	67	DT	none	Driveline Infection (135 POD)

POD 229 with INR of 1.49 and LDH 341 U/liter, which was elevated relative to the post-clinical course (between 174 and 252 U/liter), but not relative to baseline (341 U/liter). Transthoracic echocardiography was normal and log-file interrogation was negative. The patient was bridged with LMWH according to the study protocol. Control LDH level at 2 days after was 294 U/liter. No additional complications were noted through POD 413. Safety monitoring detected no thrombosis-related adverse events.

Discussion

The MAGENTUM 1 pilot trial with the HM3 LVAS suggests that low-intensity anti-coagulation is feasible within a narrow INR range (1.5 to 1.9), and is not associated with an increase in thromboembolic complications, especially pump thrombosis, in a group of closely monitored and managed patients.

Reported rates of pump thrombosis at 12 months for patients implanted with commonly used LVASs are 6% to 12% for axial-flow pumps[8,9] (HeartMate II LVAS) and 8% with hydrodynamic centrifugal-flow devices[10,11] (HeartWare HVAD, Medtronic, Minneapolis, MN). In contrast, recent observations from both a single-arm study at 2 years[12] and a randomized trial at 6 months[3] with the HM3 LVAS, a magnetically levitated centrifugal-flow assist device, reported absence of de novo pump thrombosis. Similarly, an observational study showed greater preservation of von Willebrand high-molecular-weight multimers with the HM3 LVAS as compared with the HeartMate II device.[13] However, these attributes have not translated into decreased incidence of non-surgical bleeding during LVAD support, and the incidence of gastrointestinal bleeding at 6 months was similar and unchanged in a randomized trial experience comparing the centrifugal-flow HM3 and axial-flow HeartMate II LVAS (15.9% for both devices). Thus, a clinical rationale to reduce anti-coagulation targets exists for the HM3 LVAS; however, there is concern that the observed benefit of a low rate of pump thrombosis may be attenuated if such an approach were adopted.

Anti-platelet agents are used to provide not only rheologic but also anti-inflammatory effects.[14] Controversy

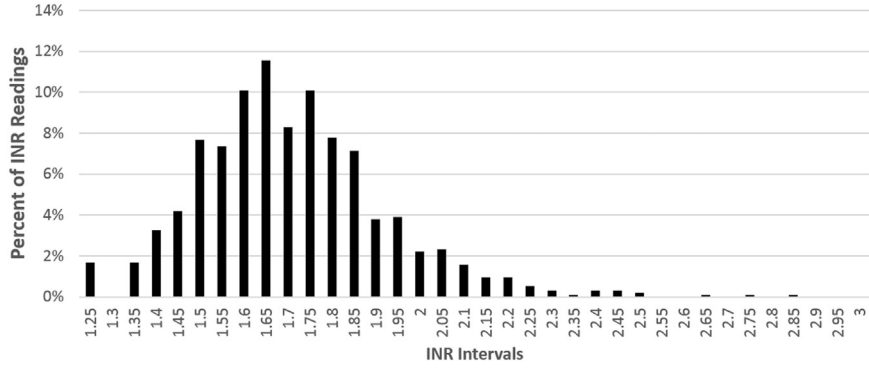

Figure 3 Proportion of INR values at various levels, with target INR 1.50 to 1.90 (INR measurements >3.0 were excluded in 4 instances, representing 0.42% of measurements).

reigns with their use and whether they represent a critical component of therapy.[15] However, knowledge of their mechanistic utility remains incomplete in the context of LVAS and recent studies have suggested that platelets activate differentially in various clinical contexts and such activation, as assessed by the platelet activity assay, may correlate with thrombotic outcomes.[16] Furthermore, in the centrifugal-flow HeartWare HVAD pump, correlations with reduced anti-platelet therapy and heightened risk of ischemic stroke have emerged.[17] Thus, we chose to maintain anti-platelet therapy so that we could reliably investigate one component of the anti-thrombotic regimen, decreasing the INR target range.

Management of anti-coagulation and maintenance of the INR in a therapeutic range remains challenging. Poor INR control (TTR $<60\%$) is typically the norm in patients with LVAS and there is emerging evidence that better control (as adjudicated by TTR $>60\%$) is associated with a reduced risk of thromboembolic and bleeding complications.[18] A multidisciplinary initiative to optimize anti-coagulation practice, by establishing a standardized anti-coagulation management protocol, standardizing INR target ranges, and integrating a clinical pharmacist as a consultant into the care team, improves the TTR achieved in patients implanted with an LVAS.[19] In MAGENTUM 1, we adopted protocol-based, centralized management, developed at Brigham and Women's Hospital/Harvard Medical School. This INR management protocol was implemented at the study center in Prague, with patient warfarin management by a dedicated anti-coagulation–trained clinical pharmacist, to ensure a strictly controlled multidisciplinary initiative. In this study, we measured INR weekly exclusively with venipuncture samples at a certified laboratory and adjusted the warfarin dose according to the INR management protocol. To ensure safety, we did not allow use of point-of-care testing at home due to the reported inaccuracy of such systems, where a difference of 0.4 to 0.8 in INR for home monitoring is commonly reported.[20] We addressed 2 other potential safety concerns within the study. First, in patients with baseline atrial fibrillation, we uniformly performed left atrial appendage exclusion and patent foramen ovale closure, if detected. Second, we established a structured algorithm for biomarker surveillance of LDH and an early alert system using clinical and advanced LVAS interrogation parameters, as we reported in a previous study.[21]

Limitations to this single-center, prospective feasibility study include the small number of patients and the tightly monitored and controlled anti-coagulation management algorithm that achieved a high center TTR. We encountered a greater frequency of supra-therapeutic INRs that required adjustment as compared with sub-therapeutic range INRs. This may reflect: (a) the lower limit INR being closer to what would be considered a "normal" INR; (b) the inherent variability in pharmacokinetics and pharmacodynamics of warfarin dosing; (c) the impact of lifestyle changes such as exercise and dietary patterns; and (d) interceding illnesses (such as an infection) or drug–drug interactions. We were unable to discern a clear pattern in the time-curves for supra-therapeutic INRs; however, we did find that this occurred only 14% of time. A center TTR of $\geq 66\%$ is considered excellent and has served as a benchmark for warfarin management in trials of atrial fibrillation with direct thrombin inhibitors or direct factor Xa inhibitors compared with vitamin K antagonists. A meta-analysis of all such trials[22] demonstrated that, once TTR increases, the advantages of direct thrombin inhibitors or direct factor Xa inhibitors compared with vitamin K antagonists decreases significantly. Furthermore, there are concerns about generalizability outside the controlled trial environment and it would be unwise to translate these preliminary pilot findings into routine clinical practice. Reproducibility and safety within larger patient cohorts will be required before these early findings can be adopted.

In conclusion, the results of this pilot study demonstrate feasibility and short-term safety at 6 months for use of closely monitored low-intensity anti-coagulation with a target INR range of 1.5 to 1.9 in patients implanted with the HM3 LVAS. We believe that this investigation has established the rationale for a large-scale, randomized, controlled clinical trial to test the clinical utility of low-intensity anti-coagulation with the HM3 LVAS on hemocompatibility-related adverse effects.

Disclosure statement

I.N. is a consultant, has received grant funds, and is on the advisory boards for Abbott and Carmat. SA. P.I., Z.T., S.G., and O.S. have received grants from Abbott. P.S. and D.C. are employees of Abbott. J.R. has no disclosures. J.M.C. is a consultant for Abbott. M.R.M. is a consultant for Abbott, Medtronic, Janssen, Portola, Mesoblast, and Bayer, and is on the advisory board for NupulseCV, Inc.

This study was supported by Abbott (Chicago, IL, USA) and the Ministry of Health, Czech Republic (Institute for Clinical and Experimental Medicine, grant IN 00023001). The authors are indebted to Laura Damme, RN, MPH for her support of this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at www.jhltonline.org.

References

1. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med 2017; 376:451-60.
2. Netuka I, Sood P, Pya Y, et al. Fully magnetically levitated left ventricular assist system for treating advanced HF: a multicenter study. J Am Coll Cardiol 2015;66:2579-89.
3. Mehra MR, Naka Y, Uriel N, et al. A fully magnetically levitated circulatory pump for advanced heart failure. N Engl J Med 2017;376: 440-50.
4. Uriel N, Pak SW, Jorde UP, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol 2010;56:1207-13.
5. Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.

6. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975-83.
7. Mehra MR. The burden of haemocompatibility with left ventricular assist systems: a complex weave [e-pub ahead of print]. Eur Heart J. http://dx.doi.org/10.1093/eurheartj/ehx036, accessed March 23, 2018.
8. Mehra MR, Stewart GC, Uber PA. The vexing problem of thrombosis in long-term mechanical circulatory support. J Heart Lung Transplant 2014;33:1-11.
9. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med 2014;370:33-40.
10. Kirklin JK, Naftel DC, Pagani FD, et al. Pump thrombosis in the Thoratec HeartMate II device: An update analysis of the INTERMACS Registry. J Heart Lung Transplant 2015;34:1515-26.
11. Najjar SS, Slaughter MS, Pagani FD, et al. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2014;33:23-34.
12. Schmitto JD, Pya Y, Zimpfer D, et al. HeartMate 3 Fully magnetically levitated left ventricular assist device for the treatment of advanced heart failure—CE Mark Study 2-year results. J Heart Lung Transplant 2017;36(suppl):S66.
13. Netuka I, Kvasnicka T, Kvasnicka J, et al. Evaluation of von Willebrand factor with a fully magnetically levitated centrifugal continuous-flow left ventricular assist device in advanced heart failure. J Heart Lung Transplant 2016;35:860-7.
14. Khan Q, Mehta JL. Relevance of platelet-independent effects of aspirin to its salutary effect in atherosclerosis-related events. J Atheroscler Thromb 2005;12:185-90.
15. Netuka I, Litzler PY, Berchtold-Herz M, et al. Outcomes in HeartMate II patients with no antiplatelet therapy: 2-year results from the European TRACE Study. Ann Thorac Surg 2017;103:1262-8.
16. Consolo F, Sferrazza G, Motolone G, et al. Platelet activation is a preoperative risk factor for the development of thromboembolic complications in patients with continuous-flow left ventricular assist device [e-pub ahead of print]. Eur J Heart Fail. http://dx.doi.org/10.1002/ejhf.1113, accessed March 23, 2018.
17. Teuteberg JJ, Slaughter MS, Rogers JG, et al. The HVAD left ventricular assist device: risk factors for neurological events and risk mitigation strategies. JACC Heart Fail 2015;3:818-28.
18. Boehme AK, Pamboukian SV, George JF, et al. Predictors of thromboembolic events in patients with ventricular assist device. ASAIO J 2015;61:640-7.
19. Kuyumjian YM, Miyares MA, Leverock J, et al. A multidisciplinary team-based process improves outpatient anticoagulation quality with continuous-flow left-ventricular assist devices. Int J Cardiol 2016;218:118-9.
20. Christensen TD, Larsen TB. Precision and accuracy of point-of-care testing coagulometers used for self-testing and self-management of oral anticoagulation therapy. J Thromb Haemost 2012;10:251-60.
21. Netuka I, Mehra MR. Ischemic stroke and subsequent thrombosis within a HeartMate 3 left ventricular assist system: a cautionary tale. J Heart Lung Transplant 2018;37:170-2.
22. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.