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FEATURED PAPERS

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

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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.

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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-

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