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ORIGINAL CLINICAL SCIENCE

Early intervention for lactate dehydrogenase elevation improves clinical outcomes in patients with the HeartMate II left ventricular assist device: Insights from the PREVENT study

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BACKGROUND: Hemolysis, assessed by elevated serum lactate dehydrogenase (LDH), is strongly associated with HeartMate II pump thrombosis (PT). However, it is unknown whether early intervention for elevated LDH circumvents the risk of serious PT requiring pump exchange. We sought to evaluate the relationship between elevated LDH and clinical outcomes, the effectiveness of early medical intervention, and risk factors for elevated LDH.

METHODS: We studied 268 patients in the prospective, multicenter PREVENT study who had 2 or more LDH measurements at ≥30 days post-implant. Elevated LDH was defined as LDH ≥2.5× upper limit of normal (ULN) for 2 consecutive measurements.

RESULTS: Fourteen percent of patients had elevated LDH. Stroke-free survival at 6 months was lower in patients with elevated LDH vs patients with normal LDH (83 ± 6% vs 93 ± 2%, $p = 0.035$). Elevated LDH resolved without intervention in 19% of patients, with intensified medical therapy in 43% and required surgical intervention in 38%. For patients receiving only medical therapy, survival was 94 ± 6% at 6 months post-treatment. In this subgroup, resolution of symptoms with intensified medical therapy was sustained in 15 of 16 patients, with PT occurring in 1 patient at 171 days after initial treatment for elevated LDH (202 days post-implant). Early medical intervention at moderately elevated LDH (2.5× to 3.2× ULN), as compared with higher levels (>3.2× ULN), led to more sustained

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resolution of symptoms without subsequent PT or need for surgical intervention (91% vs 26% at 6 months post-treatment, $p = 0.002$).

CONCLUSIONS: Early medical intervention can successfully resolve moderate LDH elevations (2.5× to 3.2× ULN) with a low incidence of death or PT at 6 months post-treatment.

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Pump thrombosis (PT) is a major complication of left ventricular assist devices (LVADs),[1] with an incidence of 2% to 4% in HeartMate II (HMII; Abbott, Pleasanton, CA) patients in the original clinical trials.[2,3] Real-world contemporary estimates have suggested an increase in PT risk from 2009 to 2013,[4] and another study from 3 large centers reported a peak incidence of 8.4% at 3 months.[5] To address this, the PREVENT study, a prospective, multicenter clinical trial, was designed to standardize surgical and medical practices for the HMII. PT rates in the PREVENT study were 2.9% and 4.8% at 3 and 6 months, respectively.[6] PT is associated with significant morbidity and mortality, including heart failure, thromboembolic stroke and reoperation for pump exchange.[7,8] Thus, early recognition and treatment of PT, along with better upfront management strategies, remains a critical focus.

An increase in serum lactate dehydrogenase (LDH), a marker of intravascular hemolysis, has been shown to identify patients at high risk of PT with high sensitivity.[5,7,9] LDH elevations may occur before symptoms of PT, making it an ideal target for early intervention. The current knowledge regarding LDH level and its relationship to PT is mainly based on single-center, retrospective analyses.[7,9] In addition, although most publications have shown that patients with elevated LDH are "at risk" for PT and stroke, little is known about the efficacy of intensified medical therapy in HMII patients presenting with elevated LDH but no evidence of heart failure or abnormal pump parameters,[8] and no study to date has provided an LDH threshold at which intensified medical therapy may actually help circumvent the risk of a serious PT event requiring pump exchange.

PREVENT is the first study to prospectively collect serial LDH levels and anti-thrombotic therapeutic interventions for patients undergoing HMII implantation. In this secondary analysis, our objectives were to: (a) characterize the relationship between elevated LDH levels and clinical outcomes; (b) determine the effectiveness of early medical intervention for elevated LDH; and (c) identify risk factors for elevated LDH.

Methods

Study design and cohort

PREVENT was a prospective, single-arm study that was conducted at 24 participating centers across the United States. Patients enrolled in the study were followed for 6 months post-implant or until an outcome was reached. The study was designed to evaluate outcomes in HMII patients with the adoption of recommended practices focused on surgical implantation technique, anti-coagulation regimen, pump speed and blood pressure management to reduce PT. Detailed inclusion and exclusion criteria of the PREVENT study have been reported previously.[6] All patients provided written informed consent and the study protocol was approved by the institutional review boards of the participating institutions. The most recent Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definition for PT was utilized in the study (see Table S1 in the Supplementary Material online at www.jhltonline.org/). All suspected and confirmed PT was adjudicated by an independent assessor.[6]

For this analysis, we included patients from PREVENT who were on HMII support for at least 30 days and had 2 or more LDH measurements taken ≥30 days post-implant. We restricted our analysis to LDH levels ≥30 days after HMII implantation to eliminate post-operative alterations in LDH levels. Of the 300 patients enrolled in PREVENT, we excluded 18 patients who were on HMII support for <30 days and 14 patients who did not have 2 LDH measurements after 30 days post-implant (Figure 1). Of all the excluded patients, there was only 1 confirmed PT event that led to subsequent pump explantation, which occurred on Day 3 post-operatively. A total of 268 patients formed the cohort for this analysis.

Serum LDH measurement and analysis

All LDH measurements obtained from patients during the follow-up period were collected as a log. LDH levels were measured routinely at each follow-up visit (1 week, 1 month, 3 months and 6 months post-implant) and at the clinical discretion of the treating physician. If a patient had multiple LDH measurements in a single day, only the highest LDH value from that day was used. Because the normal reference values for LDH differed between participating centers (see Table S2 in the Supplementary Material online), the levels were normalized to the upper limit of lab normal (× ULN) to determine whether or not LDH was elevated.

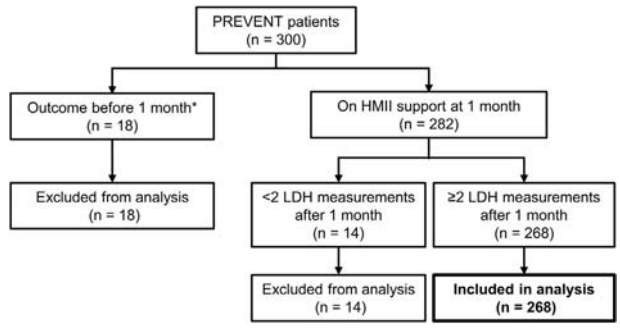

Figure 1 Flowchart of the study cohort. Patients either died (asterisk, $n = 16$), were withdrawn ($n = 1$) or were explanted after pump thrombosis ($n = 1$). HMII, HeartMate II; LDH, lactate dehydrogenase.