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Safety of reduced anti-thrombotic strategies in HeartMate II patients: A one-year analysis of the US-TRACE Study

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BACKGROUND: Patients with bleeding complications during left ventricular assist device (LVAD) support often require a reduction in the recommended warfarin plus aspirin regimen. To characterize those who can be safely managed with a reduced anti-thrombotic strategy, the TRACE (STudy of Reduced Anti-Coagulation/Anti-platelEt Therapy in Patients with the HeartMate II LVAS) study was initiated in the United States (U.S.) and Europe.

METHODS: The TRACE U.S. arm enrolled HeartMate II (HMII; Thoratec) outpatients on a regimen of reduced anti-thrombotic therapy (RT), defined as vitamin K antagonist (warfarin) only, aspirin only, or no anti-thrombotic agent. The indication for RT, changes in anti-thrombotic therapies, and patient outcomes after RT were documented. Results for patients reaching 12 months or outcome are presented here.

RESULTS: Between April 2012 and June 2013, 100 HMII outpatients (85% men) on RT (median age 64.5 [interquartile range, 32, 82] years, 61% with ischemic etiology, 69% destination therapy) were enrolled from 9 U.S. sites. The primary reason for RT initiation was in response to a bleeding event (82%). Pharmacotherapy at RT initiation included warfarin only (38%), aspirin only (28%), or no anti-thrombotic agent (34%). Freedom from ischemic stroke at 1 year was 93.8% ± 2.5%, and freedom from device thrombosis was 92.7% ± 2.7%. Despite RT, a subsequent bleeding event occurred in 52%.

CONCLUSIONS: Reducing anti-thrombotic therapies in response to bleeding among HMII patients was achievable but may be associated with a higher risk for device thrombosis. Furthermore, despite an RT strategy, bleeding often will persist in those prone to such events.

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Although the use of durable left ventricular assist device (LVAD) therapy for end-stage heart failure has demonstrably improved patient survival and quality of life, complications do occur.[1] These adverse events have become increasingly acknowledged,[2–4] with a recent focus on device

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thrombosis.[5,6] Nonetheless, bleeding remains the most commonly reported complication among contemporary continuous-flow LVAD (CF-LVAD) recipients.[7]

Bleeding, typically gastrointestinal (GI) or epistaxis, appears to be a multifactorial event, related at least in part to an acquired von Willebrand syndrome,[8,9] alterations in platelet function,[10] and angiodysplastic changes in the mucosa of the GI tract.[11] Compounding this risk is the logical but scientifically unproven recommendation that all patients with a CF-LVAD be managed with an intensive combination of anti-coagulant and anti-platelet medications.[12]

Although some centers have empirically used reduced anti-thrombotic therapy (RT) after a hemorrhagic event to mitigate the hazard of future bleeding,[13] the optimal pharmacologic response to a bleeding episode is unknown and varies widely across centers and providers. In an effort to describe current RT practices, to determine thromboembolic and bleeding rates after RT initiation, and to better characterize patients who may be safely maintained on an RT regimen, the STudy of Reduced Anti-Coagulation/Anti-platelEt Therapy in Patients with the HeartMate II LVAS (TRACE) was performed.

Methods

TRACE is a multicenter, prospective and retrospective, observational study designed to assess the risks and benefits of chronic, long-term RT regimens in advanced heart failure patients supported with a HeartMate II (HMII) LVAD (Thoratec Corp). RT was defined as (1) use of a vitamin K antagonist (VKA; warfarin) only, (2) use of aspirin only, or (3) no anti-thrombotic therapy. To be included in TRACE, a patient had to have been successfully discharged from his or her index LVAD implant hospitalization. In addition, patients had to have been on RT at the time of enrollment or maintained or initiated on RT on or after January 1, 2011, even if RT was subsequently discontinued due to an adverse event or outcome. Patients managed with alternative anti-thrombotic agents were excluded.

The TRACE United States (U.S.) arm began enrolling patients in April 2012 from 9 implanting centers (Appendix). Each site received Institutional Review Board approval before patient enrollment, and all patients provided informed consent before participation. Patients were followed up at 3, 6 , and 12 months and every 6 months up to 24 months after enrollment.

The primary study end point was the rate of thromboembolic (i.e., ischemic stroke, transient ischemic attack, or pump thrombosis) and hemorrhagic events (i.e., bleeding and hemorrhagic stroke), which were captured using Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions.[14] Data on patient demographics, medical history, and laboratory and diagnostic studies were recorded. The indication for RT and subsequent anti-thrombotic changes after RT initiation were also documented. By June 2013, 100 consecutive outpatients had been enrolled, and all had been on RT for at least 12 months or had reached an outcome. These individuals comprise the study cohort for the current analysis.

For descriptive purposes, categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means if normally distributed or as medians if the distribution was skewed. Survival analyses were performed using the Kaplan-Meier method. All analyses were conducted using SAS 9.1 software (SAS Institute Inc, Cary, NC).

Results

Demographics and comorbidities

Baseline patient characteristics at the time of TRACE enrollment are reported in Table 1. Those managed with an RT regimen were more commonly male (85%), white (72%), had an ischemic etiology to their heart failure (61%), were INTERMACS profile II at the time of device implantation (40%), and were considered destination therapy patients (69%). The median duration of HMII support at TRACE enrollment was 1.0 (interquartile range [IQR] 0.07, 7.5) year.

An RT strategy was used in 82% of the TRACE U.S. patients in response to a bleeding event, in response to stroke in 2%, due to physician preference or center standard-of-care in 1%, and for other indications in 15 of the 100 patients (15%): 10 patients were never on aspirin, 1 had hematuria due to nephrolithiasis, 1 had gastric inflammation, 1 had elevated international normalized ratio (INR), and 2 were determined to be at risk of falling. Initial RT included warfarin only in 38% of patients, aspirin only in 28%, and no anti-thrombotic agent in 34%.

Anti-thrombotic Duration, Intensity, and Changes over Time

Figure 1 shows the duration of RT at follow-up, including time on RT before enrollment, which indicates that most participants had been managed with an RT strategy for at least 1 year. Figure 2 shows the intensity of systemic anti-coagulation with the distribution of INR values for all TRACE enrollees. The median INR was 1.85 (IQR 0.9, 3.7) for those managed with a VKA antagonist, 1.11 (IQR 0.95, 1.29) for those managed with aspirin alone, and 1.12 (IQR 1.00, 1.8) for those on no anti-thrombotic agents. The

Table 1 Baseline Characteristics for the Enrolled STudy of Reduced Anti-Coagulation/Anti-platelEt Therapy in Patients with the HeartMate II LVAS (TRACE) United States Study Population

Parameter at implantation	Median (IQR) or % ($N = 100$)
Age, years	64.5 (32, 82)
Male	85
Race	
White	72
Black	22
Other	6
Ischemic etiology	61
Destination therapy	69
Bridge to transplantation	30
INTERMACS profile	
I	18
II	40
III	15
IV-VI	22

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range.