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Gastrointestinal bleeding and subsequent risk of thromboembolic events during support with a left ventricular assist device

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BACKGROUND: Modern left ventricular assist devices (LVAD) require anti-coagulation (AC) with warfarin and anti-platelet therapy to prevent thromboembolic complications in patients. Gastrointestinal bleeding (GI) is a significant adverse event in these patients and treatment typically requires reduction or elimination of AC or anti-platelet therapy. It is not known whether alterations in AC to treat GI bleeding influence subsequent risk of thromboembolic (TE) events during LVAD support.

METHODS: Between July 2003 and September 2011, 389 patients (308 male) underwent implantation of a continuous-flow LVAD at the University of Michigan Health System and the Mayo Clinic. Median age at implant was 60 years (range 18 to 79 years). Outcomes were analyzed for the association of GI bleeding events and subsequent TE events, defined as stroke, transient ischemic attack, hemolysis or suspected or confirmed pump thrombosis.

RESULTS: Median survival was 10 months (maximum 7.2 years, total 439 patient-years). TE events occurring within the first 30 days were not counted. Overall survival and freedom from an outcome event were assessed using the Kaplan–Meier method. Associations between GI bleeding and subsequent TE events and survival impact were analyzed as time-dependent covariates. One hundred ninety-nine GI bleeding episodes occurred in 116 of 389 patients (30%) for an event rate of 0.45 GI bleed/patient-year of support. One hundred thirty-eight TE events occurred in 97 of 389 patients (25%) for an event rate of 0.31 TE event/patient-year of support. Median time from LVAD implant to first GI bleed was 5 months (range 1 to 116 months) and to first TE event was 6 months (range 1 to 29 months). For patients who had a TE event after GI bleed, the median interval was 5 months (range 0.5 to 25 months). TE events were 7.4-fold more likely in patients who had a prior GI bleed (range 4.9- to 11.1-fold) ($p < 0.001$); however, neither the presence of GI bleeding (0.7 to 1.2) nor a TE event (0.8 to 2.0) portended a lower overall survival.

CONCLUSIONS: Patients who had GI bleeding were at significantly higher risk for a subsequent TE event. Although the exact cause of this relationship is unknown, it suggests that a reduction in anti-coagulation and anti-platelet management to treat GI bleeds may contribute to this risk.

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The use of left ventricular assist devices (LVADs) to treat advanced heart failure has been increasing steadily over the past decade.[1,2] Recent technological improvements in device design and surgical implantation refinement have

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significantly improved patient survival.[3] However, patients with LVADs are at increased risk for serious complications such as thromboembolism and bleeding.[4] Management of anti-coagulation and anti-platelet therapy to obtain optimum balance of these 2 risks presents a difficult challenge to the clinician.

Patients with LVADs have a significantly altered thrombotic profile compared with other patients.[5] LVAD implantation has been found to be associated with endothelial dysfunction and elevated baseline activity of the coagulation system, thus putting the patients at increased risk of a thromboembolic event.[6] Therefore, patients are managed with a regimen of an anti-coagulant (heparin, direct thrombin inhibitors, warfarin) and anti-platelet agents (aspirin, clopidogrel, dipyridamole).[4] In addition, continuous-flow devices have been found to result in an acquired von Willebrand syndrome, further complicating the thrombotic profiles of these patients.[7]

One consequence of this altered thrombotic profile is gastrointestinal (GI) bleeding. Patients with implanted LVADs are at a substantially higher risk of having GI bleeding than non-LVAD patients who are also receiving anti-thrombotic therapy for cardiovascular disease.[8] Gastrointestinal bleeding is a significant adverse event in these patients and treatment typically requires reduction or elimination of anti-coagulation or anti-platelet therapy.[4,8] It is not known whether alterations in anti-coagulation to treat GI bleeding influences subsequent risk of thromboembolic (TE) events during LVAD support.

The aim of our study was to identify a cohort of patients who had undergone implantation of a continuous-flow LVAD from our respective institutional databases and had at least 1 GI bleeding episode. We then sought to examine the association of GI bleeding and subsequent risk of TE events. The risks of GI bleeding and TE events were analyzed with respect to survival. Our hypothesis was that temporary or prolonged alterations in anti-coagulation secondary to GI bleeding may increase risk of subsequent TE events in patients with a continuous-flow LVAD.

Methods

Study population

The data collection process and analysis was performed after informed patient consent and approved by the institutional review boards of the University of Michigan and the Mayo Foundation. Between July 2003 and September 2011, 389 patients (308 men, 81 women) underwent implantation of a continuous-flow LVAD at the University of Michigan Hospital and Mayo Clinic. Median age at implant was 60 years (range 18 to 79 years).

Pre-operative clinical characteristics are presented in Table 1. Importantly, 54 (14%) patients had prior stroke, 89 (23%) had pre-operative atrial fibrillation and 142 (37%) had hypertension. All patients ($n = 389$) underwent implantation of a continuous-flow LVAD. Pump types included a HeartMate II in 330 patients, a HeartWare HVAD in 34, a DuraHeart in 10 and a VentrAssist in 6. A tricuspid valve procedure was performed in 128 (33%) patients and an aortic valve procedure was performed in 29 (7%). Mean cardiopulmonary bypass time was 92 ± 38 minutes. Early right ventricular failure occurred in 36 patients (19%) and a temporary right ventricular assist device was required in 22 patients (6%) at the time of LVAD implant. Early dialysis was required in 30 patients (16%). There were 24 operative deaths (6%; death prior to 30 days or hospital discharge) and 9 patients (2%) had a stroke or transient ischemic attack (TIA) within 30 days.

Table 1 Pre-operative Clinical Characteristics

Variable	Patients [*n* (%)]
Prior stroke	54 (14%)
Atrial fibrillation	89 (23%)
Diabetes mellitus	107 (28%)
Destination therapy	130 (33%)
Hypertension	142 (37%)
Ischemic etiology	193 (50%)
Hyperlipidemia	245 (63%)

Outcome assessment

A GI bleeding event was defined as a case of GI bleeding that required re-admission to the hospital, blood transfusion or intervention via endoscopy or interventional radiology. Multiple bleeding events that occurred during the same hospitalization were counted as a single event. A TE event was defined as a stroke (CVA), TIA, hemolysis or suspected or confirmed pump thrombus.

GI bleeding and TE events that occurred after the LVAD was explanted were not counted. TE events occurring within 30 days of implantation of the LVAD were considered to be related to the procedure and were not counted.

Statistical analysis

Demographics and other patient-related data were obtained from University of Michigan and Mayo Foundation medical records and our prospectively collected clinical databases. Follow-up information was obtained from subsequent clinic visits and written correspondence from local physicians. Data were expressed either as mean ± standard error of the mean for normally distributed data or median with range for non-normally distributed data. Data between 2 groups were compared using Student's paired *t*-test or chi-square test for continuous and dichotomous variables, respectively. Overall survival and freedom from an outcome event was performed using the Kaplan–Meier method and compared by log rank. Any association between GI bleeding and subsequent TE events and survival impact was analyzed as a time-dependent covariate. $p < 0.05$ was considered statistically significant. Early operative mortality was defined as death occurring within 30 days of operation or at any time during the index hospitalization.

Results

Median follow-up was 10 months (maximum 7.2 years, total 439 patient-years) and data were available for all early survivors ($n = 365$).

There were 119 GI bleeding events in 116 patients (30%; 116 of 389), occurring as a single event in 67 (58%; 67 of 116) patients and multiple times in 49 (42%; 49 of 116). The median time after LVAD implant to first GI bleed was 5 months (range 1 to 116 months). The rate of GI bleed in this cohort was 0.45 per patient-year of support. Overall freedom from GI bleeding in the entire cohort is shown in Figure 1.