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Heart Failure

Pre-Operative Risk Factors of Bleeding and Stroke During Left Ventricular Assist Device Support

An Analysis of More Than 900 HeartMate II Outpatients

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Objectives This study sought to determine the pre-operative risk factors related to late bleeding, stroke, and pump thrombosis in patients with HeartMate II (HMII) left ventricular assist devices (LVADs) (Thoratec Corporation, Pleasanton, California) that might influence tailored improvements in patient management.

Background Adverse events in LVAD patients remain high. It is unclear whether pre-operative characteristics influence the likelihood of the development of post-operative hemorrhagic or thrombotic complications. Knowing which patients are at greater risk might assist in tailoring anticoagulation therapy for certain patients.

Methods Advanced heart failure patients (n = 956) discharged from the hospital after LVAD implantation in the HMII bridge to transplantation (n = 405) and destination therapy (n = 551) clinical trials were retrospectively evaluated. Bleeding requiring surgery or transfusion of >2 U of packed red blood cells, stroke (hemorrhagic and ischemic), and pump thrombosis were tracked from hospital discharge until patient outcome.

Results Adverse event rates for post-discharge bleeding (0.67 events/patient-year) were higher than those for hemorrhagic stroke (0.05), ischemic stroke (0.04), and pump thrombosis (0.03). The main sites of bleeding included gastrointestinal (45% of events), wound (12%), and epistaxis (4%). Older age (>65 years) (hazard ratio [HR]: 1.31), lower pre-operative hematocrit (≤31%) (HR: 1.31), ischemic etiology (HR: 1.35), and female (HR: 1.45) were statistically significant multivariable risk factors for bleeding. Female (HR: 1.92) and 65 years of age and younger (HR: 1.94) were multivariable risk factors for hemorrhagic stroke, whereas female (HR: 1.84) and history of diabetes (HR: 1.99) were risk factors for ischemic stroke. Female (HR: 1.90) and higher body mass index (HR: 1.71/10 kg/m^2 increase) were also multivariable risk factors for pump thrombosis.

Conclusions The risk of bleeding and thrombotic events during LVAD support differs by patient demographics, including sex, age, body mass index, and etiology of heart failure. Further studies should focus on the potential of tailored anticoagulation strategies in these subgroups. (J Am Coll Cardiol 2014;63:880–8) © 2014 by the American College of Cardiology Foundation

Continuous-flow left ventricular assist devices (CF-LVADs) are becoming the standard of care for management of refractory advanced heart failure patients. Despite demonstrating significant improvements in survival with CF-LVADs compared with the older pulsatile devices, along with reductions in major adverse events including infections and pump replacements (1), bleeding continues

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to be the most frequently reported complication (1–4), whereas stroke and pump thrombosis are among the most serious.

The HeartMate II (HMII) CF-LVAD (Thoratec Corporation, Pleasanton, California) is approved by the U.S. Food and Drug Administration for both bridge to transplantation (BTT) and destination therapy (DT) for long-term support. The HMII destination therapy trial was a prospective, randomized study comparing the HMII CF-LVAD with the HeartMate XVE pulsatile-flow left ventricular assist device (LVAD) (Thoratec Corporation) (1). Bleeding was high in both the CF-LVAD and pulsatile LVAD cohorts, with >75% of the patients requiring transfusions post-LVAD surgery, and there was a trend toward a lower incidence of bleeding in the HMII cohort. The incidence of ischemic stroke (0.06 events per patient-year [EPPY] vs. 0.10 EPPY) and hemorrhagic stroke (0.07 EPPY vs. 0.12 EPPY) was not statistically different between the HMII and HeartMate XVE. More recent data from additional DT trial patients have shown a reduction in hemorrhagic stroke (from 0.07 to 0.03 EPPY) and in bleeding (from 1.66 to 1.13 EPPY) (4). Recent results from INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) for 1,496 BTT patients have also suggested some improvements, with a combined occurrence of ischemic and hemorrhagic stroke at 8% and gastrointestinal bleeding at 10% (5).

The causes of bleeding are multifactorial, but recent studies have shown that von Willebrand syndrome has developed in patients with CF-LVADs because of a loss in high-molecular-weight von Willebrand factor multimers, which results in reduced platelet activity and aggregation (6–10). Additionally, along with aspirin, HMII patients are also typically anticoagulated with warfarin, with a target international normalized ratio range of 1.5 to 2.5 in the absence of an additional indication for warfarin (11,12). Single-center studies have identified age, ischemic cardiomyopathy, hypertension, body mass index (BMI), albumin, cardiopulmonary bypass time, and history of gastrointestinal bleeding as pre-operative risk factors for bleeding post-LVAD implantation (8,13–15).

Compared with bleeding, the risks of stroke and pump thrombosis with the HMII have been shown to be low, both in single-center and multicenter experiences (11,16,17). However, these are among the most serious events that deserve continued attention for improvements. There are only a few published reports evaluating risk factors for stroke and thrombosis in CF-LVAD patients because single-center studies lack the power necessary to identify statistically significant factors when the frequency of events is low. Previous single-center studies have identified history of cerebrovascular accident, serum sodium, and serum albumin (18) and right atrial pressure and right ventricular end-diastolic dimension (19) as pre-operative risk factors for post-LVAD ischemic and hemorrhagic stroke.

The primary purpose of this study was to determine pre-operative risk factors related to post-discharge bleeding, stroke, and pump thrombosis in both BTT and DT HMII LVAD patients in the multicenter clinical trials. Because the perioperative period is associated with highly confounding factors related to surgery and post-operative recovery, which will be addressed in separate analyses, we elected to solely focus this study on the events that occurred after patients were discharged from the hospital and were being managed as outpatients.

Abbreviations and Acronyms

BMI = body mass index
BTT = bridge to transplantation
CF-LVAD = continuous flow left ventricular assist device
DT = destination therapy
EPPY = events per patient-year
HMII = HeartMate II
HR = hazard ratio
LVAD = left ventricular assist device

Methods

Study design. This study was a retrospective analysis of patients implanted with the HMII as part of the BTT and DT clinical trials. Details of the study design and trial results for BTT and DT were previously published (1,2). Between March 2005 and January 2010, 1,302 patients were enrolled in the study, including the continued access protocol phase, and received the HMII device as BTT, DT, compassionate use, or an exchange for a failing, previously implanted HeartMate XVE. For this study, HeartMate XVE exchange (n = 140) and compassionate use (n = 33) patients were excluded. As of March 6, 2012, all patients had at least 2 years of follow-up. Of the remaining 1,129 patients, a total of 956 patients were successfully discharged; they form the subjects of the present analysis. All adverse events were tracked and adjudicated by an independent clinical events committee. Bleeding, hemorrhagic and ischemic stroke, and pump thrombosis were the primary adverse events that were investigated in this study. Laboratory and hemodynamic measurements were collected every month until outcome or for up to 6 months for BTT patients and 24 months for DT patients.

Adverse event definitions. Bleeding was defined as an episode of internal or external bleeding that resulted in death, reoperation, or permanent injury or necessitated the transfusion of ≥2 U of packed red blood cells within 24 h of the event. Each bleeding event was categorized based on its location or cause into: 1) gastrointestinal bleeding; 2) epistaxis; 3) anemia; 4) wound; 5) other; 6) no site identified; or 7) no site reported. A stroke event was defined as a neurological deficit lasting >24 h or ≤24 h with a brain imaging study showing new infarction. Each stroke was categorized as either hemorrhagic or ischemic by the study center, which was subsequently confirmed by the clinical events committee. Pump thrombosis was defined as an obstructive thrombus in the device or its conduits associated with clinical symptoms of impaired pump performance (e.g., decreased pump flow, need to increase pump speed, increased power, or hemolysis) or the need for thrombolytic or surgical intervention. Definitions of all other adverse

events can be found as part of the appendixes of the HMII BTT (2) and DT (1) publications.

Statistical analysis. Continuous variables are described as mean ± SD or median (range) as appropriate, and categorical variables are described in percentages. Adverse events are presented as the percentage of patients affected, and event rates as EPPY. Statistical significance was set at $p < 0.05$ unless explicitly stated otherwise. Univariable and multivariable associations of each adverse event with pre-operative factors were evaluated using Cox proportional hazards models because of variability in support durations across different cohorts (e.g., BTT vs. DT, males vs. females). Patients were censored if they underwent transplantation, died, or had their devices explanted for myocardial recovery. Variables with significant associations as defined by $p < 0.1$ on univariate analysis were entered into a multivariable model. Variables were included in a stepwise fashion and retained if the p value was <0.05 in the multivariable model. Care was taken to not overfit the model and to limit the number of variables entered into the multivariable model to <10 per event. In certain cases, continuous variables were dichotomized based on upper or lower quartiles, except for age, which was dichotomized to 65 years of age and older. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics. Baseline characteristics of patients are shown in Table 1. A total of 956 patients were included and successfully discharged from the hospital. Median time to discharge was 24 days, and patients were supported for a median of 1.5 years for an accumulated duration of 1,799 patient-years, with 1,715 patient-years spent post-initial discharge. The average age was 58.2 ± 14.0 years, 23% were women, and 42% of the patients were BTT. Before surgery, 82% of the patients were on intravenous inotropes, 56% had cardiac resynchronization therapy devices, and 28% were supported on an intra-aortic balloon pump. Overall, the patient demographics matched the other patient cohorts whose outcomes were described in previous BTT and DT trials (1–4).

Prevalence and incidence of bleeding, hemorrhagic stroke, and pump thrombosis. The incidence of post-discharge bleeding, hemorrhagic stroke, ischemic stroke, and pump thrombosis is shown in Table 2. The overall prevalence and incidence of bleeding requiring transfusion were 38% (0.65 EPPY), with a greater incidence of bleeding in DT patients (47%, 0.72 EPPY) compared with BTT patients (25%, 0.48 EPPY) ($p = 0.001$). DT patients also had a higher incidence of gastrointestinal bleeding (29%, 0.35 EPPY) compared with BTT patients (13%, 0.19 EPPY) ($p < 0.001$). The majority of bleeding events resulting in transfusion were from the gastrointestinal tract (45%), followed by wound site (12%) and epistaxis (4%).

Table 1 Baseline Demographics of Patients Evaluated in This Study (N = 956) and Duration of LVAD Support

Characteristic	
Sex	
Male	736 (77)
Female	220 (23)
Indication	
BTT	405 (42)
DT	551 (58)
Age (range), yrs	58.2 ± 14.0 (15–87)
Ischemic etiology	506 (53)
African American	187 (20)
Body surface area	1.97 ± 0.27
BMI, kg/m^2	27.1 ± 5.8
LVEF, %	16.7 ± 6.0
LVEDD, mm	69.2 ± 11.1
ACE inhibitors	281 (29)
ARBs	66 (7)
Beta-blockers	429 (45)
Cardiac resynchronization therapy	534 (56)
Intravenous inotropes	781 (82)
Intra-aortic balloon pump	266 (28)
Duration of support	1.5 yrs (15 days, 6.8 yrs)
Duration of support post-discharge	1.4 (1 day, 6.8 yrs)
Pre-operative laboratory/hematology results	
BUN, mg/dl	31.7 ± 19.9
Creatinine, mg/dl	1.44 ± 0.53
Total bilirubin, mg/dl	1.22 ± 0.85
ALT, U/l	64 ± 163
AST, U/l	55 ± 143
INR	1.33 ± 0.57
PTT, s	25.6 ± 2.6
Hemoglobin, g/dl	11.6 ± 1.96
Hematocrit, %	35.1 ± 5.6
WBC count, 1,000/mm^3	8.2 ± 3.1
Platelet count, 1,000/mm^3	217 ± 86

Values are n (%), mean ± SD, or median (minimum, maximum), unless otherwise indicated.
ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; BTT = bridge to transplantation; BUN = blood urea nitrogen; DT = destination therapy; INR = international normalized ratio; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; PTT = partial thromboplastin time; WBC = white blood cell.

Anemia was the reason for transfusion in 14% of patients. No specific site could be identified in 15% of the patients, and in 5% of the patients, the sites of bleeding were not reported.

The overall prevalence of hemorrhagic stroke was 8% of patients, with an incidence rate of 0.05 EPPY, and there was no difference between BTT (6%, 0.05 EPPY) and DT (9%, 0.04 EPPY) patients ($p = 0.734$). Ischemic stroke occurred in 6% of the patients (0.04 EPPY), with no statistically significant difference between the BTT (4%, 0.03 EPPY) and DT (8%, 0.04 EPPY) patients ($p = 0.386$). Clinically relevant pump thrombosis was reported in 4% of the patients (0.03 EPPY), with a trend toward higher prevalence in DT patients (6%, 0.03 EPPY) compared with BTT patients (2%, 0.01 EPPY) ($p = 0.086$).

Fifty-eight patients (6%) experienced both hemorrhagic (bleeding or hemorrhagic stroke) and ischemic events

Table 2 Prevalence and Incidence of Bleeding, Stroke, and Pump Thrombosis After Discharge

Event	Patients, n (%)			Events (Event per Patient-Year)		
	All Patients (N = 956)	BTT (n = 405)	DT (n = 551)	All Patients (1,715 pt-yrs)	BTT (523 pt-yrs)	DT (1,192 pt-yrs)
Hemorrhagic events						
Bleeding requiring surgery	33 (3)	12 (3)	21 (4)	35 (0.02)	12 (0.03)	23 (0.02)
Bleeding requiring ≥2 U PRBCs	361 (38)	103 (25)	258 (47)	1,108 (0.65)	253 (0.48)	855 (0.72)
GI bleeding	213 (22)	52 (13)	161 (29)	518 (0.30)	101 (0.19)	417 (0.35)
Hemorrhagic stroke	76 (8)	25 (6)	51 (9)	80 (0.05)	27 (0.05)	53 (0.04)
Thrombotic events						
Ischemic stroke	58 (6)	15 (4)	43 (8)	61 (0.04)	16 (0.03)	45 (0.04)
Pump thrombosis	38 (4)	7 (2)	31 (6)	43 (0.03)	7 (0.01)	36 (0.03)

GI = gastrointestinal; PRBCs = packed red blood cells; pt-yrs = patient-years; other abbreviations as in Table 1.

(ischemic stroke or pump thrombosis). A total of 36 patients experienced an ischemic event after a hemorrhagic event at an average of 316 days after the initial hemorrhagic event; 10 of these 36 patients experienced the ischemic event within 90 days of the hemorrhagic event. It is certainly possible that a patient with a hemorrhagic event could be at a higher risk of an ischemic event later on if anticoagulation is withheld. However, details pertaining to the intervention for a hemorrhagic event were not captured in this study. Hence, it is difficult to say whether the ischemic event was an isolated event or due to a management response to treat a hemorrhagic event.

Pre-operative risk factors of bleeding, stroke, and pump thrombosis. The statistically significant pre-operative clinical characteristics of patients related to bleeding, stroke, and pump thrombosis are shown in Tables 3, 4, 5, and 6. DT, older age, female, ischemic etiology, higher BMI, lower left ventricular end-diastolic diameter, higher cardiac index, higher blood urea nitrogen, lower hematocrit, history of diabetes, and lower hemoglobin correlated with bleeding post-discharge. When included in a multivariable model, the independent risk factors for bleeding were >65 years of age, sex, ischemic etiology, and lowest quartile hematocrit (≤31%) (Table 3, Fig. 1).

Table 3 Pre-Operative Statistically Significant Univariable Correlates ($p < 0.1$) and Multivariable Risk Factors for Post-Discharge Bleeding

Parameter	Post-Discharge Bleeding					
	Univariable Correlates				Multivariable Risk Factors	
	No (n = 584)	Yes (n = 372)	p Value (Cox)	HR (95% CI) (Cox)	p Value (Cox)	HR (95% CI) (Cox)
DT (n = 551)	287 (52)	264 (48)	0.001	1.44 (1.15–1.81)	—	—
BTT (n = 405)	297 (73)	108 (27)				
Age, yrs	56 ± 15	61 ± 13	<0.001	1.02 (1.01–1.02)		1.31 (1.05–1.62)*
>65 (n = 340)	169 (50)	171 (50)	0.006	1.33 (1.09–1.64)*	0.015	
≤65 (n = 616)	415 (67)	201 (33)				
Female (n = 220)	117 (53)	103 (47)	0.013	1.33 (1.06–1.67)	0.022	1.45 (1.14–1.84)
Male (n = 736)	467 (63)	269 (37)				
Ischemic cardiomyopathy (n = 506)	291 (58)	215 (42)	0.01	1.31 (1.07–1.61)	0.008	1.35 (1.08–1.69)
Nonischemic cardiomyopathy (n = 450)	293 (65)	157 (35)				
Diabetes (n = 345)	177 (51)	168 (49)	<0.001	1.71 (1.391–2.09)	—	—
No diabetes (n = 611)	407 (67)	204 (33)				
Bypass time, min	99 ± 40	109 ± 56	0.003	1.003 (1.001–1.005)	—	—
BMI, kg/m^2	26.7 ± 5.7	27.7 ± 5.9	0.041	1.02 (1.00–1.03)	—	—
LVEDD, mm	70.0 ± 11.0	67.9 ± 11.0	0.005	0.99 (0.98–1.00)	—	—
CVP, mm Hg	12.2 ± 6.6	12.9 ± 6.2	0.083	1.01 (1.00–1.03)	—	—
CI, l/min/m^2	1.98 ± 0.62	2.07 ± 0.65	0.008	1.24 (1.06–1.44)	—	—
Diastolic BP	63 ± 12	61 ± 12	0.004	0.99 (0.98–1.00)	—	—
Albumin, g/dl	3.50 ± 0.59	3.44 ± 0.55	0.080	0.86 (0.72–1.02)	—	—
HCT	35.6 ± 5.8	34.4 ± 5.3	<0.001	0.97 (0.95–0.98)	—	—
>31% (n = 708)	450 (64)	258 (36)	0.003	1.41 (1.13–1.75)	0.023	1.31 (1.04–1.64)
≤31% (n = 243)	130 (54)	113 (46)				
Hemoglobin, g/dl	11.8 ± 2.0	11.4 ± 1.8	<0.001	0.91 (0.86–0.96)	—	—

Values are n (%) or mean ± SD. *Hazard ratio (HR): >65 years of age compared with ≤65 years of age.
BP = blood pressure; CI = cardiac index; CVP = central venous pressure; HCT = hematocrit; other abbreviations as in Table 1.

Table 4 Pre-Operative Statistically Significant Univariable Correlates ($p < 0.1$) and Multivariable Risk Factors for Post-Discharge Hemorrhagic Stroke

	Post-Discharge Hemorrhagic Stroke					
	Univariable Correlates				Multivariable Risk Factors	
Parameter	No (n = 880)	Yes (n = 76)	p Value (Cox)	HR (95% CI) (Cox)	p Value (Cox)	HR (95% CI) (Cox)
Age, yrs	58 ± 14	59 ± 11	0.688	—	—	—
>65 (n = 340)	319 (94)	21 (6)	0.003	2.13 (1.30–3.57)*	0.010	1.94 (1.17–3.23)*
≤65 (n = 616)	561 (91)	55 (9)				
Sex						
Female (n = 220)	189 (86)	31 (14)	0.001	2.14 (1.35–3.38)	0.006	1.92 (1.21–3.05)
Male (n = 736)	691 (94)	45 (6)				
Pre-albumin, mg/dl	18.6 ± 7.2	20.0 ± 8.2	0.038	1.03 (1.00–1.07)	—	—
Inotropes						
Yes (n = 781)	714 (91)	67 (9)	0.085	1.84 (0.92–3.70)	—	—
No (n = 175)	166 (95)	9 (5)				

Values are n (%) and mean ± SD. *Hazard ratio (HR): ≤65 years of age compared with >65 years of age.

Univariable correlates for patients with hemorrhagic strokes were age ≤65 years, female, and serum pre-albumin (Table 4). Additionally, patients on inotropes before LVAD implantation had a trend toward a higher incidence of hemorrhagic stroke ($p = 0.085$). On multivariable analysis, the variables found to be statistically significant were age ≤65 years and female (Table 4, Fig. 2).

There were trends toward higher ischemic stroke rates in patients with a higher platelet count, lower baseline international normalized ratio, lower partial thromboplastin time, history of diabetes, and lower Model for End-Stage Liver Disease score. On multivariable analysis, the independent risk factors for ischemic stroke were female and history of diabetes (Table 5, Fig. 1).

A similar analysis was performed to identify correlates of pump thrombosis. Higher BMI, pulmonary capillary wedge pressure, and white blood count were found to be statistically significant factors. However, there were trends toward a higher incidence of pump thrombosis in DT patients, female patients, and those with a nonischemic etiology. On multivariable analysis, the only statistically significant independent factor was BMI ($p = 0.031$), with a trend toward significance for female ($p = 0.057$).

Impact of age and sex on bleeding, hemorrhagic stroke, ischemic stroke, and pump thrombosis. Figure 2 shows the adverse event rates for bleeding, hemorrhagic stroke, ischemic stroke, and pump thrombosis stratified by age (≤65 and >65 years) and sex. Men who were ≤65 years of age had the lowest incidence of post-discharge bleeding events, whereas women >65 years of age had the highest incidence of bleeding. Men >65 years of age had a higher incidence of bleeding compared with men ≤65 years of age,

Table 5 Pre-Operative Statistically Significant Univariable Correlates ($p < 0.1$) and Multivariable Risk Factors for Post-Discharge Ischemic Stroke

	Post-Discharge Ischemic Stroke					
	Univariable Correlates				Multivariable Risk Factors	
Parameter	No (n = 898)	Yes (n = 58)	p Value (Cox)	HR (95% CI) (Cox)	p Value (Cox)	HR (95% CI) (Cox)
Sex						
Female (n = 220)	199 (90)	21 (10)	0.028	1.82 (1.07–3.11)	0.021	1.88 (1.10–3.34)
Male (n = 736)	699 (95)	37 (5)				
BMI, kg/m^2	27.0 ± 5.8	28.7 ± 6.6	0.033	1.56 (1.04–2.33) per 10 U	—	—
BUN, mg/dl	32.3 ± 20.2	23.5 ± 13.1	<0.001	0.964 (0.94–0.99)	—	—
TBILI, mg/dl	1.23 ± 0.85	1.03 ± 0.74	0.068	0.67 (0.44–1.03)	—	—
PLT, 1,000/mm^3	216 ± 87	235 ± 82	0.054	1.00 (1.00–1.01)	—	—
Diabetes						
Yes (n = 345)	315 (91)	30 (9)	0.011	1.95 (1.16–3.26)	0.009	1.99 (1.19–3.34)
No (n = 611)	583 (95)	28 (5)				
Baseline INR	1.34 ± 0.58	1.21 ± 0.24	0.057	0.30 (0.09–1.03)	—	—
Baseline PTT	45.5 ± 26.1	38.5 ± 14.5	0.076	0.99 (0.97–1.00)	—	—
Baseline MELD	13.4 ± 4.7	11.7 ± 3.4	0.019	0.93 (0.87–0.99)	—	—

Values shown are n (%) and mean ± SD.
MELD = Model for End-Stage Liver Disease; PLT = platelets; TBILI = total bilirubin; other abbreviations as in Table 1.

Table 6 Pre-Operative Univariable Correlates With p < 0.1 and Multivariable Risk Factors for Post-Discharge Pump Thrombosis

	Post-Discharge Pump Thrombosis					
	Univariable Correlates				Multivariable Risk Factors	
Parameter	No (n = 918)	Yes (n = 38)	p Value (Cox)	HR (95% CI) (Cox)	p Value (Cox)	HR (95% CI) (Cox)
DT (n = 551)	520 (94)	31 (6)	0.086	2.06 (0.90–4.71)	—	—
BTT (n = 405)	398 (98)	7 (2)			—	—
Age, yrs	58 ± 14	56 ± 14	0.087	0.98 (0.96–1.00)	—	—
>65 (n = 340)	329 (96.8)	11 (3.2)	0.062	0.511 (0.25–1.033)	—	—
≤65 (n = 616)	589 (95.6)	27 (4.4)			—	—
Sex						
Female (n = 220)	206 (94)	14 (6)	0.060	1.86 (0.96–3.59)	0.057	1.90 (0.98–3.67)
Male (n = 736)	712 (97)	24 (3)				
Ischemic cardiomyopathy (n = 506)	491 (97)	15 (3)	0.074	0.55 (0.29–1.06)	—	—
Nonischemic cardiomyopathy (n = 450)	427 (95)	23 (5)			—	—
BMI, kg/m^2	27.0 ± 5.8	29.1 ± 5.6	0.037	1.69 (1.03–2.77)	0.031	1.71 (1.5–2.77) per 10 U
Pulmonary capillary wedge pressure, mm Hg	24.6 ± 8.4	27.6 ± 7.1	0.027	1.05 (1.01–1.09)	—	—
CVP, mm Hg	12.4 ± 6.4	14.2 ± 7.2	0.075	1.04 (1.00–1.09)	—	—
WBC count	8.1 ± 3.1	8.9 ± 3.2	0.046	1.09 (1.00–1.19)	—	—

Values are n (%) or mean ± SD.
Abbreviations as in Tables 1 and 3.

but not higher than the incidence of bleeding in women (both ≤65 and >65 years of age). By contrast, men >65 years of age had the lowest incidence of hemorrhagic strokes, whereas women ≤65 years of age had the highest incidence of post-discharge hemorrhagic strokes. Although men ≤65 years of age were at a higher risk compared with older men for the development of hemorrhagic strokes, they were still at a lower risk compared with younger women. Men >65 years of age had the lowest incidence rates for thromboembolic events (ischemic stroke and pump thrombosis), whereas women >65 years of age had the highest incidence of thromboembolic events.

Discussion

This retrospective, multicenter analysis of 956 HMII LVAD patients shows that the risk of post-discharge bleeding, hemorrhagic stroke, ischemic stroke, and pump thrombosis during LVAD support differs substantially in subgroups of patients based on factors including sex, age, body size, history of diabetes, and etiology of heart failure. This study is the largest analysis of risk factors for hemorrhagic and thrombotic events in patients with LVADs. Identification of these risk factors may help in the development of anticoagulation and antiplatelet strategies

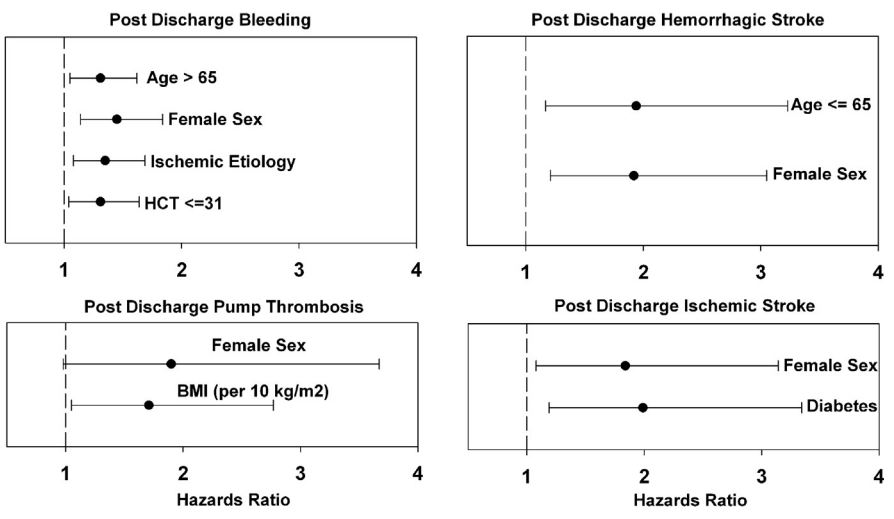

Figure 1 Multivariable Risk Factors for Bleeding, Hemorrhagic Stroke, Ischemic Stroke, and Pump Thrombosis

Hazard ratios for severe thrombotic and hemorrhagic events. BMI = body mass index; HCT = hematocrit.

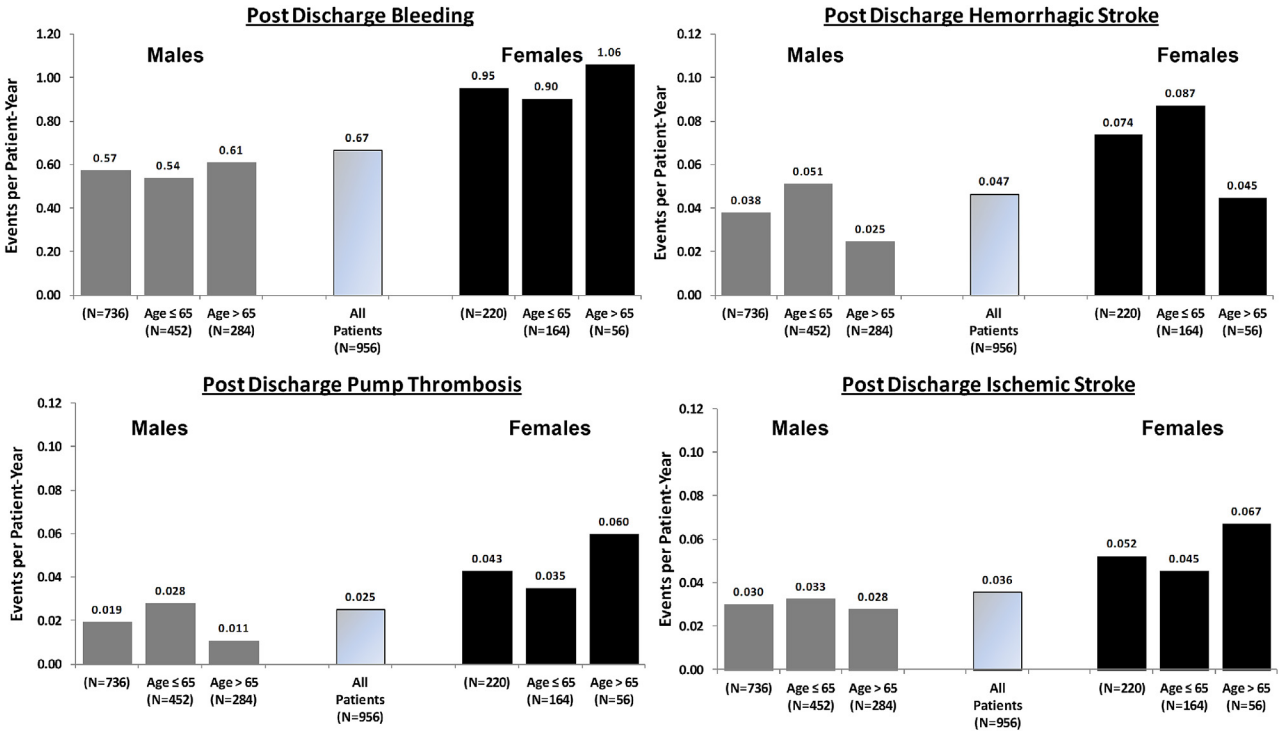

Figure 2 Impact of Age and Sex on Post-Discharge Bleeding, Hemorrhagic Stroke, Ischemic Stroke, and Pump Thrombosis

Event rates for men are shown in **gray**, and rates for women are shown in **black**.

appropriately targeted to minimize events in these subgroups.

Clinical risk factors identified for post-discharge bleeding events, 45% of which were gastrointestinal bleeding, include older age, female, ischemic etiology, and a low pre-operative hematocrit level. For hemorrhagic stroke, younger age and female were significant independent risk factors, whereas for ischemic stroke, female and a history of diabetes were found to be significant factors. For pump thrombosis, female and higher BMI were found to be the multivariable risk factors. Female patients were found to be at risk of bleeding and thrombotic adverse events. However, when stratified by age, younger women (≤65 years of age) were at a higher risk of hemorrhagic stroke, whereas older women were at a higher risk of ischemic stroke. There were no differences between younger and older women in the incidence of bleeding and pump thrombosis, but both were higher compared with men.

Older age, and its associated risk of gastrointestinal bleeding, was well documented in previous studies on CF-LVADs (8,13–15). Our study also found that older patients were at a higher risk of bleeding events, along with ischemic etiology, female, and lower pre-operative hematocrit. A lower hematocrit may be an indicator of bleeding and anemia before LVAD surgery, and when combined with acquired von Willebrand syndrome, which has been shown to occur in patients with a CF-LVAD (6–9), along with the prescribed anticoagulation and antiplatelet therapy, the risk of bleeding is increased.

We found a significantly increased incidence of thrombotic and hemorrhagic events in female patients compared with male patients. An earlier univariable analysis performed in the BTT cohort of patients from the same HMII trial by Bogaev et al. (20) in 104 women and 361 men found a higher hemorrhagic stroke rate (0.10 EPPY vs. 0.04 EPPY), but similar rates of ischemic strokes and bleeding in women versus men. Interestingly, despite the higher incidence of hemorrhagic stroke, no differences in survival were found between women and men, with women having a significant advantage over men in the incidence of other adverse events such as sepsis and driveline infection. One could hypothesize that the smaller size of women may be partly responsible for the difference in events. However, in the current study, body size area did not correlate with ischemic stroke or pump thrombosis.

Women have been found to be at higher risk of some acquired hypercoagulable states. The use of oral contraceptives or hormone replacement therapy has been associated with an increased risk of venous thromboembolism (21,22). The Framingham Heart Study found that women with natural menopause before 42 years of age had twice the ischemic stroke risk than those with a natural menopause after the age of 42 years (23). The state of menopause and

details regarding the use of oral contraceptives or hormone replacement therapy were unavailable, but these underlying risk factors could be having an impact on the higher incidence of ischemic strokes in older women and a higher incidence of hemorrhagic strokes in younger women.

The findings of this study may help to identify a unique patient profile for appropriately targeting an anticoagulation regimen to reduce the risk of bleeding. For example, an older male patient with an ischemic etiology and low pre-operative hematocrit may be able to tolerate and may be more appropriately managed on lower levels of anticoagulation compared with a younger man. However, the goal of developing targeted anticoagulation strategies specifically for female patients is complicated by the increased risk of hemorrhagic and thrombotic events in females. Increasing anticoagulation or antiplatelet therapy to reduce ischemic stroke could result in a fatal hemorrhagic stroke. Initial targeted strategies for subgroups should probably start with older male patients, in whom the risk of ischemic stroke and pump thrombosis is low, but the risk of bleeding is high. Further studies are needed to identify whether prospectively targeting anticoagulation based on identified pre-operative risk factors has an impact on the development of bleeding and thromboembolic events.

Study limitations. This was a retrospective analysis of patients in the pivotal clinical trial, which may not be representative of patients in the population as a whole. Clearly, bias and confounding effects can be introduced because there was no randomization or blinding. Therefore, caution should be used in interpreting the results of this study. Also, because the objective of the study was to evaluate risk factors for events that occurred in long-term support for outpatients, events that took place in the immediate perioperative period and during the initial hospital stay were not evaluated and will be the subject of a separate analysis. Furthermore, only pre-operative risk factors were considered in this review. Post-operative factors such as anticoagulation management, pump parameters, and other acquired risk factors were not evaluated in this study, but are also the subject of another analysis currently underway.

Conclusions

Pre-operative factors related to the risk of bleeding, stroke, and pump thrombosis after initial hospital discharge were evaluated in a large cohort of advanced heart failure patients receiving the HMII LVAD as a BTT or DT. Risks of events were found to differ between demographic groups. Older age, female, ischemic etiology, and low pre-operative hematocrit levels were the multivariable risk factors for bleeding, whereas younger age and female were multivariable risk factors for hemorrhagic strokes. Female and a history of diabetes were the multivariable risk factors for ischemic stroke, whereas female and higher BMI were the multivariable risk factors for pump thrombosis. Further prospective studies are needed to determine whether a targeted anticoagulation management regimen would be beneficial in the subgroups of patients identified to be at high risk of the development of long-term bleeding, stroke, and thrombosis.

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Key Words: bleeding ■ heart failure ■ HeartMate II ■ LVAD ■ pump thrombosis ■ stroke.