



Peer-Reviewed Original Research

Bleeding and Thromboembolic Events in Patients with Heartmate II Mechanical Circulatory Support

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Citation: Allana, S. et al. (2016).
" Bleeding and thromboembolic
events in patients with Heartmate
II mechanical circulatory
support", *The VAD Journal*, 2.
doi:
<http://dx.doi.org/10.13023/VAD.2016.07>

Editor-in-Chief: Maya Guglin,
University of Kentucky

Received: February 9, 2016

Accepted: April 29, 2016

Published: April 29, 2016

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Funding: Supported by the
Clinical and Translational
Science Award through NIH
National Center for Advancing
Translation Sciences grant
UL1TR000427.

Competing interests: none

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Abstract

Background

Bleeding and thromboembolic events (TE) are common complications following HeartMate II (HMII) implantation. The aim of the study was to review our experience related to bleeding and TE events in patients with a HMII and identify factors associated with increased risk of these events.

Methods

We retrospectively reviewed 70 consecutive patients who received a HMII between May 2006 and December 2011. The patients were followed for 12 months or until cardiac transplantation, device explantation or death. Major bleeding was defined by INTERMACS criteria with intracranial bleeding events added.



Results

There were 48 bleeding events in 28 (40%) patients with gastrointestinal bleeding (54.2%) being most common. Patients with bleeding events had significantly higher average INR ($p=0.04$) and more chronic kidney disease ($p=0.03$), although 43.8% of bleeding events occurred at an INR <2 . Twelve TE events occurred in 9 patients (12.9%), with ischemic stroke the most common (75%). TE events were associated with young age ($p=0.04$) and non-diabetes status ($p=0.03$) and were not associated with average INR. There was no association of bleeding or thromboembolism with gender, BMI, HMII speed, pulsatility index, hypothyroidism, smoking history or INTERMACS profile at the time of HMII implantation.

Conclusion

Different factors are associated with bleeding and TE events. The appropriate target INR range for HMII patients should be chosen to balance the risk between bleeding and TE events based largely on patient factors.

Keywords

mechanical circulatory support; ventricular assist device; heart failure; bleeding events; thromboembolic events

Abbreviations

HF = Heart Failure

NYHA = New York Heart Association

MCS = Mechanical Circulatory Support

HMII = HeartMate II

DM = Diabetes Mellitus

CKD = Chronic Kidney Disease

GFR = Glomerular Filtration Rate

vWF = von Willebrand Factor

HMWM = High Molecular Weight Multimers

PI = Pulsatility Index



Introduction

The burden of heart failure (HF) continues to grow, with over 500,000 cases annually¹ and increasing numbers of hospitalizations. With pharmacological and device-based therapies, 1 year mortality of HF patients with New York Heart Association class (NYHA) III and IV has decreased from 50% in 1986 to less than 15% in 2002.¹⁻⁵ Despite these advances, many patients with advanced HF continue to have severe symptoms.¹

In the last 15 years, implantation of mechanical circulatory support (MCS) has been demonstrated to prolong survival and improve quality of life.¹ Continuous flow MCS can be used as destination therapy and bridge to recovery or transplantation.⁶ The HeartMate II (HMII) by Thoratec Corporation, Pleasanton, CA is one such continuous-flow device that has become the most commonly used device for MCS in end-stage HF patients. However, there are still substantial risks and complications during the implant period and with long term HMII support.

Thromboembolic events occur with the use of HMII despite the use of anticoagulation and antiplatelet therapies. This, in turn, is thought to contribute to increased bleeding events in these patients. Indeed, bleeding complications with the HMII are more common than thromboembolic events,⁷ with its incidence varying widely between studies and influenced by the definition of bleeding used. Bleeding was reported in 15.4% of patients in the HMII bridge to transplant trial.⁸ Uriel et al in 2010 reported bleeding to occur in as high as 44.3% of the patients receiving HMII.⁹ In patients who undergo mechanical valve replacement, where a targeted INR is required, bleeding rates of only 2.68 to 4.6 events/100 patient years are seen.¹⁰ In contrast, continuous flow MCS patients have been shown to experience bleeding rates as high as 63 events/100 patient years.¹¹ Therefore, these events must be attributed to factors other than the use of anticoagulation and antiplatelet therapies. A universal loss of high molecular weight multimer (HMWM) has been reported in continuous flow MCS recipients.¹² Development of acquired von Willebrand syndrome due to loss of HMWM appears to be a potential contributor to the bleeding tendencies in HMII recipients.¹³ In the present study we review our experience related to the bleeding and thromboembolic events in patients with HMII implantation and explore factors associated with this increased risk.

Methods

Patients and Study Design

This study is a retrospective chart review of 70 consecutive subjects in whom a HMII MCS was implanted between May 2006 and December 2011 at the University of Wisconsin Hospital and Clinics, Madison, WI. The study was approved and complied with all regulations of the University of Wisconsin Institutional Review Board and the Veterans Affairs Research & Development Committee. Baseline and demographic data were collected including age,



gender, body mass index, HF etiology, NYHA class, history of diabetes mellitus (DM) and chronic kidney disease (CKD). CKD was defined as glomerular filtration rate (GFR) $<60 \text{ mL/min/1.73 m}^2$ for at least 3 months. Subjects were categorized by whether HMII was placed as a bridge to transplantation, bridge to candidacy or as destination therapy. The subjects were followed every 6-12 weeks for 12 months or until cardiac transplantation, device explantation or death. Major bleeding episodes were defined by the INTERMACS criteria¹⁴ as any internal or external bleeding event that results in death, hospitalization, reoperation or red blood cell transfusion (greater than or equal to 4 units within first 7 days post implant and any number of units after 7 days post implant). Intracranial bleeding was also included as a major bleeding episode in this analysis, although it was classified as a neurological event in INTERMACS. Thromboembolic events were defined by any arterial thromboembolic events including ischemic stroke and confirmed pump thrombosis. The HMII pump speed, pulsatility index (PI), flow and power were recorded at the time of the implantation, at 1, 2 and 3 months post implantation and every 3 months thereafter.

Clinical assessment and echocardiographic parameters were used to adjust the HMII speeds to optimize cardiac output, achieve adequate left ventricular decompression, avoid suction events, maintain target pulsatility index and provide aortic valve opening every 2-3 beats when possible. Pump speed was set between 8600 and 10000 rotations per minute (rpm) according to these factors. All patients were on a HF medication regimen titrated to maintain mean blood pressures $<85 \text{ mmHg}$ and optimize perfusion based on clinical assessment.

Anticoagulation therapy

Low dose aspirin and anticoagulation therapy with warfarin was started on post-operative day 2 or 3. INR was maintained between 2 and 3. No post-operative heparin was given. For purposes of this study patients' INRs were recorded at 1, 2 and 3 months' post hospital discharge, every 3 months thereafter and when patients presented with a bleeding or a thromboembolic event. INR at the time of bleeding and thromboembolic events was recorded. Also, average INR was calculated by taking the mean of all the INR values from the time the INR first became therapeutic after the HMII placement till the bleeding event.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0. Continuous data were compared using the t-test and presented as mean and standard deviation. Categorical data were analyzed using the chi square or the Fischer exact test. Results were considered statistically significant for a p value less than 0.05. We also used repeated measure analysis with binary outcome to test the effect of average PI on bleeding events adjusting for months since implant, age and gender. Using a binary outcome analysis, we model the odds of a "success" (bleeding event), $p(x)/(1-p(x))$. The slope= b means that the odds increase multiplicatively by $\exp(b)$ for every one-unit increase in the predictor, PI.



Results

Demographics

The baseline characteristics of the population are shown in Table 1. The INTERMACS profiles of the patients are shown in Figure 1.

Table 1. Baseline Characteristics of the Study Population

Baseline Characteristics	N=70
Average Age	53.3 +/- 11.2
Male	57 (81.4%)
Average BMI (kg/m ²)	29.5 +/- 4.9
Ischemic etiology (%)	32 (45.7%)
Non ischemic etiology (%)	38 (54.4%)
Bridge to transplantation (%)	56 (80%)
Bridge to candidacy (%)	10 (14.3%)
Destination therapy (%)	4 (5.7%)
Chronic kidney disease (%)	34 (48.6%)
Diabetes Mellitus (%)	32 (45.7%)
Tobacco use (%)	46 (65%)
Hypothyroidism (%)	17 (24.3%)

Average follow up was 238+/-168 days with a total of 45.6 patient-years of follow up. Fifteen patients (21.4%) completed 12 months of post device implantation follow up without transplantation, device explant or death; 39 (55.7%) underwent cardiac transplantation and 15 (21.4%) died. One patient developed HML dysfunction with mediastinal hematoma after a fall, requiring device explantation, and was not re-implanted due to recovery of left ventricular function.

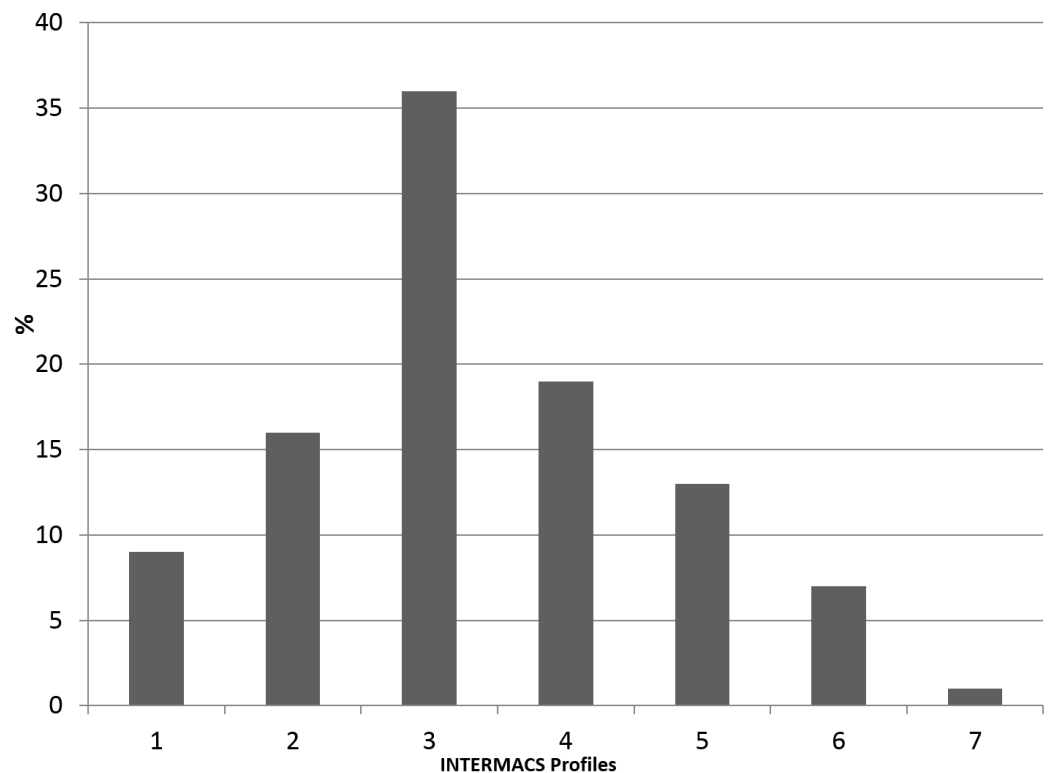


Figure 1 Percentage of study patients (y axis) in various INTERMACS profiles (x axis)

Bleeding

There were 48 bleeding events in 28 patients. Six of these (21.4%) occurred in women. Average age was 56.3 \pm 9.9 years. Blood transfusion was necessary in 27 (56.3%) bleeding events with an average of 2.1 \pm 2.6 units of packed red cells per event (range of 0-12 units, interquartile range of 0-4 units with 0 and 4 the 25th and 75th percentile respectively and median of 2 units per event). Gastrointestinal bleeding was the most common bleeding event. Intracranial bleeding occurred in 6 patients and had a case fatality rate of 50%. Traumatic bleeding occurred in four patients causing mediastinal hematoma, lower extremity hematoma, hemothorax and acute subdural hematoma occurring in one patient each. There were no post-surgical bleeding events. Five bleeding events resulted in death and 5 required major surgical interventions (laparotomy in 2 and craniotomy, thoracotomy and lower extremity debridement in 1 patient each). Bleeding events and their outcomes are summarized in Table 2.

Many bleeding events, 21 of 48 (43.8%), occurred at an INR level of less than 2; 19 (39.5%) at INR between 2 and 3 and 8 (16.7%) at an INR greater than 3 (Figure 2).

Table 2. Bleeding Events and their Outcomes



Bleeding Events	Numbers (%)	Surgical Intervention	Death
Gastrointestinal Bleeding	26 (54.2%)	2	1
Epistaxis	7 (14.6%)	0	0
Intracranial Bleeding	6 (12.5%)	1	3
Vaginal Bleeding	2 (4.2%)	0	0
Pericardial Temponade	1 (2.1%)	1	0
Hemothorax	1 (2.1%)	0	1
Tongue Bleeding	1 (2.1%)	0	0
LVAD pocket hematoma	1 (2.1%)	0	0
Hematuria	1 (2.1%)	0	0
Lower extremity hematoma	1 (2.1%)	1	0
Unknown source	1 (2.1%)	0	0

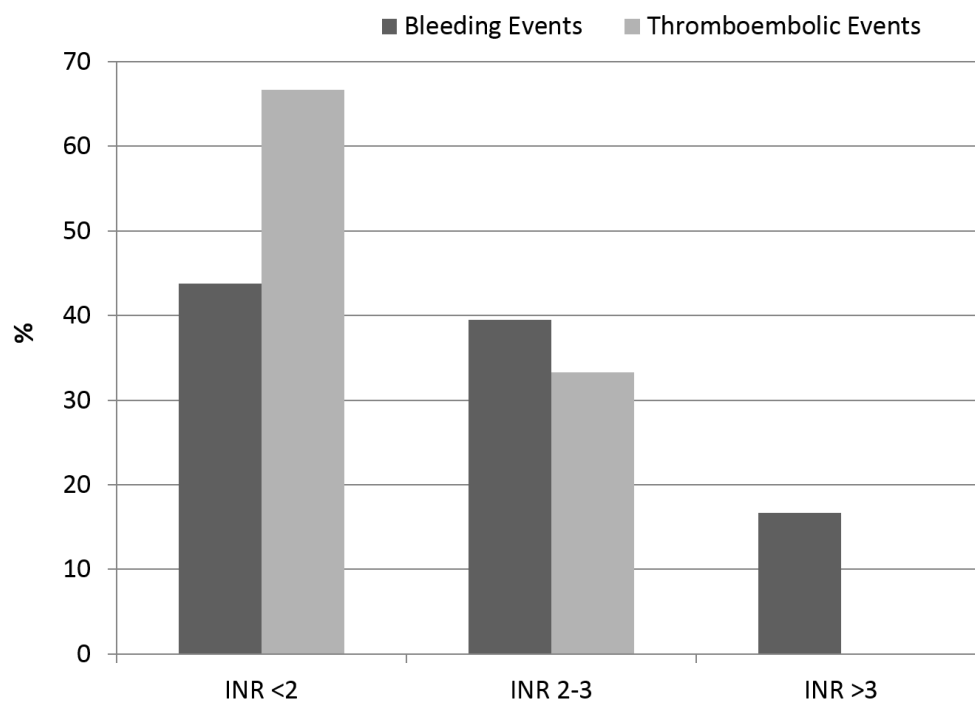


Figure 2 Percentage of bleedings and thromboembolic events (y axis) against INR (x axis)



Table 3 shows clinical characteristics of patients with bleeding compared to those without. Patients with bleeding events tended to be older and had significantly higher average INR than patients without bleeding events. Eighteen of 28 (64.2%) patients with bleeding events had CKD as compared to 16 of 42 (38.1%) without bleeding events ($p=0.03$). Greater proportion of females experienced a bleeding event as compared to males (46% vs 38.6%), although this result was not statistically significant.

Table 3. Comparison of Characteristics of Patients with and without Bleeding Events

Characteristics	Bleeding Patients	Non Bleeding Patients	p value
Avg Age (years)	56.3+/-9.9	51.2+/-11	0.06
Male Gender (%)	78.6	83.3	0.60
Avg BMI (kg/sqm)	30.2+/-5.3	29.4+/-6.3	0.29
Ischemic cardiomyopathy (%)	42.9	47.6	0.70
Avg HMII speed (rpm)	9047+/-411	9105+/-310	1.00
Avg INR	2.47+/-0.43	2.09+/-0.38	0.04
CKD (%)	64.3	38.1	0.03
Pre op GFR (ml/min/1.73 sqm)	44.9+/- 19.0	54.2+/-24.2	0.07
Diabetics (%)	53.6	40.4	0.30
Hypothyroid (%)	25.0	23.8	0.90
Smoking History (%)	60.7	69.0	0.50
INTERMACS profile ≤ 3 (%)	71.1	52.4	0.11

Bleeding was not associated with HMII speed, body mass index pre HMII implantation, HF etiology, DM, hypothyroidism, smoking status or pre-operative INTERMACS profile. We also analyzed bleeding events with the average home PI and PI recorded at each clinic visit. Bleeding events were not associated with average home PI (slope of -0.04 ± 0.29 , $p=0.88$) or the clinic PI value (slope of 0.12 ± 0.35 , $p=0.72$). Average time to a bleeding event was 109 ± 115 days with 34 (70.4%) events occurring within 4 months of device implantation (Figure 3).

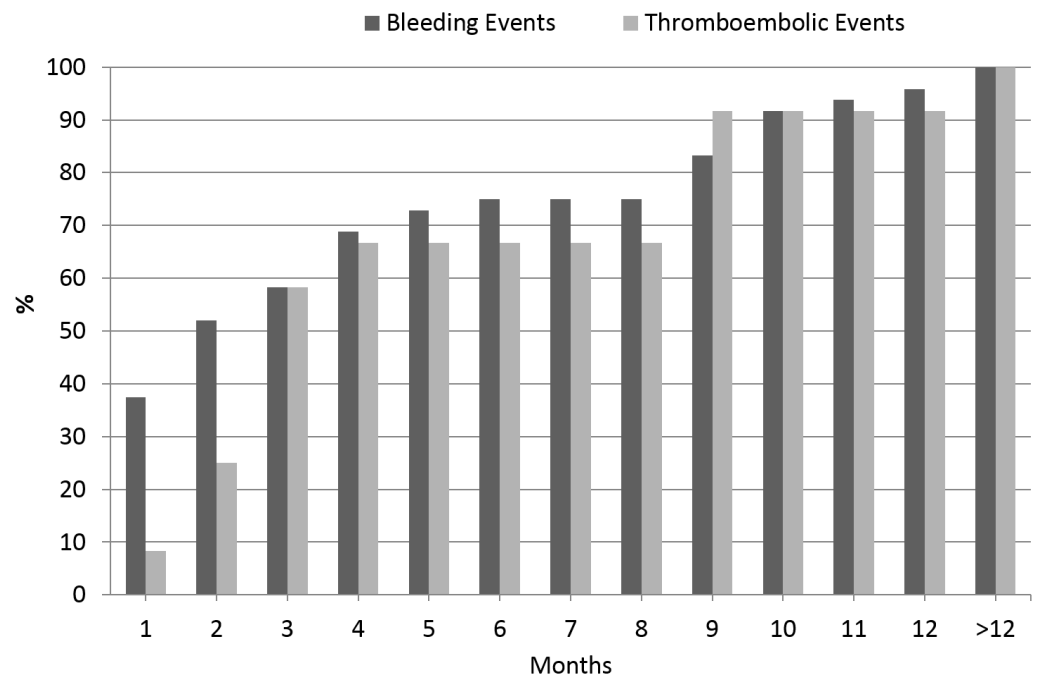


Figure 3: Cumulative percentage of bleeding and thromboembolic events (x axis) over time in months (y axis)

Thromboembolic Events

There were 12 thromboembolic events in 9 patients. All were males except one. Most events, 8 of 12 (66.7%), occurred at an INR of <2 and 4 (33.3%) at an INR between 2 and 3. None of the thromboembolic events occurred with INR >3 (Figure 2). Ischemic stroke was the most common thromboembolic event (Table 4).

Table 4. Thromboembolic Events and their Outcomes

Thromboembolic Events	Numbers (%)	Surgical Interventions	Death
Ischemic Stroke	9 (75)	0	1
Ischemic Bowel	2 (16.7)	2	0
HMI Thrombosis	1 (8.3)	1	0



Table 5 presents the clinical characteristics of patients with and without thromboembolic events. Patients who had thromboembolic events were significantly younger than those who did not. Thromboembolic events were not found to be associated with body mass index, HMII speeds, average INR, HF etiology, hypothyroidism, smoking history, CKD, gender or preoperative INTERMACS profile. Non-diabetics comprised 88.9% (8 out of 9) of the patients who had a thromboembolic event as compared to 49.2% who did not, suggesting thromboembolic events to be more common among non-diabetics ($p=0.03$). Average time to a thromboembolic event was 130 ± 140 days with 7 out of 12 events (58.3%) occurring in less than 90 days (Figure 3).

Table 5. Comparison of Characteristics of Patients with and without Thromboembolic Events

Characteristics	Patients with TE events	Patients with no TE events	p value
Avg Age (years)	46.0\pm15.6	54.2\pm10.2	0.04
Male Gender (%)	88.9	82.0	0.61
Avg BMI (kg/sqm)	32.9 \pm 5.6	29.0 \pm 5.9	0.09
Ischemic cardiomyopathy (%)	55.6	44.2	0.53
Avg HMII speed (rpm)	9017 \pm 315	9079 \pm 377	0.70
Avg INR	2.16 \pm 0.5	2.17 \pm 0.46	0.70
CKD (%)	33.3	50.8	0.33
Pre op GFR (ml/min/1.73 sqm)	33.4	34.4	0.95
Diabetics (%)	11.1	50.8	0.03
Hypothyroid (%)	22.2	24.5	0.89
Smoking History (%)	66.7	65.6	0.96
INTERMACS profile ≤ 3 (%)	44.4	62.2	0.31

Discussion

The HMII is currently the most widely used long term mechanical circulatory support device, with more than 7,000 implantations and more than 3,000 patients on support.¹⁵ It is associated with significant improvement in 2 year survival free of stroke and device failure compared with pulsatile MCS.⁷ Advantages of HMII include its reduced size, increased durability, ease of implantation, and reduced infections.⁹ However, complications can accompany the use of HMII, the most significant of which are bleeding and thromboembolic events.



With varying definitions of bleeding, bleeding rates as high as 44.4% have been reported in patients with HMII.⁹ In our study, 40% of the patients had one or more bleeding events. Using a similar definition of bleeding as in our study, Bunte et al¹⁶ reported occurrence of bleeding in 58% of the population. Notably this study also had a high rate of post-operative bleeding and classified anemia of undetermined source as a bleeding event. The average INR in the bleeding population in our study was significantly higher than the non-bleeding population, even though both values were in the therapeutic range of 2-3. This reinforces that a higher level of anticoagulation contributes to bleeding events. Keeping INR in the low therapeutic range may decrease the frequency of bleeding. However, nearly half the bleeding events in our population occurred at INR of <2. This suggests that average INR over a period of time may be a better marker of bleeding than the INR at the time of the event. Patients on chronic long term anticoagulation secondary to mechanical valve replacement or atrial fibrillation and HF patients on anticoagulation have far lower bleeding rates than those observed in continuous flow MCS populations. The WATCH trial (Warfarin and Antiplatelet Therapy in Heart Failure Trial)¹⁷ that examined the role of anticoagulation in HF patients revealed rates of bleeding on warfarin at 5.2%, significantly lower than observed in our series. Similar results were reported in the WASH (Warfarin/Aspirin Study in Heart Failure) and HELAS (Heart Failure Long Term Antithrombotic Study) studie.^{18,19} These data suggest presence of additional factors contributing to bleeding events in MCS patients.

Recent studies have supported a contribution of acquired von Willebrand deficiency to bleeding events in continuous flow MCS patients.^{9,20-22} HMII patients experience altered physiology due to the high shear stress associated with blood flow through the impeller. This shear stress is hypothesized to result in vWF conformation changes that lead to proteolysis and cleavage of the HMWM by ADAMTS13.²³ Uriel et al⁹ and Meyer et al²² reported decreased or absent HMWM forms of vWF in all patients with HMII in their studies. Similar results were produced in a recent study that showed decrease of 30+/-14% of HMWM of vWF in patients with HMII compared to normal plasma levels.²⁴ However, not all these patients had bleeding events, possibly suggesting a multifactorial etiology.

Gastrointestinal bleeding was the most common cause accounting for bleeding in 22.3% of all the study patients. This is in accordance with the other studies.^{9,25,26} Although the most common etiology, only 1 patient died secondary to a major gastrointestinal bleed. Gastrointestinal bleeding likely results from factors besides anticoagulant therapy and acquired vWF deficiency. Older patients tend to have more colonic polyps, increasing the risk of colonic bleeding. In patients with HMII the left ventricle is relatively decompressed, with minimal opening of the aortic valve creating flow patterns similar to those with aortic stenosis. Heyde et al²⁷ suggested that the abnormal pulse wave associated with aortic stenosis may cause distention of the sub-mucosal venous plexuses of the gastrointestinal tract and eventually lead to angiodysplasia and arteriovenous malformations.²⁷ Cessation of gastrointestinal bleeding has been reported in continuous flow MCS patients after cardiac transplantation.²⁸



Most bleeding events (70.4%) occurred in the first 4 months of HMII implantation. Bunte et al¹⁶ also showed cumulative incidence of bleeding peaking within the first 3 months. There was no post-surgical bleeding requiring re-sternotomy in these patients, although the reported incidence of this varies from 10-30% in literature.^{7,29-31} Previous studies have suggested age as an important risk factor for bleeding after MCS.^{9,26,30} Boyle et al³² determined age >65 a risk factor for increased bleeding in this population. Uriel et al⁹ showed that the risk of bleeding for a patient >66 years was 65%. Our study had only 5 patients (7.1%) who were greater than 65 years of age with a non-significant trend toward increased bleeding in older patients. In our study, bleeding events were more common in patients with CKD. Only 3 patients (10.7%) had 6 bleeding events while on some form of hemodialysis (chronic hemodialysis or continuous veno-venous hemofiltration). Administration of heparin or sodium citrate during the hemodialysis can contribute to bleeding, however, does not explain association of bleeding with CKD as the proportion of patient on hemodialysis was small. Bleeding can also be attributed to platelet dysfunction due to decreased platelet aggregation and impaired platelet adhesiveness in CKD.³³ The impairment in platelet adhesiveness may result at least in part from intrinsic dysfunction of glycoprotein IIb/IIIa, a platelet membrane glycoprotein that plays a major role in platelet aggregation and adhesion by interacting with fibrinogen and vWF.³⁴⁻³⁶

Boyle et al³² reported female gender as a risk factor for bleeding events. In our study although the incidence of bleeding was higher in females, this result was not statistically significant, likely due to a small proportion of female population in the study. We also hypothesized that increased HMII speed would be associated with increased bleeding events. Increased speed would decompress the left ventricle and result in decreased opening frequency of the aortic valve with flow patterns similar to those observed in aortic stenosis and predisposing to gastrointestinal arteriovenous malformations. Higher speeds would also theoretically expose red cells to increased shear stress and increase severity of acquired von Willebrand syndrome. However, in our study there was no association of bleeding with HMII speeds.

We examined the association of bleeding with PI. It has been hypothesized that decreased PI may lead to arteriovenous malformations and thus an increased risk of bleeding through a similar mechanism to the Heyde syndrome in aortic stenosis.²⁷ Wever-Pinzon et al³⁷ reported low PI to be associated with increased risk of non-surgical bleeding during the first 3 months after implantation of HMII. We, however, did not find any association between bleeding events and PI.

Recent data suggests that the bleeding risk of continuous flow MCS support may be offset by minimizing the use of anti-coagulation.³⁸ However, pump thrombus and embolic cerebrovascular accidents remain a concern. In our study, the level of INR was not statistically different in patients with and without thromboembolic events. However, 66.7% of all the thromboembolic events occurred at INR of less than 2 and none of the events occurred at an INR greater than 3. This sheds light on the efficacy of anticoagulant therapy to prevent these events in patients with the HMII. Boyle et al⁸ reported thromboembolic events in 3.3% of the population with HMII, a lower rate than that found in our study. Similar lower



rates have been reported in comparable cohorts in other studies.^{15,39} it is also important to note that the advanced heart failure population has an inherent risk of thromboembolic stroke. In the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial, patients assigned to optimal medical therapy had a yearly stroke rate of 5.2%.⁵

A recent study found significantly increased incidence of thrombotic complications in females;³² however, in our study gender was not associated with thromboembolic events. Interestingly, in our study, thromboembolic events were more common in younger patients and in non-diabetics. In clinical experience, younger patients are seen to be less compliant with medications and also have better inflammatory and clotting cascades that may account for this result. Association of thromboembolic events with non-diabetes status is curious but this could be a cofactor as young patients are less likely to have underlying diabetes mellitus. It appears in our data and the literature that younger patients are more likely to have thromboembolic events and older patients more likely to bleed; a possible implication would be that INR goals be tailored to patient age. However, further studies are needed to confirm this hypothesis.

Recently, Starling et al reported occurrence of pump thrombosis to be 7.5% during 12 months of support, and 12.3% during 24 months of support with HMII.⁴⁰ In our study, only one patient developed pump thrombosis (1.4%).

Conclusion

Our study confirms that thrombotic events in patients implanted with continuous flow MCS are significantly overshadowed by the frequency of hemorrhagic events. We did not find any association of the bleeding or thromboembolic events with HMII speed, body mass index, HF etiology, hypothyroidism, smoking status or pre-operative INTERMACS profile. Bleeding events are associated with chronic kidney disease and the level of anticoagulation, with average INR appearing to be an important factor than the INR at the time of the event. The appropriate target INR range for HMII patients should be chosen to minimize the risk of devastating hemorrhagic and ischemic strokes and reduce the incidence of major bleeding. Since most thromboembolic events in our study occurred at INR <2 and the average INR in the non-bleeding population was 2.09 (compared to 2.47 in the bleeding population), keeping INR values in the lower therapeutic range seems to be a reasonable strategy. However, INR management may best be tailored on an individual basis.



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