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Acquired von Willebrand Syndrome After Continuous-Flow Mechanical Device Support Contributes to a High Prevalence of Bleeding During Long-Term Support and at the Time of Transplantation

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Objectives The objective of the study was to determine the prevalence of bleeding during continuous-flow left ventricular assist device support and to identify potential mechanisms for those bleeding events.

Background Bleeding is frequently reported with continuous-flow left ventricular assist devices and may result from anticoagulation coupled with bleeding diathesis such as acquired von Willebrand syndrome. Accordingly, the prevalence of coagulation abnormalities including laboratory assessment for von Willebrand syndrome, bleeding events during device support, and at heart transplantation were evaluated.

Methods A retrospective study in all HeartMate II (HM II) (Thoratec Corp., Pleasanton, California) patients who underwent implantation between April 1, 2004, and August 1, 2009, was performed. Bleeding was defined as the need for transfusion >7 days after device insertion of 1 U of packed red blood cells. Transfusion at heart transplantation was compared with that in HeartMate XVE patients.

Results Seventy-nine HM II devices were implanted. Anticoagulation included warfarin in 68.3%, aspirin in 55.7%, and dipyridamole in 58.2% of the patients. Of the patients, 44.3% had bleeding episodes at 112 ± 183 days after left ventricular assist device implantation, with 50% experiencing an event within 2 months. Gastrointestinal bleeding was the most frequent event. At the index event, the international normalized ratio averaged 1.67 ± 0.53, and the platelet count was 237 ± 119 × 10^9/l. Comparison of the transfusion requirements at heart transplantation of 35 HM II patients with 62 HeartMate XVE patients demonstrated twice the transfusion requirements in HM II patients (packed red blood cells, 6.3 ± 0.8 U vs. 3.8 ± 0.5 U; platelets, 12.5 ± 5.4 U vs. 8.6 ± 6.4 U; fresh frozen plasma, 9.6 ± 4.9 U vs. 4.9 ± 3.6 U; and cryoprecipitate, 4.3 ± 3.6 U vs. 2.2 ± 3.5 U; $p < 0.05$ for all). High molecular weight von Willebrand factor multimers were measured in 31 HM II patients and were reduced in all patients; 18 of these 31 (58%) patients had bleeding.

Conclusions Patients with the HM II had a high incidence of bleeding events during device support and at heart transplantation. All HM II patients had reduced high molecular weight von Willebrand factor multimers. The role of these abnormalities in the high incidence of bleeding deserves further investigation. Furthermore, alterations in anticoagulation should be considered during device support and before surgery in patients supported with the HM II. (J Am Coll Cardiol 2010;56:1207–13) © 2010 by the American College of Cardiology Foundation

Left ventricular assist device (LVAD) therapy is being increasingly used in patients with advanced heart failure as either a bridge to transplantation or an alternative to transplantation (i.e., destination therapy [DT]). The limited durability and thrombotic complications of the first-generation mechanical support devices precluded widespread application. Newer generation mechanical devices using axial continuous-flow pumps have been increasingly used as a bridge to transplantation. Axial flow pump design includes a single moving part, the rotor, suspended by

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Abbreviations and Acronyms

DT = destination therapy
HM II = HeartMate II
HMW = high molecular weight
HM XVE = HeartMate XVE
HT = heart transplantation
INR = international normalized ratio
LVAD = left ventricular assist device
vW = von Willebrand
vWF = von Willebrand factor
vWF:Ag = von Willebrand factor antigen
vWF:Rco = von Willebrand ristocetin cofactor

bearings that quietly spin at 8,800 to 10,000 rpm. The reduced size, increased durability, ease of implantation, and reduced infections associated with these pumps are some of the advantages of these new devices. Clinical trials using these newer pump designs have demonstrated efficacy in providing hemodynamic support and a favorable risk-to-benefit ratio in both bridge to transplantation (1) and DT (2) populations. However, thromboembolic events are still frequent adverse events with these devices, which require the use of long-term anticoagulation therapy with both warfarin and antiplatelet drugs. Bleeding complications associated with these devices range from as low as 17.5% (3) to as high as 63 events/100 patient-years (4). Owing to the need for anticoagulation, a greater prevalence of bleeding is anticipated with continuous-flow devices such as the HeartMate II (HM II) (Thoratec Corp., Pleasanton, California) than with the pulsatile devices such as the HeartMate XVE (HM XVE) (Thoratec Corp.). Whether this bleeding tendency is simply a consequence of anticoagulation therapy has recently been challenged by reports that suggest that the device design affects hemostatic factors and results in acquired von Willebrand (VW) syndrome (5–7).

Accordingly, we reviewed our experience with a commonly used axial flow pump, the HM II, to better define the prevalence of bleeding in these patients and the need for transfusion during subsequent surgeries, notably heart transplantation (HT). In those patients with bleeding complications, hemostasis studies were performed to determine whether acquired WV syndrome developed in these patients.

Methods

A retrospective chart review was performed from April 1, 2004, to August 1, 2009, of all continuous-flow device patients who underwent implantation at a single large medical center. Minor bleeding was defined as observable blood loss without the need for transfusion. Major bleeding was defined as need for blood transfusion >7 days after device insertion. Hemorrhagic events analyzed included hemorrhagic stroke and bleeding requiring at least 1 U of packed red blood cells. Blood transfusion for hemolysis (n = 1) was excluded from the bleeding analysis. Thrombotic events analyzed included ischemic stroke, pump thrombosis, and systemic embolic events. Stroke was defined as any neurologic event lasting >24 h and categorized as having a hemorrhagic or thromboembolic etiology according to the results of intracranial imaging. Pump thrombosis was defined as any thrombus within the device or its conduits associated with clinical signs of impaired pump performance.

Blood product requirements during HT were collected and compared in patients bridged with HM II with patients bridged with HM XVE.

Platelet counts, prothrombin time, partial thromboplastin time, international normalized ratio (INR) were obtained in all patients. von Willebrand factor (vWF) antigen (VWF:Ag), vWF ristocetin cofactor activity (VWF:Rco), and vWF multimeric structure were measured in patients with major bleeding events or before HT and in a random group of patients with heart failure before HM II support or during support with other devices. vWF:Ag was measured using an immunoturbidiumetric assay, and vWF:Rco was measured using platelet aggregometer PAP4. The multimeric structure analysis was performed as described by Daniels et al. (8), and represents a qualitative measurement of the presence or absence of the largest vWF multimers (high molecular weight [HMW]). Acquired vW syndrome was defined as the decrease in or absence of the largest vW multimers (HMW). Serial testing was obtained in those patients who underwent HT.

Statistical analysis. Data were collected using Excel Software (2007 Microsoft Corp., Redmond, Washington). All data were analyzed using the Stata version 11.0 (StataCorp., College Station, Texas). Categorical variables were summarized by frequencies and percentages, and were analyzed using chi-square test. Student *t* test for independent samples was used to determine differences in normally distributed data. The Wilcoxon rank sum test was used to determine differences in non-normal distributions.

Results

Prevalence of bleeding in continuous-flow mechanical assist devices. Seventy-nine patients (mean age 56 ± 14 years) had an HM II implanted with 64 patients receiving the device as bridge to transplantation and 15 patients receiving it as DT. The patient population is described in Table 1. During a follow-up period of 370 ± 486 days (range 3 to 1,978 days), 40 patients underwent HT; 15 patients died.

During LVAD support, 44 patients had no significant bleeding episodes (Normal) and 35 patients (44.3%) had major bleeding episodes (Bleed). The mean time to bleeding from LVAD implantation was 112 ± 183 days with 50% of episodes occurring within 2 months (median 56 days).

The most common bleeding event was gastrointestinal; 24 patients had gastrointestinal bleeding, 21 patients underwent at least 1 endoscopy, whereas 5 patients had multiple endoscopies. Chest bleeding requiring a surgical procedure was reported in 7 patients (pericardial effusion/tamponade in 6 patients and pleural effusion in 1 patient). Other bleeding sources included oral (after dental extrac-

Table 1 HM II Patient Characteristics (n = 79)

Age (yrs)	56.3 ± 13.7
Male sex, n (%)	63 (79.8)
Body mass index (kg/m^2)	25.9 ± 5.0
BTT/DT	63/14
Heart failure etiology, n (%)	
ICM	33 (45.2)
DCM	40 (54.8)
Previous thoracic surgery, n (%)	22 (29.0)
Diabetes, n (%)	26 (33.3)
Hypertension, n (%)	37 (47.4)
Left ventricular ejection fraction	16.1 ± 7.2
Obstructive lung disease, n (%)	6 (7.7)
Lietz score (n = 63)	9.1

BTT = bridge to transplantation; DCM = dilated cardiomyopathy; DT = destination therapy; HM II = HeartMate II; ICM = ischemic cardiomyopathy.

tion, n = 1), muscle (n = 1), epistaxis (n = 1), and post-menopausal bleeding (4 episodes). Epistaxis was reported in 7 patients, but only 1 patient required blood transfusion. Transfusion requirements averaged 5.7 U of packed red blood cells per bleeding patient (range 2 to 140 U) (Table 2).

Major bleeding events were observed more frequently in older patients (Fig. 1) (60.1 ± 13.5 years vs. 53.4 ± 13.2 years, p = 0.03) and those with ischemic cardiomyopathy as their underlying heart failure etiology (58.8% vs. 33.3%, p = 0.03) Hypertension was also more common (61.8% vs. 46.4%, p = 0.026).

Anticoagulant use at the time of a bleeding event was not statistically different between the groups (Table 3). The INR averaged 1.67 ± 0.53 with an INR >2.5 noted only in 2 patients. The platelet count was 237 ± 119 × 10^9/l, with a low platelet count in 1 patient (48 × 10^9/l). Five patients experienced thromboembolic events: 2 had cerebrovascular accidents in the middle cerebral artery territory, 1 had a popliteal artery embolism, and 2 embolic events were noted after treatment with intravenous immunoglobulin (1 systemic event with a fatal outcome and 1 aortic valve thrombus event). The mean time to thromboembolic events after LVAD implantation was 126 ± 134 days, whereas 50% experienced the event within 2 months (median 30 days).

Comparison of blood transfusion requirements during HT in patients bridged with continuous-flow devices versus pulsatile flow devices. Thirty-five patients (age 53 ± 2 years, 84.2% men) with an HM II underwent HT.

Table 2 Bleeding Events Requiring Transfusion

Event Site	n	Event
GI	24	
Chest	7	6 pericardial effusion, 1 hemothorax
Other	3	Dental, LE wound, postmenopausal
Epistaxis	1	
Total	35	

GI = gastrointestinal; LE = lower extremity.

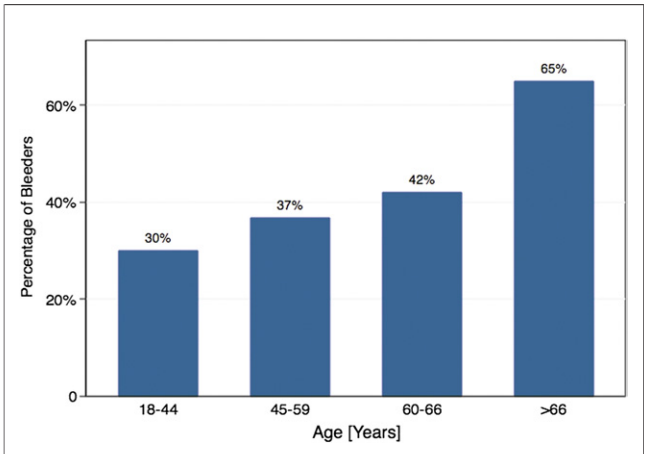

Figure 1 Bleeding Frequency per Quartile Age Group

Major bleeding events occurred more frequently in older patients, with patients older than age 66 years having twice the risk of bleeding during device support compared with patients younger than 44 years of age. Age groups: 18 to 44 years, n = 20; 45 to 59 years, n = 19; 60 to 66 years, n = 19; >66 years (n = 20); p = 0.027.

Their blood product requirements during surgery were compared with those of 62 patients (age 53 ± 2 years, 80.6% men) with an HM XVE who underwent HT during the same time period. More HM II patients were treated with warfarin (89.5% vs. 31.2%, p < 0.001), aspirin (76.3% vs. 59.0%, p = 0.078), and dipyridamole (63.2% vs. 0%, p < 0.001). Patients supported with an HM II required twice the amount of blood products during HT compared with patients supported with an HM XVE (Table 4). Comparing HM II patients with a subgroup of HM XVE patients who also received warfarin treatment revealed the same differences in transfusion requirements after HT.

Table 3 Comparison of Clinical Characteristics of Patients Who Did and Did Not Bleed

Characteristic	Bleed	Normal	p Value
Age (yrs)	60.1 ± 13.5	53.4 ± 13.2	0.031
Male sex, n (%)	30 (85.7)	33 (75)	0.239
Basic metabolic index	26.3 ± 5.4	25.3 ± 4.5	0.398
Ejection fraction (%)	16.1 ± 6.0	16.1 ± 8.3	0.998
BTT, n (%)	26/8 (76.5)	37/6 (86.1)	0.279
HF etiology, n (%)			
ICM	20 (58.8)	13 (33.3)	0.029
DCM	14 (41.2)	26 (66.7)	
Diabetes	12 (35.3)	14 (31.8)	0.747
Hypertension	21 (61.8)	16 (46.4)	0.026
COPD	3 (8.8)	3 (6.8)	1
Lietz score	9.28 ± 4.8	8.97 ± 5.8	0.822
Anticoagulation, n (%)			
Warfarin	24 (75.0)	30 (79.0)	0.695
Aspirin	19 (59.4)	25 (65.8)	0.58
Dipyridamole	20 (62.5)	26 (68.4)	0.603

BTT = bridge to transplantation; COPD = chronic obstructive pulmonary disease; HF = heart failure; other abbreviations as in Table 1.

Table 4 Transfusion Requirements During Heart Transplantation

	HM XVE (n = 62)	HM II (n = 35)	p Value
Packed red blood cells (U)	3.8 ± 0.5	6.3 ± 0.8	0.0055
Platelets (U)	8.6 ± 6.4	12.5 ± 5.4	0.0027
Fresh frozen plasma (U)	4.9 ± 3.6	9.6 ± 4.9	0.0000
Cryoprecipitate (U)	2.2 ± 3.5	4.3 ± 3.6	0.0035
CellSaver (U)	3.9 ± 2.3	5.0 ± 4.0	0.50

HM = HeartMate.

Possible mechanism: acquired VW syndrome and continuous-flow assist devices. Thirty-one patients (27 men) with HM II support were evaluated for vW syndrome; 18 patients were tested after major bleeding events and 13 were tested before anticipated surgeries. All patients had decreased or absent HMW forms of vWF needed for platelet adhesion, which is sufficient for the diagnosis of acquired vW syndrome. vWF:Ag was 204 ± 107%, and vWF:Rco was 102 ± 27%, both within normal range. When the levels of vWF:Ag and vWF:Rco were divided by the median level and the incidence of bleeding in those groups were compared, no significant differences in bleeding events were noted ($p = 0.45$ and $p = 0.275$, respectively).

All patients tested with bleeding events had vW syndrome with decreased to absent HMW vW multimers. Sixteen patients had gastrointestinal bleeding, and 2 patients had pericardial bleeding.

In all 6 patients who had vWF levels measured during HM II support and repeated after HT, there was normalization of the HMW vWF multimer levels with a statistically significant elevation in vWF:Ag and vWF:Rco (Table 5). In 1 patient, normal HMW vWF multimer levels pre-implantation decreased with HM II support.

Additionally, vWF levels were measured in a variety of advanced heart failure conditions in random fashion. Three patients with advanced heart failure on inotropic support had normal HMW vWF multimer levels. Two patients with an HM XVE and 1 patient with a Duraheart (Terumo Heart Inc., Ann Arbor, Michigan) had normal HMW vWF multimer levels. One patient with CentriMag BiVad (Thoratec Corp.) support as a bridge to transplantation had decreased HMW vWF multimers. None of the patients with normal vWF multimer levels had a bleeding event (18 of 31 vs. 0 of 6, $p < 0.001$).

Discussion

We examined the prevalence of major bleeding episodes in advanced heart failure patients supported with a continuous-flow LVAD (HM II). vWF levels were studied during the support time, and blood product requirements were collected in those patients who underwent HT. Thirty-five patients (44.3%) had major bleeding episodes at a median time of 56 days after device implantation; gastrointestinal bleeding was the most common source. At HT, HM II patients required significantly higher amounts of blood products compared with HM XVE patients, even a subgroup receiving warfarin. Acquired vW syndrome developed in all patients on device support diagnosed by the decrease in or absence of HMW vWF multimers. This hemostatic abnormality may explain the excessive bleeding in the continuous-flow device patients.

In recent years, LVADs using rotary pump technology to provide continuous flow with reduced pulsatility have shown great promise (1,2). These continuous-flow LVADs improve hemodynamics, end-organ function, quality of life, and functional capacity of patients awaiting HT (1,9). Recently, Slaughter et al. (2) reported that implantation of a continuous-flow LVAD, compared with a pulsatile-flow device, significantly improved survival at 2 years in patients with advanced heart failure who were ineligible for HT. Based on these and other clinical data, many centers have transitioned from pulsatile-flow devices to continuous-flow devices. With the recent approval of the HM II by the U.S. Food and Drug Administration as DT, an increase in LVAD implantation among patients who are ineligible for HT is anticipated.

Patients with continuous-flow devices require anticoagulation and antiplatelet agents to attenuate the risk of thromboembolic events. Results from the HM II Pivotal Trial supported the use of aspirin at a dose of 81 mg/day and warfarin achieving and maintaining an INR of 2.0 to 3.0 as soon as post-operative bleeding was controlled. Case series have suggested that gastrointestinal bleeding may be a more frequent complication with continuous-flow devices (10). Crow et al. (4) reported in a series of 101 patients that the rate of gastrointestinal bleeding was significantly higher in patients receiving continuous-flow LVADs compared with pulsatile devices. There were 63 gastrointestinal bleeding events per 100 patient-years in nonpulsatile device recipients compared with 6.8 in the pulsatile group ($p = 0.0004$). Possible pathophysiological explanations for these phenomena included the increased use of anticoagulation and/or the development of a bleeding diathesis.

Table 5 von Willebrand Factor Levels (n = 31)

	During VAD Use	After HT	p Value
Decreased or absent VW multimers	100%	0%	0.001
VW antigen	203.5 ± 107.1, median 187	309.5 ± 83.0, median 327	0.03
Ristocetin	102.4 ± 26.6, median 117	144.0 ± 53.7, median 120	0.009

VAD = ventricular-assist device; VW = von Willebrand.

Multiple studies have been done using warfarin in chronic heart failure patients. In the HELAS (Heart Failure Long Term Antithrombotic Study), 197 chronic heart failure patients were randomized to treatment with aspirin or warfarin. Major hemorrhage occurred in the warfarin group at a rate of 0.046 per patient-year and was to the result of overanticoagulation. Similar results were reported in the WASH (Warfarin/Aspirin Study in Heart Failure) (11,12). The WATCH (Warfarin and Antiplatelet Therapy in Heart Failure Trial) (13) examined the role of anticoagulation in 1,587 chronic heart failure patients and compared warfarin, aspirin, and clopidogrel. Although increased bleeding was reported in the warfarin group (5.2% vs. 3.6% vs. 2.1%, respectively), this bleeding rate is significantly lower than the event rate observed in our series. In the context of these studies, our findings suggest that the high bleeding rate seen in our cohort cannot be totally attributed to anticoagulation therapy.

In 1958, Heyde et al. (14) reported a high incidence of gastrointestinal bleeding in aortic stenosis patients (Heyde syndrome). In the 1990s, Warkentin et al. (15) raised the question of whether stenotic aortic valves predisposed patients to the development of acquired vW syndrome, which could contribute to high bleeding events from gastrointestinal angiodysplasia, which is common in these patients. Further studies by several investigators have shown that aortic stenosis and gastrointestinal bleeding are associated with acquired type 2A vW syndrome, which is characterized by the loss of HMW vWF multimers (15,16). High shear forces induce structural changes in the shape of the vWF molecule, leading to exposure of the bond between amino acids 842 and 843. This results in proteolysis of the highest molecular weight multimers of vWF, which are the most effective in platelet-mediated hemostasis under conditions of high shear stress (17,18). Aortic valve replacement reverses this hematological syndrome (19,20). Continuous-flow LVADs may cause a similar syndrome. Geisen et al. (7) reported an impaired function of vWF with respect to binding to collagen and to platelet receptor GPIb (reflected by ristocetin cofactor activity) and loss of HMW biologically active vWF multimers in 7 HM II patients. In our study, all HM II patients who underwent vWF testing had low to absent levels of HMW vWF multimers. HT reversed this phenomenon, suggesting that the LVAD support was causative of acquired VW syndrome. The vWF level changes in our cohort are especially noteworthy, given the study by Lip et al. (21) that demonstrated a positive correlation between heart failure and increased plasma vWF concentrations, with highest plasma vWF levels in patients with acute or recent decompensated chronic heart failure.

In a recent study of HM II patients by Boyle et al. (3), the rate of thromboembolic events (3%) was not dissimilar from our findings (6.3%). Anticoagulation is indicated but given the development of acquired vW syndrome in continuous-flow LVAD patients, the current guidelines recommending the use of warfarin in conjunction with antiplatelet agents needs to be reconsidered. The role of routine follow-up of vWF levels and the adjustment of antiplatelets and/or the INR levels to the degree of acquired vW syndrome severity should be studied. Although this study focused on the HM II, this phenomenon may be occurring with other continuous-flow devices. vWF abnormalities were also described in BiVad devices (7) and centrifugal pumps (6), and the clinical implication of those findings may be similar: increased major bleeding events and need for more blood products during HT.

The effects of this bleeding diathesis may change the course of the HT in patients bridged with HM II. During HT surgery, patients with HM II received double the amount of blood products than did patients bridged with the HM XVE. Kuduvalli et al. (22) reported that perioperative red blood cell transfusion after cardiac procedures was associated with an increased risk of death during a 1-year follow-up. In general, transfusions of blood products are associated with increased risk of short- and long-term complications. Minor transfusion reactions, such as fever and hypotension, occur frequently. Major transfusion reaction such as transfusion-related acute lung injury and a pulmonary leukoagglutinin reaction are less common (23). In our population, transfusion-related acute lung injury might have been masked because clinical signs can be confounded by post-operative complications such as atelectasia, congestive heart failure, and pleural fluid or as a consequence of ischemia and reperfusion injury induced by cardiopulmonary bypass (24). Other complications may result from substantial changes in the immune system after transfusion. Banbury et al. (25) reported that the risk of infection increased incrementally with each unit of blood transfused in 15,592 post-cardiac surgery patients. Those infections can include bacteria/viral (e.g., human immunodeficiency virus, hepatitis B virus, hepatitis C virus) and transmissible spongiform encephalopathies (e.g., Creutzfeldt-Jacob disease) (26). Whether the increase in blood product transfusions observed in our series carries an increased risk of the complications mentioned needs to be investigated.

The effect of LVAD on post-transplantation mortality was a subject for many studies and yielded conflicting results. Recently, Patlolla et al. (27) conducted a retrospective analysis in 11,336 patients entered into the United Network for Organ Sharing Thoracic Registry to examine the relationship between intracorporeal and extracorporeal VAD implantation and post-transplantation mortality. They reported that intracorporeal ventricular assist devices are associated with a small increase in mortality in the first 6 months and a clinically significant increase in mortality beyond 5 years. The increased use of blood products that we are reporting here may be an explanation for this report, by increasing allosensitization during LVAD support. In contrast, Pal et al. (28) compared the transplantation outcomes of patients bridged with an LVAD and intravenous inotropes. They reported no increase in post-transplantation

morbidity or mortality and did not observe an increased incidence of rejection episodes in the first year after HT. Furthermore, measured levels of anti–human leukocyte antigen antibodies were similar in the LVAD group compared with the intravenous inotrope group. Our group's analysis of the United Network for Organ Sharing data for adult heart transplant recipients from January 1, 2001, to December 31, 2006, found that the use of intracorporeal and paracorporeal devices was not associated with decreased survival after HT (29) and concurs with the report of Pal et al. (28).

Study limitations. This is a single-center study of a small number of patients who were screened for vW syndrome if bleeding was present or if surgery was anticipated. Therefore, all device-supported patients were not screened. The incidence and the timing of the development of this syndrome cannot be derived from this study.

Conclusions

Patients supported by an HM II have a high risk of major bleeding during the support time and at the time of HT. The increased prevalence of bleeding with continuous-flow devices is not explained by excessive anticoagulation therapy. Acquired vW syndrome occurs almost uniformly in patients on continuous-flow assist devices and appears to be a significant contributor to the observed bleeding. Bleeding during HM II support is particularly frequent in older patients and, unless prevented, may constitute a major limitation of DT. Routine monitoring of vWF multimers or of their activity and alteration of anticoagulation treatment in these patients should be addressed.

Given our current observations, our program has developed the following approach to bleeding complications in patients with continuous-flow devices. All anticoagulation medications are discontinued during the bleeding episode and until hemodynamic stability is achieved. The bleeding site is identified and corrected, if possible. After stabilization of hemoglobin levels, anticoagulation treatment is resumed on an individual patient basis considering the extent of bleeding, the patient's age, and the risk of thrombosis. The majority of patients are restarted on warfarin or aspirin alone. Although we can hypothesize that platelet inhibitors should be discontinued once a decrease in HMW vWF multimers is observed, we do not have enough data to recommend anticoagulation changes according to vWF studies. A randomized, multicenter, prospective trial is needed to define the optimal anticoagulation regimen for patients supported with continuous-flow devices.

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