Acquired von Willebrand syndrome and hemocompatibility-related adverse events in patients with left ventricular assist device

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Abstract Left ventricular assist device (LVAD) is an important therapeutic option for patients with end-stage advanced heart failure. LVAD can reduce cardiovascular death and improve the quality of life in patients with end-stage advanced heart failure. However, as LVAD-implanted patients increase and survival becomes prolonged, many patients experience serious complications. Major complications of LVAD include ischemic and hemorrhagic strokes, bleeding complications, device thrombosis, right heart failure, and LVAD related infections. These complications lead to worse mortality in patients with LVAD. In particular, cerebrovascular events and gastrointestinal bleeding are the most dreaded complications. High molecule weight multimers of von Willebrand factor (vWF-HMWM) play an essential role in platelet adhesion and aggregation, but high shear stress caused by LVAD pump diminishes the vWF-HMWM. In fact, in response to the shear stress of LVAD, vWF exposes cleavage domains of ADAMTS 13 to form smaller multimeric molecules. Therefore, in many patients with LVAD, the vWF reduces its large multimers and lowers the ability to bind sufficiently to platelets and sub-endothelial collagen, resulting in the acquired von Willebrand syndrome. Thus, in LVAD patients with acquired von Willebrand syndrome, vWF function is impaired, and this impairment is associated with hemocompatibility-related adverse events. Based on hemorheology, this review focuses on the pathophysiology of acquired von Willebrand syndrome and its management in patients with LVAD.

Keywords acquired von Willebrand syndrome, left ventricular assist device, shear stress, von Willebrand factor (vWF), ADAMTS13, vWF high molecular weight multimers (vWF-HMWM)

Introduction

It is estimated that 5.8 million people in the United States and at least 10 million people have congestive heart failure [1]. Heart failure is a growing public health issue affecting at least 26 million people worldwide [2]. About half of people who develop heart failure die within five years of diagnosis [1, 3]. Advanced heart failure as an indication of LVAD implantation should meet the following criteria [4]: (1) left ventricular ejection fraction (LVEF) <25% and a peak VO2 <12 mL/kg/min (if measured) (2) more than three hospital admissions within 12 months without evident precipitating factors, (3) dependence on inotropic support or mechanical circulatory supports, and (4) end-organ failure and increased left ventricular end-diastolic filling pressure (≥20 mmHg), low blood pressure (80–90 mmHg) and low cardiac index (≤2 L/min/m²).

REMATCH study demonstrated that a left ventricular assist device (LVAD), first-generation pulsatile-flow HeartMate XVE, can improve the mortality in patients with end-stage advanced heart failure [5]. After the transition to continuous flow, the new generation LVADs are classified as axial/centrifugal flow. HeartMate 2 is classified into axial-flow LVAD and HeartMate 3 centrifugal-flow LVAD (Figure 1). A propeller generates the axial-flow in the LVAD pump chamber, while the centrifugal-flow by a bladed disk rotating. According to the HeartMate 2 study, the second-generation axial continuous-flow LVAD improved mortality, quality of life (QOL), the functional capacity of patients, and device durability, compared to Heartmate XVE [6]. In addition, the ROADMAP study demonstrated that survival with improved active status was better with HeartMate 2, compared to optimal medical management [7, 8]. The latest LVAD is HeartMate 3. It is a centrifugal-flow pump with fully magnetic levitation and artificial pulsatility to minimize the
destruction of red blood cells and thrombosis [9]. Momen-
tum 3 study, the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3, demonstrated that HeartMate 3 was superior to HeartMate 2 in the survival free of stroke and reoperation to replace devices [10].

To date, LVAD has rapidly emerged as a durable and safe therapy for those patients with >22,000 implantations [11]. Now that, LVAD therapy is world-wide used as “a bridge to heart transplant (BTT),” “bridge to candidacy (BTC),” “bridge to recovery (BTR),” or “a destination therapy (DT)” [12, 13] (Table 1). LVAD types currently approved by the U.S. Food and Drug Administration and their mechanical properties are shown in Table 2. In Japan, The Japanese registry for mechanical assisted circulatory sup-
port (J-MACS) is a prospective registry to collect all data of implantable LVAD from 2010. As of Oct 2018, 711 primary

LVAD implants and 168 BTR implants were enrolled [14]. In Japan, where the number of transplant donors is extremely small, the waiting period for heart transplantation is about 7 to 8 years, which is much longer than in other countries. Because of the very long waiting period, LVAD-related complications are also common in Japan [14]. Recently, DT, which does not presuppose a heart transplant, was covered by public medical insurance. Unfortunately, despite advances in the LVAD pump design and clinical management, LVAD-related complications remain frequent and contribute to poor QOL in LVAD patients [15].

Figure 1 Axial-flow pump LVAD (A) and Centrifugal-flow pump LVAD (B). (A) Axial-flow pump. The inlet cannula is placed in the apex of the left ventricle. The blood subsequently enters the pump, the structure of which has undergone significant changes over time. The outflow graft leads to the ascending aorta. Blood have to go through the tiny lumen of the small pump. Adapted from JACC HF 2017; 5: 518–527. (B) Centrifugal-flow pump. Centrifugal-flow pump with fully magnetic levitation, and artificial pulsatility, to minimize destruction of red blood cell and thrombosis. Wide blood flow passages to reduce shear stress, frictionless with absence of mechanical bearing in the pump. And intrinsic pulse to reduce stasis and aver thrombosis. Adapted from ASAIO 2016; 62: 375–383.
LVAD induced hemocompatibility-related adverse events

Bleeding adverse events

According to the 8th annual INTERMACS report, approximately 60% of LVAD patients were hospitalized at least once during the post-LVAD-implantation period [16]. As complications related to LVAD therapy, there are stroke, aortic insufficiency, right heart failure, pump thrombosis, driveline infection, and gastrointestinal (GI) bleeding [11]. Three major adverse events are right heart failure, LVAD-related infections including driveline infection, hemocompatibility-related adverse events including bleeding and thrombosis in the cerebrovascular or gastrointestinal system. Unfortunately, hemocompatibility-related adverse events, especially GI bleeding, are the most frequent reason for readmission after LVAD implantation [17, 18].

The incidence of GI bleeding was 0.068 events per patient-year in patients with pulsatile-flow LVAD and 0.63 events per patient-year in patients with continuous-flow LVAD [19]. LVAD-associated bleeding occurs in 19% to 40% of patients on HeartMate 2 support [20, 21]. On the other hand, GI bleeding events in HeartMate 3 were significantly less frequent than those in HeartMate 2 over two years (HeartMate 3 vs. HeartMate 2: 0.31 vs. 0.49 events per patient-year) [6]. Surprisingly, the number needed to treat (NNT) over two years to avert at least thrombotic adverse events is less than 1 in HeartMate 3 [10, 22]. In addition, there was a distinct difference in hemocompatibility-related adverse events between axial-flow and centrifugal-flow LVAD. Because the shear stress and shear rate depend on the pump design [23] and LVAD-pump speed [24], the centrifugal-flow LVAD with fully magnetic levitation permits lower shear stress. The lower shear stress has a significant advantage in avoiding hemocompatibility-related adverse events (Table 2).

Thromboembolic adverse events

All LVAD patients should be on anticoagulation such as warfarin to prevent thrombosis. The target PT-INR should be between 2.0 and 3.0 in the post-LVAD-implantation period. LVAD pump thrombosis usually occurs in the bearing part of the LVAD and appears on examination as chronic fibrinous pannus formation that is not responsive to thrombolytic therapy [25]. LVAD pump exchange is the best treatment option for pump thrombosis. The incidence of pump thrombosis in HeartMate 2 was 11.3%, whereas HeartMate 3 was just 2.3% at two years after implantation [10].

Table 1 Types of LVAD therapy

| Type                  | Status                                                                 |
|-----------------------|------------------------------------------------------------------------|
| Bridge-to-Transplantation | The purpose of Bridge-to-Transplantation is to provide circulatory support to transplant-eligible patients with HFrEF until a donor’s heart becomes available. |
| Destination therapy | Destination therapy is used in patients with HFrEF who are ineligible for cardiac transplantation. |
| Bridge-to-the-Candidacy | A patient was too sick to be a candidate for a certain therapy, but the bridge may carry them to a state of being eligible. |
| Bridge-to-Recovery | Bridge-to-Recovery provides temporary ventricular support in some heart failure patients has been shown to improve myocardial function and promote recovery. |

Table 2 LVAD types currently approved by the FDA and their mechanical properties

| Device Type | HeartMate 2 | HeartMate 3 | HeartWare HVAD* |
|-------------|-------------|-------------|----------------|
| Indication | Bridge to transplant (2008) | Bridge to transplant (2017) | Bridge to transplant (2012) |
| Speed range | 6000–15,000 rpm | 3000–9000 rpm | 2400–3200 rpm |
| Rotor design | Axial pump | Centrifugal pump | Centrifugal pump |
| Pump position | Pump pocket | Intra-pericardial | Intra-pericardial |
| Blood flow gaps | ≈0.08 mm | ≈0.12 mm | ≈0.05 mm |
| Magnetic levitation | No | Yes | Yes |
| Artificial pulsatility | No | Yes | |
| High inlet suction | Yes | No | |

* Recently, Medtronic is recalling their HeartWare HVAD System due to safety issues with (1) Carrying Cases, (2) Driveline Cover Orientation, and (3) Controller Power-Up Sequence, as a Class I recall: the most serious type of recall. URL: https://www.fda.gov/medical-devices/medical-device-recalls/medtronic-inc-recalls-instructions-use-and-patient-manual-heartware-hvad-system-update-information

LVAD, left ventricular assist device; HFrEF, heart failure with reduced ejection fraction.
According to the society of thoracic surgeons INTERMACS annual report, the freedom from the first stroke, regardless of severity, at three years was 78\% for axial-flow LVAD and 93\% for continuous-flow LVAD with fully magnetic levitation [12]. In the HeartMate 2 study, a stroke rate was 0.064 events per patient-year [26]. LVAD patients who experienced a stroke had a 2-fold risk of mortality compared to stroke-free LVAD patients [26]. Over time, the centrifugal-flow LVAD with fully magnetic levitation showed superior freedom from stroke relative to the axial-flow LVAD [12]. The severity of stroke in the HeartMate 3 was lower than that in the HeartMate 2 [6]. In the MOMENTUM study, the centrifugal-flow pump HeartMate 3 was associated with a lower incidence of either ischemic or hemorrhagic strokes of any severity and fewer bleeding events [10].

**Pulsatility and Endothelial Function**

Continuous-flow LVAD has a unique physiology characterized by a non- (weak-) pulsatile and non-laminar blood flow profile without Wind-Kessel effect during diastole. LVAD patients without pulsatility have a high incidence of complications such as GI bleeding, pump thrombosis, and stroke [27]. In an animal model, reduction of pulsatility resulted in higher levels of matrix metalloproteinase activity and markers of cell proliferation [28]. It was suggested that this matrix degradation may contribute to the pathophysiology of the increased vascular resistance associated with non-pulsatility. In another animal study using LVAD, systemic vascular resistance increased and nitric oxide levels decreased with non-pulsatility [29, 30]. In the other animal experiments, a similar decrease in nitric oxide and an increase in reactive oxygen species were observed in the non-pulsatile vascular endothelial cells [31]. It has been suggested that decreased pulsatility may cause inflammatory damage to vascular endothelial cells and adversely affect their function.

**Role of von Willebrand factor (vWF) in the hemostasis**

In 1926, a Finnish physician, Erik von Willebrand, first reported a family suffering from severe hereditary bleeding [32]. The patient had multiple episodes of severe mucosal bleeding, leading to her death at 13 years. Three of four sisters had died before 4-year-old, due to severe bleeding, too. Four of her eleven siblings were also severely affected. However, their platelet counts were normal. Therefore, Dr. von Willebrand considered the illness as a disease of platelet dysfunction or vascular abnormalities leading to bleeding.

In 1985, the cloning of von Willebrand factor (vWF) was performed from a DNA library of vascular epithelial cells [33, 34]. vWF is synthesized in endothelial cells and megakaryocytes [35] and is a plasma glycoprotein with a molecular weight of approximately 250 kDa, consisting of 2,050 amino acids [36] (Figure 2). The vWF exists as a monomer and is linearly linked by double bonds to form multimers ranging from 1,000 to 20,000 kDa. It goes through a process of multimerization to become a huge multimer form [37]. First, the dimerization of vWF is performed by forming interchain disulfide bonds between the C-terminal of the vWF in the endoplasmic reticulum [38] (Figure 3). Next, the vWF dimers are transported to the Golgi apparatus and modulated with glycosylation and sulfation. Afterward, the vWF multimers are formed by disulfide bond between D3 regions of the N-terminal of the vWF [39]. Thereafter, the vWF multimers are stored in Weibel-Palade bodies and the alpha granules of platelets [40]. Smaller multimers vWF are spontaneously released to the subendothelial extracellular matrix [41]. In response to stimuli, Weibel-Palade bodies release vWF multimers into the vessel lumen [41]. The usual range of plasma vWF concentrations is 500 to 1000 μg/dL. Platelets contain approximately 15\% of the quantity of vWF present in an equal amount of platelet-poor plasma [42].

vWF plays a crucial role in primary hemostasis in the form of platelet adhesion and aggregation [43] (Figure 4). vWF exists as multimers of various sizes, and the higher the molecular weight of the multimers, the more pronounced the hemostatic effect. vWF also binds to blood coagulation proteins, such as factor VIII and von Willebrand factor (VWF) with its functional domains. An ADAMTS13 cleavage site is located in the A2 domain. Binding sites are indicated for FVIII (D’ and D3 domains), GPIb (A1 domain), collagen (A3 domain), and GPIIb/IIIa (C1 domain).

**Figure 2** The structure of von Willebrand factor (vWF) with its functional domains. An ADAMTS13 cleavage site is located in the A2 domain. Binding sites are indicated for FVIII (D’ and D3 domains), GPIb (A1 domain), collagen (A3 domain), and GPIIb/IIIa (C1 domain).
factor VIII and stabilizes coagulation factor VIII in plasma. Thus, vWF plays a substantial role in the initial coagulation cascade.

vWF-high molecular weight multimers (vWF-HMWM) and ADAMTS-13

The platelet-binding capacity of vWF is proportional to the length of its multimer. The presence of vWF ultra-large multimers in the bloodstream is associated with spontane-
ouls thrombosis, whereas its deficiency leads to bleeding. vWF high molecular weight multimers (vWF-HMWM) can have the greatest platelet-binding capacity, whereas vWF low multimers have the weakest platelet-binding capacity [44]. Thus, to maintain a balanced hemostatic system, the length of the vWF multimers must be strictly controlled. Circulating metalloprotease ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13), synthesized in megakaryocytes, platelets, hepatic stellate cells, and endothelial cells [45, 46], regulates the length of vWF multimers. As the vWF cleaving enzyme, ADAMTS13 plays a vital role in the homeostasis of coagulation. Thrombotic thrombocytopenic purpura (TTP) is caused by severely deficient activity of the ADAMTS13, clinically defined as an activity level less than 10% [47]. Thus, thrombocytopenia in TTP is due to dysfunction of ADAMTS13 in the microcirculation, resulting in excessive vWF multimers and abnormal platelet consumption.

Impacts of shear stress on vWF-HMWM

In 1958, Edward Heyde first reported that elderly patients with aortic stenosis tended to show GI bleeding [48]. Although the original description was the association between GI bleeding due to angiodysplasia and aortic stenosis, previous reports revealed that vWF-HMWM decreased in patients with aortic stenosis [49–53].

Changes in shear stress can cause alteration in the conformation of vWF-HMWM [51, 54]. The shear stress plays an essential role in controlling the hemostatic action of vWF. vWF-HMWM makes the molecular structures sensitive to changes in blood flow and shear stress. Especially in the area of higher shear stress, the vWF-HMWM can be unfolded and elongated, which is susceptible to cleavage by ADAMTS13 (Figure 5). Indeed, the unfolded vWF-HMWM exposes the cleavage site by ADAMTS13 within the A2 domain. Once the vWF A2 domain is unfolded and exposed to blood stream, it is cleaved in a shear-dependent manner by proteases other than ADAMTS13, including plasmin [55], leukocyte proteases [56], and thrombin [57]. In vitro studies demonstrated that unfolding of the A2 domain, which is required for proteolysis, occurs in <1 second [58]. Thus, an increase in fluid shear stress above a certain threshold can alter the conformation of vWF multimers, triggering cleavage of vWF by ADAMTS-13 and binding vWF to platelets [58–60].

Shear rate-induced changes in vWF conformation occur above a laminar flow threshold of 1,000/s [61], corresponding to the shear observed in non-stenotic small arteries and arterioles [62]. Proteolytic degradation of vWF-HMWM by ADAMTS13 results in the circulation of smaller multimers of vWF, thereby reducing the thrombogenic potential of vWF. The cleavage of vWF-HMWM by ADAMTS13 is not specific to aortic stenosis. It is also manifested in several types of hemodynamic situations with high-speed turbulent blood flow, including aortic or mitral regurgitation [51, 54], hypertrophic obstructive cardiomyopathy [63, 64], congenital cardiac defects [49, 65], and perivalvular leakage after valve replacement [66, 67]. Therefore, these diseases can be called the shear stress-induced acquired von Willebrand syndrome.

Figure 5 Higher shear stress and bleeding adverse events. Shear stress induces a change in vWF structure from the aggregated form to the elongated form. Given elongated vWF, the vWF multimers are degraded by ADAMTS-13, leading to the loss of function of vWF.
Pathophysiology of LVAD related acquired von Willebrand syndrome

The typical range of wall shear stress is dependent on blood vessels and reported as follows: large arteries 14–36 dyne/cm², arterioles 20–70 dyne/cm², veins 0.7–9.0 dyne/cm², and stenotic vessels 36–450 dyne/cm² [68–70]. On the other hand, LVAD and extracorporeal devices (e.g., Extracorporeal Membrane Oxygenation) can produce extremely high shear stress: axial-flow LVAD around 6000 dyne/cm² and centrifugal-flow LVAD 1500–2300 dyne/cm² [68, 69, 71]. Under these conditions, the vWF multimers are stretched and cleaved by ADAMTS13. In addition, platelet aggregation is often impaired in LVAD patients [60].

Geisen et al. first demonstrated that LVAD patients develop the acquired von Willebrand syndrome [72]. LVAD-associated acquired von Willebrand syndrome is diagnosed by laboratory data showing a lack of vWF-HMWM in the plasma of LVAD patients [73, 74]. The decreases of vWF-HMWM are observed after LVAD implantation and were not observed in heart transplant recipients [72]. High shear induces by LVAD-pump leads to a conformational change of the vWF-HMWM, predisposing the multimers to proteolytic cleavage by ADAMTS13, which results in reduced vWF adhesion activity leading to bleeding adverse events [75, 76] (Figure 5). The correlation between LVAD-pump speed and the percent of vWF-HMWM was observed [18]. In comparison with bleeding events, thrombotic events in LVAD patients with acquired von Willebrand syndrome are minor adverse effects of LVAD implantation. However, LVAD-induced marked thrombin formation as a hemostatic foreign body reaction is a risk of thrombotic events.

Another common feature in patients with LVADs is a narrow pulse pressure. The small pulse pressure underlies vascular smooth muscle relaxation and arteriolar dilatation, leading to arteriovenous malformations and bleeding [77]. In the observational study elucidating non-surgical bleeding during the first three months of LVAD support, LVAD patients with a low pulsatility index had a 4-fold higher incidence of bleeding adverse events [78]. An echocardiogram of patients with LVAD that shows no aortic valve opening is called full-bypass support, while one in which the aortic valve opens even once every few beats is called partial-bypass support. Interestingly, LVAD patients with full-bypass support tended to have a higher incidence of bleeding events than LVAD patients with partial-bypass support [78]. The full-bypass support is more likely to cause left ventricular suction, which leads to increased subsequent thrombotic and bleeding events.

Diagnosis of LVAD related acquired von Willebrand syndrome

von Willebrand disease is the most common heritable bleeding disorder and is typically divided into types 1, 2, and 3 with several sub-types [79–81]. Briefly, von Willebrand disease type 1 and 3 belong to quantitative vWF deficiency, and type 2 is qualitative vWF deficiency. The key factors distinguishing acquired von Willebrand syndrome from hereditary von Willebrand disease are the absence of family history and the late-onset disease manifestation. Therefore, history taking is essential for initial screening, and all LVAD patients with bleeding adverse events need to undergo diagnostic tests.

After confirming family history, the basic tests are helpful to diagnose hemostatic disorders, and different types of von Willebrand diseases are listed in Table 3. Acquired von Willebrand syndrome is often referred to von Willebrand disease type 2A, but each has distinct characteristics [82, 83]. Usually, acquired von Willebrand syndrome is accompanied by a loss of vWF-HWMM and an increase in low molecular weight multimers and vWF fragments [84]. Therefore, all subjects suspected of acquiring von Willebrand syndrome should undergo vWF multimer analysis [85]. In addition, LVAD-associated acquired von Willebrand syndrome is characterized by reduced collagen-binding activity and ristocetin cofactor activity of vWF [70].

Clinical management for the acquired von Willebrand syndrome in LVAD patients

The treatment targets in acquired von Willebrand syndrome related to LVAD are to control the bleeding appropriately [25, 86, 87]. In the management of GI bleeding in LVAD patients, multidisciplinary approaches are required [88]. The optimal approach to manage the LVAD patients with acquired von Willebrand syndrome should include a prophylactic strategy to minimize the severity of bleeding [89]. Therefore, the primary treatment goals are evaluating the bleeding location and its severity, withholding the anticoagulants and resuscitation to maintain stable hemostasis [90]. Adequate blood transfusion is required as needed, with attention to abnormalities in the coagulation system. Endoscopy is also required as a standard care to manage the GI bleeding in the LVAD patients as in the patients without LVAD. The upper and lower endoscopies can raise blood pressure, which in turn contributes to further bleeding. Therefore, endoscopies should be performed with careful blood pressure control.

Regarding the treatments for acquired von Willebrand syndrome, there were no specific therapeutic options for GI bleeding other than reversal or cessation of anti-thrombotic drugs and endoscopic interventions [91, 92]. Recurrent GI bleeding is a guide to initiate prophylaxis with intravenous
vWF concentrate. A previous report demonstrated that vWF concentrate 80 IU/kg daily was effective for the treatment of bleeding events in a HeartMate 2 implanted patient with refractory GI bleeding [93]. Recombinant human vWF (Vonvendi®) is the only plasma-free and factor VIII absent replacement product available. In addition, Vonvendi contains ultra-vWF-HMWM and vWF-HMWM that may be useful in the management of bleeding events in patients with acquired von Willebrand syndrome without thromboembolic complications. However, robust evidence is scanty so far in terms of the long-term efficacy and safety of such approaches in LVAD patients. Furthermore, the efficacy of vWF-concentrated preparations may be limited due to the short half-life of vWF [94]. Thus, clinical studies should be warranted to elucidate the effects of recombinant human vWF on acquired von Willebrand syndrome.

Recently, octreotide, a somatostatin analog, has begun to be used as an adjunct to current therapies and interventions [95, 96]. Factors contributing to GI bleeding may be modulated by the pharmacologic effects of octreotide which exerts platelet aggregation, increased vascular resistance, and decreased splanchnic blood stagnation [96]. Indeed, several reports have indicated that octreotide is helpful in the management of bleeding events in patients with acquired von Willebrand syndrome without thromboembolic complications. However, robust evidence is scanty so far in terms of the long-term efficacy and safety of such approaches in LVAD patients. Furthermore, the efficacy of vWF-concentrated preparations may be limited due to the short half-life of vWF [94]. Thus, clinical studies should be warranted to elucidate the effects of recombinant human vWF on acquired von Willebrand syndrome.

Table 3 Diagnostic tests in von Willebrand diseases and acquired von Willebrand syndrome

| Diagnostic test | Type 1 | Type 2A | Type 2B | Type 2M | Type 2N | Type 3 | AVWS | Reference (IU/dl) |
|-----------------|--------|--------|--------|--------|--------|--------|------|-----------------|
| vWF:Ag          | Low    | Low    | Low    | Normal/low | Normal/low | Und | Normal/low | 50–240 |
| vWF:GPIbM or vWF:RCo | Low | Very low | Very low | Low | Normal/low | Und | Normal/low | 50–240 |
| vWF:GPIbM/Ag or vWF:RCo/vWF:Ag | Normal | Low | Low | Low | Normal | — | Normal/low | >0.6 |
| vWF:CB          | Low    | Very low | Very low | Normal/low | Normal/low | Und | Low | 50–240 |
| vWF:CB/vWF:Ag   | Normal | Low | Low | Normal/low | Normal/low | Und | Normal/low | >0.6 |
| FVIII:C         | Normal/low | Normal/low | Normal/low | Normal/low | Very low | Low | Normal | 60–190 |
| FVIII:C/vWF:Ag  | Normal | Normal | Normal | Normal | Low | — | Normal/low | >0.7 |
| HMWM            | Normal | Very low | Very low | Normal | Low | Very low | Low | Normal distribution |
| vWF fragments   | NP     | NP     | NP     | NP     | NP     | NP | Present* | NP |

AVWS, Acquired Von Willebrand Syndrome; FVIII: C factor VIII; vWF, von Willebrand factor; vWF:Ag, vWF antigen; vWF:CB vWF collagen binding; vWF:GPIbM, vWF binding to mutant (gain of function) GPIb; vWF:RCo, vWF ristocetin cofactor activity; HMWM high molecular weight multimers; Und, undetectable; NP, not present. vWF:GPIbM has replaced the vWF:RCo in some centers, but vWF:RCo or any vWF platelet-dependent activity assay could be used here as well. *Particularly in patients with left Ventricular Assist Devices Adapted from Keesler DA. Res Pract Thromb Haemost 2018; 2: 34–41.

LVADs therapy provides favorable clinical impacts on mortality and QOL in patients with end-stage advanced heart failure. Despite those improvements, LVAD-related adverse effects remain critical complications, including bleeding and thromboembolic events. Especially, bleeding adverse events are significant complications occurring in the majority of LVAD patients. vWF plays a crucial role in primary hemostasis with respect to the platelet adhesion and aggregation. Especially, vWF multimers play an essential role in platelet adhesion and aggregation. However, the LVAD pump can produce extremely high shear stress, which leads to stretching and cleaving the vWF multimers by ADAMTS13. Therefore, in many patients with LVAD, the vWF multimers are diminished and insufficient to bound to the platelets and sub-endothelial collagen. This situation is the acquired von Willebrand syndrome characterized by lack of vWF-HMWM. Therefore, the vWF multimer analysis is helpful to diagnose the acquired von Willebrand syndrome. The treatment targets for the acquired von Willebrand syndrome are to control and prevent bleeding appropriately. As necessary, drugs including recombinant vWF, octreotide, or desmopressin, are applied, but the treatment has not yet been fully established. For these challenging LVAD patients with acquired von Willebrand syndrome, targeted agents...
that prevent degradation of vWF multimers need to be developed.

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