

# Acquired von Willebrand Syndrome and Platelet Function Defects during Extracorporeal Life Support (Mechanical Circulatory Support)

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## Abstract

Patients with ventricular assist devices (VADs) and extracorporeal membrane oxygenation (ECMO) suffer from an increased risk for thromboembolic events as well as for hemorrhages. High shear stress in the mechanical device results in acquired von Willebrand syndrome (AVWS), characterized by a loss of high-molecular-weight multimers of von Willebrand factor (VWF) leading to an increased bleeding risk. Onset of AVWS occurs within hours, persists during the whole period of mechanical support, and subsides rapidly after explantation. Patients with the older HeartMate II exhibit more severe AVWS than those with the newer HeartMate III, thanks to lower shear stress in the latter. All ECMO and VAD patients exhibit thrombocytopenia and often thrombocytopenia which further increases the bleeding risk. Etiological models for AVWS are increased cleavage by the metalloproteinase ADAMTS13, mechanical destruction of VWF, and shear-induced VWF binding to platelets. Platelet secretion defects may be caused by transient platelet activation leading to degranulation. AVWS can be diagnosed by detection of VWF multimers using gel-electrophoresis and functional assays of varying sensitivity (VWF ristocetin cofactor activity, VWF activity, VWF collagen binding). Platelet dysfunction is monitored using light transmission aggregometry and secretion defects are detectable using flow cytometry. Modest use of anticoagulants and a target-controlled therapy based on VWF parameters and other coagulation and platelet parameters are shown to be beneficial in this patient group. Persistent hemorrhages may be controlled with tranexamic acid and platelet concentrates. Prompt weaning from the device, when indicated, is the best therapeutic option to prevent recurrent bleeding.

## Keywords

- ▶ ventricular assist devices
- ▶ ECMO
- ▶ acquired von Willebrand syndrome
- ▶ platelet secretion

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## Introduction

Recent advances in the field of mechanical circulatory support (MCS) have led to increased survival and improved quality of life of patients suffering from advanced respiratory or heart failure.<sup>1</sup> Mortality of patients with extracorporeal membrane oxygenation (ECMO) therapy is gradually decreasing.<sup>2</sup> Ventricular assist devices (VADs) are used as a bridge to heart transplant or for recovery. VAD support also gains importance as destination therapy, because newer devices feature smaller sizes and less complications, and donor organs for transplantation are scarce. In 2018, a total of 703 patients were on the active waiting list for heart transplants in Germany, but only 296 hearts were transplanted (Yearly Statistics Overview Eurotransplant, 2018).

The HeartMate II (HM II) has been a prominent left-VAD (LVAD) with an axial continuousflow that had been implanted into 15,000 patients worldwide until 2015.<sup>3</sup> Clinical findings and long-term experience with the HM II have influenced the development of the HeartMate III (HM III), a novel LVAD featuring several modifications and potential improvements.<sup>4</sup> HM III contains a centrifugal-flow pump with wide blood-flow paths to improve hemodynamics. Additionally, an artificial pulse mode has been implemented. Clinical evaluations have attested the HM III lower shear stress, greater hemocompatibility, and better overall outcome.<sup>5</sup>

## Epidemiology

Hemostaseological alterations secondary to MCS, particularly VAD and ECMO, are issues of continued research interest. Patients with MCS are suffering from an increased risk for thromboembolic events; however, hemorrhage is the main complication resulting from VAD implantation or ECMO therapy.<sup>6,7</sup> ECMO patients exhibit bleeding from catheter insertion sites, mucous membranes, and pulmonary bleeding. Incidence of intracranial bleeding varies from 3.6 to 21% and is associated with substantially increased mortality.<sup>8,9</sup> VAD patients show elevated bleeding risk at surgical sites, occasional pulmonary and intracerebral bleeding, and an increased rate of gastrointestinal (GI) bleeds during long-term VAD support.<sup>10,11</sup> Continuous flow and reduced pulse pressure can result in arteriovenous malformations contributing to the GI bleeds.<sup>12,13</sup>

Anticoagulation is required to prevent substantial contact activation on mechanical surfaces, but incidence of nonsurgical hemorrhages exceeded those of heart transplant patients receiving heparin postoperatively.<sup>14</sup> International normalized ratio, activated partial thromboplastin time, and rotational thrombelastography cannot reliably predict clinical bleeding events in ECMO or VAD patients.<sup>15,16</sup>

In addition to contact of patients' blood with nonphysiological surfaces, MCS also induces pathological blood flow resulting in elevated shear stress.<sup>17</sup> These changes in hemodynamics lead to acquired von Willebrand syndrome (AVWS) present in VAD and ECMO, which may exacerbate bleeding symptoms.<sup>18–20</sup> AVWS is characterized by the loss of high-molecular-weight (HMW) multimers of von Willebrand factor (VWF) leading to impaired hemostatic activity.<sup>21</sup>

Patients with ECMO invariably develop severe AVWS within 1 to 6 hours after implantation. AVWS persists as long as patients remain on ECMO. After ECMO explantation, recovery from AVWS occurs rapidly within 3 to 24 hours.<sup>22</sup>

VAD patients develop AVWS as well, with rapid onset within a few hours and quick recovery after VAD explantation.<sup>18</sup> A longitudinal study with a large cohort ( $N = 198$ ) revealed that severity and progression of AVWS heavily depend on the VAD type. AVWS in patients with HM III was less severe than in patients with HM II, which correlated with less bleeding symptoms in HM III patients.<sup>14</sup>

Most ECMO and VAD patients exhibit decreased platelet counts.<sup>22,23</sup> Platelet counts recover slower than VWF activity but within 1 to 7 days after device explantation. Platelet function measured using light-transmission aggregometry is impaired in patients with ECMO and VAD, independently of low-dose aspirin administration.<sup>22,23</sup> Flow cytometric analysis of platelets from ECMO and VAD patients revealed impaired  $\alpha$ -granule and  $\delta$ -granule secretion upon stimulation with thrombin due to preactivation which finally leads to platelet hypoaggregability.<sup>14,22</sup> These platelet secretion defects in VAD and ECMO patients are similar to storage pool deficiencies associated with inherited platelet disorders.<sup>24</sup> Patients with the latter exhibit mild to moderate bleeding diathesis analogously arguing for an increased bleeding risk due to secretion defects in MCS patients.

Interestingly, platelet function defects are equally persistent with both LVADs (HM II and HM III) giving new incentives for design improvements.<sup>14</sup>

## Pathophysiology

Changes in hemodynamics lead to unfolding of HMW multimers of VWF, which allows the metalloproteinase with the thrombospondin type 1 motif, member 13 (ADAMTS13), to cleave VWF at the A2 domain into smaller multimers resulting in impaired interaction between VWF and collagen and platelets.<sup>25</sup> This consecutive loss of VWF HMW multimers leads to typical clinical bleeding symptoms characterized by AVWS. Other models emphasize the mechanical destruction of VWF within the device, and shear-induced VWF binding to platelets.<sup>26,27</sup>

VWF regulates angiogenesis and vessel maturation by controlling vascular endothelial growth factor receptor-2 signaling and binding to  $\alpha v \beta 3$  integrin on vascular smooth muscle cells.<sup>28</sup> Patients with prolonged AVWS due to extended VAD therapy can exhibit vessel malformations leading to increased mucosal and GI bleeding. The VWF is aggravated by shear-stress-induced degradation and ameliorated by endothelial release of new VWF which is triggered by pulsatility.<sup>29</sup> Hence, introduction of artificial pulsatility in newer VADs resulted in significantly lower GI bleeding incidence compared with older models.

Lower platelet counts and observed platelet defects are attributable to shear-stress-induced platelet activation resulting in platelet consumption.<sup>30</sup> Transient platelet activation potentially leads to degranulation making platelets refractory to agonistic stimuli, which explains their hyporeactivity and secretion defects.<sup>31</sup> Platelets from VAD and ECMO patients

reportedly exhibit lower surface levels of the VWF receptor GPIb $\alpha$ , which may contribute to impaired VWF–platelet interaction.<sup>32</sup>

## Diagnosis

Gold standard for detection of AVWS is separation of VWF multimers from patients' plasma via gel electrophoresis on SDS-agarose low-resolution gels followed by membrane blotting and detection with appropriate primary and secondary antibodies.<sup>33,34</sup> This method is highly sensitive for loss of VWF HMW multimers, but requires special training and is quite laborious, thus, not always suitable for routine screening.

Screening for loss of VWF HMW multimers can be performed with functional assays. Ristocetin cofactor activity (VWF:RCo) was used routinely worldwide and is based on the binding of VWF to GPIb receptors of fixed platelets. The newer VWF activity (VWF:Ac) is based on VWF binding to recombinant GPIb immobilized on particles, and features higher sensitivity for AVWS than for VWF:RCo.<sup>35</sup> The collagen-binding capacity (VWF:CB) using collagen I features even higher sensitivity than the aforementioned functional assays, but requires in-house development and special training. The commercially available VWF:CB uses collagen III, which is more stable than collagen I; however, collagen III is less sensitive to the loss of HMW multimers than collagen I. Ratios of these values (VWF:CB/VWF:Ag) are used to identify the loss of the HMW multimers (e.g., <0.7 as cut-off for the VWF:CB assay using collagen I; **Table 1**).<sup>35</sup>

Two large-scale studies were published investigating the longitudinal impact of HM II versus HM III on AVWS.<sup>14,36</sup> While Bansal et al did not observe any significant differences regarding the vWF:Ac/vWF:Ag ratio between the two devices up until 90 days after implantation, Geisen et al found a greater reduction of the vWF:CB/vWF:Ag ratio in patients with HM II than in patients with HM III support, which correlated with the more severe loss of VWF high-molecular multimers and the more severe bleeding symptoms in patients with HM II.

**Table 1** Recommended laboratory assays to establish the diagnosis of AVWS and platelet dysfunction

Laboratory assay	Sensitivity	Labor-intensiveness
VWF HMW multimer analysis	+++	+++
VWF:CB/VWF:Ag ratio	++	++
VWF:Ac/VWF:Ag ratio	+	+
VWF:RCo/VWF:Ag ratio	+	+
Light transmission aggregometry	++	++
Flow cytometry (secretion defects)	+++	+++

Abbreviations: CB, collagen binding capacity; RCo, ristocetin cofactor activity; VWF:Ac, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; VWF HMW, von Willebrand factor high molecular weight.

The discrepancies of these assays are most likely attributable to previously reported variations in functional assays, and emphasize the necessity of sufficient sensitivity when screening for AVWS routinely.<sup>35,37</sup>

Since VWF is involved in the regulation of blood vessel formation,<sup>38</sup> mucosal vascular alterations due to HMW loss may be monitored as risk stratification for GI bleeds.<sup>39</sup>

Platelet counts should be determined using standard laboratory techniques. Gold standard for platelet function testing is light transmission aggregometry. Commonly used agonists to test for platelet dysfunction are adenosine diphosphate, collagen, epinephrine, and ristocetin.<sup>23</sup> Arachidonic acid should not be used in this patient group because low-dose aspirin administration hampers informative value.

Quantification of platelet granule secretion is performed using flow cytometry.<sup>40</sup> Platelets in platelet-rich plasma are stimulated with increasing concentrations of thrombin, in the presence of the peptide Gly-Pro-Arg-Pro to prevent fibrin polymerization. Then, platelets are fixed, washed, and incubated with fluorescently labeled CD62 (for  $\alpha$ -granules) and CD63 (for  $\delta$ -granules) antibodies before analysis of surface fluorescence with a flow cytometer.

## Treatment

Patients with MCS exhibit increased risk for thrombosis as well as bleeding leaving only a narrow therapeutic window for anticoagulation. Pump thrombosis is a feared complication due to additional risks added by reoperation. Antithrombotic regimens include heparin, vitamin K antagonists (VKAs), and antiplatelet therapy. Heparin is used as a bridge to VKA anticoagulation. Presence of AVWS should be considered regarding the antithrombotic regimens, since it contributes to the bleeding risk. Recent findings suggest a modest usage of anticoagulants to be beneficial. In a study by Krueger et al, administration of 40 mg subcutaneous enoxaparin per day (the standard anticoagulation strategy for every critical care patient) in 60 ECMO patients resulted in no fatal bleeding event and no intracranial hemorrhage, while patients required only a third of blood product transfusion compared with published data.<sup>41,42</sup> Researchers recommend to minimize additional anticoagulation and suggest desmopressin as bleeding prophylaxis.<sup>43</sup> However, VWF is an acute-phase protein, and VWF storage may deplete rapidly capping the therapeutic value of desmopressin.

In a single case report, repeated transfusion of VWF concentrates successfully stopped recurrent GI bleeds.<sup>44</sup> We gathered similar outcomes in patients with AVWS and VAD or ECMO support. However, therapeutic efficacy can be limited due to short half-life of VWF and constant shredding within the device. Tranexamic acid is a suitable alternative to stop refractory bleeding, however, can be either insufficient if the wound is too large or may lead to an increased risk of thrombosis if used recurrently in a high dosage.<sup>45</sup>

Rigorous monitoring of parameters associated with acquired coagulation disorders and substitution of the appropriate coagulation factors and platelet concentrates instead of

coagulation management based on clinical bleeding symptoms has been shown to be beneficial for the management of MCS patients. Kalbhenn et al demonstrated that the risk for ECMO patients to develop intracranial hemorrhage can be reduced by identification of acquired bleeding disorders and substitution of the respective factors in a target-controlled approach.<sup>46</sup>

Platelet concentrates are an option to manage thrombocytopenia and platelet dysfunction or patients with bleeding symptoms not manageable with VWF concentrates; however, potential contraindications such as heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, or disseminated intravascular coagulation should be taken into account. Aspirin is frequently used as therapy in VAD patients, but causes an ongoing matter of debate since shear-induced platelet aggregation seems to be unaffected by aspirin.<sup>47</sup>

For both ECMO and VAD patients, the best therapeutic option to prevent bleeding as well as thrombosis is rigorous weaning from the device as soon as possible.

## Conclusion

AVWS is present in MCS patients with fast onset after implantation and recovery after explantation. AVWS is more pronounced in ECMO patients than in LVAD patients, and newer LVAD devices with lower shear stress show less pronounced AVWS and less bleeding symptoms. All MCS patients exhibit platelet secretion defects and hypoaggregability independent of the device, which adds to the already heightened bleeding risk. Close monitoring of AVWS and platelet dysfunction is recommended using VWF HMW multimer analysis, functional assays (VWF:RCO/VWF:Ag, VWF:Ac/VWF:Ag, or VWF:CB/VWF:Ag), light transmission aggregometry, and flow cytometry. To minimize the bleeding risk, antithrombotic regimens should be tailored to presence and severity of AVWS. Bleedings can be managed with tranexamic acid and platelet concentrates. In any case, proactive coagulation management based on parameters associated with acquired coagulation is preferred over treatment of clinical bleeding symptoms.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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## References

- Schramm R, Morshuis M, Schoenbrodt M, et al. Current perspectives on mechanical circulatory support. *Eur J Cardiothorac Surg* 2019;55(Suppl 1):i31–i37
- Thiagarajan RR, Barbaro RP, Rycus PT, et al; ELSO Member Centers. Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J* 2017;63(01):60–67
- Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015;34(12):1495–1504
- Bourque K, Cotter C, Dague C, et al. Design rationale and preclinical evaluation of the HeartMate 3 left ventricular assist system for hemocompatibility. *ASAIO J* 2016;62(04):375–383
- Mehra MR, Naka Y, Uriel N, et al; MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med* 2017;376(05):440–450
- Susen S, Rauch A, Van Belle E, Vincentelli A, Lenting PJ. Circulatory support devices: fundamental aspects and clinical management of bleeding and thrombosis. *J ThrombHaemost* 2015;13(10):1757–1767
- Aubron C, DePuydt J, Belon F, et al. Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation. *Ann Intensive Care* 2016;6(01):97
- Klinzing S, Wenger U, Stretti F, et al. Neurologic injury with severe adult respiratory distress syndrome in patients undergoing extracorporeal membrane oxygenation: a single-center retrospective analysis. *AnesthAnalg* 2017;125(05):1544–1548
- Cavayas YA, Del Sorbo L, Fan E. Intracranial hemorrhage in adults on ECMO. *Perfusion* 2018;33(1, Suppl):42–50
- Harvey L, Holley CT, John R. Gastrointestinal bleed after left ventricular assist device implantation: incidence, management, and prevention. *Ann Cardiothorac Surg* 2014;3(05):475–479
- Park SJ, Milano CA, Tatoes AJ, et al; HeartMate II Clinical Investigators. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. *Circ Heart Fail* 2012;5(02):241–248
- Demirozu ZT, Radovancevic R, Hochman LF, et al. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 2011;30(08):849–853
- Kim JH, Brophy DF, Shah KB. Continuous-flow left ventricular assist device-related gastrointestinal bleeding. *Cardiol Clin* 2018;36(04):519–529
- Geisen U, Brehm K, Trummer G, et al. Platelet secretion defects and acquired von Willebrand syndrome in patients with ventricular assist devices. *J Am Heart Assoc* 2018;7(02):e006519
- Panigada M, Artoni A, Passamonti SM, et al. Hemostasis changes during veno-venous extracorporeal membrane oxygenation for respiratory support in adults. *Minerva Anestesiol* 2016;82(02):170–179
- Hellmann C, Schmutz A, Kalbhenn J. Bleeding during veno-venous ECMO cannot reliably be predicted by rotational thrombelastometry (ROTEM™). *Perfusion* 2018;33(04):289–296
- Benk C, Lorenz R, Beyersdorf F, et al. Three-dimensional flow characteristics in ventricular assist devices: impact of valve design and operating conditions. *J Thorac Cardiovasc Surg* 2011;142(05):1019–1026
- Geisen U, Heilmann C, Beyersdorf F, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. *Eur J Cardiothorac Surg* 2008;33(04):679–684
- Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S, Zieger B. Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. *J AtherosclerThromb* 2015;22(03):265–271
- Tauber H, Ott H, Streif W, et al. Extracorporeal membrane oxygenation induces short-term loss of high-molecular-weight von Willebrand factor multimers. *Anesth Analg* 2015;120(04):730–736
- Baldauf C, Schneppenheim R, Stacklies W, et al. Shear-induced unfolding activates von Willebrand factor A2 domain for proteolysis. *J ThrombHaemost* 2009;7(12):2096–2105
- Kalbhenn J, Schlagenhauf A, Rosenfelder S, Schmutz A, Zieger B. Acquired von Willebrand syndrome and impaired platelet function during venovenous extracorporeal membrane oxygenation: Rapid onset and fast recovery. *J Heart Lung Transplant* 2018;37(08):985–991

- 23 Baghai M, Heilmann C, Beyersdorf F, et al. Platelet dysfunction and acquired von Willebrand syndrome in patients with left ventricular assist devices. *Eur J Cardiothorac Surg* 2015;48(03):421–427
- 24 Lambert MP. Inherited platelet disorders: a modern approach to evaluation and treatment. *Hematol Oncol Clin North Am* 2019;33(03):471–487
- 25 Rauch A, Legendre P, Christophe OD, et al. Antibody-based prevention of von Willebrand factor degradation mediated by circulatory assist devices. *ThrombHaemost* 2014;112(05):1014–1023
- 26 Restle DJ, Zhang DM, Hung G, et al. Preclinical models for translational investigations of left ventricular assist device-associated von Willebrand factor degradation. *Artif Organs* 2015;39(07):569–575
- 27 Nascimbene A, Hilton T, Konkle BA, Moake JL, Frazier OH, Dong JF. von Willebrand factor proteolysis by ADAMTS-13 in patients on left ventricular assist device support. *J Heart Lung Transplant* 2017;36(04):477–479
- 28 Schepcke L, Murphy EA, Zarpellon A, et al. Notch promotes vascular maturation by inducing integrin-mediated smooth muscle cell adhesion to the endothelial basement membrane. *Blood* 2012;119(09):2149–2158
- 29 Vincent F, Rauch A, Loobuyck V, et al. Arterial pulsatility and circulating von Willebrand factor in patients on mechanical circulatory support. *J Am Coll Cardiol* 2018;71(19):2106–2118
- 30 Nascimbene A, Neelamegham S, Frazier OH, Moake JL, Dong JF. Acquired von Willebrand syndrome associated with left ventricular assist device. *Blood* 2016;127(25):3133–3141
- 31 Kawahito K, Mohara J, Misawa Y, Fuse K. Platelet damage caused by the centrifugal pump: in vitro evaluation by measuring the release of alpha-granule packing proteins. *Artif Organs* 1997;21(10):1105–1109
- 32 Lukito P, Wong A, Jing J, et al. Mechanical circulatory support is associated with loss of platelet receptors glycoprotein Iba and glycoprotein VI. *J ThrombHaemost* 2016;14(11):2253–2260
- 33 Budde U, Bergmann F, Michiels JJ. Acquired von Willebrand syndrome: experience from 2 years in a single laboratory compared with data from the literature and an international registry. *SeminThrombHemost* 2002;28(02):227–238
- 34 Tiede A, Priesack J, Werwitzke S, et al. Diagnostic workup of patients with acquired von Willebrand syndrome: a retrospective single-centre cohort study. *J ThrombHaemost* 2008;6(04):569–576
- 35 Geisen U, Zieger B, Nakamura L, et al. Comparison of Von Willebrand factor (VWF) activity VWF:Ac with VWF ristocetin cofactor activity VWF:RCo. *Thromb Res* 2014;134(02):246–250
- 36 Bansal A, Uriel N, Colombo PC, et al. Effects of a fully magnetically levitated centrifugal-flow or axial-flow left ventricular assist device on von Willebrand factor: A prospective multicenter clinical trial. *J Heart Lung Transplant* 2019;38(08):806–816
- 37 Geisen U, Beyersdorf F, Zieger B. Acquired von Willebrand syndrome and left ventricular assist devices. *J Heart Lung Transplant* 2020;39(01):89
- 38 Randi AM, Smith KE, Castaman G. von Willebrand factor regulation of blood vessel formation. *Blood* 2018;132(02):132–140
- 39 Patel SR, Madan S, Saeed O, et al. Association of nasal mucosal vascular alterations, gastrointestinal arteriovenous malformations, and bleeding in patients with continuous-flow left ventricular assist devices. *JACC Heart Fail* 2016;4(12):962–970
- 40 Lahav J, Jurk K, Hess O, et al. Sustained integrin ligation involves extracellular free sulfhydryls and enzymatically catalyzed disulfide exchange. *Blood* 2002;100(07):2472–2478
- 41 Ang AL, Teo D, Lim CH, Leou KK, Tien SL, Koh MB. Blood transfusion requirements and independent predictors of increased transfusion requirements among adult patients on extracorporeal membrane oxygenation – a single centre experience. *Vox Sang* 2009;96(01):34–43
- 42 Esper SA, Levy JH, Waters JH, Welsby JJ. Extracorporeal membrane oxygenation in the adult: a review of anticoagulation monitoring and transfusion. *AnesthAnalg* 2014;118(04):731–743
- 43 Krueger K, Schmutz A, Zieger B, Kalbhenn J. Venovenousextracorporeal membrane oxygenation with prophylactic subcutaneous anticoagulation only: an observational study in more than 60 patients. *Artif Organs* 2017;41(02):186–192
- 44 Fischer Q, Huisse MG, Voiriot G, et al. Von Willebrand factor, a versatile player in gastrointestinal bleeding in left ventricular assist device recipients? *Transfusion* 2015;55(01):51–54
- 45 Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood* 2011;117(25):6777–6785
- 46 Kalbhenn J, Wittau N, Schmutz A, Zieger B, Schmidt R. Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy. *Perfusion* 2015;30(08):675–682
- 47 Morici N, Varrenti M, Brunelli D, et al. Antithrombotic therapy in ventricular assist device (VAD) management: From ancient beliefs to updated evidence. A narrative review. *Int J Cardiol Heart Vasc* 2018;20:20–26