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STATE-OF-THE-ART REVIEW

Management of Bleeding and Hemolysis During Percutaneous Microaxial Flow Pump Support

A Practical Approach

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ABSTRACT

Percutaneous ventricular assist devices (pVADs) are increasingly being used because of improved experience and availability. The Impella (Abiomed), a percutaneous microaxial, continuous-flow, short-term ventricular assist device, requires meticulous postimplantation management to avoid the 2 most frequent complications, namely, bleeding and hemolysis. A standardized approach to the prevention, detection, and treatment of these complications is mandatory to improve outcomes. The risk for hemolysis is mostly influenced by pump instability, resulting from patient- or device-related factors. Upfront echocardiographic assessment, frequent monitoring, and prompt intervention are essential. The precarious hemostatic balance during pVAD support results from the combination of a procoagulant state, due to critical illness and contact pathway activation, together with a variety of factors aggravating bleeding risk. Preventive strategies and appropriate management, adapted to the impact of the bleeding, are crucial. This review offers a guide to physicians to tackle these device-related complications in this critically ill pVAD-supported patient population. (J Am Coll Cardiol Intv 2023;16:1707-1720)

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ABBREVIATIONS AND ACRONYMS

Hb = hemoglobin

ICU = intensive care unit

LDH = lactate dehydrogenase

LV = left ventricle/ventricular

MCS = mechanical circulatory support

NO = nitric oxide

PAPi = pulmonary artery pulsatility index

PAWP = pulmonary artery wedge pressure

pfHb = plasma-free hemoglobin

pVAD = percutaneous ventricular assist device

RV = right ventricle/ventricular

UFH = unfractionated heparin

The use of percutaneous ventricular assist devices (pVADs) in the management of cardiogenic shock or as a bridge providing hemodynamic support during complex coronary procedures has significantly increased over the past decade, likely because of improved device design and better understanding of device management.[1] Among mechanical circulatory support (MCS) devices, microaxial pVADs such as the Impella (Abiomed) are commonly used.[1,2] The Impella supports the left ventricle (LV) and/or the right ventricle (RV) by transferring blood across the aortic or tricuspid and pulmonary valves, on the basis of the principle of Archimedes' screw. It augments systemic and/or pulmonary forward flow, maintaining end-organ perfusion and also unloads the ventricle, which results in a reduced area inside the ventricular pressure-volume loop and consequently reduced myocardial oxygen demand.[3]

Whereas the duration of indwelling pVAD support was previously on the order of days, patients may now be supported for weeks because of extended unloading, axillary implantation with de-escalation strategies, and weaning of pVAD as the last step in recovery.[3] However, despite superior hemodynamic support compared with the intra-aortic balloon pump, 3 large retrospective registries in the United States, including >5,000 patients supported by microaxial pVADs, did not demonstrate a survival benefit of using pVAD compared with intra-aortic balloon pumps.[1,4,5] This was attributed mainly to a higher rate of major bleeding complications in the pVAD group, although none of these studies mentioned a standardized intensive care unit (ICU) management strategy.[6] Furthermore, the retrospective design renders propensity-matched studies subject to selection bias that can affect outcomes. Another explanation for the disappointing outcomes with microaxial pVAD support might be the frequent occurrence of hemolysis, with a reported cumulative rate up to 62.5%.[7,8]

HIGHLIGHTS

- Bleeding and hemolysis impair outcomes during pVAD support for cardiogenic shock.
- Prevention, adequate diagnostics, and management may mitigate these complications.
- Prospective studies are needed to standardize hematological management during MCS.

As bleeding and hemolysis remain important complications, the accurate prevention, monitoring, and management of these complications is pivotal when managing a pVAD-supported patient in the ICU (**Central Illustration**).[9] Here, we discuss the mechanisms that underlie hemolysis and bleeding and vascular complications during percutaneous microaxial flow pump support and their prevention and optimal management.

MECHANISMS OF HEMOLYSIS AND BLEEDING

HEMOLYSIS. Hemolysis, the release of hemoglobin into the plasma from erythrocytes, leads to a decline in efficient oxygen delivery and may be detected as an increase in plasma-free hemoglobin (pfHb), which occurs when the capacity of protective hemoglobin-scavenging mechanisms (eg, haptoglobin) becomes saturated.[10] PfHb consumes nitric oxide (NO), resulting in vasoconstriction, platelet activation and aggregation, and arterial thrombosis.[10] Furthermore, pfHb also increases inflammation and can induce pigment nephropathy by precipitation, leading to acute kidney injury (**Figure 1**).[11-13] Although the impact of hemolysis on mortality in patients on MCS is unclear, it is important to detect hemolysis in a timely fashion, in order to prevent acute kidney injury and other pfHb-induced complications.[7]

Hemolysis is a potential complication of all MCS devices and can be pump or patient related or a

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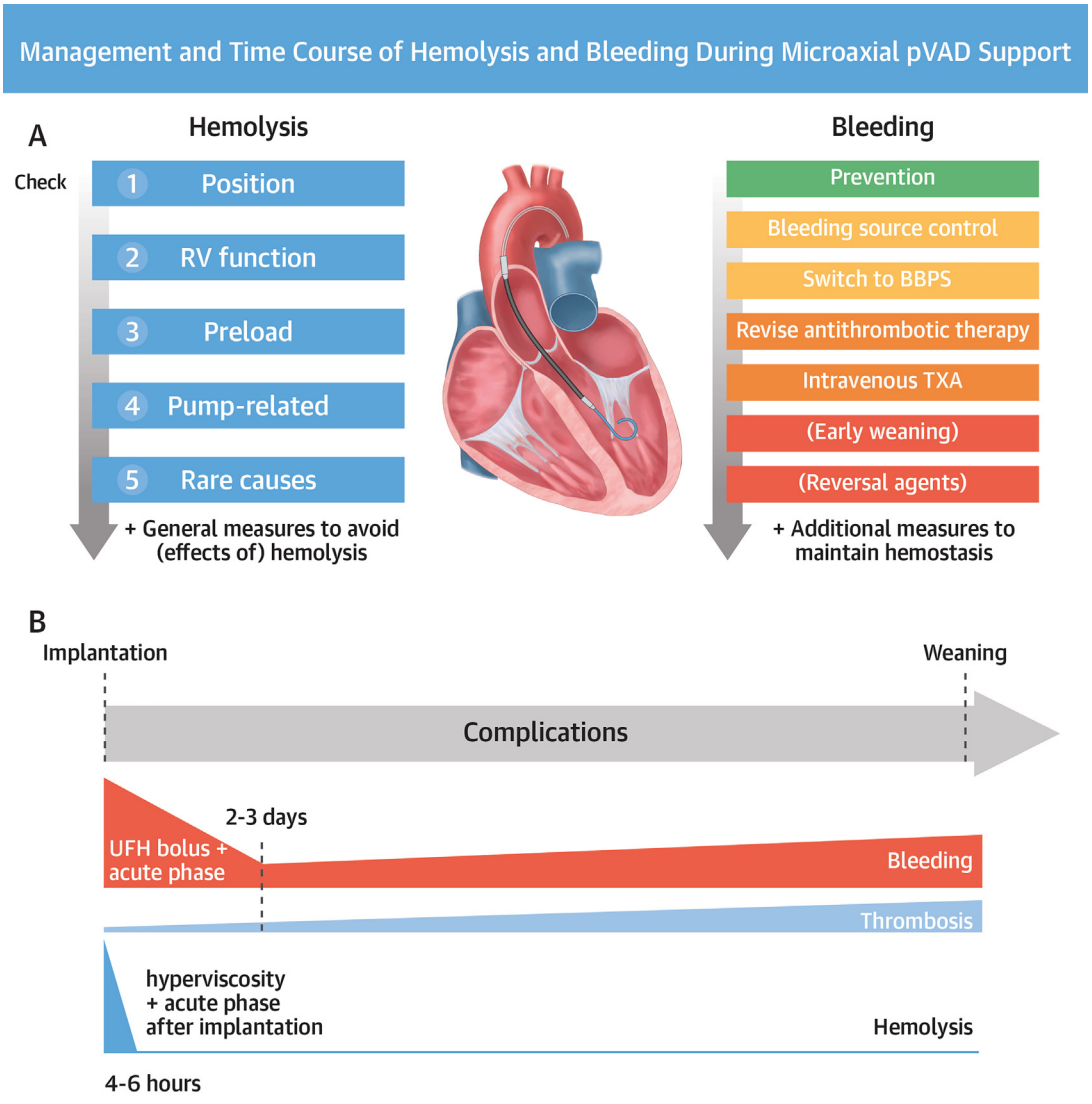
CENTRAL ILLUSTRATION **Hemolysis and Bleeding During Microaxial pVAD Support**



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(A) As bleeding and hemolysis remain important complications during microaxial percutaneous ventricular assist device (pVAD) support, accurate management using a stepwise, standardized approach is crucial. **Green color** indicates prevention. **Yellow color** indicates measures for minor bleeds. **Orange** and **red colors** indicate additional measures for intermediate and major bleeds, respectively. **(B)** Bleeding complications typically occur in the first 2 to 3 days after device implantation and rise in parallel with the duration of the microaxial pVAD support. Thrombotic complications typically rise with the duration of support. Hemolysis is mostly present shortly after implantation and can be avoided by proper device positioning and management. BBPS = bicarbonate-based purge solution; RV = right ventricular; TXA = tranexamic acid; UFH = unfractionated heparin.

combination of both. As discussed later, various patient- and/or ICU-related issues may also strongly affect its occurrence.

Device-related factors. First, inherent function-related mechanisms of the microaxial pVAD might contribute to the occurrence of hemolysis. Increased shear stress during pVAD support is an important factor resulting in erythrocyte damage. When the erythrocyte membrane is mechanically stressed, the cell's capacity to deform and perform its normal

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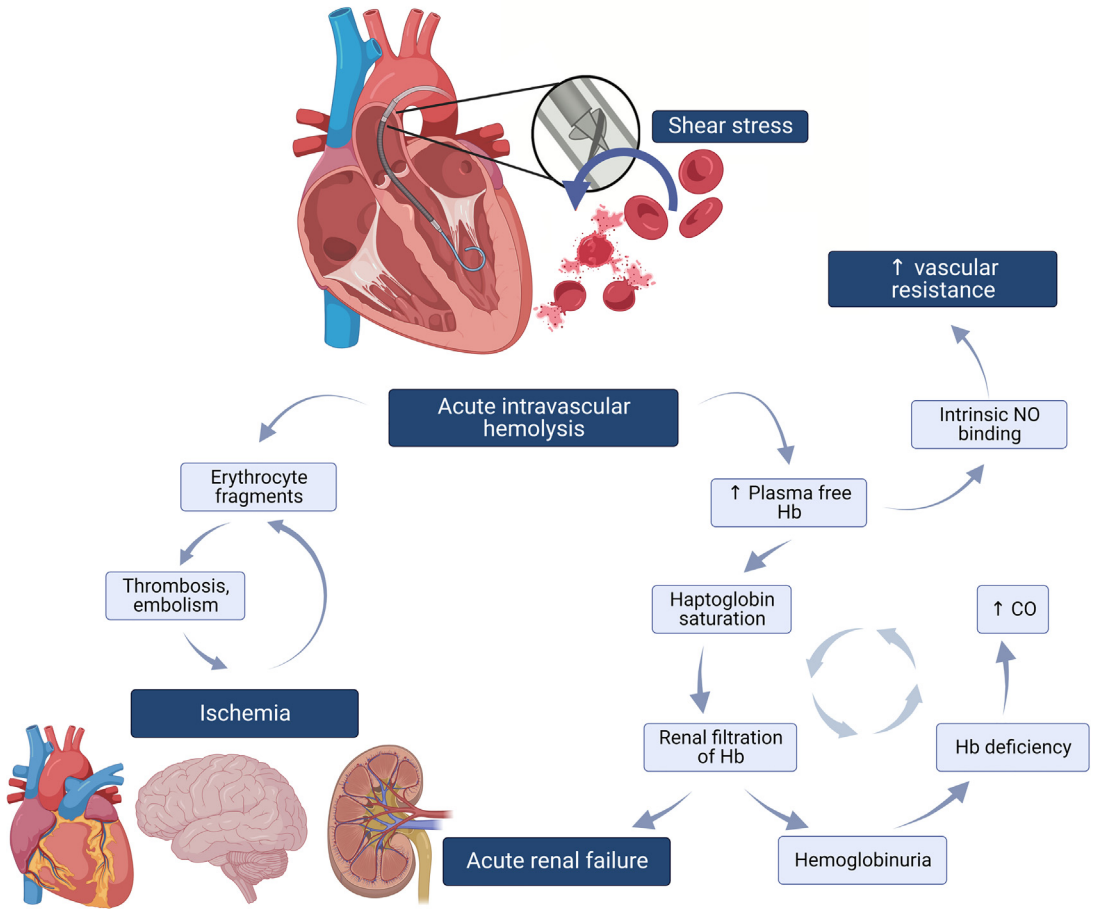
FIGURE 1 Systemic Repercussions of (Acute) Intravascular Hemolysis



Intravascular hemolysis leads to the release of erythrocyte fragments and free hemoglobin (Hb), which irreversibly bind nitric oxide (NO). This results in increased vascular resistance, vasoconstriction and platelet activation, aggregation, and arterial thrombosis, potentially resulting in ischemia in multiple organs. Furthermore, free Hb can precipitate and induce pigment nephropathy, leading to acute renal failure. Additionally, ongoing hemoglobinuria leads to Hb deficiency and reduced oxygen-carrying capacity of the blood. In an attempt to preserve end-organ oxygen delivery, cardiac output (CO) will increase. Initially this is achieved by increasing heart rate and later also by increasing stroke volume because of neurohormonal responses leading to fluid retention.

functions starts to decline. This results in hemolysis or nonreversible subhemolytic damage.[14] The computational fluid dynamics of an Impella CP show higher shear stress at the tip of the impeller blade (between the rotor and the housing), which is in line with the established formula whereby linear pump speed and, consequently, shear stress are the highest at the outer tip of the impeller blades[15]:

$$v\,(\text{linear speed}) = r\,(\text{radius}) \times \omega\,(\text{rotational speed})$$

To keep impeller tip speed, along with the shear stress, below a defined level, pumps with larger diameters are designed to generate flow with fewer rotations per minute. For example, the Impella 2.5 allowed operation up to 51,000 rotations per minute, while the Impella 5.0 allows only up to 33,000 rotations per minute, albeit with doubled output. Therefore, it is easily understandable that using a lower rotational speed in a microaxial pVAD reduces hemolysis.[16] In a case series of 23 left Impella-supported patients (7 × 5.0, 16 × CP), pfHb levels were indeed higher at high pump support levels (P7 and P8) compared with pfHb of patients on lower levels (P5 and P6). Furthermore, the investigators showed a

TABLE 1 Parameters to Obtain Proper Positioning of the Impella Device

Routine preimplantation assessment of LV dimensions and aortic and mitral annulus
Ensure unobstructed microaxial pVAD inflow
Device positioned ~3.5 cm below the aortic valve (Impella CP and 5.0) or ~5 cm (Impella 5.5); Impella RP inlet in the inferior vena cava
Pump housing in the midventricular cavity
Free from anterior mitral leaflet
Free from subannular structures
Tip of the catheter pointing toward LV apex
Aim for pVAD outflow well above the aortic valve (Impella CP and 5.0/5.5) and 2-4 cm above the pulmonary valve annulus (Impella RP)
Aim for a stable device position (avoid pump migration); consider axillary insertion for prolonged use in a mobile patient

Proper positioning is key to reduce the risk of hemolysis and bleeding.
LV = left ventricular; pVAD = percutaneous ventricular assist device.

direct correlation between P level and pfHb (Pearson's $R = 0.61$, $P = 0.0004$).[17] Another unique feature of the Impella is the purge solution, which prevents the entrance of blood into the motor, as this would inevitably lead to hemolysis and pump thrombosis. Unfractionated heparin (UFH) is conventionally used in the dextrose purge solution to protect against adsorption, deposition, and coagulation of blood components. When the purge flow is obstructed (by, eg, thrombus), hemolysis will occur immediately. In addition, reduced purge flow may be insufficient to attenuate motor heat resulting from attrition forces, resulting in increased local temperature and higher risk for clotting and hemolysis.[18]

Second, hemolysis may also be related to (transient) suboptimal intracardiac device positioning (Table 1), resulting in partial inlet or outlet obstruction and suction events. Indeed, 50% obstruction of an Impella CP outlet leads to a detrimental increase in the exposure time of blood to regions of high shear stress because of flow restriction and increase in turbulence near the impeller and the outlet windows.[15]

Patient-related factors. Patient anatomical parameters can contribute to the feasibility of proper positioning of the pump. As recently showed by Nakamura et al,[19] a narrow angle of <126.5° between the aortic and mitral annulus in the apical 3-chamber view on transthoracic echocardiography was an independent risk factor for refractory hemolysis in a group of 26 patients. The group with the narrow angle (n = 11) also showed significantly smaller left ventricular (LV) end-diastolic dimensions. This narrow angle oriented the microaxial pVAD toward the lateral or posterior wall and resulted in mechanical suction and obstruction due to improper positioning of the device. Consequently, the anatomical variability among patients should also be considered upon microaxial pVAD insertion, and a quick echocardiographic assessment of the heart before device selection is mandatory to avoid hemolytic complications afterward. Furthermore, hemodynamic issues might lead to the occurrence of hemolysis. For example, low LV preload due to hypovolemia, vasoplegia, or RV failure can result in suction events with inflow obstruction and hemolysis. This was illustrated in a retrospective study showing that patients with RV impairment, indicated by lower pulmonary artery pulsatility index (PAPi) (<1.3) following the initiation of microaxial pVAD support, have a higher risk for hemolysis.[20] Finally, other factors, including blood transfusions, primary hemolytic disorders such as sickle cell anemia or autoimmune hemolytic anemia, surgery, and tissue damage, among others, can also contribute to clinically significant hemolysis not directly related to the pVAD itself.

BLEEDING. The most common cause of morbidity and mortality during pVAD support are bleeding and thrombotic complications. This is the consequence of a complex, bidirectional interplay among different factors influencing the precarious hemostatic balance.[21] Indeed, during critical illness, a procoagulant state is often seen because of multiorgan failure and a systemic inflammatory response.[21] Also the nonbiological material of the device itself will activate not only the intrinsic (contact) pathway of coagulation but also platelets and leukocytes, resulting in increased thrombotic risk. In contrast, different factors can aggravate bleeding risk.

First, the device-induced high-shear environment and reduction in pulsatility both lead to increased cleavage of and reduced endothelial release of high-molecular weight von Willebrand factor, resulting in acquired von Willebrand syndrome and, consequently, reduced platelet-binding affinity.[22] This phenomenon might be facilitated by improper

intracardiac device position and orientation (Table 1), as suggested by a recent study demonstrating a significantly increased rate of clinically relevant bleeding events in patients with Impella malrotation inside the LV cavity.[23] Malrotation of the microaxial pVAD is defined by catheter inflow orientation away from the LV apex and toward the mitral valve apparatus and the LV inferolateral wall (Figure 2).

Second, to avoid device-related thrombotic complications, systemic anticoagulation, usually with UFH, is necessary but increases bleeding risk. Its dose management is far from easy, involving on-off phenomenon in case of bleeding further aggravating coagulopathy, UFH monitoring tests, and other issues.[22] Different tests to monitor anticoagulation and detect bleeding risk in this patient cohort have been reviewed elsewhere.[24] Next to anticoagulant therapy, patients on pVAD therapy often require antiplatelet therapy for concomitant conditions, further affecting bleeding risk.

Third, the unique purge system can further complicate anticoagulant management; the purge solution is frequently heparinized, and its flow rate is automatically controlled by the device to maintain purge pressure within a predefined range.[21]

Fourth, the development of liver failure with depletion of coagulant factors II, V, VII, IX, and X again aggravates bleeding risk. Also, the microaxial pVAD may be run in conjunction with other extracorporeal circuits (eg, continuous renal replacement therapy, venoarterial extracorporeal circulation and blood purification devices), increasing the blood-device interaction and favoring platelet consumption. Finally, larger bore femoral access is required, increasing the risk for bleeding (and vascular complications). In particular, the insertion sheath is slightly larger than the repositioning sheath, which might also contribute to the risk for access-site bleeding.[25]

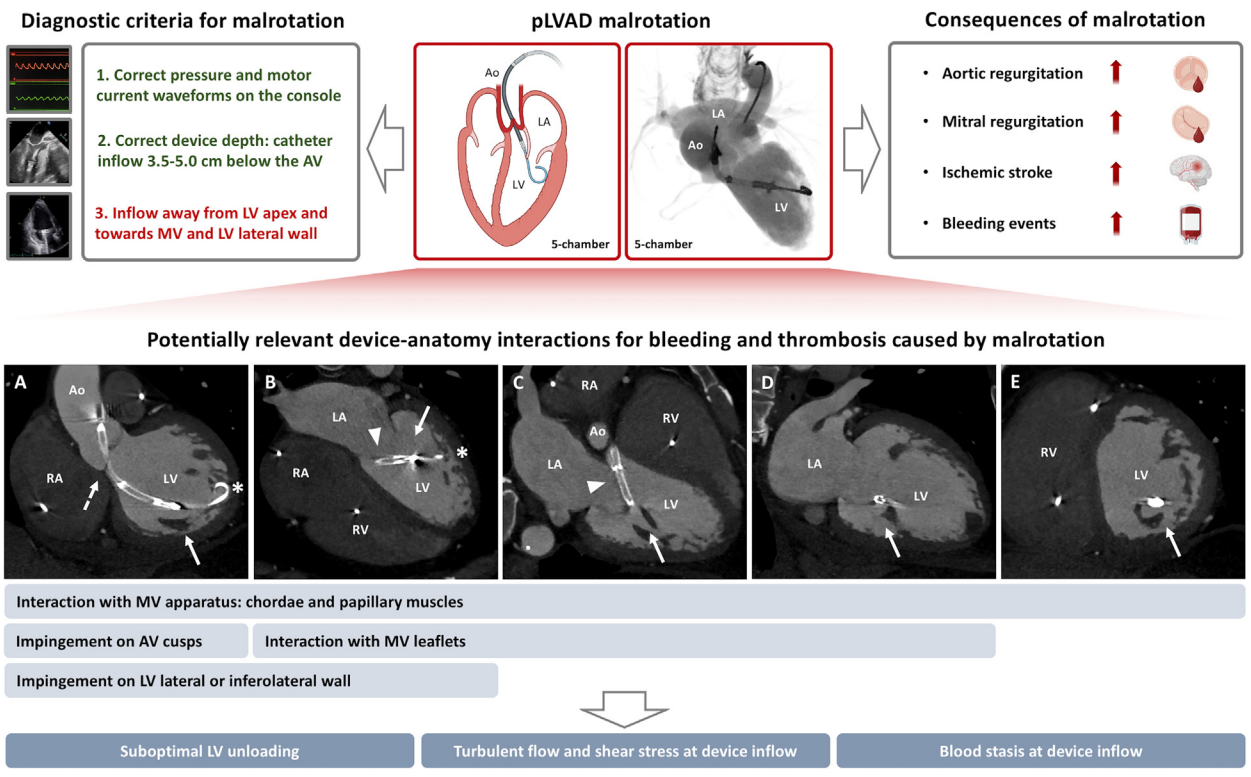
In conclusion, the complex interplay among procoagulant and antithrombogenic factors, including patient-, pump-, and drug-related variables, substantially increases the risk for bleeding, vascular, and thrombotic complications during microaxial pVAD use.

DIAGNOSIS OF HEMOLYSIS AND BLEEDING

HEMOLYSIS. Clinical as well as biochemical parameters and technical tools are useful in suspecting and confirming hemolytic events as early as possible. Clinical manifestations include a change in urine color due to hemoglobinuria ("tea colored urine") and late jaundice. Biochemical changes in case of hemolysis include increases in pfHb, lactate dehydrogenase (LDH), phosphate, unconjugated bilirubin, and potassium levels and decreases in hemoglobin and haptoglobin.[26] Importantly, preanalytical error should always be ruled out (eg, delayed handling in the laboratory). All these biochemical parameters have limitations, pertaining to the timeliness or availability of the results and specificity for detecting hemolysis. For example, pfHb may be increased because of surgery and transfusion, LDH is a nonspecific marker of tissue damage, and the production of haptoglobin can be reduced because of liver damage. Clearly, all of these scenarios may occur in patients with cardiogenic shock, independent of pVAD support. Because of this, whichever biomarker is used, the threshold for hemolysis that represents clinically or prognostically relevant hemolysis is unclear. Although the Extracorporeal Life Support Organization considers a pfHb concentration >50 mg/dL as a cutoff for serious hemolysis, recent pVAD registries have used a cutoff of >40 mg/dL.[27,28] A recent consensus document providing definitions for adverse events in patients on pVAD defines hemolysis as a pfHb concentration >20 mg/dL.[29] Others use a decrease in hemoglobin, blood transfusion requirement plus a decrease in haptoglobin, or an increase in LDH.[7] A retrospective registry showed that an increase in pfHb of >27 mg/dL within 24 hours of pVAD implantation was superior to plasma LDH level in predicting hemolysis, with sensitivity of 57% and specificity of 93%.[17] Pragmatically, the pfHb levels should be as low as possible, and any rise should prompt immediate evaluation. Therefore, frequent biochemical sampling, at least daily but more often when hemolysis is already present, is encouraged. Once hemolysis is suspected, immediate action should be undertaken.

Next, as inadequate microaxial pVAD positioning will inevitably lead to hemolysis, the aid of technical tools to assess dislocation of the pump is an important pillar in hemolysis prevention and detection. First, echocardiography is important to visualize the pump. The distance between the aortic valve and the inflow cage should preferably be approximately 3.5 cm for an Impella CP or 5 cm for an Impella 5.0/5.5. The Doppler color artifact that locates the outflow opening of the pump can be used to determine (dis) location of the pump. In addition, the observation of

FIGURE 2 **Device-Anatomy Interactions Relevant for Bleeding and Thrombosis Caused by Malrotation**



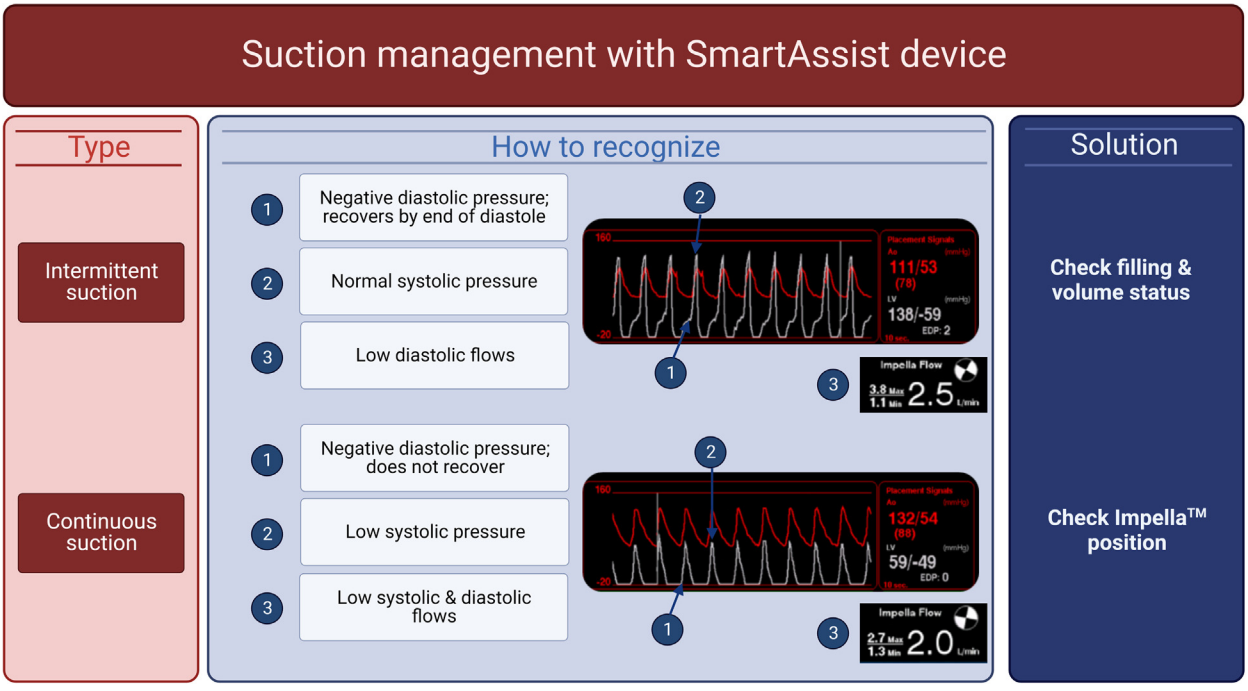
Impella malrotation within the LV **(upper panels)** generates device-anatomy interactions that might cause bleeding or thrombosis. Multiplanar reconstructions of computed tomographic images **(A to E)** illustrate interactions of device inflow with the mitral valve (MV) apparatus **(arrow)** and MV leaflets **(arrowhead)**, shaft impingement on the aortic valve (AV) cusps **(dashed arrow)**, and pigtail/inflow impingement on the LV lateral or inferolateral wall **(*)**. Ao = aorta; LA = left atrium; LV = left ventricle/ventricular; RA = right atrium; RV = right ventricle.

bubble artifacts in the LV during echocardiography is a further hint that relevant hemolysis is present.

Second, fluoroscopy and computed tomography can be helpful to confirm dislocation, for both left-sided and right-sided pumps. Last, the placement and the motor current signals on the pVAD console should be used to continuously assess pump positioning. The placement signal registers the difference between the inlet and outlet pressure (for the Impella 5.0) or the aortic pressure (for the Impella CP) during the cardiac cycle and should be accompanied by a pulsatile motor current. This specifically indicates that the inlet and the outlet are positioned in different compartments (aorta or pulmonary artery vs ventricle), which leads to variations in flow through the microaxial pVAD and therefore variations in energy consumption of the device during systole and diastole. The only exception that leads to complete lack of pulsatility of the placement signals, despite good positioning, is when there is ventriculoarterial uncoupling with consequent continuous closure of the aortic valve, and all blood being diverted through the pump.

In 2019, the SmartAssist technology was added to the Impella device to allow better positioning and avoidance of suction and, thus, hemolysis. By adding an optical placement sensor at the outlet of the pump, aortic pressure can be detected. This, in combination with registration of variability in microaxial motor current, which is proportionally related to the differential pressure between the aorta and LV, allows calculation of the LV pressure waveform. The display of the LV pressure waveform is informative to promptly detect suction, before the development of manifest hemolysis, as it can help differentiate between inadequate volume status and improper microaxial pVAD positioning. In particular, if the LV waveform shows negative diastolic pressures with normal systolic pressures, the filling and the volume status should be checked. In contrast, if the LV shows

FIGURE 3 SmartAssist Technology Allows Differentiation Between Hypovolemia and Impaired Device Positioning



The device console displays the (calculated) LV pressure waveform. **(Upper panel)** Negative diastolic pressure that recovers by the end of diastole, combined with normal systolic pressure and low diastolic flow, suggests hypovolemia. **(Lower panel)** Negative diastolic pressure that does not recover at the end of diastole, combined with low systolic pressure and low flows, suggests impaired device positioning. LV = left ventricle/ventricular.

both negative diastolic and systolic pressures, a positioning problem is more likely (Figure 3).

BLEEDING. Meticulous monitoring of the anticoagulant effect of UFH during pVAD support is key to minimizing the risk for bleeding. This is challenging, as different coagulation tests are affected by various factors during critical illness and pump support. In a recent review, our group gave an overview of the (dis) advantages of different coagulation tests and proposed an anti-Xa/activated partial thromboplastin time-driven algorithm to assess the anticoagulant effect of UFH in this critically ill patient population.[21,22] Bleeding jeopardizes patients with pVADs, as it results in both direct harm, as well as need for transfusions and eventually cessation of antithrombotic therapy, which may ultimately lead to an increased risk for thrombotic and ischemic events. Although there is general consensus on endpoint definitions for ischemic events, the classification of bleeding is far from uniform.[30,31] This has resulted in a wide variability in the reported incidence of bleeding and undermines the assessment of different bleeding mitigation strategies in clinical trials. To harmonize the definition of bleeding, different scores have been proposed in different settings. The most commonly used bleeding scores and the settings for which they were developed are listed in Table 2, along with their major limitations in the ICU population.[32-36] Given the frequency of bleeding and thrombosis in this predisposed patient cohort, a specific bleeding score designed for critically ill patients supported by pVADs is urgently needed.[29]

APPROACH AND MANAGEMENT OF HEMOLYSIS AND BLEEDING

HEMOLYSIS. Once hemolysis is suspected, immediate action should be taken. We therefore propose the following practical approach, which combines investigation of the etiology of hemolysis with

TABLE 2 The Most Commonly Used Bleeding Classification Scores With Their Original Development Cohort and Major Limitations in the ICU Setting

Name of Bleeding Score	Field of Indication for the Bleeding Score
Bleeding Academic Research Consortium	Developed for cardiovascular clinical trials of antithrombotic therapy, derived from a cohort of mainly patients with acute coronary syndrome
Valve Academic Research Consortium	Developed for clinical trials in TAVR
International Society on Thrombosis and Haemostasis	Developed for long-term oral anticoagulation exposure
Thrombolysis In Myocardial Infarction	Developed for fibrinolytic therapy after STEMI/non-CABG-related bleeding

Major Limitations in the ICU Setting
None of the scores was designed to assess bleeding on short-term intravenous anticoagulation.
No incorporation of patient's baseline Hb, which is often around the transfusion threshold in critically ill patients. Consequently, transfusions may be administered to correct pre-existing deficiencies rather than in reaction to bleeding, therefore potentially misclassifying the severity of a minor bleed.
No incorporation of repercussion of bleed on patient hemodynamics (eg, increased pressor requirements).
No weighting in the scores between severity and chronicity of bleeding (eg, chronic oozing around line insertion site or ENT area vs acute pulmonary hemorrhage).
Incorporation of endpoints determined by the response to the bleed (eg, surgical intervention) that suffer from reduced standardization and are not directly applicable to an ICU population ("surgical intervention" poorly classified; could be interpreted to include both major and minor surgical interventions (eg, resternotomy or an additional suture around an arterial or venous access site).
Classification of bleed sometimes based on "actionable" vs "nonactionable": the threshold for intervention in the ICU setting may be much higher or much lower than the threshold for intervention for the same bleed outside the ICU setting. However, this allows capture of events outside arbitrary laboratory definitions.
Incorporation of Hb levels into scores, variable laboratory cutoffs, and consequent uncertainty regarding the timing of assessment may lead to inappropriate Hb peaks and nadirs. Furthermore, alternative reasons for drop in Hb (eg, hemolysis, often present on MCS) are not taken into account.
Built on consensus rather than derived from an analysis of any specific database to identify independent risk factors.

CABG = coronary artery bypass grafting; ENT = ear, nose, and throat; Hb = hemoglobin; ICU = intensive care unit; MCS = mechanical circulatory support; STEMI = ST-segment elevation myocardial infarction; TAVR = transcatheter aortic valve replacement.

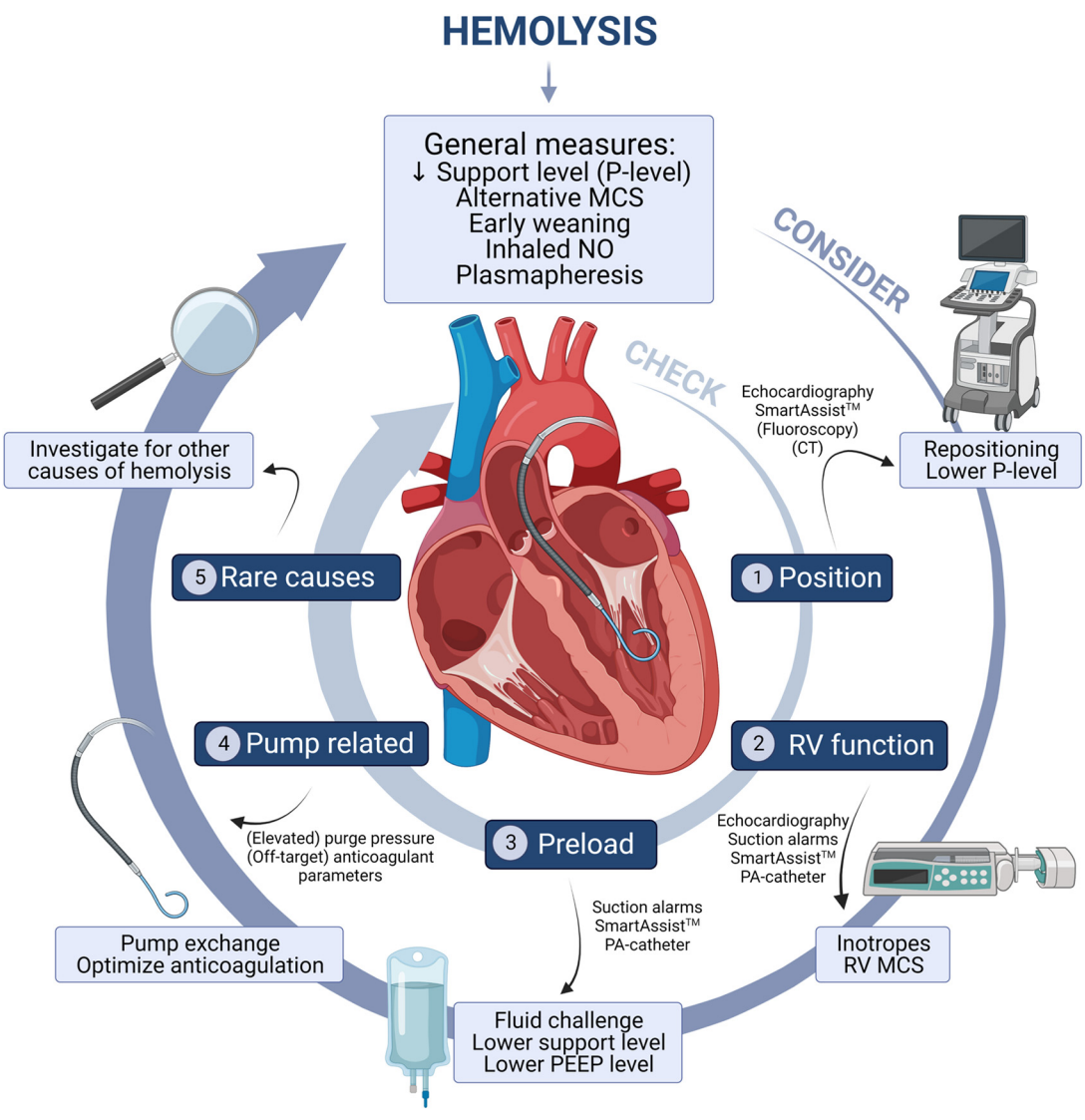
general measures to avoid further complications (Figure 4).

First, proper device positioning should be checked, as previously explained (bedside transthoracic echocardiography, SmartAssist technology). If the position of the pump is not established yet, fluoroscopy, chest radiography, or computed tomography can be diagnostic. In case the device is situated too deep in the ventricle, repositioning (pull back), guided by transthoracic echocardiography, is the first bedside option. Importantly, the P level should be lowered to P2 before the pump is manipulated to avoid structural cardiac damage. If the microaxial pVAD has been dislodged above the aortic valve, advancing it at the bedside is generally not recommended.

Second, when pump malpositioning has been excluded on transthoracic echocardiography, RV function and ventricular preload should be evaluated. The LV pressure waveform on the console can again be informative in this scenario, as normal systolic and low diastolic pressures indicate low filling status. Moreover, pulmonary artery catheterization allows the determination of right atrial pressure, pulmonary artery wedge pressure (PAWP), and calculation of PAPi. Such information can help differentiate between hypovolemia (low PAWP) and low central venous pressure and RV failure (low to normal PAWP and disproportionately high right atrial pressure, with PAPi <1.0) and pulmonary hypertension.[3] A dynamic positive end-expiratory pressure test (lowering or increasing the positive end-expiratory pressure to assess its effect on hemodynamic parameters) and/or fluid challenge might also offer valuable information. If RV dysfunction is diagnosed, inotropes or pulmonary vasodilators or the addition of RV MCS should be promptly considered. When hypovolemia is presumed to be the main cause of insufficient pump preload, an empirical but cautious fluid bolus should be administered. In case of hypovolemia, it will result in reduced suction events and increased cardiac output. This scenario is usually driven by low cardiac output as the main clinical issue, and management should focus on hemodynamic stabilization; thereafter, pump position should be reevaluated according to the modified geometry and pressures in the heart chambers.

Third, if device dislocation, RV dysfunction, and hypovolemia are excluded as the drivers of hemolysis, pump thrombosis should be considered, as a clot

FIGURE 4 Practical Step-by-Step Approach for Hemolysis Management During Microaxial Percutaneous Ventricular Assist Device Support

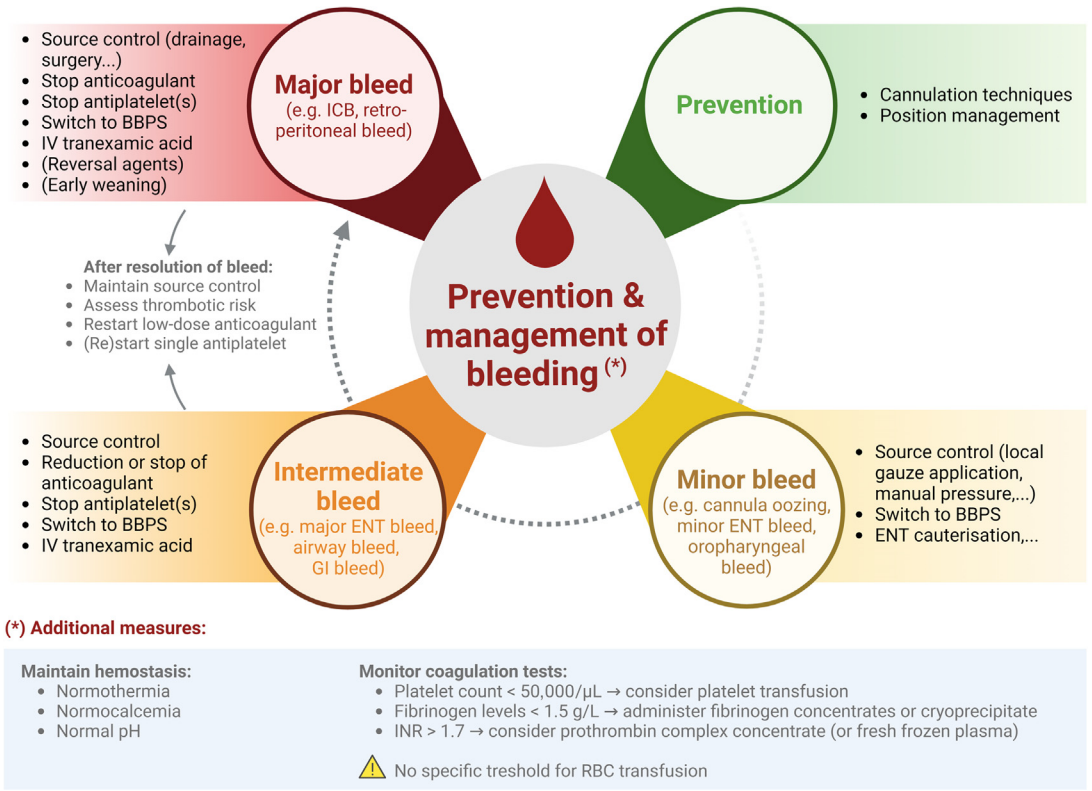


(1) Check position and reposition if necessary. **(2)** Assess right ventricular (RV) function (echocardiography or pulmonary artery [PA] catheter) and consider inotropic support or RV mechanical support. **(3)** When intermittent suction occurs, a fluid challenge or lowering the support or positive end-expiratory pressure (PEEP) level can be helpful. **(4)** Exclude pump-related problems in case of elevated purge pressures or a recent history of off-target anticoagulant parameters; consider pump exchange and/or optimize the anticoagulation therapy. **(5)** Think about less common causes of hemolysis when hemolysis remains. CT = computed tomography; MCS = mechanical circulatory support; NO = nitric oxide.

will narrow the lumen between the impeller and the housing and thereby enhance shear stress and induce hemolysis. Evidence for pump thrombosis includes elevated purge pressures and a recent history of insufficient anticoagulation, including an anti-Xa level <0.2 IU/L.[22] Pump exchange is recommended when pump thrombosis is suspected.[22] Finally, if the cause of hemolysis remains unclear, more unusual etiologies, including intrinsic reasons for hemolysis (eg, sickle cell anemia) or thrombotic microangiopathy, should be considered.

Together with the etiologic investigation, both pump and ICU management-related general actions should be considered to lower the shear stress and

FIGURE 5 **Prevention and Management of Bleeding Complications on Microaxial pVAD Support**

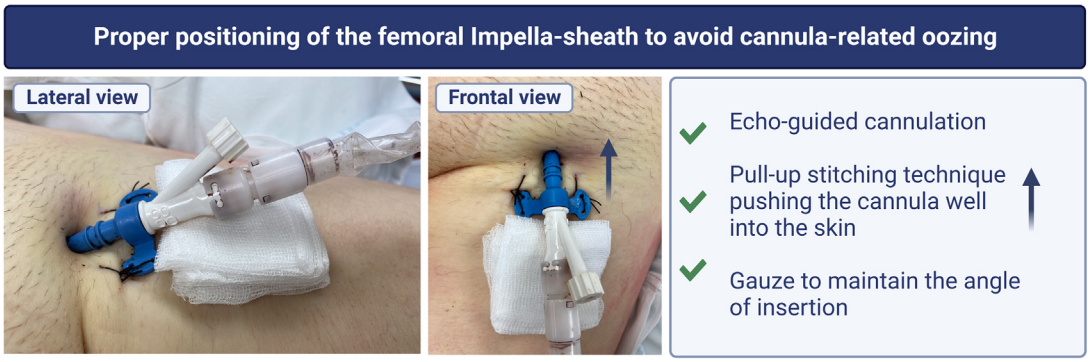


Overview of strategies to prevent bleeding complications and suggested treatment modalities in case of minor, intermediate, or major bleeding. Source control should be central, aided by additional interventions depending on the type, location, and severity of the bleed. Furthermore, general measures based on maintenance of hemostasis and monitoring of coagulation tests are provided. BBPS = bicarbonate-based purge solution; ENT = ear, nose, and throat; GI = gastrointestinal; ICB = intracranial bleed; INR = international normalized ratio; IV = intravenous; pVAD = percutaneous ventricular assist device.

avoid direct complications of hemolysis. A first step is lowering the P level as much as possible, as this will reduce shear stress. If lower P levels are well tolerated, early weaning from microaxial pVAD should be attempted. Alternatively, if lower support is not sufficient, pump exchange or upgrade to another MCS should be considered. Upgrading patients on Impella CP support experiencing refractory hemolysis to a surgically implanted Impella device because of better fixation of the pump position was suggested.[37] As general management, prevention of hypovolemia and increased anticoagulation levels may be necessary. Counteracting the devastating effects of pfHb during excessive hemolysis is equally important. In the presence of severe pfHb-induced vasoconstriction, irreversible pfHb-NO binding may be countered by administering high doses of inhaled NO.[38,39] Ideally, pfHb should be removed from the systemic circulation as soon as possible to counter thrombosis, renal failure, vasoconstriction, and other adverse effects. This can be done by plasmapheresis (against 50% albumin, 50% fresh-frozen plasma) and/or by hemoadsorption (eg, CytoSorb, CytoSorbents).[40]

BLEEDING. The most important step if bleeding occurs during pVAD support is to obtain bleeding source control (**Figure 5**). As most bleeds are access site related, local measures are the first step. Meticulous (ultrasound-guided) cannulation techniques, proper positioning, and stitching of the sheath to the skin are key to avoid complications (pull-up technique; **Figure 6**). Manual pressure and/or local application of gauze soaked in tranexamic acid or adrenaline (concentration 1:1,000 with a limited application time of 20 minutes to avoid necrosis of the skin) is often effective. For ear, nose, and throat bleeds, local treatments are also recommended (eg, mouth packing

FIGURE 6 Measures to Ensure Proper Positioning of the Femoral Impella Sheath



Ultrasound-guided cannulation techniques, proper positioning, and stitching with pull-up technique of the sheath to the skin are important measures to avoid local oozing or bleeding.

with tranexamic acid-soaked gauze, intranasal balloon compression, or local cauterization interventions); such bleeds can be prevented by the use of orogastric instead of nasogastric tubes. To avoid increasing the risk for thrombotic complications, reducing the anticoagulant target should be considered only when previous measures are insufficient. When indicated, the administration of peripheral UFH should be reduced. Recently, the U.S. Food and Drug Administration has approved the switch to a bicarbonate-based purge solution (25 mEq/L) in case of a contraindication to UFH or bleeding. Pump speed should be maximized when ceasing to use UFH, to minimize the risk for pump thrombosis and/or systemic embolism. Generally, the administration of reversal agents such as protamine or fresh-frozen plasma without device removal is not recommended. This reversal step should be reserved only for life-threatening bleeds. Finally, more data are needed to assess whether the increased bleeding risk outweighs the ischemic risk in patients receiving pVAD support, thus justifying less intensive antithrombotic therapy in this cohort.[41] Additional measures based on the maintenance of hemostasis and monitoring of coagulation test with recommendations concerning transfusions are provided in Figure 5.[42]

CONCLUSIONS

Bleeding and thrombotic complications can jeopardize outcomes in patients on pVAD support. Correct device and patient selection, together with a standardized approach to the prevention and treatment of microaxial pVAD-induced severe complications, are mandatory. A comprehensive understanding of the literature concerning the mechanisms of shear-induced hemolysis and bleeding in microaxial flow pump-supported patients, as well as the different diagnostic tools, and their strengths and limitations, is vital. Combining prevention, etiologic investigation and ICU management may help mitigate complications related to bleeding and hemolysis. Prospective studies are needed to provide additional guidance to optimize and standardize hematological management in critically ill MCS-supported patients.

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APPENDIX For an interactive version of the Central Illustration, please see the online version of this paper.