JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 79, NO. 19, 2022

JACC REVIEW TOPIC OF THE WEEK

Anticoagulation for Percutaneous Ventricular Assist Device-Supported Cardiogenic Shock

JACC Review Topic of the Week

Christophe Vandenbriele, MD, PhD,[a,b,c] Deepa J. Arachchillage, MD,[d,e] Pascal Frederiks, MD,[a,c] Gennaro Giustino, MD, PhD,[f] Diana A. Gorog, MD, PhD,[g,h] Mario Gramegna, MD,[i] Stefan Janssens, MD, PhD,[a,b] Bart Meyns, MD, PhD,[a,b] Amin Polzin, MD, PhD,[j] Mara Scandroglio, MD, PhD,[k] Benedikt Schrage, MD,[l,m] Gregg W. Stone, MD, PhD,[f] Guido Tavazzi, MD, PhD,[n,o] Thomas Vanassche, MD, PhD,[a,b] Pascal Vranckx, MD, PhD,[p,q] Dirk Westermann, MD, PhD,[r] Susanna Price, MD, PhD,[s,*] Alaide Chieffo, MD, PhD[t,*]

ABSTRACT

Interest in the use of mechanical circulatory support for patients presenting with cardiogenic shock is growing rapidly. The Impella (Abiomed Inc), a microaxial, continuous-flow, short-term, ventricular assist device (VAD), requires meticulous postimplantation management. Because systemic anticoagulation is needed to prevent pump thrombosis, patients are exposed to increased bleeding risk, further aggravated by sepsis, thrombocytopenia, and high shear stress–induced acquired von Willebrand syndrome. The precarious balance between bleeding and thrombosis in percutaneous VAD–supported cardiogenic shock patients is often the main reason that patient outcomes are jeopardized, and there is a lack of data addressing optimal anticoagulation management strategies during percutaneous VAD support. Here, we present a parallel anti-Factor Xa/activated partial thromboplastin time-guided anticoagulation algorithm and discuss pitfalls of heparin monitoring in critically ill patients. This review will guide physicians toward a more standardized (anti)coagulation approach to tackle device-related morbidity and mortality in this critically ill patient group. (J Am Coll Cardiol 2022;79:1949–1962)

From the [a]Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium; [b]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium; [c]Department of Adult Intensive Care, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; [d]Department of Haematology, Royal Brompton Hospital, London, United Kingdom; [e]Centre for Haematology, Department of Immunology and Inflammation, Imperial College London, London, United Kingdom; [f]Department of Cardiology, The Zena & Michael A. Wiener Cardiovascular Institute, Mount Sinai, New York, New York, USA; [g]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom; [h]School of Life and Medical Sciences, Postgraduate Medical School, University of Hertfordshire, Hertfordshire, United Kingdom; [i]Cardiac Intensive Care Unit, San Raffaele Scientific Institute, Milan, Italy; [j]Division of Cardiology, Pulmonology, and Vascular Medicine, Heinrich Heine University Medical Center Düsseldorf, Düsseldorf, Germany; [k]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy; [l]Department of Cardiology, University Heart & Vascular Center Hamburg, Hamburg, Germany; [m]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; [n]Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; [o]Anaesthesia and Intensive Care, Fondazione Policlinico San Matteo IRCCS, Pavia, Italy; [p]Department of Cardiology and Intensive Care Medicine, Jessa Ziekenhuis, Hasselt, Belgium; [q]Faculty of Medicine and Life Sciences, University of Hasselt, Hasselt, Belgium; [r]Department of Cardiology and Angiology, University Heart Center Freiburg-Bad Krozingen, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [s]Departments of Critical Care & Cardiology, Royal Brompton & Harefield Hospitals, London, United Kingdom, National Heart & Lung Institute, Imperial College, London, United Kingdom; and the [t]Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy. *Drs Price and Chieffo contributed equally to this work as joint senior authors.
Navin K. Kapur, MD, served as Guest Associate Editor for this paper. Athena Poppas, MD, served as Guest Editor-in-Chief for this paper.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on JACC.org.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2022.02.052

JACC VOL. 79, NO. 19, 2022
MAY 17, 2022:1949–1962

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

APTT = activated partial thromboplastin time

AVWS = acquired von Willebrand syndrome

CS = cardiogenic shock

DAPT = dual antiplatelet therapy

ECMO = extracorporeal membrane oxygenation

HIT = heparin-induced thrombocytopenia

IV = intravenous

MCS = mechanical circulatory support

PCI = percutaneous coronary intervention

pfHb = plasma-free hemoglobin

pVAD = percutaneous ventricular assist device

UFH = unfractionated heparin

VAD = ventricular assist device

The Impella (Abiomed Inc) is a form of short-term percutaneous ventricular assist device (pVAD)[1] approved for high-risk percutaneous coronary interventions (PCI)[2] and cardiogenic shock (CS).[3] It is intended to restore hemodynamics, unload the ventricle, and protect the myocardium from further ischemia.[4] pVADs are increasingly used as a bridge to a permanent ventricular assist device (VAD) or heart transplant and, by 2019, had been used in >50,000 patients in the United States alone.[5,6]

The Impella is a catheter-based continuous microaxial flow pump[7] comprising an impella (a rotating screw within a covered miniaturized housing) that drains blood from the left ventricle or inferior vena cava and expels it into the ascending aorta or pulmonary artery. Here, the use of anticoagulation is mandatory to counteract activation of the coagulation system caused by shear force stress and the foreign body surfaces of the pump. This is further compounded because CS causes a systemic inflammatory response syndrome, leading to disruption of the normal coagulation system.[8] Moreover, acute coronary syndrome (ACS), multiorgan dysfunction, and infection (and mostly a combination) further contribute to a procoagulant acute-phase response. Additionally, factors related to the device's mechanical functioning, optimal positioning, and hydrodynamics may further negatively alter the equilibrium between bleeding and thrombosis.

Bleeding complications are a major challenge in pVAD-supported patients, as recently shown in 2 large retrospective U.S. studies, both including >25,000 patients supported by microaxial flow pumps.[6,9] Mortality was even higher in the microaxial flow pump group than in the group supported by more conventional intra-aortic balloon pumps, mainly because of a higher rate of major bleeding complications in the microaxial flow group.[6,9] Disappointingly, neither of these studies discussed the anticoagulation management strategy (which anticoagulant agent, monitoring strategies, management of bleeding complications, guiding anticoagulation protocols, prevention of hemolysis). The precarious balance between bleeding and thrombosis in patients supported by microaxial flow pumps is often the main reason that patient outcomes are jeopardized (**Central Illustration**), and there is a lack of data addressing optimal anticoagulation management strategies during pVAD support in critically ill patients. Therefore, we aim to provide a practical and rational approach to this key topic.

HIGHLIGHTS

- Bleeding and thrombotic complications jeopardize outcomes in patients with cardiogenic shock supported with pVADs.
- A standardized anticoagulation management protocol guided by parallel measurements of anti-Xa activity and APTT can reduce the risks of these complications.
- Randomized trials are needed to confirm the optimum anticoagulation regimen in patients with cardiogenic shock requiring mechanical circulatory support.

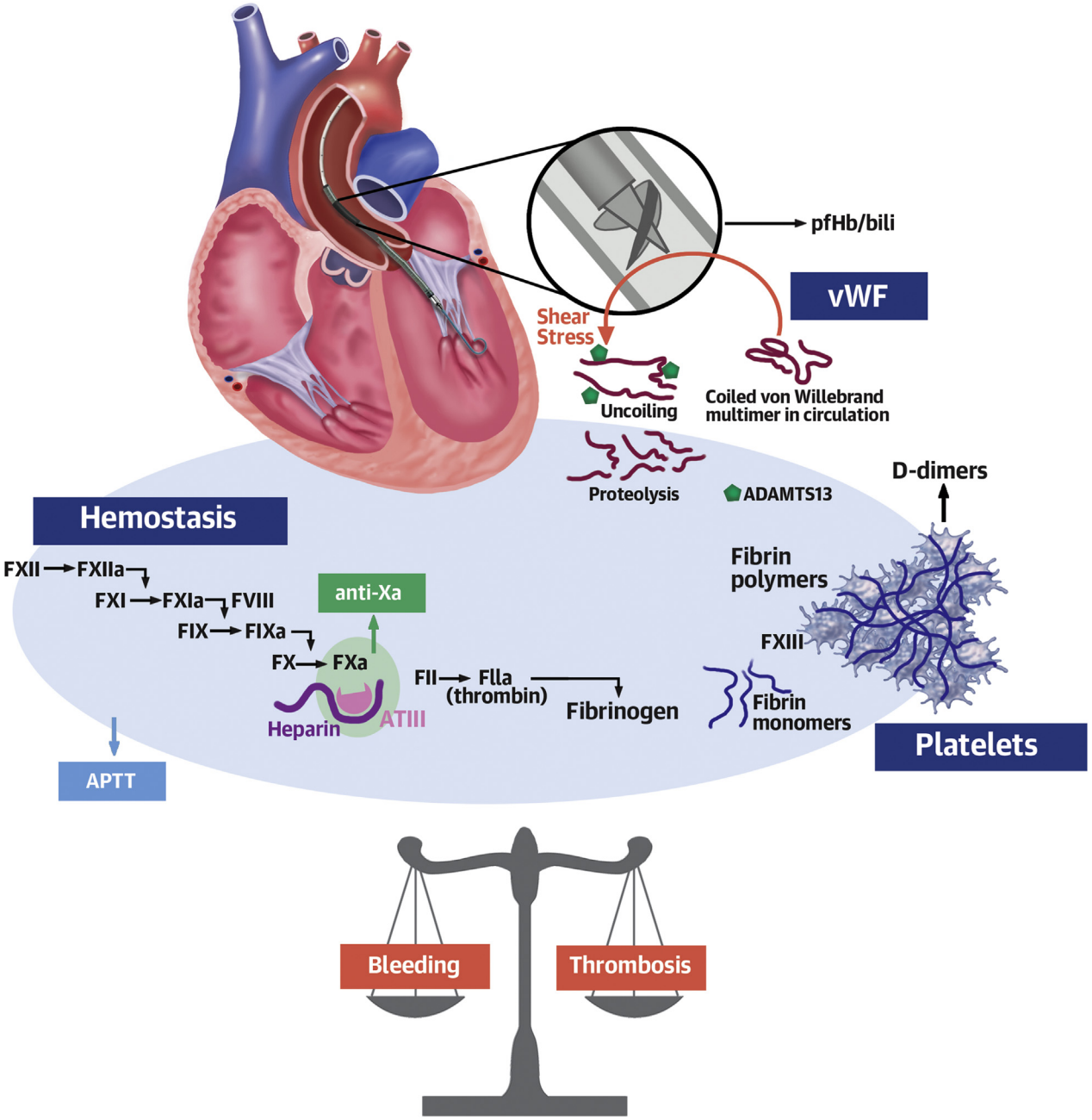
BLEEDING AND THROMBOTIC COMPLICATIONS ON SHORT-TERM MECHANICAL CIRCULATORY SUPPORT

Bleeding and vascular complications are frequent with short-term mechanical circulatory support (MCS) and increase mortality.[10] These complications also vary with different pVAD devices. Anticoagulation, usually with intravenous (IV) unfractionated heparin (UFH), is required during MCS to avoid clotting of the circuit and to reduce the risk of device-related thrombus formation and embolization.[11] Over-anticoagulation, the effects of dual antiplatelet therapy (DAPT) in patients with ACS and/or PCI, as well as the frequent development of acquired von Willebrand syndrome (AVWS) all increase the risk of bleeding. The high shear and continuous flow in MCS, particularly with extracorporeal membrane oxygenation (ECMO) and microaxial flow pumps, leads to proteolysis of high molecular weight von Willebrand factor. This results in reduced platelet-binding affinity and the development of AVWS in the majority of patients within 24 hours of starting MCS, which resolves rapidly after discontinuation (**Figure 1**).[12] The only treatment to date for MCS-induced AVWS

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 22, 2021; revised manuscript received February 8, 2022, accepted February 22, 2022.

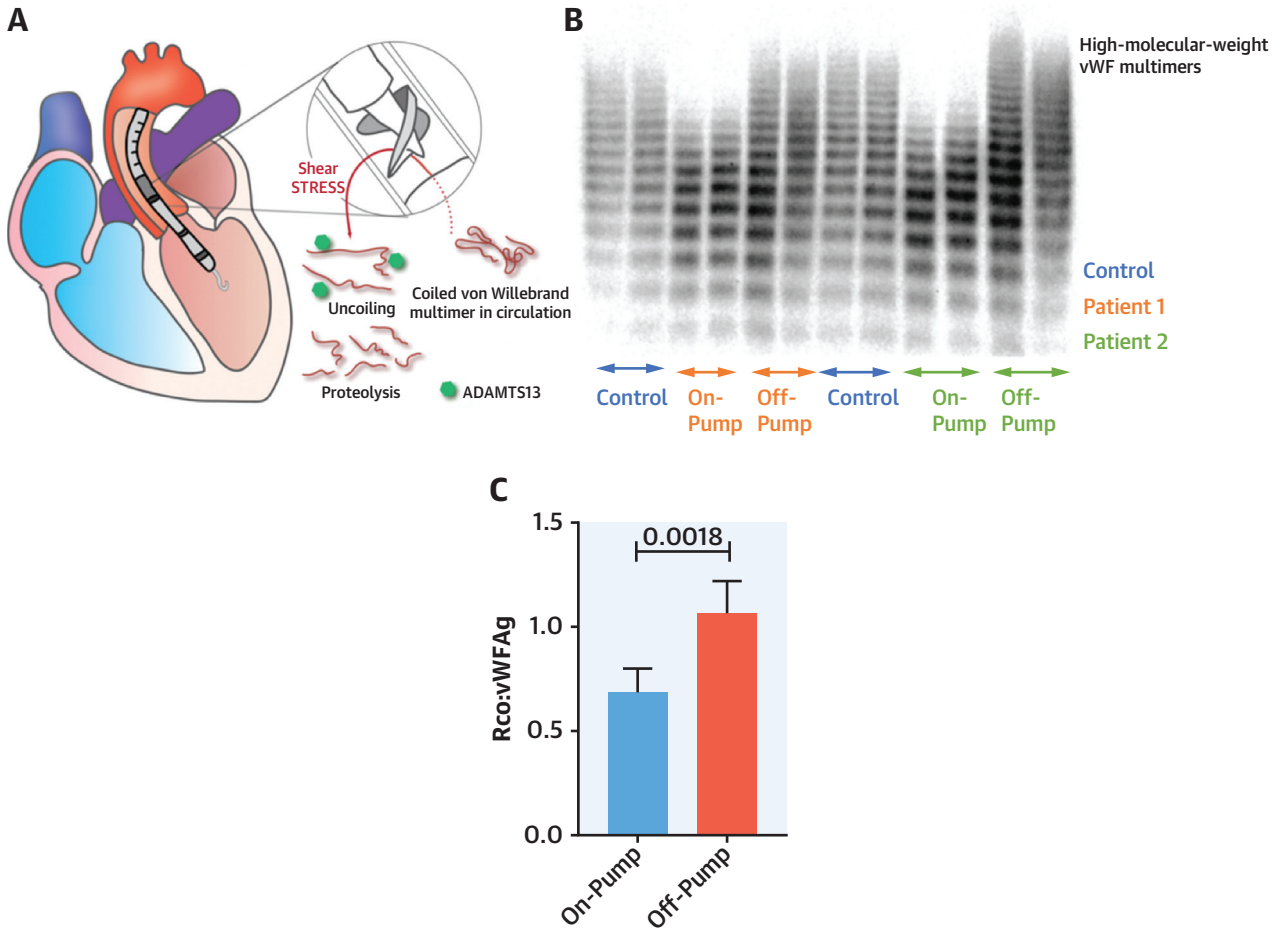
CENTRAL ILLUSTRATION **Precarious Balance Between Bleeding and Thrombosis in Critically Ill Patients Supported by Microaxial Flow Devices**



Vandenbriele C, et al. J Am Coll Cardiol. 2022;79(19):1949–1962.

Hemostasis/unfractionated heparin is monitored via parallel measurements of anti-Factor Xa/activated partial prothromboplastin time. Thrombosis is measured indirectly via D-dimer levels (product of fibrinolysis). Shear-stress–induced acquired von Willebrand factor is measured via von Willebrand factor antigen and functional von Willebrand testing. Hemolysis is measured via plasma-free hemoglobin levels.

FIGURE 1 Shear Stress-Induced AVWS



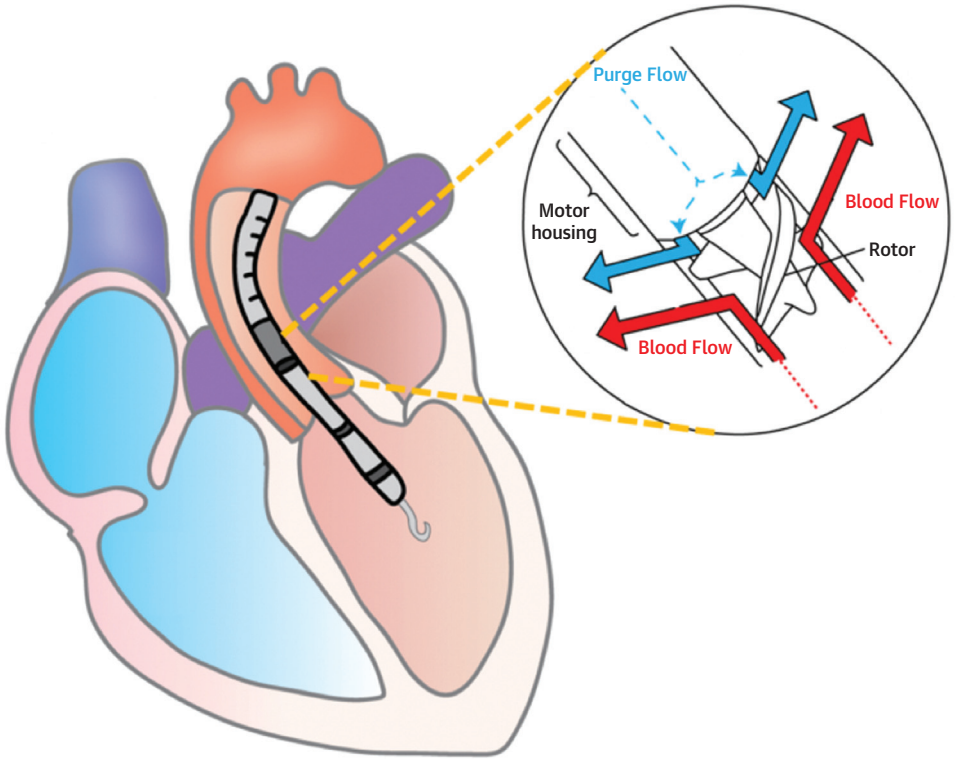
(A) Mechanically-induced shear stress causes uncoiling of large von Willebrand factor (vWF) multimers and subsequently cleaving by ADAMTS13. **(B)** Electrophoresis, loss of high-molecular-weight vWF multimers in 2 patients (1 hour after pump initiation), and regain 1 hour after pump explantation. **(C)** 8 microaxial flow pump-supported cardiogenic shock patients; a significant drop in the ristocetin (Rco) to von Willebrand factor antigen (vWFAg) ratio on-pump as compared with on-pump, compatible with acquired von Willebrand syndrome (AVWS). Paired Student's *t-test*. **Error bars** indicate mean ± SD.

is removal of the pump, although novel techniques (eg, ADAMTS13-blocking agents) are under investigation.[13,14]

Bleeding is more common with nonpulsatile, continuous-flow devices, is greater at lower flow rates,[15] and also varies with different pVAD devices. Among ACS patients with CS, bleeding complications occur in ~20% of those treated with intra-aortic balloon pumps[16] and in 40%-70% with ECMO.[17] Most data pertaining to the frequency of bleeding and thrombotic complications come from retrospective analyses of large national databases. Evaluation of PCI registry data from the United States indicates that the microaxial flow pump brings an increased risk of major bleeding requiring transfusion, but highlight wide variation between hospitals in the reported incidence of bleeding (>2.5-fold variation) and stroke (~1.5-fold variation).[6] A meta-analysis of 17 studies involving 3,933 patients with CS supported by microaxial flow pumps reported vascular complications and major bleeding in 7.4% and 15.2% of patients, respectively.[18]

A recent prospective evaluation of MCS in the ACS setting comes from a subanalysis of the CULPRIT-SHOCK (PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock) randomized trial. Among 684 patients, of whom 193 received MCS, bleeding complications occurred in 21.5%, mainly within the first 2 days of hospitalization, and treatment with ECMO or a microaxial flow pump emerged as the major risk factor for bleeding (ORs: 1.84 and 3.31, respectively). Bleeding was

FIGURE 2 The Unique Heparinized Purge System



The microaxial flow pump is equipped with an integrated purge system using heparinized dextrose in water (purge flow), designed to protect blood from entering the motor compartment by creating a pressure barrier against the blood flow to which the device is exposed.

associated with an increased risk of death (HR: 2.11; $P < 0.0001$) and with prolonged inotropic and ventilatory requirement.[19]

Risk factors associated with pVAD-related vascular complications and major bleeding include older age, female sex, obesity, prior hypertension, and peripheral arterial disease.[18,20] In addition, optimizing the sheath to femoral artery ratio,[18] use of Doppler ultrasound and fluoroscopic guidance, and use of a micropuncture technique and low stick angle can help reduce access-site complications. With increasing operator experience, the rate of bleeding complications with MCS implantation is reduced.

WHICH ANTICOAGULANT STRATEGY?

Anticoagulation in pVAD-supported CS patients is often challenging because of pre-existing coagulopathy, access-site vascular complications, and the

TABLE 1 APTT vs Anti-Xa for Monitoring UFH

APTT	Heparin Anti-Xa
• Cheap, easily available.	• Expensive.
• Frequent measurements are needed.	• Less frequent measurements needed.
• Various confounding factors (pre-analytical and analytical) and reagents from different batches can vary.	• Not affected by confounding factors.
• Required for DTI monitoring.	• Not useful in case of DTI anticoagulation.
• Inflammatory response of the patient, coagulation activation with artificial surfaces, pre-existing coagulation factor deficiency (especially factor XII deficiency; both congenital and acquired), presence of lupus anticoagulant, liver failure or nonspecific inhibitors can affect APTT.	• Measures the amount of UFH available to produce an anticoagulant effect within the patient. • Presence/absence of exogenous AT in the assays needs to be known to interpret the results accurately in patients with AT deficiency.
• May be more useful in assessing the overall bleeding tendency because APTT is affected by coagulation factor deficiency.	• May be more useful for predicting thrombosis because the anti-Xa level is a marker of the overall anticoagulant effect of UFH.

Anti-Xa = anti-factor Xa; APTT = activated partial thromboplastin time; AT = antithrombin; DTI = direct thrombin inhibitor; UFH = unfractionated heparin.

TABLE 2 Case Vignettes Illustrating the Importance of Parallel Anti-Xa and APTT Monitoring in CS Patients[a]

Case Presentation	Heparin Dosage (U/h)	APTT (s)	Anti-Xa (U/mL)	AT-III (%)	Fibrinogen (g/L)	FVIII (%)
1. A 58-year-old man (weight: 75 kg) was supported on VA-ECMO and Impella CP for cardiogenic shock (SCAI stage D) after acute myocardial infarction. On day 3, he developed high APTT, with anti-Xa levels in the anticoagulation range. Oozing from the cannula insertion sites was observed (Figure 3A).	1,350	136.1	0.41	55	**0.66**	–
	Targets: APTT: 60-80 s, anti-Xa: 0.3-0.5 U/ml *What is the first laboratory test you want to know?*					
2. A 20-year-old female patient (weight: 71 kg) with a recent diagnosis of dilated cardiomyopathy was hospitalized with overwhelming pneumonia. After intubation, she developed asystole and was resuscitated with VA-ECMO. An Impella CP was inserted on day 2 for left ventricular venting. At that moment, levels of APTT were high, with undetectable anti-Xa levels (Figure 3B).	1,900	103.5	<0.15	**17**	**0.71**	–
	Targets: APTT: 60-80 s, anti-Xa: 0.3-0.5 U/mL *Which would be your next laboratory tests?*					
3. A 66-year-old male patient (weight: 83 kg) was supported with BiPella (CP + RP) for cardiogenic shock (SCAI stage C) in an acute decompensated toxic cardiomyopathy. APTT levels remained high on day 2, with anti-Xa levels in anticoagulation range (Figure 3C).	1,000	140	0.31	65	2.71	120.7
	Targets: APTT: 60-80 s, anti-Xa: 0.3-0.5 U/mL *If fibrinogen is normal, which laboratory tests would give you the answer?*					
4. A 56-year-old female patient (weight: 88 kg) was admitted to the hospital with late presentation of anterior myocardial infarction. Shortly after admission, she developed CS (SCAI stage D) and was supported with Impella 5.0. On day 4, laboratory results showed extremely high aminotransferase levels and signs of poor hepatic synthesis function (Figure 3D).	850	110.2	0.26	55	1.22	44.4
	Targets: APTT 40-60 s, anti-Xa: 0.2-0.3 U/mL *What is the most likely reason for this coagulation profile?*					

Relative frequencies of the described cases in patients on mechanical circulatory support are currently unknown. The answers to the questions are indicated in **bold**. Normal range of laboratory tests: APTT: 25.1-36.5 s; anti-Xa: <0.15 U/mL; AT-III (antithrombin III): 80%-130%; fibrinogen: 2.00-3.93 g/L; FVIII: 50-150%; FIX: 70%-130%; FXI: 70%-130%; FXII: 70%-130%. [a]In addition to Figure 4. [b]Lupus anticoagulant activity may prolong phospholipid-dependent coagulation tests such as APTT.

CS = cardiogenic shock; DIC = disseminated intravascular coagulation; FIX = factor IX; FVIII = factor VIII; fXI = Factor XI; FXII = factor XII; SCAI = Society for Cardiovascular Angiography and Intervention; VA-ECMO = veno-arterial extracorporeal membrane oxygenation; other abbreviations as in Table 1.

Continued on the next page

concomitant use of antithrombotic therapies or UFH allergies. UFH is the anticoagulant agent of choice in patients on pVAD support,[21] although some centers prefer the use of direct thrombin inhibitors (DTIs) (eg, bivalirudin or argatroban) because of its shorter half-life and safety in case of heparin-induced thrombocytopenia (HIT).[22] Given that some of heparin's protection is related to its specific ionic charge resulting in decreased protein adsorption to the surface, an alternative agent should ideally have a similar charge. Recent publications suggested that using sodium bicarbonate (25 mEq/L; similar ionic charge to UFH) in the purge solution may provide more sustainable support in patients who are unable to tolerate anticoagulation/UFH.[23]

DAPT IN pVAD-SUPPORTED CS PATIENTS

DAPT with aspirin and a $P2Y_{12}$-receptor inhibitor constitutes the mainstay of treatment in patients with ACS and those undergoing PCI.[24] Patients with ACS complicated by CS are at higher risk of periprocedural thrombotic complications.[25] The more potent oral $P2Y_{12}$-receptor inhibitors ticagrelor and prasugrel have both been shown to be more effective than clopidogrel in the setting of ACS.[26,27] However, prasugrel cannot be used as an upfront antiplatelet strategy in patients with unknown coronary anatomy.[24] The antiplatelet effects of oral $P2Y_{12}$-receptor inhibitors are delayed in CS patients because of slower absorption and metabolism and inadequate enteral access in intubated patients. Crushing ticagrelor or prasugrel tablets may lead to faster drug absorption and more prompt and potent antiplatelet effects compared with whole-tablet ingestion.[28] Cangrelor is an IV ATP analogue that directly, potently, and reversibly inhibits ADP binding to the $P2Y_{12}$ receptor in a dose-dependent manner after an IV bolus followed by continuous infusion.[29] In addition, cangrelor has a very short half-life (3-6 minutes) and allows fast recovery of platelet function (≈60 minutes) after infusion. Therefore, use of an IV antiplatelet agent—when available locally—offers multiple advantages, including rapid onset of action, rapid return of platelet function after cessation, and ease of administration in intubated patients. After the acute phase of acute myocardial infarction/CS, cangrelor can be transitioned to ticagrelor to maintain adequate levels of platelet inhibition because ticagrelor reversibly binds the $P2Y_{12}$ receptor at a site distinct from the ADP-binding site of cangrelor. Whether DAPT on top of UFH in MCS-supported patients significantly

TABLE 2 Continued

FIX (%)	FXI (%)	FXII (%)	Extra	Treatment	Rationale
–	–	–	Mild DIC	Supplementation of fibrinogen, watch for signs of hemorrhage.	High APTT and anti-Xa in range: **fibrinogen depletion**, caused by liver failure and DIC.
–	–	–	Negative lupus anticoagulant[b]	Supplementation of recombinant antithrombin and fibrinogen. Alternatively, replace anticoagulant (eg, bivalirudin).	High APTT and immeasurable anti-Xa: heparin resistance caused by antithrombin deficiency, in combination with hypofibrinogenemia, common in critical illness. High APTT with immeasurable anti-Xa in this setting should raise suspicion of isolated **antithrombin deficiency**.
66.5	**20.2**	**29.0**	DIC excluded	Continue heparin based on anti-Xa levels.	High APTT and anti-Xa in range: **FXI and FXII** deficiency (contact factors) caused by foreign surface-induced consumption coagulopathy. Anti-Xa reflects the antithrombotic effect of UFH, while prolonged APTT in these cases is not associated with increased bleeding risk.[52]
38.5	67.0	59.0	Liver failure, no overt DIC	Continue heparin based on APTT measurements, consider viscoelastic hemostatic assays, watch for signs of hemorrhage.	High APTT and anti-Xa in range: **FVIII and FIX deficiency,** caused by liver failure. In this setting, frequently associated with AT deficiency, where anti-Xa assay is less useful to monitor AT-dependent anticoagulant drugs (UFH).

increases the already high bleeding rate remains to be elucidated.

ANTICOAGULATION IN PATIENTS SUPPORTED BY MICROAXIAL FLOW PUMPS: THE UNIQUE HEPARINIZED PURGE SYSTEM

The microaxial flow pump is equipped with an integrated dextrose in water purged seal system designed to prevent blood from entering the motor compartment by creating a pressure barrier (**Figure 2**).[1] This purge solution enhances device protection against ingress, adsorption, deposition, and coagulation of blood components and therefore improves the duration of the pump.[30,31] The purge solution (25,000 or 12,500 U/500 mL UFH) is in addition to systemic heparinization, with a starting dose of 11-12 U/kg bodyweight (Formula 1). In case of HIT, alternative systemic anticoagulation (eg, bivalirudin or argatroban) systemically or via the purge solution is recommended.[30] In a survey of 182 centers in the United States, 25% reported using an anticoagulant-free (ie, dextrose-only) purge solution for HIT and more than one-half reported using a purge solution containing argatroban, bivalirudin, or either in this scenario.[32]

The dextrose concentration (5% D5 or 20% D20) determines the viscosity and flow rate of the purge fluid. The D5 concentration is less viscous and flows quickly through the purge system, thereby increasing the amount of UFH delivered.[31] D20 is more viscous, resulting in a slower purge flow rate and less UFH infusion but increased risk of purge obstruction. D20 concentrations may be used in patients with higher anti-Xa levels (even after cessation of systemic UFH) or those anticipated to have lower anticoagulation needs (ie, patients with a lower body surface area).[30,31] A change from D20 to D5 results in an increase in purge flow rates of approximately 30%-40% with consequent greater systemic exposure to UFH. UFH exposure may also change over time, as flow rates of the purge solution are automatically regulated by the device to maintain a pressure range (300-1,100 mm Hg).[33] To maintain an appropriate purge pressure of 300 mm Hg, flow rates may therefore range from 2-30 mL/h.

FORMULA: CALCULATE THE INITIAL UFH INFUSION RATE

Purge rate calculation assumes pump use of 50 U/mL UFH for a patient weighing, eg, 85 kg and a purge rate of, eg, 10 mL/h:

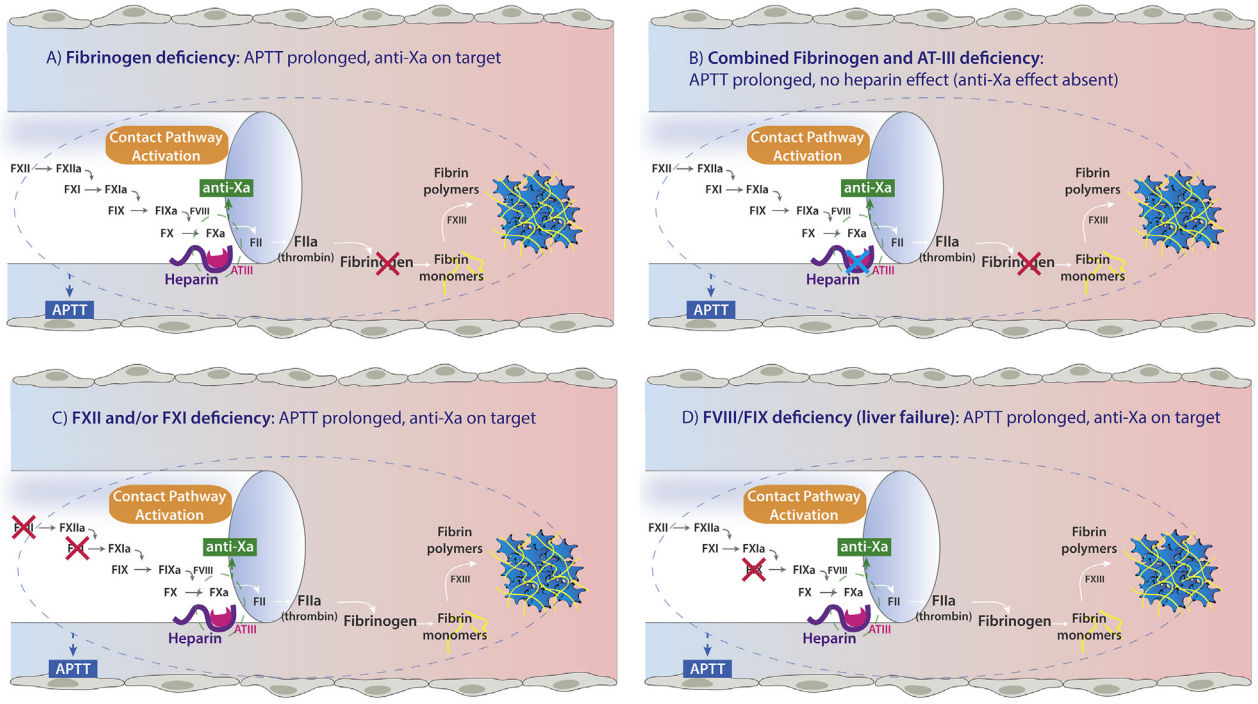
- Total UFH (purge plus systemic) to reach therapeutic anticoagulation levels:

  12 U/kg bodyweight (in kg)/h = 1,020 U/h (do NOT exceed the maximum of 1,800 U/h).

- Microaxial flow pump purge rate: 10 mL/h × 50 U/mL = 500 U/h
- Systemic heparin infusion rate = total UFH - purge UFH = 1,020 U/h − 500 U/h = 520 U/h of UFH = 6 IU/kg/h of UFH

JACC VOL. 79, NO. 19, 2022
MAY 17, 2022:1949–1962

FIGURE 3 Clinical Scenarios of the APTT/Anti-Xa Effect in Critically ill Patients on UFH



(A) Low levels of fibrinogen prolong contact pathway activation (APTT) and do not affect anti-Xa. **(B)** Low levels of both fibrinogen and AT result in prolonged APTT and the absence of the heparin effect (no anti-Xa effect). **(C)** Low levels of FXII and FXI prolong APTT with preserved anti-Xa levels. **(D)** Deficiency of FVIII and/or FIX (eg, liver failure) prolong APTT and preserve anti-Xa levels. Anti-Xa = anti–factor Xa; APTT = activated partial thromboplastin time; AT = antithrombin; FIIa = factor IIa (thrombin); FIX/a = factor IX/a; FX/a = factor X/a; FXI = factor XI/a; fXII/a = factor XII/a; FXIII = factor XIII; UFH = unfractionated heparin.

The purge rate should be checked at least daily because significant changes in flow rate can often be found.

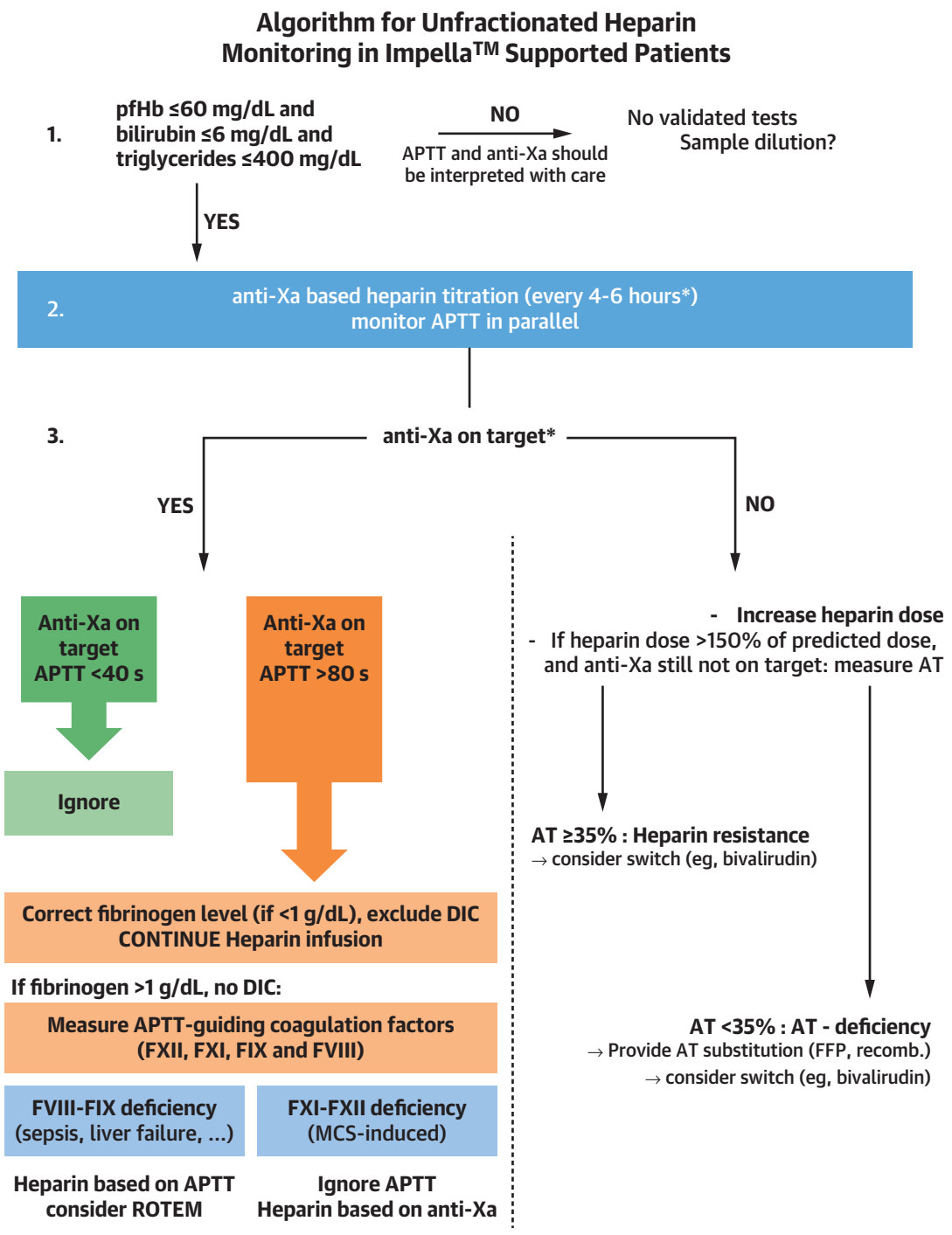
MONITORING UFH IN CRITICALLY ILL PATIENTS: A PRACTICAL APPROACH

ACTIVATED PARTIAL THROMBOPLASTIN TIME VS ACTIVATED CLOTTING TIME VS ANTI–FACTOR-XA. UFH exhibits marked variability in anticoagulant response among individual patients. The variability is especially high in those who are critically ill, because UFH is a highly negatively charged molecule that binds to positively charged plasma proteins, proteins released from platelets, and endothelial cell proteins/surfaces.[34] Standard practice is to measure the heparin anti-factor Xa level (anti-Xa), activated partial thromboplastin time (APTT) or, when very high doses UFH are used, the activated clotting time. The ideal test to monitor UFH should have the following characteristics:

- A well-defined and preferably linear relationship with clinical outcome in terms of recurrent thrombosis and bleeding;
- Good precision;
- Well standardized among laboratories and assay reagents;
- Readily available and inexpensive.

Thus, to assess the local APTT/anti-Xa correlation, the range of APTT corresponding with therapeutic anti-Xa levels of 0.3-0.7 IU/mL should be assessed from control samples obtained from (noncritically ill) patients on stable UFH infusion without confounding factors that affect APTT.[35] Although APTT is widely available and inexpensive, it does not have linear relationship with bleeding or thrombosis, and standardization is challenging and affected by various confounding factors (Table 1). Currently, there are no prospective randomized controlled trials directly comparing APTT vs anti-Xa levels available in patients on microaxial flow pump support. Various factors (eg, fibrinogen or antithrombin depletion caused by acute

FIGURE 4 Algorithm for UFH Monitoring in Critically Ill Patients Supported by Microaxial Flow Pumps



This flowchart provides an overview of 3 important steps in assessing anticoagulation management in critically ill patients on microaxial flow pump support. Anti-Xa (standard target 0.3-0.5 IU/mL, unless otherwise defined by the treating physician) and APTT should be assessed in parallel every 4-6 hours. *Frequency of monitoring and anti-Xa targets should be reconsidered case by case and on a daily basis.
DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; pfHb = plasma-free hemoglobin; ROTEM = rotational thromboelastometry; other abbreviations as in Figure 3.

TABLE 3 Routine Daily Anticoagulation Monitoring in a Cardiac ICU

Measurement	Time Frame
ACT	(Initial phase, only for short-term monitoring)
APTT	Every 4-6 h (in parallel)
Anti-Xa levels	
Prothrombin time (INR)	
D-dimer	At least daily (more often on indication)
pfHb	
Fibrinogen levels	
Platelet counts	At least daily (more often if indicated)
vWFAg, functional vWF testing	Situationally (mainly for research purposes)
Other coagulation factors (FVIII, FIX, FXI, FXII)	Situationally, based on APTT/anti-Xa mismatch

Proposed daily assessment of anticoagulation parameters in critically ill patients on pVAD-support.

ACT = activated clotting time; ICU = intensive care unit; INR = international normalized ratio; pfHb = plasma-free hemoglobin; vWF = von Willebrand factor; vWFAg = von Willebrand factor antigen; other abbreviations as in Tables 1 and 2.

inflammation/following surgery, factor VIII depletion caused by AVWS or liver failure, or factor XI/XII depletion caused by plastic surface adherence) all contribute to APTT fluctuation in patients on pVADs. Because anti-Xa levels are not affected by those factors, monitoring UFH in these critically ill patients is preferably undertaken using heparin anti-Xa levels (with APTT *in parallel* to rule out any coagulation factor deficiency, as further discussed). Various reports have shown increased 30-day mortality in critically ill UFH-treated patients when APTT is prolonged relative to the corresponding anti-Xa level.[36]

Target anti-Xa levels in patients supported by microaxial flow pumps should be between 0.3-0.5 IU/mL in the absence of acute thrombosis; otherwise, escalation to 0.5-0.7 IU/mL should be considered. In case of DTIs, APTT is the preferred way of monitoring (target range 40-60 seconds). There are currently no studies in pVAD-supported patients evaluating the ideal UFH anti-Xa anticoagulation level.[37]

THE IMPORTANCE OF PARALLEL ANTI-Xa/APTT MONITORING: 4 CLINICAL VIGNETTES. To illustrate APTT fluctuations and the important added value of *parallel* anti-Xa/APTT level assessment during UHF therapy, we provide 4 clinical vignettes (Table 2, Figure 3) describing the effects of fibrinogen and/or antithrombin depletion, FVIII deficiency (eg, AVWS or liver failure), or factor XII/XI deficiency, as is often seen in critically ill patients supported by pVADs.

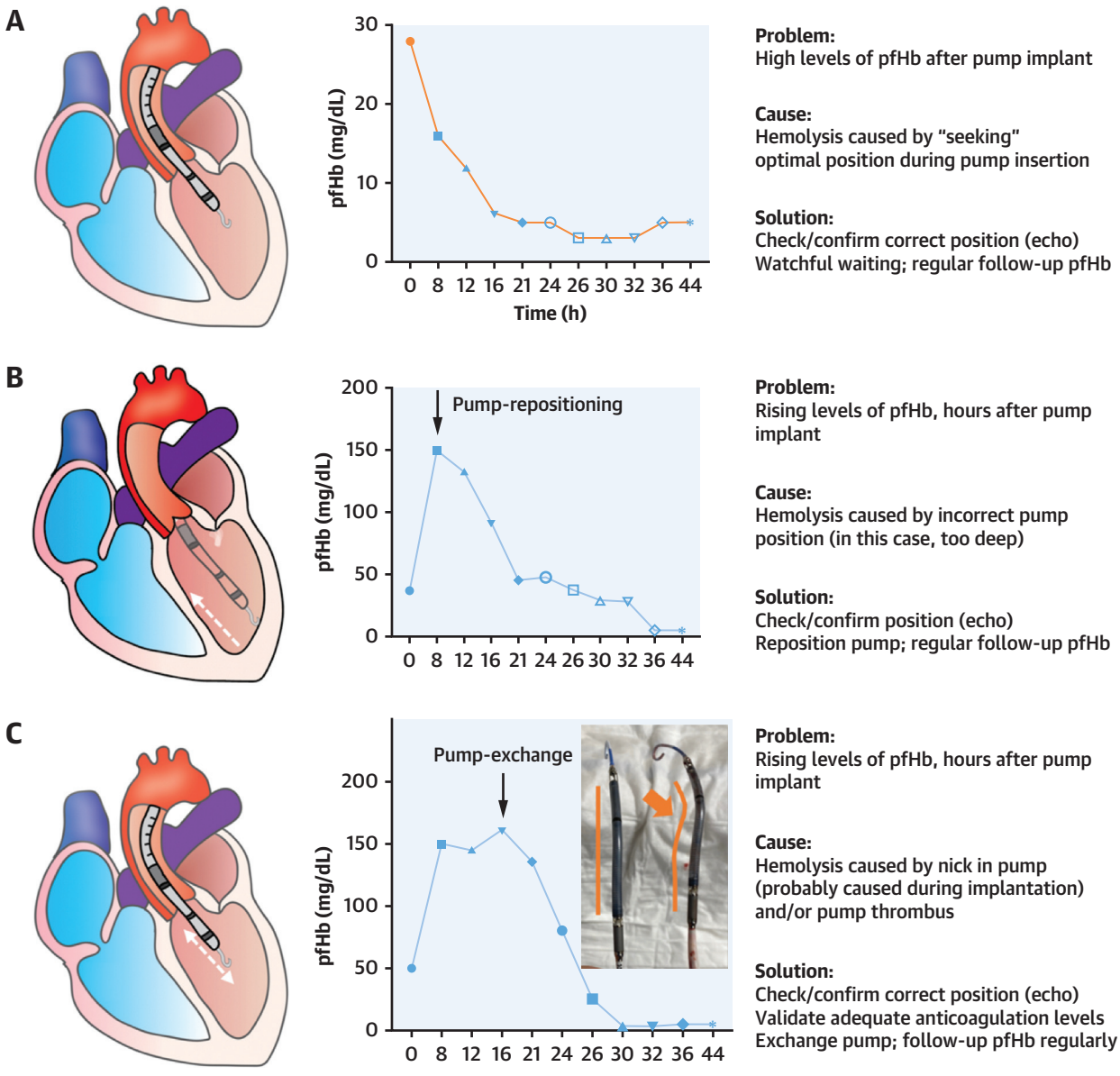
A PRACTICAL ALGORITHM FOR MONITORING pVAD-SUPPORTED CS PATIENTS. A 3-step algorithm to monitor UFH anticoagulation in a microaxial flow pump-supported patient is shown in Figure 4. First, one needs to exclude high levels of plasma-free hemoglobin (pfHb), bilirubin, and/or triglycerides, because this disturbs the correct analysis of both APTT and anti-Xa. Next, the UFH dose is titrated based on anti-Xa with APTT measured *in parallel*; the ideal sampling frequency is every 4-6 hours but should be reconsidered based on local resources and case by case. When anti-Xa reaches its target (0.3-0.5 IU/mL, unless decided differently) but APTT is disproportionally prolonged, further investigations should be performed to assess the cause of this discrepancy (Figure 4). In patients not achieving therapeutic anti-Xa despite an adequate dose of UFH, the antithrombin level should be tested. If the antithrombin level is low, antithrombin supplementation or a switch to alternative, nonheparin anticoagulant agents (eg, DTIs) could be considered.

DAILY COAGULATION MONITORING OF THE pVAD-SUPPORTED CS PATIENT: PRACTICAL SCHEME. An overview of routine daily anticoagulation monitoring in a cardiac intensive care unit is shown in Table 3. ACT only roughly reflects the anticoagulative state, and should therefore only be used after the UFH bolus. If anti-Xa is not available 24/7, it should be performed at least once daily. D-dimers reflect the thrombotic state of the patient's coagulation and pfHb/lactate dehydrogenase (LDH) levels (as a marker for hemolysis) should be performed at least once daily, more often when hemolysis is present. Prothrombin time reflects the tissue factor pathway (vitamin K-dependent coagulation factors) and especially reflects liver function.

HEMOLYSIS

Patients supported with pVADs are at high risk of shear-induced hemolysis as erythrocytes pass through the device. The extent of shear stress, the pVAD device used, and the duration of MCS increase the risk of hemolysis.[38] The reported incidence of hemolysis with the microaxial flow pump varies widely, from 5%-63%, at least in part based on the definition used.[39] Regular inspection of the urine for increasing red discoloration is a good initial indicator. The recognized definition of hemolysis in patients on MCS is not uniform, and its extent can be quantified by pfHb, LDH, and haptoglobin. A recent consensus document providing definitions for adverse events in patients on percutaneous MCS

FIGURE 5 3 Different Scenarios Causing Pump-Related Hemolysis



(A) Hemolysis after pump implant, spontaneous resolution. **(B)** Hemolysis caused by deep pump position in the left ventricle, resolution after repositioning. **(C)** Hemolysis caused by kink and/or thrombus in the microaxial flow pump device, resolution after pump exchange. pfHb = plasma-free hemoglobin.

defines hemolysis as a pfHb concentration >20 mg/dL or a serum LDH level >2.5 times the upper normal range (more than 72 hours postimplantation).[40] Isolated LDH elevations may be attributable to laboratory error or hepatic or pulmonary dysfunction. Here, parallel monitoring of indirect bilirubinemia can be helpful in differentiating between hemolysis and alternative causes of LDH rise. As LDH is more widely available and is an easier assay to perform,[41] LDH measurement should be performed daily and with complementary use of pfHb according to local availability.

The main consequence of hemolysis is a drop in hemoglobin, but additionally, released hemoglobin scavenges nitric oxide,[42] which can result in enhanced vascular tone, platelet activation,

aggregation, and arterial thrombosis.[43,44] Furthermore, pfHb can precipitate and aggravate kidney injury.[45] However, whether hemolysis contributes to excess mortality in pVAD patients is unclear.[38]

The optimal ways of managing pVAD-associated hemolysis are not clear. Suboptimal pump positioning or a change in position during patient transit (particularly outlet obstruction by the aortic valve) importantly contribute to hemolysis.[46] If hemolysis is present, positioning should immediately be checked with bedside echocardiography, and stringent pfHb/LDH follow-up is mandatory. A recent case series indicated that an aortic/mitral annulus angle $<126.5^{\circ}$ on echocardiography was associated with a 7.8-fold increased risk of hemolysis.[47] Another important determinant is pump performance, with flow rate directly correlating with erythrocyte damage. In patients with hemolysis, one should rapidly intervene by the following: 1) optimizing pump position; 2) reducing pump speed; or 3) exchanging the pump. **Figure 5** illustrates 3 cases of microaxial flow pump-related hemolysis by describing the problem, cause, and possible solution. Basic principles should additionally be followed, including blood transfusion, hemodiafiltration, stringent anticoagulation management and/or plasmapheresis, as needed.[48]

HOW TO MANAGE pVAD-SUPPORTED CS PATIENTS WITH BLEEDING COMPLICATIONS

Most microaxial flow pump-related bleeding is access site-related, caused by the need for large-bore access as well as continuous anticoagulation, with a lower incidence of major bleeding compared with venoarterial ECMO therapy.[18,49] Meticulous cannulation techniques are required, based on best clinical practice. In patients with CS, protamine sulfate can inhibit the coagulation process or induce thrombocytopenia in rare cases.[50] Therefore, it should not be used to reverse UFH-based anticoagulation without device removal, and local source control is the best way to control access site-related bleeding.

Adapting the device skin level with an underlying gauze is often effective in stopping as well as preventing bleeding from the access site, combined with proper stitching of the sheath to the patient's skin. This is because of reduced force from the microaxial flow pump sheath directly into the artery and better closing of the arteriotomy by the sheath. It should be combined with local pressure applied manually or preferably by compression devices (ie, FemoStop, St. Jude Medical). However, control of distal perfusion is mandatory during prolonged compression and can be a limiting factor in controlling blood loss. Oozing at the access site can be controlled by tranexamic acid- or adrenalin-soaked gauze (1:100 concentration, only 20 minutes to avoid skin necrosis) in conjunction with pressure. Ear-nose-throat bleeds are common in patients on MCS, and bleeding prevention and source control are key to success (eg, orogastric instead of nasogastric tubes, mouth packing with tranexamic acid-soaked gauze, ear-nose-throat interventions, intranasal balloon compression). Only when no proper hemostasis is obtained after optimal source control should lowering the UFH target (and thus increasing the thrombotic risk) be a next reasonable step. Cessation of UFH treatment in combination with (surgical or endovascular) source control should only be considered for severe bleeding events (eg, retroperitoneal or intracerebral bleeding) and should be kept as short as possible to prevent pump thrombosis and/or systemic embolism. If possible, only systemic UFH treatment should be stopped, and the purge system solution might be changed to bicarbonate solutions, as discussed previously. Pump speed should be maximized. Ultimately, if long-term cessation of UFH treatment is required, one should consider explanting the pVAD device.

CONCLUSIONS

pVAD support is associated with a complex process of activation of both thrombosis and bleeding. Here, we present a practical approach for optimal anticoagulation management in pVAD-supported critically ill patients. UFH remains the anticoagulant therapy of choice in the critically ill CS patient (parenteral administration, short-acting, readily reversible, low cost, low renal excretion). Other, possibly safer antithrombotic/anticoagulation strategies (eg, DTIs, anticoagulant device coatings, factor XI inhibitors), however, deserve further investigation because of the ongoing challenges with the high risk of bleeding/thrombosis complications in these critically ill patients.[37] Monitoring UFH levels using *parallel* assessment of APTT/anti-Xa is the preferred strategy in critically ill MCS patients, supported by rising evidence that mortality increases when APTT and anti-Xa start to diverge.[36] Concerning optimal UFH levels, anticoagulation is mostly based on experience, rather than on evidence; prospective trials comparing different target levels (eg, intermediate vs therapeutic levels) of UFH are lacking but urgently needed.[51]

There is clearly a need for research toward identifying new, individualized anticoagulant strategies, tailored to the specific needs of an ICU patient and on the device itself. Optimization of coagulation

strategies would help us to tackle an important hurdle in optimizing safety, outcomes, and efficacy in critically ill pVAD patients.

ACKNOWLEDGMENT The authors sincerely thank the members of the UZ Leuven and Brompton ECMO-MDT for fruitful discussions.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Vandenbriele, Meyns, Chieffo, Schrage, and Westermann have received research and/or travel funding, as well as speaker fees, from Abiomed outside of this paper. Dr Vandenbriele has received grant support from University Hospitals Leuven (Klinische onderzoeks-en opleidingsraad); and is funded by MRC Uk (MR/V037633/1). Dr Polzin has received support from the Forschungskommission of the Medical Faculty of the Heinrich Heine University (No. 18-2019) and from the German Research Foundation (PO 2247/2-1 and SFB1116). Dr Vranckx has received personal fees from Bayer, Daiichi-Sankyo, and CLS Behring. Dr Schrage has received speaker fees from AstraZeneca. Dr Chieffo has received consultant/speaker fees from Abbott, Biosensor, Boston Scientific, Edwards, and Magenta. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Prof Christophe Vandenbriele, Department of Cardiovascular Diseases, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail: Christophe.vandenbriele@gmail.com. Twitter: @CVandenbriele, @susannaprice, @alaide_chief, @BenediktSchrage, @GreggWStone, @MarioGramegnaMD, @amin_polzin.

REFERENCES

1. Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. *Lancet*. 2020;396:199–212.

2. Chieffo A, Dudek D, Hassager C, et al. Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices. *Eur Heart J Acute Cardiovasc Care*. 2021;10(5):570–583.

3. Schäfer A, Werner N, Westenfeld R, et al. Clinical scenarios for use of transvalvular microaxial pumps in acute heart failure and cardiogenic shock - a European experienced users working group opinion. *Int J Cardiol*. 2019;291:96–104.

4. Kapur NK, Alkhouli MA, DeMartini TJ, et al. Unloading the left ventricle before reperfusion in patients with anterior ST-segment-elevation myocardial infarction. *Circulation*. 2019;139:337–346.

5. Vaduganathan M, Mehra MR. Reappraisal of the safety and effectiveness of Impella pumps. *Nat Rev Cardiol*. 2020;17:203–204.

6. Amin AP, Spertus JA, Curtis JP, et al. The evolving landscape of Impella use in the United States among patients undergoing percutaneous coronary intervention with mechanical circulatory support. *Circulation*. 2020;141:273–284.

7. Meyns B, Dens J, Sergeant P, Herijgers P, Daenen W, Flameng W. Initial experiences with the Impella device in patients with cardiogenic shock - Impella support for cardiogenic shock. *Thorac Cardiovasc Surg*. 2003;51:312–317.

8. Cuinet J, Garbagnati A, Rusca M, et al. Cardiogenic shock elicits acute inflammation, delayed eosinophilia, and depletion of immune cells in most severe cases. *Sci Rep*. 2020;10:7639.

9. Dhruva SS, Ross JS, Mortazavi BJ, et al. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA*. 2020;323:734–745.

10. Chieffo A, Ancona MB, Burzotta F, et al. Observational multicentre registry of patients treated with IMPella mechanical circulatory support device in ITaly: the IMP-IT registry. *EuroIntervention*. 2020;15:e1343–e1350.

11. Gorog DA, Price S, Sibbing D, et al. Antithrombotic therapy in patients with acute coronary syndrome complicated by cardiogenic shock or out-of-hospital cardiac arrest: a joint position paper from the European Society of Cardiology (ESC) Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J Cardiovasc Pharmacother*. 2021;7:125–140.

12. Vandenbriele C, Balthazar T, Engelen M, et al, for the Coagulation group. University of Leuven. Acquired von Willebrand Syndrome in left Impella supported cardiogenic shock patients. *Eur Heart J*. 2020;41(Suppl 2). ehaa946.1538.

13. Bartoli CR, Kang J, Restle DJ, et al. Inhibition of ADAMTS-13 by doxycycline reduces von Willebrand Factor degradation during supraphysiological shear stress: Therapeutic implications for left ventricular assist device-associated bleeding. *J Am Coll Cardiol HF*. 2015;3:860–869.

14. Deconinck SJ, Nix C, Bennek-Schopping E, et al. Inhibition of adamts13: a novel therapy to treat mechanical circulatory support-induced acquired von Willebrand syndrome. *Eur Heart J*. 2020;41(suppl 2). ehaa946.3836.

15. Ki KK, Passmore MR, Chan CHH, et al. Low flow rate alters haemostatic parameters in an ex-vivo extracorporeal membrane oxygenation circuit. *Intensive Care Med Exp*. 2019;7:51.

16. Thiele H, Zeymer U, Thelemann N, et al, for the IABPSHOCK II Trial (Intraaortic Balloon Pump in Cardiogenic Shock II) Investigators. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: Long-term 6-year outcome of the randomized IABP-SHOCK II Trial. *Circulation*. 2019;139:395–403.

17. Mazzeffi M, Greenwood J, Tanaka K, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECLS Working Group on Thrombosis and Hemostasis. *Ann Thorac Surg*. 2016;101:682–689.

18. Iannaccone M, Albani S, Giannini F, et al. Short term outcomes of Impella in cardiogenic shock: a review and meta-analysis of observational studies. *Int J Cardiol*. 2021;324:44–51.

19. Freund A, Jobs A, Lurz P, et al. Frequency and impact of bleeding on outcome in patients with cardiogenic shock. *J Am Coll Cardiol Intv*. 2020;13:1182–1193.

20. Pahuja M, Ranka S, Chehab O, et al. Incidence and clinical outcomes of bleeding complications and acute limb ischemia in STEMI and cardiogenic shock. *Catheter Cardiovasc Interv*. 2021;97:1129–1138.

21. Balthazar T, Vandenbriele C, Verbrugge FH, et al. Managing patients with short-term mechanical circulatory support: JACC review topic of the week. *J Am Coll Cardiol*. 2021;77:1243–1256.

22. Fabrizio C, Levito MN, Rivosecchi R, et al. Outcomes of systemic anticoagulation with bivalirudin for Impella 5.0. *Int J Artif Organs*. 2021;44:681–686.

23. Vladimir Gilman SD, Mark Popovsky, Shannon McMinn, et al. Bicarbonate as an alternative to heparin in Impella purge fluid: understanding the biochemical basis. Paper presented at: ASAIO 66th Annual Conference; June 10-12, 2021; Washington DC.

24. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

25. van Diepen S, Katz JN, Albert NM, et al, for the American Heart Association Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e232–e268.

26. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute

coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.

27. Wiviott SD, Braunwald E, McCabe CH, et al, for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.

28. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. *J Am Coll Cardiol*. 2015;65:511–512.

29. Bhatt DL, Stone GW, Mahaffey KW, et al, for the CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368:1303–1313.

30. Dietrich JN, Kazmi H. Bleeding risks in patients on percutaneous ventricular assist devices receiving two different dextrose concentrations of heparinized purge solution: a case series. *J Pharm Pract*. 2019;32:464–469.

31. Succar L, Sulaica EM, Donahue KR, Wanat MA. Management of anticoagulation with Impella percutaneous ventricular assist devices and review of new literature. *J Thromb Thrombolysis*. 2019;48:284–291.

32. Reed BN, DiDomenico RJ, Allender JE, et al. Survey of anticoagulation practices with the Impella percutaneous ventricular assist device at high-volume centers. *J Interv Cardiol*. 2019;2019:3791307.

33. Jennings DL, Nemerovski CW, Kalus JS. Effective anticoagulation for a percutaneous ventricular assist device using a heparin-based purge solution. *Ann Pharmacother*. 2013;47:1364–1367.

34. Arachchillage DRJ, Kamani F, Deplano S, Banya W, Laffan M. Should we abandon the APTT for monitoring unfractionated heparin? *Thromb Res*. 2017;157:157–161.

35. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl 3):311S–337S.

36. Price EA, Jin J, Nguyen HM, Krishnan G, Bowen R, Zehnder JL. Discordant aPTT and anti-Xa values and outcomes in hospitalized patients treated with intravenous unfractionated heparin. *Ann Pharmacother*. 2013;47:151–158.

37. Vandenbriele C, Vanassche T, Price S. Why we need safer anticoagulant strategies for patients on short-term percutaneous mechanical circulatory support. *Intensive Care Med*. 2020;46:771–774.

38. Badiye AP, Hernandez GA, Novoa I, Chaparro SV. Incidence of hemolysis in patients with cardiogenic shock treated with Impella percutaneous left ventricular assist device. *ASAIO J*. 2016;62:11–14.

39. Esposito ML, Morine KJ, Annamalai SK, et al. Increased plasma-free hemoglobin levels identify hemolysis in patients with cardiogenic shock and a trans valvular micro-axial flow pump. *Artif Organs*. 2019;43:125–131.

40. Kormos RL, Antonides CFJ, Goldstein DJ, et al. Updated definitions of adverse events for trials and registries of mechanical circulatory support: a consensus statement of the Mechanical Circulatory Support Academic Research Consortium. *J Heart Lung Transplant*. 2020;39:735–750.

41. Chung HJ, Chung JW, Yi J, et al. Automation of Harboe method for the measurement of plasma free hemoglobin. *J Clin Lab Anal*. 2020;34:e23242.

42. Donadee C, Raat NJH, Kanias T, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. *Circulation*. 2011;124:465–476.

43. Kelm M, Schrader J. Control of coronary vascular tone by nitric oxide. *Circ Res*. 1990;66:1561–1575.

44. Loscalzo J. Nitric oxide insufficiency, platelet activation, and arterial thrombosis. *Circ Res*. 2001;88:756–762.

45. Fervenza FC, Croatt AJ, Bittar CM, et al. Induction of heme oxygenase-1 and ferritin in the kidney in warm antibody hemolytic anemia. *Am J Kidney Dis*. 2008;52:972–977.

46. Roberts N, Chandrasekaran U, Das S, Qi Z, Corbett S. Hemolysis associated with Impella heart pump positioning: in vitro hemolysis testing and computational fluid dynamics modeling. *Int J Artif Organs*. 2020:391398820909843.

47. Nakamura M, Imamura T, Fukui T, et al. Impact of the angle between aortic and mitral annulus on the occurrence of hemolysis during Impella support. *J Artif Organs*. 2020;23:207–213.

48. Dalton HJ, Cashen K, Reeder RW, et al. Hemolysis during pediatric extracorporeal membrane oxygenation: associations with circuitry, complications, and mortality. *Pediatr Crit Care Med*. 2018;19:1067–1076.

49. Schrage B, Ibrahim K, Loehn T, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation*. 2019;139:1249–1258.

50. Bakchoul T, Jouni R, Warkentin TE. Protamine (heparin)-induced thrombocytopenia: a review of the serological and clinical features associated with anti-protamine/heparin antibodies. *J Thromb Haemost*. 2016;14:1685–1695.

51. Kanji R, Vandenbriele C, Arachchillage DRJ, Price S, Gorog DA. Optimal tests to minimise bleeding and ischaemic complications in patients on short-term mechanical circulatory support. *Thromb Haemost*. Published online May 13, 2021. https://doi.org/10.1055/a-1508-8230

52. Weitz JI. Factor XI and factor XII as targets for new anticoagulants. *Thromb Res*. 2016;141(suppl 2):S40–S45.

KEY WORDS anticoagulation management, bleeding, thrombosis