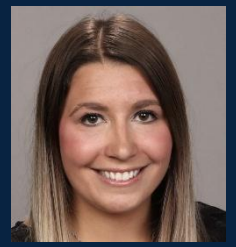
Pharmacists at the Pump: Anticoagulation & Bleeding Management in Mechanical Circulatory Support

A presentation for HealthTrust Members
May 13, 2026



Courtney Cianci, PharmD

PGY2 Critical Care Pharmacy Resident

HCA Centennial Medical Center

Preceptors:
Kelsey-Anne Forrest, PharmD, Cardiovascular Critical Care Pharmacy Clinical Specialist
Chelsea Mitchell, PharmD, BCCCP, Medical-Surgical Critical Care Pharmacy Clinical Specialist
TriStar Centennial Medical Center, Nashville, TN

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Learning Objectives for Pharmacists & Nurses

1. Recall the incidence, pathophysiology and device-specific risk factors contributing to bleeding in patients with Mechanical Circulatory Support (MCS)
2. Identify anticoagulant strategies used in patients receiving MCS to include thrombosis prevention, bleeding risks and monitoring strategies
3. Recognize current and emerging evidence on reversal agents and novel pharmacologic therapies to treat and prevent bleeding in patients on MCS

Learning Objectives for Pharmacy Techs

1. Recognize patients needing additional education from the pharmacist while receiving anticoagulant medications in the treatment of Mechanical Circulatory Support (MCS)
2. Identify anticoagulant medication schedules in the treatment of MCS
3. Recall anticoagulation medications and potential side effects for patients with MCS

Abbreviations

- Mechanical Circulatory Support (MCS)
- Left Ventricle (LV)
- Right Ventricle (RV)
- Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO)
- Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO)
- Left Ventricle Assist Device (LVAD)
- Heart Failure (HF)
- Acquired Von Willebrand Syndrome (AVWS)
- Acute Coronary Syndrome (ACS)
- Percutaneous Coronary Intervention (PCI)
- Extracorporeal Life Support Organization (ELSO)
- Unfractionated Heparin (UFH)
- Activated Partial Thromboplastin Time (APTT)
- Anti-factor Xa (Anti-Xa)
- Activated Clotting Time (ACT)
- Gastrointestinal Bleed (GIB)
- International Normalized Ratio (INR)
- Angiotensin-Converting Enzyme Inhibitor (ACEi)
- Angiotensin-Receptor Blocker (ARB)
- Long-Acting Release (LAR)
- International Society for Heart and Lung Transplantation (ISHLT)
- Heparin Induced Thrombocytopenia (HIT)

Overview of Mechanical Circulatory Support (MCS)

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MCS

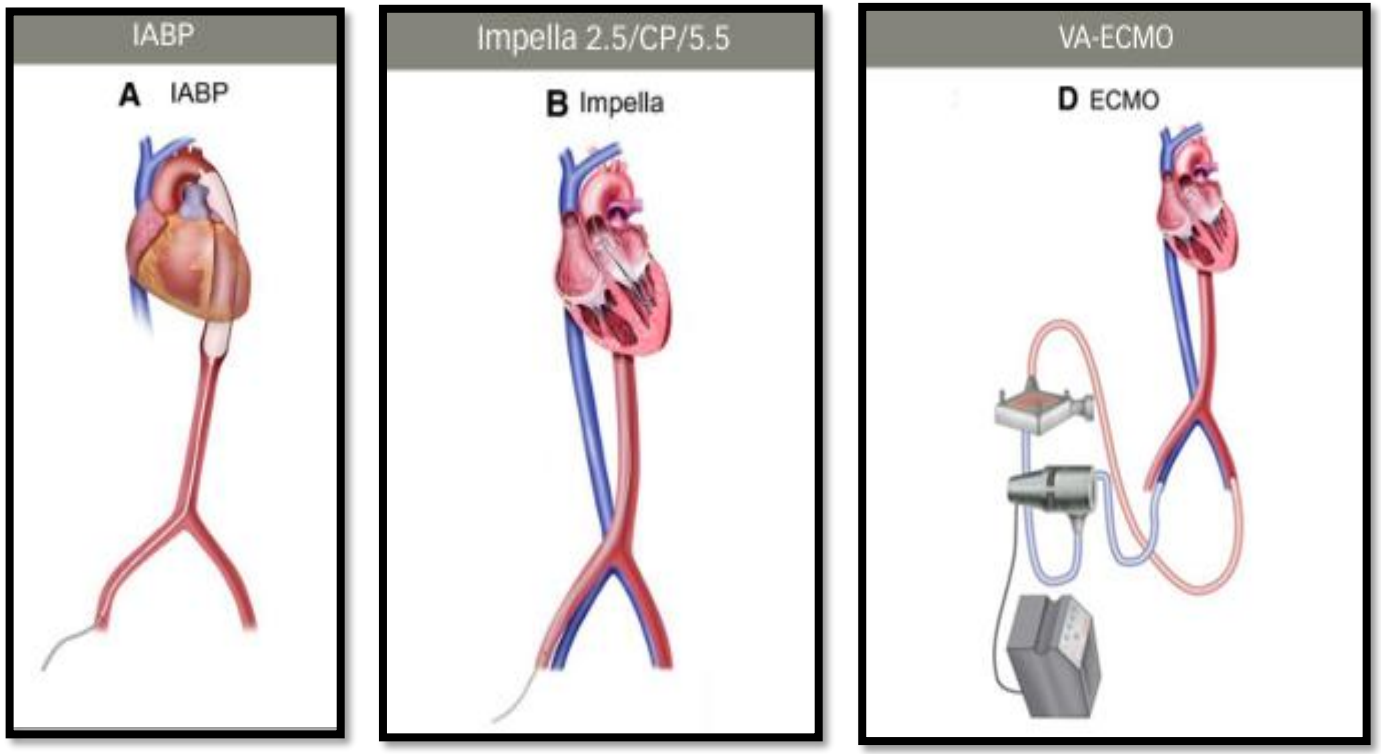
- Used as bridge to recovery, bridge to transplantation, or destination therapy
- Provide short and/or long-term support
- Both temporary and durable MCS

Primary Indications:
Cardiogenic shock
Refractory heart failure
Acute Respiratory Distress Syndrome
Emergency Cardiopulmonary Resuscitation
Pulmonary Embolism

Source: *Heart Int*. 2022;16(1):37-48

Temporary MCS

- **Classified according to the type of support provided:**
  - Ventricular support devices (IABP, Impella)
  - Respiratory support (VV-ECMO)
  - Circulatory +/- respiratory support (VA-ECMO)
  - Multiple devices may be used together in certain situations



Source: *Heart Int*. 2022;16(1):37-48

Durable MCS

- Offers long-term support from months to years for advanced heart failure
- Surgically implanted device
- Requires evaluation from multi-disciplinary team to be a candidate
- Destination therapy or bridge to transplant

	First generation	Second generation	Third generation
Pump design	Pulsatile flow	Continuous flow (axial pump)	Continuous flow (centrifugal pump)
LVAD type	Heartmate IP10000, XVE	HeartMate II	HVAD Heartmate 3

Source: *Heart Int*. 2022;16(1):37-48.

Complications in MCS

- **Bleeding –** most common complication across all devices
- **Thrombosis –** pump thrombosis, circuit clots, stroke
- **Infection**
- **Vascular complications –** limb ischemia, vascular injury (especially with femoral cannulation)
- **Hemolysis**
- **Neurologic events –** stroke, hypoxic injury

Sources:
Heart Int. 2022;16(1):37-48,
Circulation. 2012;126(22):2648-2667

Anticoagulation Strategies in MCS

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Anticoagulant Recommendations in MCS

Device	Recommendation
IABP	• Systemic anticoagulation may be considered with 1:1 balloon support • Systemic anticoagulation is recommended when balloon support is provided every other (1:2) or every third (1:3) cardiac cycle
Impella	• Heparinized purge solution is recommended • Additional systemic UFH may be needed if the purge alone does not achieve therapeutic targets
VV-ECMO	• ELSO guidelines (2021) cannot recommend the routine use of no anticoagulation
VA-ECMO	• ELSO guidelines (2021) recommended routine use of anticoagulation
LVAD	• ISHLT Clinical Expert Consensus Document (2019) states that antithrombotic therapy with warfarin and aspirin 81-325 mg daily is necessary for all patients

Sources:
ASAIO J. 2022;68(3):303-310,
J Am Coll Cardiol. 2015;65(19):e7-e26,
Heart Lung Transplant. 2019;38(7):677-698

Anticoagulation in Temporary MCS

- The use of anticoagulation is necessary to counteract activation of the coagulation system caused by shear force stress and the foreign body surfaces of the pump

Anticoagulant	Mechanism of action	Half-life	Advantages	Disadvantages
Heparin	Binds to antithrombin to inhibit thrombin and Xa	60-90 minutes	Inexpensive, has reversal agent (protamine)	Binds to other plasma proteins, HIT
Bivalirudin	Reversibly binds to thrombin	25 minutes	Does not require antithrombin	No reversal agent, caution in renal dysfunction
Argatroban	Reversibly binds to thrombin	39-51 minutes	Does not require antithrombin, not degraded by serine proteases	No reversal agent, variable dosing, caution in hepatic dysfunction

Source: *ASAIO J*. 2022;68(3):303-310

Heparin vs. Bivalirudin in ECMO

Study Outcomes	Seelhammer (2021)	Rivosecchi (2021)	Lofy (2026)
Mortality	Decreased with bivalirudin in adults	Not reported	Not reported
Major bleeding	Not significantly different	Decreased with bivalirudin	No difference
Circuit/device thrombosis	Not significantly different	Decreased with bivalirudin	Decreased with bivalirudin
Systemic thrombosis	No difference	Not reported	No difference
Transfusion requirements	Decreased in pediatric group only	Decreased with bivalirudin	Not reported
Time in therapeutic range	No difference	Not reported	Increased with bivalirudin

Sources:
Crit Care Med. 2021;49(9):1481-1492
CritCare Med. 2021;49(7):1129-1136,
Ann Pharmacother. 2026;60(5):455-465

Anticoagulation in Durable MCS

International Society for Heart and Lung Transplantation guidelines:

- Recommend anticoagulation with warfarin and aspirin for LVAD's
  - Warfarin with an INR goal of 2.0 to 3.0
  - Aspirin is 325mg for patients with an HMII or HeartWare device, 81 mg for an HM3 device
- Direct-oral anticoagulants (DOAC's) are NOT recommended
- Intravenous unfractionated heparin bridging within 48 hours after LVAD implantation

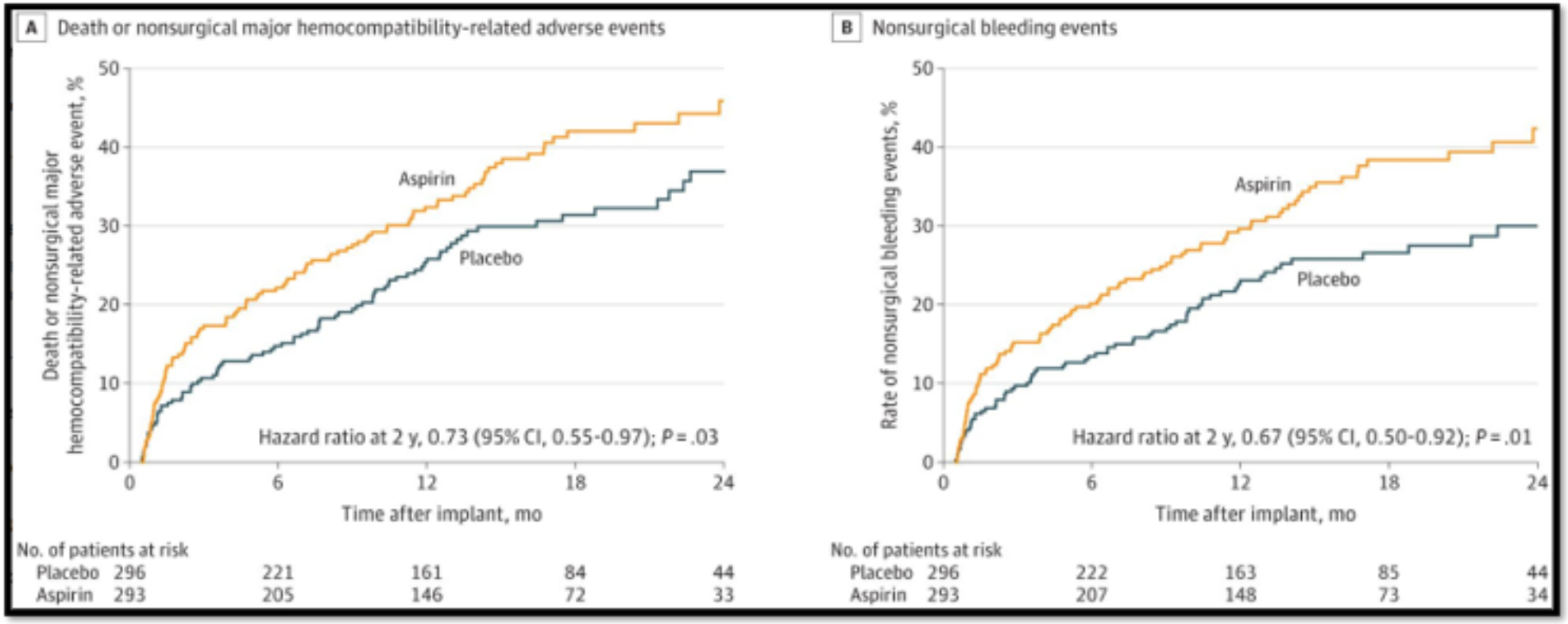
Source: *J Heart Lung Transplant*. 2019;38(7):677-698

Aspirin Discontinuation in LVAD Patients

ARIES-HM3 Trial (2023)	Aspirin and Hemocompatibility Events With a Left Ventricular Assist Device in Advanced Heart Failure
Design	Multicenter, prospective, randomized, double-blind, noninferiority trial
Intervention	Randomized 1:1 to receive aspirin 100 mg/day or placebo, both in combination with a vitamin K antagonist (VKA) to target INR of 2.0–3.0
Population	Patients with advanced heart failure implanted with HeartMate 3 LVAD, randomized
Outcomes	Composite of survival free of stroke, pump thrombosis, major nonsurgical bleeding, arterial peripheral thromboembolism at 12 months, assessed for noninferiority
Results	Aspirin avoidance met noninferiority at 12 months of survival free of stroke, pump thrombosis, major nonsurgical bleeding, arterial peripheral thromboembolism (74.2% vs. 68.1%) Demonstrated superiority at 24 months (HR 0.73, p = 0.03) 34% reduction in cumulative bleeding (RR 0.66, p = 0.002) No increase in stroke or pump thrombosis

Source: JAMA. 2023;330(22):2171-2181

Time to Event Analysis ARIES-HM3 Trial



Aspirin may be withheld in LVAD patients depending on facility protocols

Source: JAMA. 2023;330(22):2171-2181

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Summary

- **MCS types:**
  - Temporary devices (IABP, Impella, ECMO)
  - Durable devices (LVADs)

- **Temporary MCS anticoagulation:**
  - Heparin is the standard anticoagulation, protamine as reversal agent
  - Bivalirudin- more time within therapeutic range, may reduce bleeding and circuit thrombosis
  - Routine anticoagulation is required for VA-ECMO
  - May be safe to hold anticoagulation in VV-ECMO if patient is bleeding

- **Durable LVAD anticoagulation:**
  - ISHLT recommends warfarin (INR 2.0–3.0) plus aspirin with heparin bridging post-implantation
  - ARIES-HM3 trial: Aspirin discontinuation in HeartMate 3 patients reduced bleeding without increasing thrombotic events

Monitoring Strategies for Anticoagulation in MCS

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Monitoring of Parenteral Anticoagulation MCS

Activated Clotting Time (ACT)	Activated Partial Thromboplastin Time (aPTT)	Anti-Xa Level
• Should only be used for initial bolus monitoring or when other tests are unavailable • Not approved for direct thrombin inhibitors	Cheap, easily available, but frequent measurements are required	More expensive, but less frequent measurements once in range
	Various confounding factors and reagents from batches can vary; inflammatory response of patient can affect result	Measures the amount of UFH available to produce an anticoagulant effect, not affected by confounding factors
	Bivalirudin or argatroban	Can only be used for UFH, LMWH
	May be more useful in assessing the overall bleeding tendency	May be useful for predicting thrombosis

Sources:
J Am Coll Cardiol. *2022;79(19):1949-1962,*
Journal of Cardiac Failure, 2023; 29, 304-374

International Society of Heart and Lung Transplant (ISHLT) Recommendations for Anticoagulant Goals

- The ISHLT/HFSA 2023 guideline in acute MCS states ideal monitoring method is not defined, but offers these targets

Device	ACT Goal	aPTT Goal	Anti-Xa Goal
IABP	N/A	50-70 seconds	0.2-0.5 U/mL
Impella	250 seconds or longer at device insertion	55-80 seconds	0.15-0.3 U/mL
VA-ECMO	180-220 seconds at device insertion	**Heparin:** 1.5-2.5 times baseline **Argatroban:** 1.5-3 times baseline ***Bivalirudin-** not mentioned in guideline	0.3-0.7 U/mL (for UFH only)

Source: *J*ournal of Cardiac Failure, 2023; 29, 304-374

Anti-Xa vs. APTT to Monitor Heparin in MCS

Study	Objective	Population	Key Findings
Moussa et al. (2021)	To analyze paired anti-Xa and aPTT samples and assess concordance and correlation	Adult patients with refractory cardiogenic shock on VA-ECMO	• Concordance rate between aPTT and anti-Xa was only 50.7% • 39.3% of samples had subtherapeutic aPTT despite therapeutic anti-Xa
Hla et al. (2024)	To compare the accuracy and precision of anti-Xa vs aPTT for monitoring UFH	Adult patients with viral respiratory failure requiring VV-ECMO	• No significant difference in time within therapeutic range: 51% (anti-Xa) vs. 47% (aPTT), $p = 0.28$ • Anti-Xa was significantly more precise (0.21, anti-Xa) vs. (1.61, aPTT), $p < 0.05$
Van Edom et al. (2025)	To analyze paired anti-Xa and aPTT samples	Adults with cardiogenic shock on impella support	• Weak correlation ($r = 0.50$), conflicting information about anticoagulation status. • When anti-Xa was in the therapeutic range, aPTT was discordant nearly half the time

For both ECMO and Impella, anti-Xa was more precise than aPTT for UFH titration

Sources:
J Clin Med. 2021;10(10):2158,
ASAIO J. 2024;70(4):313-320,
J Thromb Haemost.2025;23(6):1810-1816

Warfarin Monitoring in LVAD's

- **INR goal 2.0–3.0** is the typical target for continuous-flow LVADs
- Lowering the INR target range is a common strategy for **secondary prevention after a bleeding event:**

Study	Device	INR target	Thromboembolic events	Bleeding
Nassif et al (2016)	HM II, HVAD	<1.5 vs. 1.5-1.99 vs. ≥2.0	Highest at INR <1.5	53 GI bleeds and 9 ICHs reported
Sowder et al. (2023)	HM3	1.8-2.2	0 to 7.1% at 12 months	28.6% at 12 months; Reported overall "bleeding events" did not provide a breakdown by bleeding location or type
Magentum 1 (2018)	HM3	1.5-2.0	0 at 6 months	1 patient with recurrent GIB

HM3 device may allow for lower targets, INR goal of **1.5–1.9** or **1.8–2.2 for patients with bleeding events**

Sources:
J Heart Lung Transplant. 2018;37(5):579-586,
Circ Heart Fail. 2016;9(5):e002680,
Artif Organs. 2023;47(10):1613-1621

Assessment Question #1: Pharmacists and Nurses

Parenteral anticoagulants used for MCS, such as heparin or bivalirudin, are administered as continuous infusions and require careful titration of the dose based on frequent laboratory values (aPTT or Anti-Xa)

True or False

Assessment Question #1: Pharmacists and Nurses

Parenteral anticoagulants used for MCS, such as heparin or bivalirudin, are administered as continuous infusions and require careful titration of the dose based on frequent laboratory values (aPTT or Anti-Xa)

TRUE

Assessment Question #2: Pharmacy Techs

Which of the following are symptoms that patients receiving warfarin might share that indicate additional education from the pharmacist is needed?

A. Minor nosebleed that stopped after five minutes of direct pressure
B. Small purple spots on arms after my blood draw, that are not painful
C. Dark and tarry bowel movements for the past 2 days
D. Slight bruising on leg after bumping into coffee table

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Assessment Question #3: Pharmacy Techs

A patient with a newly implanted LVAD is managing warfarin therapy at home. **Which of the following best demonstrates a pattern of nonadherence to anticoagulant medication schedules?**

A. Consistent daily administration with a variation of less than one hour between doses
B. Frequent "drug holidays" or omitting doses during weekends and social events
C. Filling prescriptions at the same pharmacy every 30 days without interruption
D. Maintaining a stable INR within the therapeutic target range

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Pathophysiology of Bleeding in Mechanical Circulatory Support (MCS)

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Pathophysiology of Bleeding in MCS

- **High shear stress:** hemolysis of RBCs, platelet damage
- **Acquired von Willebrand Syndrome (AVWS):** High shear flow → ADAMTS-13 proteolysis of vWF multimers → reduced platelet-binding
- **Consumptive coagulopathy:** Extracorporeal circuit activates and consumes platelets/clotting factors → thrombocytopenia and fibrinolysis
- **Loss of pulsalility**
- **Anticoagulation**
- **Antithrombic Therapy**
- **Shock Physiology and Critical Illness**
- **Vascular Access Complications**

Sources:
J Am Heart Assoc. 2022;11(24):e027251,
J Am Coll Cardiol. 2022;79(19):1949-1962

Device Specific Bleeding Risk Factors

Device	Risk factors
IABP	Vascular-access related
Impella	Hemolysis, Device malrotation in the LV
ECMO	Hemodilution, Consumptive coagulopathy
LVAD	Loss of pulsatility

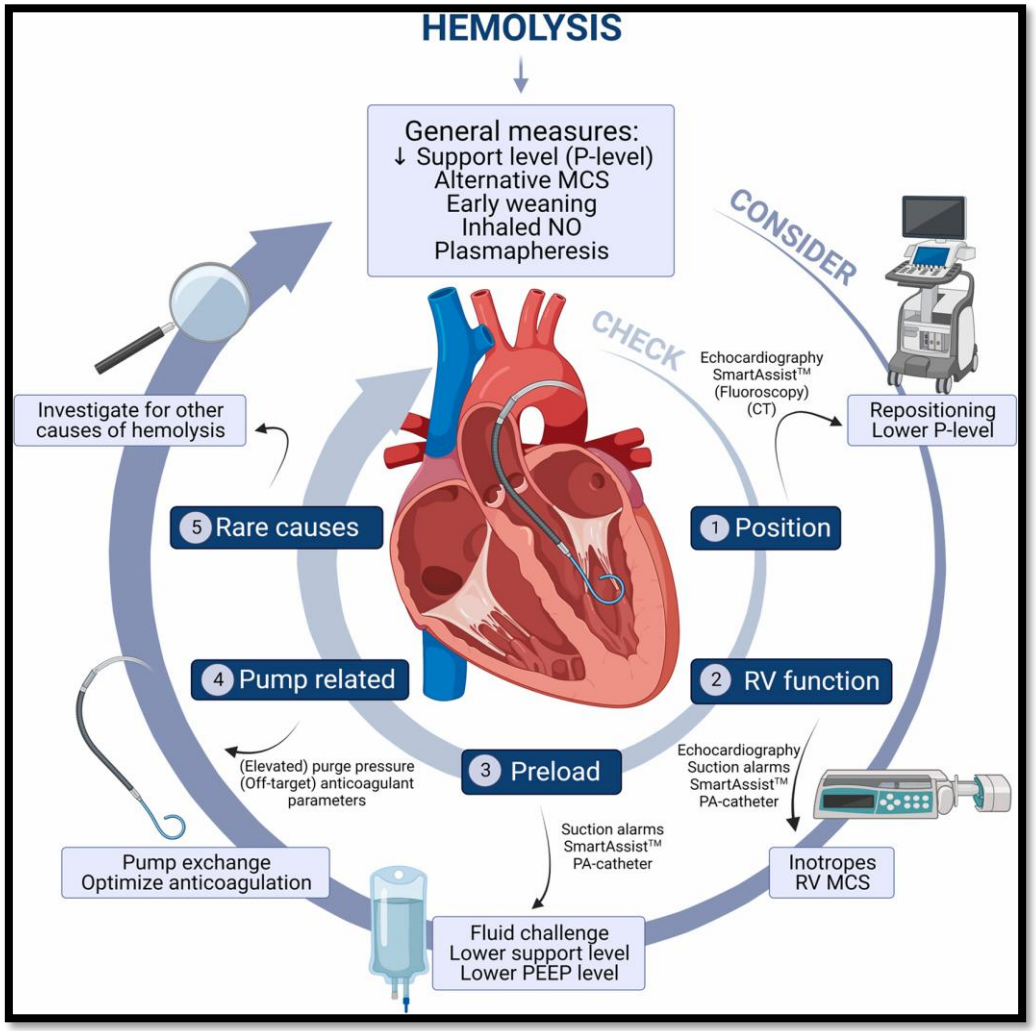

Image adapted from *JACC Cardiovasc Interv*. 2023;16(14):1707-1720

Sources:
JACC Cardiovasc Interv. 2023;16(14):1707-1720
CritCare Med. 2020;48(5):e400-e408
J Am Heart Assoc. 2022;11(24)

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Pathophysiology of GIB in LVADs

Devices with continuous flow have lower peak shear stress than pulsatile devices, however, they have increased exposure time to moderate shear stress

- Shear stress on platelets = platelet dysfunction, inappropriate platelet activation
- vWF degradation from shear stress/degradation by ADAMTS13→ AVWS = reduced platelet binding
- Angiodysplasia from loss of pulsatility → arteriovenous malformation creation in GI tract = weak blood vessels

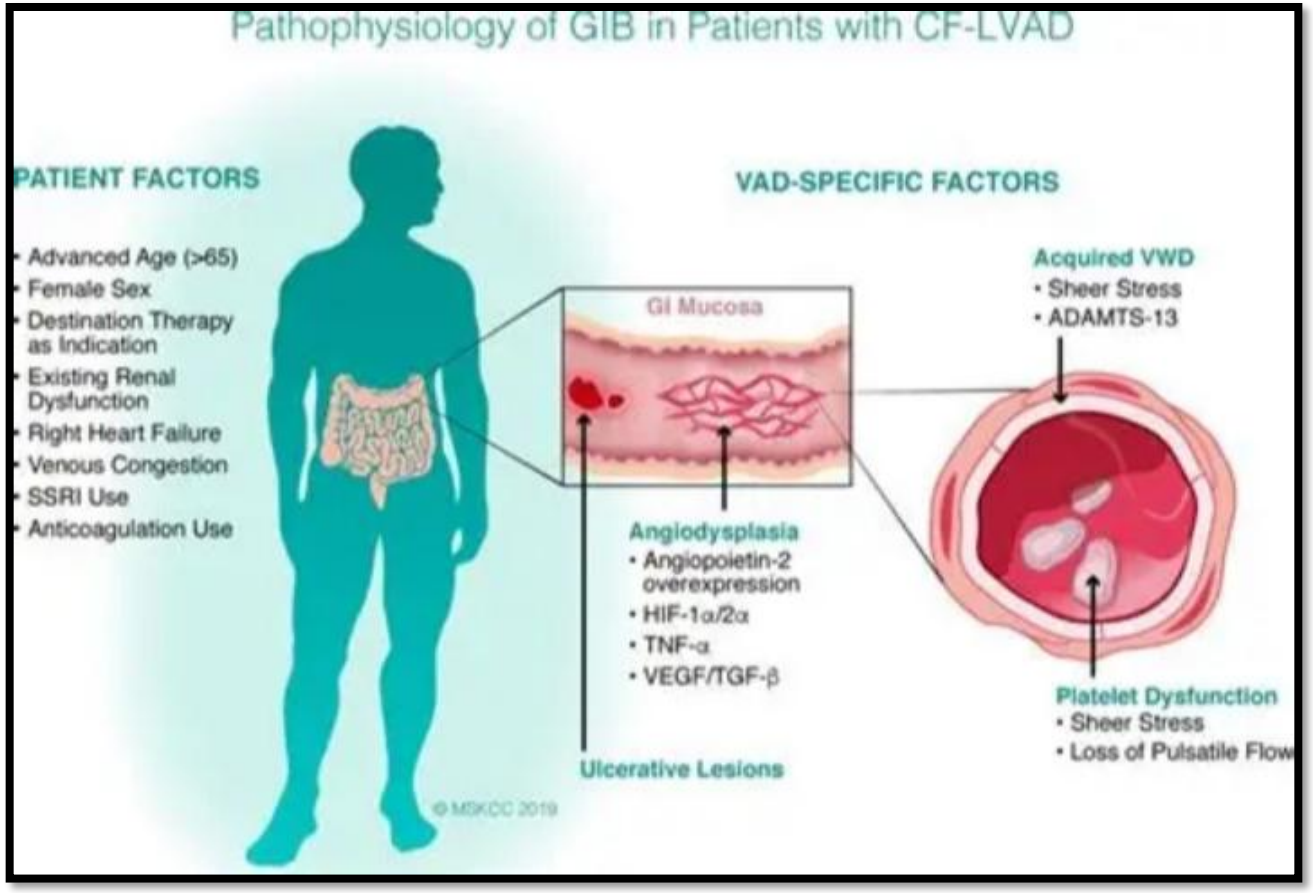

Image was adapted from researchgate.net

Source: J Am Heart Assoc. 2022;11(24):e027251

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Incidence of Bleeding in Mechanical Circulatory Support

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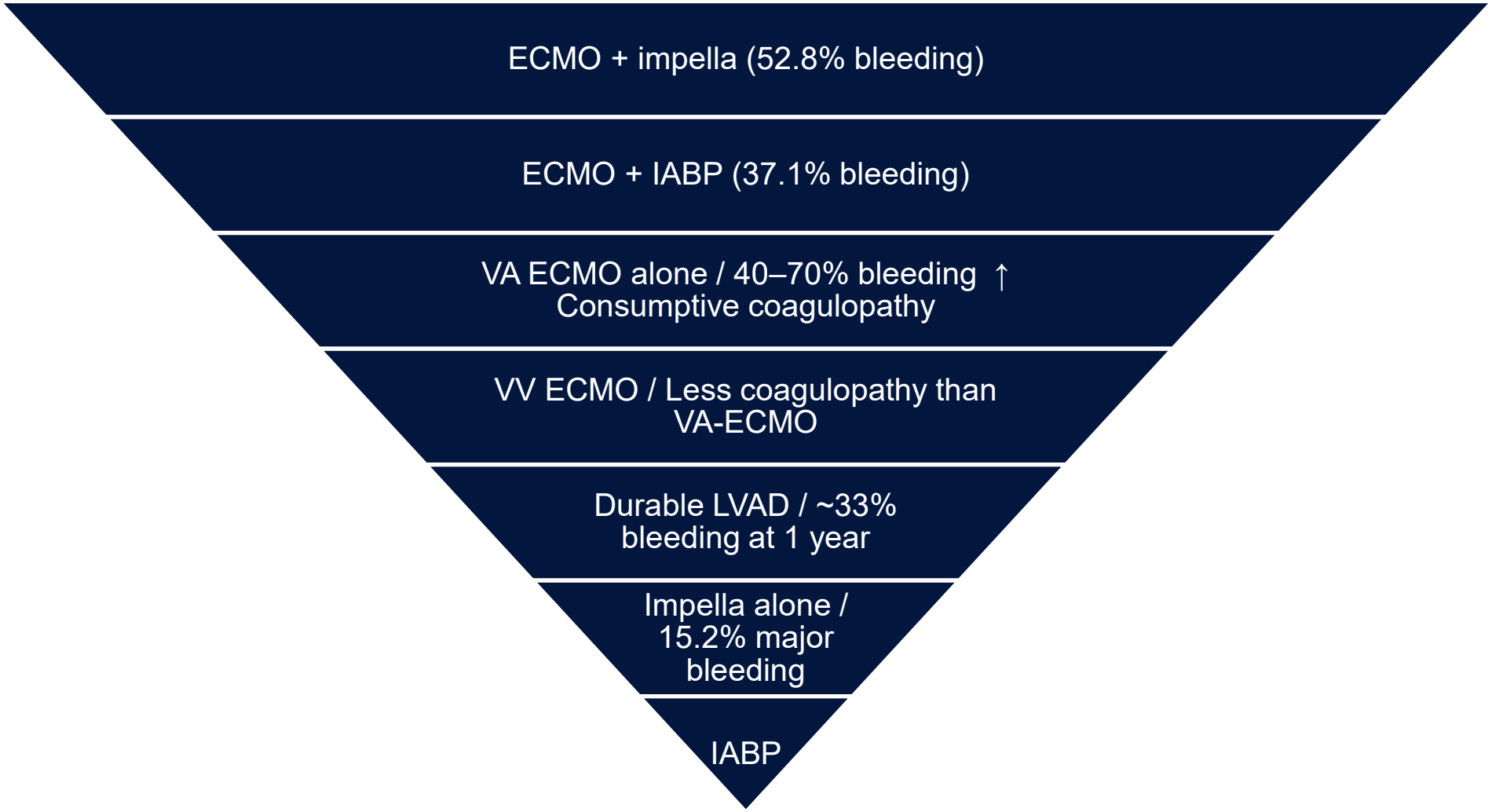
Incidence of Bleeding in Temporary MCS

- Meta-analysis by Stub et al. (2025): Highest level of evidence currently available **comparing impella to VA-ECMO**
  - Impella was associated with significantly fewer bleeding events requiring transfusion (39% relative reduction)
- **Retrospective review of ECMO alone vs ECMO + LV unloading (IABP or Impella)**
  - ECMO alone (17.7% bleeding)
  - ECMO + Impella group: 52.8% bleeding vs 37.1% with ECMO + IABP (p= 0.0001)
- **More devices = more bleeding**

Sources:
Shock. 2025;63(4):512-519,
J Thorac Cardiovasc Surg. 2023;165(2):699-707.e5

Incidence of Bleeding in MCS



Sources:
J Am Coll Cardiol. 2022;79(19):1949-1962
J Thorac Cardiovasc Surg. 2023;165(2):699-707
J Am Coll Cardiol. 2023;82(14):1464-1481

Incidence of Bleeding in Durable MCS

- Nearly 1/3 of LVAD patients experience a bleeding event at 1 year
- GIB accounts for ~60% of all LVAD-associated bleeding

	Early Bleeding <90 days	Late Bleeding ≥90 days
Common cause	Surgical complications/surgical site	GIB, ICH (8-11%)
Risk factors	• Pre-implant VA ECMO • Post-operative thrombocytopenia • Re-sternotomy • Cardiopulmonary bypass time	• Post LVAD implant infection • Elevated INR, lower platelet count • Elevated right atrial pressure • Low body mass index, female sex • Destination therapy indication for implantation

Sources:
J Am Heart Assoc. 2022;11(24):e026227,
Eur J Cardiothorac Surg. 2018;54(1):176-182.

Assessment Question #4: Pharmacy Techs

Which of the following are potential side effects of anticoagulation medications for patients with MCS might indicate that a patient needs additional education from the pharmacist?

A. Ischemic stroke and pump thrombosis
B. Nose bleeding, gastrointestinal bleeding and intracranial hemorrhage
C. Vascular complications
D. Drive-line site infection

Assessment Question #4: Pharmacy Techs

Which of the following are potential side effects of anticoagulation medications for patients with MCS might indicate that a patient needs additional education from the pharmacist?

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C. Vascular complications
D. Drive-line site infection

Assessment Question #5: Pharmacists & Nurses

The incidence of gastrointestinal bleeding is significantly higher in patients with continuous-flow LVADs compared to pulsatile-flow models

True or False

Assessment Question #5: Pharmacists & Nurses

The incidence of gastrointestinal bleeding is significantly higher in patients with continuous-flow LVADs compared to pulsatile-flow models

TRUE

Classification, Prevention and Management of Bleeding in MCS

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Bleeding Definitions

Bleeding Definitions	Bleeding Academic Research Consortium (BARC)	ESLO Bleeding Definitions	ISTH Bleeding Definitions	INTERMACS Bleeding Definition
Minor Bleeding	Type 1: Bleeding not actionable Type 2: Overt bleeding requiring nonsurgical intervention	Not defined	Overt bleeding not meeting major	Any other bleeding requiring medical attention or transfusion 4 units
Major Bleeding	Type 3a: Hgb drop 3–5 g/dL Type 3b: ≥5 g/dL drop, tamponade, or surgery Type 3c: ICH/intraocular Type 4: CABG-related Type 5: Fatal	Clinically overt bleeding requiring >3 units PRBCs/24 hours	• Fatal • Critical organ (7 sites); Hb drop ≥2 g/dL; or ≥2 units PRBCs	Death, reoperation, hospitalization, or ≥4 units PRBCs

****No universal bleeding definition exists across MCS devices**

Sources:
J Card Fail. 2023;29(3):304-374,
J Heart Lung Transplant. 2019;38(7):677-698,
Circulation. 2011;123(23):2736-2747
Cochrane Database Syst Rev. 2024;6:CD015685

Prevention Strategies for Bleeding

- Ultrasound-guided cannulation techniques
- Proper positioning and stitching of the sheath to skin
- Change device specific factors (maximize pump speed, change purge solution, decrease cannula size)

For Ear, Nose, and Throat Bleeding:

- De-escalate nasogastric tubes when possible
- Consider orogastric tube before nasogastric tube

Source: JACC Cardiovasc Interv. 2023;16(14):1707-1720

Steps for Management of Bleeding

Step 1: Source Control (First-Line)

- **Cannula/Access Site Oozing:**
  - Manual pressure ± compression device
  - Optimize device-skin angle and sheath stitching
  - Topical agents
- **ENT Bleeding**
  - Intranasal balloon compression
  - Local cauterization
  - Invasive intervention including em bolization may be required to stop bleeding

Type of Agent	Topical Hemostatic Agent	Mechanism of Action	When to Use/Special Considerations
Physical	Gauze	Direct pressure compresses blood vessels to reduce blood flow	Effective in stopping as well as preventing bleeding from the access site
	Gelatin sponge (GelFoam)	Absorbs blood and fluid; matrix for clot formation, mechanical barrier	May be useful for mechanical hemostasis
	Oxidized cellulose (Surgicel)	Activates extrinsic clotting cascade and provides scaffold for platelet aggregation and clot formation	Do not use with topical thrombin
Combination agent	Thrombin combined with gelatin matrix (Floeseal)	Converts fibrinogen to fibrin and absorbs blood and fluid	Higher cost compared to others
	Thrombin and fibrinogen sealant (Tisseel)	Combines thrombin and fibrinogen; allowing for fibrin clot formation	Takes time to thaw, contraindicated if anaphylaxis to plasma products or IgA deficiency
Biologic	Tranexamic acid (Gause soaked in TKA solution)	Antifibrinolytic	When there is oozing at the access site
Other	Epinephrine (1:1,000 (1 mg/mL or 1:100)	Causes vasoconstriction to area	Avoid on end-artery sites, due to concerns about ischemic necrosis

Sources:
J Am Coll Cardiol. 2022;79(19):1949-1962,
ASAIO J. 2022;68(3):303-310
Obstet Gynecol. 2020;136(4):e81-e89

Steps for Management of Bleeding

- **Step 2: Reduce Antithrombotic Therapy**
  - Stop antiplatelets
  - Switch to bicarbonate-based purge solution (BBPS) for Impella if indicated
  - Reduce or hold anticoagulant (lower target)

Sources:
J Am Coll Cardiol. 2022;79(19):1949-1962,
ASAIO J. 2022;68(3):303-310

SAVE-ECMO Pilot Trial

Low-Intensity vs Moderate-Intensity Anticoagulation for VV ECMO	
Intervention	Low-intensity group: UFH titrated to lower targets (aPTT <50 seconds or anti-Xa <0.3 IU/mL) Moderate-intensity group: UFH titrated to standard therapeutic targets (aPTT 50–70 seconds or anti-Xa 0.3–0.7 IU/mL)
Population	26 critically ill adults on VV ECMO for respiratory failure
Outcomes	**Primary efficacy outcome:** Major bleeding (enrollment through 24 hours after decannulation) • Major bleeding defined as: Clinically overt bleeding requiring transfusion of >3 units of packed red blood cells (PRBCs) per 24 hours in adults **Primary safety outcome:** Thromboembolic events (from enrollment through 24 hours after decannulation
Results	**Major bleeding:** Occurred in 1 of 12 patients (8.3%) in the low-intensity group versus 4 of 14 patients (28.6%) in the moderate-intensity group **Thromboembolic events:** One patient (8.3%) in the low-intensity group experienced a thromboembolic event compared with none in the moderate-intensity group

Source: Chest. 2025;168(3):639-649.

Critique of the SAVE-ECMO Pilot Trial

- Small sample size (n=26)
- Open-label design
- Short follow-up
- Limited generalizability
  - Excluded patients with pre-existing indications for therapeutic anticoagulation
  - VV-ECMO only—findings may not apply to VA-ECMO
- Heterogeneous monitoring
- Bleeding definition- aligns with ELSO definition

****This study is hypothesis-generating only, but demonstrated larger study is feasible**

Source: Chest. 2025;168(3):639-649

Steps for Management of Bleeding

- **Step 3: Systemic Hemostatic Support**
  - Blood product support as needed
  - Reversal agents

Sources:
J Am Coll Cardiol. 2022;79(19):1949-1962,
ASAIO J. 2022;68(3):303-310

Blood Product Goal and Replacement

- Lack of studies to guide blood product transfusion practices in ECMO patients
- Below is an approach from the 2021 ELSO Guidelines blood product replacement

Product type	Product	Goal	Dose
Blood products	PRBC	Hgb ≥7-9 g/dL	10 mL/kg (max of 2 units)
	Platelets	≥50,000 (non-bleeding)-100,000 (bleeding)	2 units(max of 2 units)
	FFP	INR <3 (non-bleeding); <1.5 (bleeding)	10 mL/kg (max of 2 units)
	Cryoprecipitate	Fibrinogen >100 (non-bleeding); >150 (bleeding)	1 unit/5 kg (max 6 units
	Antithrombin	>0.5-0.8 U/mL	Thombate III dose (IU)= Desired AT- current AT x weight in kg

Source: *J Card Fail*. 2023;29(3):304-374

Reversal Agents

- 4-Factor Prothrombin Complex Concentrate (4F-PCC)
- Phytonadione (vitamin K1)
- Protamine
- Antifibrinolytic agents – Tranexamic acid (TXA), aminocaproic acid
- Recombinant factor VIIa

4-Factor Prothrombin Complex Concentrate (4F-PCC)

- Contains factors II, VII, IX, X and proteins C and S
- Contains heparin and is contraindicated in patients with heparin induced thrombocytopenia within 12 months

Dosing	Onset	Duration of Action	Monitoring
• Variable • Weight-based • Fixed dosing • 50 units/kg (5000 units=max dose)	Immediate	• Lasts approximately 12–24 hours when used for warfarin reversal • Duration varies by individual clotting factor • Half-lives may be significantly reduced in severe hepatocellular damage or disseminated intrvascular coagulopathy	• INR (baseline and post-dose) • Modern viscoelastic point-of-care tests • Chest tube output • Thromboembolic complications

Sources:
Anaesthesia. 2021;76(3):381-392
Prothrombin Complex Concentrate: Drug information. UpToDate

4F-PCC in ECMO

- Evidence for use specifically in ECMO patients in limited
- Most data extrapolated from cardiac surgery and general critical bleeding literature
- **European Association of Cardiothoracic Anesthesiology recommends:**
  - Initial bolus of 25 IU/kg for massively bleeding patients with coagulopathy
  - Consider initial half-dose of 12.5 IU/kg for cardiac surgery patients at high risk for thromboembolic complications (recent valve replaced or cardiopulmonary bypass surgery)

Source: *Anaesthesia*. 2021;76(3):381-392

4-PCC for Warfarin Reversal in LVAD Patients

Stevenson et al. (2025)	Temporarily Reversing Warfarin With Low-Dose 4F-PCC in Left Ventricular Assist Device Patients Undergoing an Invasive Procedure
Design	Retrospective, single-center cohort review of patients with LVAD undergoing elective or emergent procedure
Intervention	Administration of 4-factor prothrombin complex concentrate (4F-PCC)
Population	14 patients with continuous-flow LVADs who received 4F-PCC 82% (14/17) of administrations were for low bleed-risk procedures 76% (13/17) were for elective procedures
Outcomes	Composite incidence of pump thrombosis, venous thromboembolism, and ischemic stroke within 30 days of 4F-PCC administration
Results	• Low-dose 4F-PCC (median dose of 500 units) • Pump thrombosis at 30 days: 0/17 (0%) • Venous thromboembolism at 30 days: 0/17 (0%) • Ischemic stroke at 30 days: 0/17 (0%) • Composite thrombotic endpoint: 0/17 (0%)

Source: *Ann Pharmacother*. 2025;59(1):5-12

Critique of Study by Stevenson et al.

- **82% low bleed-risk procedures:** The study predominantly included low-risk procedures, limiting applicability to high bleed-risk or emergent surgeries where more aggressive reversal may be needed
- **76% elective procedures:** Emergent cases (where rapid reversal is most critical) were underrepresented
- **30-day follow-up only:** May miss delayed thrombotic events; pump thrombosis can occur weeks to months after
- **No bleeding outcomes reported:** The study focused on thrombotic safety but did not systematically report whether the low-dose PCC achieved adequate hemostasis or procedural bleeding rates

4F-PCC for Intracranial Hemorrhage in LVAD Patients

Lai et al. (2021)	Prothrombin Complex Concentrate for Emergent Reversal of Intracranial Hemorrhage in Patients with Ventricular Assist Devices
Design	Single-center, retrospective cohort study
Intervention	Four-factor PCC administered for rapid anticoagulation reversal Mean time from imaging diagnosis to PCC administration: 3.3 ± 0.3 hours
Population	16 ICH events in 14 patients with VADs ICH types: 11 intraparenchymal (69%), 4 subdural (25%), 1 subarachnoid (6%)
Outcomes	**Primary:** Survival, occurrence of thromboembolic events
Results	• Overall mortality was 63% (10 of 16 ICH events) **Thromboembolic events:** • 0 events occurred between PCC administration and anticoagulation resumption • 3 events occurred after anticoagulation was resumed (within 3 months)

Source: *Neurocrit Care*. 2021;35(2):506-517

Critique of Study by Lai et al.

- The study does not clearly define which patients were excluded and why, making it difficult to assess generalizability
- **Heterogeneous population:**
  - Mixed ICB types (ICH, SDH, SAH, EDH) with median GCS 15 suggesting mild presentations
- The study reported hemostatic efficacy and survival but did not assess modified Rankin Scale (mRS) or other meaningful functional outcome
- Mean dose 46.6 units/kg: Higher than some protocols (fixed 2000 units or 25 units/kg)

Phytonadione (Vitamin K1)

- Specific reversal agent for VKAs — restores hepatic carboxylation of vitamin K-dependent clotting factors
- Used in combination with 4F-PCC to reverse warfarin
- IV route preferred due to quick onset of action and more predictable absorption
- Vitamin K 10 mg IV for major/life-threatening bleeding, like intracranial hemorrhage
- Oral vitamin K may be appropriate non-urgent minor/ non-life threatening bleeding

Dosing	Onset	Duration of Action	Monitoring
2.5-10 mg IV	12-14 hours	24-72 hours	• INR at baseline and 6–8 hours post-dose • Repeat INR at 24 hours • Monitor for anaphylactoid reaction during infusion

Source: Phytonadione (vitamin K1): Drug information. UpToDate

Protamine

- Reversal agent for heparin

Mechanism of action

- Protamine is strong base, heparin is strong acid-->Forms stable salt and inactivates heparin

Dosing:

- 1 mg of protamine neutralizes ~100 units of heparin, maximum single dose of 50 mg
- Administer by slow IV injection due to risk of hypotension

Place in therapy:

- Life-threatening bleeding, like intracranial hemorrhage or massive GI bleed

****The Protamine Paradox:** While it is an antidote for anticoagulation, protamine itself has weak anticoagulant properties when administered in the absence of heparin or in significant excess it can inhibit platelets and interact with coagulation factors, which may paradoxically worsen bleeding

Source: Protamine: Drug information. UpToDate

Antifibrinolytic Agent – Tranexamic Acid (TXA)

- **Mechanism of action:** Inhibition of plasminogen conversion and thus prevent fibrinolysis
- **Place in therapy:**
  - Nebulized TXA- Used for pulmonary hemorrhage
  - Systemic TXA- Viscoelastic testing (TEG/ROTEM) showing hyperfibrinolysis

Formulation of TXA	Dosing
Nebulized	500 mg via endotracheal tube every 6-8 hours
Systemic	Low-dose regimens (10 mg/kg loading + 2 mg/kg/hr infusion, total ~20 mg/kg)

- **Duration-** No standardized duration of TXA therapy exists for MCS patients
  - For nebulized TXA, reassess in 24-48 hours- up to 5 days maximum has been seen in trials
  - For systemic TXA, repeat viscoelastic testing in 4-6 hours and discontinue when LY30 is normalized-ideally limit infusion to <24 hours)

Sources:
Clin Pharm Ther. 2022;47(1):125-128,
JAMA. 2022;328(4):336–347

Antifibrinolytic Agent- Aminocaproic Acid

ELSO Adult and Pediatric Anticoagulation Guidelines:

- Aminocaproic acid may reduce incidence of surgical bleeding when used prophylactically or after surgical operation
  - ECMO patients who received aminocaproic acid prophylactically for anticipated surgical procedures had surgical site bleeding in only 10% compared to 30% reported in ELSO registry
- **Dosing:**
  - Extrapolated from landmark study in 2003 examining the impact of aminocaproic acid on hemorrhagic complications in pediatric ECMO patients
  - **Loading dose:** 100 mg/kg, **Continuous infusion:** 30 mg/kg/hour for 72 hours
- **Place in therapy:**
  - ECMO patients with preexisting or anticipated surgical procedures — this is the strongest indication
  - Cardiac surgical patients on ECMO showed the most dramatic reduction in surgical site bleeding

Sources:
Journal of Pediatric Surgery. 2003;38(8):1212-1216,
ASAIO Journal. 2022;68(3):303-310.

Aminocaproic Acid

Buckley et al. (2016)	Aminocaproic acid for the management of bleeding in patients on extracorporeal membrane oxygenation: Four adult case reports and a review of the literature
Design	Single-center case series with literature review
Intervention	Aminocaproic acid administration (dosing not standardized in the report)
Population	4 adult patients with bleeding on ECMO who had evidence of fibrinolysis (high D-dimer, low fibrinogen)
Results	Bleeding was controlled in all 4 patients, shown by clinical and laboratory parameters One patient suffered a cardiac arrest and care was withdrawn No thrombotic complications attributed were reported
Limitations	Only 4 patients — cannot draw definitive conclusions Dosing was not standardized in the report No control group for comparison Single-center experience

Source: Heart Lung. 2016;45(3):232-236

Recombinant Factor VIIa (rFVIIa)

- Promotes hemostasis by activating extrinsic pathway of clotting cascade and replaces deficient activated factor VII
- **Place in therapy:**
  - Reserved as a last resort therapy for life-threatening, refractory bleeding after all other hemostatic measures have failed
    - Surgical/interventional source control attempted
    - Anticoagulation reduced or held
    - Coagulopathy corrected (FFP, cryoprecipitate, platelets)
    - 4F-PCC
    - Antifibrinolytics tried (TXA or aminocaproic acid)
- **Significant thrombotic risks** associated with its use
- Lack of studies on rFVIIa efficacy in ECMO; dosing extrapolated from cardiac surgery

Sources:
Eur J Cardiothorac Surg. 2016;49(1):78-84
Interdiscip Cardiovasc Thorac Surg. 2025;40(8)
Recombinant Factor VII: Drug Informaton. UptoDate

Dosing of Recombinant Factor VIIa

- The current **European Guidelines (2024) for blood management in cardiac surgery** recommendation reserving use as a last resource only in patients with uncontrollable bleeding refractory to conventional interventions
- Recent studies suggest that administration of rFVIIa at a **low (20-40 µg/kg)** or at a **very-low dose (10-20 µg/kg)** are effective controlling the bleeding without increasing mortality or morbidity
- 2021 clinical practice guidelines on patient blood management in cardiac surgery states a level IIB recommendation for low dose (20-40 µg/kg) rFVIIa
- Start low dose, can always re-dose

Dosing	Onset	Duration of Action	Monitoring
Variable	10-20 minutes	2-4 hours	PT/INR Viscoelastic testing

Source: Interdiscip Cardiovasc Thorac Surg. 2025;40(8)

Recombinant Factor VIIa in ECMO

Anselmi et al. (2016)	Safety of recombinant factor VIIa in patients under extracorporeal membrane oxygenation
Design	Retrospective analysis of prospectively collected data from a tertiary referral cardiothoracic surgery center
Intervention	Group A: ECMO patients who received rFVIIa treatment, dose of 60 mcg/kg Group B: 43 ECMO patients who did not receive rFVIIa (case-matched controls)
Population	Patients on VA or VV ECMO support
Outcomes	Primary Efficacy Outcome- bleeding control rate Safety Outcomes- thromboembolic events Survival Outcomes- Survival at ECMO explantation, 30-day survival
Results	Bleeding control rate: 93.3% (28 of 30 patients achieved hemostasis) No significant difference in thromboembolic events (p = 0.99) Comparable survival at ECMO explantation and 30 days

Source: Eur J Cardiothorac Surg. 2016;49(1):78-84

Critique of Study by Anselmi et al.

- Refractory to all conventional therapies not clearly defined
- Survivor bias: Only patients who survived long enough to receive rFVIIa were included
- No standardized bleeding definition (INTERMACS, BARC, ISTH) was used
- Confounding interventions: Patients received multiple concurrent interventions (blood products, surgical re-exploration, anticoagulation adjustments) — difficult to isolate rFVIIa effect

Prevention of GIB in LVAD Patients

TriStar Centennial MEDICAL CENTER

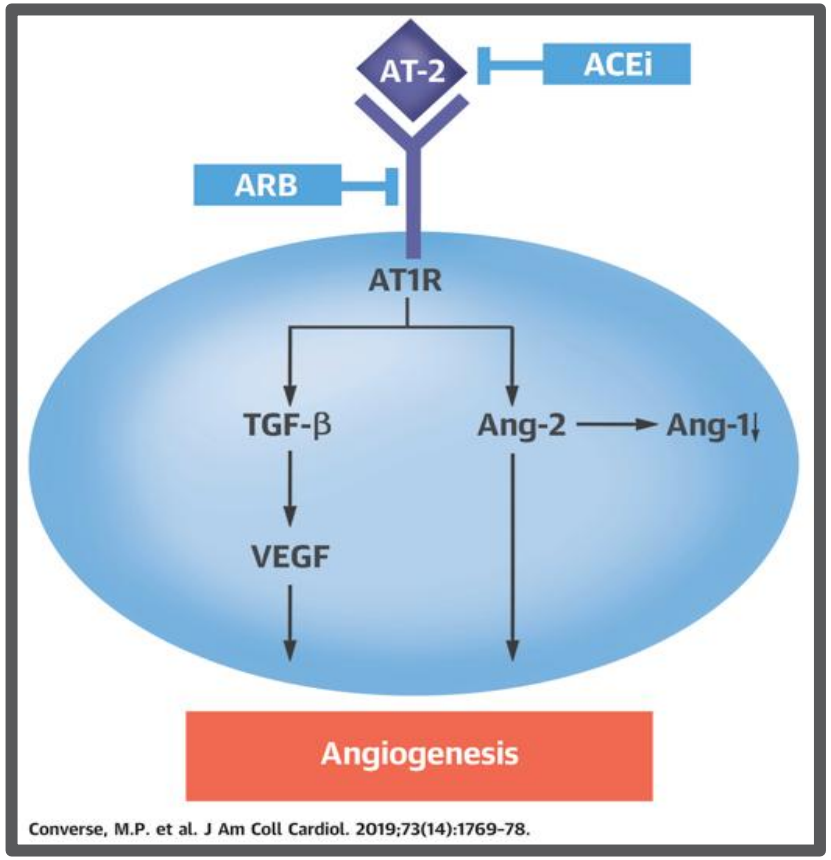
Pharmacological Therapy for Prevention of GIB in LVAD Patients

- **ACEi/ARBs**
- **Octreotide**
- Omega-3 agents
- Digoxin
- Desmopressin
- Thalidamide

Source: Pharmacotherapy. 2017;37(11):1432-1448

Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

- ACE inhibitors block angiotensin II formation, reducing downstream TGF-β and VEGF signaling
- ARBs directly antagonize the AT1 receptor, blocking the proangiogenic signal at the receptor level
- Both approaches reduce Ang-2 expression and VEGF-driven angiogenesis
- Provides hypothesis for the observed reduction in AVM-related GIB with ACEI/ARB use



Source: Pharmacotherapy. 2017;37(11):1432-1448

Angiotensin II Inhibitors in Left Ventricular Assist Devices

Effect of Angiotensin II Inhibitors on Gastrointestinal Bleeding in Patients With Left Ventricular Assist Devices	
Design	Retrospective cohort study
Intervention	ACE inhibitor or ARB therapy initiated within 30 days post-operatively
Population	53 adult patients who received continuous-flow LVADs (HeartMate II or HeartWare HVAD) between 2008 and 2016
Outcomes	Primary outcomes- major gastrointestinal bleeding (GIB) and arteriovenous malformation (AVM)-related GIB
Results	**ACE inhibitor/ARB use within 30 days post-operatively:** • 57% reduction in major GIB (adjusted HR 0.43, 95% CI 0.24-0.77, p=0.004) • 63% reduction in AVM-related GIB (adjusted HR 0.37, 95% CI 0.17-0.81, p=0.013)

Initiate ACE inhibitor or ARB at a dose-threshold effect >5 mg lisinopril-equivalent daily within 30 days post-op LVAD to reduce GIB

Source: *J Am Coll Cardiol*. 2019;73(14):1769-1778

Octreotide

Mechanism of action:

- Somatostatin analog, produces vasoconstriction of the splanchnic artery, causing a decrease in duodenal and splanchnic blood flow
- Inhibits cell proliferation and angiogenesis through mediation of the high-affinity somatostatin subtype 2 receptor

- **Most evidence comes from case reports and case series**

Source: Pharmacotherapy. 2017;37(11):1432-1448

Summary of Studies for Octreotide

Study Year	Study Design	Dosing Strategies	Outcomes
2012	Single-center retrospective	Not provided	No significant difference
2013	Case report (n=1)	100 mcg SQ twice daily, then long-acting (20 mg) at discharge	Patient was readmitted with bleeding 1 month after depot injection
2015	Case series (n=7)	50 mcg SQ twice daily or monthly injections	No subsequent episodes of bleeding, nonsignificant finding
2016	Multicenter interim analysis (n=34)	Daily SQ injection of LAR depot	Depot injection 29% bleeding rate, daily SQ injection 42 % bleeding rate
2017	Case series (n=51)	SQ injection or LAR depot	No rebleeding at 6 months

- **Many different formulations for Octreotide to prevent GIB in LVAD patients**
- **Low quality of evidence, but supports the use**

Source: Pharmacotherapy. 2017;37(11):1432-1448

Assessment Question #6: Pharmacists & Nurses

Which of the following agents could be used to prevent gastrointestinal bleeding in LVAD patients?

A. Spironolactone
B. Metoprolol
C. Amlodipine
D. Lisinopril

Assessment Question #6: Pharmacists & Nurses

Which of the following agents could be used to prevent gastrointestinal bleeding in LVAD patients?

A. Spironolactone
B. Metoprolol
C. Amlodipine
D. Lisinopril

Conclusions

MCS- Temporary (IABP, Impella, ECMO) and durable (LVAD) devices each carry unique anticoagulation and bleeding considerations

Anticoagulation Strategies: Heparin (UFH), bivalirudin, argatroban, warfarin — agent selection is device- and patient-specific

Monitoring: ACT, anti-Xa, aPTT, and INR — modality depends on anticoagulant used and institutional protocol

Bleeding Pathophysiology- Multifactorial: acquired von-Willebrand, platelet dysfunction, shear stress, coagulopathy, and device-specific factors

Incidence varies by device; more devices = more bleeding risk

- **Bleeding Management:**
- First-line: Preventitive measures, topical and hemostatic agents (local source control)
- Blood product replacement (FFP, platelets, cryoprecipitate)
- Antifibrinolytics: Nebulized TXA → pulmonary hemorrhage, IV TXA → hyperfibrinolysis
- Aminocaproic acid (Amicar) → strongest evidence for prophylaxis in cardiac MCS patients
- Last-resort agents: 4-factor PCC (4F-PCC) → reserved for life-threatening bleeding, Recombinant factor VIIa → last resort only; significant risk of thromboembolic events

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Thank you!!

Courtney Cianci, PharmD

PGY2 Critical Care Pharmacy Resident

Courtney.Cianci@hcahealthcare.com

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