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# Anticoagulation in Critically Ill Adults during Extracorporeal Circulation

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## Abstract

Extracorporeal circuits including renal replacement therapy, extracorporeal membrane oxygenation, and ventricular assist devices are increasingly used in critically ill patients. The need for anticoagulation to provide circuit patency and avoid thrombosis remains a challenging task for treating physicians. In the presence of overall low scientific evidence concerning the optimal anticoagulants, monitoring tests, and therapeutic target ranges, recommendations are largely expert opinions and most centers use individual “in-house” anticoagulation protocols. This review gives a practical view on current concepts of anticoagulation strategies in patients with extracorporeal assist devices.

### Keywords

- anticoagulants
- blood coagulation tests
- continuous renal replacement therapy
- extracorporeal membrane oxygenation
- heart-assist devices

## Zusammenfassung

Extrakorporale Organersatzverfahren (Nierenersatzverfahren, extrakorporale Membranoxygenierung und ventrikuläre Unterstützungssysteme) finden zunehmend Verwendung in der modernen Notfall- und Intensivmedizin. Die Notwendigkeit einer Antikoagulation, um eine Thrombosierung extrakorporaler Kreisläufe zu verhindern, bleibt jedoch eine Herausforderung für die/den behandelnde/n Ärztin/Arzt. Angesichts der insgesamt schwachen wissenschaftlichen Evidenz bezüglich des optimalen Antikoagulans, optimaler Tests zur Steuerung und anzustrebender therapeutischer Zielbereiche basieren aktuelle Empfehlungen weitgehend auf Expertenmeinungen. Die meisten Zentren verwenden daher eigene ‘hausinterne’ Antikoagulations-Protokolle. Dieses Review soll einen praktischen Überblick über aktuelle Antikoagulationsstrategien bei Patienten/innen mit extrakorporalen Organersatzverfahren geben.

### Schlüsselwörter

- Antikoagulantien
- Blutgerinnungstests
- kontinuierliche Nierenersatztherapie
- extrakorporale Membranoxy-Genierung
- Herzersatzverfahren

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## Introduction

The increasing frequency with which extracorporeal circuits are used in critically ill patients presents treating physicians with daily challenges. Continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices (LVADs) provide essential opportunities for organ support, but are accompanied by potentially fatal complications, including but not limited to hemorrhage and thrombosis.

Exposure to foreign surfaces in extracorporeal circulation provides contact activation and an associated risk for thrombus formation within the circuits or throughout the human circulation.[1] Thus, effective anticoagulation is usually required during extracorporeal circulation. Aside from this, circuit-related clotting factor and platelet consumption, increased fibrinolysis, and von Willebrand factor deficiency may all contribute to an increased bleeding risk. Treating physicians thus need to balance a fragile equilibrium between bleeding and clotting tendency by choosing the right anticoagulants, dosage, and monitoring tests according to the type of circuit and individual patient requirements.

This concise review aims to provide a practical view on current anticoagulation and monitoring strategies in patients receiving CRRT, ECMO, or LVAD and to help clinicians in appraising available evidence.

### General Considerations on Anticoagulation in Critically Ill Patients with Extracorporeal Circuits

Coagulation is a complex process, especially during critical illness and even more in patients on extracorporeal circuits. Both may substantially affect the effectiveness and safety of anticoagulants and interfere with the reliability of coagulation assays. A serious anticoagulation strategy thus needs to incorporate several critical aspects. Patient-specific factors including preexisting coagulopathies, comorbidities, underlying disease, associated organ dysfunctions, and the individual risk for thromboembolism and bleeding must be considered, as well as drug-specific factors (mechanism of action, pharmacokinetics, test sensitivity, adverse effects, and contraindications), circuit-related effects on coagulation (clotting factor and platelet consumption/dysfunction, fibrinolysis), and the methodology and limitations of different coagulation assays (clotting-based tests, chromogenic assays, viscoelastic tests).

#### Anticoagulants and Dosing

There are insufficient data from randomized studies on the efficacy and safety of anticoagulants (other than heparin) in extracorporeal circuits, particularly ECMO and LVAD. Intravenous unfractionated heparin (UFH) is most widely used,[2] but is limited by complex pharmacokinetics and variable effect response, a risk of heparin-induced thrombocytopenia (HIT) and drug resistance. Parenteral direct thrombin inhibitors (DTIs) may provide a more consistent effect, but experience is limited, costs are high, and their use in extracorporeal circuits may generally be questioned given that their mechanism of action does not target the contact pathway of coagulation (which is primarily activated by nonbiological surfaces).

While direct oral anticoagulants (DOACs) including direct thrombin and factor Xa inhibitors are widely used in daily practice for prophylaxis of stroke in nonvalvular atrial fibrillation as well as the prevention and treatment of deep vein thrombosis and pulmonary embolism, they have no role in anticoagulation during extracorporeal circulation. Vitamin K antagonists (VKAs) represent the standard treatment for long-term oral anticoagulation in patients on contemporary continuous-flow LVADs.

►Table 1 shows mechanisms of action and characteristics of anticoagulants most commonly used during extracorporeal circulation.

Proposed dosing regimens for anticoagulants (along with target ranges) are likewise largely derived from patients without extracorporeal circuits and thus need to be adjusted individually according to patients' requirements. Examples of dosage regimens are provided in ►Table 2.

#### Coagulations Assays and Target Ranges

Monitoring is required during anticoagulation of patients with extracorporeal circulation, but is complicated by a lack of assay standardization and uncertainties regarding therapeutic effect targets.

Activated clotting time (ACT), activated partial thromboplastin time (aPTT), and anti-factor Xa activity (anti-Xa) are the most commonly used assays for anticoagulation monitoring during extracorporeal circulation. Clotting-based tests (ACT, aPTT) are widely available and low in cost but nonspecific to heparin and sensible to various confounders. Anti-Xa assays provide a direct measure of heparin effect, but assess only a small part of the coagulation cascade and may miss coexistent coagulopathies. Viscoelastic tests reflect *in vivo* hemostasis more accurately, but are limited by high interobserver variability and lack of available therapeutic target ranges. ►Table 3 gives an overview of the advantages and disadvantages of various coagulation assays.

Lack of standardized coagulation assays and uncertainties regarding anticoagulation effect targets render anticoagulation monitoring during extracorporeal circulation challenging. Not only do patients' individual coagulation profiles need to be considered, but test systems also vary among different centers. Individualized anticoagulation and monitoring policies limit their reproducibility and complicate the interpretation and wider application of available evidence. Therefore, physicians treating patients on extracorporeal circuits need to be familiar with the reagents and principles used in their laboratory. Every center should thus use in-house protocols for the monitoring of anticoagulation, considering the availability and respective reference ranges of tests used.

### Anticoagulation during CCRT, ECMO, and LVAD

#### Continuous Renal Replacement Therapy

Kidney injury occurs in approximately 50% of all patients admitted to the intensive care unit (ICU). Every forth patient

 

**Table 1** Anticoagulants used in extracorporeal circulation

| Drug | Mechanism of action | Advantages | Disadvantages |
|---|---|---|---|
| **Parenteral anticoagulants** | | | |
| UFH | - Potentiates AT-dependent inhibition of thrombin and FIXa–XIIa<br>Thrombin/FXa inhibition ratio 1:1<br>- Increases the effect of TFPI to inactivate FXa and FVIIa/TF complex | - Long-term experience and good evidence for use in extracorporeal circuits<br>- Standard in ECMO and LVAD perioperatively<br>- Short half-life, easily titratable<br>- Antidote available (protamine)<br>- Low costs and widely available | - Risk of HIT<br>- Complex pharmacokinetics and -dynamics<br>- AT-dependent effect<br>- Complex interactions with coagulation and inflammation pathways<br>- No linear dose–response/anticoagulatory effect (variable fraction of AT-binding penta-saccharides)<br>- Risk of heparin resistance[a] (AT consumption/degradation, heparin binding to acute phase reactants and cells, increased renal heparin clearance)<br>-No inhibition of fibrin-bound thrombin or platelet-bound FXa |
| LMWH | Potentiates AT-dependent inhibition of thrombin and FXa in a 1:4[b] ratio | - 10 times lower risk of HIT than UFH<br>- Lower AT dependency<br>- More predictable pharmacokinetics (less cell- and protein-binding)<br>- Convenient, easy to administer<br>- Good experience in RRT<br>- RRT: hemofilter survival better compared to UFH | - Limited data and no controlled trials in ECMO and LVAD<br>- aPTT not sensitive, monitoring only through anti-Xa level<br>- Accumulation in kidney failure<br>- Only partly dialyzable<br>- Can only be partially antagonized<br>- Costs higher than with UFH (in CRRT)<br>- RRT: increased bleeding risk compared to RCA |
| **DTIs**<br>Parenteral:<br>argatroban<br>bivalirudin | Direct reversible inhibition of circulating and clot-bound thrombin, independent of AT | - No risk of HIT<br>- Short half-life, more predictable pharmacokinetics, and consistent anticoagulant effect<br>- Inhibition of clot-bound thrombin and thrombin-induced platelet activation<br>- No risk of antiplatelet antibodies<br>- Specific monitoring assays available (ECT, thrombin time, anti-IIa level)<br>- Bivalirudin: hemodialyzable | - Limited experience in extracorporeal circuits<br>- No antidote available<br>- Not sensitive to aPTT, ceiling effect<br>- Higher costs than UFH<br>- Dose adjustment in hepatic (argatroban, bivalirudin) and renal failure (bivalirudin)<br>- DTIs do not target contact pathway, questioning reasonability of its use in extracorporeal circuits |
| Citrate (regional citrate anticoagulation) | Citrate inhibits local clotting by complexing calcium. Hypocalcemia inhibits thrombin generation in the circuit | - Regional (not systemic) anticoagulation<br>- Feasible and safe in RTT<br>- Superior to systemic heparin in terms of bleeding risk and hemofilter survival | - Use only in RRT<br>- Cannot be used in patients requiring systemic anticoagulation, severe liver failure, cardiogenic shock/poor tissue perfusion (lactate acidosis)<br>- Risk of citrate accumulation (requires monitoring of systemic $iCa^{2+}$ or t/iCa ratio[c])<br>- Hypocalcemia due to rapid citrate infusion may cause severe hemodynamic compromise (hypotension, cardiac arrest)<br>- Risk of metabolic derangements: alkalosis, acidosis, hypomagnesemia, hypernatremia (with trisodium citrate), hypocalcemia<br>- No data in ECMO<br>- No use in LVAD |
| **Oral anticoagulants** | | | |
| VKAs | Inhibit vitamin K–dependent clotting factors II, VII, IX, X | - Low costs, widely available<br>- Antidote available (vitamin K) | - Repetitive INR testing necessary<br>- Variable pharmacokinetics<br>- Long half-lives<br>- No use in ECMO |

Abbreviations: AT, antithrombin; DTIs, direct thrombin inhibitors; ECMO, extracorporeal membrane oxygenation; ECT, Ecarin clotting time; ELSO, extracorporeal support organization; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; LVAD, left ventricular assist device; RRT, renal replacement therapy; TFPI, tissue factor pathway inhibitor; UFH, unfractionated heparin; VKAs, vitamin K antagonists.

[a]Heparin resistance means an inadequate effect response despite high doses of UFH. It can be proposed if doses exceed 35,000 IU/day,[44] aPTT remains <45 seconds after administration of 1,200 IU/hour UFH for at least 2 hours[45] or ACT remains <400 seconds after bolus administration of 400 IU/kg UFH.[46]

[b]Enoxaparin.

[c]A t/iCa ratio >2.25 may indicate citrate accumulation.

 

**Table 2** Dosing of commonly used anticoagulants during extracorporeal circulation

| Circuit | Drug | | Initiation/Bolus | Maintenance |
|---|---|---|---|---|
| RRT | UFH | | 500–1,000 IU | 500 IU/h (aPTT target: 40–45 s) |
| | LMWH | Enoxaparin | 0.15 mg/kg | 0.05 mg/kg/h (anti-Xa target 0.25–0.30) |
| | | | 40 mg twice daily | |
| | Citrate (RCA) | | – | Depending on protocol:<br>- Conventional citrate dose: 3–5 mmol/L blood flow<br>- Citrate dose is adjusted to blood flow +/– post filter $iCa^{2+}$ (target $iCa^{2+}$ concentration in the filter <0.4 mmol/L) |
| ECMO | UFH | | 50–100 IU/kg | 7.5–20 IU/kg/h (aPTT target: 1.5–2.5 × baseline) |
| | LMWH | Enoxaparin | – | - Half-therapeutic dose: enoxaparin 0.5 mg/kg twice daily, or<br>- Prophylactic dose: enoxaparin 40 mg once daily |
| | DTI | Argatroban | 100–200 µg/kg (optional) | 0.2–1.0 µg/kg/min (aPTT target: 1.5–2.5 × baseline, or anti-IIa level) |
| | | Bivalirudin | 0.05–0.5 mg/kg | 0.025–0.10 mg/kg/h (aPTT target 1.5–-2.5 × baseline, or anti-IIa level) |
| LVAD | UFH | | Perioperative during CPB: 50–100 IU/kg | 7.5–20 IU/kg/h |
| | | | Early postoperative period: 50–100 IU/kg (Start at postoperative day 1–2 if there is no evidence of bleeding and chest tube drainage is less than 50 mL/h) | - aPTT target range: 45–50 s in first 24 h<br>- aPTT target range: 55–65 s after 24 h |
| | DTI | Argatroban | 2 mg/h | - aPTT target range: 70–80 s |
| | | Bivalirudin | 50 mg | - 1.25–2 mg/kg/h<br>- ACT target >300 s |
| | LMWH | | – | - Early postoperative period: start 24 h after surgery<br>- Peak anti-Xa target: 0.12–0.15 U/mL (4 h after administration)<br>- Postoperative day 4: peak anti-Xa target: 0.2–0.4 U/mL |
| | VKAs | Warfarin | INR target range: 2–2.5: e.g.: Phenprocoumon 5 mg daily for 3 d (start at postoperative days 2–3 when there is no evidence of bleeding and chest drains have been removed; heparin can be discontinued when target INR is reached; daily INR check) | INR target range: 2–2.5 (may be adapted individually according to thrombosis/bleeding risk) |
| | | Phenprocoumon | | |
| | Acetylsalicylic acid (aspirin) | | 81–200 mg daily (start at postoperative days 2–3) | 81–200 mg daily<br>Dose is device dependent[a]: e.g.:<br>- 100 mg of aspirin once daily for Abbott HeartMate II + III<br>- 100 mg twice daily for HeartWare HVAD recipients (some centers add a second platelet inhibitor, most commonly dipyridamole or clopidogrel) |

Abbreviations: aPTT, activated partial thromboplastin time; AT, antithrombin; CPB, cardiopulmonary bypass; DTIs, direct thrombin inhibitors; ECMO, extracorporeal membrane oxygenation; ELSO, extracorporeal support organization; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; LVAD, left ventricular assist device; RCA, regional citrate anticoagulation; RRT, renal replacement therapy; UFH, unfractionated heparin.

[a]This dosage regimen is used at the Medical University of Vienna.

Please note: Doses given are examples and must be adjusted to a patient's individual requirements.



 

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**Table 3** Coagulation assays most commonly used during extracorporeal circulation

| Assay, unit, and reference range[a] | Method | Target range | Advantages | Disadvantages |
|---|---|---|---|---|
| **ACT, s**<br>Reference: 70–120 s | - Whole blood point-of-care test measuring time to clot formation after activation by kaolin, celite, or glass beads | 160–220 s | - Readily available point-of-care assay<br>- Easy to use<br>- Low costs<br>- Useful at high heparin doses (aPTT > 180 s) | - Sensitive to all anticoagulants to a variable extent<br>- Nonspecific to heparin<br>- Insensitive to low doses of UFH (developed for high-dose heparin monitoring)<br>- Affected by low platelet count <30–50 G/L, platelet dysfunction, fibrinolysis, hypothermia, hemodilution, anticoagulation therapy, GPIIb/IIIa inhibitors, deficiencies of FI, II, V, VII, IX, XI, XII<br>- Not well standardized, limited reproducibility, test precision operator-dependent<br>- Depends on the presence of platelet phospholipids<br>- Least related to heparin dose on ECMO |
| **aPTT, s**<br>Reference: 27–41 s | - Platelet poor citrated plasma-based test<br>- Measures time to fibrin formation after activation by silica or ellagic acid | 1.5–2.5 × baseline<br>Depending on bleeding/thrombosis risk:<br>- 40–60 s<br>- 60–80 s<br>e.g.: higher aPTT target when ECMO flow can be reduced to < 2 L/min (increased risk of cannula thrombosis) | - Most experience, widely available<br>- Standard laboratory test (increases reliability)<br>- Not affected by hematocrit or platelets<br>- Whole blood point-of-care tests available<br>- Better correlation with heparin dose than ACT during ECMO | - Sensitive to all anticoagulants to a variable extent<br>- Nonspecific to heparin<br>- Ceiling effect with high doses of heparin<br>- Sensitive to clotting factor deficiencies I, II, V, VII, IX, XI, XII, lupus inhibitor, massive bleeding, DIC, liver failure, anticoagulation therapy<br>- Sensitive to high fibrinogen and FVIII (may underestimate heparin activity in inflammation)<br>- Not well standardized, limited inter-assay/interinstitution reproducibility, >300 reagents with different sensitivity to UFH<br>- Poorly reflects in vivo hemostasis (does not account for cellular blood components) |
| **Anti-factor Xa, U/mL**<br>Reference: 0 U/mL | - Plasma-based chromogenic test<br>- Spectroscopic measure of chromophore linked to FX substrate | 0.3–0.7 U/mL<br>(derived from adult non-ECMO patients with deep vein thrombosis) | - Specific to heparin<br>- Direct measure of heparin effect (inhibition of FXa)<br>- Highest correlation with heparin dose and less variation than other tests<br>- Not affected by dilution<br>- Its use may decrease transfusion requirements, bleeding, thrombosis, and circuit changes in ECMO | - Different assays with and without addition of AT (differences between in vitro and in vivo heparin activity)<br>- Separate calibration needed for each type of heparin<br>-Affected by plasma-free hemoglobin, hyperbilirubinemia, and hypertriglyceridemia (false low anti-Xa activity)<br>- Insensitive to AT, fibrinogen, and platelets (may over- or underestimate heparin effect) |
| **Viscoelastic tests: TEM**<br>References:<br>EXTEM: CT = 42–74 s;<br>CFT = 46–148 s;<br>MCF = 49–71 mm<br>INTEM: CT = 137–246 s, | - Citrated whole blood-based test<br>- TEM and TEG measure all phases of clotting including clotting/reaction time (CT; R), clot formation time/kinetics (CFT; K), maximum clot | - TEM: no defined targets<br>- TEG: R-K time of 16–24 min (= 2–3 times upper limit of normal) in ECMO | - Global measure of hemostasis and clot dynamics<br>- Incorporates contribution of platelets, red blood cells, and fibrinogen to hemostasis (more accurate reflection of *in vivo* hemostasis)<br>- May help distinguishing | - Little data available on use in extracorporeal circuits<br>- Lack of available threshold parameters or therapeutic targets<br>- Lack of standardization<br>- Uncertain quality control<br>- High interobserver variability<br>- Insensitive to (acquired) vWF deficiency (may occur in ECMO, LVAD) |

**Table 3** (*Continued*)

| Assay, unit, and reference range[a] | Method | Target range | Advantages | Disadvantages |
|---|---|---|---|---|
| CFT = 40–100 s, MCF = 52–72 mm<br>**TEG**<br>References:<br>R: *4–8 min*, K: *1–4 min;* α-angle: *47–74°; MA*: *55–73 mm;* LY 30%: *0–8%* | firmness/amplitude (MCF; MA), and lysis index/clot lysis (LY; CL) | | clotting factor deficiency from platelet dysfunction or hyperfibrinolysis<br>- Detects heparin resistance and hypercoagulability<br>- Use of heparinase enables evaluation of both baseline coagulation status and heparin effect<br>- Additional platelet function testing available (ROTEM platelet) | |
| **ECT, s**<br>Reference: 18–38 s<br>**Quantitative thrombin time, s**<br>Reference: 13–15 s | - Plasma-based tests<br>- Measure time to fibrin formation<br>- Indirect measure of anti-IIa activity | No defined targets | - Specific to DTIs<br>- Not affected by coagulation factors other than FIa, FIIa, or lupus anticoagulant | - Insensitive to heparin<br>- Lack of therapeutic targets<br>- Not routinely available<br>- Little data available on use in extracorporeal circuits |

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; AT, antithrombin; DTIs, direct thrombin inhibitors; ECMO, extracorporeal membrane oxygenation; ECT, Ecarin clotting time; ELSO, extracorporeal support organization; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; LVAD, left ventricular assist device; RRT, renal replacement therapy; TEG, thromboelastography; TEM, thromboelastometry; UFH, unfractionated heparin.

[a]Reference ranges vary depending on the test/activator and laboratory.

Please note: Reference ranges may vary depending on the test/activator and laboratory. There is no evidence-based consensus regarding optimal target ranges—these must be adjusted individually.

 

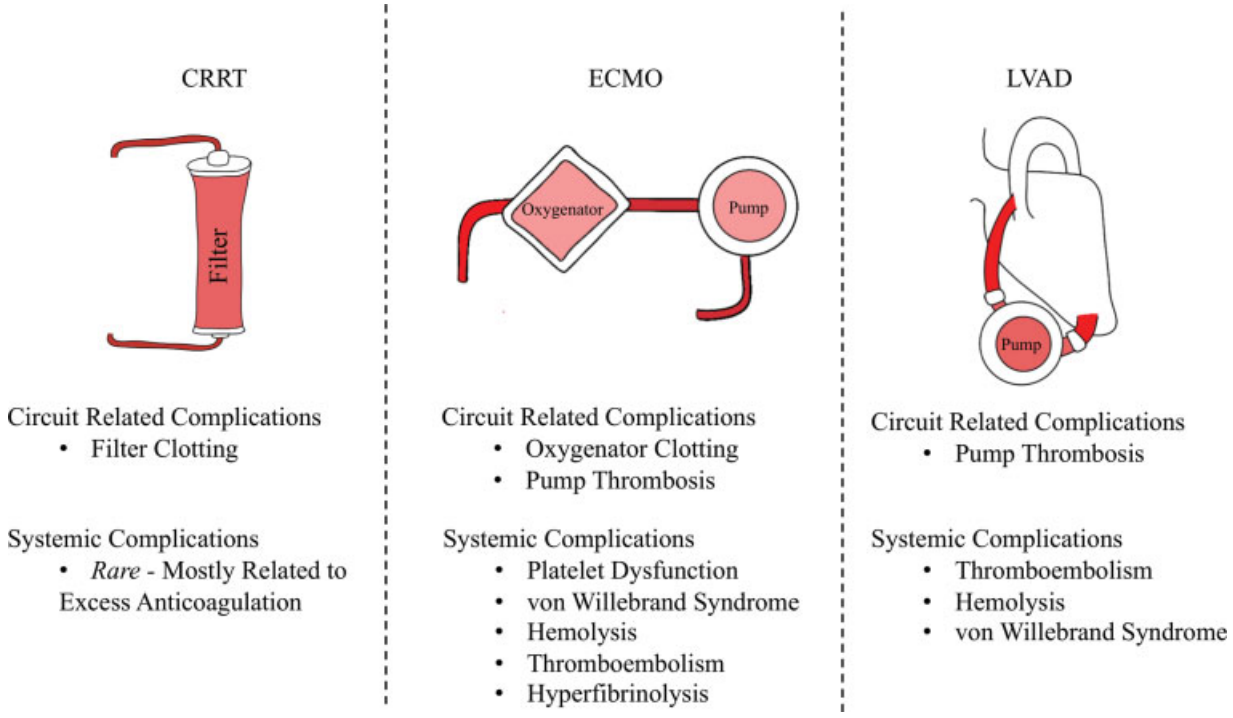


**Fig. 1** Hematological complications of extracorporeal circuits. CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device.

with kidney injury requires renal replacement therapy (RRT).[3] Several modalities are currently available for RRTs in the intensive care setting, including continuous and intermittent strategies of hemodialysis, hemofiltration, or hemodiafiltration. Given the lack of clear benefit of any modality, the choice of RRT remains at the discretion of the treating physician. A large international cross-sectional study performed at over 97 ICUs showed that the generally preferred RRT procedure was any continuous modality,[3] which will therefore be discussed in this review.

## How to Anticoagulate

The rationale of anticoagulation in RRT is to maintain patency of the extracorporeal filter and prevent reduction in membrane permeability and loss of function. Systemic bleeding and thrombotic complications are rare in RRT and are mostly related to excessive anticoagulation rather than to the circuit (►Fig. 1).

In the absence of an increased bleeding risk, coagulopathy, or previously established systemic anticoagulation for other reasons (e.g., mechanical heart valves), the Kidney Diseases—Improving Global Outcomes (KDIGO) guidelines suggest the use of regional citrate anticoagulation (RCA) in continuous RRT (►Table 4). Citrate binds and chelates free ionized calcium, an essential component for clotting initiation. Approximately 60% of formed citrate–calcium complexes are removed by the extracorporeal circuit due to its low molecular weight. Remaining chelates enter the systemic circulation and get rapidly metabolized, predominantly within the liver, into three bicarbonate molecules and calcium. As citrate binds calcium in a 1:2 ratio, calcium lost via the effluent needs to be replaced by an exogenous infusion. To

**Table 4** Complications of regional citrate anticoagulation and management

| Complication | Mechanism | Laboratory features | Management |
|---|---|---|---|
| Citrate accumulation | Incomplete citrate metabolism | $Ca_{tot}/Ca_i$ ratio: >2.5 | Decrease blood flow and/or increase dialysate flow |
| | | Metabolic acidosis | Consider alternative anticoagulation if severe |
| Citrate net overload | Excess citrate administration | $Ca_{tot}/Ca_i$ ratio: <2.5 | Decrease blood flow and/or increase dialysate flow |
| | | Metabolic alkalosis | |
| Insufficient trisodium-citrate delivery | Insufficient alkalotic load | $Ca_{tot}/Ca_i$ ratio: <2.5 | Increase blood flow and/or decrease dialysate flow |
| | | Metabolic acidosis | |

Abbreviations: $Ca_{tot}$, total calcium in plasma; $Ca_i$, ionized calcium in plasma.

 

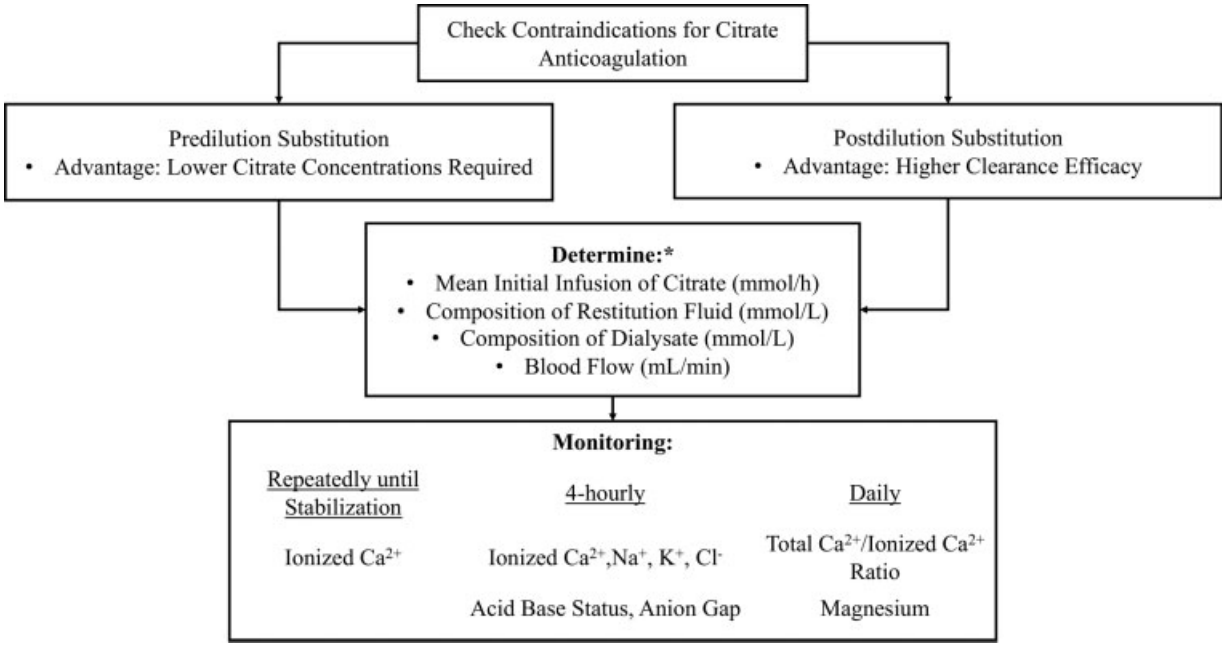


**Fig. 2** Establishment of regional citrate anticoagulation in CRRT. *Individual determination of settings depends on availability at the center's pharmacy and patient's body weight.

avoid complications of RCA, strict protocol adherence is vital, and this needs to be considered as a major limitation of this strategy. In most centers, adapted device-specific protocols give guidance on amounts of calcium and citrate infusion, composition of dialysate/replacement fluid and required monitoring of acid–base status, sodium, and total ionized calcium levels. ►Fig. 2 offers an algorithm for the establishment of RCA in CRRT.

In patients in whom impaired metabolic clearance of citrate is suspected (e.g., acute liver failure or cardiogenic shock with lactate acidosis), low-molecular-weight heparin (LMWH) or UFH provide alternatives for systemic anticoagulation. The choice between heparins relies on the discretion of the treating physician. Many centers prefer LMWH, given the convenience of single bolus injections.[4] However, due to preliminary renal elimination, anti-Xa levels should be monitored to avoid drug accumulation. The American College of Chest Physicians recommends use of UFH in patients with a severe decrease in kidney function (glomerular filtration rate $< 30$ mL/min) under monitoring of aPTT. The targeted aPTT range, however, needs to be determined individually, considering bleeding risk and filter performance. Additionally, platelet counts should be obtained on a regular basis to detect (the generally rare) occurrence of HIT. In this case, DTIs (argatroban, bivalirudin) and prostacyclin may be used as non–heparin-based systemic anticoagulants. Finally, no anticoagulation may be applied in patients with a very high risk of bleeding (<48 hours postsurgery, low platelet count, prolonged aPTT/reduced PT), or those who are actively bleeding.

### Clinical Evidence

A meta-analysis including more than 1,100 patients receiving CRRT concluded that RCA improves filter-lifespan and reduces bleeding risk compared to UFH and LMWH. This, however, did not translate into survival benefit. A large randomized controlled trial including 638 patients has recently been completed and may strengthen the evidence on RCA (ClinicalTrials.gov Identifier: NCT02669589). When interpreting the applicability of these data, it needs to be noted that patients with increased bleeding risk were excluded from these trials, including those with severe liver failure and thrombocytopenia.

While big data comparing different types of heparin in CRRT or intermittent hemodialysis are currently lacking, a large body of evidence in patients on chronic hemodialysis suggests equal effectiveness and safety between LMWH and UFH,[5] which may also be applicable to CRRT.

### Continuous renal replacement therapy: What is known about this topic?

- The goal of anticoagulation in CRRT is to prevent filter clotting.
- RCA has proven superior to heparin in terms of filter lifespan, bleeding complications, and costs and is therefore the modality of choice.
- Strict protocol adherence is required to avoid citrate overload in RCA.
- Regional heparin anticoagulation is rarely used in practice.
- Systemic anticoagulation with heparin (UFH or LMWH) can be used as alternative.
- For anticoagulation with heparin, serial monitoring with aPTT (UFH) and/or anti-Xa activity (LMWH, UFH) according to individualized targets is recommended.
- In case of (suspected) HIT or heparin resistance, DTIs can be used if systemic anticoagulation is required.

 

### Extracorporeal Membrane Oxygenation

Over past decades, the use of ECMO has exponentially increased as an emerging rescue therapy for isolated or combined respiratory and circulatory failure.[6] The effectiveness of ECMO relies on the combination of a cannulation system with an incorporated pump and oxygenator. A veno-venous configuration (VV ECMO) thereby provides pulmonary support, while a veno-arterial configuration (VA ECMO) additionally provides hemodynamic support. There has been a dramatic increase in ECMO runs,[7] but its application is still associated with potentially life-threatening complications, predominantly related to thrombosis and hemorrhage (►Fig. 1).

### How to Anticoagulate

The extracorporeal circuit provides artificial surfaces requiring continuous anticoagulation. Oxygenator membrane, pump head, and canula tips are predilection sites for thrombus formation. The extracorporeal life support organization (ELSO) guidelines suggest therapeutic anticoagulation with UFH.[8] In agreement with this, UFH remains the anticoagulant of choice in more than 95% of centers,[9] but LMWH or DTIs may be used as alternatives.

Upon cannulation, an intravenous bolus of 50 to 100 U/kg body weight UFH should be administered, followed by continuous infusion of UFH at a dose of 7.5 to 20 U/kg/h, which should be titrated according to anticoagulation targets.

LMWH may provide an alternative to UFH, but experience in ECMO is limited.[10,11] Advantages of LMWH include a fixed dosing regimen with more convenient application and a lower risk of developing HIT, but drug accumulation should be considered in patients with concomitant renal compromise. Published dosing regimens for anticoagulation with LMWH include twice daily 0.5 mg enoxaparin/kg body weight (i.e., half-therapeutic dose) or a fixed dose of 40 mg enoxaparin once daily (i.e., prophylactic dose).[10,11]

DTIs may be used as an alternative to heparin. In most centers, argatroban and bivalirudin are available. Although DTIs theoretically provide several advantages over heparin, experience in ECMO remains limited. According to ELSO, use of argatroban does not require bolus administration; instead a continuous infusion is started with 0.5 to 1 µg/kg/min and adjusted to aPTT target values. While most data on the use of bivalirudin come from pediatric populations, starting doses reported for adults vary largely. Regarding bolus administration, available literature states doses from 0 to 0.5 mg/kg. Continuous doses range from 0.025 to 0.10 mg/kg/h.[12–16]

In patients with active bleeding or those with high risk of major bleeding (e.g., postsurgery, severe thrombocytopenia), an anticoagulation-free strategy may be feasible. A recent systematic review found relatively low rates of circuit and patient thrombosis in anticoagulant-free ECMO in adults, which might also be attributable to the fact that ECMO circuits themself are coated with anticoagulants (e.g., heparin). Prospective randomized trials are needed, however, to evaluate the safety and efficacy of such an approach and identify patients who may benefit from an anticoagulation-free management.[17,18]

### Clinical Evidence

In the absence of high-quality evidence, recommendations for anticoagulation strategies in ECMO remain largely expert opinions. This applies to the choice of the optimal anticoagulant as well as to appropriate monitoring, including the test system and frequency at which coagulation tests are performed.

Weight-based intravenous UFH is predominantly used for systemic anticoagulation in both VV and VA ECMO, but the need for an alternative in patients with HIT specifically led to an increase in the use of DTIs.[12,19] Both argatroban and bivalirudin appear to be safe and provide a predictable and stable anticoagulation profile. Evidence from randomized trials comparing UFH and DTIs in regard to clinical endpoints is currently lacking. As of yet, however, retrospective studies have shown no benefit of DTIs over UFH. Prospective randomized controlled trials are currently evaluating the use of bivalirudin in adult and pediatric ECMO, which hopefully will shed some light on this critical issue (ClinicalTrials.gov Identifier: NCT03318393; NCT03965208).

Experience with LMWH in ECMO is also limited; two retrospective studies, one in lung transplant patients and one in nonsurgical patients, showed that LMWH appears to be safe and effective at half-therapeutic and prophylactic doses, respectively.[10,11] One of these studies compared clinical outcome events of patients treated with LMWH to those receiving UFH, where less thromboembolic complications were reported in patients receiving LMWH.[10]

Data assessing the most adequate test to monitor anticoagulation regimes are inconclusive and evidence is largely based on retrospective studies.[20] No randomized trials have yet compared different anticoagulation tests for the monitoring of anticoagulation and for the adjustment of treatment in ECMO. ACT and aPTT poorly correlate with both each other and UFH dose.[21] Different test reagents and analyzers, along with a variable fraction of AT-binding penta-saccharides, complicate a reliable correlation of test results and heparin level. Comparably weak correlation has been shown for viscoelastic tests.[22] In a small randomized study, however, thromboelastography-guided anticoagulation appeared to be safe without increase in thrombotic complications and was associated with lower heparin doses compared to an aPTT-guided strategy.[23] Anti-Xa activity accurately reflects UFH concentrations in vivo[24]; and retrospective studies have shown improved patient outcomes with its use during ECMO.[25] However, anti-Xa activity displays only an isolated part of the coagulation cascade and may miss coexistent coagulopathies. In this context, experts suggest that it might be misleading to rely on one single test to assess the complex interaction between hemostasis, extracorporeal circuit, and anticoagulant therapy during ECMO. From an evidence-based perspective, there is still no consensus regarding the optimal monitoring strategy. No coagulation assay accurately predicts the individual risk of bleeding or thrombosis. Therapeutic targets, however, should rely on this information and are thus difficult to define. As of yet, no coagulation test has been

 

proven superior to another and correlations between specified "therapeutic ranges" and clinically relevant outcome benefit have not been demonstrated.

### Extracorporeal membrane oxygenation: What is known about this topic?

- Goal of anticoagulation is the reduction of thrombin and fibrin formation triggered by blood contact with nonbiological ECMO surfaces and turbulent flow.
- Weight-based intravenous UFH is standard and most widely used for parenteral anticoagulation in both VV and VA ECMO.
- DTIs are emerging alternatives to heparin and are currently used in case of HIT or heparin resistance.
- Anticoagulation dosing in ECMO should be premised on multiple means of assessment including different coagulation assays (clotting-based and chromogenic assays with or without viscoelastic tests), the underlying disease, and clinical evidence of bleeding or circuit clotting.
- ACT, aPTT, and anti-Xa activity are most widely used for anticoagulation monitoring, but are not well standardized and poorly correlate with each other and heparin levels.
- An individual anticoagulation protocol and monitoring policy may reduce bleeding complications and prolong circuit lifespan.

### Contemporary Continuous-Flow Left Ventricular Assist Devices

Technical improvements and increased expertise in mechanical assist devices have led to expanded indications for LVAD implantation. While initially use of LVAD was limited to a bridging option until heart transplantation, it is now increasingly used as definite therapy in end-stage heart failure.[26] In contrast to the extracorporeal circuits discussed earlier, this presents the need for anticoagulation not only in hospital, but also in an outpatient setting.

Continuous flow rates and the artificial pump provide overall altered hemostasis. Especially LVADs providing axial flow are associated with a high risk of device thrombosis and embolic complications, leading to high mortality and morbidity (►Fig. 1). However, introduction of centrifugal pumps, as used in the HeartMate III device (Abbott), significantly reduced thrombotic complications, with more than 75% of patients alive and free from disabling stroke 2 years after implantation.[27] This game changer also manifested in increased use of the HeartMate 3 device, which was used in almost four out of five LVAD patients in 2019.[28]

## How to Anticoagulate

### Perioperative Anticoagulation Management

In the process of preparing a patient for the LVAD implantation procedure, coagulation parameters should be optimized. This may be challenging in the acute setting, especially in patients in cardiogenic shock with impaired hepatic function.

For the implantation of an LVAD, a cardiopulmonary bypass is temporarily established, which requires continuous anticoagulation with UFH. After successful weaning from cardiopulmonary bypass, complete heparin reversal with protamine is recommended. Additionally, some centers administer tranexamic acid prophylactically to reduce microvascular bleeding.[29]

In the early postoperative period, anticoagulation should be initiated within 48 hours after surgery, as soon as chest tube drainage is less than 50 mL/h. aPTT is used to monitor anticoagulation effect. Initial anticoagulation is achieved with continuous intravenous UFH with a target aPTT of 40 to 60 seconds in the first 48 hours postsurgery, and increased to achieve a target aPTT of 60 to 80 seconds after 48 hours.[30]

Alternatively, LMWH can be used. At our center, LMWH is started 24 hours after surgery targeting a peak anti-Xa level of 0.12 to 0.15 U/mL 4 hours after administration on days 2 to 3 following surgery. Starting from postoperative day 4, a peak anti-Xa level of 0.2 to 0.4 U/mL should be aimed for. For patients with known HIT, argatroban, bivalirudin, or fondaparinux can be used instead of heparins, but experience remains highly limited. The use of DTIs during LVAD implantation is associated with increased risk of thrombus formation within the device. According to a published case series of patients with suspected HIT who were treated with argatroban, increasing the anticoagulation target to an aPTT of 70 to 80 seconds prevented acute thrombus formation, but four of six patients even needed postsurgical revision due to bleeding complications.[31]

In the absence of bleeding complications and chest tube drainage in regular postoperative ranges, antiplatelet therapy with acetylsalicylic acid (aspirin) is initiated on day 3 postsurgery. The aspirin dosage is device dependent and also varies among specialized centers between 81 and 325 mg aspirin daily.[31] At our institution, we use 100 mg of oral aspirin once daily for HeartMate II + III devices, and 100 mg twice daily for HeartWare HVAD (Medtronic) recipients. Platelet aggregometry may be used to identify aspirin nonresponders, but is not yet routinely performed.[32] Some centers use a second platelet inhibitor; mostly dipyridamole in the United States and clopidogrel in Europe.[33]

### Postimplantation Anticoagulation Long-Term Management

Aiming to prevent hemocompatibility-related adverse events, anticoagulation using VKAs (warfarin or phenprocoumon) with a target international normalized ratio (INR) of 2 to 3, as well as antiplatelet therapy with aspirin is the standard therapy in the majority of implant centers for patients on contemporary continuous-flow LVADs (CF-LVADs, HeartMate II + III, and HeartWare HVAD).[30]

Patients are transitioned from LMWH to a VKA after chest tubes have been removed. Transitioning from parenteral to oral anticoagulation may be challenging in the individual patient and thus needs to be carried out with great care to avoid bleeding or thromboembolic complications.

LMWH can be discontinued as soon as the target INR range of 2 to 2.5 is reached. Daily INR checks should be performed until discharge. Upon transfer to the rehabilitation center, patients are trained to perform at-home INR

 

testing, which is convenient and feasible for the majority and provides reliable results according to a recent study.[34] The target INR range is commonly set at 2 to 2.5 but may be adapted individually considering risk factors for thrombosis and hemorrhage.

### Temporary Cessation of Anticoagulation

In case of bleeding complications, anticoagulation can and should be temporarily withheld with close clinical and laboratory monitoring of hemolysis. Particularly in case of intracranial hemorrhage, reversal of anticoagulation is advisable and bears only low risk of pump thrombosis.[35] In patients with recurrent bleeding complications (e.g., gastrointestinal), individualized anticoagulation regimens should be considered (e.g., lower target INR and/or permanent discontinuation of antiplatelet therapy).

In case of planned invasive procedures or surgeries that require cessation of anticoagulation, bridging with subcutaneous injections of LMWH three times daily, with a target peak anti-Xa level of 0.2 to 0.4 U/mL, should be administered as soon as the INR is below 2, and LMWH should be stopped 12 hours before the planned intervention.

## Clinical Evidence

Comparative studies regarding different regimes concerning agents and targets used for anticoagulation remain scarce. Current practice guidelines thereby mostly rely on manufacturer's instructions and expert opinions with a resulting low level of evidence.[36]

Determining the ideal target range for VKA remains challenging, as conflicting data exist regarding whether the intensity of anticoagulation (assessed by INR) is associated with bleeding events. Outpatient follow-up of more than 300 patients on LVAD showed that bleeding occurred more frequently when INR was above 3.0. However, this included only one-third of hemorrhagic strokes, which indicates that no specific cutoff was applicable.[37] Comparable associations were observed for thromboembolic events, although rates were much lower; 40% of ischemic strokes occurred in patients with an INR less than 1.5. Another retrospective study determined the optimal therapeutic range for anticoagulation to be between 2.0 and 3.2.[38] It needs to be noted, however, that both studies report data before the introduction of centrifugal pumps. Likewise, the commonly used approach of an INR target between 2 and 3 overall is based on evidence gained before the release of the fully magnetically levitated HeartMate III[27]; thus, reevaluation and adaption of this regimen for patients on this device may be necessary in the future. Most recent studies suggest that reduction of anticoagulation and antiplatelet therapy might be possible without increase in thrombotic complications in patients who have the HeartMate III device implanted.[39] Regarding antiplatelet therapy, no difference in hemocompatibility-related adverse events and survival was detected with different dose regimens (81 vs. 325 mg of aspirin daily) for patients with the HeartMate III device.[40]

Recently, a large retrospective analysis of more than 13,000 patients showed that use of phosphodiesterase 5 inhibitors, mostly sildenafil, significantly reduced pump thrombosis, stroke, and all-cause mortality up to 48 months after implantation. However, intake was associated with an increased risk for gastrointestinal bleeding and future prospective trials need to be performed to prove its apparent benefit.[41]

DTIs could be an alternative to overcome disadvantages of VKA overall, including requirement of INR monitoring as well as fluctuations of anticoagulation levels upon changes in diet and during states of inflammation.[42] However, a prospective, open-label phase 2 trial investigating the efficacy of the oral DTI dabigatran in LVAD patients was terminated prematurely due to thromboembolic safety concerns.[43]

## Left ventricular assist devices: What is known about this topic?

- Anticoagulation and antiplatelet therapy in LVAD patients are required to prevent hemocompatibility-related adverse events.
- In the early postoperative period, anticoagulation should be initiated 12 to 24 hours after surgery, as soon as chest tube drainage is less than 50 mL/hours.
- Postoperative heparins are switched to oral VKA and antiplatelets (mostly aspirin ± dipyridamole or clopidogrel) after chest tubes have been removed.
- Anticoagulation and antiplatelet therapy are continued after discharge from hospital with at-home INR testing aiming at an INR target between 2.0 and 2.5.
- Temporary cessation of anticoagulation in case of bleeding complications bears only a low risk of pump thrombosis.
- The value of DOACs for anticoagulation in LVAD is currently unknown, but the use of oral dabigatran was associated with an increased rate of thromboembolic events compared to VKA in a previous, prematurely terminated, clinical trial.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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