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Bleeding news

Reversal of anticoagulation: Haemostatic efficacy or clinical benefit?

Bianca Rocca, Hugo Ten Cate

PMID: 42269153 DOI: 10.1056/NEJMra2506021

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The growing use of anticoagulants, particularly in elderly patients with multiple comorbidities, has turned its urgent reversal in a common clinical challenge. In this excellent review, Rocca and ten Cate analyse the available antidotes, their mechanisms of action and the evidence supporting their use, highlighting a fundamental issue: **an effective pharmacological reversal does not always translate into a proven clinical benefit.**

Of particular relevance is the analysis of **andexanet alfa**, with an ability to reverse the activity of factor Xa inhibitors, yet some uncertainties surrounding its safety. In the ANNEXA-I trial, andexanet showed an improved haemostatic efficacy compared with the conventional treatment (67% versus 53.1%), but without significantly reducing mortality and with a higher incidence on thrombotic events (10.3% versus 5.6%). Its withdrawal from the US market in December 2025, while retaining conditional authorisation in Europe, illustrates the difficulties in establishing a favourable risk-benefit balance.

In this scenario, **four-factor prothrombin complex concentrates** represent a pragmatic alternative, particularly in cases of severe haemorrhage or emergency surgery. However, their use to reverse the effects of direct oral anticoagulants is still based on limited evidence, and neither the optimal doses nor their comparative efficacy against specific antidotes have been conclusively established.

The review also points out that even well-established treatments, such as protamine or idarucizumab, still have unresolved issues, particularly related to dosing, monitoring and a potential rebound of anticoagulant activity.

From the perspective of perioperative haemostasis, the **lack of evidence available for patients requiring emergency surgery**—an under-represented population in clinical trials—warrants particular attention. Furthermore, there are still significant limitations in monitoring reversal. Viscoelastic testing and point-of-care systems offer interesting possibilities, but they still require specific validation for this purpose.

The main strength of this article lies in its balanced analysis of the efficacy and safety of available treatments, but since it is a narrative review, it does not provide a systematic assessment of the certainty of the evidence. Besides, a better integration of antidotes would be desirable into overall strategies to treat haemorrhage, including control of the source of bleeding and the resumption of anticoagulation.

Thus, this review reminds us that reversing anticoagulation doe not necessarily improve the prognosis. The real challenge lies in identifying which patients benefit from reversal, selecting the most appropriate strategy, and ensuring that the attempts to control a haemorrhagic complication ends up leading to another complication of a thrombotic nature.

The availability of increasingly specific antidotes is undoubtedly a step forward, but their use should always be guided by clinically relevant outcomes and not exclusively by the normalisation of analytical parameters.

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Point-of-care visco-elastic testing for postpartum haemorrhage: A narrative review

Hans Vandersmissen, Eva Roofthooft, Sarah Devroe, Steven Thiessen, Hendrik Stragier

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The authors carry out a narrative review on the use of viscoelastic testing (VET), primarily ROTEM, in postpartum haemorrhage (PPH), with a particular focus on the indication of fibrinogen and tranexamic acid (TXA). Its main limitation is the lack of a systematic literature review, as the authors themselves acknowledge the selection bias in the articles.

It is important no note that coagulopathy is rare at the onset of PPH and will develop as blood loss increases. Thus, with around 1,200 ml of blood loss, only a minority have a Clauss <2 g/L. In this context, **fibrinogen is the key marker:** A Clauss value <2 g/L or a low FIBTEM A5 predict progression to severe PPH.

VET in PPH have made it possible to avoid unnecessary plasma transfusions and to optimise fibrinogen replacement, which, particularly in pregnant women, should be carried out using fibrinogen concentrate. The ROTEM model should be considered, since the authors suggest that with ROTEM Sigma, and the change of cartridges, the replacement threshold becomes FIBTEM A5 ≤8 mm, equivalent to the previous ≤11–12 mm (ROTEM Delta), corresponding to the 2 g/l threshold according to Clauss. The use of VET in the context of PPH has resulted in less plasma transfusions, less TACO and less blood products in large cohorts (particularly the OBS Cymru programme in Wales). However, RCTs are small or show negative results; it should be assessed whether this is due to an inappropriate endpoint: OBS-2 reported fibrinogen with FIBTEM <15 mm and showed no benefit, and only the subgroup with A5 ≤12 mm or Clauss ≤2 g/L suggested an effect.

With regard to tranexamic acid, it should be administered as soon as possible following the PPH diagnosis. However, routine prophylaxis is not supported and should be reserved for high-risk patients. VET results cannot be trusted either, since they are not very sensitive to hyperfibrinolysis. Other limitations of VET include the fact that the platelet function is poorly assessed (the role of PLTEM in PPH is unclear), and the devices and their thresholds are not interchangeable.

A different scenario is acute obstetric coagulopathy (AOC), which occurs as a distinct condition (≈1/1000 births), associated with placenta abruption and amniotic fluid embolism. It combines hypo-/dysfibrinogenemia with massive hyperfibrinolysis (very high PAP levels, elevated aPC, and consumption of FV/FVIII/FXIII). The treatment should be early fibrinogen plus TXA.

As key points, I would highlight the indication of VET to guide fibrinogen (with the right threshold depending on the cartridge) and to *avoid* plasma transfusion. Conversely, the information from VET cannot be regarded as reliable on platelets or fibrinolysis. Therefore, early TXA should always be administered, without waiting for the tracing. In case of abruption or amniotic fluid embolism, a completely different scenario must be considered, that of AOC, and an aggressive early treatment with fibrinogen must be applied.

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The Year in Coagulation and Transfusion: Selected Highlights

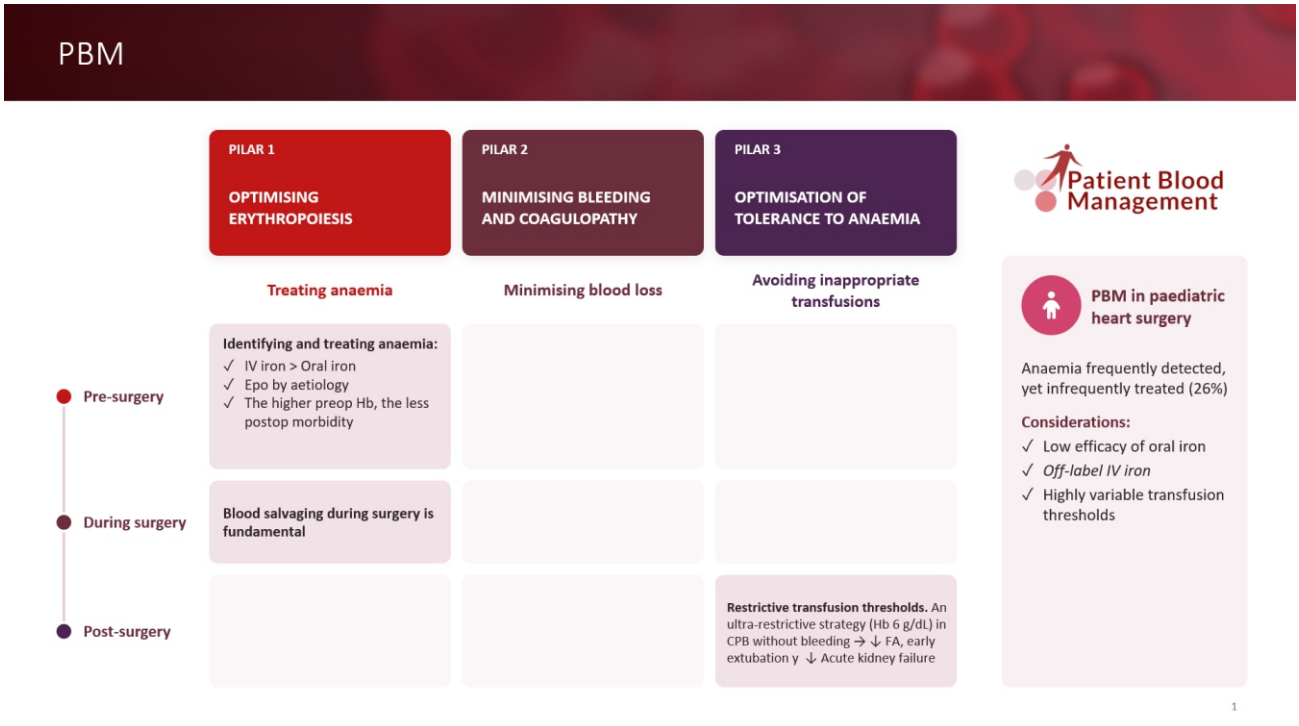
Gabor Erdoes, Andreas Koster, Linda Shore-Lesserson, Yefim Vilnits, Marie E Steiner, Hugo Ten Cate, Michael Mazzeffi

PMID: 41876318 DOI: 10.1053/j.jvca.2026.03.005

Author of the comment: *Dra. Pilar Marcos.* *Intensive Medicine. Hospital Germans Trias i Pujol, Badalona, Barcelona.*

This article **summarises** the most significant advances in the management of **coagulation and transfusion** in **cardiothoracic and vascular surgery** that took place throughout **2025.**

1. About **Patient Blood Management**



Bleeding news

2. About **Prothrombin Complex Concentrate**

4-FACTOR PROTHROMBIN COMPLEX CONCENTRATE (4F-PCC)

The body of scientific evidence confirms 4F-PCC as the cornerstone of perioperative bleeding management in cardiac surgery

Reversal of anti-vitamin K anticoagulants with 4F-PCC — Recommendation: Class IIa Level A

4F-PCC is superior to FFP in factor replacement during cardiac surgery — Recommendation: Class IIa Level B

Study	Intervention	Key results
Initial single-site RCT (n = 100 patients)	• **4F-PCC:** 15 U/kg *vs.* • **FFP:** 10–15 mL/kg	‣ Significant reduction of pRBC transfusions in haemorrhage following cardiac surgery
FARES-II Multicentre Trial	• **4F-PCC:** : 1,500–2,000 UI *vs.* • **FFP:** 3 to 4 units	‣ Superiority of 4F-PCC in bleeding due to coagulopathy following CPB: Lower transfusion of pRBCs, FFP and PLT ‣ Reduction in bleeding from drains ‣ Similar reoperation rates
Meta-analysis of RCTs	• **PCC** versus **FFP**	‣ More effective correction of INR ‣ Improved Hb levels ‣ Reduction in pRBC transfusion and use of recombinant Factor VIIa ‣ No increase in thromboembolic events

↓ Transfusion of pRBC, FFP, PLT

Faster and more effective correction of coagulation

Safe profile: no further thrombotic events

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3. About **Direct Oral Anticoagulants**

DIRECT ORAL ANTICOAGULANTS (DOACs)

SCENARIO

- Active **DOAC** levels in **emergency cardiac surgery** indicate a scenario with **a very high risk of bleeding**
- **We do not have an antidote**, since the specific antidote of anti-Xa DOACs (**andexanet alfa**) lacks sufficient scientific evidence in cardiac surgery, and it is not marketed in Europe

EVIDENCE ON INTRAOPERATIVE HAEMOADSORPTION

The first clinical assessment was the study by Frering et al. on the elimination of **apixaban** using **CytoSorb** in **emergency cardiac surgery**:

- It demonstrates **clinical feasibility** with no device-related adverse events
- It shows a **reduction in bleeding** compared to historical controls
- Aligned with *in vitro* data supporting effective intraoperative removal of DOACs

Haemoadsorption using **CytoSorb** in the **ECC** circuit could be a promising alternative for the **intraoperative removal of DOACs in emergency cases**, although it requires further rigorous pharmacokinetic and clinical validation

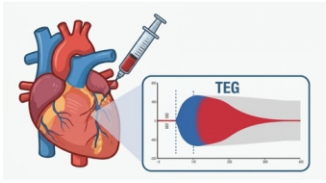
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Bleeding news

4. About **Advances in Coagulation Monitoring**

ADVANCES in COAGULATION MONITORING

Recent innovation is focused on monitoring using **TEG**, which complements the sound body of evidence previously accumulated with **ROTEM**



Studies prove that the **TEG 'R'** (ROTEM 'CT') is a good predictor of factor deficiency coagulopathy, and that the **TEG 'MA'** (ROTEM 'MA') is a good predictor of PLT and/or fibrinogen deficiency

Furthermore, **TEG-6S** (point-of-care monitor) proves that in coronary revascularisation surgery:

01
The **R** correlates with **anti-Xa activity** (R^2>0.8)

02
It is a good predictor of the **lack of heparin reversal** in ECC

03
A useful alternative to ***measure*** **heparin anticoagulation**, when aPTT, ACT, or anti-Xa levels are inconsistent. This could happen in clinical situations involving **heparin resistance, such as:**

- AT III deficiency
- Inflammation
- Prior exposure to heparin
- Hyperfibrinogenemia
- Obesity

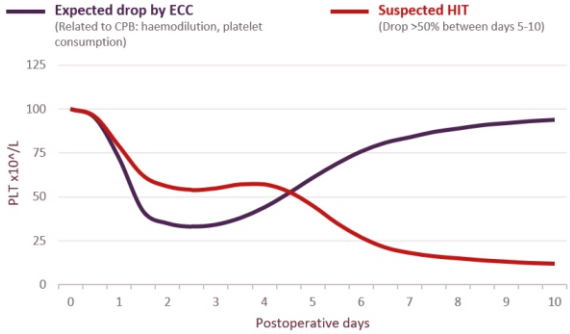
Viscoelastic tests (ROTEM and TEG) show a **strong correlation with Anti-Xa levels** and a **good predictive performance for the residual effect of postoperative heparin**

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5. About **Heparin-induced Thrombocytopenia**

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

DIFFERENTIAL DIAGNOSIS



MANAGEMENT, in cases of suspected HIT

01 **Immediate discontinuation of heparin**

02 Alternative and effective intravenous direct thrombin inhibitors (Anti-IIa): Argatroban or Bivalirudin

HIT in paediatric heart surgery

A paediatric clinical case was recently published describing the successful management of HIT in a patient on ECMO and VAD support, using bivalirudin as an anticoagulant, as a bridge to heart transplantation

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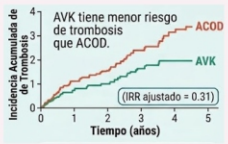
6. About **Antithrombotic therapy**

ANTIAGGREGANT and ANTICOAGULANT THERAPY

ESC/EACTS 2025 GUIDELINES

Mechanical valves
Lifelong anticoagulation with AVK

Surgical bioprostheses
- ✓ **Aortic**: AVK or AAS low doses
- ✓ **Tricuspid**: AVK
- ✓ **Mitral**: AVK



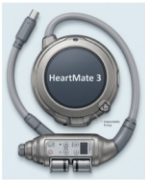
It is not recommended to **switch from AVK to DOACs** to treat AF in patients **over 75**, since it involves a higher risk of bleeding

(FRAIL-AF RCT)

GENDER DIFFERENCES

Women present a **greater vascular and haemorrhagic risk** in **percutaneous valve procedures**

ARIES-HMR TRIAL

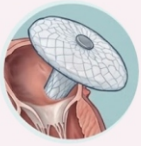


NOT combining AAS with **AVK** anticoagulation reduces bleeding (mainly digestive bleeding) without increasing the risk of thrombosis

The robustness of **HeartMate 3**'s haemocompatible design has spurred research into **DOACs**, particularly **apixaban**. Initial studies are promising, yet without conclusive evidence

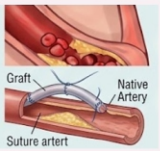
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FURTHER ACTIONS AND FUTURE STRATEGIES



ANDES RCT

Thrombosis of the atrial appendage closure device is similar with **DOACs or antiPLT dual therapy**, with a **lower incidence of bleeding**



In CPB

- Although a case-by-case approach is required, it is recommended to **withdraw P2Y12 and continue with ASA**
- When the use of **DOACs** is indicated, the recommendation is to add **a single anti-PLT**

EMERGING AGENTS and SECONDARY PREVENTION

Glycoprotein IV inhibitors and **PAR-4 antagonists**

Fast-acting: Zalunfiban and Selatogrel (safer, but further studies are required)

In **CPB, clopidogrel > ASA** in secondary prevention of major cardiovascular and cerebrovascular events, without increased bleeding. CYP2C19 genotyping is still under study

New **factor XI inhibitors** are currently under development

IN SUMMARY

THROMBOTIC PREVENTION ⚖ **ACCEPTABLE BLEEDING RISK**

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7. About **Mechanical Circulatory Systems**

MECHANICAL CIRCULATORY SYSTEMS

ECMO: BLEEDING AND THROMBOSIS

ECMOVV in COVID-19

75%
bleeding or thrombosis

10%
cerebral or pulmonary haemorrhage, especially if PLT < 100x10^9/L

ECMOVA

44.3%
bleeding

22.3%
major bleeding



Mechanisms associated with coagulopathy in ECMO therapy

- ↓ Thrombin formation
- ↓ Von Willebrand factor activity
- ↑ Fibrinolysis
- ↓ Coagulation factor deficiency

Anticoagulation strategies: Rise of direct thrombin inhibitors

ECMO + Newborns + Bivalirudin	→ ↓Transfusions. Equal mortality
ECMO + Paediatrics + Bivalirudin	→ ↓ Thrombosis. Longer time within range
ECMOvv + COVID-19 + Argatroban	→ ↓ Bleeding and thrombosis

PLT transfusion in case of bleeding: Target > 50x10^9/L

ECMOVA and pRBC transfusion A comparison between liberal (Hb 9 g/dL) and restrictive (Hb 7 g/dL) transfusion strategies has not shown conclusive results, and so high-quality randomised studies are required to establish the optimal strategy

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8. About **Paediatric population**

PAEDIATRIC POPULATION

Experience in adults does not correlate with that in paediatrics

Priming strategies of ECC in CPB

- Priming with FFP does not reduce bleeding, except in infants under 6 Kg
- A high priming volume is associated with greater inflammation, infection, renal dysfunction and length of stay in ICU

New viscoelastic testing technologies require validation

- TEG 5000 vs TEG 6S: good correlation in infants
- QUANTRA vs TEG 5000: good correlation, but clinically not interchangeable

4F-PCC dosage

Further studies are needed to define optimal dose, due to:

- ✓ ↑ Risk of thrombosis
- ✓ No differences in bleeding or transfusions between low doses (<35UI/Kg) and high doses (≥35UI/Kg)

Postoperative thrombosis and costs:

- Fibrinogen > 400 mg/dL: 8.4% thrombosis, longer stays and higher costs
- Other risk factors: preoperative hypercoagulability, pRBC transfusion, single ventricle

APRICOT and NECTARINE studies

- Paediatric patients who die following cardiac surgery are the youngest, with the lowest weight and undergoing longer surgeries
- Morbidity is high, particularly among newborns

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Abbreviations:

DOACs: Direct Oral Anticoagulants
ASA: Acetylsalicylic acid
CBP: *Cardiopulmonary Bypass*
PCC: Prothrombin Complex Concentrate
ECC: Extracorporeal Circulation
pRBCs: Packed Red Blood Cells
RCT: Randomised Clinical Trial
ECMO: *Extracorporeal Membrane Oxygenation*
Hb: Hemoglobin
HIT: *Heparin-induced trombocytopenia*
AF: Atrial fibrillation
ESC guidelines: *European Society of Cardiology*
EACTS guidelines: *European Association for Cardio-Thoracic Surgery*
IV: Intravenous
FFP: Fresh frozen plasma
PLT: Platelet
ROTEM: *Rotational Thromboelastometry*
TEG: *Thromboelastography*
VAD: *Ventricular Assist Device*
VO: Oral