CSL Behring

The new shape of coagulation

Moderators: Ravishankar Raobaikady and Diana Castro Pauperio

Thursday, April 24, 2025

1. REVERSAL OF DIRECT ORAL ANTICOAGULANTS: GUIDANCE FROM ISTH

Marc Samama

There are three ways to revert the effect of anticoagulants, especially direct oral anticoagulants (DOACs).

Reversion of anticoagulation	Type	Reverted anticoagulant
Drug removal 	· Dialysis · Antibody (Idarucizumab) · False target	· Dabigatran · Dabigatran · Dabigatran / FXa inhibitors
Drug absorption 	· Activated charcoal	· Dabigatran / Apixaban
Molecules with different mechanisms of action 	· Prothrombin Complex Concentrate (PCC) · Activated Prothrombin Complex Concentrate (aPCC) · Recombinant factor VIIa (rFVIIa)	· Dabigatran / FXa inhibitors · Dabigatran / FXa inhibitors · Dabigatran / FXa inhibitors

PCC

A meta-analysis published in 2019, including case series in a single arm, concluded that it is difficult to determine whether using PCC provides any benefit to the interruption of DOACs (FXa inhibitors) in patients with severe DOAC-related hemorrhage[1].

Percentage of patients with an effective treatment of severe hemorrhage:

IN 2 STUDIES WITH ISTH CRITERIA	IN 8 STUDIES WITHOUT ISTH CRITERIA
69% (95% CI, 61-76)	**77%** (95% CI, 63-92)

In a retrospective study assessing the efficacy and safety of PCC to revert apixaban/rivaroxaban before an emergency surgery, the following results were observed[2]:

- No patient required additional PCC
- **5%** of bleedings during the intervention
- **26%** of patients received cell concentrates
- **21%** of mortality within 30 days
- **3%** of thrombosis within 30 days

According to the *International Society on Thrombosis and Haemostasis* (ISTH)[3] four-factor PCC (4F-PCC) presents:

- Global efficacy **80%**
- **4%** incidence of thromboembolism
- Preventive efficacy in patients treated with DOACs without bleeding that must undergo an emergency invasive procedure
  - Comparative studies with placebo are required
- No differences between the fixed dose and the weight-based dose

aPCC

According to ISTH, aPCC[3] is associated with:

- Increases in thrombin generation higher than PCC or rFVIIa
- **56%** of patients with massive bleeding that achieve moderate-good hemostasis
- **84%** of patients undergoing emergency surgery that achieve Normal surgical hemostasis

rFVIIa

According to ISTH, there is no evidence supporting its use in patients with DOAC-related bleeding, and there are not enough concluding safety data[3].

IDARUCIZUMAB

- Its affinity for dabigatran es 350 times higher than for thrombin[4].
- 2.5 hours on average until the bleeding stops in patients with uncontrolled hemorrhage (intracranial or gastrointestinal)[5].
- 93,4% of patients with normal perioperative hemostasis before the emergency procedure[5].
- 6-7% thrombotic events[5].
- 19% mortality[5].

ANDEXANET ALFA

- Approved by the FDA with a safety warning, on account of its risk of thromboembolism, ischemia, cardiac arrest, and death.
- Efficacy after 2-5 minutes and short $T_{1/2}$ (1 h) ➡ the desired effect is achieved through continuous infusion + bolus[6].
- In a prospective open study, with a single group including 352 patients with predominantly gastrointestinal or intracranial hemorrhage, using questionable hemostasis criteria (primary outcome), the following results were observed[6]:
  - 82% of patients with excellent hemostasis 12 hours after infusion.
  - 10% of patients with thrombotic events within 30 days.
  - 14% mortality.
- Results vs Standard treatment[7]:

	Andexanet	Standard treatment
Hemostasis efficacy	67%	53,1%
Xa activity reduction	94,5%	26,9%
Thrombotic events	10,3%	5,6%
Ischemic stroke	6,5%	1,5%

- Better hemostasis control, but with no differences in the results at discharge vs. PCC[8].

CURRENT RESEARCH STRATEGIES

- Ciraparantag
- FXa variants

KEY MESSAGES:

- **DOAC reversion must consider both targeted drugs and clear stepped institutional strategies.**
- **Ciraparantag offers a promising option as a multi-specific reverter, although it clinical role is still under study.**
- **Designing rapid-action algorithms and setting up clinical teams are cornerstones for the modern management of bleeding under direct anticoagulation.**

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2. FACTOR XIII

Elisabeth Adam

FXIII is a thrombin-activated transglutaminase, and it is essential for clot stability, increasing its rigidity and providing resistance to proteins, as well as for wound healing[9]. FXIII not only stabilizes coagulation, but it also protects, repairs, and heals.

There are two types of FXIII deficiency (FXIII activity < 70%)[10,11]:

Congenital	Acquired
Homozygotes • 1-3 cases / 4 million • Experience bleedings **Heterozygotes** • 1 case / 1000 • Normally asymptomatic	1 case / 1000 **Causes:** • Burned/large wounds • Surgeries and polytrauma • Disseminated intravascular coagulation and sepsis • Liver parenchyma lesion / Cirrhosis • Cancer • Hematological / autoimmune diseases • Inflammatory bowel disease

It has been observed that FXIII availability per generated thrombin unit is significantly lower in patients with bleeding before, during, and after surgery[12], and that cancer patients with a high risk of intraoperative hemorrhage treated with FXIII during surgery experience less blood loss and use of fibrinogen than those treated with placebo[13].

FXIII deficiency often goes unnoticed, and standard analysis are not enough[14].

Quantitative tests (ELISA, chromogenic tests) are required to specifically determine FXIII deficiency.

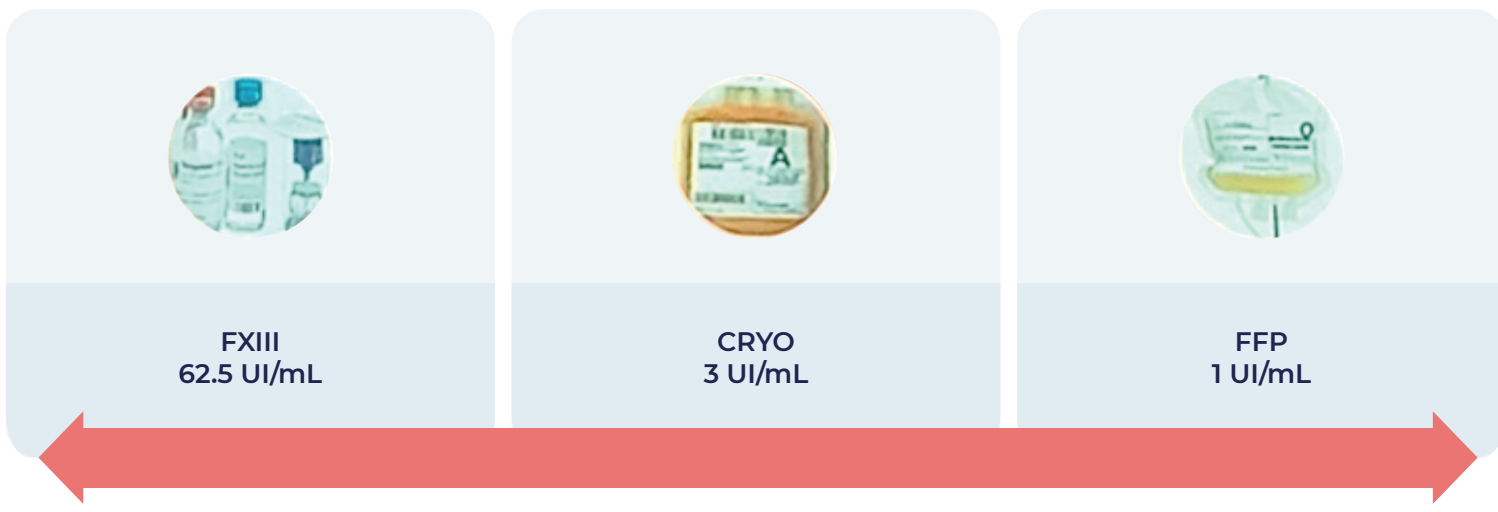
Standard coagulation tests	Many patients will present normal international normalized ratio (INR) and activated partial thromboplastin time (aPTT).
Viscoelastic tests	ROTEM, TEG, ClotPro may show FXIII deficiency, through the reduction of the clot rigidity, but they are not specific for FXIII determination.
Qualitative trials	A clot solubility test may be used, but the specificity is only shown in case of severe deficiency.

The *European Society of Anaesthesiology and Intensive Care* (ESAIC) suggests monitoring the FXIII and correcting the deficiency in case of a continuous hemorrhage not responding to the multimodal coagulation therapy or in critical patients presenting cicatrization defects (2C)[15].

- However, the use of FXIII is considered off-label in several settings, and it is indicated according to clinical judgment.
- Activity levels at which it should be administered vary between different authors, and a consensus is required on the desired levels[15,16].
- An FXIII concentration <60-70% may affect clinical results in trauma, surgery, and wounded patients.

FXIII DOSING:

10-40 UI/kg (20 UI, if tests cannot be performed and it is an empirical treatment). Considering FXIII concentration in each one of the available products, it makes sense to administer FXIII concentrate.



In summary, conducting tests and administering FXIII should be considered in high-risk patients.

KEY MESSAGES:

- **FXIII is essential for clot stability, but it is rarely assessed.**
- **FXIII deficiency should be suspected in persistent bleeding with normal hemostasis studies.**
- **Targeted replacement may have a relevant impact in complex hemorrhage contexts.**

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3. OLD AND NEW FIBRINOLYSIS INHIBITORS

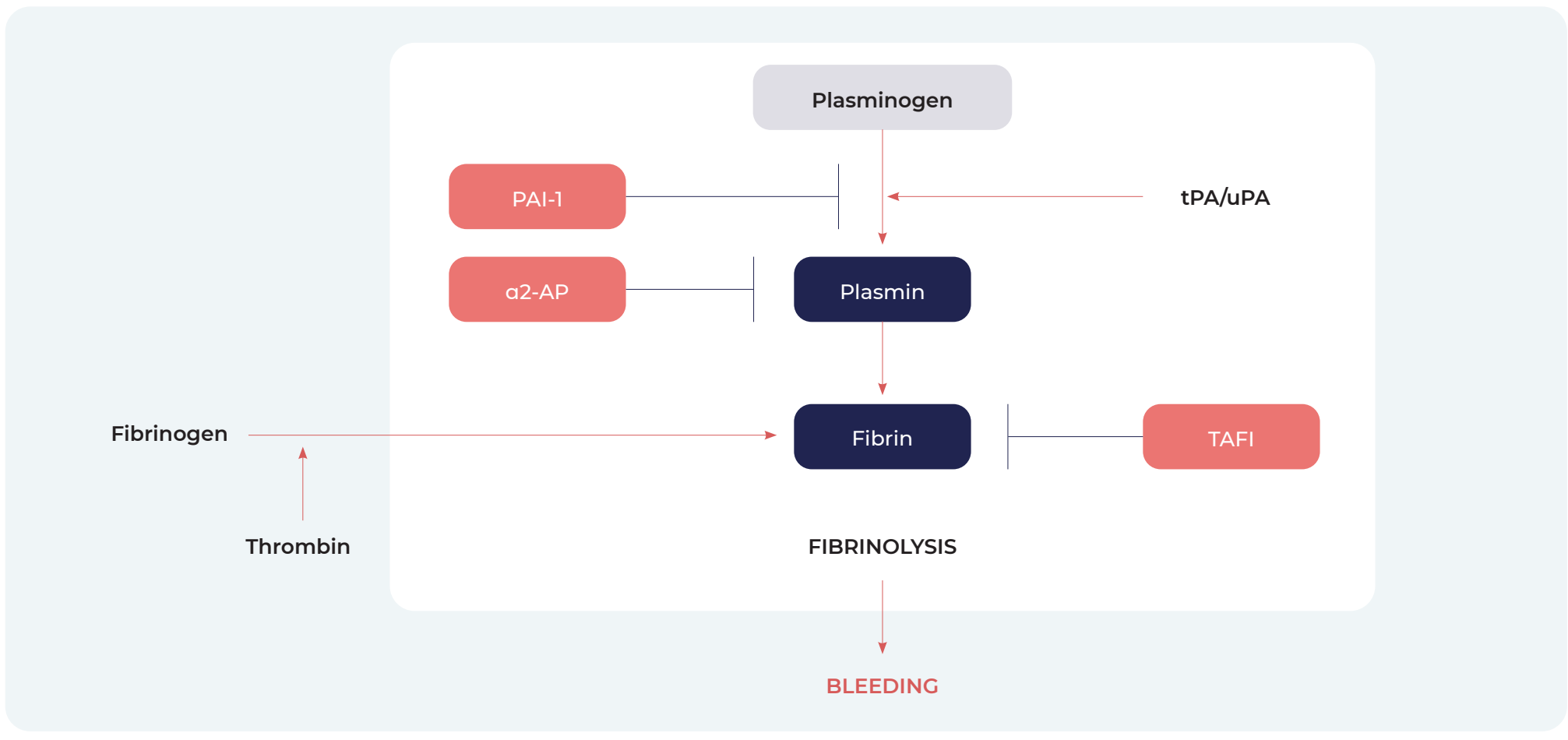
José Antonio Paramo

Acute hemorrhages are a significant health problem[17,18]:

Uncontrolled hemorrhage causes over a quarter of injury-related deaths and over 40% of post-injury deaths

Postpartum hemorrhage is still a frequent obstetric emergency and the main cause of maternal mortality worldwide

Hyperfibrinolysis appears as a result of an unbalance between pro- and antifibrinolytic molecules (due to situations such as surgery, trauma or delivery), and it can produce potentially-lethal hemorrhages in surgical and medical settings.



Antifibrinolytic agents used so far:

Aprotinin	Bovine pulmonary tissue isolate protein.
Tranexamic acid	Synthetic lysine analogue.
Aminocaproic acid	Synthetic lysine analogue.

TRANEXAMIC ACID

Tranexamic acid blocks plasminogen lysine binding sites, and thus it inhibits binding to fibrin and activation of plasminogen to plasmin. It also reduces fibrinolysis and stabilizes the clot[19].

Indications[20–22]:

- Trauma
- Postpartum hemorrhage
- Major surgery

Non-recommended use in[23]:

- Prevention of postpartum hemorrhage
- Gastrointestinal or intracranial hemorrhage
- Traumatic brain injury

Therefore, further safe antifibrinolytics need to be approved to manage patients with major bleeding.

CM-352

CM-352 is a new molecule with a new mechanism of action (pan-MMP inhibitor) that inhibits fibrinolysis and proteolysis[24,25].

0.7 nM concentration → 50% delay in lysis time[26]

T1/2 = 1,4 h → It allows effect regulation during infusion[26]

PRECLINICAL RESULTS:

- Significant reduction of bleeding time compared to control and to tranexamic acid and aprotinin, in a hyperfibrinolytic model[26].
- Significant reduction of blood loss compared to control in a hepatectomy model, whereas tranexamic acid and aprotinin cannot get there[26].
- Reduction of hematoma expansion and lesion volume after 3 and 24 hours in an intracranial hemorrhage model, both with early (1 hour) and late (3 hours) administration[27].
  - Reduction of sensorimotor development
  - Reduction of neurological deficit
- Very effective in controlling rivaroxaban-related intracranial hemorrhage[27].
- Reduction of the number of neutrophils in the hemorrhage area[27].

In summary, CM-352 presents a great bleeding control potential in surgical and medical settings, including intracranial hemorrhage cases.

KEY MESSAGES:

- **Tranexamic acid is effective, but not universally applicable or risk-free.**
- **New antifibrinolytics seek more molecular specificity with less toxicity.**
- **Fibrinolytic phenotype identification will be key for hemostasis personalized medicine.**

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