

Factor Concentrates in the Perioperative Management of Coagulopathy

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Speakers

Donat R Spahn

University and University Hospital Zurich, Switzerland

Jerrold H Levy

Duke University Medical Center, Durham, NC, USA

Marco Ranucci

IRCCS Policlinico San Donato, Milan, Italy



Donat R Spahn
Professor
Institute of Anaesthesiology
University and University Hospital
Zurich
Zurich, Switzerland

Donat.Spahn@usz.ch

Pathophysiology of Trauma and Revised European Trauma Guidelines

The fifth edition of the European Trauma Treatment Guidelines that have already been cited 1650 times and downloaded from the original home page nearly 600,000 times.

The European trauma treatment guidelines have significantly changed the treatment modalities of trauma patients around the world. The guidelines have also been endorsed by major European professional societies including European Society of Anaesthesiology (ESA), European Society of Intensive Care Medicine (ESICM), European Shock Society (ESS), European Society for Trauma and Emergency Surgery (ESTES), European Society for Emergency Medicine (EuSEM), Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA). There is, therefore, profound consensus with respect to these guidelines.

This updated version of the guidelines considers all the scientific evidence that has been produced during the last three years as well as evidence from current clinical practice. The existing suggestions and recommendations were revised by a group of experts, mainly delegates of European professional societies.

In the fifth version, there is more elaboration on the pathophysiology of trauma-induced coagulopathy. The organisation of the guidelines reflects the decision-making process along the patient pathway and less the treatment modalities. There are now nine chapters which are comparatively more patient and problem-oriented. The former chapter on resuscitation measures has been reorganised into three separate chapters (Chapters VI, VII, VII). **Table 1** outlines the major issues/topics discussed in the new chapters (Spahn et al. 2019).

Key Recommendations in the Revised Guidelines

Some of the key recommendations in the revised guidelines include the following (Spahn et al. 2019):

- Routine practice should include the early and repeated monitoring of haemostasis, using either a combined traditional laboratory determination [prothrombin time (PT), platelet counts and fibrinogen] and/or point-of-care (POC) PT/international normalised ratio (INR) and/or a viscoelastic method (VEM). As per the new addition, laboratory tests are graded equally to the VEM test, and the Activated Partial Thromboplastin Time (APTT) is deleted because it is unspecific and does not offer any interpretation in the context of major trauma. Also, early and repeated are both very important terms in this recommendation because it is important to get an idea about the problem early on in order to determine whether it has been treated or whether there is a need for a second round of treatment with the same or with other treatment modalities.
- Patients treated or suspected of being treated with anticoagulant agents should be screened.
- Tranexamic acid (TXA) should be administered to the trauma patient who is bleeding or at risk of significant haemorrhage as soon as possible and within 3h after injury at a loading dose of 1g infused over 10 minutes, followed by an IV infusion of 1g over 8 hours. This is still in place as the last version.
- Protocols for the management of bleeding patients should consider the administration of the first dose of TXA en-route to the hospital. The important thing is to give it as early as possible.
- The administration of TXA should not await results from a viscoelastic assessment. It should always be given and it should be given as early as possible.
- In the initial management of patients with expected massive haemorrhage, it is recommended that one of the two following strategies should be followed:
 1. FFP (fresh frozen plasma) or pathogen-inactivated FFP in an FFP:RBC (red blood cells) ratio of at least 1:2 as needed.
 2. Fibrinogen concentrate and RBC.
- As per the revised guidelines, both measures are graded equally and should be determined based on a goal-directed strategy.
- Resuscitation measures should be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM.
- Treatment with fibrinogen concentrate or cryoprecipitate should be initiated if major bleeding is accompanied by hypofibrinogenaemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤ 1.5 g/L).
- Reversal of the effect of antithrombotic agents in patients with ongoing bleeding is recommended. The need for reversal should be weighed against the prothrombic state of the patient. This is because patients taking antithrombotic medications have an

• Chapter VI: Further goal-directed coagulation management

- Goal-directed therapy (R25)
- FFP-based strategy (R26)
- CFC-based management (R27), including the use of FXIII
- Fibrinogen supplementation (R28)
- Platelet administration (R29)
- Calcium (R30)
- rFVIIa (R31)

• Chapter VII: Reversal of antithrombotic agents

- Monitoring and treatment (VKA and DOACs: R33, R34, R35)
- Monitoring and treatment of trauma patients who are being treated with platelet inhibitors (R36)

• Chapter VIII: Thromboprophylaxis

- Recommendation for the prophylactic prevention of thromboembolic complications (R37) in major trauma patients
- Which is increasingly recognised as important, particularly in patients treated prior to traumatic injury with oral anticoagulants and/or platelet inhibitors

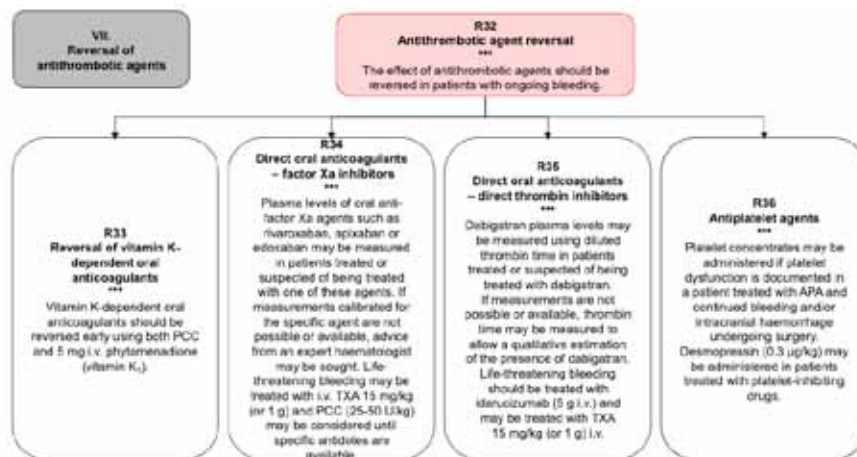
• Chapter IX: Guideline implementation and quality control

- Encouragement of local implementation (R38) of evidence-based guidelines for the management of the bleeding patient following traumatic injury
- Local quality and safety management systems (R39) specifically assess key measures of bleeding control and outcome

Table 1. New Chapters in the Fifth Version of the European Trauma Treatment Guidelines (Spahn et al. 2019).

underlying thrombotic risk. Full reversal of the anticoagulant is only justified if there is life-threatening bleeding (ema.europa.eu/en/medicines/human/summaries-opinion/ondexxya). This is a new chapter in the guidelines, details of which are outlined in **Figure 1** (Spahn et al. 2019).

- Appropriate thromboprophylaxis should be initiated as soon as possible after bleeding has been controlled.
- In the bleeding trauma patient, the emergency reversal of vitamin K-dependent oral anticoagulants is recommended with the early use of both prothrombin complex concentrates (PCC) and 5mg IV phytonadione (vitamin K1).
- Measurement of plasma levels of oral direct



anti-factor Xa agents such as apixaban, edoxaban, or rivaroxaban should be done in patients treated or suspected of being treated with one of these agents.

- Measurement of anti-Xa activity should be calibrated for the specific agent. If measurement is not possible or available, advice from an expert haematologist should be sought.
- If bleeding is life-threatening, TXA 15 mg/kg (or 1g) should be administered intravenously, and the use of PCC (25-50 U/kg) be considered until specific antidotes are available.
- Dabigatran plasma levels should be measured using diluted thrombin time in patients treated or suspected of being treated with dabigatran.
- If measurement is not possible or available, standard thrombin time should be measured to allow a qualitative estimation of the presence of dabigatran.
- If bleeding is life-threatening in those receiving dabigatran, patients should be treated with idarucizumab (5g intravenously) and with TXA 15 mg/kg (or 1 g) intravenously. ■

Abbreviations

APTT	activated partial thromboplastin time
FFP	fresh frozen plasma
INR	international normalised ratio
PCC	prothrombin complex concentrates
PCC	point-of-care
PT	prothrombin time
RCB	red blood cells
TXA	tranexamic acid
VEM	viscoelastic method

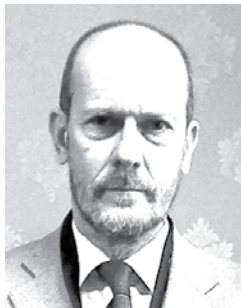
Key Points

- Injured patients should be transported quickly and treated by a specialised trauma centre whenever possible
- Measures to monitor and support coagulation should be initiated as early as possible and used to guide a goal-directed treatment strategy
- A damage control approach to surgical intervention should guide patient management
- Coagulation support and thromboprophylactic strategies should consider trauma patients who have been pre-treated with anticoagulants or platelet inhibitors
- Local adherence to a multidisciplinary, evidence-based treatment protocol should serve as the basis of patient management and undergo regular quality assessment

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**Marco Ranucci**

Director of Clinical Research
Department of Cardiothoracic
and Vascular Anesthesia and
Intensive Care
IRCCS Policlinico San Donato
Milan, Italy

marco.ranucci@grupposando-
nato.it

Coagulopathy During Cardiac Surgery: The Role of Factor Concentrates

The EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery.

The EACTS/EACTA guidelines were published jointly by the Society of Cardiothoracic Anesthesia and Cardiac Surgery for patient blood management. In the bleeding patient with a low fibrinogen level (<1.5 g/L), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions. However, the prerequisite is a bleeding patient. In patients where bleeding is related to coagulation factor deficiency, prothrombin complex concentrates (PCC), or fresh frozen plasma (FFP) administration should be considered to reduce bleeding and transfusions (Boer et al. 2017).

As far as clinical evidence is concerned, there is conflicting data with respect to fibrinogen supplementation. In a study conducted about four years ago, patients were randomised to receive either fibrinogen or placebo. This was a non-pragmatic trial conducted in an artificial environment where patients that had bleeding due to other reasons were excluded. The goal was to demonstrate that a first-line fibrinogen supplementation would avoid the need for FFP and would reduce the need for any kind of transfusions. The primary endpoint was achieved (Figure 1), and the group treated with fibrinogen had zero need for FFP or platelets (Ranucci et al. 2015).

However, the Randomized Evaluation of Fibrinogen vs. Placebo in Complex Cardiovascular Surgery (REPLACE) study provided different results. Fibrinogen administration resulted in higher reduction of bleeding (Figure 2). Medication was administered to patients with a 5 minute bleeding mass of 60-250g after separation from bypass and

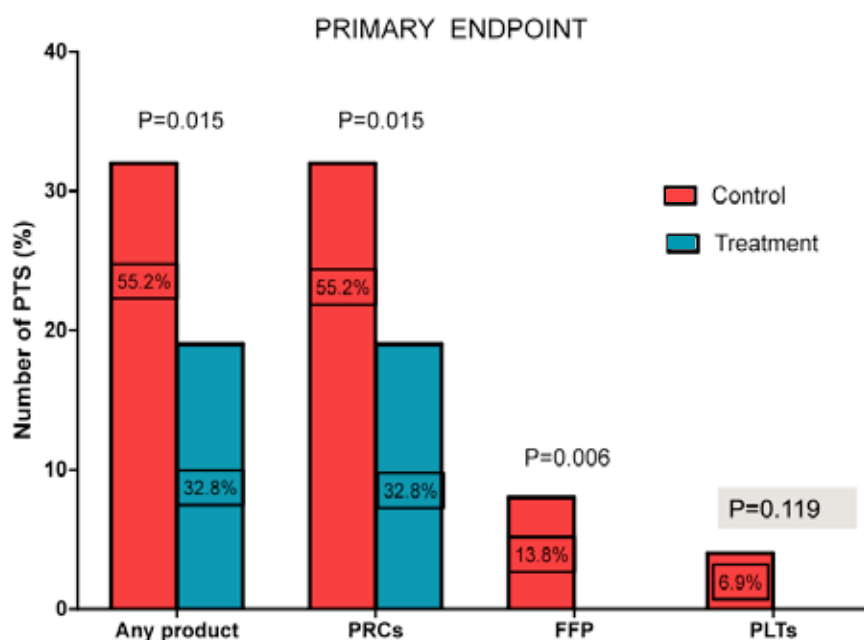


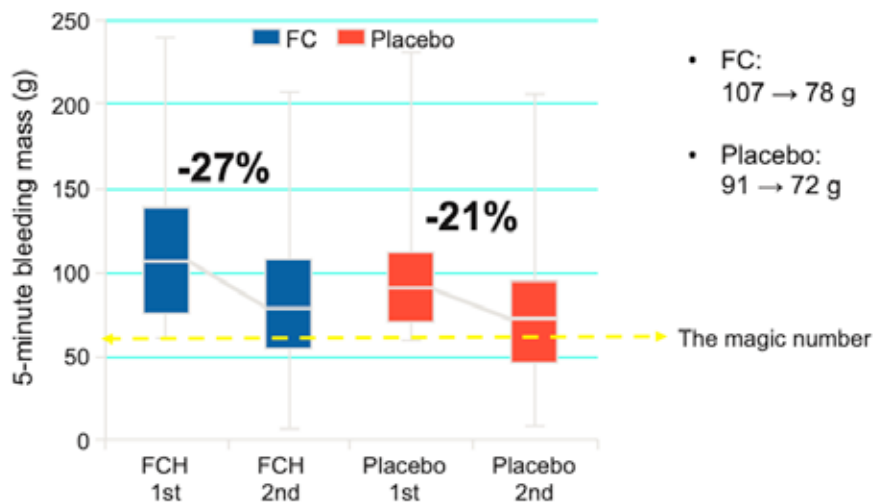
Figure 1. Fibrinogen Concentrate Supplementation After Complex Cardiac Surgery (Ranucci et al. 2015)

surgical haemostasis. Study findings did not demonstrate a reduction in total units of allogenic blood products (ABP) [FFP, platelets, and/or RBCs] transfused over 24 hours with

in the bleeding patient with a low fibrinogen level, fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions

fibrinogen concentrate compared with placebo. Surprisingly, human fibrinogen concentrate was found to be associated with increased blood product transfusion compared to placebo (Rohe-Meyer N et al. 2016).

Yet another very well-designed study that focused on intraoperative bleeding showed different findings. Patients were randomised into two groups where they received an intravenous, single dose of fibrinogen concentrate or placebo. The primary outcome was blood loss between intervention and closure of chest. In patients with intraoperative bleeding during high-risk cardiac surgery, administration of fibrinogen concentrate resulted in no significant



Key Points

- FFP is a poor source of fibrinogen and prothrombin complexes
- Cryoprecipitate is a moderately good source of fibrinogen but has multi-donor risks
- PCC and fibrinogen are both elegant ways to replace FFP
- In the bleeding patient with a low fibrinogen level (<1.5 g/L), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions in bleeding patients with a low fibrinogen level
- PCC or FFP administration should be considered to reduce bleeding and transfusions when bleeding is related to coagulation factor deficiency

Figure 2: Fibrinogen administration resulted in higher reduction of bleeding [Rohr-Meyer N et al. 2016].

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difference in the amount of intraoperative blood loss compared to placebo (Bilecen S. et al. 2017). There was one problem, however. The window of observation of bleeding was incredibly short. The observation time of bleeding was six minutes. The control group bled 70 millilitres and the study group 50 millilitres.

Blood, Blood Products And Derivatives - Use In Trauma And Cardiac/ Liver Surgery

There are different solutions that are available for clinicians to reduce postoperative bleeding and transfusions. Here is a quick overview of the primary ones:

Fresh Frozen Plasma (FFP)

- Poor source of fibrinogen and prothrombin complexes
- Huge quantity needed
- Increasingly not considered the best product but still largely used
- Offers benefits whenever large volumes of fluids are required (e.g. in trauma patients)
- Very inexpensive

Cryoprecipitate

- Moderately good source of fibrinogen
- Limited volume overload

- Unavailable in many countries/hospitals but still largely used
- Multi-donor risks
- Probably will become less popular in the years to come

Prothrombin Complex Concentrate (PCCs)

- An elegant way to replace FFP
- Triggered by point-of-care haemostatic testing (POC) tests
- Associated with increased thromboembolic events and acute kidney injury (AKI)
- Effective but expensive
- Use likely to moderately increase in the years to come

Fibrinogen

- The main component of clot firmness
- Elegant way to replace FFP or cryoprecipitates
- Triggered by POC (mainly rotational thromboelastometry)
- Not associated with increased thromboembolic events
- Effective but expensive
- Dose unclear (both target concentration and dose calculation)

Therefore, to answer the question as to when to supplement with fibrinogen, the guidelines recommend that in the bleeding

patient with a low fibrinogen level (<1.5 g/L), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions. In patients where bleeding is related to coagulation factor deficiency, PCC, or FFP administration should be considered to reduce bleeding and transfusions. ■

Abbreviations

ABC	allogenic blood products
AKI	acute kidney injury
FFP	fresh frozen plasma
PCC	prothrombin complex concentrates
PLT	platelets
RBC	red blood cells

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Jerrold Levy
Professor of Anesthesiology
Professor of Surgery (Cardiothoracic)
Co-Director, Cardiothoracic ICU
Duke University School of Medicine
Durham, North Carolina
USA

jerrold.levy@duke.edu

@JerroldLevy

Treatment Options for Factor-Xa Inhibitor-Related Bleeding

Specific treatment options for factor Xa inhibitor-related bleeding, focusing on drugs like rivaroxaban, apixaban, and edoxaban.

Non-vitamin K oral anticoagulants (NOACs/DOACs) are direct reversible inhibitors of factor Xa. These drugs are also reversible inhibitors versus warfarin or other vitamin K antagonist that are used in Europe. Anticoagulants decrease circulating levels of factor II, VII, IX and X. In patients with acute bleeding, the concept of factor concentrates is to restore the levels of these agents. When a patient comes in on a NOAC and needs emergency surgery or is actively bleeding, two important questions must be asked. One is what's their renal function as it can have an impact on drug elimination, and the other is coagulation testing.

Measuring the effects of these new oral anticoagulants and nonvitamin K can be confusing for clinicians. There are some important caveats to consider (Heidbuchel H et al. 2013):

- Prothrombin time (PT)/ International normalised ratio (INR)/partial thromboplastin time (PTT) are relatively insensitive to the effects of anti-FXa agents and are reagent-dependent
- Normal PT and PTT do not rule out significant blood level of DOACs, especially anti-FXa agents
- In case of elevated PT, this may represent high blood levels of DOACs or coagulopathy

With respect to when to decide to potentially consider drug levels, it should be done:

- o If the patient is bleeding or there is a risk of potential overdose
- o In case of impaired renal or liver function
- o To evaluate for low level prior to surgery

Managing bleeding is important, and developing a bleeding, and therapeutic plan is critical. The two specific state of the art reversal agents (also called antidotes) that can be used to manage a major bleed include idarucizumab and andexanet. Andexanet reverses FXa inhibitors. Once bound to andexanet, inhibitors are unable to bind/inhibit FXa (Ansell 2013). Andexanet comes in vials that require mixing, and is given as a loading dose followed by an infusion of two hours. The drug effect on reversal is about three hours (Figure 1). A large study was conducted, which led to the drug's approval both in the U.S. and in Europe. However, it is important to note

bleeding and coagulopathy is a multi-modal defect that requires a multi-modal therapy

that there is no current surgical data supporting this particular use. The drug is approved for emergency medical bleeds only, in particular, intracranial haemorrhages. Of the 352 patients in the final New England Journal of Medicine study, 64% were intracranial hemorrhage, and about 26% were GI bleeds.

As demonstrated in **Figure 2**, anti-factor Xa activity among persons who had received anticoagulation treatment with apixaban or rivaroxaban was measured before and after the administration of andexanet or placebo on study day 4. Dashed lines indicate the end of administration of the bolus or infusion. Panel A shows data from participants in the apixaban study (ANNEXA-A) who received andexanet, as a 400-mg intravenous bolus, or placebo; Panel B participants in the rivaroxaban study (ANNEXA-R) who received andexanet, as an 800-mg intravenous bolus, or placebo; Panel

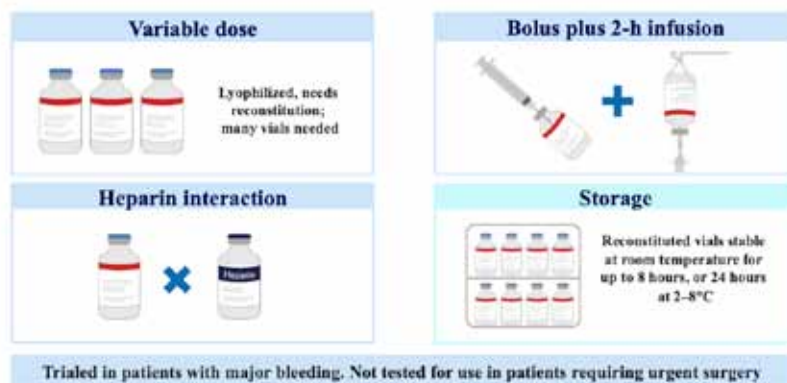


Figure 1. Andexanet Rx: IV load + infusion (Levy et al. 2018)

C participants in the apixaban study who received andexanet, as a 400-mg intravenous bolus plus a 4-mg-per-minute infusion for 120 minutes, or placebo; and Panel D participants in the rivaroxaban study who received andexanet, as an 800-mg intravenous bolus plus a 8-mg-per-minute infusion for 120 minutes, or placebo. Different scales along the x axis in each graph are used to enable visualisation of the immediate, short-term dynamics as well as the longer-term dynamics of anti-factor Xa activity after andexanet treatment. The points on the graph represent the mean anti-factor Xa activity level, and I bars indicate the standard error. There was a significant difference ($P < 0.05$) in the percent change in anti-factor Xa activity (relative to the pre-bolus activity level) between andexanet and placebo until 2 hours after administration of the bolus or infusion (Siegel et al. 2015).

As far as the use of prothrombin complex concentrates (PCC) is concerned, they have the potential to treat bleeding, but there is a lack of correlation between laboratory tests and bleeding or treat of anticoagulation. PCCs are used as part of an off-label multimodal approach with haemodynamic and haemostatic resuscitation (Zahir et al. 2014; Dickneite et al. 2014; Heidbuchel et al. 2015; Levy et al. 2014; Weitz et al. 2015; Levi et al. 2014; Brown et al. 2016).

One of the most important things to remember is that bleeding and coagulopathy is a multi-modal defect that requires a multi-modal therapy. PCCs and other factor concentrates should be part of this multi-modal strategy.

With respect to managing bleeding with DOACs, some important factors to consider and certain important elements to remember:

- How urgent/emergent is the bleeding
- Whether there is time to decide if drug levels are contributing
- Whether the patient needs procedural intervention for the bleed
- Standard coagulation tests should be performed with bleeding and followed
- Reversal strategies are part of a multi-modal strategy in addition to fixing the bleeding lesion
- Reversal agents will only remove the role of the anticoagulant
- Identify and take out the source while minimising the amount of blood loss
- Critically ill patients require haemodynamic and haemostatic resuscitation

Finally, it is important to develop institution-wide protocols for emergencies. Also, it must be noted that reversal of anticoagulation does not always mean improved clinical outcomes because patients bleeding are already at great risk for adverse outcomes (Crowther et al. 2016). ■

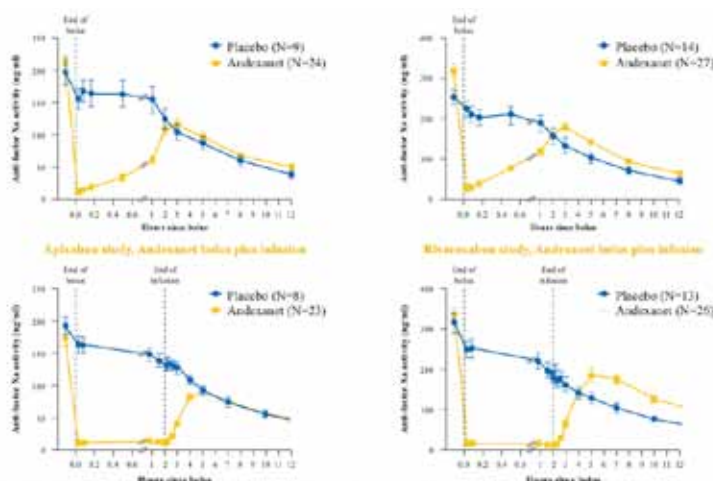


Figure 1. Time Courses of Anti-Factor Xa Activity before and after Administration of Andexanet (Siegel et al. 2015). Reprinted with permission from Massachusetts Medical Society

Key Points

- Managing bleeding is important, and developing a bleeding, and therapeutic plan is critical.
- Two of the state of the art reversal agents that can be used to manage a major bleed include idarucizumab and andexanet.
- PCCs can be used as part of an off-label multimodal approach with haemodynamic and haemostatic resuscitation.
- Reversal of anticoagulation does not always mean improved clinical outcomes because patients bleeding are already at great risk for adverse outcomes.

Abbreviations

NOAC	non-vitamin K oral anticoagulants
DOAC	direct oral anticoagulants
INR	international normalised ratio
PCC	prothrombin complex concentrates
PT	prothrombin time
PTT	partial thromboplastin time

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