



**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.

**N**on-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:

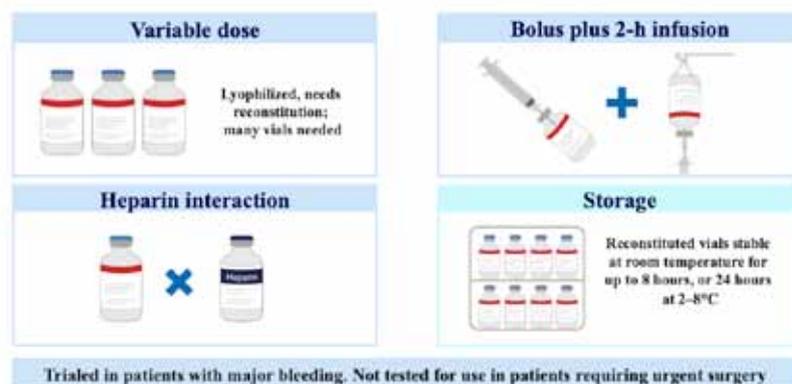
- o If the patient is bleeding or there is a risk of potential overdose
- o In case of impaired renal or liver function
- o To evaluate for low level prior to surgery

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

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

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



**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).

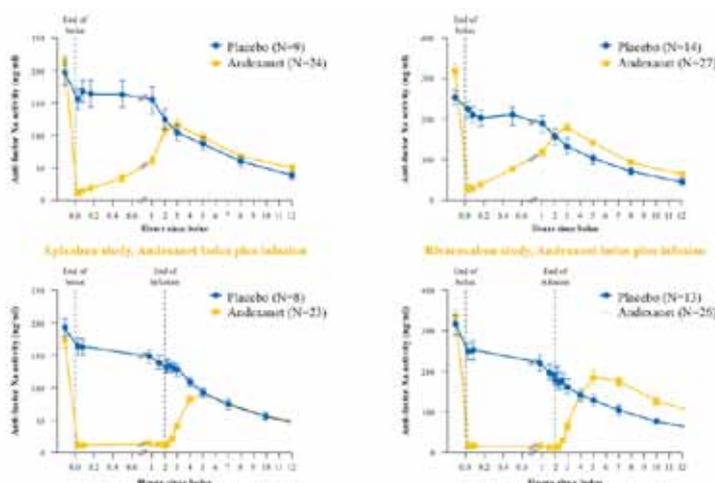
As far as the use of prothrombin complex concentrates (PCC) is concerned, they have the potential to treat bleeding, but there is a lack of correlation between laboratory tests and bleeding or treat of anticoagulation. PCCs are used as part of an off-label multimodal approach with haemodynamic and haemostatic 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 2.** 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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