



EM CASES SUMMARY

Episode 89 – DOACs Part 2: Bleeding and Reversal Agents

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In this episode we discuss how to weigh the risks and benefits of stopping the DOAC, when reversal of the DOAC is advised, how best to accomplish the reversal, the evidence for the newest reversal agent and when we should and should not stop DOACs for different procedures.

Three categories of illnesses for bleeding risk in patients taking DOACs

It is helpful to divide patients in to low, moderate and high risk for poor outcomes from bleeding when considering whether to hold or stop DOACs.

Low Risk: Bleeding where there is easy access to local bleeding control measures such as epistaxis and hemorrhoidal bleeding

Moderate Risk: Stable GI bleed

High Risk: Intracranial bleed, unstable GI bleed, bleeding into a closed space (eye, spinal cord, pericardium)

Case 1: Low Risk Bleed

“Treat local problems with local solutions”

An 89 year-old man with a history of atrial fibrillation and TIA on a DOAC for stroke prevention comes in with a few hours of brisk epistaxis that isn't controlled with local pressure. You try some of the usual local maneuvers but the bleeding continues. His hemoglobin is normal.

Would you stop the DOAC? Would you reverse the DOAC?

Holding 1-2 doses of DOAC is akin to giving vitamin K to a warfarin-treated patient as vitamin K takes approximately 6-12 hours to take effect, similar to the time it takes for the anticoagulation effect of DOACs to wear off.

Our experts recommend *not* stopping the DOAC in this case, as the patient likely has a high CHADS2 score and the increased risk of cardioembolic stroke would likely outweigh the risk of complications of the anticoagulation effect of the DOAC. Efforts to stop the bleeding should be centered on employing local methods such as wrapping a tampon in gelfoam or surgicel, a nasal balloon, apply ice to the palate (popsicles, ice in the mouth) which has been shown to reduce nasal blood flow up to 25%.

For epistaxis, tonsillar or oral bleeding consider local application of 5% oral tranexamic acid solution (25mg of IV tranexamic acid) in addition to your local measures (soak gauze or surgical or gelfoam in this solution and directly apply or swish and spit).

Go to [Episode 38: ENT Emergencies Pearls Pitfalls and Tricks](#) for step by step management of epistaxis

Case 2: Moderate Risk Bleed

A 42 year-old woman who was told by her internist that she would be on a DOAC for life after being diagnosed with a pulmonary embolism six months prior comes into your ED with a one day history of hematochezia and no other symptoms. Her vitals are normal, there is a small amount of bright red blood on rectal exam and her hemoglobin comes back a bit low.

Would you stop the DOAC? Would you reverse the DOAC?

Our experts recommend *not* stopping the DOAC in this case, monitoring the patient carefully, admitting them to hospital, repeating the hemoglobin and arranging endoscopy. The risk of life-threatening or life-altering pulmonary embolism for this patient not being anticoagulated outweighs the risk of serious complications from the GI bleed.

Indications for consideration of reversing the anticoagulant effects of DOACs

1. Intracranial hemorrhage
2. Hemodynamically unstable GI bleed not controlled by endoscopy or interventional radiology

3. Bleeding into an enclosed, fixed space (intraocular, pericardium, spinal cord)
4. Failure of local measures and ongoing bleeding
5. Emergency surgery necessary for aortic dissection or aneurysm repair

Management of non-traumatic hemorrhagic shock in patients taking DOACs

The most important principle to remember in the management of hemodynamically unstable patients who are bleeding and taking DOACs is that reversing or withholding a DOAC does not stop bleeding, but rather, returns the patient to an un-anticoagulated state. It is therefore imperative that resuscitative measures to stop the bleeding are taken as a priority over reversing the DOAC.

1. Maintain a good **urine output** because DOACs are excreted renally (especially dabigatran and rivaroxaban).
2. Use all the usual **local measures**.
3. **Call for help** early – interventional radiology, ICU, hematology, for GI bleed call GI for early endoscopy.
4. This is not the time to get too obsessed with a restrictive policy for **red cell transfusion** (in the event of major bleeding); if massive bleeding > 5 units in 3 hrs and ongoing: begin your institutional **massive transfusion protocol** and don't forget the cryoprecipitate after 10 units of blood if the fibrinogen is low.
5. Activated **charcoal 1g/kg** if DOAC taken in within 1-2 hours or for massive intentional overdose and the patient is protecting their airway.

Another important consideration is the **time of last ingestion** of the DOAC. If it was more than 12-14hrs, then the anticoagulation effects have likely worn off and reversal is likely unnecessary.

Reversing the anticoagulant effects of DOACs

The reversal of DOACs is different depending on the specific DOAC. The following recommendations are based on expert opinion taking into account the paucity of evidence on this topic.

For Xa inhibitors apixaban or rivaroxaban

First line: 4-factor PCC (Octaplex, Beriplex) at a dose of 50 IU/kg up to 2,000 units.

Note that if you highly suspect a Xa inhibitor head bleed *before* obtaining a CT head, it is reasonable to give 1,500 units of 4 factor PCC on spec.

Second Line: *Tranexamic acid*, 1 gm over 10 minutes and then 1 gm over the next 8 hrs if 4-factor PCC is ineffective.

For Dabigatran

First Line: Idarucizumab (Praxbind)

Idarucizumab (Praxbind): Antidote for Dabigatran

Idarucizumab is a monoclonal antibody that works immediately to reverse bleeding parameters.

Dose: 5 gm IV over 15 minutes

Cost: wholesale cost in U.S is \$3500

The *REVERSE-AD study* from NEJM included 90 patients with either a major bleed or having to undergo emergency surgery. Almost all of the patients were taking dabigatran for atrial fibrillation. Reversal, as assessed by both the dilute thrombin time and ecarin clotting time within 4 hrs, was 100%. However, it took an average of 11.4 hrs to reach clinical hemostasis. For the subgroup that required emergency surgery, the majority of patients who were given idarucizumab had clinical hemostasis as assessed by the surgeon in the O.R.

Bottom Line: While *Idarucizumab* appears to reverse bleeding parameters effectively in patients taking Dabigatran, it's effectiveness in clinical outcomes have yet to be determined and their safety requires further study.

Idarucizumab is the best we've got.....so far.

Andexanet Alfa*: Antidote for Rivaroxiban and Apixaban

*not available in Canada as of this publication date

Andexanet Alfa is a decoy antigen; it competitively binds rivaroxaban and apixaban and is given as an ongoing infusion.

The Siegal et al article from NEJM enrolled 65 patients on Apixaban and 80 patients on Rivaroxiban. All of these patients were healthy volunteers given DOAC for 4 days followed by either Adexanet Alfa or placebo. The primary outcome a lab measure – anti factor Xa

activity was decreased by >90% in the DOAC groups compared to 45% in the placebo groups.

The Connolly et al article from NEJM was a prospective open label trial which included 67 patients with major bleeding on Apixiban or Rivaroxiban. All patients received Adexanet Alfa. There was no control group. 80% of patients had “good” or “excellent” hemostasis by 12 hours. However, remember that the half-life of these drugs is only about 6-12 hours. Thrombotic events occurred in 18% of patients. Mortality was 15%.

Bottom Line: We don’t know if Andexanet Alfa is clinically effective or safe. We need more robust clinical outcome data before we start to use Andexanet Alfa in the ED to reverse Xa inhibitors.

Periprocedural Management of DOACs

For patients taking DOACs whom you need to a procedure on, the approach stems from whether or not the procedure is low risk or high risk.

Case 3: To LP or not to LP

A patient on Apixiban post surgery for a femur fracture comes in with a rigors, headache and neck stiffness. He’s got jolt accentuation, a rigid neck and you think he might have the words bacterial meningitis written on his forehead. You order up 2g of Ceftriaxone and 1g of Vancomycin, and as you’re getting set up for the LP you pause because your resident asks you if it’s okay to do the LP if the patient is on Abixiban.

Would you do an LP on this patient in the ED?

The simple answer is no. Bleeding into a closed space such as the spinal epidural space is a real risk and can be devastating.

High risk procedures for patients on DOACs include non compressible areas including LP and subclavian central line.

Low risk procedures for patients on DOACs include paracentesis, thoracentesis and non-subclavian central line.

The **skill of the operator** is the number one predictor of bleeding complications for these procedures, so be sure that the provider with the best skills does the procedure.

Periopertative Management of DOACs

For major surgery it is normally recommended to stop DOACs 2 days before surgery (i.e. skip 2 doses), which corresponds to approximately 4-5 half-lives elapsed between stopping the DOAC and surgery, assuming normal renal function. However, for patients needing to go for emergency surgery – reverse them, but only if it’s a true emergency surgery. Reversal should not be used for patients who require a non-emergent operation just to speed up the time to surgery.

Dose reduction for older patients taking DOACs for stroke prevention in atrial fibrillation

Apixiban

The dose of Apixiban should be reduced from 5 mg bid to 2.5 mg bid in patients with 2 of 3 of the following characteristics:

1. serum creatinine \geq 133 $\mu\text{mol/L}$
2. age \geq 80 years or
3. body weight \leq 60 kg

Dabigatran

The dose of Dabigatran should be reduced from 150 mg bid to 110 mg bid in patients aged 80 years and older, or over 75 years old with 1 risk factor for bleeding.

Rivaroxiban dose not require dose adjustment in the elderly and should be given as 20 mg daily.

It is important to remember that DOAC dosing for venous thromboembolism is fixed and no dose reduction is required in older patients.

For calculating DOAC dosing on shift taking into account patient age, renal function and weight try the [Thrombosis Canada app](http://thrombosiscanada.ca/?page_id=245) http://thrombosiscanada.ca/?page_id=245

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