NATIONAL NURSE PRACTITIONER SYMPOSIUM

Anticoagulation Reversal

Janhavi Athale, MD
Critical Care and Hematology/Oncology Departments
Mayo Clinic Arizona

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DISCLOSURES

- No Financial Disclosures
- Non-FDA approved use of medications in this case will be discussed and outlined as such

LEARNING OBJECTIVE

- Review the options available for anticoagulation and their indications
- Discuss reversal strategies with risks and benefits
- Discuss agents used in Heparin-induced thrombocytopenia (HIT) and reversal options, including when not to reverse with concern for thrombosis in hypercoagulable patients.

CASE 1

- A 74yo patient with DM, HTN and chronic A fib ($CHADS_2$ 5) on dabigatran is admitted to the ICU with abdominal sepsis. On admission, his WBC is 23K with L shift, Cr 2.1, lactate 2.6 with normal LFTs. CT with nonspecific thickening of the duodenum with fat stranding, and the patient was scheduled for an EGD.
- The patient deteriorated overnight despite fluids and antibiotics and was started on vasopressors. Abdominal exam with worsening tenderness and guarding. Repeat labs: WBC 31.4K, Hgb 8.5g/dL, platelets 145K, and Cr 2.5. CXR with pneumoperitoneum and general surgery is consulted for an ex-lap. It has now been 18hr since the patient's last dose of dabigatran.

CASE 1 (A)

- Which lab test is most suggestive of ongoing dabigatran effect

A) Prolonged INR/PT
B) Prolonged APTT
C) Prolonged TT (thrombin time)
D) Prolonged Anti-Xa

CASE 1 (B)

- What is the most appropriate treatment to reduce the risk of serious bleeding during surgery?

A) Idarucizumab
B) Andexanet
C) Novo-7
D) Prothrombin complex concentrate

CASE 1 (C)

•After surgery and idarucizumab (5mg), the patient continues to bleed, and after careful consideration received a second dose. His TT remains prolonged and in the setting of ongoing bleeding, what is the best next step.

A) Administration of PCC
B) Administration of cryoprecipitate
C) Administration of FFP
D) Initiation of dialysis

NOACS REVERSAL GUIDELINES

EXAMPLE of a "Serious Bleeding on NOAC PROTOCOL"

General Measures

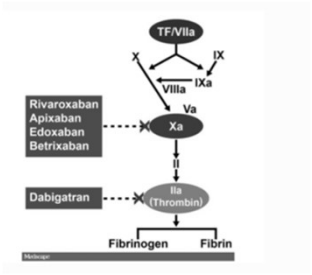
- mechanical compression if possible
- two sites of IV access
- determine timing of last NOAC dose
- CBC, BUN, Creatinine, liver enzymes
- plasma expanders/PRBC's as necessary
- consider activated charcoal if NOAC ingestion <2hours
- notify on-call hematologist
- Refer to chart below for specific measures

NOAC	Blood tests for NOAC presence or effect	Specific Antidote	Alternative Treatments Options
Dabigatran	PTT , TT	Idarucizumab 5 grams IV (2 infusions of 2.5 grams)	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV Hemodialysis
Rivaroxaban	Anti-Factor Xa	Andexanet Alfa	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Apixaban	Anti-Factor Xa	Andexanet Alfa	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Edoxaban	Anti-Factor Xa	Andexanet Alfa	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV

TT = thrombin time, PTT = partial thromboplastin time, PCC = prothrombin complex concentrate

Raval AN et al. Circulation. 2017;135:e604–e633

NOACS AND THE CLOTTING CASCADE



https://coreem.net/journal-reviews/idarucizumab/

FDA APPROVED INDICATIONS OF DOACS

DRUG	Non-valvular Afib	VTE	Reduction of Risk of VTE	Ppx after Ortho surgery	Ppx during hospitalization
Dabigatran	Y	Y	Y	Y/N	N/A
Apixaban	Y	Y	Y	Y	N/A
Edoxaban	Y	Y*	N/A	Y/N	N/A
Rivaroxaban	Y	Y	Y	Y	N/A
Betrixaban	N/A	N/A	N/A	N/A	Y

* following 5 to 10 days of initial therapy with a parenteral anticoagulant

Verma A et al. JAMA Surg. 2018. 153(6): 577-585

TIMELINE OF APPROVAL

DABIGATRAN

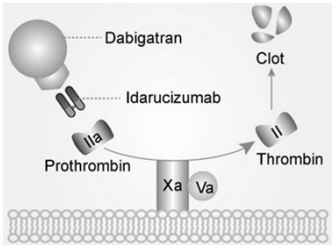
•Oral Direct Thrombin Inhibitor

•Reversed with Idarucizumab (Praxbind): humanized monoclonal Ab with very high affinity for dabigatran and its metabolites

•Neutralization within minutes, and can consider re-dose

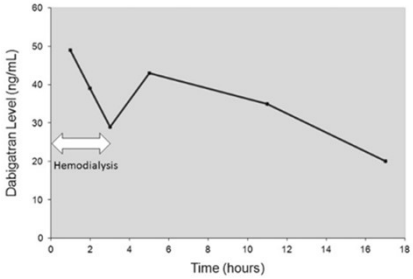
Schiele F, et al. Blood. 2013.121(18): 3554-3562

MECHANISM OF ACTION



https://www.creativebiolabs.net/idarucizumab-overview.htm

DABIGATRAN AND DIALYSIS



Chang DN *et al*. American Journal of Kidney Diseases. 2013. 61 (3): 487-489

ORAL XA INHIBITORS

- Work by blocking Factor X
- Andexanet alfa: a recombinant modified version of human activated factor X (FXa) which acts as a decoy receptor
- Dosing depends on timing of NOAC use

ANDEXANET ALPHA

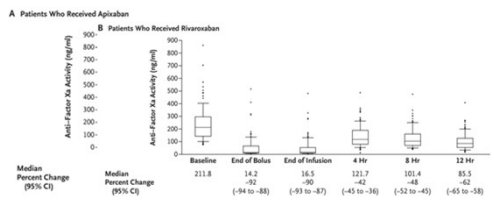
Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose			
FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation	
		<8 Hours or Unknown	≥8 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg or unknown	High dose	

Low dose: 400 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 4 mg/minute for up to 120 minutes

High dose: 800 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 8 mg/minute for up to 120 minutes

- Low Dose: 400mg bolus, 480mg follow-on
- High Dose: 800mg bolus, 960mg follow-on

ANNEXA-4 TRIAL



Connolly SJ *et al*. NEJM. 2019. 380:1326-1335

2020 30;18(

COMPLICATIONS OF ANDEXANET-ALFA

- In addition to sequestering factor Xa inhibitors rivaroxaban and apixaban, it also inhibits the activity of Tissue Factor Pathway Inhibitor, increasing tissue factor-initiated thrombin generation.
- Incidence of thrombosis of 16-20% (post-hoc analysis including arterial thromboses)

Connolly SJ *et al*. NEJM. 2019. 380:1326-1335

Barra ME *et al*. J Thromb Haemost. 2020.18:1637-1647

Jan-Dec 2021

ANDEXANET ALFA VS. PCC FOR REVERSAL

- Consider underlying reason for anticoagulation (hypercoagulable state)
- Retrospective study assessed 32 patients who received either andexanet alfa or 4-factor PCC:
  - Equivalent time to hemostasis, and interestingly equivalent thromboembolic events and overall mortality.

Stevens VM *et al.* Clin Appl Thromb Hemost. 2021. 27

ANDEXANET ALFA VS. PCC FOR REVERSAL

- Several studies looked at outcomes in ICH
- A recent retrospective study of 44 patients w/ ICH (16 traumatic and 28 spontaneous):

	Andexanet Alfa (n = 28)	PCC (n = 16)	P value
CT stability at 6 hrs	21 (78%)	10 (71%)	0.71
CT stability at 24 hrs	15 (88%)	6 (60%)	0.15
Good mRS on discharge	10 (36%)	6 (38%)	0.81
Thromboembolic events	2 (7%)	0 (0%)	0.53

Ammar AA *et al.* Neurocrit Care. 2021. 35: 255-261

FACTOR REPLACEMENT PRODUCTS

- PCC:
  - 3-factor
  - 4 factor PCC
  - Activated factor VII
- Activated Factor VII
- Others

ACTIVATED FACTOR VII

- Originally developed for hemophilia patients with antibodies
- FDA approved indications:
  - Congenital hemophilia with inhibitors
  - Congenital Factor VII deficiency
  - Acquired hemophilia
  - Glanzmann's thrombasthenia

ACTIVATED FACTOR VII

- In a database survey, 97% of the use was for off label indications
- Non-FDA approved use for bleeding:
  - In thrombocytopenia and other platelet dysfunctions
  - Warfarin over anticoagulation
  - Bleeding: trauma, HSCT, liver failure

Logan AC et al, Ann Int Med. 2011; 154(8): 516
Kristensen J. Haemostasis. 1996; 26(1): 159-164

2012 Mar 14

OUTCOMES AFTER USE OF FACTOR VII

- 29 RCTs were included:
- 16 trials examined **prophylactic use**: no mortality benefit (RR 1.04; 95% CI 0.55 to 1.97), decreased blood loss (mean difference (MD) -297 mL; 95% CI -416 to -178), and RBC requirement; trend in favor of outcomes rFVIIa in the number of participants transfused (RR 0.85; 95% CI 0.72 to 1.01). However, there was a trend against rFVIIa with respect to thromboembolic adverse events (RR 1.35; 95% CI 0.82 to 2.25).
- 13 examined **therapeutic use** of rFVIIa: no outcomes where any observed advantage or disadvantage of rFVIIa over placebo could not have been observed by chance alone. There was a trend in favour of rFVIIa for reducing mortality (RR 0.91; 95% CI 0.78 to 1.06). However, there was a trend against rFVIIa for increased thromboembolic adverse events (RR 1.14; 95% CI 0.89 to 1.47).
- When all trials were pooled together to examine the risk of thromboembolic events, a significant increase in total arterial events was observed (RR 1.45; 95% CI 1.02 to 2.05).

Simpson E et al. Cochrane Database Syst Rev. 2012. 14:CD005011

PCC

- 4 Factor PCCs and 3 Factor PCCs available, along with activated PCC
- 3 factor is missing factor VII, but otherwise contains all the other Vit K dependent factors: II, IX, and X, and some protein C/S
- Fixed dosing is non-inferior, though commonly weight based dose is given

Khorsand N. Blood. 2013. 122: 3639
Dentali F. Thromb Haemost. 2011. 106(3): 429

PCC

- Thrombotic complications in about 1-2% of patients
- The current US approved 3 Factor PCC (Profilnine) does not contain heparin
- Activated PCC: contains activated factor VII and thus is more prothrombotic; in the US we have FEIBA: Factor Eight Inhibitor Bypassing Activity

Dentali F. Thromb Haemost. 2011. 106(3): 429

WARFARIN REVERSAL

Clinical setting	2018 ASH guideline	2012 ACCP guideline
▪ Serious or life-threatening bleeding ▪ Any INR	▪ 4-factor PCC ▪ Vitamin K (intravenous) ▪ Hold warfarin	▪ 4-factor PCC* ▪ Vitamin K (intravenous) ▪ Hold warfarin
▪ No bleeding ▪ INR >10	(No recommendations given)	▪ Vitamin K (oral) ▪ Hold warfarin
▪ No bleeding ▪ INR 4.5 to 10	▪ Hold warfarin ▪ No vitamin K	▪ Hold warfarin ▪ Vitamin K (low dose, oral) is optional

www.uptodate.com

WARFARIN REVERSAL AND VITAMIN K

- Important to give Vitamin K to reverse the underlying acquired deficiency.
- Dosing is debatable, but with a life-threatening bleed, would reverse fully with 10mg (or at least 5mg) IV Vitamin K (risk of anaphylaxis mitigated generally with longer infusion)
- Should see effect within a couple of hours (re-check INR at 12hrs), with full effect by 24hrs

WARFARIN REVERSAL AND VITAMIN K

- Fixed dose is non-inferior to weight-based dosing
- Consider underlying indication, and can always give more

Pretreatment INR	Dose Basis	Max Dose
2 to < 4	25 units/kg	2500 units
4 to 6	35 units/kg	3500 units
> 6	50 units/kg	5000 units

4 FACTOR PCC FACTOR HALF-LIVES

Factor	Half-life (hrs)
Factor II	48-60
Factor VII	1.5-6
Factor IX	20-24
Factor X	24-48
Protein C	1.5-6
Protein S	24-48

HEPARIN REVERSAL

- Reversed with protamine based on POC heparin-protamine titration assay, after an initial 10mg challenge dose if on pump (0.7mg per 100U of heparin)
- 1mg per 100u of heparin administered. For example: if a 100kg patient is receiving 18U/kg/hr of heparin and develops ICH, you would reverse with 36mg protamine (18 x 2hrs of heparin infusion)
- https://clincalc.com/Protamine/

Lu C, *et al.* CMAJ. 2022;194 (4):E122.

SIDE-EFFECTS OF PROTAMINE

- Maximal single dose of 50mg
- Hypersensitivity reactions: mitigated by running product slowly (especially consider slow drip if reversing heparin subQ)
- Be prepared to treat reactions since these can be severe and involve hemodynamic collapse

REVERSAL OF ENOXAPARIN

- Can partially reverse with protamine
  - 1mg per 1mg enoxaparin dose given if within 8hrs (max 50mg)
  - 0.5mg per 1mg enoxaparin dose if > 8hrs (max 50mg)
  - If > 12hrs, protamine generally not recommended
- Can "treat" with PCC, and technically also with andexanet alfa

Hirsh J et al. CHEST. 2008; 133(6 Suppl):141S

OTHER ANTICOAGULANTS

- Fondaparinux: reversed fully with andexanet alfa, although generally use PCC
- Bivalirudin and Argatroban: direct thrombin inhibitors with short half-lives; can temporize with product, and can consider PCC

SUMMARY TABLE

DRUG	REVERSAL
Heparin	Protamine
Lovenox	Partially with protamine; andexanet alfa; PCC
Warfarin	Vitamin K and PCC
Dabigatran	Idarucizumab; can consider PCC and/or iHD
Xa Inhibitors[1]	PCC or andexanet alfa
Fondaparinux	Can consider andexanet alfa or PCC
IV DTIs[2]	Can consider PCC

[1] Apixaban, Rivaroxaban, Edoxaban, and Betrixaban
[2] Dabigatran and Argatroban

PLATELET REVERSAL

- Challenging to measure platelet functional status
- Some institutions have a PFA 100 assay that measures platelet-collage plug formation with epinephrine and ADP (a quick version of platelet aggregometry); challenges with interpretation
- Some have access to aspirin platelet function tests; additional tests

PLATELET REVERSAL

- In general, do not need to reverse NSAIDs or ASA
- PATCH trial: 190 patients on ASA w/ ICH randomized to platelet transfusion or not
- Higher odds of death (or dependence) at 3 months in the platelet transfusion group (adjusted OR 2.05; 95% CI 1.18 – 3.56; p = 0.0114)

Baharoglu MI *et al.* Lancet. 2016. 387: 2605-2613

PLATELET REVERSAL

- With life-threatening bleeding, would transfuse platelets to reverse effects of anti-platelet agents, such as clopidogrel
- A novel drug: bentracimab (PB2452), a recombinant IgG1 monoclonal antibody, has been developed to reverses the effect of ticagrelor
- REVERSE-IT trial preliminary results presented and are promising

Bhatt DL *et al.* NEJM. 2019. 380: 1825-1833

UTILITY OF TEG AND ROTEM IN ANTICOAGULATION

- Measurements of clot formation and stability
- Recent studies demonstrate that R time in TEG (initial clot formation) is prolonged after NOACs (dabigatran, rivaroxaban, and apixaban) in 9 healthy men w/ 100% sensitivity and ≥ 90% specificity
- Another study demonstrated in 20 healthy donors that ex-vivo addition of apixaban, edoxaban, rivaroxaban or dabigatran at varying concentration and noted a dose dependent increase in CT (clotting time)

Artang R *et al.* Res Pract Thromb Haemost. 2019. 3(3): 391–396
Seyve L *et al.* Int J Lab Hematol. 2018. 40: 84-93

OTHER ADJUNCTS

- Anti-fibrinolytic agents can be used in bleeding patients
- When concerned about factor deficiency, can use plasma and products
- Consider desmopressin for uremic platelets

THANK YOU!

- Email with questions: Athale.Janhavi@mayo.edu

CASE 2

- A 58yo man w/ HTN, BPH, homozygous FV Leiden was discharged 5 months ago after a PE on apixaban. He returns to the ED with 2 days of melena and 1 day of lightheadedness and confusion. VS in the ED: 85/40, HR 145 (irregularly irregular), and he is oriented to person only. Abdomen is soft, ND and NT. His extremities are cold with mottling. Type and cross is sent, and the patient is given 2L saline and 2 units of unmatched blood. Later, the patient is transfused 4u PRBCs via two large bore PIVs and 40mg IV PPI is also given without improvement in BP. Labs with Hgb 8.4, plts 106K, Cr 1.6, LA 3.4, APTT 25.4, PT 12.2 (INR 1.1), thrombin time 13, and he is admitted the ICU.

CASE 2

- In addition to preparing for endoscopy, what additional treatment should be started?

A) Vitamin K 10mgIV
B) Idarucizumab 5gm IV
C) 4 factor PCC 50U/kg IV
D) FFP 15mL/kg and 2u platelets