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PEARLS OF LABORATORY MEDICINE

V. Direct Oral Anticoagulants (DOACs):
Reversal strategies for DOACs: Laboratory role?

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DOAC reversal – the early years

In the early years of DOAC use, there were no specific reversal agents.

- Reversal strategies for dabigatran included:
  - Activated charcoal if recent ingestion
  - Dialysis
  - Pharmaceutical intervention of low efficacy:
    Pooled normal plasma
    Activated factor VII (FVIIa)
- Reversal strategies for factor X DOACs included the used of FVIIa, prothrombin complex concentrates both activated and inactivated.

DOAC reversal – current practice

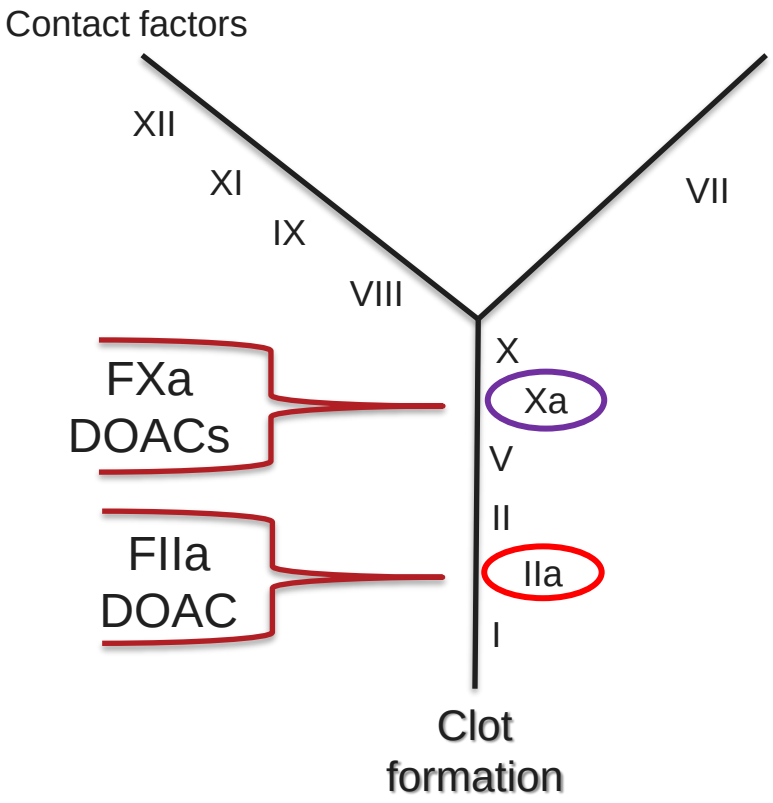
- In 2015, Praxbind® was FDA approved as a specific reversal agent for dabigatran
- In 2018, Andexxa® was FDA approved as a specific reversal agent for rivaroxaban and apixaban
- Use of activated and nonactivated PCCs

DOAC reversal – clinical indications[1-4]

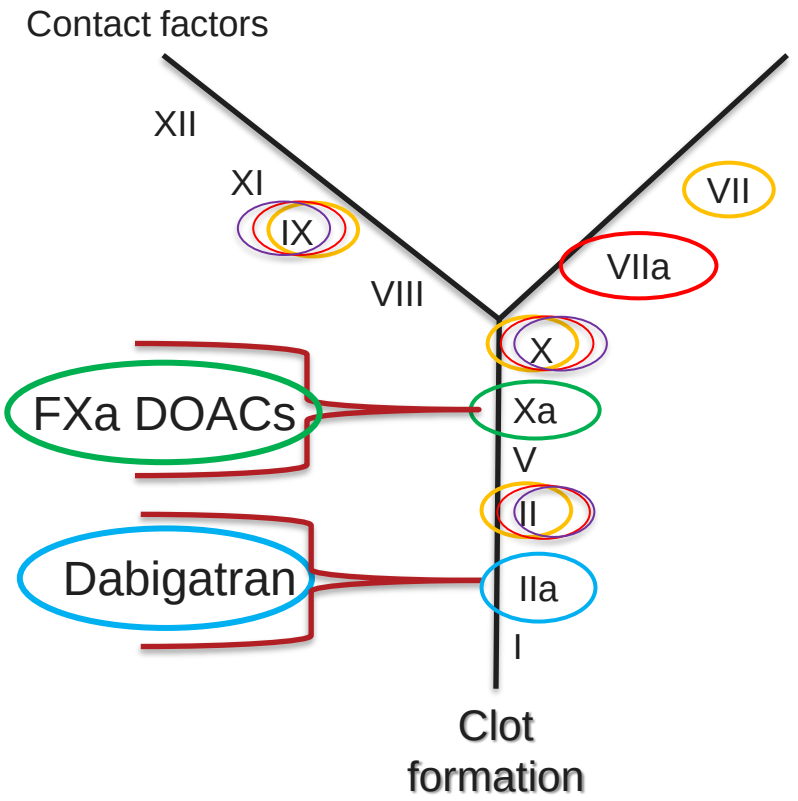
- Hemorrhage or major bleeds
- Emergent invasive procedures*
- Thrombolysis for acute thrombotic stroke*
- Demonstrable DOAC levels

*Safe or acceptable thresholds for interventions are based on case reports, small series of patients, or consensus guidance from opinion leaders

DOAC Targets



Reversal strategies targets or factor supplements



Praxbind® target

Andexxa® target

FEIBA® target

Profilnine® : 3 factor PCC

Kcentra: 4 factor PCC

Praxbind® (idarucizumab)[5]

(Boehringer Ingelheim)

Praxbind® is a humanized monoclonal antibody fragment derived from IgG1 molecule

The total dose is administered as two separate 2.5g doses that will bind to dabigatran and its acylglucuronide metabolites

One 5g dose will neutralize 1,000ng/mL of dabigatran

Drug “rebound” or drug dissociation noted in some patients between 12 – 24 hours after treatment

Praxbind® (idarucizumab) - Laboratory

Praxbind® does not have thrombogenicity

Praxbind® will correct the PT, APTT, thrombin time, dilute thrombin time, ecarin clotting time

These tests may also detect dabigatran “reappearance”

Consider more sensitive methods to assess post-treatment efficacy, especially if dabigatran values are >1,000ng/mL

Andexxa® (andexanet alfa)[6]

(Portola Pharmaceuticals)

Andexxa® is recombinant factor Xa, inactivated - zhzo

FDA approval only for rivaroxaban and apixaban DOACs

Two doses:

- Low dose: 400 mg
- High dose: 800 mg

Andexxa® has some thrombogenicity:

- Inhibition of TFPI
- Increase in thrombin generation

Andexxa® (andexanet alpha) - Laboratory

Andexxa® efficacy can be measured using Anti-Xa assays

Andexxa® will reduce the Anti-Xa levels

Initial studies indicated Anti-Xa activity rebound, but this effect was due to in-vitro dissociation of drug:substrate

No FDA recommendation for Anti-Xa testing and dosing

Dosing predicate on last exposure, or if unknown, highest dose

FEIBA®[7]
(Baxalta)

Factor Eight Inhibitor Bypass Agent – FDA approved in 1986 for use in hemophilia A patients with inhibitors

Also known as activated prothrombin complex concentrate (aPCC)

Contains non-activated factors II, IX, and X, with mostly activated factor VII

Case reports of use in DOAC reversal

FEIBA® - Laboratory

Per prescribing information, the administration of FEIBA® will reduce the APTT in factor VIII inhibitor patients

This product contains factors II and X, and therefore FEIBA® treatment in DOAC treated patients would presumably reduce the PT

However, there is unclear utility of laboratory for assessing reversal efficacy in FXa DOAC patients.

Profilnine®, a 3 factor PCC[8]

(Grifols Biologics, LLC)

Lyophilized concentrate of factors II, IX and X

FDA approved indications for use are for Hemophilia B patients

Case reports for use in DOAC reversal

Case reports for use in warfarin reversal

Profilnine®, a 3 factor PCC - Laboratory

As this product contains a concentrate of factors II, IX and X, would presumably correct PT and/or APTT associated with these deficiencies

Unclear utility of laboratory for assessing efficacy in FXa DOAC reversal

Kcentra®, a 4 factor PCC[9]
(CSL Behring)

Lyophilized concentrate of non-activated factors II, VII, IX and X

FDA approved indications for use are for reversal of vitamin K dependent factor deficiency (factors II, VII, IX and X) induced by warfarin

Case reports for use in DOAC reversal

KCentra®, a 4 factor PCC - Laboratory

As this product contains a concentrate of factors II, VII, IX and X, would presumably correct PT and/or APTT associated with these deficiencies

Unclear utility of laboratory for assessing efficacy in FXa DOAC reversal

Cautionary use of UFH/LMWH targets for emergent interventions[1,2]

Alteplase could be given if LMWH <0.1IU/mL

Alteplase should be avoided if LMWH >0.50UI/mL

Heparin kit	LMWH level	Apixaban (ng/mL)	Edoxaban (ng/mL)	Rivaroxaban (ng/mL)
Coamatic®[1]	0.50IU/mL	80	96	70
Berichrom®[2]		90	118	82
STA®-Liquid Anti-Xa		36	36	22

Tables data from Rimsans, et al Curr Pharmacol Report 2020 doi: doi:10.1007/s40495-020-00232-7

Summary: DOAC and reversal strategies

For dabigatran: Praxbind® is generally accepted as the ideal choice for reversal

For FXa DOACs: Due to the cost of Andexxa®, there is less of a universal acceptance for using this drug for reversal

- Published reports have indicated efficacy of PCCs in reducing DOAC related bleeding

There are no recommendations for laboratory guidance for reversal strategies.

- However, our institutional experience indicates that providing clinicians with DOAC levels were useful for reversal management decisions

Local determination of heparin derived thresholds are required if this practice is used to determine interventions or reversal

References

1. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol. 2019;94(6):697-709.
2. Rimsans J, Douxfils J, Smythe M, Gosselin RC. Overview and Practical Application of Coagulation Assays in Managing Anticoagulation with Direct Oral Anticoagulants (DOACs). Curr Pharmacol Rep 2020 (in press) doi:10.1007/s40495-020-00232-7
3. Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, et al. Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management-a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2017;38(22):1710-1716.
4. Frontera JA, Bhatt P, Lalchan R, Yaghi S, Ahuja T, Papadopoulos J, Joset D. Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. J Thromb Thrombolysis. 2020;49(1):121-131.
5. Praxbind prescribing information. Boehringer Ingelheim Pharmaceuticals. Revised March 2018.
6. Andexxa prescribing information. Portola Pharmaceuticals INc. Version ADX-US-v1.4.
7. FEIBA prescribing information. Baxalta US Inc. Revised 12/2018.
8. Profilnine prescribing information. Grifols Biologicals Inc. Revised August 2010.
9. Kcentra prescribing information. CSL Behring GmbH. Revised October 2018.

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenters completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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