DOAC management: reversal options with case study discussion

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Overview

Initiation of anticoagulation

Reversal options, pharmacology and evidence

- Supportive care and current practice
- Idarucizumab (Praxbind)
- Andexanet alfa
- Ciraparantag

Case studies

Introduction

DOACs are at least as effective as VKAs

Shorter half-life and without some of the treatment limitations

Less life-threatening bleeding, particularly intracranial haemorrhage

GI bleed more frequent

Outcomes of major bleeds with DOACs are no worse than those with VKAs even in the absence of clinically available antidotes

Initiation and monitoring of DOACs

Assess bleed risk systematically and review periodically

Modify risk factors where able

Review interacting drugs e.g. NSAIDs, antiplatelet, 3A4 and P-gp inhibitors

Consider use of PPI for gastric protection

Prescribe appropriate dose

De-escalate therapy- dose/duration

Set appropriate follow-up and monitoring plan

Supportive care

for anticoagulation related bleeds

Hold DOAC: short half life

Local haemostasis

Treat effects of bloods loss: oxygen and IV fluids

Packed red cell, plasma (FFP) and platelets: supportive measure for major blood loss indicated in trauma

FFP: not shown to reverse abnormal coagulation tests and drug action still relevant

Activated charcoal: reduce the absorption if ingested within 2 to 6 hours or in overdose

Tranexamic acid: anti-fibrinolytic used for trauma-related bleeding

Haemodialysis: dabigatran

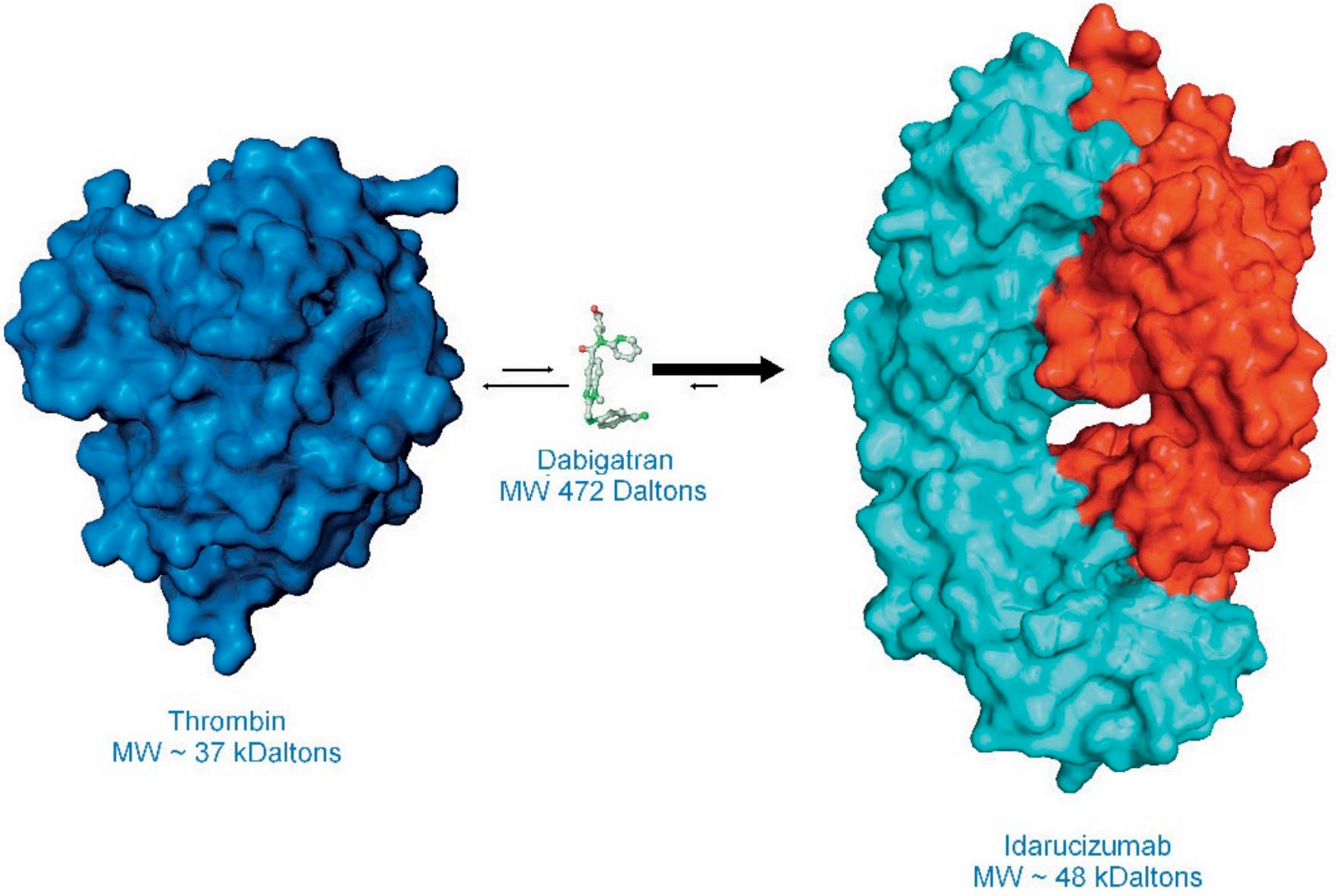
Idarucizumab

Humanised mouse monoclonal antibody anti-dabigatran fragment

- Approximately 300-fold more potent than the binding affinity of dabigatran for thrombin
- Binds both free and thrombin-bound dabigatran
- Bind active glucuronide metabolites
- Forms stable complex
- Complex is renally cleared

Despite structural similarities to thrombin

- Does not exhibit any thrombin-like activity
- Does not effect coagulation or platelet aggregation tests



Thromb Haemost 2015; 114: 198–205

Dosing

Licenced in UK for rapid reversal of its anticoagulant effects is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding.

Short half-life ~45mins

Two x 2.5g intravenous infusions over 5–10 min or boluses

A further course of two x 2.5g can be administered as necessary

NHS indicative price £2400 for 2x2.5g vials

Evidence: RE-VERSE AD

Multicentre, open-label study of idarucizumab (n=503)

- Uncontrollable/life-threatening bleeding (n= 301) GI bleeding 46%; ICH 33%; trauma 26%
- Emergency surgery/procedure (n=202)

Outcomes: monitoring of dabigatran-specific assays and clinical assessment of haemostasis

Rapidly corrected laboratory indices of anticoagulation and reduced the level of active drug

Recurrent elevation in clotting time seen 12-24 hours after treatment (n=114)

- Associated with bleeding (n=10)
- Can give additional doses of idarucizumab if clinically necessary

Impact of intervention on clinical outcomes could not be assessed

Mortality rate at 30 days: 13.5% (bleeding group) and 12.6% (surgery group)

Thrombotic event rate 4.8% at 30 days and 6.8% at 90 days

- Contributing factors: delay in re-starting anticoagulation and prothrombotic state

Current treatments for anticoagulation related bleeds

Factor Xa inhibitors

Nonspecific indirect reversal strategies used in clinical practice:

- Prothrombin complex concentrates (PCCs), activated PCCs, and recombinant FVIIa

Prothrombin complex concentrate (PCC):

- 4 factor PCC (factors II, VII, IX, X with protein C and S)

Efficacy in DOAC-associated bleeding: observational studies

- Support the use in life-threatening bleeding or bleeding associated with significant long-term morbidity
- Risk of thrombosis similar to that of PCC used for VKA reversal (~8%)

Dosing: 50 units/kg (actual body weight)

Price: Octaplex ~£1500 per reversal (weight dependent)

Andexanet-alfa

Genetically modified variant of human form of factor Xa

Designed to reverse factor Xa inhibitors, LMWH and fondaparinux

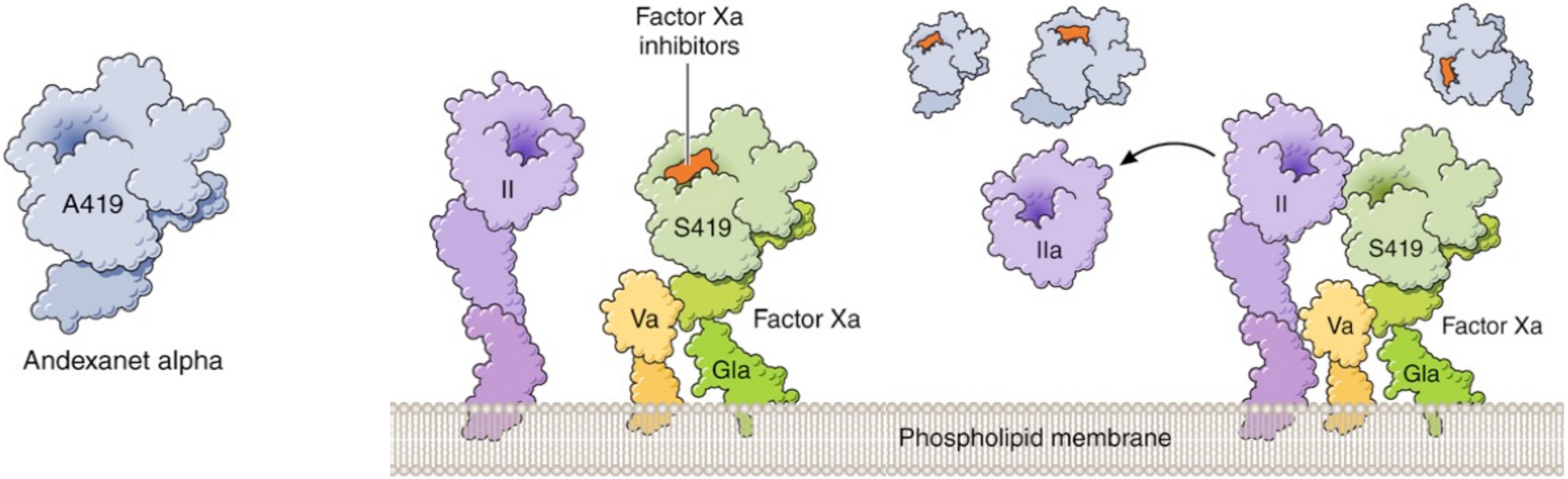
Catalytically inactive

Binds to factor Xa inhibitors

- with affinities similar to those of native factor Xa
- preventing the inhibitors from binding

Also binds tissue factor pathway inhibitor (TFPI) to form non-productive andexanet–TFPI complex

- reduces TFPI activity
- increases tissue factor initiated thrombin



II indicates factor II (prothrombin); IIa, activated factor II (thrombin); Va, activated factor V; antagonist GLA, γ-carboxyglutamic acid-rich; factor Xa, activated factor X;

Circulation. 2016;134:248–261

Dosage

Approved by FDA for patients treated with rivaroxaban and apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

Half life ~1hr

Bolus followed by a continuous infusion up to 120mins

Dose dependent on drug dose and time of ingestion

Lower doses are needed to reverse apixaban than rivaroxaban

Cost reported at around $30,000 to 50,000 per reversal

NICE technology appraisal expected March 2020

Evidence: ANNEXA-4

Multicentre, open-label study of andexanet-alfa (n=352)

- Uncontrollable/life-threatening bleeding; ICH 64%; GI bleeding 26%; other 10%
- Prescribed rivaroxaban (n=128); apixaban (n=194); edoxaban (n=10) or enoxaparin (n=20)
- EXCLUDED patients requiring planned surgery/procedure and no trauma patients

Outcomes monitoring of FXa-specific assays and clinical assessment of haemostasis

Rapidly and markedly reduced anti-factor Xa activity

82% patients excellent or good haemostatic efficacy at 12 hours

Impact of intervention clinical outcomes could not be assessed

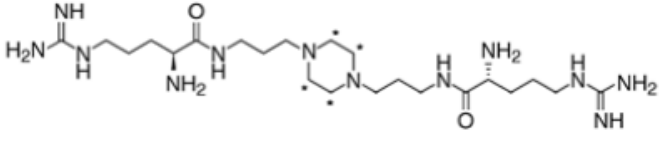
Mortality rate at 30 days: 14%

Thrombotic event rate 10% at 30 days

- Most due to delay in re-starting anticoagulation

Ciraparantag

universal antidote



Ciraparantag (PER977)

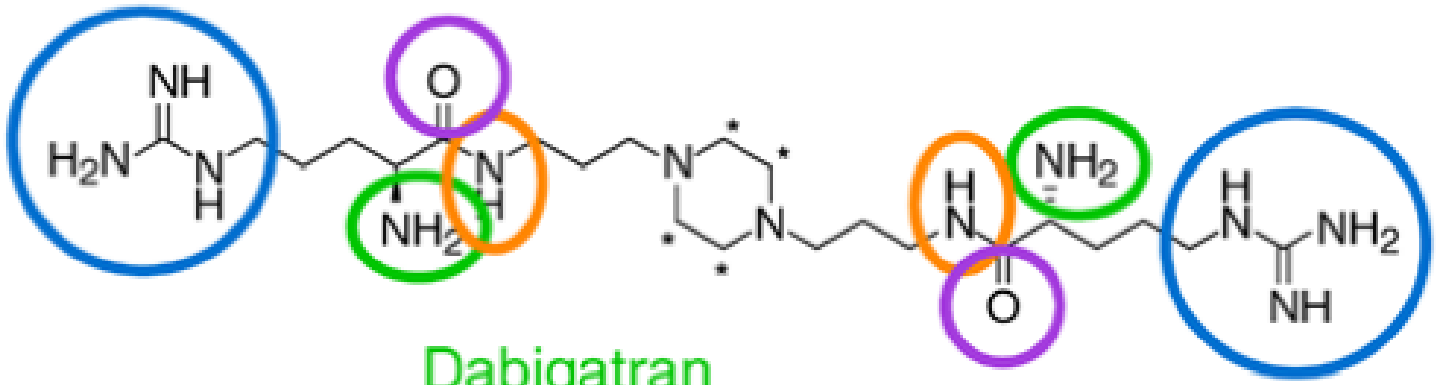
Synthetic, cationic small molecule, ciraparantag binds anticoagulant via hydrogen bonds

Prevents the anticoagulants from binding to their endogenous targets

Designed to reverse direct thrombin inhibitors, factor Xa inhibitors, LMWH and UFH

Phase 2 clinical trials still ongoing in healthy volunteers

Demonstrated complete and sustained reversal of apixaban, rivaroxaban, edoxaban, and enoxaparin with a single IV bolus



Edoxaban	Dabigatran		
Dabigatran	Rivaroxaban	Dabigatran	
Rivaroxaban	Apixaban	Rivaroxaban	
UFH/LMWH	Argatroban	UFH/LMWH	Edoxaban
Fondaparinux	UFH/LMWH	Fondaparinux	Apixaban
	Fondaparinux		

Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins

Circulation. 2016;134:248–261

Case Study 1

troublesome minor bleeding

78 year old female patient

CHA_2DS_2-VASc = 5 (HTN,age2,Diabetes,Sex)

HAS BLED = 2 (Elderly, Drugs)

CrCL = 53ml/min. Weight 74kg

DHx Rivaroxaban 20mg daily started 4 weeks ago; Ramipril 5mg daily, Metformin 500mg twice daily; Atorvastatin 20mg at night; Sertraline 50mg daily

NKDA

Non smoker, teetotaller

Presents to anticoagulation clinic c/o recurrent self-limiting epistaxis

No trauma or other cause

Observations normal, and show no haematological compromise

How would you proceed?

1. Prescribe naseptin cream
2. Refer to ENT for review +/- cauterisation
3. Hold rivaroxaban
4. Stop rivaroxaban and switch to:
   a) edoxaban
   b) apixaban
   c) dabigatran

How would you proceed?

Prescribe naseptin cream QDS for 10 days

Refer to ENT for review if ineffective

Switch to apixaban 5mg twice daily

Case Study 2

Persistent major bleed

78 year old female patient

CHA_2DS_2-VASc = 5 (HTN,age2,Diabetes,Sex)

HAS BLED = 2 (Elderly, Drugs)

CrCL = 53ml/min. Weight 74kg

DHx Rivaroxaban 20mg daily started 4 weeks ago; Ramipril 5mg daily, Metformin 500mg twice daily; Atorvastatin 20mg at night; Sertraline 50mg daily

NKDA

Non smoker, teetotaller

Presents to A&E with prolonged epistaxis, unresponsive to self-tamponade and nasal packing

No trauma or other cause

Observations: HR 105bpm BP 95/53 mmHg

Key questions and investigations

When was the last dose taken?

Concurrent medication?

Check renal function

Check FBC

Check coagulation screen

Check anti Xa (if available)

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Half-life of rivaroxaban = 11-13hrs (elderly)

Within 2 hours: give active charcoal and withhold

2-6 hours: consider charcoal and withhold

6+ hours: withhold only

Sertraline: can inhibit platelet function, hold until bleeding resolved

Key questions and investigations

When was the last dose taken?

Concurrent medication?

Check renal function

Check FBC

Check coagulation screen

Check anti Xa (if available)

Renal impairment: prolongs half-life

Assess for other abnormalities

Assessment of coagulation function though not necessarily predictive of drug level

Check PT: may be elevated, normal PT does not exclude clinically relevant levels

Check anti-Xa level: if available or can be processed rapidly

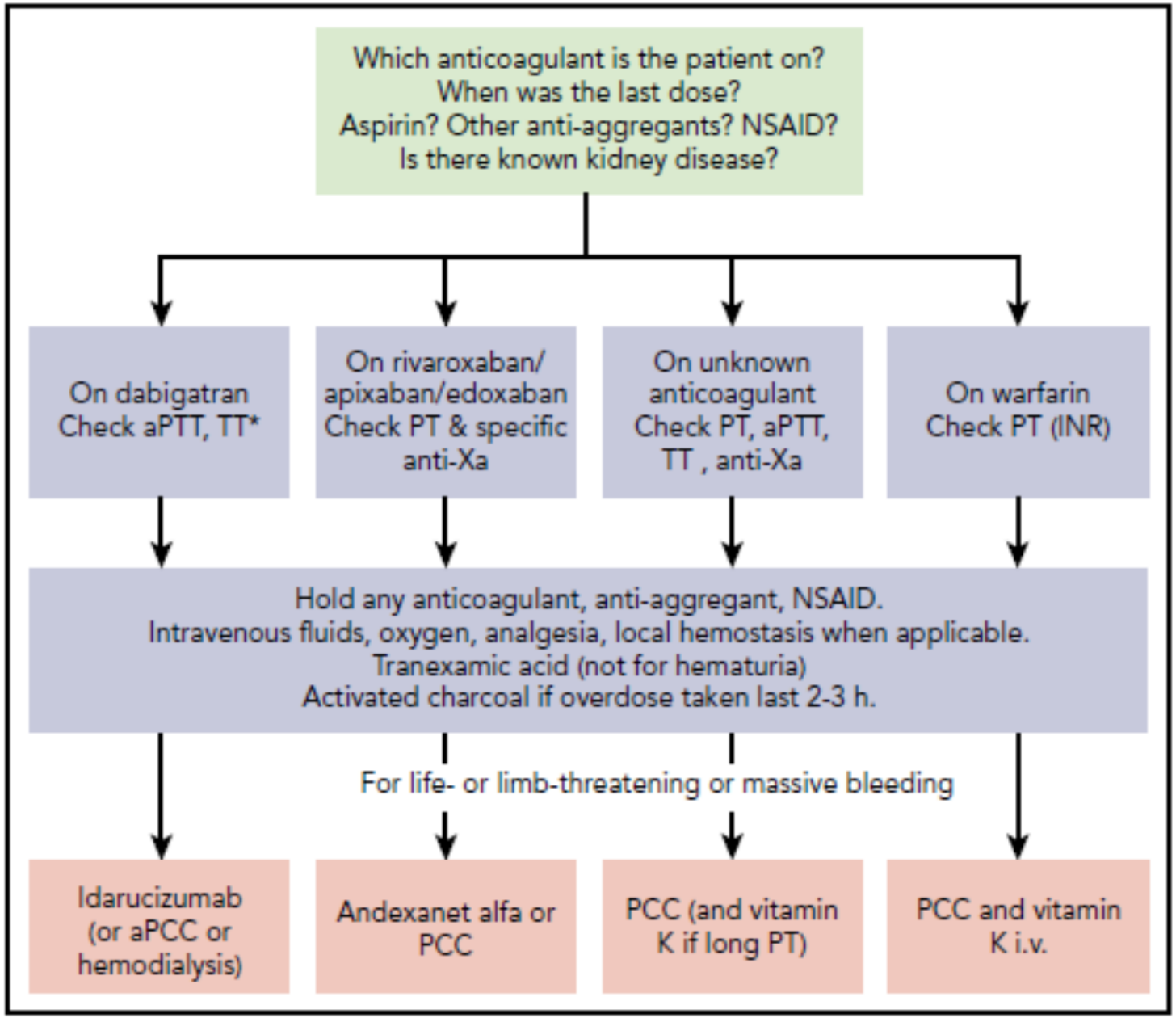
How would you proceed?

Refer to ENT for review +/- cauterisation or nasal packing

Haematology review for consideration of PCC

Role andexanet-alfa or ciraparantag (when available)?

Dialysis not effective (factor Xa inhibitors are highly protein bound)



Blood. 2019;133(5):425-435

Limitations of antidotes

Cost

Frequency of use, especially at smaller general hospitals

- Universal antidote may be preferable

Lack of head-to-head RCT comparing reversal options

- Impossible to know whether 4F-PCC or antidotes are more effective than supportive care alone

Risk of thromboembolic complications

Summary

Reversal should only be used in:

- Life-threatening bleeding or bleeding in a closed space
- Persistent major bleeding
- Emergency surgery or intervention with high bleed risk

Restart long-term anticoagulation when clinically safe

- Resuming anticoagulation following a major bleed (ICH or GI) is associated with a reduced risk of all-cause mortality

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