GI bleeding on anticoagulants

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Overview

- **Available anticoagulants in the UK**
- **DOACs**
  - Indications
  - Bleeding risk
- **Factors to consider in management of GI bleeding on DOACs**
  - Which drug
  - Patient characteristic
  - Renal function
- **DOACs and the coagulation screen**
- **Management of GI bleeding in patients on DOACs**
  - General measures
  - Specific reversal agents: idarucizumab & Andexanet alpha
  - Role of prothrombin complex concentrate
- **Restarting anticoagulation after a GI bleed**

Available Anticoagulant Drugs in the UK

Injectable therapies	Vitamin K Antagonists	Direct Oral Anticoagulants (DOACs)
UFH	Warfarin	**Dabigatran**
LMWH	Sinthrome (Acenocoumarol)	**Rivaroxaban**
Fondaparinux	(Phenindione)	**Apixaban**
Argatroban		**Edoxaban**
Bivalirudin		

Licensed DOAC indications in the UK

	Dabigatran (IIa inhibitor)	Rivaroxaban (Xa inhibitor)	Apixaban (Xa inhibitor)	Edoxaban (Xa inhibitor)
Orthopaedic thromboprophylaxis	+	+	+	-
General thromboprophylaxis	-	-	-	-
NVAF	+	+	+	+
DVT	+	+	+	+
PE	+	+	+	+
Prophylaxis atherothrombotic events after ACS (+aspirin or aspirin and clopidogrel)		+		

Bleeding on DOACs

Data from RCT and post marketing studies[1]

	Major bleeding	ICH	GI bleeding
Dabigatran – Rely	RR 0.93 (0.81 – 1.07)	RR 0.40 (0.27-0.60)	RR 1.50 (1.19-1.89)
Post marketing	HR 0.66 – 0.97	HR 0.08 – 0.49	HR 0.97 – 1.28
Rivaroxaban – Pocket AF	HR 1.04 (0.90-1.20)	HR 0.67 (0.47-0.93)	RR 1.46 P < .001
Post marketing (non comparative)	IR 2.86 – 2.89	IR 0.22	IR 2.53
Apixaban – Aristotle	HR 0.69 (0.60-0.80)		
Post marketing	HR 0.75 (0.63-0.88)		

- **In general post marketing studies support findings from RCT.**
- **Majority major bleeding events are GI but have low mortality.**
- **ICH rare but high mortality.**

Villines & Peacock The American Journal of Medicine (2016) 129, S41-S46

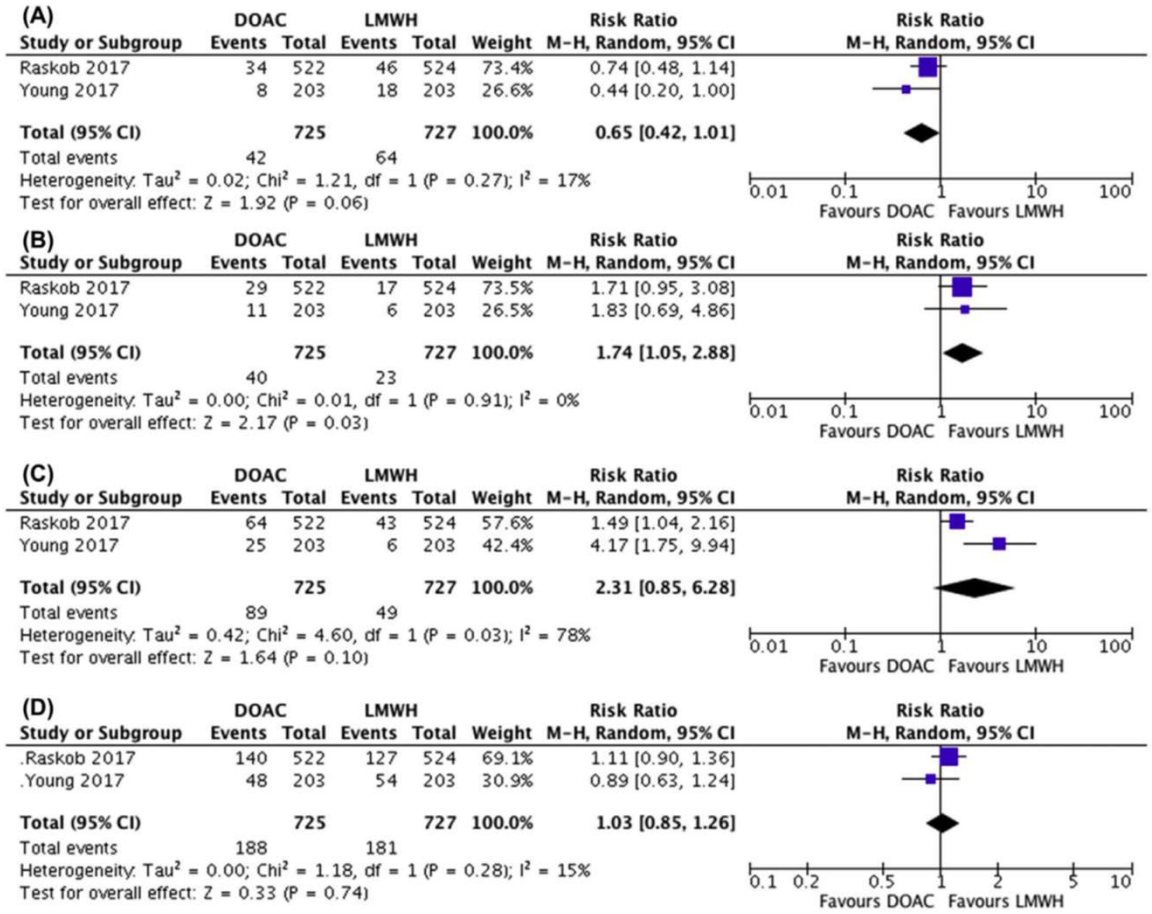
DOACs for VTE in malignancy
Select-D and Hokusai trials: meta-analysis[1]

Recurrent VTE at 6 months

Major bleeding at 6 months

CRNMB at 6 months

Overall mortality at 6 months



Bleeding particularly in GI or urologic malignancy

1. Li et al in press https://doi.org/10.1016/j.thromres.2018.02.144

Management of bleeding DOACs

	Dabigatran (IIa inhibitor)	Rivaroxaban (Xa inhibitor)	Apixaban (Xa inhibitor)	Edoxaban (Xa inhibitor)
Licensed for	SPAF Treatment and 2nd prevention of VTE	SPAF Treatment and 2nd prevention of VTE	SPAF Treatment and 2nd prevention of VTE	SPAF Treatment and 2nd prevention of VTE
Protein binding	35%	high	high	High
Peak effect, h	0.5–2	2–4	3–4	1–2
Excretion	Renal	Renal/hepatic	Renal/hepatic	Renal/hepatic
$T_{½}$, h	11–14 (27 h CrCl <30 ml/min)	5–13	~12	10–14

- **Patient characteristics**
- **Which drug is the patient taking?**
- **When was the last dose?**
- **FBC, renal function, coagulation screen.**

Heidbuchel *et al, Europace* doi:10.1093/europace/euv309

Mortality in upper GI bleeding – Rockall score[1]

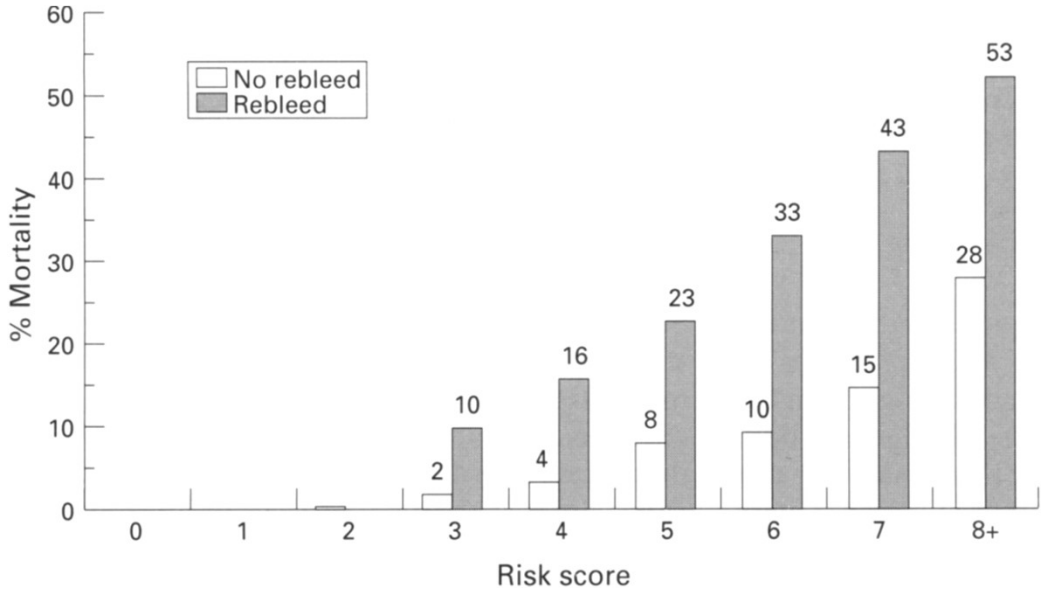


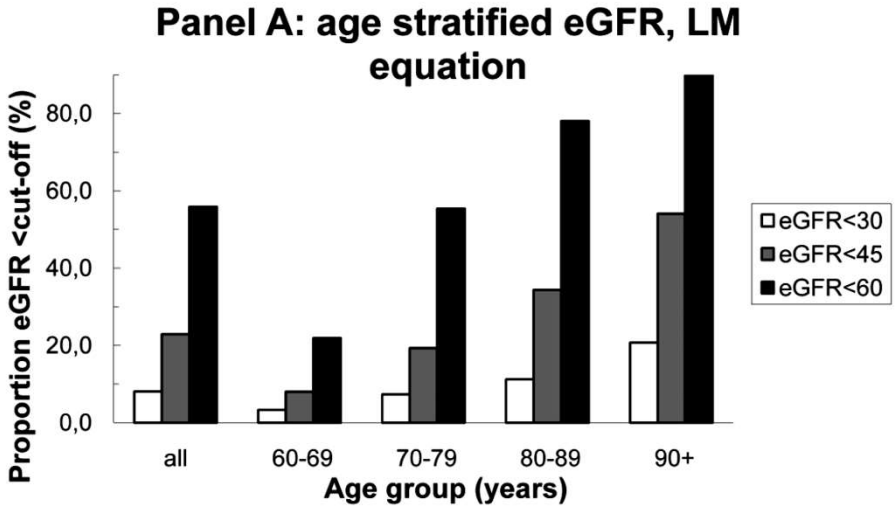
Table 1 The Rockall risk scoring system for upper-gastrointestinal haemorrhage

	Score			
Component	0	1	2	3
Age (years)	< 60	60–79	⩾ 80	
Pulse rate (beat/min)	< 100	⩾ 100		
SBP (mmHg)	⩾ 100	⩾ 100	< 100	
Comorbidity	None	None	IHD, cardiac failure, any other major comorbidity	Renal failure, liver failure or disseminated malignancy
Diagnosis	Mallory–Weiss lesions or no lesion, no SRH	All other diagnoses	Malignant lesions of the upper-gastrointestinal tract	
Stigmata of recent haemorrhage	No stigmata or dark spot in ulcer base		Any other signs	

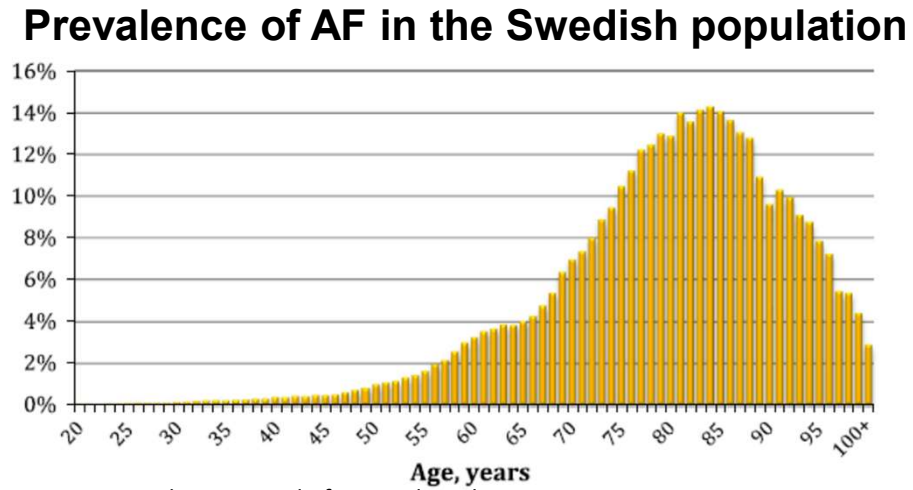
IHD, ischaemic heart disease; SBP, systolic blood pressure; SRH, stigmata of recent haemorrhage.

Rockall et al Gut 1996; 38: 316-321

Prevalence of renal dysfunction in patients with AF



Jönsson et al. Thromb Res. 2011 Oct;128(4):34



Friberg Journal of Internal Medicine, 2013, 274; 461–468

Approximate $T_{1/2}$ by renal function

CrCl (ml/min)	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
> 80	14	8	7 - 8	8 – 9
50 - 79	17	9	7 - 8	8 – 9
30 - 49	19	9	17 - 18	9 – 10
15 - 29	28	10	17 - 18	17
< 15	NA	NA	NA	NA

Adapted from Burnett et al J Thromb Thrombolysis 2016 41:206–232

Dabigatran

- Estimate normalization of plasma levels:
  - Normal renal function: 12–24 h
  - CrCl 50–80 mL/min: 24–36 h
  - CrCl 30–50 mL/min: 36–48 h
  - CrCl <30 mL/min: ≥48 h

Anti Xa agents

- Normalization of plasma levels: 12–24 h

Adapted from Steffel et al, ESC Guideline, EHJ 2018

Can routine coagulation testing be used to determine the presence/degree of anticoagulation with DOACs?

Expected levels in DOAC steady state plasma concentrations

Table 9 Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist oral anticoagulants

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Steffel et al, ESC Guideline, EHJ 2018

Normal APTT in dabigatran or normal PT in anti Xa agents does not always exclude the presence of therapeutic drug levels.

Do not use for apixaban.

Normal TT excludes dabigatran but too sensitive.

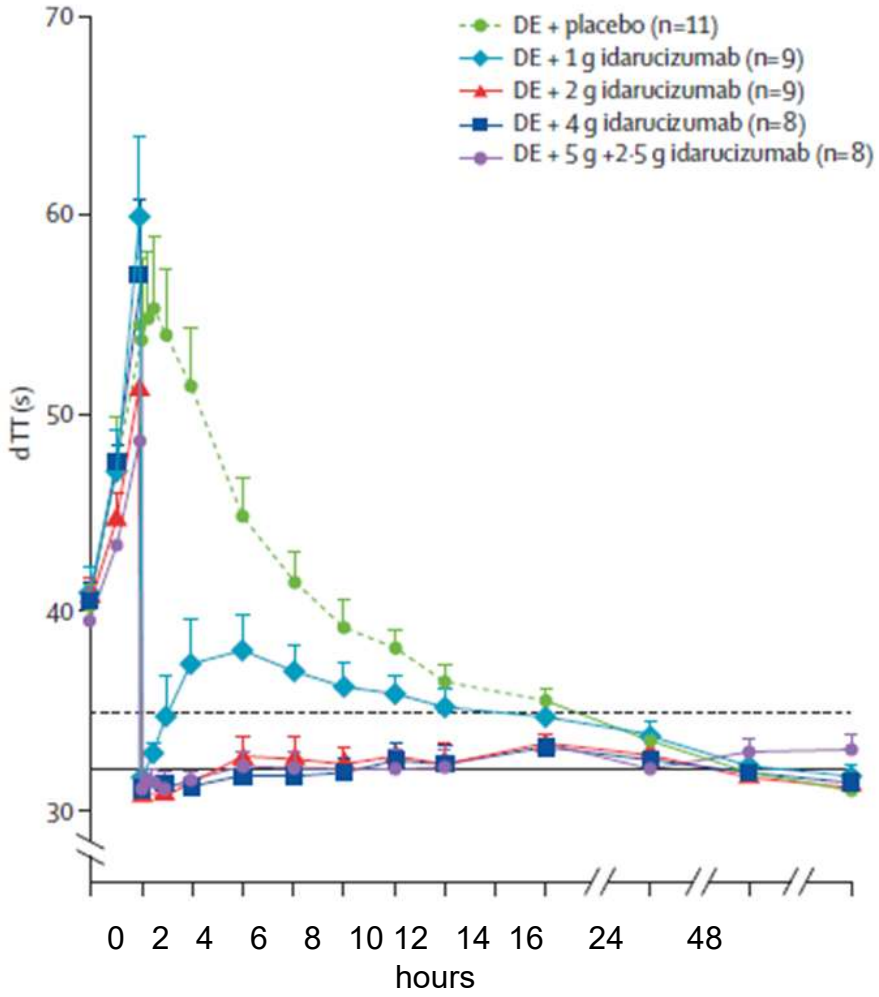
Use specific assays if possible.

Management of bleeding on DOACs

	General measures	Specific reversal agent	Charcoal after ingestion	Haemodialysis
Dabigatran	Yes	Idarucizumab	Yes within 2 h	Yes
Rivaroxaban	Yes	No in Europe Yes in USA: Andexanet alpha	Yes, can be considered	No
Apixaban	Yes		Yes within 2 – 6 hours	No
Edoxaban	Yes		Yes, can be considered	No

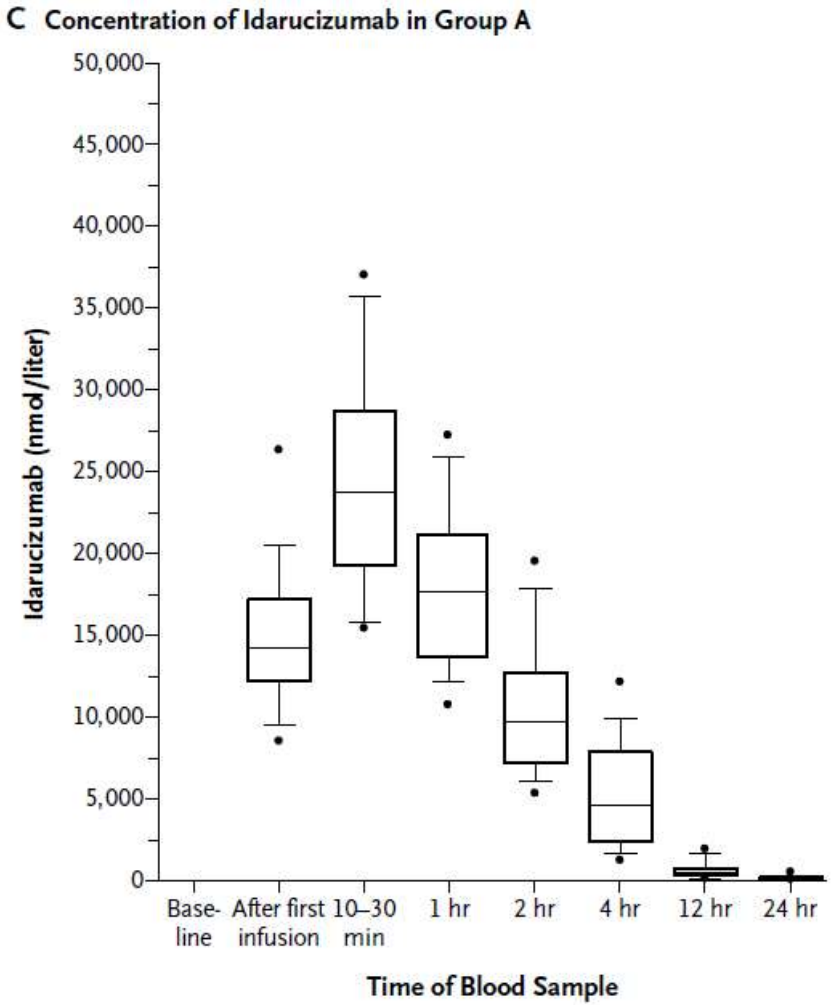
Dabigatran reversal with iv Idarucizumab (Praxbind®)

Healthy volunteers



Glund et al. Lancet 2015; 386:680-690

Emergency surgery



Pollack CV et al. NEJM 2015; 373:511-520

Praxbind® Administration[1]

Praxbind® is the specific reversal agent for Pradaxa®

Praxbind® should be used when rapid reversal of the anticoagulation effects of Pradaxa® is required:

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

The dose is 5 g

Two 50-mL vials of ready-to-use solution equal 1 dose of Praxbind® (2 x 2.5 g).

Pradaxa® can be restarted after 24 hours.[1]

Praxbind®:

- Is specifically designed as a reversal agent for Pradaxa® and will not reverse the effects of other anticoagulants
- May be used with standard supportive measures that are considered medically appropriate[2]

[1] If the patient is clinically stable and adequate haemostasis has been achieved.

[2] Consider standard supportive measures as medically appropriate: surgical haemostasis, haemodialysis, volume replacement, blood products, platelet concentrates (with thrombocytopenia or long-acting antiplatelet drugs), aPCCs (eg, FEIBA), recombinant Factor VIIa, or concentrates of coagulation Factors II, IX, or XI. Blood factors and dialysis have not been evaluated in clinical trials, and clinical experience for the management of medical emergencies is limited. Approximately 50% of dabigatran can be cleared from plasma over 2 hours.[1]

Infuse intravenously

Give the complete 5-g dose as 2 consecutive intravenous infusions over 5 to 10 minutes each.

or

Inject intravenously

Give the complete 5-g dose in 2 separate bolus injections as quickly as possible.

A pre-existing intravenous line that has been fully flushed may be used for administration of Praxbind®.*

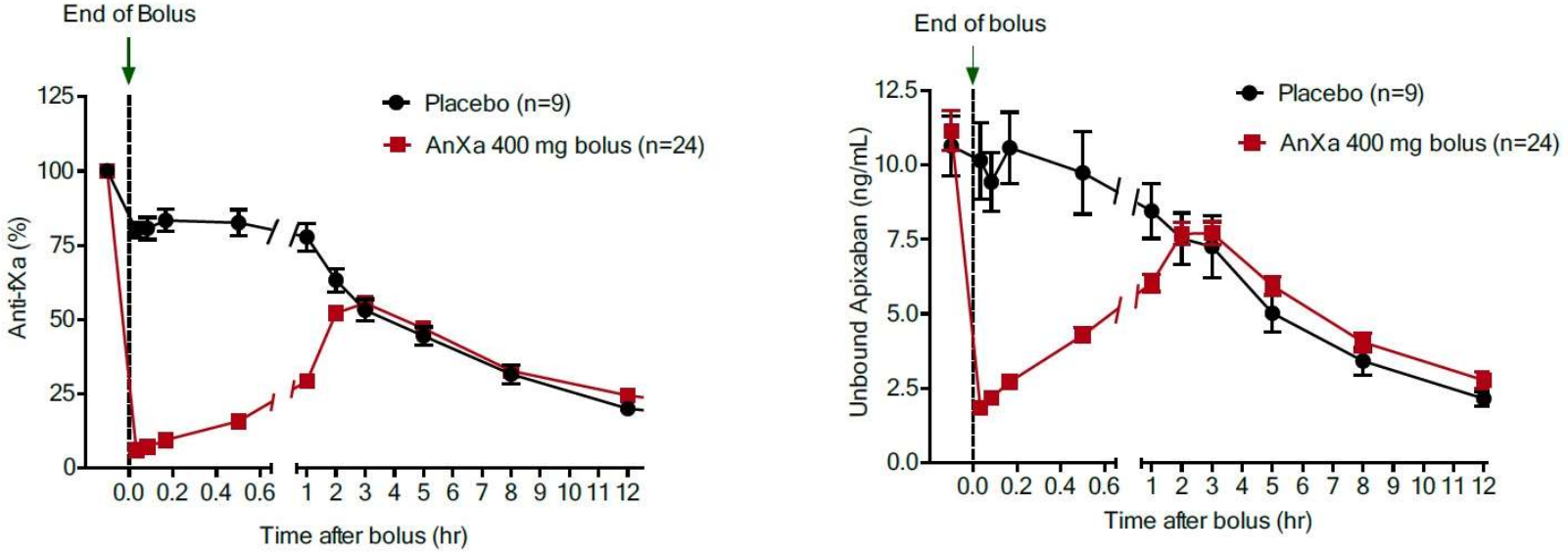
*The line must be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection prior to and at the end of infusion.

Preparation and administration considerations

- Solution is clear to slightly opalescent, colourless to slightly yellow
- Do not mix or coadminister with other medications
- Once Praxbind® has been removed from the vial, administration should begin promptly or within 1 hour
- Do not freeze

Andexanet alpha

Annexa-A trial



Adapted from: Crowther *et al*. https://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469639.pdf . Accessed 12/9/2015

Annexa-4 trial, interim analysis

Number of Major Bleeds Adjudicated	Number of Patients who Achieved Excellent or Good Hemostasis	Percent of Patients who Achieved Excellent or Good Hemostasis	95% Confidence Interval
132	109	83%	76% - 89%

Adapted from ACC, slide presentation 12/03/2018. Accessed 06/10/2018
http://www.crtonline.org/presentation-detail/interim-report-on-annexa-4-study-andexanet-reversa

Andexanet alpha – Annexa-4 trial, interim analysis

- **Thrombotic events occurred within 3 days of andexanet in 6 (2.6%) patients and by 30 days in 24 (11%)**
- **Anticoagulation re-started in 129 patients (57%) by 30 days**
- **Therapeutic anticoagulation was re-started in only 9 patients before a thrombotic event occurred**
- **27 deaths occurred by 30 days (12%), of which 11 were cardiovascular**

Adapted from ACC, slide presentation 12/03/2018. Accessed 06/10/2018
http://www.crtonline.org/presentation-detail/interim-report-on-annexa-4-study-andexanet-reversa

FDA approved dosing, EMA awaited.

Dose*	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

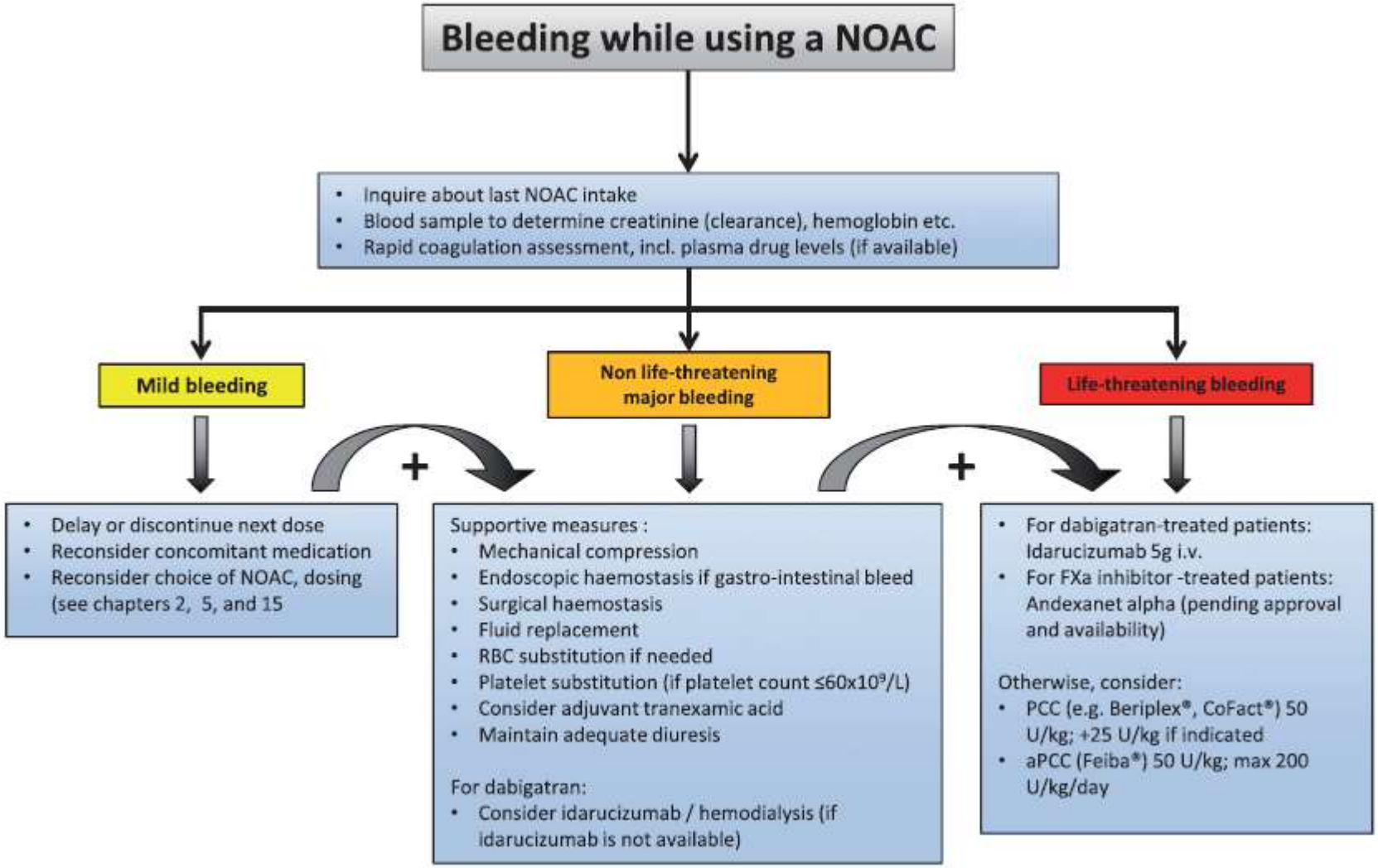
https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM606687.pdf
Accessed 06/10/2018

Rivaroxaban reversal with PCC/aPCC

Reference	Reversal agent	Model	Lab test	Bleeding
Perzborn 2013	PCC	Rat mesenteric bleeding	✓	✓
Zhou 2013	PCC	Mouse ICH	✗	✓
Godier 2012	PCC	Rabbit hepatosplenic bleeding	✓	✗
Eerenberg 2012	PCC	Human volunteers	✓	
Dinkelaar 2013	PCC	Human in vitro	✓	
Marlu 2012	PCC	Human ex vivo	✓	
Marlu 2012	aPCC	Human ex vivo	✓	
Perzborn 2013	aPCC	Rat mesenteric bleeding	✓	✓
Perzborn 2013	aPCC	Baboon mesenteric bleeding	✓	✓

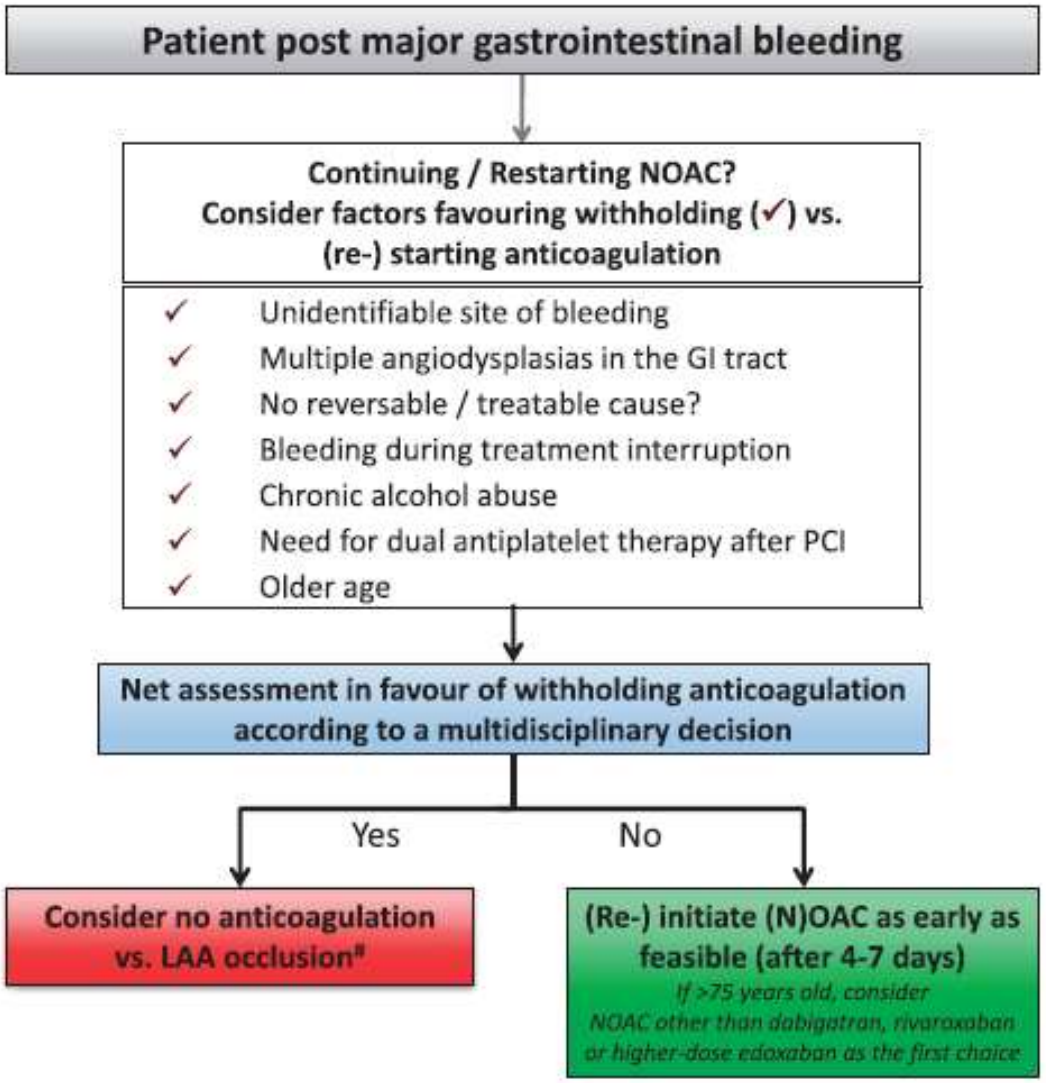
Recommended PCC (Beriplex/Octaplex) dose 50 units/kg (Steffel et al, ESC Guideline, EHJ 2018)

Management of Bleeding



Steffel et al, ESC Guideline, EHJ 2018

Anticoagulation after a GI bleed?

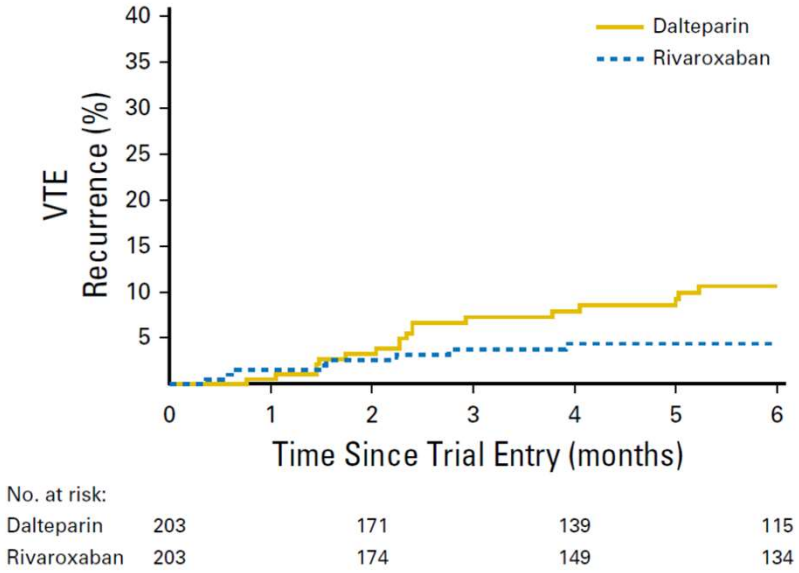


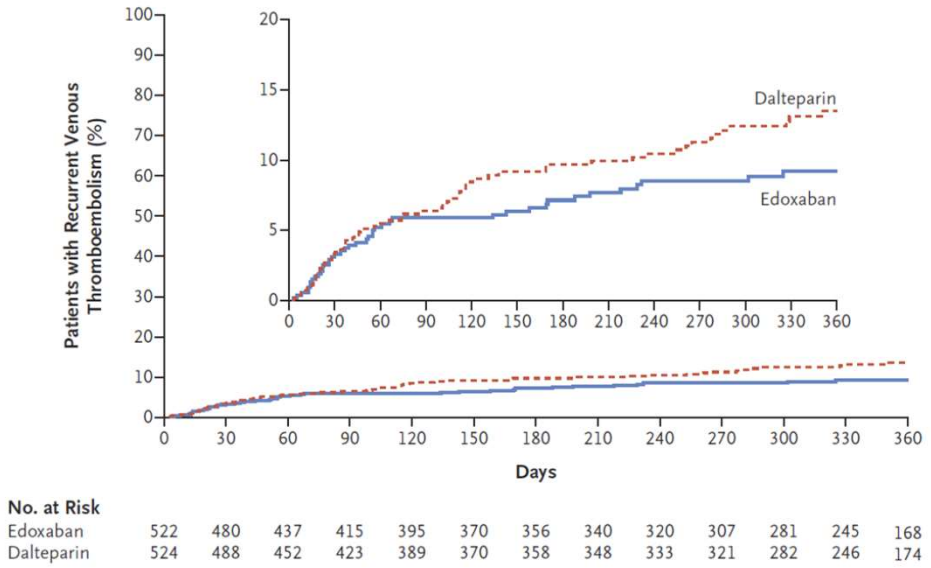
Steffel et al, ESC Guideline, EHJ 2018

Conclusion

- **DOACs are increasingly used in AF and VTE**
- **Major/life-threatening bleeding similar or less than with warfarin.**
  - ICH significantly less than with warfarin
  - GI bleeding slightly more than with warfarin (rivaroxaban, dabigatran, edoxaban)
- **Patient characteristics, drug and renal function important in assessing the risk/severity of a bleed.**
- **Routine coagulation testing on of limited use.**
- **Use general measures for all bleeds**
  - Idarucizumab for dabigatran reversal
  - PCC probably effective for bleeding with anti Xa agents
  - Andexanet alpha for rivaroxaban and apixaban reversal awaited
- **Individual approach to re-starting anticoagulation after GI bleed**

DOACs for VTE in malignancy
Select-D[1] and Hokusai[2] trials



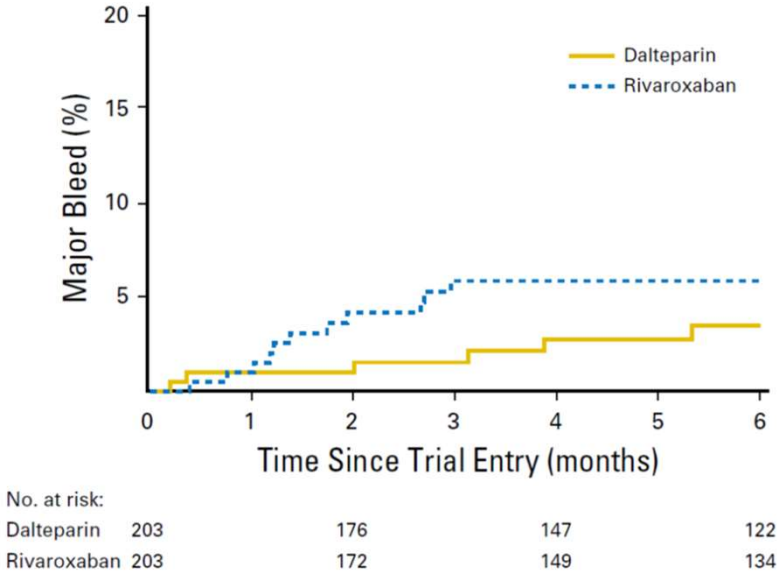


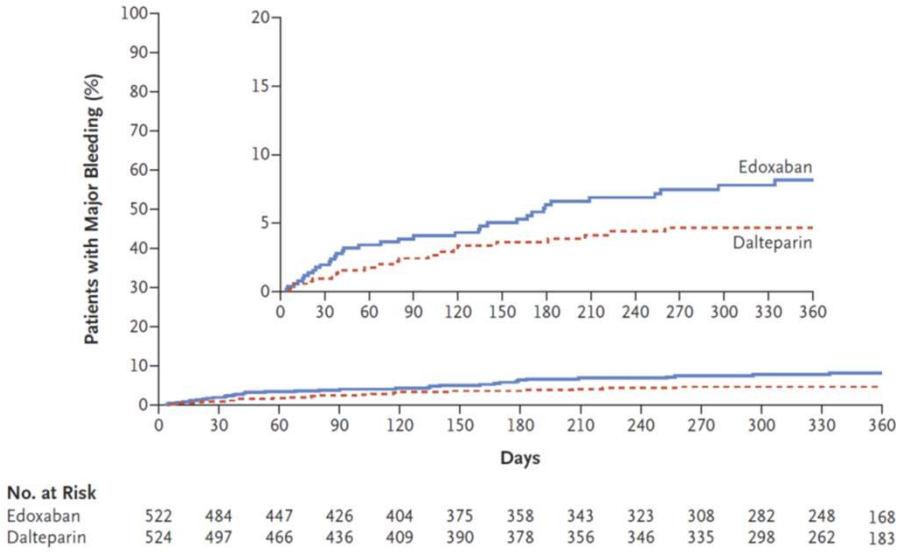
- Select-D recurrence at 6 months 11% vs 4%, HR 0.43; 95% CI, 0.19 to 0.99
- Hokusai recurrence at 12 months 11.3% vs 7.9%, HR 0.71 95% CI, 0.48 to 1.06;

1. Young et al J Clin Oncol 2018, 36:2017-2023.
2. Raskob et al N Engl J Med 2018;378:615-24.

DOACs for VTE in malignancy

Select-D[1] and Hokusai[2] trials



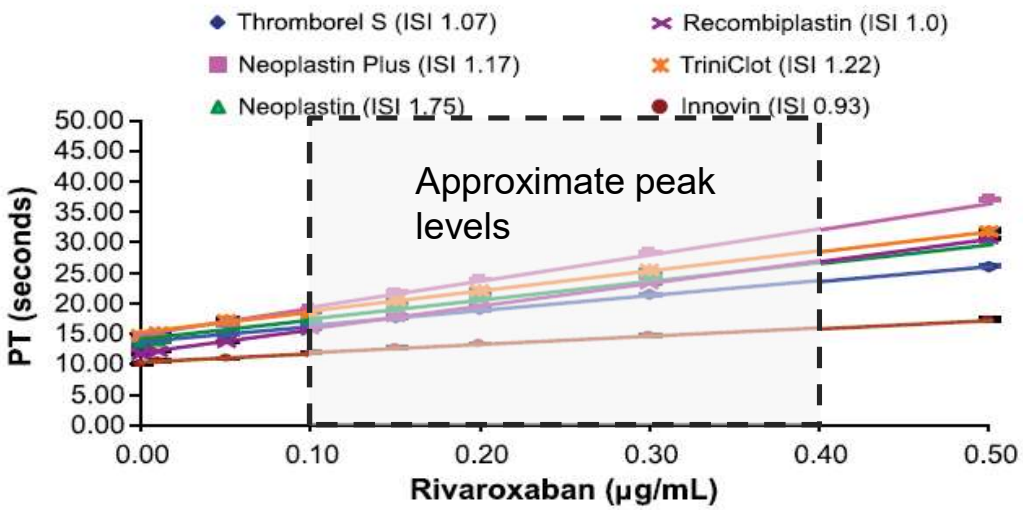


- Dalteparin vs rivaroxaban bleeding at 6 months 4% vs 6% HR,1.83; 95% CI, 0.68 to 4.96
- Dalteparin vs edoxaban bleeding at 12 months 4% vs 6.9% HR 1.77;95% CI, 1.03 to 3.04

Bleeding particularly in GI or urologic malignancy

1. Young et al J Clin Oncol 2018, 36:2017-2023.
2. Raskob et al N Engl J Med 2018;378:615-24.

The PT and anticoagulant intensity of Anti Xa agents

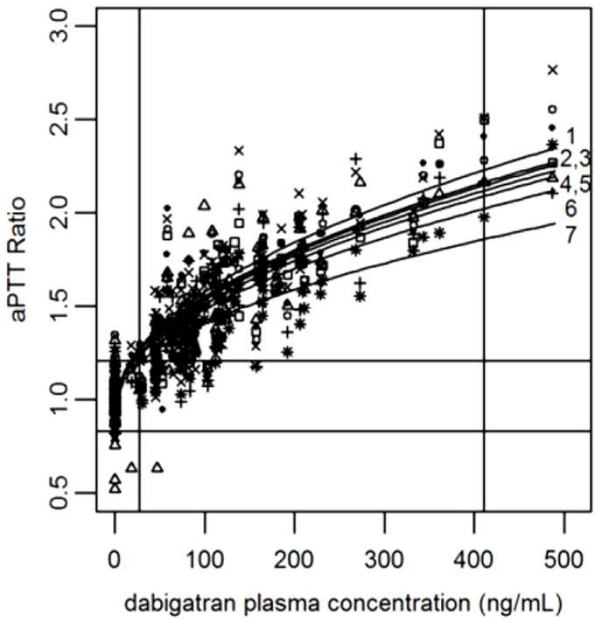


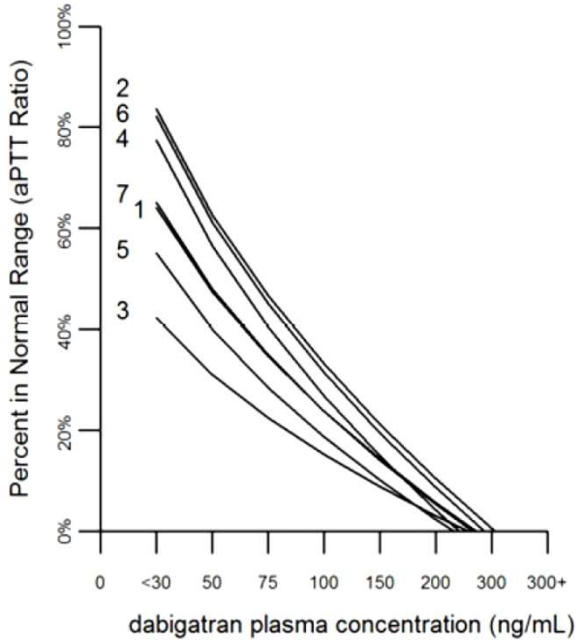
Adapted from Samama *et al* Thromb Haemost 2010; 103: 815–825

- **Rivaroxaban & Edoxaban: PT more sensitive than APTT**
  - Dependent on reagent used. Normal result does not exclude therapeutic levels.
- **Apixaban: PT more sensitive than APTT.**
  - Dependent on reagents but normal results are frequently found despite therapeutic levels.

Dabigatran and coagulation testing

Hawes et al Jth 2013. doi: 10.1111/jth.12308





- **15 – 35% of patients >100 ng/ml had normal APTT depending on reagent**
- **Normal thrombin time excludes the presence of dabigatran but too sensitive**