De waarde van stolling assays bij couperen van directe Xa en IIa remmers

Global coagulation tests; their applicability for measuring direct factor Xa- and thrombin inhibition and reversal of anticoagulation by prothrombin complex concentrate

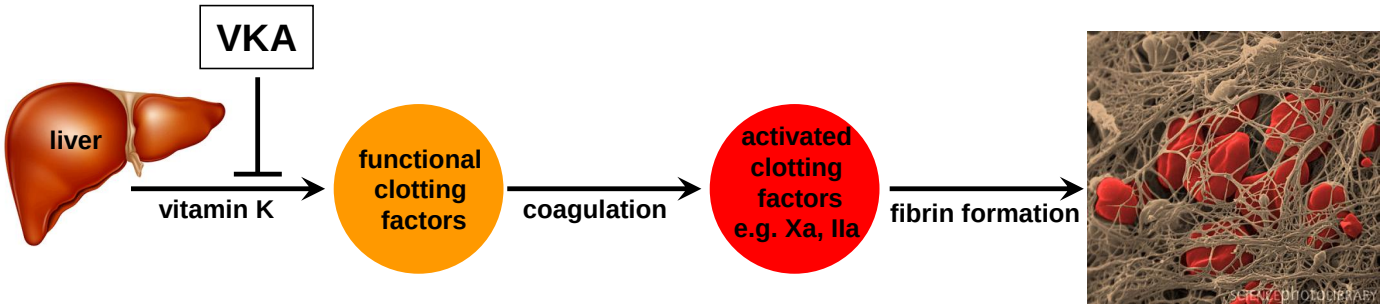
Jasper Dinkelaar, Sanne Patiwael, Job Harenberg, Anja Leyte, Herm Jan M. Brinkman

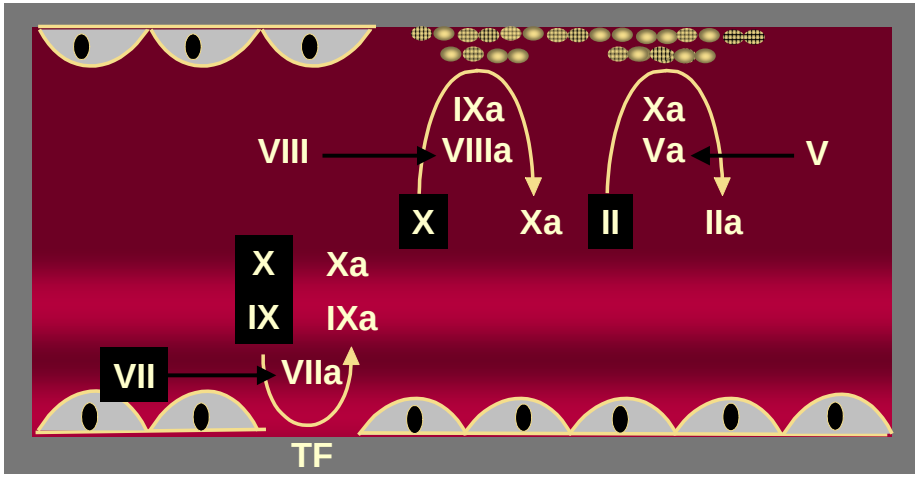
Jasper Dinkelaar

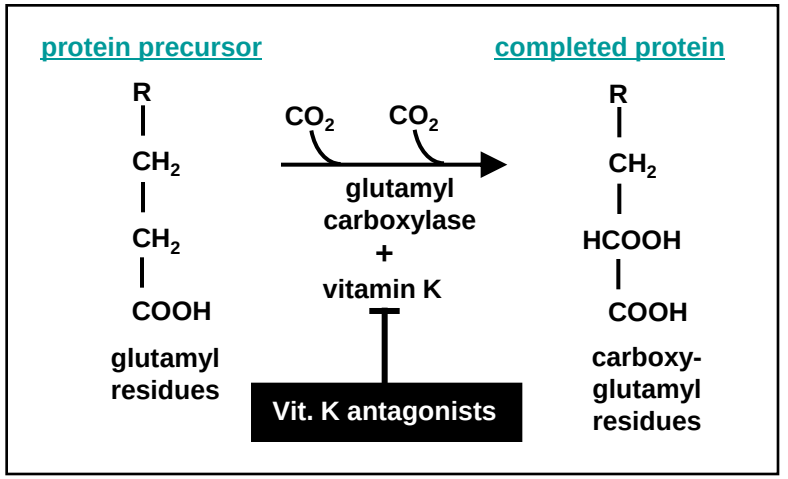
een santeon ziekenhuis

olvg

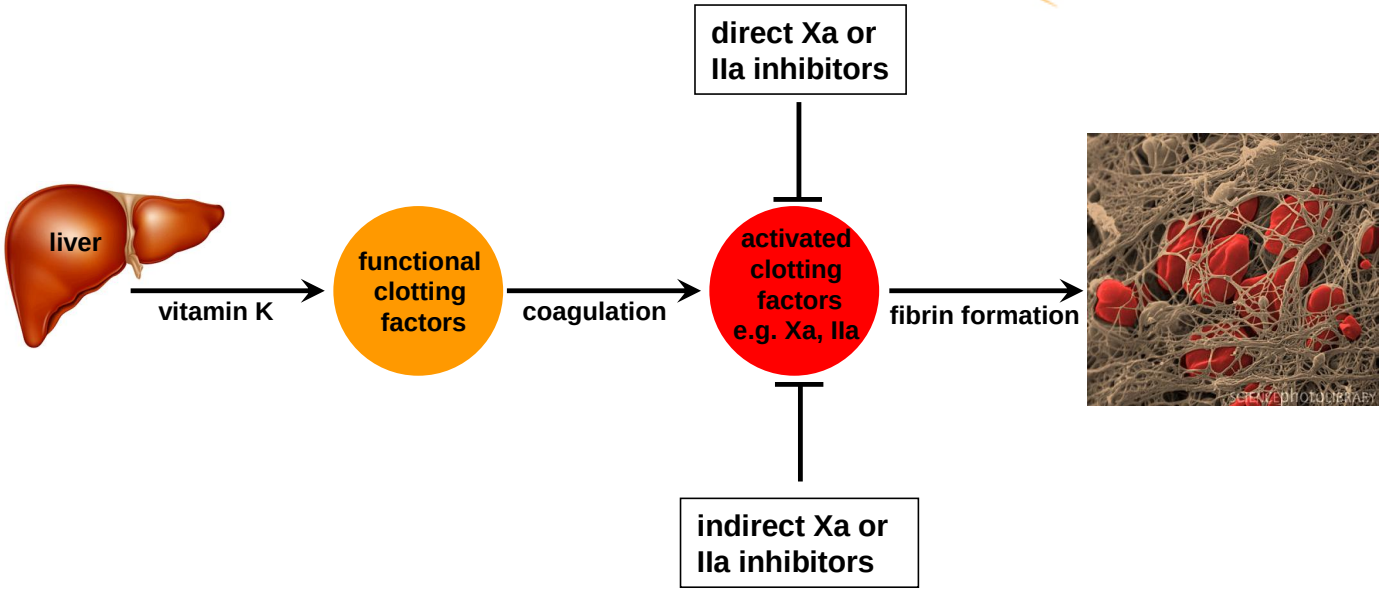
Vitamin K Antagonists (VKA)

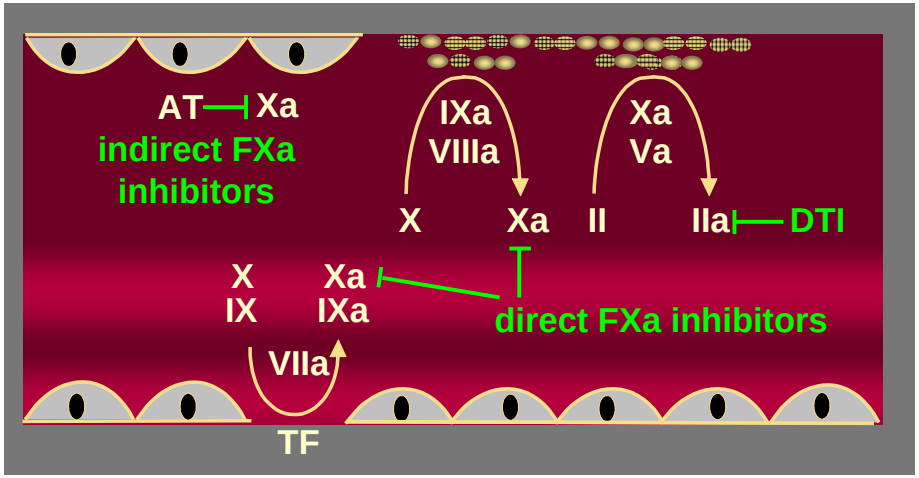






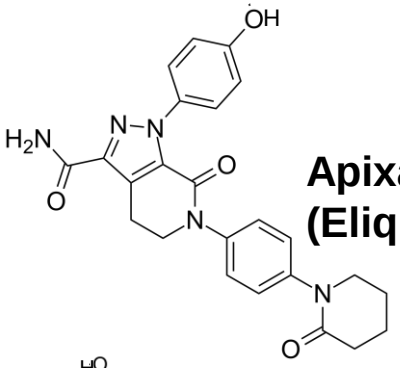
Target specific oral anticoagulants



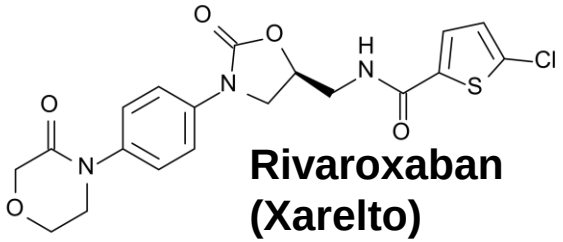


Non-vitamin K Direct Oral Anticoagulants

Xa inhibitors

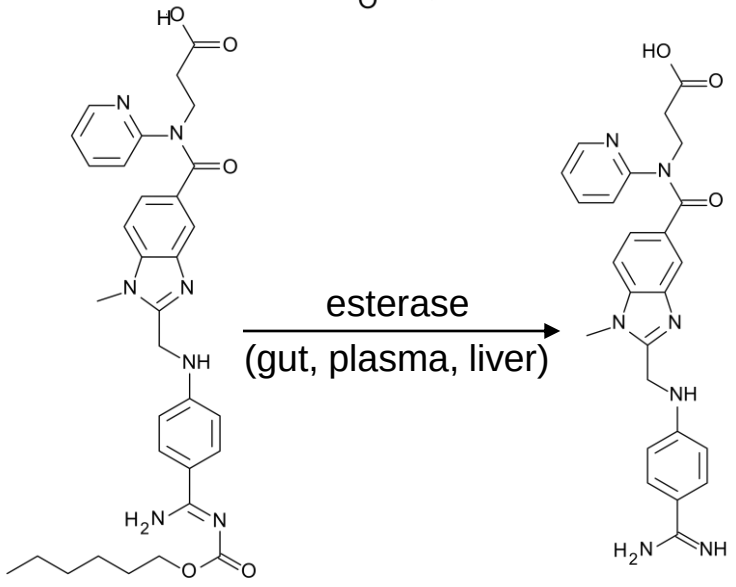


Apixaban (Eliquis)



Rivaroxaban (Xarelto)

IIa inhibitor



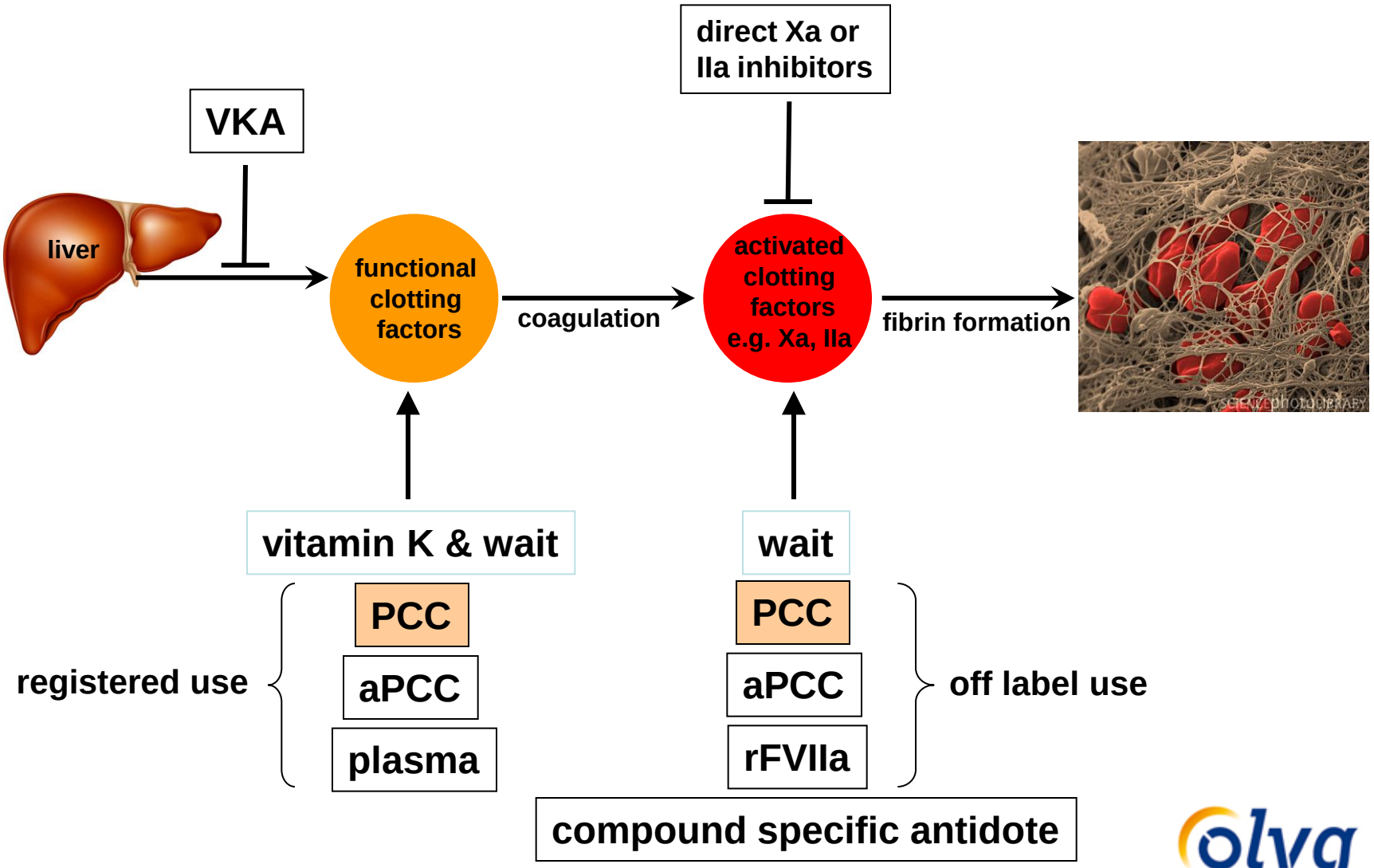
Dabigatran-etexilate (Pradaxa)

Dabigatran

DOACs

- competitive and reversible inhibitors
- bind to active site of Xa or IIa
- affect any assay that depends on Xa or IIa activity

Emergency reversal of oral anticoagulation



Emergency reversal of oral anticoagulation

VKA reversal by PCC

- Established clinical practice

DOAC reversal by PCC

- effective in animal bleeding studies:
  - Dabigatran: 5/6
  - Rivaroxaban: 3/4
- no clinical data
- correction of laboratory parameters: inconsistent data

Study Design

Plasma & Whole blood samples:

- Spiked with Dabigatran and Apixaban, up to 800 ug/l
  - Dabigatran: 150 mg -> mean plasma concentration 93-184 ug/l[1]
  - Apixaban: 5 mg -> mean plasma concentration 50-128 ug/l[1]
- Spiked with PCC up to 4 IU/ml plasma
  - Approximately 1 IU/ml to normalize an INR of 7.5[2]

Plasma:

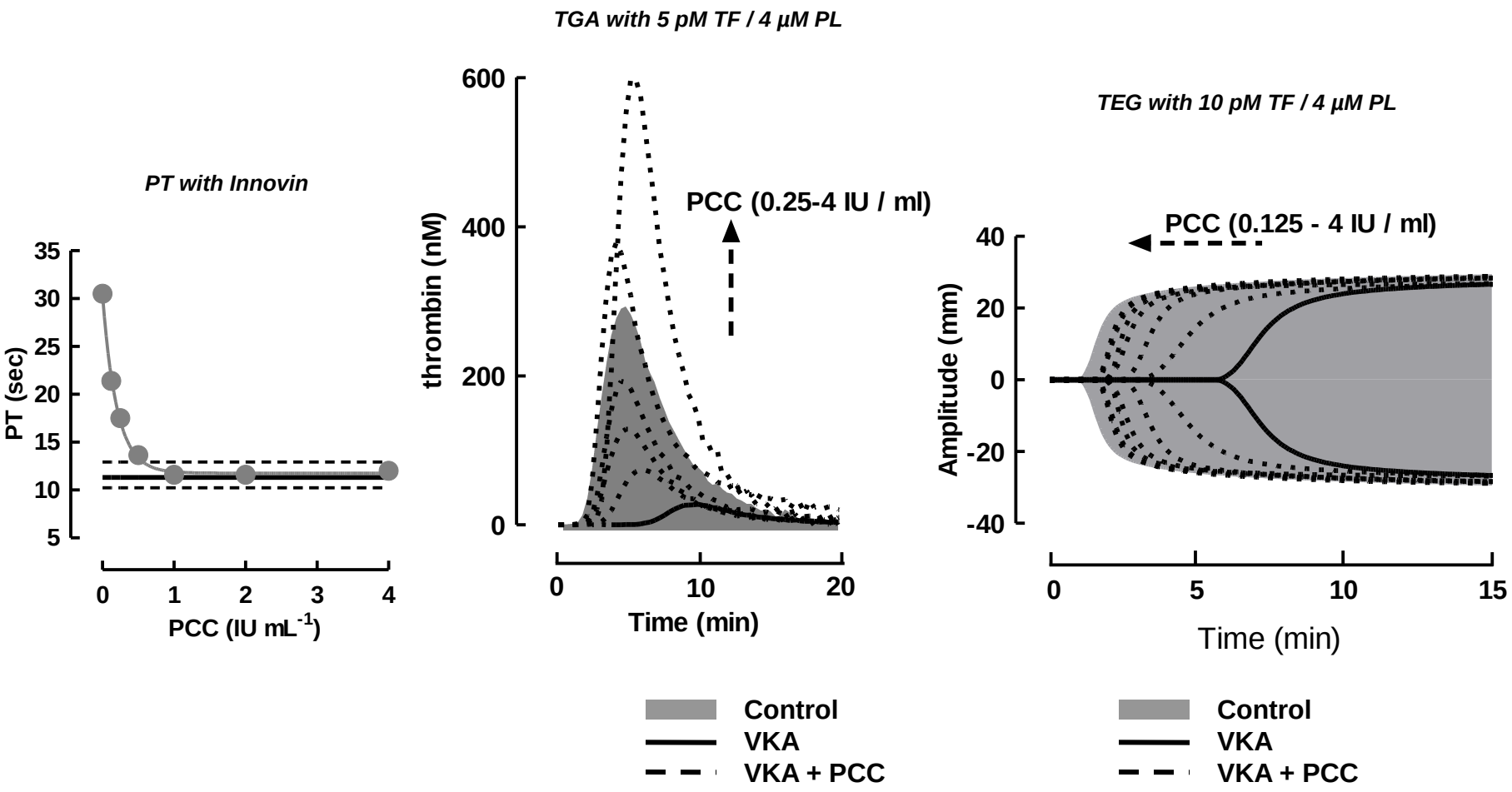
- Prothrombin Time (PT)
- Thrombin generation (CAT)
- Thromboelastography (TEG)

Whole blood:

- Thromboelastography
  - TEG
  - ROTEM

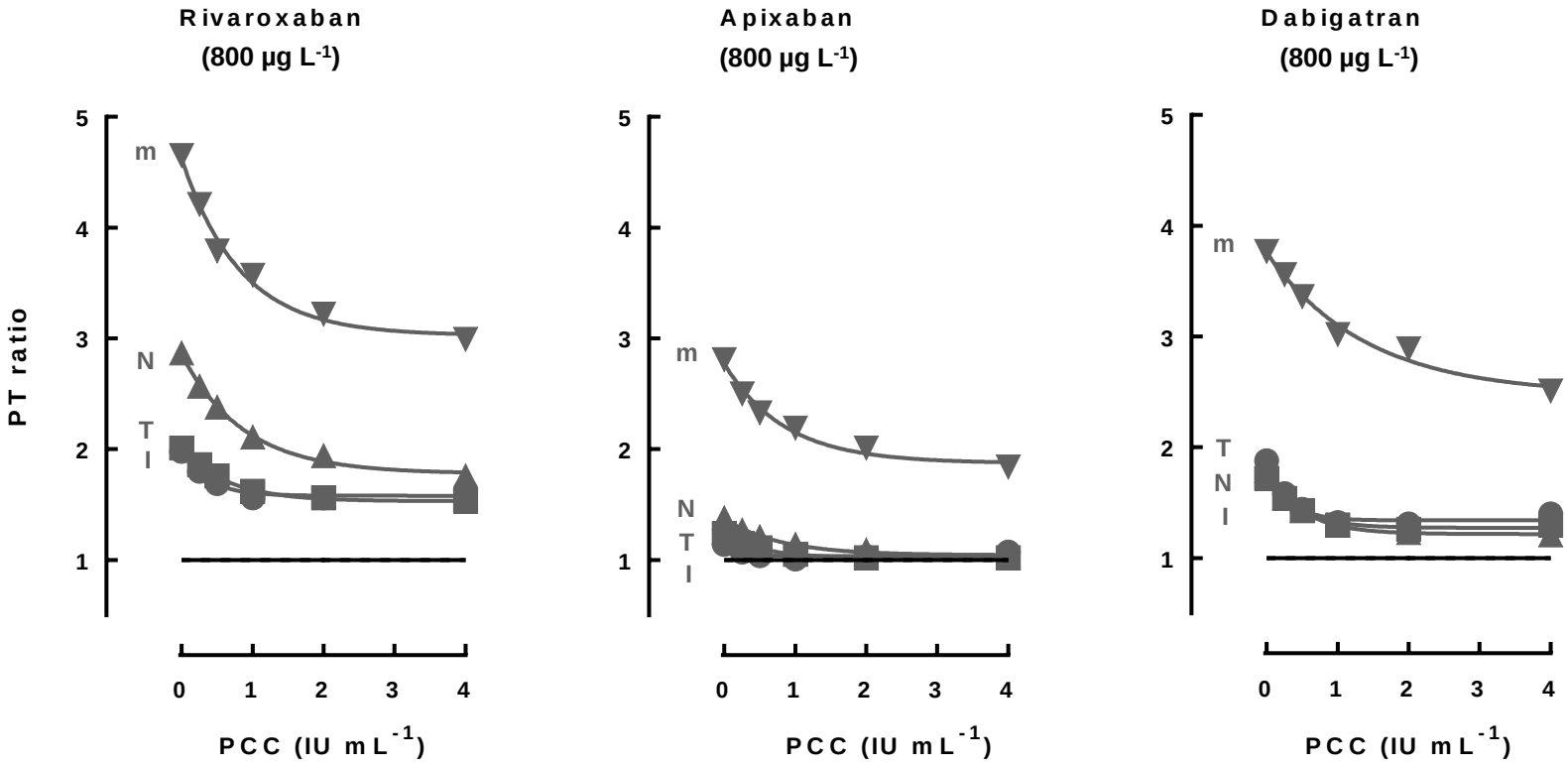
[1] Frost C, et al. Br J Clin Pharmacol. 2013; 76: 776-86, Clemens et al. A Curr Med Res Opin. 2012; 28: 195-201
[2] Sanquin product information

VKA reversal by PCC



Sanquin 2013

DOAC reversal by PCC with PT



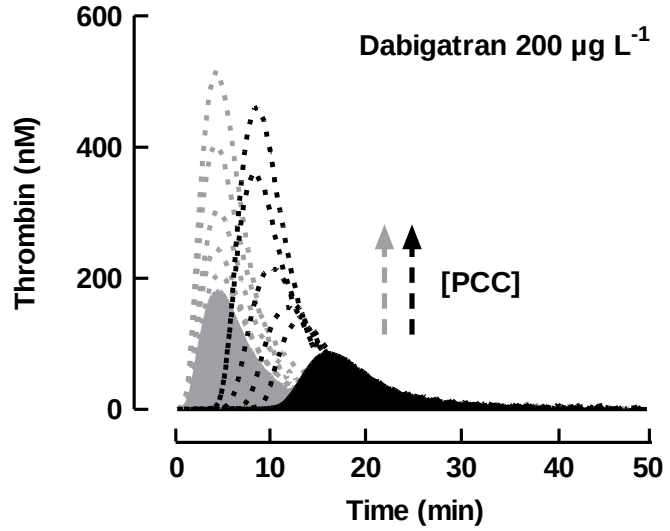
▲, N Neoplastine

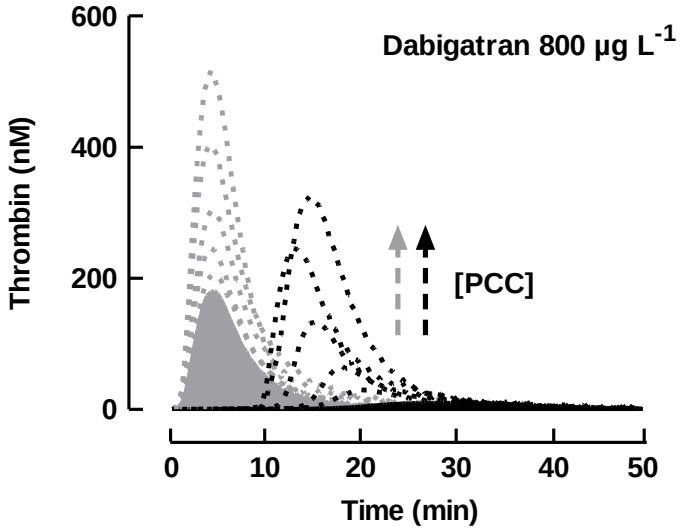
■, T Thromborel

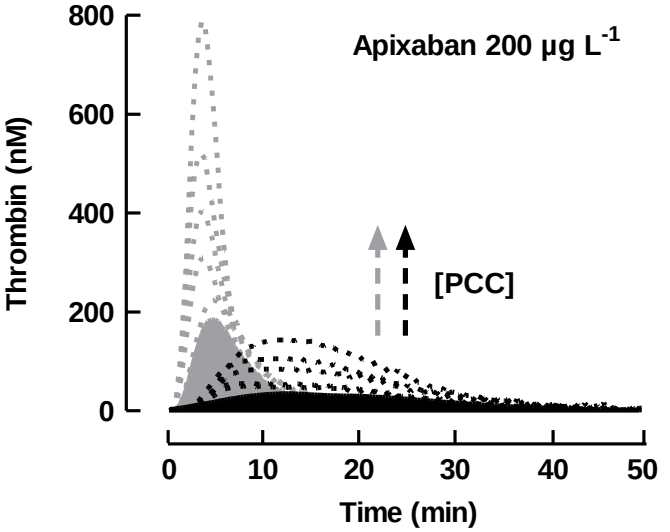
●, I Innovin

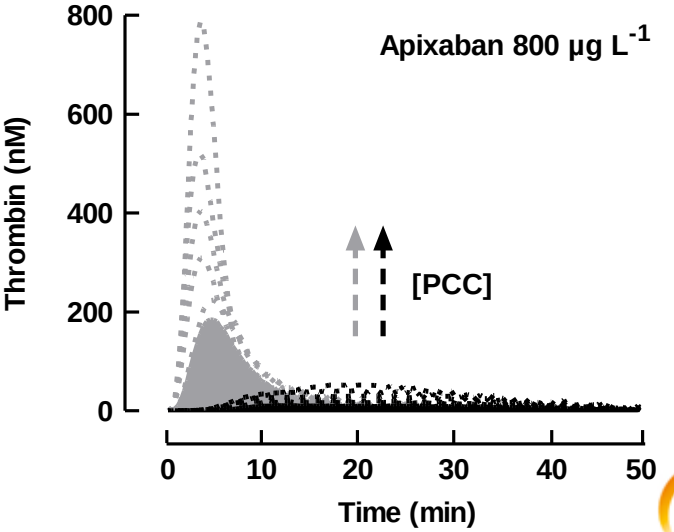
▼, m modified: Thromborel diluted 2.25 fold in 80 mM $CaCl_2$ (Frost 2013 Br J Clin Pharmacol)

DOAC reversal by PCC with Thrombin generation

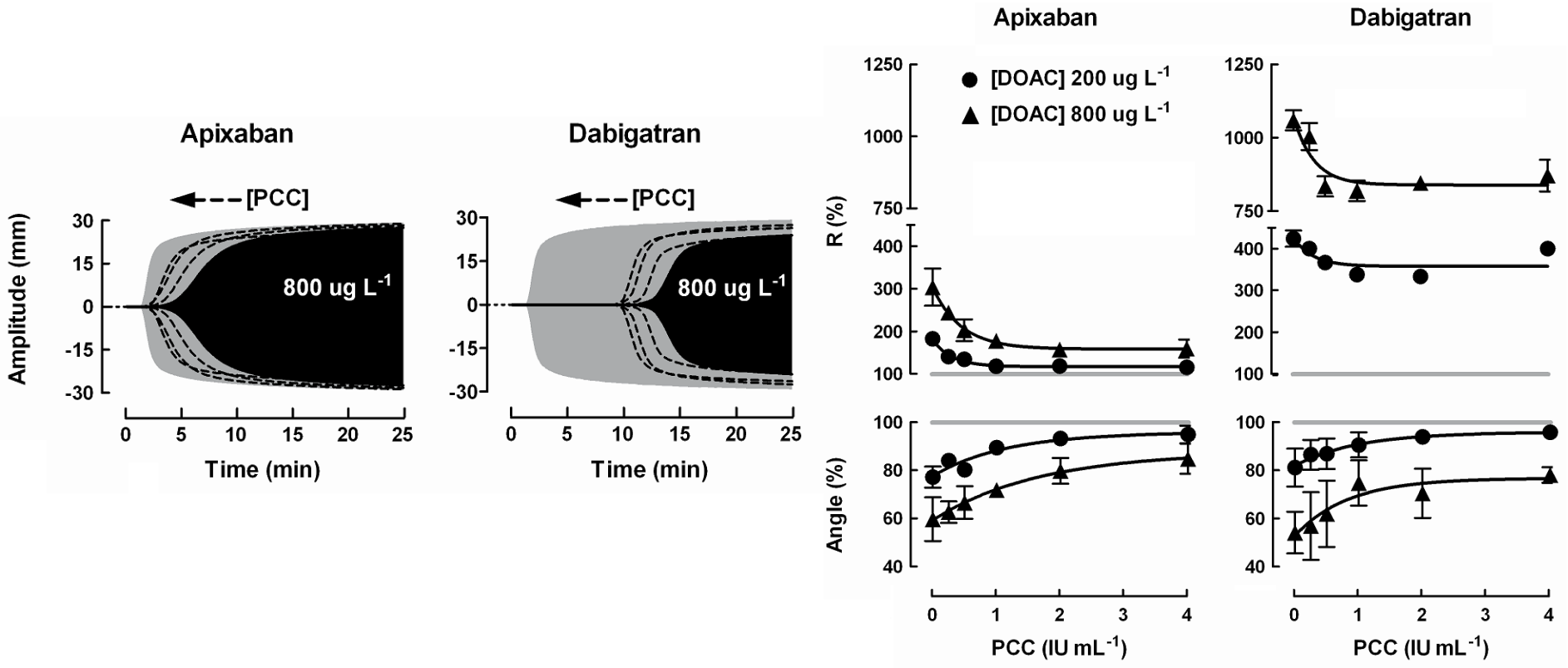




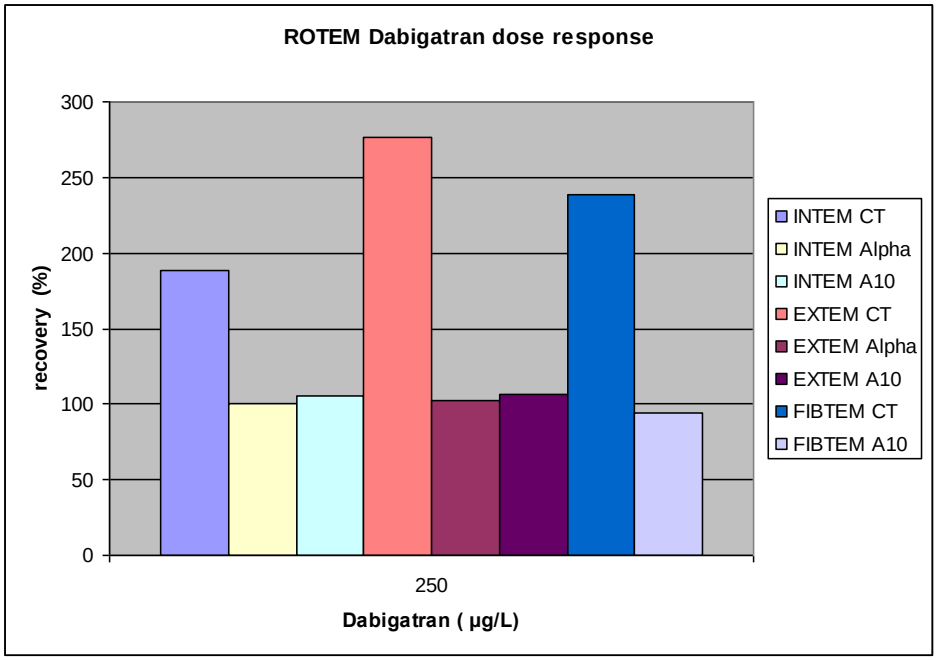


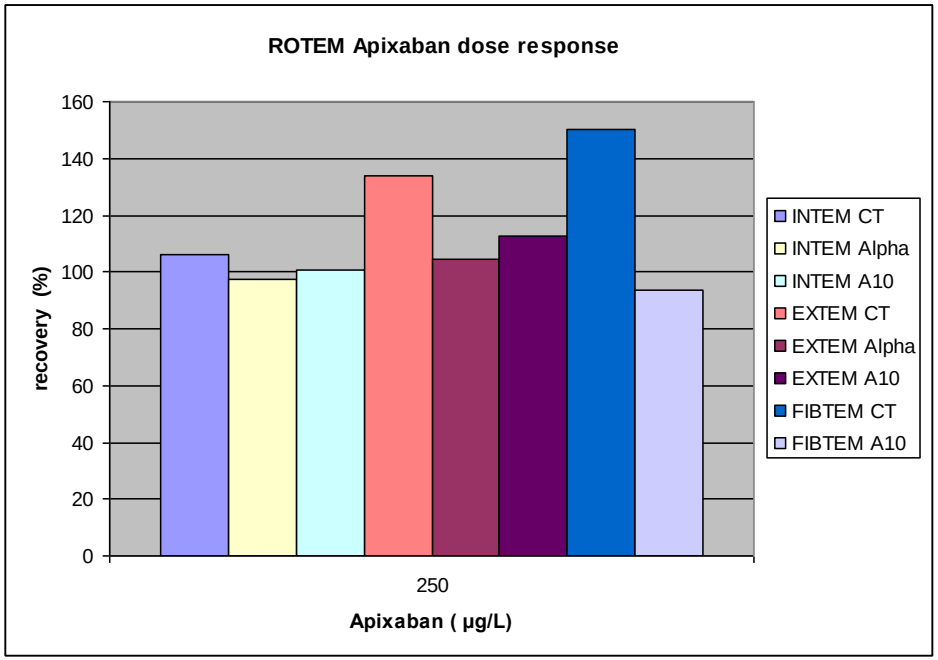


DOAC reversal by PCC with Thromboelastography (Plasma)



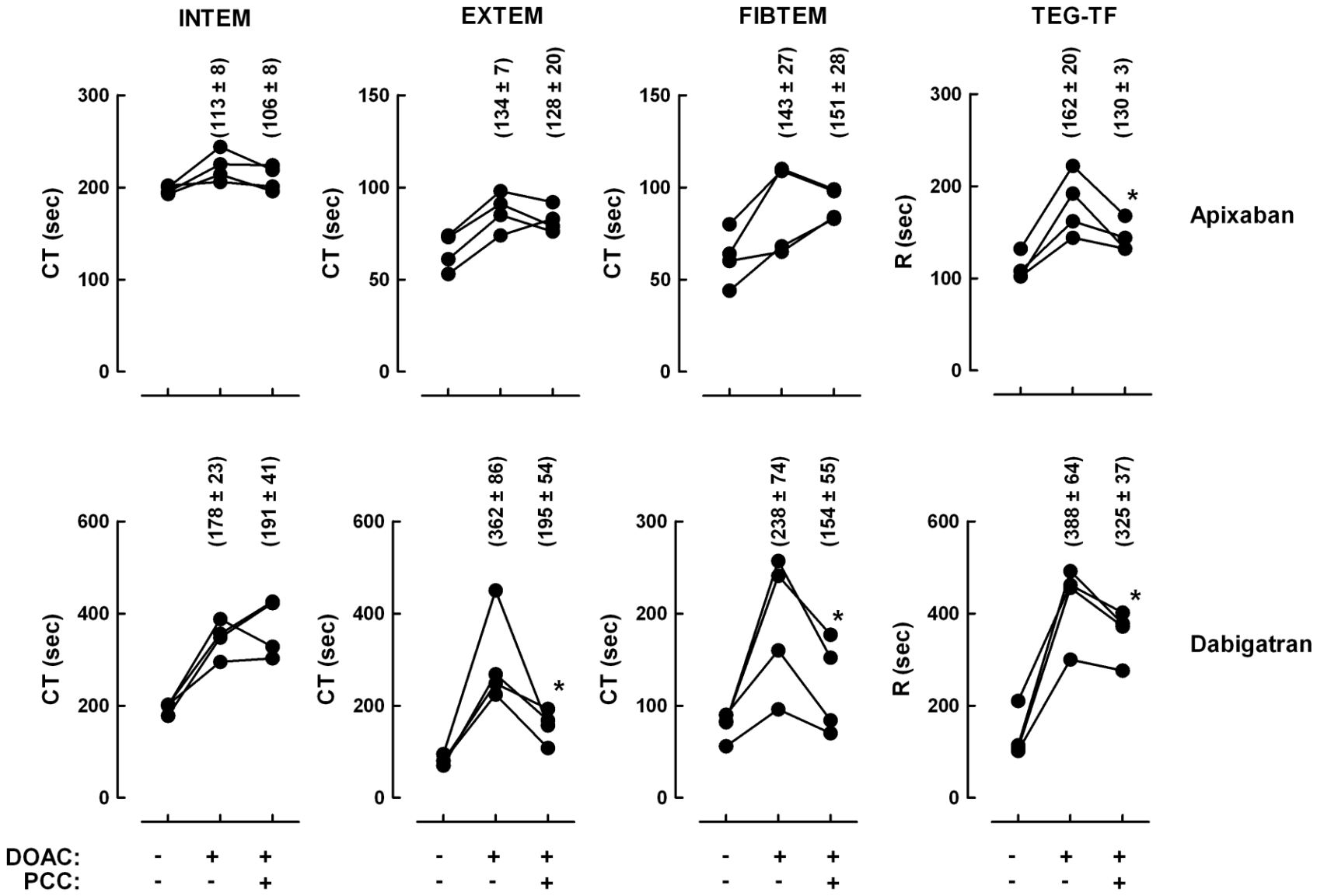
ROTEM response to DOAC





- Concentration in whole blood: 250 ug/l -> +/- 500 ug/l in plasma
- Only CT is affected
- Contact activation (INTEM) less response
- Apixaban smaller dose response

DOAC reversal by PCC in Whole Blood



conclusion

- Concentration TF is crucial in DOAC sensitivity
- Contact activation shows less response (INTEM)
- Increasing coagulation factors restores AUC (CAT)
- PT, CT-CAT, R-TEG (TF) and CT-ROTEM (EXTEM) reach plateau values

Assay	Applicability in monitoring DOAC reversal by PCC
APTT	- Not applicable
PT	- Extent of reversal depends on DOAC type, and [DOAC]
TGA	- Extent of reversal depends on DOAC type, [DOAC], [TF] - AUC: general applicable (normalization / overcorrection) - Dabigatran in reference wells containing calibrator (CAT assay) should be avoided
TEG, ROTEM	- Extent of reversal depends on DOAC type, [DOAC], reagent - R or CT general applicable (partial normalization) - INTEM not applicable