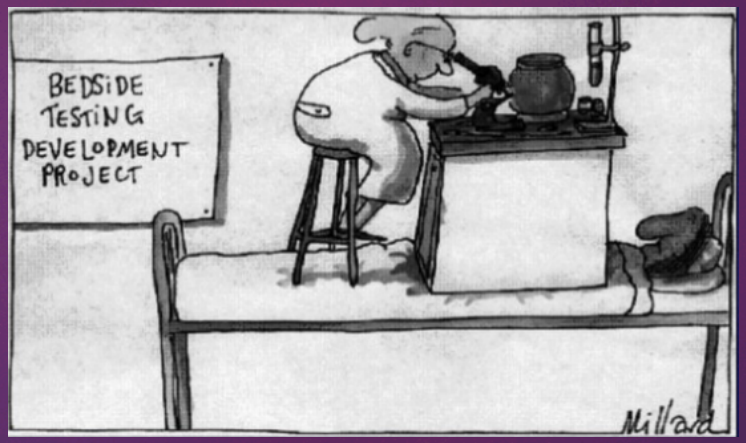
Can we bring the lab to the OR?

"The heparin monitoring dilemma"



DR. E. KEMNA, LABORATORY SPECIALIST CLINICAL CHEMISTRY AND HEMATOLOGY, MEDLON, ENSCHEDE, THE NETHERLANDS

Where…?

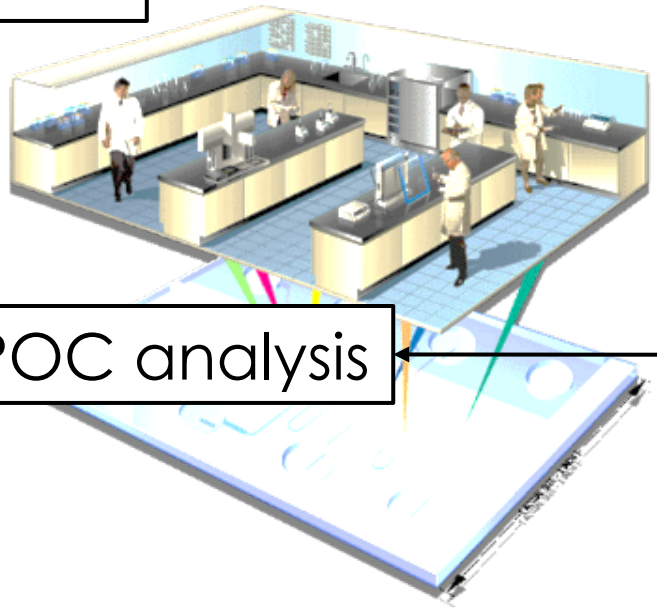
POC devices at the GP

- urinary dip sticks
- CRP
- HBA1c
- Glucose
- D-dimer, etc

POC devices at the hospital

- urinary dip sticks
- Blood gass, electrolytes
- Viscoelastic testing
- HBA1c
- Glucose
- D-dimer
- PT(INR) etc

What has the lab to offer?



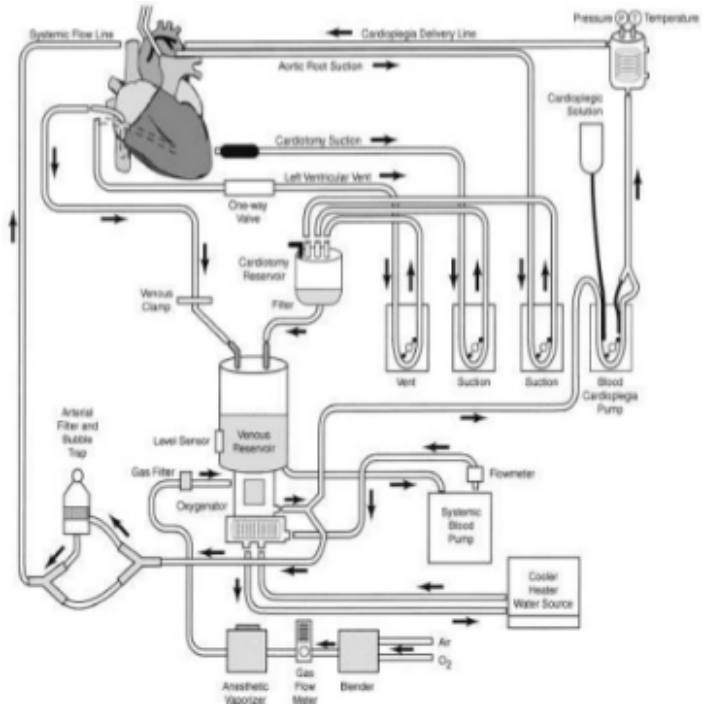
What has the lab to offer?

Vital function	Central lab	POCT
Acid base	pH pCO2 bicarbonate	
Energy and perfusion	Glucose Hemoglobin pO2 Saturation Lactate	
Conduction	Potassium Sodium Calcium Magnesium	
Osmolality	Measured osmol	
Haemostasis	Ht, PT/APTT ACT PT # and function D-dimer Viscoelastic testing etc	

(anti)coagulation monitoring in the OR

"The heparin monitoring dilemma"

VS



Cardiac Operation - diagnostics

Operations follow the same pattern:

- pre – CPB
  - Baseline coagulation profile, ABG before CPB,
- During CPB
  - ABG and ACT every 20 – 30 min, Assess coagulopathy
- post – CPB
  - ABG after weaning form CPB, ACT after protamine, Coagulation assessment

What would you do?

Patiënt A. Preparing for CPB

Baseline ACT value -> 124 s

Start heparin infusion of 400 U/kg

First ACT result is 460 s (local target to go on CPB is >440s)

Heparin monitoring – Once upon a time…

1918 Discovery of heparin.

1930s Perfectioning for safe clinical use.

1939 Used in animal CPB

1953 Used in human CPB

Still, monitoring was empirically done…

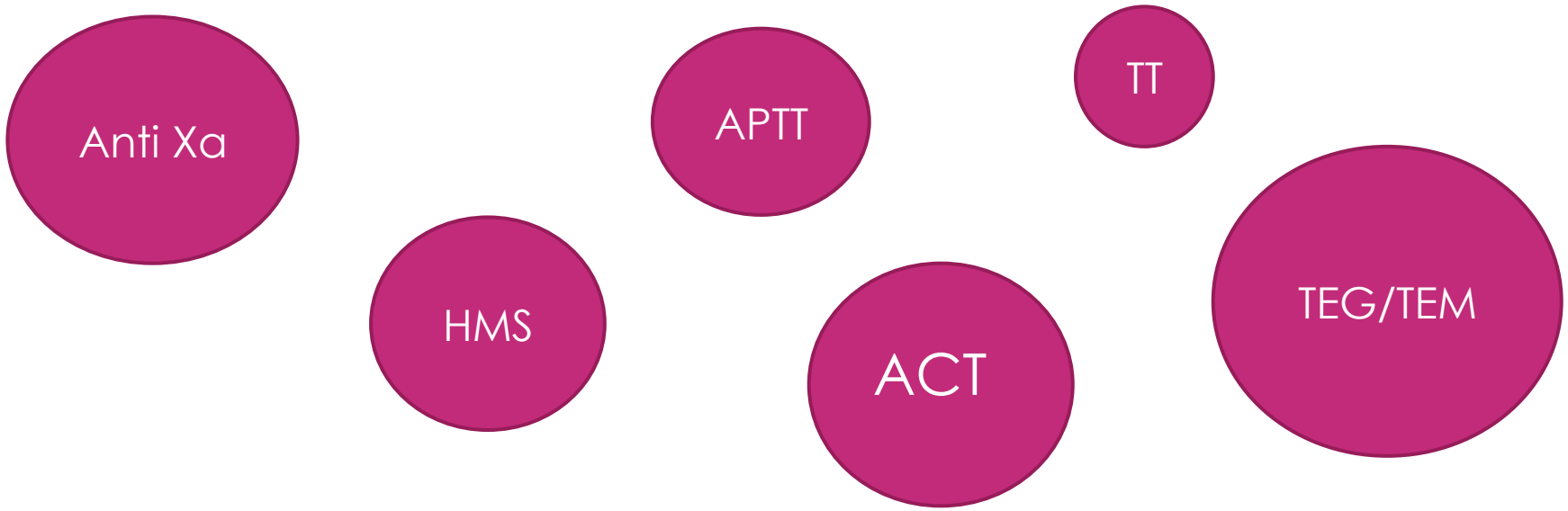
1966 Hattersley first described ACT and it was introduced by Bull in cardiac surgery in the 70's

ACT evolved from virtually nonexistent to widespread during next 5 years.

Overview - Standard tests of coagulation

	Screening/monitoring	Confirming lab
Whole blood	~~Hb, Ht~~ ~~Thrombocyte count~~ ~~PFA/Multiplate~~ ROTEM/TEG ACT Heparin Management System	
Plasma	~~PT/INR~~ APTT ~~APTT 1:1~~ Thrombin time ~~HIT~~ ~~D dimeer~~	~~Fibrinogen~~ ~~AT~~ ~~Factor analysis~~ Anti-Xa ~~Platelet aggregetaion~~

The Heparin Monitoring Dilemma Bring it to the OR

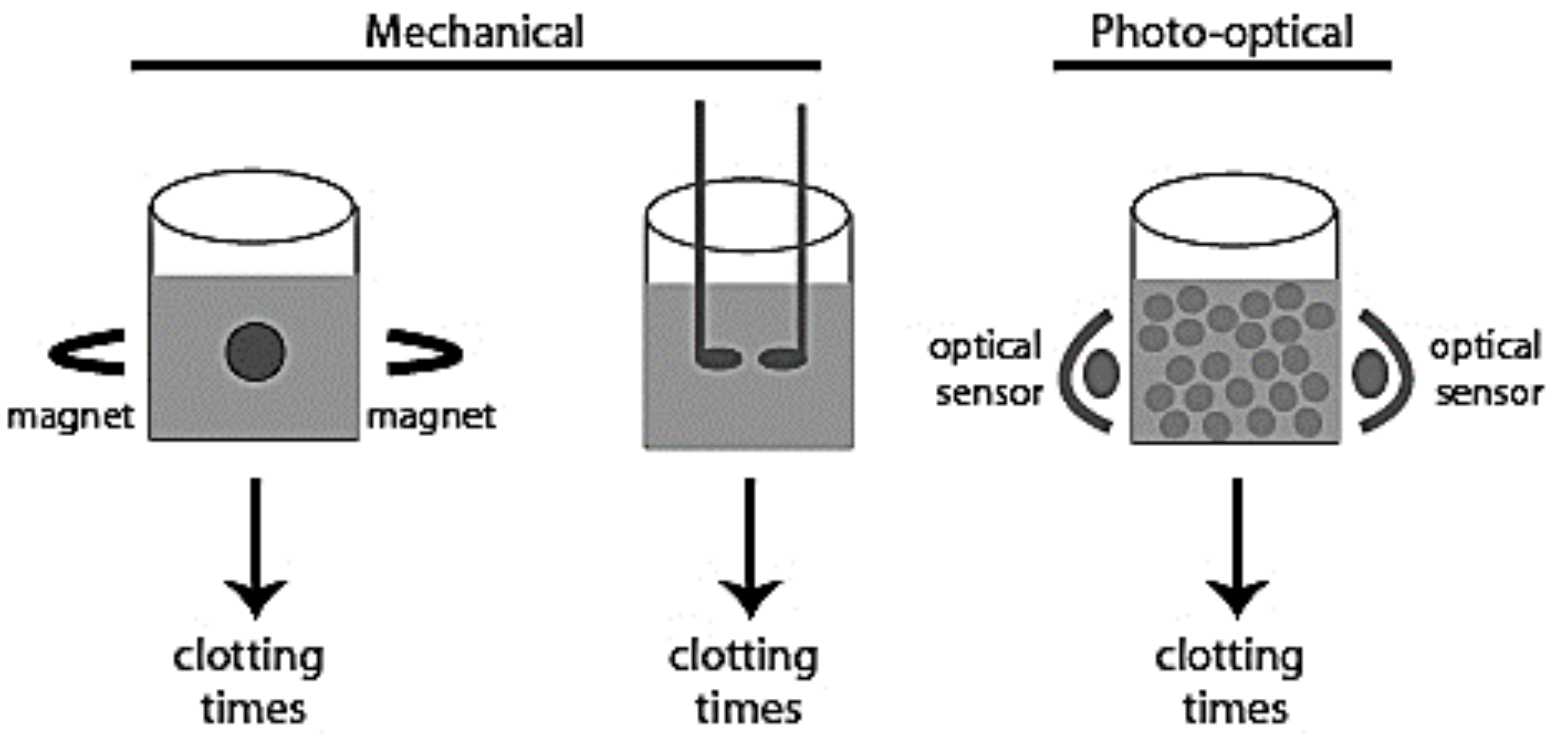


Which test and/or value gives best representation of anticoagulation level?

ACT - Today

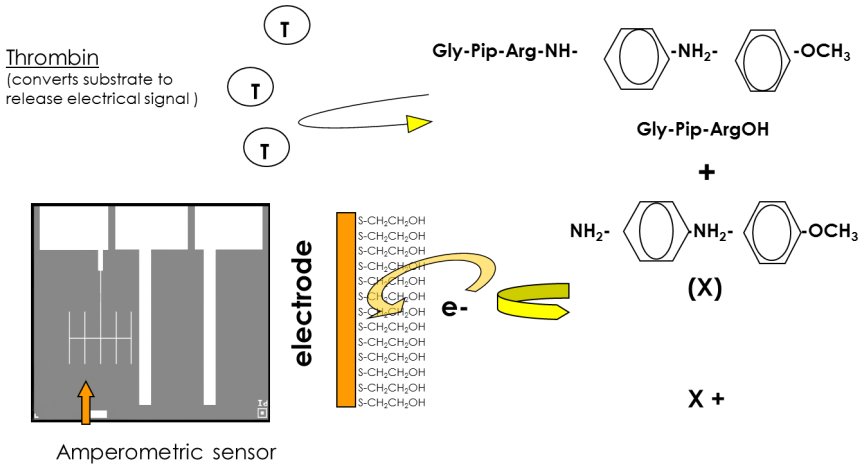
- Hemochron Response
- Hemochron *Signature* Elite
- Medtronics ACT Plus
- Medtronics HMS+
- Helena Actalyke XL / Mini
- Gem PCL
- Abbott i-STAT
- ,,,,,,,

ACT - Detection systems



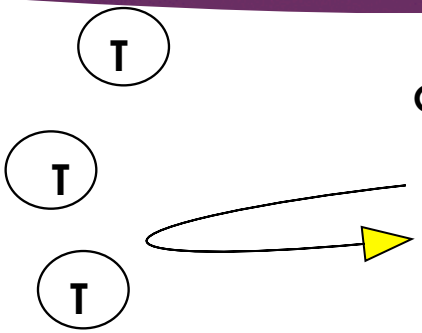
ACT - iSTAT

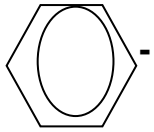
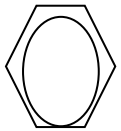
- Chemical detection of thrombin formation
  - Derivation of lab chromogenic testing
- Electrochemical sensor measures specific substrate conversion
- Amperometrical detection of electroactive substance in seconds



Thrombin detection

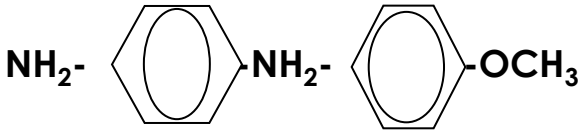
Thrombin
(converts substrate to release electrical signal)



Gly-Pip-Arg-NH-  -NH_2-  -OCH_3

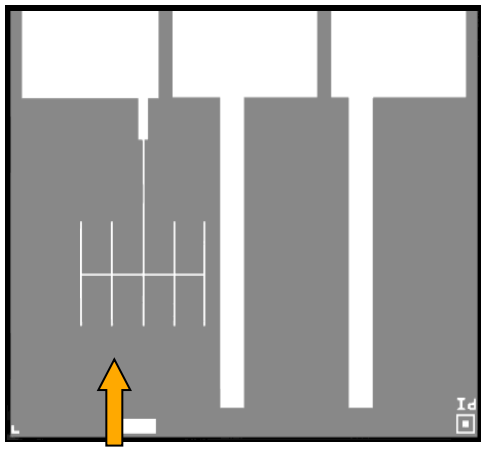
Gly-Pip-ArgOH

+

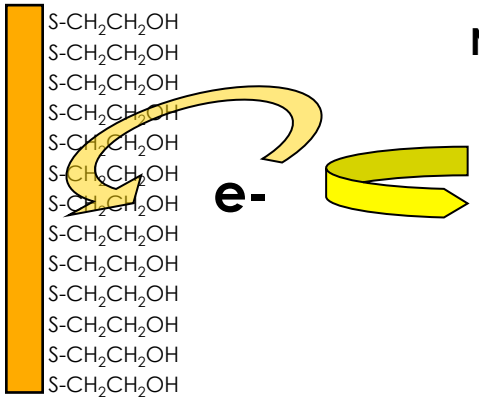


(X)

X +



Amperometric sensor




ITC
HEMOCHRON
Signature Elite
ITC
CHARGE
START
NOTE
ID
QC
DATA BASE
PRINT/ SCAN
CANCEL
ENTER
MENU


i-STAT
BLOOD GASES
ELECTROLYTES
CHEMISTRIES
Hgb & Hct
ACT
GLUCOSE STRIPS
CARDIAC Troponin I
Scan

Laboratory guidelines

Guidelines for medical laboratories ISO 15189 (2012): "Specifies requirements for quality and competence in medical laboratories "

POCT ISO 22870 (2006) 'Point-of-Care -requirements for quality and competence':

- Procedures for selection and use of POCT are under supervison of the laboratory.
- Adequate training programs
- POCT linking with lab information systems, certificating en re-certification

Laboratory guidelines

CLSI (clinical & laboratory Standards Institute) (2004): "POC Monitoring of Anticoagulation Therapy "

- Tests should be performed according to manufacturer's directions
- No "standard" ACT, need to establish normal and therapeutic ranges for each system and activator used.
- Select appropriate system for clinical application and heparin ranges.
- Be aware of (pre)analytical variables
  - Platelet # and function
  - Hypothermia and/or hemodilution
  - Different detection systems
  - Deviation from the manufacturer's instructions

  Etcetera

CLINICAL AND LABORATORY STANDARDS INSTITUTE ™

(Formerly NCCLS)
Providing NCCLS standards and guidelines, ISO/TC 212 standards, and ISO/TC 76 standards

Recommendations

Extracorporeal Life Support Organization (2014):

- ACT most commonly used test to dictate UFH dosage. However, state potential shortcomings of ACT alone and mention complementing with more elaborate tests like aXa.

European Society of Cardiology: Guidelines on myocardial revascularization (2014):

- No role for ACT during PCI

Recommendations

British Committee for Standards in Hematology and National Academy of Clinical Biochemistry (2006)

- Recommend ACT to monitor heparin dose during cardiac surgery

Is there evidence of improved clinical outcome with ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In interventional cardiology?

Guideline 31. *We strongly recommend ACT monitoring of heparin anticoagulation and neutralization during interventional cardiology procedures.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials, nonrandomized controlled trials, and case-controlled analytic studies from more than 1 center or research group)

Guideline 32. *We recommend the use of target times specific to ACT system used that differ if specific platelet inhibitors are used concurrently with heparin. Without intravenous platelet inhibitors, the evidence suggests that targets of >250 seconds with the Medtronic ACTII or >300 seconds with the Hemochron FTCA510 tube assay are appropriate.*

Strength/consensus of recommendation: B

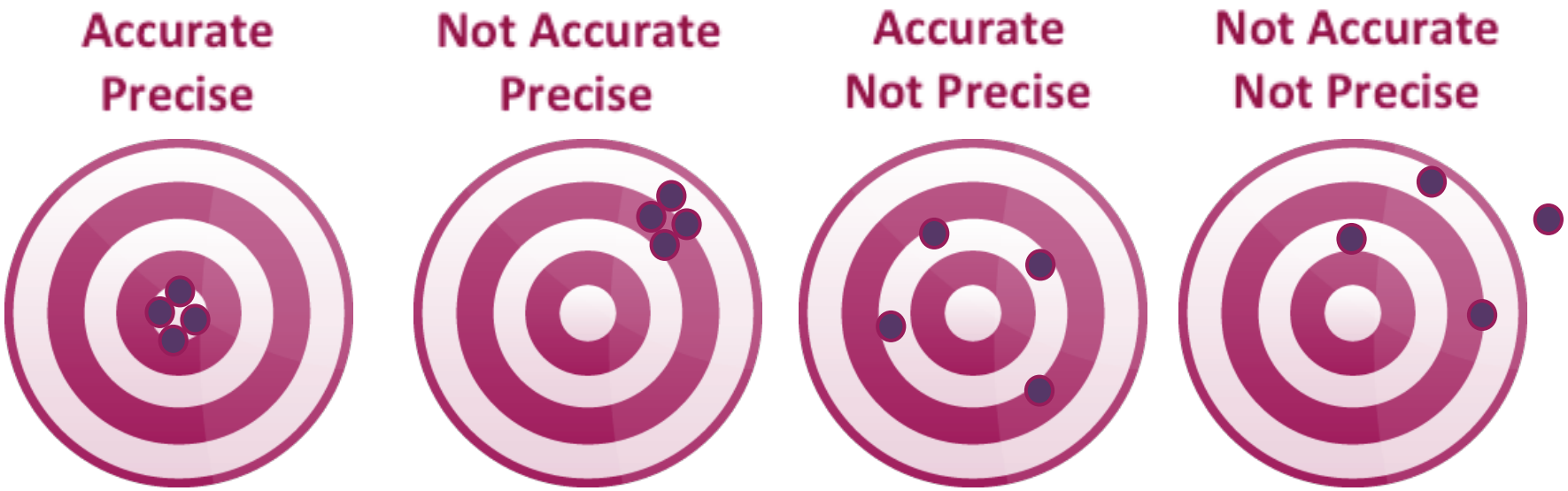
Level of evidence: II (small randomized controlled trials, nonrandomized controlled trials, case-controlled analytic studies from more than 1 center or research group)

Guideline 33. *With the intravenous platelet inhibitors abciximab or eptifibatide, a target of 200–300 seconds is recommended; with tirofiban, a somewhat tighter range of 250–300 seconds is recommended.*

Strength/consensus of recommendation: B

Level of evidence: I (at least 1 randomized controlled trial)

Laboratory test interpretation



ACT and quality assurance

- Some form of external assessment is essential to confirm accuracy and is recommended in the ISO22870.
- No agreed formal EQA program for ACT measurement at this point in time
- no ‘gold standard’ ACT method, which makes EQA even more important when attempting to achieve some sort of standardization.

What would you do? Part 2

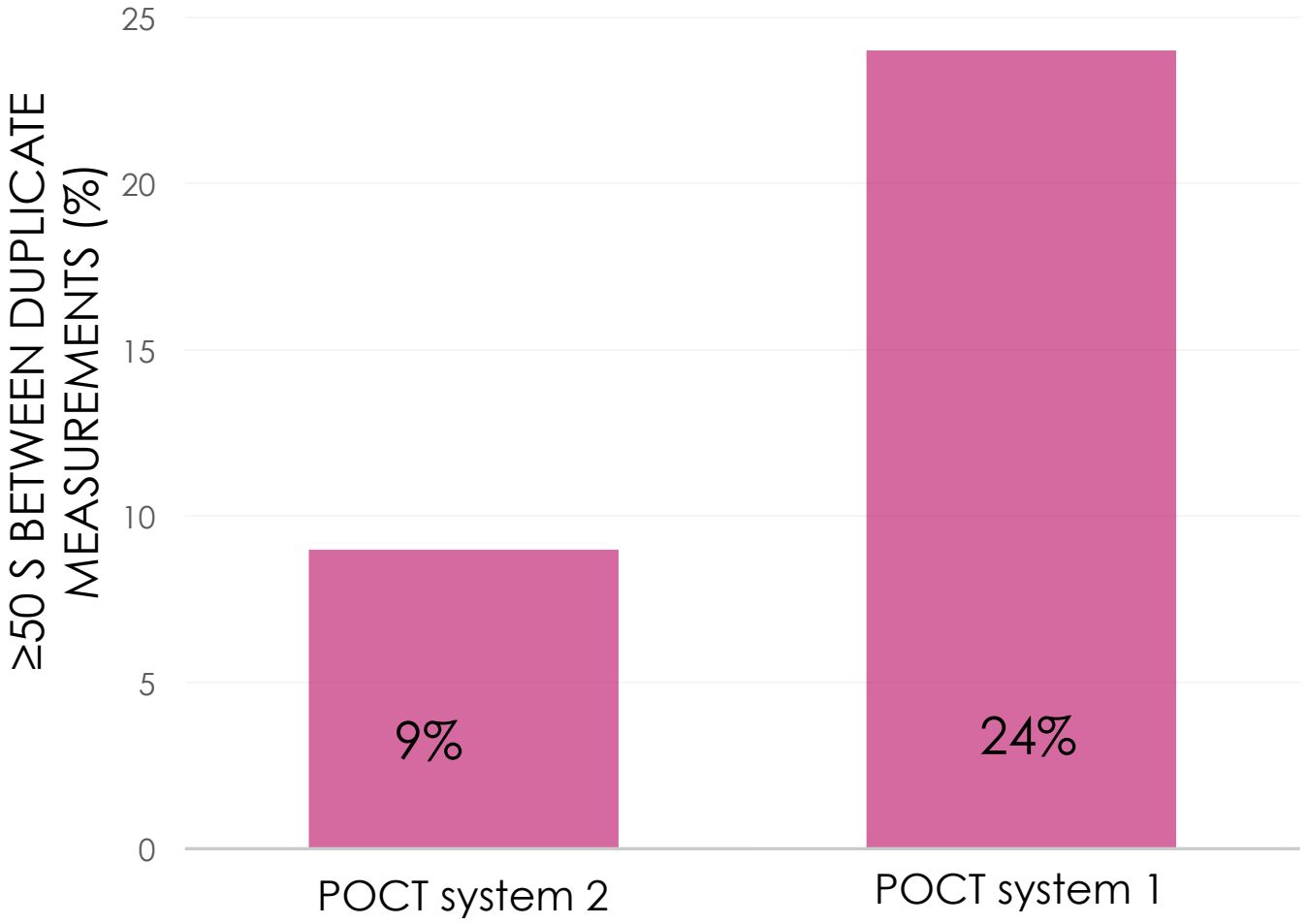
Patiënt A, had an ACT of 460 and is starting on CPB.

After 20 minutes the ACT is checked again.

First result is 420 sec and extra heparin is administered (10000 EH)

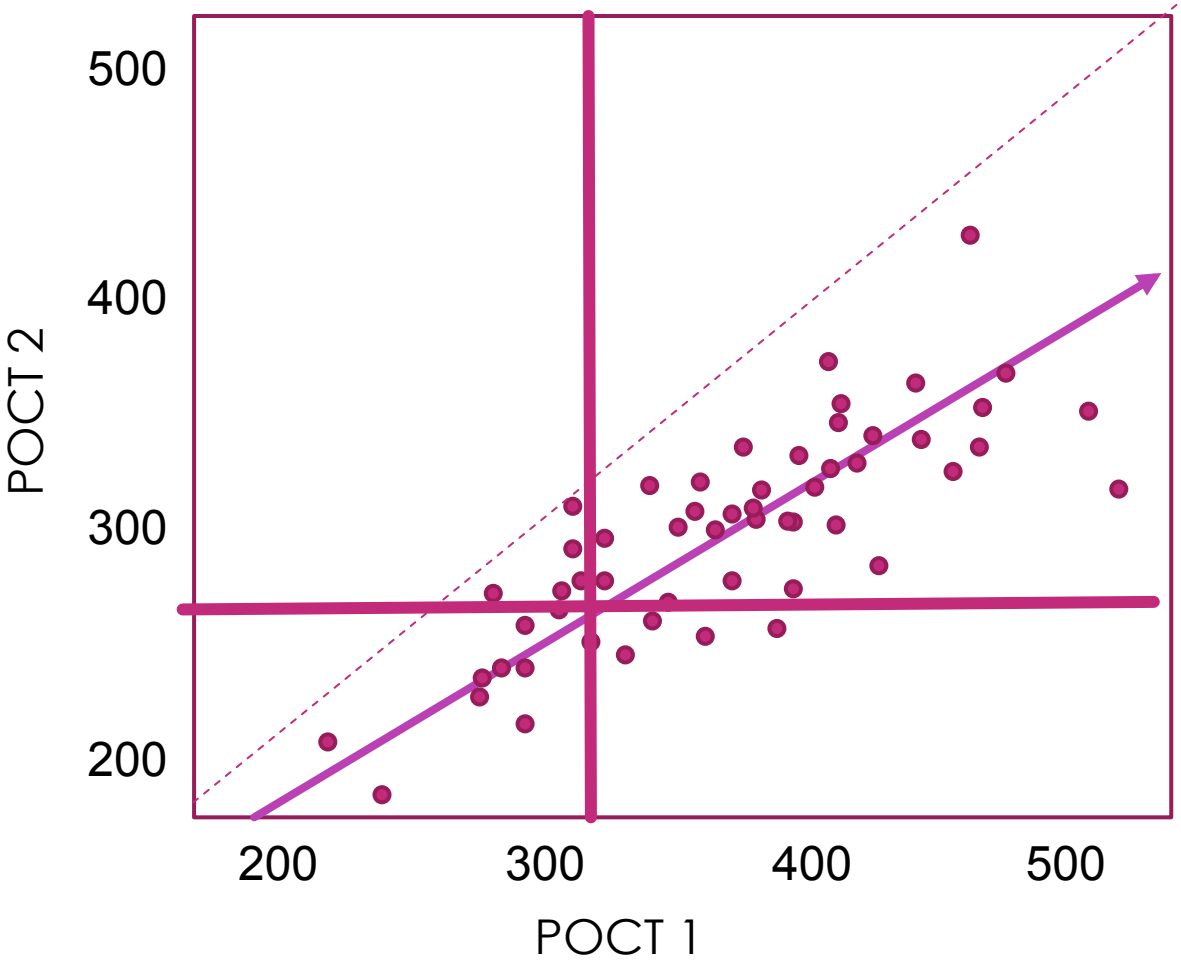
ACT is checked again and it is 440 sec

>50 sec difference between duplicates (n=177)



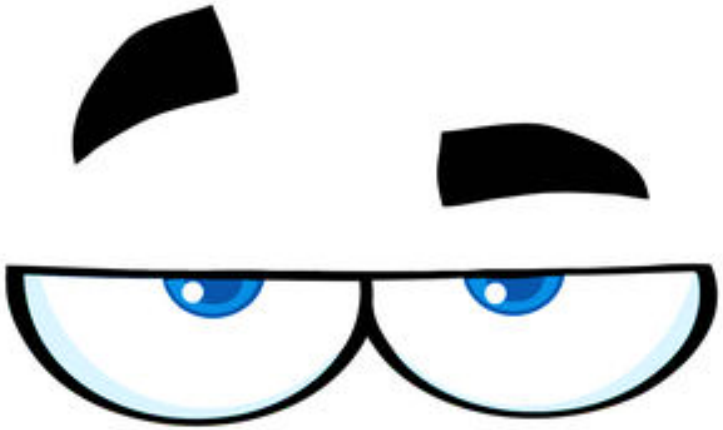
Correlation POCT 1 POCT 2

N=88, no baseline, unpublished results



Healthy critisism when interpreting ACT result on your specific device

Although all systems correlate to a certain extent, they yield different results.



Know your ACT!

Special cases, ask for special approach

- Lupus anticoagulans prolongs initial ACT values.
  - doubling baseline ACT
  - anti-Xa
  - Heparin management system.

- DOAC: The IIa agent interferes more than anti-Xa agents on the ACT. But stays below 300-400 range. However the effect on this range should be investigated.

- Platelet # or inhibitors: <30-50 * 10^6/L and platelet inhibitors prolongate ACT. Target range adjustment or anti Xa measurement.

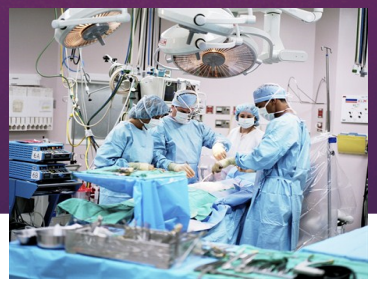
Take home messages

Intraoperative testing is the domain of Point of Care

No golden ACT standard, no true ACT

Know your ACT system and the influencing variables

Heparin monitoring requires a multidisciplinary approach



Acknowledgements

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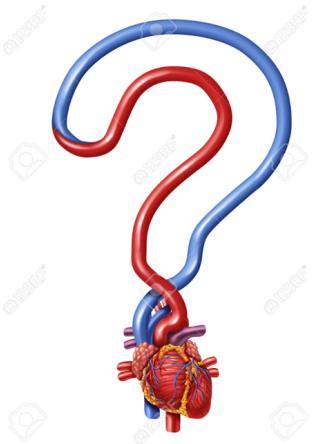
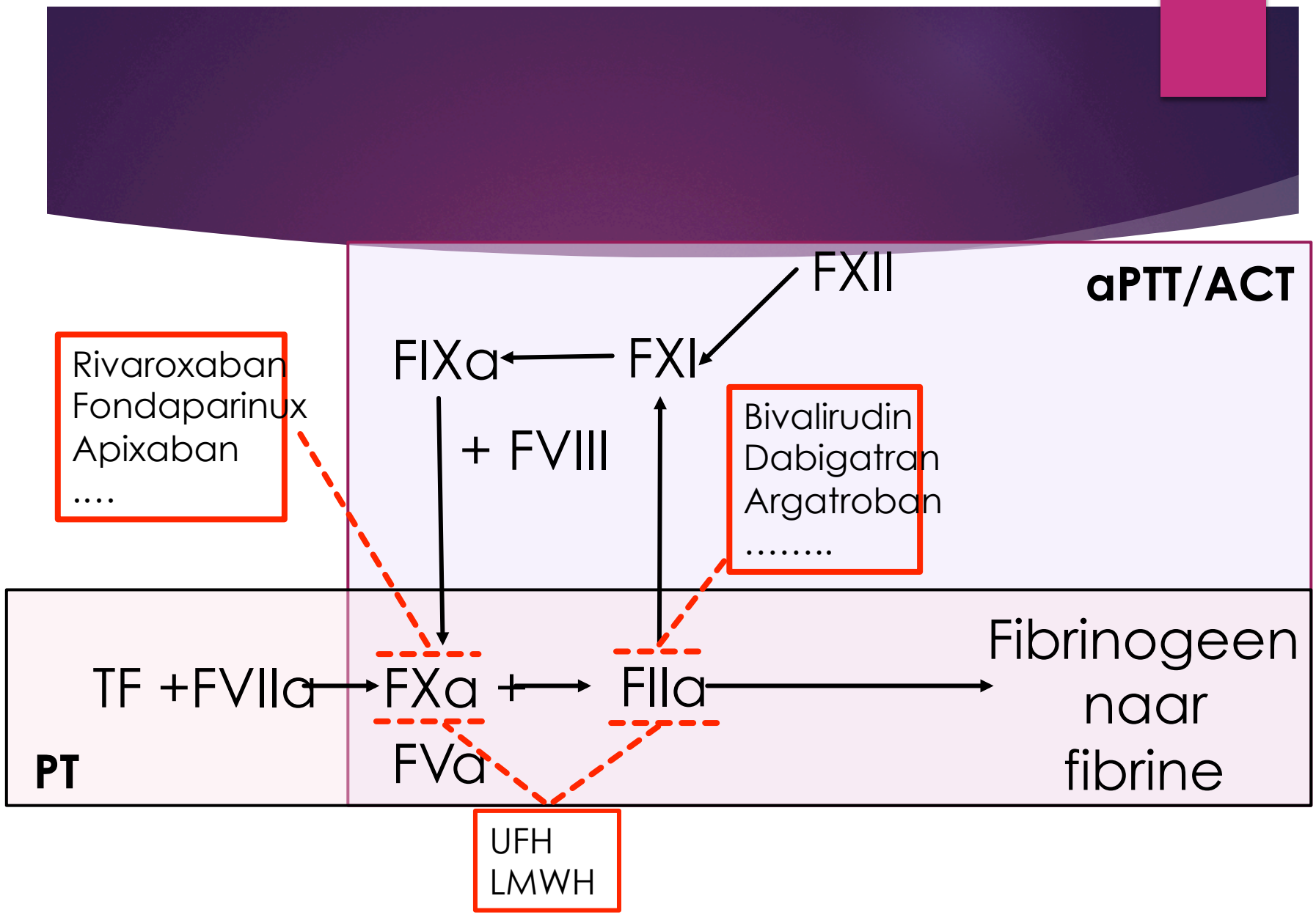
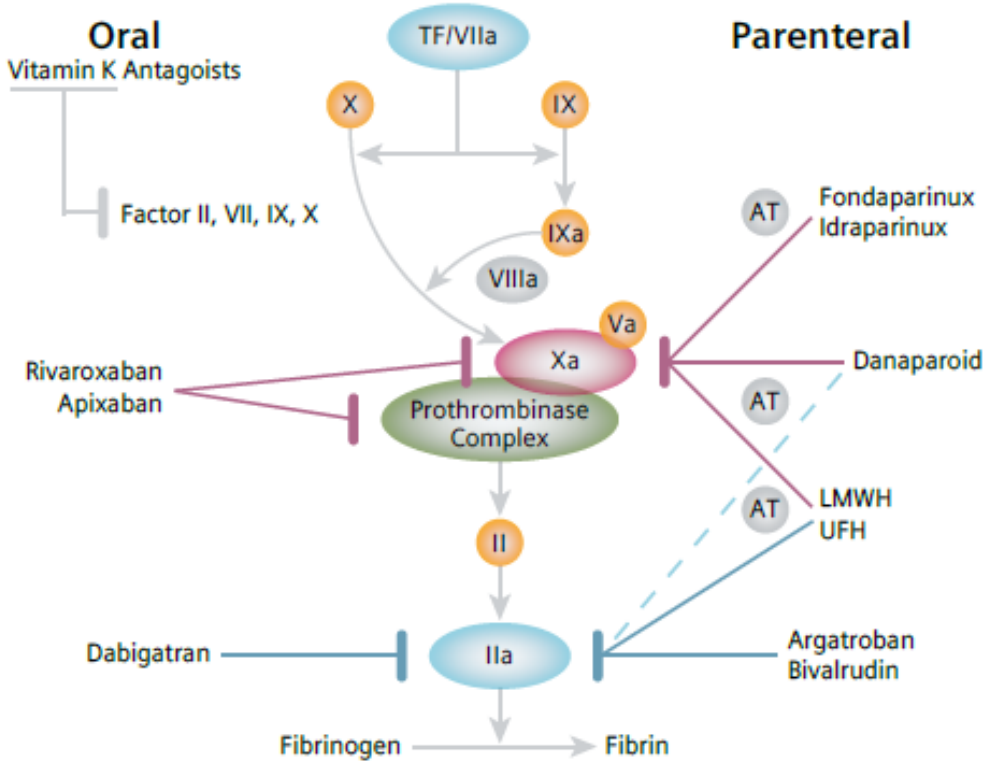



FXII
aPTT/ACT
FIXa
FXI
+ FVIII
Rivaroxaban
Fondaparinux
Apixaban
....
Bivalirudin
Dabigatran
Argatroban
.....
TF +FVIIa
FXa +
FVa
FIIa
Fibrinogeen
naar
fibrine
PT
UFH
LMWH

Heparin



TF – Tissue factor
AT – Antithrombin
UFH – Unfractionated heparin
LMWH – Low-molecular-weight heparin

CLSI: 49-A POCT

Table 1. Classification of Heparin Dose Regimens Used in the Prevention and Treatment of Venous and Arterial Thromboembolic Complications

Heparin Dose	Heparin Concentration, U/mL	Clinical Use	Methods for Monitoring
Standard	0.2 - 0.5	Venous thromboembolism	APTT; Heparin Concentration
Intermediate	0.5 - 3.0	Hemodialysis ECMO/VADs Diagnostic Catheterization PCI	ACT; APTT; Heparin Concentration
High	3.0 - 8.0	Cardiac surgery (CPB)	ACT; Heparin Concentration

Junior, drink your blood before it clots"

Effect of DOACs on ACT

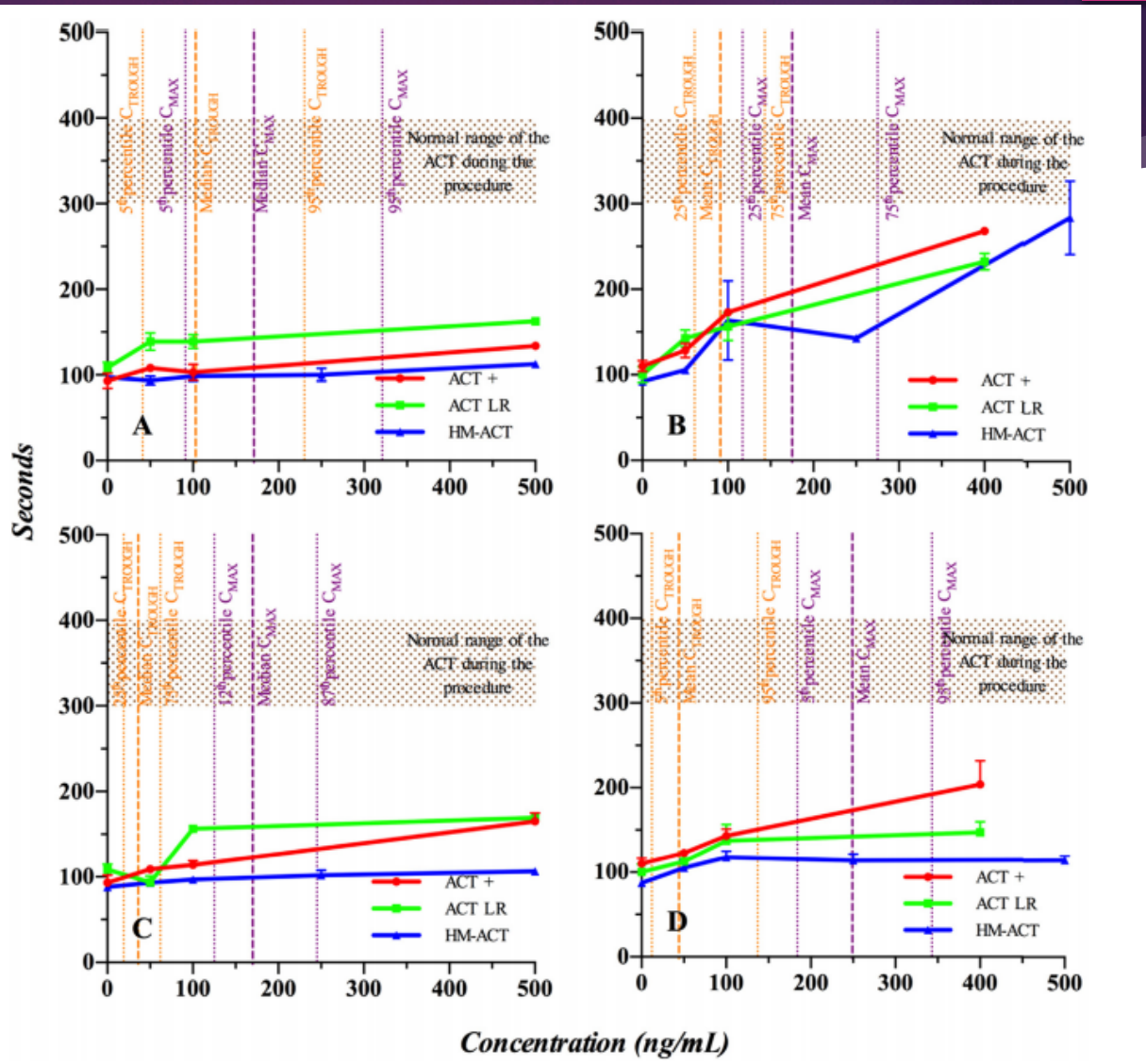


Fig 1. Impact of (A) apixaban, (B) dabigatran, (C) edoxaban, and (D) rivaroxaban on the ACT. Results are reported in seconds. Plasma concentration range at TTROUGH (orange) and TMAX (purple) are represented for information.

DOAC ACT

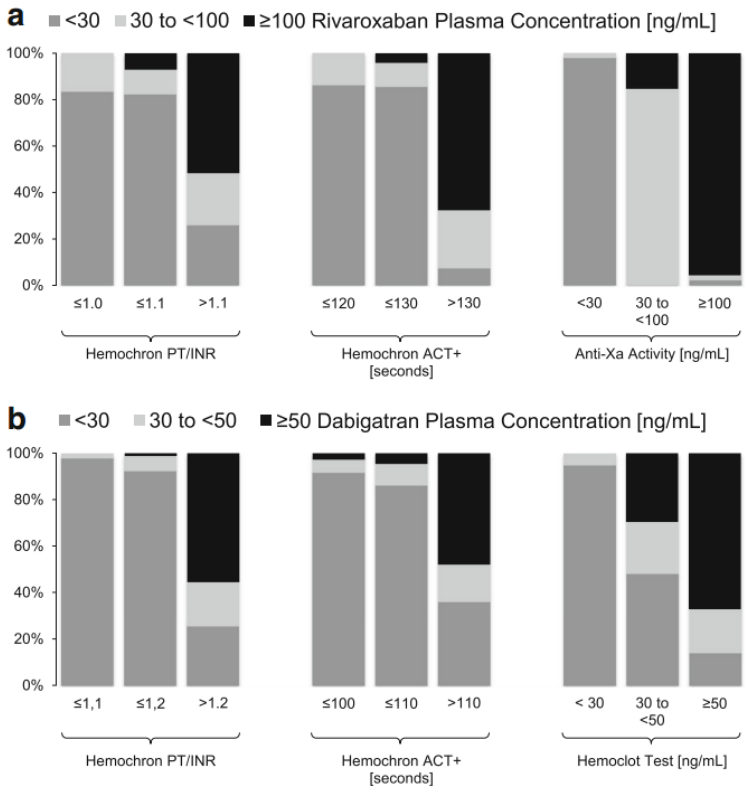
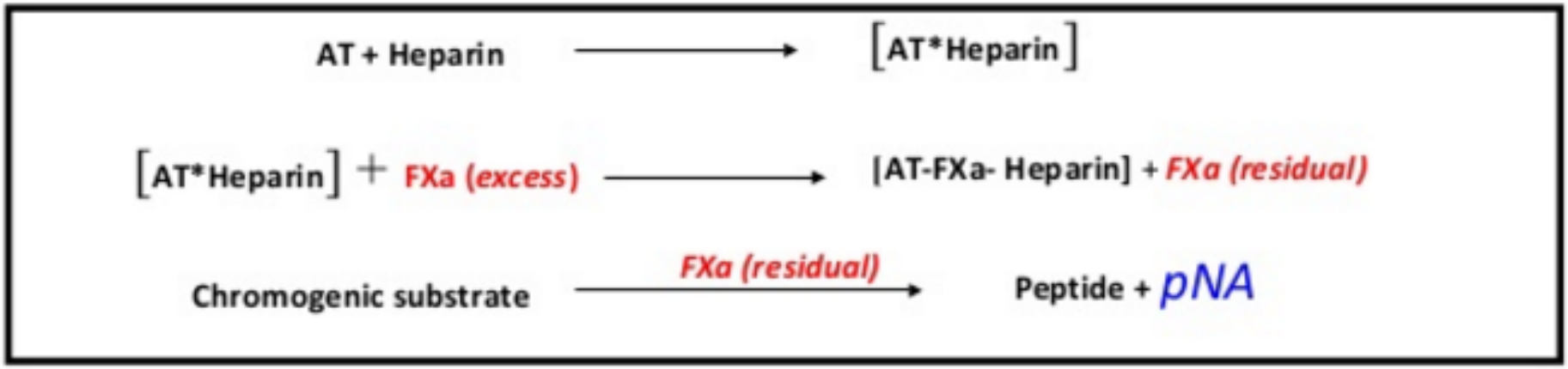


Fig. 2 **a** Distribution of rivaroxaban concentrations found at different Hemochron® Signature POCT results of prothrombin time/international normalized ratio (*PT/INR*) and activated clotting time plus (*ACT+*) test cards and at different anti-Xa activities ($n = 118$ samples). **b** Distribution of dabigatran concentrations found at different Hemochron® Signature POCT results of PT/INR and ACT+ test cards, and at different Hemoclot assay results ($n = 168$ samples)


AT + Heparin
[AT*Heparin]
[AT*Heparin] + FXa (excess)
[AT-FXa- Heparin] + FXa (residual)
Chromogenic substrate
FXa (residual)
Peptide + pNA