

# High variability in rivaroxaban and apixaban Pharmacokinetics (PK) and pharmacodynamics (PD) assessed with thrombin generation in patients over 80 years

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## INTRODUCTION & AIMS

- ❖ Thrombin generation (TG) assay is a valuable approach to evaluate xaban PD. Few data are available in elderly patients at high risk of both thrombosis and bleeding.
- ❖ To assess the PK/PD profiles in patients >80 years included in the prospective ADAGE study (NCT02464488), receiving rivaroxaban or apixaban for atrial fibrillation (AF)
- ❖ To determine the relationships between xaban plasma concentration and thrombin generation (TG) parameter studied under different conditions.

## CONCLUSION

- ❖ In ADAGE patients, we showed substantial PK inter-individual variability with both xabans.
- ❖ TG allowed evidencing i/ a **high variability in PD response to xaban**, ii/ an underlying **baseline hypercoagulable state** in most patients.
- ❖ Whether PD parameters may predict clinical events remains to be demonstrated.

## MATERIALS & METHODS

### 1) *ex vivo* study



- 129 elderly patients from the ADAGE study (mean age  $86 \pm 3$  y.)
- Treated with **rivaroxaban (R)** / **apixaban (A)** for AF: 250 samples

### 2) *in vitro* study



- 36 plasmas spiked with **rivaroxaban**
- 36 plasmas spiked with **apixaban**

Xaban concentration range  
0 to 400 ng/mL

### Anti-Xa activity

Liquid anti-Xa,  
Stago®

### TG assay

ST-Genesia,  
Stago®

### ST-DrugScreen (DS)

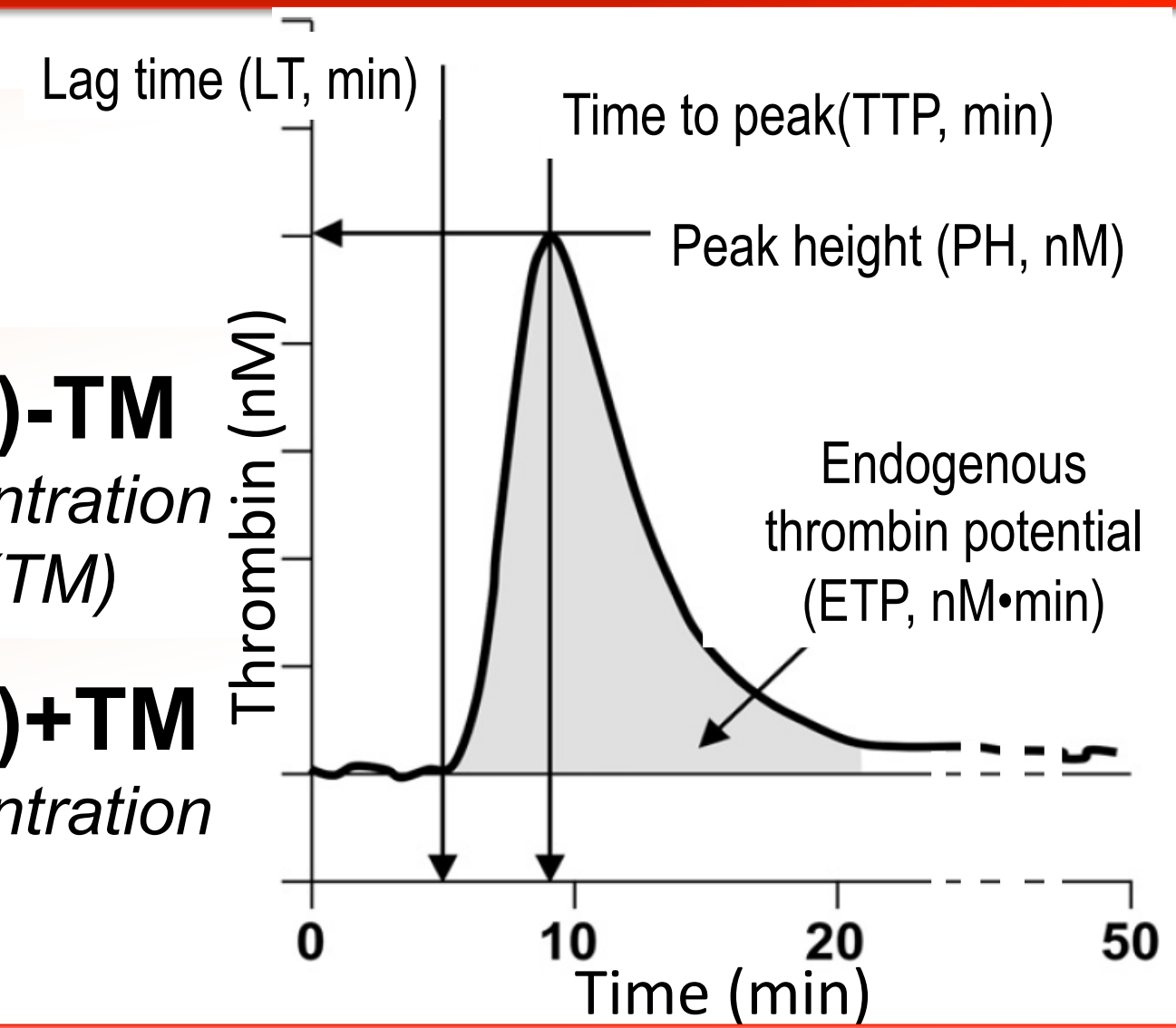
High tissue factor concentration

### ST-ThromboScreen (TS)-TM

Intermediate tissue factor concentration  
in absence of thrombomodulin (TM)

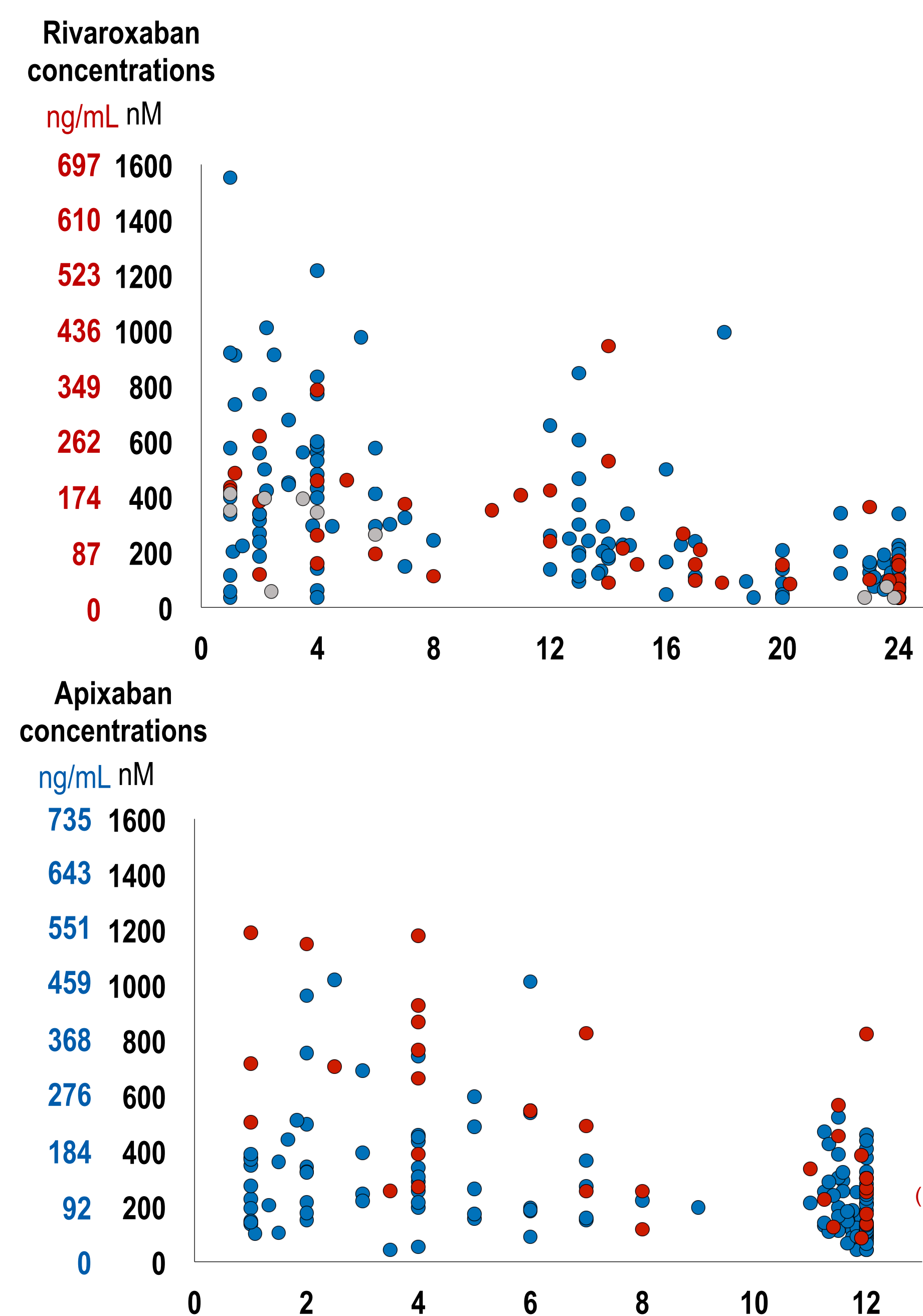
### ST-ThromboScreen (TS)+TM

Intermediate tissue factor concentration  
in presence of thrombomodulin



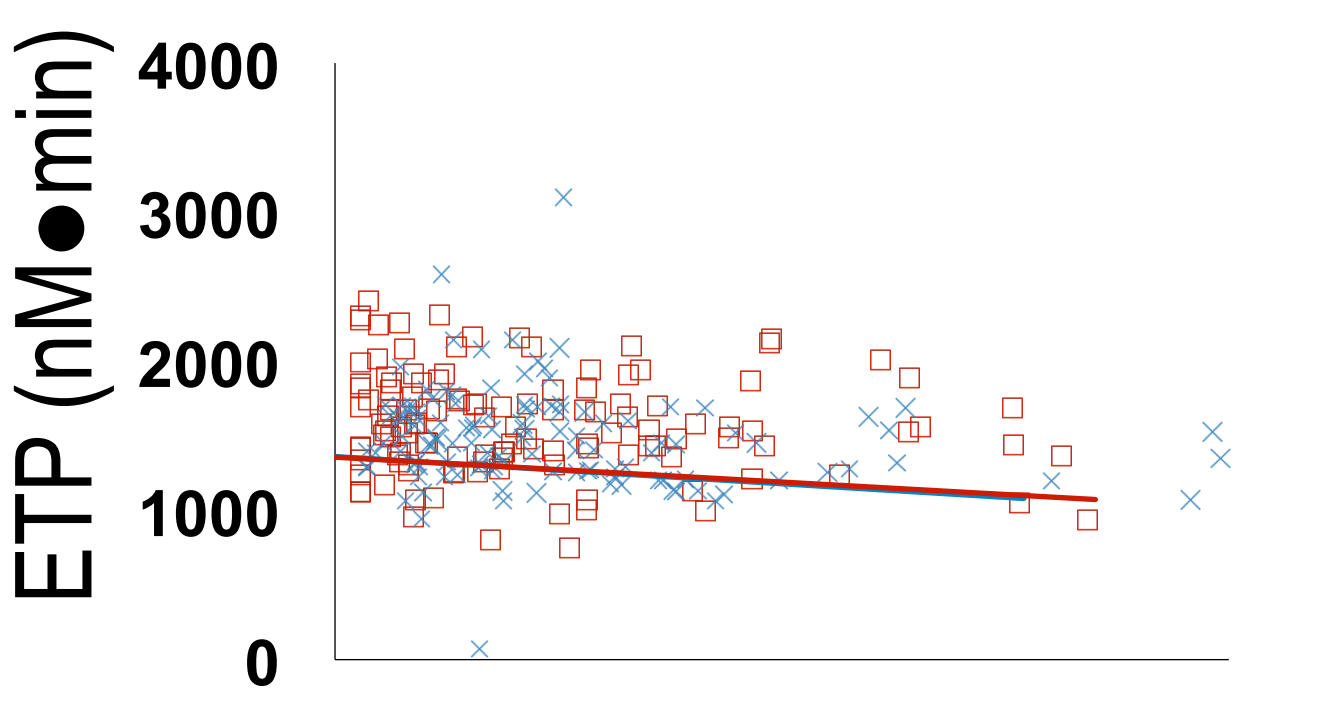
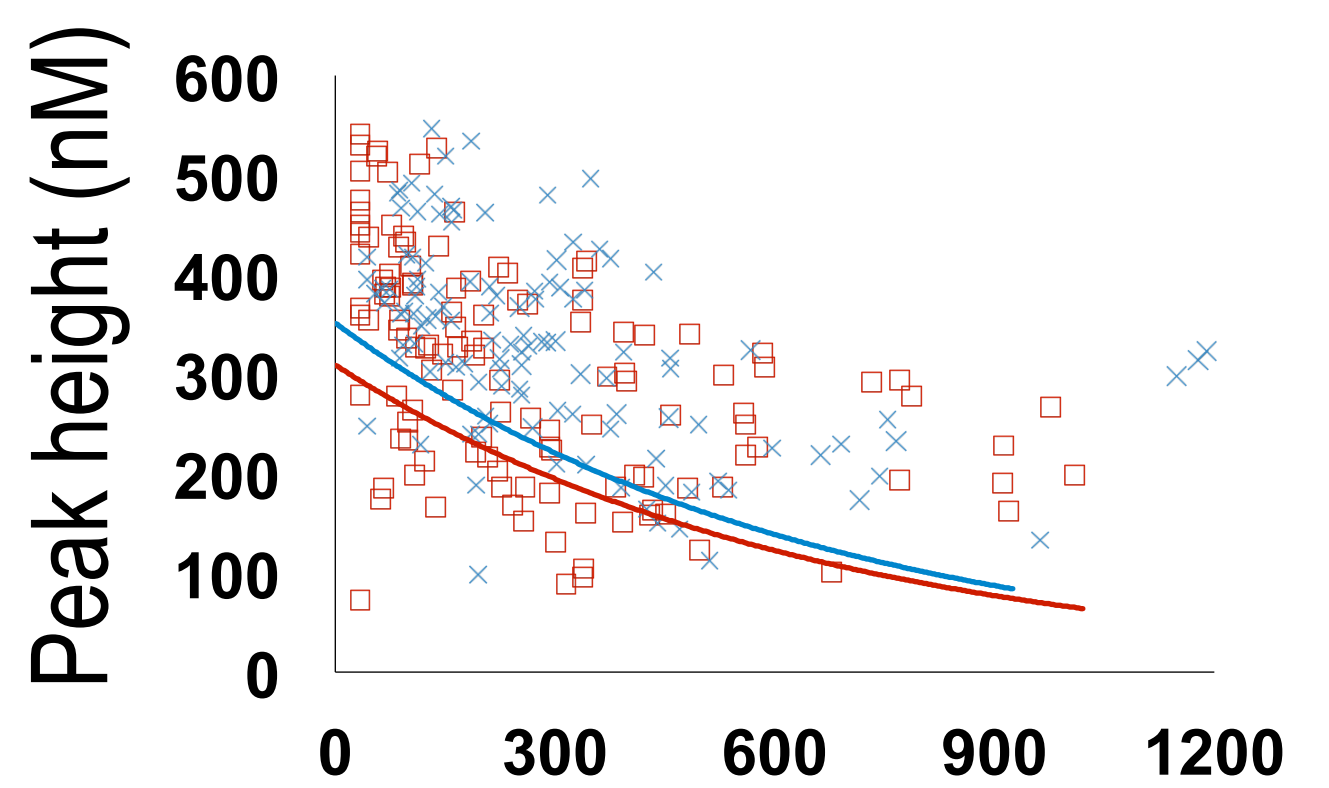
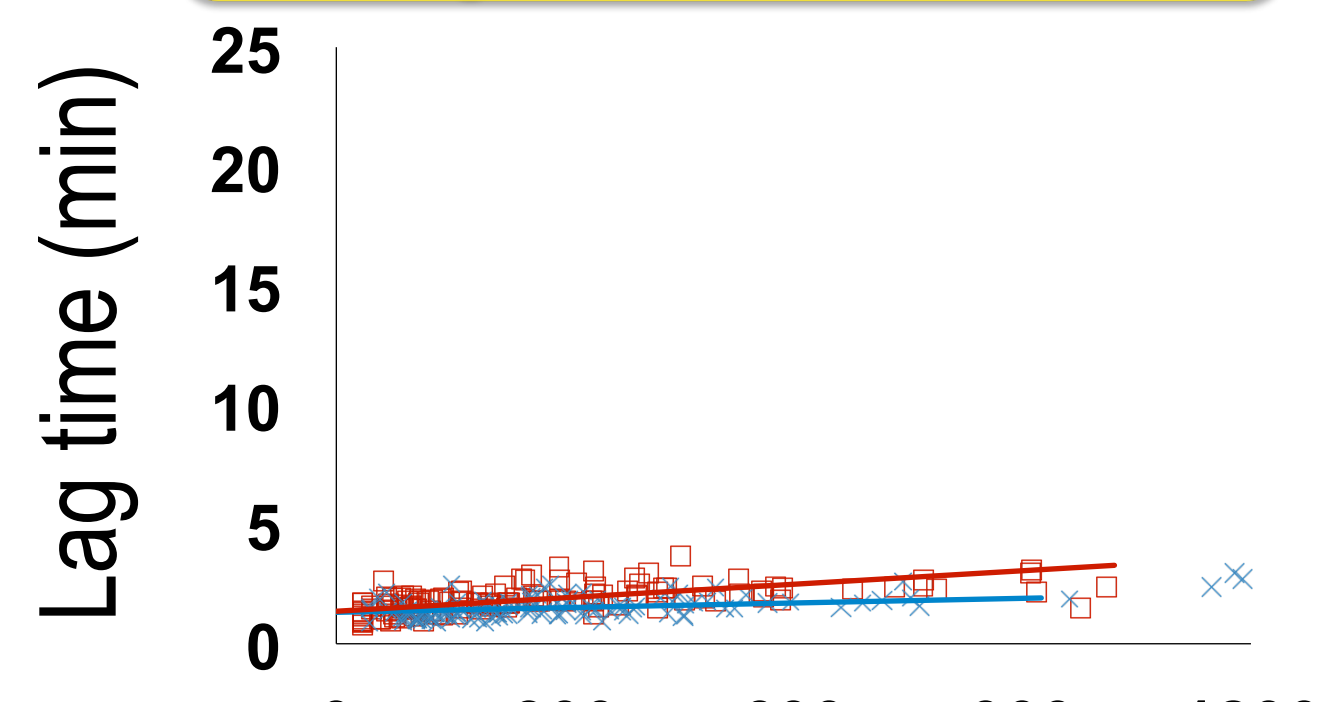
## RESULTS

### PK



### DrugScreen

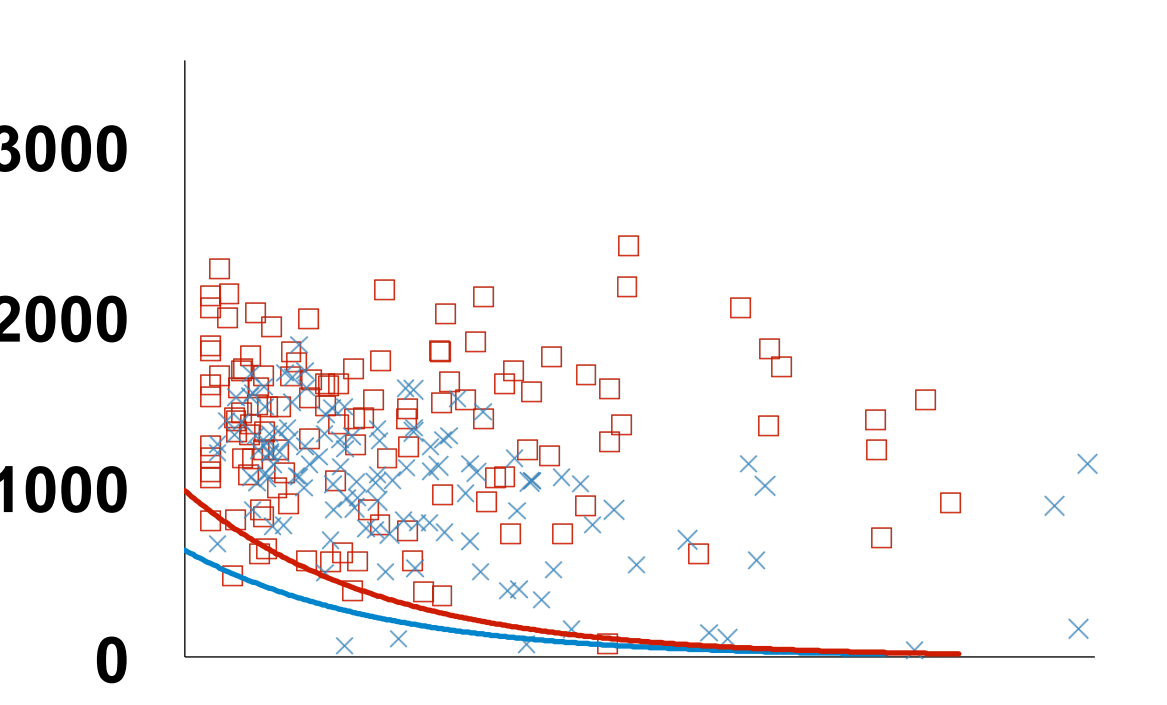
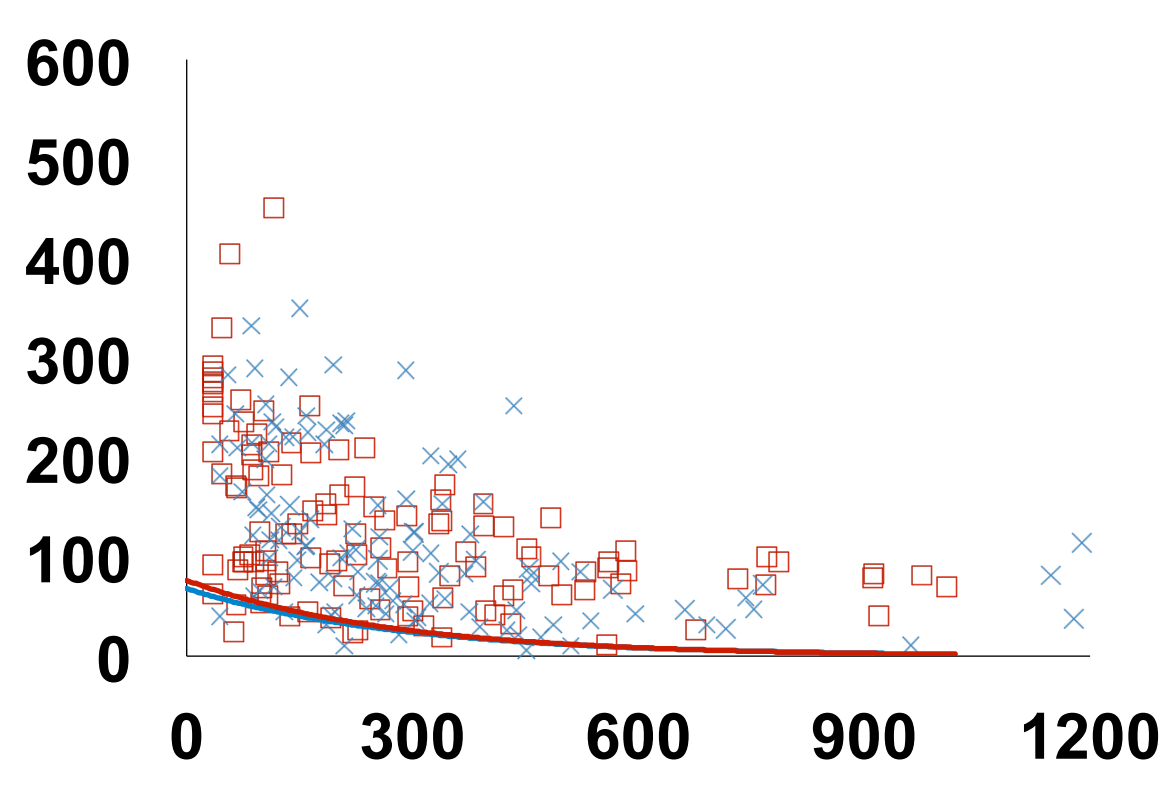
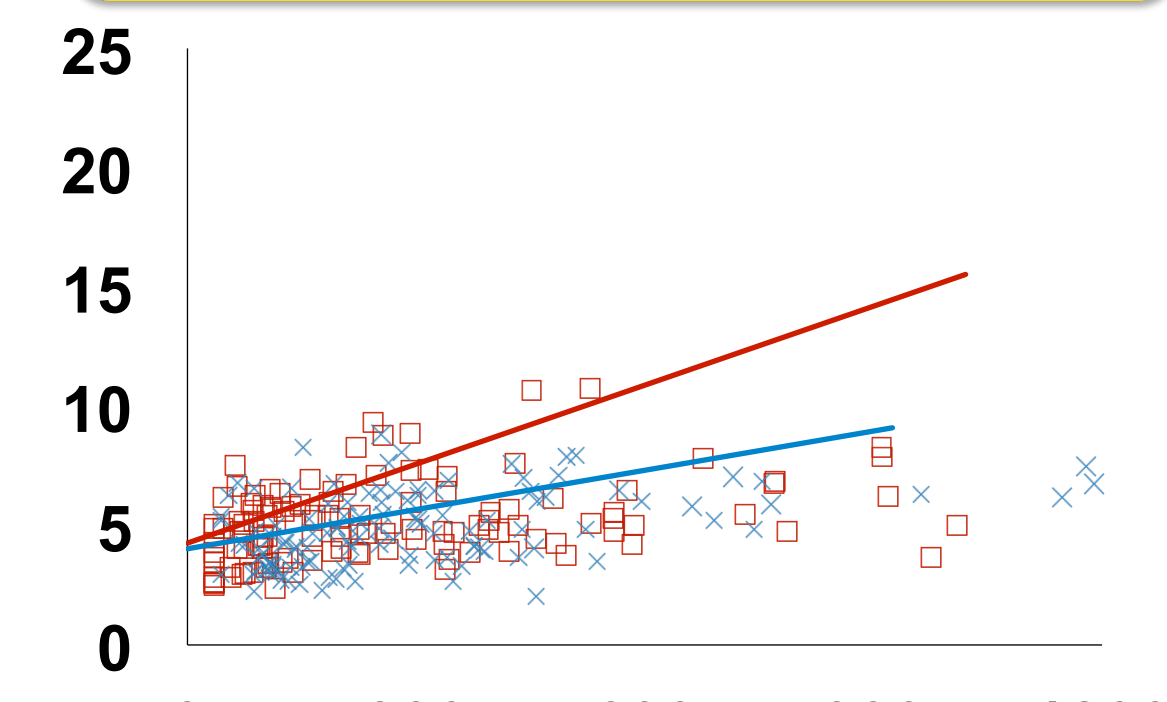
High TF concentration



(nM)	0	300	600	900	1200
(rivaroxaban ; ng/mL)	0	131	262	392	523
(apixaban ; ng/mL)	0	138	276	414	551

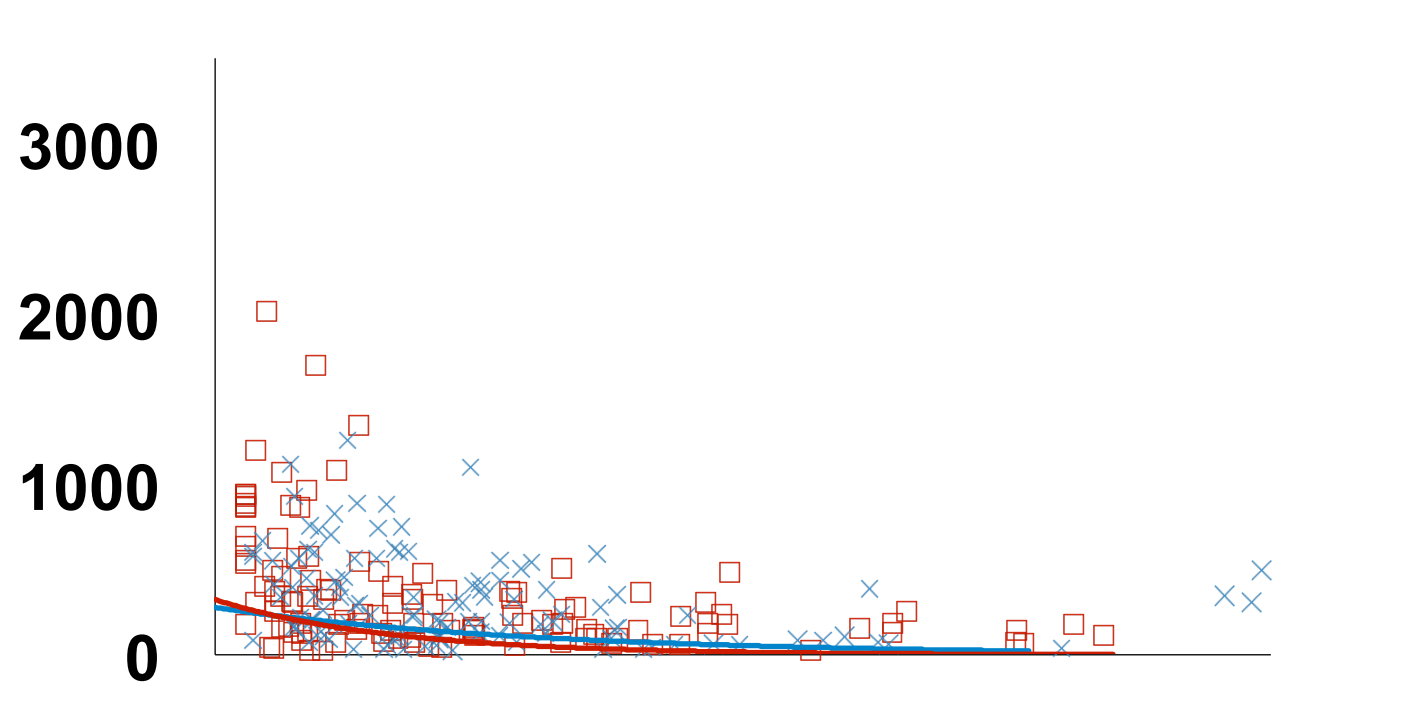
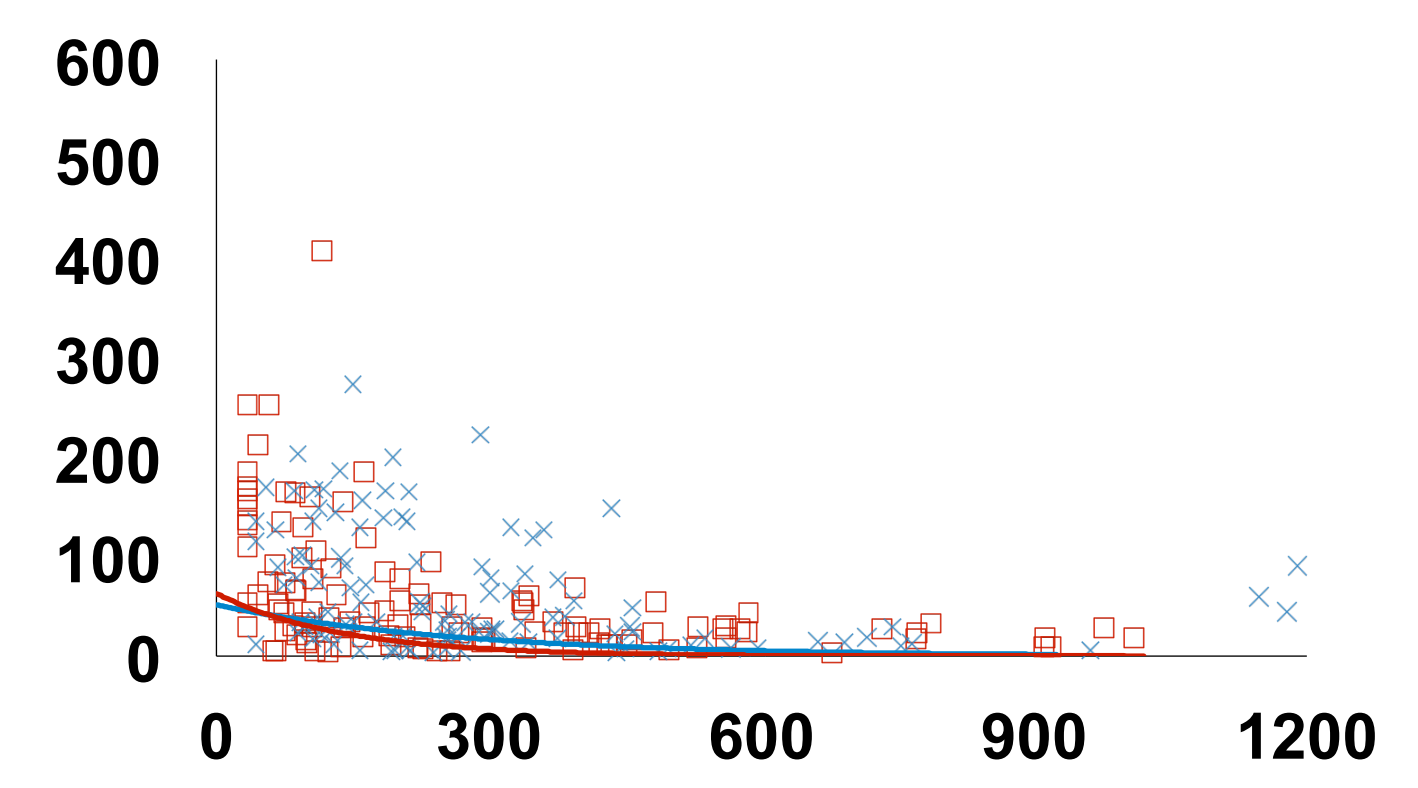
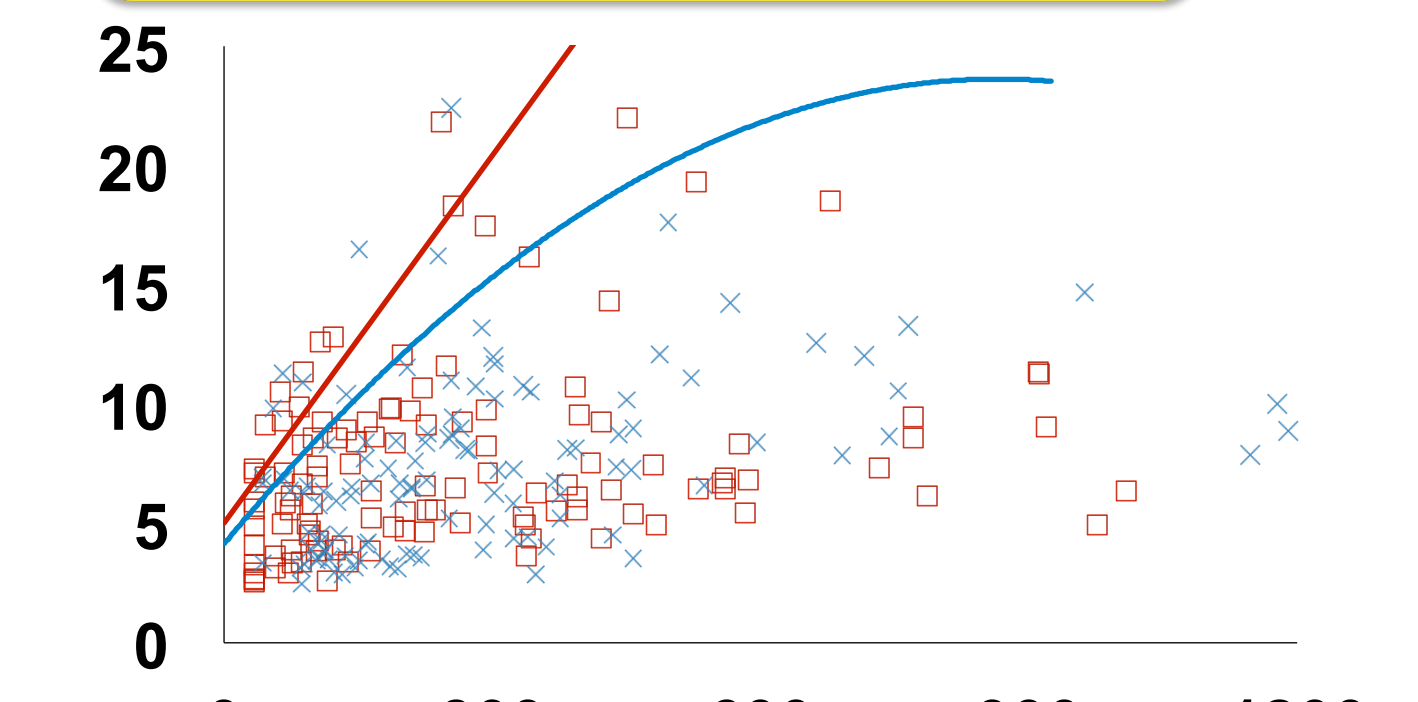
### ThromboScreen -TM

Intermediate TF concentration



### ThromboScreen +TM

Intermediate TF concentration



Xaban plasma concentrations (nM)

**Rivaroxaban** 15 mg o.d. → 54 patients  
• Median C<sub>max</sub> **213** ng/ml (IQR 147 – 301)  
• Median C<sub>min</sub> **44** ng/ml (IQR 29 – 69)

**Apixaban** 2.5 mg bid. → 54 patients  
• Median C<sub>max</sub> **149** ng/ml (IQR 97 – 200)  
• Median C<sub>min</sub> **73** ng/ml (IQR 50 – 117)

Legend  
■ ADAGE patient receiving rivaroxaban  
× ADAGE patient receiving apixaban  
— Normal plasma spiked with rivaroxaban  
— Normal plasma spiked with apixaban

- ❖ Xaban prolonged temporal parameters (LT, TTP) and lowered the value of quantitative parameters (PH, ETP).
- ❖ In spiked plasma samples, all TG parameters were highly correlated with xaban concentrations ( $p < 10^{-4}$ ).
- ❖ In ADAGE patients receiving either rivaroxaban or apixaban, LT, PH and TTP were more significantly associated with xaban concentrations ( $p < 10^{-3}$  to  $< 10^{-4}$ ) than ETP in the different conditions, in agreement with data of the literature.
- ❖ A high variability of the PD response was observed in ADAGE patients, especially regarding PH and ETP.
- ❖ Most ADAGE patients had PH and ETP values higher than those obtained with spiked plasma, suggesting an underlying hypercoagulable state.