ASSESSMENT OF DIRECT ORAL ANTICOAGULANT PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) EVALUATED BY THROMBIN GENERATION IN GERIATRICS: RESULTS OF THE ADAGE STUDY

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Innovations Thérapeutiques en Hémostase

DISCLOSURES

- Participation to expert meetings (Aguettant, Bayer, Boehringer Ingelheim, BMS, Leo-Pharma, Pfizer, Stago)
- None related to the present work

RATIONALE

- A growing number of very elderly patients with atrial fibrillation (AF) receive direct oral anticoagulants (DOAC) for stroke prevention.

Hindricks, Eur Heart J 2021

- Management of anticoagulated patients is challenging in this age group:
  - → numerous comorbid conditions *(e.g. chronic renal impairment)*
  - → polymedicated

- Scarce specific data available in frail elderly patients with AF regarding <u>both</u> DOAC pharmacokinetics (PK) and pharmacodynamics (PD)

ADAGE STUDY

ADAGE: Assessment of Direct oral Anticoagulant PK and PD in Geriatric patients

❖ Academic prospective multicenter cohort study (NCT02464488)

Aims

- **Characterize**

→ rivaroxaban / apixaban concentration time-profiles

→ thrombin generation (TG) time-profiles

in **patients with atrial fibrillation ≥ 80 years**

- **Evaluate** the potential influence of individual characteristics on DOAC concentrations and TG peak-height at T_{max} and T_{min}

- **Record** clinical outcomes (bleedings, thrombosis, deaths) at 6 months

METHODS (1)

❖ **Inclusion criteria**

- Patients ≥ **80** years recruited in 5 university hospitals (2015-2019)
- Receiving **rivaroxaban** or **apixaban** for AF
- DOAC taken since at least **4 days** (regimen at the discretion of the physician)

❖ **Exclusion criteria**

- Acute unstable comorbid conditions
- No consent

❖ **Blood sampling**

- Up to **5 blood samples per patient over a 20-day period** collected in addition to usual care (no extra vein puncture) **at different time-points** at the discretion of the physician
  → **time since last DOAC intake recorded**

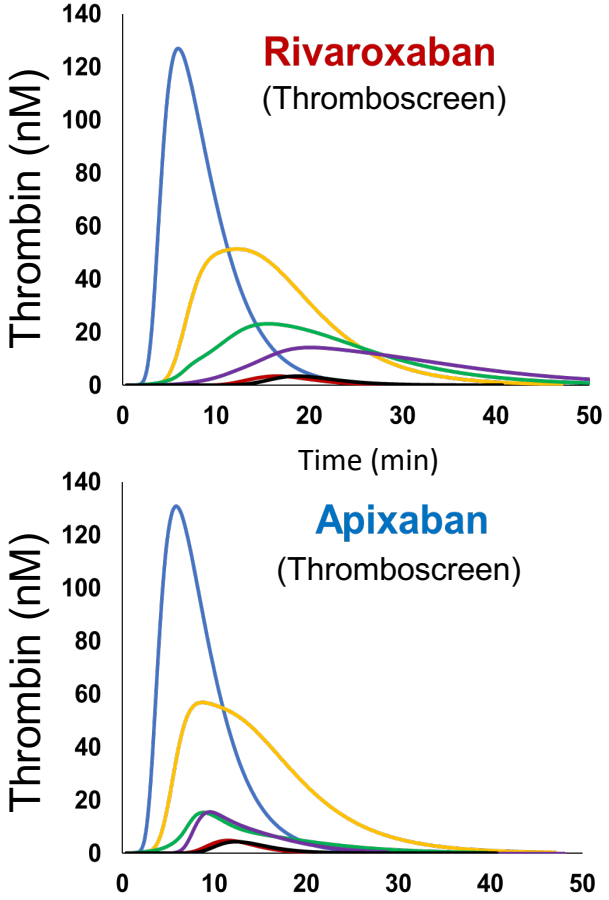
METHODS (2)

- **DOAC concentration** (ng/mL) → chromogenic assay (STA-Liquid-anti-Xa Stago) (centrally measured)

- **Thrombin generation**: ST-Genesia® analyser (Stago, Asnières, France)

  → **STG-ThromboScreen (TS):** *intermediate [TF]*
  - without addition of thrombomodulin (-TM)
  - with addition of TM (+TM)

In addition:
Normal Pool Plasma (Cryocheck®) **spiked with DOAC**
→ 0 to 450 ng/mL



Foulon-Pinto, IJLH, 2021

METHODS (3)

❖ **Demographic, clinical, laboratory data prospectively collected** at inclusion

❖ **Genotyping:**

- ***ABCB1*** (rs2032582, rs1045642) (→ P-gp transporter)
- ***CYP2J2*7, CYP3A5*3*** (→ metabolism of ‘’xaban’’)

❖ **Clinical outcomes at six months** (blinded of PK/PD results)

→ bleedings: major / clinically relevant non-major bleeding (CRNMB)

Schuman, J Thromb Haemost, 2005

→ thrombosis events

→ deaths

ADAGE PATIENT CHARACTERISTICS (N=215) (1)

	rivaroxaban (n=104)	apixaban (n=111)	P value
Age (yrs)	**86.4 ± 4.4**	**86.8 ± 4.3**	0.4911
Females (%)	**68.3**	**73.9**	0.3713
Body-weight (kg)	64.9 ± 12.6	66.4 ± 16.5	0.5430
CHA_2DS_2VASc score	4.9 ± 1.4	5.2 ± 1.4	0.1223
$HEMORR_2HAGES$ score	**2.1 ± 1.0**	**2.5 ± 1.0**	0.0218
CIRS-G score	**9.3 ± 3.7**	**11.4 ± 4.8**	0.0023
Creatinine clearance (mL/min)	50.5 ± 17.1	47.9 ± 15.9	0.3135

CIRS-G : Cumulative Illness Rating Scale in Geriatrics

ADAGE PATIENT CHARACTERISTICS (N=215) (2)

Therapeutics	Rivaroxaban (n=104)	Apixaban (n=111)	P value
Xaban: full dose* (%)	17.3	23.4	0.3116
reduced dose** (%)	**82.7**	**76.6**	0.3116
Number of comedications (mean)	5.9 ± 2.5	6.5 ± 2.9	0.2558
≥ 1 P-gp moderate substrate/inhibitor (%)	44.6	51.8	0.2915
≥ 1 CYP3A4/5 moderate inhibitor (%)	17.8	26.4	0.1363

**20-mg rivaroxaban o.d.; 5-mg apixaban b.i.d.*

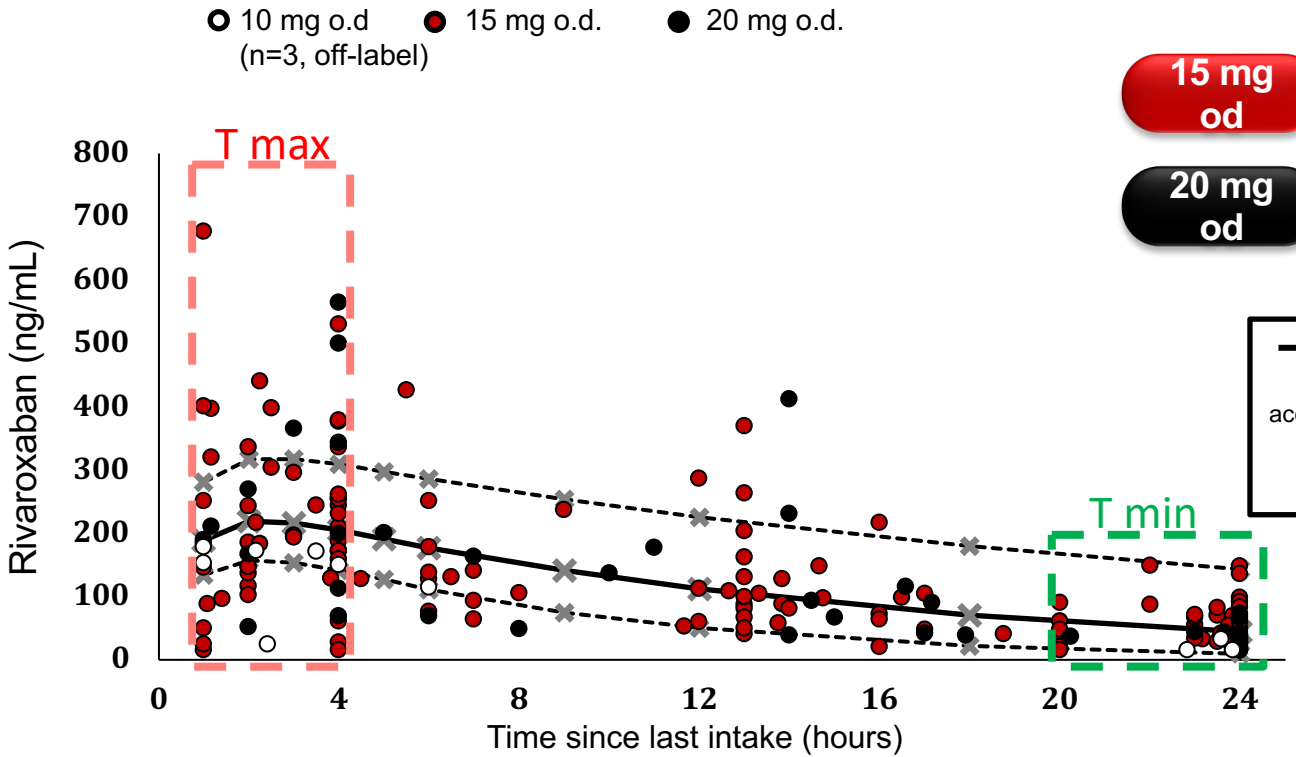
SmPC: Summary of Product Characteristics

*** 15-mg rivaroxaban o.d (or 10-mg: n=3 – off label); 2.5-mg apixaban b.i.d.*

~ 30% of patients did not receive the dose according to SmPC's criteria (of whom 90% underdosed).

RIVAROXABAN PLASMA CONCENTRATION TIME-PROFILES

- 230 samples from 104 ADAGE patients



		Conc (ng/mL) *mean ± SD*	CV (%)
15 mg od	T_{max}	273 ± 133	64
	T_{min}	52 ± 34	75
20 mg od	T_{max}	321 ± 151	47
	T_{min}	46 ± 18	37

mean ▪▪▪▪ 5th and 95th percentiles

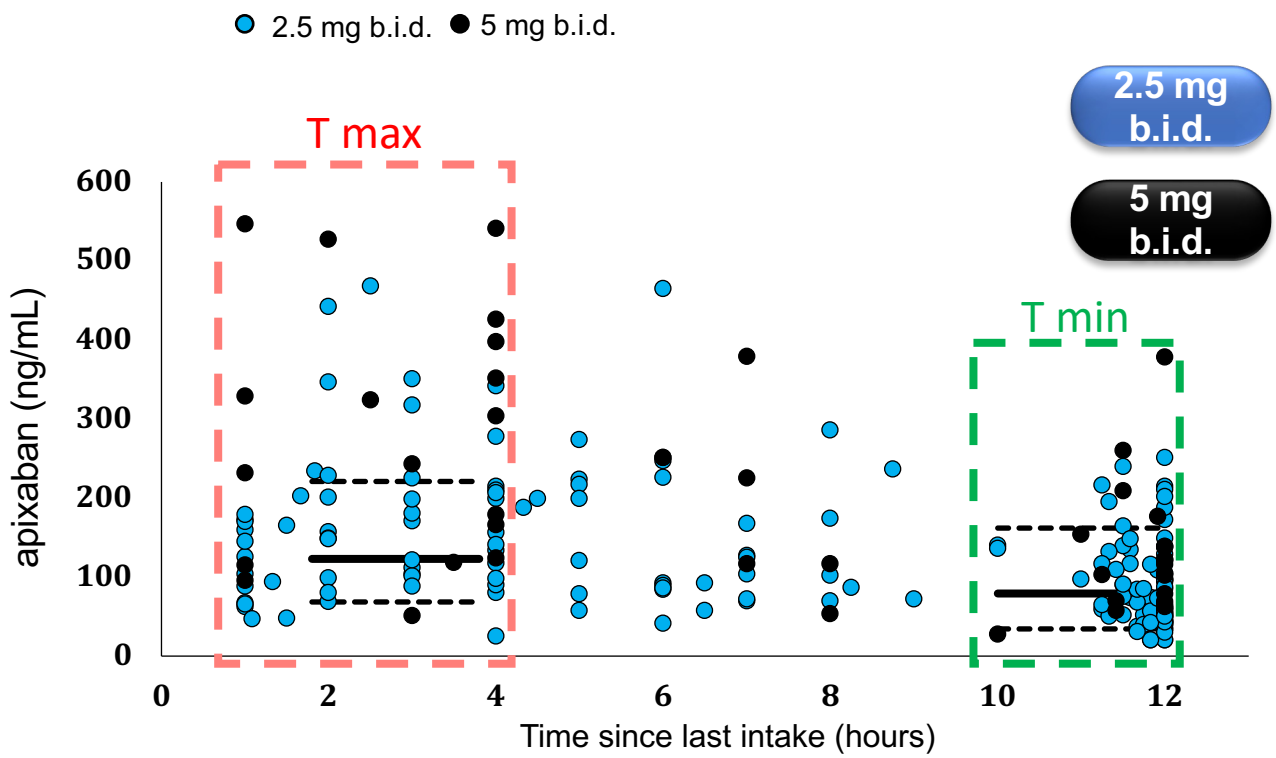
according to patients receiving **15 mg rivaroxaban**

Mueck W, Thromb J. 2013

Great variability of results at Tmax and at Tmin as shown by high CVs

APIXABAN PLASMA CONCENTRATION TIME-PROFILES

- 222 samples from 111 ADAGE patients



	Conc.(ng/mL) *mean ± SD*	CV (%)
2.5 mg b.i.d.		
T_{max}	195 ± 91	46
T_{min}	88 ± 53	61
5 mg b.i.d.		
T_{max}	285 ± 131	47
T_{min}	130 ± 107	68

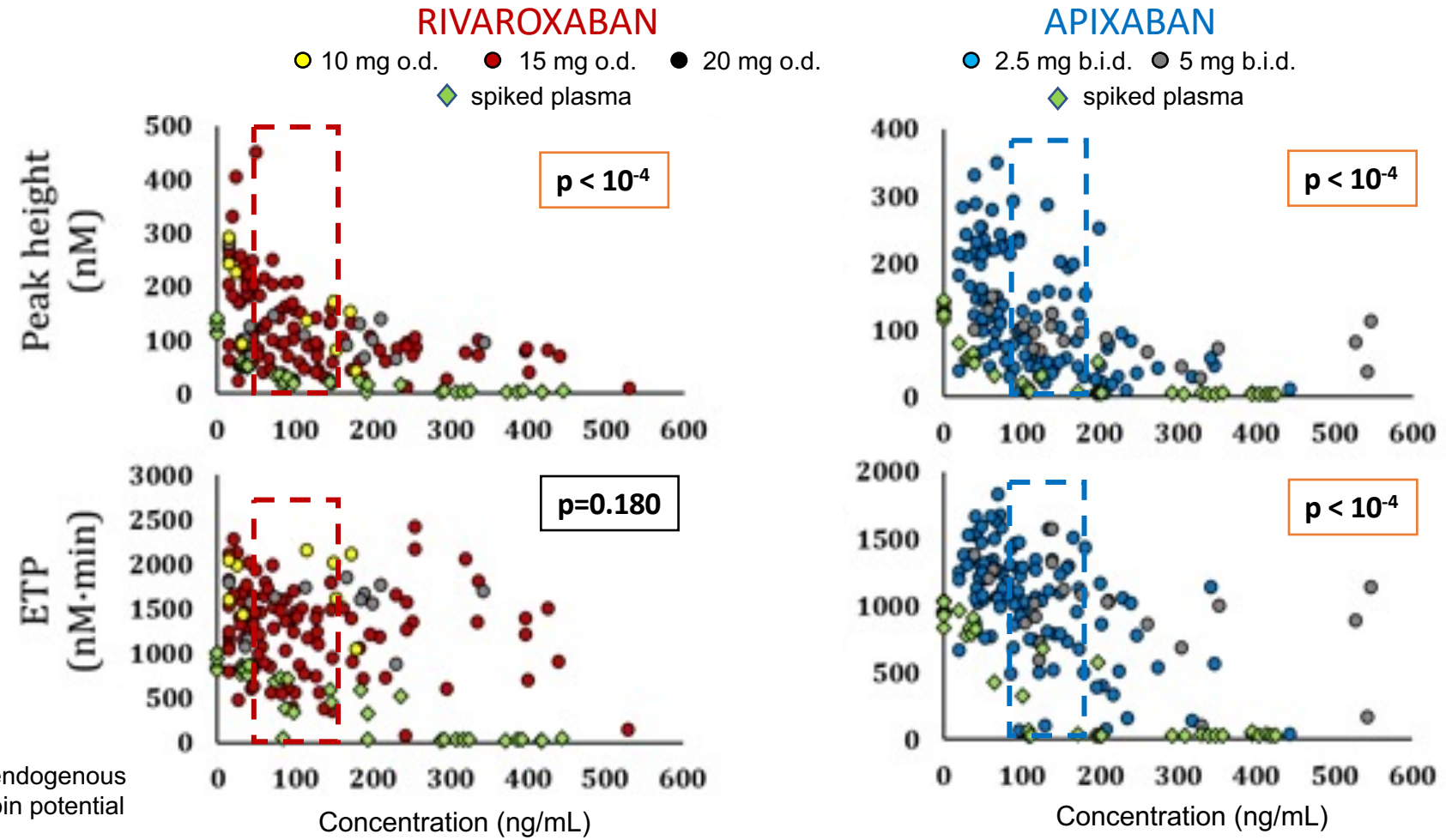
median

5th and 95th percentiles in 2.5 mg bid patients

(BMS apixaban SmPC, 2022)

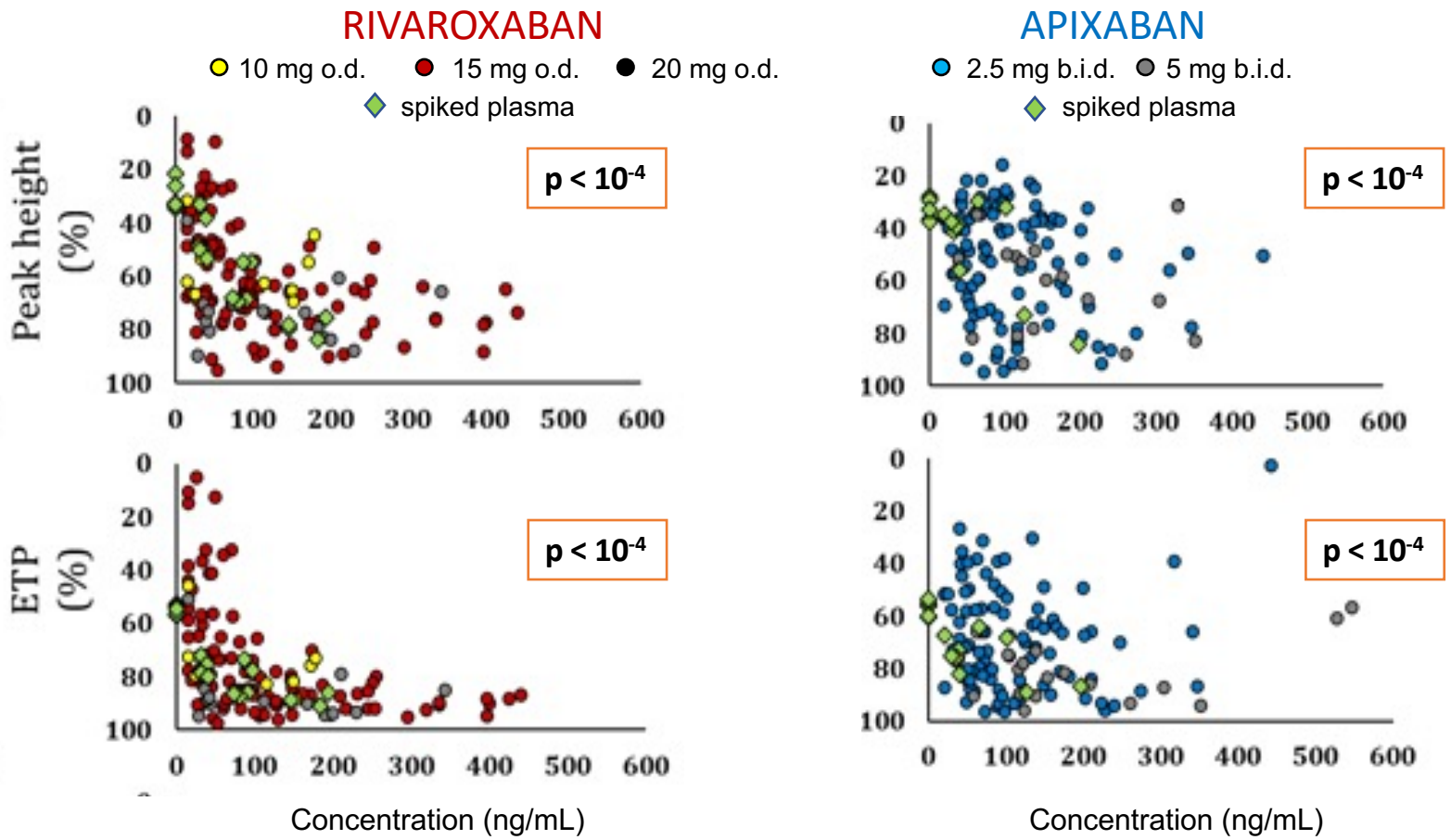
Great variability of results at Tmax and at Tmin as shown by high CVs

PEAK HEIGHT / ETP (STG-Thromboscreen without TM)



ETP: endogenous thrombin potential

PERCENTAGES OF INHIBITION (STG-Thromboscreen withTM)



INFLUENCE OF PATIENT CHARACTERISTICS ON XABAN CONCENTRATIONS AT Tmax and Tmin: MAIN RESULTS

Covariate	*Univariate analysis*				*Multivariate analysis*			
	Cmax		***Cmin***		***Cmax***		***Cmin***	
	Effect	*p*	Effect	*p*	Effect	*p*	Effect	*p*
				RIVAROXABAN				
Dose regimen	+20.3 %	NS	+9.2 %	NS	13.89 %	NS	−1.59 %	NS
Female gender	+12.2 %		−14.2 %	NS	+11.79 %		−10.98 %	NS
Creatinine clearance	+1.89 %		+5.5 %	NS	+3.35 %		+5.04 %	NS
Amiodarone	+4.73 %		+47.8 %	**0.0315**	−26.06 %		99.82 %	**0.0232**
CYP3A4/5 modulator*	+9.46 %		+31.2 %	**0.0361**	+10.57 %		+43.05 %	**0.0228**
				APIXABAN				
Dose regimen	+44.9 %	**0.025**	+45.61 %	**0.0317**	+64.77 %	**0.0058**	+54.78 %	**0.0222**
Female gender	+43.9 %	**0.017**	+15.65 %	NS	+28.70 %	NS	14.50 %	NS
Creatinine clearance	+3.29 %	NS	+4.60 %	NS	+4.51 %	NS	+4.50 %	NS
Amiodarone	+43.5 %	**0.010**	+14.38 %	NS	+79.26 %]	**0,0319**	+44.09 %	NS
CYP3A4/5 modulator*	+4.01 %	NS	+20.76 %	NS	+12.08 %	0.2838	+23.40 %	NS

*other than amiodarone

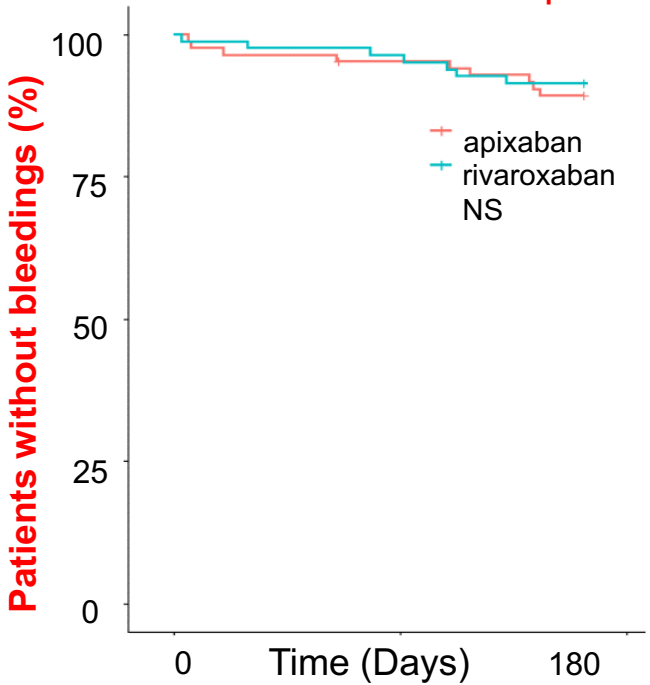
INFLUENCE OF PATIENT CHARACTERISTICS ON PEAK HEIGHT AT Tmax and Tmin (STG-Thromboscreen without TM): : MAIN RESULTS

Covariate	*Univariate analysis*				*Multivariate analysis*			
	PH at Tmax		***PH at Tmin***		***PH at Tmax***		***PH at Tmin***	
	Effect	***p***	**Effect**	***p***	**Effect**	***p***	**Effect**	***p***
RIVAROXABAN								
Plasma concentrations *per 10 ng/mL increase*	−1.85 %	0.0614	**-7.79**	**0.004**	−5.03 % †	0.7002	+20.96 % †	0.1033
Creatinine clearance *per 10 mL/min decrease*	−16.5 % ‡	**0.0016**	-8.15 %	0.098	−16.35 % ‡	**0.0085**	−6.76 % ‡	0.1561
Heart failure	−36.6 %	**0.0414**	−31.4 %	0.0546	−22.33 %	0.1427	−12.65 %	0.4217
Amiodarone	*N.A**	*N.A.*	−52.2 %	**0.0144**	*N.A.**	*N.A.**	−44.6 %	0.2277
APIXABAN								
Plasma concentrations *per 10 ng/mL increase*	−3.10 %	**0.0224**	−5.09 %	**0.0017**	+86.77 % †	0.0516	+32.69 %	**0.0074**
Creatinine clearance *per 10 mL/min decrease*	−0.42 %	0.9030	-1.73 %	0.5664	−2.42 % ‡	0.8248	−1.94 %	0.7526
Heart failure	−26.73 %	0.4262	3.21 %	0.9347	−9.17 %	0.8256	+0.84 %	0.9647
Amiodarone	+3.67 %	0.9364	−37.23 %	**0.0426**	−25.98 %	0.7586	−57.47 %	0.1292

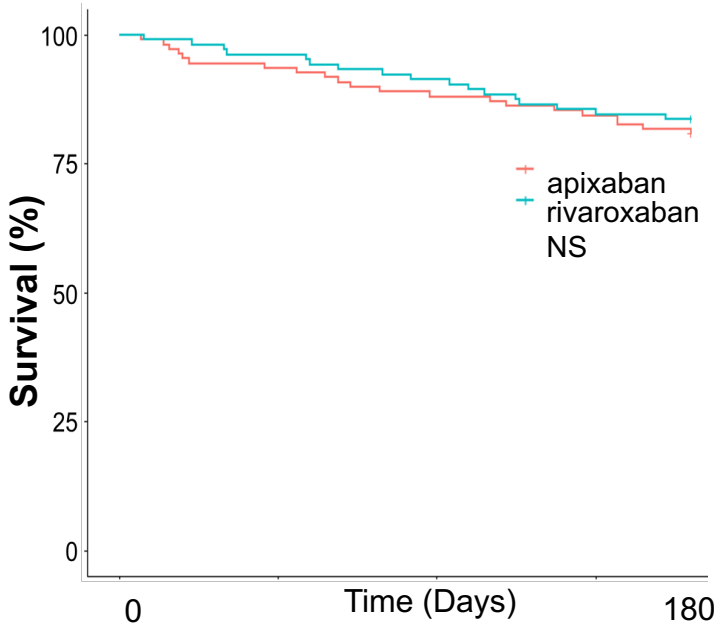
** number of patients on amiodarone < 5*

CLINICAL EVENTS AT SIX MONTHS

❖ **20 bleedings:** major → 13 patients (6.0%)
CRNMB → 7 patients (3.3%)



❖ **39 deaths** (18.1%)



❖ **5 thrombosis** (1 rivaroxaban, 4 apixaban)

→ **No association between clinical events and patients characteristics**

DISCUSSION

- **Strength of ADAGE:** academic study conducted in a real-life cohort of well characterized very elderly AF patients (mean age 87 years)
  → substantial comorbid conditions and polymedicated

- We provided specific data:

→ confirming the **great variability of both DOAC concentrations** in agreement with previous studies in real-life patients (rather younger)

Al-Aieshy et al. Eur J Clin Pharm 2016
Testa et al. Thromb Res 2016
Testa et al. JTH 2018

Miklič et al. Eur J Clin Pharm 2019
Suwa et al. Circulation J 2019
Roşian et al. Genes 2020
Bendayan et al. JAGS 2021
Sukumar, JAGS, 2022

→ showing a significant **impact of the regimen** (full dose *vs* reduced) on both **apixaban concentrations and TG peak-height**

DISCUSSION

- At a given DOAC concentration interval, we evidenced a **high interindividual variability of thrombin peak-height** suggesting an impact of the underlying coagulation status, thus modulating anticoagulation intensity
  → Deserves further investigation

- **Limitations**

→ limited number of patients and samples

→ not sized to assess a relationship between DOAC concentrations / peak-heights and clinical events

- **Perspective**
  → to build a PK model using a PK population approach

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