BASSI LIVELLI DELL'ANTICOAGULANTE ORALE DIRETTO (NAO) E COMPLICANZE TROMBOTICHE IN PAZIENTI CON FIBRILLAZIONE ATRIALE A RISCHIO ELEVATO (START- LABORATORIO)

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START-LABORATORIO

- START-Laboratorio afferisce a START-Register, data base elettronico informatizzato con propria Direzione e Statuto, affidato all'Azienda Ospedaliera-Universitaria Sant'Orsola Malpighi di Bologna.
- Coordinatore di START-Register: Prof. Gualtiero Palareti
- Referenti di START Laboratorio: Cristina Legnani (BO), Vittorio Pengo (PD), Sophie Testa (CR), Armando Tripodi (MI)

PERCHE' START-LABORATORIO?

- La gestione dei pazienti in terapia antitrombostica ed anticoagulante in particolare (orale e parenterale) ha trovato nel laboratorio, attraverso l'individuazione del test più adeguato, (monitoraggio/controllo) uno dei mezzi per garantire sicurezza ed efficacia dei trattamenti
- Per il "buon uso clinico" del dato di laboratorio è indispensabile conoscere la metodologia, la qualità, il vantaggio/svantaggi dei mezzi diagnostici disponibili

BACKGROUND

- At present, DOACs are administered at fixed dose in relation to clinical indications, individual characteristics and renal function without need for laboratory monitoring.
- Nevertheless, a high inter-individual variability was demonstrated with all DOACs and post-hoc analyses of phase III clinical trials showed a relationship between DOACs plasma levels (measured at trough) and thrombotic and bleeding complications in the follow up period.

Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

Sophie Testa [a,*], Armando Tripodi [b], Cristina Legnani [c], Vittorio Pengo [d], Rosanna Abbate [e], Claudia Dellanoce [a], Paolo Carraro [f], Luisa Salomone [c], Rita Paniccia [e], Oriana Paoletti [a], Daniela Poli [f], Gualtiero Palareti [g], for the START-Laboratory Register

Drug	Trough (ng/ml) mean (min-max)	Peak (ng/ml) media (min-max)
Dabigatran 110 mgx2/die	93 (14-386)	190 (31-651)
Dabigatran 150mgx2/die	91 (16-494)	210 (43-538)
Rivaroxaban 15mg/die	27 (0-88)	208 (77-393)
Rivaroxaban 20mg/die	41 (5-119)	235 (61-449)
Apixaban 2,5mgx2/die	79 (26-248)	192 (55-300)
Apixaban 5 mgx2/die	113 (42-283)	200 (102-416)

Thrombosis Research, 2016

EDOXABAN: INTER-INDIVIDUAL VARIABILITY

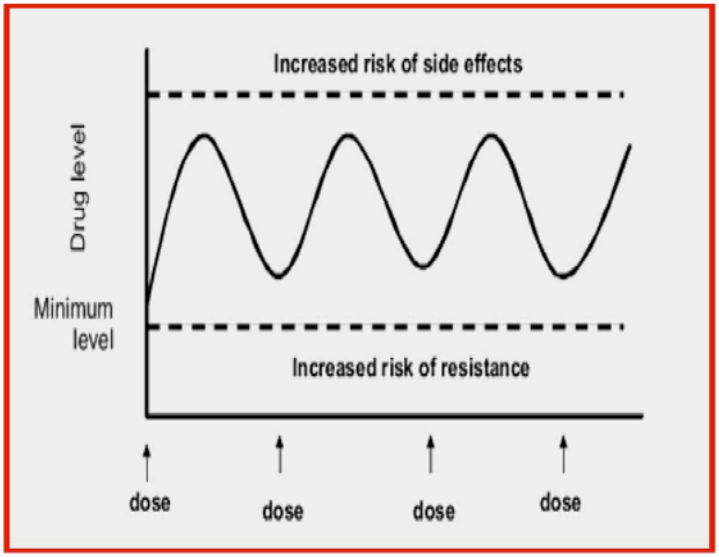
Drug	Trough (ng/ml) mean (min-max)	Peak (ng/ml) media (min-max)
Edoxaban 60 mg/die	39 (13-114)	294 (136-569)
Edoxaban 30 mg/die	37 (11-147)	184 (10-529)

Cremona 2017, unpublished

DOACs INTER-INDIVIDUAL VARIABILITY

Population	CV%
Healthy and young volunteers	~ 20
Phase III randomized clinical studied	~ 40
"Real world" patients	~ up to 75

FURTHERMORE…



Based on phase II and III clinical trials, it has been assumed that during time:

- anticoagulant levels are always "acceptable"
- do not occur: 1. persistent drug accumulation and 2. persistent absence or insufficient drug activity

If we compare:

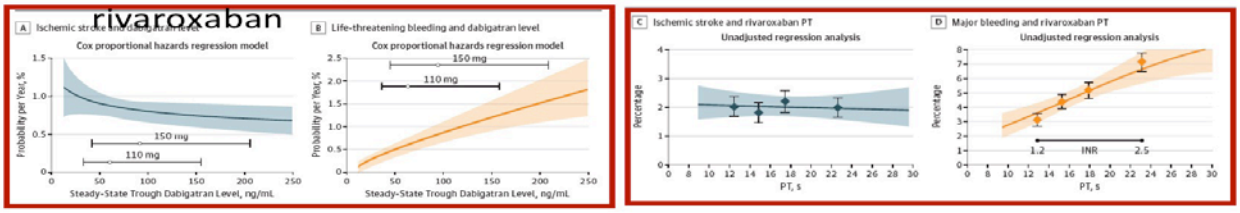
a) AVK complications are correlated with TTR

b) LMWH, not generally monitored, are administered for short period

FDA REPORTS: DOACs EXPOSURE-RESPONSE ASSOCIATION FOR EFFICACY AND SAFETY

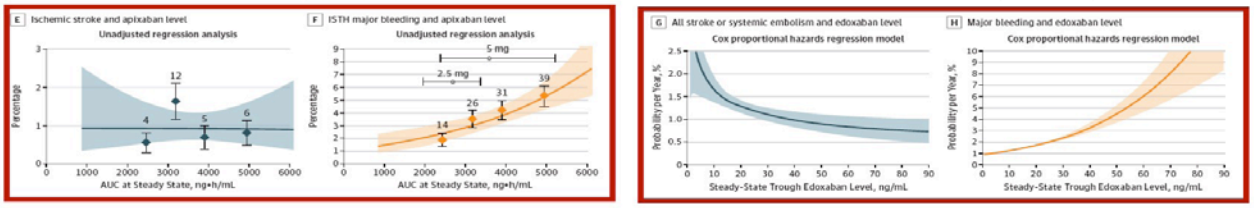
dabigatran

rivaroxaban



apixaban

edoxaban



Eikelboom JW et al, JAMA Cardiol 2017

LOW DRUG LEVELS AND THROMBOTIC COMPLICATIONS IN HIGH RISK ATRIAL FIBRILLATION PATIENTS TREATED WITH DIRECT ORAL ANTICOAGULANTS

Testa S, Paoletti O, Dellanoce C, Cosmi B, Morandini R, Pengo V, Poli D, Salomone L, Tala M, Testa R, Tripodi A, Palareti G *for the START-Lab Registry.*

JTH 2018, submitted

AIMS

- To evaluate a possible relationship between DOACs trough anticoagulant levels, measured at steady state within the first month of treatment, and thromboembolic events observed during one year follow up.

DESIGN

This is a prospective, observational, multicenter study in patients with non valvular atrial fibrillation (NVAF) treated with DOACs and conducted into 4 anticoagulation clinics affiliated with the Italian Federation of Anticoagulation Clinics (FCSA) and engaged in the Start Register (Survey on anTicoagulated pAtients RegisTer) (www.start-register.org).

METHODS (I)

- 565 consecutive naïve patients, aged =>18years, with NVAF referred to 4 Italian Anticoagulation Clinics, were enrolled.
- Patients received type and dosage of DOACs on the base of clinical characteristics at the discretion of the attending physician.
- Baseline characteristics (demographic, clinical, risk factors, CHA_2DS_2-VASc score, HAS-BLED, kidney/liver function, concomitant medications) were recorded into a structured data base.
- Follow up, as defined by FCSA guidelines (Federation of Italian Anticoagulation Clinics), included clinical evaluation within the first month and each 3 months for one year.
- Thromboembolic complications (Stroke, TIA, peripheral embolism, AMI, DVT/PE, SVT) were registered and patient lost at follow up

METHODS (II)

- Plasma samples were collected within the first month of treatment at trough level, obtained at 12 hours from the last dose intake for dabigatran and apixaban, and at 24 hours for rivaroxaban.
- Diluted thrombin time (dTT) calibrated for dabigatran, anti-FXa calibrated for rivaroxaban and apixaban were performed locally, within 3 months from plasma collection, to determine drug concentration.

RESULTS (I)
Main clinical characteristics

	dabigatran	rivaroxaban	apixaban	Total
Pts (n)	185	172	208	565
Age (yr) Mean (min/max)	78 (44-94)	82 (57-97)	80 (49-94)	80 (44-97)
Gender (M/F)	105/80	95/77	115/93	315/250
BMI	26.9 (17.4-43.3)	25.5 (16.6-34.7)	26.2(16.4-40.1)	26.2 (16.4-43.3)
Drug daily dose (n° patients)	2x150mg (82) 2x110mg(103)	20mg (100) 15mg (72)	2x5mg (154) 2x2.5mg (54)	- -
Cr Cl (mL/min/ 1.73m^2)	70.5 (39-149)	66.5 (36-117)	69 (33-117)	69 (33-149)
CHA_2DS_2VASc Mean (min-max)	3.0 (0-7)	3.0 (0-7)	3.0 (0-9)	3.0 (0-9)
Thrombosis n° (%)	5 (2.7) 4 Strokes, 1 AMI	3 (1.7) 2 AMI, 1 TIA	2 (1.0) 1 DVT, 1 Systemic Embolism	10 (1.8)

RESULTS (III)
Thromboembolic complications and DOAC plasma levels

- During 1 year follow up we observed 10 thromboembolic events (1.8%), all occurred after the first 6 months of treatment.
- All events were recorded in patients with drug trough levels below the mean value of biological variability, calculated for each drug

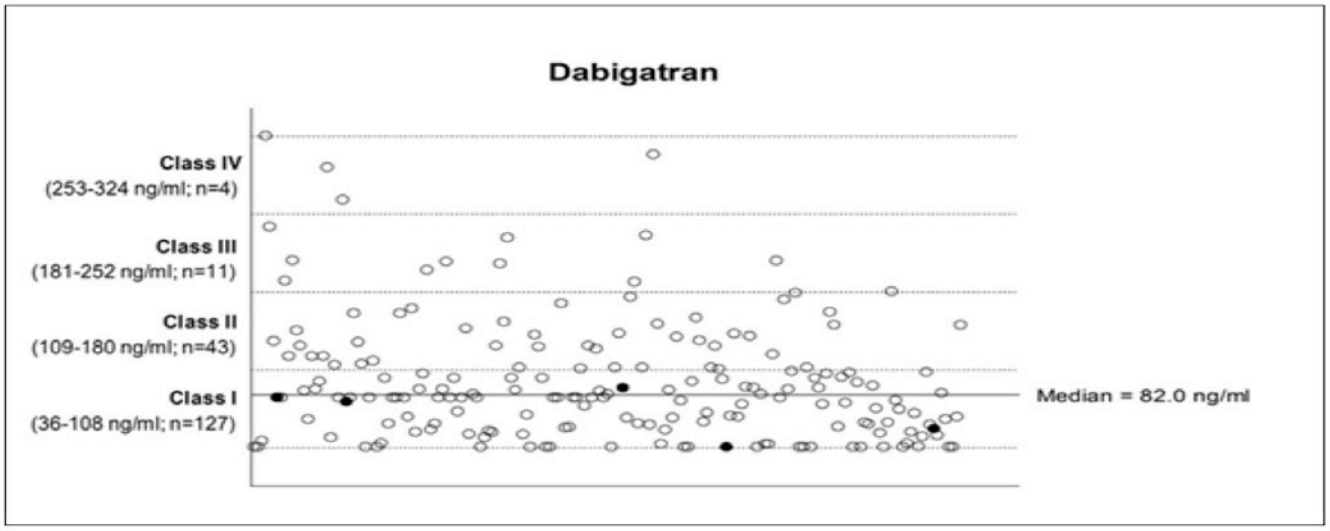
RESULTS (II)
DOAC plasma levels (ng/ml)

	dabigatran	rivaroxaban	apixaban	Total
All patients	82 (36-324)	39 (17-273)	111 (22-515)	-
Patients with thrombosis	67 (36-91)	28 (23-39)	79 (45-113)	-
Patients without thrombosis	82 (36-324)	39 (17-273)	111 (22-515)	-

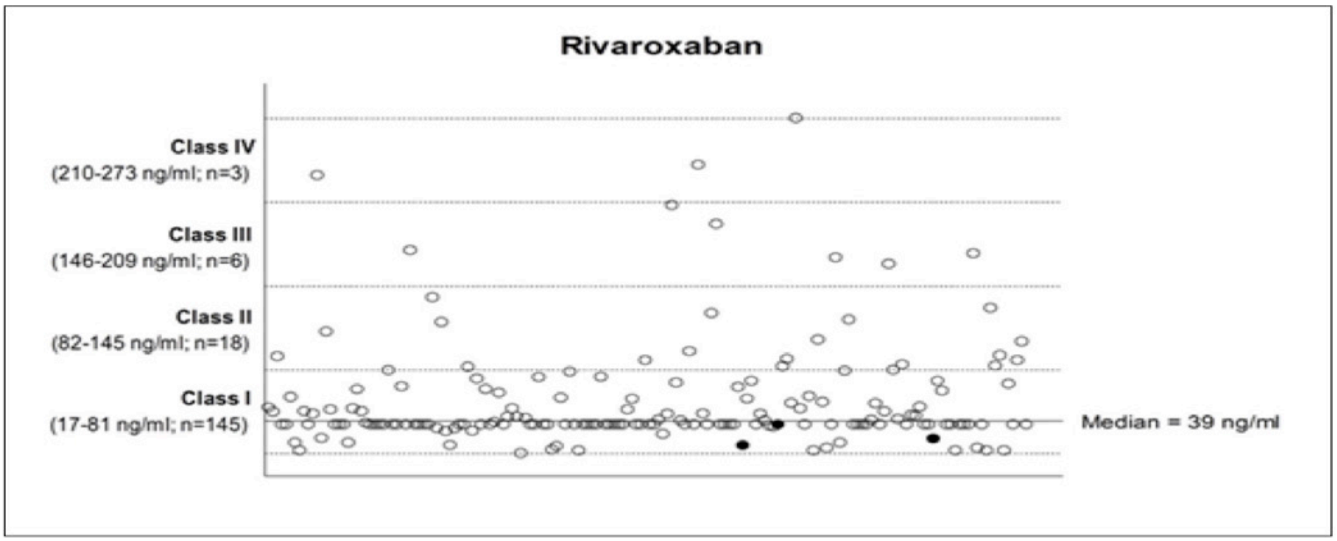
THROMBOEMBOLIC EVENTS AND DOAC c-TROUGH LEVELS (ng/ml)

	dabigatran	rivaroxaban	apixaban
Pts (n°)	185	172	208
Thromboembolic Events n (%)	5 (2.7) (4 strokes, 1 AMI)	3 (1.7) (2 AMI, 1 TIA)	2 (1.0) (1 DVT, 1 Syst. Emb.)
Patients without thrombosis	82 (36-324)	39 (17-273)	111 (22-515)
Patients with thrombosis	67 (36-91)	28 (23-39)	79 (45-113)

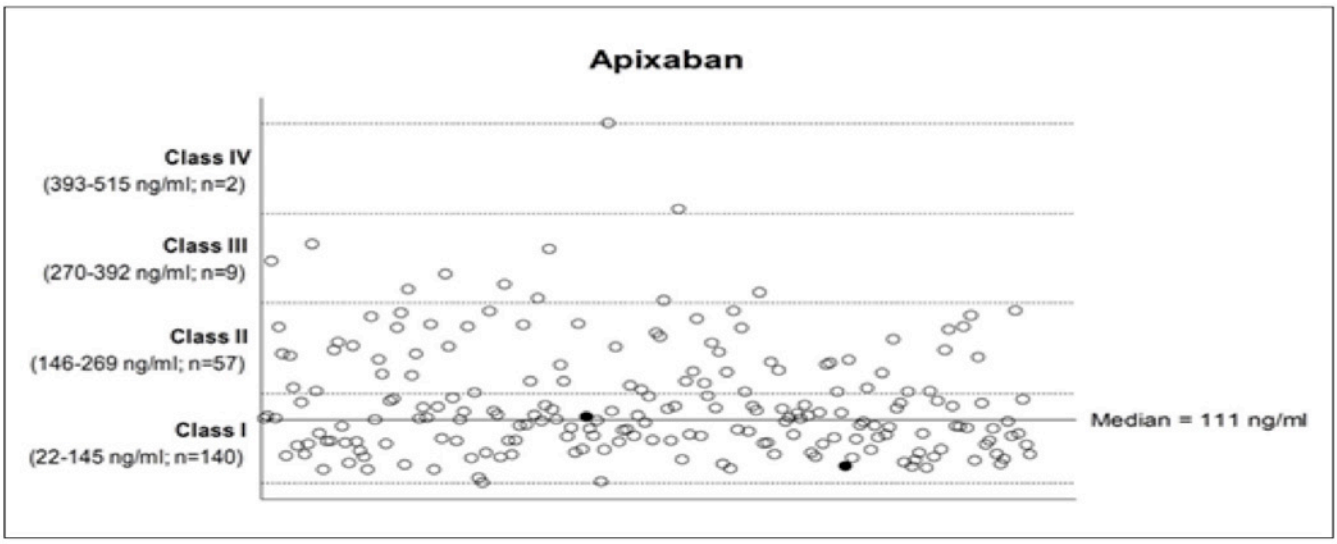
DABIGATRAN



RIVAROXABAN



APIXABAN



Thromboembolic complications, CHA_2DS_2VASc score and DOAC C-trough levels

Pt	Drug	Posology	CHA_2DS_2VASc	ASA	Amiodaron	CrCl (mL/min/1.73m²)	DOACs ng/ml	Thromboembolic Complication
1	Dabigatran	150mgx2	5	yes	yes	79	36	Stroke
2	Dabigatran	110mgx2	7	no	no	67	67	Stroke
3	Dabigatran	110mgx2	3	no	yes	53	53	Stroke
4	Dabigatran	110mgx2	4	no	no	67	78	Stroke
5	Dabigatran	150mgx2	7	no	no	76	91	AMI
6	Rivaroxaban	20mg	7	no	no	69	39	TIA
7	Rivaroxaban	15mg	5	no	no	56	23	AMI
8	Rivaroxaban	15mg	5	no	no	47	28	AMI
9	Apixaban	2.5mgx2	6	yes	no	44	113	Systemic Embolism
10	Apixaban	5x2mg	4	no	no	79	45	DVT

THROMBOEMBOLIC RISK IN PATIENTS WITH LOW DOACs LEVEL AND HIGHER CHA_2DS_2-VASc

CHA_2DS_2-VASc ≥3.0 (291/595pts; 51.5%)	Class I n° (Lower drug levels)	Class II, III,IV n° (Highest drug levels)	Total (n)
Thrombosis	10	0	10
No Thrombosis	117	164	281
	10/127 (7.9%)	0/164 (0%)	

LIMITS

- Relatively limited number of patient
- Locally and not centralized DOACs measurements

CONCLUSION

- Our data show a relationship between low DOACs trough plasma levels and subsequent thrombotic events
- Higher cardiovascular risk patients with low DOACs levels show significantly higher risk of thrombosis compared to patients with higher DOACs levels.
- DOACs measurement seems particularly indicated in higher cardiovascular risk patients
- To confirm this preliminary results a large prospective, multicenter, observational study - The MAS (Measure And See) Study, conducted within FCSA and the START Registry- has been planned and will start within February 2018.