START–Register

SURVEY ON ANTICOAGULATED PATIENTS – REGISTER

Registro computerizzato per la raccolta dei dati di pazienti trattati cronicamente con anticoagulanti

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 antitrombotica 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

DRUGS

UH

AVK

UH / LMWH

DOAC

Table. **Major Advances in the Treatment of Venous Thromboembolism**

1960s	Barritt and Jordan demonstrate that anticoagulant therapy reduces death and recurrent venous thromboembolism in patients with pulmonary embolism
	The Mobin–Uddin umbrella is introduced
1970s	Recurrent venous thromboembolism is found to occur more often in patients who have subtherapeutic activated partial thromboplastin times within the first 24 hours of treatment
	The Kimray–Greenfield filter is introduced
	Low-molecular-weight heparin is discovered
1980s	Lower-intensity oral anticoagulation is shown to be as effective as but safer than high-intensity regimens
	The international normalized ratio is introduced for oral anticoagulant monitoring
1990s	4 to 5 days of initial heparin therapy is found to be as effective as 10 days
	The combination of initial heparin therapy and oral anticoagulation is demonstrated to be more effective than oral anticoagulation alone in deep venous thrombosis
	Low-molecular-weight heparin is found to be as effective as intravenous unfractionated heparin in deep venous thrombosis and pulmonary embolism
	Outpatient treatment with low-molecular-weight heparin is shown to be safe and effective
	It is recognized that patients with idiopathic venous thromboembolism are at higher risk for recurrence than those with thrombosis secondary to transient risk factors
	A randomized trial demonstrates that inferior vena caval filters increase the long-term risk for recurrent venous thrombosis and do not reduce long-term mortality rates in patients who receive 3 months of anticoagulant therapy
2000	Designer anticoagulants are compared with established anticoagulants

LAB

aPTT

PT INR

Anti-FXa

dTT/ECA

Anti-FXa

DOAC: PREMESSA

Studi farmacodinamici e farmacocinetici hanno mostrato che la risposta anticoagulante e' prevedibile in condizioni cliniche "standard".

Da ciò è derivato:

1) Somministrazione a dosaggio fisso giornaliero
2) La non indicazione al monitoraggio di laboratorio routinario

MA…

- Subito dopo la loro introduzione nella pratica clinica si è evidenziata l'importanza della misurazione dell'attività anticoagulante.
- Inoltre, l'utilizzo degli antidoti specifici richiederà la pronta disponibilità del dosaggio dei DOAC per garantire la corretta somministrazione e guidare la gestione del paziente.

Pengo V et al JTH 2011, Bauer N Engl J Med 2015, Pollack et al N Engl J Med 2015

START-LABORATORIO: SCOPO

- Raccogliere informazioni relative agli aspetti di laboratorio dei pazienti trattati con DOAC (misura dell'attività anticoagulante, scelta e utilizzo dei test, qualità dei metodi, appropriatezza diagnostica)
- Favorire la ricerca attraverso la proposta di studi nell'ambito della diagnostica di laboratorio relativamente agli aspetti di: metodologia (test, reagenti, strumenti, valutazione della sensibilità e della specificità), analisi delle variabili biologiche, preanalitiche ed analitiche, validazione clinica del test di laboratorio.

COSA E' STATO FATTO?

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

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

Objective: To evaluate inter- and intra-individual variability in real-world atrial fibrillation patients on dabigatran, rivaroxaban or apixaban in four Italian anticoagulation clinics and to assess the correlation between DOAC plasma concentration and creatinine-clearance (CrCl).

Thrombosis Research 137 (2016) 178–183

MATERIALI E METODI

Materials and Methods: A total of 330 consecutive patients were enrolled, of which 160 were on dabigatran (70 and 90 taking 150 mg or 110 mg twice-daily, respectively), 71 on rivaroxaban (37 and 34 taking 20 mg or 15 mg once-daily) and 99 on apixaban (73 and 26 taking 5 mg or 2.5 mg twice-daily). Blood was taken at trough and peak within the first month (15–25 days) of treatment. Diluted-thrombin-time (dTT) calibrated for dabigatran and anti-FXa calibrated for rivaroxaban or apixaban was performed.

METODI

Methods, analytical performances, in house intra- and inter-assay coefficient of variation (CV%).

	Bologna (A)	Cremona (B)	Padua (C)	Florence (D)
Coagulometer	STA compact (Stago)	STA-R (Stago)	CA7000 (Sysmex)	ACL TOP 700 (Werfen)
Reagents				
Dabigatran	Thrombin Siemens	Thrombin Stago	Hyphen Hemoclot	Hyphen Hemoclot
Rivaroxaban	Liquid antiXa Stago	Liquid antiXa Stago	Hyphen DiXal	-
Apixaban	Liquid aXa Stago	Liquid aXa Stago	-	Hyphen DiXal
Calibrators				
Dabigatran	Hyphen Biomed	Hyphen Biomed	Hyphen Biomed	Hyphen Biomed
Rivaroxaban	Calibrator Stago	Calibrator Stago	Biophen Stago	-
Apixaban	Calibrator Stago	Calibrator Stago	-	Biophen apixaban
d-TT intra-assay CV%	2.4–5.1	2.7–5.8	2.8–3.6	1.4–7.6
dTT inter-assay CV%	1.9–7.3	3.1–7.9	4.2–8.1	3.1–6.0
Anti-FXa rivaroxaban intra-assay CV%	0.5–2.2	0.8–3.3	2.2–2.6	-
Anti-FXa rivaroxaban inter-assay CV%	0.6–4.4	1.0–4.3	2.2–6.2	-
Anti-FXa apixaban intra-assay CV%	1.3–2.4	1.1–3.6	-	1.5–6.6
Anti-FXa apixaban inter-assay CV%	1.7–3.6	2.0–4.5	-	2.2–6.9

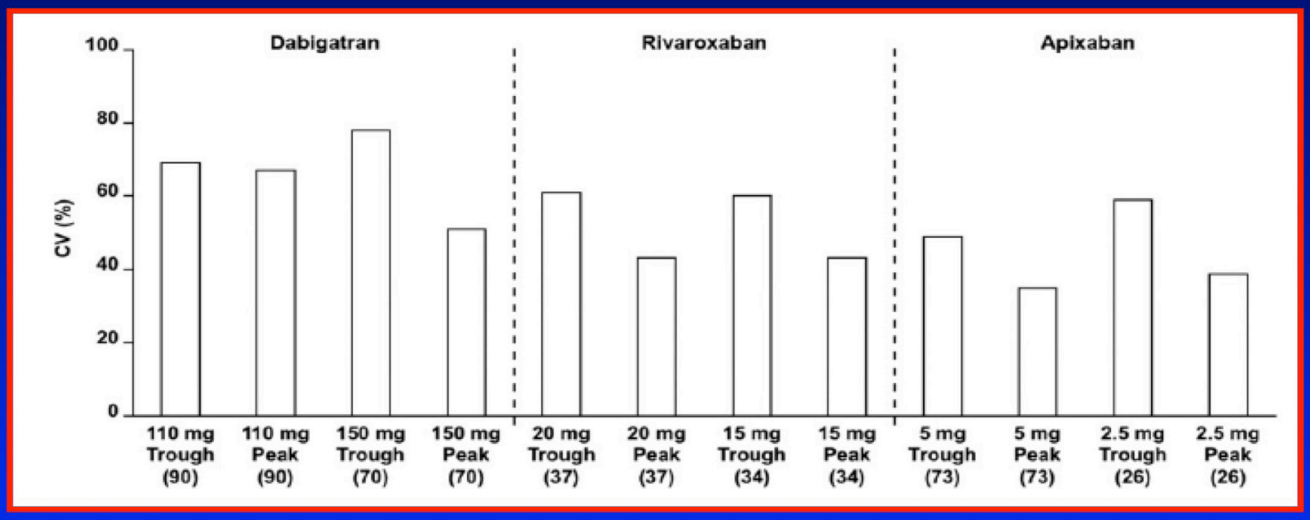
Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

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

FARMACO	Basale (ng/ml) media (min-max)	Picco (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

DOAC: INTER-INDIVIDUAL VARIABILITY



S. Testa et al / Thrombosis Research 137 (2016) 178–183

DOAC: INTRA-INDIVIDUAL VARIABILITY

	Intra-individual variability (ng/mL) mean (min-max)	CV% mean (min-max)
DABIGATRAN		
C_{trough}	80.3 (20-341)	36.0 (8.3-64.4)
C_{peak}	205.0 (37.0-465.1)	38.8 (23.8-49.8)
RIVAROXABAN		
C_{trough}	31.0 (20-75.5)	25.2 (1.5-52.6)
C_{peak}	197 (24.6-426.8)	30.7 (5.4-75.7)
APIXABAN		
C_{trough}	122.1 (40.8-249.5)	26 (13.6-54.4)
C_{peak}	224.6 (116-419.2)	25.7 (6.6-40.5)

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DOAC E ClCr

Drug and dose (mg)	C trough (r/r^2)	p	C peak (r/r^2)	p
Dabigatran 110	−0.25/0.0625	0.04	−0.12/0.014	ns
Dabigatran 150	−0.32/0.1024	0.03	−0.18/0.0324	ns
Rivaroxaban 20	−0.18/0.0324	ns	−0.15/0.0225	ns
Rivaroxaban 15	−0.09/0.0081	ns	0.07/0.0049	ns
Apixaban 5	−0.03/0.0009	ns	−0.17/0.0289	ns
Apixaban 2.5	−0.02/0.0004	ns	−0.01/0.0001	ns

CONCLUSIONI

Questo studio multicentrico conferma l'ampia variabilità inter/intra individuale dei livelli anticoagulanti dei DOAC

L'ampia variabilità non è associata ai valori di clearence della creatinina, in quanto non risultano correlazioni significative, fatta eccezione per dabigatran misurato a valle (peraltro molto basse)

L'assenza o scarsa correlazione suggerisce cautela nell'utilizzare la ClCr quale unico parametro di laboratorio per valutare indirettamente l'attività anticoagulante residua dei DOAC

Poor reliability of coagulation screening test in patients treated with direct oral anticoagulants: results from a multicenter multiplatform observational study

Sophie Testa[*], Cristina Legnani[†], Armando Tripodi[‡], Oriana Paoletti[*], Vittorio Pengo[§], Rosanna Abbate[¶], Laura Bassi[*], Paolo Carraro[#], Michela Cini[†], Rita Paniccia[¶], Daniela Poli[¶], Gualtiero Palareti[**] for the START-Laboratory Register

Aims. To evaluate correlation, responsiveness and variability of PT and aPTT vs DOAC anticoagulant levels measured with specific coagulation tests performed with different platforms in 4 anticoagulation clinics.

JTH 2016

METODI

Methods. 635 patients with non valvular atrial fibrillation participated in the study: 240 were on dabigatran, 264 on rivaroxaban and 131 on apixaban. Blood was taken at trough and peak within the first month (15-25 days) of treatment. PT, aPTT, diluted-thrombin-time (dTT) calibrated for dabigatran and anti-FXa calibrated for rivaroxaban or apixaban were performed.

JTH 2016

RISULTATI

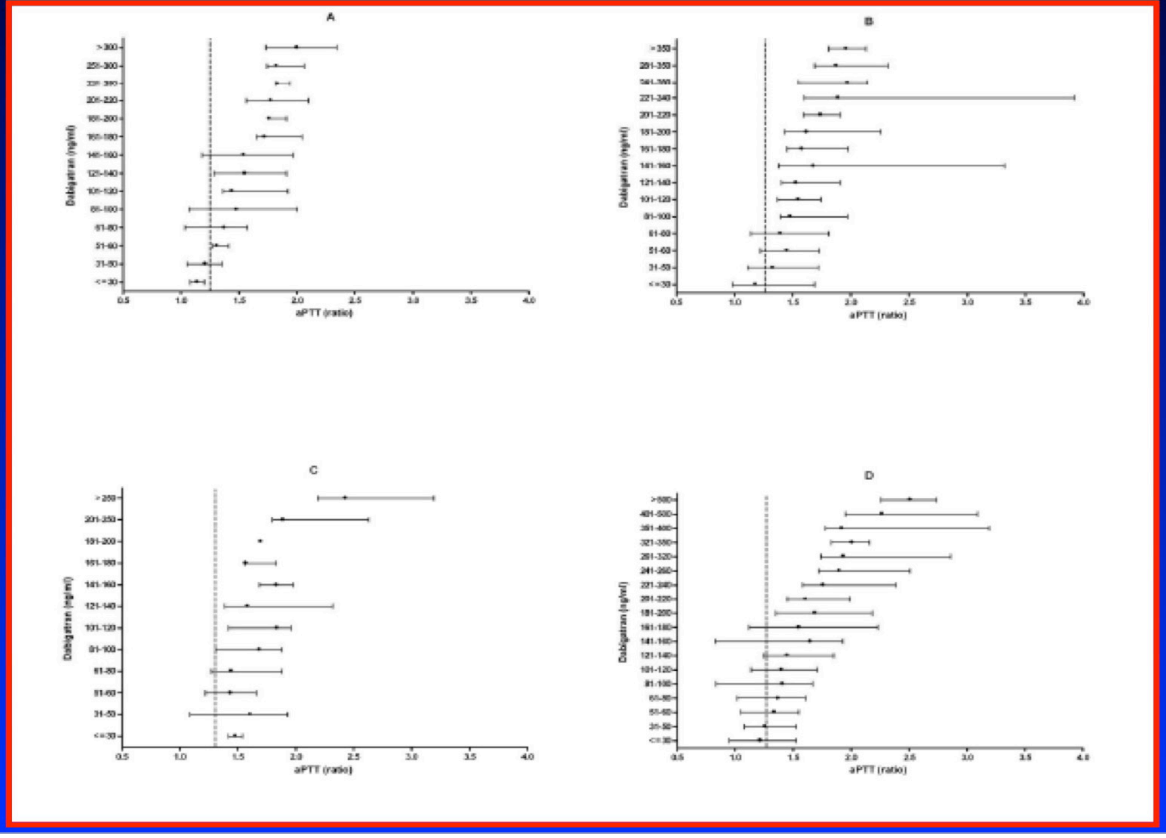
	Center A	Center B	Center C	Center D
dabigatran (aPTT)	1.67	1.74	1.97	1.68
rivaroxaban (PT)	1.57	1.88	1.31	1.53
apixaban (PT)	1.28	1.29	NA	1.32
Normal aPTT and dabigatran > 50 ng/ml	6/87 (6.9%)	6/107 (5.6%)	19/158 (12.0%)	3/42 (7.1%)
Prolonged aPTT and dabigatran ≤ 50 ng/ml	1/7 (14.3%)	22/51 (43.1%)	9/20 (45.0)	5/8 (62.5%)
Normal PT and rivaroxaban > 50 ng/ml	7/75 (9.3%)	3/119 (2.5%)	34/109 (31.2%)	2/26 (7.7%)
Prolonged PT and rivaroxaban ≤ 50 ng/ml	7/69 (10.1%)	11/97 (11.3%)	3/13 (23.1%)	5/20 (25.0%)
Normal PT and apixaban > 50 ng/ml	25/58 (43.1%)	73/172 (42.4%)	NA	6/18 (33.3%)
Normal PT and apixaban ≤ 50 ng/ml	0/2 (0%)	0/10 (0%)	NA	1/2 (50.0%)

Table 2: Responsiveness of PT or aPTT to DOAC. Numbers represent the aPTT or PT ratio (patient-to-normal clotting time) corresponding to 200 ng/ml DOAC concentration (see also Fig 1-3).

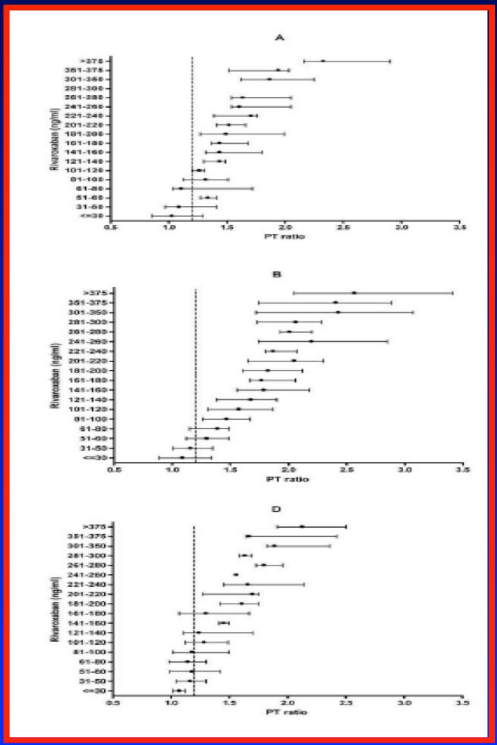
Number and percentage of discrepancies between global test and DOAC anticoagulant activity measured with specific tests.

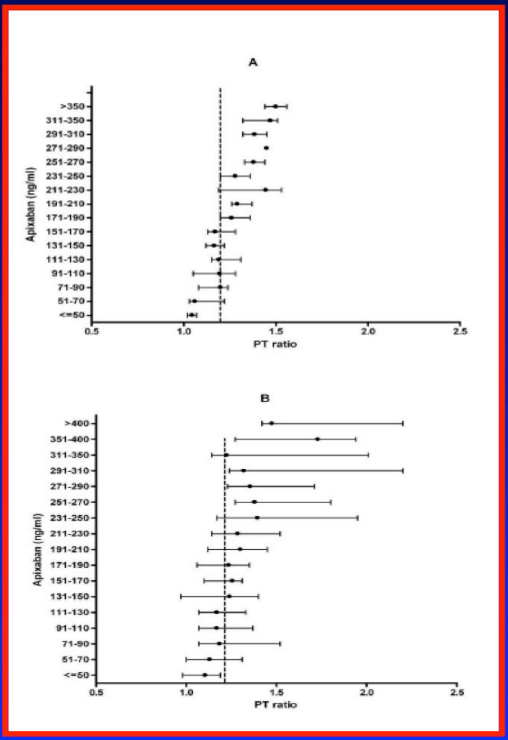
For Peer Review

DABIGATRAN



RIVAROXABAN E APIXABAN





CONCLUSIONI

In conclusion, the present study shows that: (a). PT and aPTT react differently with DOAC in relation to the type of drug and to the type of reagent, suggesting that each laboratory should be aware of their own performances. (b). Patients having the same anticoagulant activity can have significant different results in coagulation screening test. (c) Normal aPTT or PT tests for dabigatran and anti-FX drugs respectively cannot exclude significant anticoagulant activity exerted by DOAC, especially with poorly responsive PTT or PT reagents. (d) The use of PT or aPTT in clinical practice to evaluate DOAC anticoagulant activity could cause dangerous misinterpretations.

Review

JTH 2016

DOAC: CONFRONTO TRA METODI

Coordinatore Cristina Legnani

- Confronto dei risultati relativi ai livelli dell'attività anticoagulante dei DOAC, misurati con 6 diverse piattaforme commerciali
- Confronto dei risultati ottenuti con test specifici rispetto alle misurazioni cromatografiche.

MATERIALI E METODI

550 plasmi in dabigatran, 550 plasmi in rivaroxaban 450 plasmi in apixaban sono stati distribuiti ai 4 centri partecipanti

Bologna	Cremona	Padova	Firenze
DASIT SIEMENS TECHNOCLONE	STAGO	HPLC	WERFEN

PT, aPTT, TT, Fattori, Inibitori, dTT, ECA, aXa

SISET 2016

-Poster: HEPARIN INTERFERENCE IN SEVEN ANTI-Xa ASSAYS FOR RIVAROXABAN DETERMINATION

-Poster: ANALYTICAL PERFORMANCE OF SEVEN ANTI-Xa ASSAYS FOR RIVAROXABAN DETERMINATION

-Poster: ANALYTICAL PERFORMANCE OF SEVEN ANTI-Xa ASSAYS FOR APIXABAN DETERMINATION

-Comunicazione orale:COMPARISON OF TWO ANTI-Xa ASSAYS FOR RIVAROXABAN LEVELS DETERMINATION WITH OR WITHOUT EXOGENOUS ANTITHROMBIN

Legnani C et al.

COSA STIAMO FACENDO?

I

Analytical performances of five assays for dabigatran determination at low drug levels

II

Analytical performance of seven different anti-Xa assays for rivaroxaban determination at low drug levels

Legnani C et al.

III

Analytical performances of 5 different commercial assays in comparison with HPLC for dabigatran determination

Legnani C et al.

COSA FARE NEL PROSSIMO FUTURO?

- Valutare le molecole di più recente o futura introduxione (edoxaban, betrixaban)
- Valutare la possibilità di individuare cut-off di intervento e range terapeutici (da non confondere con la variabilità biologica osservata)
- Valutare la relazione tra livelli misurati e complicanze

- ...

RELATIONSHIP BETWEEN DOAC LEVELS AND SUBSEQUENT THROMBOEMBOLIC EVENTS

Our data show a relationship between low DOAC levels and thrombotic events. Further prospective analysis will be needed to confirm this preliminary observation

ISTH 2017 sub

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