Livelli anticoagulanti dei DOACs e complicanze trombotiche e emorragiche: risultati recenti dello START Laboratorio, Studio MAS

Sophie Testa
Haemostasis and Thrombosis Center
Cremona Hospital, Italy

INTRODUCTION

At present, DOACs are administered at fixed dose in relation to clinical indications, individual characteristics and renal function without need for laboratory monitoring, because:

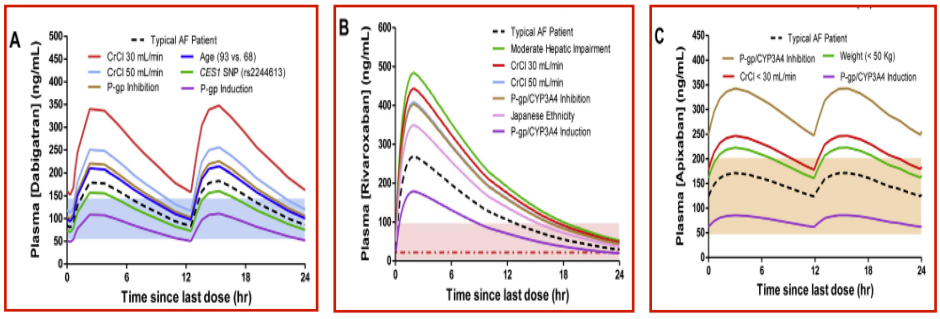
1. Pharmacologycal studies have shown that DOAC have predictable anticoagulant response in “standard” clinical condition
2. Clinical trials have been successfully conducted at fixed-dose regimen, without laboratory controls and without the availability of specific antidotes, in two clinical conditions (NVAF and VTE)

BUT, THE REALITY IS THAT …

- High inter/intra individual variability has been demonstrated in the real world patient population
- Pharmacological modifications have been showed in relation to: drug interaction, liver and renal function, age , weight, comorbidities….
- After DOAC introduction in clinical practice specific antidotes have been requested and are now available
- Laboratory measurements are recommended, at the moment, in particular clinical conditions

VARIABILITY

Drug interactions, renal and liver function, age, weight, genetic polymorphisms…



dabigatran rivaroxaban apixaban

Gong IY et al, 2013

EXPECTED PEAK AND TROUGH DOAC LEVELS IN NVAF AND VTE PATIENTS ENROLLED IN PHASE II-III CLINICAL STUDIES

	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Indication	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE
Dose	150 mg bid	150 mg bid	20 mg qd	20 mg qd	5 mg bid	5 mg bid	60 mg qd	60 mg qd
Peak concentration, ng/mL	175[a] (117–275)	175[a] (117–275)	249[b] (184–343)	270[b] (189–419)	171[c] (91–321)	132[c] (59–302)	170[d] (125–245)	234[e] (149–317)
Trough concentration, ng/mL	91[a] (61–143)	60[a] (39–95)	44[b] (12–137)	26[b] (6–87)	103[c] (41–230)	63[c] (22–177)	36[e] (19–62)	19[e] (10–39)

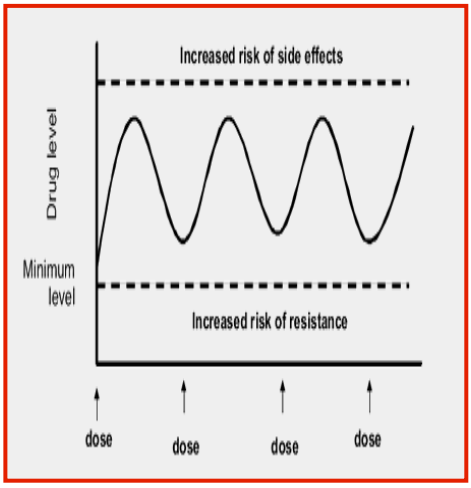
aMean (25th–75th percentile); **b**Mean (5th–95th percentile); **c**Median (5th–95th percentile); **d**Median (1.5 x IQR); **e**Median (IQR).

Gosselin R et al, Thromb Haemost 2018

DOACs INTER-INDIVIDUAL VARIABILITY

Population	CV%
Healthy and young volunteers	~ 20
Phase III randomized clinical studied	~ 40
"Real world" patients	**~ up to 100**

WHAT WE KNOW AND OUR ASSUMPTIONS IN DAILY CLINICAL PRACTICE



1. We know the **biological variability** of DOACs (**NOT the therapeutic range**), in population enrolled in phase II-III studies and few data are available in real life patient populations

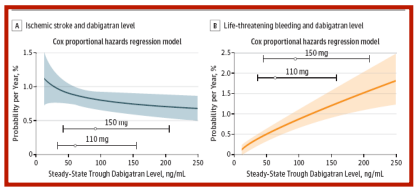
2. DOAC biological variability **differs between NVAF and VTE patients**

3. It has been assumed that DOAC levels, "individually" and "a priori", also during time, are "acceptable" and do not occur persistent accumulation or absence of drug

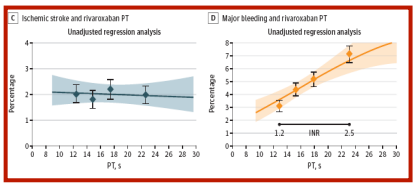
ARE THESE PHARMACOLOGICAL INFORMATIONS USEFUL FROM A CLINICAL POINT OF VIEW?

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

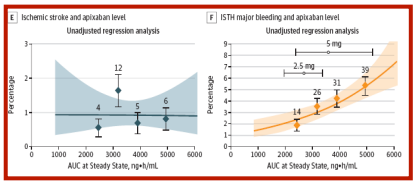
dabigatran



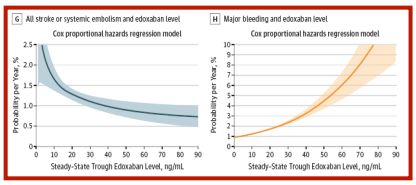
rivaroxaban



apixaban



edoxaban



Eikelboom JW et al, JAMA Cardiol 2017

DOACs AND THE LAB

Test	Recommendation	Comments
ClCr	1.Before starting DOACs and in the follow up to continue treatments (or adapt posology). 2. CrCl is also considered as surrogate of good anticoagulant action	- ClCr not validated in older population - CrCl>30ml/min not correlate with aXa drugs
AST/ALT	1. Before starting DOACs and in the follow up to continue treatments	No clear timing of controls
Blood Cell Count	Should be recommended	Before starting and during the follow up
PT/aPTT	Not recommended to assess levels of anticoagulation	Should be recommended before starting DOAC to assess haemostatic status
DOAC specific test	In special clinical conditions	There is still no unanimous consensus

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

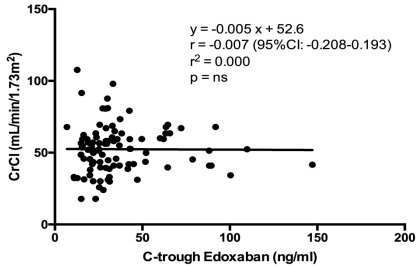
Sophie Testa [a,*], Armando Tripodi [b], Cristina Legnani [c], Vittorio Pengo [d], Rosanna Abbate [e], Claudia Dellanoce [a], Paolo Carraro [f], Luisa Salomone [c], Rita Paniccia [e], Oriana Paoletti [a], Daniela Poli [f], Gualtiero Palareti [g], for the START-Laboratory Register

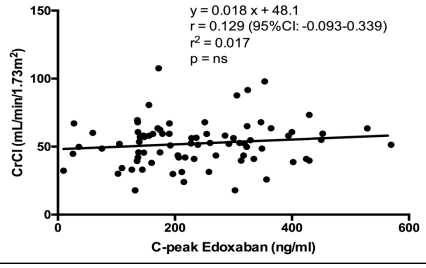
Table 6. Correlation (r value), coefficient of determination (r^2) and statistical significance (p) of DOAC plasma concentrations (at peak or trough) vs. creatinine clearance.

Drug and Dose (mg)	C Trough (r/r^2)	p	Cpeak (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

Tromb Res, 2016

EDOXABAN PLASMA LEVELS IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION: INTER AND INTRA-INDIVIDUAL VARIABILITY, CORRELATION WITH COAGULATION SCREENING TEST AND RENAL FUNCTION





Thromb Res, 2019

DOACs MEASUREMENT

1. *PERIODICAL MEASUREMENT (MONITORING) TO FREQUENT DOSE-ADJUSTEMENT (currently no evidences…)*

2. *MEASUREMENT IN SPECIAL CLINICAL CONDITIONS (Patients presenting in emergency with bleeding/thrombosis, immediate reverse of anticoagulation, perioperative management, renal disease, liver disease, suspicion or known interaction with other drugs, elderly patients, under/over weight….but no still unanimous consensus)*

3. **MEASUREMENT (CONTROL) TO HIGHLIGHT UNDER/OVER ANTICOAGULATION IN RELATION TO RISK OF BLEEDING AND THROMBOSIS**

Eikelboom JW et al, 2017; Tripodi A et al 2017

IN RECENT LITERATURE

Direct oral anticoagulant drug level testing in clinical practice: a single institution experience

Karlyn Martin and **Stephan Moll** *Thromb Res.* 2016

Laboratory measurement of the direct oral anticoagulants: Indications and impact on management in clinical practice

C. Wright | R. Brown | A. Cuker *Int J Lab Hem.* 2017

Direct-acting oral anticoagulant drug level monitoring in clinical patient management

Amihai Rottenstreich[1] · Netanel Zacks[1] · Geffen Kleinstern[2] · Bruria Hirsh Raccah[3,4] · Batia Roth[1] · Nael Da'as[5] Yosef Kalish[1]

Journal of Thrombosis and Thrombolysis (2018)

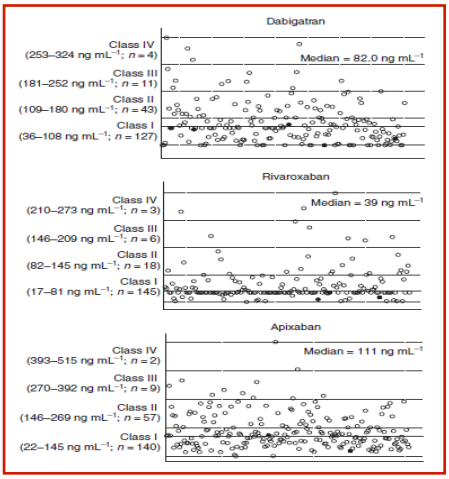
These retrospective observational studies, conducted on small cohort of patient population, highlighted :

1. A role in drug monitoring in the management of patients in selected circumstances (surgery, bleeding thromboembolic complications, renal failure, drug interactions, overweight)
2. No current indications in routine (frequent) drug level monitoring because it rarely affected clinical management
3. The necessity of studies to further establish association between drug-specific DOAC levels and clinical outcomes, to define appropriate indications for testing

Thromb Res 2016; Int J Lab Hem 2017; JTH 2018

Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants

S. TESTA,* O. PAOLETTI,* C. LEGNANI,† C. DELLANOCE,* E. ANTONUCCI,‡ B. COSMI,† V. PENGO,§ D. POLI,¶ R. MORANDINI,* R. TESTA,** A. TRIPODI†† and G. PALARETI‡



Patients with thromboembolic events are identified as filled circles

- 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 whose C-trough drug levels were in the lowest level class, calculated for each drug

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%)	

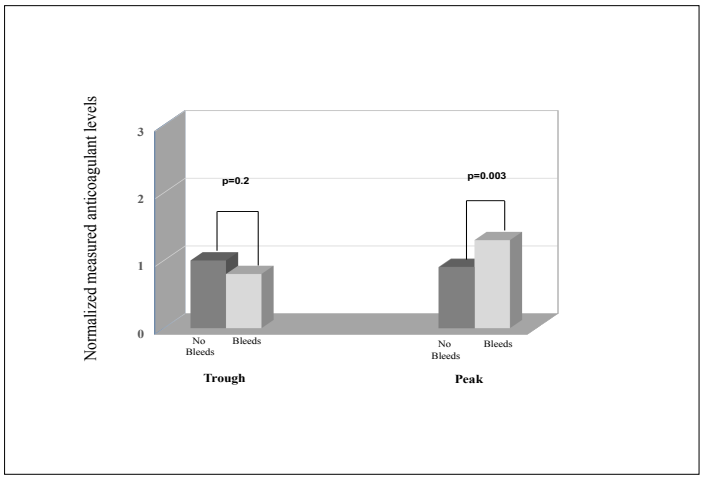
CONCLUSION

- Our data show a relationship between low DOACs trough plasma levels and subsequent thrombotic events
- Especially in high cardiovascular risk patients with low DOACs levels
- DOACs measurement seems particularly indicated in these 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 is started in June 2018.

DRUG LEVELS AND BLEEDING COMPLICATIONS IN ATRIAL FIBRILLATION PATIENTS TREATED WITH DIRECT ORAL ANTICOAGULANTS

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

Submitted JTH



The MAS study ("Measure And See")

Measurement of the anticoagulant levels in patients treated with Direct Oral Anticoagulants (DOACs) and observation of bleeding and thrombotic complications during follow up.

Promoted and funded by the «Arianna Anticoagulazione Foundation» (Bologna, Italy), Coordinator: prof. Gualtiero Palareti

In collaboration with: FCSA (Federation of Italian Anticoagulation Clinics)

STUDY DESIGN

- The MAS study is a cohort, observational, prospective, double blind, multicenter, study in patients with NVAF treated with DOAC.
- The study doesn't influence DOAC treatment of the included study population, that will be treated following the defined rules of the current clinical practice

PARTECIPANTS

- Centers affiliated to FCSA and others
- All partecipating centers should be available to organize the clinical follow up and blood sampling as requested by the study

PATIENT POPULATION

- Consecutive patients during their first year of DOAC treatment
- 4000 pazients with NVAF (1000 for each drug)
- Type and dosage of DOACs will be defined on the base of clinical characteristics at the discretion of the attending physician
- Baseline characteristics (patient identification number, demographic, clinical, risk factors, CHA_2DS_2-VASc score, HAS-BLED, kidney/liver function, concomitant medications) will be recorded on electronic CRFs
- Follow up, as defined by FCSA guidelines , includes clinical evaluation within 15-30 days and each 3 months for one year.
- Bleeding and Thromboembolic complications will be registered and patient lost at follow up promptly called back.

PLASMA SAMPLES

- Plasma samples will be collected within 15-30 days of treatment at trough level, obtained at 12 hours from the last dose intake for dabigatran and apixaban, and at 24 hours for rivaroxaban and edoxaban.
- It's strongly suggested, to collect blood samples at peak (after 2 hours from last dose intake) at the first control and only at C-trough , each three months, during the routine clinical controls
- Plasma samples, identified in anonymous , will be quickly frozen, locally, conserved at -80°, and periodically centralized for measurements

PLASMA MEASUREMENTS

- DOAC plasma samples will be centralized at Arianna Foundation in Bologna
- Plasma measurements of the four different DOACs will be performed with commercial test (whose performancies are already known)
- It's expected to perform the following measurements: dTT and ECA for dabigatran and specific chromogenic test for aXa drugs
- Each method will be performed on all samples , in a single laboratory, to reduce inter-laboratory variability
- Results will be blind for clinicians and patients and, only at the end of the study, they will be communicated

PRIMARY OUTCOMES

- Major bleeding (criteria as defined by ISTH)*
- Non major clinical relevant bleedings (NMCRB)*
- The total number of MB and NMCRB
- Venous and arterial thrombosis
- Deaths (cardiovascular deaths and total mortality)

SECONDARY OUTCOMES

- Drug discontinuation
- DOACs adverse reactions (causing a change of anticoagulant treatment)

* Schulman S and Kearon C, JTH 2005

THE MAS STUDY

Promoter	Gualtiero Palareti
Principal Investigator	Sophie Testa
Pharmacovigilance	Emilia Antonucci
Study Core Team	Cristina Legnani Sophie Testa Armando Tripodi
Statistical Analysis	Alberto Tosetto
Adjudication and Safety Committee	Giancarlo Castaman Giovanni de Gaetano Francesco Marongiu

For information

info@start-register.org

Totale 37 centri di cui:

- 12 centri: hanno ricevuto approvazione CE e autorizzazione DG (11 di questi hanno già ricevuto tutto il materiale necessario per l'arruolamento dei pazienti)
- 9 centri: in seduta CE
- 4 centri: parere sospensivo da parte del CE (tra cui Cacciola è il 3° parere sospensivo e hanno valutato lo studio non osservazionale; Fregoni hanno richiesto assicurazione)
-7 centri: in attesa di ricevere dal PI la documentazione richiesta
-2 centri: stiamo preparando la documentazione da inviare al CE
-3 centri: rinvio temporaneo/ritiro della partecipazione

Nuove richieste di partecipazione allo studio (ancora da presentare emendamento per aggiornamento centri):
- Ida Martinelli (Milano)
- Erica De Candia (Roma)

STATO RICHIESTA CE	Città	PI	N° PAZIENTI IN CRF
In attesa di documenti dal PI	Udine	Barillari Giovanni	
Parere sospensivo	Catania	Cacciola Rossella	
Approvato 22/11/18	Roma	Chistolini Antonio	0
Approvato 12/12/18	Avellino	Ciampa Antonio	0
In attesa di documenti dal PI	Bari	Colucci Antonietta	
In attesa di documenti dal PI	Bologna	Cosmi Benilde	
Ritirata partecipazione	Manerbio (BS)	Del Giudice Giorgia	
In seduta	Genova	Duce Rita	
In attesa di documenti dal PI	Oglio Po (CR)	Esteban Maria Del Pilar	
In seduta	Milano	Faioni Elena Maria	
Parere sospensivo	Sondalo (SO)	Fregoni Vittorio	
In attesa di documenti dal PI	San Giovanni Rotondo (FG)	Grandone Elvira	
Approvato 19/07/18	Perugia	Gresele Paolo	0
In attesa di documenti dal PI	Salerno	Guida Anna	
Approvato 18/09/18	Rozzano (MI)	Lodigiani Corrado	0
rinvio temporaneo partecipazione	Parma	Manotti Cesare	
Approvato 06/11/18	Modena	Marietta Marco	0
rinvio temporaneo partecipazione	Brescia	Martini Giuliana	
In preparazione documentazione	Milano	Molteni Mauro	
In preparazione documentazione	Namur (Belgio)	Mullier François	
Approvato 14/11/18	Chieri (TO)	Paparo Carmelo	0

In seduta	Padova	Pengo Vittorio	
Approvato 22/11/18	Roma	Pignatelli Pasquale	0
In seduta	Firenze	Poli Daniela	
In seduta	Nocera Inferiore (SA)	Rescigno Giuseppe	
Parere sospensivo-In seduta	Gallipoli (LE)	Ria Luigi	
In seduta	Cosenza	Rossi Vincenza	
In attesa di documenti dal PI	Pisa	Ruocco Lucia	
In seduta	Milano	Russo Umberto	
Parere sospensivo - In seduta	Brindisi	Santoro Angelo	
In seduta	Catanzaro	Santoro Rita Carlotta	
In seduta	Genova	Serra Domizio	
Approvato 10/07/18	San Fermo della Battaglia (CO)	Serricchio Giuseppina	0
Approvato 26/06/18	Varese	Squizzato Alessandro	0
Approvato 02/05/18	Cremona (Centro coord.)	Testa Sophie	62
Approvato 11/07/18	Negrar (VR)	Turrini Anna	0
Approvato 13/12/18	Chieti	Verna Sandra	2

The question:
Is DOAC testing usefull to highlight patient at higher risk of complication?

The answer: The MAS Study

> Even though the one-size-fits-all DOAC dosing may perform as well as or better than warfarin on average... patient safety can be further improved through individualized patient dosing.

Powell JR, JAMA 2015