STUDIO MAS

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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

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

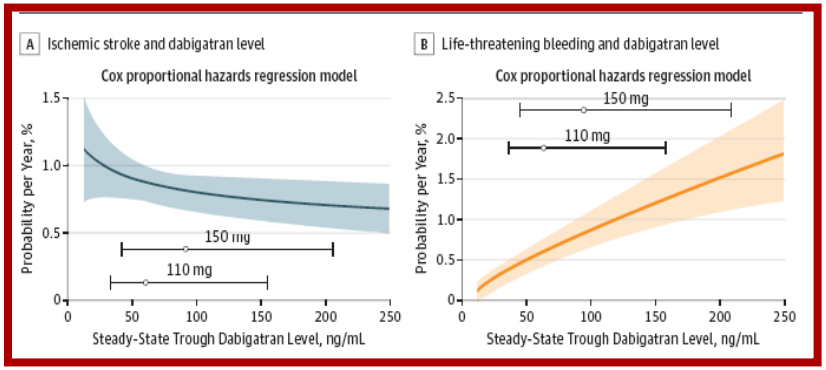
DOACs INTER-INDIVIDUAL VARIABILITY

Population	CV%
Healthy and young volunteers	~ 20
Phase III randomized clinical studies	~ 40
“Real world” patients	~ up to 100

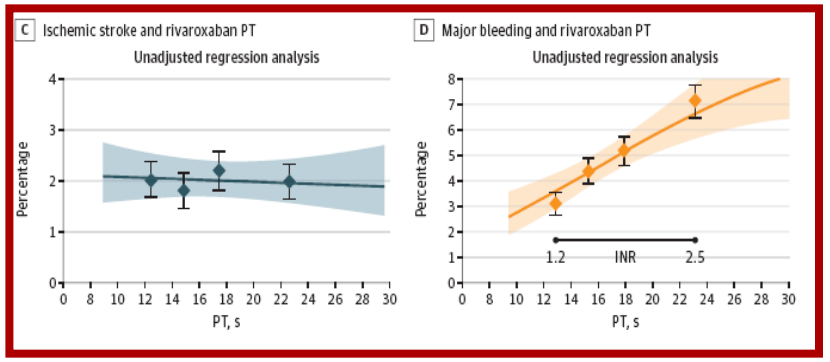
IS THIS PHARMACOLOGICAL INFORMATION USEFUL FROM A CLINICAL POINT OF VIEW?

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

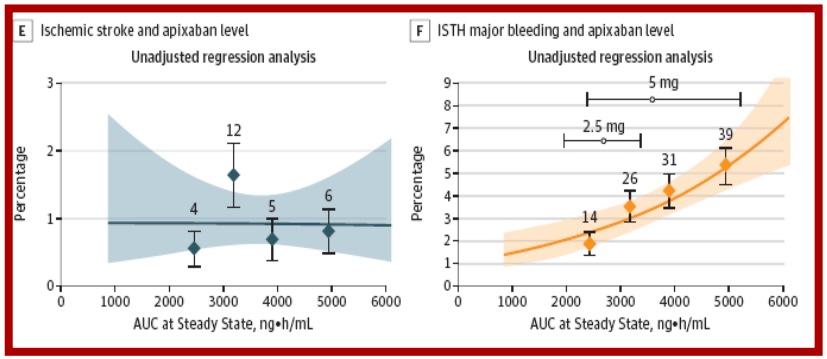
dabigatran



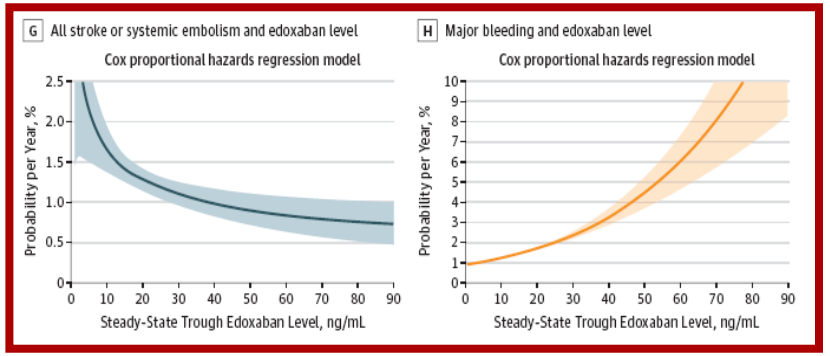
rivaroxaban



apixaban



edoxaban



Eikelboom JW et al, JAMA Cardiol 2017

DOACs 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‡

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: 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).

JTH 2018

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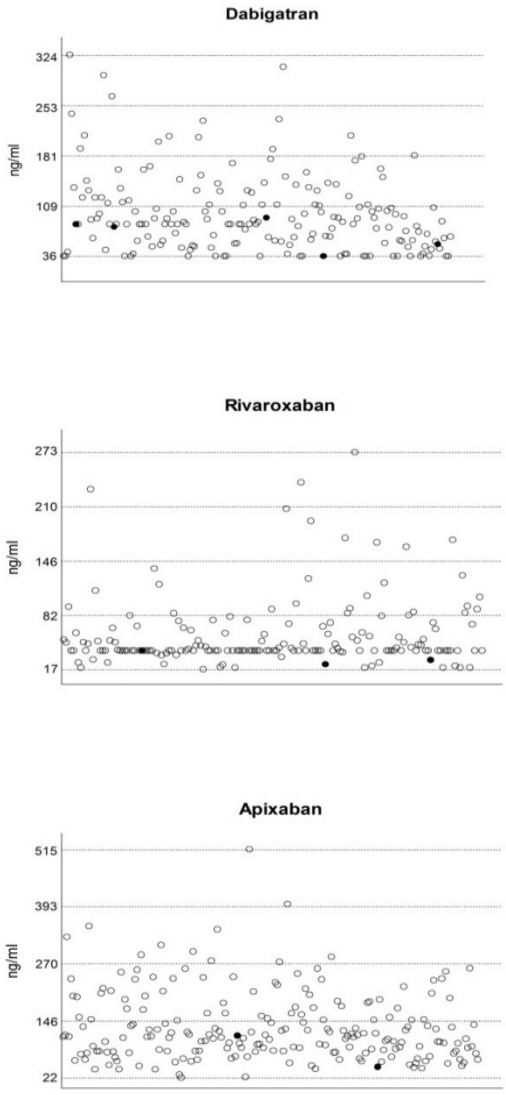


CHA_2DS_2-VASc **>3.0** (291/595pts; 51.5%)	**Class I (n)** (Lower drug levels)	**Class II, III,IV (n)** (Highest drug levels)	**Total** (n)
Thrombosis	10	0	10
No Thrombosis	117	164	281
	10/127 (7.9%)	0/164 (0%)	

Testa S, et al. J Thromb Haemost 2018;16:842-8

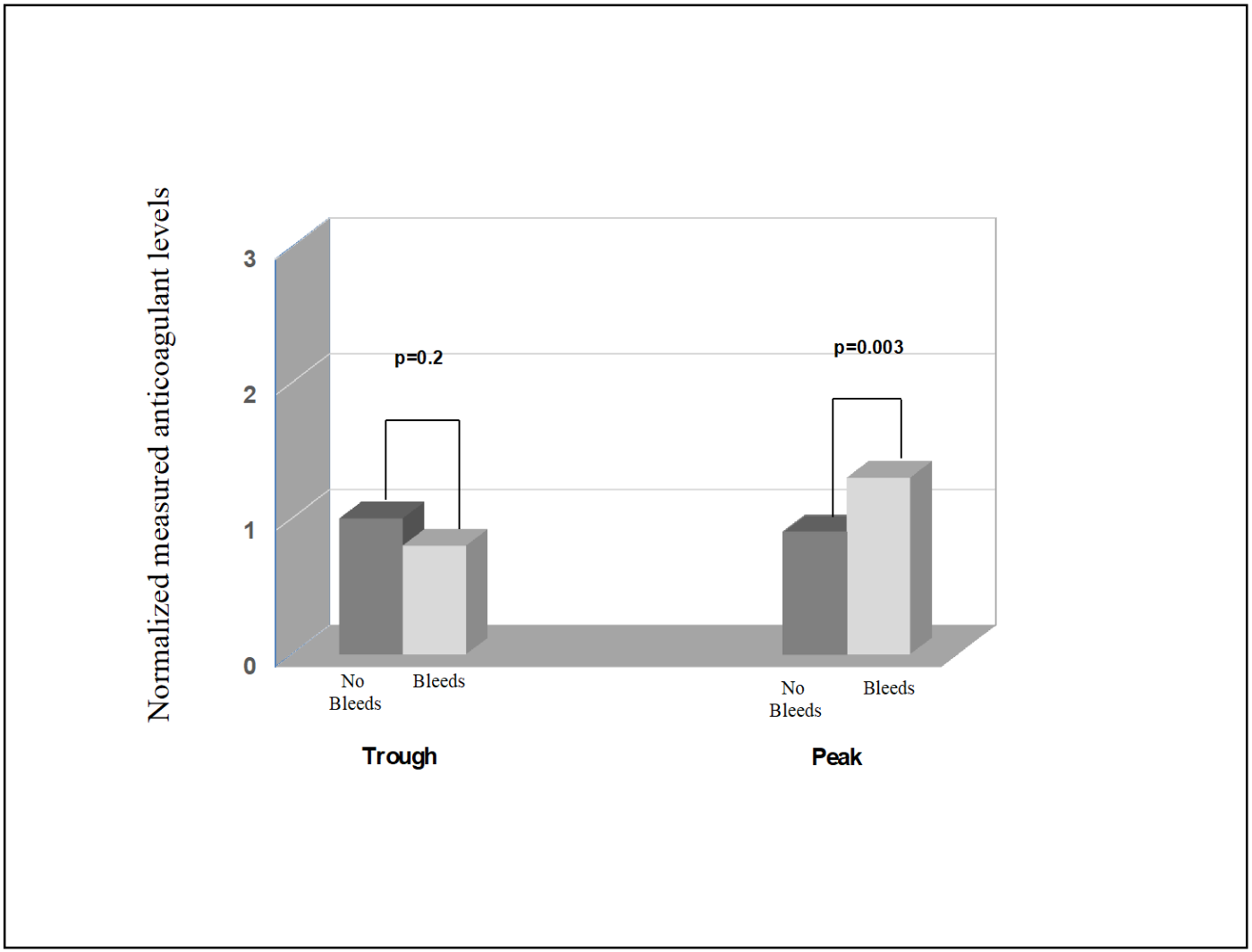
CONCLUSION

- 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.

Testa S, 2018 submitted



Testa S, 2018 submitted

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 (obtained at 12 hours from the last dose intake for dabigatran and apixaban, and at 24 hours for rivaroxaban and edoxaban) and at peak (two hours after last dose intake).

- It's suggested, but not mandatory, 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

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