I pazienti "low-responder" agli anticoagulanti orali ad azione diretta (DOAC) possono avere problemi per l'efficacia dei trattamenti? Dati della letteratura recente

Cristina Legnani

Fondazione Arianna Anticoagulazione, Bologna

DOAC: livelli e complicanze

Gli studi clinici di fase III hanno dimostrato che la variabilità inter-individuale dei livelli dei DOAC è piuttosto alta (≈ CV 40%)

Analisi post-hoc di questi trial hanno dimostrato che esiste una relazione tra il livello dei DOAC e le complicanze emorragiche e tromboemboliche intercorse nel follow-up

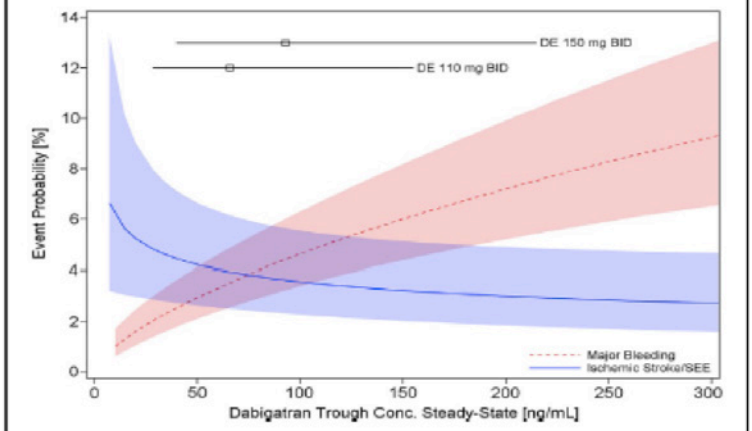


Figure 2 **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles.
Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,† Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPhil,§ John W. Eikelboom, MB BS,§ Michael D. Ezekowitz, MD, PhD,‖ Gerhard Nehmiz, PhD,† Susan Wang, PhD,* Lars Wallentin, MD, PhD,¶ on behalf of the RE-LY Investigators

(J Am Coll Cardiol 2014;63:321–8)

Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, David A Morrow, Sabina A Murphy, Julia F Kuder, Naveen Deenadayalu, Petr Jarolim, Joshua Betcher, Minggao Shi, Karen Brown, Indravadan Patel, Michele Mercuri, Elliott M Antman

Lancet 2015; 385: 2288–95

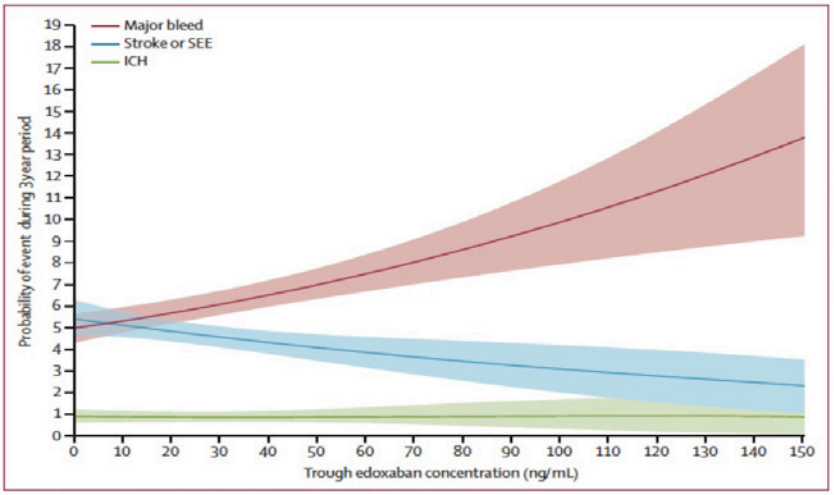


Figure 2: **Probability of clinical outcomes versus edoxaban concentration**
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

DOAC: livelli e complicanze

Negli studi di "real world" è stata dimostrata una ancora più alta variabilità inter-individuale dei livelli dei DOAC (≈ CV 70%)

Data la più alta variabilità inter-individuale è ragionevole che il numero di pazienti con livelli estremi (low- and high-responders) sia maggiore nel "real world" rispetto ai trial registrativi

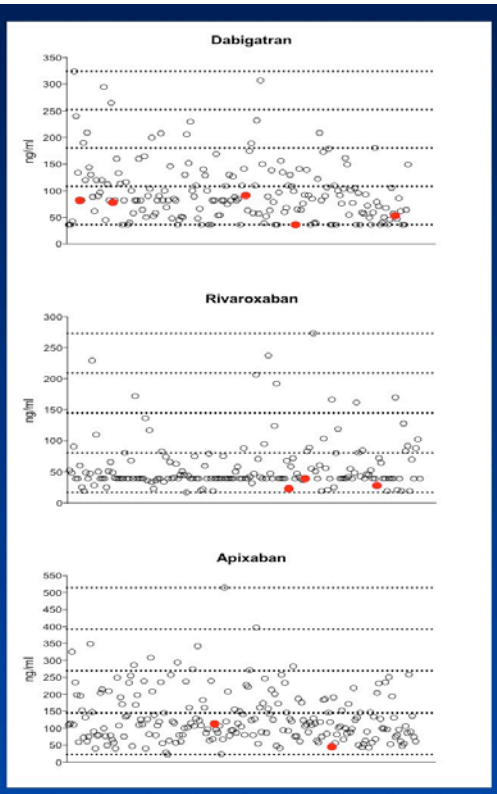
Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants

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‡

J Thromb Haemost 2018; **16**: 842–8

- Observational multicenter study (4 FCSA clinics – Ancona, Bologna, Cremona, Padova)
- 565 consecutive naive patients with atrial fibrillation (within the START Laboratory Registry) treated with DOACs (Dabigatran n=185, Rivaroxaban n=172, Apixaban n=208)
- DOAC specific measurements performed locally at C-trough 15-25 days after treatment start
- Follow up = 1 years

- Thromboembolic complications in 10 patients



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J Thromb Haemost 2018; **16**: 842–8

Incidenza complicanze tromboemboliche = 2.4% in classe I e 0% nelle altre classi

CHA_2DS_2-VASc = significativamente più alto in pazienti con complicanze tromboemboliche

Complicanze tromboemboliche = in pazienti con più alto CHA_2DS_2-VASc e bassi livelli di DOAC a valle

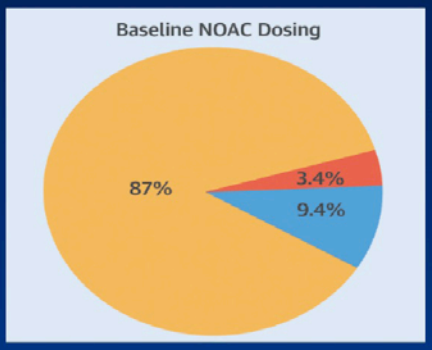
Low-responders: potenziali fattori

- Età e sesso
- BMI
- Livello albumina ed emoglobina
- Malassorbimento gastro-intestinale
- Funzionalità renale
- Interazioni con altri farmaci
- Fattori genetici
- Aderenza
- Errori prescrittivi

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes

The ORBIT-AF II Registry

Steinberg, B.A. et al. J Am Coll Cardiol. 2016;68(24):2597-604.



Recommended Dose | Under-Dosed | Over-Dosed

TABLE 2 Unadjusted and Adjusted Association Between Appropriateness of NOAC Dosing and Clinical Outcomes

	Number of Events	Adjusted HR (95% CI)	Adjusted p Value
First CV hospitalization			
Appropriately dosed	1,093 (24.16)	Reference	
Underdosed	129 (26.11)	1.26 (1.07-1.50)	0.0065

Patients receiving lower than recommended doses had more cardiovascular hospitalization than those prescribed the recommended doses

Risk of Recurrent Ischemic Stroke with Unintended Low-Dose Oral Anticoagulant Therapy and Optimal Timing of Review

J **Stroke** Cerebrovasc Dis 2018; 27:1546-1551

Recurrent ischemic stroke:
1.9% in the appropriate DOAC dose group
20.0% in the intended and unintended inappropriate DOAC low-dose group

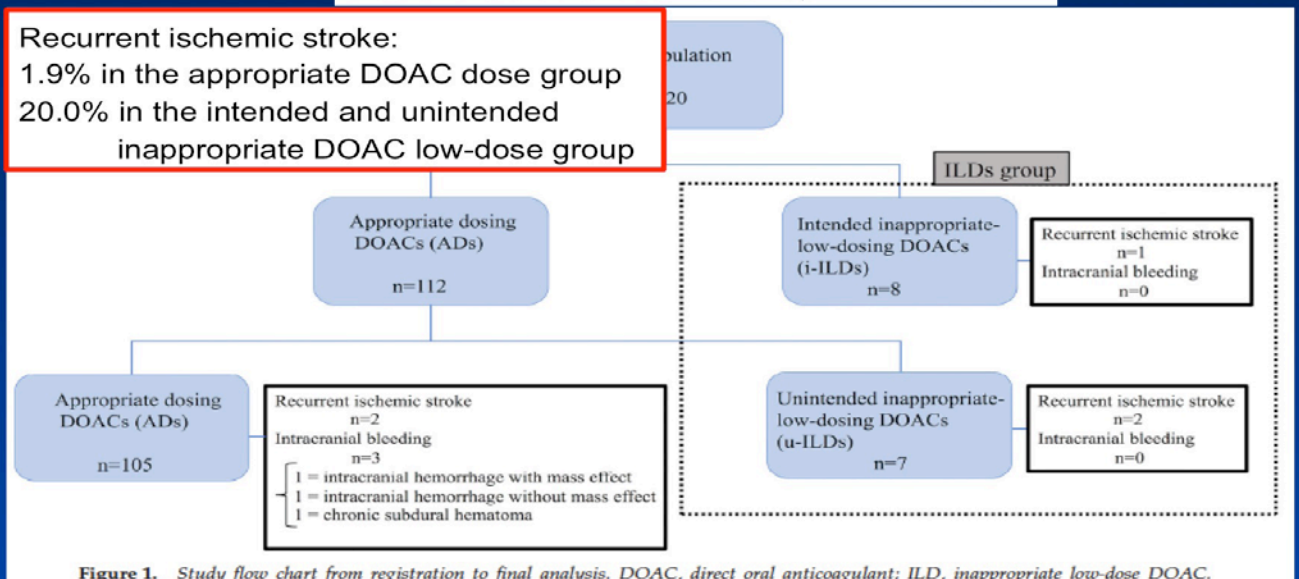


Figure 1. *Study flow chart from registration to final analysis. DOAC, direct oral anticoagulant; ILD, inappropriate low-dose DOAC.*

Appropriateness of direct oral anticoagulant dosing and its relation to drug levels in atrial fibrillation patients

J Thromb Thrombolysis 2019; 47: 550-557

Bruria Hirsh Raccah[1,2] · Amihai Rottenstreich[3] · Netanel Zacks[3] · Ilan Matok[2] · Haim D. Danenberg[1] · Arthur Pollak[1] · Yosef Kalish[3]

	Appropriate dose			Inappropriate low dose (N = 56)
	Appropriate dose# (N = 87)	Appropriate normal dose (N = 67)	Appropriate low dose (N = 20)	
DOAC levels according to the expected range				
Level under the range (%)	11.9	9.3	20.0	21.4
Level in the range (%)	64.3	68.7	50.0	71.4
Level above the range (%)	23.8*	21.9*	30.0*	7.1
DOAC quartile level				
1 (%)	15*	13.3*	20	41.5
2 (%)	25	23.3	30	24.5
3 (%)	27.5	30.3	20	24.5
4 (%)	32.5*	33.3*	30*	9.4

*P value of comparisons to an inappropriate low dose < 0.05

#Appropriate dose: includes appropriate normal dose and appropriate low dose

Progress in the monitoring of direct oral anticoagulant therapy

Jignesh P. Patel,[1,2] Rosalind A. Byrne[1] Raj K. Patel,[1] and Roopen Arya,[1]

bjh review 2019; 184: 912

L'uso dei DOAC a dosi fisse si è dimostrato efficace e sicuro sia nei trial clinici da fase III che nel "real world"

La domanda è: POSSIAMO FARE MEGLIO?

Ovvero, la misura del livello dei DOAC, almeno nei casi in cui si sospettino livelli non ottimali, può contribuire a migliorare l'efficacia e la sicurezza di questi farmaci?

Progress in the monitoring of direct oral anticoagulant therapy

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bjh review 2019; 184: 912

Per rispondere a questa domanda sono necessari ulteriori studi che definiscano i range terapeutici dei DOAC

Some are trying to address this question.

The *Measure And See* (MAS) study is an observational, prospective cohort study in AF patients managed in Italy. This study will evaluate the possible relationship between DOAC levels at trough at steady state (within the first 2–4 weeks) and occurrence of bleeding and thromboembolic events during a 1 year follow-up