2021

Progetto
Ematologia
Romagna

# *Implicazioni laboratoristiche dei farmaci anticoagulanti*

**Giovanni Poletti**

*Patologia Clinica (Ematologia) AUSL Romagna*


GRAZIE PROF TURA
19-9-2020

PAZIENTE

**RISCHIO EMORRAGICO DA PROCEDURE INVASIVE**

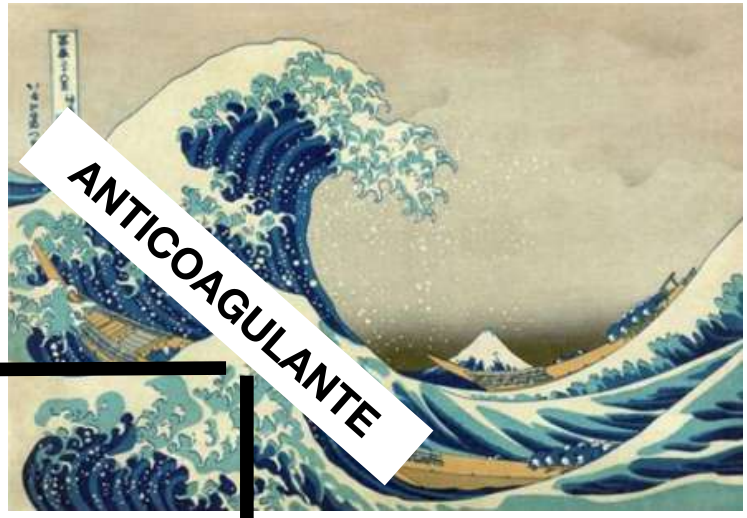
- *'high'*
- *'low-moderate'*
- *'minimal'*

*JTH 2019;17:1966-1972*

**EMORRAGIE**

- *'major'*
- *'clinical relevant nonmajor'*
- *'minor'*

*Blood 2019;133(5):425-435*




*La grande onda di Kanagawa*
*Katsushika Hokusai*
*1830 /1831*

Emocromo PT APTT Fibrinogeno

Livello di Anticoagulazione

LABORATORIO

# ANTICOAGULANTE: LE INFORMAZIONI

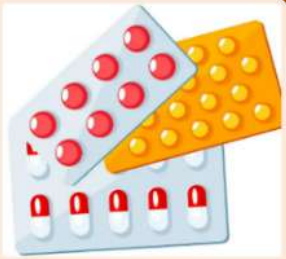
UFH
LMWH
Fondaparinux
Argatroban

1. Tipo di farmaco
2. Dosaggio
3. Ultima dose

AVK

DOAC

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban



# CONSIDERAZIONI FARMACOCINETICHE

| Anticoagulant type | Half-life, h | Route of elimination |
|---|---|---|
| Vitamin K antagonists | 20-60 (warfarin) | Liver metabolism; metabolites primarily eliminated in the urine (warfarin) |
| UFH | 1-2 | Therapeutic dose: nonrenal elimination; very high doses: possible renal contribution |
| LMWH | 3-7 | Renal |
| Fondaparinux | 17-21 | Renal |
| Dabigatran | 12-17 | Renal (80%) |
| Apixaban | 8-15 | Renal (25%) |
| Betrixaban | 19-27 | Renal (11%) |
| Edoxaban | 9-11 | Renal (35%) |
| Rivaroxaban | 9-13 | Renal (66%) |

***Blood.* 2020;135(10):724-734**

farmacocinetica

**Livello di Anticoagulazione**

laboratorio

ruolo causale

sicurezza

se..
quale..
quanto..

**EMORRAGIA**

**RISCHIO DA PROCEDURA**

**'REVERSE'**

**TOGLIERE DI MEZZO L'ANTICOAGULANTE QUANDO E' DANNOSO…**

# MISURA DELL'ANTICOAGULAZIONE

**'testing'** **'monitoring'**
(dose-adjustment)

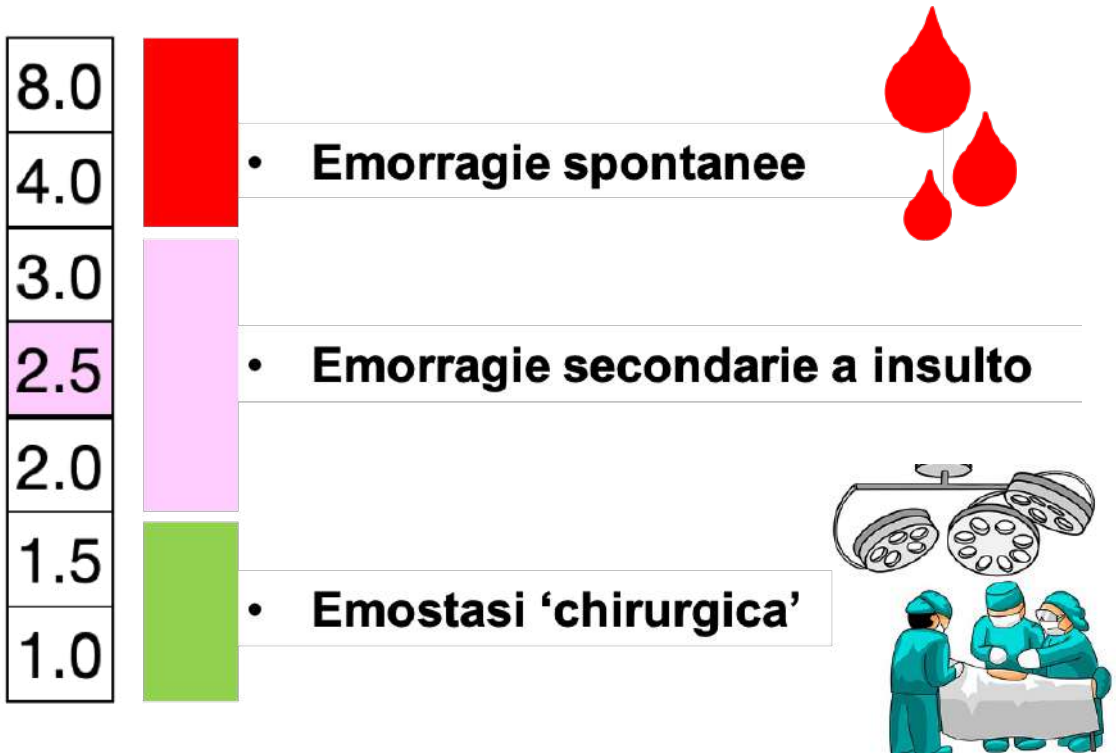
- AVK
- UFH
- Argatroban

- LMWH
- Fondaparinux
- DOAC

# VKA

## PT-INR

1. **Target (range)**
2. **Correlazione clinica**
3. **Lunga emivita: 60 h**
4. **Reverse** *(Stop VKA +/-Vit K +/- PCC)*




- *NEJM 2003;349:1019-26*
- *BJH 2005;128,513-19*
- *Stroke 2018 Mar 49(3):e46-e110*

# EPARINA NON FRAZIONATA

**UFH** **aPTT Ratio**

- In terapia: **'dose 'aggiustata' con aPTTratio** (range terapeutico: **1.5-2.5**)
- **Breve emivita** (1-2 h)

- **Molti effetti 'non eparinici' su aPTT**
  - ✓ *FVIII*
  - ✓ *FII*
  - ✓ *LAC*
  - ✓ *Farmaci*
  - ✓ *…*

aPTT: può avere un'implicazione clinica poco affidabile

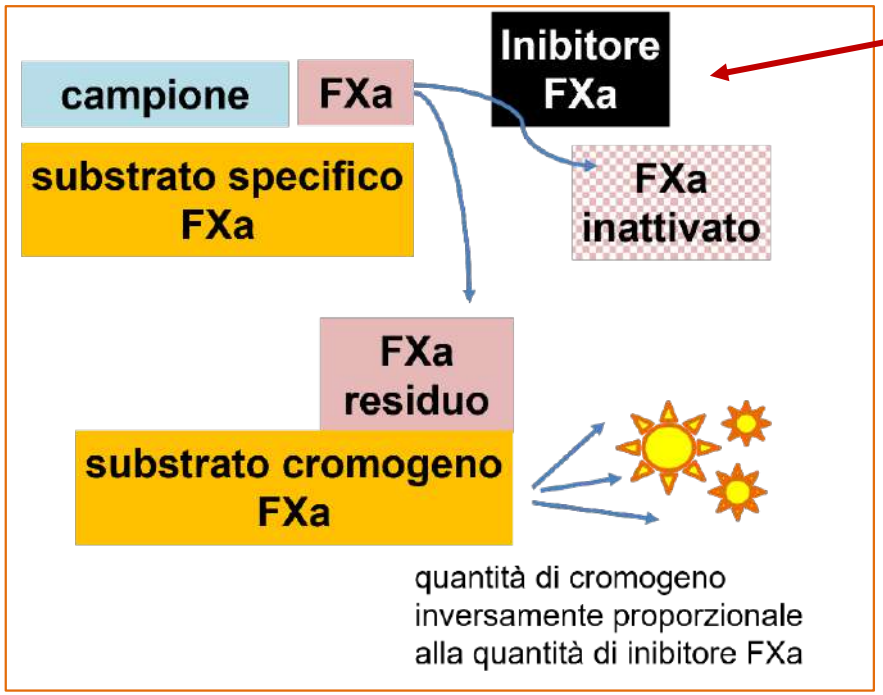
Considerare l'utilità del dosaggio eparinico attività anti-Xa (0.3-0.7 UI/ml)


- *D Basu et al. NEJM 1972;287(7):324-27*
- *RD Hull et al. Arch Intern Med 1997;157(22):2562-68.*
- *J Hirsh. et al. JTH 2004;2:2254-6*
- *MA Smythe et al. J Thromb Thrombolysis 2016;41:165-186*
- *JW Vandiver. Pharmacotherapy vol 32 numb 6 2012*

# Dosaggio con metodo cromogenico

attività anti-Xa

Eparina




| UFH/LMWH IU/ml calibrator | dOD |
|---|---|
| 0.00 | 0.7368 |
| 0.42 | 0.5206 |
| 0.79 | 0.3921 |
| 1.17 | 0.2946 |
| 1.56 | 0.2238 |

*Eparinemia (terapia): 0.3-0.7 UI/ml*

# LE 'PICCOLE' EPARINE (LMWH - Fondaparinux)

1. **LMWH: 4-6 h**
2. **Fondaparinux: 17-21 h**
3. **Eliminazione renale**

1. **Poco visibili con aPTT**
2. **Attività anti-Xa**

- *LMWH: 0.4-1.2 UI/ml*
- *Fondaparinux: 0.5-1.5 UI/ml*

| **UFH/LMWH** IU/ml calibrator | **dOD** |
|---|---|
| 0.00 | 0.7368 |
| 0.42 | 0.5206 |
| 0.79 | 0.3921 |
| 1.17 | 0.2946 |
| 1.56 | 0.2238 |

| **Fondaparinux** IU/ml calibrator | **dOD** |
|---|---|
| 0.00 | 0.7159 |
| 0.91 | 0.3107 |
| 1.83 | 0.1435 |

CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 86 • NUMBER 6 JUNE 2019 4

# ANTICOAGULANTI ORALI DIRETTI (DOAC)

- La terapia non richiede un monitoraggio di laboratorio
- Breve emivita

- **PT e aPTT non sono affidabili**
- **Usare test specifici per misurare l'anticoagulazione**

| DOAC | Test specifici |
|---|---|
| Dabigatran | anti-IIa, dTT, ECT |
| Rivaroxaban | anti-Xa |
| Apixaban | anti-Xa |
| Edoxaban | anti-Xa |
| Betrixaban | anti-Xa |

REVIEW ARTICLE

WILEY ISLH International Journal of Laboratory Hematology

The danger of relying on the APTT and PT in patients on DOAC therapy, a potential patient safety issue

D. M. Adcock[1] | R. C. Gosselin[2]

*Int J Lab Hem.* 2017;39(Suppl. 1):37–40.

**Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians**

J. DOUXFILS,*† W. AGENO,‡ C.-M. SAMAMA,§ S. LESSIRE,¶ H. TEN CATE,** P. VERHAMME,†† J.-M. DOGNÉ* and F. MULLIER‡‡

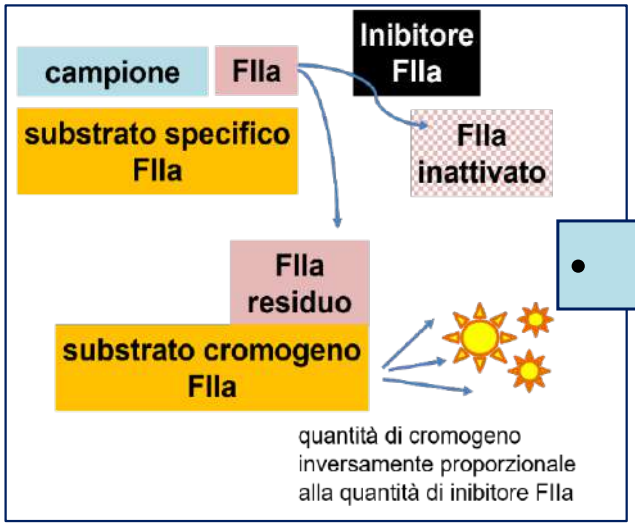
*Department of Pharmacy, Namur Thrombosis and Hemostasis Centre (NTHC), Namur Research Institute for Life Sciences (NARILIS), University of Namur, †Qualiblood s.a., Namur, Belgium; ‡Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; §Cochin University Hospital, Department of Anaesthesiology and Intensive Care, Université Paris Descartes, Paris, France; ¶Department of Anaesthesiology, Namur Thrombosis and Haemostasis Centre (NTHC),Namur Research Institute for Life Sciences (NARILIS), Université catholique de Louvain, CHU UCL Namur, Yvoir, Belgium; **Department of Internal Medicine, Maastricht University Medical Centre and Cardiovascular Research Institute (CARIM), Maastricht, the Netherlands; ††Department of Cardiovascular Sciences, Vascular Medicine and Haemostasis, University of Leuven, Leuven; and ‡‡CHU UCL Namur, Laboratory Hematology, Namur Thrombosis and Haemostasis Centre (NTHC), Namur Research Institute for Life Sciences (NARILIS), Université catholique de Louvain, Yvoir, Belgium

*J Thromb Haemost 2018; 16: 209–19*

# Dosaggio con metodo cromogenico

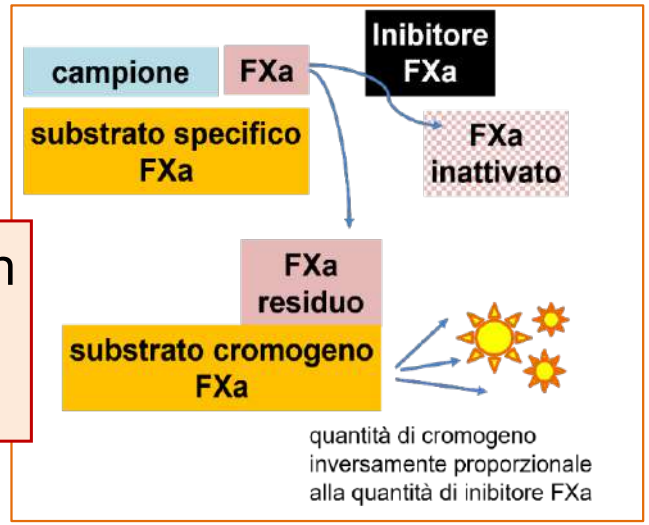
calibratori e controlli dedicati

attività anti-IIa




- Dabigatran

attività anti-Xa




- Rivaroxaban
- Apixaban
- Edoxaban

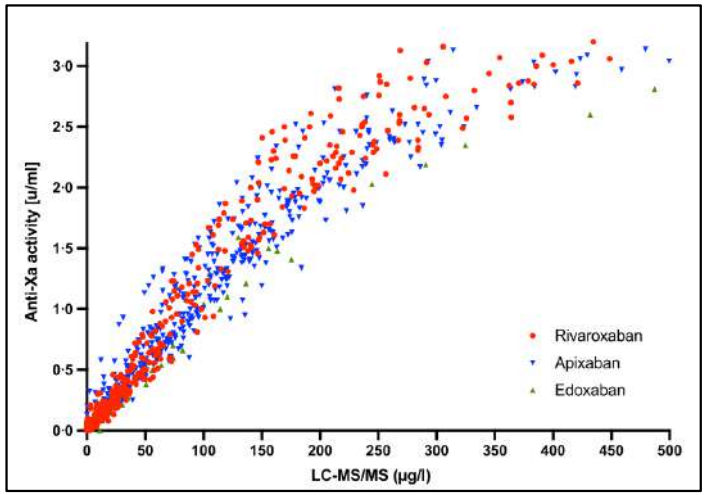
bjh research paper

# A universal anti-Xa assay for rivaroxaban, apixaban, and edoxaban measurements: method validation, diagnostic accuracy and external validation

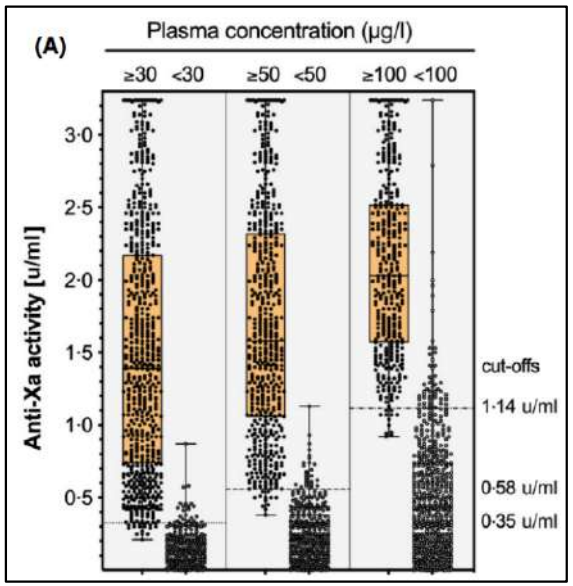
*British Journal of Haematology*, 2021, **193**, 1203–1212

Guido Willekens,[1,2,*] Jan-Dirk Studt,[3,*] Adriana Mendez,[4] Lorenzo Alberio,[5] Pierre Fontana,[6] Walter A. Wuillemin,[7] Adrian Schmidt,[8] Lukas Graf,[9] Bernhard Gerber,[10] Cedric Bovet,[2] Thomas C. Sauter[11] and Michael Nagler[2,12]

[1]*Department of Epidemiology, Maastricht University, Maastricht, the Netherlands,* [2]*Department of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern,* [3]*Division of Medical Oncology and Hematology, University Hospital Zurich, Zurich,* [4]*Department of Laboratory Medicine, Kantonsspital Aarau, Aarau,* [5]*Service and Central Laboratory of Hematology, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne,* [6]*Division of Angiology and Hemostasis, Geneva University Hospital, Geneva,* [7]*Division of Hematology and Central Hematology Laboratory, Cantonal Hospital of Lucerne, University of Bern, Bern,* [8]*Institute of Laboratory Medicine and Clinic of Medical Oncology and Hematology, City Hospital Waid and Triemli, Zurich,* [9]*Cantonal Hospital of St Gallen, St Gallen,* [10]*Clinic of Hematology, Oncology Institute of Southern Switzerland, Bellinzona,* [11]*Department of Emergency Medicine, Inselspital, Bern University Hospital, Bern, and* [12]*Department of Hematology, Inselspital, Bern University Hospital, Bern, Switzerland*




| Sensitivity | % |
|---|---|
| 30 ug/l | 96.2 |
| 50 ug/l | 96.4 |
| 100 ug/l | 96.7 |



# Richiedere il dosaggio del farmaco e non attività anti-Xa né FX

1. In un plasma la presenza di uno qualunque dei farmaci con attività anti-Xa, sia indiretta che diretta, causa una misurabile attività anti-Xa. Per risalire al livello di farmaco, l'attività anti-Xa misurata deve essere rapportata ad una curva di calibrazione eseguita con il farmaco specifico

2. **Non è disponibile un esame 'attività anti-Xa' bensì il dosaggio dell'anticoagulante specifico**

3. Il dosaggio del '**FX'** è un altro test da non confondere in questo contesto. Quest'ultimo esame dosa l'attività funzionale di FX presente in un plasma e non la capacità di un plasma di inibire FXa.


**LOQ**
Dabigatran: 20 ng/ml
Rivaroxaban/Apixaban/Edoxaban: 10-15 ng/ml

**TAT: 1 h (esame disponibile in urgenza)**
**Variabilità inter-laboratorio (VEQ): 10%**

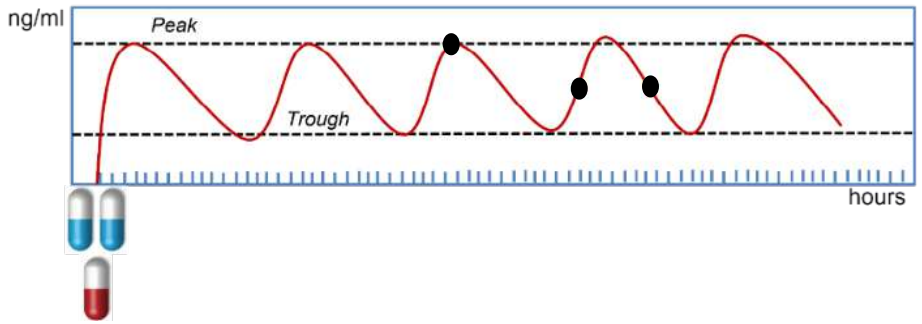
*Journal of Thrombosis and Haemostasis*, **14**: 1325–1327 DOI: 10.1111/jth.13344

FORUM

# To measure or not to measure direct oral anticoagulants before surgery or invasive procedures

A. TRIPODI
*Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Clinical Sciences and Community Health, Università degli Studi di Milano and IRCCS Cà Granda Maggiore Hospital Foundation, Milan, Italy*

## DOAC: la farmacocinetica è sufficiente per garantire la sicurezza **oppure dosare** anche il livello di anticoagulazione?

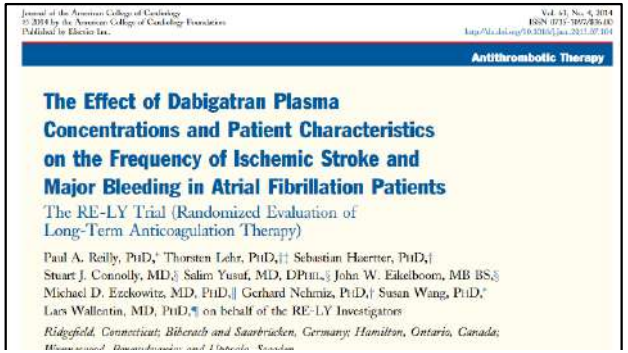



# LIVELLO DI ANTICOAGULAZIONE (DOSAGGIO) DOAC

- **I livelli più alti sembrano associati a più emorragie**

- **Esistono pazienti con valori più elevati**

# LIVELLI DI DOAC : IMPLICAZIONE EMORRAGICA



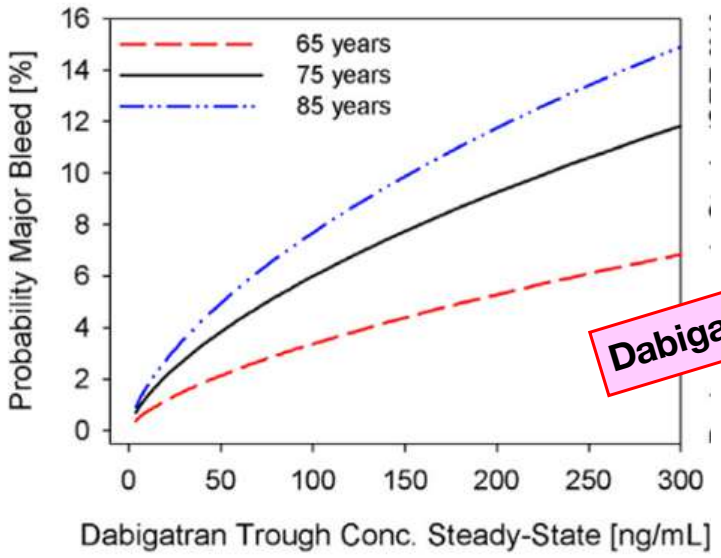
Antithrombotic Therapy

**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)

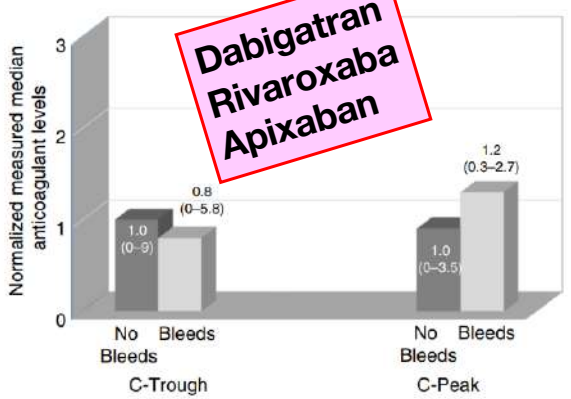
Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,†
Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPhil,§ John W. Eikelboom, MB BS,§
Michael D. Ezekowitz, MD, PhD,‖ Gerhard Nehmiz, PhD,† Susan Wang, PhD,*
Lars Wallentin, MD, PhD,¶ on behalf of the RE-LY Investigators

*Ridgefield, Connecticut; Biberach and Saarbrücken, Germany; Hamilton, Ontario, Canada;*




**Dabigatran**

**Dabigatran**
**Rivaroxaba**
**Apixaban**




ORIGINAL ARTICLE

jth

**Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants**

Sophie Testa[1] | Cristina Legnani[2] | Emilia Antoniucci[3] | Oriana Paoletti[1] | Claudia Dellanoce[3] | Benilde Cosmi[4] | Vittorio Pengo[4] | Daniela Poli[5] | Rossella Morandini[1] | Roberto Testa[6] | Armando Tripodi[7] | Gualtiero Palareti[2] | Coordinator of START2-Register

*J Thromb Haemost. 2019;17:1064–1072*

**Edoxaban**

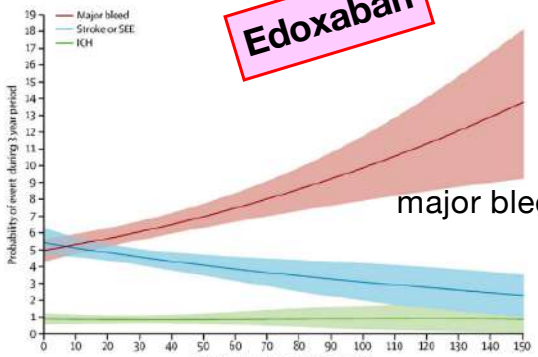
*British Journal of Haematology*, 2019, **184**, 912–924

bjh review

**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]

[1]*Department of Haematological Medicine, King's Thrombosis Centre, King's College Hospital Foundation NHS Trust, and* [2]*Institute of Pharmaceutical Science, King's College London, London, UK*




major bleed

*Trough Edoxaban concentration (ng/ml)*

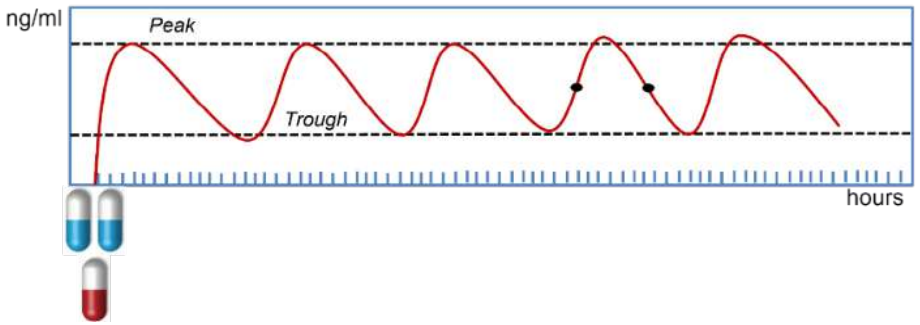
# La misura dei DOAC: risultati attesi

**Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians**

J. DOUXFILS,*† W. AGENO,‡ C.-M. SAMAMA,§ S. LESSIRE,¶ H. TEN CATE,** P. VERHAMME,†† J.-M. DOGNÉ* and F. MULLIER‡‡

*Department of Pharmacy, Namur Thrombosis and Hemostasis Centre (NTHC), Namur Research Institute for Life Sciences (NARILIS), University of Namur, †Qualiblood s.a., Namur, Belgium; ‡Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; §Cochin University Hospital, Department of Anaesthesiology and Intensive Care, Université Paris Descartes, Paris, France; ¶Department of Anaesthesiology, Namur Thrombosis and Haemostasis Centre (NTHC),Namur Research Institute for Life Sciences (NARILIS), Université catholique de Louvain, CHU UCL Namur, Yvoir, Belgium; **Department of internal Medicine, Maastricht University Medical Centre and Cardiovascular Research Institute (CARIM), Maastricht, the Netherlands; ††Department of Cardiovascular Sciences, Vascular Medicine and Haemostasis, University of Leuven, Leuven; and ‡‡CHU UCL Namur, Laboratory Hematology, Namur Thrombosis and Haemostasis Centre (NTHC), Namur Research Institute for Life Sciences (NARILIS), Université catholique de Louvain, Yvoir, Belgium

*J Thromb Haemost* 2018; **16**: 209–19.




| **DABIGATRAN** *150 mg BID* | **Peak** *ng/ml* | **Trough** *ng/ml* |
|---|---|---|
| **NVAF** | 175 (117-275) | 91 (61-143) |
| **VTE** | 175 (117-275) | 60 (39-95) |

| **RIVAROXABAN** *20 mg OD* | **Peak** *ng/ml* | **Trough** *ng/ml* |
|---|---|---|
| **NVAF** | 249 (184-343) | 44 (12-137) |
| **VTE** | 270 (189-419) | 26 (6-87) |

| **APIXABAN** *5 mg BID* | **Peak** *ng/ml* | **Trough** *ng/ml* |
|---|---|---|
| **NVAF** | 171 (91-321) | 103 (41-230) |
| **VTE** | 132 (59-302) | 63 (22-177) |

| **EDOXABAN** *60 mg OD* | **Peak** *ng/ml* | **Trough** *ng/ml* |
|---|---|---|
| **NVAF** | 170(125-245) | 36 (19-62) |
| **VTE** | 234 (149-317) | 19(10-39) |

# VARIABILITA' INTER-INDIVIDUALE

Thrombosis Research 137 (2016) 178–183

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

- Dabi>Riva>Api
- Specie nei valori di valle
- Più spesso con i bassi dosaggi

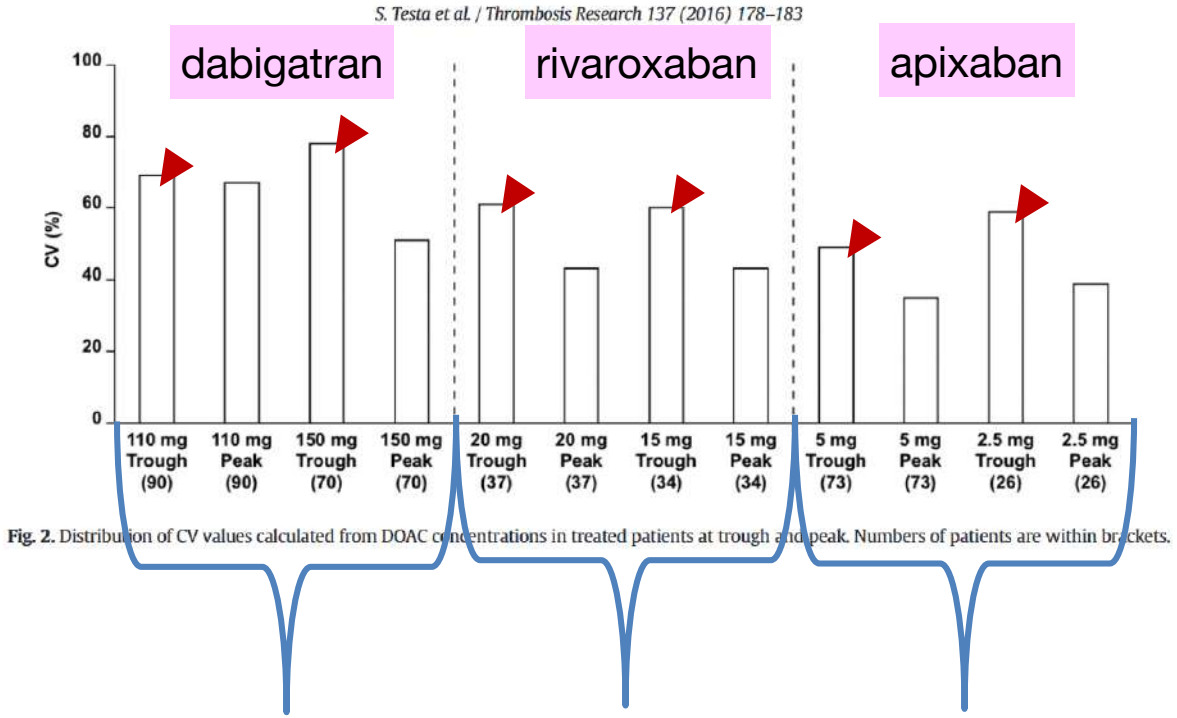



Fig. 2. Distribution of CV values calculated from DOAC concentrations in treated patients at trough and peak. Numbers of patients are within brackets.

*min-max: x 20 x 15 x 7*

# VARIABILITA' INTRA-INDIVIDUALE

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| DOAC assay (ng/ml) CV% | Dabigatran 110 mg | Dabigatran 150 mg | Rivaroxaban 20 mg | Rivaroxaban 15 mg | Apixaban 5 mg | Apixaban 2.5 mg |
|---|---|---|---|---|---|---|
| **Trough** | 59 | 49 | 39 | 35 | 23 | 15 |
| **Peak** | 60 | 51 | 27 | 31 | 22 | 14 |

Dabigatran > Rivaroxaban > Apixaban

# Fattori pre-procedurali associati a livelli alti di DOAC

- *Interruption time*
- ***Female***
- *Age >/= 75*
- *CrCl < 50 ml/min*
- ***Rivaroxaban/Apixaban***
- *Standard dose*
- ***Weight < 70 Kg***

>/= 30

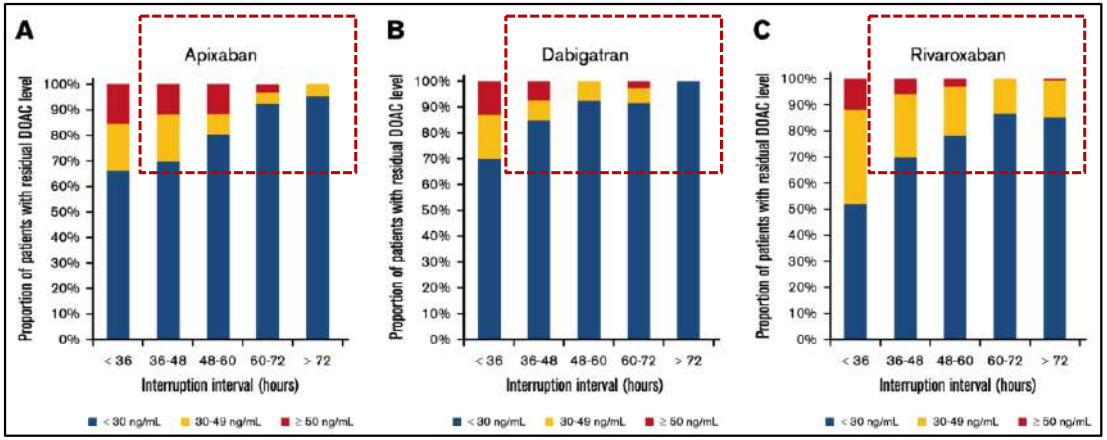
>/= 50

## Predictors of preprocedural direct oral anticoagulant levels in patients having an elective surgery or procedure

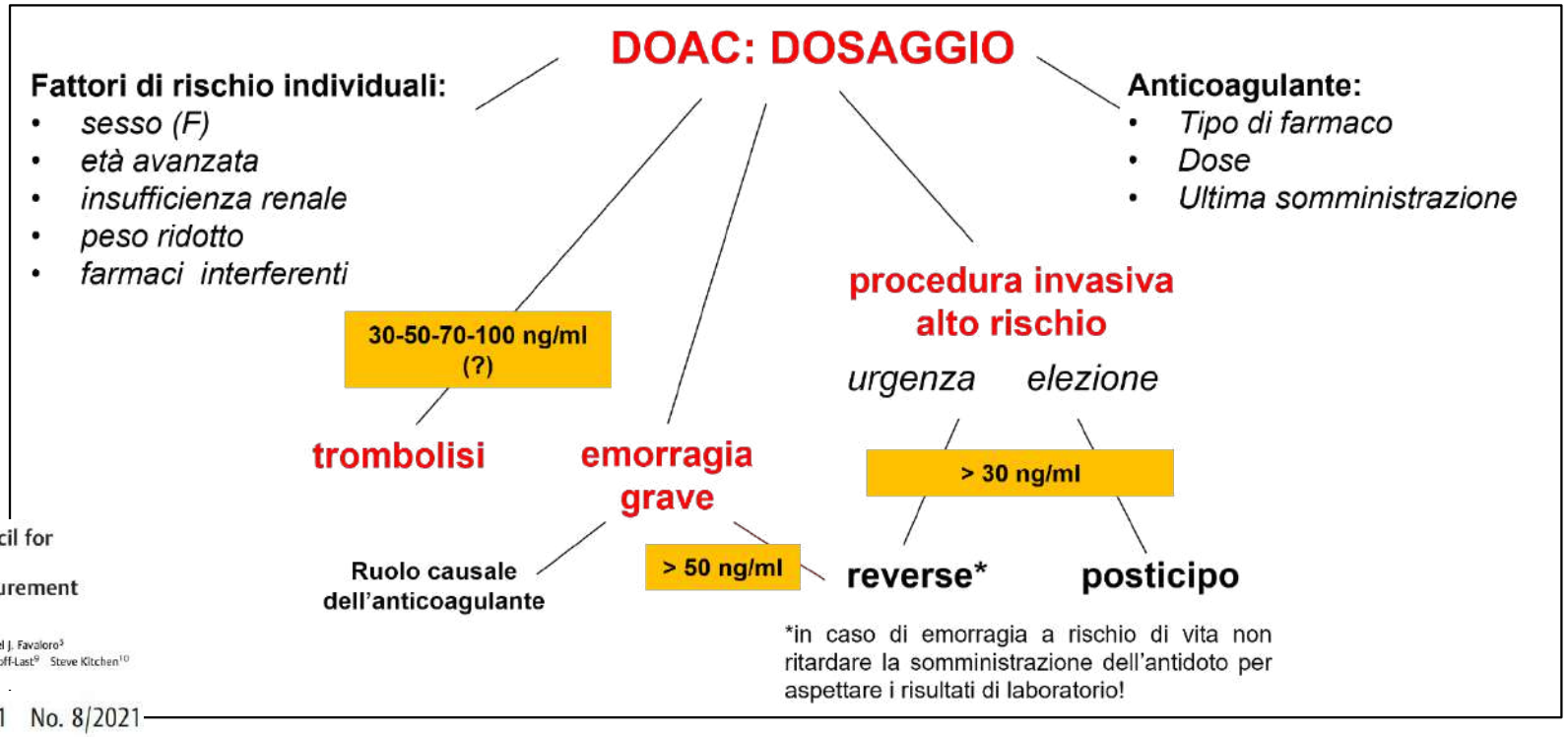
Joseph R. Shaw,[1,2] Na Li,[3] Thomas Vanassche,[4] Michiel Coppens,[5] Alex C. Spyropoulos,[6] Summer Syed,[7] Mansoor Radwi,[8] Joanne Duncan,[3] Sam Schulman,[3,9] and James D. Douketis[3]

[1]Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [2]The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]Department of Medicine, McMaster University, Hamilton, ON, Canada; [4]Center for Molecular and Vascular Biology, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; [5]Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [6]Department of Medicine, Zucker School of Medicine at Hofstra/Northwell, Northwell Health at Lenox Hill Hospital, New York, NY; [7]Department of Anesthesiology, McMaster University, Hamilton, ON, Canada; [8]Department of Hematology, Faculty of Medicine, University of Jeddah, Jeddah, Saudi Arabia; and [9]Department of Obstetrics and Gynecology, I. M. Sechenov First Moscow State Medical University, Moscow, Russia

11 AUGUST 2020 · VOLUME 4, NUMBER 15 blood advances



# DOSARE PUO' AUMENTARE LA SICUREZZA NELLE CONDIZIONI PIU' A RISCHIO




2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants

Jonathan Douxfils[1,2] Dorothy M. Adcock[2] Shannon M. Bates[4] Emmanuel J. Favaloro[5] Isabelle Gouin-Thibault[6] Cecilia Guillermo[7] Yohko Kawai[8] Edelgard Lindhoff-Last[9] Steve Kitchen[10] Robert C. Gosselin[11]

Thrombosis and Haemostasis Vol. 121 No. 8/2021

*«Omnia venenum sunt:*
*nec sine veneno quicquam existit. Dosis*
*sola facit, ut venenum non fit»*

*Philippus Aureolus Theophrastus Bombastus von Hohenheim*
*-Paracelsus-*
*(1493-1541)*

*…solo la dose fa in modo che l'anticoagulante non abbia un effetto dannoso*