TERAPIE ANTICOAGULANTI:
EVIDENZE ED OPINIONI A CONFRONTO

# MISURARE L'EFFETTO ANTICOAGULANTE: si o no e perché?

Domenico Prisco
DMSC Università di Firenze
SOD Medicina Interna Interdisciplinare
AOU Careggi Firenze

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## Disclosure

Fees for lectures and Advisory board membership: Bayer, Boehringer Ingelheim, BMS-Pfizer, Daiichi Sankyo

# The Laboratory & the New Drugs

- **Monitoring**

– **Implies dosage adjustment based on the test results**

- **Measuring**

– **Implies determining the anticoagulant effect**

# Why not to Monitor New Drugs

- Clinical trials have been carried at a fixed dose
- Relatively wide therapeutic window
- Short half-life
- Cost cutting
- Easier management (both for patients and physicians)
- Appealing (both for patients and physicians)

# Monitoraggio ?

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

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

EUROPACE 2015

# 2. How to measure the anticoagulant effect of non-vitamin K antagonist oral anticoagulants?

Non-VKA anticoagulants do not require routine monitoring of coagulation: neither the dose nor the dosing intervals should be altered in response to changes in laboratory coagulation parameters for the current registered indications. However, assessment of drug exposure and anticoagulant effect may be needed in emergency situations, such as a serious bleeding and thrombotic events, need for urgent surgery, or in special clinical situations such as patients who present with renal or hepatic insufficiency, potential drug–drug interactions or suspected overdosing.

When interpreting a coagulation assay in a patient treated with a NOAC, much more than with VKA coagulation monitoring, it is paramount to know when the NOAC was administered relative to the time of blood sampling. The maximum effect of the NOAC on the clotting test will occur at its maximal plasma concentration, which is ~3 h after intake for each of these drugs. A coagulation assay obtained on a blood sample taken 3 h after the ingestion of the NOAC (at peak level) will demonstrate a much larger impact on the coagulation test than when performed at trough concentration, i.e. 12 or 24 h after ingestion of the same dose. Moreover, depending on the clinical profile of the patient, an estimation of the elimination

# Dosaggio ?

**Dosaggio: misurazione della concentrazione di un farmaco** *(come valutazione puntiforme e non in modo sistematico*)

# Dosaggio dei NAO:

**1-** to monitor patient adherence

An assay that could confirm the presence or absence of drug **may be useful** to monitor patient adherence, and, in cases of thrombosis, would help to distinguish treatment failure from non-adherence

*Garcia et al, JTH 2012*

# Dosaggio dei NAO:

1- to monitor patient adherence

An assay that [illegible]firm the presence or absence of [illegible]**be useful** to monitor patie[illegible]nce, and, in cases of thrombosis, v[illegible] to distinguish treatment failure from non-adherence

*Garcia et al, JTH 2012*

# Dosaggio dei NAO:

2-To determine the offset of activity (strumento utile)

Qualitative assessment of the presence of drug in plasma at the time of presentation may impact on treatment decisions (e.g. thrombolysis for ischemic stroke).

*Garcia et al, JTH 2012*

# Dosaggio dei NAO:

2-To determine the offset of activity (strumento utile)

If a patient requires a semi-urgent invasive procedure associated with an increased risk of bleeding or in cases of unexpected trauma, qualitative assessment could identify the presence of anticoagulant;

a quantitative assessment of drug concentration or anticoagulant activity may be helpful so that ***the risk of bleeding*** can be weighed against the risk of delaying the procedure

*Garcia et al, JTH 2012*

# Dosaggio dei NAO:

3-To detect overdose or drug accumulation (strumento utile)

Assessment of the drug concentration or level of anticoagulant activity may help to identify cases of suspected overdose or drug accumulation in patients with impaired renal function. For potential accumulation assessment, collection of a sample at trough is likely to be most useful

*Garcia et al, JTH 2012*

# Dosaggio dei NAO:

4-To identify the mechanism of bleeding (strumento utile ?)

In patients who present with bleeding, assessment of drug concentration or, if possible, the level of anticoagulant activity may help to identify the contribution of the anticoagulant to the bleeding event

*Garcia et al JTH 2012*

# Variabilità INTER ed INTRA-individuale

- Studi clinici dimostrano che c'è estrema variabilità nella risposta anticoagulante dopo esposizione ai NAO sia nello stesso individuo sia tra individui diversi

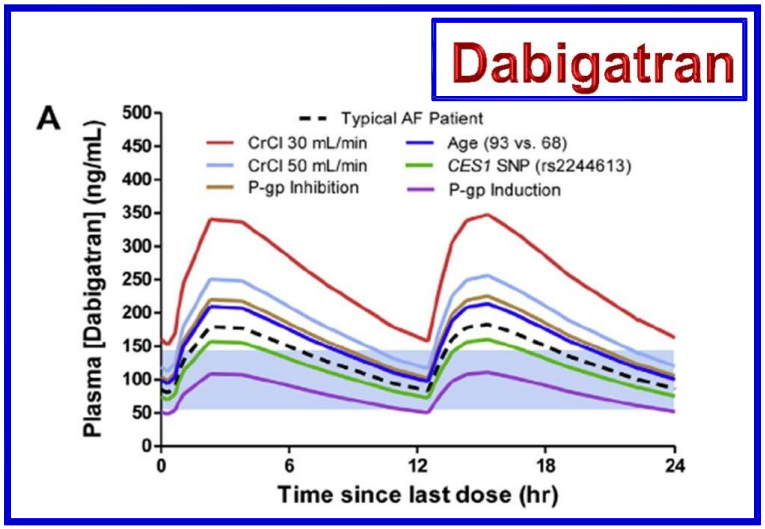
- Quindi estrema difficoltà nell'estrapolare le indicazioni fornite dai test di laboratorio

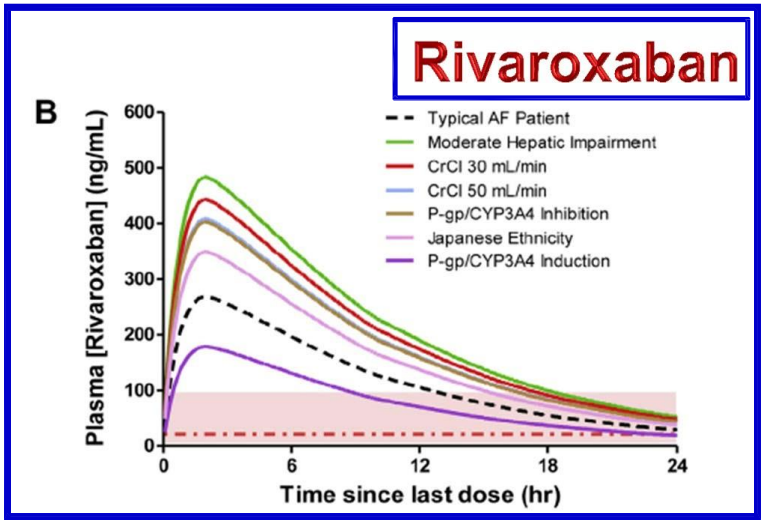
***Tabella 1.*** *Intervalli di concentrazioni plasmatiche nei pazienti in trattamento con NAO*

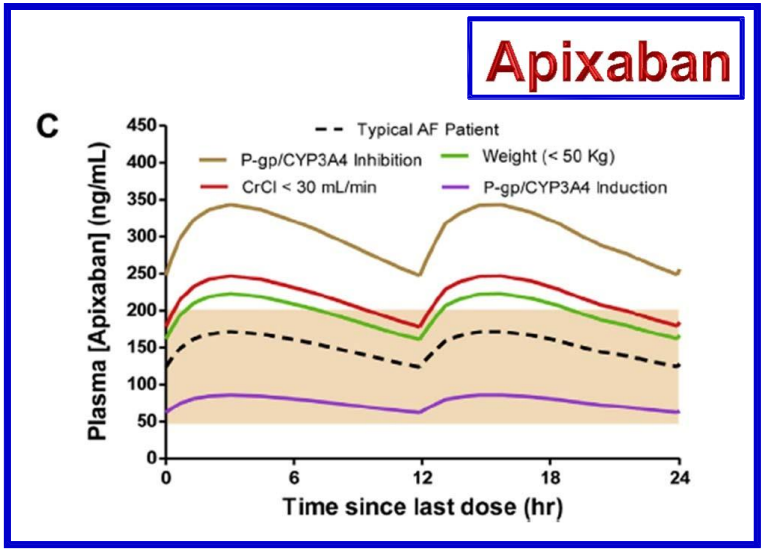
| **Farmaco** | **Punto di valle** (prima della assunzione successiva) | **Punto di picco** (2-3 ore dall'ultima assunzione) |
|---|---|---|
| Dabigatran (150 mg/2 volte die) | 40-215 ng/ml* | 74-383 ng/ml* |
| Dabigatran (110 mg/2 volte die) | 28-155 ng/ml* | 52-275 ng/ml* |
| Rivaroxaban (20 mg/die) | 12-137 ng/ml# | 184 - 343 ng/ml# |
| Rivaroxaban (15 mg/die) | 18-136 ng/ml# | 178-313 ng/ml# |
| Apixaban (5 mg/2 volte die) | 40-60 ng/ml§ | 115 - 141 ng/ml§ |
| Apixaban (2,5 mg/2 volte die) | 17-25 ng/ml§ | 39-85 ng/ml§ |

**[Reilly PA 2014] #[Mueck W 2014] §[Frost C 2013]*

# Importance of Pharmacokinetic Profile and Variability as Determinants of Dose and Response to Dabigatran, Rivaroxaban, and Apixaban




Gong IY et al. Can J Cardiol 2013; 29:S24-33

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# 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

Ad una attenta lettura  dei dati cosa possiamo notare che sicuramente c'è una **variazione  della concentrazione plasmatica del farmaco in relazione alle caratteristiche demografiche della popolazione analizzata**

# Impact of demographic characteristics on dabigatran plasma concentrations

| Characteristic | Measure | Subgroup 1 | Subgroup 2 | Subgroup 3 | Subgroup 4 |
|---|---|---|---|---|---|
| Sex | | Male (n = 5,524) | Female (n = 2,925) | | |
| | gMean | 0.727 | 0.942 | — | — |
| | gCV, % | 78.2 | 69.3 | — | — |
| | Median | 0.736 | 0.967 | — | — |
| | P10 | 0.324 | 0.419 | — | — |
| | P90 | 1.7 | 2.21 | — | — |
| Age, yrs | | <65 (n = 1,466) | 65 to <75 (n = 3,787) | ≥75 (n = 3,196) | |
| | gMean | 0.586 | 0.749 | 0.982 | — |
| | gCV, % | 86 | 75.2 | 76 | — |
| | Median | 0.595 | 0.761 | 0.994 | — |
| | P10 | 0.241 | 0.341 | 0.45 | — |
| | P90 | 1.43 | 1.69 | 2.22 | — |
| Weight, kg | | <50 (n = 163) | 50 to <100 (n = 6,852) | ≥100 (n = 1,433) | |
| | gMean | 0.998 | 0.824 | 0.652 | — |
| | gCV, % | 83.8 | 80.6 | 77.1 | — |
| | Median | 1.01 | 0.84 | 0.66 | — |
| | P10 | 0.41 | 0.365 | 0.281 | — |
| | P90 | 2.63 | 1.94 | 1.56 | — |
| CrCl, ml/min | | <30 (n = 18) | 30 to <50 (n = 1,512) | 50 to <80 (n = 3,937) | ≥80 (n = 2,690) |
| | gMean | 1.87 | 1.29 | 0.828 | 0.564 |
| | gCV, % | 51.9 | 78 | 71.7 | 70.2 |
| | Median | 2.11 | 1.33 | 0.857 | 0.582 |
| | P10 | 0.905 | 0.601 | 0.395 | 0.262 |
| | P90 | 3.16 | 2.83 | 1.77 | 1.2 |

Reilly P, JACC 2014

In ogni caso anche **la concentrazione rilevata nei pazienti con evento emorragico era nel range di normalità**, anche se più elevata rispetto a chi non ha avuto emorragia.

Importante sottolineare **che  la concentrazione plasmatica dei pazienti con evento ischemico in corso di terapia è anch'essa nel range di normalità** e soprattutto non è diversa da chi non ha avuto evento ischemico

# Trough Concentrations of Dabigatran (ng/ml/mg) Grouped by Outcome Event Occurrence

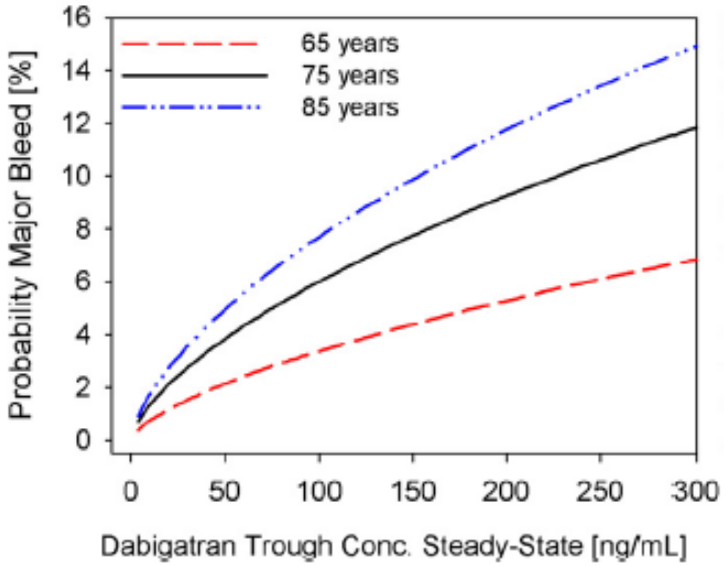
| | Major Bleed (n = 323) | Any Bleed (n = 2,319) | No Bleed (n = 5,899) |
|---|---|---|---|
| gMean | 113 | 86.9 | 72.8 |
| gCV, % | 79.8 | 81.4 | 84 |
| Median | 116 | 88.2 | 75.3 |
| P10 | 46.7 | 35.7 | 30.7 |
| P90 | 269 | 211 | 175 |

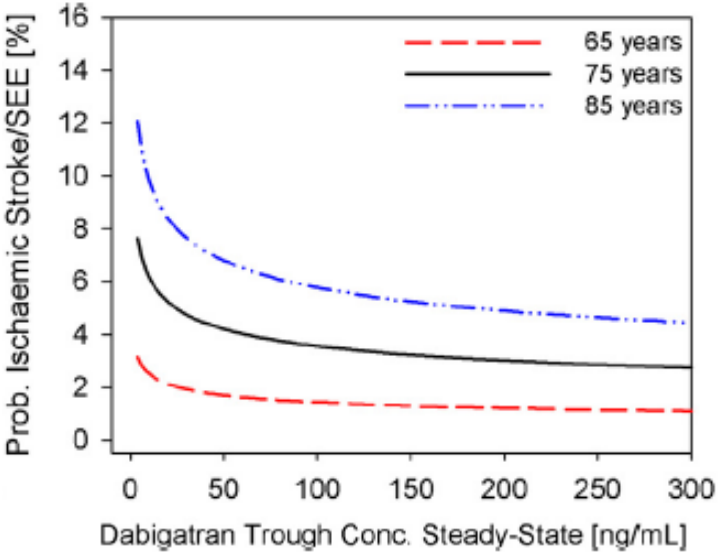
| | Stroke/SEE (+) (n = 129) | No Stroke/SEE (−) (n = 8,250) | Stroke/SEE/Death (+) (n = 387) | No Stroke/SEE/Death (−) (n = 7,789) | CV Events* (+) (n = 391) | No CV Events (−) (n = 7,865) |
|---|---|---|---|---|---|---|
| gMean | 76.6 | 76.5 | 88.5 | 75.4 | 87.8 | 75.6 |
| gCV, % | 84.1 | 83.9 | 84.7 | 83.3 | 89.5 | 83.1 |
| Median | 80.6 | 78.3 | 91.4 | 77.6 | 90.7 | 77.6 |
| P10 | 26.4 | 32.1 | 33.1 | 31.8 | 31.2 | 32 |
| P90 | 185 | 186 | 226 | 181 | 229 | 182 |

Reilly P, JACC 2014

# Probability of Clinical Outcomes Versus Dabigatran Plasma Concentrations

In relation to AGE

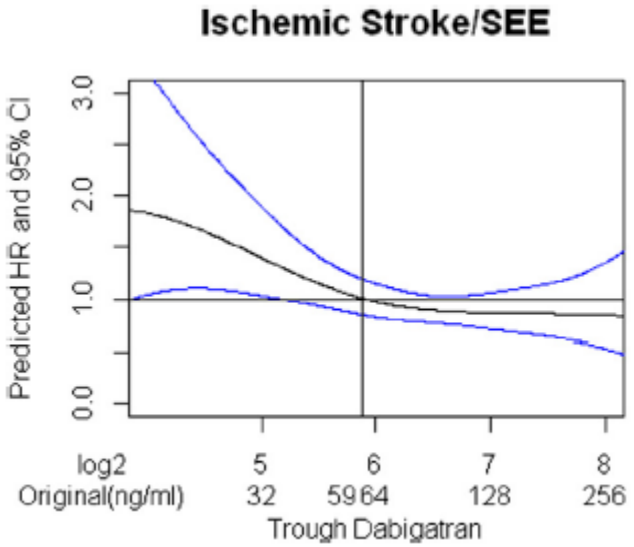


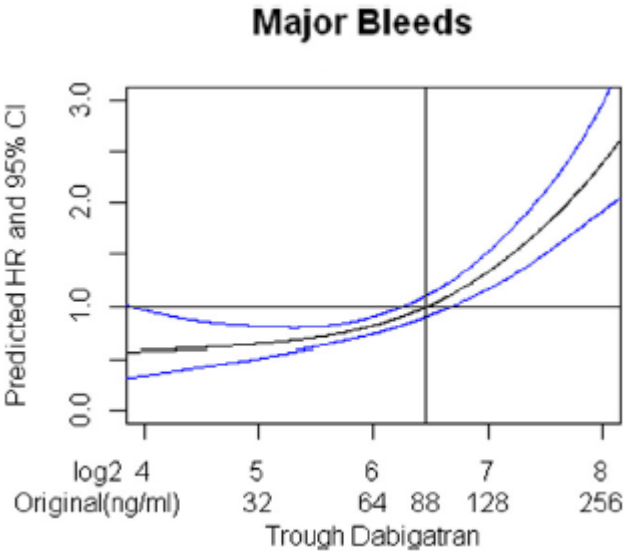




Reilly P, JACC 2014

# Cox Regression Analyses of Ischemic Stroke/SEE and Major Bleeding Versus Trough Plasma Concentration of Dabigatran

In relation to median $CHADS_2$ score




Reilly P, JACC 2014

# Conclusions of Reilly's study

Both doses of Dabigatran in RE-LY were associated with a more than 5-fold variation in plasma concentrations, indicating a **wide therapeutic range**. ……

Safety and efficacy outcomes were correlated with plasma concentrations of dabigatran, with age as the most important covariate **but there is no single plasma concentration range that provides optimal benefit–risk ratio for all patients**.

The balance between stroke risk and bleed risk varied with concentration, suggesting that **there is a subset of AF patients who may improve their benefit–risk balance with dabigatran by a tailoring of the dose in relation to patient characteristics**

Reilly P, JACC 2014

**MA……**

Sicuramente le popolazioni più a rischio di emorragia sono quelle con determinate caratteristiche:

Età avanzata, insufficienza renale (che va di pari passo con l'aumentare dell'età) etc…

E queste caratteristiche sono determinanti nel verificarsi dell'evento

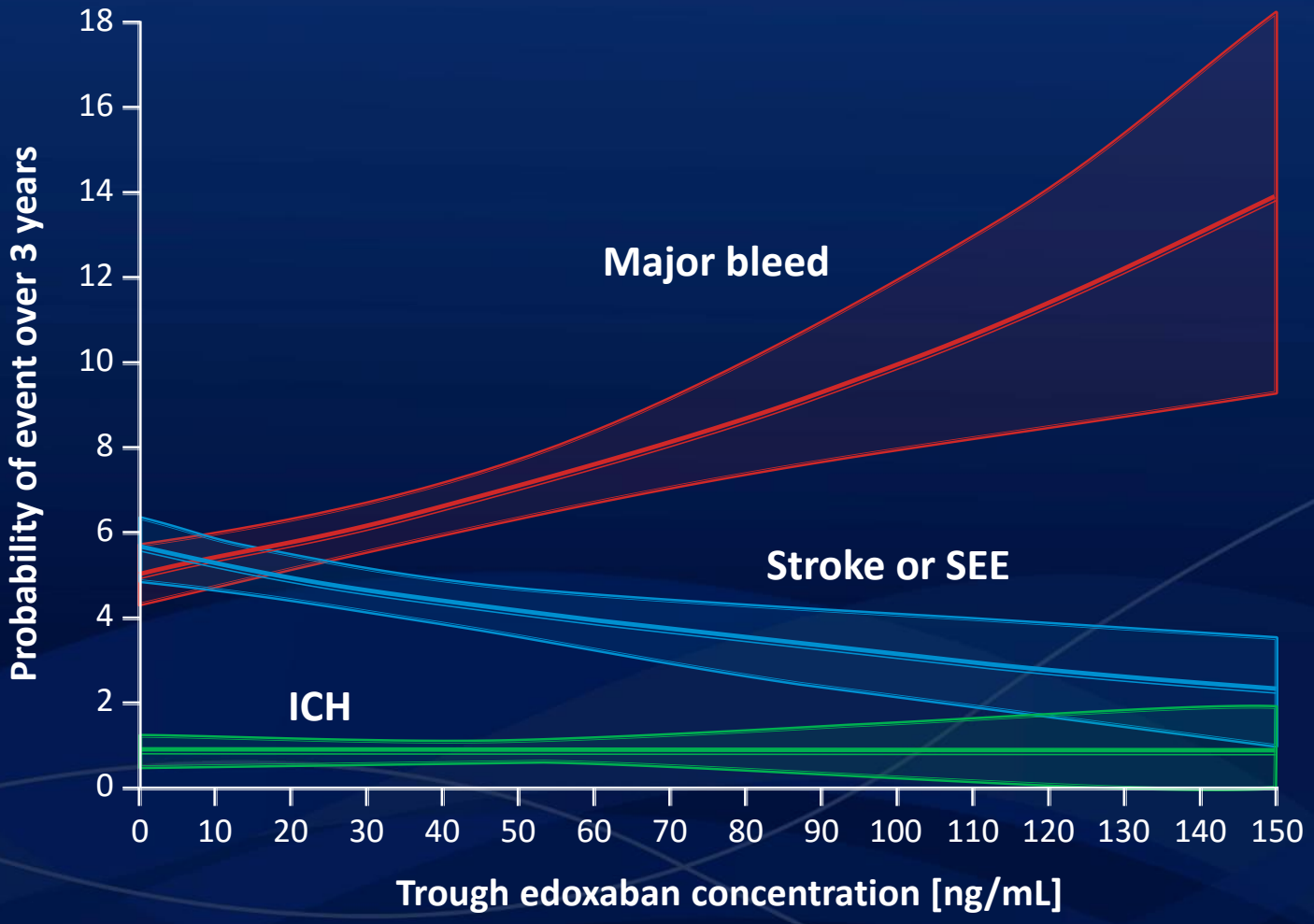
Quindi **non è solo la concentrazione del farmaco che determina l'evento avverso**

# Dosing adjustments based on pharmacokinetic considerations

| | Dabigatran (mg BID) | Rivaroxaban (mg OD) | Apixaban (mg BID) |
|---|---|---|---|
| Renal impairment | | | |
| Mild (CrCl 51-80 mL/min) | 150 | 20 | 5 |
| Moderate (CrCl 30-50 mL/min) | 110 | 15 | 5 |
| Severe (CrCl < 30 mL/min) | n.r. | 15 | 2.5 |
| Hepatic impairment | | | |
| Mild (Child-Pugh A) | 150 | 20 | 5 |
| Moderate (Child-Pugh B) | 150 | n.r. | 5 |
| Severe (Child-Pugh C) | n.r. | n.r. | n.r. |
| Hepatic dysfunction | n.r. | n.r. | n.r. |
| Demographic variables | | | |
| Ethnicity, Asian | 150 | 15 | 5 |
| Age, older than 75-80 y | 110 | 20 | 2.5 |
| Weight, < 50 kg | 150 | 20 | 2.5 |
| Drug-drug interactions | | | |
| P-gp inhibitor | 110 | 15 | 2.5 |
| CYP3A4 inhibitor | 150 | 15 | 2.5 |
| P-gp/CYP3A4 inducer | n.r.* | n.r. | n.r. |

Gong IY, Can J Card 2013

# ENGAGE AF: Edoxaban trough concentration and outcomes



# NOACs and lab

Although DOAC do not require dose-adjustment based on lab testing, **assessment of anticoagulant effect is useful in many circumstances**

**Specific lab testing** should be used
dTT or ECT (dabigatran)
Anti-FXa or PT with sensitive thromboplastins (?) (rivaroxaban)
Anti-FXa (apixaban)

# When to measure the anticoagulant effect of NOACs

Routine monitoring of coagulation not required, but quantitative assessment of drug exposure **may be needed** in emergency situations:

- **serious bleeding and thrombotic events**
- **urgent surgery**
- **renal or hepatic insufficiency**
- **potential drug-drug interaction**
- **suspected overdosing**

**LG EHRA ESC 2013**

# Targeted Anti-Anticoagulants

Kenneth A. Bauer, M.D.

…..group of patients had little or no circulating anticoagulant in their blood and would not be expected to benefit from the administration of idarucizumab.

Thus, it will be **useful to have activity measurements available for the various direct oral anticoagulants in real time to help guide the treatment of such patients and to prevent overutilization** of what will surely be a costly medication

Bauer K, NEJM 2015

# Peak or trough values?

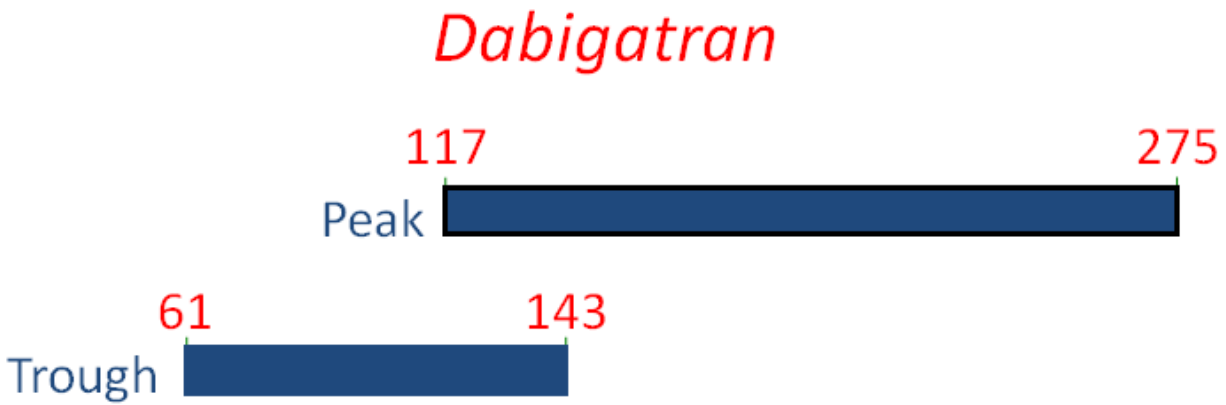
DOAC reach peak value (Cmax) approximately 2 hours after ingestion

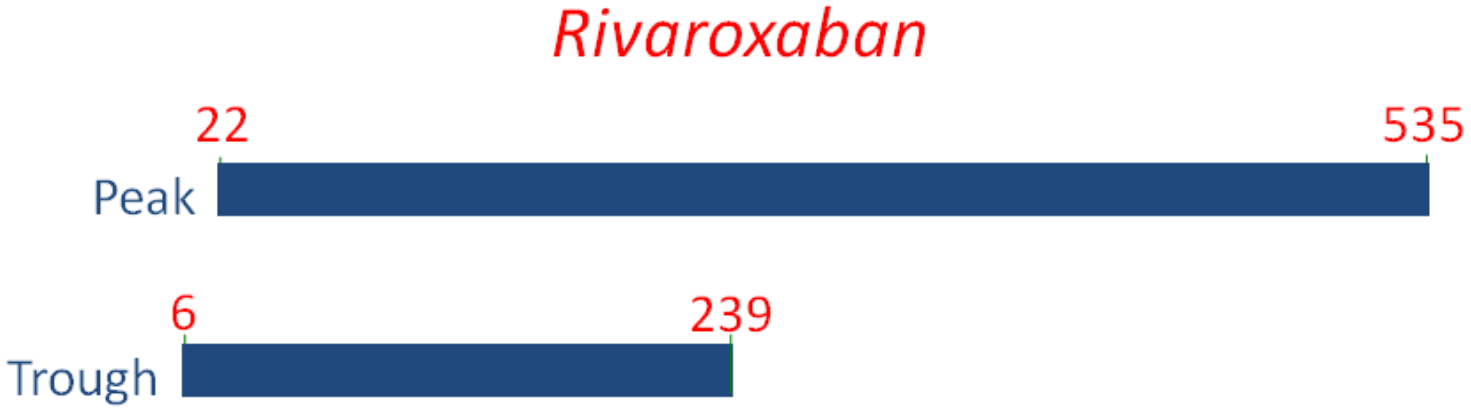
DOAC reach Ctrough values approximately 12h (bid) or 24h (od) after ingestion

Knowledge of timing of blood draw relatively to the last dose is essential for results interpretation

# Inter-individual variability plasma concentrations

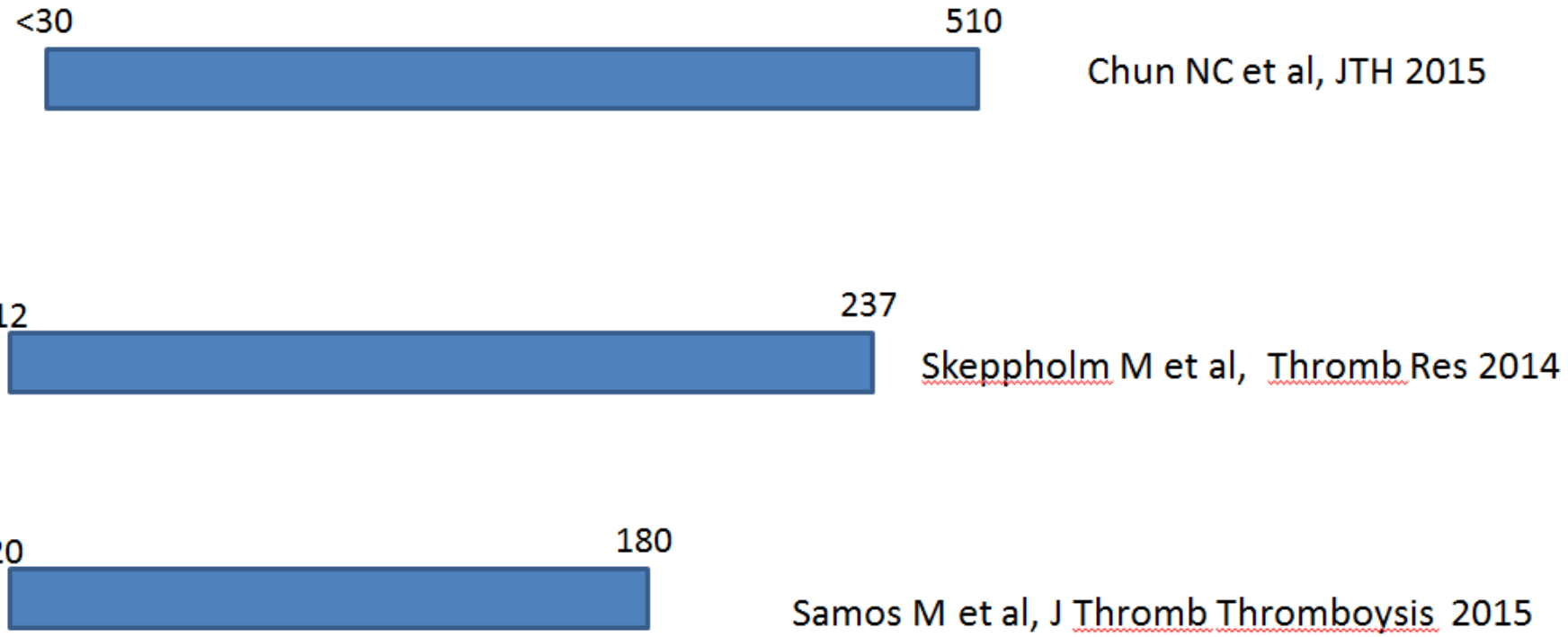
## *Data from Clinical trials*




***[ng/mL (min-max)]***

# Inter-individual (trough levels) Dabigatran variability
# Data from real life




*[ng/mL (min-max)]*

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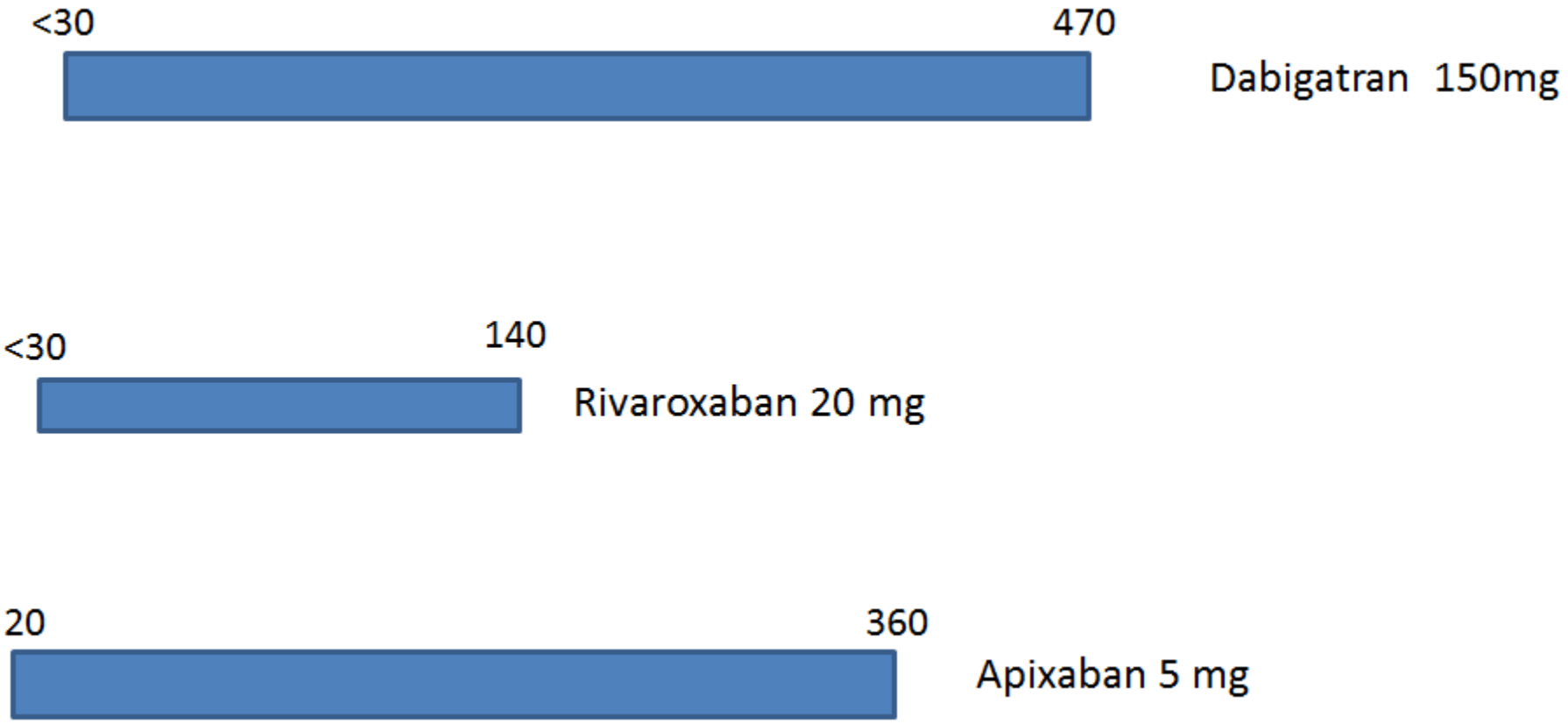
# Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

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

# Inter-individual (trough levels) DOACs variability
# Data from real life




**Ma seppur meno anche la variabilità intraindividuale è alta!!!**

Testa S, TR 2015

# Blood levels variability

No significant relation with Cr Cl except for dabigatran!

Testa S, TR 2015

# Alerting values

Owing to the interindividual variability and limited clinical experience, **no accurate alerting values are currently known**

ORIGINAL ARTICLE

# Effect of standardized perioperative dabigatran interruption on the residual anticoagulation effect at the time of surgery or procedure

J. D. DOUKETIS,*† G. WANG,* N. CHAN,*† J. W. EIKELBOOM,*† S. SYED,‡ R. BARTY,* K. A. MOFFAT,*§ F. A. SPENCER,*† M. BLOSTEIN¶ and S. SCHULMAN*†

*Department of Medicine, McMaster University; †Thrombosis and Atherosclerosis Research Institute, McMaster University; ‡Department of Anesthesia, McMaster University; §Hamilton Regional Laboratory Medicine Program, McMaster University, Hamilton, Ontario; and ¶Department of Medicine, McGill University, Montréal, Quebec, Canada

Methods: A prospective cohort study of patients receiving dabigatran (110 mg or 150 mg twice daily) who required an elective surgery/procedure and received a standardized dabigatran interruption protocol based on surgery/procedure bleeding risk and renal function was performed. Before the surgery/procedure, a blood sample was taken for measurement of PT, APTT, TT and dTT

Douketis JD, JTH 2013

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*Department of Medicine, McMaster University; †Thrombosis and Atherosclerosis Research Institute, McMaster University; ‡Department of Anesthesia, McMaster University; §Hamilton Regional Laboratory Medicine Program, McMaster University, Hamilton, Ontario; and ¶Department of Medicine, McGill University, Montréal, Quebec, Canada

…….the rates of major bleeding and thromboembolism were both low (0.5%), thereby precluding any associations between coagulation test results and clinical outcomes

Douketis JD, JTH 2013

# Effect of dabigatran interruption on coagulation test results

| Coagulation test | All patients $n = 181$ | Low bleeding risk surgery/procedure $n = 118$ | High bleeding risk surgery/procedure $n = 63$ |
|---|---|---|---|
| PT | | | |
| Median (IQR) (s) | 13.1 (12.6–13.7) | 13.0 (12.6–13.7) | 13.2 (12.7–14.0) |
| Normal (11–15 s), *n* (%) | 168 (92.8) | 109 (92.4) | 59 (93.7) |
| Increased (> 15 s), *n* (%) | 13 (7.2) | 9 (7.6) | 4 (6.3) |
| APTT | | | |
| Median (IQR) (s) | 32.0 (29.0–35.0) | 32.0 (30.0–35.0) | 30.0 (29.0–34.0) |
| Normal (22–35 s), *n* (%)† | 147 (81.2) | 91 (77.1) | 56 (88.9) |
| Increased (> 35 s), *n* (%) | 34 (18.8) | 27 (22.9) | 7 (11.1) |
| TT | | | |
| Median (IQR) (s) | 35.0 (28.0–55.0) | 40.0 (31.0–70.0) | 29.0 (25.0–36.0) |
| Normal (20–30 s), *n* (%) | 60 (33.1) | 24 (20.3) | 36 (57.1) |
| Increased (> 30), *n* (%) | 121 (66.9) | 94 (80.0) | 27 (42.9) |
| dTT | | | |
| Median (IQR) (ng $mL^{-1}$)‡ | 19 (19–19) | 19 (19–19) | 19 (19–19) |
| Normal (< 20 ng $mL^{-1}$), *n* (%) | 146 (80.7) | 91 (77.1) | 55 (87.3) |
| Increased (≥ 20 ng $mL^{-1}$), *n* (%) | 35 (19.3) | 27 (22.9) | 8 (12.7) |
| Dabigatran level | | | |
| Median (IQR) (ng $mL^{-1}$)§ | 13.2 (6.0–27.2) | 17.9 (10.8–31.8) | 6.7 (3.4–12.6) |
| Normal (< 20 ng $mL^{-1}$), *n* (%) | 120 (66.3) | 67 (56.8) | 53 (84.1) |
| Increased (≥ 20 ng $mL^{-1}$), *n* (%) | 61 (33.7) | 51 (43.2) | 10 (15.9) |

…….the interpretation of dabigatran levels in a clinical setting is uncertain.

Thus, the detection of low plasma levels of dabigatran (< 20 ng $mL^{-1}$) may not reflect an in vivo anticoagulant effect; moreover, the correlation between dabigatran levels and a pharmacodynamic (anticoagulant) effect is uncertain

Douketis JD, JTH 2013

# Conclusion

….it is possible that there may be a therapeutic range for dabigatran to mitigate the risk of thromboembolic and bleeding outcomes; however, this may be difficult to define, owing to considerable interpatient and intrapatient variability in peak and trough anticoagulant levels of dabigatran

Douketis JD, JTH 2013

ORIGINAL ARTICLE

# Real-world variability in dabigatran levels in patients with atrial fibrillation

N. C. CHAN,* M. COPPENS,† J. HIRSH,‡ J. S. GINSBERG,‡§ J. I. WEITZ,‡§ T. VANASSCHE,* J. D. DOUKETIS,‡§ S. SCHULMAN‡§ and J. W. EIKELBOOM*‡§

*Population Health Research Institute, Hamilton, ON, Canada; †Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; ‡Department of Medicine, McMaster University; and §Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada*

The objectives of the study were to

(i) estimate the inter- and intra-patient variability in dabigatran levels with 110 mg (DE110) and 150 mg (DE150) doses,

(ii) examine the effect of physicians' dose selection on levels in DE110 and DE150 subgroups, and

(iii) explore whether a single trough measurement identifies patients with extreme levels on subsequent visits.

Methods:

In this prospective observational study of 100 patients with atrial fibrillation (AF), peak and trough levels of dabigatran were measured with the Hemoclotassay at baseline and every 2 months thereafter (maximum four visits)

Chan NC, JTH 2015

ORIGINAL ARTICLE

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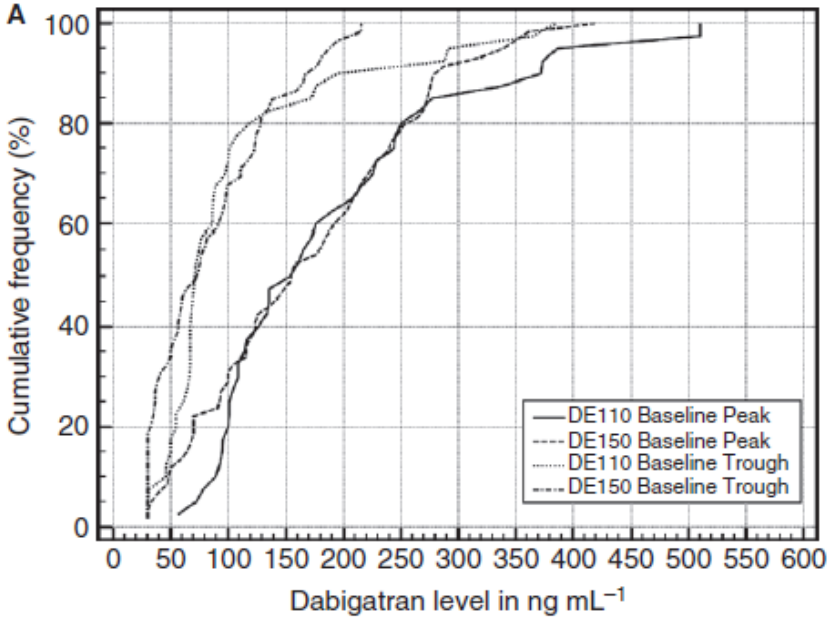
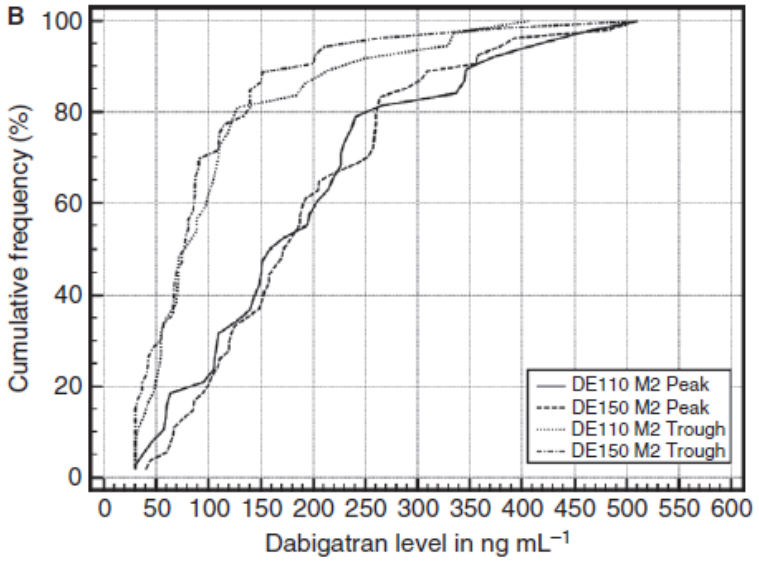
*Population Health Research Institute, Hamilton, ON, Canada; †Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; ‡Department of Medicine, McMaster University; and §Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada

## Inter-patient variability in levels of the DE110 and DE150




……. Our data support the practice of selecting the dabigatran dose based upon clinical characteristics ……. **They do not support the concept that a single…. measurement reliably identifies patients with consistently high or low values**

Chan NC, JTH 2015

# Comment

……. These findings contrast with those of RE-LY , in which patients randomly assigned to DE150 had higher drug levels (38% and 55% higher median peak and trough, respectively) than those assigned to DE110.

The divergent findings suggest that in our study, informed physicians who had a choice of using either dose, appropriately selected the lower dose based on known clinical determinants of increased bleeding risk, which in turn correlate with drug levels

Our findings provide an explanation for the results of a post-hoc analysis of the RE-LY study which reported that the efficacy and safety of dabigatran was improved when dose allocation was based on clinical characteristics according to recommendations by European regulators

Chan NC, JTH 2015

# In Which Patients and When Should We Measure Plasma Concentrations or Estimate the Intensity of Anticoagulation? A 2016 perspective

**…. The use of dedicated assays, using validated platforms, may probably improve the benefit-risk profile of NOACs by identifying poor- or high-responders**

Monitoring such therapies that were claimed to be independent of any biological testing may be useful to provide guidance in case of bleeding, thrombosis recurrence, before urgent surgery or procedure, for populations excluded from clinical trials, and for those with several comorbidities

**However and importantly, the clinical benefit of such monitoring still needs to be proven in a large, sufficiently powered, clinical trial designed to compare standard treatments with dose-adjusted regimen of these NOACs**

Douxfil J, BioMed Research International

# Riflessioni

-Conoscere i range di VARIABILITA' delle concentrazioni del farmaco in vivo NON significa conoscere i range TERAPEUTICI

- una volta in possesso di quel numero...cosa ne facciamo? come lo traduciamo in un atto medico?
-non è sufficiente sapere se siamo ON/OFF/OVER/UNDER? semaforo verde o rosso?
-non mi basterebbe un test che mi dice sovra o sottodosaggio o che mi dice se c'è farmaco in circolo?

- Quando avremo gli studi (per ora solo Reilly con DABI) che dimostrano le concentrazioni terapeutiche o che mostrano, ad es. quanto antidoto dare in rapporto alle concentrazioni trovate....allora dovremo sempre usare il dosaggio.

# Cosa fare subito

- **Attrezzarsi prima possibile con i test consigliati**
- **Valutare il comportamento dei test di base (PT, APTT) mediante la loro esecuzione su plasmi calibranti a titolo noto del farmaco**
- **Organizzare riunioni aziendali con tutti i soggetti coinvolti, per stabilire linee di comportamento condivise**
- **In una prima fase eseguire al bisogno test specifici ma anche di base per capire meglio il loro comportamento**

A. Tripodi

# Conclusioni

**Non modificare la concentrazione in base alla concentrazione plasmatica**

**Necessità di effettuare uno studio (con sponsor istituzionale – AIFA?) in cui i pazienti con rilievo di concentrazioni plasmatiche alterate vengono randomizzati ad un diverso tipo di trattamento:**

**A) Dose più alta di farmaco**

**B) Dose più bassa di farmaco**

**End point: valutare safety e efficacy nei due bracci di randomizzazione**

Pengo et al 2016