# Monitoraggio di laboratorio dei NOA: NO

Daniela Poli

Firenze

**Vietri 8 Ottobre 2016**

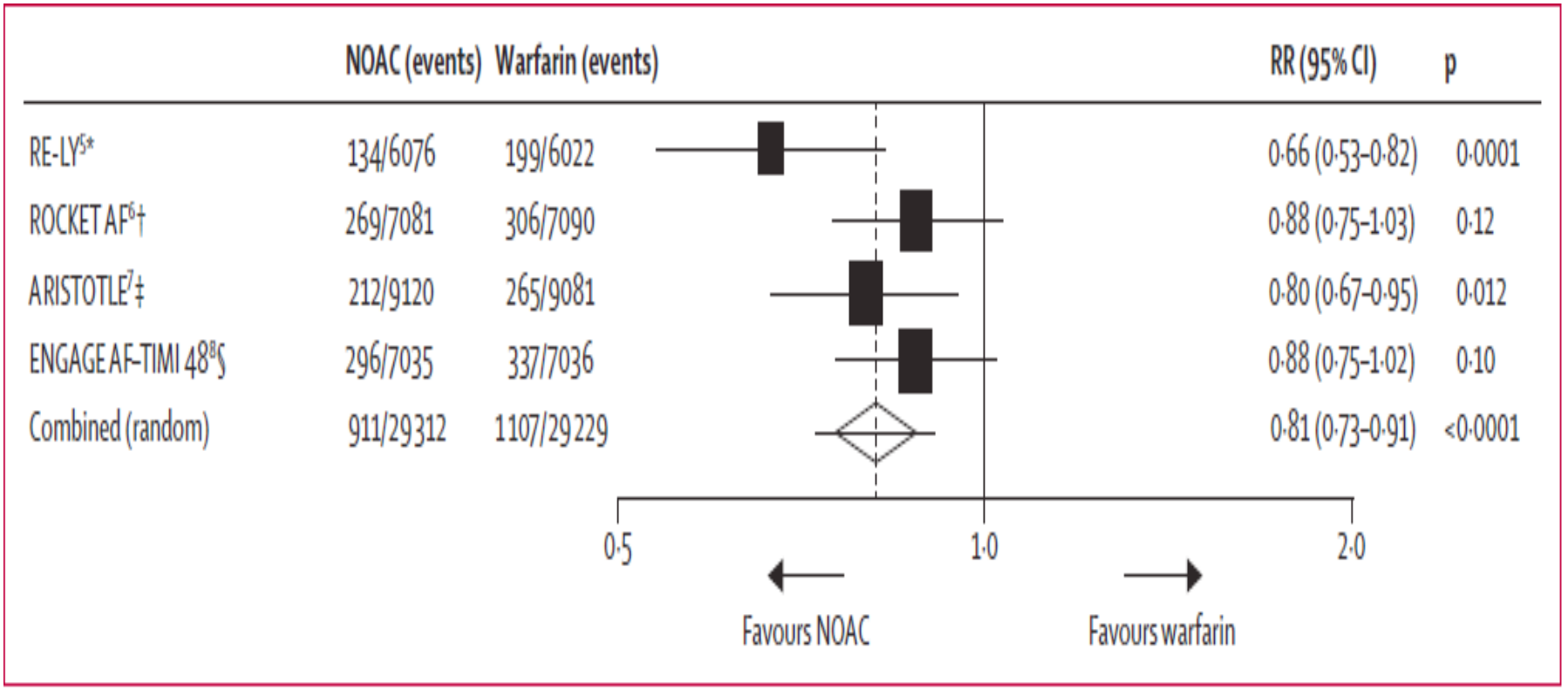
# Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

*Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman*

| | RE-LY[5] | | | ROCKET-AF[6] | | ARISTOTLE[7] | | ENGAGE AF-TIMI 48[8] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Dabigatran 150 mg (n=6076) | Dabigatran 110 mg (n=6015) | Warfarin (n=6022) | Rivaroxaban (n=7131) | Warfarin (n=7133) | Apixaban (n=9120) | Warfarin (n=9081) | Edoxaban 60 mg (n=7035) | Edoxaban 30 mg (n=7034) | Warfarin (n=7036) |
| Age (years) | 71·5 (8·8) | 71·4 (8·6) | 71·6 (8·6) | 73 (65–78) | 73 (65–78) | 70 (63–76) | 70 (63–76) | 72 (64–68) | 72 (64–78) | 72 (64–78) |
| ≥75 years | 40% | 38% | 39% | 43% | 43% | 31% | 31% | 41% | 40% | 40% |
| Women | 37% | 36% | 37% | 40% | 40% | 36% | 35% | 39% | 39% | 38% |
| CHADS2* | 2·2 (1·2) | 2·1 (1·1) | 2·1 (1·1) | 3·5 (0·94) | 3·5 (0·95) | 2·1 (1·1) | 2·1 (1·1) | 2·8 (0·97) | 2·8 (0·97) | 2·8 (0·98) |

Ruff C, Lancet 2013

# Stroke or systemic embolic events




Dabigatran 150 mg bid

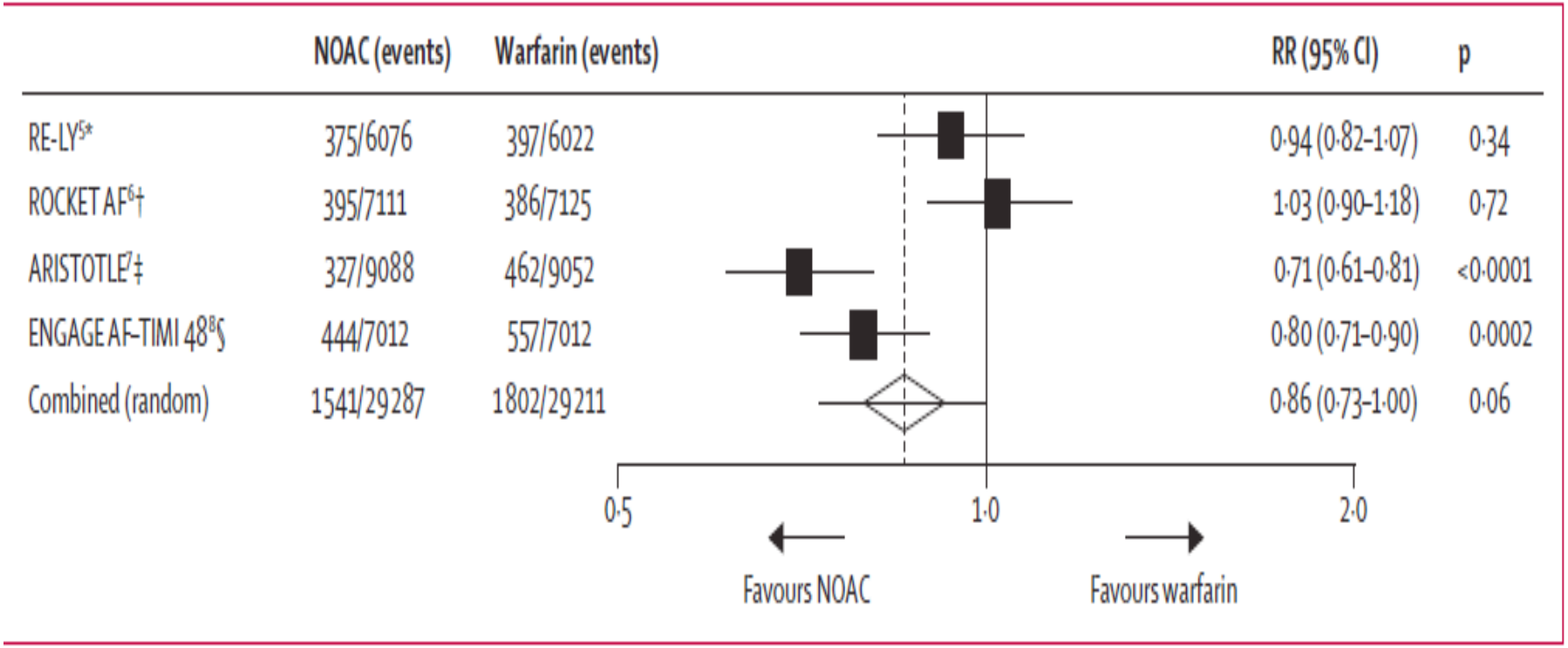
Rivaroxaban 20 mg od

Apixaban 5 mg bid

Edoxaban 60 mg od

Ruff C, Lancet 2013

# Major bleeding




Dabigatran 150 mg bid

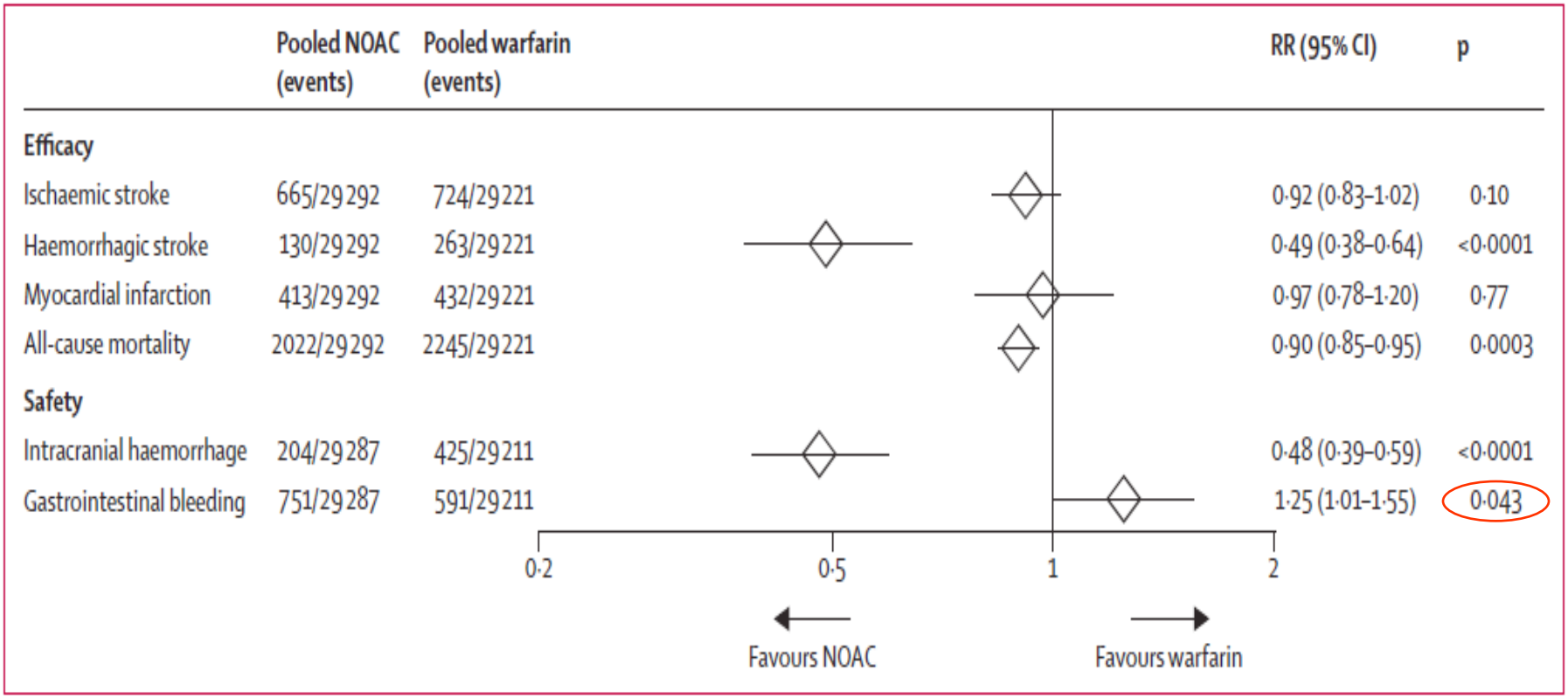
Rivaroxaban 20 mg od

Apixaban 5 mg bid

Edoxaban 60 mg od

Ruff C, Lancet 2013

# Secondary efficacy and safety outcomes




Dabigatran 150 mg bid

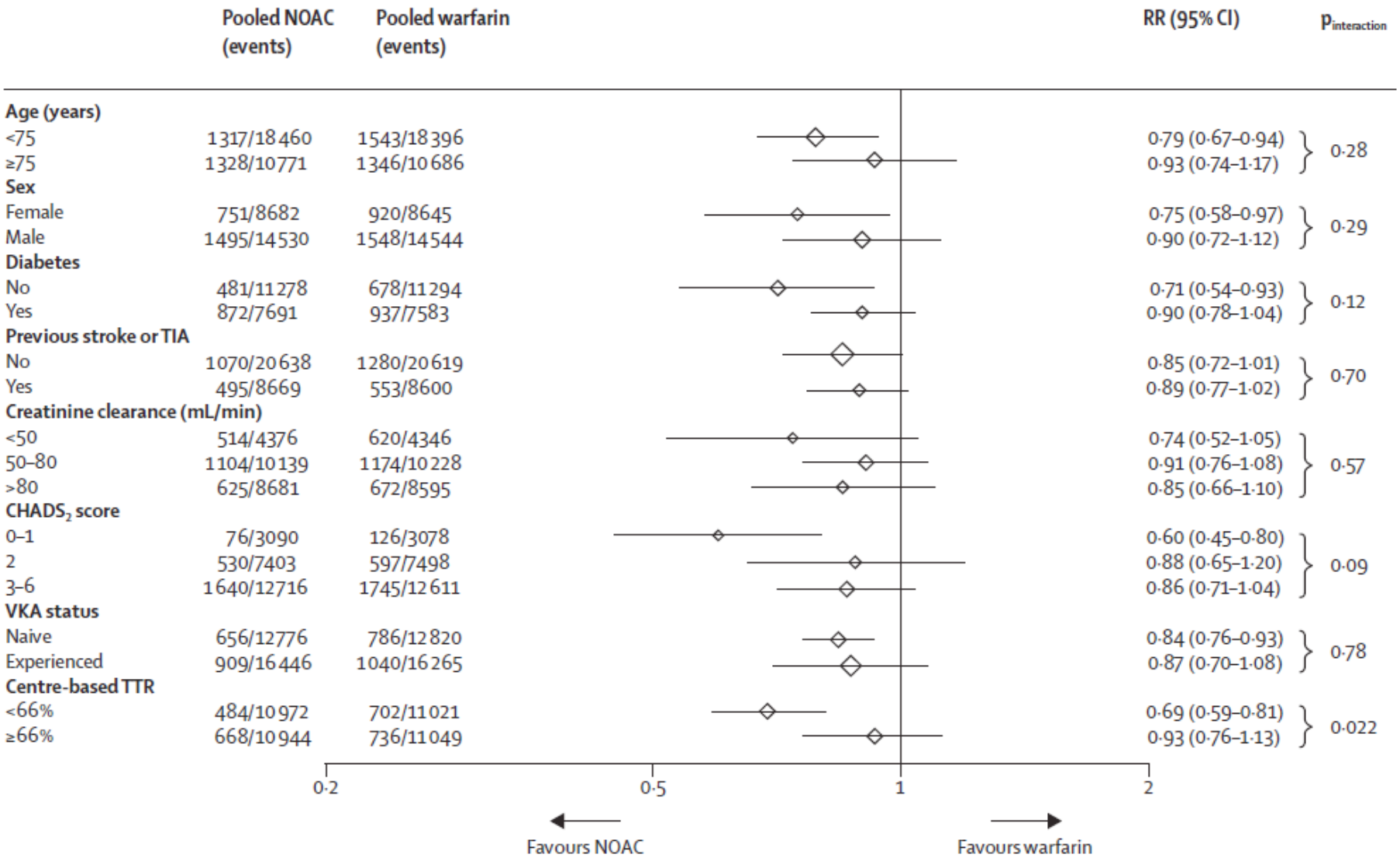
Rivaroxaban 20 mg od

Apixaban 5 mg bid

Edoxaban 60 mg od

Ruff C, Lancet 2013

# Major bleeding subgroups




Ruff C, Lancet 2013

# 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

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Antithrombotic Therapy

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

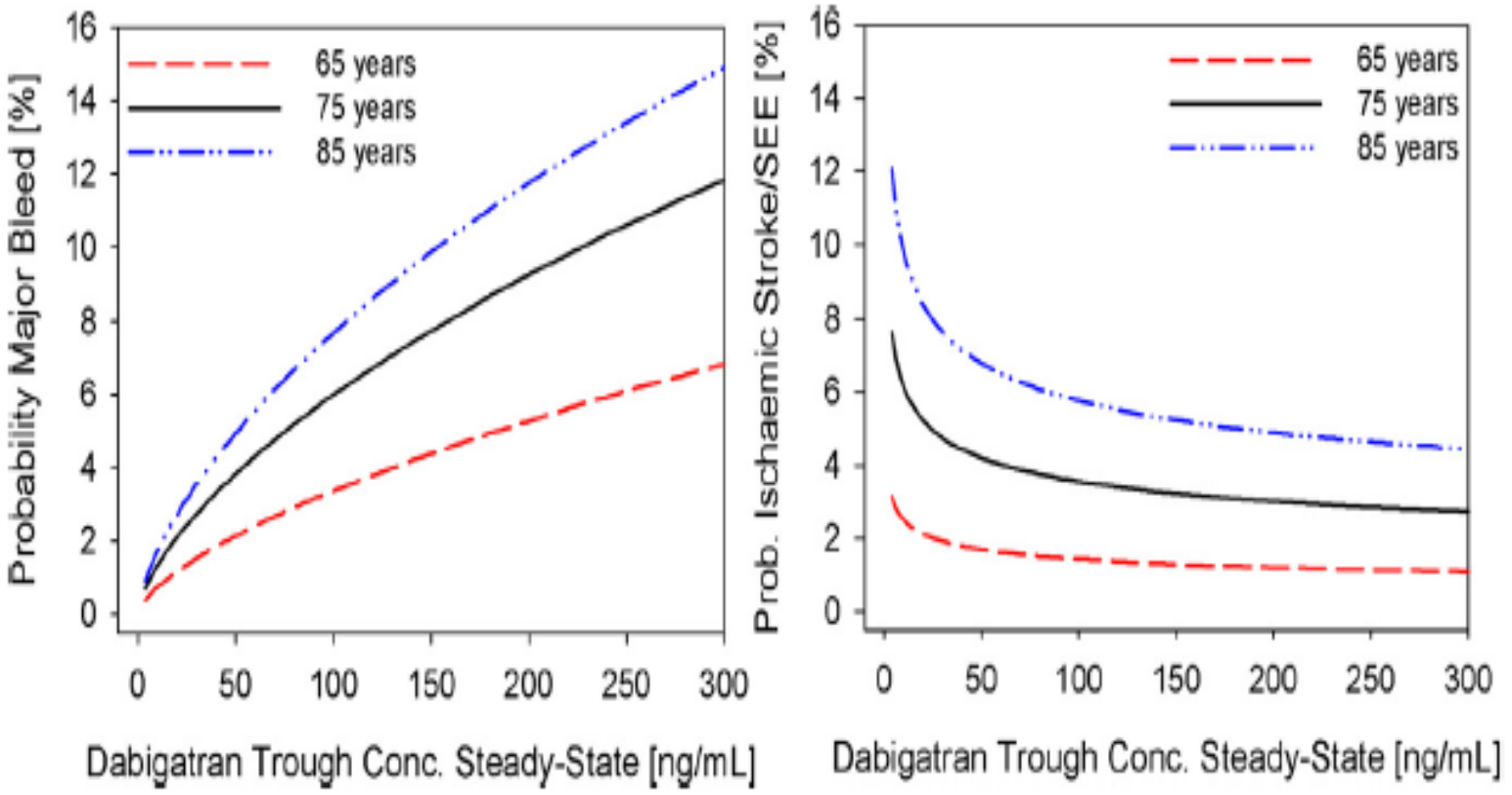
## The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

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; Wynnewood, Pennsylvania; and Uppsala, Sweden*

Reilly PA, JACC 2014

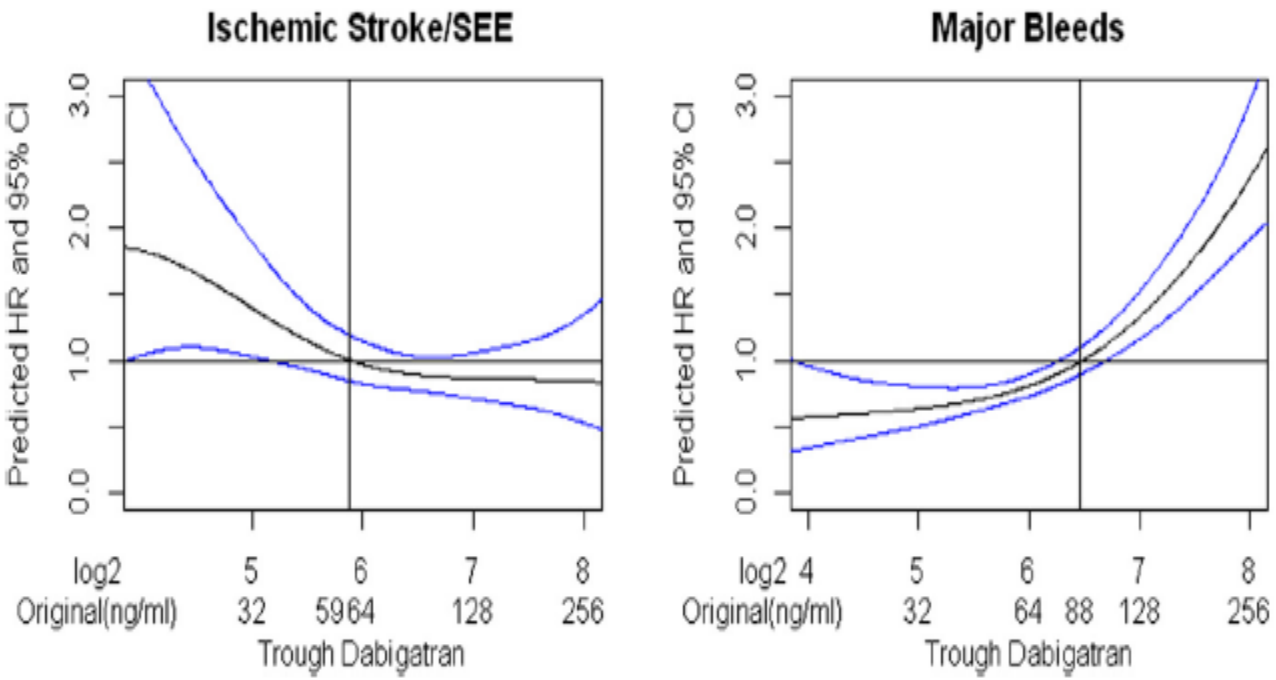
# Probability of Clinical Outcomes Versus Dabigatran




Reilly PA, JACC 2014

# Dabigatran etexilate

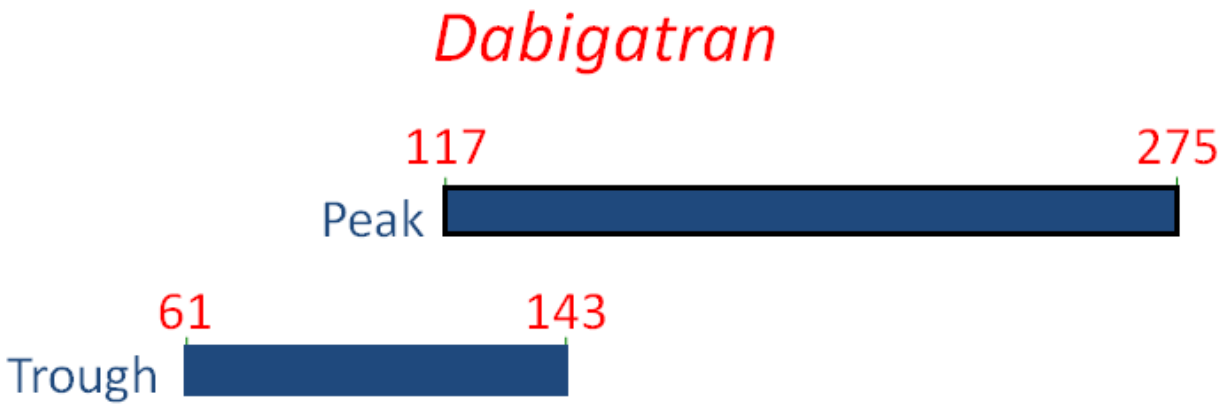
**Cox Regression Analyses of Ischemic Stroke/SEE and Major Bleeding Versus Trough Plasma Concentration of Dabigatran**

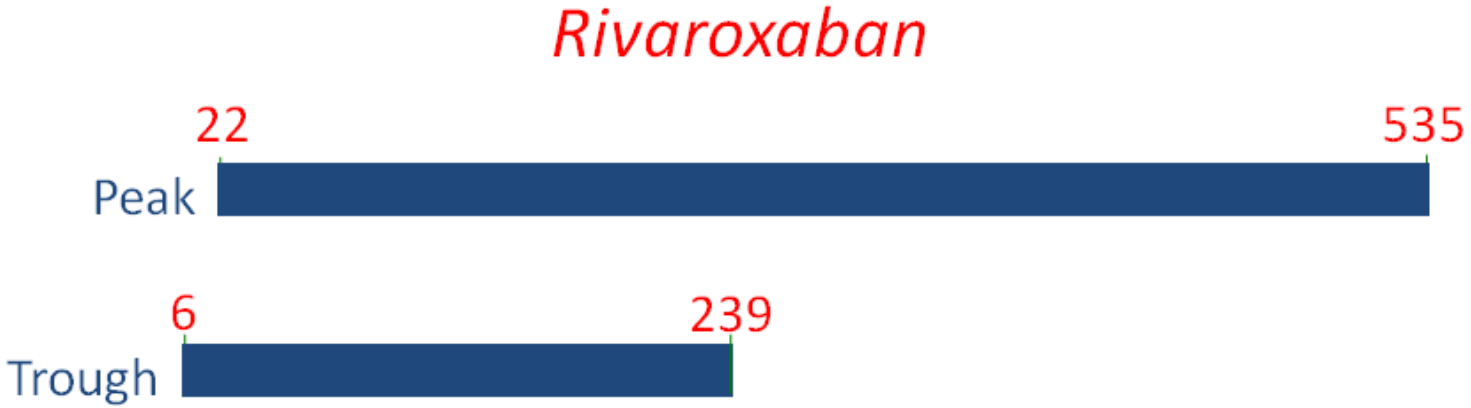



Reilly PA, JACC 2014

# Inter-individual variability plasma concentrations

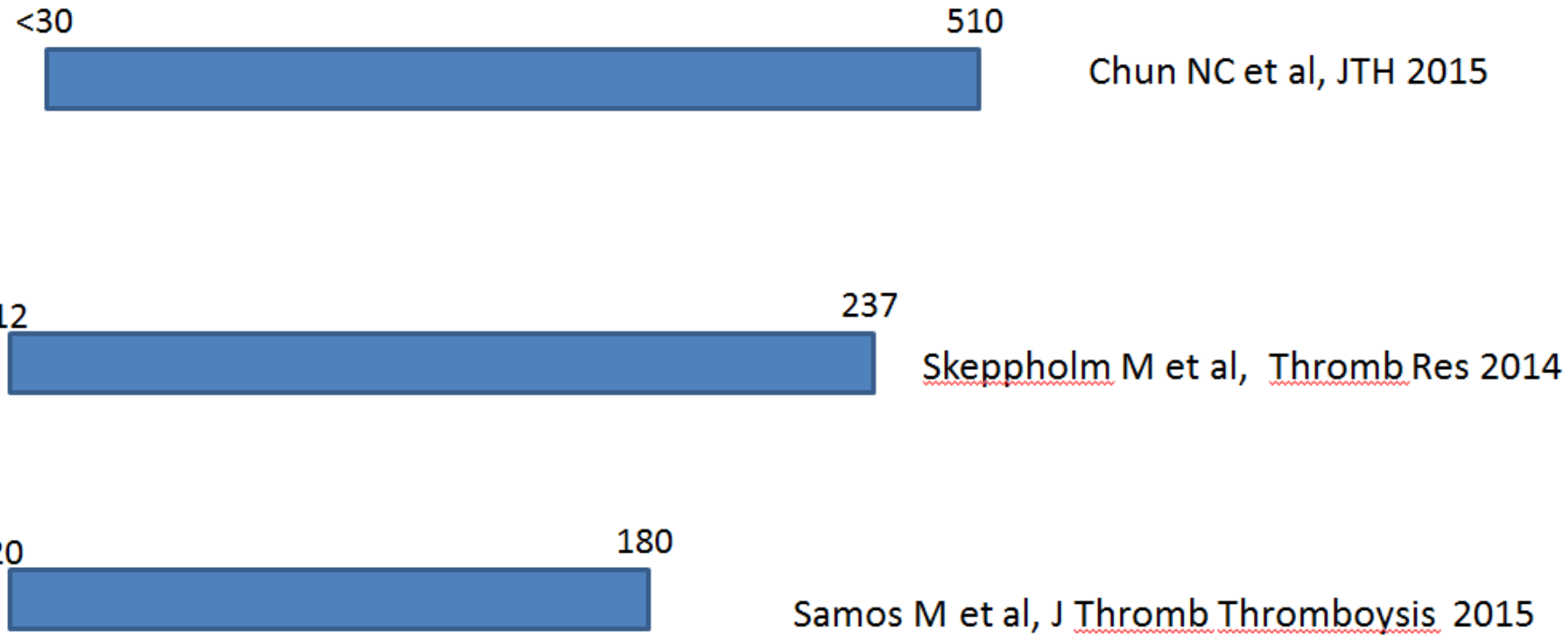
## *Data from Clinical trials*



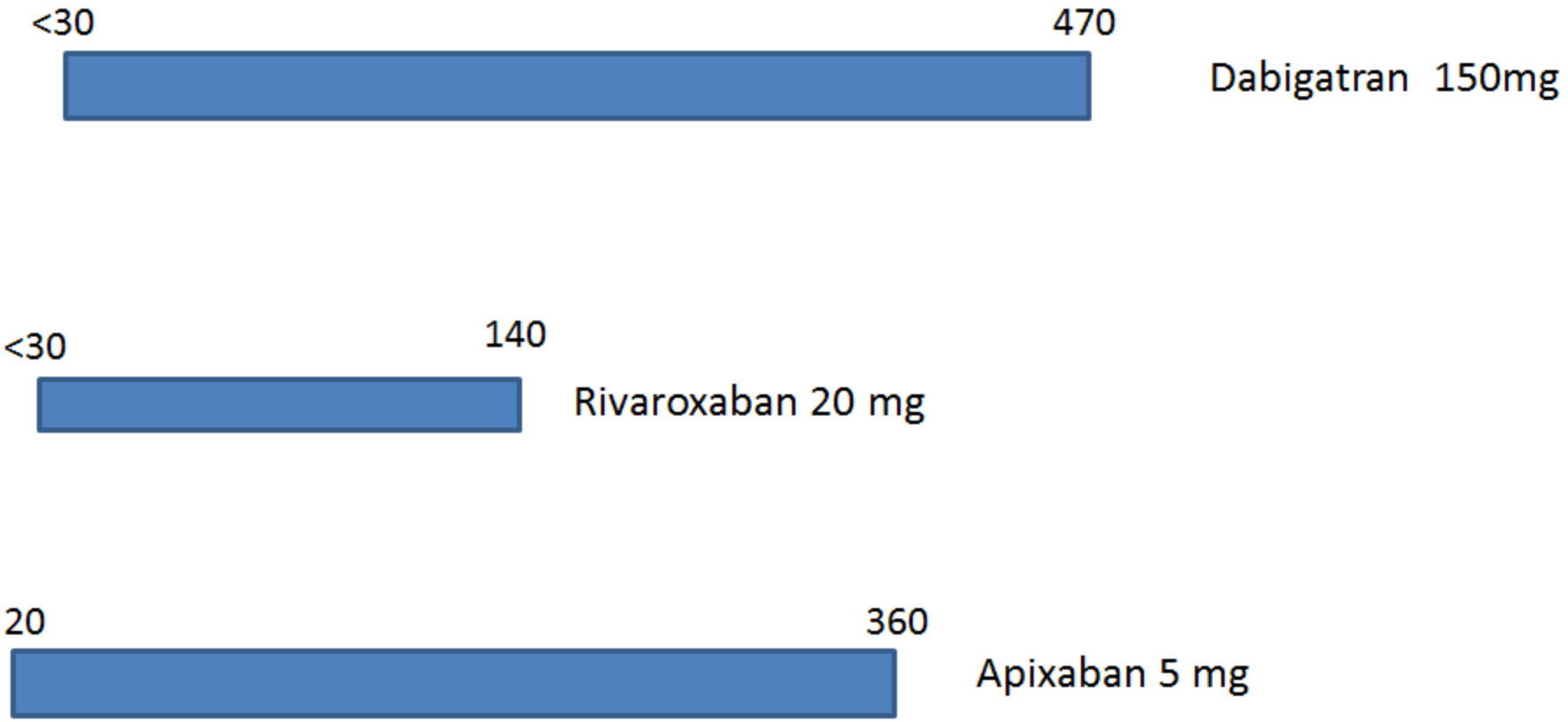

***[ng/mL (min-max)]***

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




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

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




Testa S, TR 2015

# Alerting values

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

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

# DOAC a dosaggio ridotto: indicazioni cliniche

| | |
|---|---|
| **DABIGATRAN 110** | **Età≥ 80**<br>**Verapamil**<br>**(Gastrite, età 75-80, eGFR 30-50 mL/min)**<br><br>**Combinazione di farmaci (amiodarone..)** |
| **RIVAROXABAN 15** | **eGFR<50 mL/min**<br><br>**Combinazione di farmaci (amiodarone..)** |

# DOAC a dosaggio ridotto: indicazioni cliniche

**APIXABAN 2.5**
**2 volte al dì**

**Almeno 2 delle seguenti condizioni:**
**Età≥ 80**
**Peso ≤ 60 Kg**
**Creatinina sierica ≥1.5**
**oppure**
**eGFR 15-30 mL/min**

**Combinazione di farmaci (amiodarone..)**

**Edoxaban 30 mg**
**1 volta al dì**

**Peso ≤ 60 Kg**
**eGFR 15-50 mL/min**
**Uso concomitante di dronedarone, ciclosporina…**

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

Variability in levels of the DE110 and DE150

100 patients

Dab dosage chosen on clinical basis

Peak and trough levels baseline, every 2 months

| | |
|---|---|
| CV inter-patient | 51-64% |
| CV intra-patient | 32-40% |

Chan NC, JTH 2015

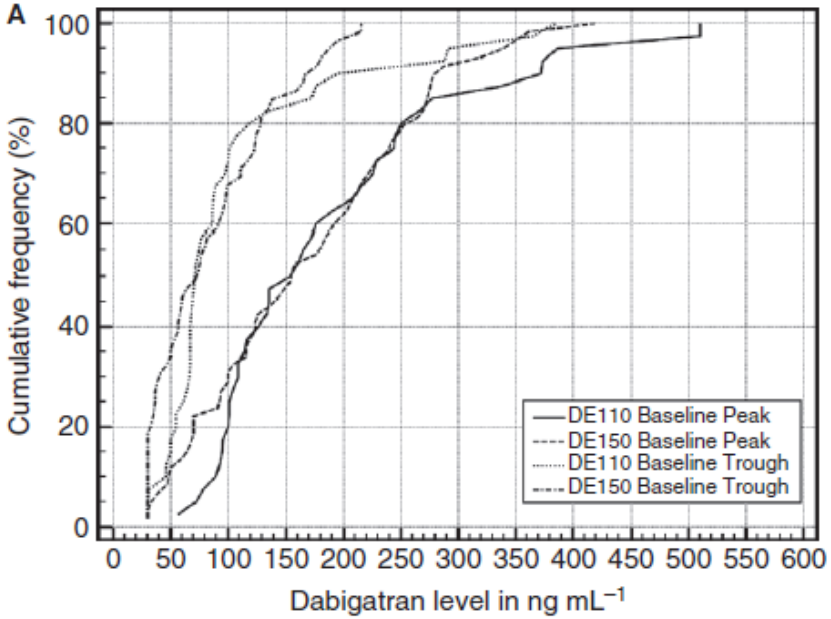
ORIGINAL ARTICLE

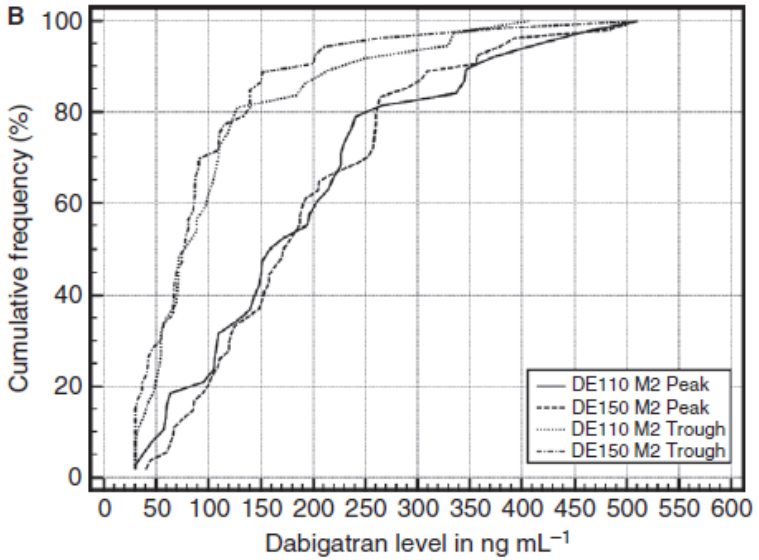
# Real-world variability in dabigatran levels in patients with atrial fibrillation

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

## 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

# Conclusion

……. 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

Taken together, these findings support adoption of the two doses of DE evaluated in the RE-LY trial and also support recommendations made by professional bodies that the lower dose should be considered for older patients or patients with clinical risk factors for bleeding

Chan NC, JTH 2015

# DOAC: need to measure

To determine the offset of activity

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

If a patient requires a semi-urgent invasive procedure associated with an increased risk of bleeding or in cases of unexpected trauma

*Garcia et al, JTH 2012*

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

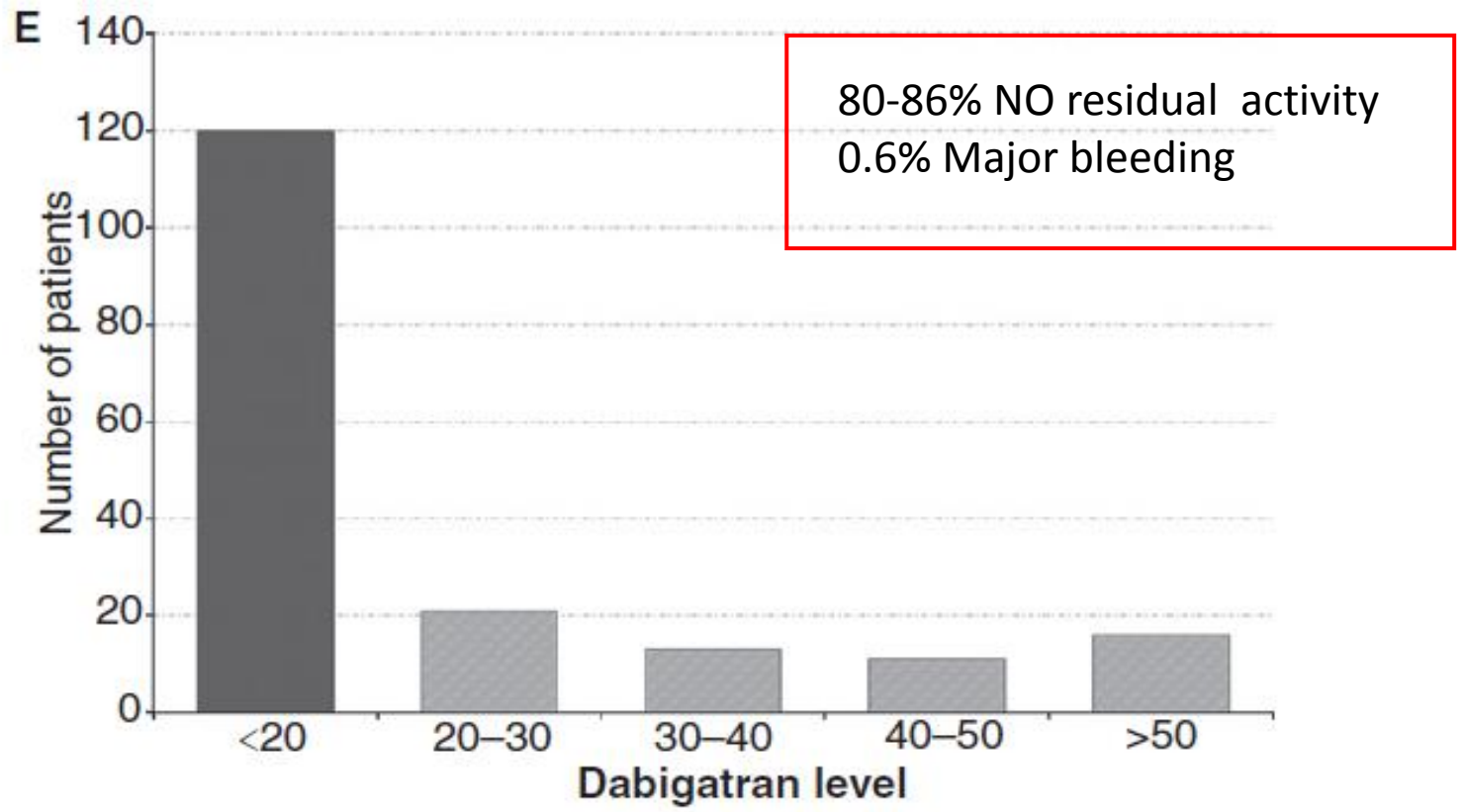
181 patients on DE who need elective surgery

Pre-op Stop Dabigatran

| | |
|---|---|
| low bleeding-risk procedure | 24 h |
| high bleeding risk | 48 h |
| CrCl 30-50 mL/min | +24h |

JTH, 2016

# Effect of dabigatran interruption on coagulation test results




…….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 2016

# Effect of dabigatran interruption on coagulation test results

…..there were more patients with a detectable anticoagulant effect at the time of a surgery/procedure than patients with bleeding.

- The interpretation of dabigatran levels in a clinical setting is uncertain.

- The detection of low plasma levels of dabigatran (< 20 ng mL -1) may not reflect an in vivo anticoagulant effect.

- The correlation between dabigatran levels and a pharmacodynamic (anticoagulant) effect is uncertain.

- One explanation for this finding is that many surgeries/procedures may be safely performed despite a mild (in this case drug-induced) coagulopathy

Douketis JD, JTH 2016

# Conclusions

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

- 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 intra-patient variability in peak and trough anticoagulant levels of dabigatran.

Douketis JD, JTH 2016

# PAUSE Study

- Aim: to establish a safe, standardized protocol for the perioperative management of AF patients who are receiving a DOAC (dabigatran, rivaroxaban, apixaban) and require elective surgery.
- Study outcomes: Major Bleedings and Arterial Thromboembolism
- >3000 patients (1100 patients per DOAC)
- Follow-up: starts the day of DOAC interruption – ends 30 day after

Douketis JD, 2016

ON MY MIND

# Urgent Need to Measure Effects of Direct Oral Anticoagulants

Jeffrey I. Weitz & John W. Eikelboom

Circulation 2016

# What tests are currently available, and why do we need new ones?

Although routine coagulation monitoring is unnecessary, there is an urgent need for readily and rapidly available tests to measure the DOACs. This need will increase with the introduction of costly reversal agents such as idarucizumab for dabigatran and andexanet alfa for rivaroxaban, apixaban, and edoxaban Idarucizumab is already licensed, and andexanet is undergoing regulatory review and could be approved later this year.

Weitz JI, Circulation 2016

# Can we achieve this goal?

All modern coagulometers are capable of performing chromogenic assays with a turnaround time similar to that for the aPTT or PT, and anti–factor Xa assays are already available for quantifying levels of heparin or low-molecular-weight heparin.

Commercial anti–factor Xa assays for rivaroxaban and apixaban and a diluted thrombin time and ecarin chromogenic assay for dabigatran are available

Weitz JI, Circulation 2016

# Can we achieve this goal?

Adoption of these assays into practice requires their regulatory approval for clinical use and their widespread introduction into busy emergency departments.

We urge regulatory agencies and hospitals to get on board to make this happen.

Weitz JI, Circulation 2016

GRAZIE PER L’ATTENZIONE

# Usefulness of measuring the effect of DOAC

Required

At baseline (before initiation of treatment)

Before surgical/invasive procedures

Adverse events (hemorrhage or thrombosis)

Make decision on thrombolytic therapy in stroke patients

Useful

- Soon before and after introducing additional drugs
- Extreme body weight

Potentially useful

- When chronic anticoagulation is achieved (1-2 weeks after initiation)
- At regular intervals during clinical visits
- Need for reversal of anticoagulation

# Conclusion

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)

Caution should be exerted when interpreting results of hemostatic parameters in patients on DOAC

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

…. 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

# What tests are currently available, and why do we need new ones?

Although routine coagulation monitoring is unnecessary, there is an urgent need for readily and rapidly available tests to measure the DOACs. This need will increase with the introduction of costly reversal agents such as idarucizumab for dabigatran and andexanet alfa for rivaroxaban, apixaban, and edoxaban Idarucizumab is already licensed, and andexanet is undergoing regulatory review and could be approved later this year.

*What tests are currently available, and why do we need new ones?*

Weitz JI, Circulation 2016

# What tests are currently available, and why do we need new ones?

…. aPTT and PT can be useful to assess the anticoagulant effects of dabigatran and some of the oral factor Xa inhibitors, respectively, the sensitivity of these tests is variable and reagent dependent.

Such tests are currently available in research facilities and include the diluted thrombin time and ecarin clot time or ecarin chromogenic assay for dabigatran, as well as chromogenic anti–factor Xa assays for rivaroxaban, apixaban, and edoxaban. Unfortunately, these tests are not widely available, and even if available, the turnaround time is often too slow to be useful. This needs to change

Weitz JI, Circulation 2016

# Why is the need for these tests so urgent?

Quantification of plasma concentrations of the DOACs is critical when assessing their potential contribution to serious bleeding, when making decisions about the timing of urgent surgery or interventions, or when determining whether patients with acute ischemic stroke can safely be given fibrinolytic therapy. Patients with elevated drug levels in these settings may benefit from the administration of a reversal agent, whereas those with little or no circulating drug will not.

Weitz JI, Circulation 2016

# Why is the need for these tests so urgent?

In urgent situations, clinicians may administer reversal agents without waiting for the results of laboratory testing, but how do we otherwise identify patients who need reversal, and how do we monitor the extent of reversal achieved when reversal agents are given?

Weitz JI, Circulation 2016

# Assays Available to Measure Plasma Levels of the DOACs

| Target | Drug | Test | Manufacturers |
|---|---|---|---|
| Thrombin | Dabigatran | Diluted thrombin time | Hyphen-BioMed, Neuville-Sur-Oise, France |
| | | | Instrument Laboratory, Bedford, MA |
| | | Ecarin chromogenic assay | Diagnostica Stago, Asnieres, France |
| Factor Xa | Rivaroxaban | Calibrated anti–factor Xa | Hyphen-BioMed |
| | | | Instrument Laboratory |
| | | | Diagnostica Stago |
| | | | Technoclone, Vienna, Austria |
| | Apixaban | Calibrated anti–factor Xa | Hyphen-BioMed |
| | | | Diagnostica Stago |
| | | | Technoclone |
| | Edoxaban | Calibrated anti–factor Xa | Diagnostica Stago (not yet commercially available) |

Weitz JI, Circulation 2016

# Why is the need for these tests so urgent?

Idarucizumab is licensed for dabigatran reversal in patients with life-threatening bleeding or in those requiring urgent surgery or intervention. An elevated aPTT at baseline provides sufficient grounds to administer idarucizumab, but a normal aPTT may not exclude the potential benefit from reversal because the aPTT is less responsive to dabigatran than the ecarin clot time.

Weitz JI, Circulation 2016

# Why is the need for these tests so urgent?

In patients taking rivaroxaban, apixaban, or edoxaban, the PT will not identify patients requiring reversal with andexanet or inform the timing of urgent surgery. Although blood is collected for central laboratory determination of anti–factor Xa activity, the treating physician cannot access this information. Instead, the dose of andexanet is determined by which oral factor Xa inhibitor the patient is taking and the time from the last dose. If implemented in practice, this approach could lead to unnecessary administration or underdosing of andexanet if the clinical information is incorrect.

Weitz JI, Circulation 2016

# Why is the need for these tests so urgent?

Although the cost of andexanet has not been revealed, it will be at least as expensive as idarucizumab, which costs about $3500 per dose in the United States.

Therefore, ready access to rapidly available, calibrated tests is needed to ensure that reversal agents are given appropriately

Weitz JI, Circulation 2016

# FARMACI AVK

## reversibilità dell'effetto anticoagulante

| AZIONE | EFFETTO |
|---|---|
| Sospensione TAO | 3-7 gg |
| Vit.K x os | 24 ore |
| Vit.K ev | 10-12 ore |
| Plasma Fresco congelato | 3-6 ore |
| CCP | 5 minuti |

**Poor reliability of coagulation screening test in patients treated with direct oral anticoagulants: results from a multicenter multiplatform observational study**

| | | | | |
|---|---|---|---|---|
| Normal aPTT and dabigatran > 50 ng/ml | 6/87 (6.9%) | 6/107 (5.6%) | 19/158 (12.0%) | 3/42 (7.1%) |
| Prolonged aPTT and dabigatran ≤ 50 ng/ml | 1/7 (14.3%) | 22/51 (43.1%) | 9/20 (45.0) | 5/8 (62.5%) |
| Normal PT and rivaroxaban > 50 ng/ml | 7/75 (9.3%) | 3/119 (2.5%) | 34/109 (31.2%) | 2/26 (7.7%) |
| Prolonged PT and rivaroxaban ≤ 50 ng/ml | 7/69 (10.1%) | 11/97 (11.3%) | 3/13 (23.1%) | 5/20 (25.0%) |
| Normal PT and apixaban > 50 ng/ml | 25/58 (43.1%) | 73/172 (42.4%) | NA | 6/18 (33.3%) |
| Normal PT and apixaban ≤ 50 ng/ml | 0/2 (0%) | 0/10 (0%) | NA | 1/2 (50.0%) |

PT/PTT nella norma non escludono presenza di concentrazioni significative di DOAC così come PT/PTT allungati si osservano in assenza di farmaco.

Testa S et al, JTH 2016

*Journal of Thrombosis and Haemostasis*, 14: 1–8 DOI: 10.1111/jth.13486

ORIGINAL ARTICLE

# Poor comparability of coagulation screening test with specific measurement in patients receiving direct oral anticoagulants: results from a multicenter/multiplatform study

S. TESTA,* C. LEGNANI,† A. TRIPODI,‡ O. PAOLETTI,* V. PENGO,§ R. ABBATE,¶ L. BASSI,* P. CARRARO,** M. CINI,† R. PANICCIA,¶ D. POLI¶ and G. PALARETI††

| | | | | |
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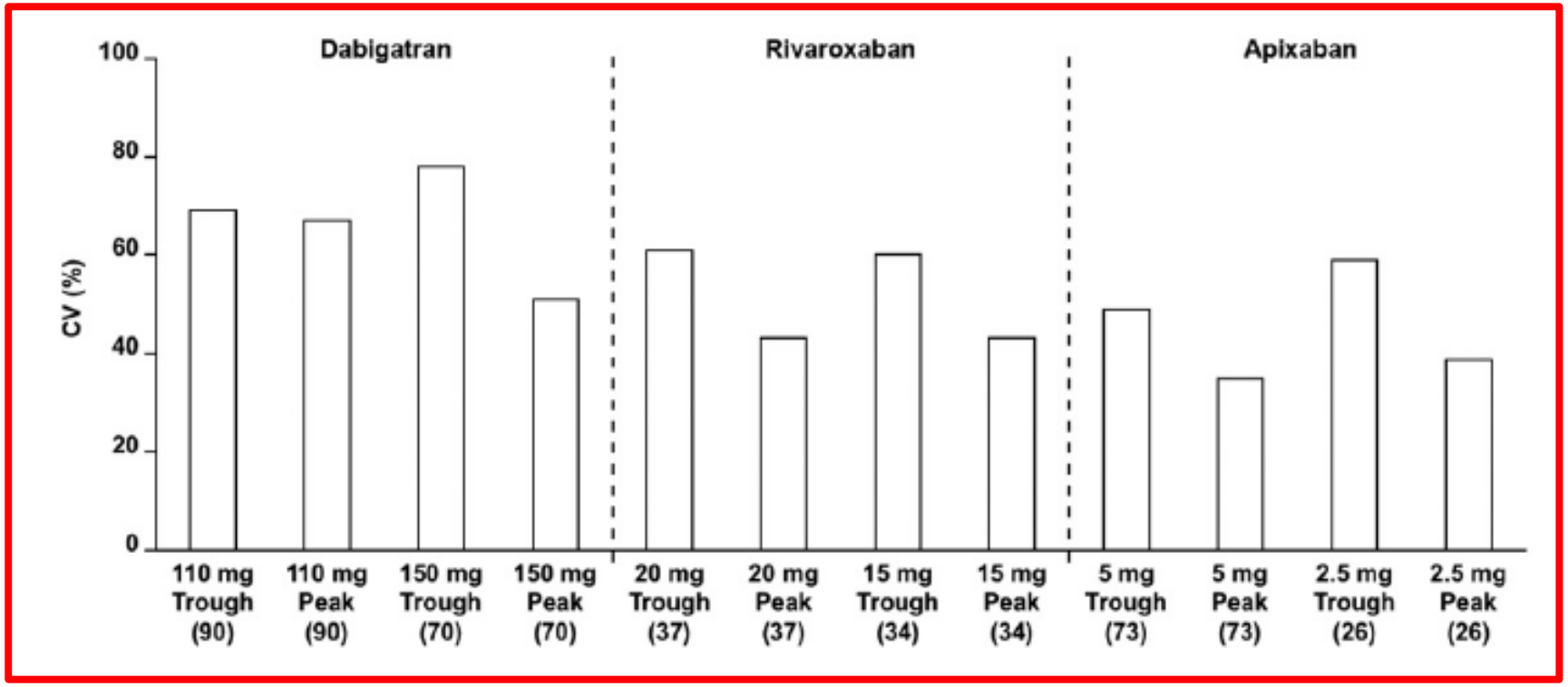
PT/PTT nella norma non escludono presenza di concentrazioni significative di DOAC così come PT/PTT allungati si osservano in assenza di farmaco.

Testa S et al, JTH 2016

# DOAC: INTER-INDIVIDUAL VARIABILITY




S. Testa et al. / Thrombosis Research 137 (2016) 178–183

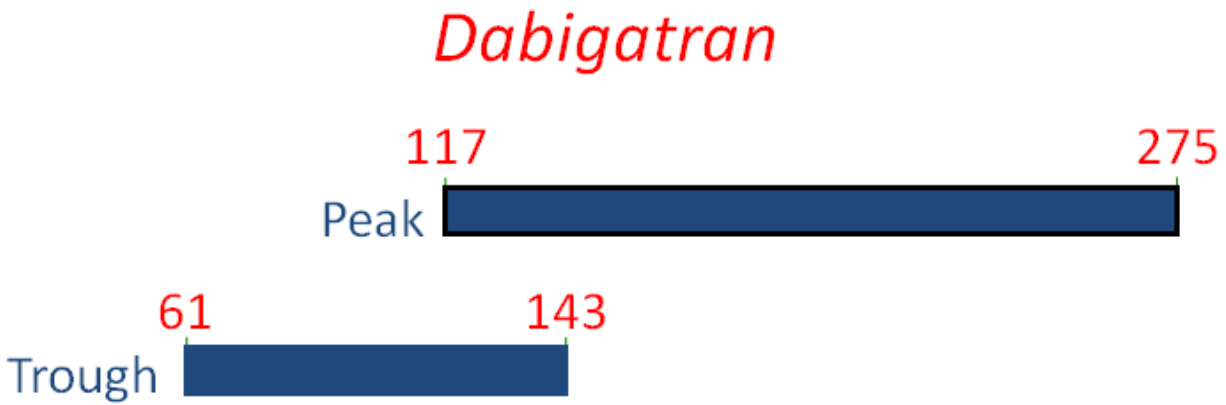
***Tabella 1.*** *Intervalli di concentrazioni plasmatiche nei pazienti in trattamento con NAO*

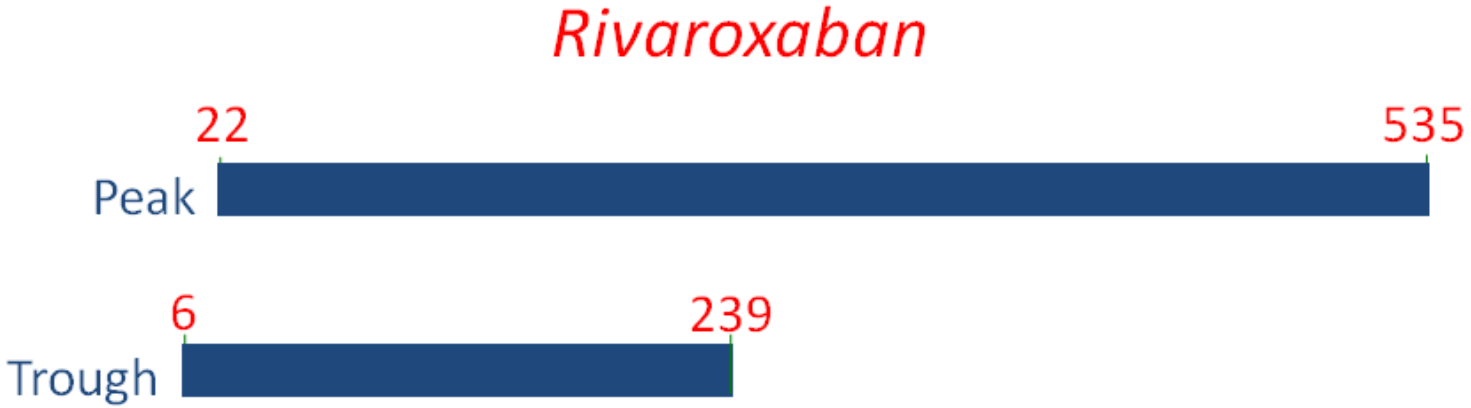
| **Farmaco** | **Punto di valle** (prima della assunzione successiva) | **Punto di picco** (2-3 ore dall'ultima assunzione) |
|---|---|---|
| Dabigatran (150 mg/2 volte die) | 40-215 ng/ml* | 74-383 ng/ml* |
| Dabigatran (110 mg/2 volte die) | 28-155 ng/ml* | 52-275 ng/ml* |
| Rivaroxaban (20 mg/die) | 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]*

# Inter-individual variability plasma concentrations

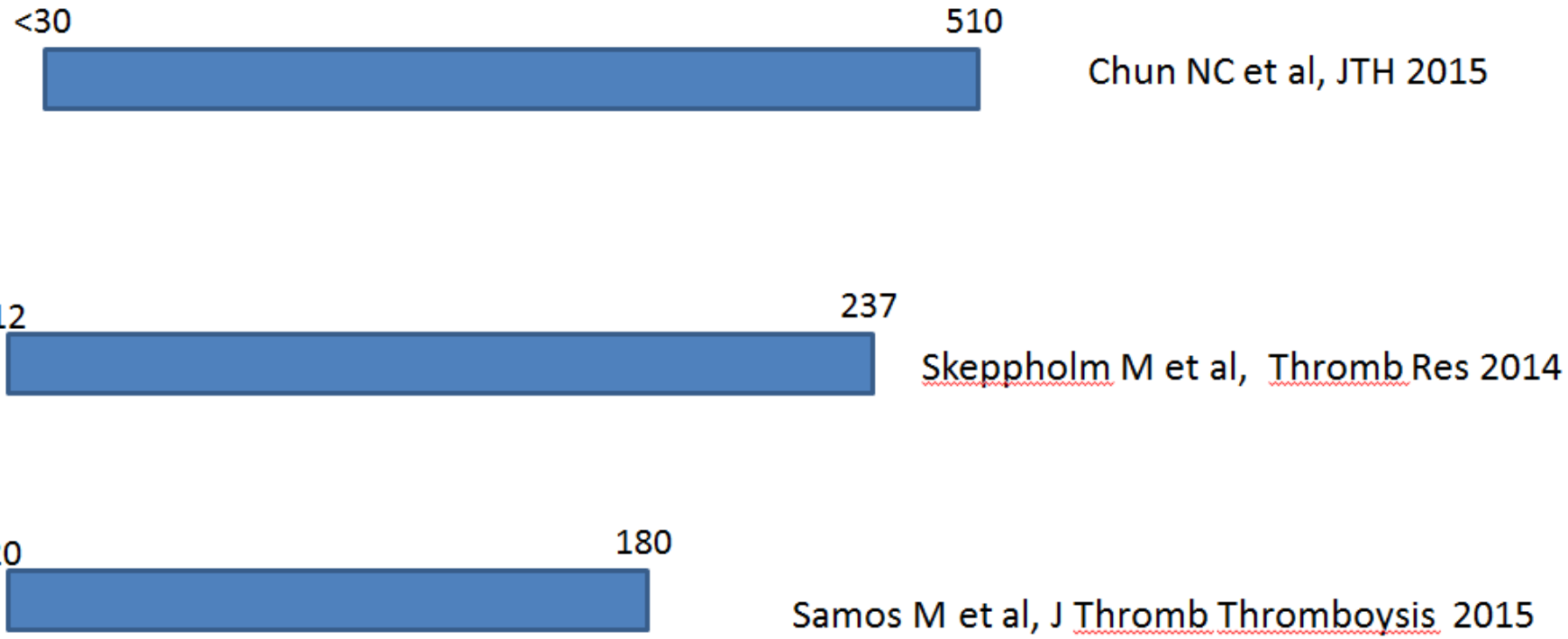
## *Data from Clinical trials*



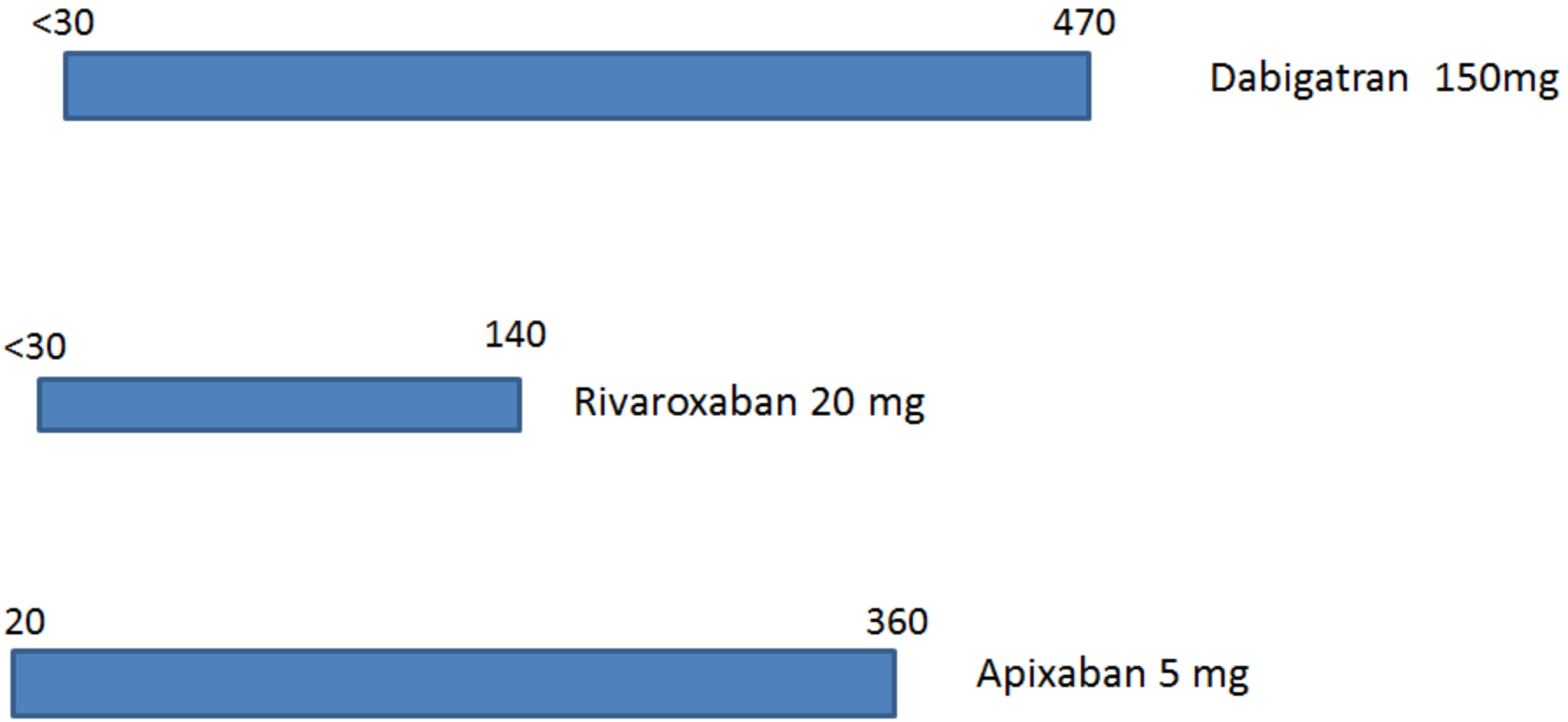

***[ng/mL (min-max)]***

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



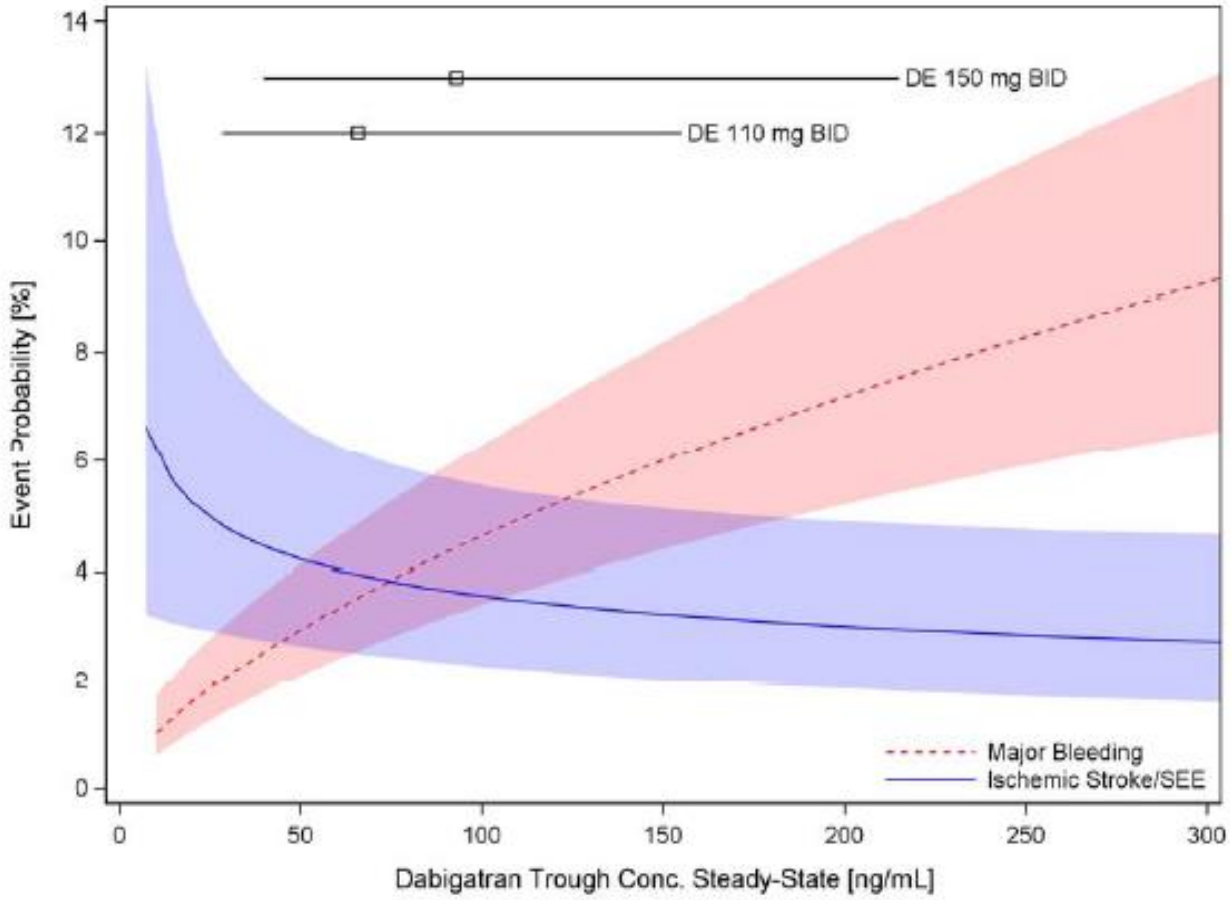

*[ng/mL (min-max)]*

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




Testa S, TR 2015


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




Reilly PA, JACC 2013

# Management of bleeding individualized according to:

- Severity of bleeding
- Site of bleeding
- Patient characteristics (renal function)
- Indication of anticoagulation
- Specific anticoagulant used and dosage
- Timing of the last dose
- Presence of anticoagulant effect
- Interacting or concomitant anti-hemostatic therapy,
- Comorbidities

# Possible measures to take in case of bleeding

| | Direct thrombin inhibitors (dabigatran) | FXa inhibitors (apixaban, edoxaban, and rivaroxaban) |
|---|---|---|
| None life-threatening bleeding | Inquire last intake + dosing regimen.<br>Estimate normalization of haemostasis:<br>Normal renal function: 12–24 h<br>CrCl 50–80 mL/min: 24–36 h<br>CrCl 30–50 mL/min: 36–48 h<br>CrCl < 30 mL/min: ≥48 h<br>Maintain diuresis.<br>Local haemostatic measures.<br>Fluid replacement (colloids if needed).<br>RBC substitution if necessary.<br>Platelet substitution (in case of thrombocytopenia ≤60 × $10^9$/L or thrombopathy).<br>Fresh frozen plasma as plasma expander (not as reversal agent)<br>Tranexamic acid can be considered as adjuvans.<br>Desmopressin can be considered in special cases (coagulopathy or thrombopathy)<br>Consider dialysis (preliminary evidence: −65% after 4 h).[122]<br>Charcoal haemoperfusion can be considered (based on preclinical data) | Inquire last intake + dosing regimen.<br>Normalisation of haemostasis: 12–24 h<br>Local haemostatic measures.<br>Fluid replacement (colloids if needed).<br>RBC substitution if necessary.<br>Platelet substitution (in case of thrombocytopenia ≤60 × $10^9$/L or thrombopathy).<br>Fresh frozen plasma as plasma expander (not as reversal agent)<br>Tranexamic acid can be considered as adjuvans.<br>Desmopressin can be considered in special cases (coagulopathy or thrombopathy) |

LG EHRA ESC 2015

# Possible measures to take in case of bleeding

| | | |
|---|---|---|
| Life-threatening bleeding | All of the above.<br>Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata).<br>Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.<br>Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)<br>Idarucizumab 5 g IV (approval waiting) | All of the above.<br>Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data)<br>Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.<br>Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence) |

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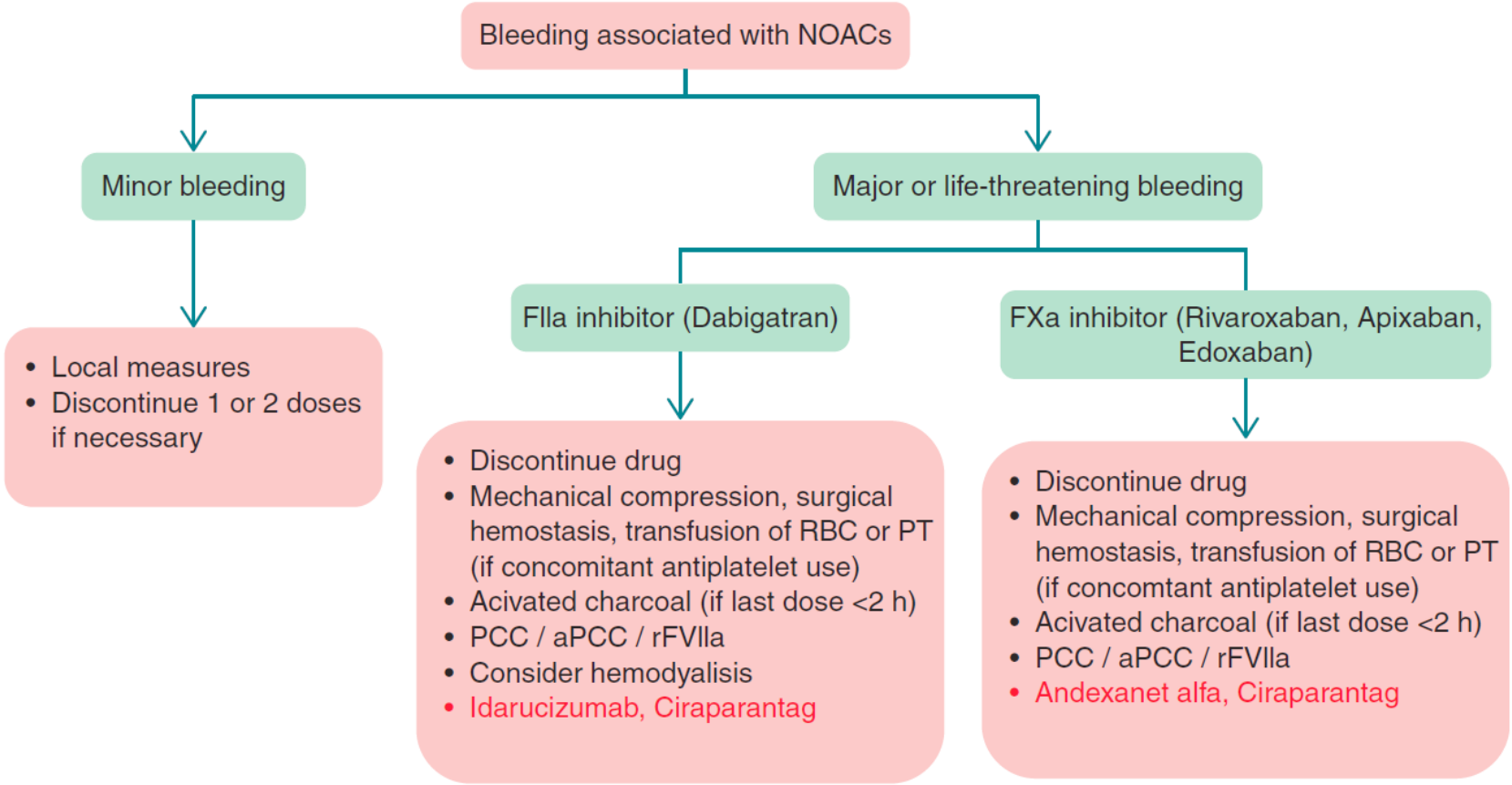
# ANTIDOTI

# Strategies for anticoagulation reversal in bleeding associated with warfarin and new oral anticoagulants

| | Warfarin | Dabigatran | Rivaroxaban, apixaban, and edoxaban |
|---|---|---|---|
| General measures | Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support | Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support | Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support |
| Activated charcoal | Consider if last dose <2 h | Consider if last dose <2 h | Consider if last dose <2 h |
| Haemodialysis | No benefits (highly protein bound) | Removes 62–68% of circulating drug | No benefits (highly protein bound) |
| Coagulation factors | PCC (25 U/kg, repeat if necessary)<br>FFP (10–15 ml/kg)<br>rFVIIa (90 ug/kg) | PCC (25 U/kg, repeat if necessary)<br>rFVIIa (90 ug/kg) | PCC (25 U/kg, repeat if necessary) or<br>FEIBA (50 IE/kg, max 200 IE/day)<br>rFVIIa (90 ug/kg) |
| Specific inhibitors | Vitamin K (5–10 mg IV) | Idarucizumab (Phase 1)<br>Ciraparantag (preclinical) | Andexanet alfa (Phases 1–3)<br>Ciraparantag (Phase 1) |

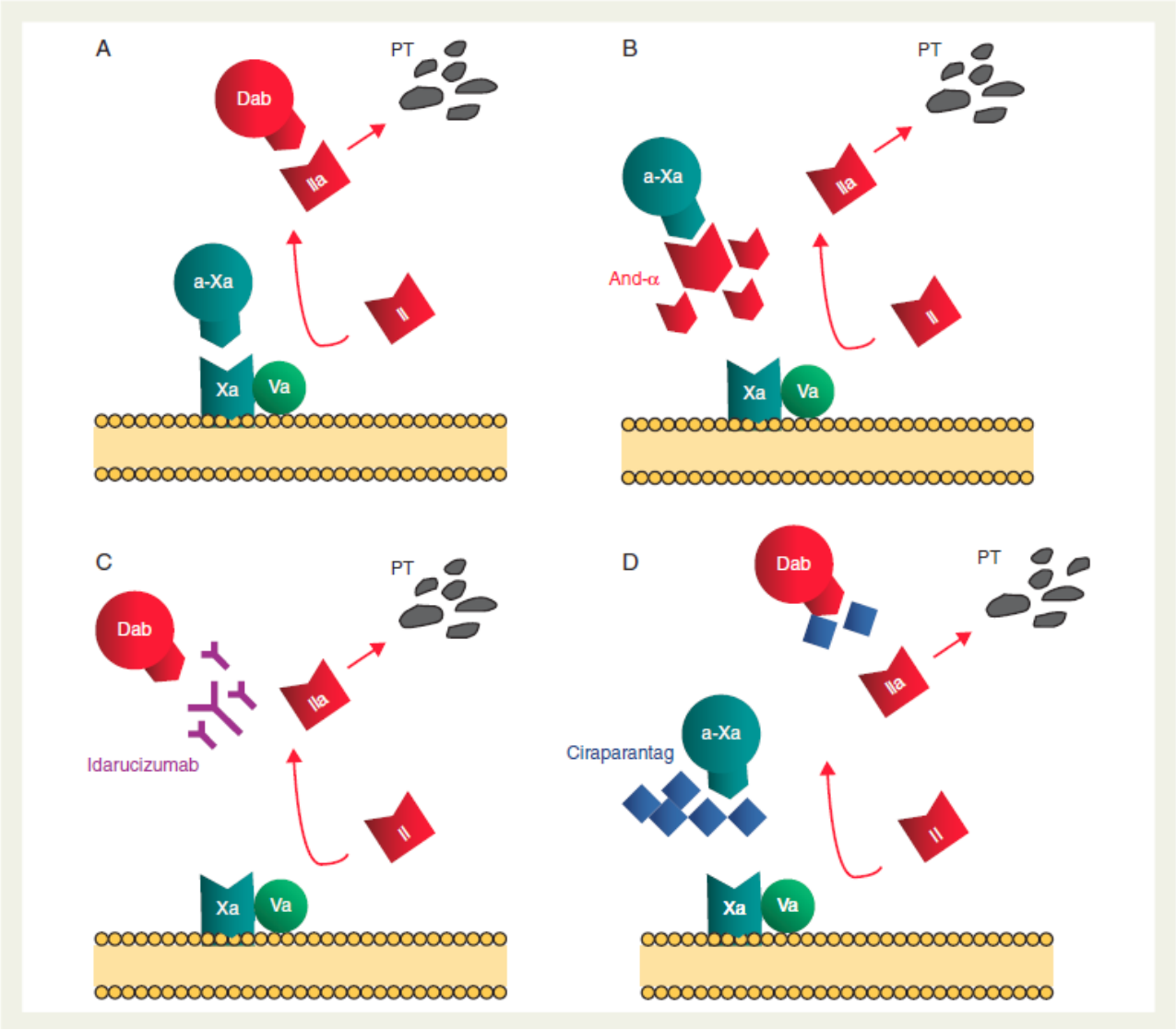
Enriquez A, Europace 2015

# Management of bleeding associated with NOACs




Enriquez A, Europace 2015

# Mechanism of NOACs and their antidotes




Enriquez A, Europace 2015

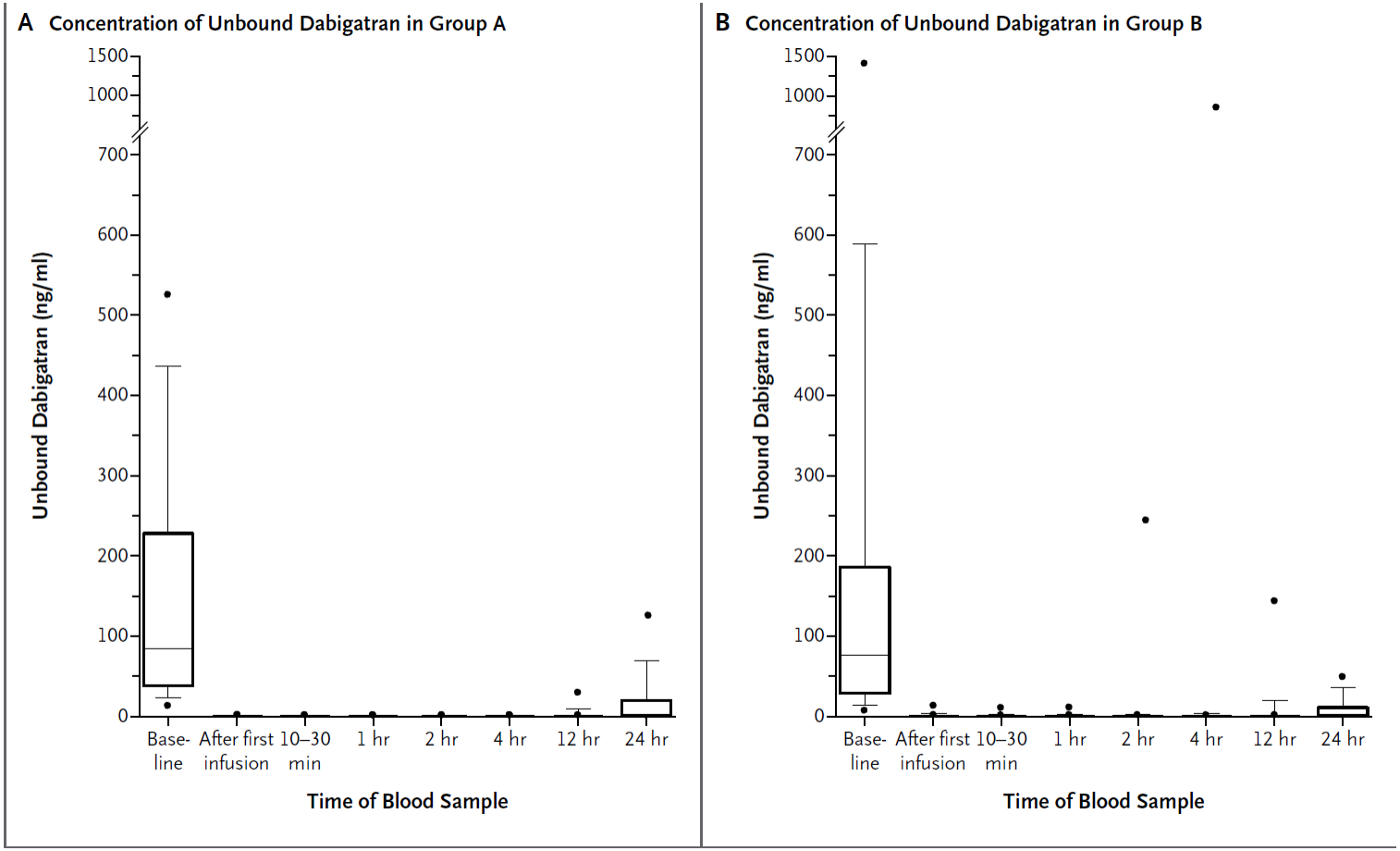
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

# Time Courses of Plasma Concentrations of Unbound Dabigatran before and after the Administration of Idarucizumab

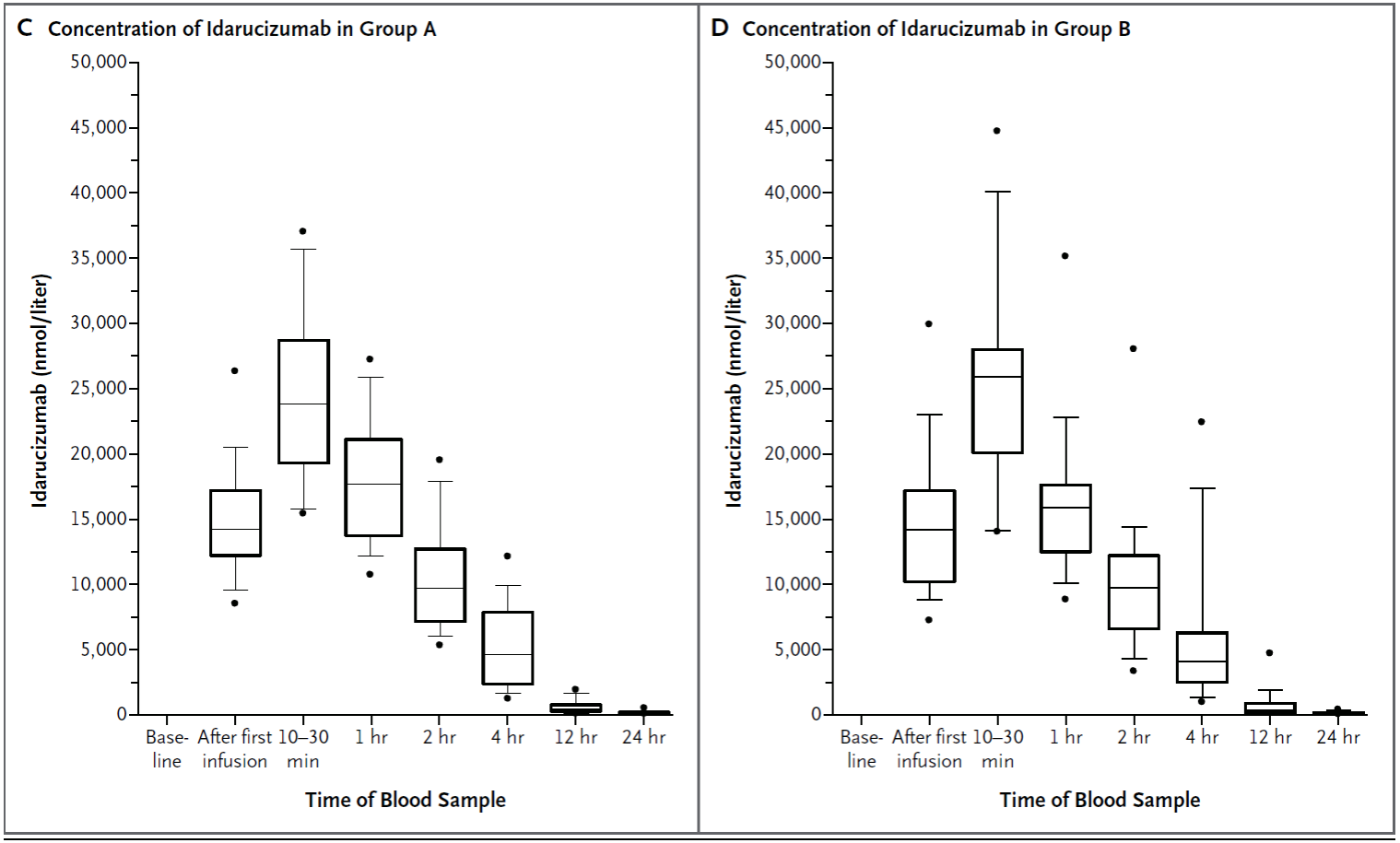



patients who had serious bleeding

patients who required urgent surgery

Pollack V, NEJM 2015

# Time Courses of Plasma Concentrations of Idarucizumab before and after the Administration of Idarucizumab




patients who had serious bleeding

patients who required urgent surgery

Pollack V, NEJM 2015

# Idarucizumab for dabigatran reversal

- Rapidly and complete reversal of the anticoagulant activity of dabigatran in 88 to 98% of patients

- No safety concerns among the 90 patients involved in this study — including patients who were given idarucizumab on clinical grounds but were later found to have had normal results on clotting tests at baseline — or among the more than 200 volunteers who were administered idarucizumab in previous studies

Pollack V, NEJM 2015

The NEW ENGLAND JOURNAL of MEDICINE

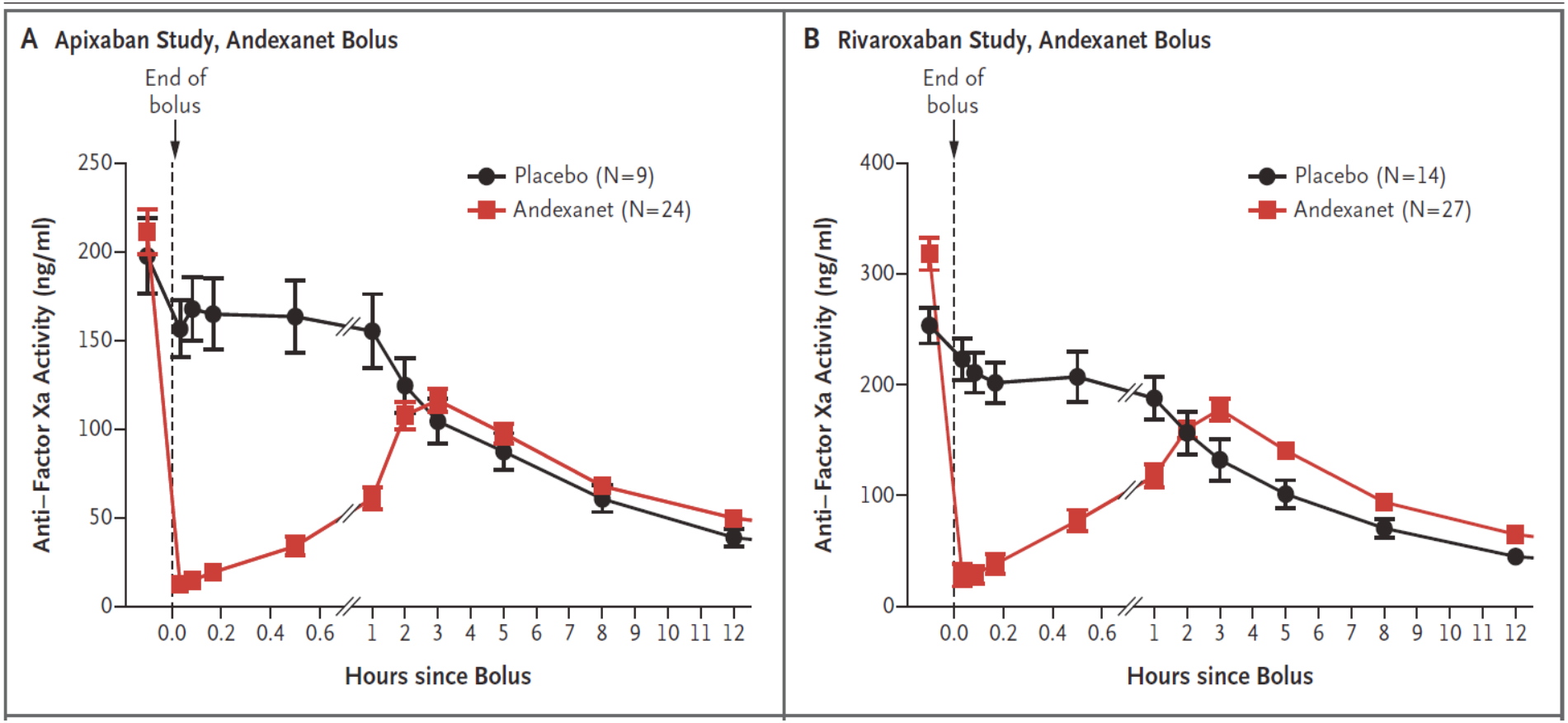
ORIGINAL ARTICLE

# Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

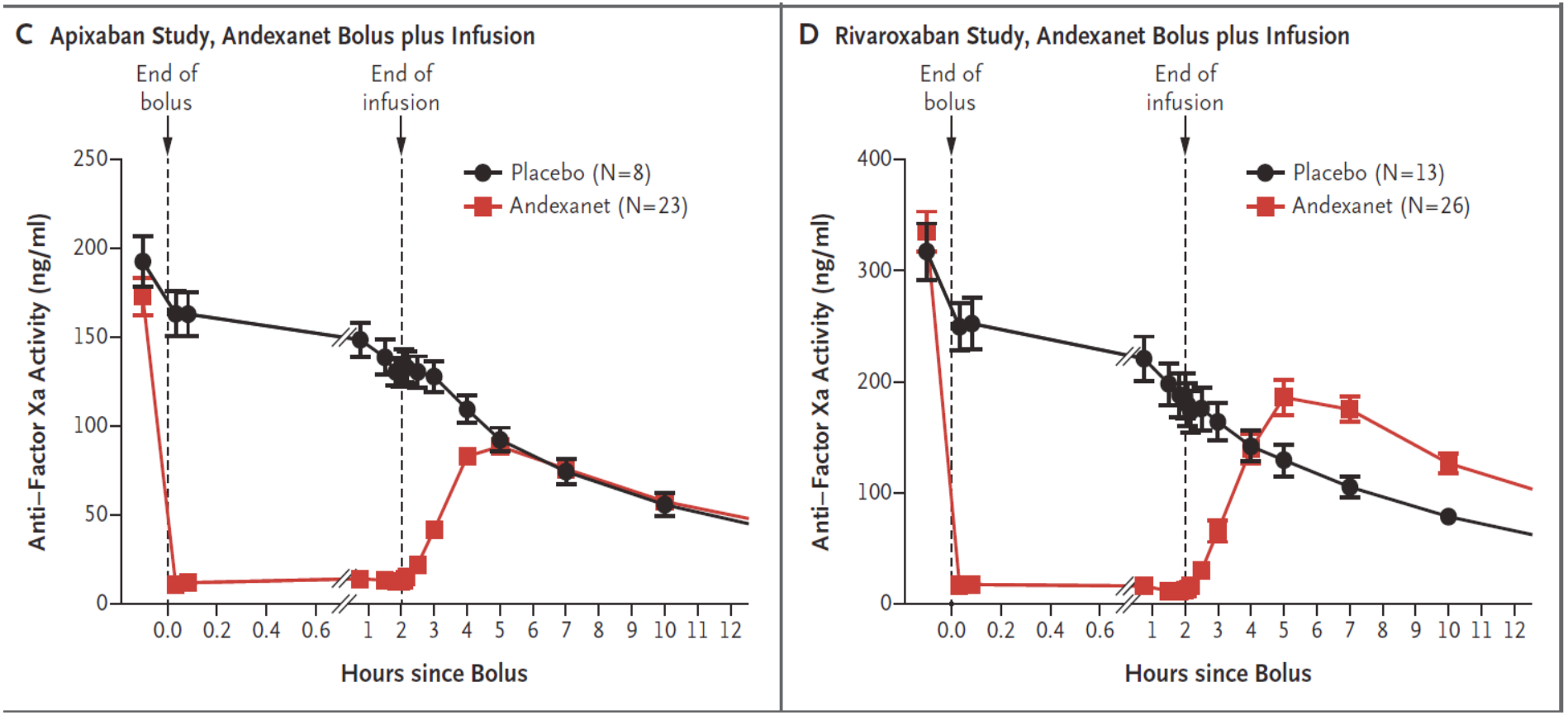
Siegal D, NEJM 2015

# Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet



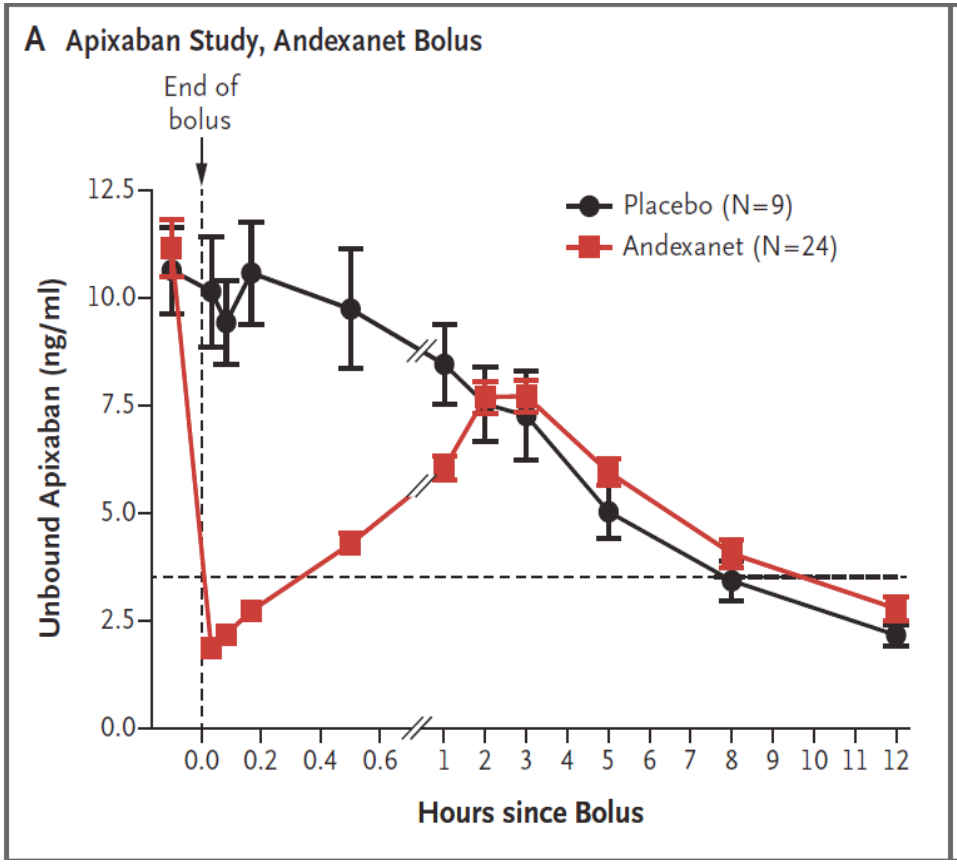

Siegal D, NEJM 2015

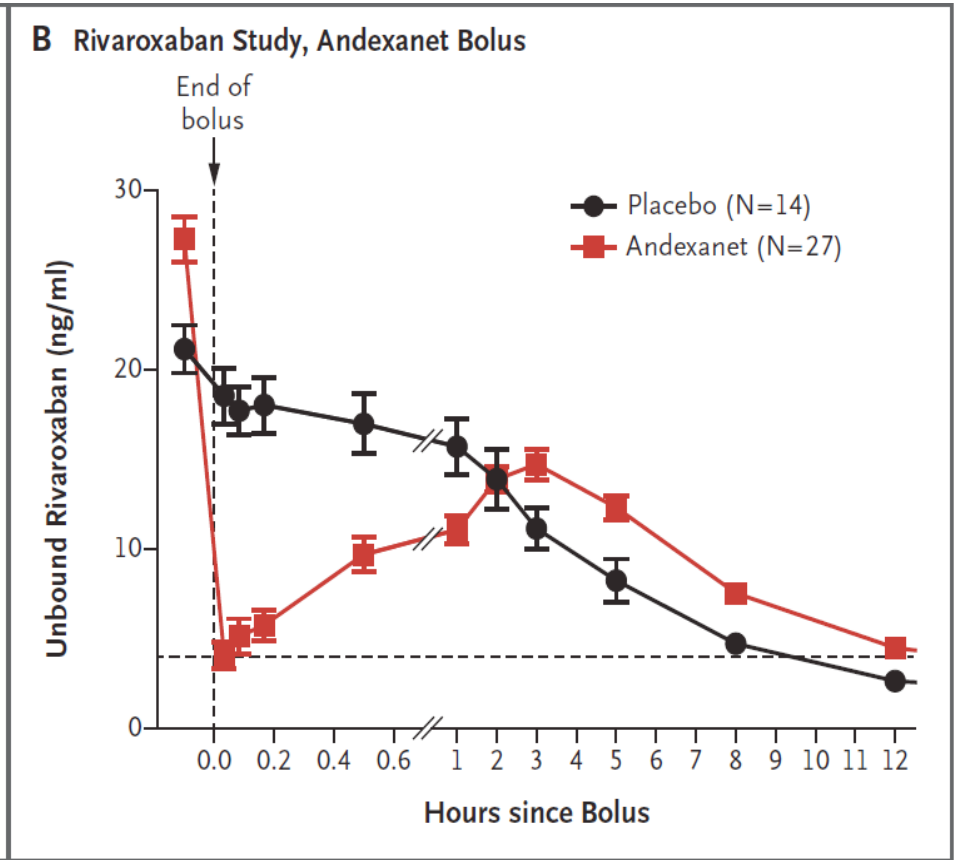
# Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet




Siegal D, NEJM 2015

# Time Courses of Plasma Concentrations of Unbound Apixaban or Rivaroxaban before and after Administration of Andexanet




Siegal D, NEJM 2015

# Drug Related Events

| Event | Apixaban | | Rivaroxaban | | Placebo (N=44) |
|---|---|---|---|---|---|
| | Bolus (N=24) | Bolus + Infusion (N=24) | Bolus (N=27) | Bolus + Infusion (N=26) | |
| | *number of events* | | | | |
| Gastrointestinal disorders | 2 | 2 | 0 | 0 | 0 |
| Constipation | 0 | 2 | 0 | 0 | 0 |
| Dysgeusia | 2 | 0 | 0 | 0 | 0 |
| General disorders and administration-site conditions | 3 | 4 | 2 | 0 | 1 |
| Feeling hot | 1 | 2 | 0 | 0 | 1 |
| Flushing | 2 | 2 | 2 | 0 | 0 |
| Immune system disorders | 0 | 1 | 1 | 0 | 0 |
| Urticaria | 0 | 1 | 1 | 0 | 0 |

Siegal D, NEJM 2015

# Conclusion

Andexanet is a specific, rapidly acting antidote that is being developed for urgent reversal of factor Xa inhibitor anticoagulant activity.

Siegal D, NEJM 2015

# Conclusion

In our studies, andexanet rapidly restored factor Xa activity and thrombin generation and reduced unbound factor Xa inhibitor concentrations in apixaban-treated and rivaroxaban-treated older participants. The reversal of anticoagulation with andexanet was not associated with safety concerns or thrombotic events.

The ongoing ANNEXA-4 phase 3b–4 study (ClinicalTrials.gov number, NCT02329327) is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor–associated acute major bleeding

Siegal D, NEJM 2015

# Dubbi sugli antidoti

La loro efficacia/sicurezza sarà valutata in RCT di adeguata potenza e con sample size decisi su end-point clinici (e non solo farmacologici)?

Quale l'appropriatezza del loro uso?

Quali i possibili effetti indesiderati?

Quale rapporto costo/efficacia?

# Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

**Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.***

| Analysis | Dabigatran | | | Warfarin | | |
|---|---|---|---|---|---|---|
| | No. of Patients | No. of Events | Incidence *no. of events/ 100,000 days at risk* | No. of Patients | No. of Events | Incidence *no. of events/ 100,000 days at risk* |
| **Gastrointestinal hemorrhage** | | | | | | |
| Analysis with required diagnosis of atrial fibrillation | 10,599 | 16 | 1.6 | 43,541 | 160 | 3.5 |
| Sensitivity analysis without required diagnosis of atrial fibrillation | 12,195 | 19 | 1.6 | 119,940 | 338 | 3.1 |
| **Intracranial hemorrhage** | | | | | | |
| Analysis with required diagnosis of atrial fibrillation | 10,587 | 8 | 0.8 | 43,594 | 109 | 2.4 |
| Sensitivity analysis without required diagnosis of atrial fibrillation | 12,182 | 10 | 0.9 | 120,020 | 204 | 1.9 |

This article was published on March 13, 2013, at NEJM.org.

# Efficacy and safety of dabigatran and warfarin in ‘real world’ patients with atrial fibrillation: A prospective nationwide cohort study

- Danish Registry of Medicinal Product Statistics
- Dabigatran: n=4978  Warfarin: n=8936
- Less intracranial bleeding with dabigatran (110mg BID: aHR: 0.24 150mg BID: 0.08,
- Less gastrointestinal bleeding with dabigatran 110mg BID (aHR: 0.60), but not dabigatran 150mg BID.

Larsenet , al. JACC  2013

# 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