# Le complicanze emorragiche in corso di terapia anticoagulante e loro gestione

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Cremona 20 Settembre 2016

# Eventi emorragici in pazienti in terapia anticoagulante

Valutare:
Entità della perdita ematica e compenso emodinamico
Sede
Durata
Valore di INR (in caso di VKA)
Concentrazioni ematiche (in caso di DOAC)
Compliance alla terapia
Interazioni farmacologiche
Identificare possibili cause locali
Trauma
Patologie concomitanti:
- piastrinopenia
- insufficienza renale
- insufficienza epatica/ cirrosi
- ipertensione non controllata

# Major Bleeding Definition

Palareti G et al. Iscoat Study 1996

Fatal intra-cranial (documented by imaging); ocular (with blindness); articular; retroperitoneal; if surgery or angiographic intervention are necessary to stop bleeding; haemoglobin drop of 2 g/dL or need for transfusion of ≥2 blood units

ISTH 2005

Fall in haemoglobin of 2 g/dL or transfusion of 2 or more units of blood, bleeding that is symptomatic in a critical organ (intra-cranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular or peri-cardial, or intra-muscular with compartment syndrome) or fatal

## Clinically Relevant non Major Bleeding

All bleeding episodes that were clinically relevant but did not qualify as major bleeding (e.g., epistaxis that required an intervention or spontaneous macroscopic hematuria).

The van Gogh Investigators. N Engl J Med, 2007

## Minor Bleeding

All bleeding episodes that cannot be defined ad MB or CRNMB

# Eventi emorragici minori

Epistassi
Gengivorragia
Emorragia congiuntivale
Microematuria
Ecchimosi
Ematomi muscolari di piccole dimensioni
Metrorragie

## Che fare?

-Possono essere sintomatiche di iperdosaggio: verificare
-Correggere condizioni facilitanti locali
-Limitare la sospensione del trattamento per non esporre il paziente ad un aumento del rischio tromboembolico

# Farmaci anti Vitamina K

- § Warfarin (emivita 36 - 42 ore)
- § Acenocumarolo (emivita 9 ore)
- § Fenprocumone (emivita 84 ore)*

* non disponibile in Italia

# 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 |

# VITAMINA K1 (Konakion®)

DOSE RACCOMANDATA: 10 mg in 100 mL di soluzione fisiologica in 30’

VANTAGGI
- Antidoto specifico
-Rari gli effetti collaterali
-Basso costo
-Ampia disponibilità

LIMITI
-Tempi di reverse 12-24 ore

# PLASMA FRESCO CONGELATO (FFP)

DOSE RACCOMANDATA: 15 mL/Kg (3-4 Unità per un peso medio di 70 Kg) (*)

VANTAGGI
-Contiene tutti i fattori vitamina K dipendenti
-Basso costo, facile accessibilità e ampio utilizzo

LIMITI
-Tempi di attesa per la disponibilità per effettuare prove di compatibilità ABO, riscaldamento e infusione
- Rischio di sovraccarico di volume
-Possibili reazioni allergiche
-Rischio di emodiluizione con aggravamento del sanguinamento
-Rischio di Transfusion-related Acute Lung Injury

(*) è richiesto il consenso come tutti gli emoderivati

# CONCENTRATI DI COMPLESSO PROTROMBINICO (CCP)

VANTAGGI
Rari gli eventi avversi
Non rischi infettivi (virus inattivati)

LIMITI
Costi elevati
Scarsa conoscenza e uso limitato da timori di effetto pro-trombogeno
Mancanza di disponibilità immediata in molti PS

# CONCENTRATI DI COMPLESSO PROTROMBINICO (CCP)

Emoderivati ottenuti da un pool di plasma di donatori.
In un piccolo volume in forma liofila sono concentrati i fattori del complesso protrombinico la cui sintesi epatica è inibita dai farmaci AVK.

Sono disponibili 2 tipi:
A 3 fattori (II, V e X)
A 4 fattori (II, V, X e VII)

Modalità di somministrazione e dosaggio:
Flaconi da 20 mL da ricostruire con solvente e infondere in 15-20' (*)
20 UI/Kg di peso corporeo se INR<2.0
30 UI/Kg di peso corporeo se INR 2.0 - 4.0
40 UI/Kg di peso corporeo se INR 4.0 – 5.9
50 UI/Kg di peso corporeo se INR >6.0

(*) è richiesto il consenso come tutti gli emoderivati

# CONCENTRATI DI COMPLESSO PROTROMBINICO (CCP)

Controllare INR dopo 10’ dalla fine dell’infusione

Se INR<1.5 reverse concluso
Se INR >1.5 ripetere un’infusione

Nel paziente con Emorragia Maggiore severa se l’INR non è prontamente disponibile, iniziare l’infusione alla dose di 20 UI/kg in attesa del risultato

# Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding

## A Randomized, Plasma-Controlled, Phase IIIb Study

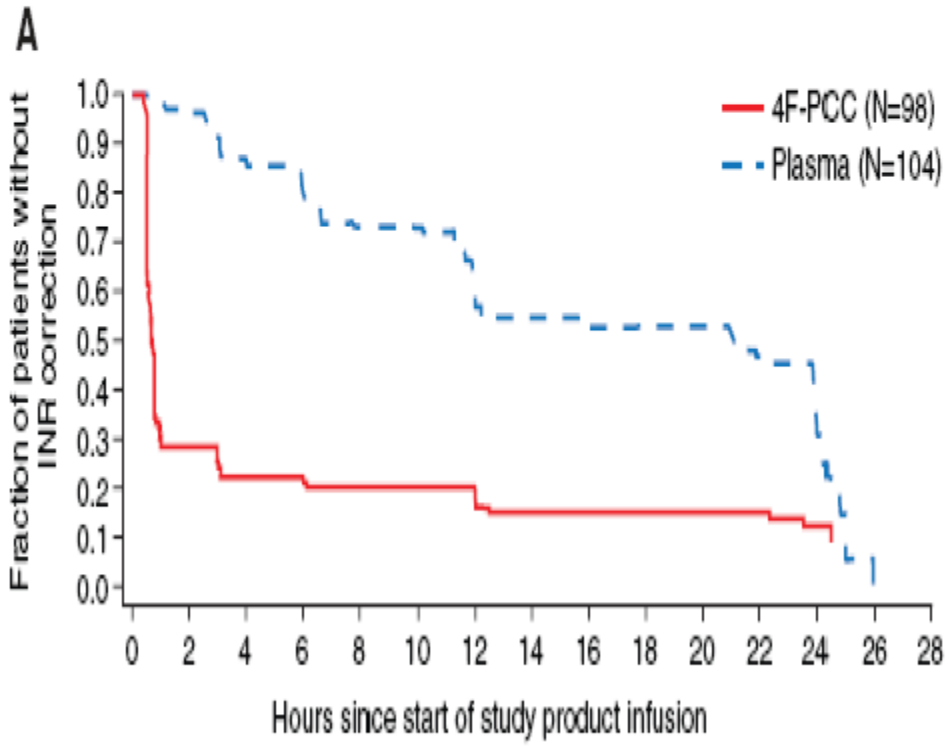



**Table 7. Rapid INR Reduction (Intention-to-Treat Efficacy Population)**

| | No. (%) of Patients [95% CI] | | |
|---|---|---|---|
| | 4F-PCC (n=98) | Plasma (n=104) | Difference 4F-PCC Minus Plasma, % (95% CI) |
| Rapid INR reduction* | 61 (62.2) [52.6 to 71.8] | 10 (9.6) [3.9 to 15.3] | 52.6† (39.4 to 65.9) |

Sarade R et al, Circulation 2013

# Anticoagulanti orali diretti (DOAC)

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| **Target** | **IIa (thrombin)** | **Xa** | **Xa** | **Xa** |
| **Hours to Cmax** | **1.25-3** | **2-4** | **3-4** | **1-2** |
| **CYP metabolism** | **None** | **32%** | **Minimal** | **NR** |
| **Bioavailability** | **6.5%** | **80-100%** | **50%** | **62%** |
| **Transporters** | **P-gp** | **P-gp/BCRP** | **P-gp/ BRCP** | **P-gp** |
| **Protein binding** | **35%** | **92-95%** | **87%** | **40-59%** |
| **Half-life** | **12-14h** | **9-13h** | **8-15h** | **8-10h** |
| **Renal elimination** | **80%** | **33%** | **~25%** | **~50%** |
| **Linear PK** | **Yes** | **Yes** | **Yes** | **Yes** |

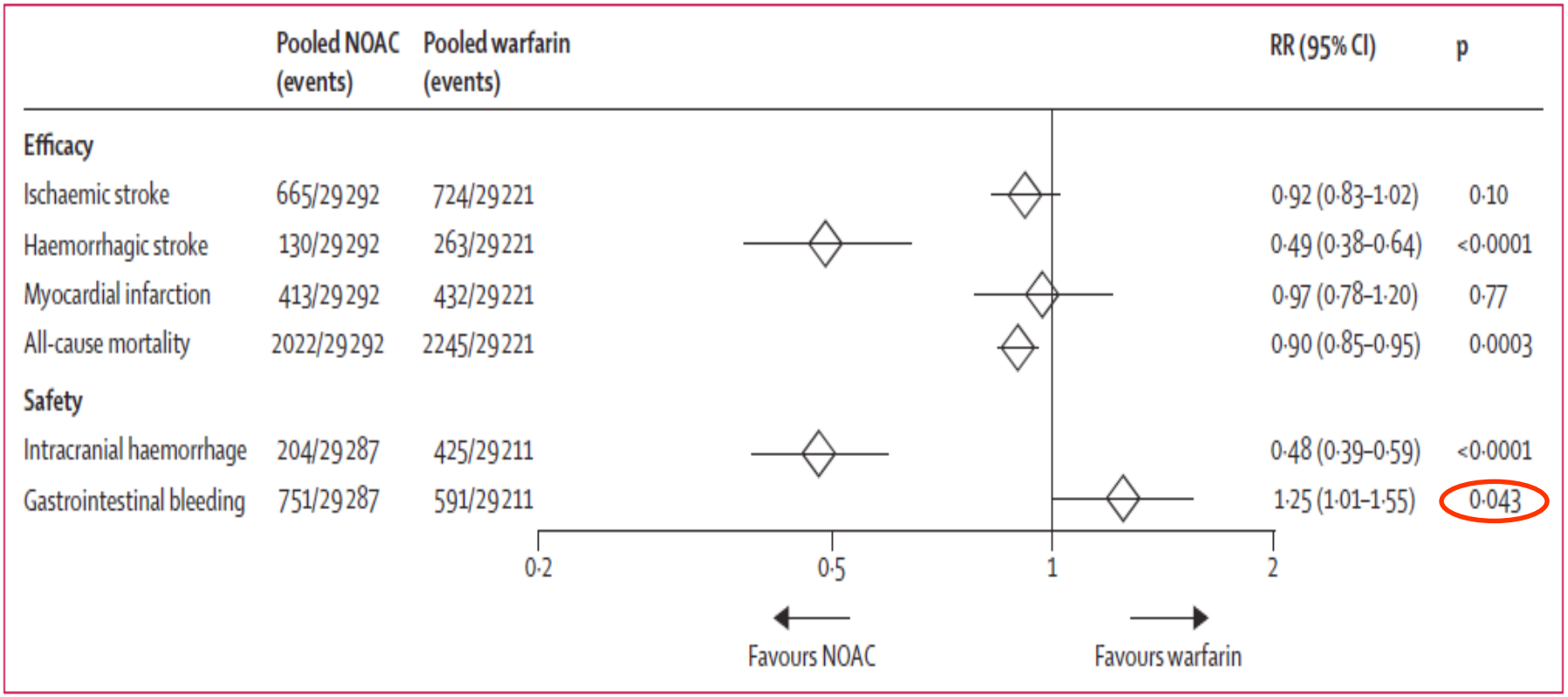
BCRP = breast cancer resistance protein
CYP = cytochrome P450; P-gp = P-glycoprotein
NR = not reported

# 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) |

# Secondary efficacy and safety outcomes




Dabigatran 150 mg bid

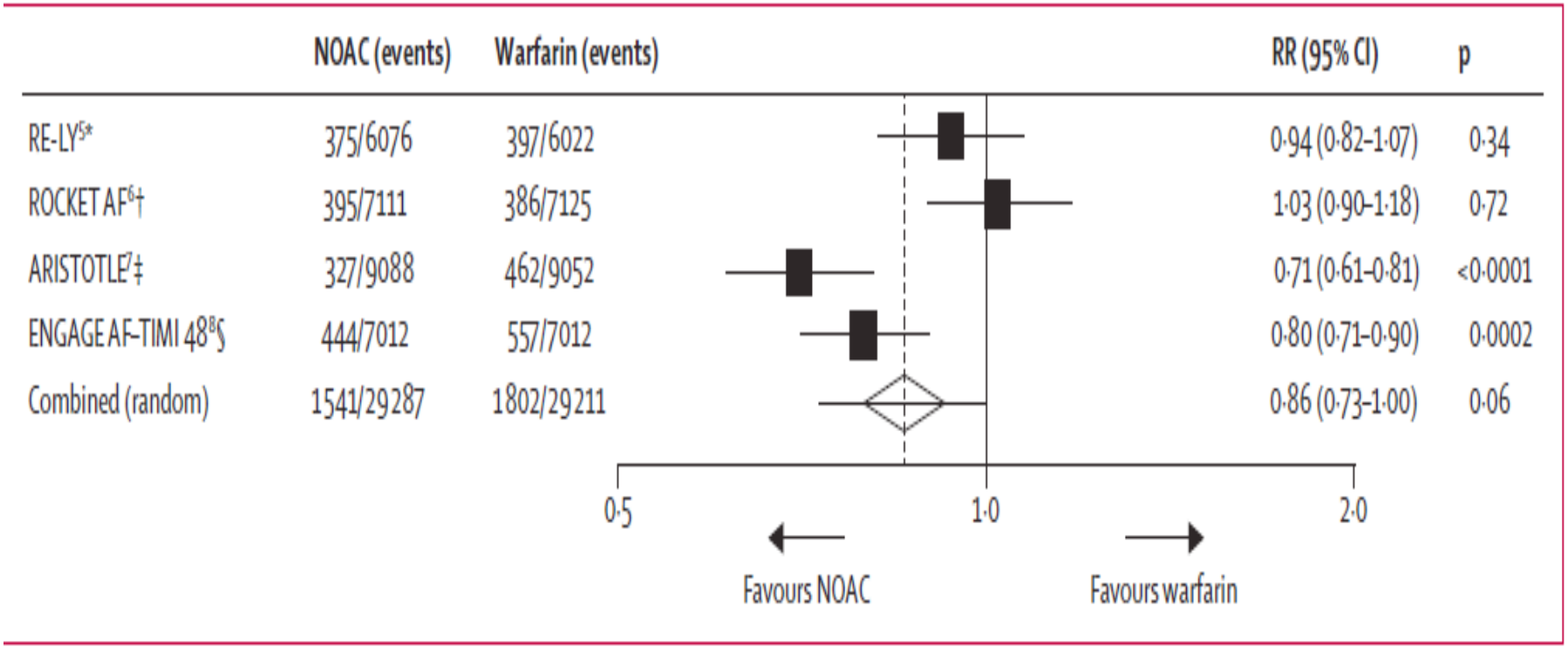
Rivaroxaban 20 mg od

Apixaban 5 mg bid

Edoxaban 60 mg od

Ruff C, Lancet 2013

# Major bleeding




Dabigatran 150 mg bid

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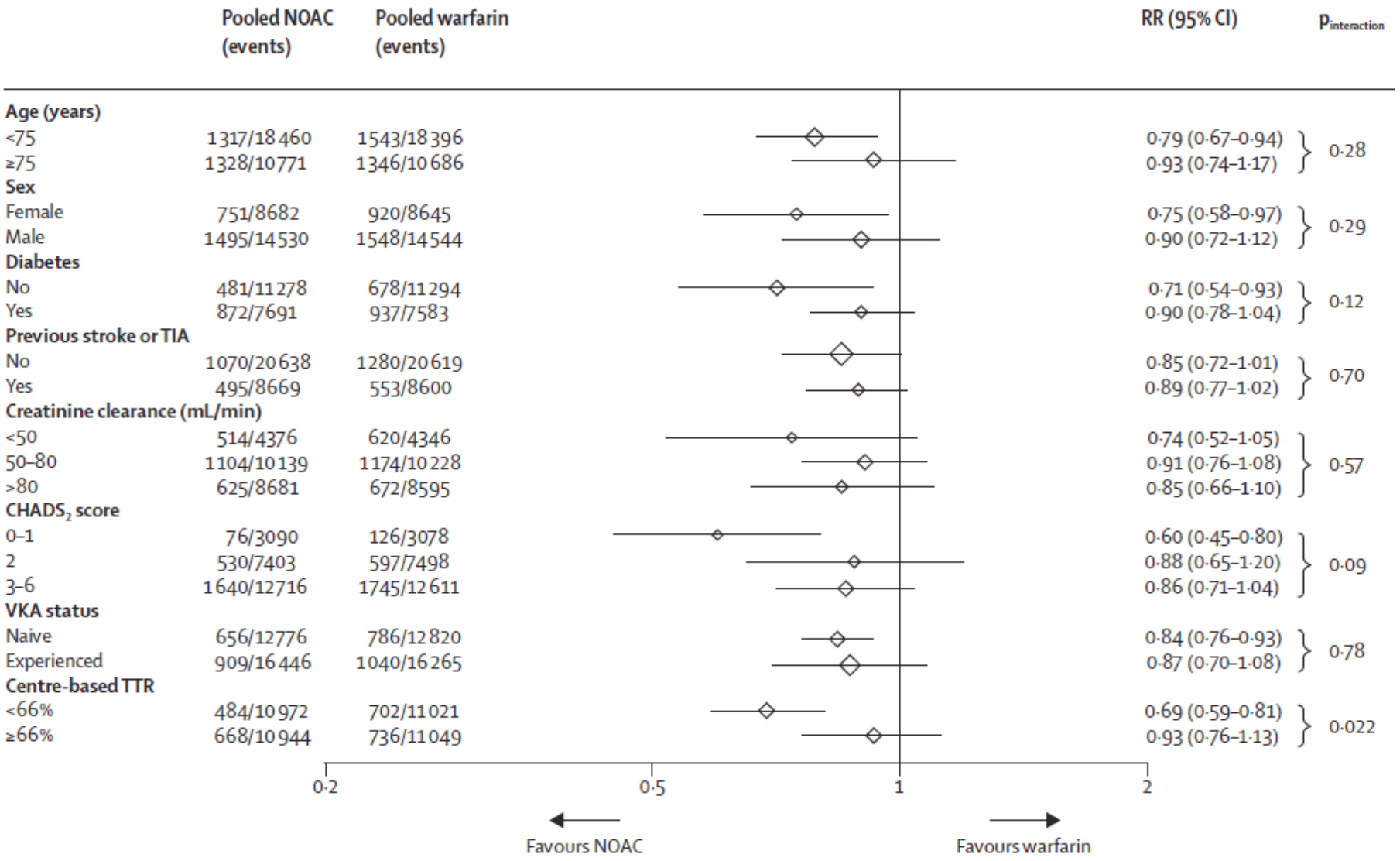
Edoxaban 60 mg od

Ruff C, Lancet 2013

# Major bleeding subgroups




Ruff C, Lancet 2013

# Interpretation

This meta-analysis is the first to include results from all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention in patients with atrial fibrillation. New oral anticoagulants showed a favourable risk–benefit profile with significant reductions in stroke, intracranial haemorrhage, and mortality with similar major bleeding as warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of the anticoagulants was consistent across a wide range of patients with atrial fibrillation. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

Ruff C, Lancet 2013

## Quanto tempo dovrebbe passare tra la sospensione dei NAO ed un intervento chirurgico elettivo ?

| Creatinina clearance | Dabigatran | | Apixaban | | Rivaroxaban | |
|---|---|---|---|---|---|---|
| | Chirurgia a basso rischio | Chirurgia ad alto rischio | Chirurgia a basso rischio | Chirurgia ad alto rischio | Chirurgia a basso rischio | Chirurgia ad alto rischio |
| ≥80 ml/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| 50-80 ml/min | ≥36 h | ≥72 h | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| 30-50 ml/min | ≥48 h | ≥96 h | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| 15-30ml/min | Non indicato | Non indicato | ≥36 h | ≥48 h | ≥36 h | ≥48 h |

Heidbuchel H et al. Europace, 2013

**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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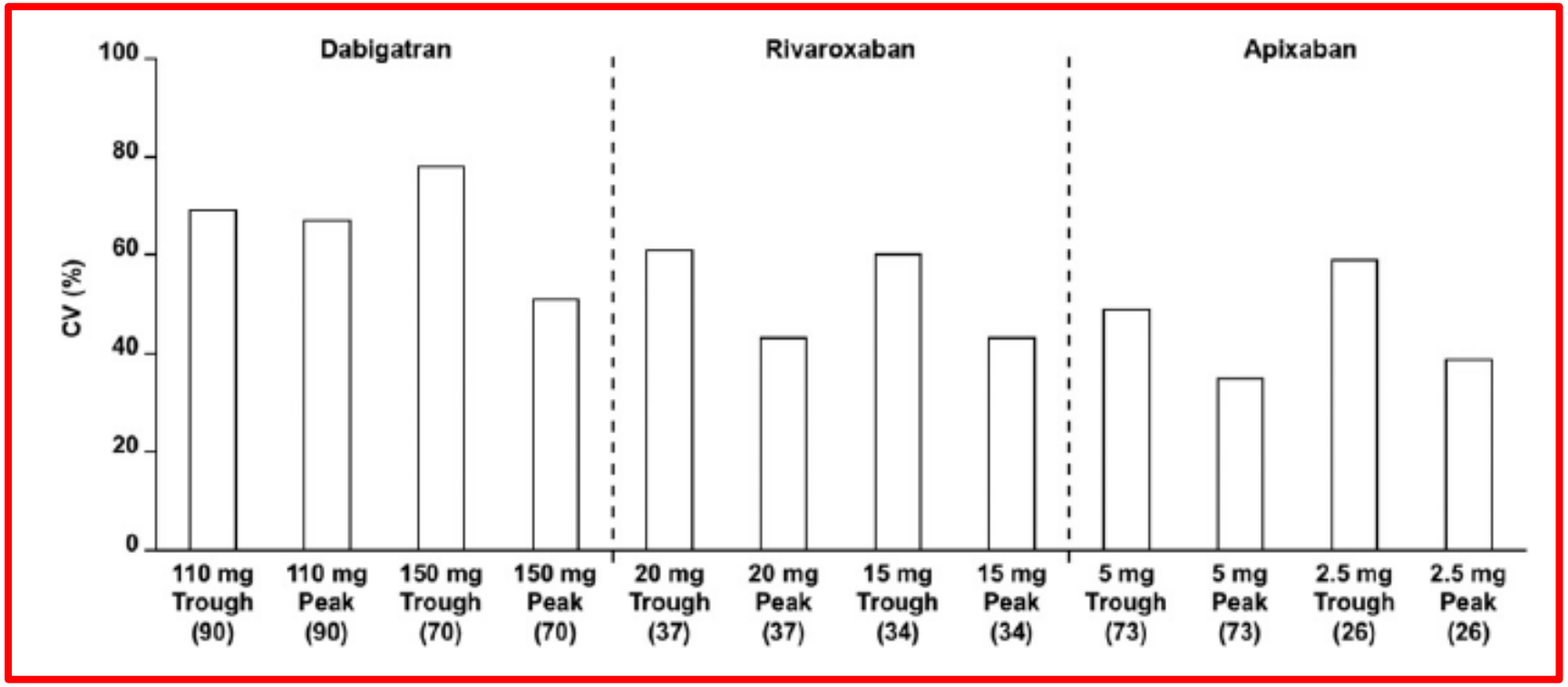
Testa S et al, JTH 2016

# DOAC: INTER-INDIVIDUAL VARIABILITY




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

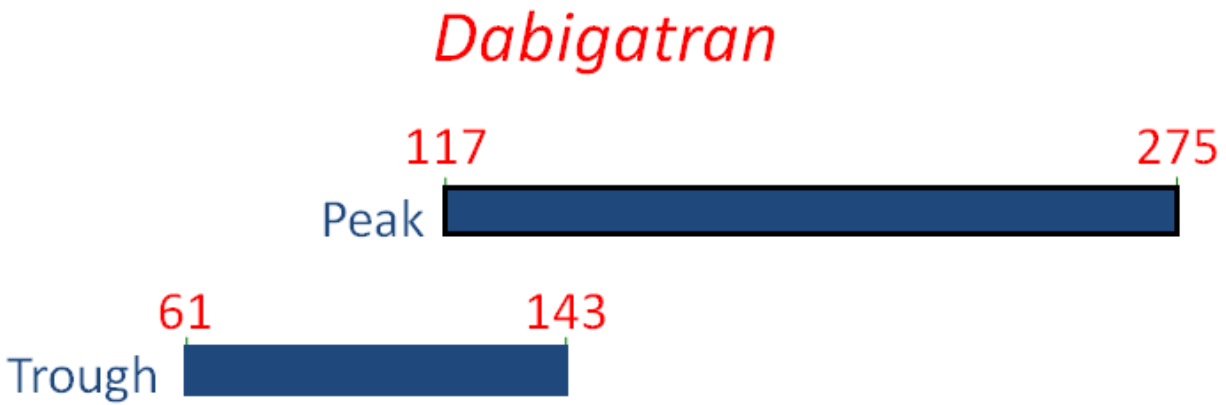
***Tabella 1.*** *Intervalli di concentrazioni plasmatiche nei pazienti in trattamento con NAO*

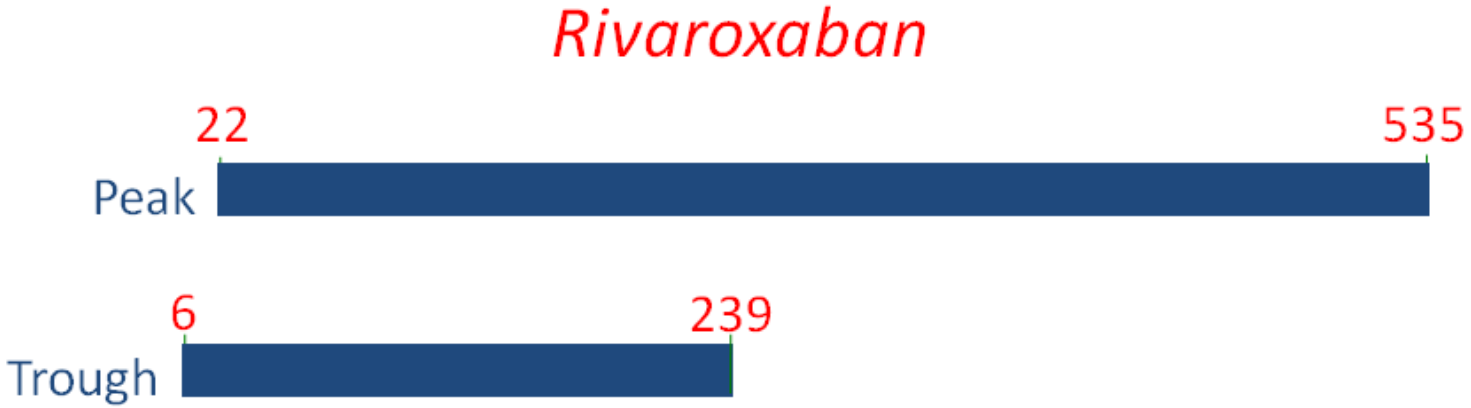
| **Farmaco** | **Punto di valle** (prima della assunzione successiva) | **Punto di picco** (2-3 ore dall'ultima assunzione) |
|---|---|---|
| Dabigatran (150 mg/2 volte die) | 40-215 ng/ml* | 74-383 ng/ml* |
| Dabigatran (110 mg/2 volte die) | 28-155 ng/ml* | 52-275 ng/ml* |
| Rivaroxaban (20 mg/die)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

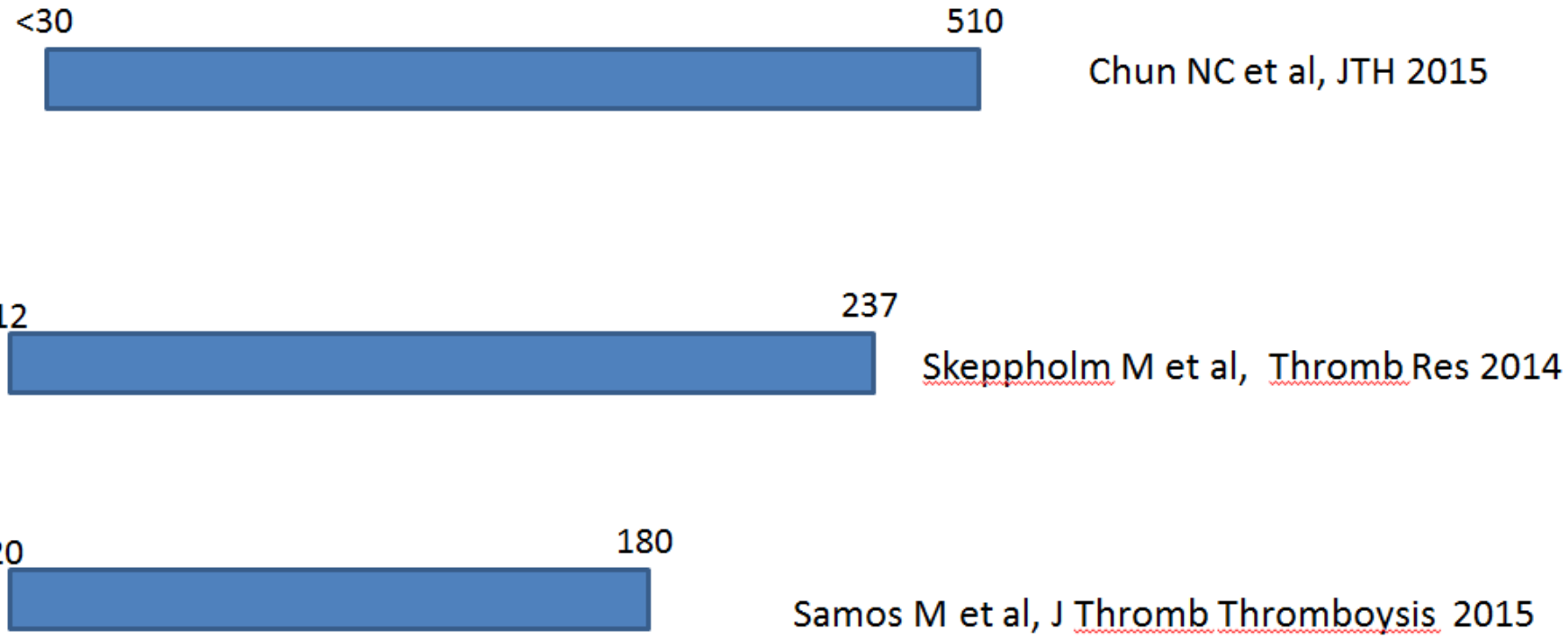
## *Data from Clinical trials*



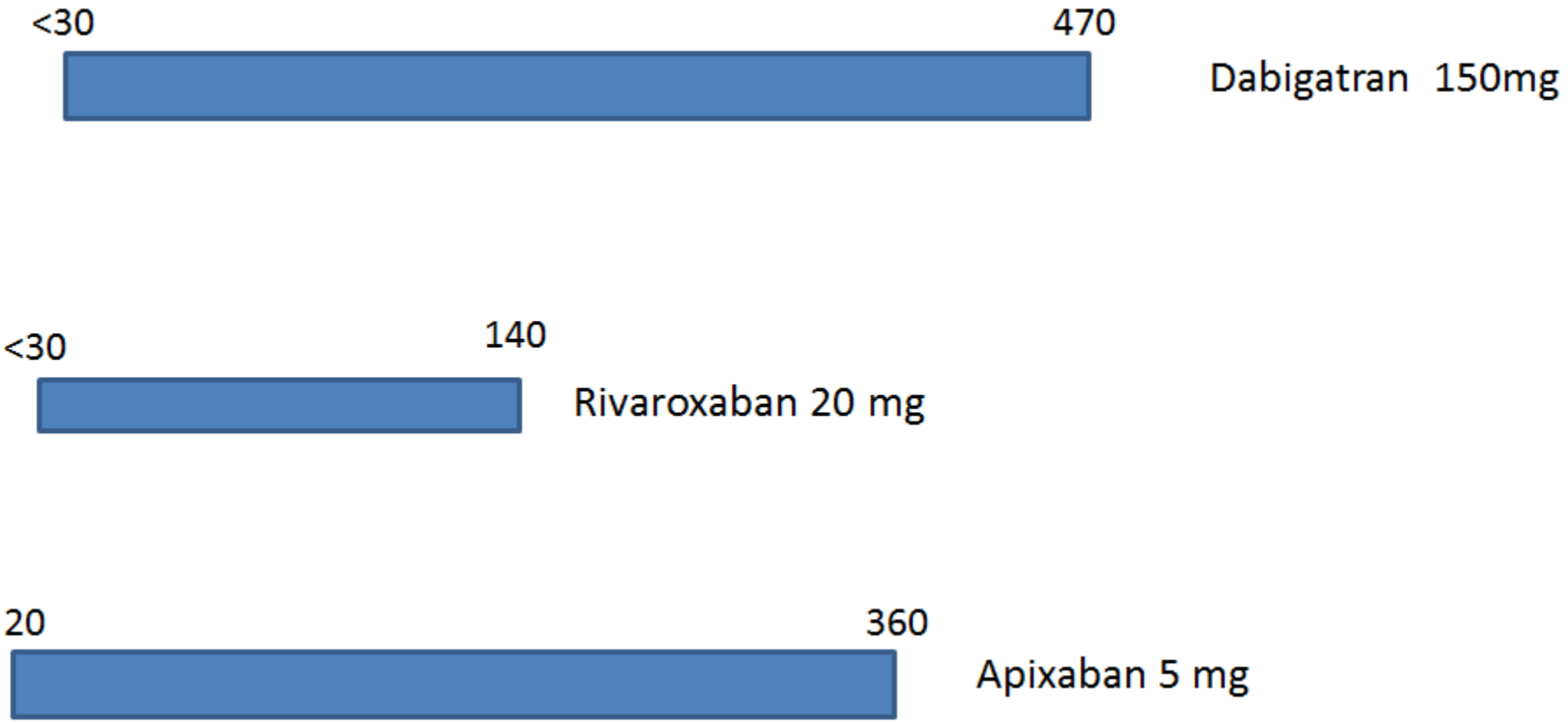

***[ng/mL (min-max)]***

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



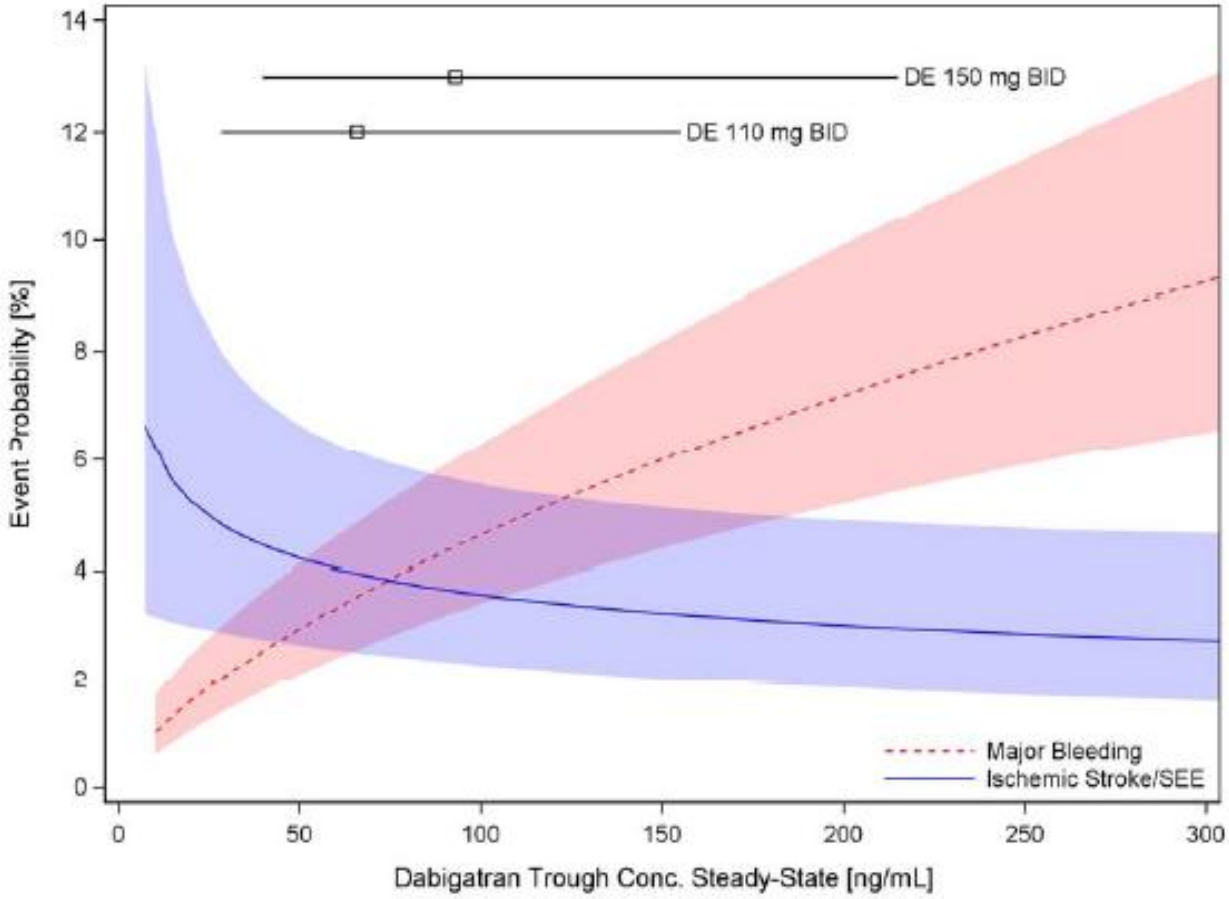

*[ng/mL (min-max)]*

# 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) |

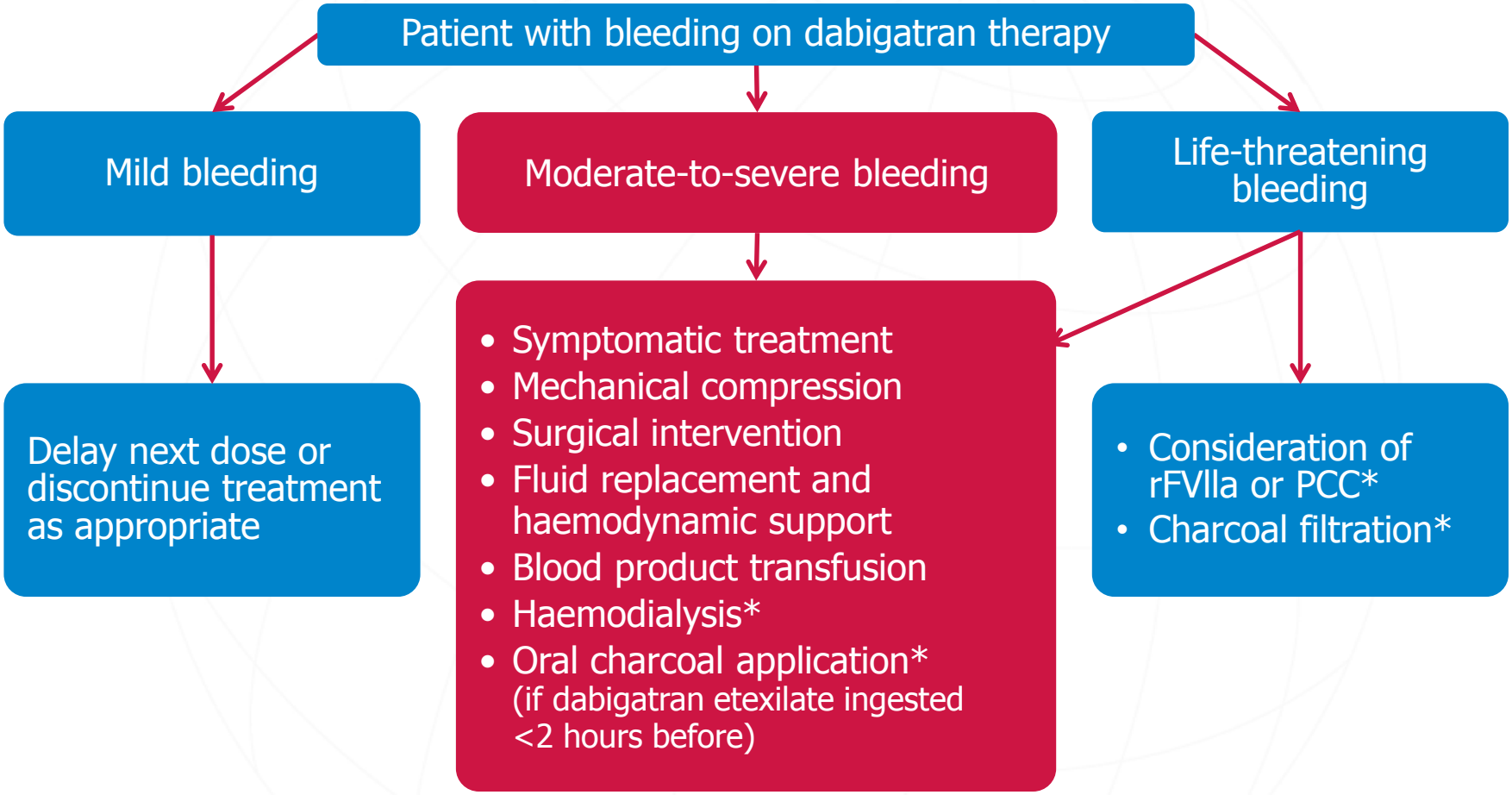
LG EHRA ESC 2015

# 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) |

LG EHRA ESC 2015

# Managing bleeding complications in patients treated with NOACs




*For dabigatran. Recommendation based only on limited non-clinical data; no experience in volunteers or patients

rFVIIa = recombinant activated clotting Factor VIIa;
PCC = prothrombin complex concentrates (non-activated or activated)

van Ryn J et al. Thromb Haemost 2010;103:1116–27

# Management options:

Supportive mesures

Specifical reversal strategies

# Support for circulation and oxygenation

Intravenous access

- Volume expanders
- Other hemodynamic support
- Oxygen on mask or nasal prongs
- Red cellsc oncentrates
- Correct acidosis
- Counteract hypothermia

# Reduction of drug exposure

- Delay or stop next dose of DOAC
- Hold antiplatelet therapy
- Active charcoal orally if last dose < 3 h
- Hemodialysis (dabigatran)

# Local measures

- Compression of bleeding source (if possible)
- Apply topical thrombin or fibrin glue
- Invasive maneuvers
- Coiling or regional embolization
- Surgical intervention

# Activated Charcoal

- In vitro it absorbs 99.9% of dabigatran suspended in acidic water
- its adminstration should be done within 1–2 h after intake of the drug
  (van Ryn et al. Thromb Haemost 2010)

# Improvment of hemostasis

- Correct hypocalcemia
- Antifibrinolytic agents
- Desmopressin – if platelet inhibition has occurred
- Platelet transfusion – for thrombocytopenia or if clopidogrel or prasugrel has been given
- Fresh frozen plasma for dilution coagulopathy
- Prothrombin complex concentrates (PCC)
- Activated PCC (FEIBA)
- Recombinant activated Factor VII

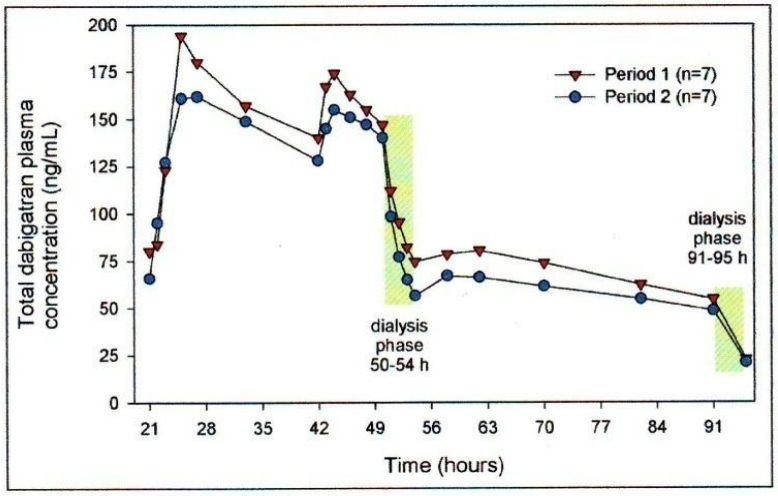
# Hemodialysis and hemoperfusion

- Only for dabigatran (low protein binding)
- One study on patients on hemodialysis: hemodialysis after a single dose of dabigatran: 62% drug removed after 2 h and 68% after 4 h of dialysis
  (Stangier et al. Clin Pharmacokinet 2010)
- Successful and safe use of hemodialysis to remove dabigatran in several case reports
- However, difficult the insertion of central dialysis catheters in a patient fully anticoagulated (risk of bleeding)

# Dialisi

- Basso legame di Dabigatran con le proteine plasmatiche (solo il 35% ha un legame con albumina) la dialisi con carbone attivato può rimuovere il 60% dei Dabigatran in 4 ore mentre
- Priva di efficacia nei pazienti in Rivaroxaban e Apixaban per il loro legame all'albumina) .
- La procedura è complessa , necessita di un catetere venoso centrale

  (femorale eco-guidato ) ma è tecnicamente possibile , centralizzando il paziente in strutture in cui è possibile un trattamento emodialitico in urgenza.
- Il trattamento dialitico in emergenza rappresenta attualmente l'unica efficace possibilità di ripristinare una sufficiente emostasi nel paziente con emorragia critica in trattamento con Dabigatran




Effective eliminationof Dabigatran by hemodialysis: a fase 1 single centre study
In patients with end stage renal disease. (7 pts)
Khadzhynov D. et al. Thrombosis and Haemostasis 2013

# Prothrombin complex concentrate

- Non-activated:
  - '4-factor-concentrates' contain Factors II, VII, IX, and X (e.g. Beriplex, Octaplex, Proplex T, Cofact)
  - '3-factor-concentrates' contain lower amounts of Factor VII (e.g. Prothrombinex-HT, Profilnine and BEBULIN)
- Activated:
  - FEIBA VH contains Factors II, IX, X and protein C mainly in non-activated forms and Factor VII mainly in the activated form

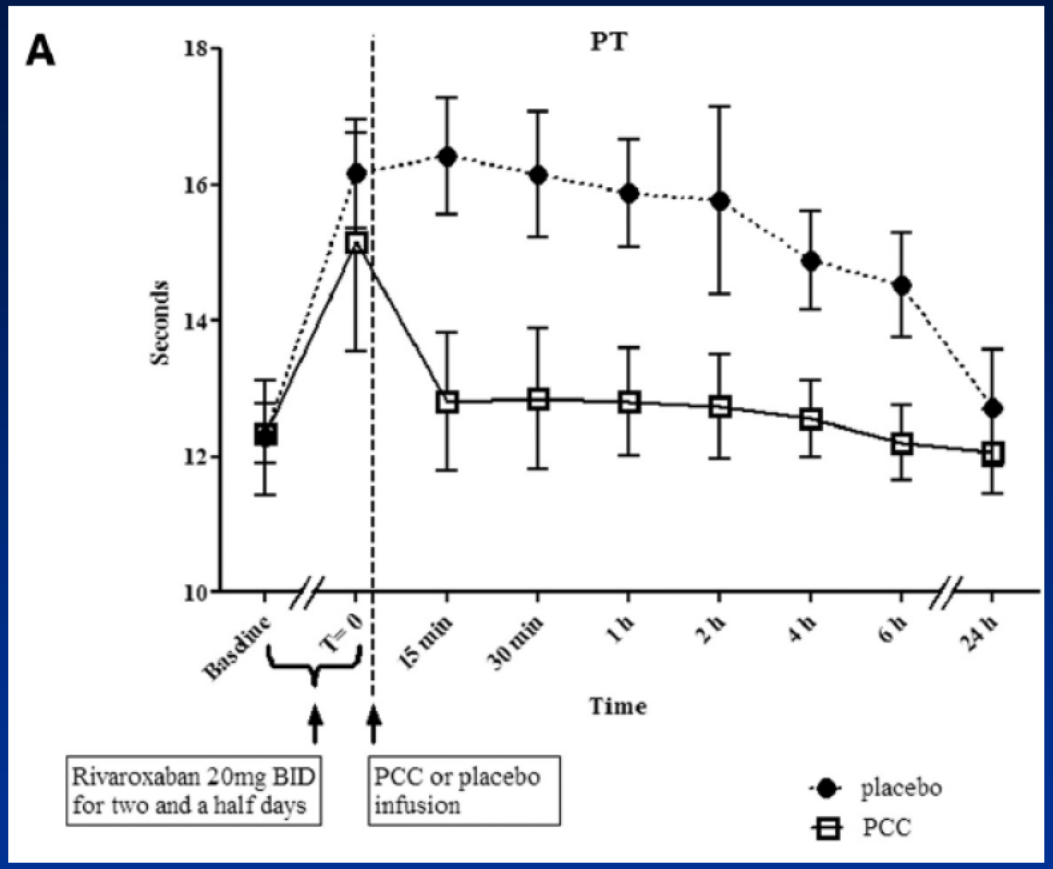
# PCC

- Given at a dose of 50 IU/kg normalized the rivaroxaban induced prolongation of prothrombin time
(Eerenberg et al. Circulation 2011)

- No study evaluated the effect of PCC in patients on rivaroxaban with active bleeding

- A small case series reported failure of PCC to manage massive dabigatran-associated bleeding
(Lillo-Le Louetet al. Thromb Haemost2012)

# Prothrombin complex concentrate




(from Eerenberg et al., Circulation 2011)

EXPERT OPINION

Expert Opin. Pharmacother. [Early Online]

# Clinical management of rivaroxaban-treated patients

Gualtiero Palareti†, Walter Ageno, Annamaria Ferrari, Alessandro Filippi, Davide Imberti, Vittorio Pengo, Andrea Rubboli & Danilo Toni

2013

**Bleeding patient**

→ Information on personal characteristics and anticoagulant therapy: indication, rivaroxaban dosage, time of the last dose assumption, concomitant therapies, previous bleeding episodes

→ Routine blood test, measurement of rivaroxaban activity, CrCl

→ **Minor bleeding** →

- Possible local measures
- Tranexamic ac. 1 g per os 3 times/day
- Delay or temporarily discontinue the next doses in presence of rivaroxaban activity
- Look for local bleeding sources
- Avoid a prolonged dose reduction or treatment discontinuation if not strictly necessary

EXPERT OPINION

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# Clinical management of rivaroxaban-treated patients

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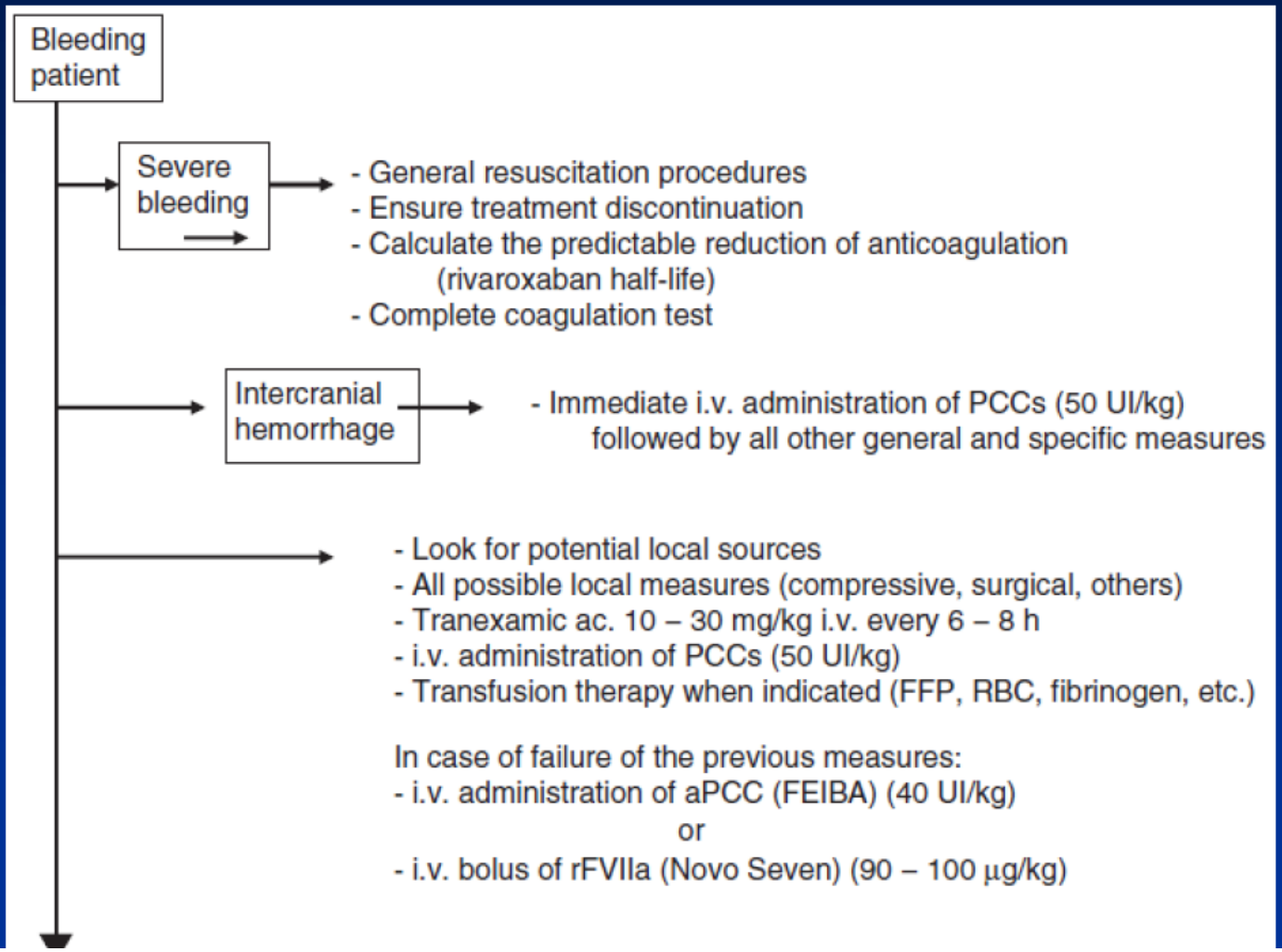


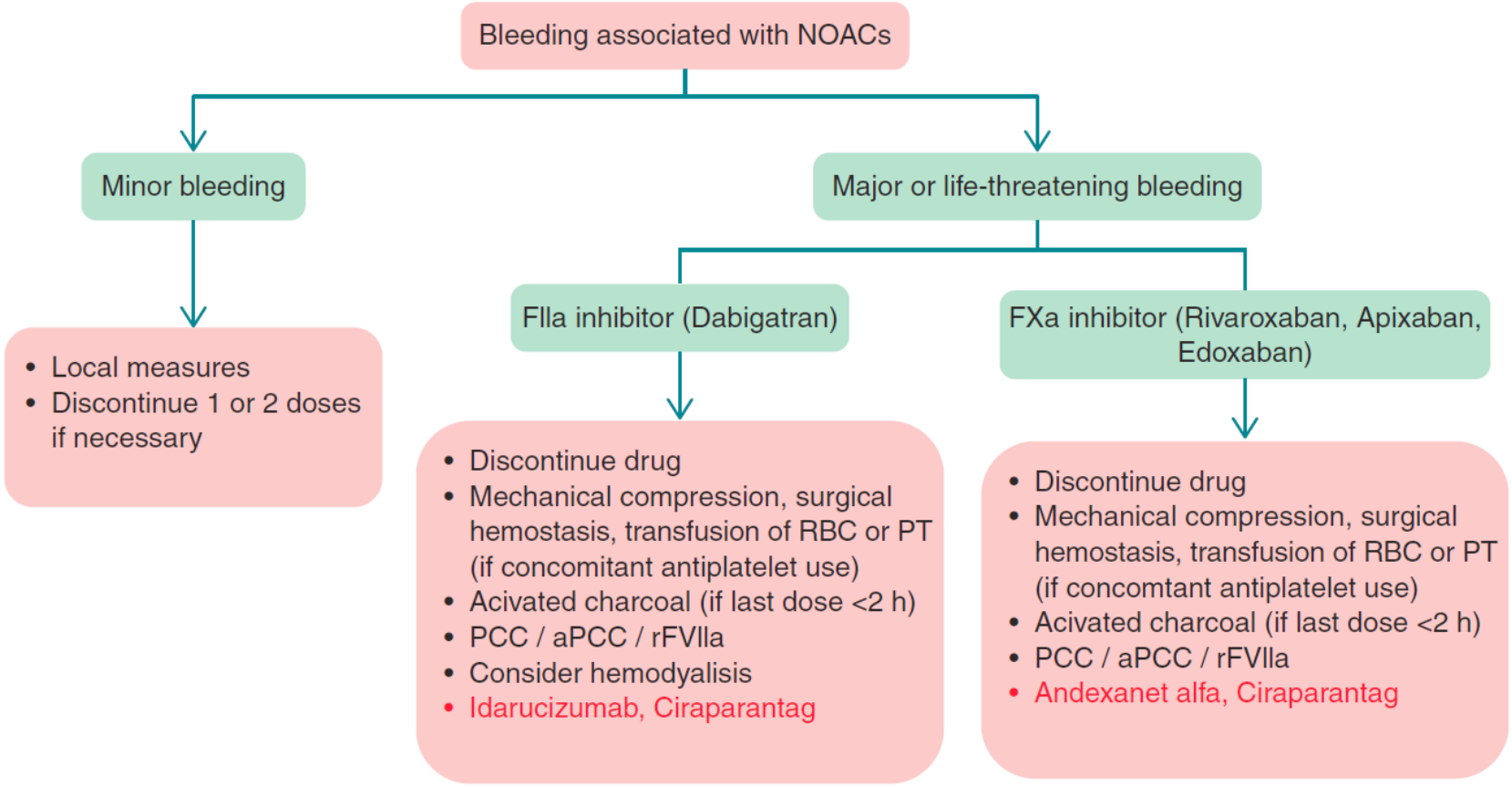
# ANTIDOTI

# 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) |

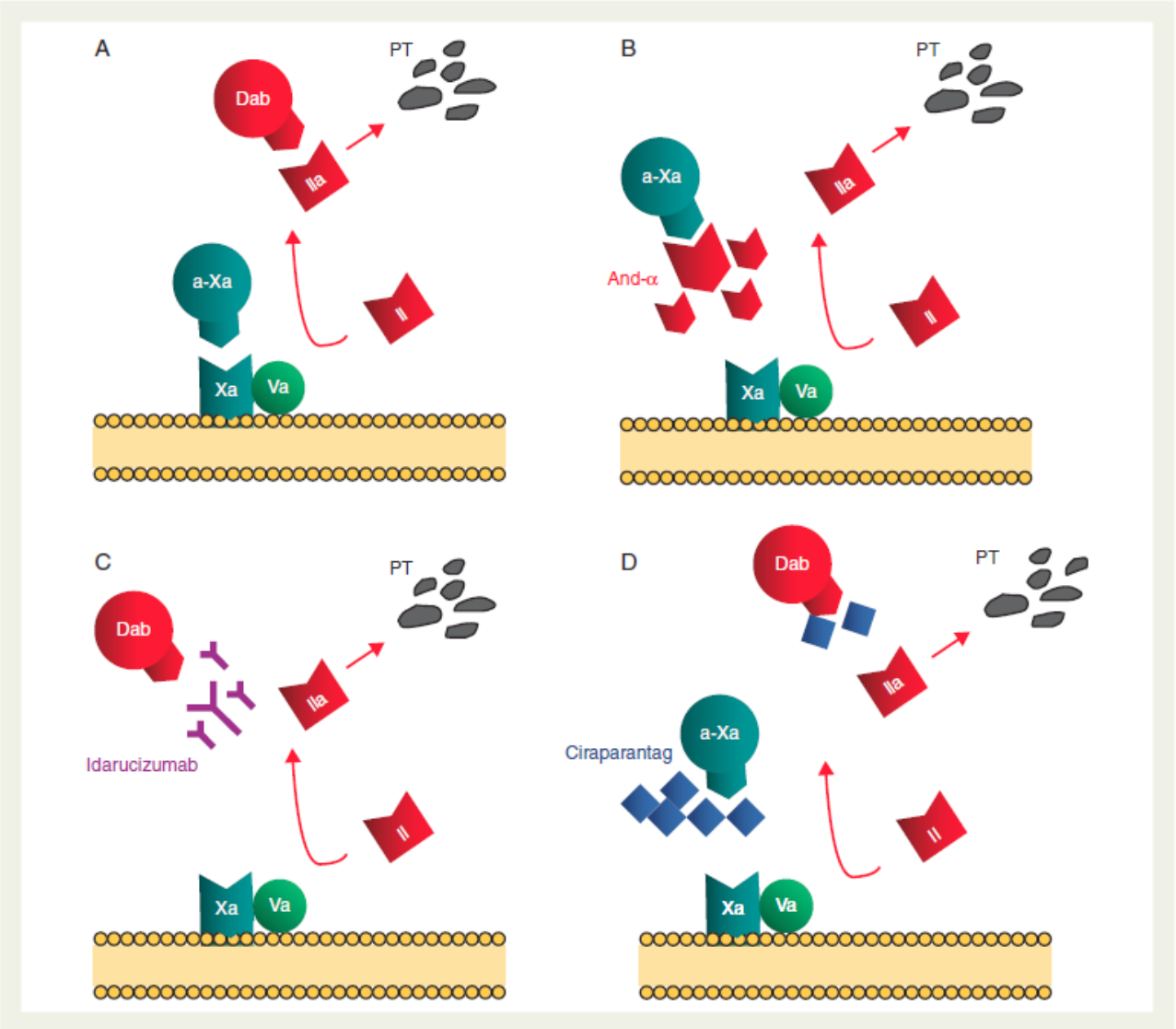
Enriquez A, Europace 2015

# Management of bleeding associated with NOACs




Enriquez A, Europace 2015

# Mechanism of NOACs and their antidotes




Enriquez A, Europace 2015

# Comparison of specific antidotes for NOACs

| Agent | Idarucizumab (Boehringer Ingelheim) | Andexanet alfa (Portola Pharmaceuticals) | Ciraparantag (Perosphere) |
|---|---|---|---|
| Target | Dabigatran | FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban, Betrixaban) | Dabigatran, FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban, Betrixaban), Fondaparinux, heparin |
| Structure | Humanized antibody fragment | Recombinant human FXa, catalytically inactive | Synthetic small molecule (512 Da) |
| Mechanism | Non-competitive binding to Dabigatran with 350 times greater affinity than thrombin | Binds competitively to direct FXa inhibitors | Binds to heparins and oral FXa and IIa inhibitors through hydrogen bonding |
| *In vitro* studies | Reversal of prolonged clotting time induced by Dabigatran | Complete and dose-dependent reversal of Rivaroxaban, Apixaban and Betrixaban in human plasma | Complete reversal of anti-Xa activity of Rivaroxaban, Apixaban and Edoxaban |
| Animal models | Reduction in blood loss and mortality in a porcine liver trauma model | Reduced blood loss induced by Rivaroxaban in mouse (tail transection) and rabbit (liver laceration) models | Decreased bleeding in a rat-tail transaction model |
| Clinical trials | Phase 1: Immediate, complete and sustained reversal of Dabigatran-induced anticoagulation in healthy humans<br>Phase 3: Ongoing (RE-VERSE AD) | Phase 1: Dose-dependent reversal of Rivaroxaban in healthy volunteers<br>Phase 2: Rapid reversal of Rivaroxaban and Apixaban. Ongoing trial with Edoxaban<br>Phase 3: Rapid reversal of Apixaban (ANNEXA-A). Ongoing trial with Rivaroxaban (ANNEXA-R) and planned trial with Edoxaban (ANNEXA-E) | Phase 1: Rapid and sustained reversal of edoxaban |

Enriquez A, Europace 2015

The NEW ENGLAND JOURNAL of MEDICINE

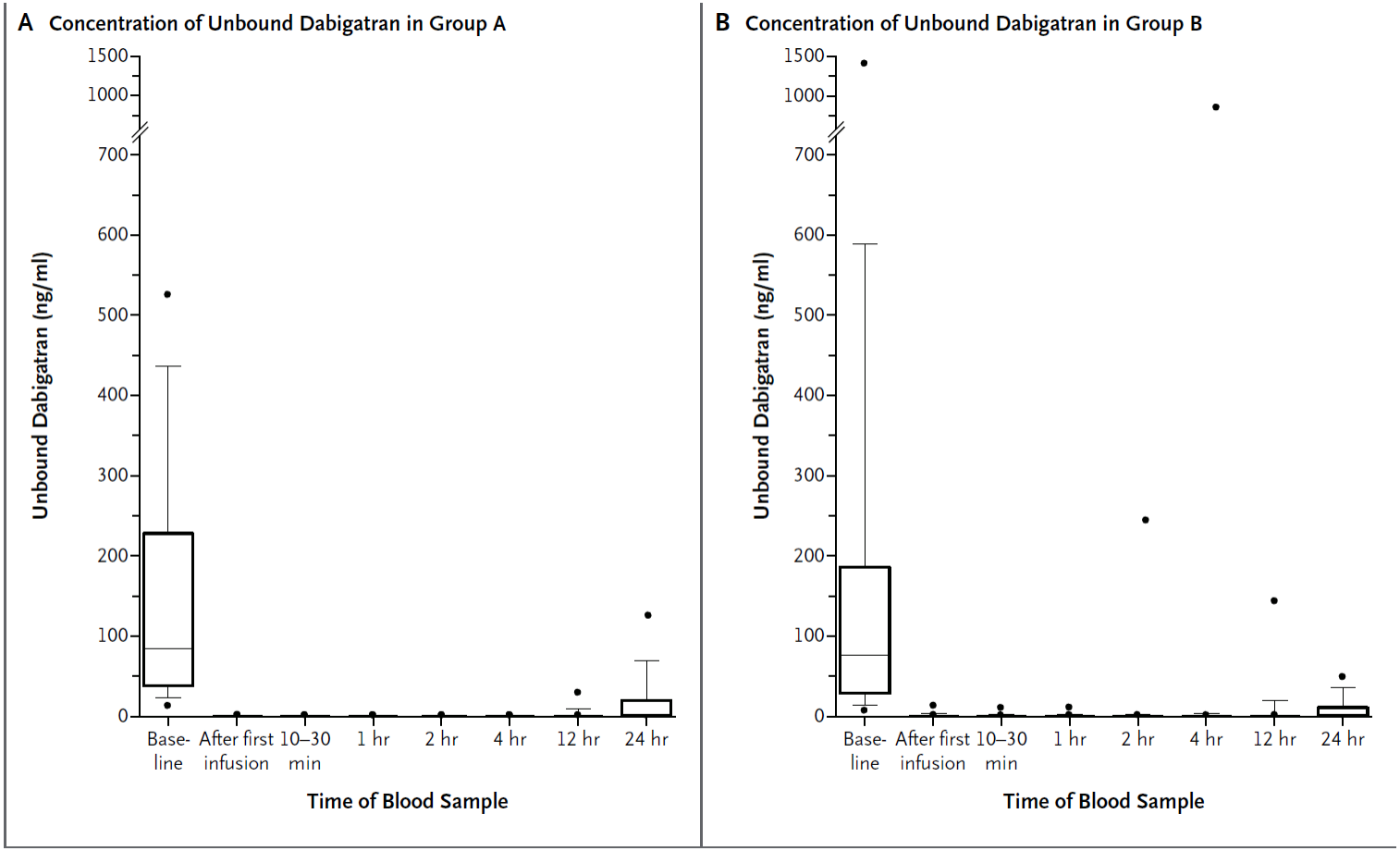
ORIGINAL ARTICLE

# 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.

Pollack V, NEJM 2015

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

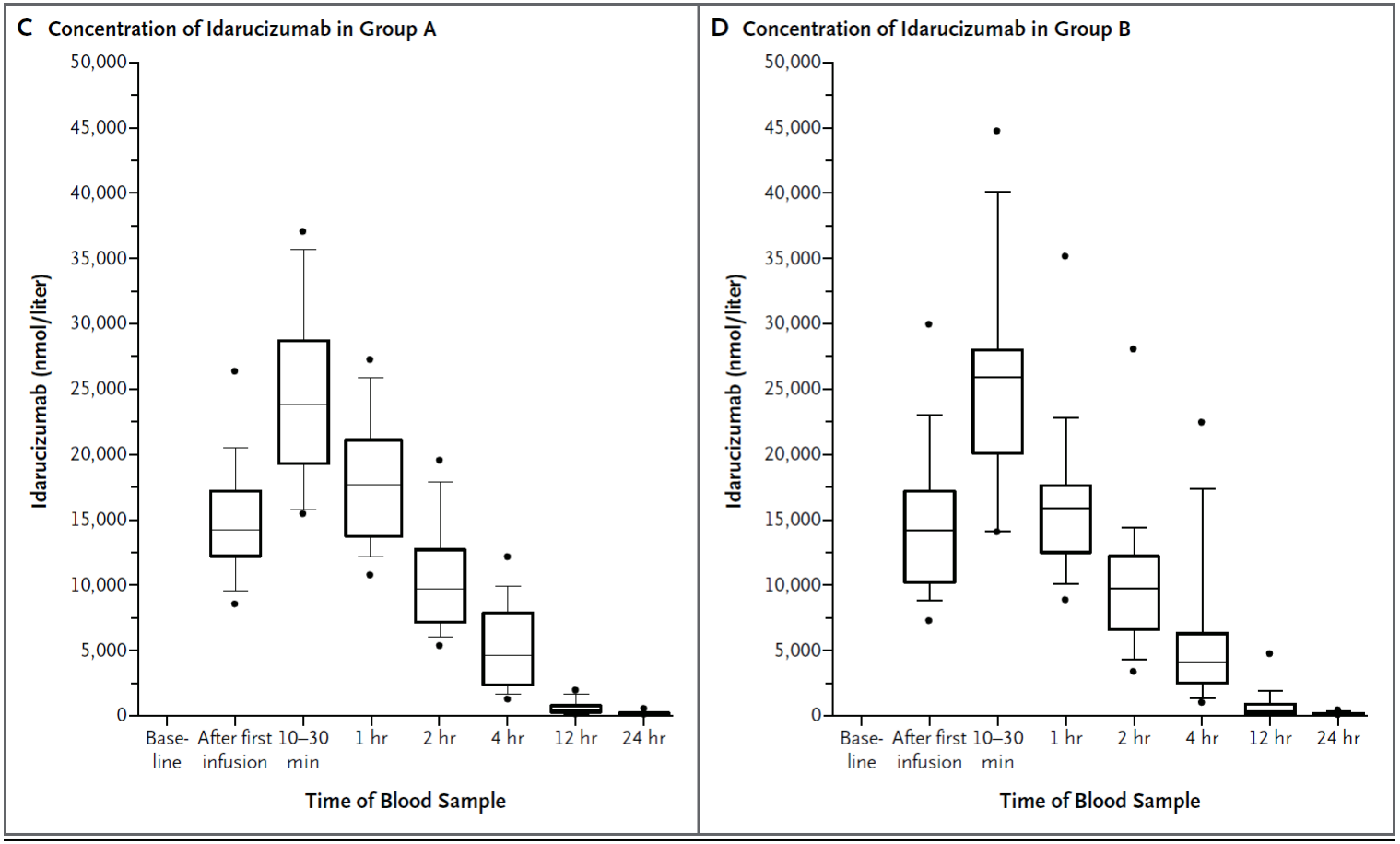



patients who had serious bleeding

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

- Thrombotic events occurred in 5 patients
- 18 patients died

Pollack V, NEJM 2015

The NEW ENGLAND JOURNAL of MEDICINE

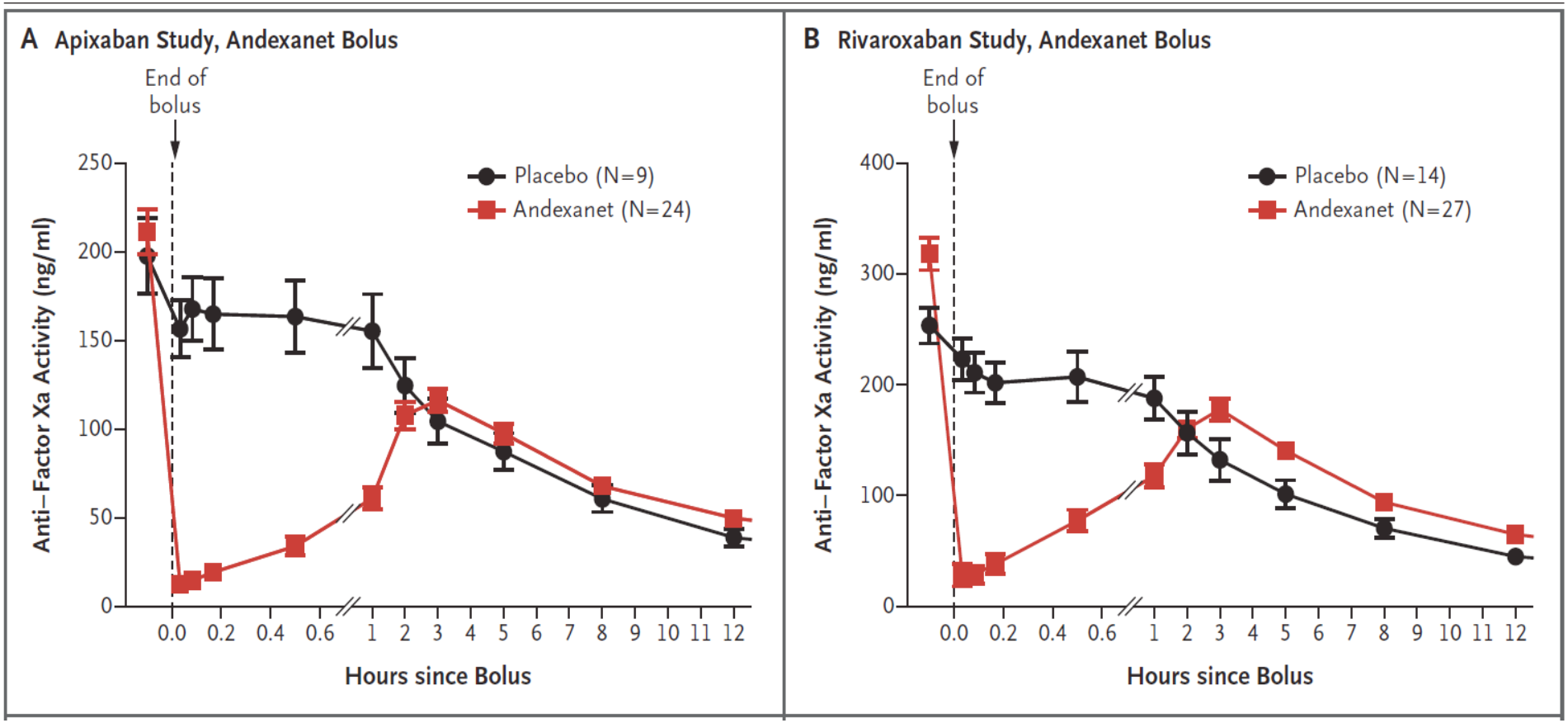
ORIGINAL ARTICLE

# 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

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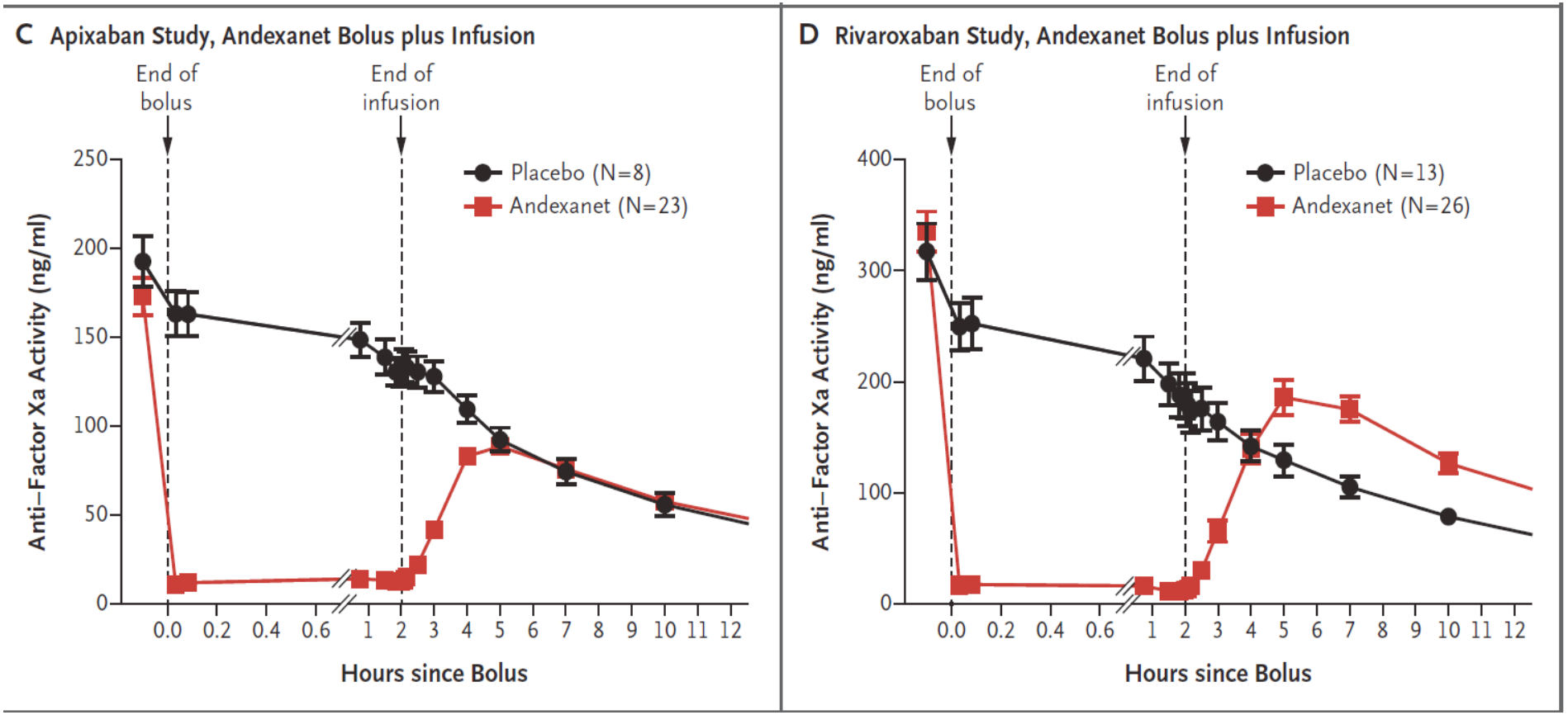
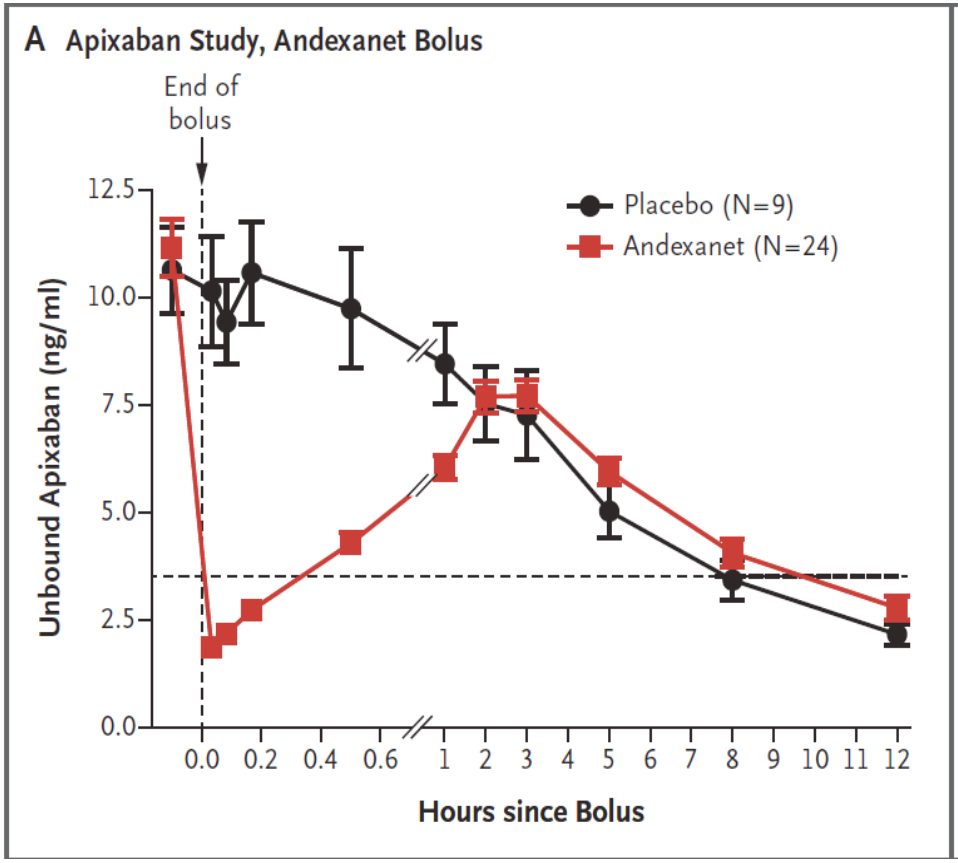
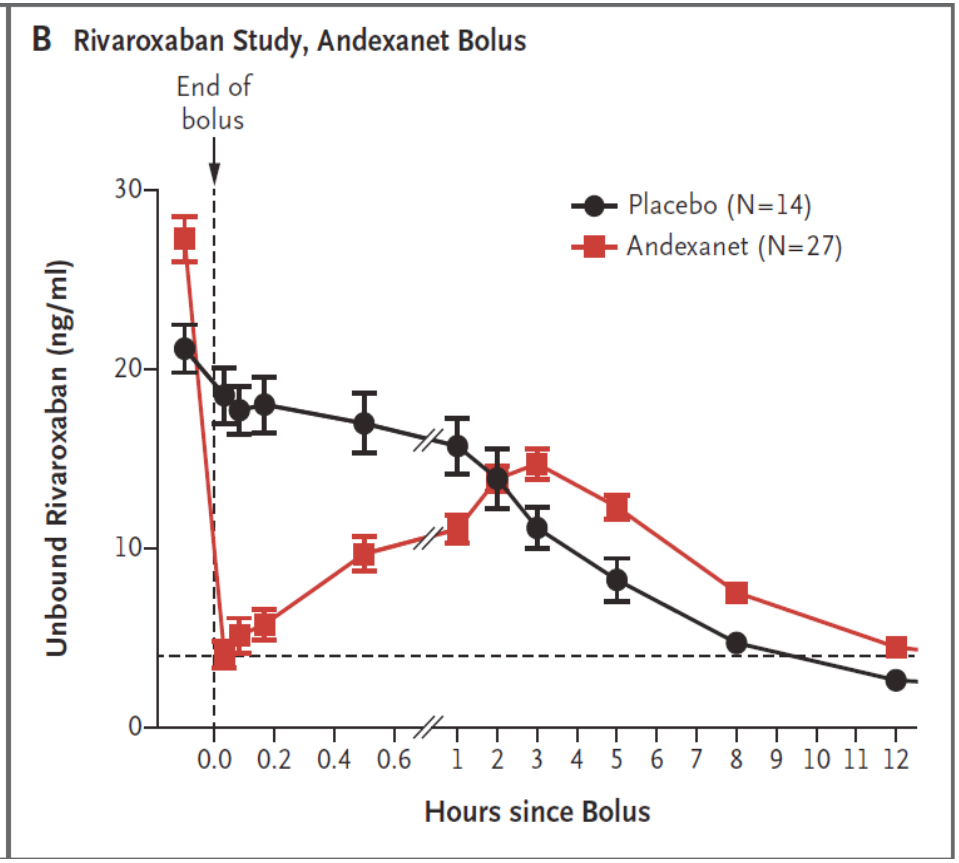



Siegal D, NEJM 2015

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



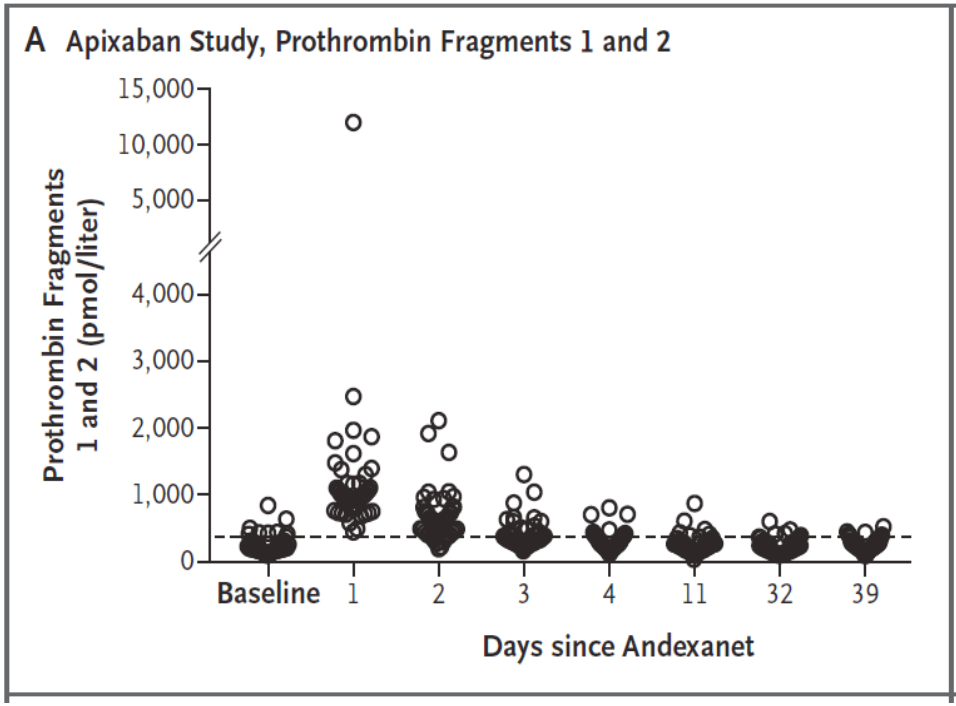

Siegal D, NEJM 2015

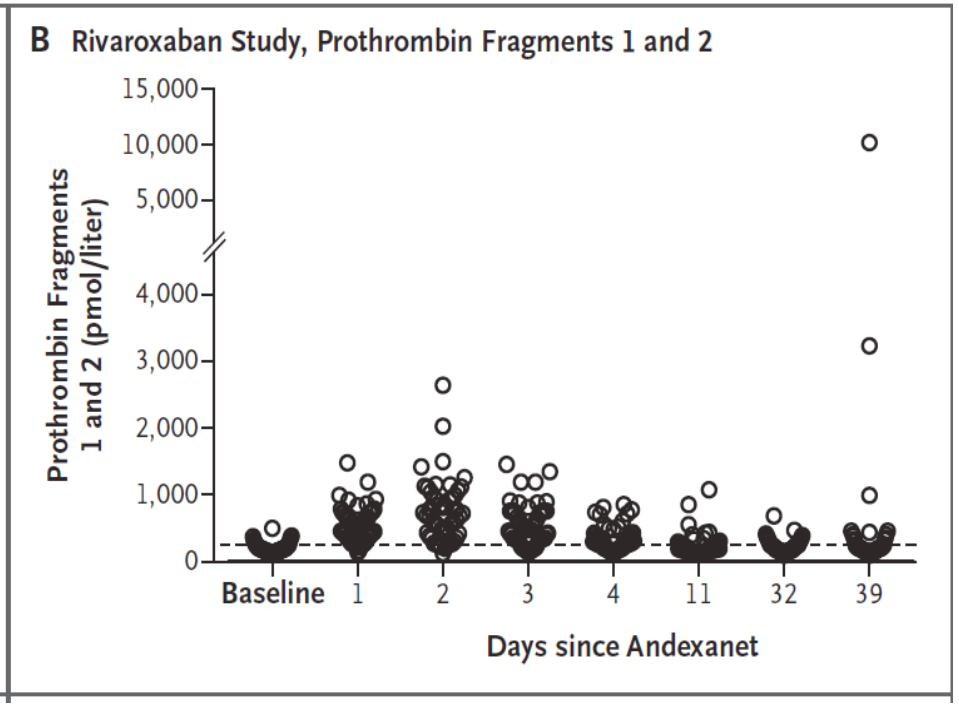
# Drug Related Events

| 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

# Prothrombin Fragments 1 and 2 and d-Dimer Levels before and after the Administration of Andexanet




Siegal D, NEJM 2015

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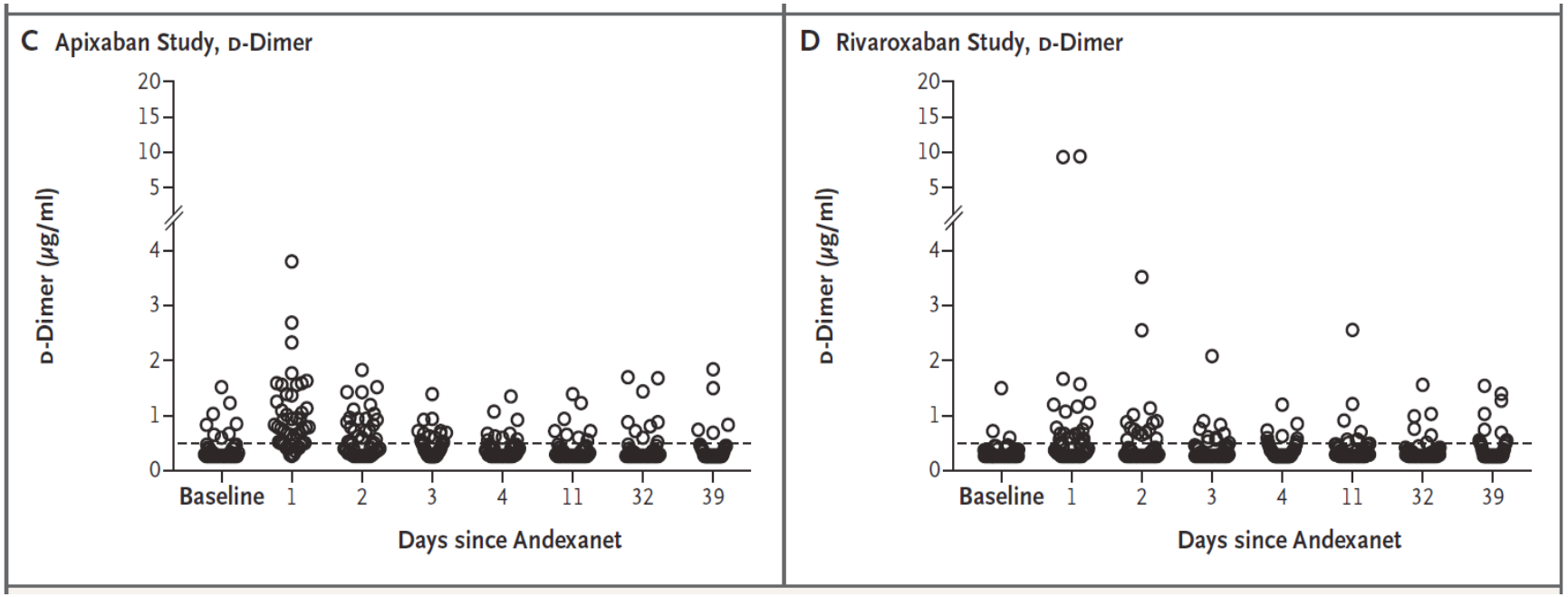


Siegal D, NEJM 2015

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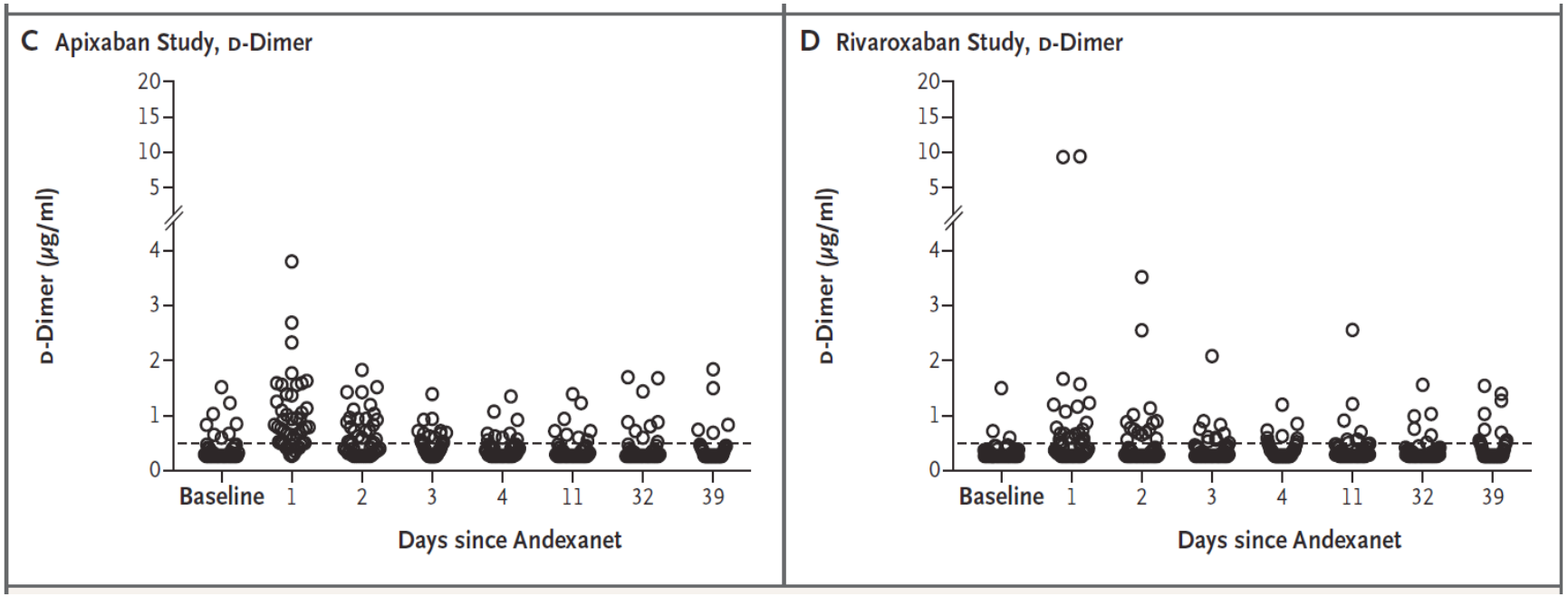


Siegal D, NEJM 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Safety Population (N=67) | Efficacy Population (N=47) |
|---|---|---|
| Age — yr | 77.1±10.0 | 77.1±10.1 |
| Male sex — no. (%) | 35 (52) | 24 (51) |
| White race — no. (%)† | 54 (81) | 36 (77) |
| Body-mass index‡ | 28.1±6.3 | 28.8±6.7 |

20/67 pazienti avevano concentrazione <75 ng/mL

Connoly S et al.2016

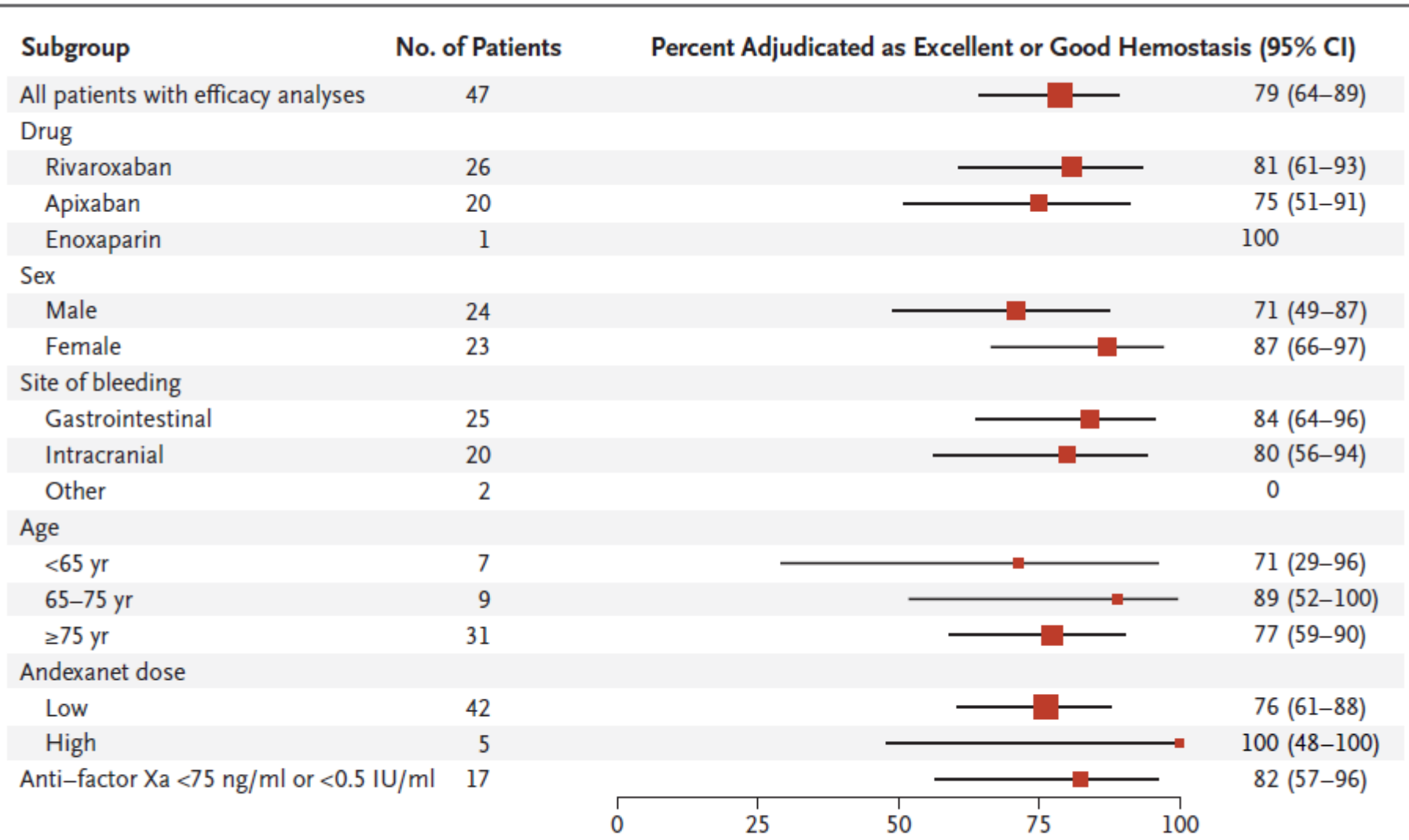


**Figure 2. Subgroup Analysis of Hemostatic Efficacy.**

Connoly S et al.2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Rivaroxaban patients
After the bolus administration, the median anti– factor Xa activity decreased by 89% (95% [CI], 58 to 94) from baseline
Apixaban patients
After the bolus administration the median anti– factor Xa activity decreased by 93% (95% CI, 87 to 94) from baseline

These levels remained similar during the 2-hour infusion.
Four hours after the end of the infusion, there was a relative decrease from baseline of 39% for rivaroxaban and of 30% for apixaban.
Twelve hours after the andexanet infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%; 95% CI, 64 to 89).

Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up.

Connoly S et al.2016

# 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?