



# La gestione delle emergenze con Rivaroxaban: quali test e come gestire le emorragie

Enrico Bernardi

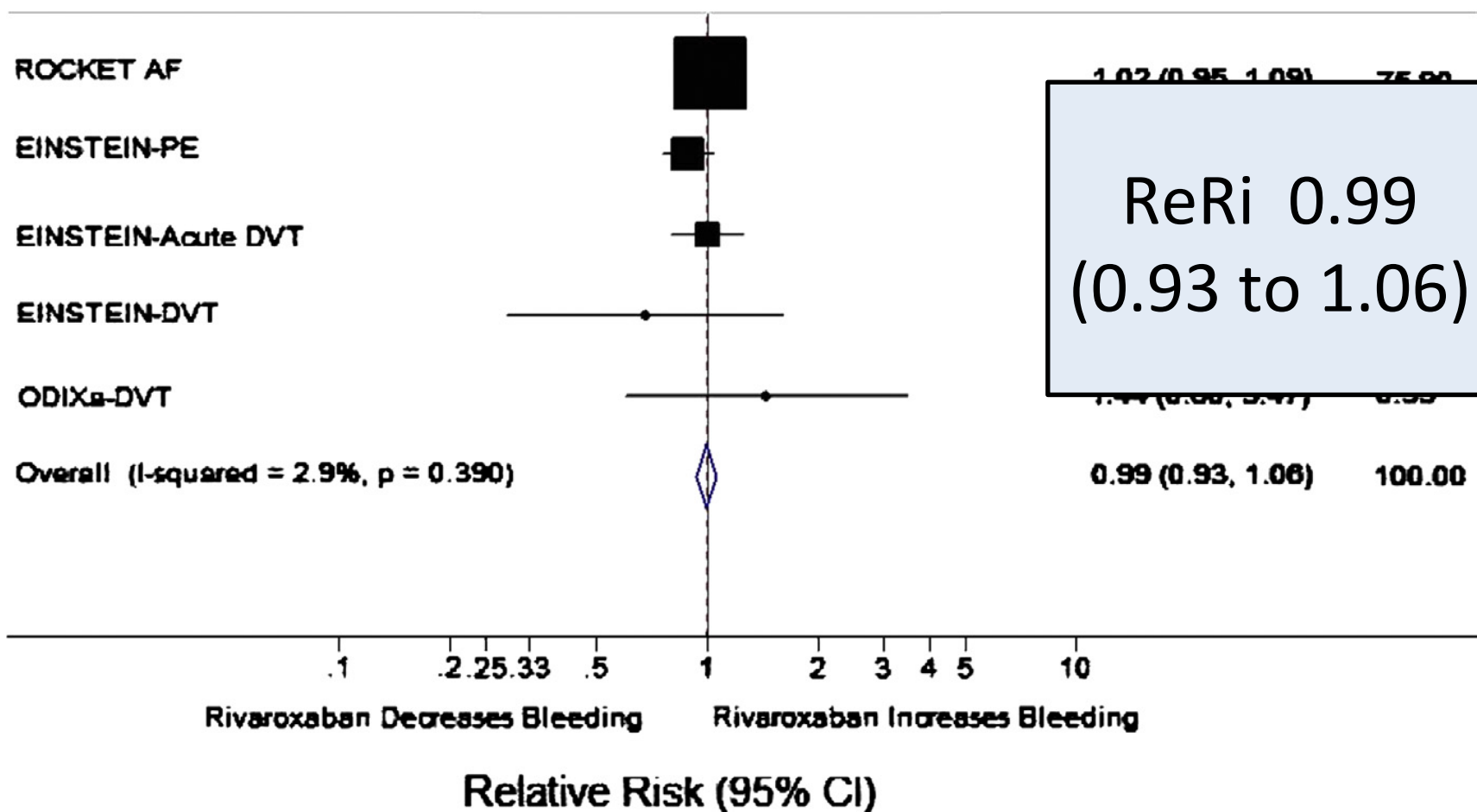


# Meta-Analysis of *Rivaroxaban* and Bleeding Risk

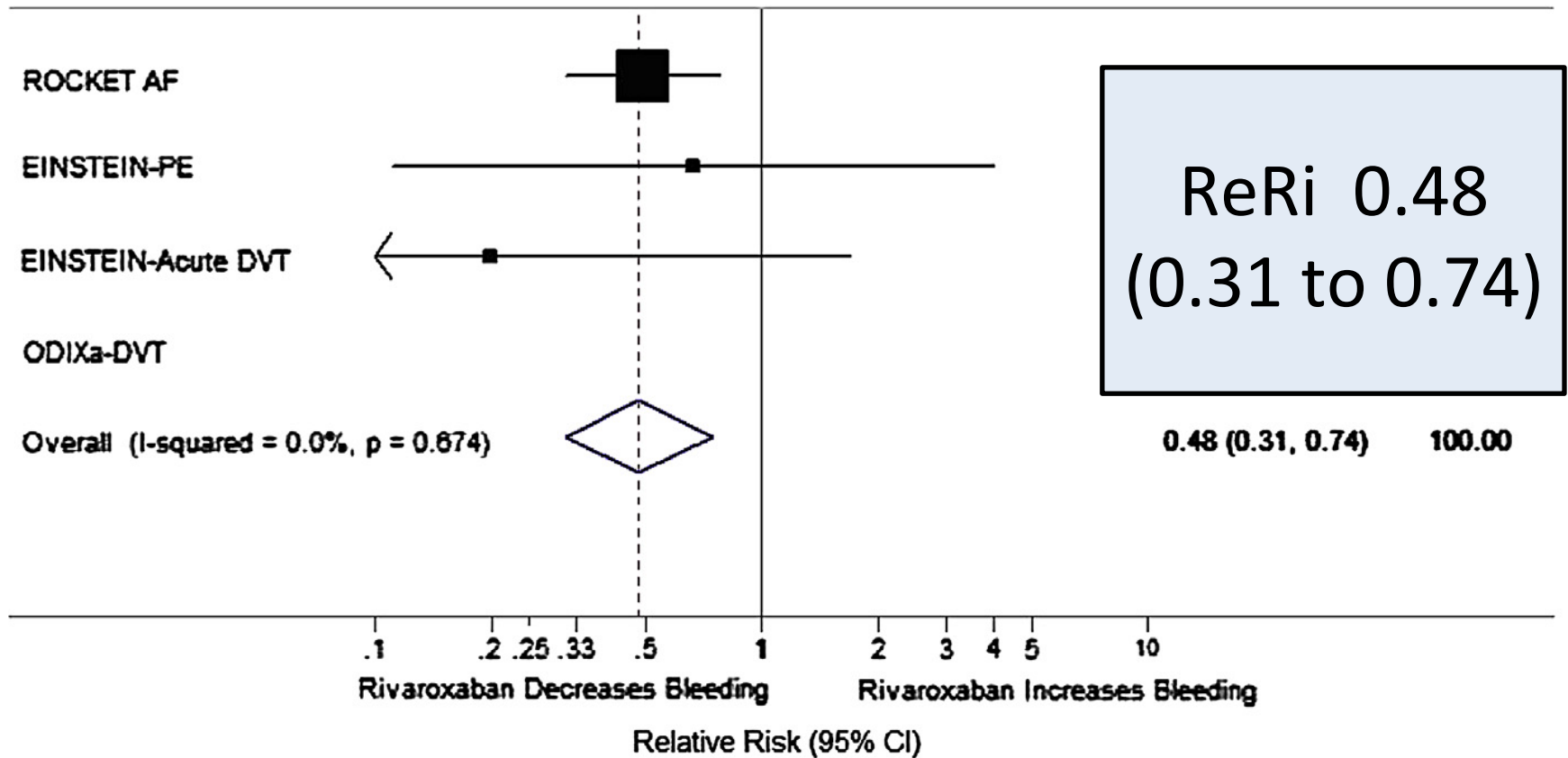
Guila Wasserlauf<sup>a,c</sup>, Sonia M. Grandi, MSc<sup>a</sup>, Kristian B. Fillion, PhD<sup>a</sup>,  
and Mark J. Eisenberg, MD, MPH<sup>a,b,c,\*</sup>

- 5 RCTs, >26.000 pazienti (nvAF, DVT, PE)
- Età (media/mediana): 58-73 anni
- Follow-up (mediana): 84-707 giorni
- Giorni in trattamento (mediana): 85-590
- Outcomes (emorragia):
  - emorragia maggiore o non-maggiore clinicamente rilevante
  - emorragia fatale
  - mortalità globale

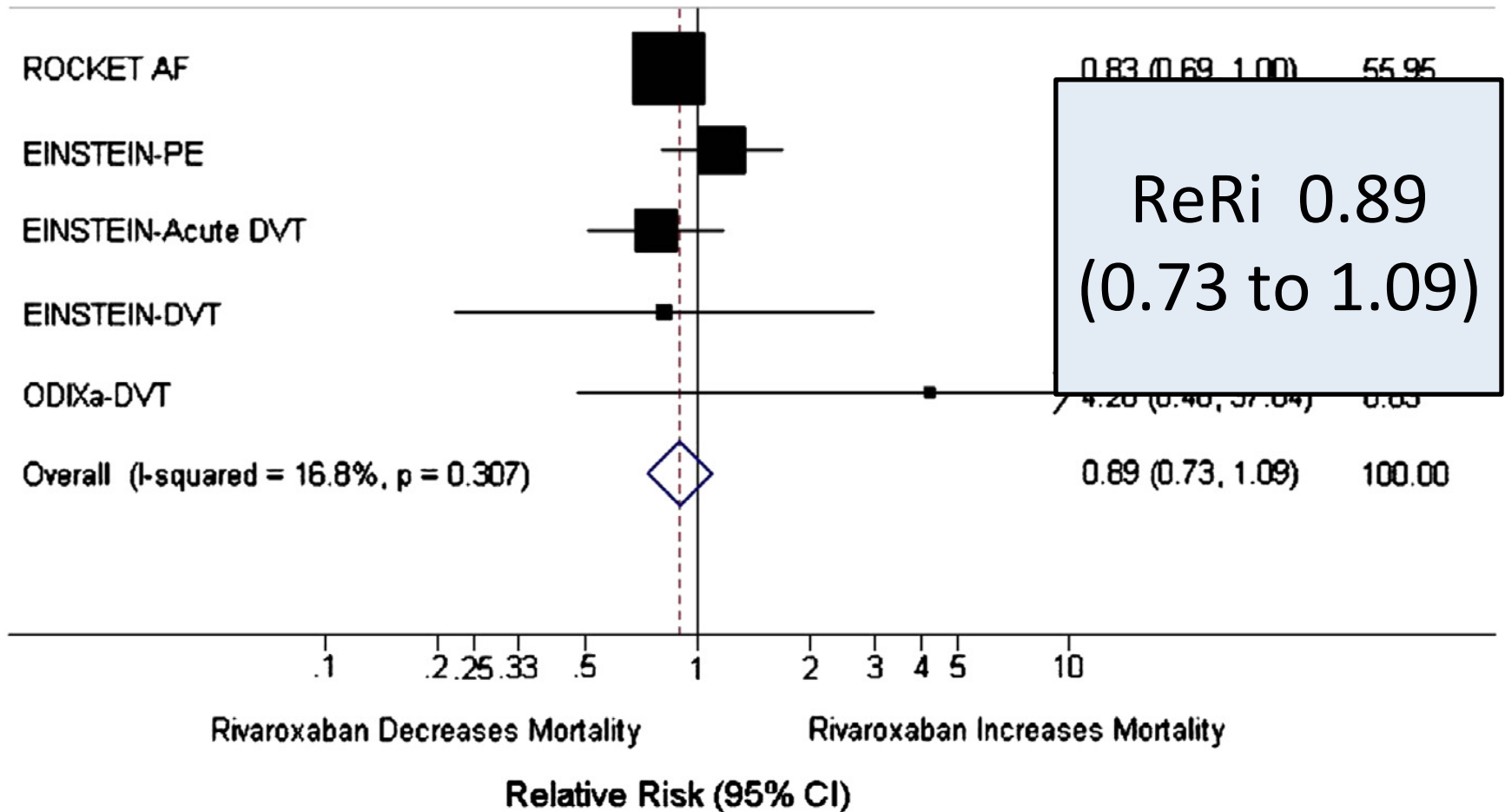
# Emorragia maggiore, o EMNCR



# Emorragia fatale



# Mortalità globale



# Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism

## A Systematic Review and Meta-analysis

Lana A. Castellucci, MD; Chris Cameron, MSc; Grégoire Le Gal, MD, PhD; Marc A. Rodger, MD, MSc; Doug Coyle, PhD; Philip S. Wells, MD, MSc; Tammy Clifford, PhD; Esteban Gandara, MD, MSc; George Wells, PhD; Marc Carrier, MD, MSc

- 2 RCTs
- 4150 pazienti

	Rivaroxaban VS LMWH+VKA
Emorragia maggiore	HR 0.55 (0.35 to 0.89)
EM a 3 mesi	HR 0.49 (0.29 to 0.85)

JAMA 2014;312(11):1122-1135

## Regular Article

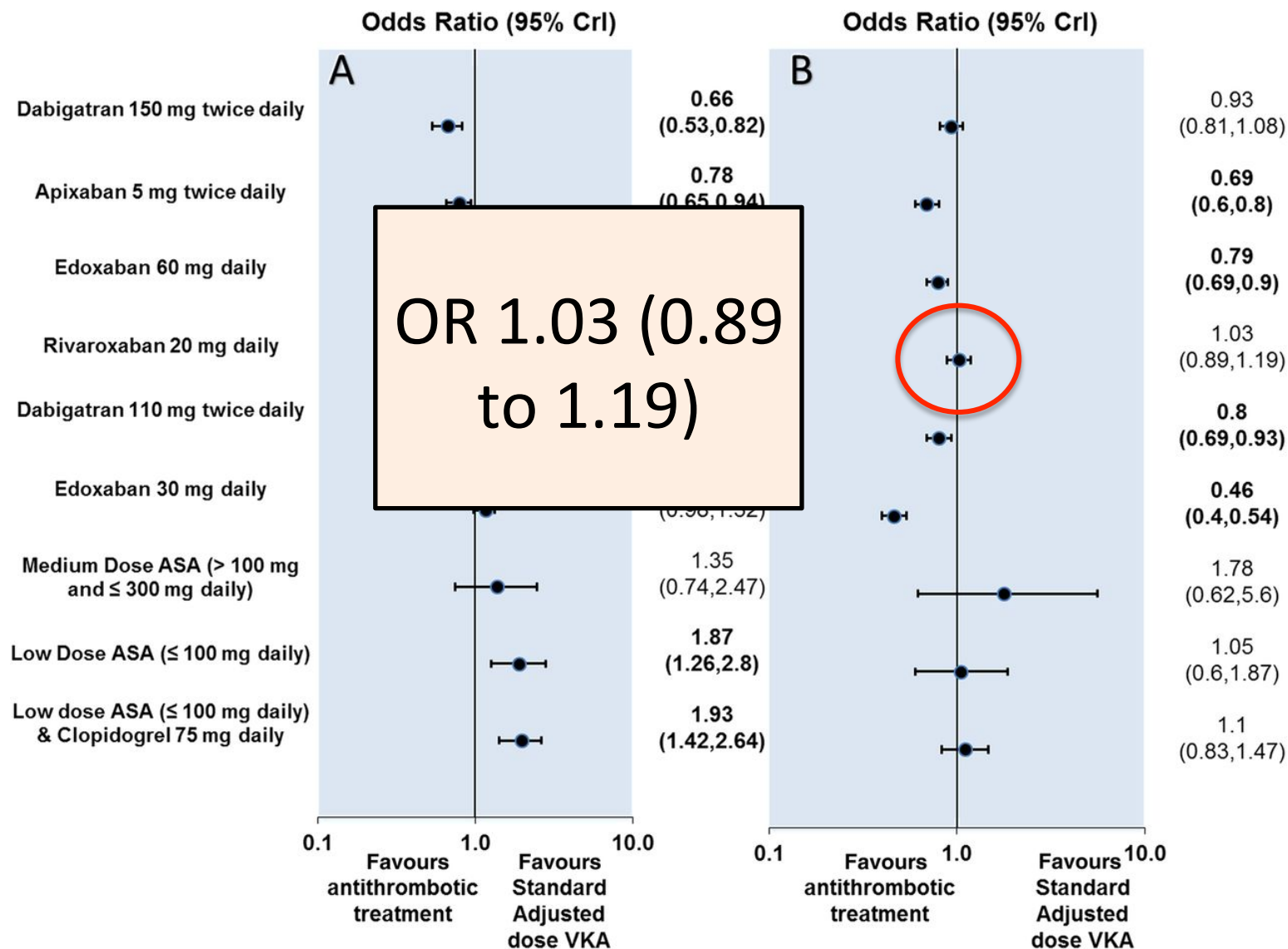
### Direct oral anticoagulants in the treatment of acute venous thromboembolism: A systematic review and meta-analysis

Antonio Gómez-Outes <sup>a,\*</sup>, Ana Isabel Terleira-Fernández <sup>b,c</sup>, Ramón Lecumberri <sup>d</sup>,  
M. Luisa Suárez-Gea <sup>a</sup>, Emilio Vargas-Castrillón <sup>b,c</sup>

- 2 RCTs
- 4151 pazienti

	Rivaroxaban VS LMWH+VKA
Emorragia maggiore	RiRa 0.55 (0.38 to 0.82)

# Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation



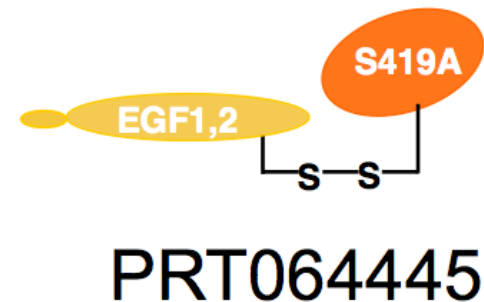
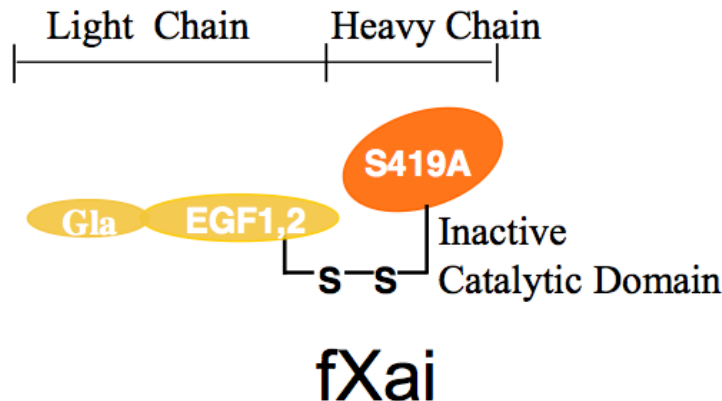


# Antidoto?

- Non disponibile antidoto specifico
- Andexanet alfa / PRT064445 (Portola) → Fase 3
  - *In vitro* e *in vivo* (animale) inibisce l'attività degli xabani e ne neutralizza gli effetti FD (test coagulativi / emorragia).
  - Neutralizza l'effetto *in vivo* (uomo) su diversi test di laboratorio (rivaroxaban / apixaban)
- PER977 (Perosphere) → Fase 2
  - *in vitro* e *in vivo* (animale) inibisce l'attività degli inibisce l'attività degli xabani, di dabigatran UFH/LMWH

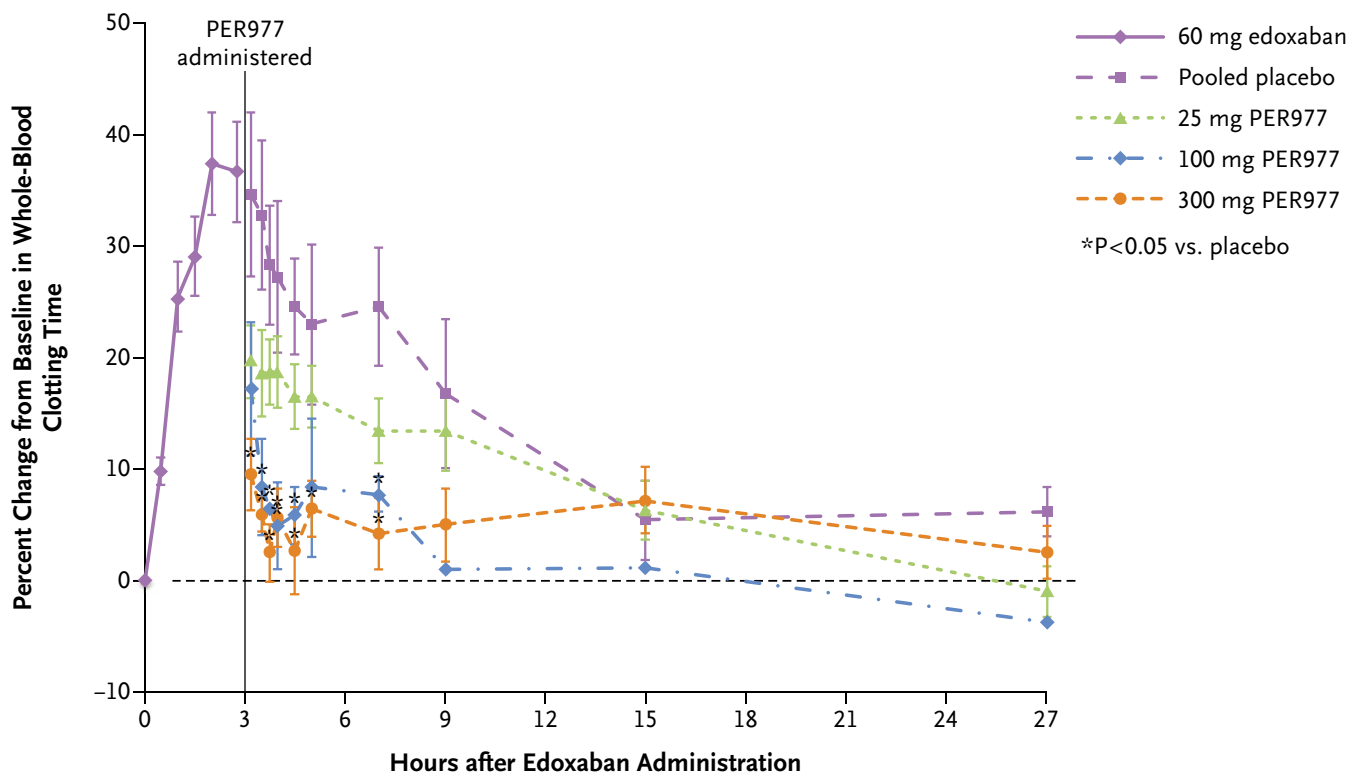
# PRT064445 (Portola)

- PRT064445 (Portola)
- Analogo ricombinante del FXa
- Elevata capacità legante per xabani
- Non partecipa alla formazione del complesso della protrombinasi e all'attivazione del FII

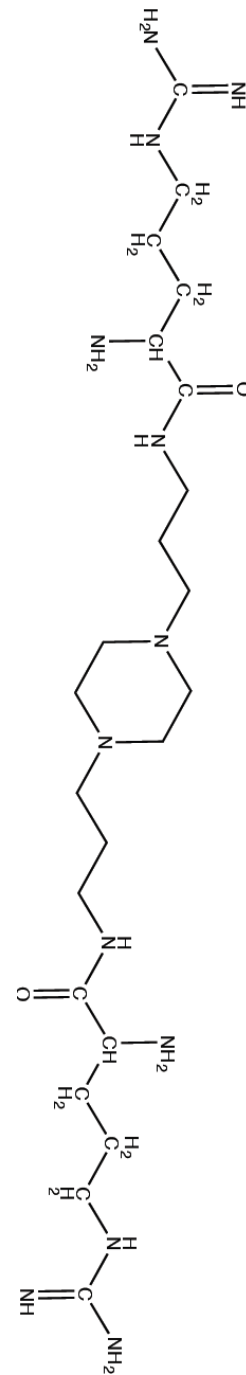


# PER977 (Perosphere)

- 80 pazienti sani, single dose (5-300 mg EV)
- Double-blind, placebo controlled



Ansell J, et al. NEJM 2014 DOI: 10.1056/NEJMc1411800



# Fattori di rischio per emorragia

- Età > 75-80 anni
- Peso < 50 Kg
- ↓ clearance creatinina (Cockcroft)
  - 30-50 ml/min
  - <30 ml/min
- Interazioni farmacologiche

European Heart Rhythm Association Practical  
Guide on the use of new oral anticoagulants in  
patients with non-valvular atrial fibrillation

2012 focused update of the ESC Guidelines  
for the management of atrial fibrillation



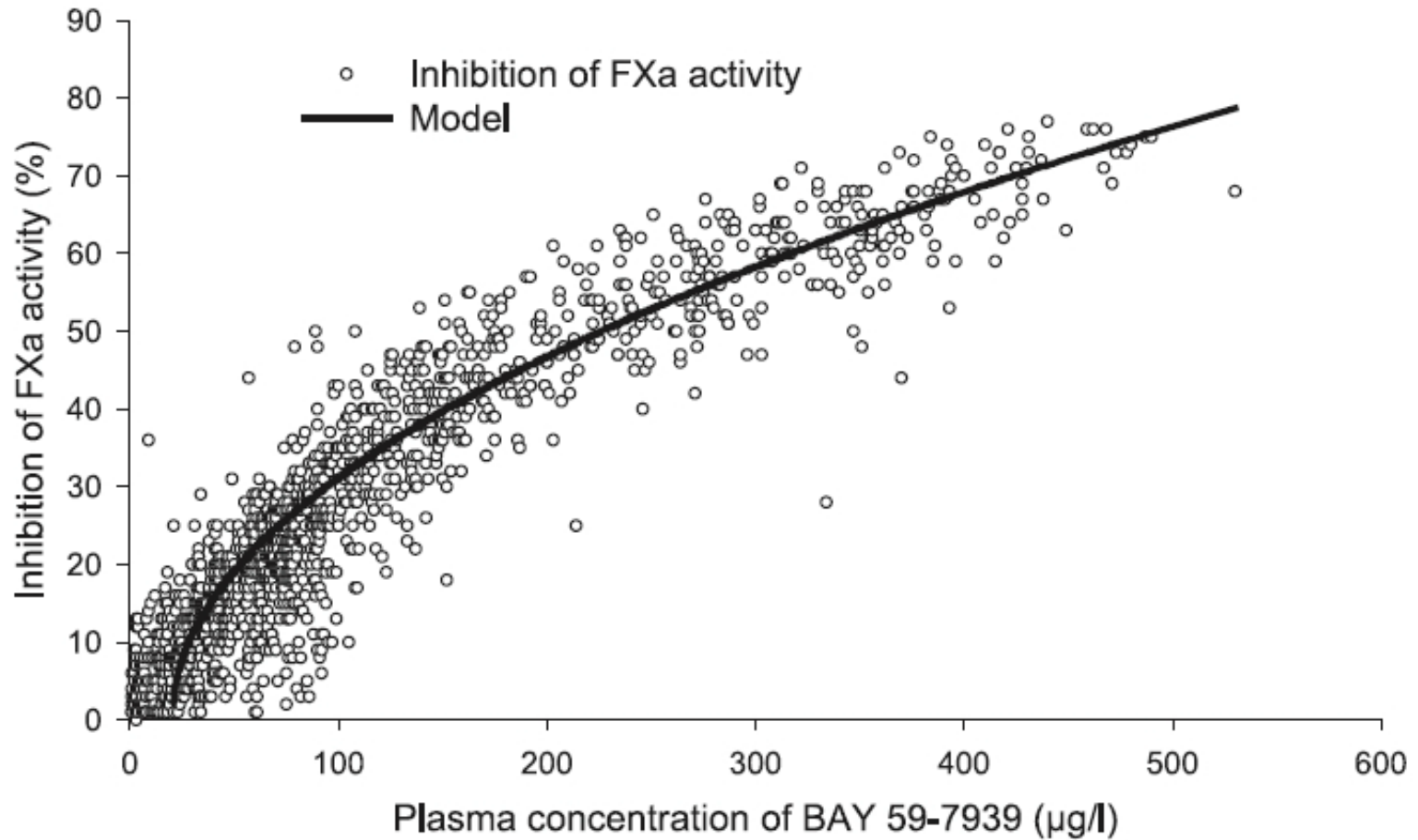
# Fattori di rischio per ICH

- Età: HR 1.35 (1.13 to 1.63) / 10 aa
- Razza
  - africana: HR 3.25 (1.43 to 7.41)
  - asiatica: HR 2.02 (1.39 to 2.94)
- Albumina: HR 1.39 (1.12 to 1.73) / ↓0.5 g/dL
- Precedente stroke/TIA: HR 1.42 (1.02 to 1.96)
- ↑ PAD: HR 1.17 (1.01 to 1.36) / 10 mmHg

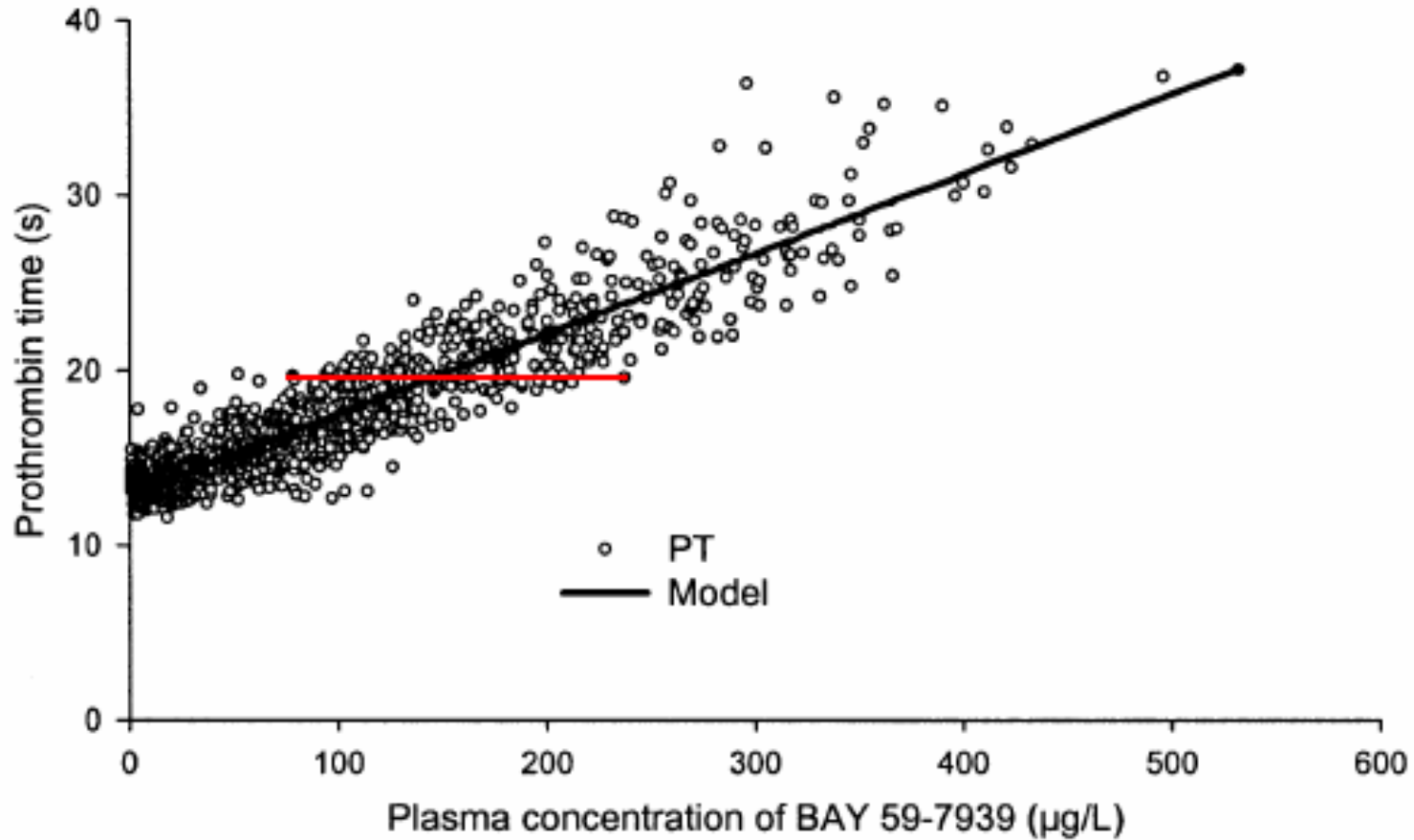
# Test della coagulazione

- Anti-Xa (10 studi) → **QUANTITATIVO**
  - con calibratori specifici → correlazione **lineare** ( $r^2 = 0.95$  to  $1.00$ ) meno robusta se [ $<100$  ng/mL]
- PT (11 studi) → **QUALITATIVO**
  - prolungato, ma ampia variabilità tra reagenti
  - possibile standardizzazione con INR specifico
- aPTT → **NON UTILIZZABILE**
  - correlazione non lineare, ampia variabilità tra reagenti

# Rivaroxaban e FXa



# Rivaroxaban e PT





# Anti-Xa / PT (INR)

Anti-Xa negativo → esclude  
[Rivaroxaban] clinicamente rilevanti

PT prolungato → indica presenza di  
Rivaroxaban (*qualitativamente*)

Cucker A, J Am Coll Cardiol 2014;64:1128–39

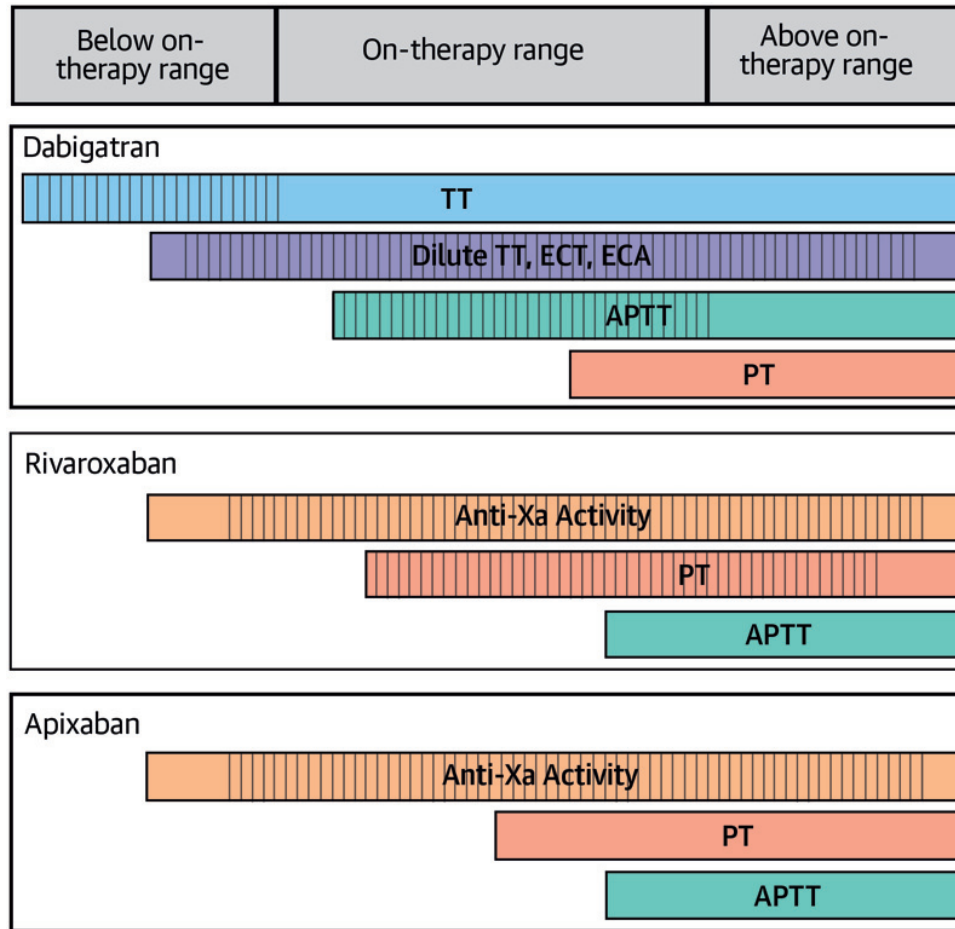
# Anti-Xa / PT (INR)

PT → “SCREENING”

Anti-Xa → RIFERIMENTO

Cucker A, J Am Coll Cardiol 2014;64:1128–39

# Test della coagulazione



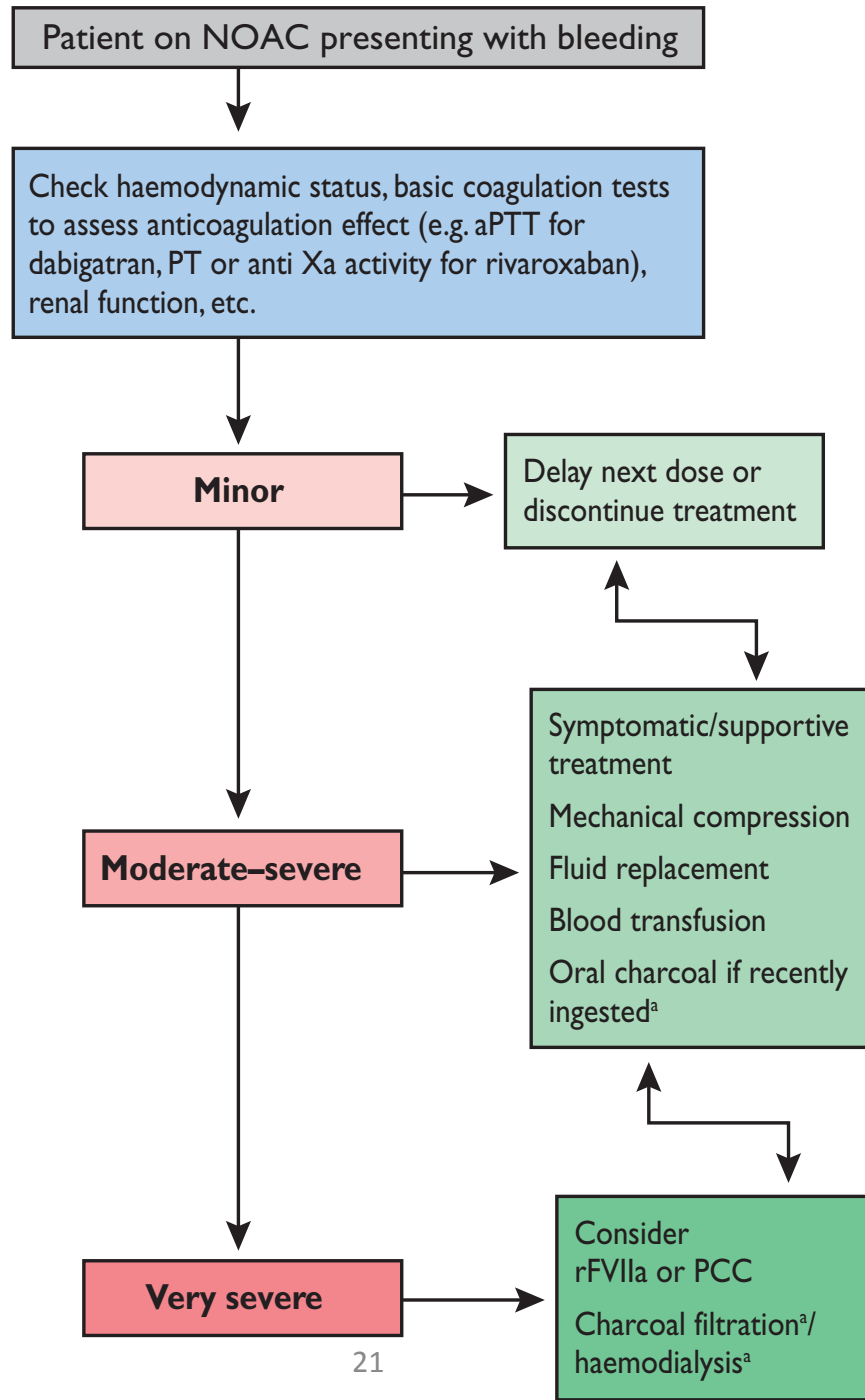
Cucker A, J Am Coll Cardiol 2014;64:1128–39

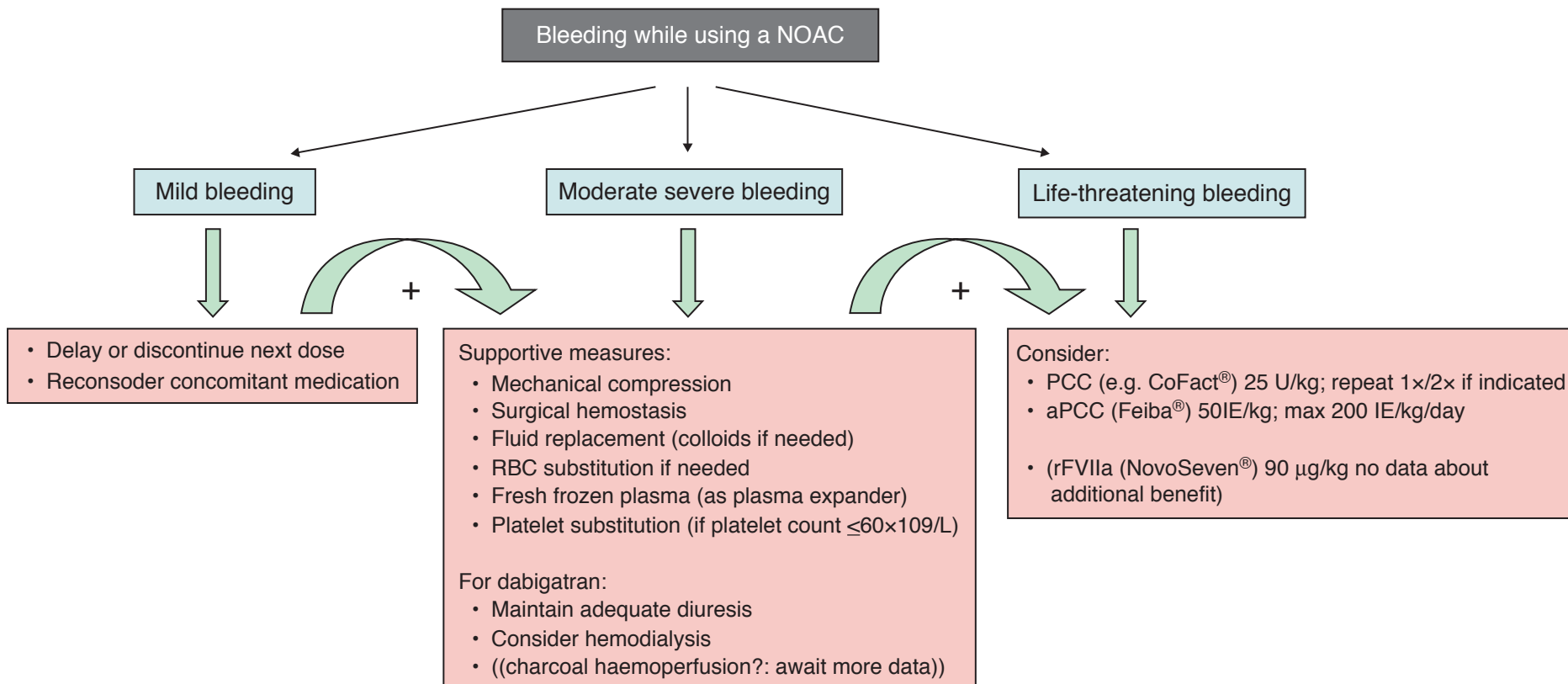
# Test anti-Fxa / PT

Anti-Xa	Distributore	Test	CE
Diagnostica Stago	Stago Italia (MI)	STA <sup>®</sup> Rotachrom <sup>®</sup>	SI
Hyphen Biomed	Cabru (MI)	Biophen DiXal <sup>®</sup>	SI
Technoclone	Alifax (PD)	Technochrom <sup>®</sup> anti-Xa	Si

Autore	Test
Dale, et al JTH 2014	TriniCLOT PT Excel S
Douxfls, et al. Thromb Res 2012	Triniclott PT Excel S
Van Bierk,et al. Thromb Haemost 2014	Neoplastin R

## 2012 focused update of the ESC Guidelines for the management of atrial fibrillation





Europace (2013) **15**, 625–651  
doi:10.1093/europace/eut083

**EHRA PRACTICAL GUIDE**

## European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

# Emorragie minori

- Solo trattamento di supporto:
  - compressione diretta (se possibile)
  - anti-Xa (PT), funzione renale
  - ritardare la successiva dose ( $\uparrow$ PT)
  - sospendere (se emorragia non controllata)

**European Heart Rhythm Association Practical  
Guide on the use of new oral anticoagulants in  
patients with non-valvular atrial fibrillation**

**2012 focused update of the ESC Guidelines  
for the management of atrial fibrillation**



# Emorragie severe

- Come “minore” + sintomatico:
  - compressione, intervento chirurgico
  - supporto (cristalloidi, PRBC / emoderivati)
  - acido tranexamico EV
  - considera CCP

**European Heart Rhythm Association Practical  
Guide on the use of new oral anticoagulants in  
patients with non-valvular atrial fibrillation**

**2012 focused update of the ESC Guidelines  
for the management of atrial fibrillation**





# Emorragie minacciose per la vita

- Somministrazione di:
  - concentrati complesso protrombinico (CCP)
- Considera:
  - concentrato complesso protrombinico attivato (aPCC) [FEIBA<sup>®</sup>]
  - fattore VII attivato ricombinante (rFVIIa)

**European Heart Rhythm Association Practical  
Guide on the use of new oral anticoagulants in  
patients with non-valvular atrial fibrillation**

**2012 focused update of the ESC Guidelines  
for the management of atrial fibrillation**



# Evidenze a supporto

- L'uso dei CCP, dell'aCCP e del rFVII è sostenuto da studi:
  - su volontari sani
  - ex-vivo
  - su modelli animali

Marlu R, et al. Thromb Haemost 2012; 108(2): 217-24

Eerenberg ES, et al. Circulation 2011; 124: 1573–1579

Zhou W, et al. Stroke 2013; 44: 771-778

Khoo TL, et al. Int J Lab Hematol 2013;35(2):222-4

Gruber A, et al. Blood 2008;112:1307

Perzborn E, et al. Haemost Thromb 2008;36:A40

Dinkelaar J, et al. JTH 2013 doi: 10.1111/jth.12236

Perzborn E, et al. Thromb Haemost 2013;110(1)

