VII Congresso Nazionale di
EcoCardioChirurgia

Milano – 6 maggio 2014

Terapia medica 2014:

i nuovi anticoagulanti orali

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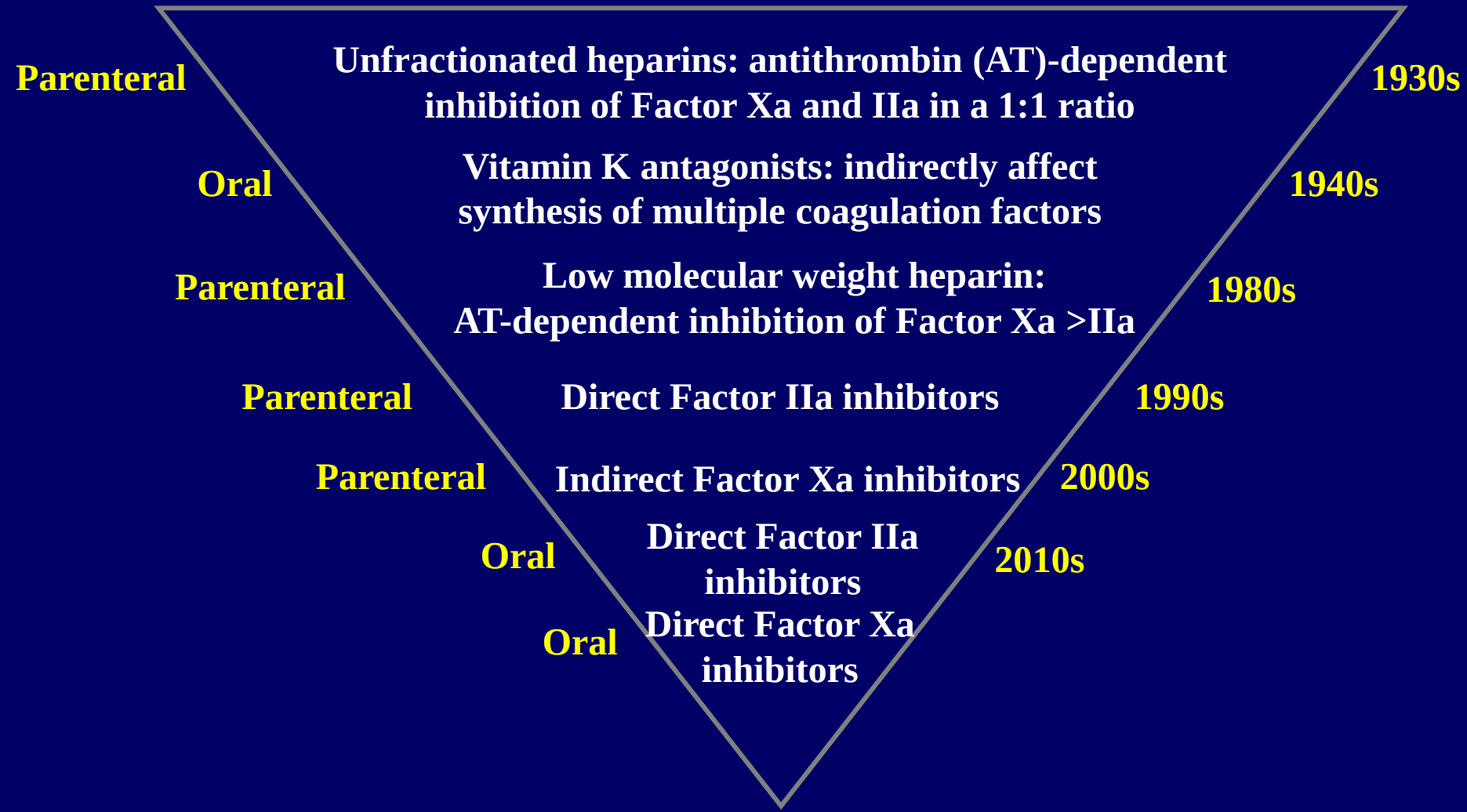
Dipartimento di Medicina Clinica e Sperimentale

Università dell'Insubria - Varese

Agenda

- **Introduzione ‘farmacologica’**
- **Evidenze disponibili**
- **Considerazioni pratiche**

Breve storia della terapia anticoagulante

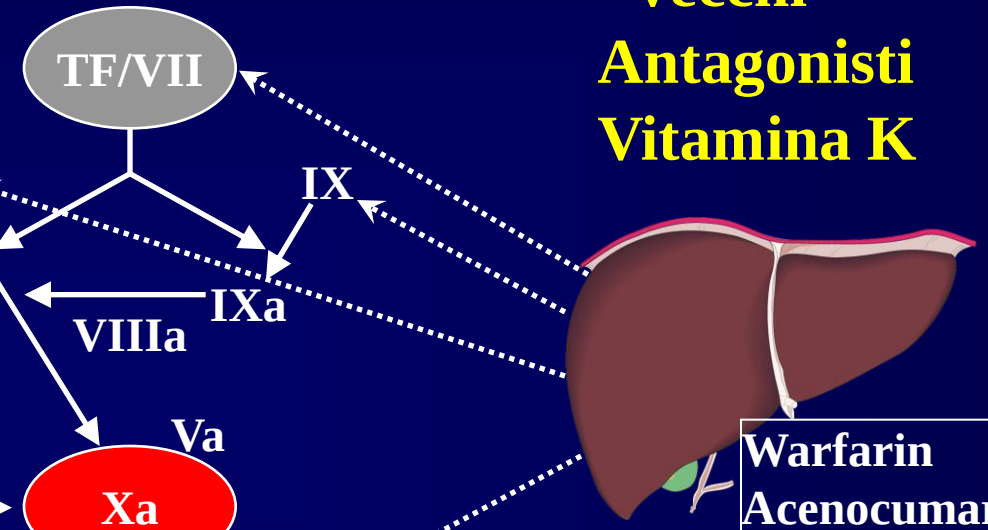


Alban, Eur J Clin Invest 2005; Link, Circulation 1959

Nuovi e "Vecchi"

Nuovi Anticoagulanti Orali (NAO)

"Vecchi" Antagonisti Vitamina K



Rivaroxaban
Apixaban
Edoxaban
Betrixaban

Dabigatran

Warfarin
Acenocumarolo

Adapted from Weitz & Bates, *J Thromb Haemost* 2007

Farmaco -dinamica / -cinetica

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Time to C-max (hrs)	0.5-2.0	2.0-4.0	3.0-4.0	1.0-2.0	3.0-4.0
Half-Life	14-17 h	9-13h	12-15h	8-10h	19-20h
Renal Elimination	80%	33%	27%	50%	17%
Interactions	P-gp	P-gp and CYP3A4	P-gp and CYP3A4	P-gp	P-gp

CYP = cytochrome P450

Indicazioni approvate dei NAO

(EMA ed AIFA)

- **Prevenzione del TEV in chirurgia protesica ortopedica**

  dabigatran, rivaroxaban, apixaban

- **Trattamento di TVP ed EP acute e prevenzione secondaria**

  rivaroxaban

- **Prevenzione del cardioembolismo nella FA non valvolare**

  dabigatran, rivaroxaban, apixaban

- **Prevenzione aterotrombosi in SCA**

  rivaroxaban

Chirurgia Ortopedica

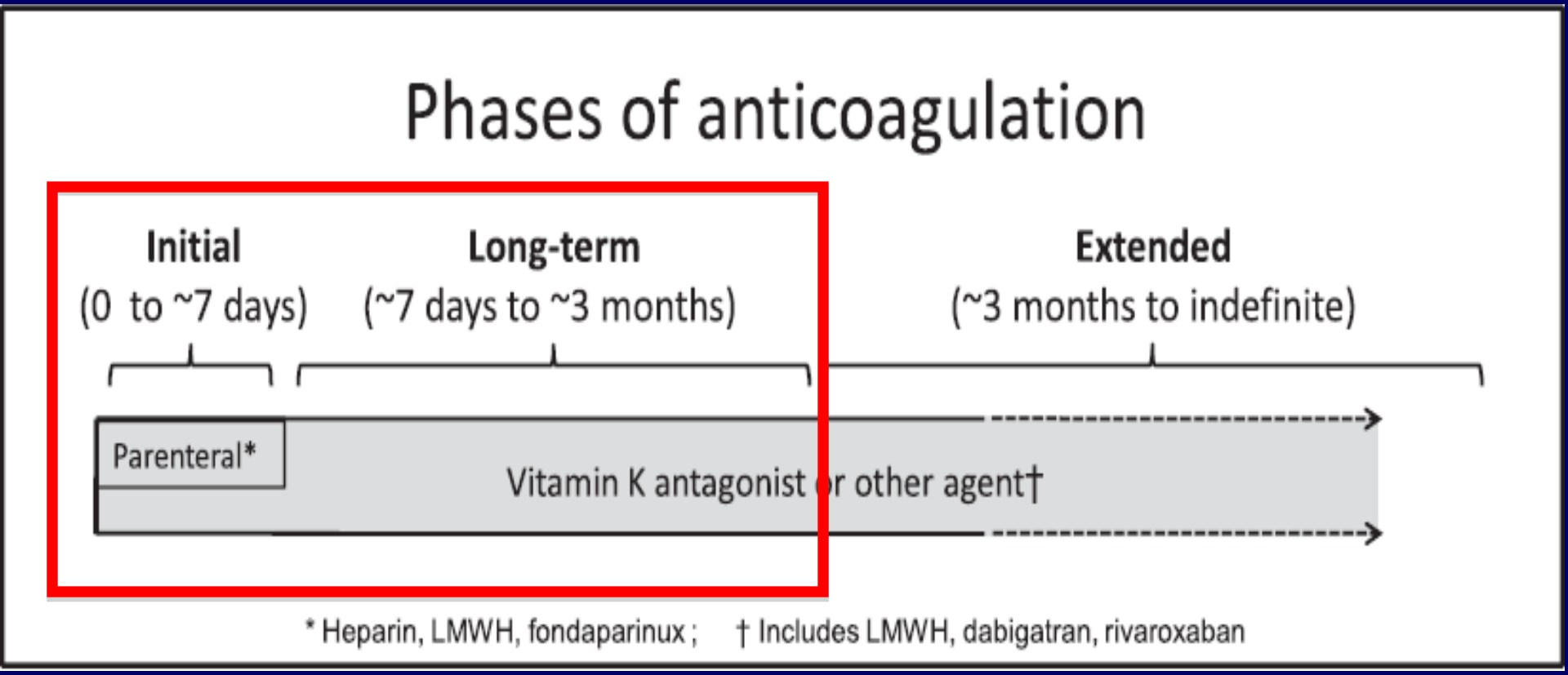
- **Interventi ortopedici maggiori elettivi:**

  protesi di anca e ginocchio

- **RCT, fase III, non-inferiorità versus enoxaparina**

  - **RECORD I-IV (rivaroxaban)**
  - **ADVANCE I-III (apixaban)**
  - **RE-MODEL/RE-NOVATE I and II/RE-MOBILIZE (dabigatran)**

Trattamento di TVP ed EP



AT9 Clinical Practice Guidelines - ACCP 2012

Evidenze - TVP ed EP acute

- **Studi RCT, fase III, non-inferiorità versus warfarin**

rivaroxaban	**- EINSTEIN**
apixaban	**- AMPLIFY**
edoxaban	**- HOKUSAI**
dabigatran	**- RE-COVER**

- **Outcome primario:** **Recidiva di TEV**
- **Sicurezza:** **Emorragia maggiore**

Trattamento di TVP ed EP

I NAO sono stati sviluppati:

1. Per ‘sfidare’ entrambi i trattamenti parenterale e dicumarolico

- **dose iniziale** ottimale per la fase acuta iniziale
- **dose di mantenimento** ottimale per il trattamento a lungo termine

Rivaroxaban e Apixaban

2. Per ‘sfidare’ SOLO i dicumarolici, mantenendo un trattamento parenterale iniziale ≥ 5 gg

- poi passare direttamente a **dose di mantenimento** ottimale

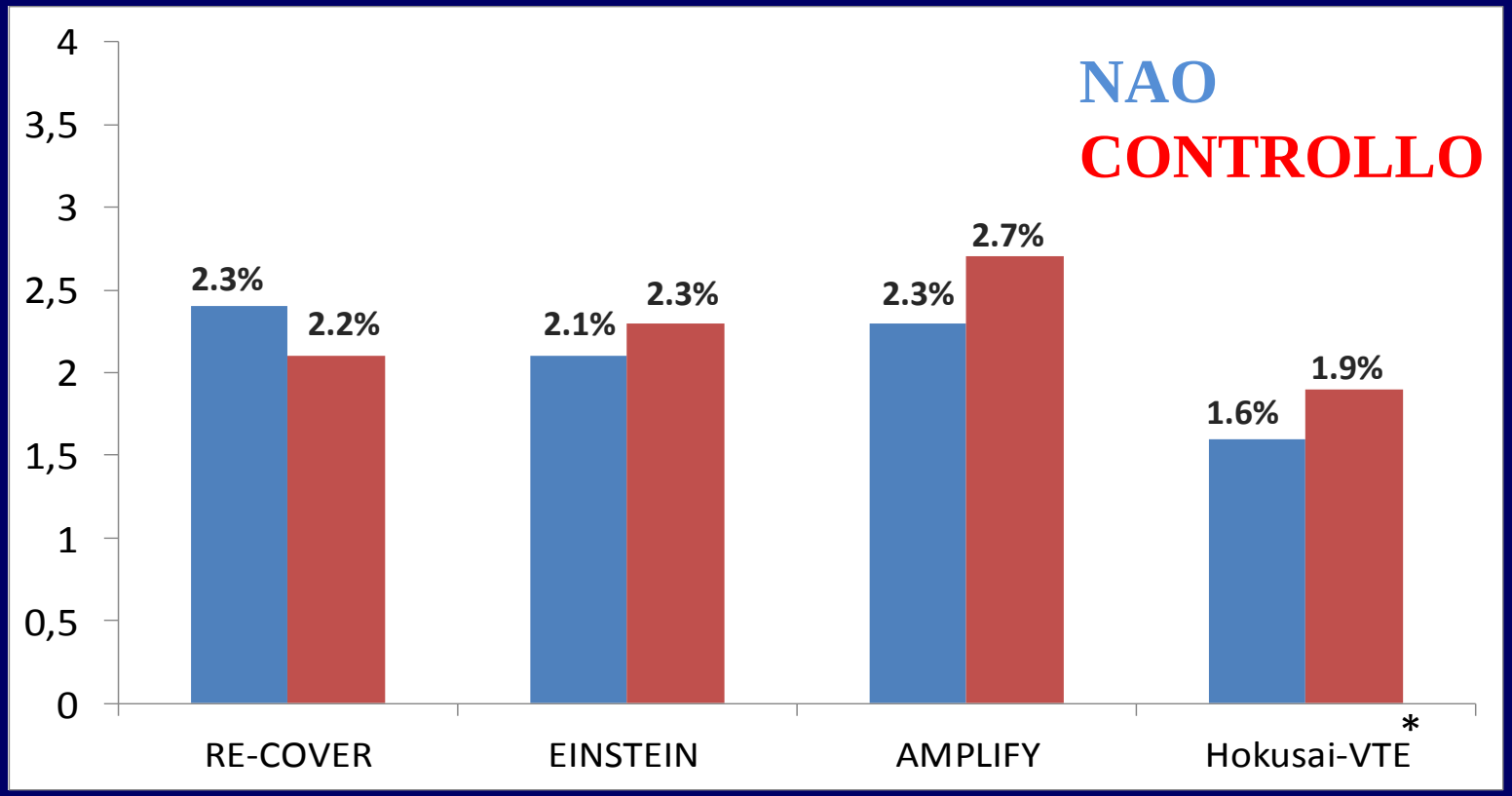
Dabigatran e Edoxaban

Evidenze - TVP ed EP acute

Studio	Farmaco (dosaggio)	RECIDIVA TEV	P for non-inf	EMORRAGIA MAGGIORE
RE-COVER	Dabigatran (EBPM x 9 gg, poi 150 mg bid)	1.10 (0.65-1.84)	<0.001	0.82 (0.45-1.48)
RE-COVER II		1.08 (0.64-1.80)	<0.0001	0.69 (0.36-1.32)
EINSTEIN - DVT	Rivaroxaban (15 mg bid x 21 gg, poi 20 mg od)	0.68 (0.44-1.04)	<0.001	0.65 (0.33-1.30)
EINSTEIN - PE		1.12 (0.75-1.68)	0.003	0.49 (0.31-0.79)
AMPLIFY	Apixaban (10 mg bid x 7 gg, poi 5 mg bid)	0.85 (0.60 - 1.18)	<0.001	0.31 (0.17-0.55)
HOKUSAI	Edoxaban (EBPM per 7 gg, poi 60 mg od)	0.89 (0.70-1.13)	<0.001	0.84 (0.59-1.21)

Evidenze - TVP ed EP acute

Recidiva di TEV

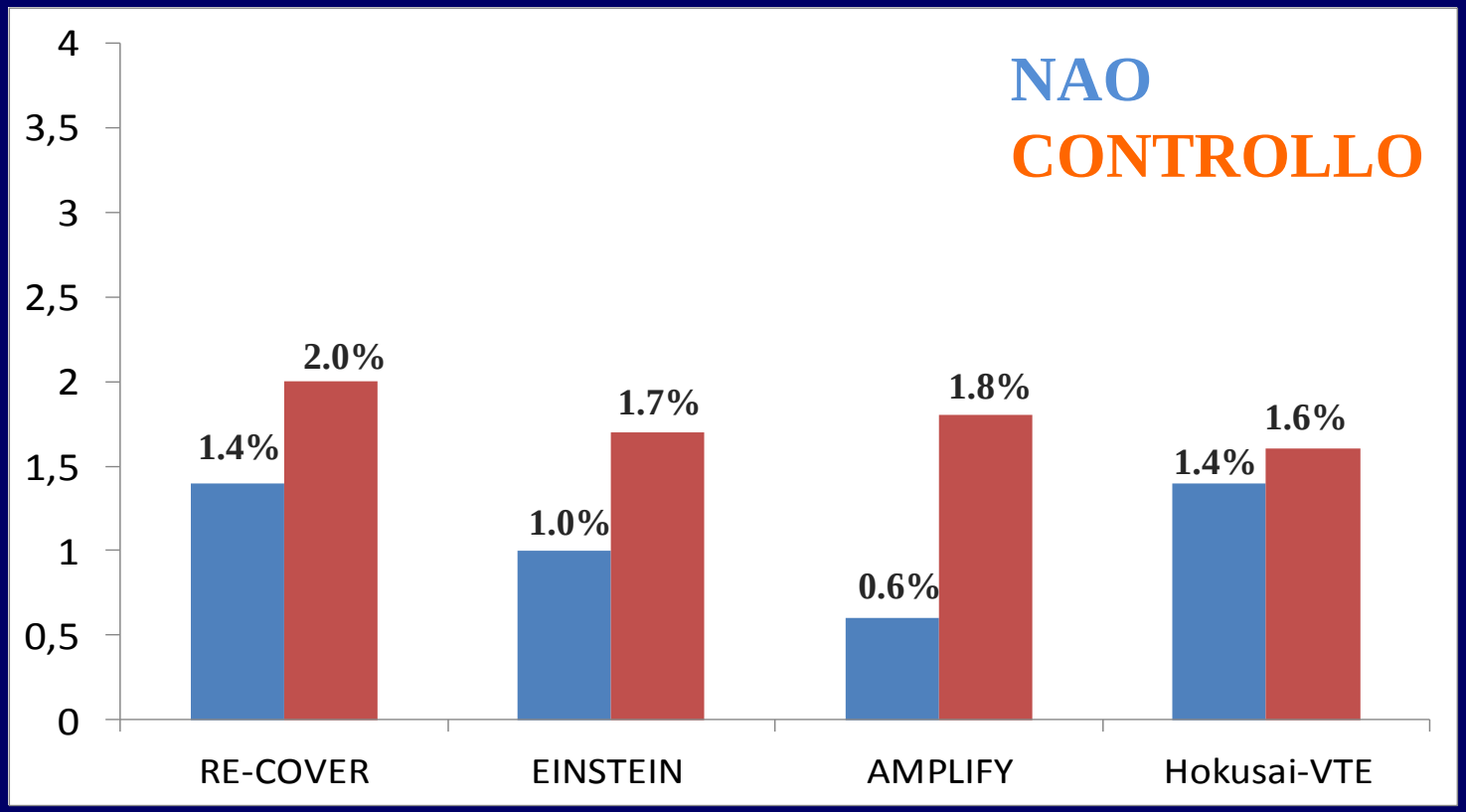


* On Treatment

1. Schulman et al. N Engl J Med 2009;361:2342–2352
2. EINSTEIN Investigators. N Engl J Med 2010; 3. EINSTEIN–PE Investigators. N Engl J Med
4. Agnelli et al. N Engl J Med 2013; 5. The Hokusai-VTE Investigators. N Engl J Med 2013

Evidenze - TVP ed EP acute

Emorragia maggiore



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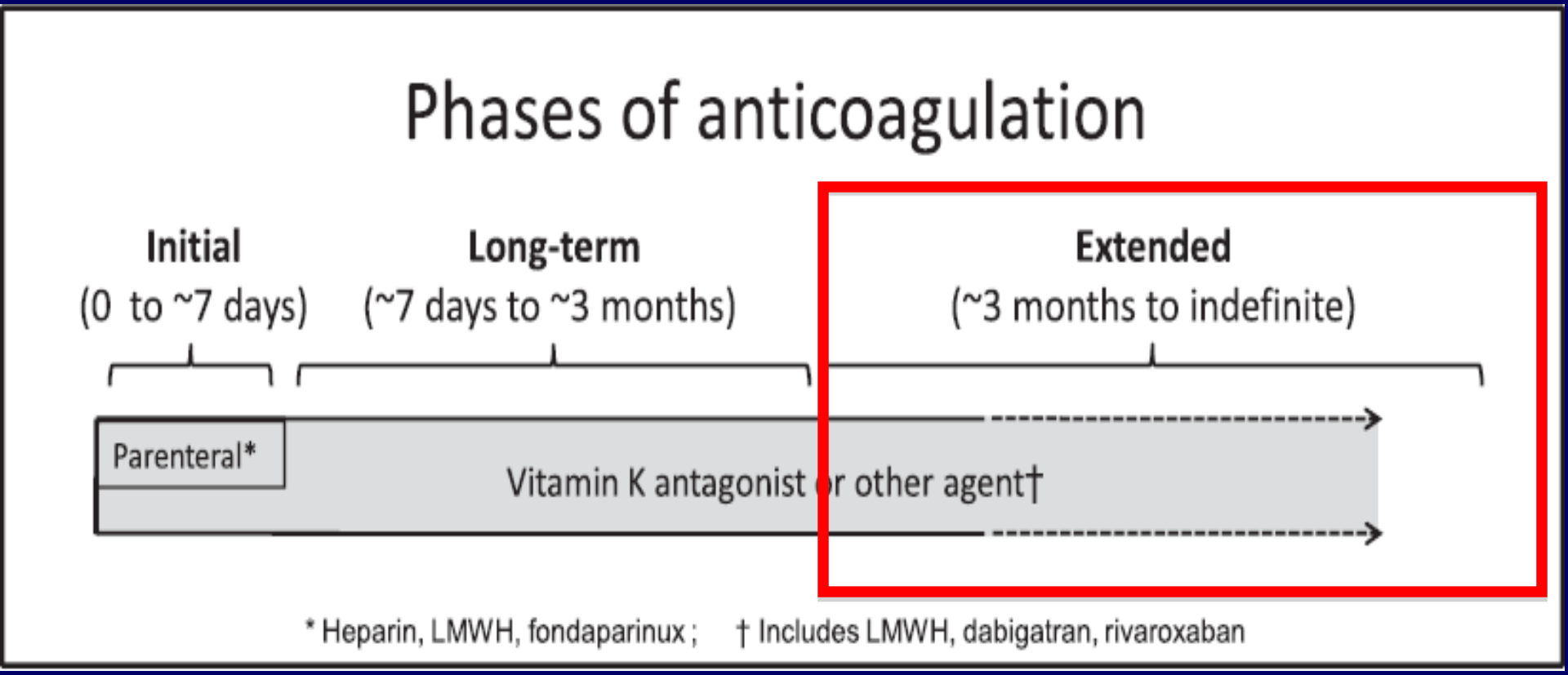
Trattamento di TVP ed EP



AT9 Clinical Practice Guidelines - ACCP 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism

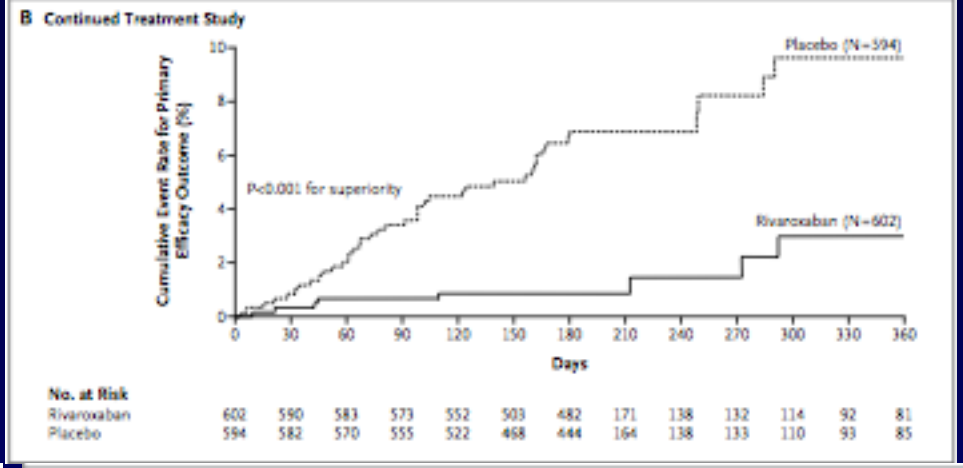
Sam Schulman, M.D., Ph.D., Clive Kearon, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., Ph.D., David Baanstra, M.Sc., Anne Mathilde Kvamme, M.Sc.Pharm., Jeffrey Friedman, M.D., Patrick Mismetti, M.D., and Samuel Z. Goldhaber, M.D., for the RE-MEDY and the RE-SONATE Trials Investigators*

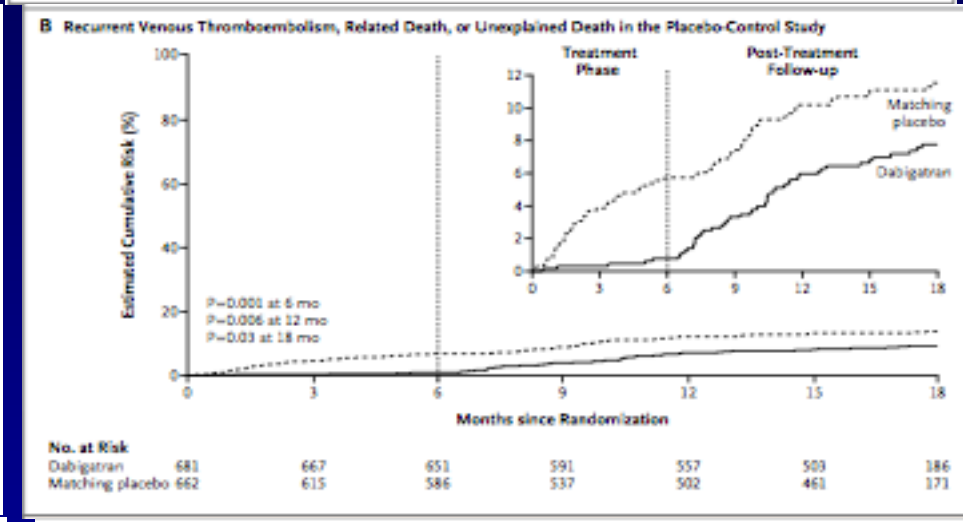
The NEW ENGLAND JOURNAL of MEDICINE

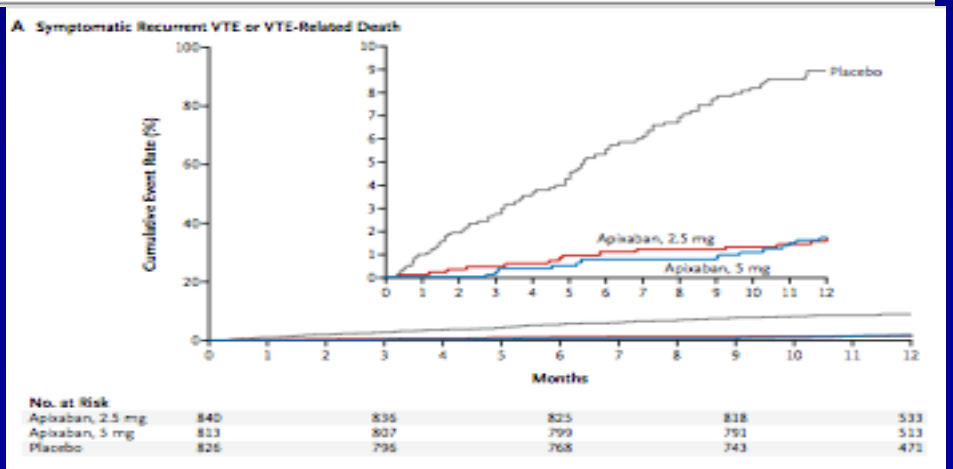
ORIGINAL ARTICLE

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*







FA non valvolare

- **Studi RCT, fase III, non-inferiorità versus warfarin**

  rivaroxaban - ROCKET - AF

  apixaban - ARISTOTLE

  edoxaban - ENGAGE

  dabigatran - RE-LY

- **Outcome primario: Stroke (ischemico o emorragico) ed embolismo sistemico**
- **Sicurezza: Emorragia maggiore**

Evidenze - FA non valvolare

	RELY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg) Freq	150, 110 BID	20 (15*) QD	5 (2.5*) BID	60*, 30* QD
N	18,113	14,266	18,206	21,105
Design	PROBE	2x blind	2x blind	2x blind
AF criteria	AF ≥ 1 risk factor	AF ≥ 2 risk factors	AF ≥ 1 risk factor	AF ≥ 2 risk factor
% VKA naive	50%	38%	43%	41%

*Dose adjusted in patients with ↓drug clearance.

PROBE = prospective, randomized, open-label, blinded end point evaluation VKA = Vitamin K antagonist

Evidenze - FA non valvolare

Studio	Farmaco (dosaggio)	STROKE/EMBOLISMO SISTEMICO	P for non-inf	EMORRAGIA MAGGIORE
RE-LY	110 mg bid Dabigatran	0.91 (0.74–1.11)	<0.001	0.80 (0.69–0.93)
	150 mg bid	0.66 (0.53–0.82)	<0.001	0.93 (0.81–1.07)
ROCKET - AF	Rivaroxaban 20 mg od	0.79 (0.66–0.96)	<0.001	1.03 (0.89-1.18)
ARISTOTLE	Apixaban 5 mg bid	0.79 (0.66–0.95)	<0.001	0.69 (0.60–0.80)
ENGAGE - AF	30 mg od Edoxaban	1.07 (0.87–1.31)	0.005	0.47 (0.41–0.55)
	60 mg od	0.79 (0.63–0.99)	<0.001	0.80 (0.71–0.91)

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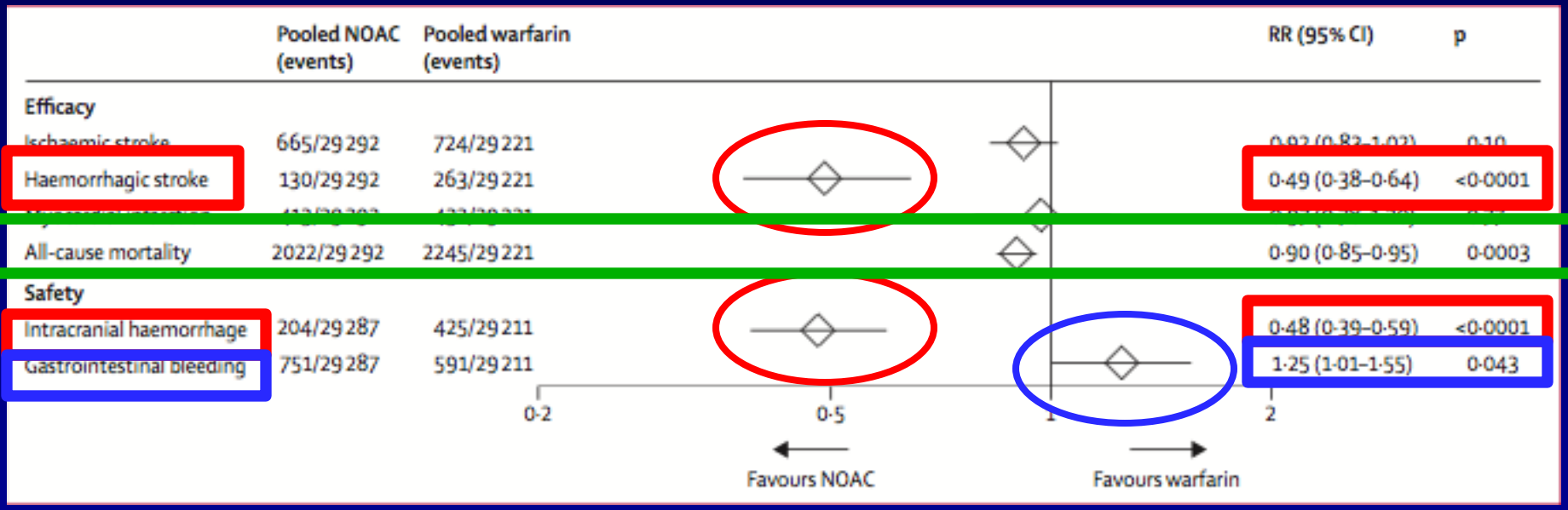
Evidenze - FA non valvolare



Ruff et al. – Lancet 2014;383

Sindromi coronariche acute

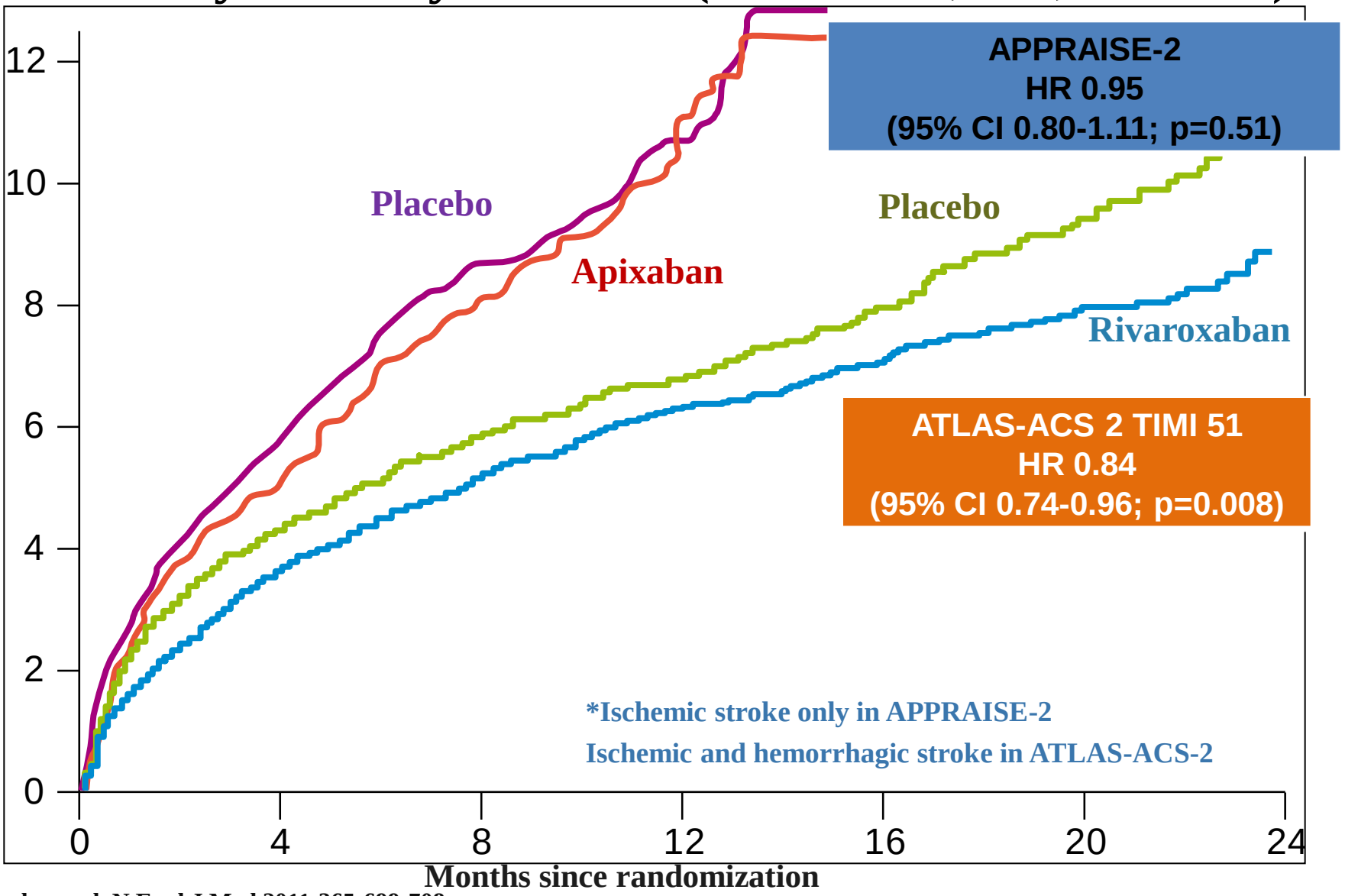
- **Studi RCT, fase III**

rivaroxaban - ATLAS ACS 2 - TIMI 51 (versus placebo)

apixaban - APPRAISE II (versus placebo)

APPRAISE-2 and ATLAS-ACS-2:

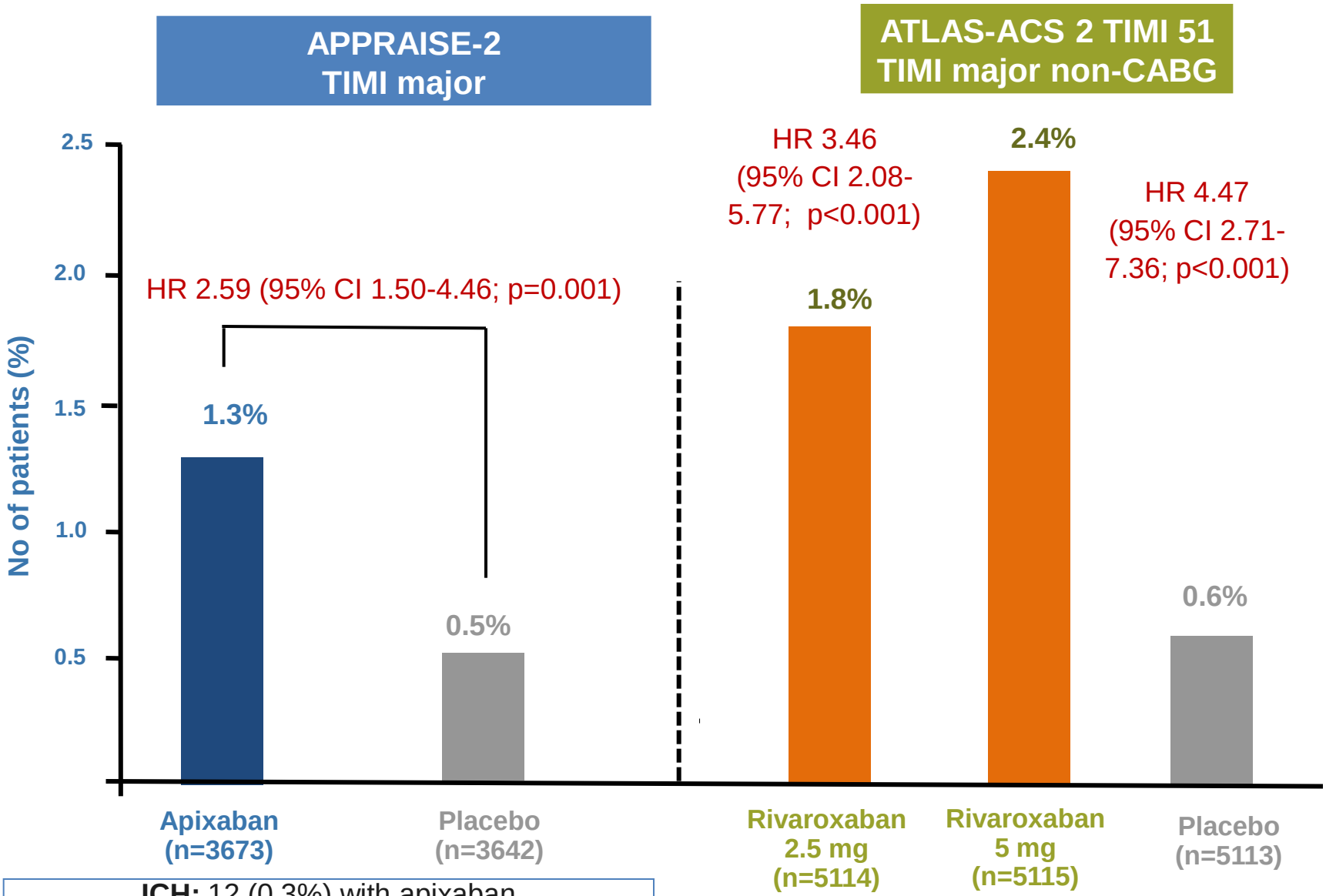
Primary Efficacy outcome (CV Death, MI, Stroke*)



Alexander et al. N Engl J Med 2011;365:699-708.

Mega et al. N Engl J Med 2012;366:9-19.

APPRAISE-2 and ATLAS-ACS-2: Safety



ICH: 12 (0.3%) with apixaban
vs 3 (0.1%) with placebo: p=0.03

ICH: 32 (0.6%) with rivaroxaban
vs 5 (0.2%) with placebo

Alexander et al. N Engl J Med 2011;365:699-708.

Mega et al. N Engl J Med 2012;366:9-19.

Conclusioni

- **Nei trial di fase III tutti i NAO hanno mostrato almeno uguale efficacia, rispetto ai controlli, per la prevenzione del TEV in ortopedia maggiore, nel trattamento della TVP/EP e per la prevenzione del cardioembolismo nella FANV**

- **Sono risultati più sicuri per quanto concerne l'incidenza di emorragie cerebrali**

- **Nella prevenzione dell'aterotrombosi in corso di SCA, rivaroxaban si è dimostrato più efficace di placebo, essendo tuttavia associato ad una incidenza maggiore di sanguinamento maggiore**

Cosa manca (ancora) ?

- **Fibrillazione atriale valvolare**
- **Trombosi intraventricolare**
- **TEV in sedi inusuali**
- **Ipertensione polmonare**
- **Cardiomiopatia dilatativa**
- **…**

Cosa mancherà?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

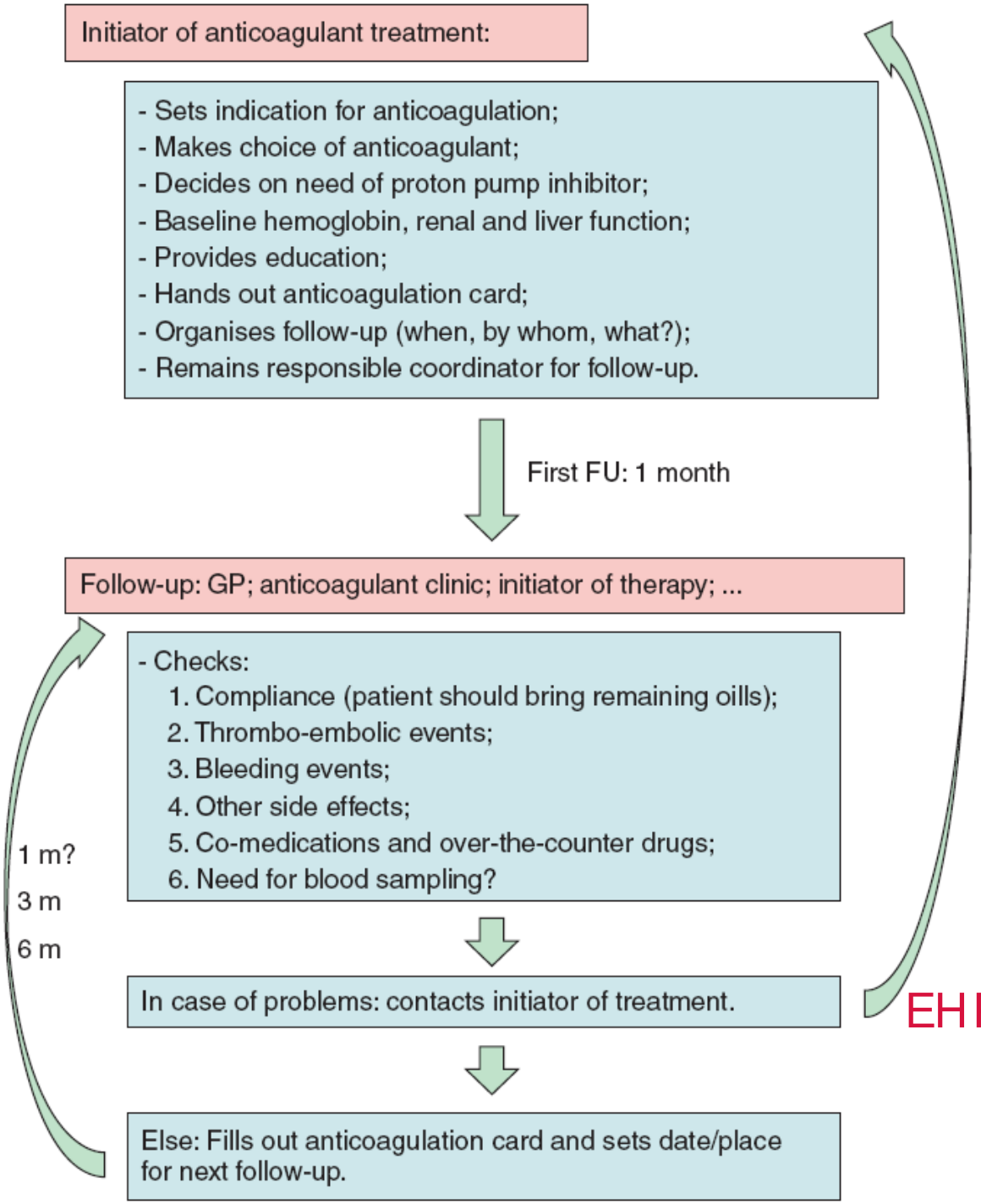
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

RESULTS

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of

N Engl J Med 2013

NAO: valutazione preliminare ed indicazioni per il follow-up



EHRA PRACTICAL GUIDE

EUROPEAN SOCIETY OF CARDIOLOGY®
Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

1. CHI NON PUO' (…non deve…) FARE i NAO?

(controindicazioni)

PRE-

1. Valutazione clinica
   - Compliance
   - Farmaci
   - Eventi avversi

2. Esami ematochimici
   - Funzione renale
   - Funzione epatica

3. Ecografia
   - Eco cuore

Compliance

Drugs don't work in patients who don't take them.

C. Everett Koop, M.D.

N Engl J Med 2005;353:487-97.

5. Ensuring compliance with new oral anticoagulant intake

(8) In NOAC patients in whom low compliance is suspected despite proper education and additional tools, conversion to VKAs (preferably with long half-life like phenprocoumon?) could be considered.

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Compliance

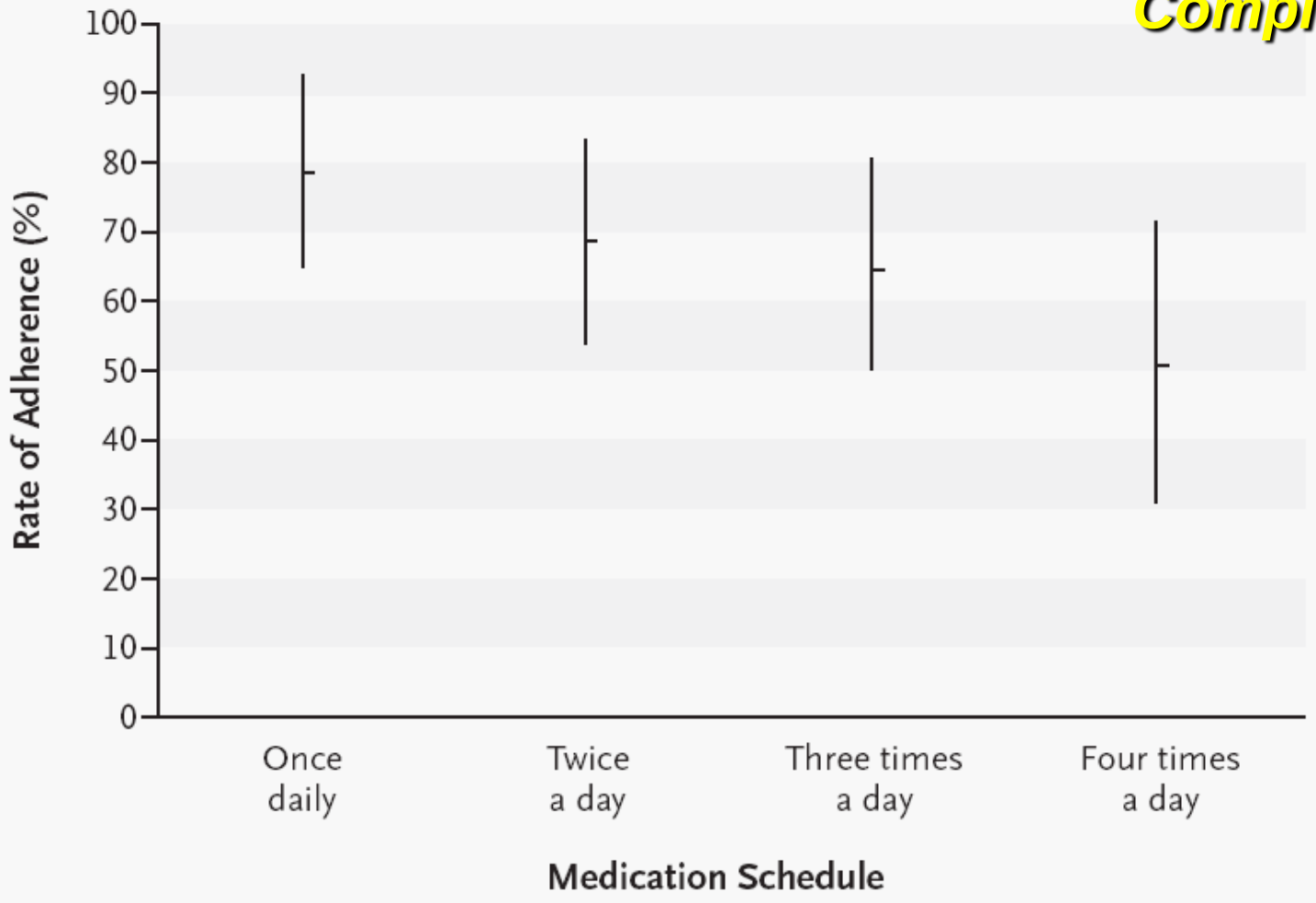

Figure 1. Adherence to Medication According to Frequency of Doses.

Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars). Data are from Claxton et al.[7]

N Engl J Med 2005;353:487-97.

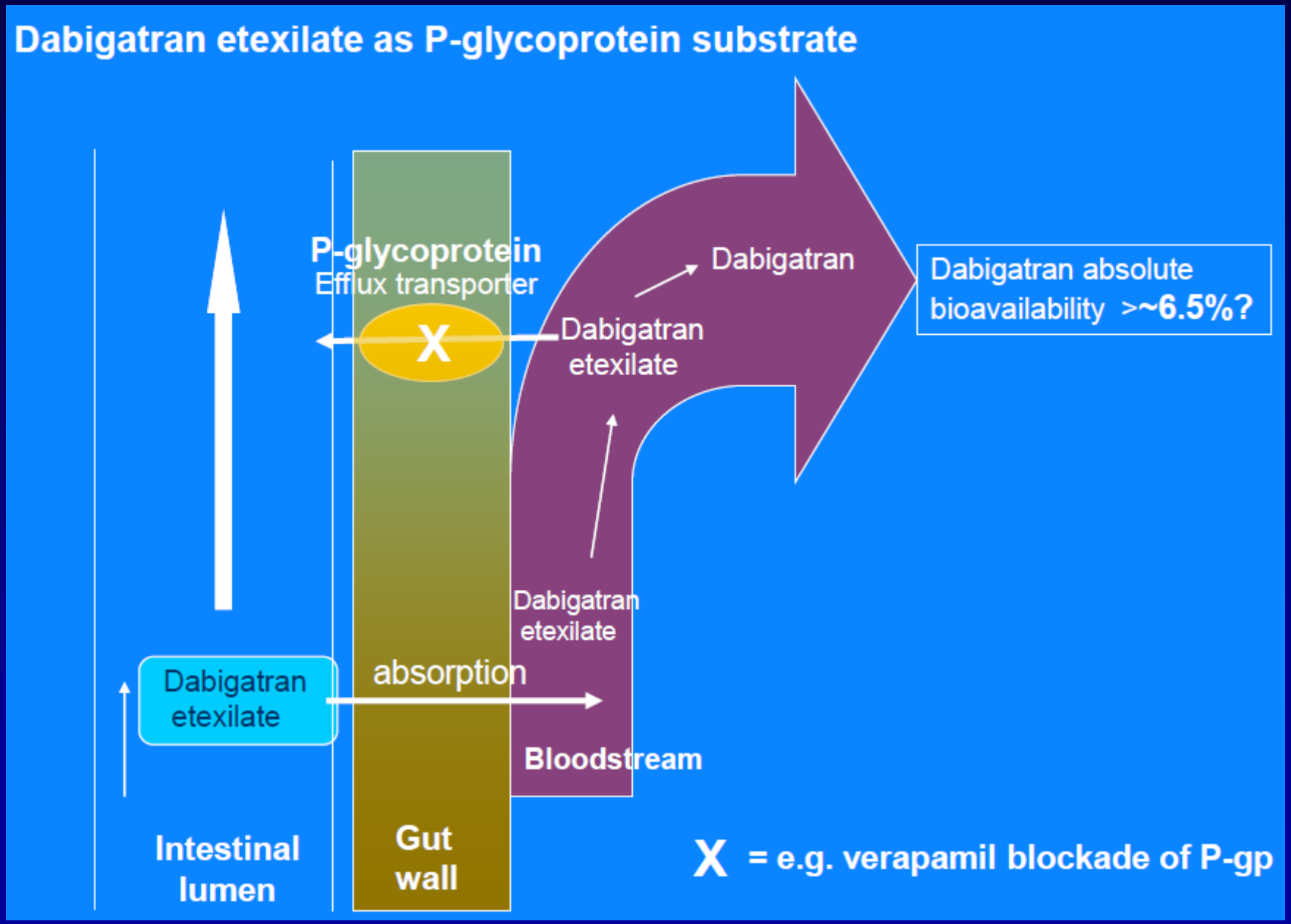
Dabigatran etexilate as P-glycoprotein substrate
P-glycoprotein
Efflux transporter
X
Dabigatran
Dabigatran etexilate
Dabigatran absolute bioavailability >~6.5%?
Dabigatran etexilate
absorption
Dabigatran etexilate
Bloodstream
Intestinal lumen
Gut wall
X = e.g. verapamil blockade of P-gp

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors, and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level	No data yet			
Age ≥75 years	Increased plasma level	No data yet			
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Farmaci

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

Table 12 Recommendations concerning new onset AF in patients with a recent (<1 year) ACS

4. If a NOAC would be indicated, a FXa inhibitor might be preferred in view of the small but insignificant increase in the risk of myocardial infarction with dabigatran, but this needs to be weighed against the overall perceived clinical effect (which was not impacted for dabigatran)
5. If dabigatran would be indicated, a lower dose (110 mg bid) might be preferred, in combination with low-dose aspirin or with clopidogrel

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Funzione renale

Table 7 NOACs in renal dysfunction: Approved European labels and dosing in chronic kidney disease

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Approved for CrCl ≥ ...	≥30 ml/min	≥15 ml/min	Not available	≥15 ml/min
Dosing recommendation	CrCl ≥50 ml/min: no adjustment (i.e. 150 mg bid)	Serum creatinine ≥1.5 mg/dl: no adjustment (i.e. 5 mg bid)	Not available	CrCl ≥50 ml/min: no adjustment (i.e. 20 mg qd)
Dosing if CKD	When CrCl 30–49 ml/min, 150 mg bid is possible (SmPC) but 110 mg bid if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[2] Note: 75 mg bid approved in US only:[b] • if CrCl 15–30 ml/min • if CrCl 30–49 ml/min and other orange factor Table 5 (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg bid Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg,[SmPC] or with other 'yellow' factor (Table 5): 2.5 mg bid	Not available	15 mg qd when CrCl 15–49 ml/min
Not recommended if	CrCl <30 ml/min	CrCl <15 ml/min	Not available	CrCl <15 ml/min

Insufficienza epatica

Rivaroxaban

Child-Pugh B e C: controindicato

Apixaban

Child-Pugh C: controindicato

Child-Pugh A e B: da usare con cautela (senza aggiustamento dose)

Dabigatran

Insufficienza epatica o malattia epatica che possa avere un qualsiasi impatto sulla sopravvivenza: controindicato

AST/ALT > 2 x ULN sono stati esclusi nello studio ROCKET-AF, ARISTOTELE e RELY-AF

2. QUANDO LO DEVO RIVEDERE ?

(seguirli regolarmente)

POST-

1. Valutazione clinica

   Compliance (educazione !!)

   Farmaci

2. Esami ematochimici

3. Prossimo controllo

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Table 2 Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Compliance	Each visit	• Instruct patient to bring remaining medication: note and calculate average adherence • Re-educate on importance of strict intake schedule • Inform about compliance aids (special boxes; smartphone applications; . . .)
2. Thrombo-embolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? (PPI; haemorrhoidectomy; . . .). Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication or dose?
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug.
	Yearly	• Haemoglobin, renal and liver function
	6 monthly	• Renal function if CrCl 30–60 ml/min, or if on dabigatran and >75 years or fragile
	3 monthly	• If CrCl 15–30 ml/min
	On indication	• If intercurring condition that may impact renal or hepatic function

TIA, transient ischaemic attack; PPI, proton pump inhibitor; CrCl, creatinine clearance (preferably measured by the Cockroft method).

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

SE …

1. Emorragia

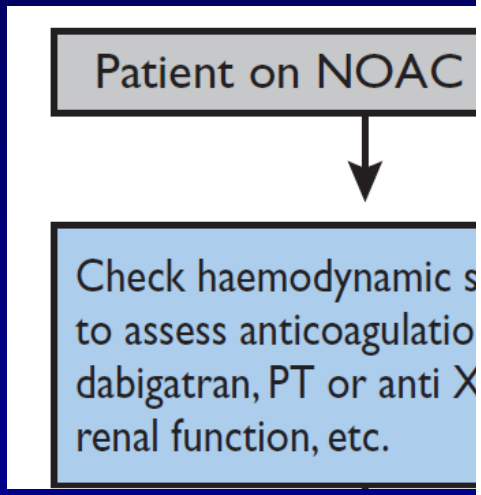
2. Intervento chirurgico

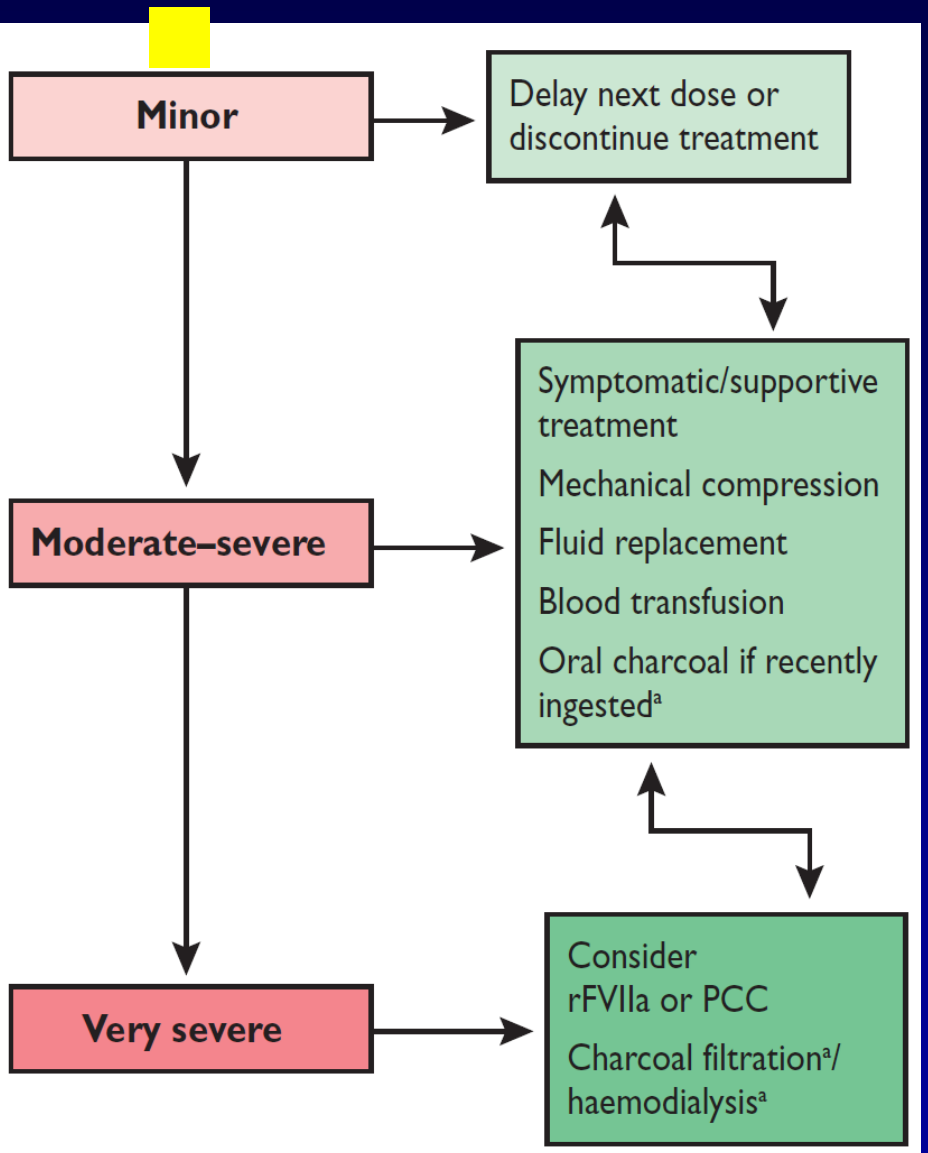
3. Insufficienza renale severa intercorrente

European Heart Journal
doi:10.1093/eurheartj/ehs253

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

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association





aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII.
[a]With dabigatran.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

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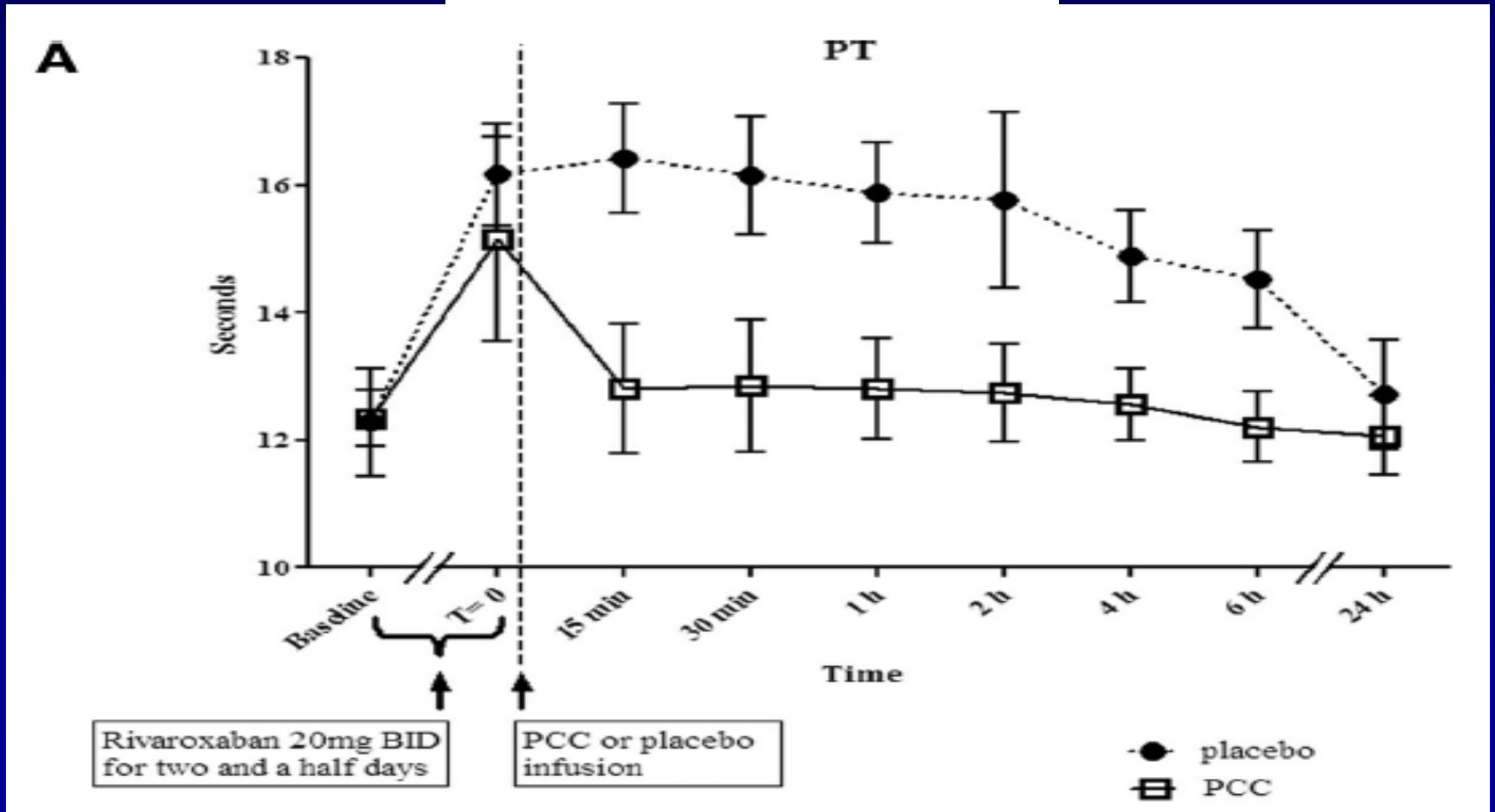

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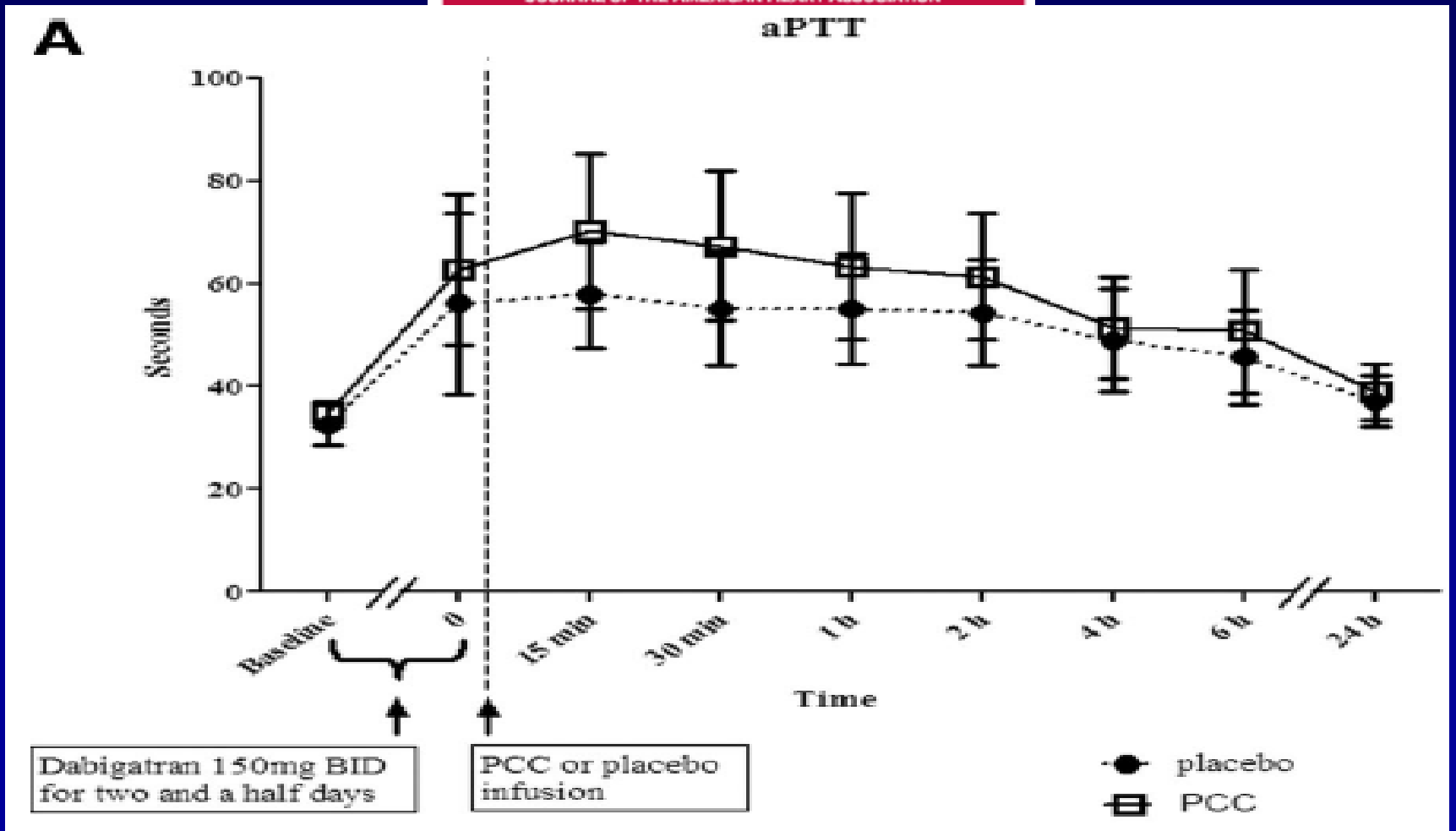

EHRA PRACTICAL GUIDE

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.

[a]No EMA approval yet. Needs update after finalisation of SmPC.

[b]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD). Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.

CrCl, creatinine clearance.

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1. SE …

Febbre

Infezione

Vomito

Diarrea

Digiuno

Rifiuto di alimentarsi

Anoressia

Bleeding Risk with Dabigatran in the Frail Elderly

TO THE EDITOR: Since July 1, 2011, the thrombin inhibitor dabigatran has been available in New Zealand for stroke prevention in patients with atrial fibrillation. There are no restrictions on prescribing, and access is free to patients through government funding. Approximately 7000 patients started treatment in the first 2 months.

Concerns from hematologists led to an audit of bleeding events that was initiated in collaboration with the Haematology Society of Australia

Table 1. Details of Episodes of Bleeding in 44 Patients Taking Dabigatran.*

Patient No.	Age	Sex	Weight	Daily Dose†	Site of Bleeding	Degree of Renal Impairment‡	Required Blood Products§
	yr		*kg*	*mg*			
1	65	M	129	300	Mucosal	Severe	No
2¶	71	M	NA	300	Hematuria	Moderate	No
3‖	77	M	60	300	Rectal	Moderate	Yes
4	78	F	NA	220	Rectal	Moderate	No
5‖	40	M	94	220	Rectal	Mild	Yes
6	65	F	79	300	Postoperative	Mild	Yes
7	71	M	75	300	Hematuria	Mild	No
8	74	M	100	220	Hematuria	Mild	No
9	75	F	NA	220	Rectal	Mild	Yes

DON'T *'FILL AND FORGET'*

”I may not speak, but I have much to say”

The ‘Angel’ Pietro

Table 3 **Interpretation of coagulation assays in patients treated with different NOACs**

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
ECT	At trough: ≥3× ULN: excess bleeding risk	Not affected	Not affected	Not affected

[a]No EMA approval yet. Needs update after finalization of SmPC.

Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as dis

PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; INR, international nor

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Dabigatran: concentrazioni plasmatiche

Donne vs uomini: 30% in +

Età > 75 vs < 65: 68% in +

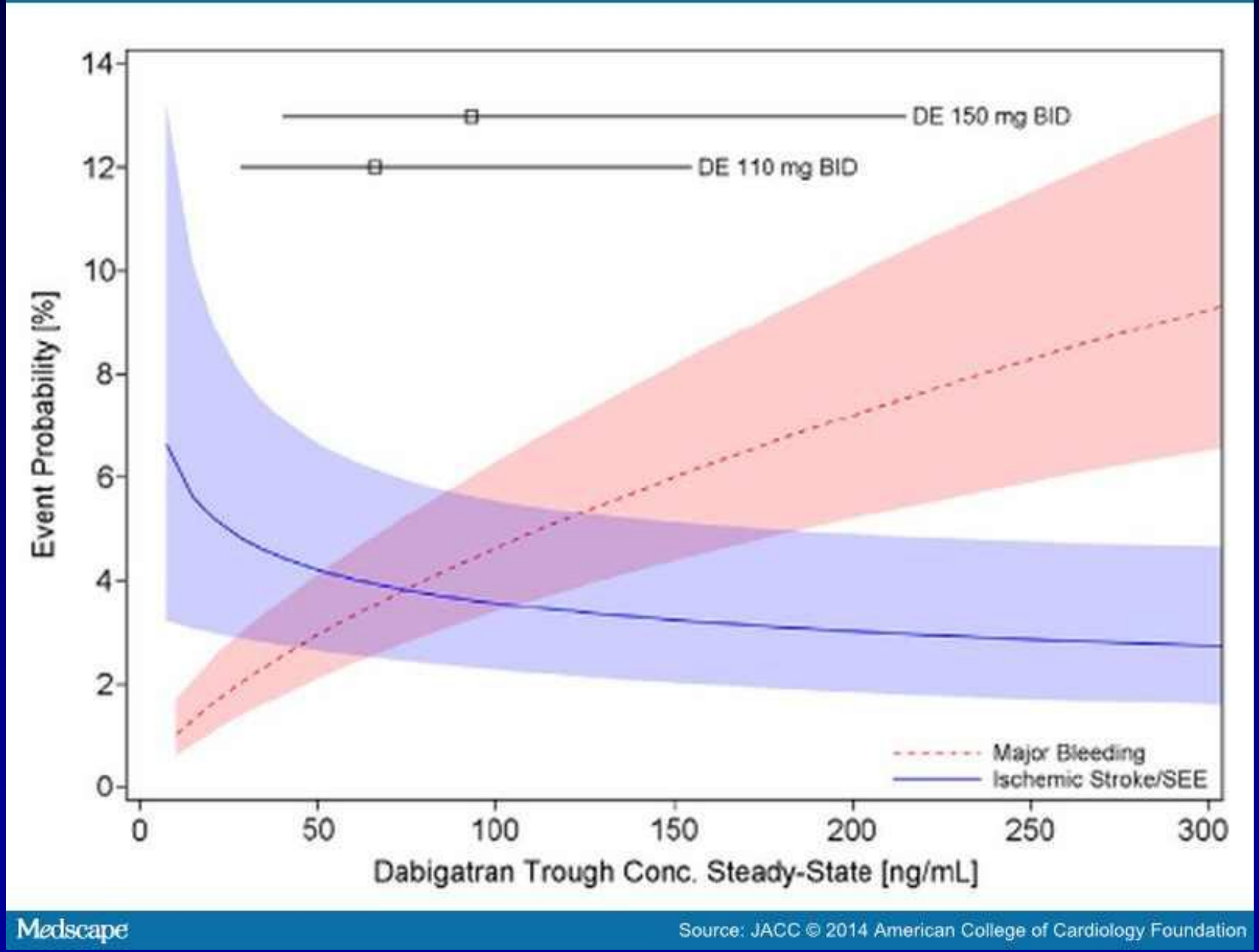
Peso <50 vs >50 Kg: 21% in + (53% se > 100 Kg)

RELY Investigators. JACC 2014

Reilly PA[1], Lehr T[2], Haertter S[3], Connolly SJ[4], Yusuf S[4], Eikelboom JW[4], Ezekowitz MD[5], Nehmiz G[3], Wang S[6], Wallentin L[7]; RE-LY Investigators.

CONCLUSIONS: Ischemic stroke and bleeding outcomes were correlated with **dabigatran plasma** concentrations. Age was the most important covariate. Individual benefit-risk might be improved by tailoring **dabigatran** dose after considering selected patient characteristics. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With **Dabigatran** Etexilate; NCT00262600).

J Am Coll Cardiol. 2014 Feb 4;63(4):321-8. doi: 10.1016/j.jacc.2013.07.104. Epub 2013 Sep 27.



Medscape

RE-LY Investigators. JACC 2014