Advances in Cardiac Arrhythmias

and

Great Innovations in Cardiology

Turin, October 25-27 2012

- Session VI -

New concepts on stroke prevention in atrial fibrillation

October 26, 2012 – 10:45-13:15

Sala Agnelli

New antithrombotic drugs: Factor Xa inhibition

Raffaele De Caterina

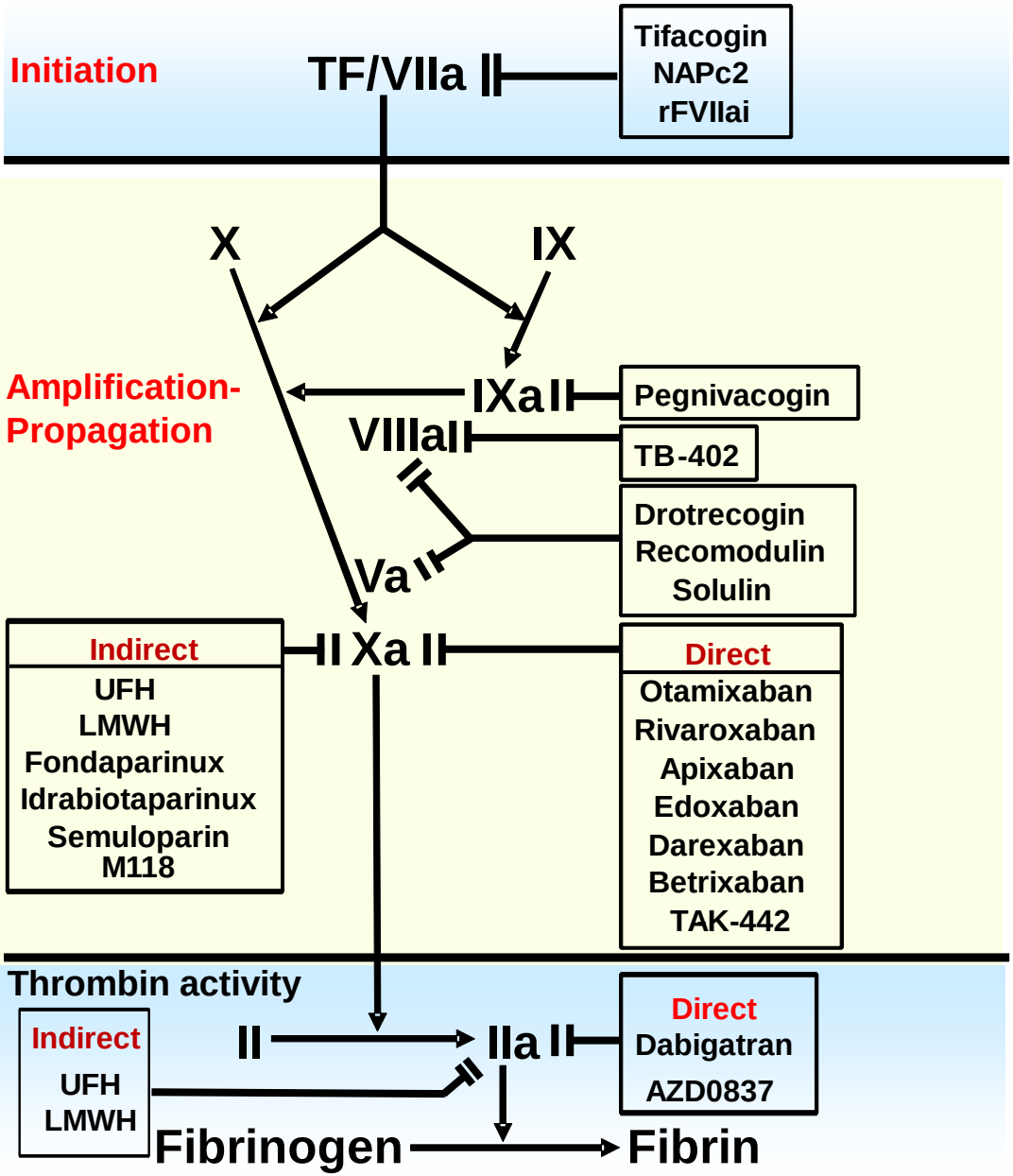
"G. d'Annunzio" University – Chieti and

"G. Monasterio" Foundation – Pisa, Italy

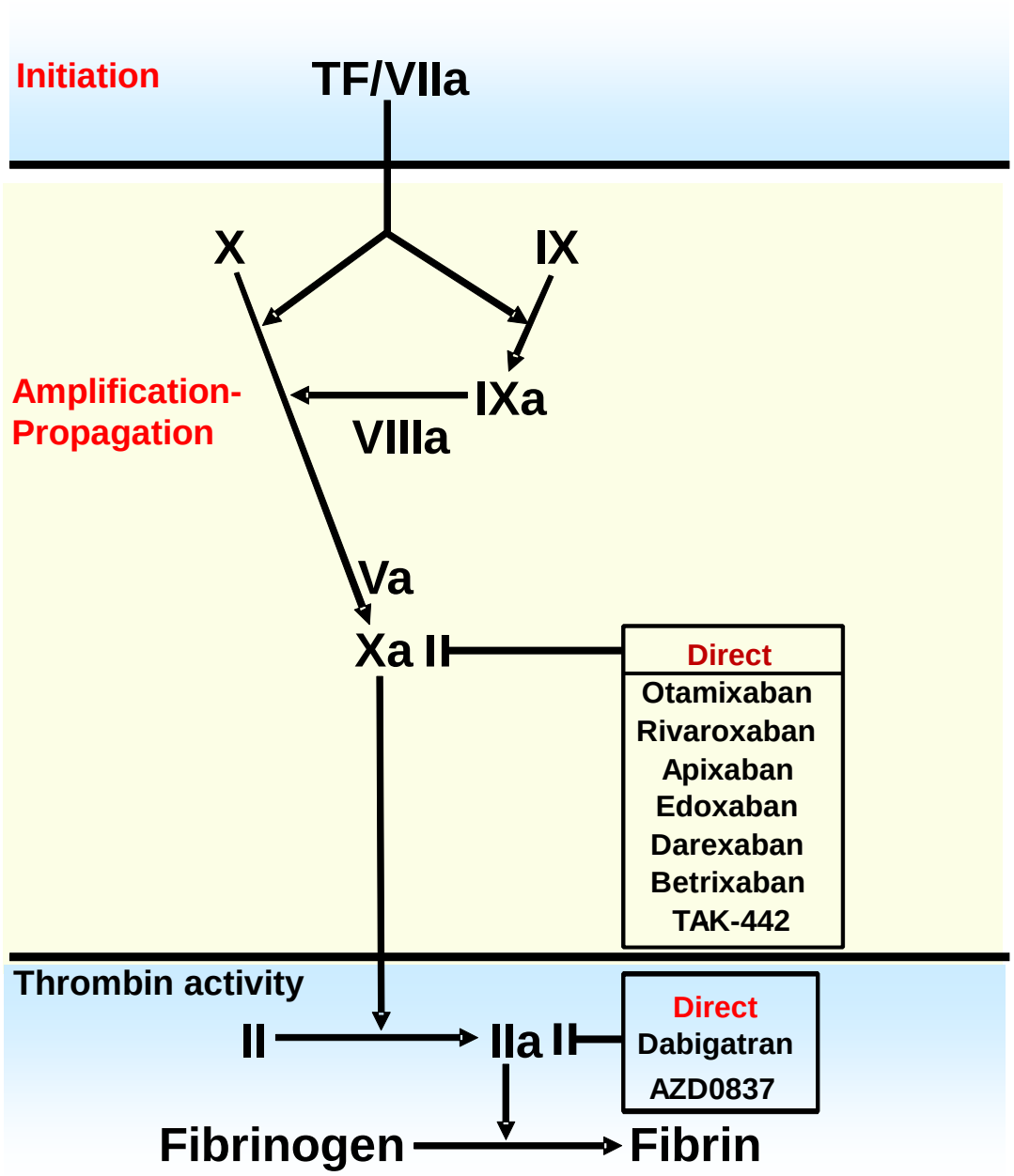
October 26, 2012 – 12:15-12:45

Prof. Raffaele De Caterina
Disclosures

- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES
- Co-author of ESC Guidelines on Atrial Fibrillation
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo



De Caterina R, Husted S, Wallentin L et al. Thromb Haemost, 2012, submitted



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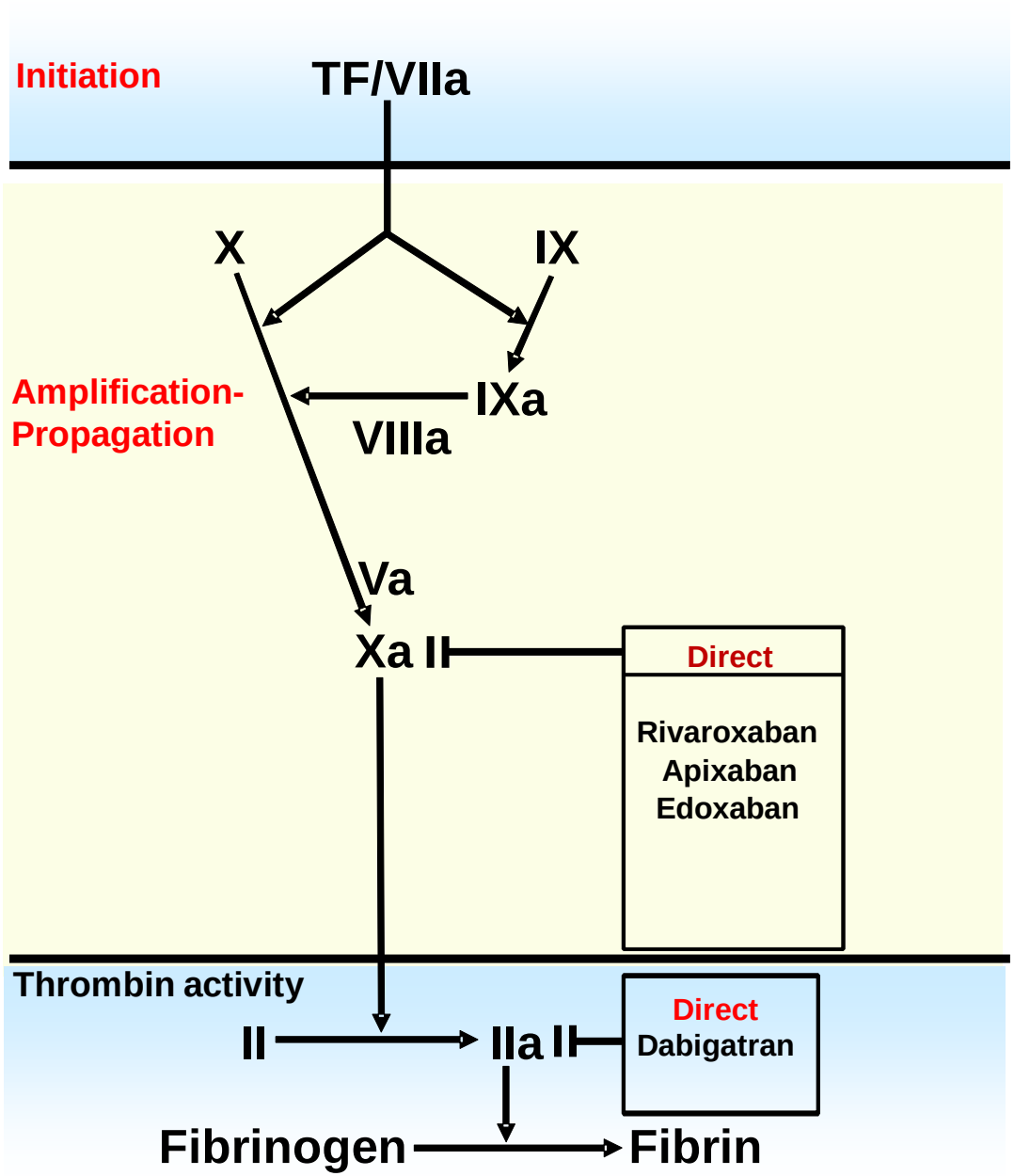

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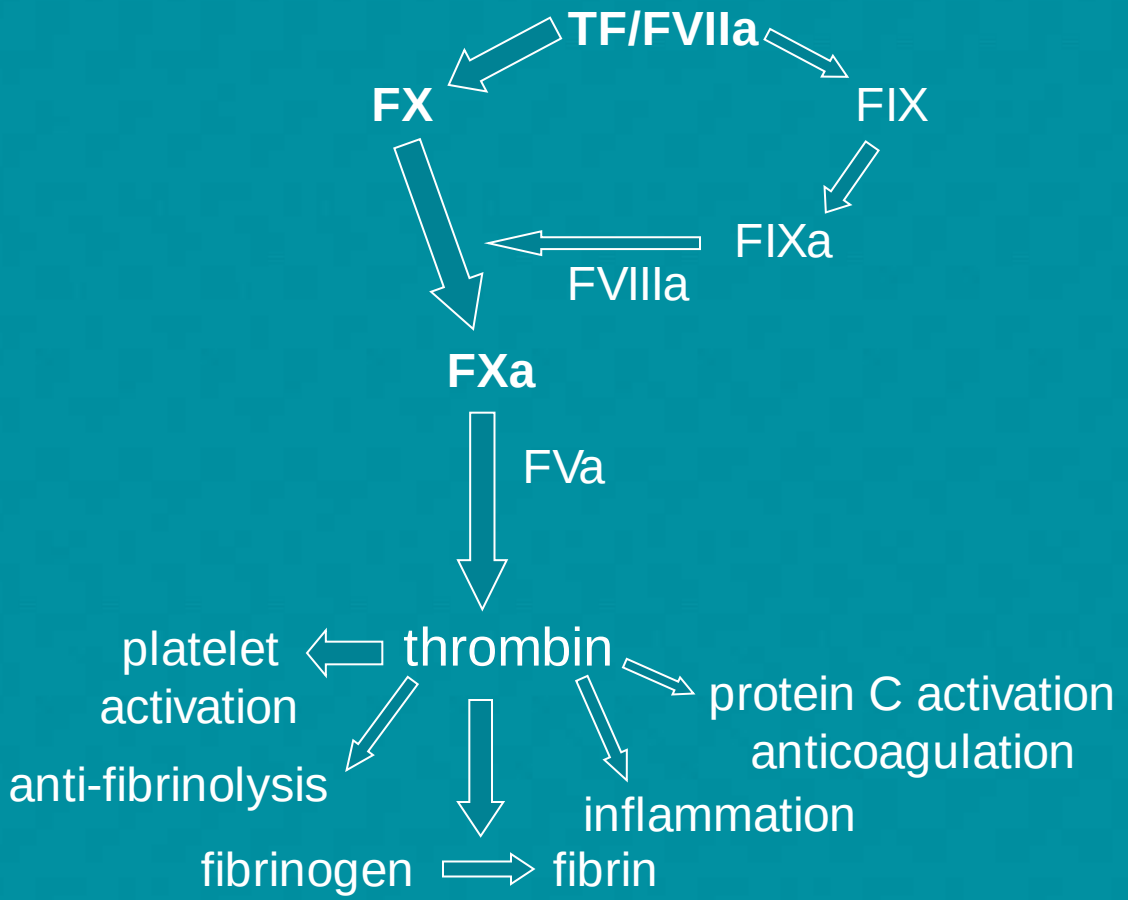
Xa inhibitors - Xabans

Is FXa a better target than thrombin?

Coagulation: an amplifying cascade



1 molecule of FXa

1000 molecules of thrombin

Mann KG, et al..J Thromb Haemost 2003; 1: 1504–14.

Early vs late inhibition of coagulation

- Because of the amplifying effect of coagulation, FXa, on a molar basis, is more thrombogenic than thrombin*
- It requires less heparin to inhibit thrombosis prior to thrombin formation than afterwards*
- Proof of concept: LMWH and pentasaccharides

*** Yin ET, Wessler S. Investigation of the apparent thrombogenicity of thrombin. Thromb Diath Haemorrh 1968; 20: 465–8.**

Early vs late inhibition of coagulation (ii)

- Within LMWH limited clinical data support the idea that compounds with a higher anti-Xa/IIa activity are more effective (efficacy to safety ratio)(Howard AW, et al. Thromb Haemost 1998; 79: 902–6; Turpie AGG, et al. Arch Intern Med 2002; 162: 1833–40)
- Not fully confirmed by later data

Is FXa a better target than thrombin?

We don't actually know, but we know that FXa is a good target

Pharmacology

Features of novel oral anticoagulants

	Dabigatran[1]	Rivaroxaban[1,2]	Apixaban[1,3]	Edoxaban[4-6]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to Cmax	1.25-3	2-4	3-4	1-2
CYP metabolism	None	32%	Minimal	<4%
Bioavailability	6%	80%	60%	62%
Transporters	P-gp	P-gp/BCRP	P-gp/ BCRP	P-gp
Protein binding	35%	93%	87%	50%
Half-life	14-17 h	7-11 h	8-15 h	8-10 h
Renal elimination	80%*	33%#	25%#	35%#

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

*Of absorbed substance

#Of ingested substance

1. Eriksson et al. Clin Pharmacokinet 2009;48:1-22; 2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2011; 3. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK; 4. Ruff et al. Hot Topics in Cardiology 2009;18:1-32; 5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract; 6. Ogata et al. J Clin Pharmacol 2010;50:743-53

JACC Vol. 59, No. 16, 2012
April 17, 2012:1413–25

Table 1 Pharmacological Characteristics of Oral Direct Thrombin Inhibitors and Oral Direct Factor Xa Inhibitors in Phase III Clinical Development

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Oral bioavailability, %	6.5	80–100	50	62
Half-life, h	12–17	5–13	8–15	6–11
Renal elimination, %	85	66 (36 unchanged and 30 inactive metabolites)	27	50§
Time to maximum inhibition, h	0.5–2	1–4	1–4	1–2
Potential metabolic drug interactions	Inhibitors of P-gp:verapamil, reduce dose; dronedarone: avoid Potent inducers of P-gp†: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid Potent inducers of CYP3A4‡ and P-gp: use with caution	Potent inhibitors of CYP3A4 and P-gp*: avoid Potent inducers of CYP3A4‡ and P-gp† use with caution	Potent inhibitors of P-gp*: reduce dose Potent inducers of P-gp†: avoid

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. †P-gp inducers include rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, and phenytoin. ‡Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort. §Of the absorbed drug.

CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein.

Once or twice daily dosing?

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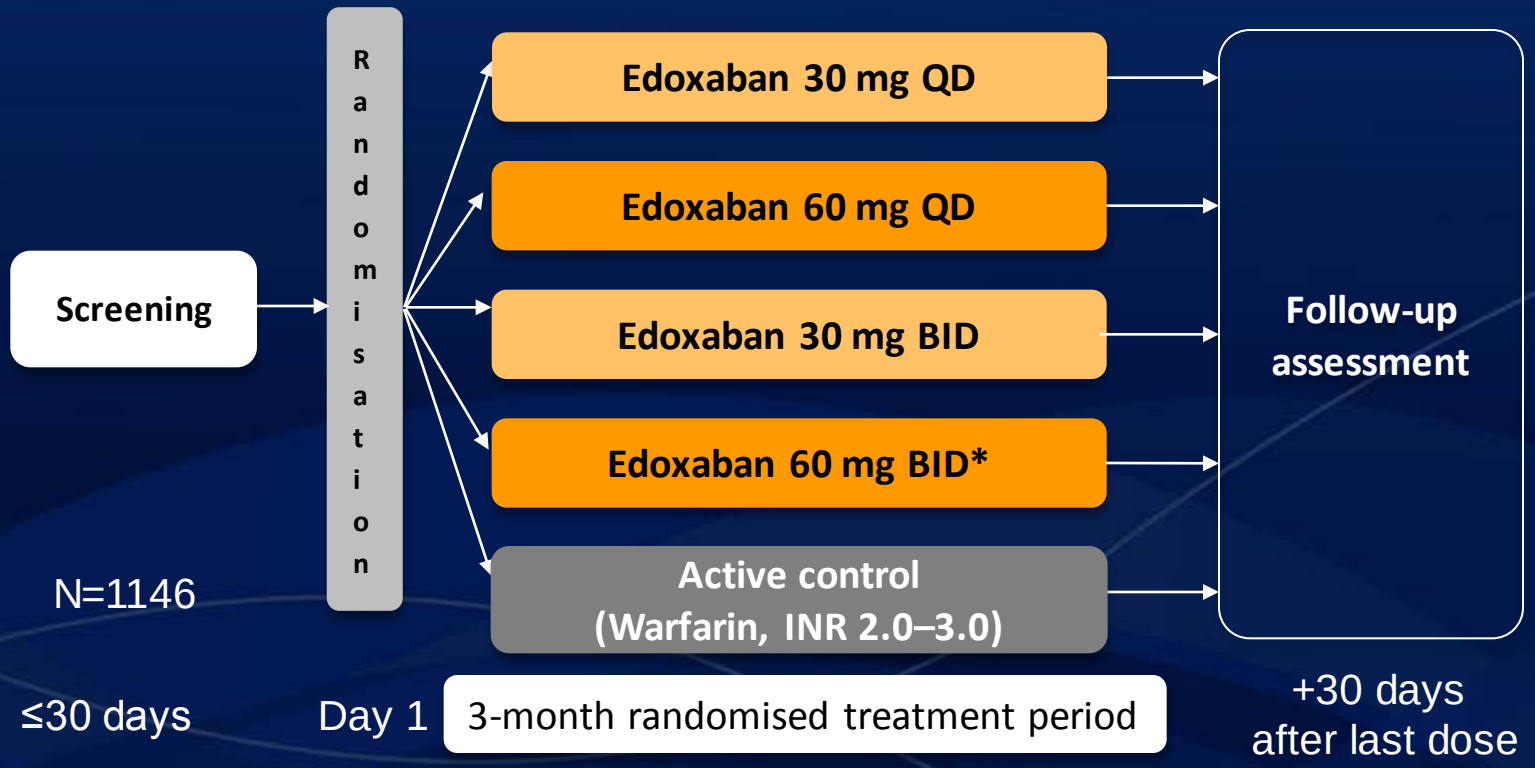
Daily dosing of FXa inhibitors in AF

- Rivaroxaban: OD
- Apixaban: BID
- Edoxaban: OD

Edoxaban phase II dose finding study in atrial fibrillation: design

Study design:
Randomised, double blind edoxaban dose regimens, open-label warfarin, parallel treatment groups

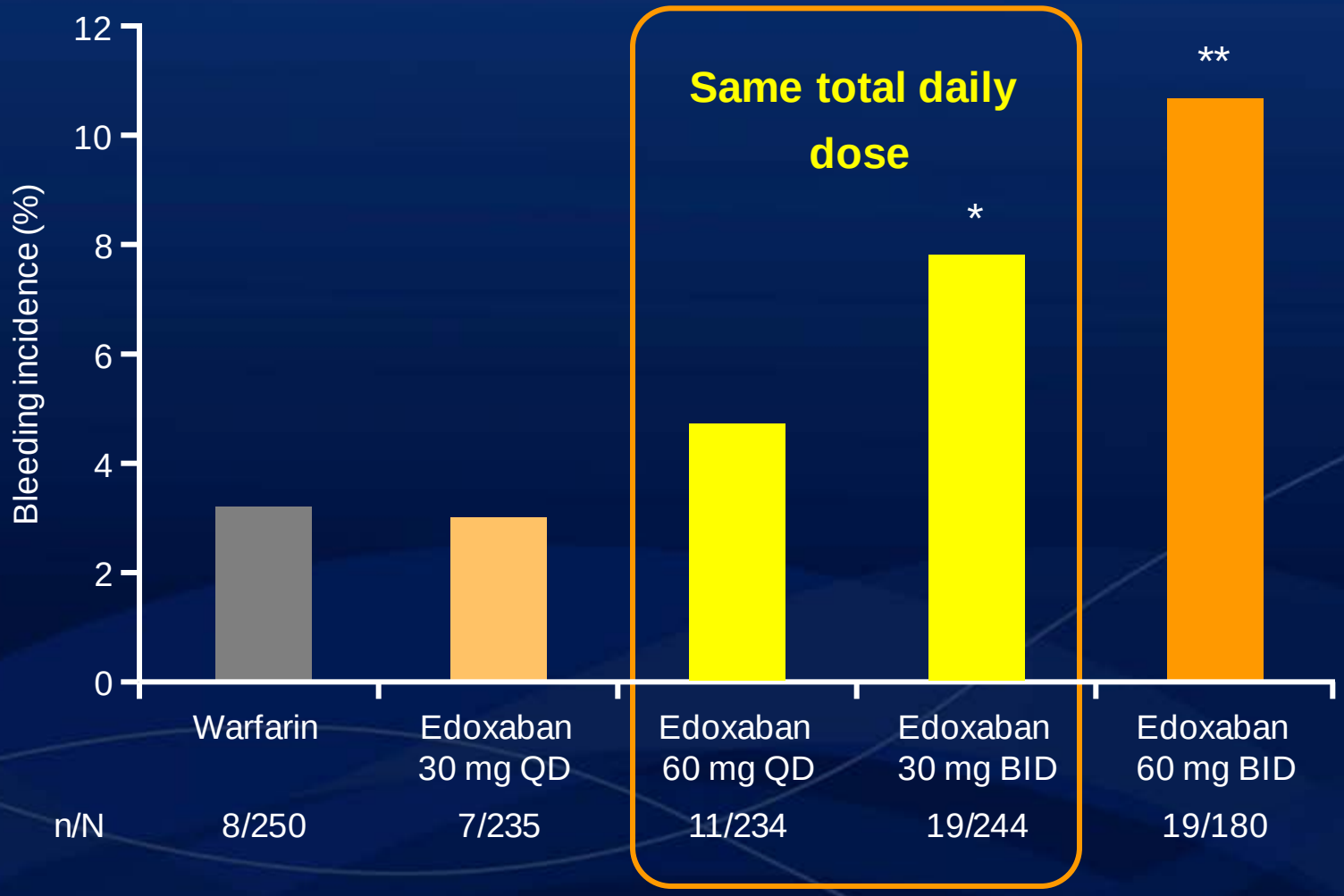
Primary endpoints:
Occurrence of major and/or clinically relevant non-major bleeding, elevated hepatic enzymes and/or bilirubin



*Stopped prematurely
QD, once daily; BID, twice daily; INR, International Normalised Ratio

Weitz et al. Thromb Haemost 2010;104:633-41

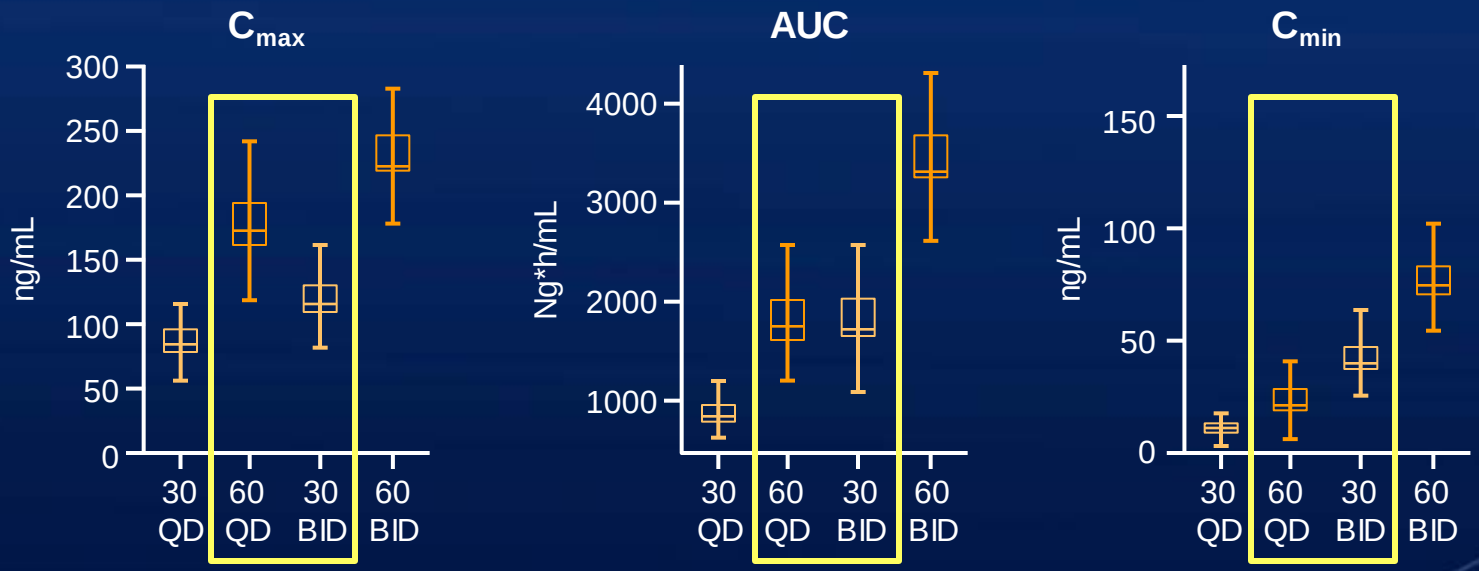
Edoxaban Phase II dose finding study in atrial fibrillation: major and clinically relevant non-major bleeding

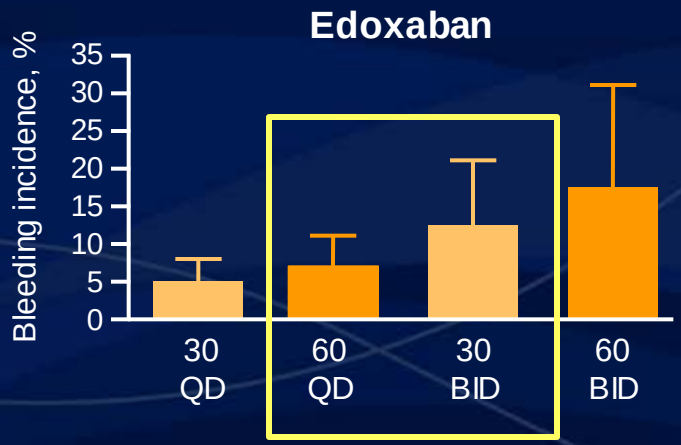


*p<0.05, **p<0.01, vs warfarin
QD, once daily; BID, twice daily

Weitz et al. Thromb Haemost 2010;104:633-41

Edoxaban phase II dose finding study in atrial fibrillation: exposure and bleeding





AUC, area under the plasma concentration-time curve from 0 to 24 hours at steady-state;
C_{max}, maximum steady-state plasma concentration;
C_{min}, minimum steady-state concentration;
QD, once daily;
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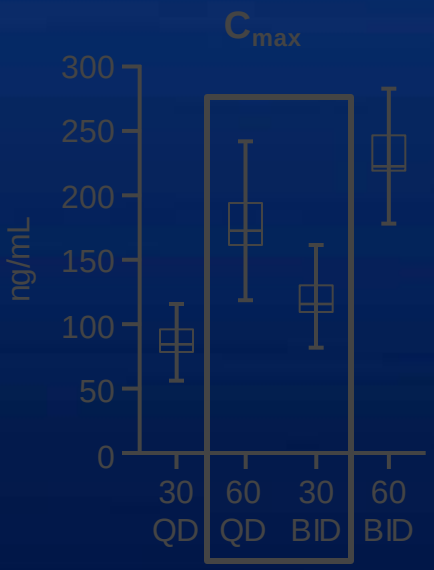

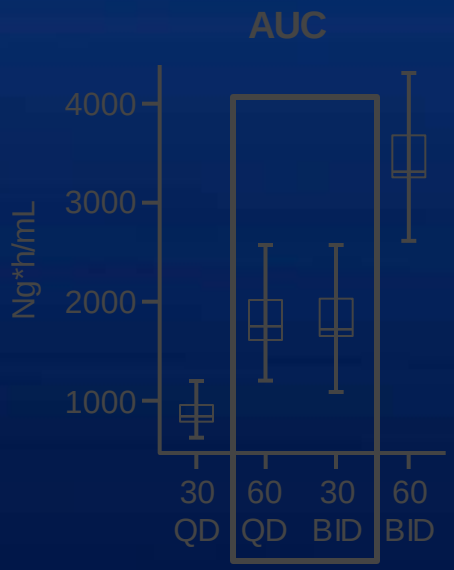

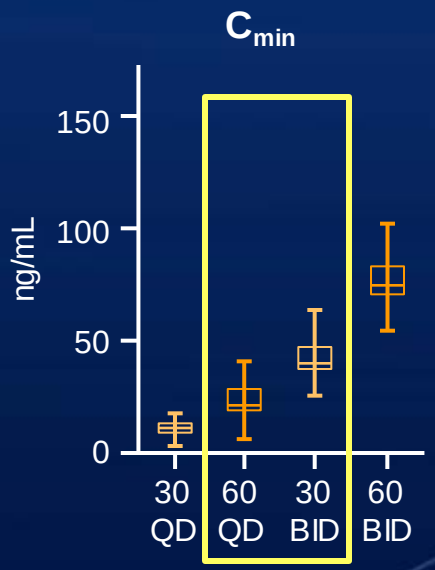

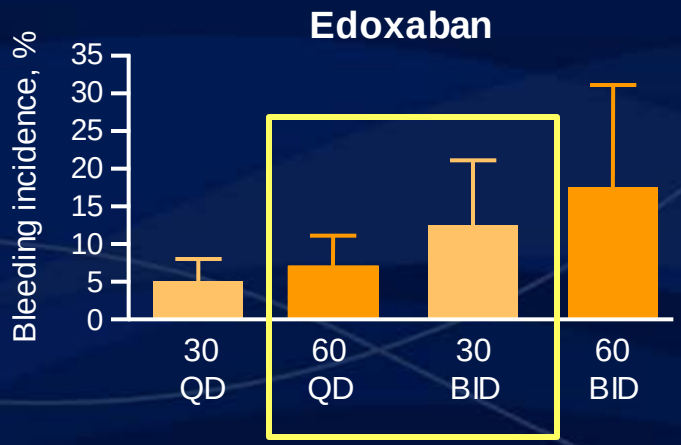

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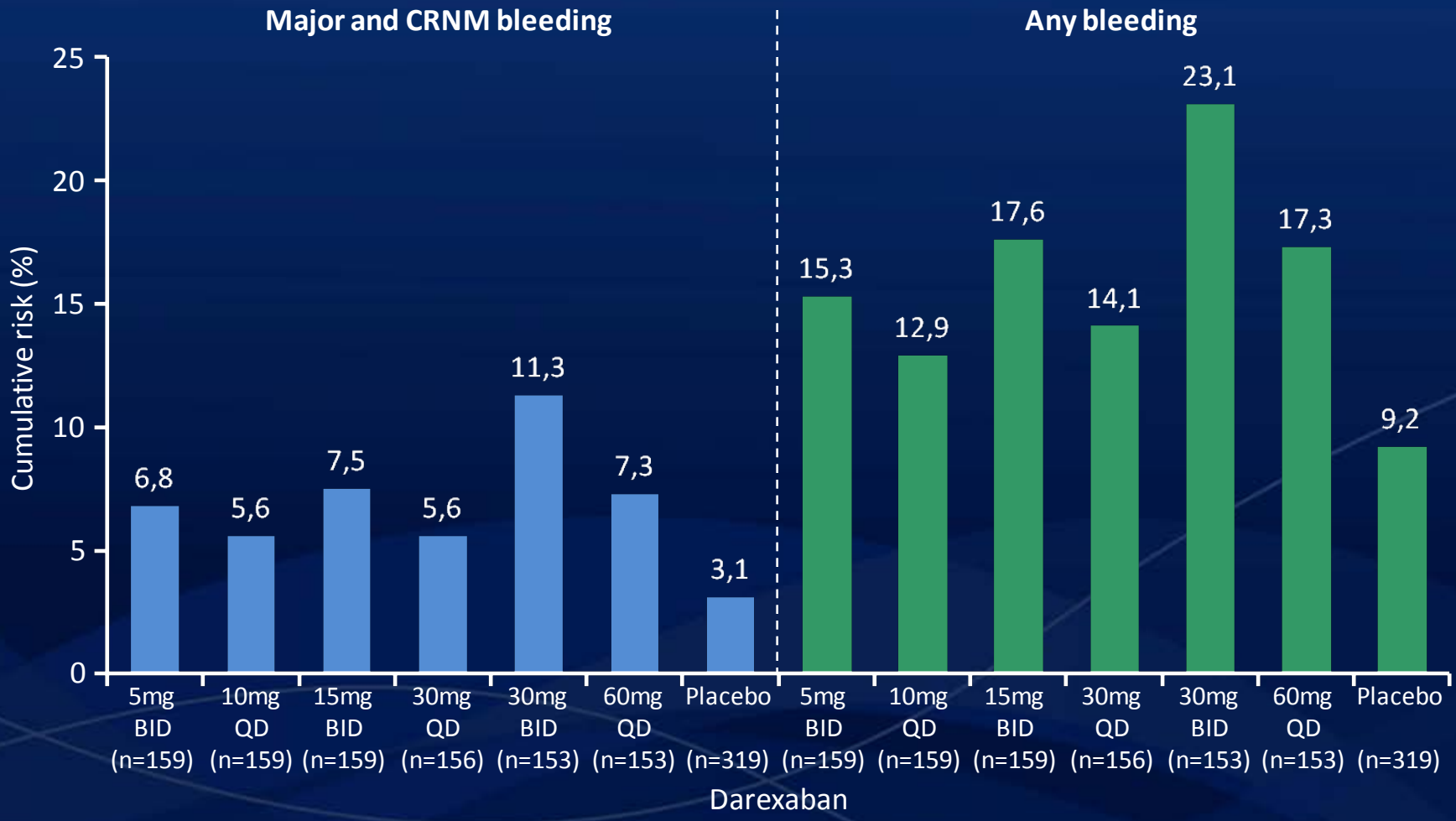
RUBY-1: cumulative risk of major and clinically relevant non-major bleeding and any bleeding events at 6 months (safety analysis set)



CRNM, clinically relevant non-major
BID, twice daily; QD, once daily

Steg et al. Eur Heart J 2011;32:2541–4

Dependence on renal function

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STATE-OF-THE-ART PAPER

New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes

ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper

Coordinating Committee: Raffaele De Caterina, MD, PhD,* Steen Husted, MD, DSc,† Lars Wallentin, MD, PhD,‡

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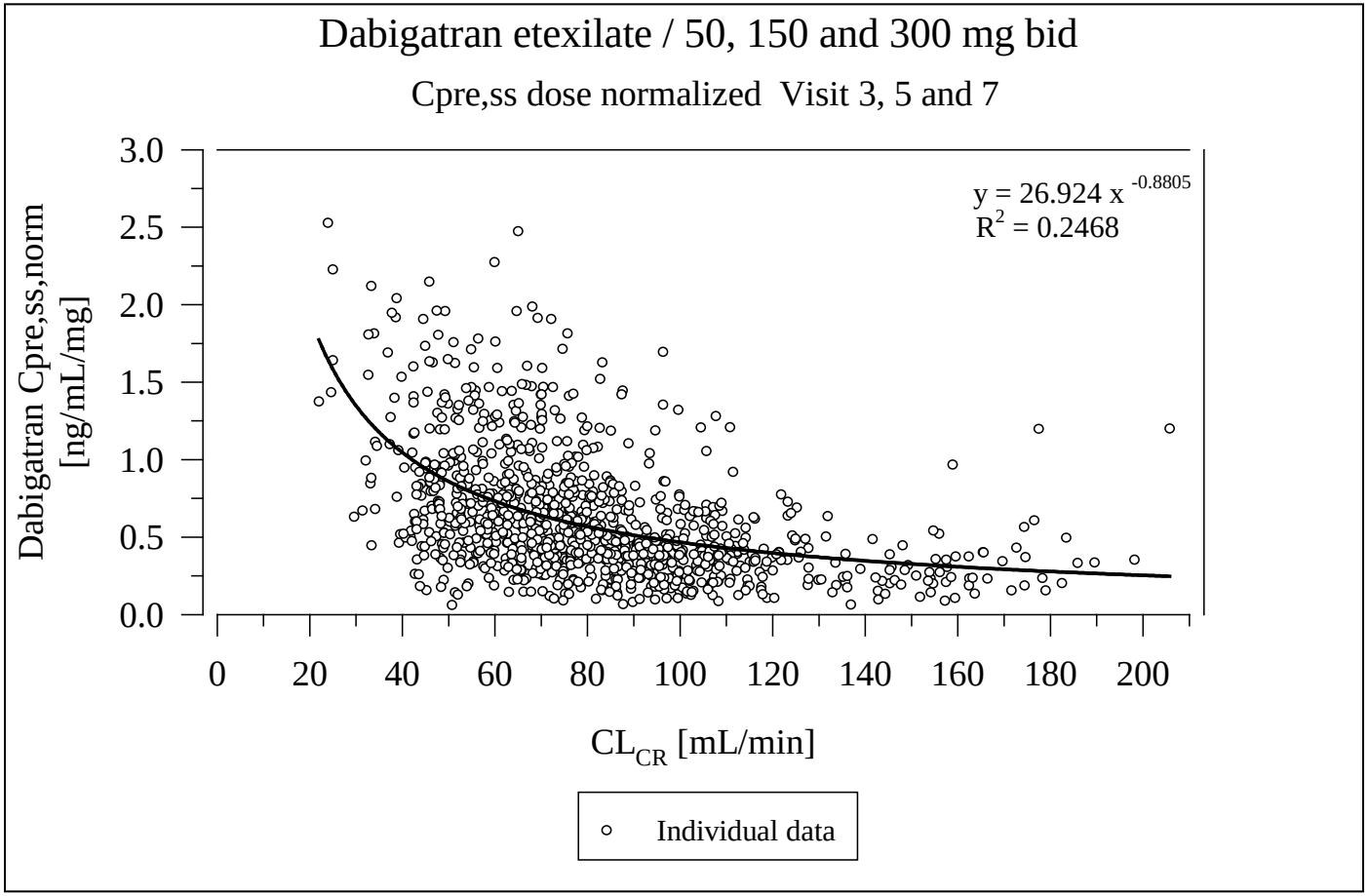
Plasma Concentrations of Dabigatran Strongly Depend on Renal Clearance



25 % of interindividual variability is explained by differences in CRCL

For FXa inhibitors – policy adopted in AF trials

- Rivaroxaban: "…*20 mg daily, or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml per minute*"
- Apixaban: "*twice daily, with apixaban given in 5-mg doses; 2.5-mg doses were used in a subset of patients with two or more of the following criteria: an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg per deciliter (133 µmol per liter) or more*".

Patel MR, et al. N Engl J Med. 2011; 365:883-91
Granger CB, et al. N Engl J Med. 2011; 365981-92

For FXa inhibitors – policy adopted in AF trials

- Edoxaban: "*Patients are randomized to edoxaban 60 mg in the high-exposure group, 30 mg in the low-exposure group, or warfarin. If patients randomized to 1 of the 2 edoxaban groups have an anticipated increased drug exposure (any one or multiple of the following: creatinine clearance [CrCl] 30-50 mL/min calculated with the Cockcroft-Gault formula, 17 body weight ≤60 kg, or concomitant administration of verapamil or quinidine [strong P-gp inhibitors]), they receive a 50% dose reduction (60 mg reduced to 30 mg in the high-exposure group; 30 mg reduced to 15 mg in the low-exposure group). This dose reduction can occur at randomization or at anytime during the trial if subjects develop moderate renal dysfunction, have a drop in body weight to ≤60 kg, or are prescribed verapamil or quinidine*".

Ruff CT et al., Am Heart J 2010;160:635-641.e2

Control of anticoagulant activity

For rivaroxaban, apixaban, edoxaban

- FXa activity probably the best test
- Some idea of whether a patient is on the drug by the PT/INR test, BUT NOT RELYING ON THE USUAL COAGULATION RANGES

Handling of bleeding

Handling of bleeding

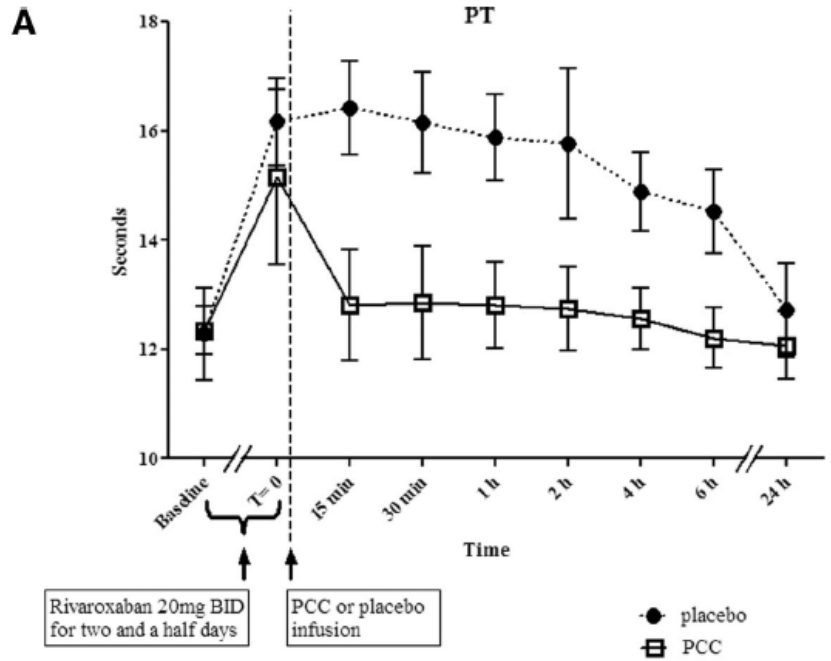
- None of the NOACs currently has specific antidotes
- For Xa inhibitors (especially rivaroxaban and apixaban) – dialysis unlikely to be effective
- PCC o aPCC, o FVIIa (NovoSeven®)?

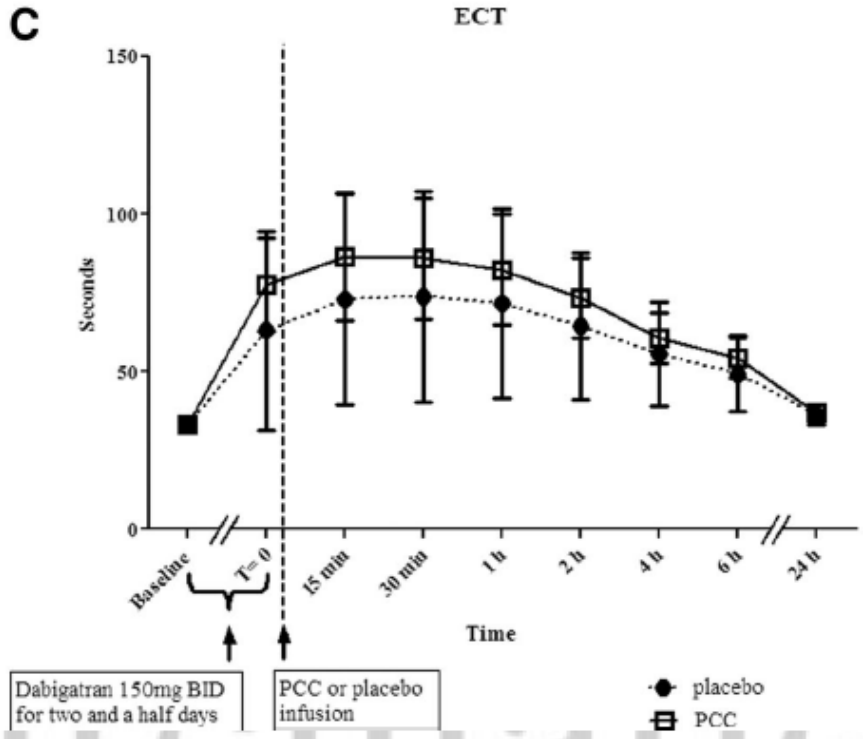
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc;
Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

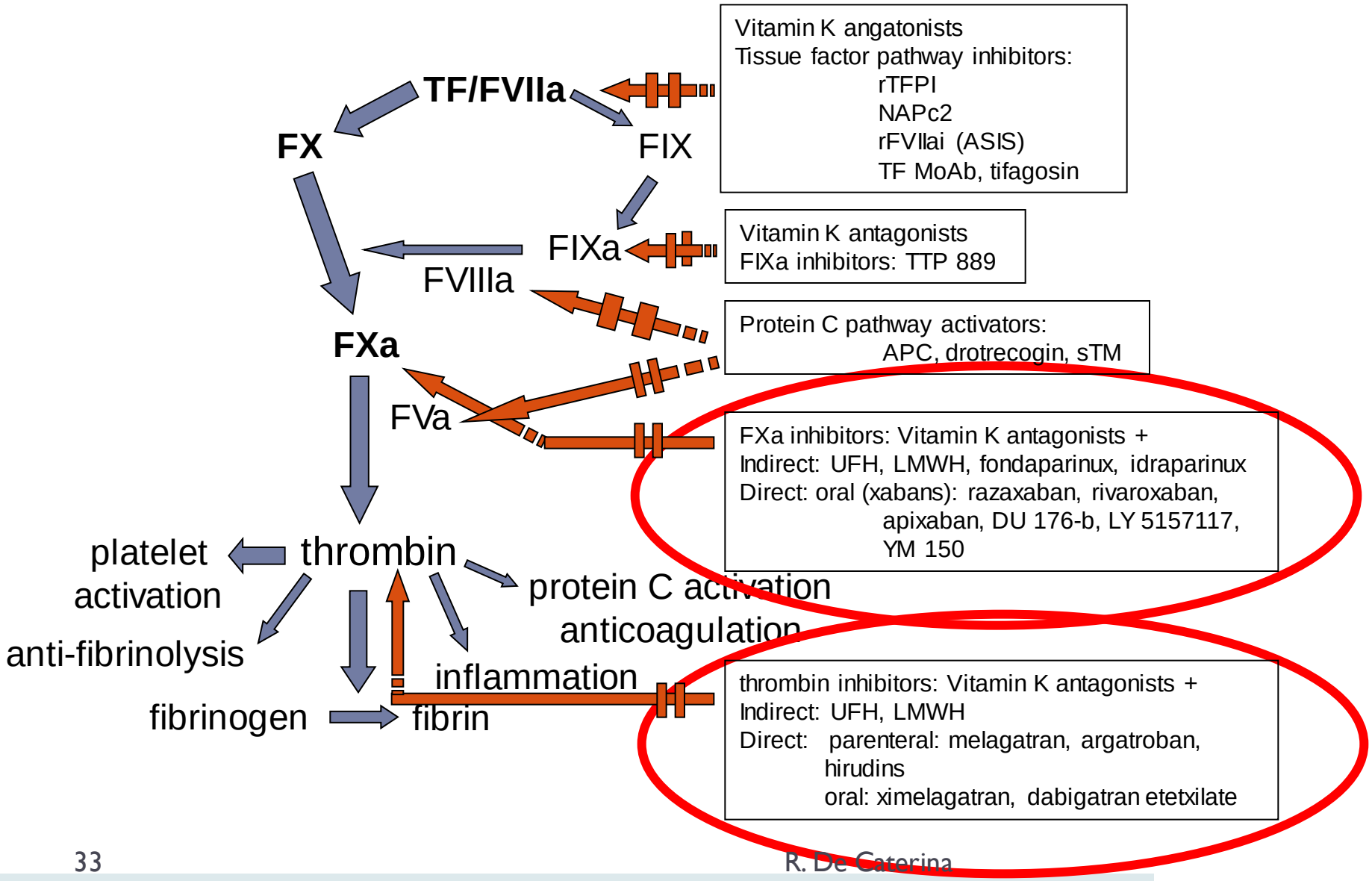
(*Circulation*. 2011;124:00-00.)





rivaroxaban

dabigatran



De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease – EHJ 2007; 28: 880-913

Beriplex P/N Reverses Bleeding in an Acute Renal Injury Model after Dabigatran Overdose in Rabbits

I. Pragst[1], B. Dörr[1], F. Kaspereit[1], W. Krege[1], S. Zeitler[1], J. van Ryn[2]
[1]CSL Behring GmbH, 35041 Marburg, Germany;
[2]Boehringer Ingelheim Pharma GmbH & Co KG, 88397 Biberach, Germany

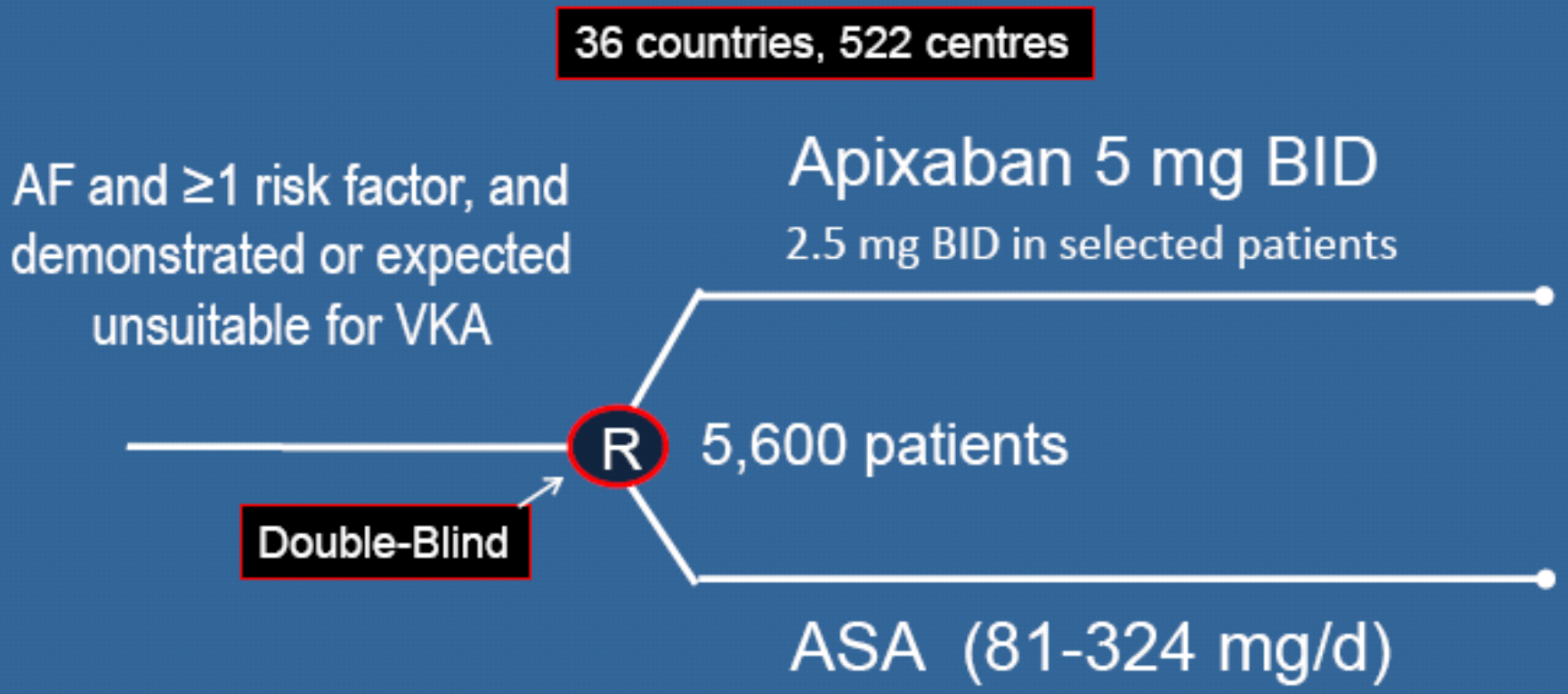
The Successful Reversal of Dabigatran-Induced Bleeding by Coagulation Factor Concentrates in a Rat Tail Bleeding Model Does Not Correlate with Ex Vivo Markers of Anticoagulation

J. van Ryn, H. Schurer, M. Kink-Eiband, A. Clemens
Depts. CardioMetabolic Disease Research and Medical Affairs, Boehringer Ingelheim Pharma GmbH & Co KG, 88397 Biberach, Germany

Boehringer Ingelheim

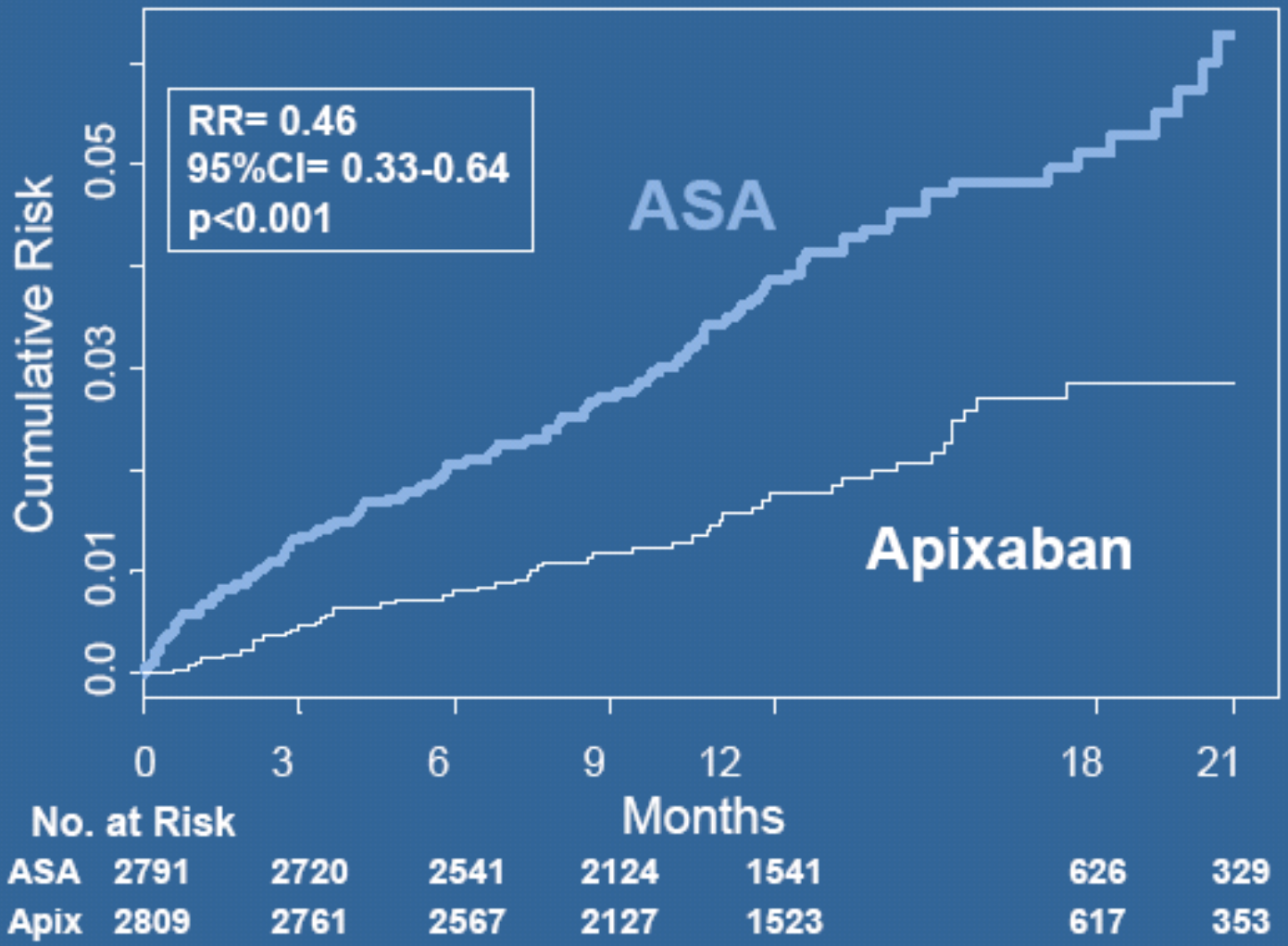
Oral FXa inhibitors in atrial fibrillation

AVERROES Design



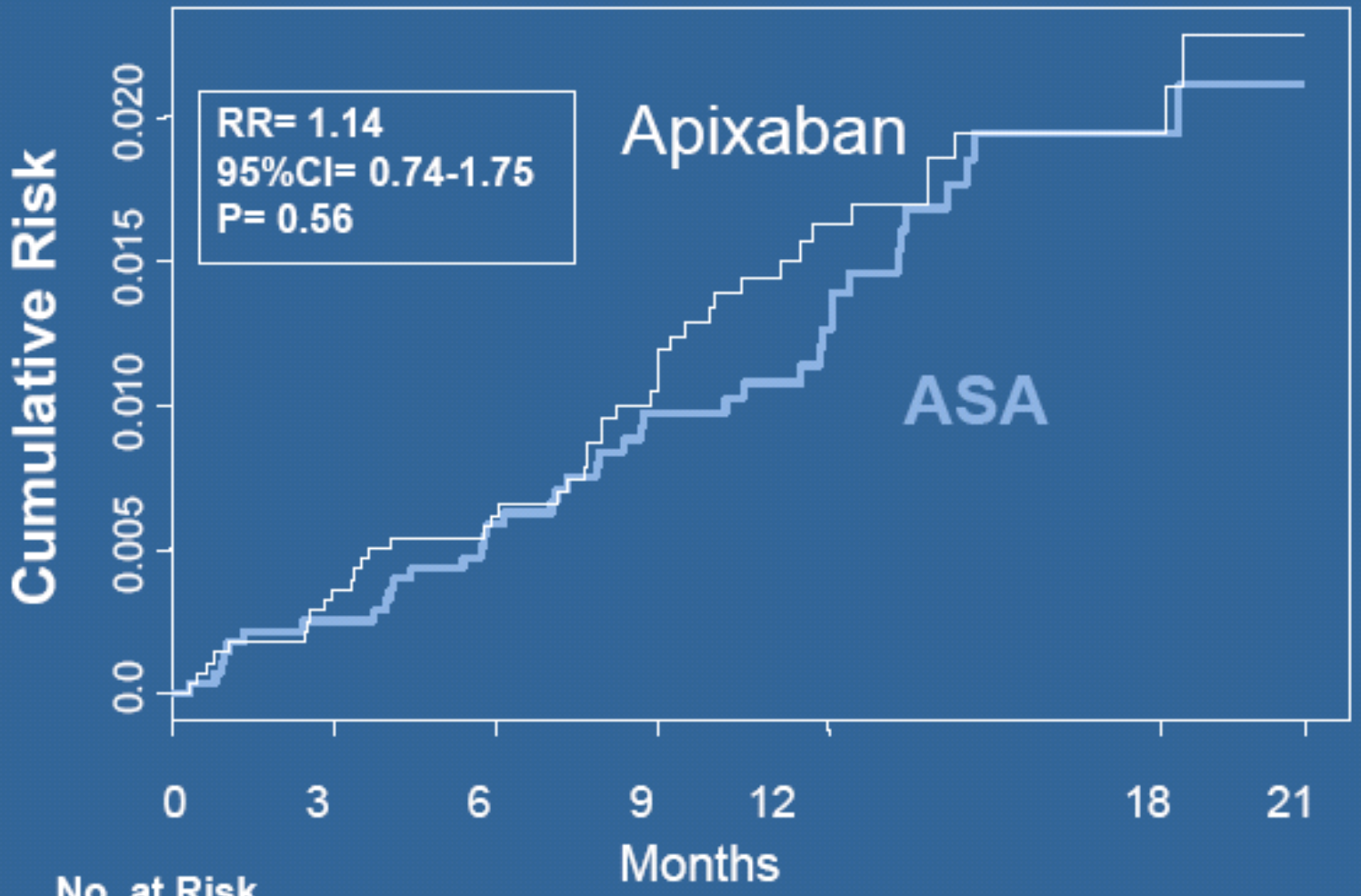
Primary Outcome: Stroke or Systemic Embolic Event (SEE)

Stroke or Systemic Embolic Event



preliminary Results

Major Bleeding



No. at Risk							
ASA	2791	2744	2572	2152	1570	642	340
Apix	2809	2763	2567	2123	1521	622	357

preliminary Results

Study Design

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Atrial Fibrillation

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind / Double Dummy
(n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

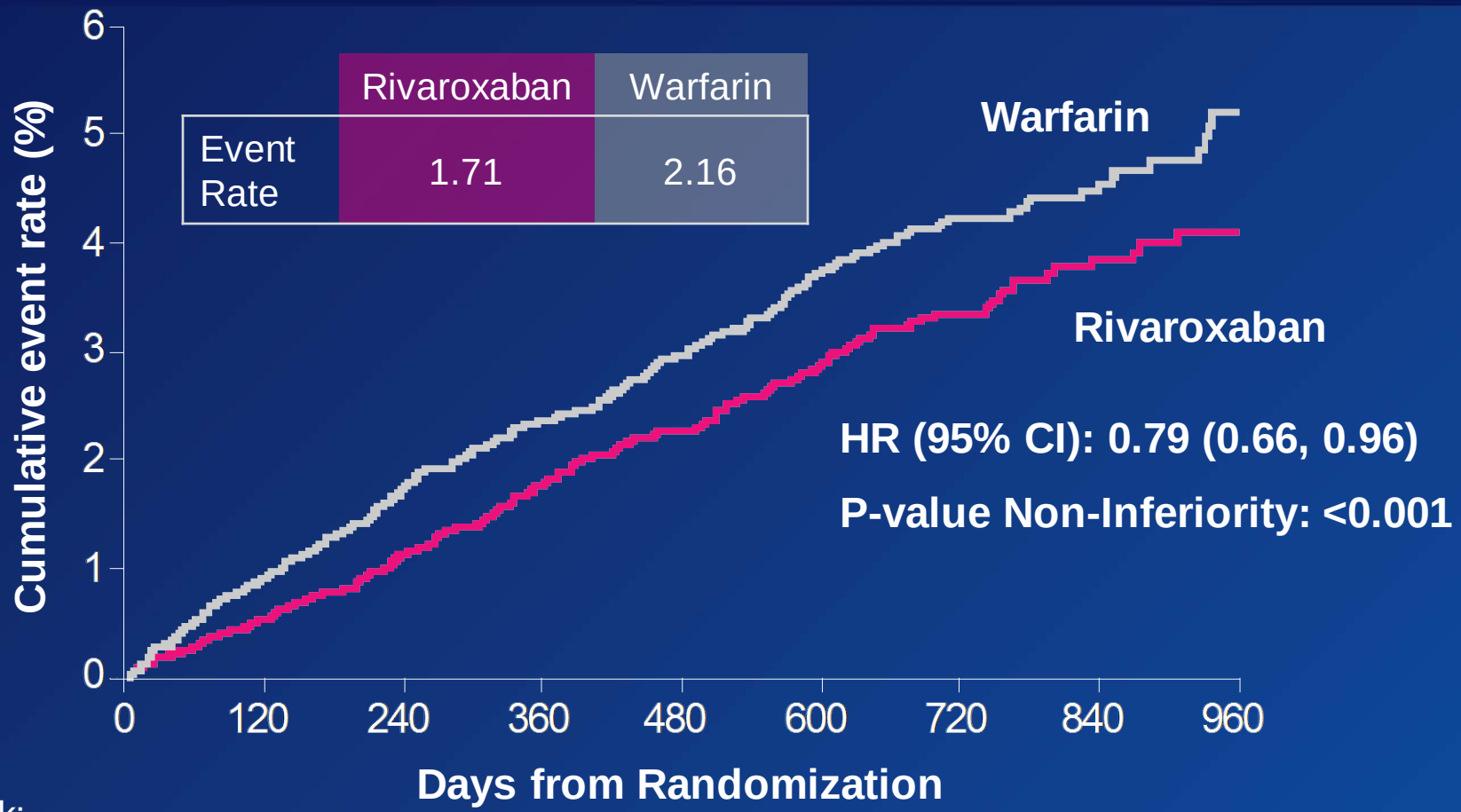
Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

ROCKET AF

Primary Efficacy Outcome
Stroke and non-CNS Embolism



No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

ROCKET AF

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

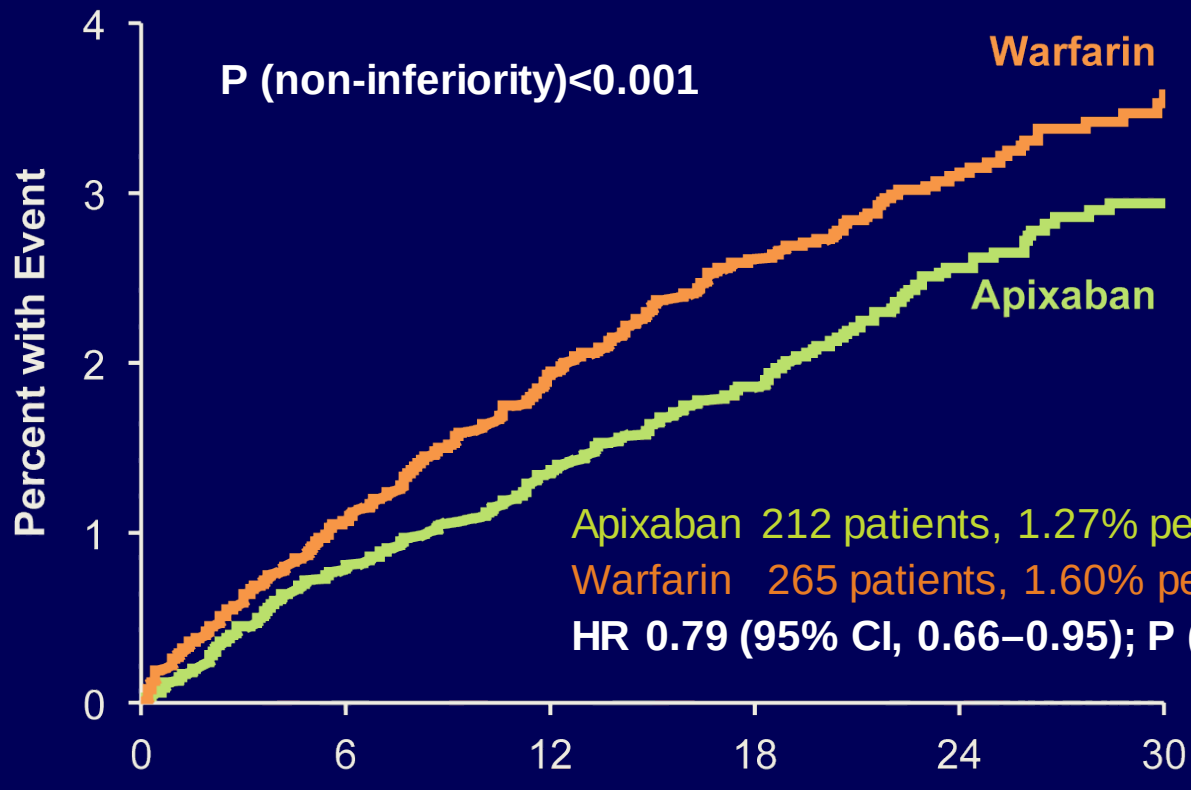
Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Duke Clinical Research Institute

UCR
UPPSALA CLINICAL RESEARCH CENTER

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Duke Clinical Research Institute

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Study design

Largest Study in AF

N = 20,500

AF on Electrical Recording ≤ 12 mo
Intended oral A/C
CH

Double blind

Only Factor Xa inhibitor with two doses in phase III

R

Low Exposure Strategy
Edoxaban 30 mg QD

High Exposu Strategy
Edoxaban 60 mg QD

Once daily

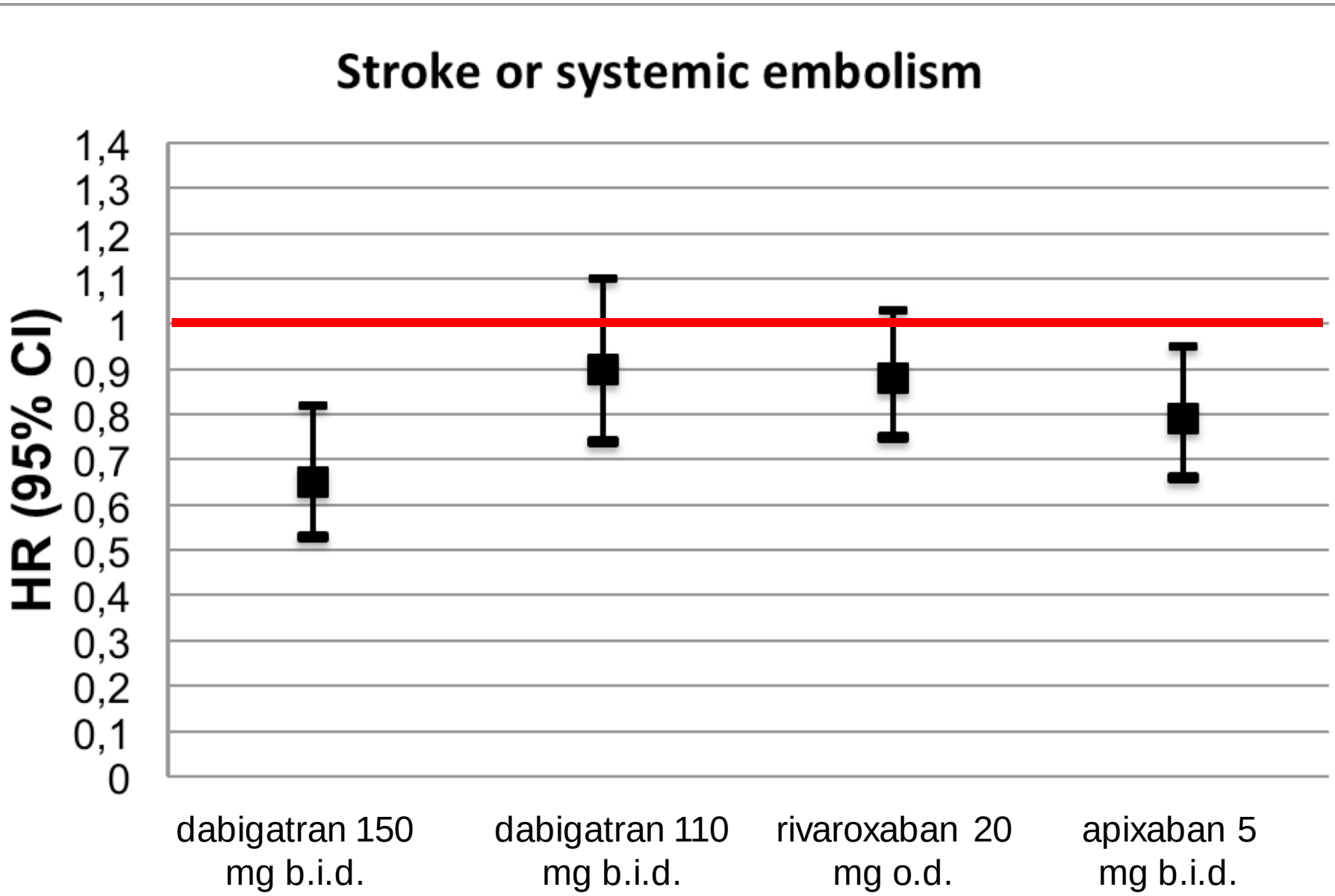
Active Control
Warfarin
(INR 2.0 – 3.0)

Median duration of follow up 24-months

Primary Objective
Edoxaban: Therapeutically as good as Warfarin

1º EP = Stroke or SEE (Non inferiority Boundary HR 1.38)
2º EP = Stroke or SEE or All-Cause Mortality
Safety EPs = Major Bleeding, Hepatic Function

SEE=systemic embolic event



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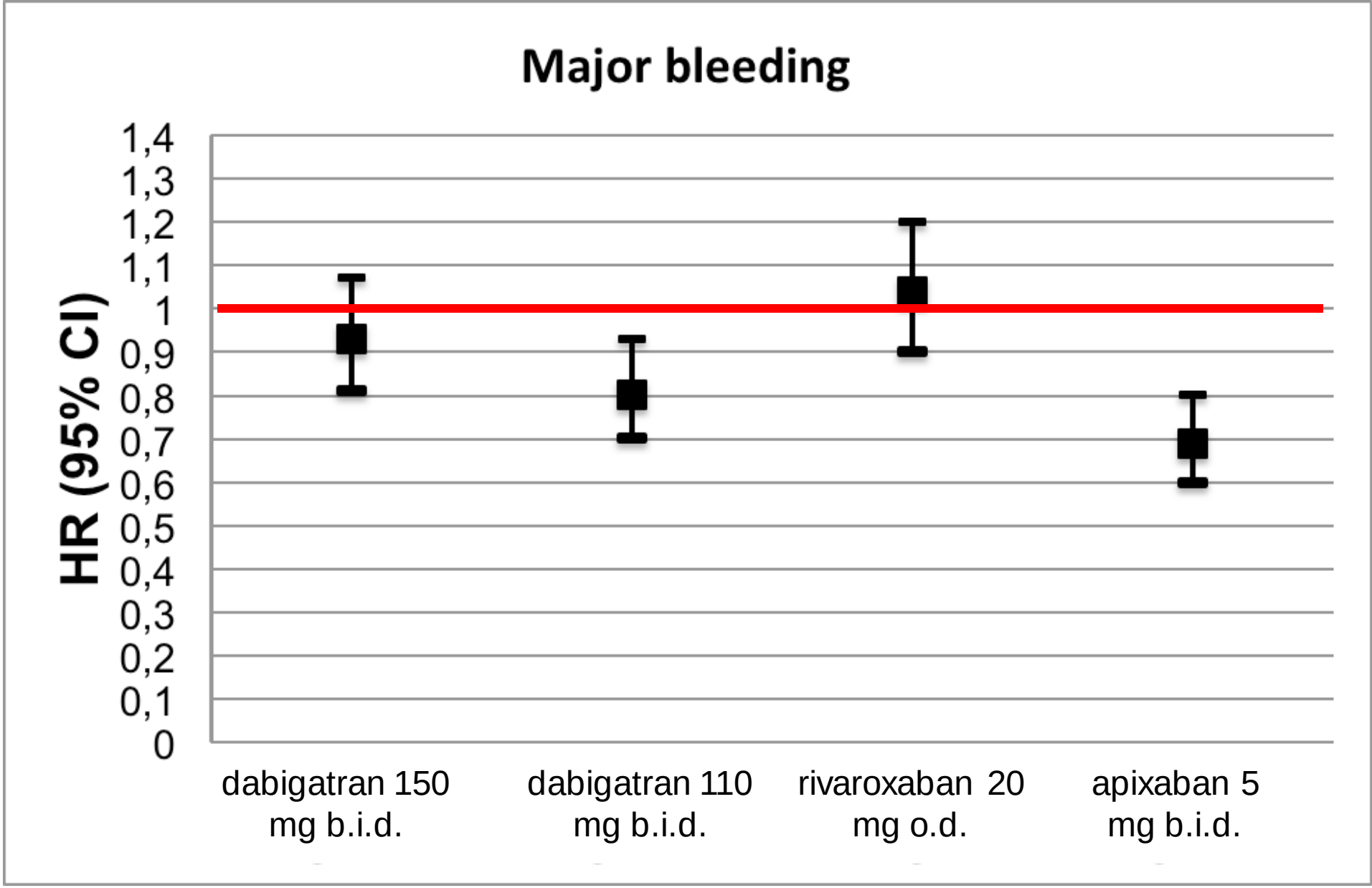
April 17, 2012:1413–25



De Caterina R, Husted S, Wallentin L et al.

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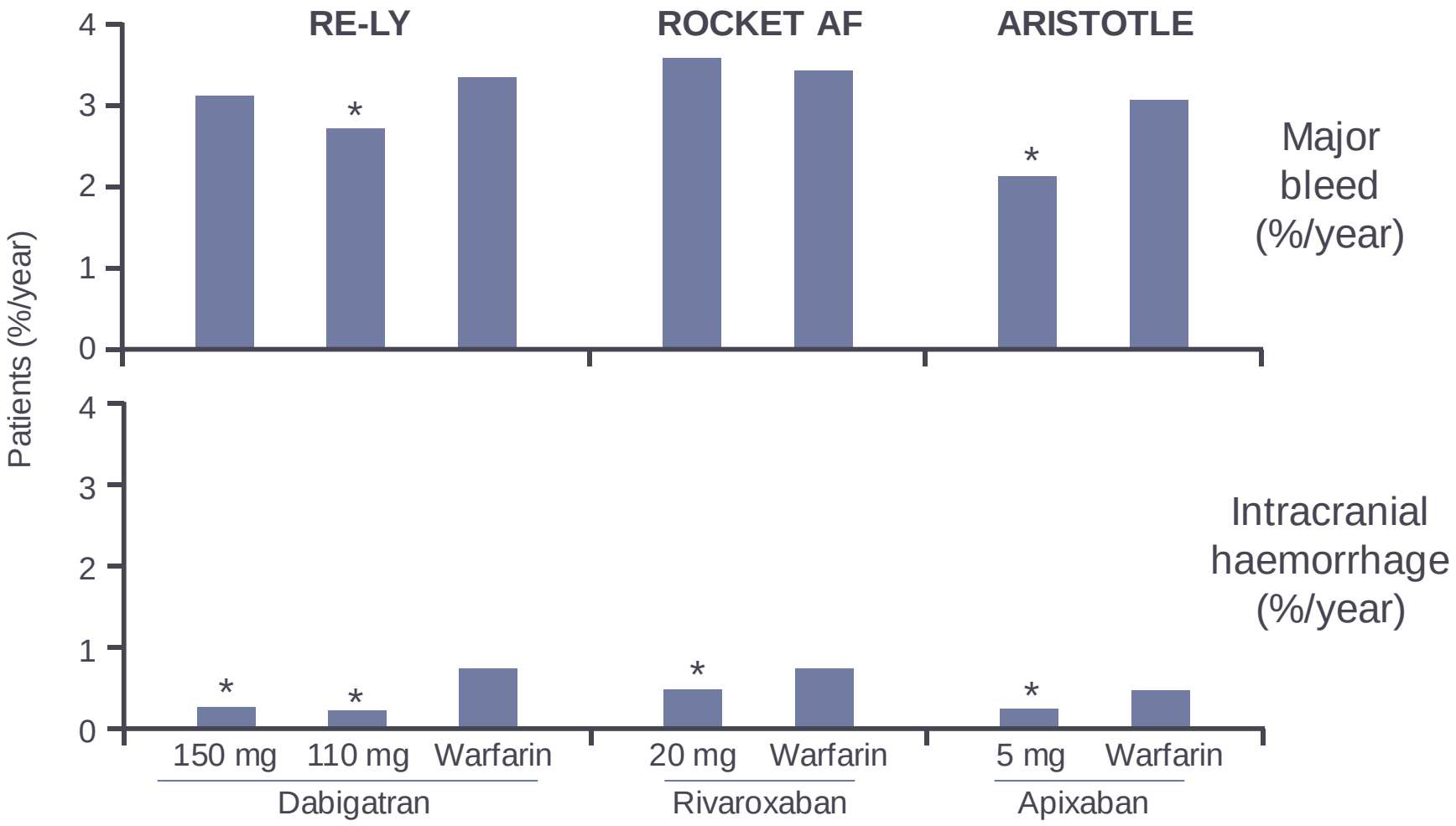
Less intracranial bleeding (consistently)



*P<0.05 vs warfarin

Connolly SJ, et al. N Engl J Med 2009;Aug 30:[Epub]
Patel MR, et al. N Engl J Med 2011;Aug 10:[Epub]
Granger CB, et al. N Engl J Med 2011 (doi 10.1056/NEJMoa1107039)

Weighted Net Clinical Benefit of Antithrombotic Therapy: An Evidenced-Based Method For Its Assessment and Application to ACTIVE A - *The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events*

Running title: Weighted Net Clinical Benefit

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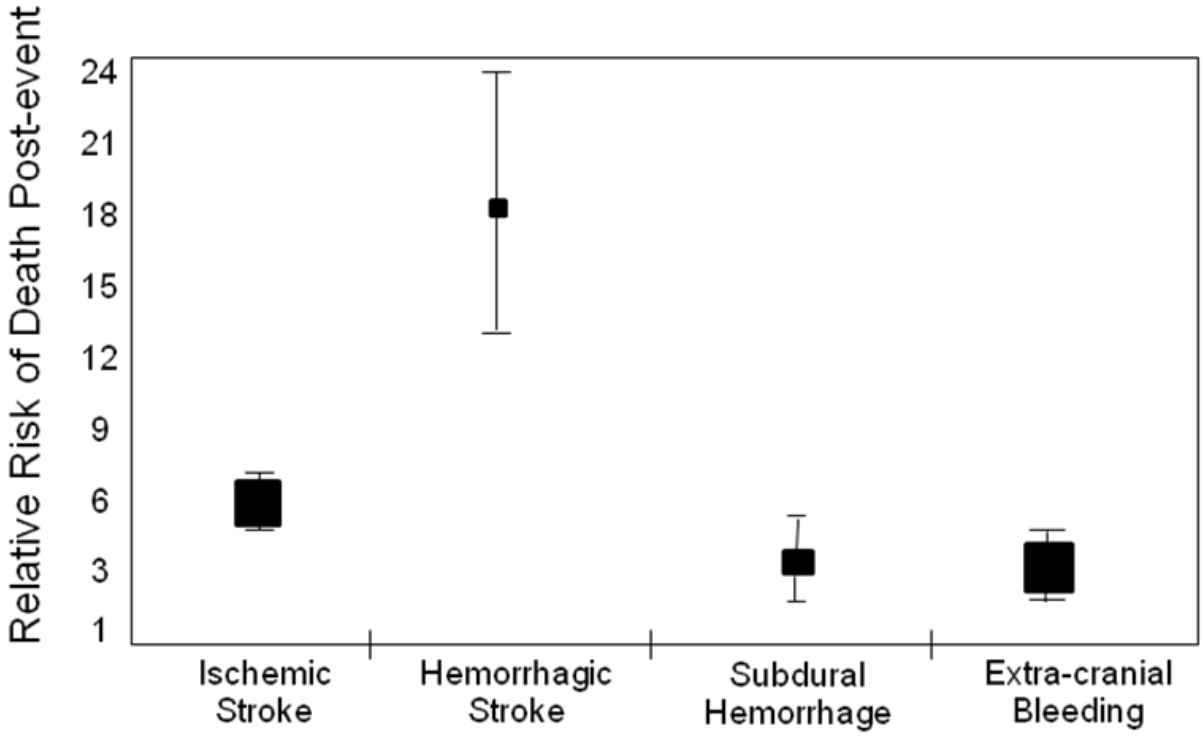
On behalf of the ACTIVE Steering Committee and Investigators
(Drs. Hart and Connolly contributed equally to this paper)

Ann Intern Med, 2011



Event	Ischemic Stroke	Hemorrhagic Stroke	Subdural Hemorrhage	Extracranial Hemorrhage
Weighting	1.00	3.00	0.64	0.63

New OACs vs Warfarin: 2012 Summary

Effect on outcome event	D150	D110	Riva	Apx
Non inferiority stroke	√	√	√	√
↓ Hemorragic stroke	√	√	√	√
↓ ischemic stroke	√			
↓ mortality	(√)			√
↓ major bleeding		√		√
↑ GI bleeding	√		√	
↑ MI	(√)	(√)		

Grazie!