NOACs: pharmacological differences

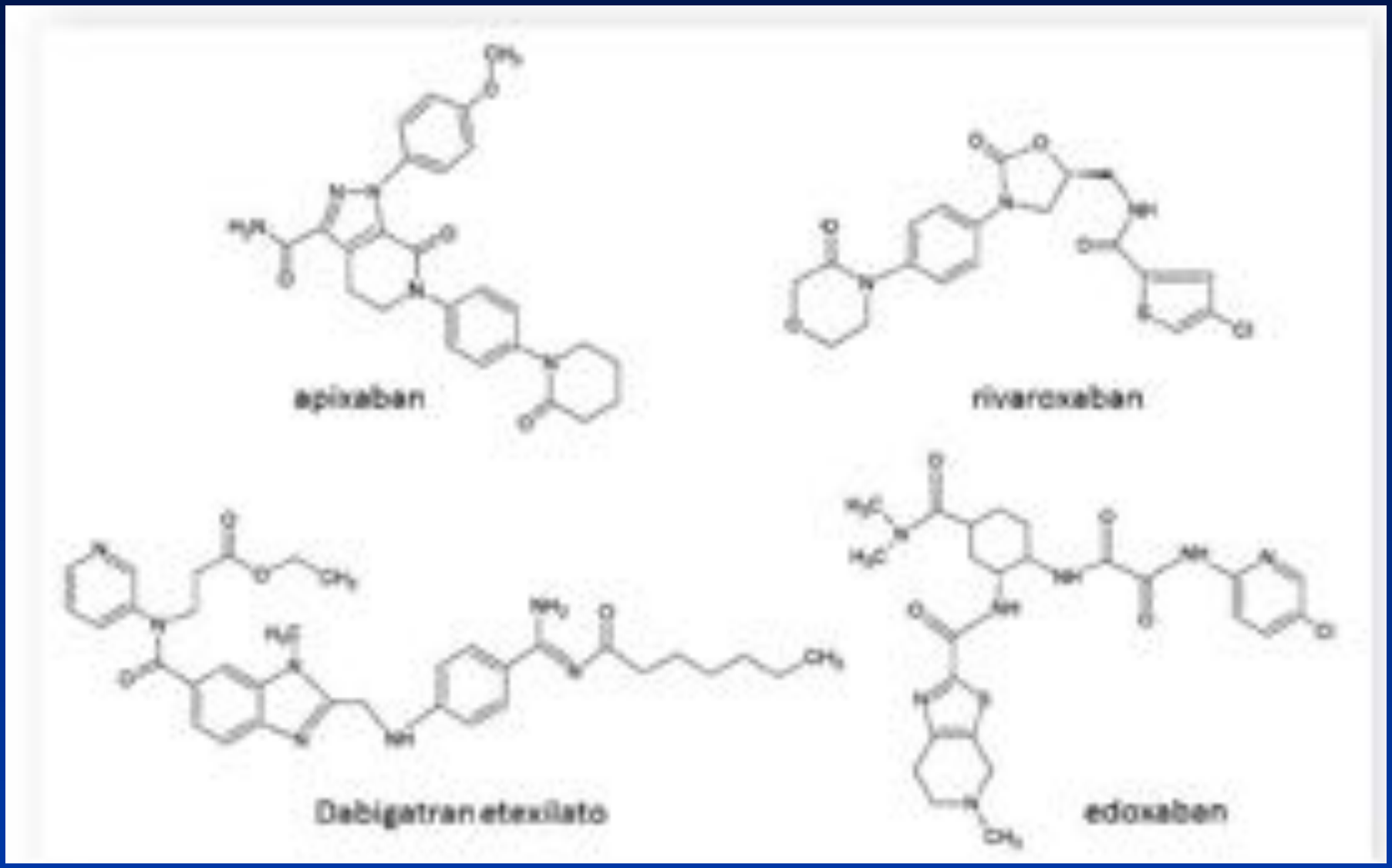
Prof. Alberto Corsini

University of Milan, Italy

NOAC - Differences

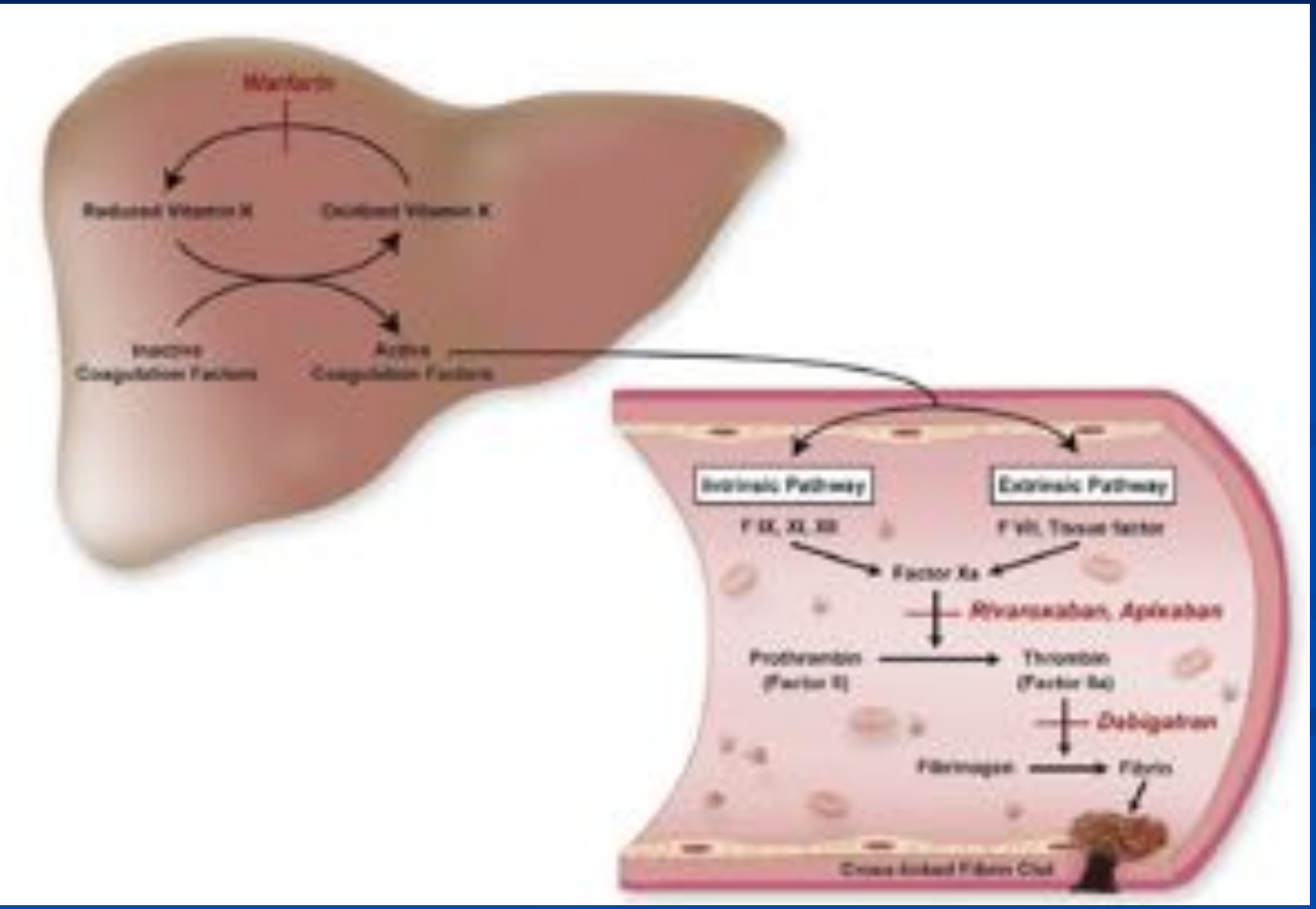
- Mechanism of action
- Pharmacokinetics
- Pharmacodynamics
- Documentation of health benefits and long-term safety

NOACs: chemical structure



Ferri N and Corsini A G Ital Cardiol 2015;16(9 Suppl 1):3S-16S

Sites of action of warfarin, apixaban, dabigatran, and rivaroxaban



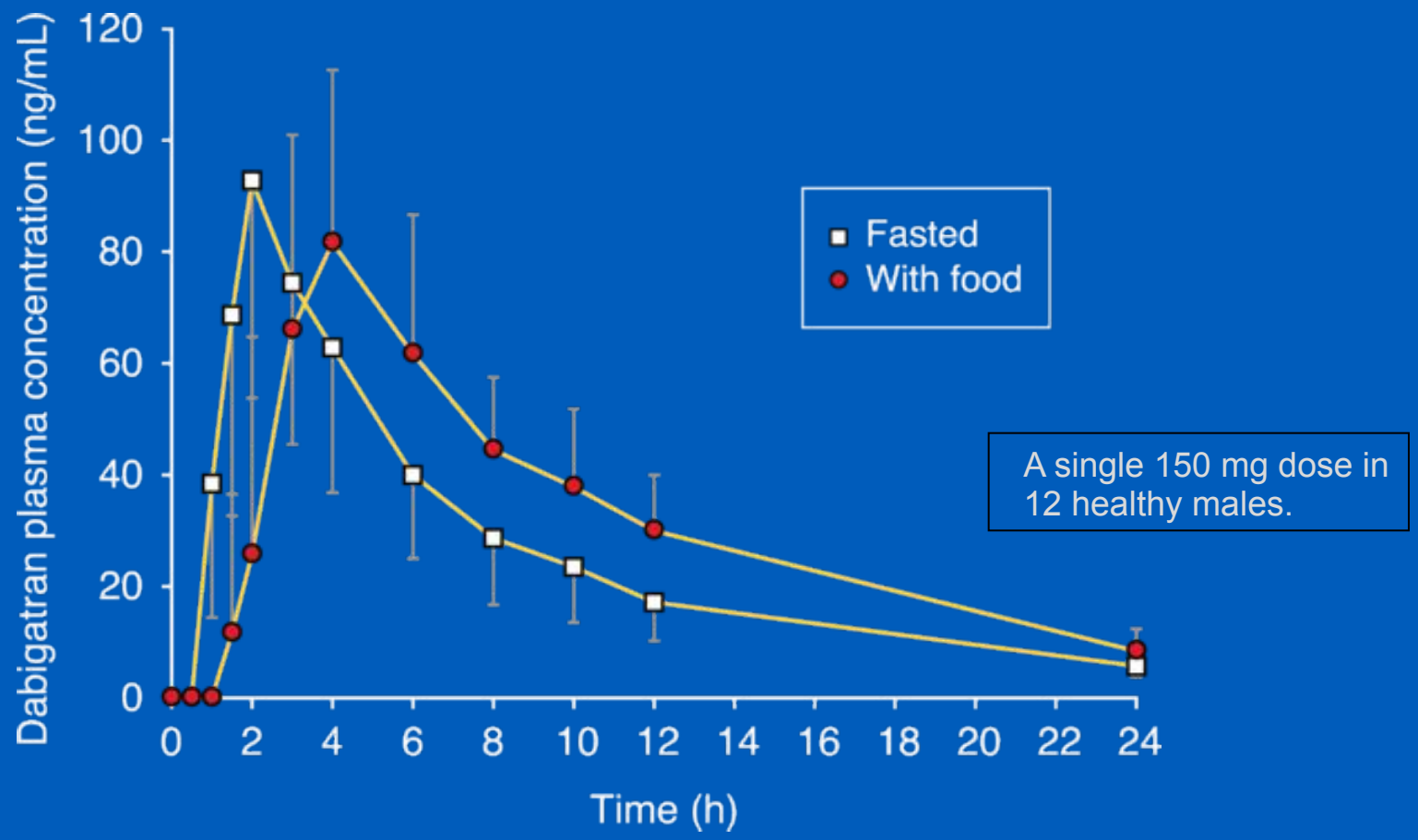
Desai J et al Gast End 78:227-239 2013

Summary pharmacokinetic characteristics of newer anticoagulants

Agent	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	FIIa (thrombin)	FXa	FXa	FXa
Bioavailability	6.5 % (absolute)	80 %	50 % (absolute)	60 % (absolute)
Food effect	Absorption delayed, not reduced	Absorption delayed, not reduced	None	None
Vd	60–70 L	50 L	21 L	>300 L
Protein binding	35 %	>90 %	87 %	40–59 %
Prodrug	Yes	No	No	No
Hours to Cmax	1–3	2–4	3–4	1–2
Half-life (h)	12–17	5–9 (healthy) 9–13 (elderly)	8–15	8–11
CYP Metabolism	No (conjugation)	30 %	15 %	Yes
Metabolism	Conjugation	CYP3A4, 2J2, CYP-independent mechanisms	CYP3A4	CYP 3A4
Substrate P-gp	Yes (prodrug only)	Yes	Yes (minimal)	Yes
Substrate for other Drug transporter	No known	BCRP/ABCG2	BCRP/ABCG2	Unknown
Renal excretion	80 %	65 %	27 %	35 %
Accumulation	None	None	NR	Negligible
Removed with HD	60–70 %	Unlikely	Unlikely	Possibly-NR
Antidote	No known	Possibly PCC	No known	No known-NR

DeWald TA, Becker RCJ Thromb Thrombolysis. 2014 Feb;37(2):217-33

Rapid Absorption



- Rapid absorption (C_{max} in up to 2 hours)
  - Food delayed C_{max} by 2 hours
  - Surgery delayed C_{max} by 4 hours

Stangier J.: *Clin Pharmacokinet* 2008:47:285-295

International Journal of Clinical Pharmacology and Therapeutics, Vol. 51 – No. 7/2013 (549-561)

Original

The effect of food on the absorption and pharmacokinetics of rivaroxaban

Jan Stampfuss[1], Dagmar Kubitza[1], Michael Becka[2] and Wolfgang Mueck[1]

[1]Clinical Pharmacology, and [2]Department of Biometry, Pharmacometry, Bayer Pharma AG, Wuppertal, Germany

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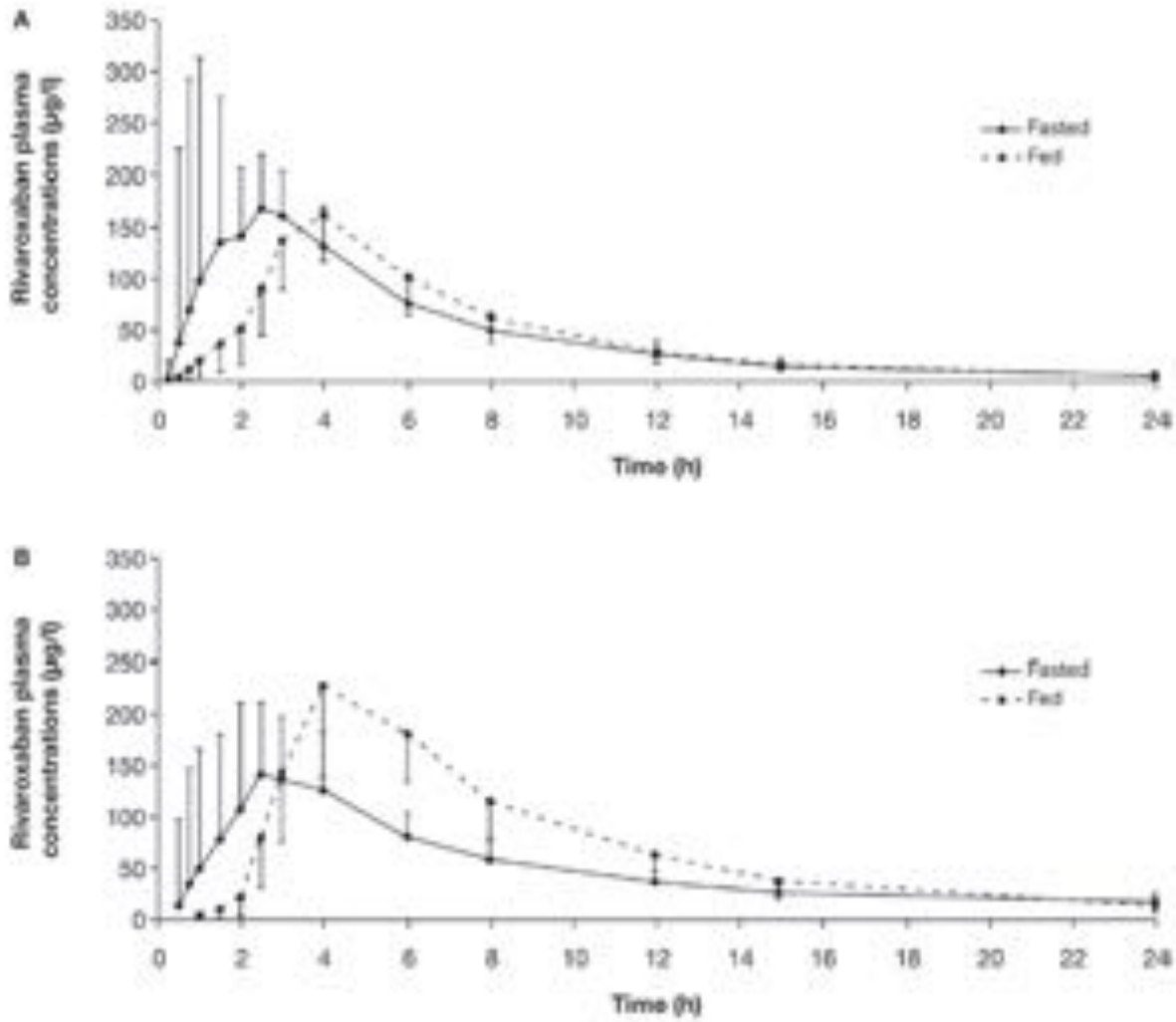
ISSN 0946-1965

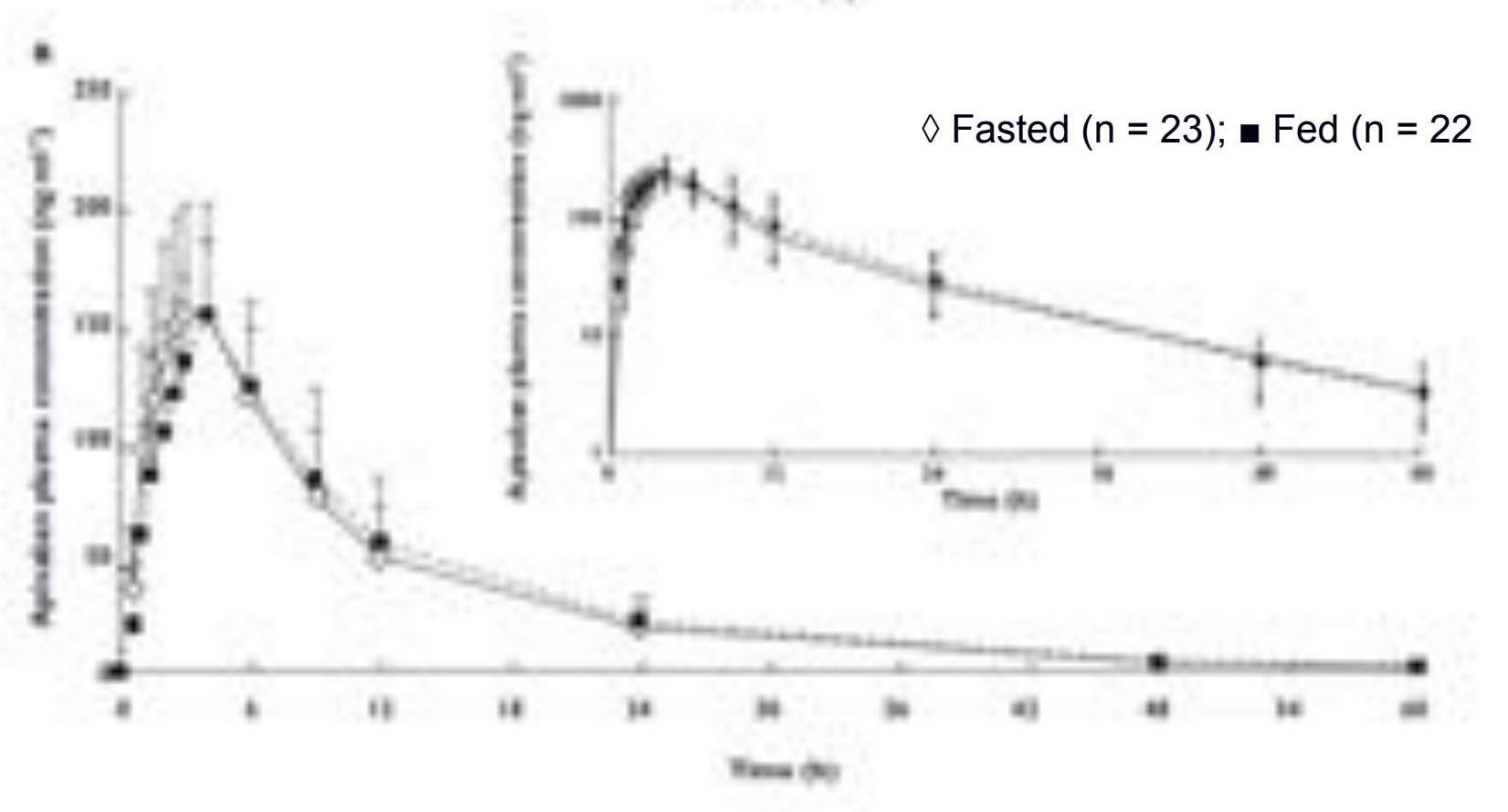
DOI 10.5414/CP201812
e-pub: March 5, 2013

Food-effect studies with 10 mg and 20 mg rivaroxaban



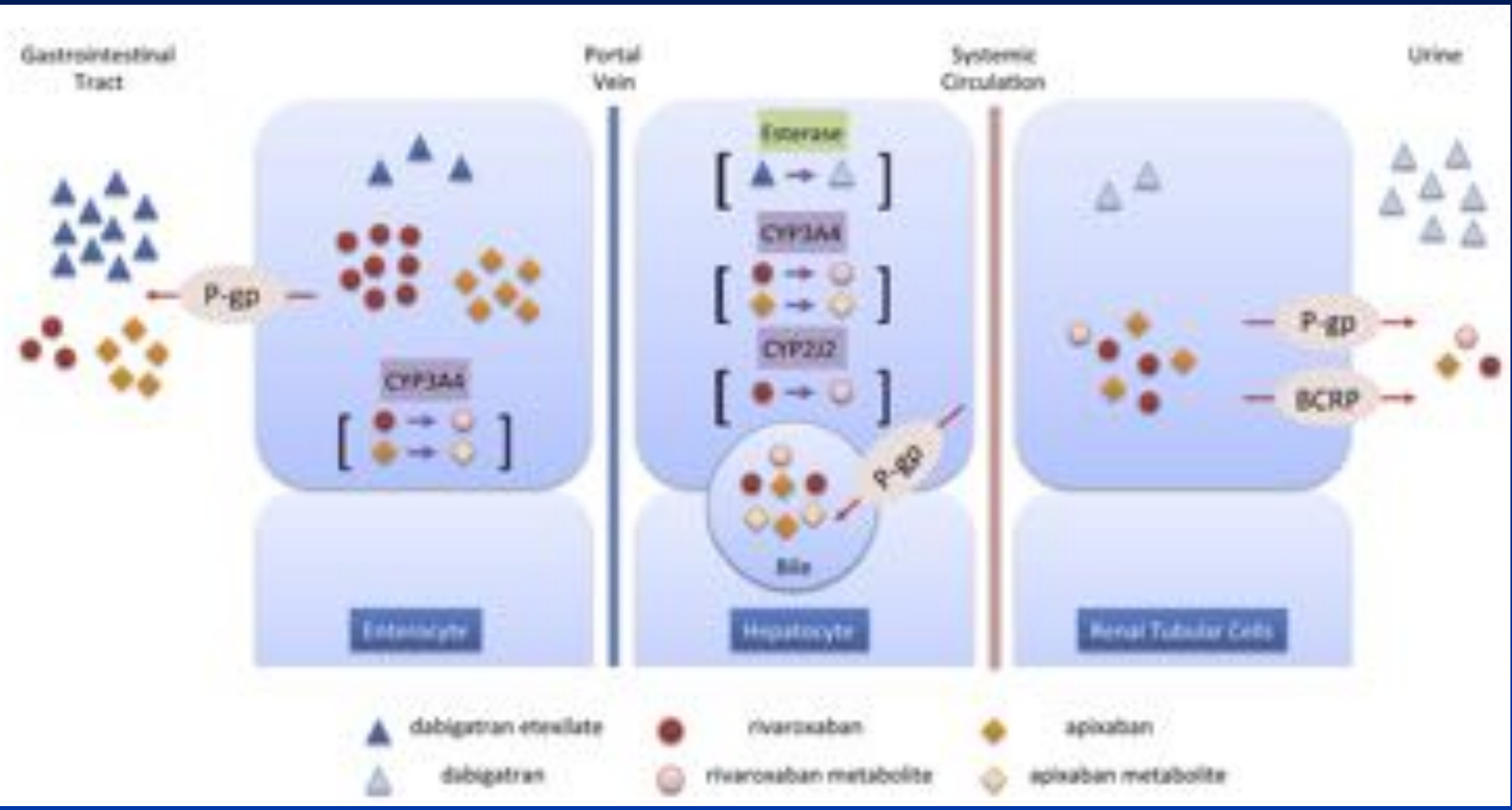
In line with US food-effect guidelines [21], the study drug was administered in the morning after a fasting period of at least 10 hours or within 5 minutes after a standardized high-fat, high-calorie American breakfast, which had to be eaten within 30 minutes. This breakfast consisted of two large eggs, two slices of fried ham, two slices of toast, 20 g butter, 25 g of pan-fried potatoes, 250 ml milk (3.5% fat), and 100 – 200 ml decaffeinated coffee. This meal contained a total of 1,051 kcal with 42 g proteins, 67 g carbohydrates, and 63.5 g fat.

Foods does not affect the pharmacokinetic profile of apixaban



Frost C et al Br J Clin Pharmacol. 2013 Nov;76(5):776-86

Summary of absorption, metabolism, and excretion of dabigatran, rivaroxaban, and apixaban



Gong IY and Kim RB Canadian Journal of Cardiology 29 (2013) S24eS33

Table 8. Examples of In Vivo CYP3A and P-gp Inhibitors and Their Relative Potency

	P-gp Inhibitor	Non-P-gp Inhibitor
Strong CYP3A Inhibitor	Itraconazole, lopinavir/ritonavir, telaprevir, clarithromycin, ritonavir,* ketoconazole,* indinavir/ritonavir,*conivaptan	Voriconazole
Moderate CYP3A Inhibitor	Verapamil, erythromycin,* diltiazem, dronedarone	None identified
Weak CYP3A Inhibitor	Lapatinib, quinidine, ranolazine, amiodarone, felodipine, azithromycin*	Cimetidine

FDA 2012

P-GP Inhibitors

- **Amiodarone:** Dabigatran exposure in healthy subjects was increased by 60 % in the presence of amiodarone
- **Verapamil:** When dabigatran 150 mg was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased,but the magnitude of this change differs, depending on timing of administration and formulation of verapamil
- **Clarithromycin:** Dabigatan exposure (AUC) in healthy subjects was increased by about 19 % in the presence of clarithromycin without any clinical safety concern
- Current US labeling for dabigatran with **rifampicin a P-GP inducers** should be avoided

Pradaxa® – Summary of Product Characteristics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
	Mean exposure ratio (90% CI)[b]			
Antimicrobials				
Ketoconazole	2.50 (NR)	2.58 (2.36–2.82)[83]	1.99 (1.81–2.18)[84]	1.87 (1.76–1.98)[58]
Fluconazole	NR	1.42 (1.29–1.56)[83]	NR	NR
Erythromycin	NR	1.34 (1.23–1.46)[83]	NR	1.85 (1.75–1.96)[58]
Clarithromycin	1.49 (NR)[85]	1.54 (1.44–1.64)[83]	NR	NR
Rifampicin	0.33 (0.27–0.41)[58]	0.50 (NR)[57]	0.46 (0.42–0.49)[75]	0.66 (NR)[c]
Ritonavir	NR	2.53 (2.34–2.74)[58,83]	NR	NR
Cardiovascular				
Dronedarone	1.99 (1.79–2.21)[86]	NR	NR	1.85 (1.78–1.91)[87]
Quinidine	1.50 (NR)[88]	NR	NR	1.77 (1.65–1.89)[87]
Amiodarone	1.60 (NR)[88]	NR	NR	1.40 (1.34–1.46)[87]
Verapamil	1.71 (1.34–2.15)[89]	NR	NR	1.53 (1.41–1.65)[87]
Diltiazem	NR	NR	1.40 (1.23–1.59)[84]	NR
Atenolol	NR	NR	0.85 (0.78–0.92)[77]	NR
Clopidogrel	1.35 (1.07–1.69)[90]	NS[91]	NR	NR
Ticagrelor	1.49 (NR)[25]	NR	NR	NR
Atorvastatin	0.82 (0.73–0.93)[92]	NS[93]	NR	NS[87]
Musculoskeletal				
Naproxen	NR	1.13 (1.00–1.27)[94]	1.54 (1.39–1.69)[95]	NR
Other				
Pantoprazole	0.80 (0.67–0.95)[67]	NR	NR	NR
Ciclosporin	NR	NR	NR	1.73 (1.63–1.83)[58]

Semin Thromb Hemost. 2015 Mar;41(2):195-207

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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http://dx.doi.org/10.1016/j.jacc.2014.07.947

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ORIGINAL INVESTIGATIONS

Amiodarone, Anticoagulation, and Clinical Events in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

Greg Flaker, MD,* Renato D. Lopes, MD, PhD,† Elaine Hylek, MD, MPH,‡ Daniel M. Wojdyla, MS,§ Laine Thomas, PhD,§ Sana M. Al-Khatib, MD, MHS,§ Renee M. Sullivan, MD,* Stefan H. Hohnloser, MD,‖ David Garcia, MD,‖ Michael Hanna, MD,¶ John Amerena, MBBS,# Veli-Pekka Harjola, MD, PhD,** Paul Dorian, MD,†† Alvaro Avezum, MD, PhD,‡‡ Matyas Keltai, MD, DSc,‖‖ Lars Wallentin, MD, PhD,‖‖ Christopher B. Granger, MD,§ for the ARISTOTLE Committees and Investigators

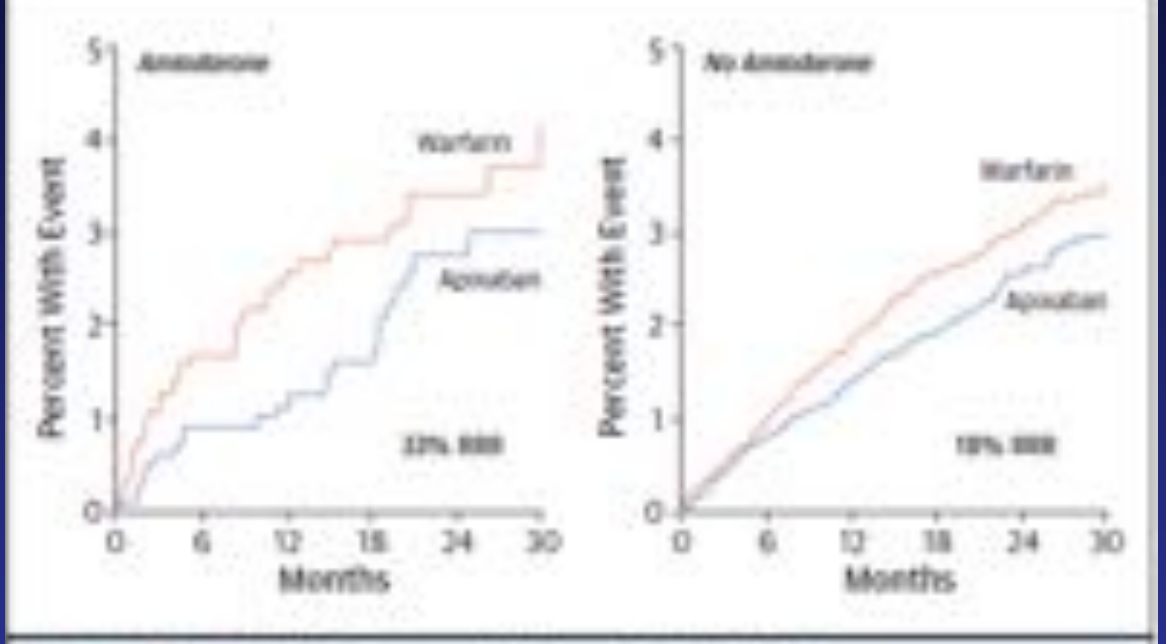


FIGURE 1 Kaplan-Meier Curves of Stroke or Systemic Embolism

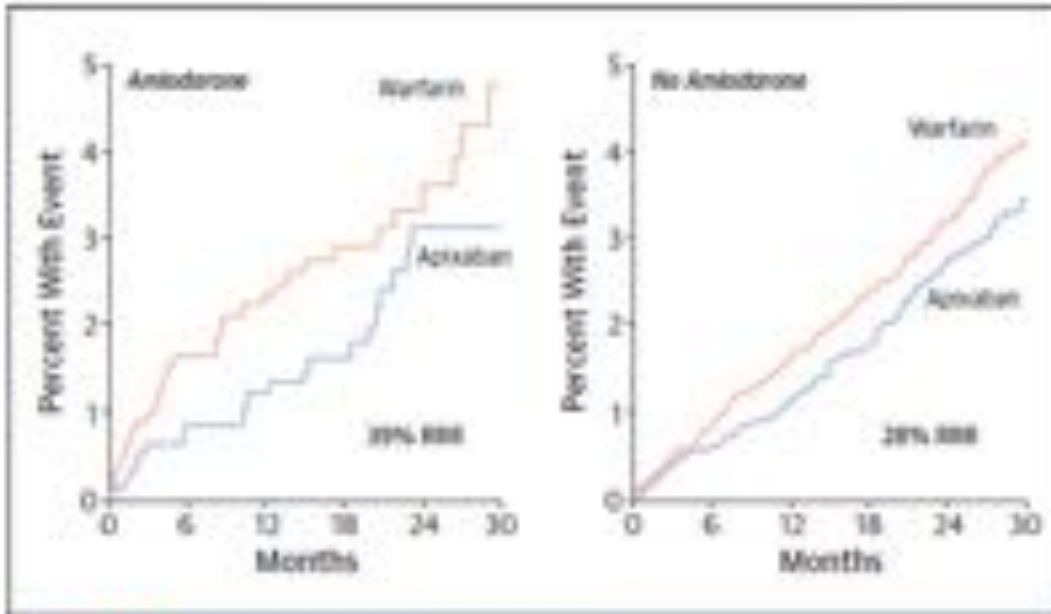


FIGURE 2 Kaplan-Meier Curves of Major Bleeding

JACC VOL. 64, 2014 Flaker et al.
OCTOBER 14, 2014: 1541–50

Adjusted outcomes of rivaroxaban vs warfarin stratified by amiodarone use at baseline

Outcome	Amiodarone			No AAD			Interaction P (amiodarone and treatment)
	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	
Stroke or non-CNS embolism	2.14 (19)	1.74 (15)	1.71 (0.80–3.65)	2.16 (237)	2.54 (279)	**0.82 (0.68–0.98)**	.063
Bleeding							
Major or NMCR bleeding	15.90 (108)	13.82 (92)	1.35 (0.94–1.92)	15.00 (1284)	14.53 (1261)	**1.12 (1.00–1.25)**	.33
Major bleeding	3.84 (29)	1.88 (14)	2.20 (0.98–4.91)	3.61 (343)	3.58 (347)	1.05 (0.90–1.24)	.078
ICH	0.52 (4)	0.27 (2)	2.42 (0.37–16.0)	0.50 (48)	0.78 (77)	**0.61 (0.42–0.88)**	.16
GI	1.70 (13)	0.40 (3)	4.58 (0.92–22.8)	1.75 (168)	1.14 (112)	**1.68 (1.30–2.18)**	.23
Fatal	0.13 (1)	0.40 (3)	0.48 (0.06–3.83)	0.25 (24)	0.50 (49)	**0.49 (0.30–0.80)**	.98
NMCR bleeding	12.28 (85)	12.03 (81)	1.24 (0.84–1.83)	11.92 (1035)	11.28 (993)	**1.15 (1.01–1.31)**	.71

AAD = antiarrhythmic drug; CI = confidence interval; CNS = central nervous system; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; NMCR = nonmajor clinically relevant.

Steinberg BA et al. Heart Rhythm 2014;11:925–932)

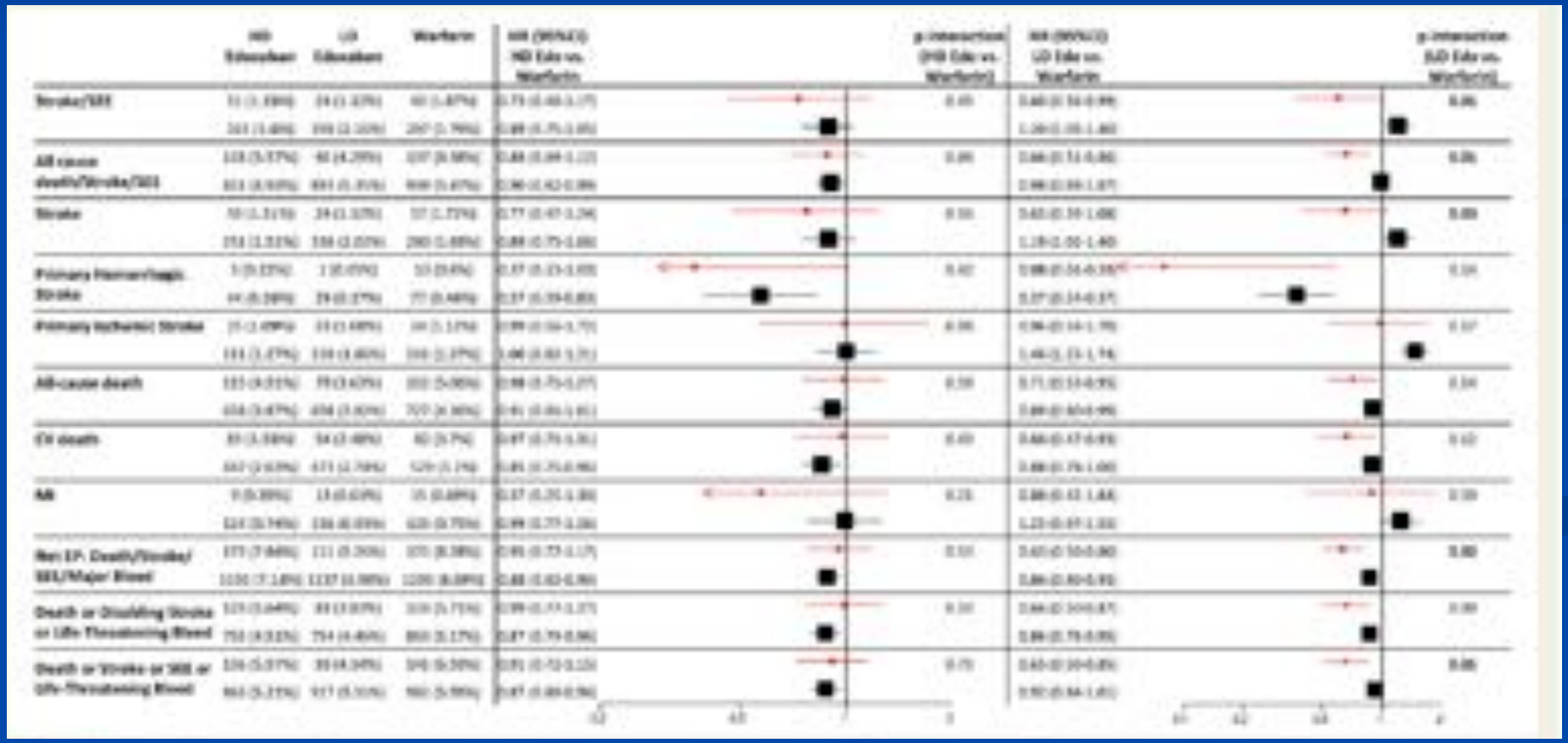
European Heart Journal (2015) 36, 2239–2245
doi:10.1093/eurheartj/ehv201

FASTTRACK CLINICAL RESEARCH
Thrombosis and anti-thrombotic therapy

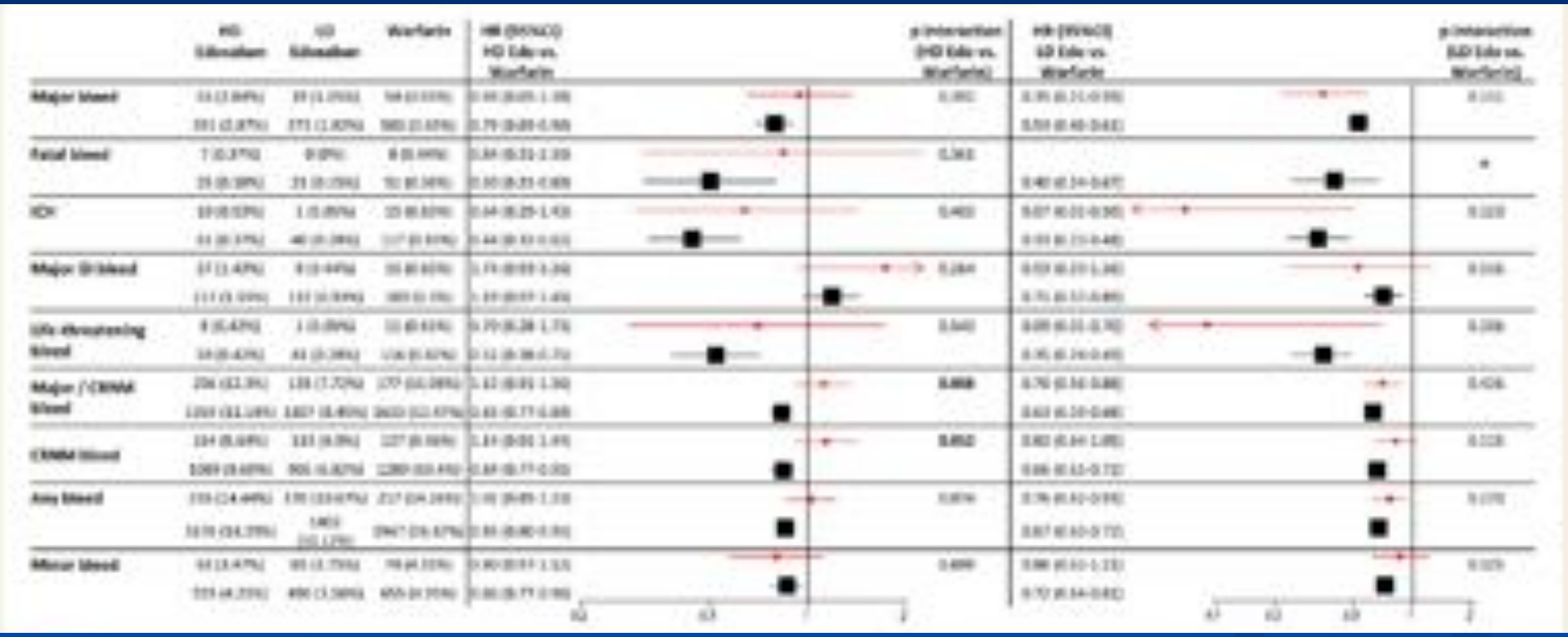
Edoxaban vs. warfarin in patients with atrial fibrillation on amiodarone: a subgroup analysis of the ENGAGE AF-TIMI 48 trial

J. Steffel[1], R.P. Giugliano[2], E. Braunwald[2], S.A. Murphy[2], D. Atar[3], H. Heidbuchel[4], A.J. Camm[5], E.M. Antman[2], and C.T. Ruff[2*]

Efficacy of edoxaban vs. warfarin in patients with and without amiodarone at baseline



Safety of edoxaban vs. warfarin in patients with and without amiodarone at baseline



European Heart Journal (2015) 36, 2239–2245

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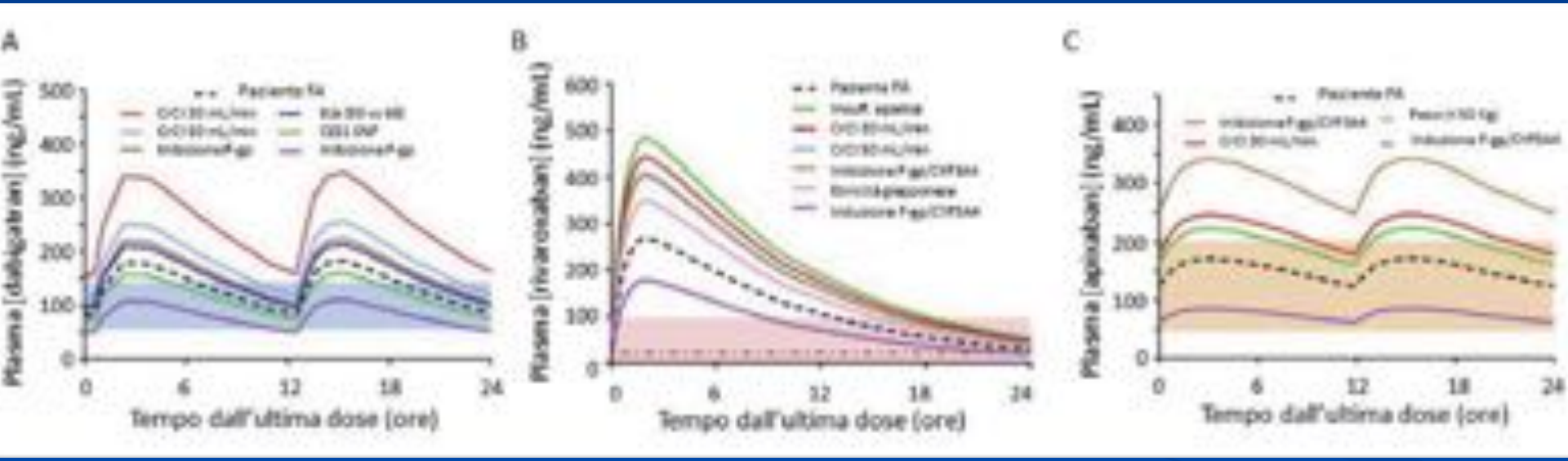
Food effect	Absorption delayed, not reduced	Absorption delayed, not reduced	None	None
Vd	60–70 L	50 L	21 L	>300 L
Protein binding	35 %	>90 %	87 %	40–59 %
Prodrug	Yes	No	No	No
Hours to Cmax	1–3	2–4	3–4	1–2
Half-life (h)	12–17	5–9 (healthy)	8–15	8–11
		9–13 (elderly)		
CYP Metabolism	No (conjugation)	30 %	15 %	Yes
Metabolism	Conjugation	CYP3A4, 2J2, CYP-independent mechanisms	CYP3A4	CYP 3A4
Substrate P-gp	Yes (prodrug only)	Yes	Yes (minimal)	Yes
Substrate for other Drug transporter	No known	BCRP/ABCG2	BCRP/ABCG2	Unknown
Renal excretion	80 %	65 %	27 %	35 %
Accumulation	None	None	NR	Negligible
Removed with HD	60–70 %	Unlikely	Unlikely	Possibly-NR
Antidote	No known	Possibly PCC	No known	No known-NR

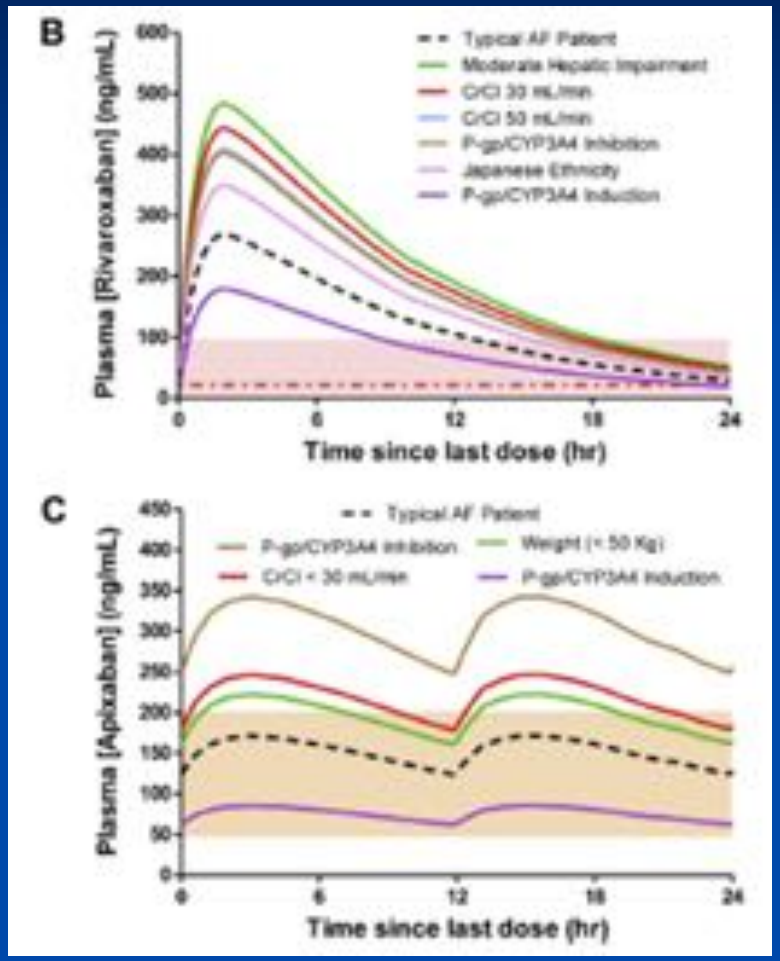
DeWald TA, Becker RCJ Thromb Thrombolysis. 2014 Feb;37(2):217-33

Profilo concentrazione-tempo dei NOA in base alla funzionalità renale ed epatica, alla co-somministrazione di inibitori ed induttori di P-gp e CYP3A4

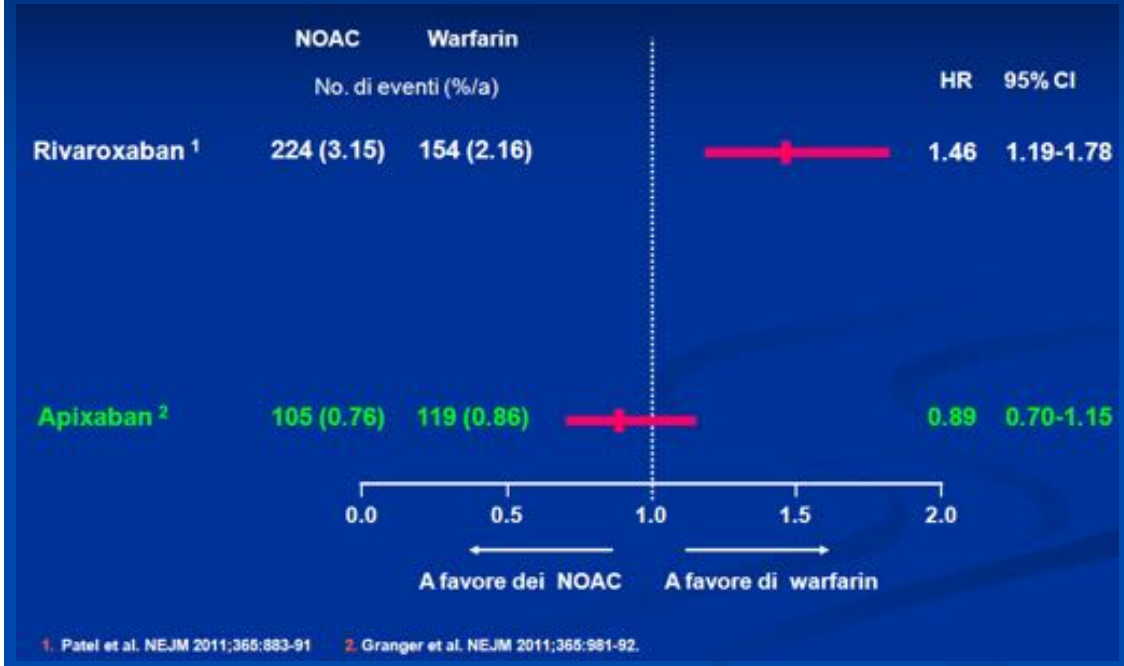


Gong IY and Kim RB Canadian Journal of Cardiology 29 (2013) S24eS33

Plasma concentration profiles of rivaroxaban and apixaban in atrial fibrillation patients



NOAC *vs.* warfarin: sanguinamenti maggiori gastrointestinali



Gong IY and Kim RB
Canadian Journal of Cardiology 29 (2013) S24eS33

NOAC - Differences

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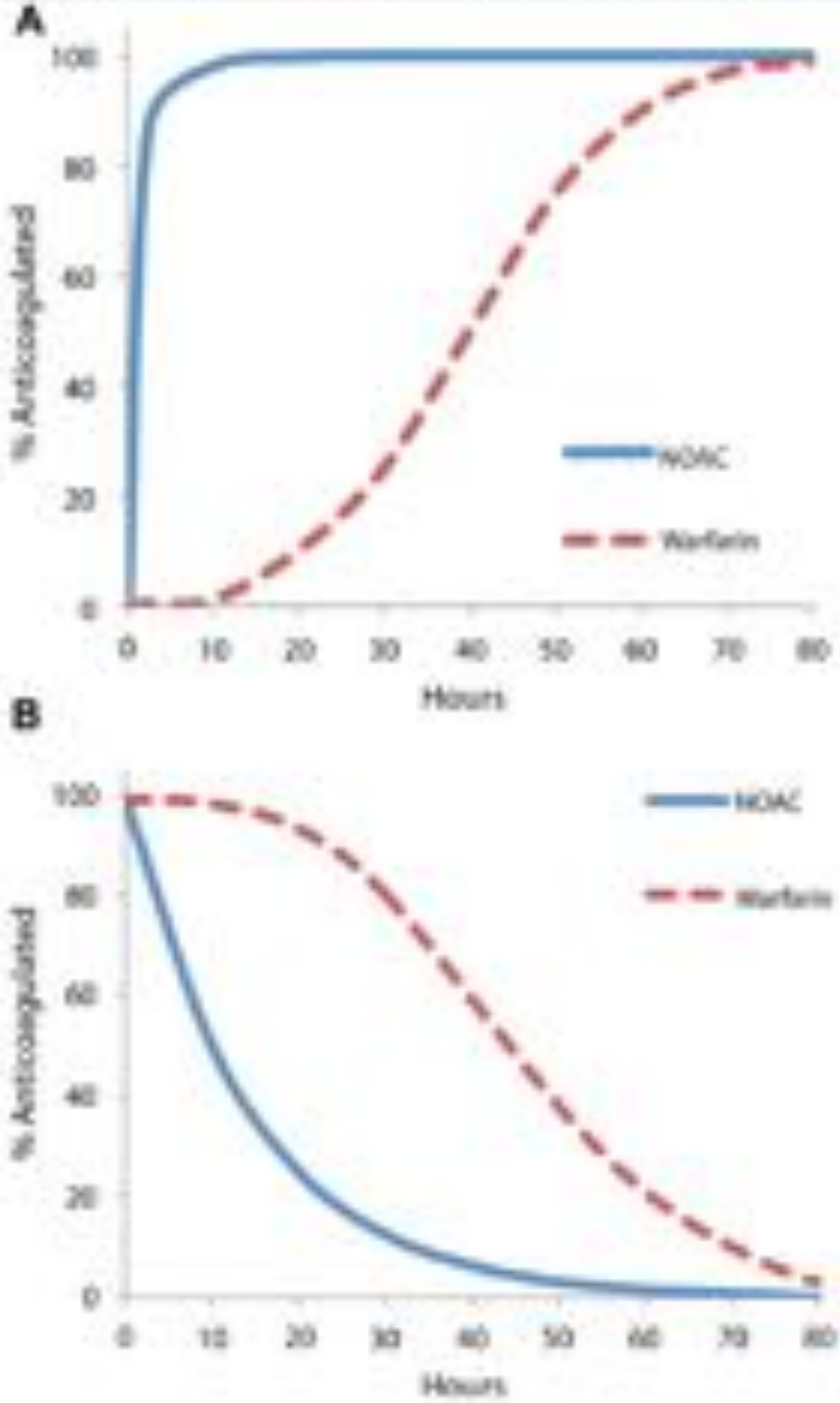
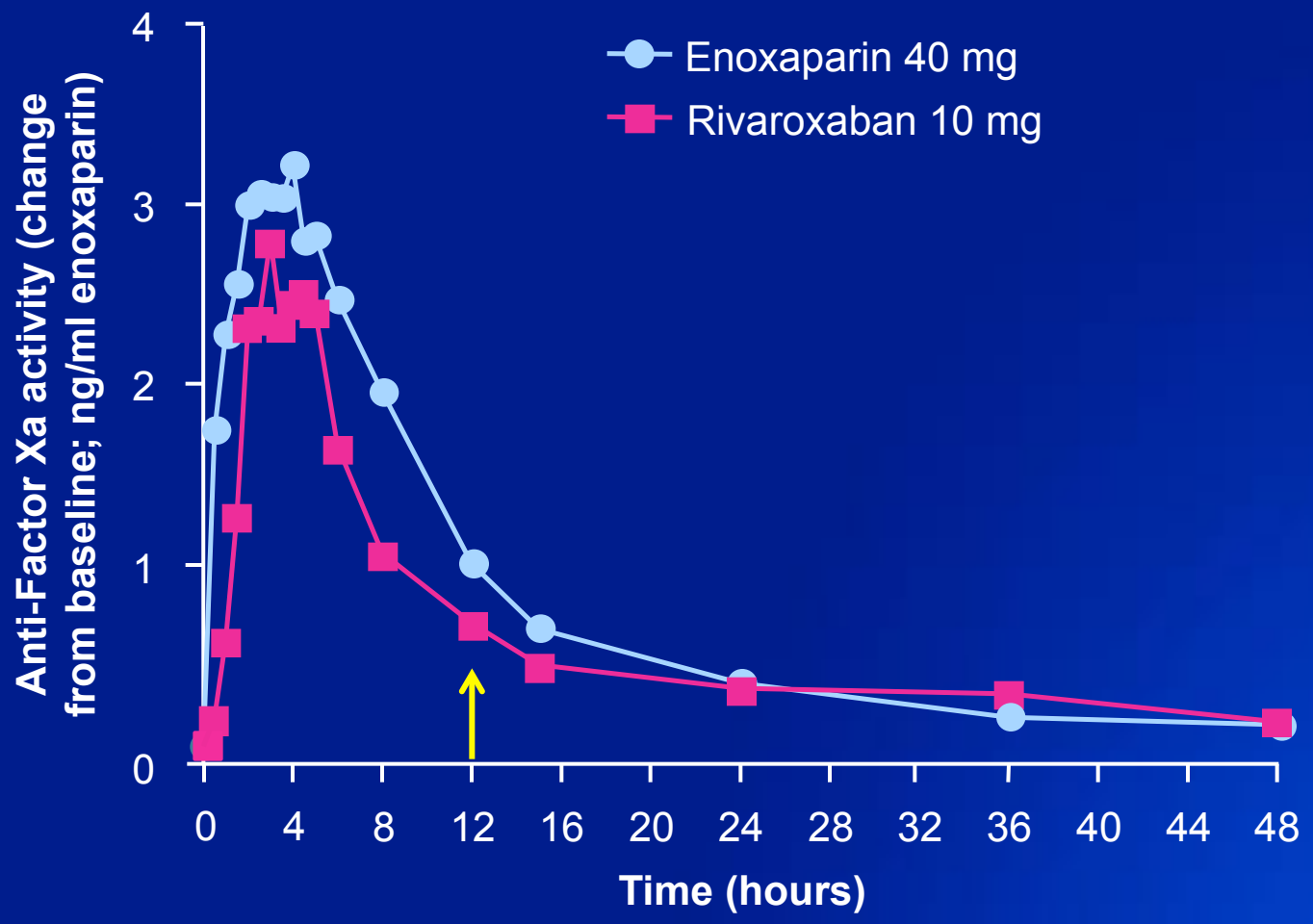


Comparative pharmacodynamics of warfarin and of NOAs

Desai J et al Gast End 78:227-239 2013

Rivaroxaban: similar onset and offset of action to enoxaparin

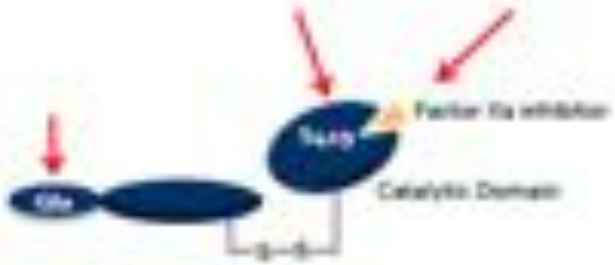


Kubitza *et al*, 2005

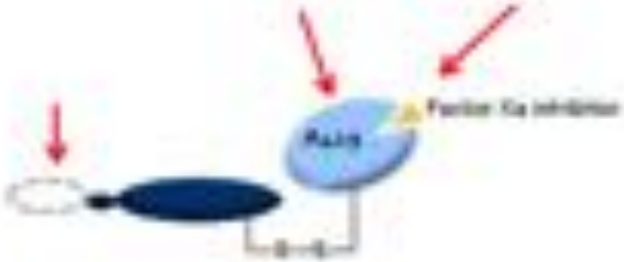
Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors Through a Well-Defined Mechanism of Action

Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all fXa inhibitors
- Change of Serine to Alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect



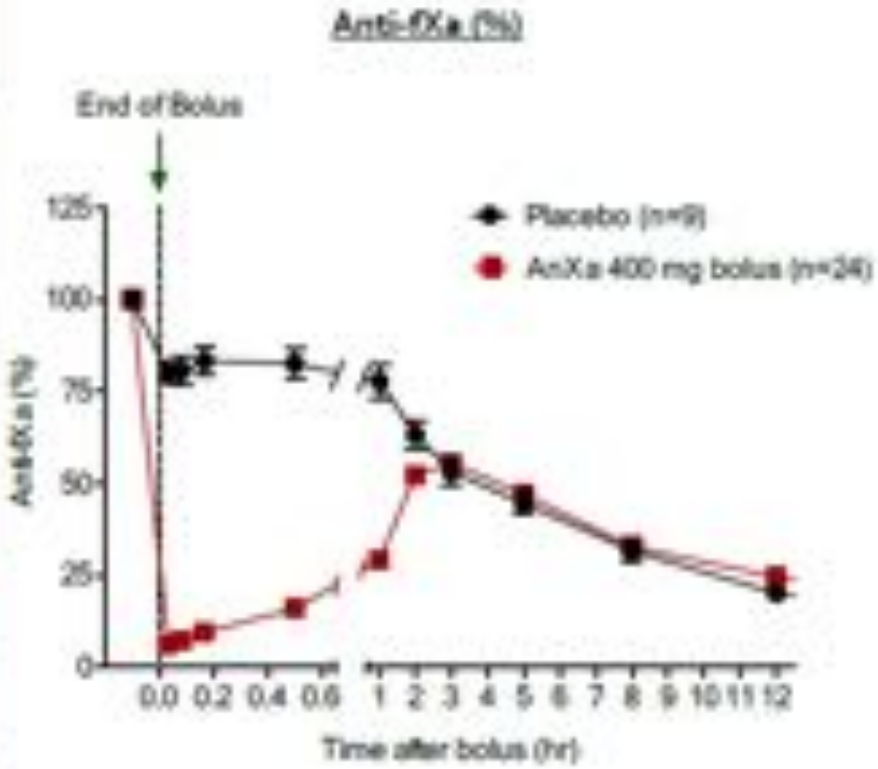
Factor Xa



Andexanet

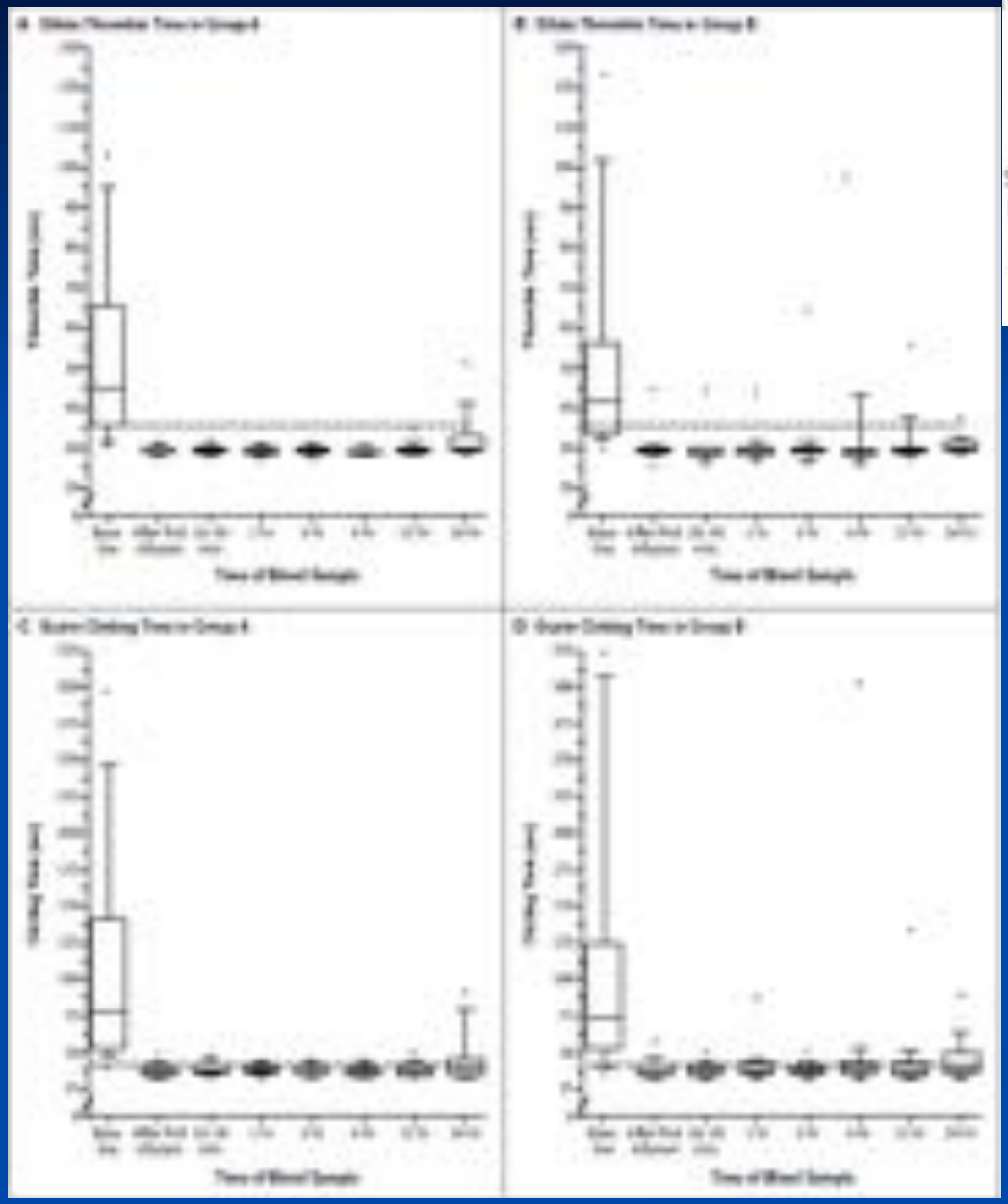
- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)
- No significant antibody signal found in development program to date

ANNEXA™-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial, Demonstrating Reversal of Apixaban-Induced Anticoagulation in Older Subjects by Andexanet alfa (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors



- **Met Primary Endpoint:**
  - Percent change anti-fXa from baseline to nadir (= 94%)
    - p< 0.0001
- **Met first Secondary Endpoint:**
  - Number of subjects with > 80% reversal: andexanet (100%) vs. placebo (0%)
    - p< 0.0001
  - All andexanet subjects achieved ≥ 90% reversal

- 100% of andexanet treated subjects had ≥ 90% reversal of anti-fXa activity and restoration of thrombin generation to baseline (pre-anticoagulant) levels
- Andexanet produced near complete normalization of all coagulation parameters measured within 2 minutes of completion of infusion



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.

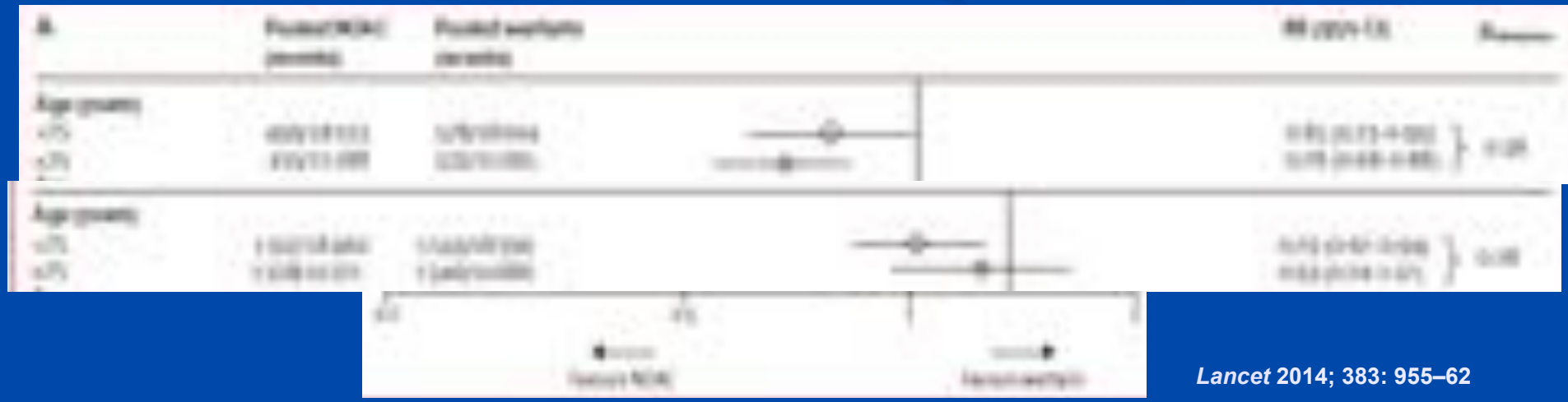
Time Course of the Dilute Thrombin Time and Ecarin Clotting Time before and after the Administration of Idarucizumab

N Engl J Med 2015;373:511-20.

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

Christian Tilluß, Robert P Giugliano, Eugene Braunwald, Elaine B Hylek, Steven Grossbard, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takashi Yamashita, Elliott M Antman

Stroke or systemic embolic events subgroups (A) and major bleeding subgroups (B)



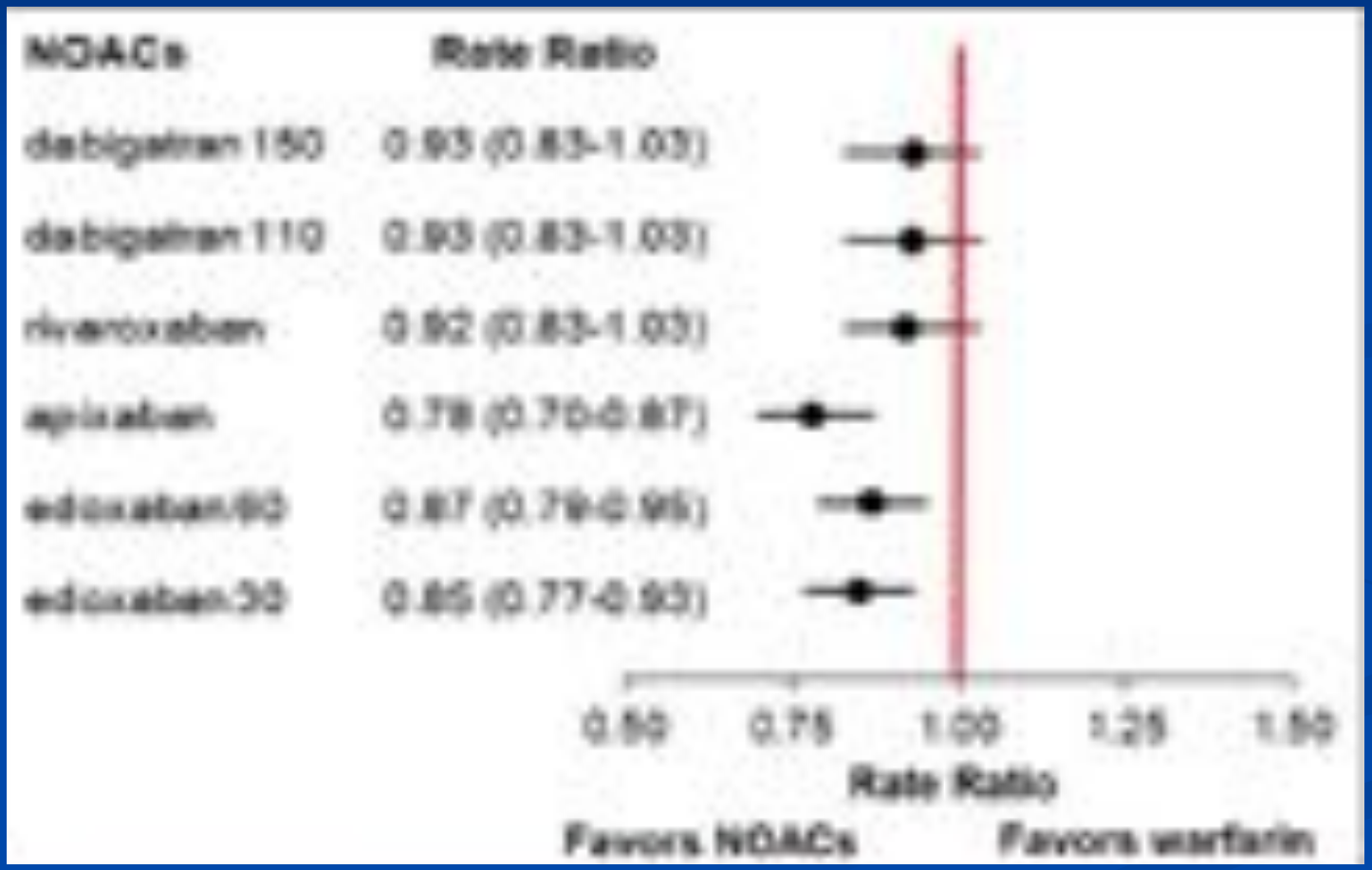
Lancet 2014; 383: 955–62

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Net Clinical Benefit of Non-vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Phase III Atrial Fibrillation Trials

Giulia Renda, MD, PhD,[a] Marta di Nicola, PhD,[b] Raffaele De Caterina, MD, PhD[a,c]



RR and 95% CI of all treatment arms in the phase III trials comparing NOAC with warfarin for the overall composite outcome

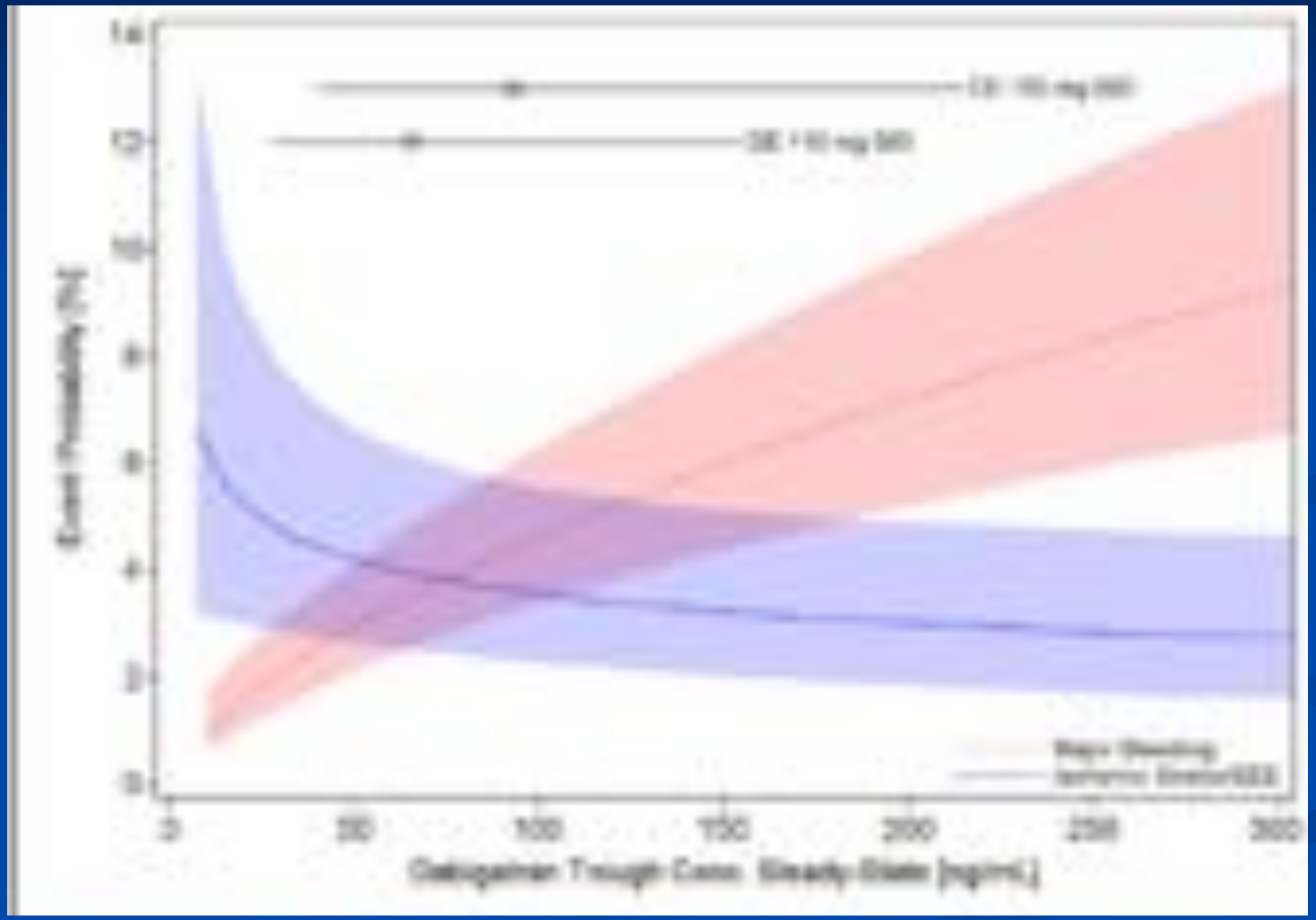
The American Journal of Medicine (2015) 128, 1007-1014

Bleeding rates of newer anticoagulants

Anticoagulant	Major bleeding (%/years)	Intracranial bleeding (%/years)	Extracranial bleeding (%/years)	GI bleeding
Dabigatran (RE-LY)				
Dabigatran 110 mg	2.71	0.23	2.51	1.12 %/years
Dabigatran 150 mg	3.11	0.30	2.84	1.51 %/years
Warfarin	3.36	0.74	2.67	1.02 %/years
Rivaroxaban (ROCKET AF)				
Rivaroxaban	3.6	0.5		3.15 % (not per years)
Warfarin	3.4	0.7		2.16 % (not per years)
Apixaban (ARISTOTLE)				
Apixaban	2.13	0.33	1.39	0.76 %/years
Warfarin	3.09	0.80	2.27	0.86 %/years

DeWald TA, Becker RCJ Thromb Thrombolysis. 2014 Feb;37(2):217-33

Major Bleeding Event and Ischemic Stroke/SEE Vs Trough Plasma Concentration of Dabigatran



Reilly PA et al. J Am Coll Cardiol 2014;63:321–8

Clinical Pharmacology: Advances and Applications

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ORIGINAL RESEARCH

A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban

This article was published in the following Dove Press journal:
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13 November 2014
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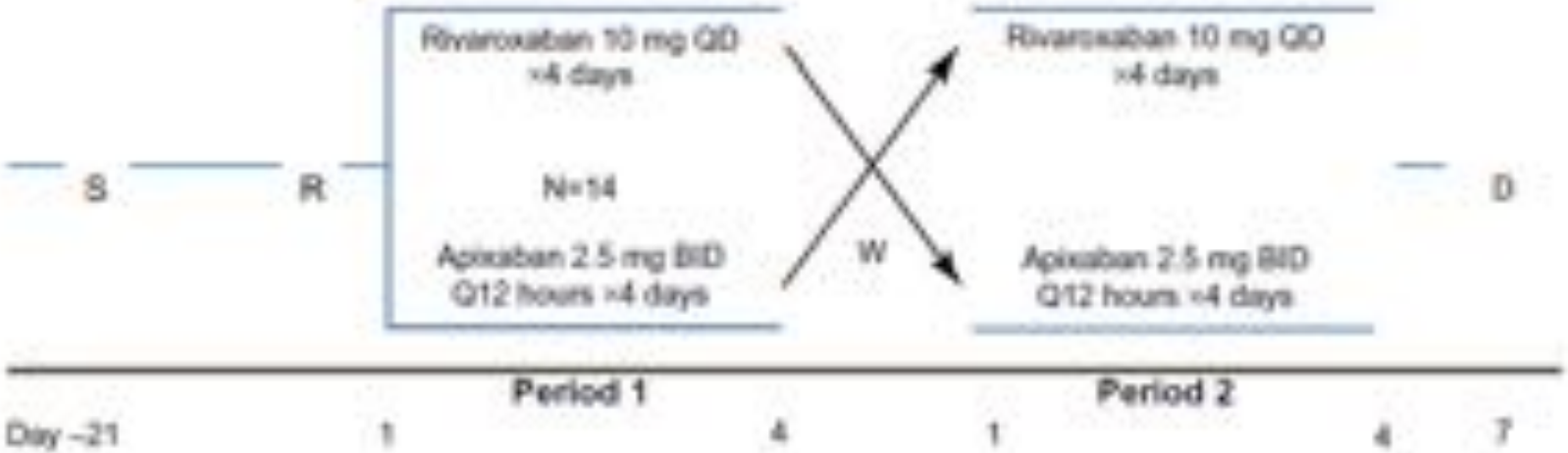
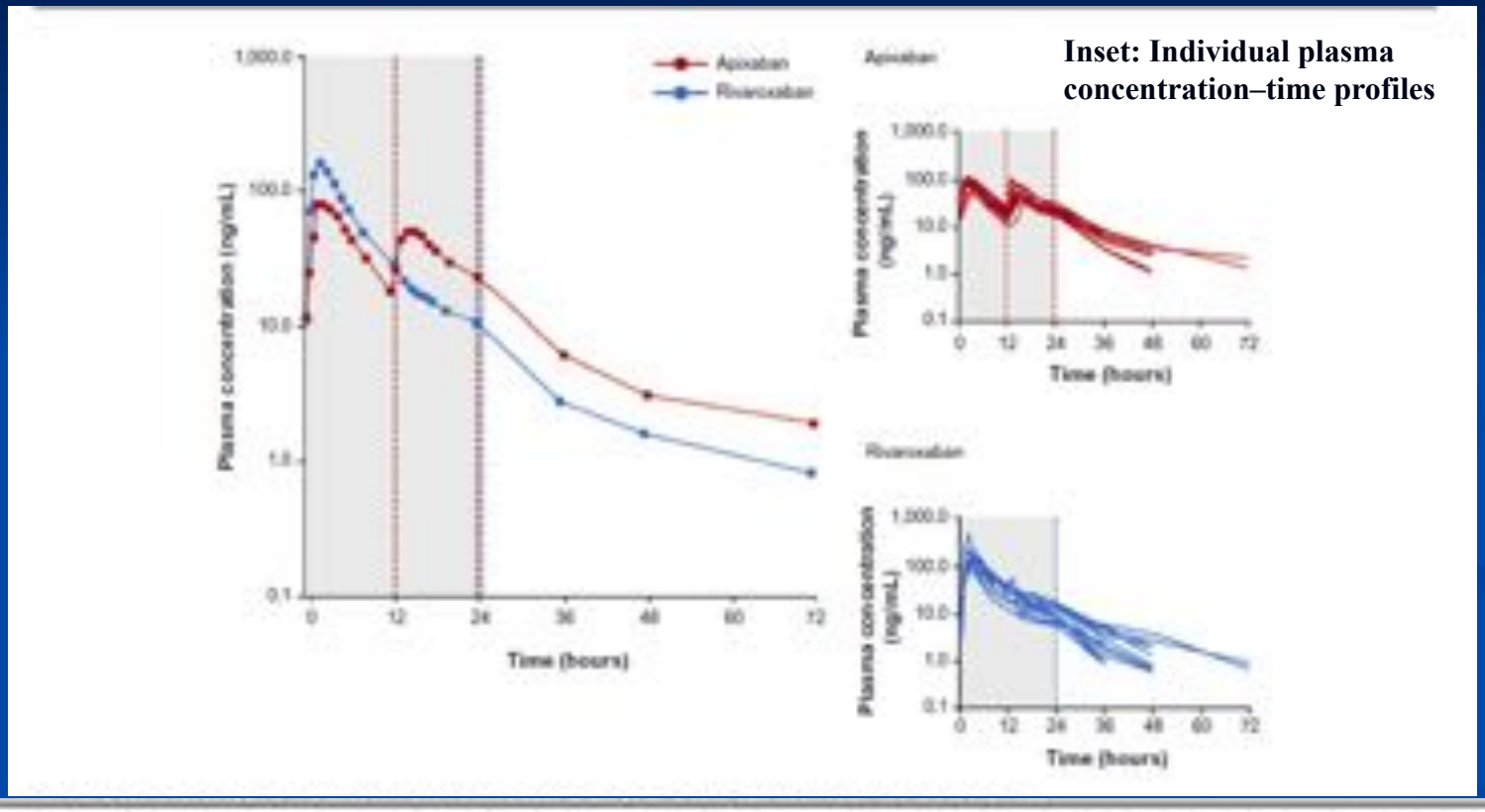


Figure 1 Study design schematic.

Abbreviations: BID, twice daily; D, discharge; Q12 hours, every 12 hours; QD, once daily; R, randomization; S, screening; W, washout (≤4.5 days).

Plasma concentration over time at steady state after treatment with rivaroxaban or apixaban



N=14	C_{max} (ng/mL) G mean (%CV)	C_{min} (ng/mL) G mean (%CV)	C_{max}:C_{min} G mean (%CV)	T_{max} (h) median (min–max)	$AUC_{(0-12)}$ (ng·h/mL) G mean (%CV)	$AUC_{(0-24)}$ (ng·h/mL) G mean (%CV)	$T_{1/2}$ (h) Mean (SD)
Rivaroxaban 10 mg QD	171 (46)	10.1 (39)	16.9 (53.5)	2.00 (1.0–3.0)		1,094 (29)	7.89 (3.00)
Apixaban 2.5 mg BID	80.5 (23)	17.1 (20)	4.7 (16.9)	2.00 (1.0–3.0)	527 (22)	535 (24)	8.65 (2.19)*

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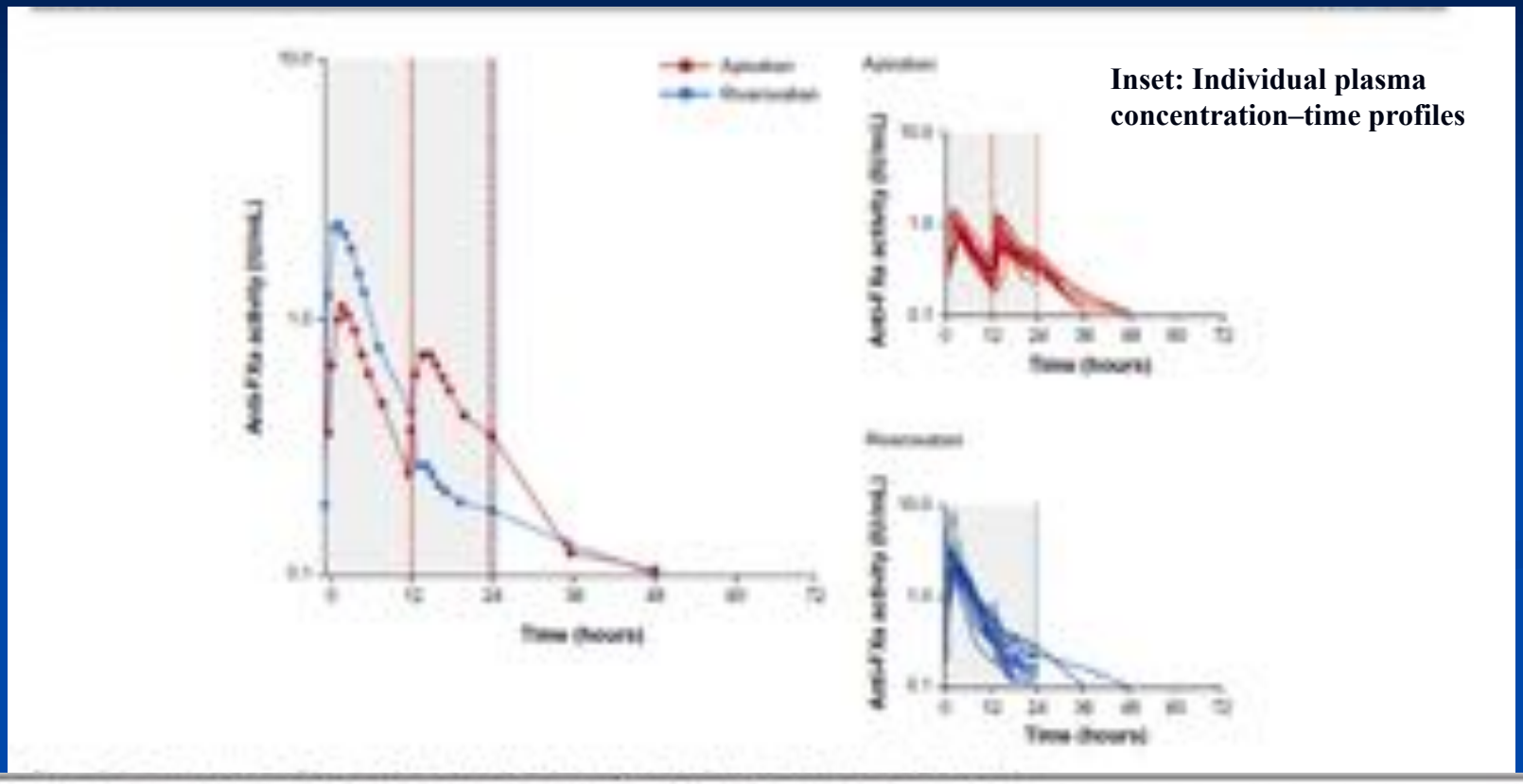
Anti-FXa activity over time at steady state on day 4 of treatment with rivaroxaban or apixaban



N=14	Peak (IU/mL) G mean (CV)	Trough (IU/mL) G mean (CV)	Peak:trough G mean (CV)	T_{peak} (h) median (min–max)	$AUC_{(0-t)}$ (IU·h/mL) G mean (CV)	$AUC_{(0-\infty)}$ (IU·h/mL) G mean (CV)	$T_{1/2}$ (h) Mean (SD)
Rivaroxaban 10 mg QD (0–24 h)	2.82 (51)	0.170[a] (32)	16.5[a] (57.4)	2.00 (1.00–3.00)		17.8 (29)	NE[a]
Apixaban 2.5 mg BID (0–12 h)	1.13 (21)	0.240 (22)	4.7 (19.5)	2.00 (1.00–3.00)	7.42 (21)	13.3 (22)	8.91 (2.46)[b]

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REVIEW

Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence

Bernard Vrijens[1,2] and Hein Heidbuchel[3*]

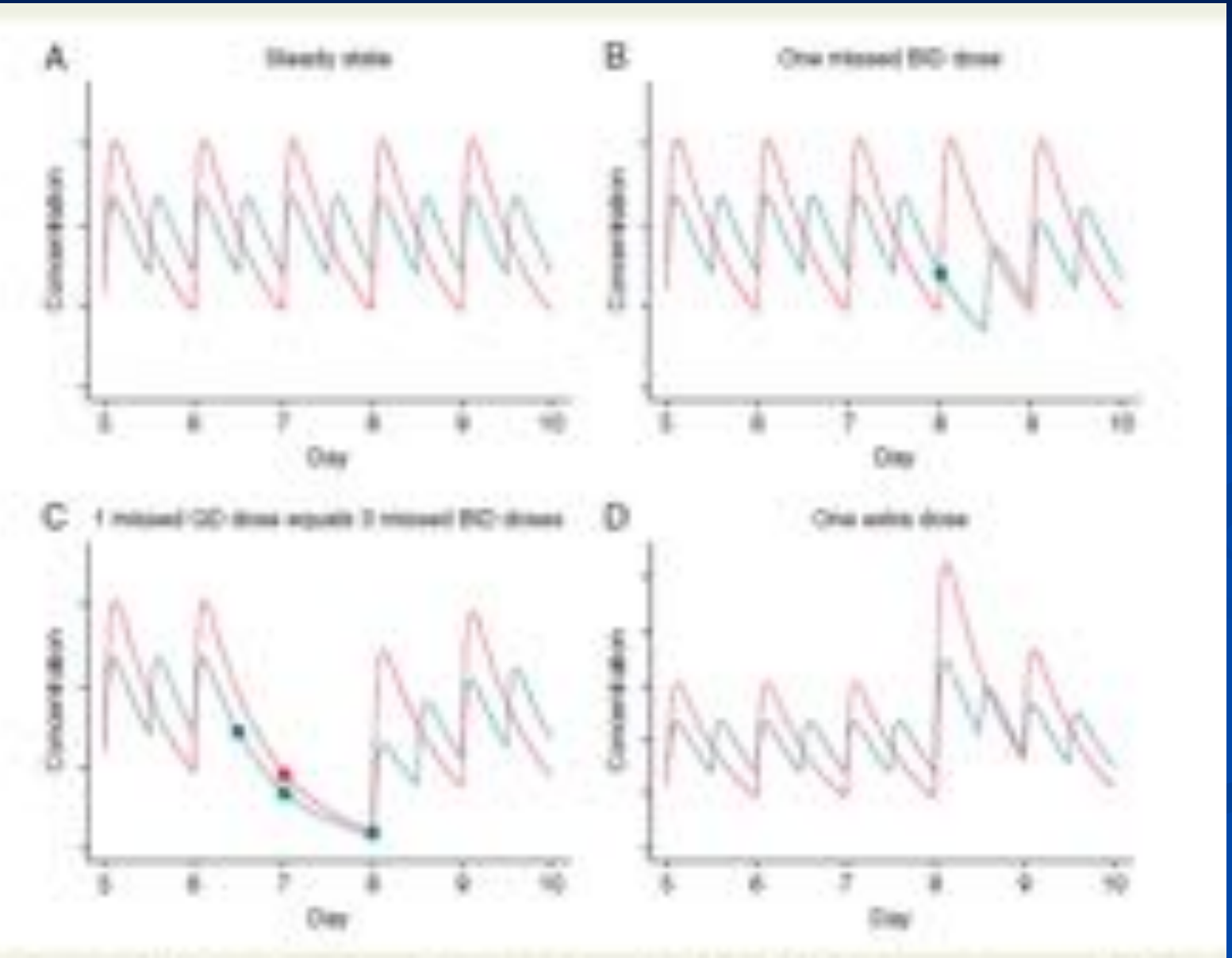
- Because NOACs have plasma half-lives of12 h, the twice-daily dosing regimen is less prone than the once-dailydosing regimen to hazardously high peaks or hazardously low troughs in anticoagulant concentrations and associated actions.

- The continuity of drug action is greater with twice-daily than with once-daily dosing, despite the fact that a few more doses are skipped with twice-daily than with once-daily dosing.

- This paradox is explained by the disproportionately greater impact on drug action of skipping a once-daily than a twice-daily dose.

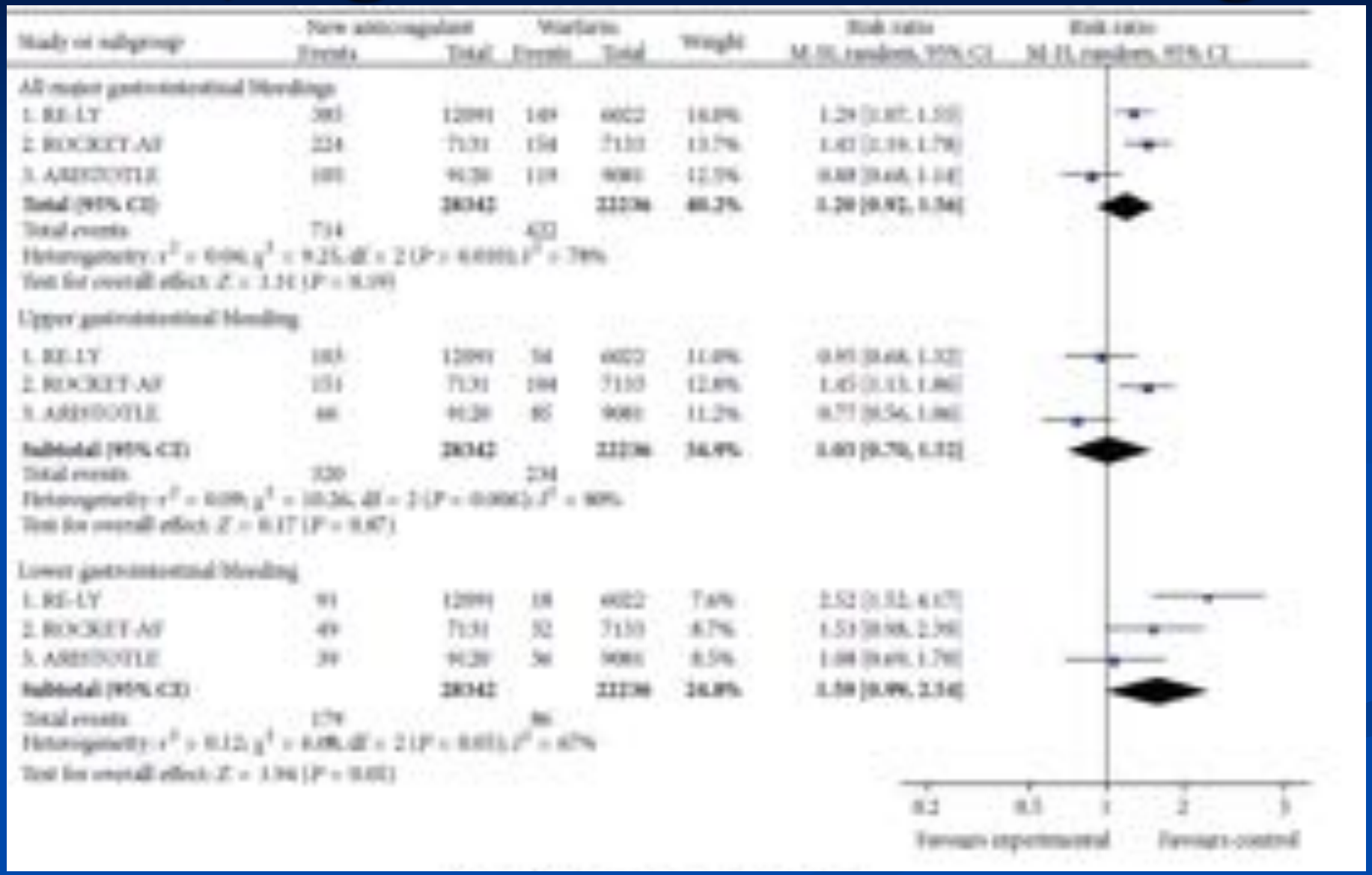
Europace Advance Access published February 17, 2015

Once-daily vs. twice-daily dosing: difference between intake and predicted biological impact in general



Europace.
2015 Feb 17.
pii: euu311.

Major gastrointestinal bleeding



Gomez-Outes A et al Thrombosis. 2013;2013:640723

AdverseEvents
REDEFINING DRUG SAFETY

SPECIAL REPORT

Examining the Comparative Safety of Blood Thinners:

An Analysis Utilizing AdverseEvents Explorer

Indeed, Adverse Events (AEs) from Food and Drug Administration (FDA) approved drugs are a major public safety concern. In fact, almost one million new AE reports are currently reported to the FDA each year, across ~2,000 approved drugs[4].

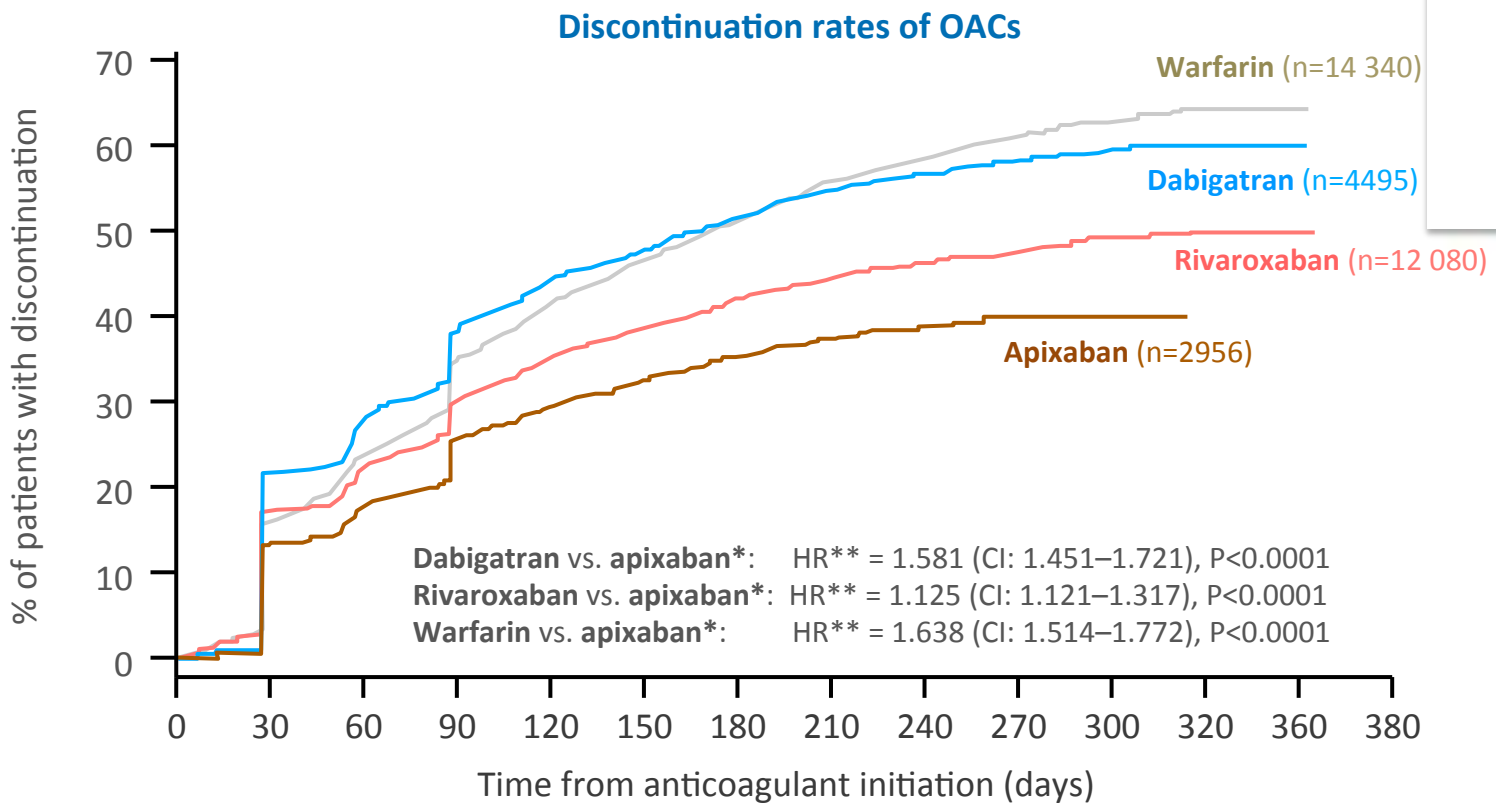
Oral anticoagulants such as warfarin (**Coumadin**) and antiplatelets agents such as aspirin and clopidogrel (**Plavix**) have been on the market for decades. New orally active anticoagulants (NOACs) include dabigatran (**Pradaxa**), rivaroxaban (**Xarelto**), and apixaban (**Eliquis**).

Table 1: Anticoagulants

Drug Name	Date Range	Primary Suspect Cases	Stroke* Cases (%)	Heart Attack* Cases (%)	Hospitalization Cases (%)	Death Cases (%)	Top 3 Adverse Events
apixaban (Eliquis)	Dec 2012-Dec 2013	1,031	54 (5.24%)	10 (0.97%)	212 (20.56%)	51 (4.95%)	Haemoglobin decreased, Ischaemic stroke, Haematoma
dabigatran (Pradaxa)	Oct 2010-Dec 2012	20,965	1,467 (6.99%)	324 (1.55%)	8,095 (38.64%)	2,529 (12.06%)	Gastrointestinal haemorrhage, Haemorrhage, Dyspepsia
rivaroxaban (Xarelto)	July 2011-Dec 2012	10,075	747 (7.41%)	107 (1.06%)	4,357 (43.25%)	1,115 (11.07%)	Pulmonary embolism, Deep vein thrombosis, Gastrointestinal haemorrhage
warfarin (Coumadin)	Nov 1997*-Dec 2012	22,338	687 (3.08%)	228 (1.02%)	11,152 (49.92%)	1,841 (8.24%)	International normalised ratio increased, Gastrointestinal haemorrhage, Haemorrhage

Discontinuation rates of NOACs in real world

Retrospective cohort study NVAF patients newly prescribed a NOAC or newly prescribed warfarin without knee/hip replacement surgeries in the time period of Jan 1 – Dec 31, 2013



* Effect size is versus apixaban which acts as a reference category.

** Analysis controlled for other variables including age, gender, onset of embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of TIA or stroke and history of bleeding.

Pan *et al*. Presented at the ESC Congress 2014. Abstract #5112.

Characteristics of Novel Oral Anticoagulants Compared With Warfarin

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	Synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, and X)	Thrombin	Factor IIa	Factor Xa
Bioavailability	~95%	~6%	~80%	~50%
Time to peak activity	72–96 hours	2 hours	2.5–4 hours	3 hours
Half-life	40 hours	14–17 hours	5–9 hours (young healthy patients), 11–13 hours (elderly patients)	8–15 hours
Dosing frequency in patients with AF	Once daily	Twice daily	Once daily	Twice daily
Interactions	Numerous drugs including substrates of CYP2C9, CYP3A4, and CYP1A2; various foods	Strong P-gp inhibitors and inducers	Strong CYP3A4 inducers, strong inhibitors of both CYP3A4 and P-gp	Strong inhibitors/inducers of both CYP3A4 and P-gp
Renal elimination (absorbed active drug)	~1%	~80%	~33%[a]	~27%

Abbreviations: AF, atrial fibrillation; CYP, cytochrome P450; P-gp, P-glycoprotein.
[a]An additional 33% of the absorbed rivaroxaban dose inactivated in the liver is also eliminated renally.

Savelieva I and Camm JA Clin Cardiol 2014 Jan;37(1):32-4