SGAIM SSMIG SSGIM
Kongresse • Veranstaltungen *Congrès • manifestations*

Médecin durable:
nachhaltig, zukunftsfähig, verlässlich
20. bis 21. September 2018 – *20 au 21 septembre 2018*
Montreux Music & Convention Centre

Montreux, 21. September 2018

DOAC
bei Krankenhauspatienten und in der Praxis

Vanessa KRAEGE & Lorenzo ALBERIO

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Médecin chef
Hématologie générale et Hémostase
Service et Laboratoire centrale d'Hématologie
CHUV, Lausanne

Outline

DOAC at a glance

DOAC : How to ... ?

New Direct Oral Anticoagulant Drugs

New Direct Oral Anticoagulant Drugs

Celle qui fut la belle Heaulmière
Rodin

“New” Direct Oral Anticoagulant Drugs

On the CH market since 12.2008

anti-fIIa — Dabigatran

anti-fXa — Rivaroxaban, Apixaban, Edoxaban

Dabigatran-etexilate: pro-drug

Rivaroxaban, Apixaban, Edoxaban: active compound

No requirement for antithrombin

Inhibit both free and surface-bound coagulation factors

Pharmacokinetics

Pharmacokinetics

Dabigatran

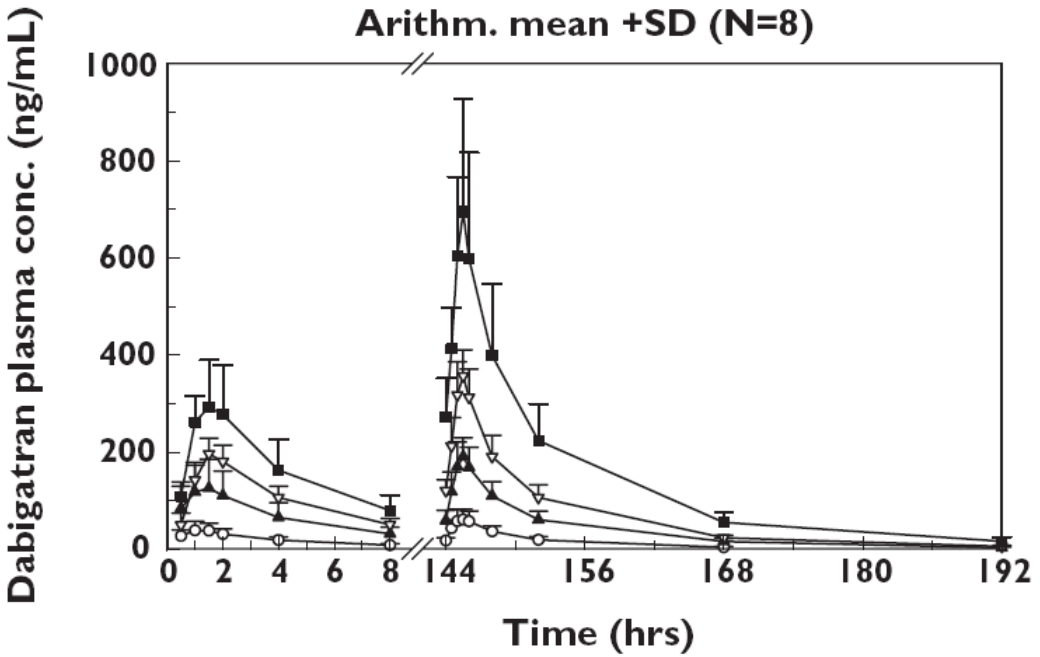


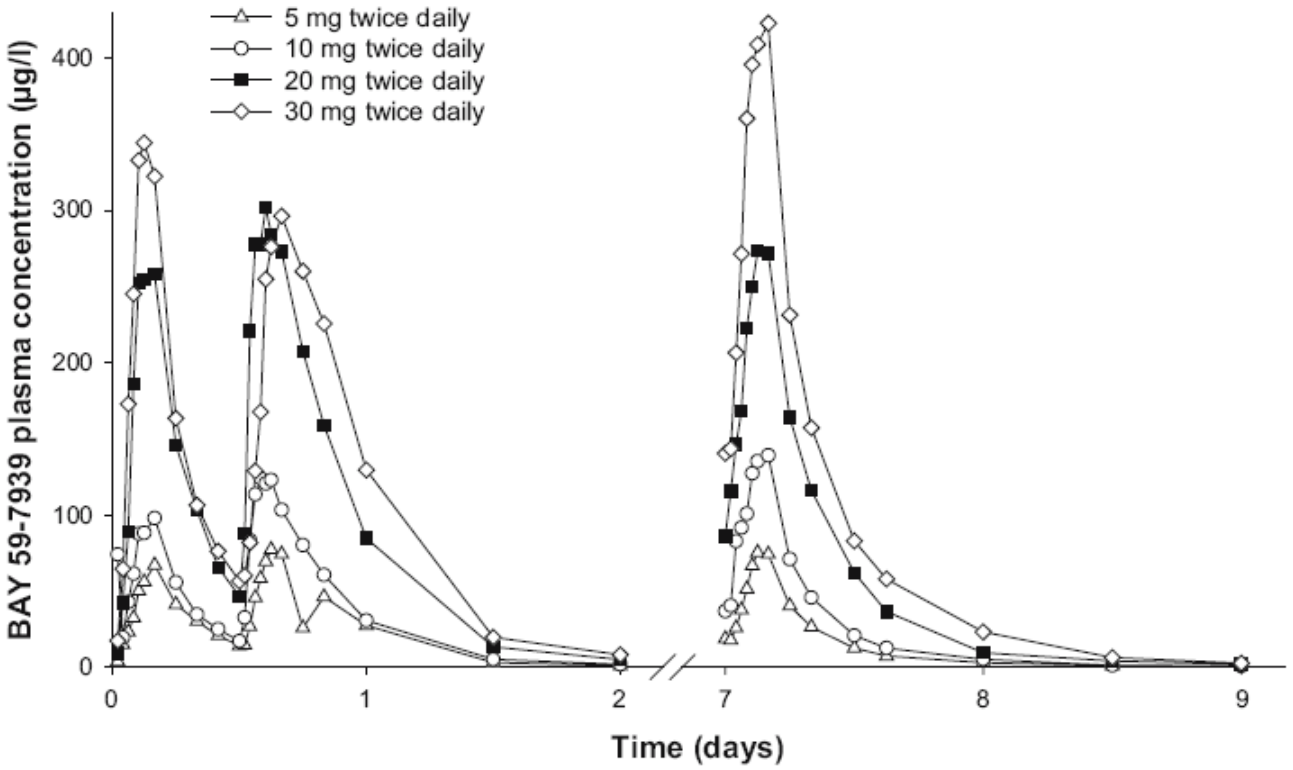
Figure 1

Arithmetic mean plot (+SD) of dabigatran plasma concentration *vs*. time following three times daily oral administration of 50 mg (○), 100 mg (▲), 200 mg (▽) or 400 mg (■) dabigatran etexilate solution for 7 days. (Note $n = 7$ for the 50 mg dose group as one subject withdrew consent)

Br J Clin Pharmacol 2007;64:292

Pharmacokinetics

Rivaroxaban



Eur J Clin Pharmacol 2005;61:873

DOAC : Pharmaco-dynamics & -kinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct, reversible inhibitor of free and clot-bound thrombin	Direct, reversible inhibitors of free and prothrombinase bound factor Xa		
Bioavailability	3–7%	80–100%	50%	62%
Protein binding	35%	92–95%	87%	55%
Primary clearance	80% renal	67% renal	56% faecal	50% renal
Tmax	1.5–3 h	2–3 h	3–4 h	1–2 h
Half-life[a]	12–14 h	5–13 h	12 h	10–14 h

Abbreviation: Tmax, time to peak drug concentration after dose.
[a]Half-life varies with renal function, with increasing half-life with increased renal impairment.

Thromb Haemost 2018;118:437

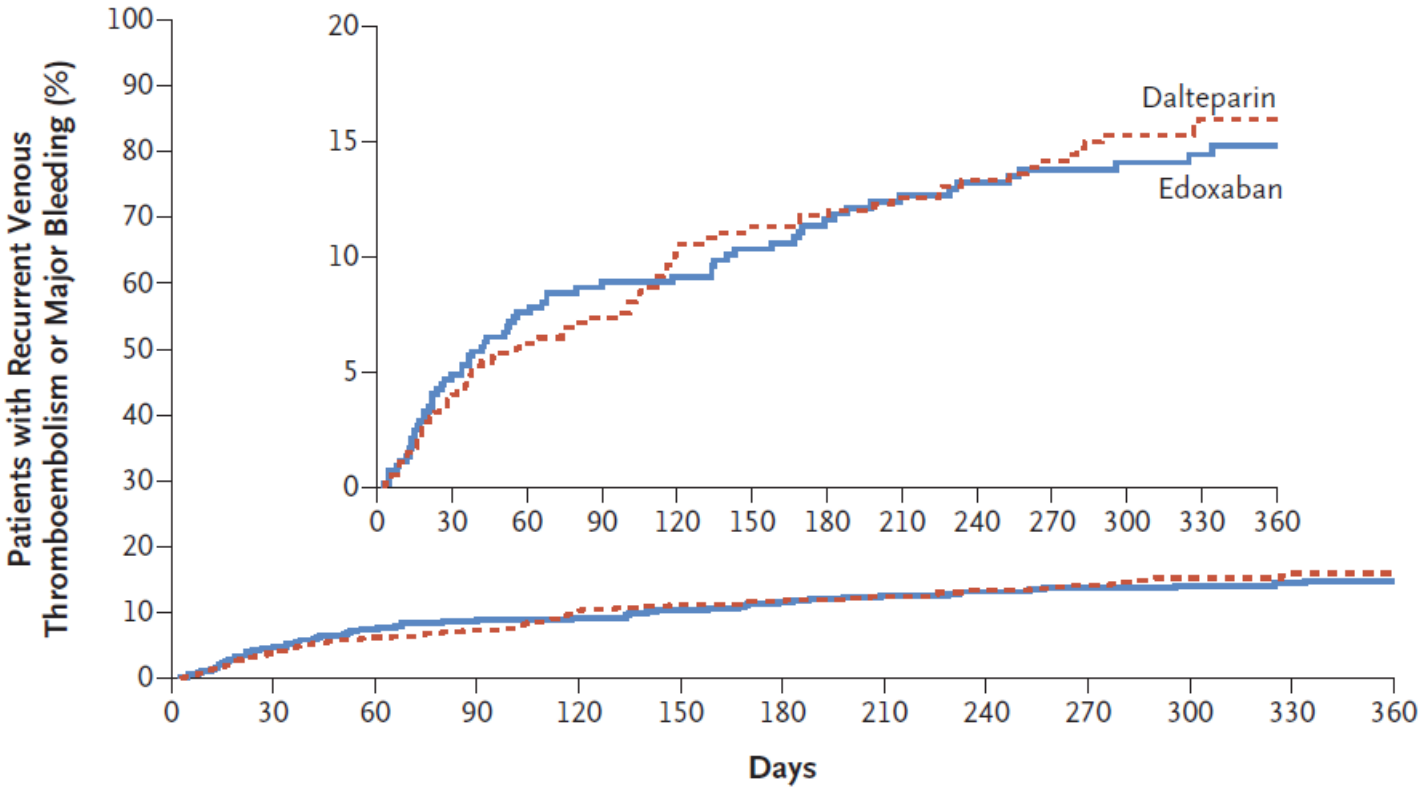
DOAC: Indications in CH

	Primary prophylaxis			Treat-ment	Secondary prophylaxis	
	Ortho	Medic	nv-AF	VTE	VTE	nv-AF
Apixa	YES	---	YES	YES	YES	YES
Edoxa	---	---	YES	YES	YES	YES
Riva	YES	---	YES	YES	YES	YES
Dabi	---	---	YES	YES	YES	YES

N.B.: NOT licensed for Mechanical cardiac valves BUT ...
Cancer
Antiphospholipid syndrome
HIT
VTE in unusual sites
Hepatic disease
Arterial (other than in nv-AF)

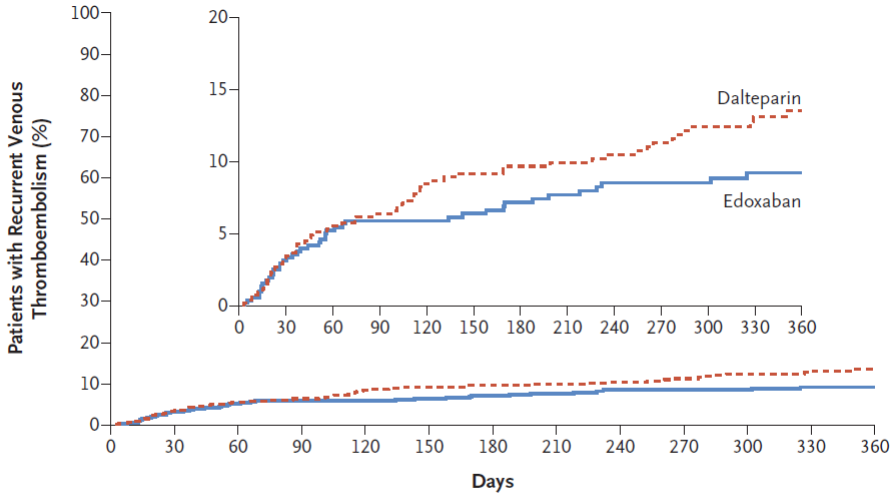
Legend:
nv-AF, non-valvular atrial fibrillation
VTE, venous thromboembolism

DOAC for cancer related VTE ?

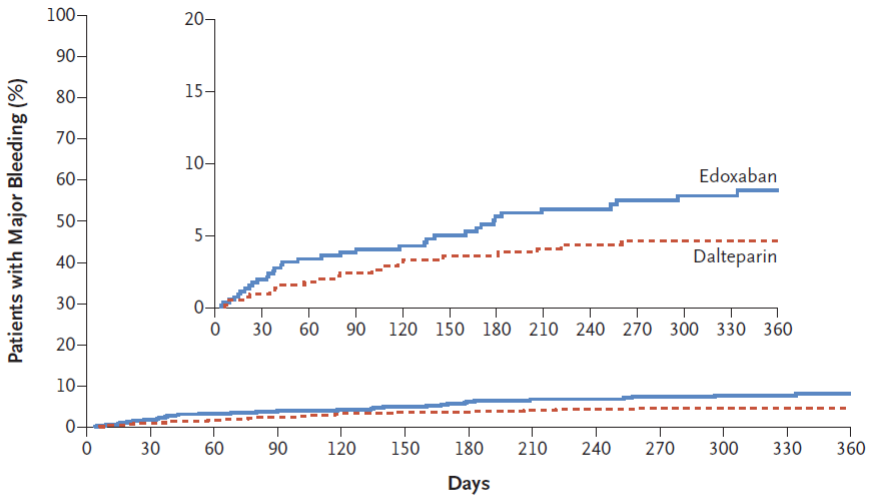


N Engl J Med 2018;378:615

DOAC for cancer related VTE ?



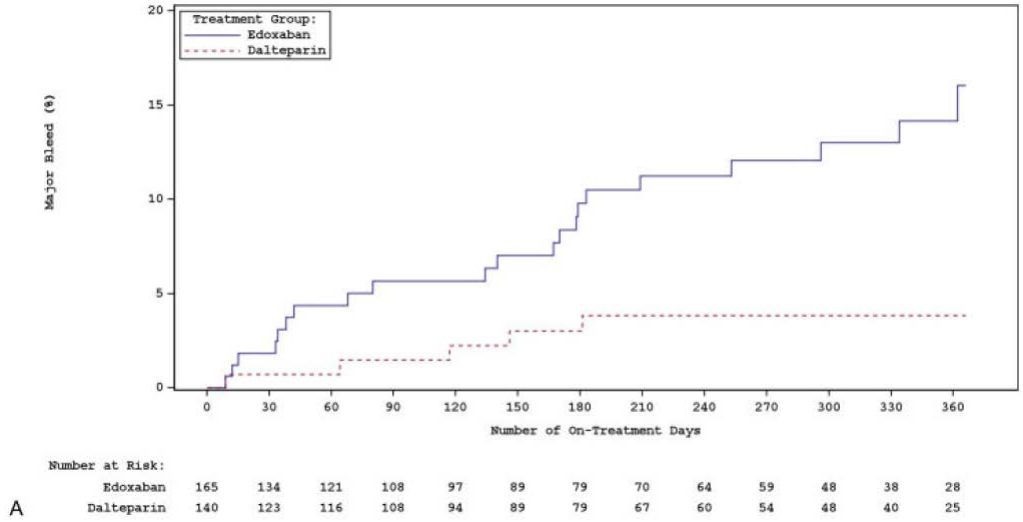
No. at Risk													
Edoxaban	522	480	437	415	395	370	356	340	320	307	281	245	168
Dalteparin	524	488	452	423	389	370	358	348	333	321	282	246	174



No. at Risk													
Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

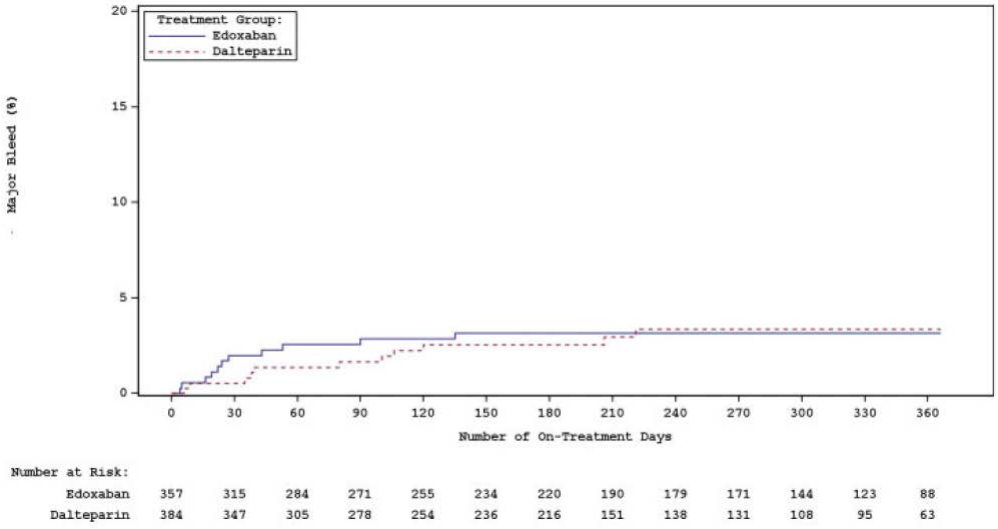
N Engl J Med 2018;378:615

DOAC for cancer related VTE ?



A

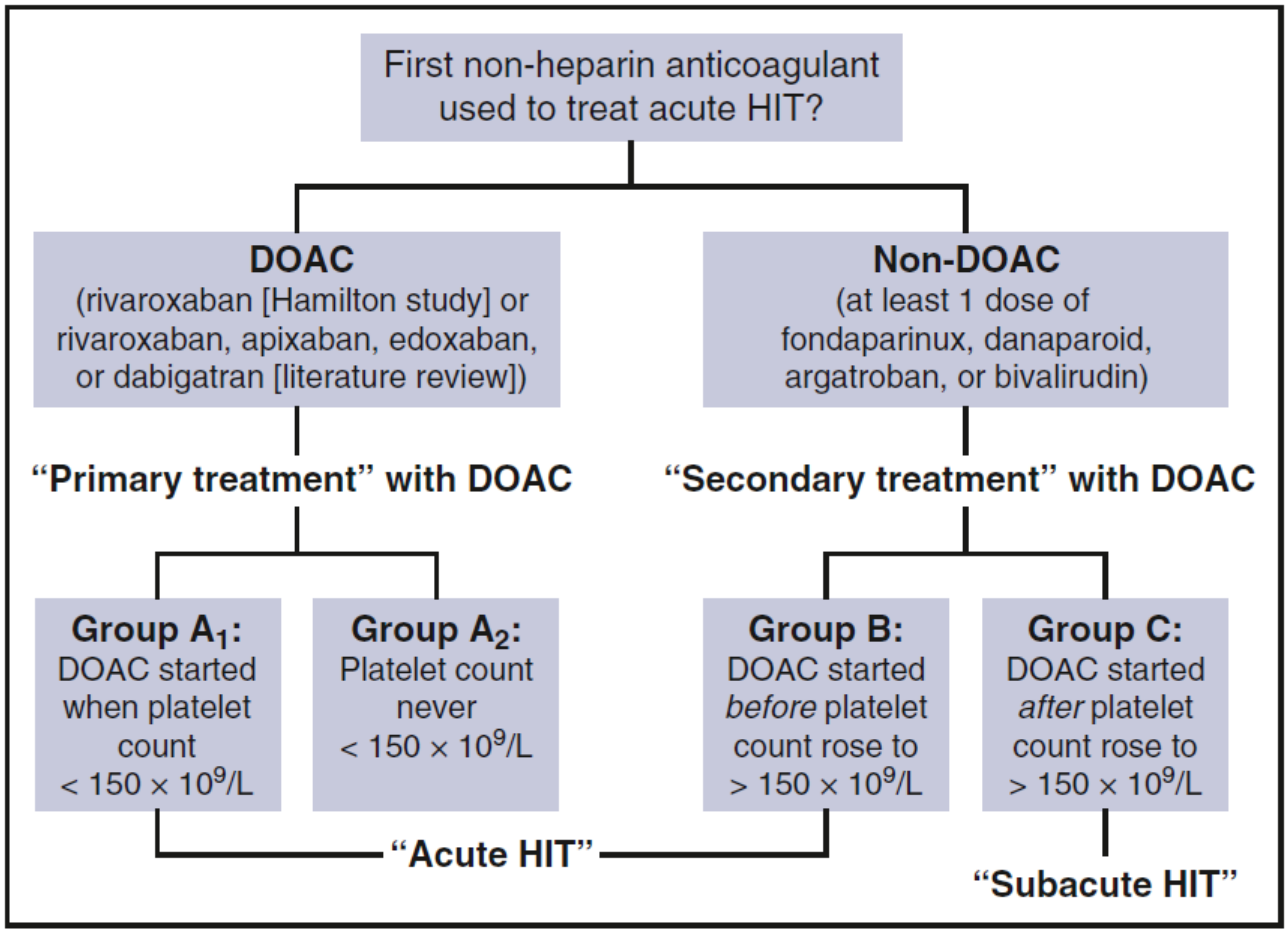
Fig. 1 Cumulative event rates of major bleeding in gastrointestinal cancer and non-gastrointestinal cancer. Shown are cumulative event rates for major bleeding with edoxaban and dalteparin in patients with gastrointestinal cancer (A) and non-gastrointestinal cancer (B).



B

Thromb Haemost 2018;118:1439

DOAC for HIT ?



Blood 2017;130:1104

DOAC for HIT ?

Table 2. Literature review of rivaroxaban for probable HIT (including new patients reported in this article): primary or secondary treatment during acute HIT (groups A_1, A_2, and B)

Study author	Reference	No. of patients	Group			Median platelet count at rivaroxaban start	HIT-associated thrombosis*		Outcome			
			A_1	A_2	B		No.	%	Thrombosis No.	Thrombosis %	Bleed No.	Bleed %
Rivaroxaban-Hamilton experience												
Linkins et al	17	12	3	2	7	56	6		1		0†	
This study		10	7	1	2	64	5		0		0	
Rivaroxaban-other (non-Hamilton) centers												
Kopolovic and Warkentin	28	1	0	0	1	30	0		0		0	
Ng et al, Ong et al‡	29, 36	9	9	0	0	64	9		0		0	
Sharifi et al§	30	9‡	0	0	9	90‡	4		0		0	
Hantson et al	31	1	0	0	1	30	1		0		0	
Abouchakra et al	32	1	1	0	0	25	1		0		0	
Sartori et al	33	1	0	1	0	150	1		0		0	
Casan et al	34	1	0	0	1	48	1		0		0	
Samoš et al	35	1	1	0	0	65	1		0		0	
Summary		46	21	4	21	73	29/46‖	63.0	1/46	2.2	0/46	0

Blood 2017;130:1104

DOAC for HIT ?

Table 3. Literature review of apixaban or dabigatran for probable acute HIT (including new patients reported in this article): primary or secondary treatment (groups A_1, A_2, and B)

			Group				HIT-associated thrombosis*		Outcome: Thrombosis		Outcome: Bleed	
Study author	Reference	No. of patients	A_1	A_2	B	Median platelet count at DOAC start	No.	%	No.	%	No.	%
Apixaban												
Sharifi et al†	30	5	0	0	5	90‡	1		0		0	
Larsen et al	37	1	1	0	0	112	0		0		0	
Delgado-García et al§	38, 39	1	1	0	0	25	1		0		0	
Kunk et al	40	5	0	0	5	111	3		0		0	
Total		12	2	0	10	90‡	5/12‖	41.7	0/12	0	0/12	0
Dabigatran												
Sharifi et al†	30	6	0	0	6	90‡	2		0		0	
Anniccherico et al	41, 42	1	0	0	1	120	1		0		0	
Mirdamadi§	43	1	1	0	0	32	1		0		0	
Tardy-Poncet et al	44	1	0	0	1	56	0		0		0	
Noel et al	45	1	0	1	0	216	1		1¶		0	
Bircan and Alanoglu§	46	1	1	0	0	52	1		0		0	
Total		11	2	1	8	58	6/11‖	54.5	1/11	9.1	0/11	0

Blood 2017;130:1104

DOAC for APS ?

Table 2 Characteristics and status of completed and recruiting randomized controlled trials (RCTs) of direct oral anticoagulants in thrombotic antiphospholipid syndrome (APS)

	RAPS [79]	TRAPS [7,82]	ASTRO-APS [7,83]
Chief Investigator	H. Cohen	V. Pengo	S. Woller
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT
No. of patients	116	536	200
APS subgroups	Previous VTE, target INR of 2.5; no thrombosis > 3 months; patients with arterial thrombosis excluded	Triple-positive thrombotic APS; arterial, venous and/or biopsy-proven microthrombosis	Thrombotic APS, VTE or arterial, target INR of 2.3, 3.0 or 3.5; no thrombosis > 6 months; definite, likely or historical APS
Intervention	Rivaroxaban 20 mg once daily versus warfarin target INR of 2.5	Rivaroxaban 20 mg once daily versus warfarin target INR of 2.5	Apixaban 2.5 mg or 5 mg twice daily versus warfarin target INR of 2.5
Primary outcome(s)	Thrombin generation – endogenous thrombin potential	Thrombosis – arterial or venous, major bleeding or death (composite)	Thrombosis - arterial and/or venous, bleeding
Duration of recruitment	Jun 2013 to November 2014	December 2014 to January 2018	February 15 to December 2019
Status	Completed and results published	Terminated January 2018 (see text)	Ongoing: protocol modified after potential safety signal (see text)

ASTRO-APS, Apixaban for the Secondary Prevention of Thromboembolism Among Patients With Antiphospholipid Syndrome (ClinicalTrials.gov: NCT02295475); INR, International Normalized Ratio; RAPS, Rivaroxaban in Antiphospholipid Syndrome (ISRCTN68222801); RCT, randomised controlled trial; TRAPS, Rivaroxaban in Thrombotic Antiphospholipid Syndrome (ClinicalTrials.gov: NCT02157272); VTE, venous thromboembolism.

JTH 2018;16:1028

RAPS : Results – Thrombin generation

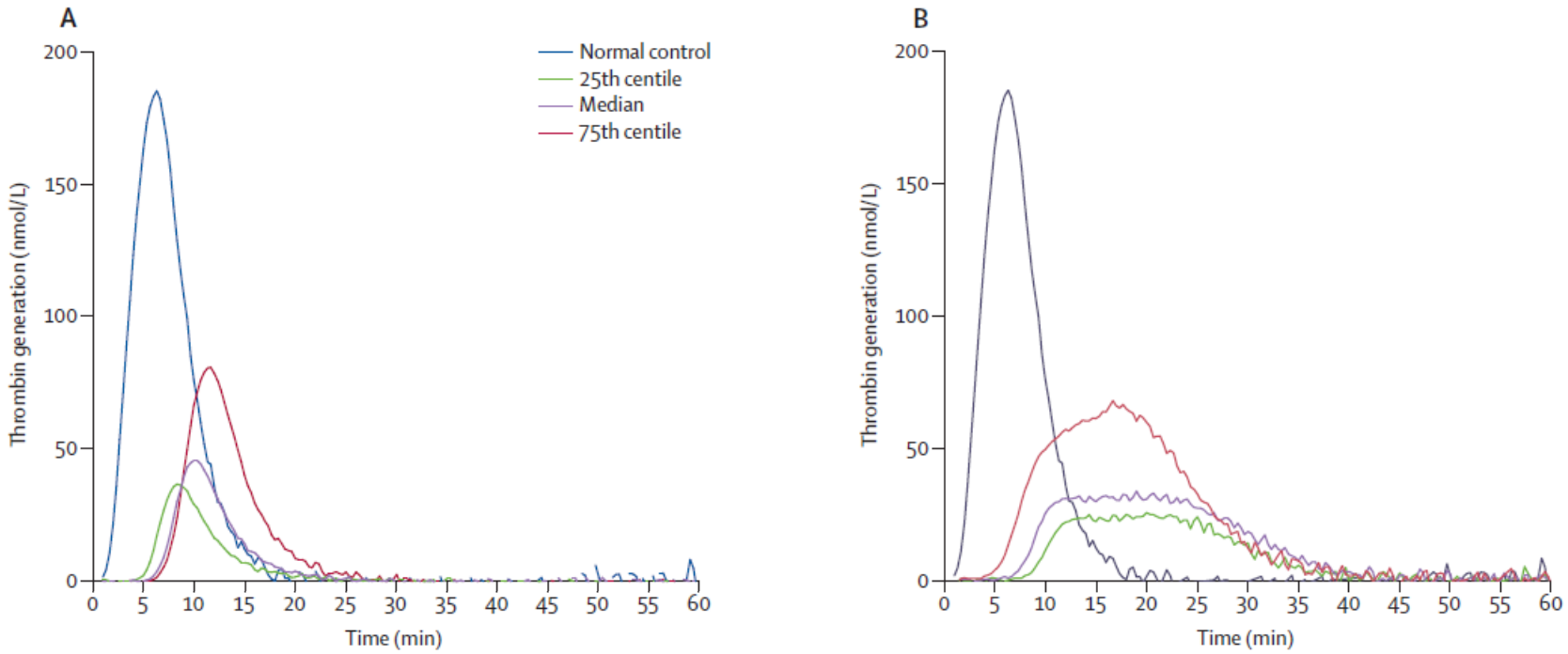


Figure 3: Thrombograms for median (25th and 7th percentiles) ETP values in RAPS, compared with a typical normal control value
(A) Patients taking warfarin. (B) Patients taking rivaroxaban.

Lancet Hematology 2016;3:e426

DOAC: How to prescribe ?

Remember to check:

Hb/Hct, Tc
PT, aPTT, thrombin time (TT), fibrinogen
Creatinine (calculate CrCl according to Cockcroft-Gault)
Liver function

Patient's age and weight

Medication

Legend:
CrCl, Creatinine clearance

DOAC: Drug interactions

Dabi

Riva

Apixa

Edoxa

P-gp	Inhibitors	Inducers
	AUC ↑	AUC ↓
Contraindicated	Quinidine Antifungal (ketokonazole, itrakonazole) Immunosuppres. (ciclosporine, tacrolimus)	
Avoid	Amiodarone Verapamil Ritonavir Clarithromycin	Rifampicin Phenytoin Carbamazepine St. John's wort

CAVE:
Always check for potential interactions with any concomittant drug

D'après Swiss Med Wkly 2016;146:w14286

Legend:
P-gp, P-glycoprotein; AUC, Area under the DOAC plasma concentration curve

DOAC: Drug interactions

~~Dabi~~

Riva

Apixa

~~Edoxa~~

CYP3A4	Inhibitors	Inducers
	AUC ↑	AUC ↓
Contraindicated	Antifungal (ketoconazole, itraconazole, voriconazole, posaconazole) HIV protease inhibitors (ritonavir)	Rifampicin Phenytoin, Carbamazepine St. John's wort
Avoid	Clarithromycine	
Unclear	Erythromycine Diltiazem	

CAVE:
Always check for potential interactions with any concomittant drug

D'après Swiss Med Wkly 2016;146:w14286

Legend:
CYP3A4, cytochrome P3A4 isoemzyme 3A4; AUC, Area under the DOAC plasma conc. curve

DOAC: Which dose ?

VTE prevention in major orthpaedic surgery

N.B.:
CrCl (Cockcroft-Gault) ≥30 ml/min

Legend:
b.i.d, *bis in die* (twice a day)
o.d., *omni die* (once daily)

DOAC: Which dose ?

Prevention of arterial TE events in nv-AF	
Apixa	5 mg b.i.d.
Edoxa	60 mg o.d. (30 mg if weight ≤60 kg and/or strong P-gp inhibitors)
Riva	20 mg o.d., with food
Dabi	150 mg b.i.d. (110 if age ≥80 yrs)

N.B.:
CrCl (Cockcroft-Gault) ≥50 ml/min

Legend:
b.i.d, *bis in die* (twice a day)
o.d., *omni die* (once daily)

D'après Swiss Med Wkly 2016;146:w14286

DOAC: Which dose ?

VTE treatment	
Apixa	*Upfront* 10 mg b.i.d. for the first 7 days 5 mg b.i.d. from day 8
Edoxa	*LMWH for 5 days* 60 mg o.d. (30 mg if weight ≤60 kg and/or strong P-gp inhibitors)
Riva	*Upfront* 15 mg b.i.d. for the first 21 days 20 mg o.d., with food
Dabi	*LMWH for 5 days* 150 mg b.i.d. (110 if age ≥80 yrs)

N.B.:
CrCl (Cockcroft-Gault) ≥50 ml/min

Legend:
b.i.d, *bis in die* (twice a day)
o.d., *omni die* (once daily)

D'après Swiss Med Wkly 2016;146:w14286

DOAC: Which dose ?

Long-term prevention of VTE recurrence	
Apixa	5 / 2.5 (*) mg b.i.d.
Edoxa	60 mg o.d. (30 mg if weight ≤60 kg and/or strong P-gp inhibitors)
Riva	20 / 10 (*) mg o.d., with food
Dabi	150 mg b.i.d.

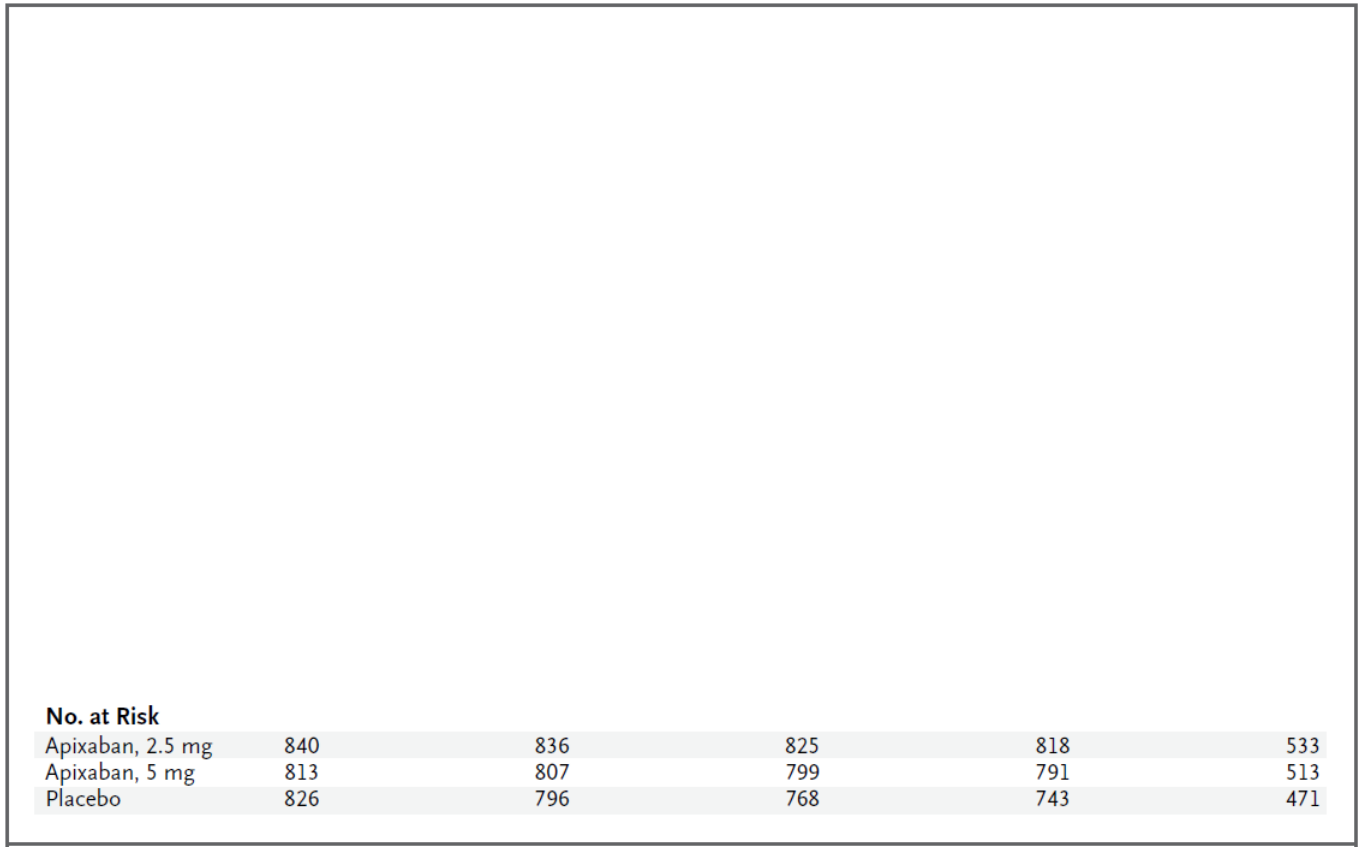
N.B.:
CrCl (Cockcroft-Gault) ≥50 ml/min

(*) clinical equipoise regarding the continuation or cessation of anticoagulation therapy

Legend:
b.i.d, *bis in die* (twice a day)
o.d., *omni die* (once daily)

D'après Swiss Med Wkly 2016;146:w14286

Long-term prevention of VTE recurrence

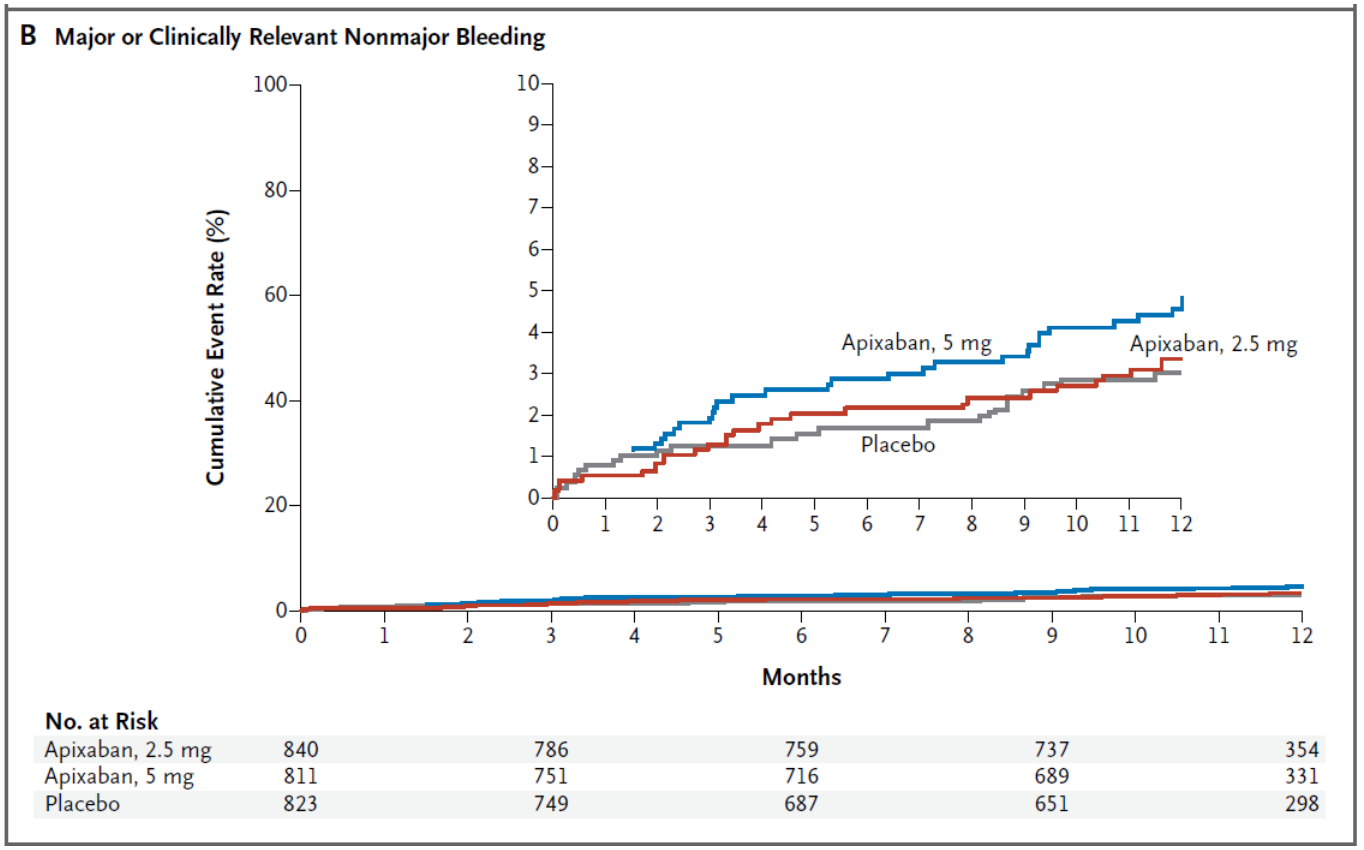


No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

(*) clinical equipoise regarding the continuation or cessation of anticoagulation therapy

AMPLIFY-EXT / N Engl J Med 2013;368:699

Long-term prevention of VTE recurrence

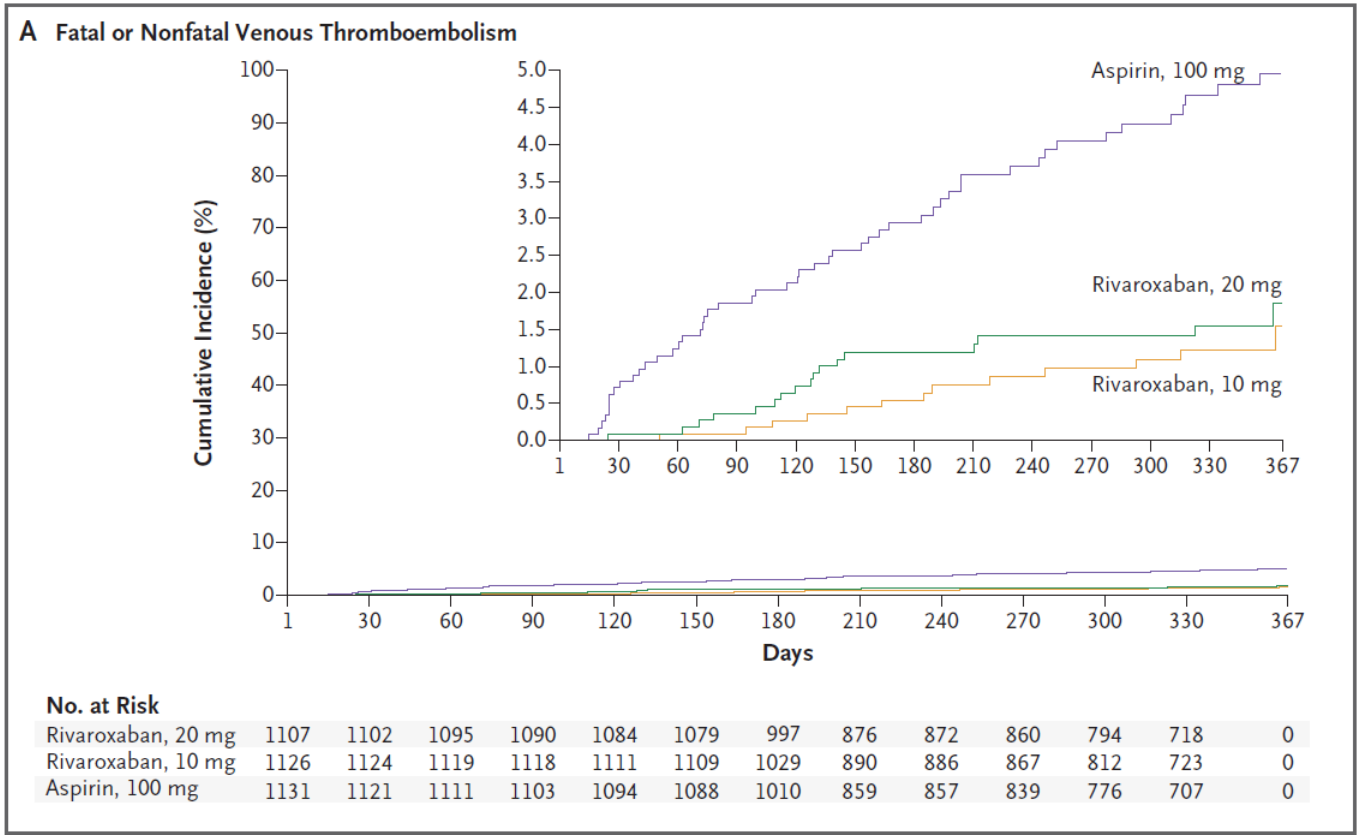


No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

(*) clinical equipoise regarding the continuation or cessation of anticoagulation therapy

AMPLIFY-EXT / N Engl J Med 2013;368:699

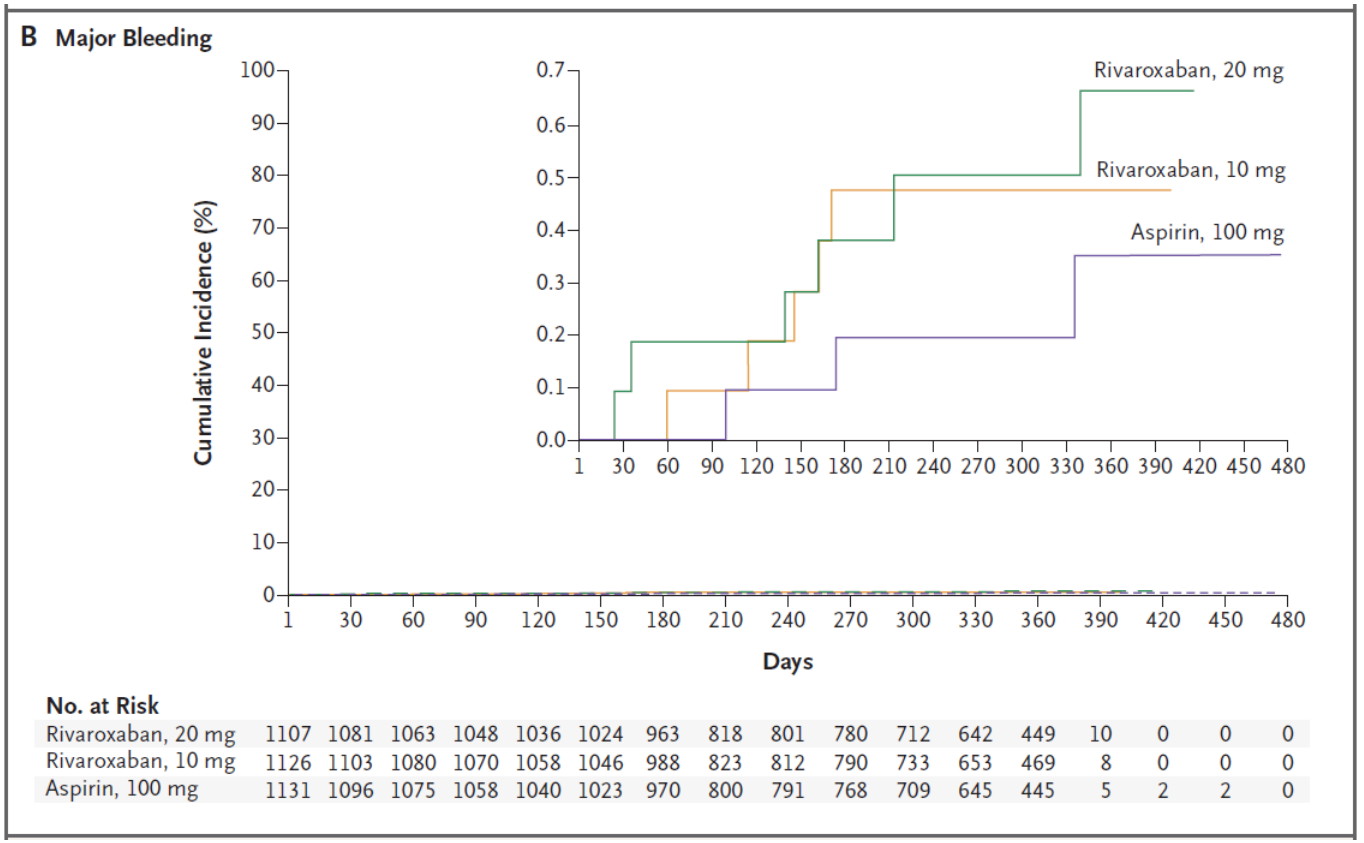
Long-term prevention of VTE recurrence



(*) clinical equipoise regarding the continuation or cessation of anticoagulation therapy

EINSTEIN-CHOICE / N Engl J Med 2017;376:1211

Long-term prevention of VTE recurrence



(*) clinical equipoise regarding the continuation or cessation of anticoagulation therapy

EINSTEIN-CHOICE / N Engl J Med 2017;376:1211

Crude incidence of recurrent VTE

Risk factor	Recurrent VTE, n (%)	
	Rivaroxaban 10 and 20 mg	Placebo/aspirin
Provoked by minor persistent risk factors, n (%)		
Inflammatory bowel disease	0/26 (0.0)	0/14 (0.0)
Lower extremity paralysis or paresis	0/12 (0.0)	0/4 (0.0)
Congestive heart failure	2/23 (8.7)	0/10 (0.0)
Body mass index >30 kg/m^2	13/907 (1.4)	25/536 (4.7)
Creatinine clearance <50 mL/min	2/122 (1.6)	8/104 (7.7)
Family history of VTE	2/31 (6.5)	0/13 (0.0)
Hereditary thrombophilia	3/173 (1.7)	8/102 (7.8)
Acquired thrombophilia	1/20 (5.0)	0/5 (0.0)
Provoked by minor transient risk factors, n (%)		
Immobilization	1/99 (1.0)	5/68 (7.4)
Travel >8 h	0/11 (0.0)	0/9 (0.0)
Use of estrogen therapy	0/75 (0.0)	1/64 (1.6)
Pregnancy or puerperium	0/17 (0.0)	0/2 (0.0)
Leg injury with impaired mobility	0/76 (0.0)	2/40 (5.0)

Minor persistent risk factors are listed for the patient who did not have a major persistent risk factor; minor transient risk factors are listed for patients who did not have persistent risk factors. Hereditary thrombophilia includes deficiency of antithrombin, protein C, or protein S, and factor V Leiden or the prothrombin gene mutation. Acquired thrombophilia includes antiphospholipid syndrome. A patient can contribute to multiple rows.

Blood advances 2018;2:788

DOAC: How to choose ?

DOAC: How to choose ?

Patient characteristic	Drug choice	Rationale
Not currently anticoagulated	NOAC[a]	NOACs are at least as effective and safe as VKAs, produce less intracranial bleeding and are more convenient because they do not require routine monitoring and have a low propensity for food and drug interactions.

Legend:
[a], Non-VKA Oral Anti-Coagulant

My commentary
- Not licensed for all indications
- Not licensed/recommended for CrCl ≤30 ml/min
- Extreme low / high body weight
- More gastro-intestinal bleedings (Edoxaban, Rivaroxaban, Dabigatran)
- DOAC drug interactions
- Treatment adherence cannot be verified
- Patient preference

Thromb Haemost 2016; 115:257

DOAC: How to choose ?

Patient characteristic	Drug choice	Rationale
Already receiving warfarin, stable INR and satisfactory TTR	Maintain VKA therapy or consider switching to NOAC[a]	Depends on patient and physician preference

Legend:
TTR, Time in Therapeutic Range

My commentary
- Keep VKA
- Patient preference

Thromb Haemost 2016; 115:257

DOAC: How to choose ?

Patient characteristic	Drug choice	Rationale
Already receiving warfarin, unsatisfactory TTR	Any NOAC[a]	NOACs produce a more predictable and stable anticoagulant effect and do not require routine coagulation monitoring

My commentary

- Why unsatisfactory TTR ?
  - Therapeutic adherence ?
  - Drug interactions ?
  - Alimentary habits ?

- Consider: VKA self-monitoring
  Half-life Sintrom ~6 hours *versus* Marcoumar 5 days
  Vitamin K supplementation

Thromb Haemost 2016; 115:257

Pharmacie Internationale
Lausanne
021 / 310 20 71

Correct labile INR

Spital-Apotheke
KS Luzern
041 / 205 55 51

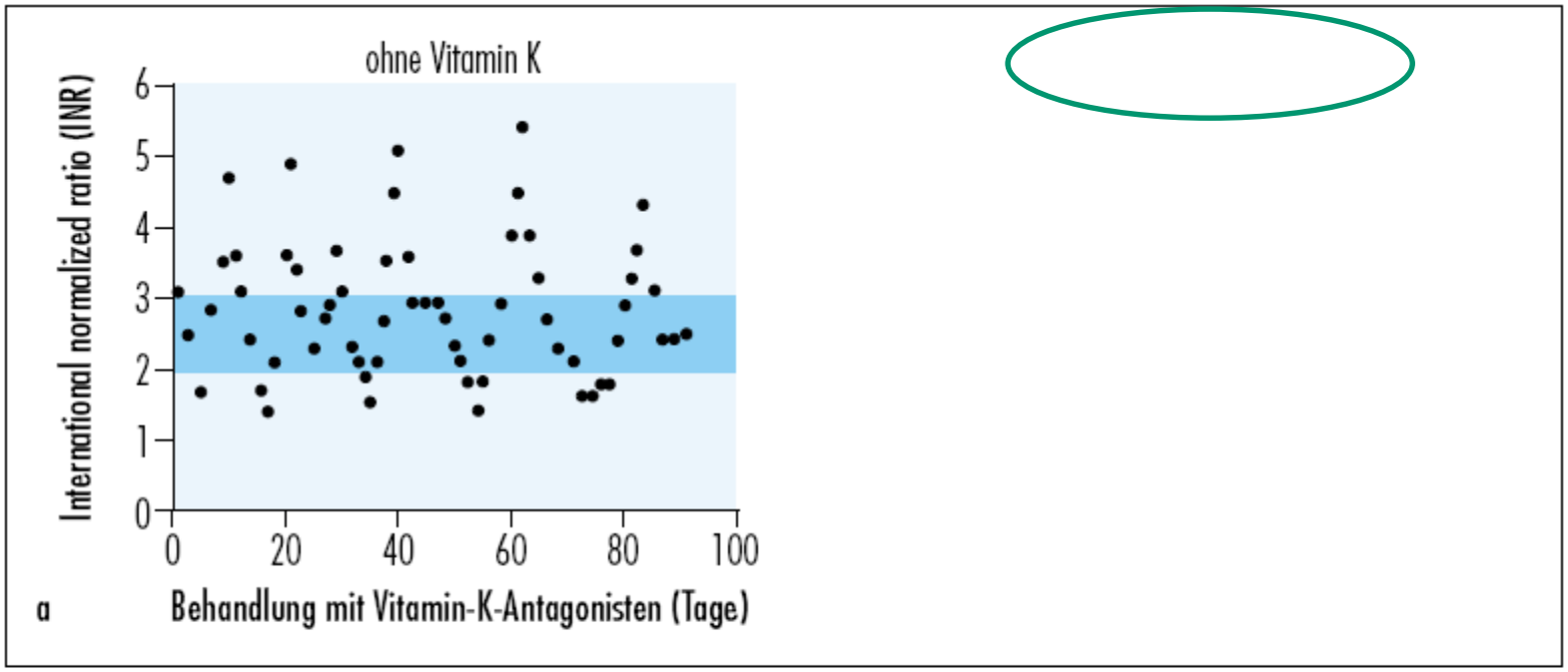


Abb. 2 INR-Verlauf bei einem 56-jährigen Patienten mit ischämischen Insult im Alter von 48 Jahren bei PFO und homozygoter Faktor-V-Leiden-Mutation: unter Sekundärprävention mit Warfarin (Ziel-INR: 2,0–3,0) exzessiv fluktuierende INR-Werte und intrakraniellen Blutungskomplikationen sowie zerebrovaskuläre Ereignisse unter dualer plättchenhemmender Medikation

a) ohne Vitamin K (ITTR: 68%, Warfarin-Dosis: 5,4 ± 1,8 mg/Woche)

b) bei Gabe von 100 µg Vitamin K/täglich (ITTR:84%, Warfarin-Dosis: 8,7 ± 0,85 mg/Woche).

Hämostaseologie 2008;28:44

J Thromb Haemost 2007;5:2043

DOAC: How to choose ?

Patient characteristic	Drug choice	Rationale
CrCl 30–50 ml/min	Apixaban[b], rivaroxaban[c] or edoxaban[d]	Less affected by renal impairment than dabigatran

Remember

- Lower dose

Apixaban 2.5 mg b.i.d. in nv-AF and age >80 yrs / weight <60kg
Edoxaban 30 mg o.d.
Rivaroxaban 15 mg o.d. in nv-AF (*but <u>not</u> in VTE !?*)
Dabigatran 110 mg b.i.d.

Thromb Haemost 2016; 115:257

Age & Renal Function

Table 1. Clinical Characteristics of Patients

Characteristic	
n	4093
Men, n (%)	1762 (43)
Median age (range)	84 (80–102)
Follow-up period, person-y	9603
Mean±SD follow-up period, y	2.35±2.1
Indication for VKA treatment, n (%)	
Atrial fibrillation	3015 (73.7)
Venous thromboembolism	1078 (26.3)
History of major bleeding	114/3933 (2.9)
History of falls	151/3595 (4.2)
≥3 Associated drugs	2367/3817 (62.0)
Creatinine clearance ≤30 mL/min	251/2477 (10.1)
Creatinine clearance ≤50 mL/min	1500/2477 (60.6)
Quality of anticoagulation (IQR), %	
Time in the therapeutic range	62 (49–75)
Time above the therapeutic range	11 (5–18)
Time below the therapeutic range	24 (13–35)

Circulation 2011;124:824

DOAC: How to choose ?

Patient characteristic	Drug choice	Rationale
Ischaemic stroke on warfarin, rivaroxaban, apixaban, or edoxaban	Dabigatran	Lower risk of ischaemic stroke with dabigatran (150 mg)

My commentary

- Unsatisfactory therapeutic adherence *versus* Treatment failure ?

Thromb Haemost 2016; 115:257

DOAC: How to choose ?

Patient characteristic	Drug choice	Rationale
Dyspepsia or upper GI complaints	Rivaroxaban, apixaban, or edoxaban	Dyspepsia with dabigatran in up to 10% of patients

Thromb Haemost 2016; 115:257

DOAC: How to choose ?

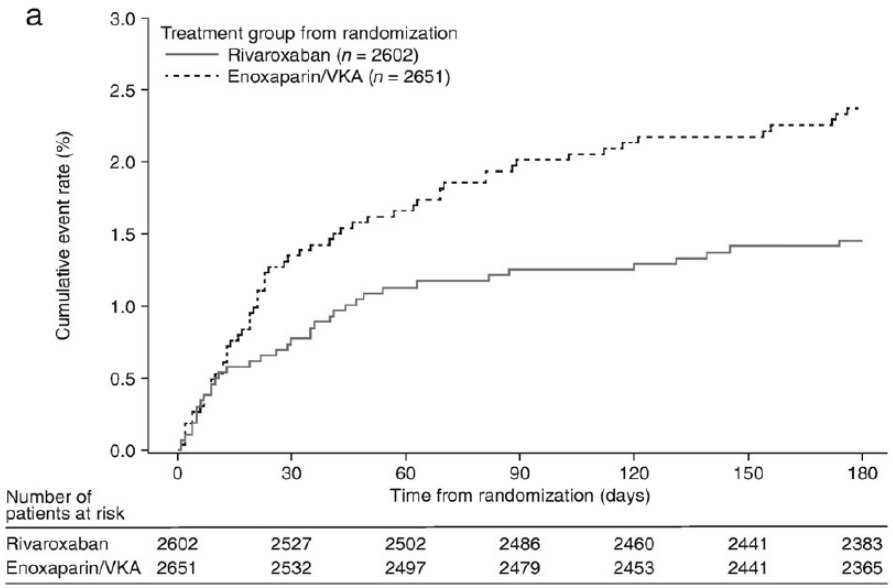
Patient characteristic	Drug choice	Rationale
Recent GI bleed	Apixaban	Dabigatran (150 mg), rivaroxaban, and edoxaban (but not apixaban) produce more GI bleeding than warfarin

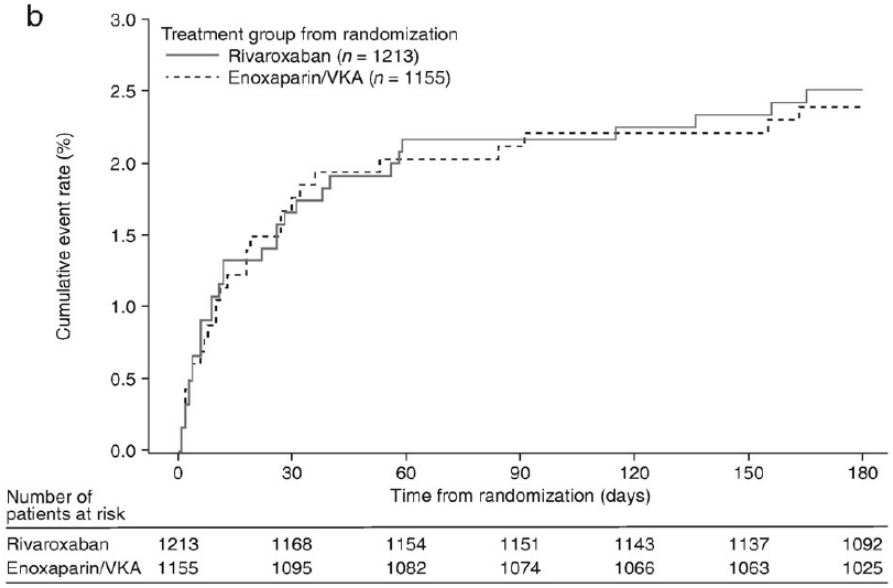
My commentary
- Diagnostic bleeding ?
- Study patient selection (Thromb Res 2017;149:29)

Thromb Haemost 2016; 115:257

CAVE : Study patient selection

Time to first VTE recurrence





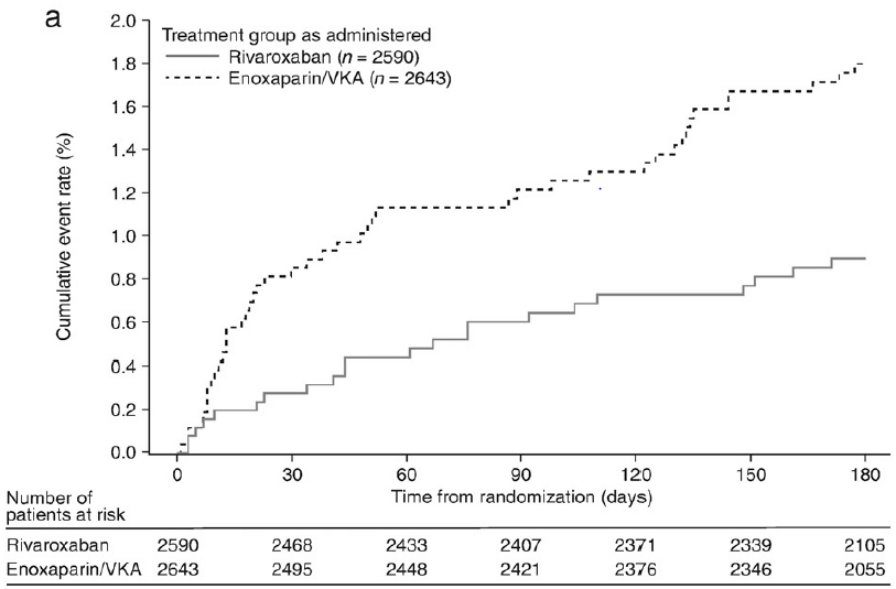
EINSTEIN-DVT/PE patients eligible for AMPLIFY

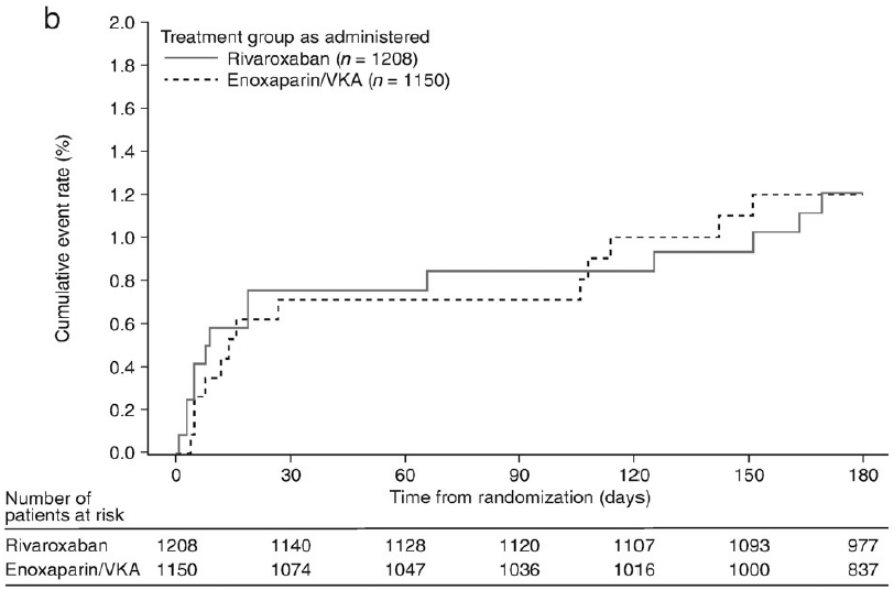
EINSTEIN-DVT/PE patients ineligible for AMPLIFY

Thromb Res 2017;149:29

CAVE : Study patient selection

Time to first major bleeding



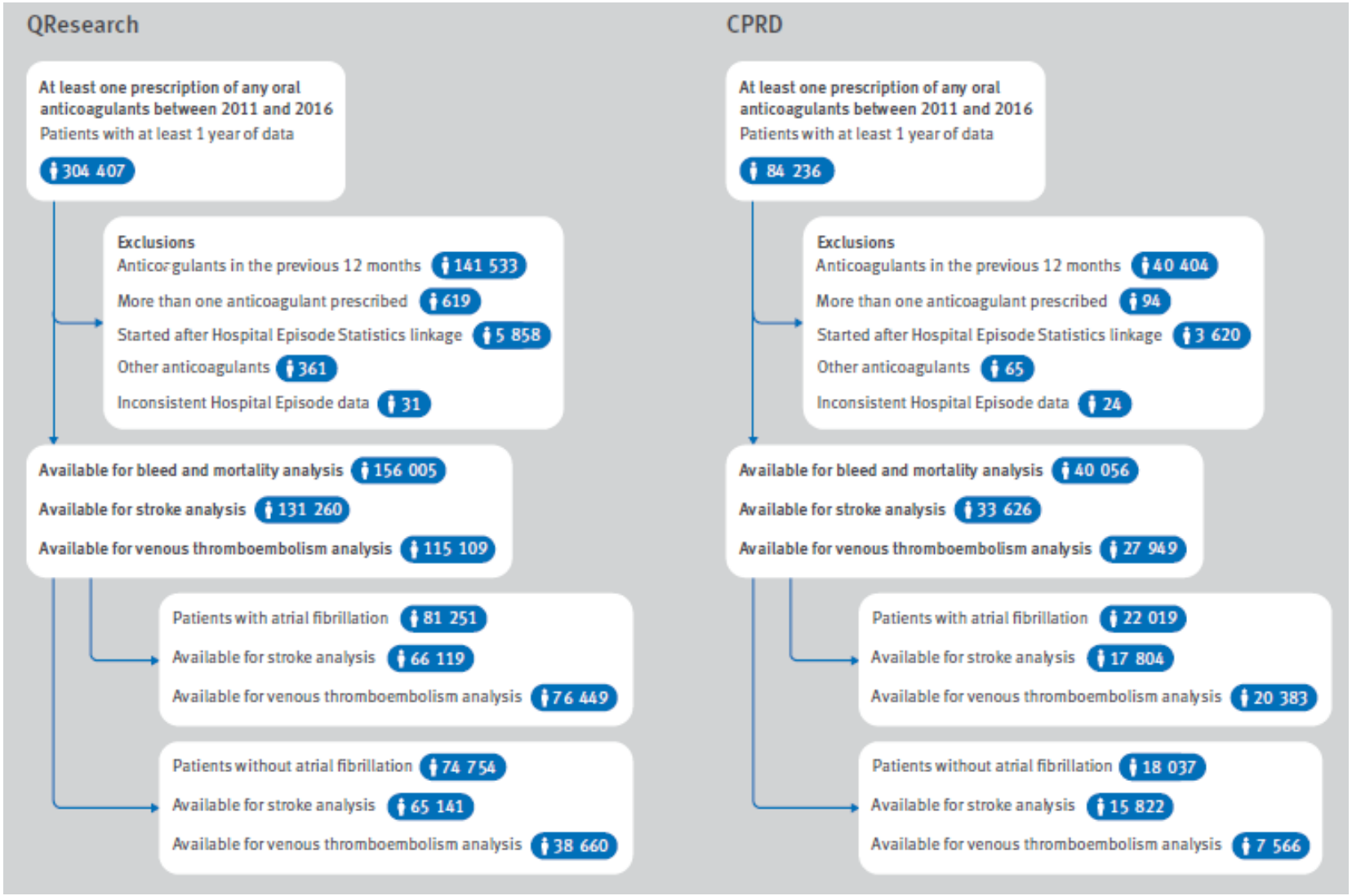


EINSTEIN-DVT/PE patients eligible for AMPLIFY

EINSTEIN-DVT/PE patients ineligible for AMPLIFY

Thromb Res 2017;149:29

DOAC in the real world (UK)



BMJ 2018;362:k2505

DOAC in the real world (UK)

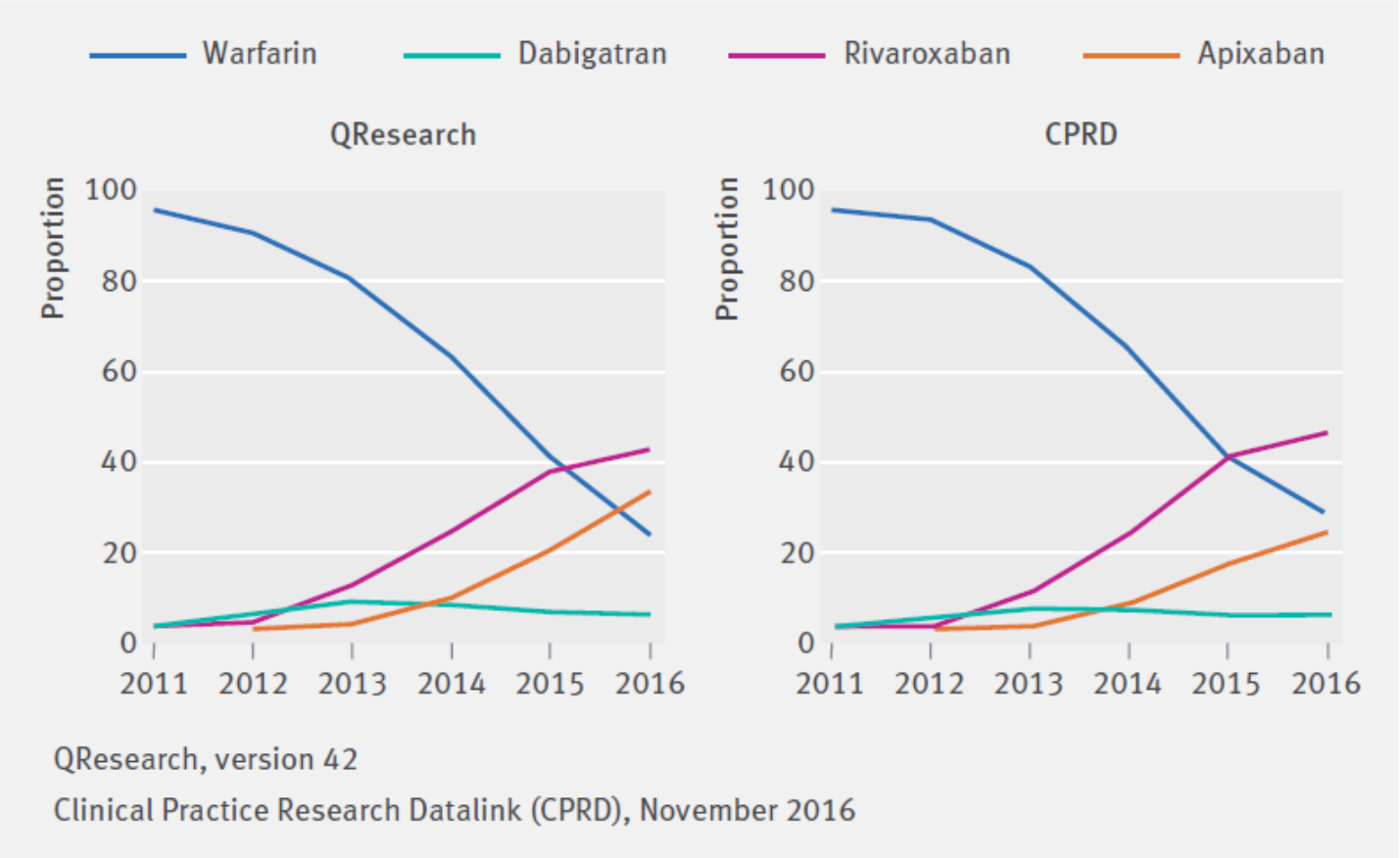


Fig 2 | Proportion of patients prescribed different anticoagulants in each year by database

BMJ 2018;362:k2505

DOAC in the real world (UK)

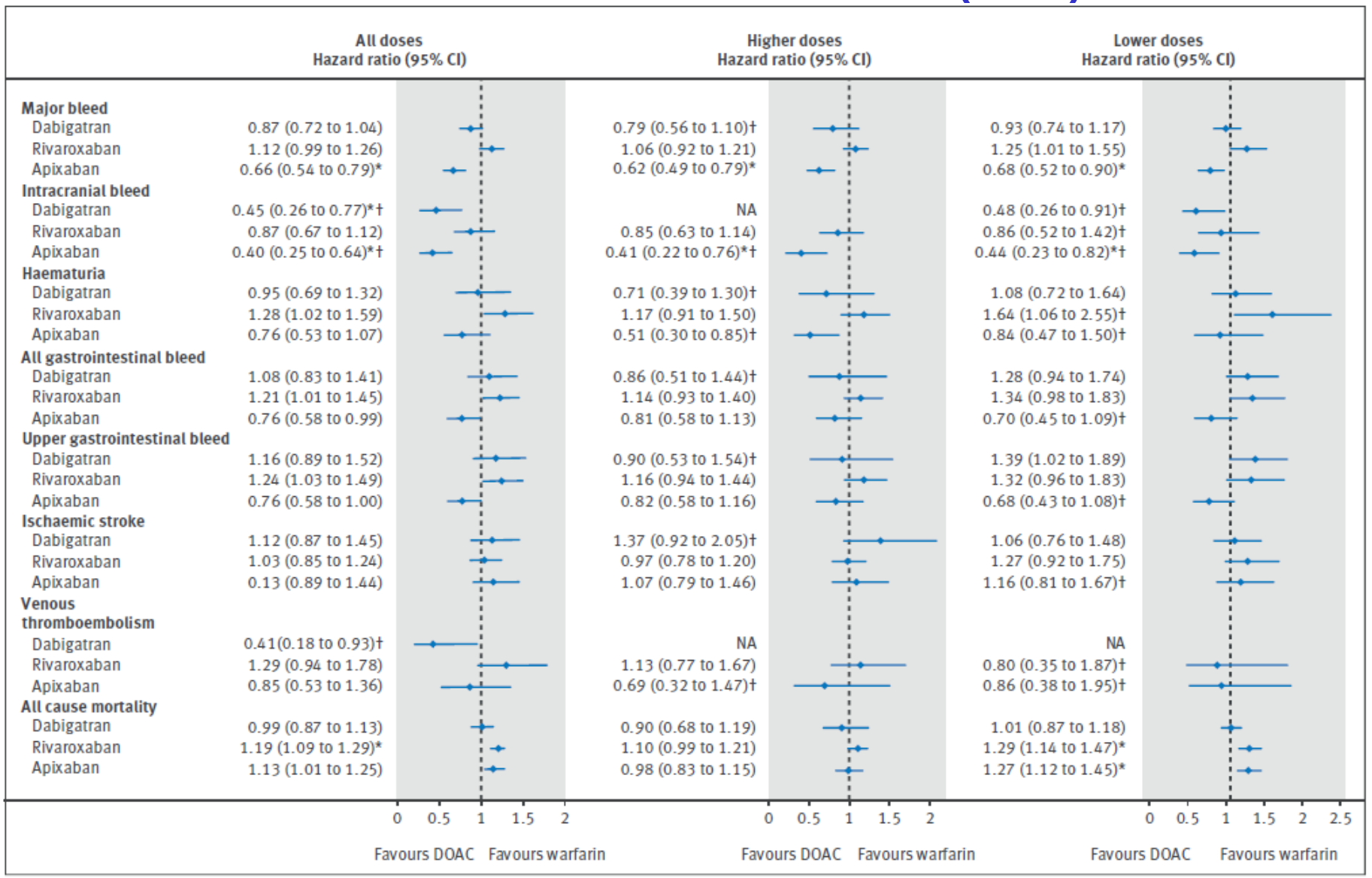


Fig 3 | Patients with atrial fibrillation: adjusted Cox hazard ratios (95% confidence interval) for outcomes associated with exposure to study drugs overall and by prescribed dose compared with warfarin. NA=not available. *P value<0.01. †The results were only available from the QResearch database.

DOAC in the real world (UK)

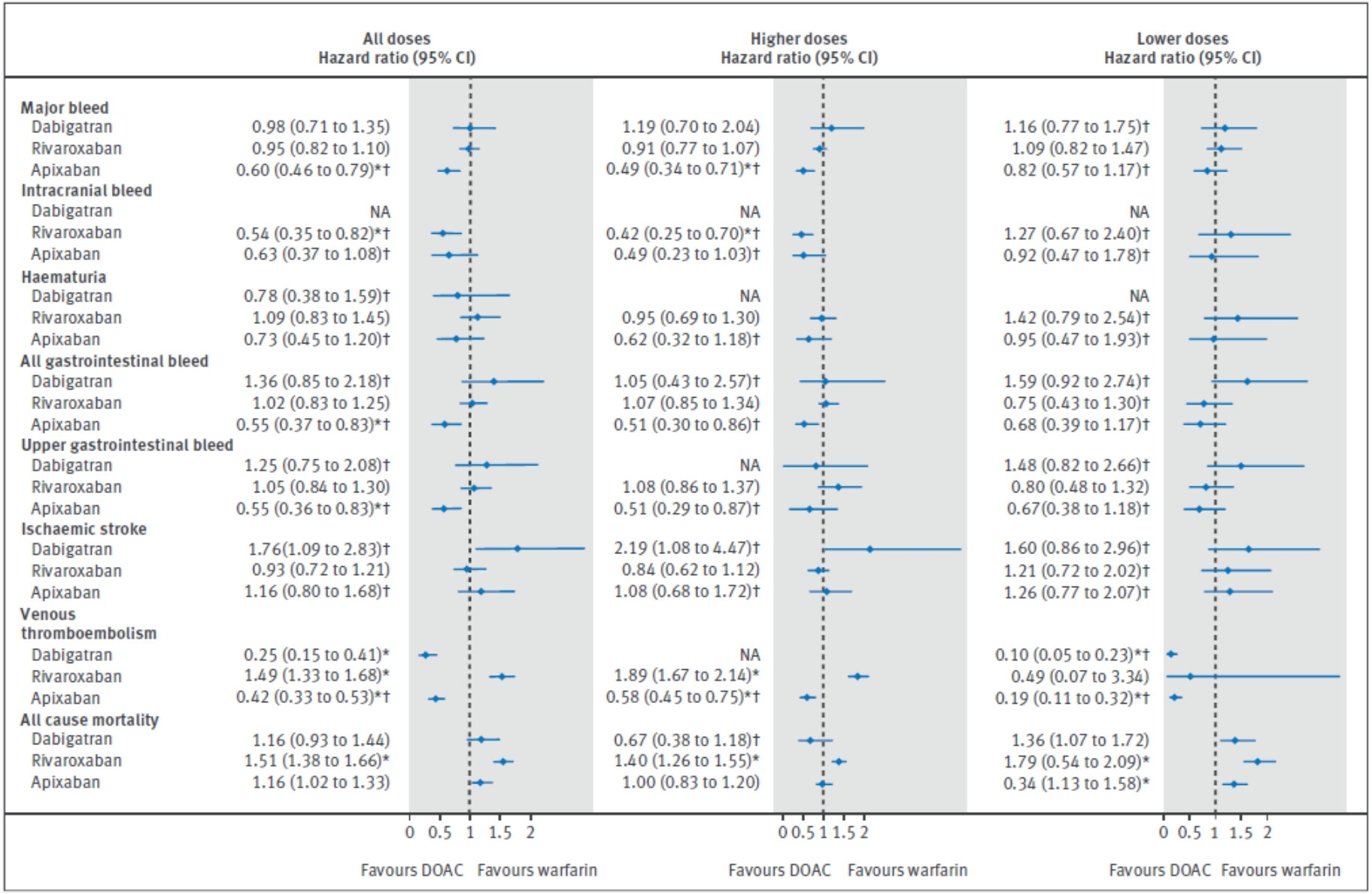


Fig 4 | Patients without atrial fibrillation: adjusted Cox hazard ratios (95% confidence interval) for outcomes associated with exposure to study drugs overall and by prescribed dose compared with warfarin. NA=not available. *P value<0.01. †The results were only available from the QResearch database.

DOAC: How to manage elective surgery ?

Perioperative bridging of DOAC ?

No bridging with LMWH

	Rivaroxaban	Enoxaparine
C_{max}	2-4 heures	3-5 heures
DV	5-9 heures 11-13 heures chez les patients âgés	4-7 heures 17 heures chez les patients avec insuffisance rénale sévère

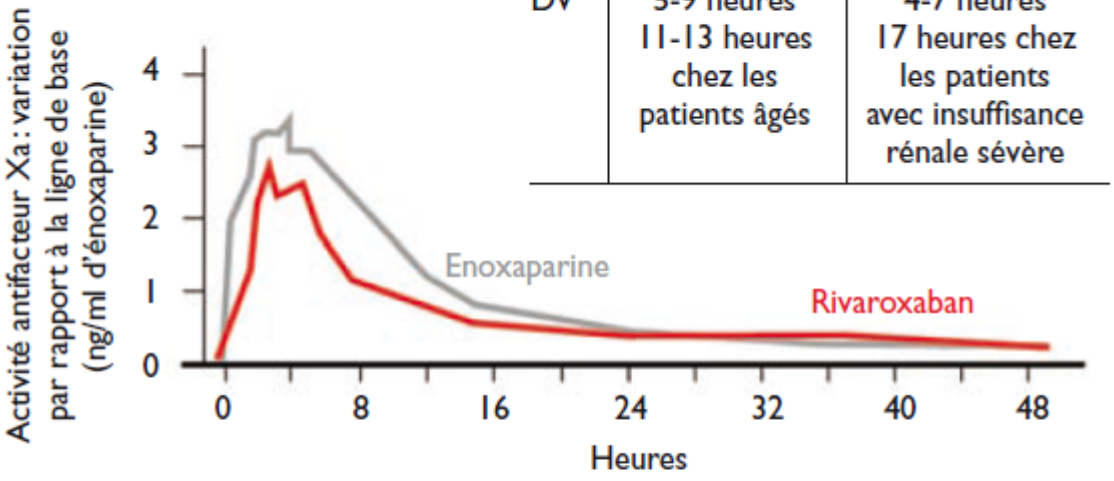


Figure 1. Profil pharmacocinétique du rivaroxaban et de l'énoxaparine

Rev Med Suisse 2013;9:1375

When to stop DOAC before surgery ?

Drug and CL_{cr}	Hold Time Before Minor Procedure	Hold Time Before Major Surgery

Adapted from:

J Thromb Thrombolysis 2016;41:206
Am J Health-Syst Pharm 2016;73(suppl 2):S5

DOAC level and perioperative bleeding risk

CAVE : Estimate
(no clinical data!)

“safe for spinal anesth”:	<30 ng/ml
“safe for surgery”:	<100 ng/ml
“high bleeding risk”:	>400 ng/ml

French guidelines	Arch Cardiovac Dis 2013;106:382
German guidelines	Clin Res Cardiol 2013;102:399

DOAC: How to treat major bleeding ?

DOAC: Treatment of major bleeding

Type of DOAC ?	anti-IIa: Dabi anti-Xa : Apixa, Edoxa, Riva
Indication & dosage ?	
Time of last intake ?	peak : 2-4 hours half-life, anti-IIa: 12-17 hrs half life, anti-Xa : 9-14 hrs
Other drugs ?	Drug interactions ? Impairment of hemostasis ?

French guidelines	Arch Cardiovac Dis 2013;106:382
German guidelines	Clin Res Cardiol 2013;102:399

DOAC: Treatment of major bleeding

Laboratory ?	Hb/Hct, Tc Creatinine Liver function
Coagulation assay ?	TP, aPTT, Thrombin time, fibrinogen anti-IIa: Thrombin time, dosage anti-Xa : dosage

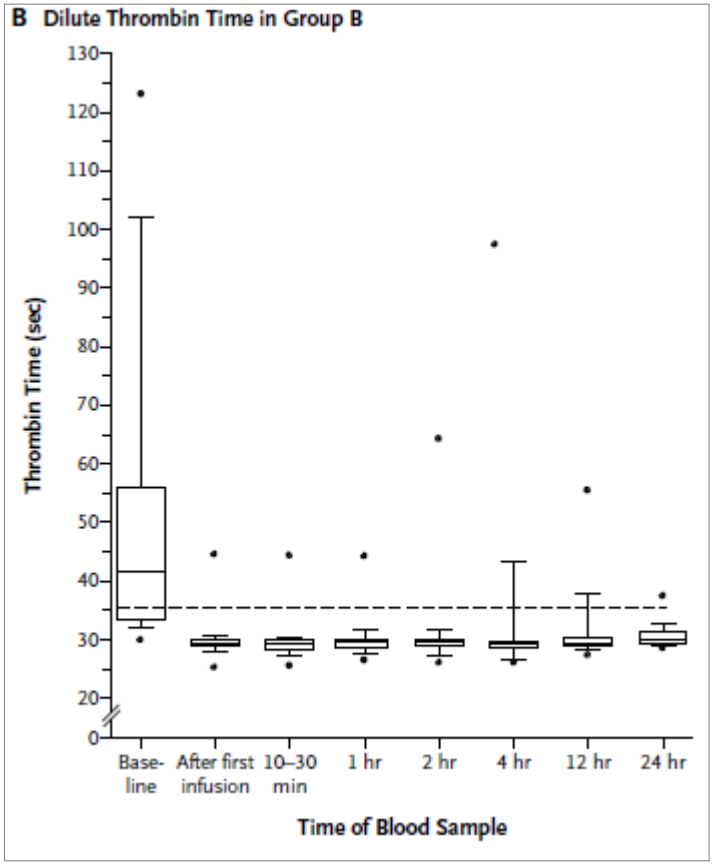
French guidelines	Arch Cardiovac Dis 2013;106:382
German guidelines	Clin Res Cardiol 2013;102:399

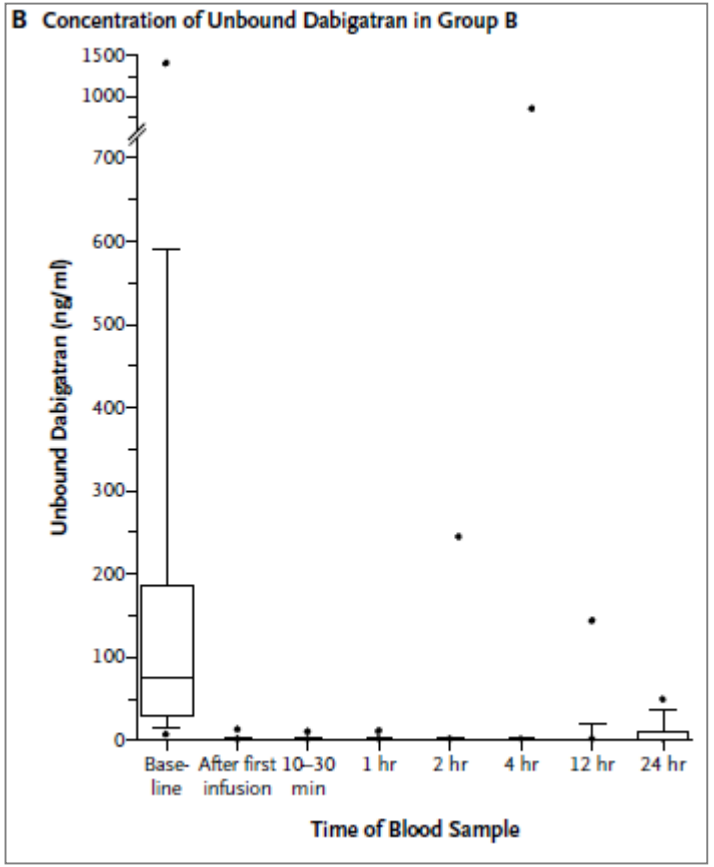
DOAC: Treatment of major bleeding

Activated charcoal	up to 8 hrs after ingestion
Tranexamic acid	1g i.v., repeat as needed
PCC (Beri/Prothrom-plex®) aPCC (FEIBA®)	25-50 U/kg 30-50 U/kg
Antidote	For Dabigatran : Idarucizumab (Praxbind®) 2x 2.5 g i.v. 15 min apart For Anti-Xa: Andexanet alfa (2018 in USA)
Hemodialysis Plasma exchange	Dabigatran Apixa, Edoxa, Riva

French guidelines	Arch Cardiovac Dis 2013;106:382
German guidelines	Clin Res Cardiol 2013;102:399

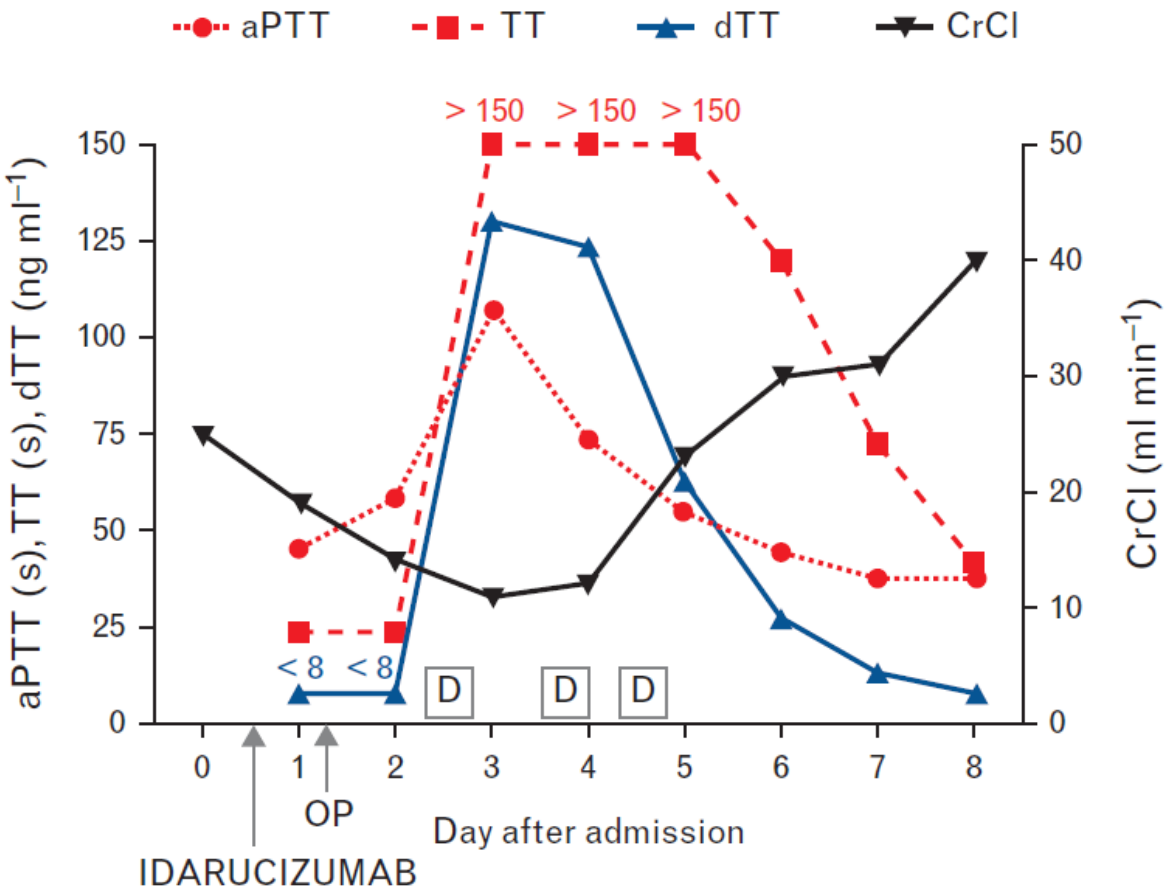
Idarucizumab (Praxbind®)





N Engl J Med 2015;373:511

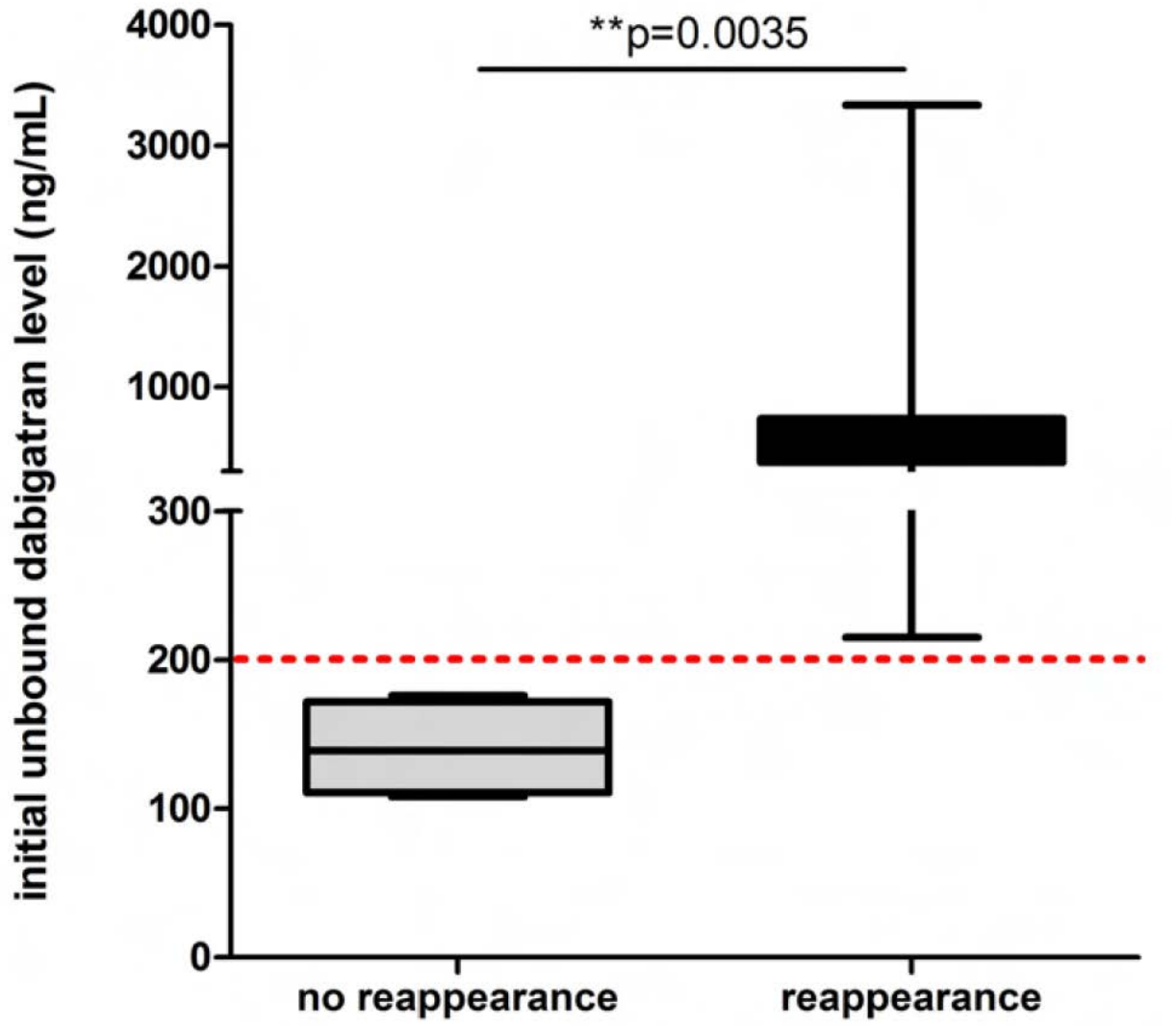
Dabigatran rebound after Idarucizumab



Activated partial thromboplastin time, thrombin time, diluted thrombin time, creatinine clearance and the time of idarucizumab administration in case 1. aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; D, haemodialysis, dTT, diluted thrombin time; OP, surgical fixation of a femoral fracture; s, seconds; TT, thrombin time.

JTH 2017;15:1317

Prediction of Dabigatran rebound



Haematologica 2018;103:e226

Dabigatran rebound

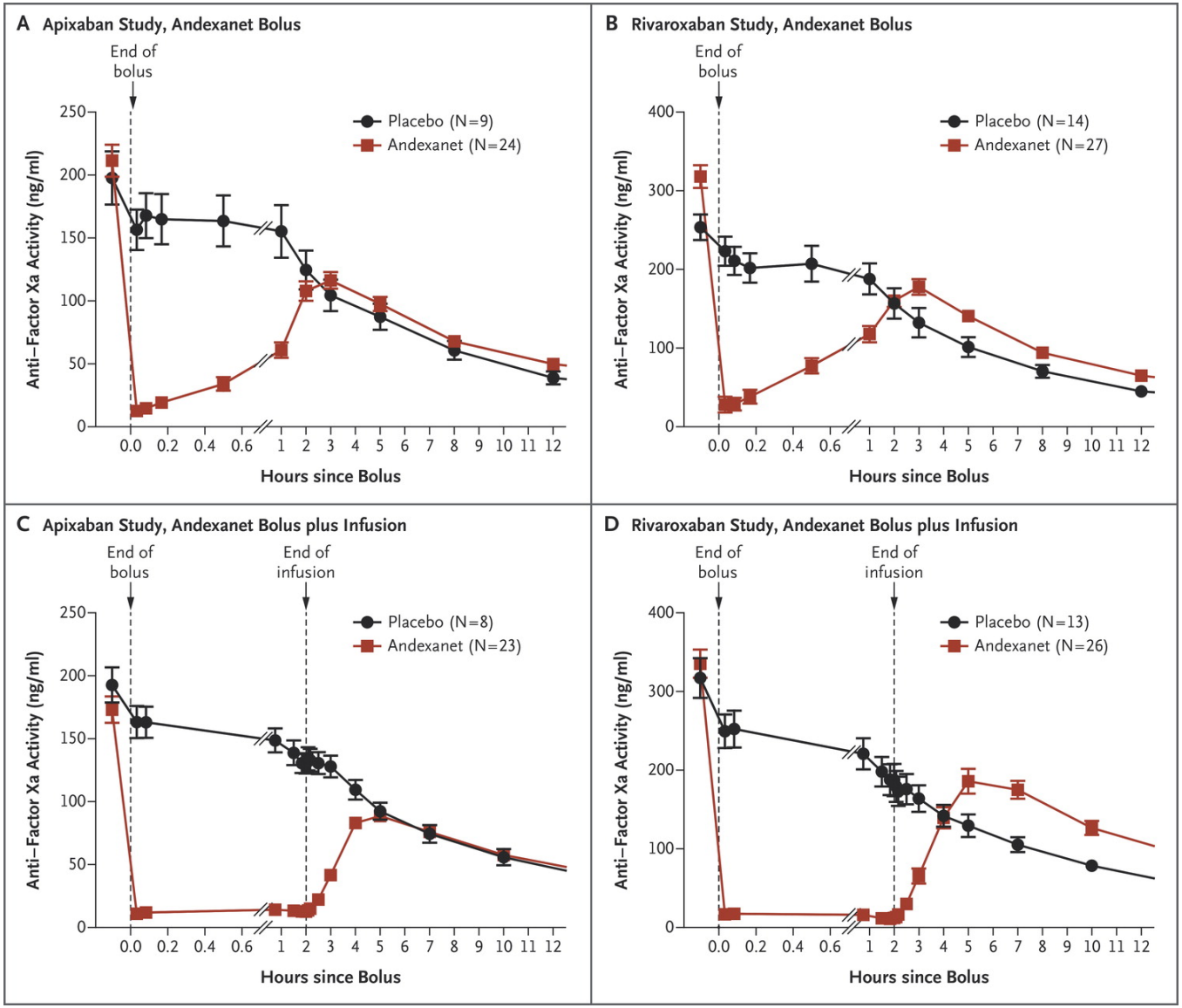
Dabigatran reappearance is indeed likely due to a shift back from extravascular dabigatran into plasma in response to the concentration gradient occurring after neutralization.

In case of Dabigatran reversal:

- Baseline lab: PT, aPTT, TT, fibrinogen
  [Dabigatran]
- Follow-up lab: TT and [Dabigatran] in case of:
  - o High initial [Dabigatran] (≥ 200 ng/ml)
  - o Renal insufficiency

Haematologica 2018;103:e226

Andexanet alfa



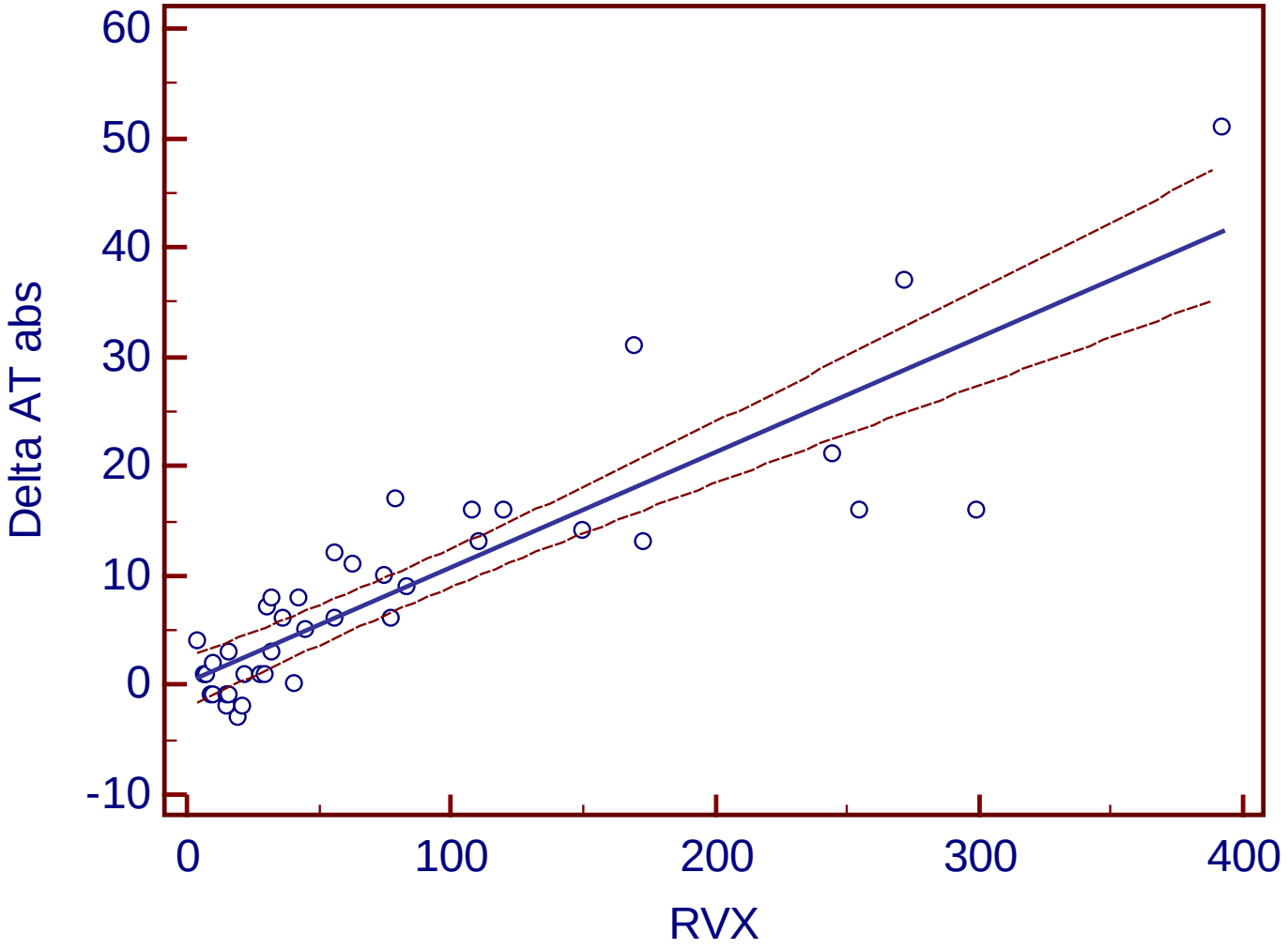
N Engl J Med 2015;373:2413

DOAC & laboratory issues

DOAC & laboratory issues

1. DOAC impact on thrombophilia tests
2. Assays for detecting / quantitating DOAC
3. DOAC monitoring

DOAC : Impact on Antithrombin



DOAC : Impact on Protein C

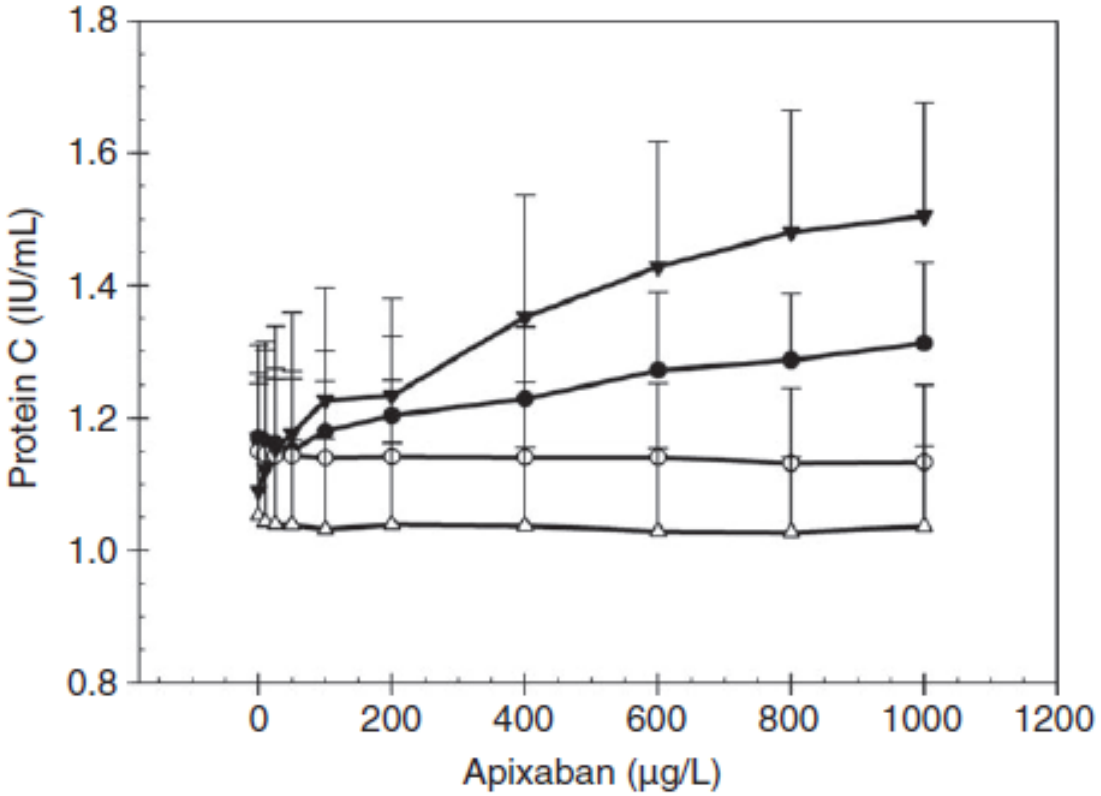


Fig. 3. Effects of apixaban on protein C assays. Two coagulation-based assays, Protein C coag (●) and Staclot Protein C (▼), and two chromogenic assays, Coamatic Protein C (△) and Berichrom Protein C (○), were used in the evaluation. Results are shown as the activity (IU mL^{-1}; mean + standard deviation) of nine different healthy donors.

JTH 2014;12:1545

DOAC : Impact on Lupus anticoagulans

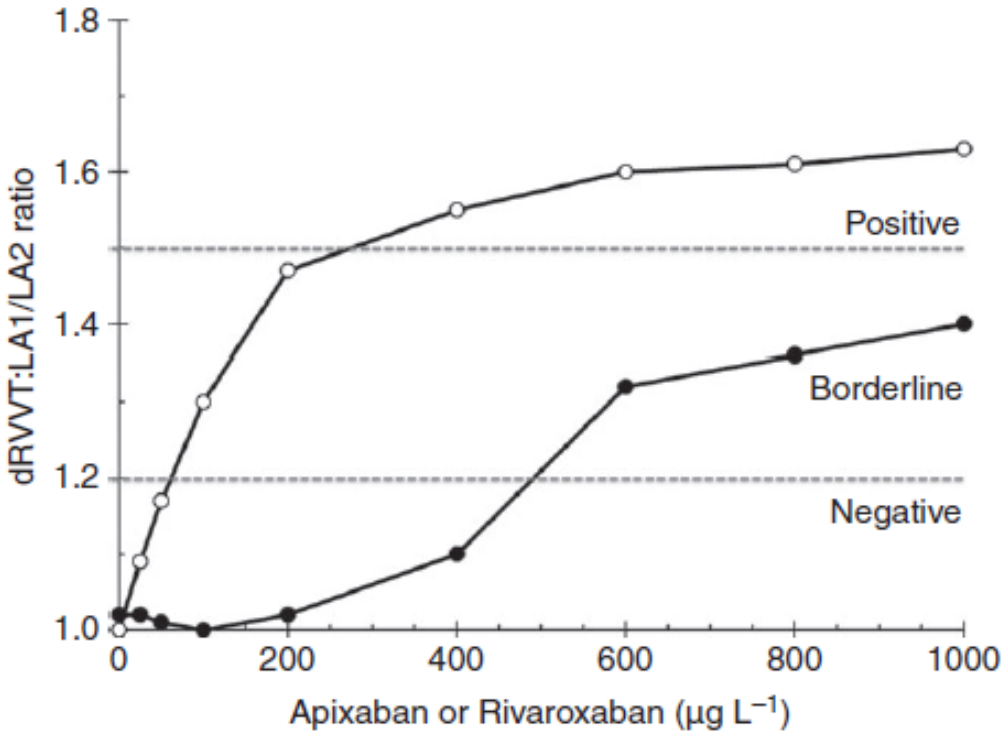


Fig. 5. Effects of direct anti-factor Xa inhibitors on the lupus anticoagulant test. Samples of pooled normal plasma were spiked with rivaroxaban (○) or apixaban (●) in 10 different concentrations ranging from 0 µg L^{-1} to 1000 µg L^{-1}, and analyzed with an integrated dilute Russell's viper venom time (dRVVT) assay. The assay consists of an LA1 screening (low phospholipid) test and an LA2 confirmatory (phospholipid-rich) clotting test. The results are shown as the LA1/LA2 ratio. The hatched lines indicate the limits for negative, borderline and positive lupus anticoagulant test results.

JTH 2014;12:1545

DOAC : Impact on Lupus anticoagulans

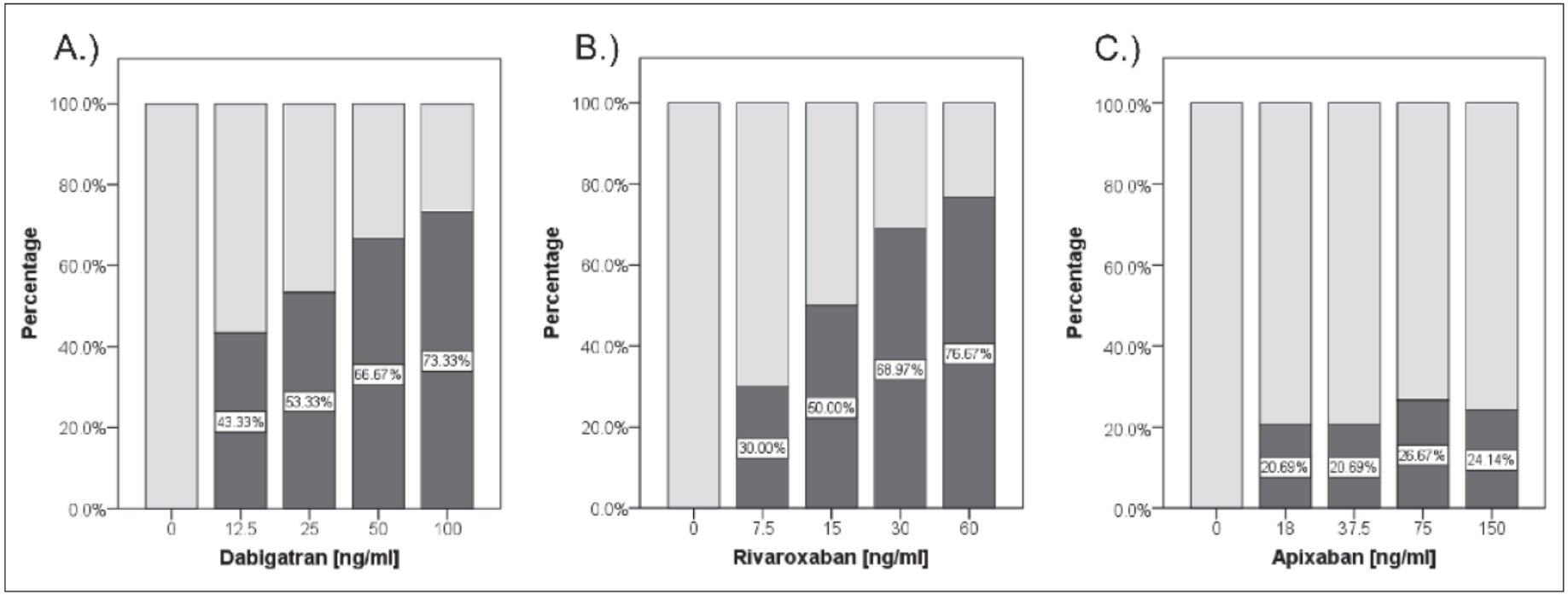
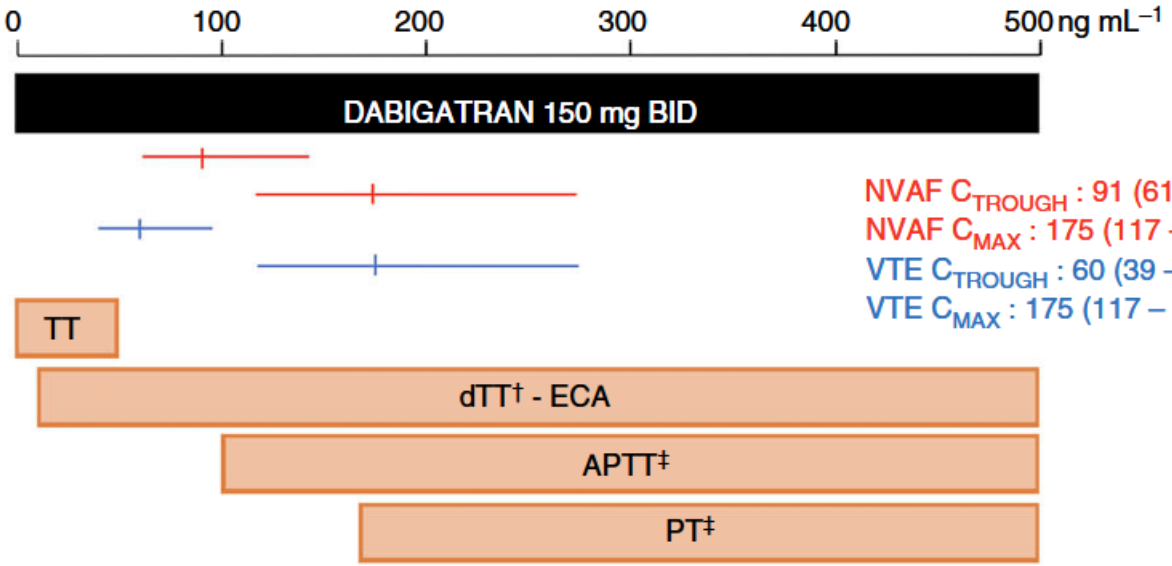


Figure 1: Dichotomised results of the influence of NOACs on confirmation DRVVT testing. Dark grey: percentage of LA-positive results; concentrations of dabigatran (A), rivaroxaban (B) and apixaban (C) are given in ng/ml.

Thromb Haemost 2016;116:235

Detecting & Quantitating Dabigatran

Drugs	Laboratory tests	Utility/interpretation	Availability	Dependence of the reagent
Dabigatran	APTT*	Interpretation: Normal APTT excludes above on-therapy dabigatran levels but does not exclude the presence of dabigatran in the on-therapy range	24/7, all laboratories	Yes
	TT	Interpretation: Normal TT excludes the presence of dabigatran. A prolonged TT could suggest either the presence of clinically relevant or trivial levels of dabigatran.	24/7, all laboratories	Yes
	dTT	Interpretation: Based on plasma concentration estimation in relation to the clinical context. Note: Some methodologies (i.e. the Hemoclot Thrombin Inhibitors (HTI)) require specific calibrators for plasma concentrations < 50 ng mL^{-1}	Can be implemented with all coagulometers	No

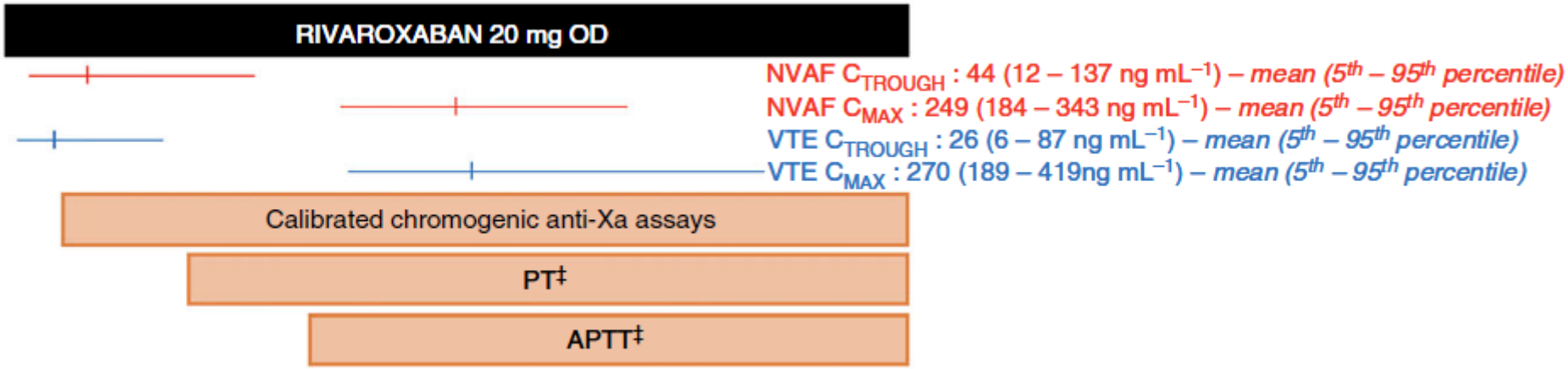


NVAF C_{TROUGH} : 91 (61 – 143 ng mL^{-1}) – *mean (25^{th} – 75^{th} percentile)*
NVAF C_{MAX} : 175 (117 – 275 ng mL^{-1}) – *mean (25^{th} – 75^{th} percentile)*
VTE C_{TROUGH} : 60 (39 – 95 ng mL^{-1}) – *mean (25^{th} – 75^{th} percentile)*
VTE C_{MAX} : 175 (117 – 275 ng mL^{-1}) – *mean (25^{th} – 75^{th} percentile)*

JTH 2018;16:209

Detecting & Quantitating Rivaroxaban

Drugs	Laboratory tests	Utility/interpretation	Availability	Dependence of the reagent
Rivaroxaban (Edoxaban)	PT*	Interpretation: Rivaroxaban: normal PT (with sensitive reagents) excludes above on-therapy rivaroxaban levels but does not exclude the presence of rivaroxaban in the on-therapy range. Edoxaban: normal PT (with sensitive reagents) would exclude above on-therapy edoxaban levels at peak but would not exclude the presence of above on-therapy edoxaban at trough.	24/7, all laboratories	Yes
Rivaroxaban Apixaban Edoxaban	Chromogenic anti-Xa assays*	Interpretation: Based on plasma concentration estimation in relation to the clinical context. Note: Some methodologies (i.e. the Biophen Direct Factor Xa Inhibitors (DiXaI)) require specific calibrators for plasma concentrations < 30–50 ng mL^{-1}. Note: If near to the LOQ, heparin or LMWH-calibrated chromogenic anti-Xa assays can be used to rule out the presence of clinically relevant direct FXa inhibitors.	Can be implemented with all coagulometers	No



JTH 2018;16:209

DOAC & laboratory issues

1. DOAC's impact on thrombophilia testing
   - Antithrombin
   - Protein C coagulometric
   - Lupus anticoagulant

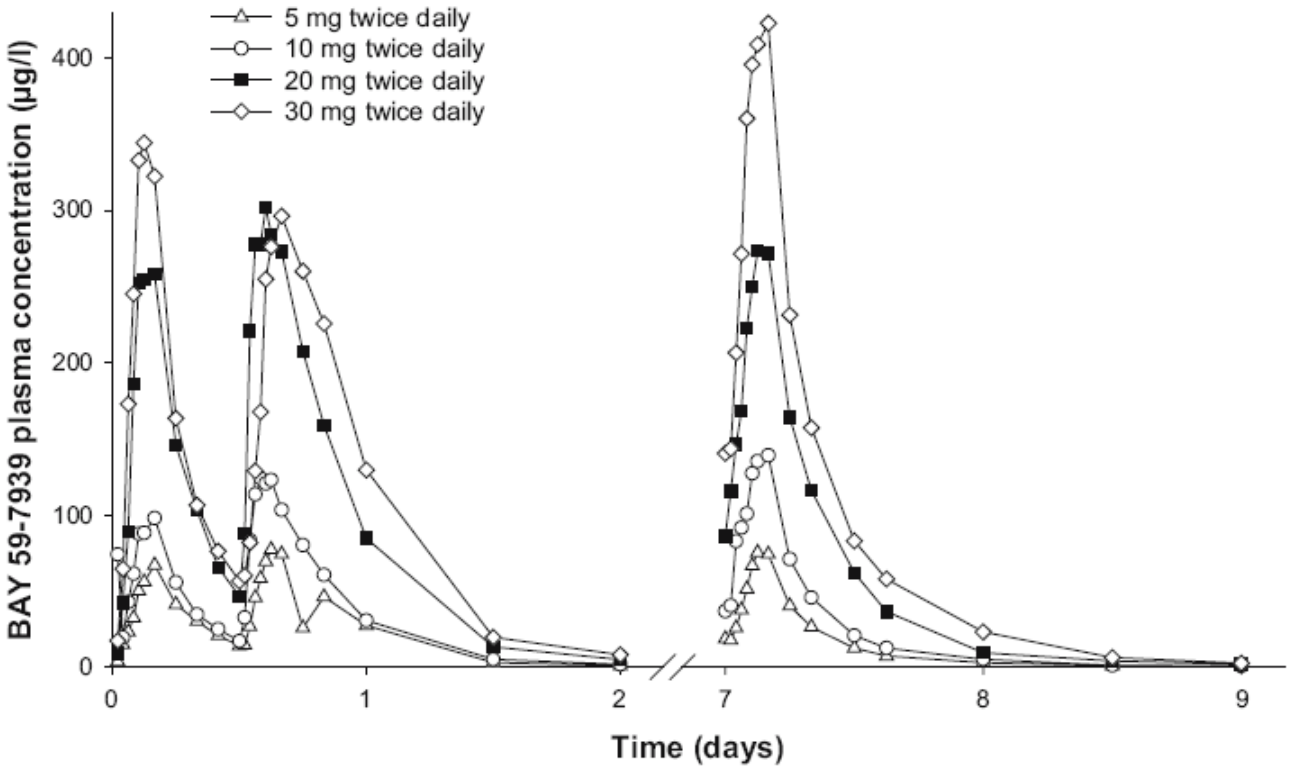
2. Assays for detecting & quantitating DOAC
   - A normal TT excludes Dabigatran
   - Calibrated dTT for [DOAC.aIIa]

   - A normal PT cannot exclude Riva/Apixa/Edoxa
   - Calibrated anti-Xa assay for [DOAC.aXa]

DOAC: Monitoring ?

Pharmacokinetics

Rivaroxaban



Eur J Clin Pharmacol 2005;61:873

Rivaroxaban peak and trough levels

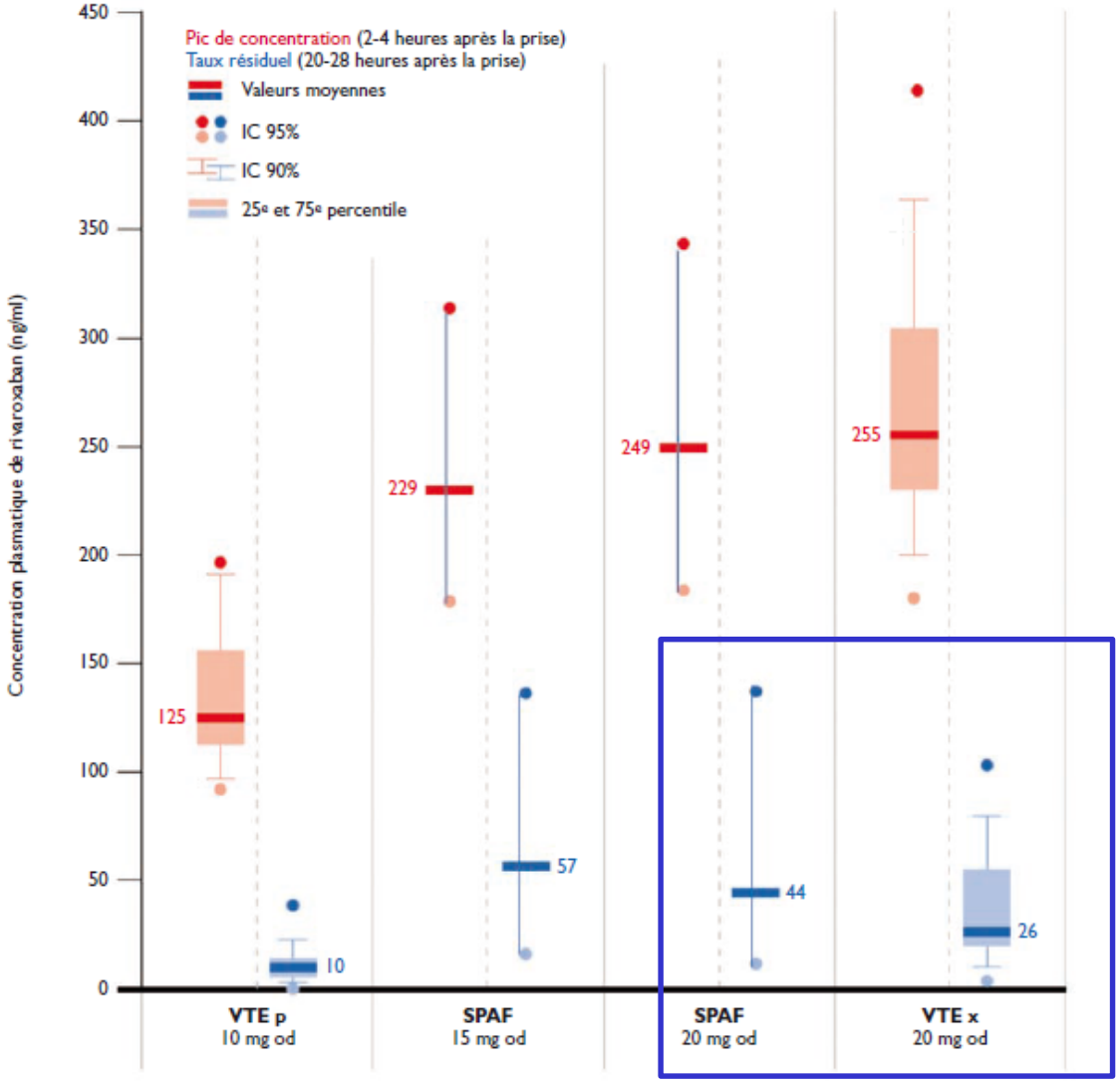


Figure 3. Domaine de C_{max} et C_{min} plasmatiques du rivaroxaban lors d'une administration 1 x/jour, mesurées 2 à 4 heures et 20 à 28 heures après la prise du comprimé

Legend:
RVX, Rivaroxaban

Rev Med Suisse 2013;9:1375

Apixaban peak and trough levels

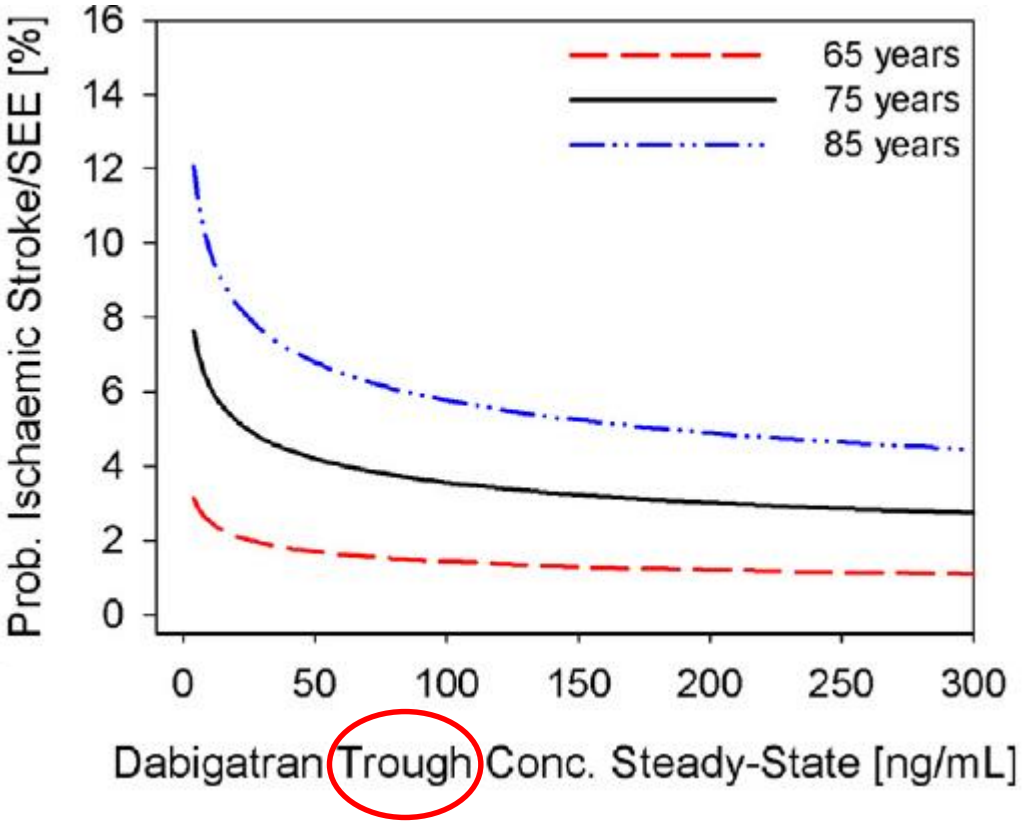
Table 3: Predicted Apixaban Steady-state Exposure and Anti-Xa Activity				
	Apix. C_{max} (ng/mL)	**Apix. C_{min} (ng/mL)**	**Apix. Anti-Xa Activity Max (IU/mL)**	**Apix. Anti-Xa Activity Min (IU/mL)**
	Median [5th, 95th Percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg twice daily	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg twice daily	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

* Dose adjusted population based on 2 of 3 dose reduction criteria in the ARISTOTLE study.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf

Dabigatran plasma concentration and

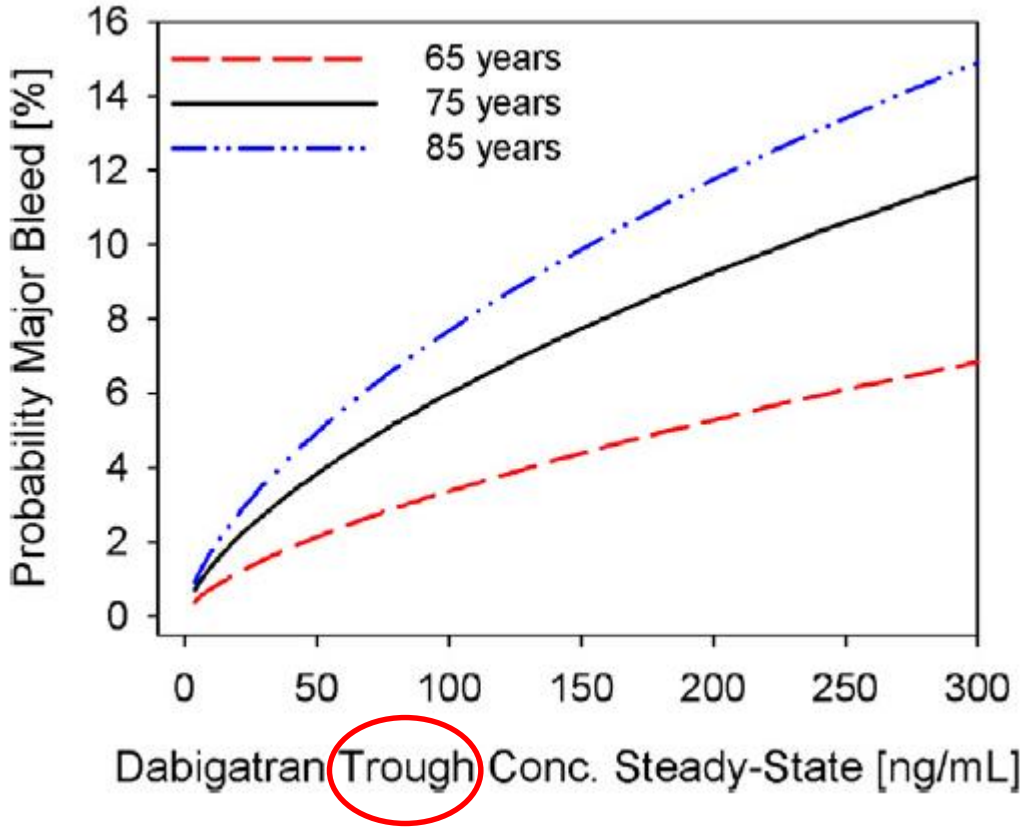
probability of ischemic stroke or systemic embolic events



JACC 2014;63:321

Dabigatran plasma concentration and

probability of major bleeding



JACC 2014;63:321

Dabigatran trough plasma concentration

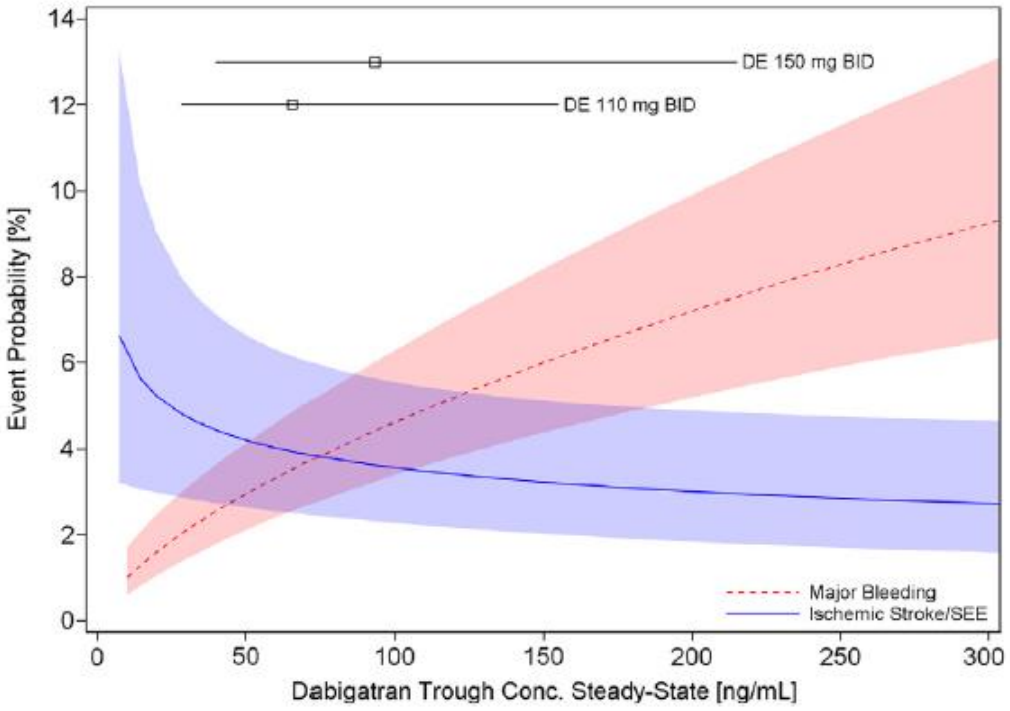
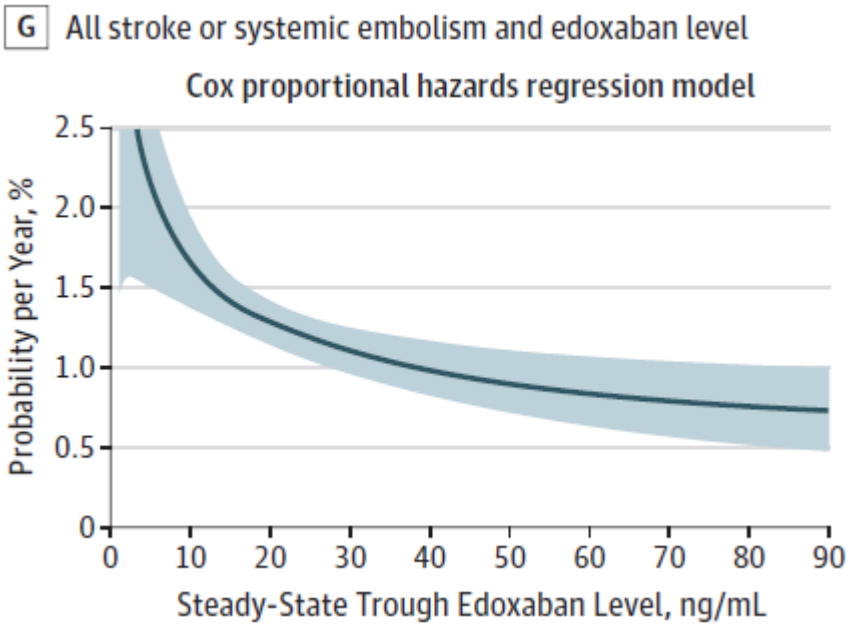


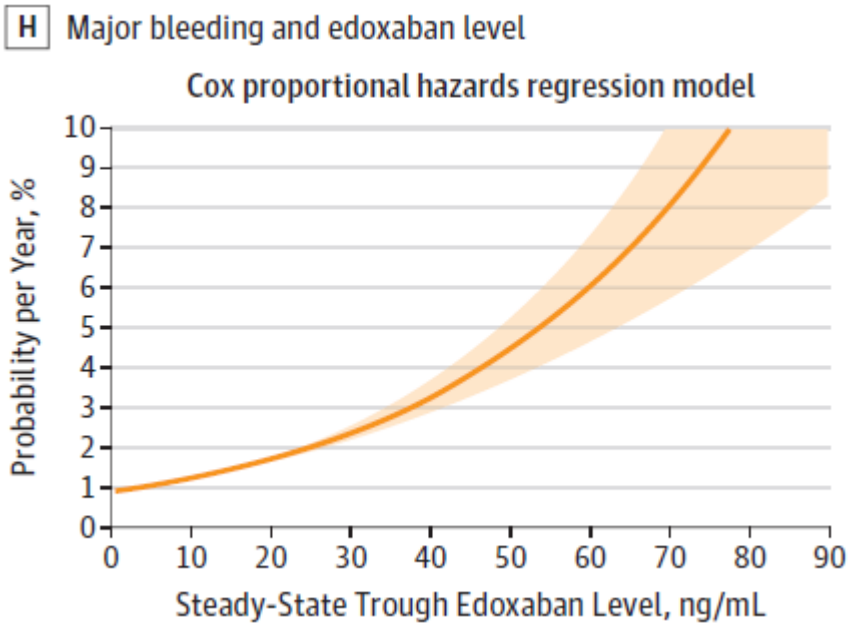
Figure 2 **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles.
Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).

JACC 2014;63:321

Exposure-Response : Edoxaban





Trial (Data Source)	Comparisons	No. of Patients in Analyses (% of the Population)	PK or PD Variable Measured	Analysis Performed (Source)	Association With Stroke	Association With Bleeding	Significant Risk Factors for Stroke or Bleeding Events	Analysis Limitations
ENGAGE AF-TIMI 48[23] (FDA[8] and Ruff et al,[9] 2015)	Edoxaban (30 or 60 mg once daily) vs warfarin	Ruff et al: 6780 (48%)	Edoxaban trough plasma levels	Cox proportional hazards regression model (FDA and Ruff et al)	Reduced risk of stroke or SEE with higher plasma drug levels	Increased risk of MB with higher plasma drug levels	Stroke or SEE and IS: trough level, age, prior stroke or TIA, weight, $CHADS_2$ score MB and LTB or FB: trough level, age, concomitant aspirin use, $CHADS_2$ score	Edoxaban level and anti-factor Xa activity measured at only a single time point (1 mo after randomization)

JAMA Cardiology 2017;2:566

Criteria for TDM : DOAC

1. INTER-individual variability	YES
2. INTRA-individual instability	YES
3. Robust assay method	YES
4. Correlation (therapeutic range)	Probably
5. Validation (clinical outcome)	No

Legend:
TDM, Therapeutic Drug Monitoring

Criteria for TDM : DOAC

1. INTER-individual variability	YES
2. INTRA-individual instability	YES
3. Robust assay method	YES
4. Correlation (therapeutic range)	Probably
5. Validation (clinical outcome)	No
6. Verify compliance	No

Legend:
TDM, Therapeutic Drug Monitoring

Take-home message

hand-out

Grazi*a*! Grazi*e*! Merc*i*! Danke! Thank y*ou*!

Rivaroxaban treatment in VTE patients with APS
RAPS trial results

National Rivaroxaban VTE Advisory Board – Bayer

Bern, 23.11.2016

Lorenzo ALBERIO

Service et Laboratoire Central d'Hématologie

UNIL | Université de Lausanne
Faculté de biologie et de médecine

RAPS (RIVAROXABAN IN APS): RCT OF RIVAROXABAN VS WARFARIN IN THROMBOTIC APS PATIENTS, WITH OR WITHOUT SLE

Hannah Cohen on behalf of the RAPS trial group

University College London (UCL) Hospitals NHS Foundation Trust and UCL, & Guy's and St Thomas' (GSTT) Hospitals NHS Foundation Trust and Kings College London, London, UK

XXV ISTH Congress, Toronto June 2015

RAPS

Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial

Hannah Cohen, Beverley J Hunt, Maria Efthymiou, Deepa R J Arachchillage, Ian J Mackie, Simon Clawson, Yvonne Sylvestre, Samuel J Machin, Maria L Bertolaccini, Maria Ruiz-Castellano, Nicola Muirhead, Caroline J Doré, Munther Khamashta, David A Isenberg*, for the RAPS trial investigators*

Lancet Hematology 2016;3:e426

RAPS Aims

Primary aim

to demonstrate that the intensity of anticoagulation achieved with rivaroxaban is not inferior to that of warfarin using thrombin generation testing

Secondary aims

to compare rates of bleeding and recurrent thrombosis, and the quality of life in both patient groups

Trial design

- Prospective phase II/III non-inferiority RCT
- APS patients, warfarin target INR 2.5 for VTE
- Randomised:
  1:1 to warfarin or rivaroxaban 20mg OD
- Open label
- Primary end point 42 days
- Treatment continued 180 days

ISRCTN 68222801; EUDRACT 2012-002345-38

TSC Chair: Prof Mike Greaves; IDMC: Prof Peter Maddison

Primary outcome

- Percentage change in ETP from randomisation to day 42
- Rivaroxaban non-inferior to warfarin if percentage change in ETP no more than 20% higher (i.e. less anticoagulant effect) than that for warfarin
  - Non-inferiority limit of 20% based on:
    - inter centre assay variability of test performance
    - clinical relevance

Secondary end points

a) Efficacy

- Recurrent VTE
- composite of recurrent VTE + other thrombotic events
- other thrombin generation test parameters
- markers of *in vivo* coagulation activation

b) Safety

- serious adverse events (SAE)
- all bleeding events

Inclusion criteria

- Patients with thrombotic APS:
  - single episode of VTE whilst not on anticoagulation or
  - recurrent episode(s) whilst off anticoagulation or on sub-therapeutic anticoagulation
- Target INR 2.5 (range 2.0 – 3.0)
- On warfarin for at least 3 months since last VTE
- Adequate contraception with the exception of postmenopausal or sterilised women

RAPS : Exclusion criteria

Patients with
- previous arterial thrombotic events due to antiphospholipid syndrome
- recurrent venous thromboembolism when taking warfarin at a therapeutic INR of 2.0–3.0
- younger than 18 years

Lancet Hematology 2016;3:e426

RAPS : CONSORT flow chart

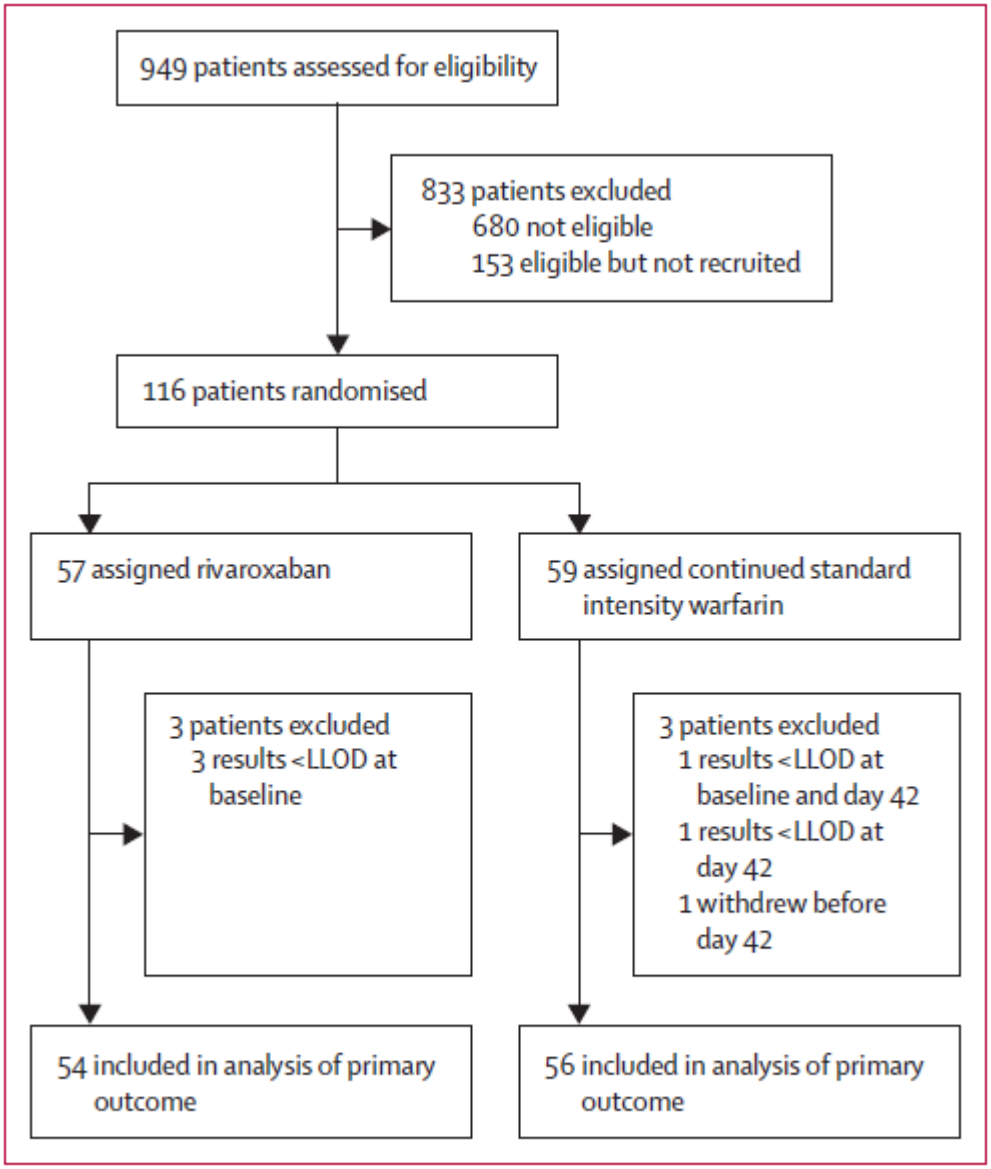


***Figure 1*: Trial profile**
LLOD=lower limit of detection.

Lancet Hematology 2016;3:e426

RAPS : Baseline characteristics

	Rivaroxaban (n=57)	Warfarin (n=59)
Demographics		
Mean (SD) age (years)	47 (17)	50 (14)
Women	42 (74%)	42 (71%)
Men	15 (26%)	17 (29%)
Mean (SD) BMI (kg/m²)	28 (6)	30 (6)
Stratification variables		
SLE	11 (19%)	11 (19%)

Lancet Hematology 2016;3:e426

RAPS : Baseline characteristics

	Rivaroxaban (n=57)	Warfarin (n=59)
aPL (Miyakis categories¶)		
I (excluding triple-positive aPL)	16 (28%)	19 (32%)
I (including triple-positive aPL‖)	7 (12%)	12 (20%)
IIa	30 (53%)	23 (39%)
IIb	3 (5%)	1 (2%)
IIc	1 (2%)	4 (7%)

¶Category I, presence of more than one aPL in any combination; category IIa, presence of lupus anticoagulant alone; category IIb, presence of antibodies against cardiolipin alone; category IIc, presence of antibodies against β_2 glycoprotein I alone. ‖14 rivaroxaban patients, 19 warfarin patients; all patients tested for triple positivity at baseline, thus numbers are higher than for antiphospolipid syndrome-defining aPL; before trial entry, persistence of aPL was established in all patients but triple positivity was not.

Lancet Hematology 2016;3:e426

Miyakis categories at baseline

	Allocated to	Allocated to	
	Rivaroxaban	**Warfarin**	**Total (%)**
Category I Double positive (any combination)	5	8	13 (11.2)
Category I Triple positive	14	19	33 (28.4)
Category IIa, IIb, IIc One aPL type only	21	14	35 (30.2)
aPL not detected	17	18	35 (30.2)
Total	**57**	**59**	**116**

Miyakis et al, JT&H 2006; 4: 295–306

RAPS : Baseline characteristics

	Rivaroxaban (n=57)	Warfarin (n=59)
Thrombin generation		
ETP (nmol/L per min)†	555 (497–619)	542 (469–626)
Lag time (min)	7·3 (6·4–8·2)	7·6 (6·6–8·7)
Time to peak thrombin generation (min)	10·8 (9·7–12·0)	11·7 (10·3–13·2)
Peak thrombin generation (nmol/L)	93·8 (78·8–111·7)	79·9 (64·9–98·2)
In-vivo coagulation activation markers		
Prothrombin fragment 1·2 (pmol/L)	43·3 (38·0–49·3)	43·1 (37·5–49·6)
Thrombin–antithrombin complex (µg/L)	2·9 (2·5–3·4)	2·7 (2·6–2·9)
Median (IQR) D-dimer (mg/L FEU)	0·19 (0·19–0·25)	0·19 (0·19–0·22)
Raised in-vivo coagulation activation markers (n)		
Prothrombin fragment 1·2	0	1
Thrombin–antithrombin complex	2	2
D-dimer	3	4
Any marker	5	6

Lancet Hematology 2016;3:e426

RAPS : Baseline characteristics

	Rivaroxaban (n=57)	Warfarin (n=59)
Thrombotic event with no or subtherapeutic anticoagulation‡		
Deep vein thrombosis§	32 (56%)	37 (63%)
Pulmonary embolism	25 (44%)	22 (37%)
Previous bleeding events while taking anticoagulation		
Major	0	0
Clinically relevant	0	4 (7%)
Mean (SD) percentage of time in therapeutic range while taking warfarin**	64 (28)	53 (24)
Rivaroxaban dose		
20 mg once daily	55 (96%)	N/A
15 mg once daily*	2 (4%)	N/A

Lancet Hematology 2016;3:e426

RAPS : Results – Clinical endpoints

	Rivaroxaban (n=57)	Warfarin (n=58)	Treatment effect† (95% CI)	p value
New thrombotic events at day 210				
Deep vein thrombosis	0	0	N/A	N/A
Pulmonary embolism	0	0	N/A	N/A
Arterial thrombosis	0	0	N/A	N/A
Other	0	0	N/A	N/A
Any combination	0	0	N/A	N/A

Lancet Hematology 2016;3:e426

RAPS : Results – Clinical endpoints

	Rivaroxaban (n=57)	Warfarin (n=58)	Treatment effect† (95% CI)	p value
Bleeding events at day 210 ¶				
Major	0	0	N/A	N/A
Clinically relevant	3 (5%)	2/55 (4%)	1·7 (–5·9 to 9·3)	N/A
Minor	10 (18%)	8/55 (15%)	3·0 (–10·5 to 16·5)	N/A
Unclassified, insufficient information	1 (2%)	0	1·8 (–1·7 to 5·3)	N/A
Site of bleed§				
Intracranial	1‖	0	N/A	N/A
Skin (bruise)	3	0	N/A	N/A
Oral	0	1	N/A	N/A
Nasal	5	3	N/A	N/A
Vaginal	1	0	N/A	N/A
Rectal	0	3	N/A	N/A
Lower ureteric	1	0	N/A	N/A
Other	9	7	N/A	N/A

Lancet Hematology 2016;3:e426

RAPS : Results – Thrombin generation

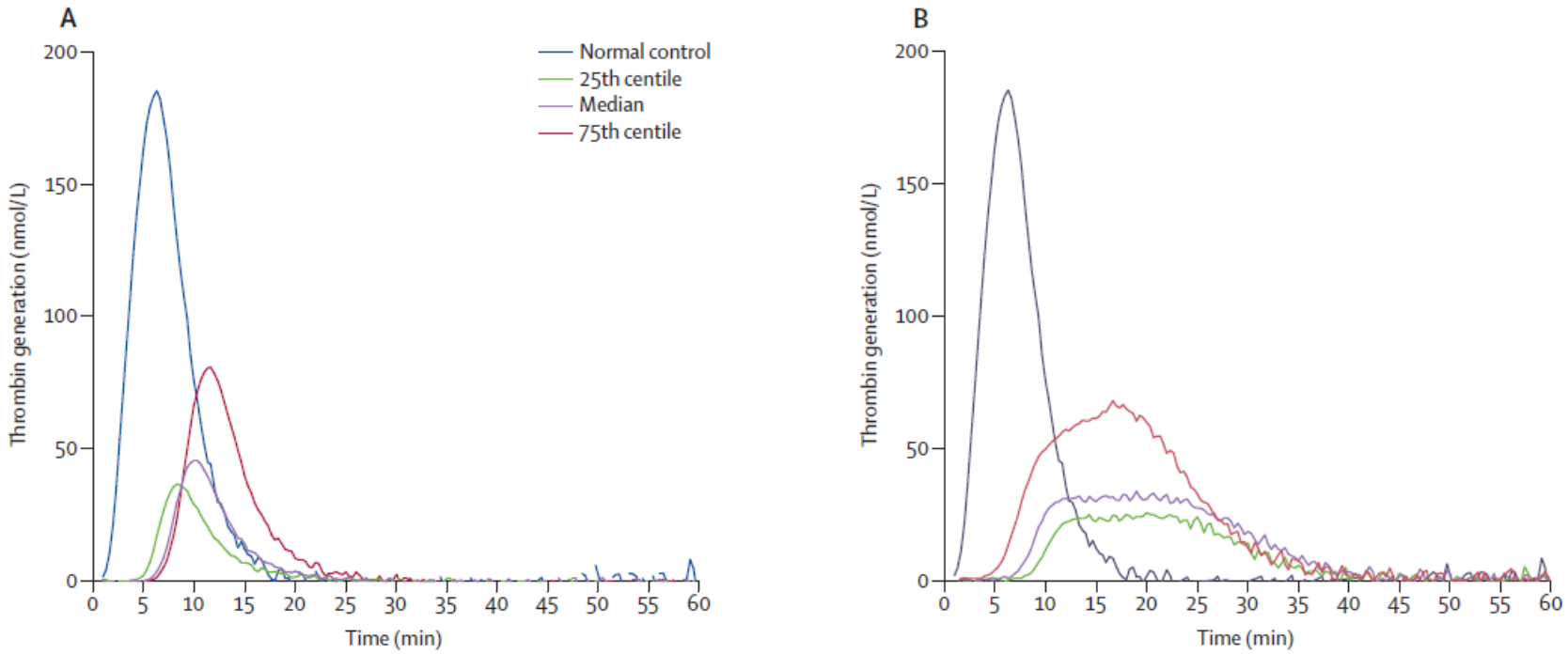
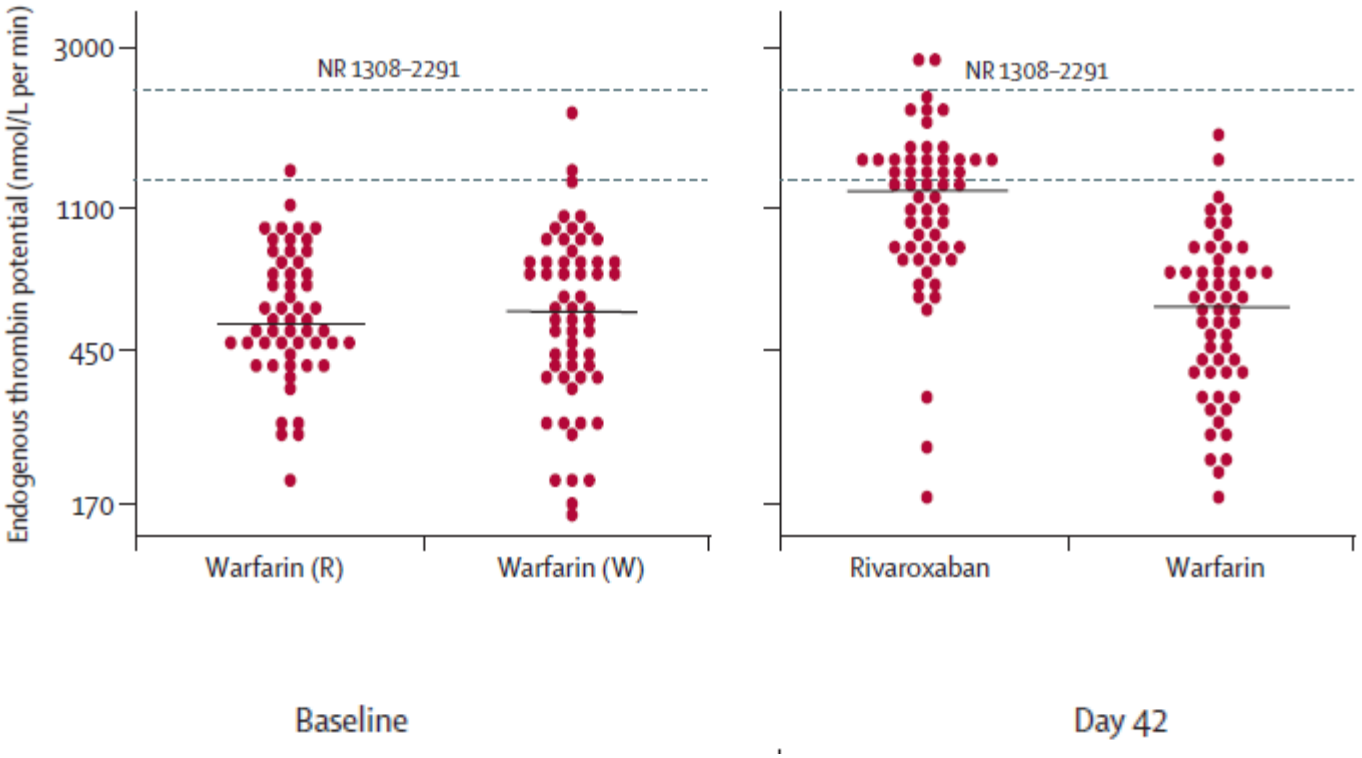


Figure 3: Thrombograms for median (25th and 7th percentiles) ETP values in RAPS, compared with a typical normal control value
(A) Patients taking warfarin. (B) Patients taking rivaroxaban.

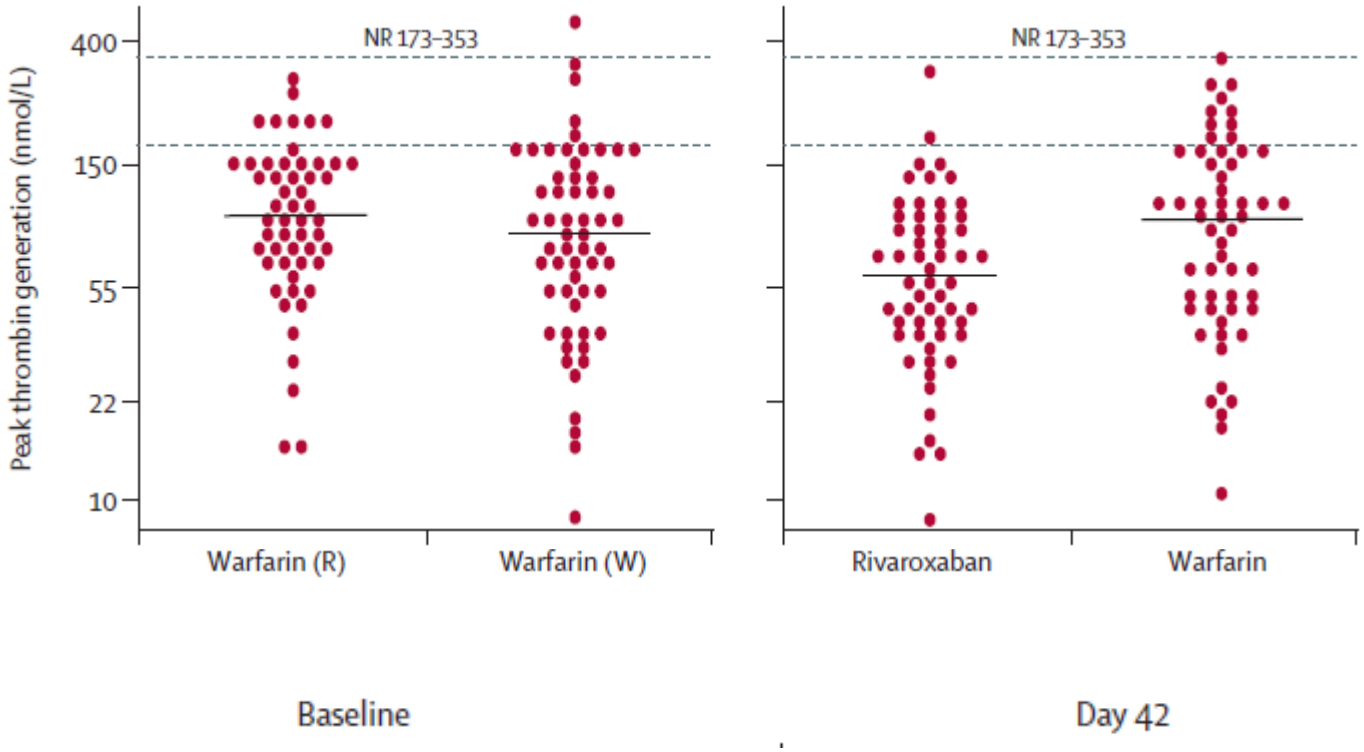
Lancet Hematology 2016;3:e426

RAPS : Results – ETP



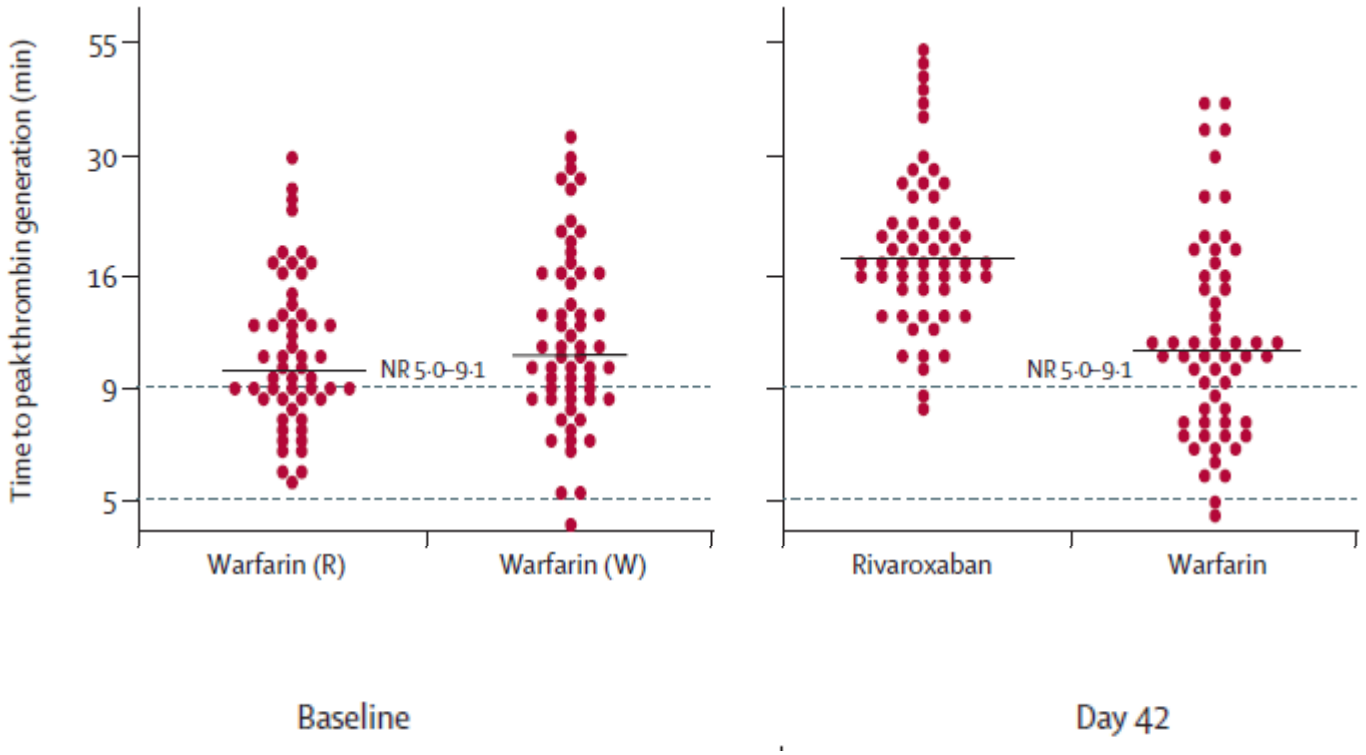
Lancet Hematology 2016;3:e426

RAPS : Results – Peak thrombin



Lancet Hematology 2016;3:e426

RAPS : Results – Time to peak



Lancet Hematology 2016;3:e426

RAPS : Results

	Rivaroxaban (n=57)	Warfarin (n=58)	Treatment effect† (95% CI)	p value
Thrombin generation at day 42				
ETP (nmol/L per min)	1086 (957 to 1233)	548 (484 to 621)	2·0 (1·7 to 2·4)	<0·0001
Lag time (min)	8·9 (8·1 to 9·8)	7·3 (6·7 to 8·0)	1·2 (1·1 to 1·4)	0·0052
Time to peak thrombin generation (min)	19·2 (17·7 to 20·9)	11·2 (10·3 to 12·1)	1·7 (1·5 to 1·9)	<0·0001
Peak thrombin generation (nmol/L)	55·6 (46·8 to 66·1)	85·7 (72·3 to 101·5)	0·6 (0·5 to 0·8)	0·00061
In-vivo coagulation activation markers at day 42				
Prothrombin fragment 1.2 (pmol/L)	93·6 (82·1 to 106·9)	45·6 (40·1 to 52·0)	2·1 (1·7 to 2·5)	<0·0001
Thrombin–antithrombin complex (µg/L)	2·4 (2·3 to 2·6)	2·6 (2·5 to 2·8)	0·9 (0·9 to 1·0)	0·14
D-dimer (mg/L fibrinogen equivalent units)	0·19 (0·19 to 0·23)	0·19 (0·19 to 0·20)	0 (0 to 0)	1
Raised concentrations (also raised at baseline [n])				
Prothrombin fragment 1.2 (pmol/L)	2 (0)	0	N/A	N/A
Thrombin–antithrombin complex (µg/L)	0	3 (1)	N/A	N/A
D-dimer (mg/L FEU)	2 (1)	4 (1)	N/A	N/A
Any marker	3 (1)	6 (2)	N/A	N/A
Adherence at day 42				
Median (IQR) rivaroxaban (µg/L)	162 (101 to 245)	N/A	N/A	N/A
Factor X amidolytic (IU/dL)	N/A	25·3 (23·5 to 27·3)	N/A	N/A
International normalised ratio	N/A	2·7 (2·6 to 2·9)	N/A	N/A
Mean (SD) time in therapeutic range at day 180 (%)‡	N/A	55 (23)	N/A	N/A

Lancet Hematology 2016;3:e426

Summary

- Rivaroxaban inferior to warfarin based on ETP
- Rivaroxaban superior to warfarin based on Time to Peak and Peak Thrombin
- Higher ETP with rivaroxaban explained by altered reaction kinetics
- ETP / Time to Peak ratio corrected for rivaroxaban-induced protracted ETP
- *In vivo* coagulation activation markers

  - no difference in risk rivaroxaban vs warfarin

Conclusions

- No difference in risk between rivaroxaban and warfarin, based on:
  - Overall assessment of anticoagulation intensity using thrombin generation
  - D-dimer/coagulation activation markers
  - Clinical outcomes over 6 months follow up

BAYER

- The primary endpoint (ETP) was not met.
  How do you judge the relevance of

  1. this endpoint (ETP)?

  2. secondary TG endpoints (e.g. peak thrombin)?

  3. the clinical outcomes?

- Based on these and previous data,
  what would be your recommendation about the use of Rivaroxaban
  for treatment and
  secondary prevention of VTE in patients with APS?

L.A. personal comments : weaknesses

- Numbers
  n=116 : randomized
  n=110 : primary endpoint (54 RVX, 56 VKA)
  n=115 : secondary endpoint (57 RVX, 58 VKA)

- Previously treated patients (>3 months on VKA)

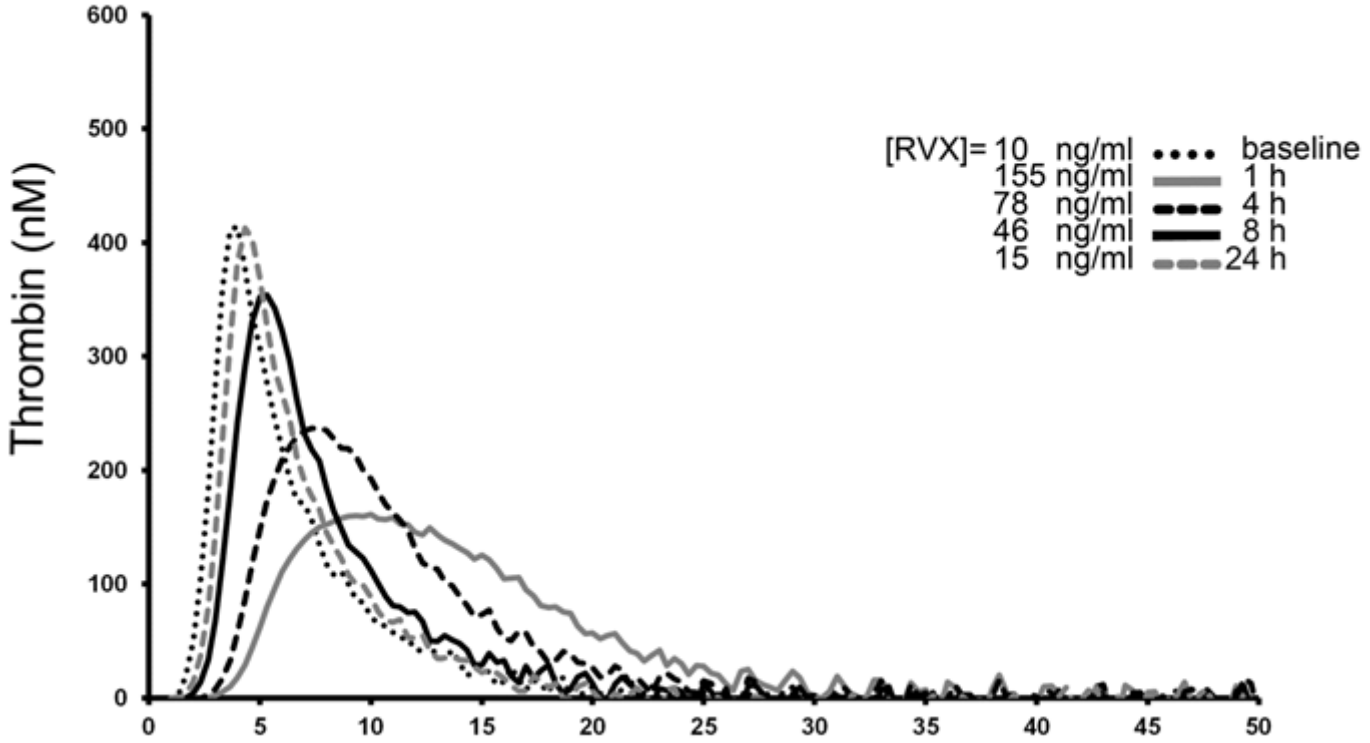
- High risk patients excluded
  (arterial TE, recurrent VTE on INR 2-3)
  or
  underrepresented
  (SLE 19%, APLA triple positive 28%)

- Timing [RVX] on day 42 : peak !

- F1+2 at day 42 in the RVX group

- Effect of RVX on TG : ETP ≠ velocity index (initial TG rate)

L.A. personal comments : RVX & TG



Bertaggia Calderara D et al. *Manuscript in preparation*

L.A. personal comments : strenghts

- Homogeneous patient population (low risk APS patients)
- D-dimers on day 42

BAYER

- The primary endpoint (ETP) was not met.
  How do you judge the relevance of

  1. this endpoint (ETP)?

  2. secondary TG endpoints (e.g. peak thrombin)?

  3. the clinical outcomes?

- Based on these and previous data,
  what would be your recommendation about the use of Rivaroxaban
  for treatment and
  secondary prevention of VTE in patients with APS?