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Contemporary Approach to Anticoagulation Management

Reversal Agents and Peri-procedural Management

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Disclosure

- Received research support and/or honoraria for educational activities from all manufacturers of NOACs currently available in the UAE (Boehringer Ingelheim, Bayer, Pfizer) related/not related to topic of this session.

Learning Objectives

- Coagulation testing with NOACs
- Peri-Procedural bleeding in NOACs RCTs
- Peri-Procedural Management of NOACs
- Reversal strategies and antidotes

NOACs for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban *
Action	Direct thrombin inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	150 mg BID 110 mg BID	5 mg BID 2.5 mg BID	20 mg QD 15 mg QD	60 mg QD 30 mg QD 15 mg QD
Phase III clinical trial	RE-LY [1]	ARISTOTLE [2] AVERROES [3]	ROCKET-AF [5]	ENGAGE-AF [4]

* not available in UAE

1. Connolly et al, N Engl J Med 2009; 361:1139-51
2. Granger et al, N Engl J Med 2011; 365:981-92
3. Connolly et al, N Engl J Med 2011; 364:806-17
4. Ruff et al, Am Heart J 2010; 160:635-41
5. Patel et al, N Engl J Med 2011;365:883-91

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

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

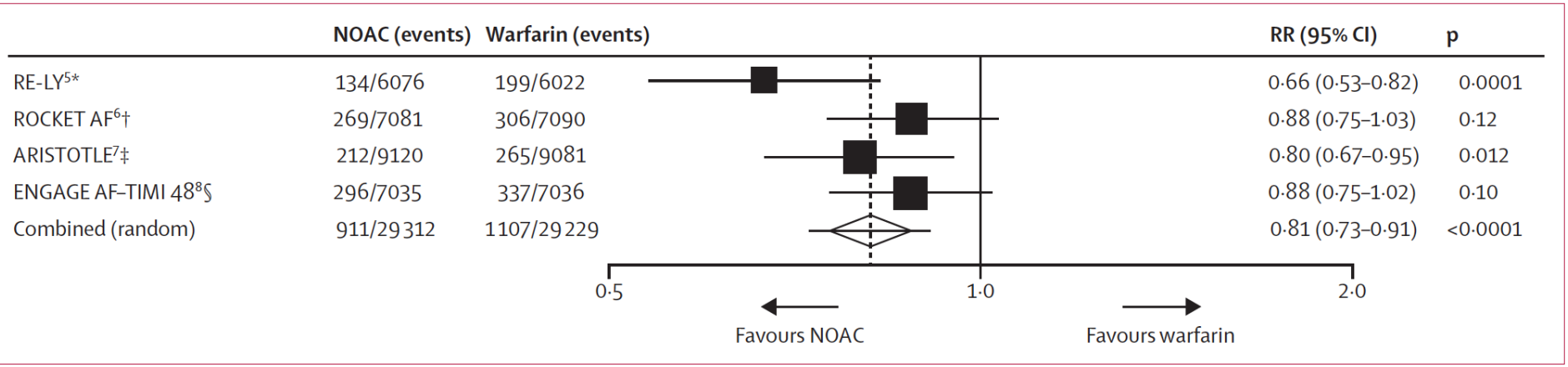

***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

~ 20% reduction in risk of stroke/systemic embolism

Lancet 2014; 383:955-962

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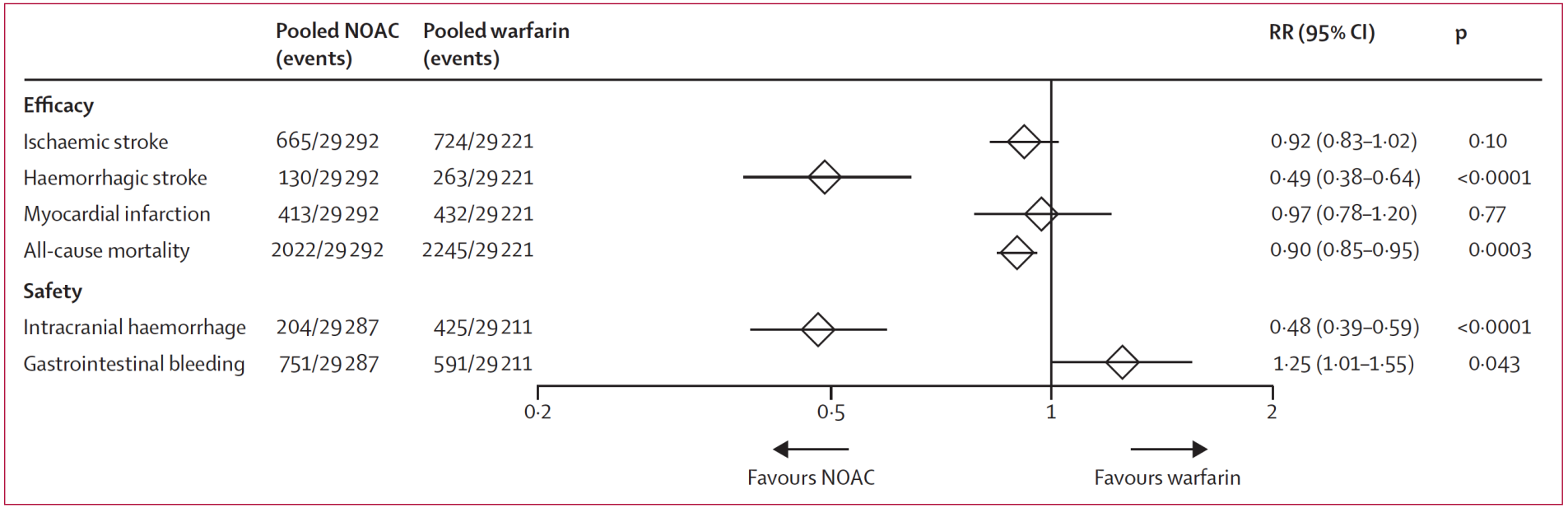

***Figure 2*: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

~ 50% reduction in risk of hemorrhagic stroke

Lancet 2014; 383:955-962

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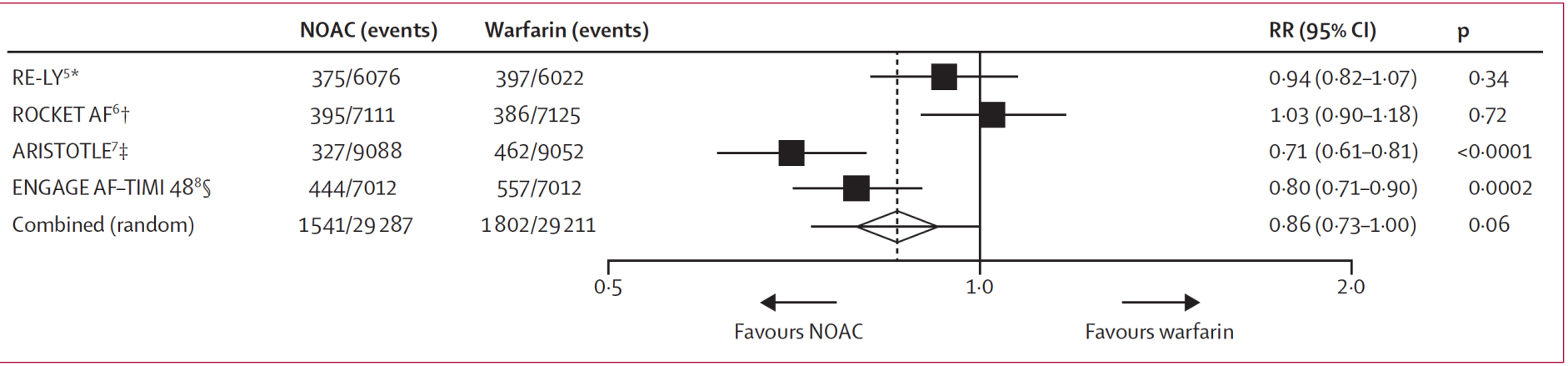


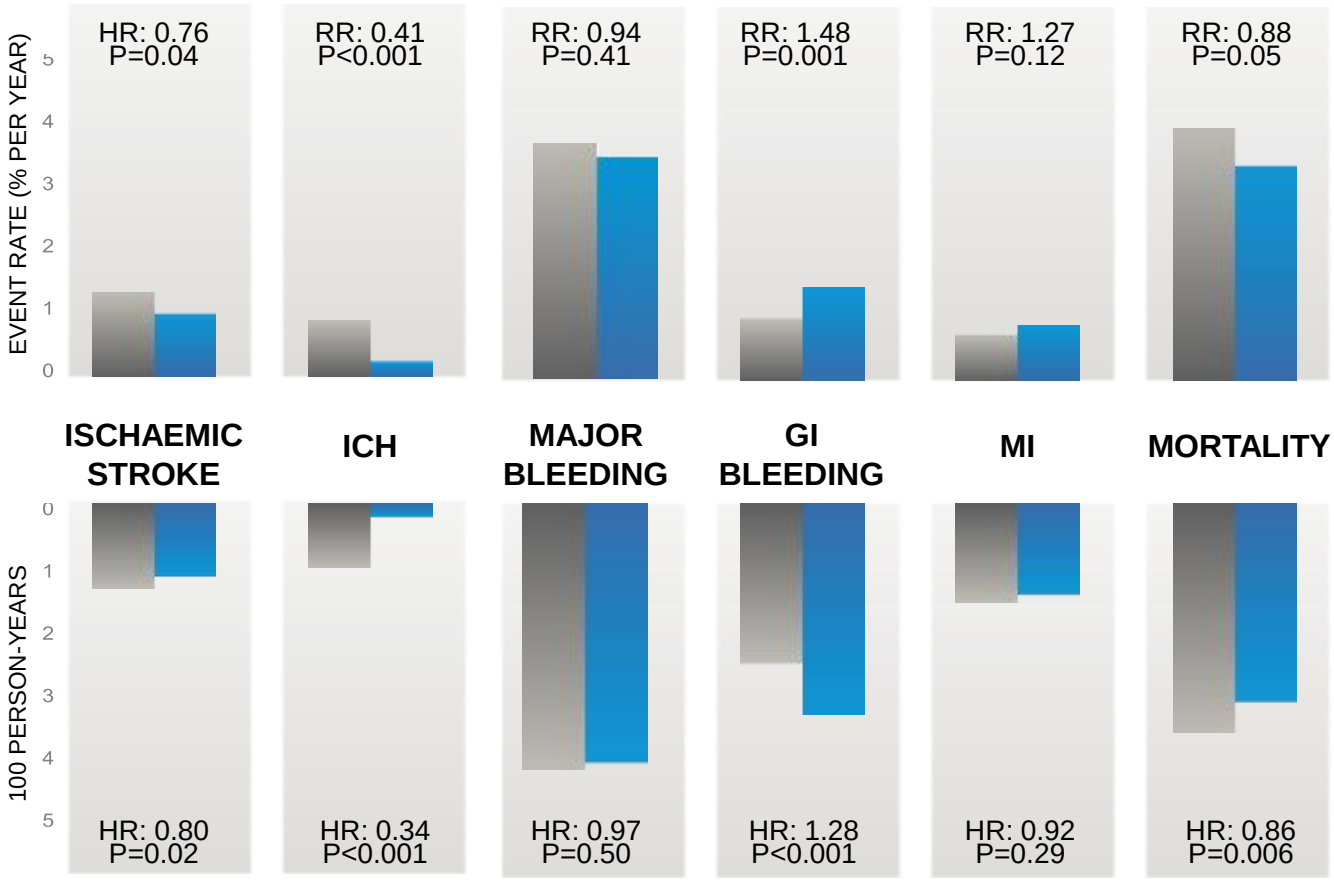
***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

~ 15% reduction in risk of major bleeding

Lancet 2014; 383:955-962

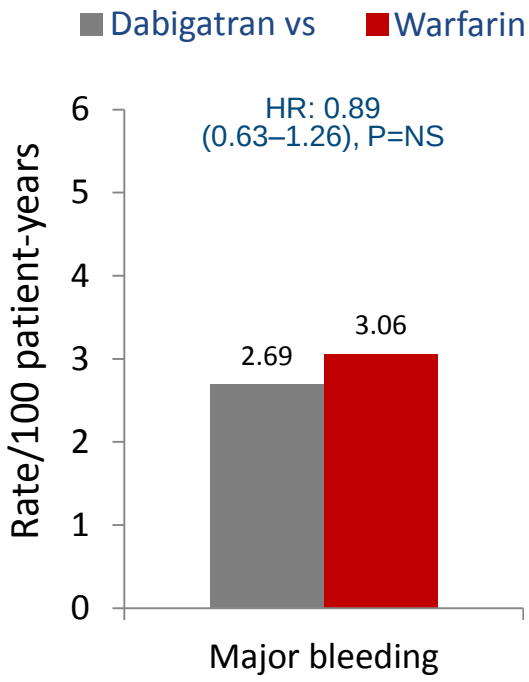
Independent FDA study of Medicare patients mirrors the findings from RE-LY

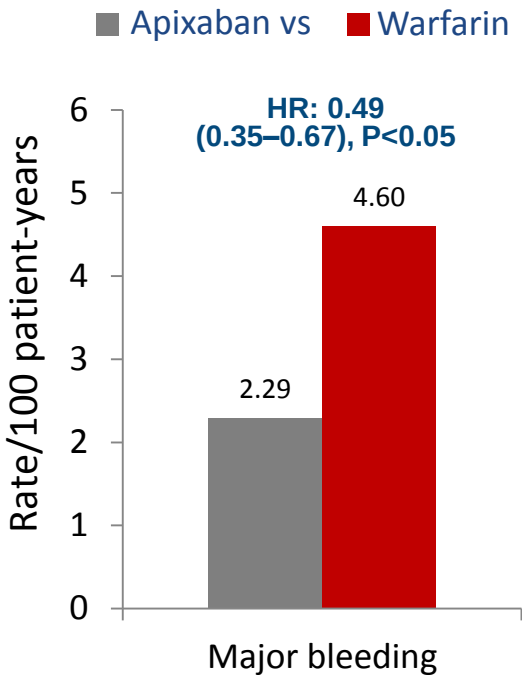


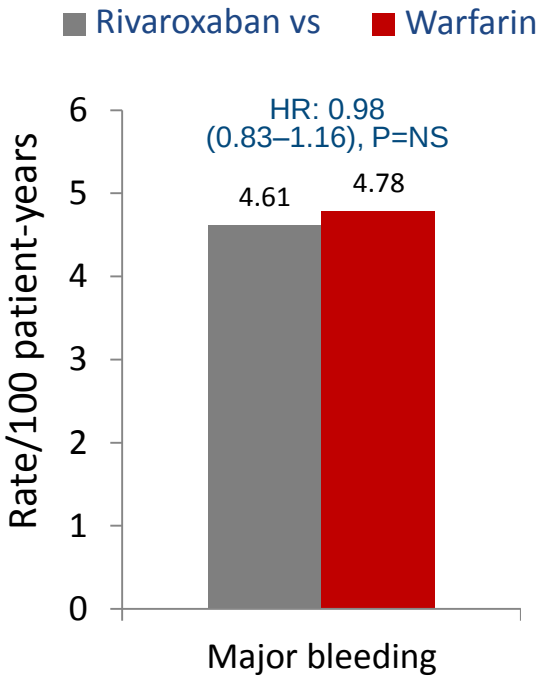
*Primary findings for dabigatran are based on analysis of both 75 mg and 150 mg together without stratification by dose.

1. Connolly et al. NEJM 2009; **2.** Connolly et al. NEJM 2010; **3.** Pradaxa®: EU SPC, 2015; **4.** Graham et al. Circulation 2014l; **5.** Connolly S et al. NEJM 2014

- Retrospective analysis of US MarketScan and Medicare supplemental databases
- Follow up until bleeding, discontinuation or switch, or end of study
- Analysis based on propensity-score-matched cohorts (Dabigatran vs warfarin, n=5255 in each group; apixaban vs warfarin, n=6441 in each group; rivaroxaban vs warfarin, n=13 320 in each group)







Propensity-score-matched HR (95% CI). Baseline patient characteristics differ between the matched cohorts; no indirect comparison of NOACs can be made. Bold values indicate statistical significance. Limitations: abstract only; moderate sample size; limited variables used for adjustment. Lip GY et al. ACC 2016

Coagulation Testing with NOACs

Coagulation Testing with NOACs

- Unlike VKA, neither the dose nor the dosing interval of NOACs is determined by laboratory coagulation parameters.
- Assessment of drug exposure or anticoagulant effect may be needed in emergency situations (serious bleeding, thrombotic event, or urgent surgery)
- Interpretation of coagulation parameters in patients taking NOACs depends on:
  - The coagulation test itself/assay
  - Timing of test relative to drug intake: peak versus trough
  - Patient characteristics: age, kidney function, liver function, concomitant medications

Measuring the anticoagulant effect of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak	2h after ingestion	1-4h post ingestion	1-2h after ingestion	2-4h after ingestion
Plasma trough	12-24h after ingestion	12-24h after ingestion	12-24h after ingestion	16-24h after ingestion
PT	cannot be used	cannot be used	prolonged but no known relation with bleeding risk	prolonged: may indicate excess bleeding risk but local calibration required
INR	cannot be used	cannot be used	cannot be used	cannot be used
aPTT	at trough >2x ULN suggests excess bleeding risk	cannot be used	prolonged but no known relation with bleeding risk	cannot be used
dTT	At trough >200ng/ml ≥ 65s: excess bleeding risk	cannot be used	cannot be used	cannot be used
Anti-FXa assays	n/a	no data yet	quantitative; no data on threshold values for bleeding or thrombosis	quantitative; no data on threshold values for bleeding or thrombosis
Ecarin clotting time	at trough >2x ULN: excess bleeding risk	not affected; cannot be used	not affected; cannot be used	not affected; cannot be used

Heidbuchel et. al. **Europace** 2015; 17:1467-1507

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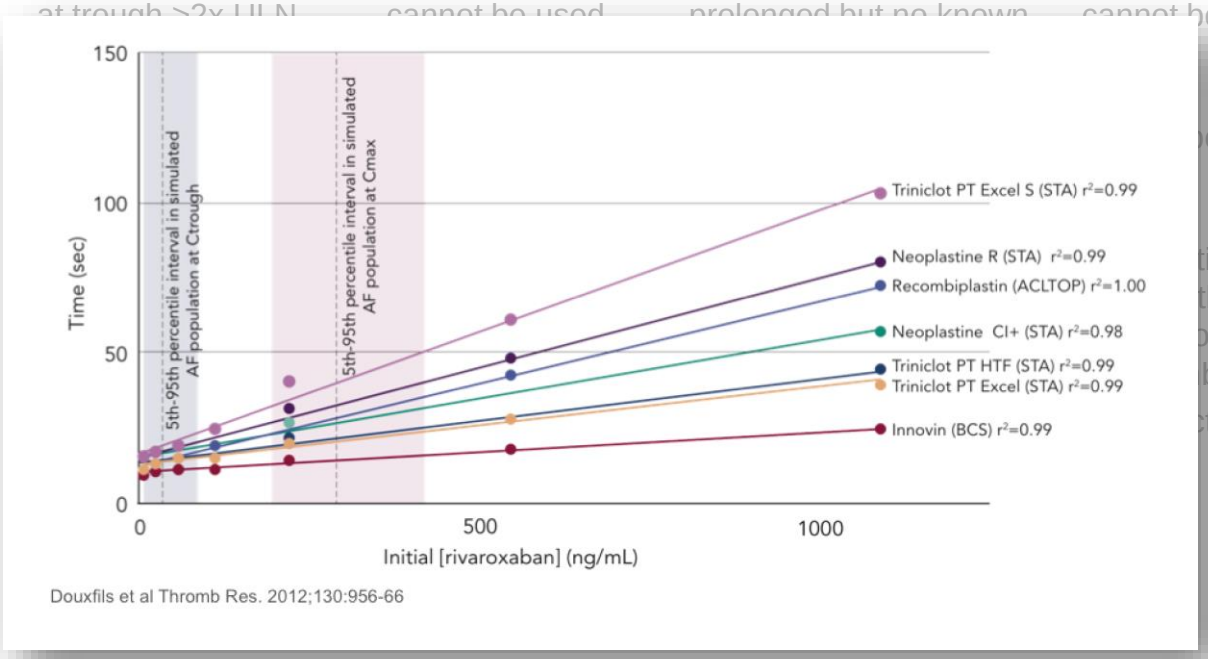
dTT				be used
Anti-FXa assays				tive; no threshold or bleeding bosis
Ecarin clotting time				cted; cannot



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dTT	At trough >200ng/ml ≥ 65s: excess bleeding risk	cannot be		
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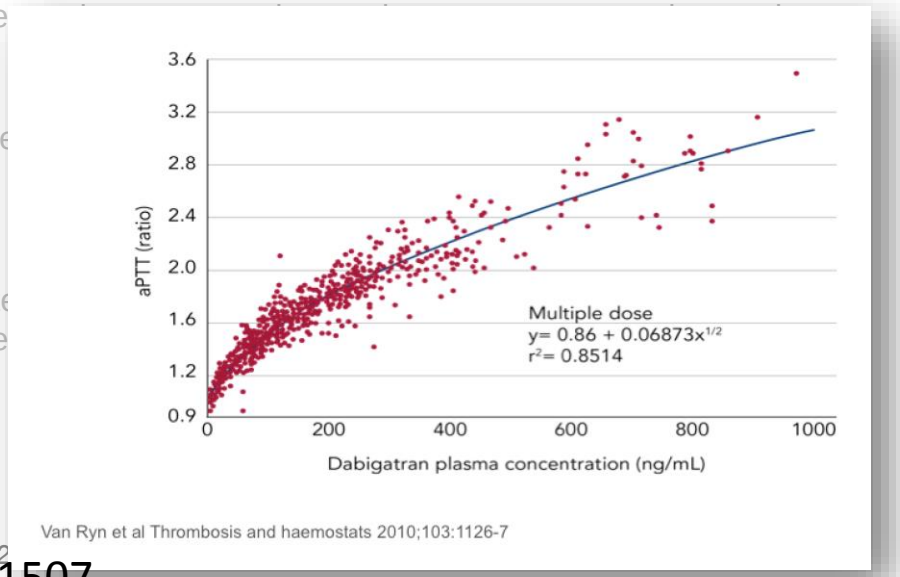
Ecarin clotting time	at trough >2x ULN: excess bleeding risk	not affecte cannot be		



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Anti-FXa assays	n/a	no data yet	quantitative: no data on	quantitative; no data on threshold values for bleeding or thrombosis
Ecarin clotting tim				not affected; cannot be used

Normal dTT = no relevant anticoagulant effect of dabigatran

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INR				cannot be used
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dTT				cannot be used
	65s: excess bleeding risk			
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Ecarin clotting time	**at trough >2x ULN: excess bleeding risk**	**not affected; cannot be used**	**not affected; cannot be used**	**not affected; cannot be used**

ECT close to baseline = no relevant anticoagulant effect of dabigatran

Heidbuchel et. al. **Europace** 2015; 17:1467-1507

Coagulation Testing with NOACs

- Important to know exactly when NOAC was administered
- **No data on cut-off values of any coagulation test below which elective or urgent surgery is possible without excess bleeding risk**
- **No studies on whether measurement of drug levels and dose adjustment based on coagulation parameters improve outcomes**
- ff
  below which surgery is safe.
- Anti-FXa chromogenic assays: commercially available for quantitative assessment, but no data to associate level with bleeding or thrombo-embolism risk.

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Peri-Procedural Bleeding in NOACs RCTs

RE-LY peri-procedural outcomes subgroup analysis: bleeding outcomes

- No significant difference in risk of bleeding for either dose vs warfarin

	% patients			D110 vs warfarin		D150 vs warfarin	
	D110 n=1487	D150 n=1546	Warfarin n=1558	RR (95% CI)	P value	RR (95% CI)	P value
Major bleeding	3.8	5.1	4.6	0.83 (0.59–1.17)	0.28	1.09 (0.80–1.49)	0.58
Fatal bleeding	0.2	0.1	0.1	1.57 (0.26–9.39)	0.62	1.01 (0.14–7.15)	0.99
Re-operation	0.6	1.4	1.0	0.59 (0.26–1.33)	0.20	1.39 (0.73–2.63)	0.32
RBC transfusion	3.3	3.5	4.0	0.81 (0.56–1.18)	0.27	0.86 (0.60–1.23)	0.42
Minor bleeding	8.1	9.0	7.8	1.03 (0.81–1.31)	0.81	1.15 (0.91–1.45)	0.24

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily;
RBC = red blood cell; RR = relative risk

Healey JS et al. Circulation 2012;126:343–8

RE-LY peri-procedural outcomes subgroup analysis: major bleeding by type of surgery

- Similar risk of bleeding within each surgery type; no significant interaction between surgery type and treatment

	% patients			D110 vs warfarin		D150 vs warfarin	
	D110	D150	Warfarin	RR (95% CI)	P value	RR (95% CI)	P value
Urgent surgery	17.8	17.7	21.6	0.82 (0.48–1.41)	0.47	0.82 (0.50–1.35)	0.43
Elective surgery	2.8	3.8	3.3	0.83 (0.55–1.26)	0.38	1.14 (0.77–1.67)	0.51
P (interaction)					0.90		0.31
Major surgery	6.1	6.5	7.8	0.78 (0.49–1.24)	0.30	0.82 (0.53–1.29)	0.40
Minor surgery	1.9	3.2	1.8	1.03 (0.39–2.71)	0.96	1.75 (0.74–4.14)	0.19
P (interaction)					0.61		0.13

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily; RR = relative risk

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: major bleeding by timing of anticoagulation interruption

- Significantly lower rate of bleeding with dabigatran (both doses) for patients undergoing surgery within 48 hours of anticoagulation interruption

	% patients (n/N)			D110 vs warfarin		D150 vs warfarin	
	D110	D150	Warfarin	RR (95% CI)	P value	RR (95% CI)	P value
<24 hrs	2.8	6.8	15.4	0.18 (0.07–0.50)	<0.001	0.44 (0.21–0.92)	0.027
24–48 hrs	3.2	3.3	9.0	0.35 (0.16–0.80)	0.01	0.36 (0.16–0.82)	0.01
48–72 hrs	4.5	4.5	5.7	0.79 (0.33–1.90)	0.60	0.79 (0.33–1.91)	0.60
>72 hrs	4.7	6.2	3.6	1.28 (0.77–2.12)	0.34	1.70 (1.08–2.68)	0.02
P-trend				0.002		0.001	

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily; RR = relative risk

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Peri-Procedural Outcomes in NOAC RCTs

	RE-LY*	ROCKET-AF	ARISTOTLE†
No. of patients	4,591	2,150	5,439
$CHADS_2$ score, mean (SD)	2.1 (1.1)	3.41 (0.95)‡	2.1 (1.1)
Most frequent procedures	Pacemaker/defibrillator insertions (10%)	GI colonoscopies or endoscopies (17%)	Dental extraction/oral surgeries (15%)
	Dental procedures (10%)	Dental work (17%)	Colonoscopies (10%)
	Diagnostic procedures (10%)	Abdominal/thoracic/orthopedic surgeries (13%)	Ophthalmic surgeries (8%)
30-day risk for stroke or systemic embolism (OR/HR)	1.01 [0.35-2.89], $P = .99$	0.75 [0.31-1.77], $P = .40$	0.61 [0.32-1.12]
30-day risk for major bleeding (OR/HR)	1.09 [0.80-1.49], $P = .58$	1.02 [0.51-2.06], $P = .96$	0.85 [0.61-1.17]

*Includes only patients treated with dabigatran 150-mg twice-daily dose.
†Includes patients with and without interruption of apixaban.
‡$CHADS_2$ score for all patients with a temporary interruption of anticoagulation regardless of indication.

Krishnamurthy et. al. **AHJ** 2015; 169:315-322

Peri-procedural Management of NOACs

Peri-procedural Management of NOACs

Interventions not necessarily requiring discontinuation of anticoagulant

Perform procedures at '**through**' levels of NOAC. Consider scheduling intervention 18-24 h after last intake and then restart 6 h later (i.e. skipping 1 dose with BID NOAC)

- Dental interventions
  - Extraction of 1 to 3 teeth
  - Paradontal surgery
  - Incision of abscess
  - Implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (e.g. abscess incision, small dermatological excision)

Heidbuchel et. al. **Europace** 2015; 17:1467-1507

Classification of surgical interventions according to bleeding risk

Low risk

- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation (unless complex anatomical setting e.g. congenital heart disease)

High risk

- Complex left-sided ablation: pulmonary vein isolation, VT ablation
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy

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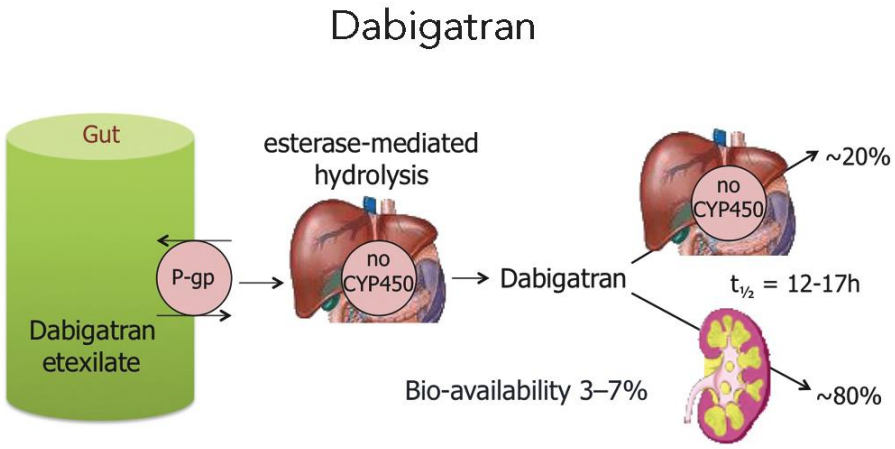
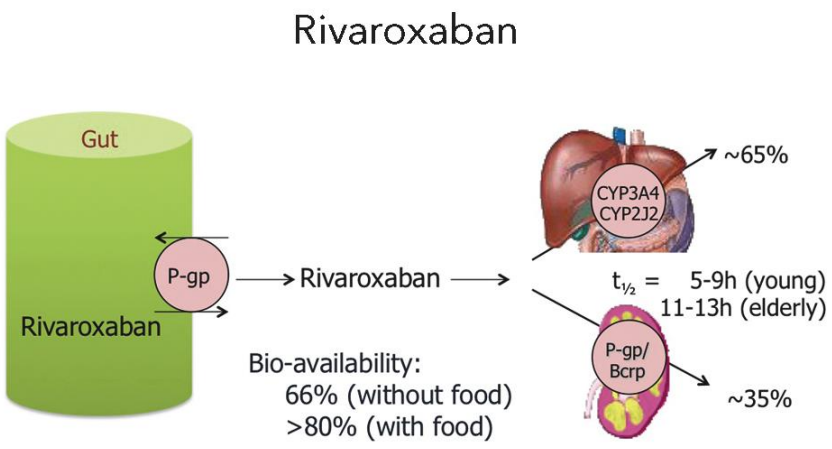
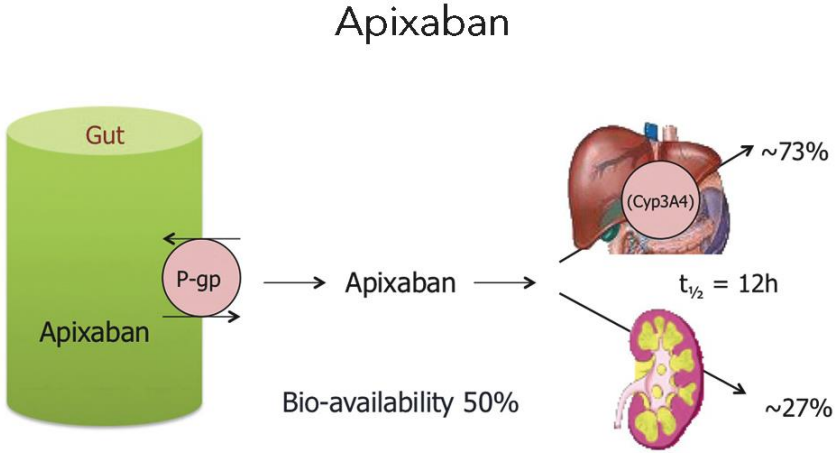
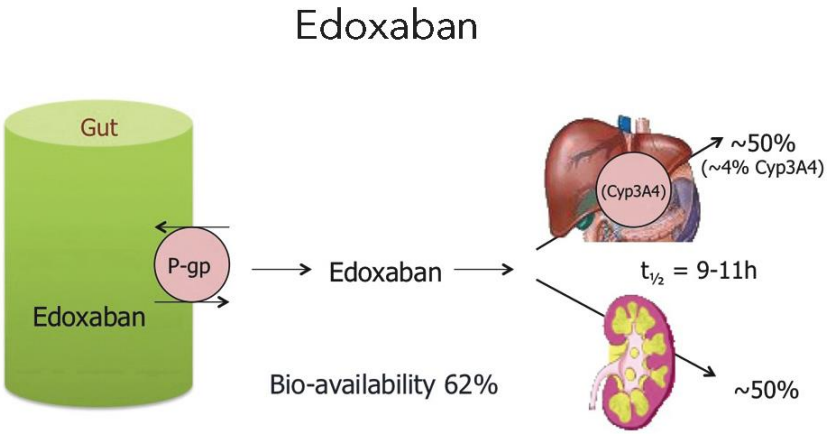
Absorption and metabolism of NOACs









Heidbuchel et. al. **Europace** 2015; 17:1467-1507

When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Rivaroxaban	
	Low risk	**High risk**	**Low risk**	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h
CrCl 50–80 ml/min	≥36h	≥72h	≥24h	≥48h	≥24h	≥48h
CrCl 30–50 ml/min §	≥48h	≥96h	≥24h	≥48h	≥24h	≥48h
CrCl 15–30 ml/min §	not indicated	not indicated	≥36h	≥48h	≥36h	≥48h

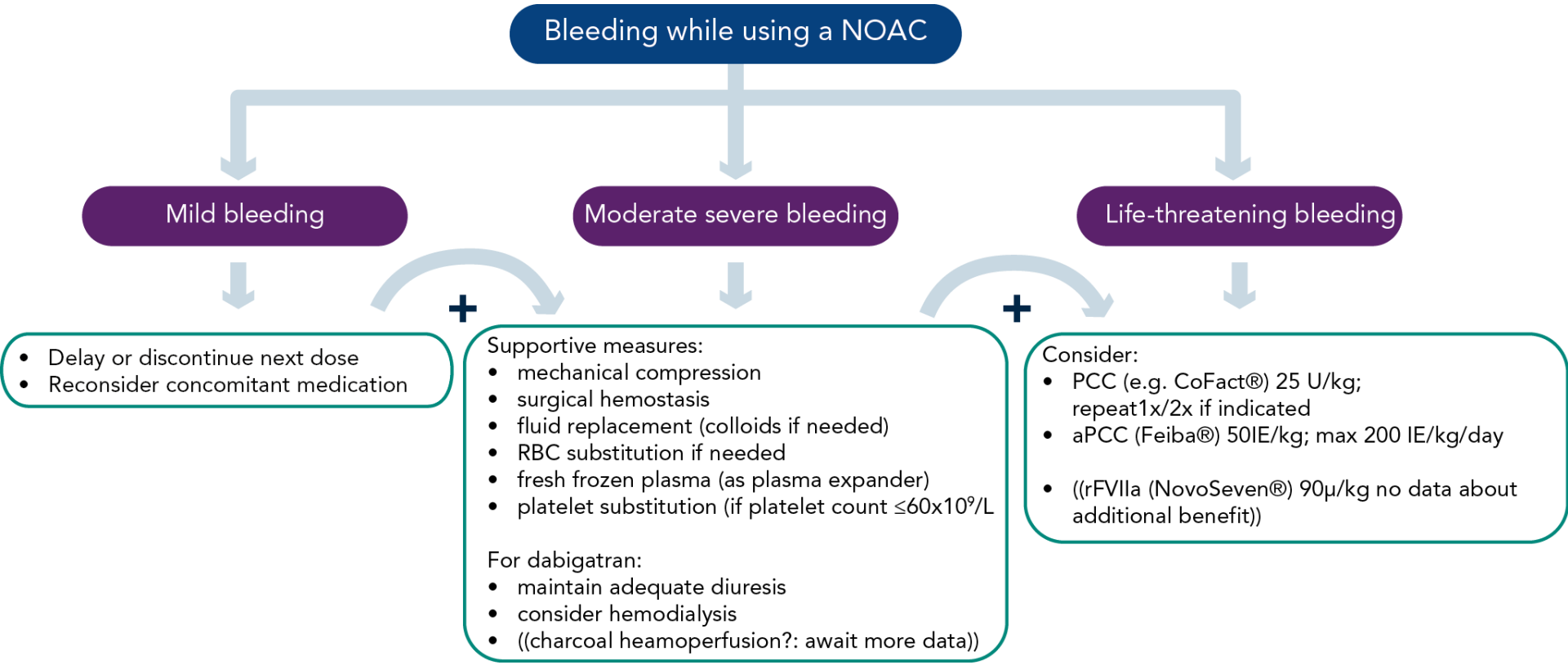
Heidbuchel et. al. **Europace** 2015; 17:1467-1507

When to restart NOACs after a planned surgical intervention

Procedures with immediate and complete haemostasis: Atraumatic spinal/epidural anethesia Clean lumbar puncture	Resume 6–8 h after surgery
Procedures associated with immobilization: Procedures with post-operative risk of bleeding:	Initiate reduced venous or intermediate dose of LMWH 6–8 h after surgery if haemostasis achieved. Restart NOACs 48–72h after surgery upon complete haemostasis Thromboprophylaxis (e.g. with LMWH) can be initiated 6-8 h after surgery

Heidbuchel et. al. **Europace** 2015; 17:1467-1507

Possible measures to take in case of bleeding



Van Ryn et al Am J Med 2012;125:417

Reversal of NOACs Anticoagulant Effect

Vitamin K as an Antidote

- There is a perception that, for patients treated with VKAs, vitamin K is a fast acting antidote
  - However, reversing the anticoagulant effect of warfarin with vitamin K is a slow and complex process[1,2]
  - It has also been shown that prognosis in VKA-associated ICH is poor despite reversal[3,4]

- Prognosis (survival) after a major bleed on NOACs appeared, despite the lack of a specific antidote, better than after a warfarin-associated bleed[5]

NOAC = novel oral anticoagulant; VKA = vitamin K antagonist

1. Camm AJ et al. Eur Heart J 2012;33:2719–47; **2.** Hanley J. J Clin Pathol 2004;57:1132–39; **3.** Wiedermann CJ et al. Thrombosis Res 2008;122(Suppl):S13–18; **4.** Dowlatshahi WT et al. Stroke 2012;43:1812–17; **5**. Majeed et. al. Circulation 2013

Nonspecific Reversal of NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Oral activated charcoal	Adsorbs and neutralizes, in vitro data[1]	Adsorbs and neutralizes	Adsorbs and neutralizes, in vivo data[10]	No data
Haemodialysis	Human volunteers, case report[2]	Not possible	Not possible	No data
Fresh frozen plasma	Mouse ICH[3] model	No data	No data	No data
Activated FVIIa	Mouse[3], rat[4] model	Baboon[8], rabbit trauma[9] models	Rabbit trauma[11] model	Rat[12] model
3-factor PCC	No data	No data	No data	No data
4-factor PCC	Mouse[3], rat[4] , rabbit trauma[5] model, human volunteers[6]	Rat[7], baboon[8], rabbit trauma[9], human volunteers[6]	Rabbit trauma[11] model	Rat[11] model

[1]van Ryn et al Blood 114 Abstr 1065, 2009
[2]Warkentin et al, Blood 119, 2012
2012
[3]Zhou et al, Stroke 42:3594, 2011
[4]van Ryn et al Blood 118 Abstr 2316, 2011
[5]Pragst et al, ICT Abstr P486, 2010
[6]Eerenberg et al, Circulation,124, 2011
[7]Perzborn et al, ISTH Abst PP-MO-183, 2009
[8]Perzborn et al, EHA Abst 853, 2009
[9]Godier et al Anesthesiology 116, 2012
[10]Wang et al Clin Pharmacol Ther 91 Abstr PI-90,
[11]Martin et al, ACC Abstr 904, 2012
[12]Fukuda et al, T&H 107(2), 2012

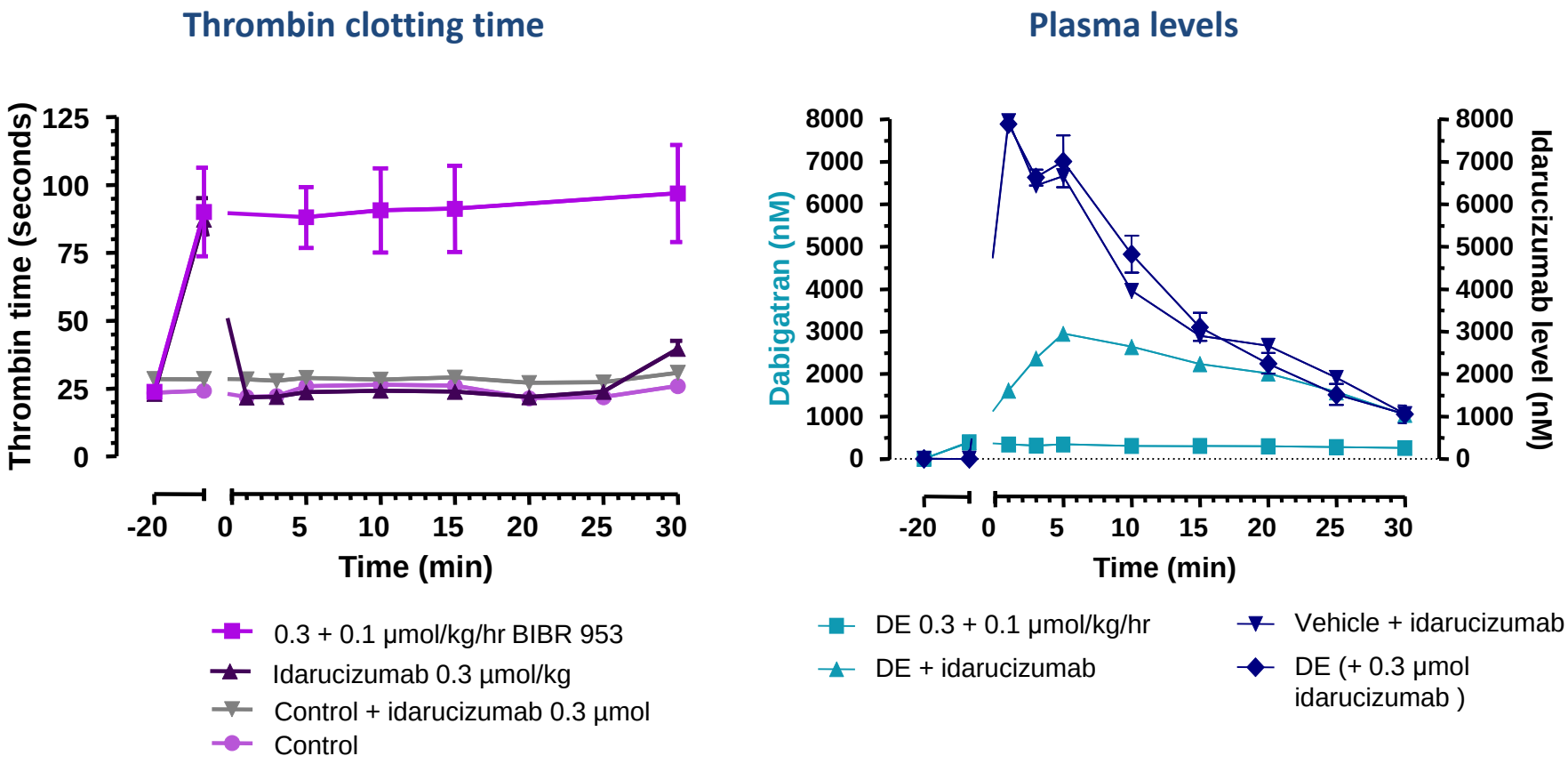
Dabigatran antidote (Idarucizumab)

- Fully humanized antibody fragment (Fab)
- Potently binds dabigatran
- No prothrombotic or anti-thrombotic effects
- Short half-life
- No endogenous targets
- Allows for intravenous administration

van Ryn J. Presented at the AHA Congress, Los Angeles, USA. 5 November 2012. Presentation 9928;
van Ryn J et al. Circulation 2012;126:A9928

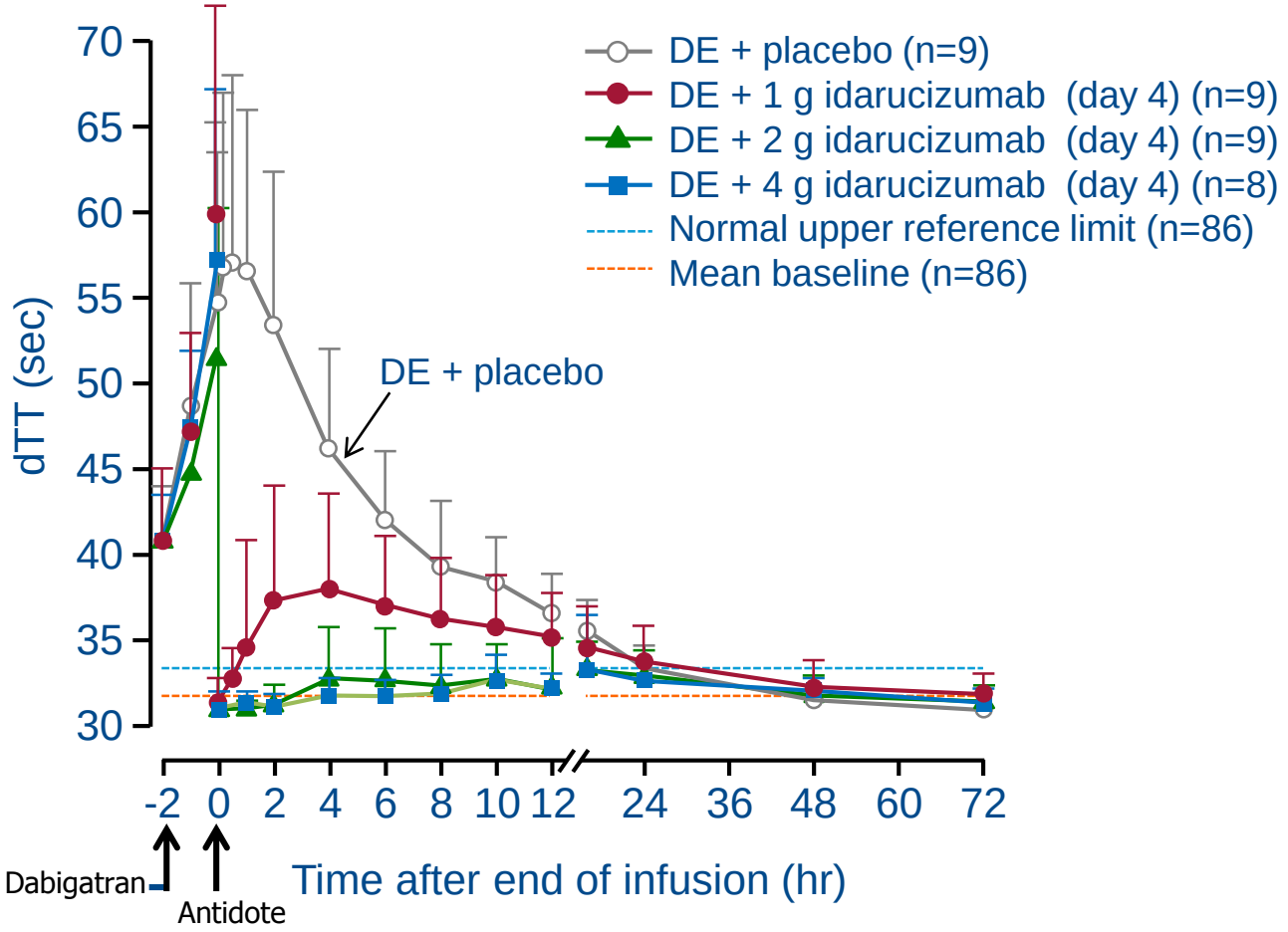
Reversal of anticoagulation *ex vivo*

- Antidote reverses the anticoagulant activity of dabigatran within 1 min of IV bolus injection to rats



Schiele F et al. Blood 2013;121:3554–62;

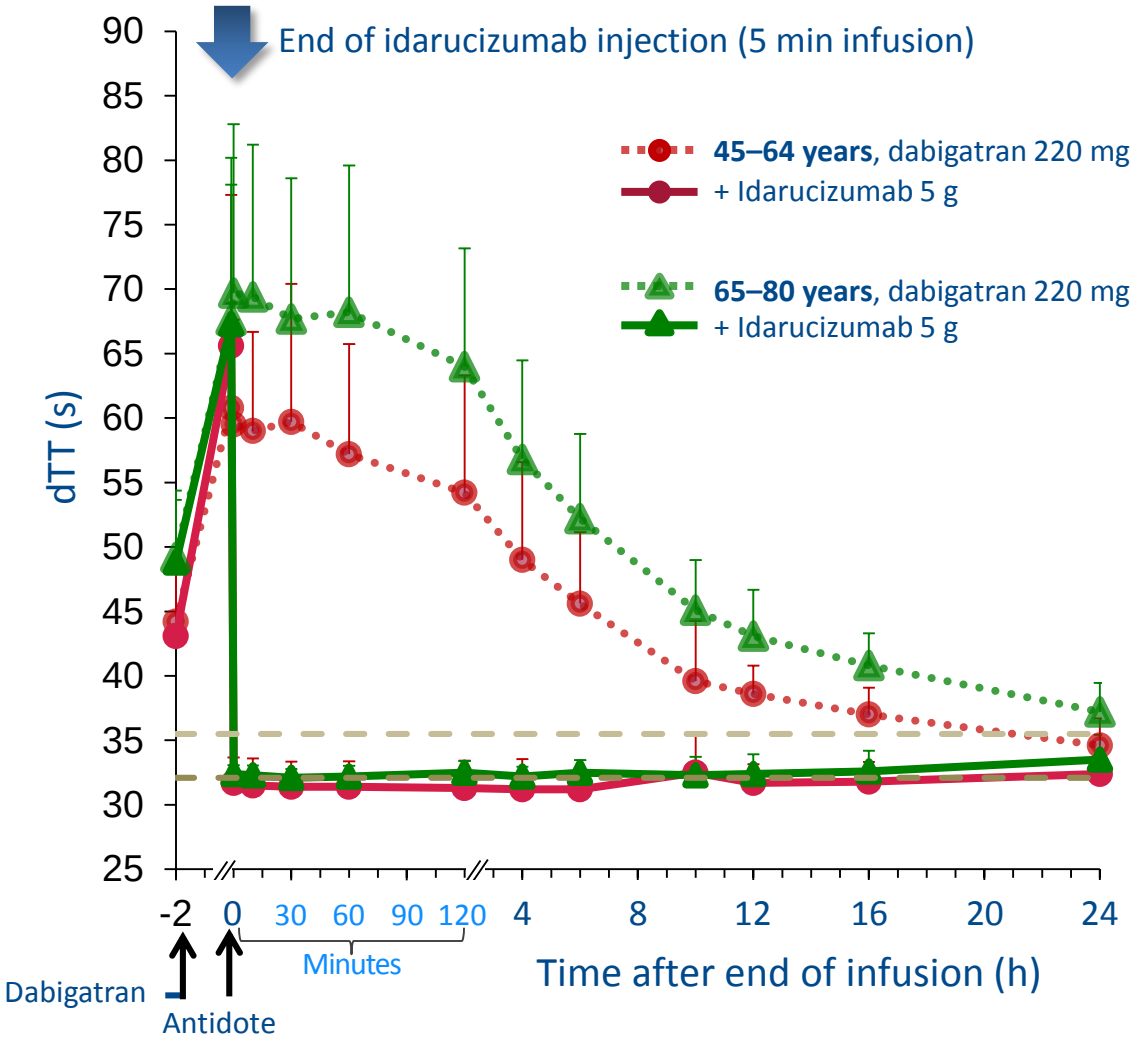
Idarucizumab in Healthy Volunteers



'Normal upper reference limit' refers to (mean+2SD) of 86 pre-dose measurements from a total of 51 subjects

Glund S et al. Presented at AHA, Dallas, TX, USA, 16–20 November 2013; Abstract 17765

Idarucizumab in elderly subjects



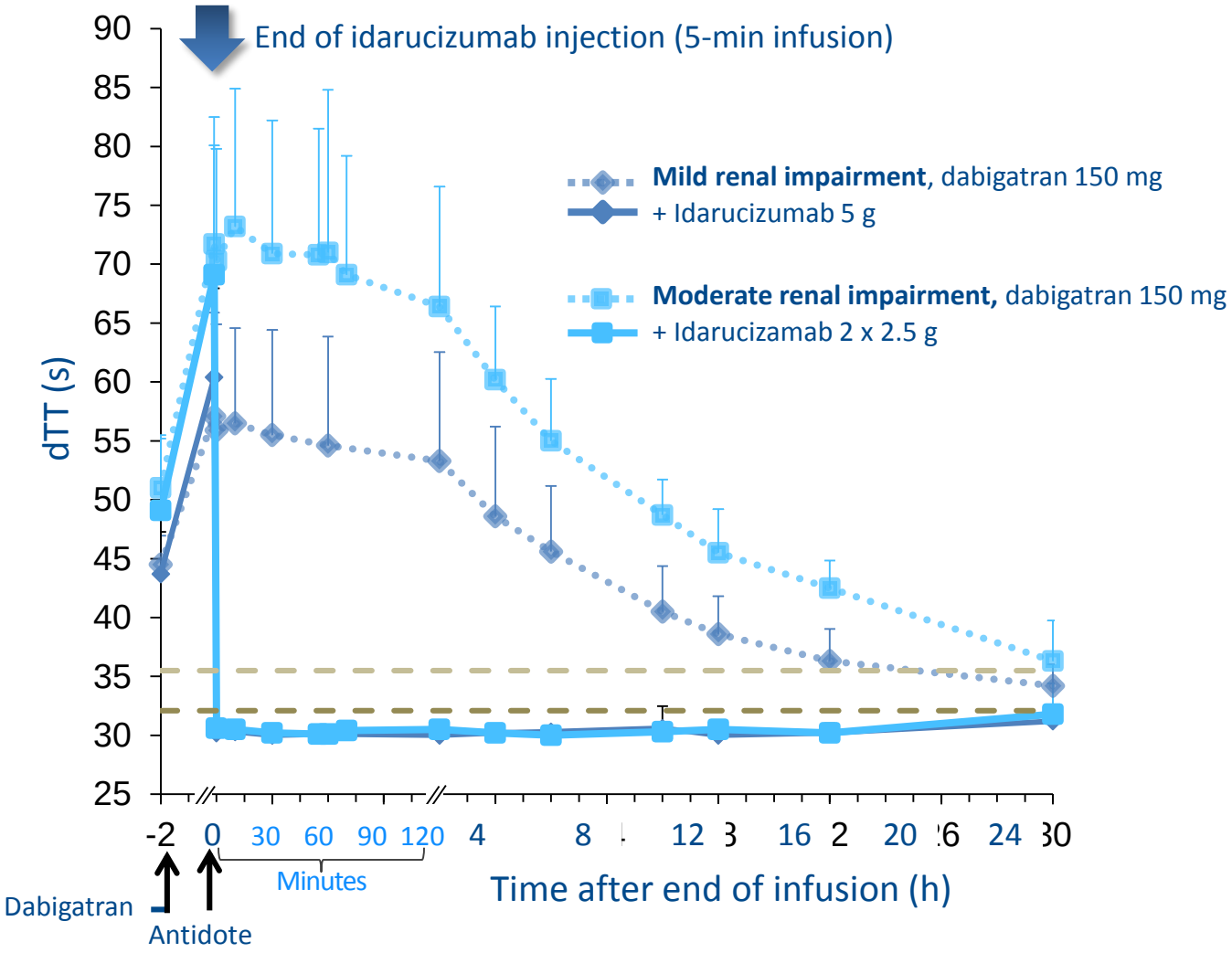
Dabigatran levels in middle-aged and elderly subjects are consistent with those in the AF population

Idarucizumab action in middle-aged and elderly subjects consistent with previous studies of healthy subjects

Idarucizumab is currently in development and is not approved for use in any country
The information presented here is intended for medical education purposes only

Glund S et al. ASH 2014; Abstract 334

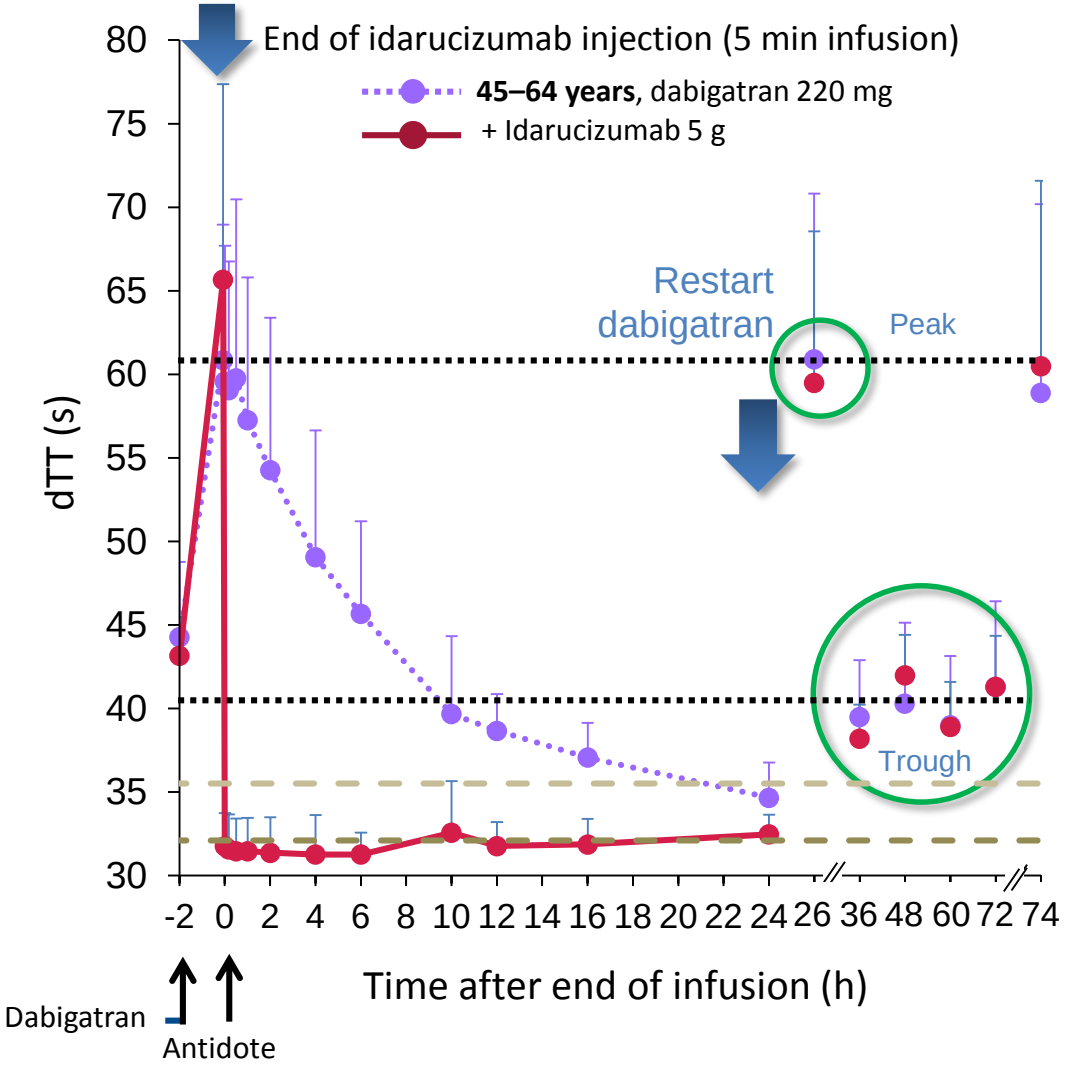
Idarucizumab in Renal Impairment



CL_{cr}: mild impairment ≥ 60–< 90 mL/min; moderate impairment ≥ 30–< 60 mL/mi

Glund S et al. ASH 2014; Abstract 334

Re-administration of dabigatran 24 hours after idarucizumab restores anticoagulation



Idarucizumab reversed dabigatran anticoagulation

24 hours later, dabigatran was restarted in all subjects

Dabigatran anticoagulation restored to levels similar to baseline regardless of prior use of antidote

Antidote effect does not last >24 hours

Glund S et al. ASH 2014; Abstract 334

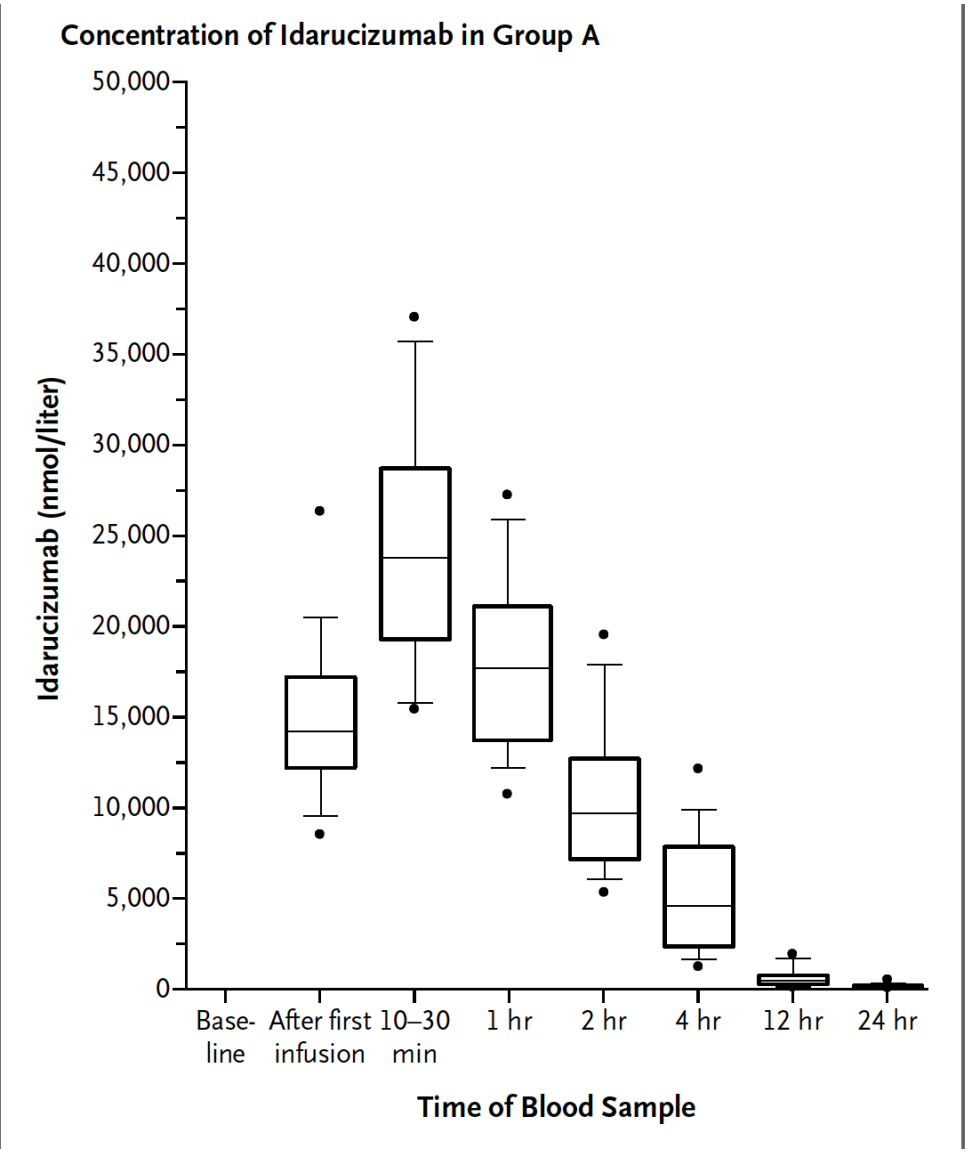
The NEW ENGLAND JOURNAL of MEDICINE

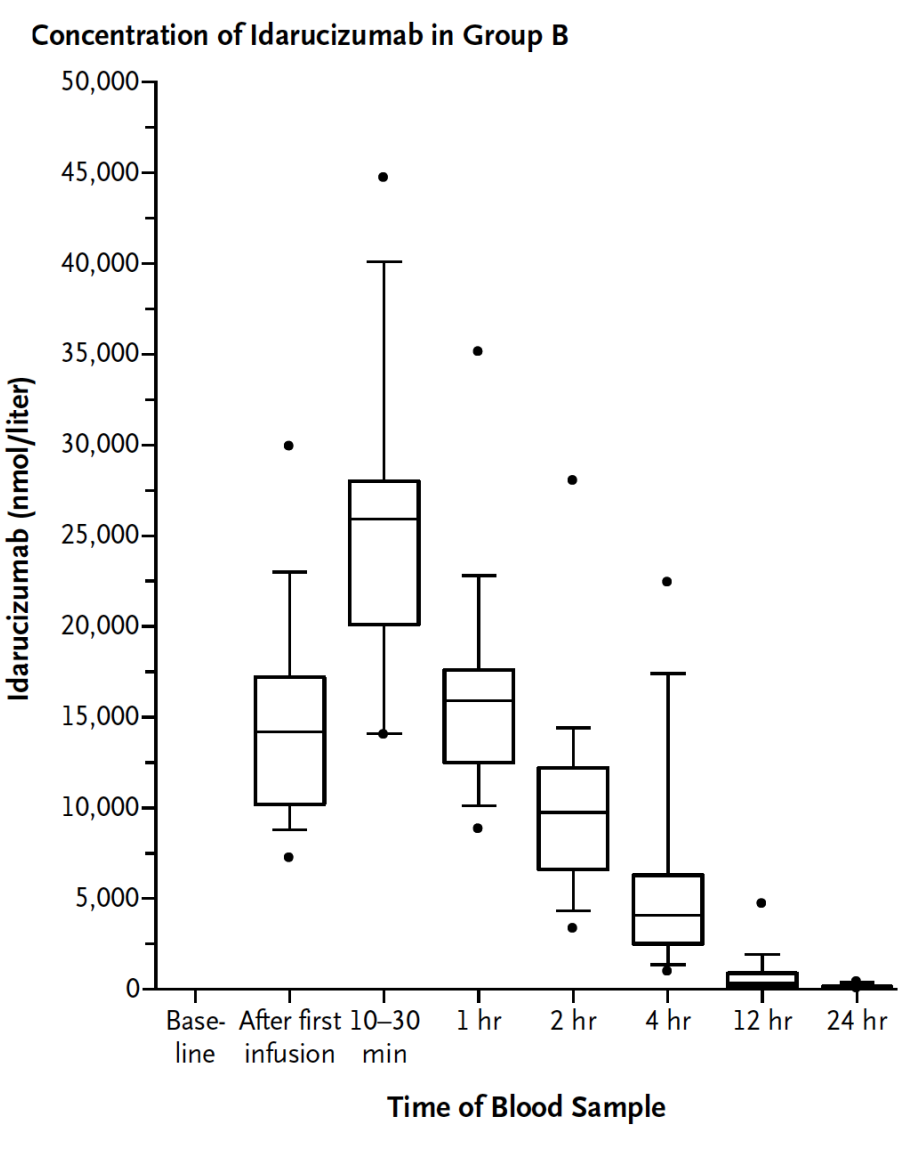
ORIGINAL ARTICLE

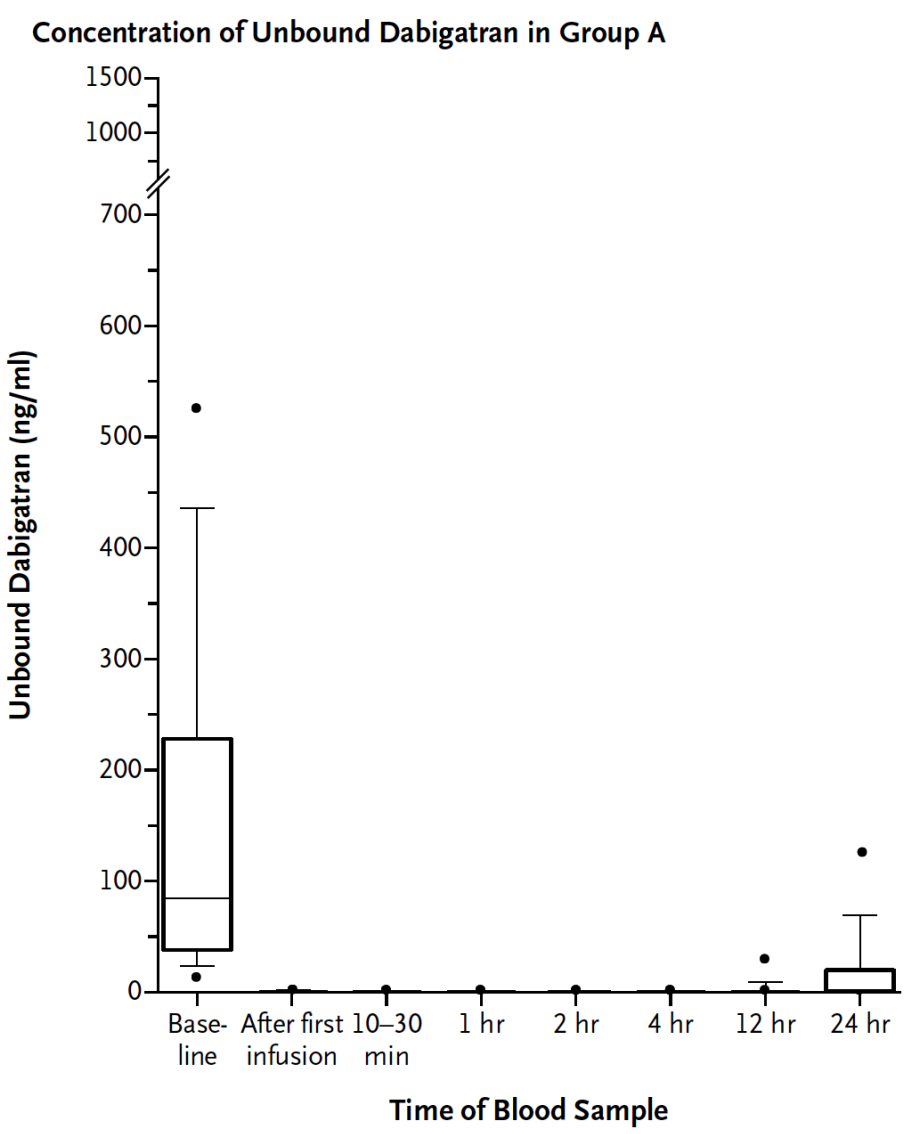
Idarucizumab for Dabigatran Reversal

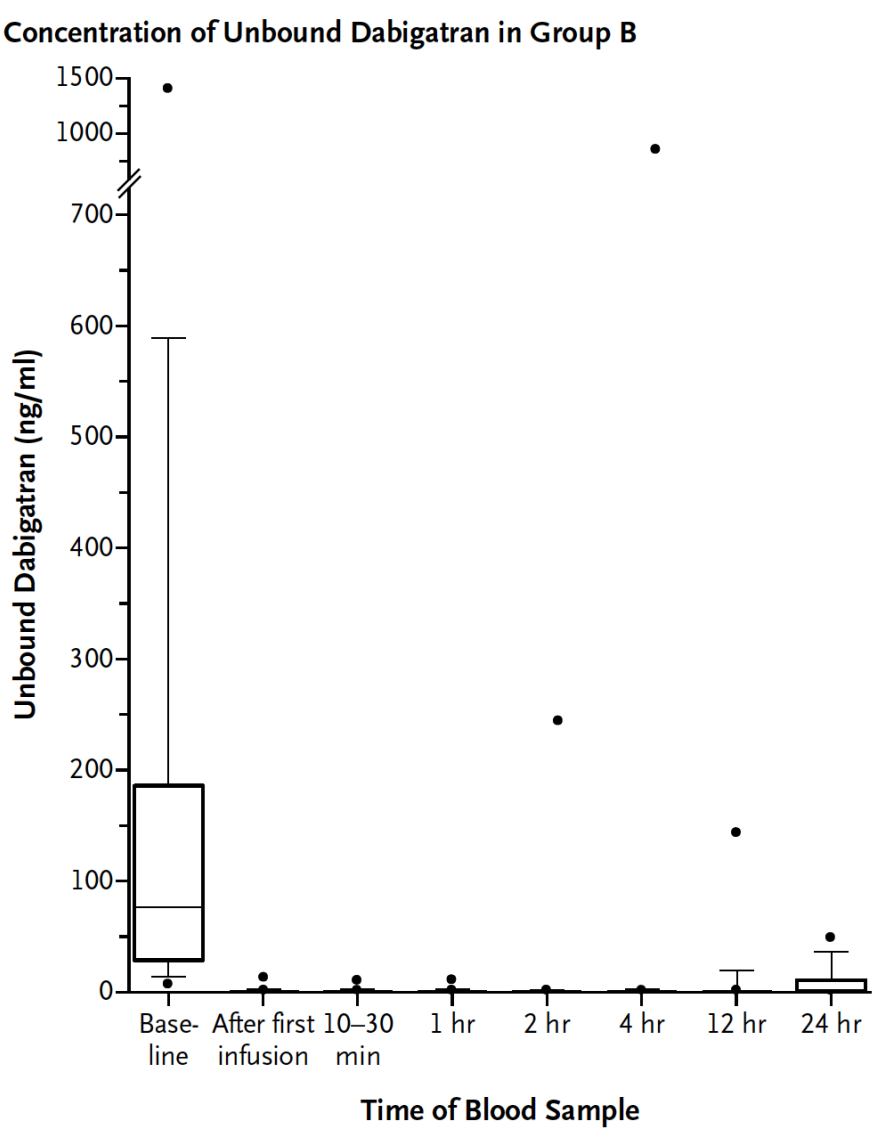
- Prospective cohort study to determine the safety of intravenous idarucizumab and its capacity to reverse the anticoagulant effect of dabigatran in patients with serious bleeding (Group A) or required an urgent procedure (Group B)
- Primary endpoint: maximum percentage reversal of anticoagulant effect of dabigatran within 4 hours after administration on the basis of dilute thrombin time or ecarin clotting time.

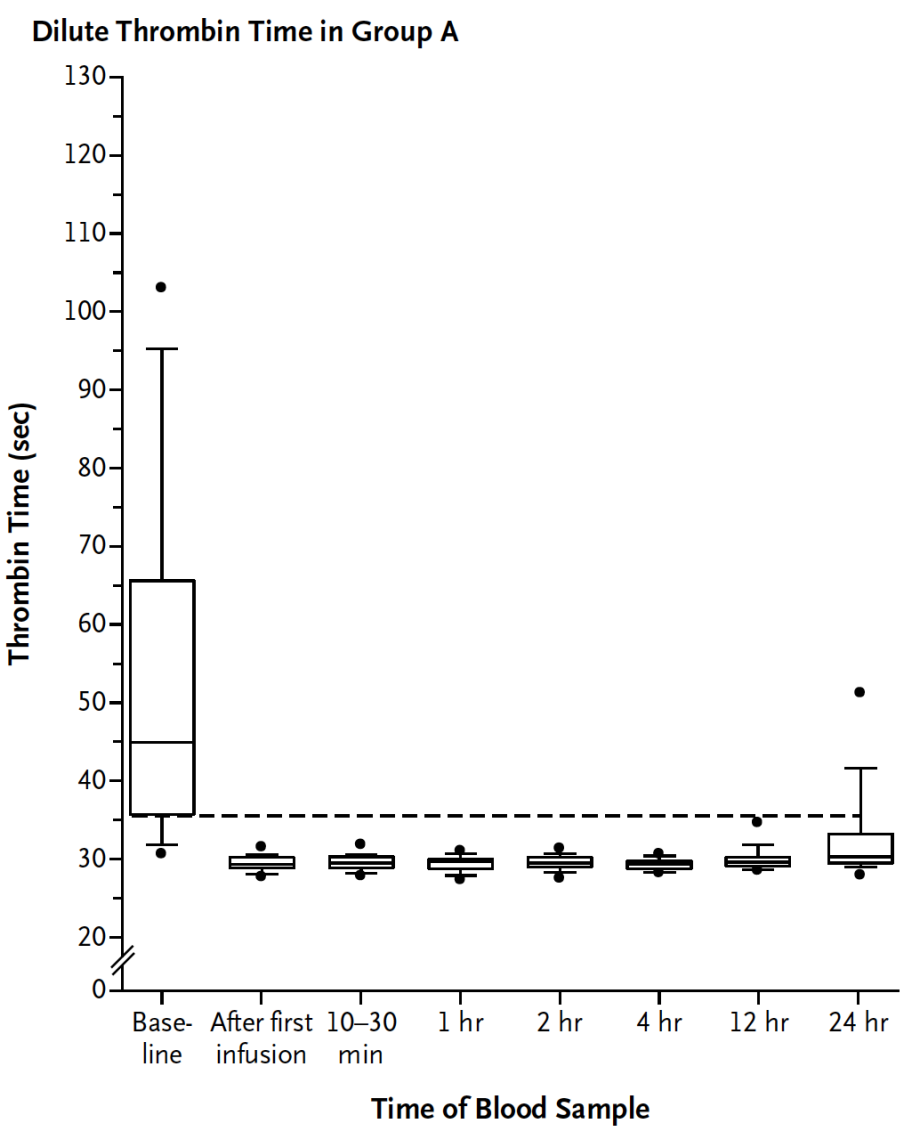
Pollack et. al. NEJM 2015; 373:511-20

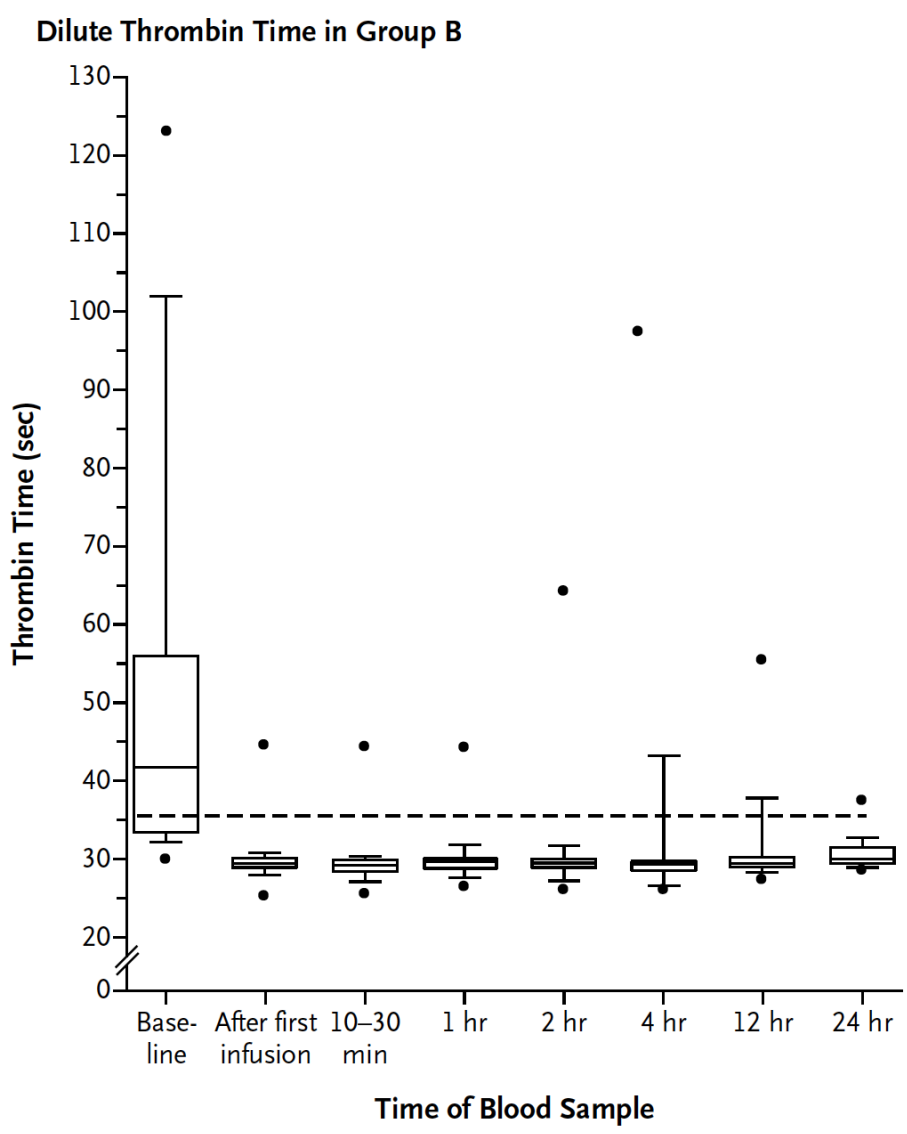

Concentration of Idarucizumab in Group A
Idarucizumab (nmol/liter)
50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
Base-line
After first infusion
10–30 min
1 hr
2 hr
4 hr
12 hr
24 hr
Time of Blood Sample

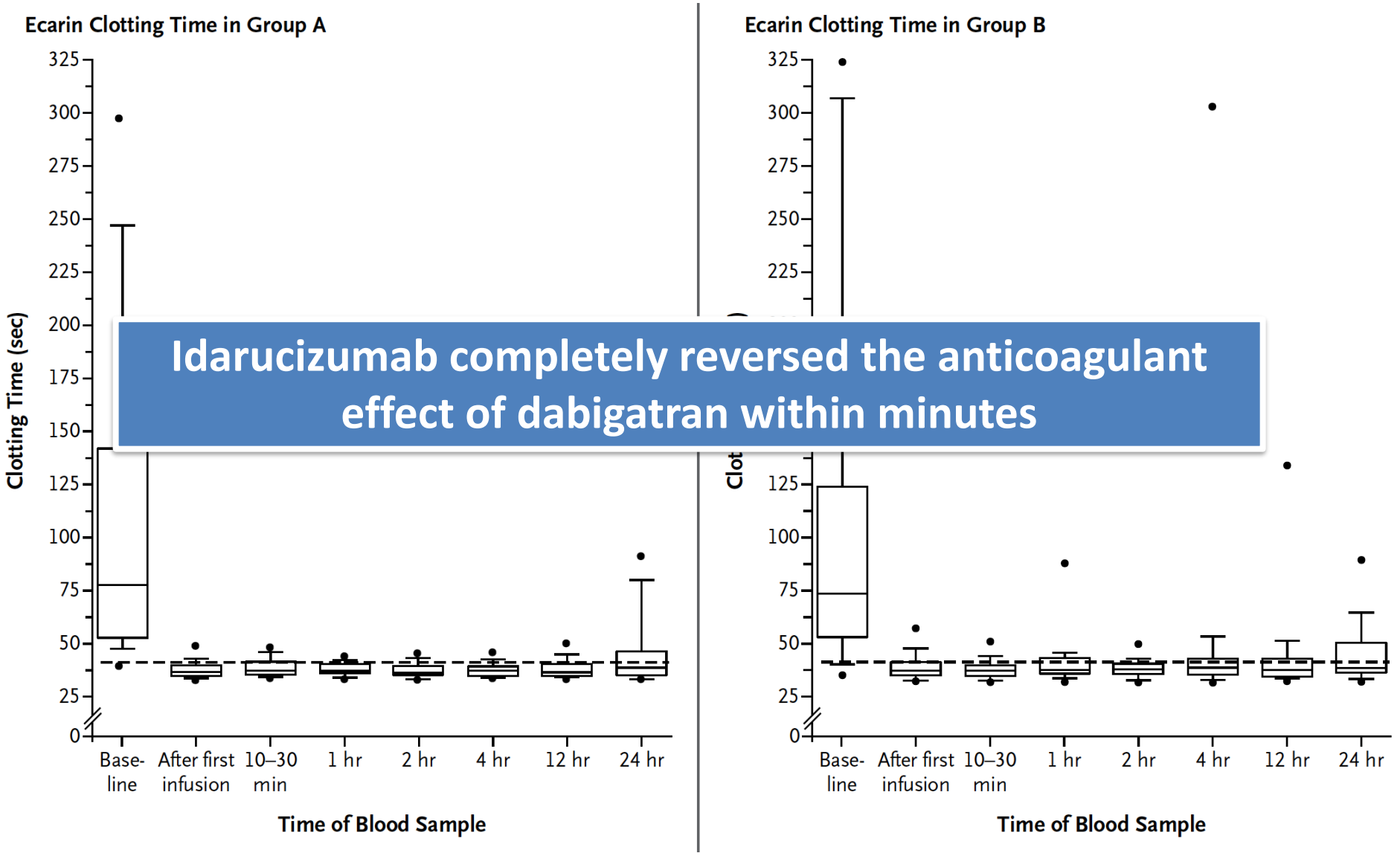

Concentration of Idarucizumab in Group B
Idarucizumab (nmol/liter)
50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
Base-line
After first infusion
10–30 min
1 hr
2 hr
4 hr
12 hr
24 hr
Time of Blood Sample


Concentration of Unbound Dabigatran in Group A
Unbound Dabigatran (ng/ml)
1500
1000
700
600
500
400
300
200
100
0
Base-line
After first infusion
10–30 min
1 hr
2 hr
4 hr
12 hr
24 hr
Time of Blood Sample


Concentration of Unbound Dabigatran in Group B
Unbound Dabigatran (ng/ml)
1500
1000
700
600
500
400
300
200
100
0
Base-line
After first infusion
10–30 min
1 hr
2 hr
4 hr
12 hr
24 hr
Time of Blood Sample


Dilute Thrombin Time in Group A
Thrombin Time (sec)
130
120
110
100
90
80
70
60
50
40
30
20
0
Base-line
After first infusion
10–30 min
1 hr
2 hr
4 hr
12 hr
24 hr
Time of Blood Sample


Dilute Thrombin Time in Group B
Thrombin Time (sec)
130
120
110
100
90
80
70
60
50
40
30
20
0
Base-line
After first infusion
10–30 min
1 hr
2 hr
4 hr
12 hr
24 hr
Time of Blood Sample



Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes

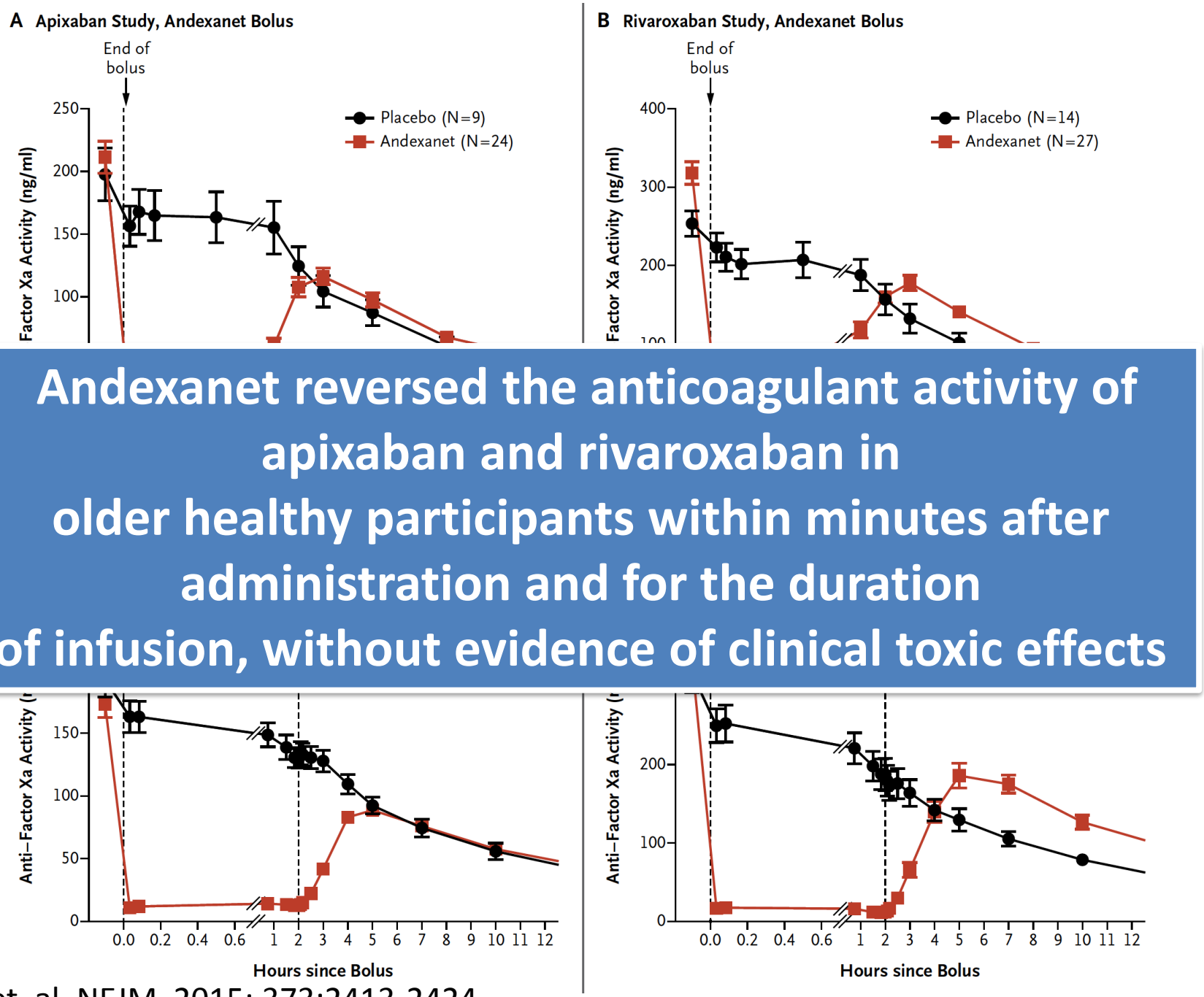
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

- Andexanet is a recombinant modified human factor Xa decoy protein that is catalytically inactive but that retains the ability to bind factor Xa inhibitors in the active site with high affinity and a 1:1 stoichiometric ratio.
- Healthy volunteers (~ 57 years) on apixaban or rivaroxaban (101) or placebo (44)

Seigal et. al. NEJM 2015; 373:2413-2424



Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects

Seigal et. al. NEJM 2015; 373:2413-2424

NOACs Reversal Agents

Reversal agent	Target	Mechanism of action	Investigation status
Idarucizumab	Dabigatran	Humanized Fab: specifically binds dabigatran (binding affinity ~350 x higher than binding of dabigatran to thrombin)	Bleeding patients and surgical patients[2]
Andexanet alfa (PRT064445)	FXa inhibitors	Recombinant human FXa variant: competitive affinity for direct FXa inhibitors	Healthy volunteers[3,4]
Aripazine (PER977)	Universal	Synthetic small molecule: charge–charge interactions (heparin); hydrogen bonds (NOACs)[5]	Phase 2[6]

1. Lauw et. al. Can J Cardiol 2014, 2. Clinicaltrials.gov NCT02104947, 3. Clinicaltrials.gov NCT02220725,
4. Clinicaltrials.gov NCT02207725, 5. Bakhru et. al. AHA 2013, 6. Clinicaltrials.gov NCT02207257

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1*], Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Heidbuchel et. al. **Europace** 2015; 17:1467-1507