The direct oral anticoagulants : Management of bleeding and urgent surgery

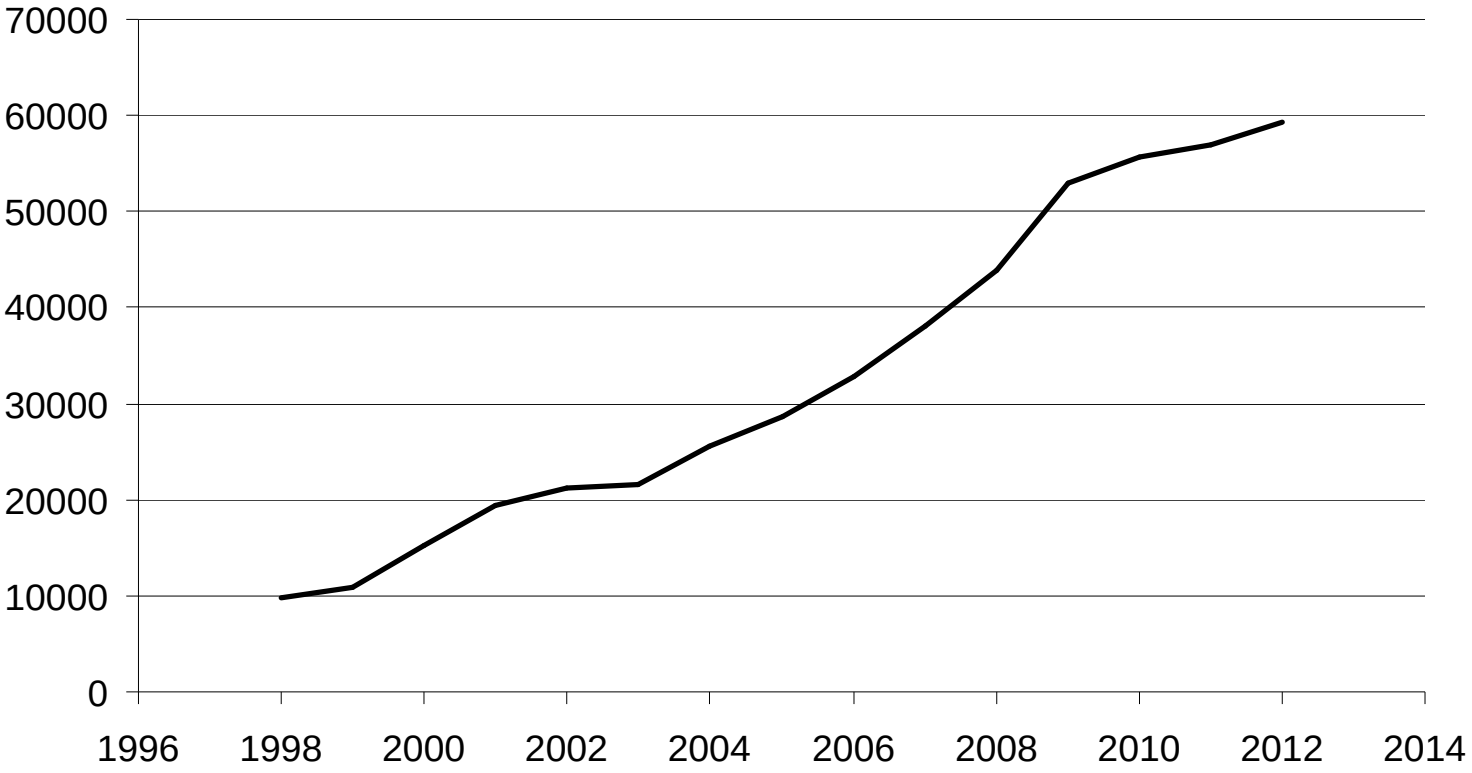
Dr Tina Biss
Consultant Haematologist
Newcastle Hospitals NHS Foundation Trust

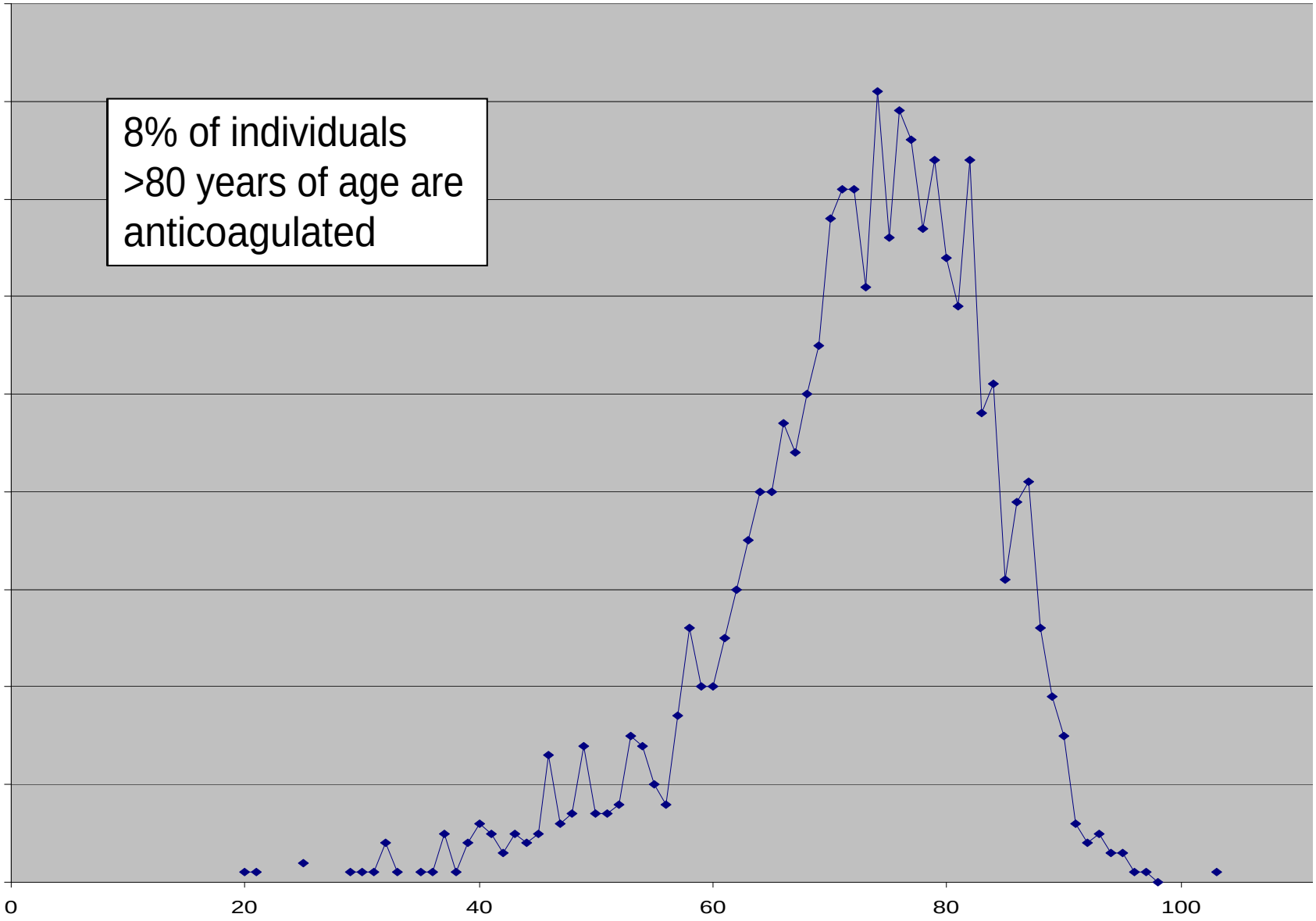
North East RTC Annual Education Symposium
16th October 2014

The extent of the problem

≈1-2% of the UK population are anticoagulated

AF	70%
VTE	25%
Other	5%





AGE DISTRIBUTION OF PATIENTS ON WARFARIN

CHA_2DS_2VASc stroke risk score

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

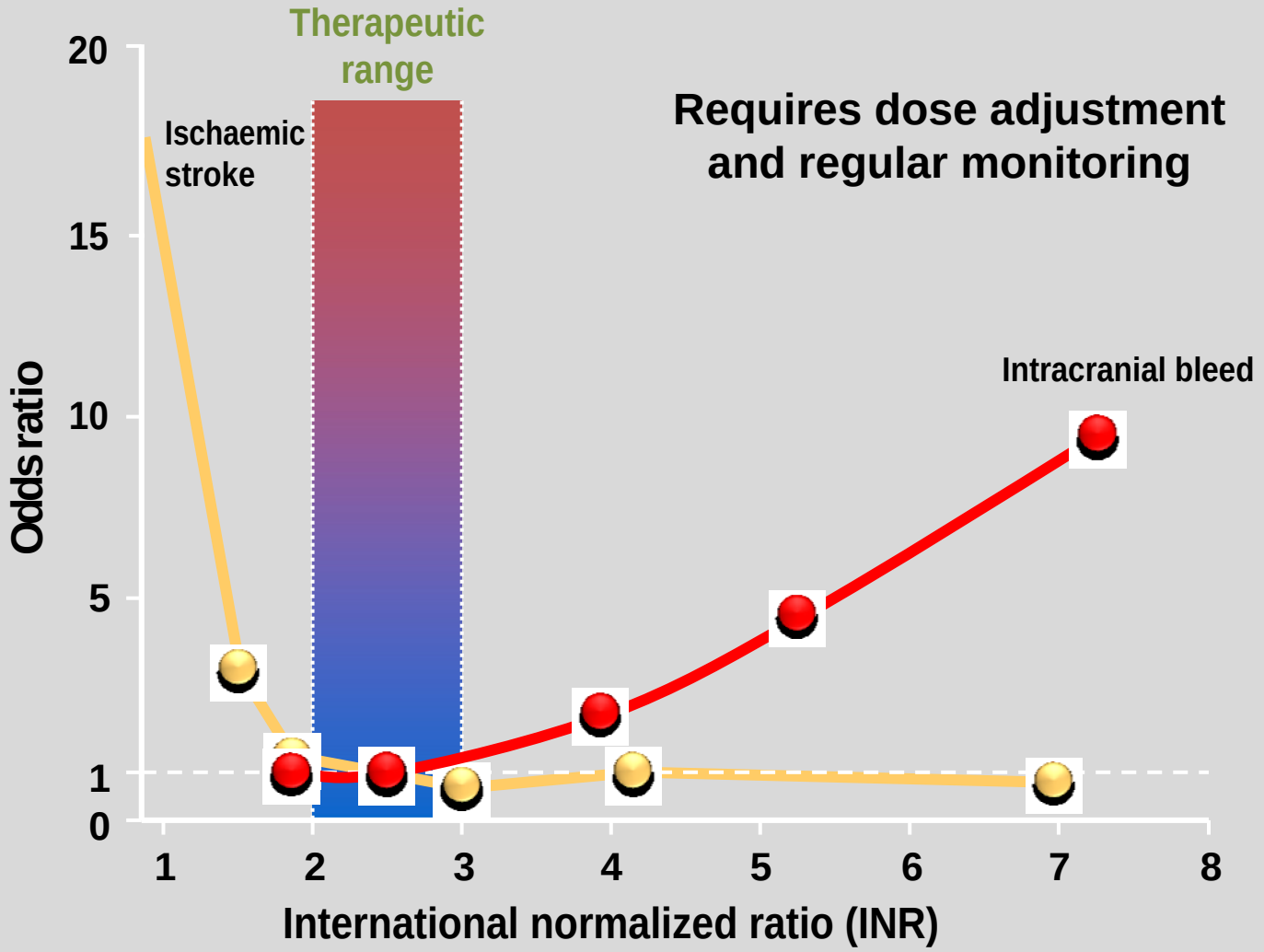
Score 2 or above
➔Offer anticoagulation

Score 1 or above in a male
➔Consider anticoagulation

Annual Stroke Risk[17]

CHA_2DS_2-VASc Score	Stroke Risk %	95% CI
0	0	-
1	1.3	-
2	2.2	-
3	3.2	-
4	4.0	-
5	6.7	-
6	9.8	-
7	9.6	-
8	??	-
9	15.2	-

Warfarin and its challenging therapeutic window



ACC/AHA/ESC guidelines: Fuster V *et al. Circulation* 2006;114:e257–e354.

Problems with warfarin

- Narrow therapeutic window
- Variable dosing:- Inter- and intra-individual
- Unpredictable response therefore requires monitoring:- inconvenience, cost
- Slow onset; slow offset
- Numerous interactions with other medications
- Anticoagulant response altered by diet and alcohol

Atrial fibrillation: the management of atrial fibrillation

Issued: June 2014 last modified: August 2014

NICE clinical guideline 180

guidance.nice.org.uk/cg180

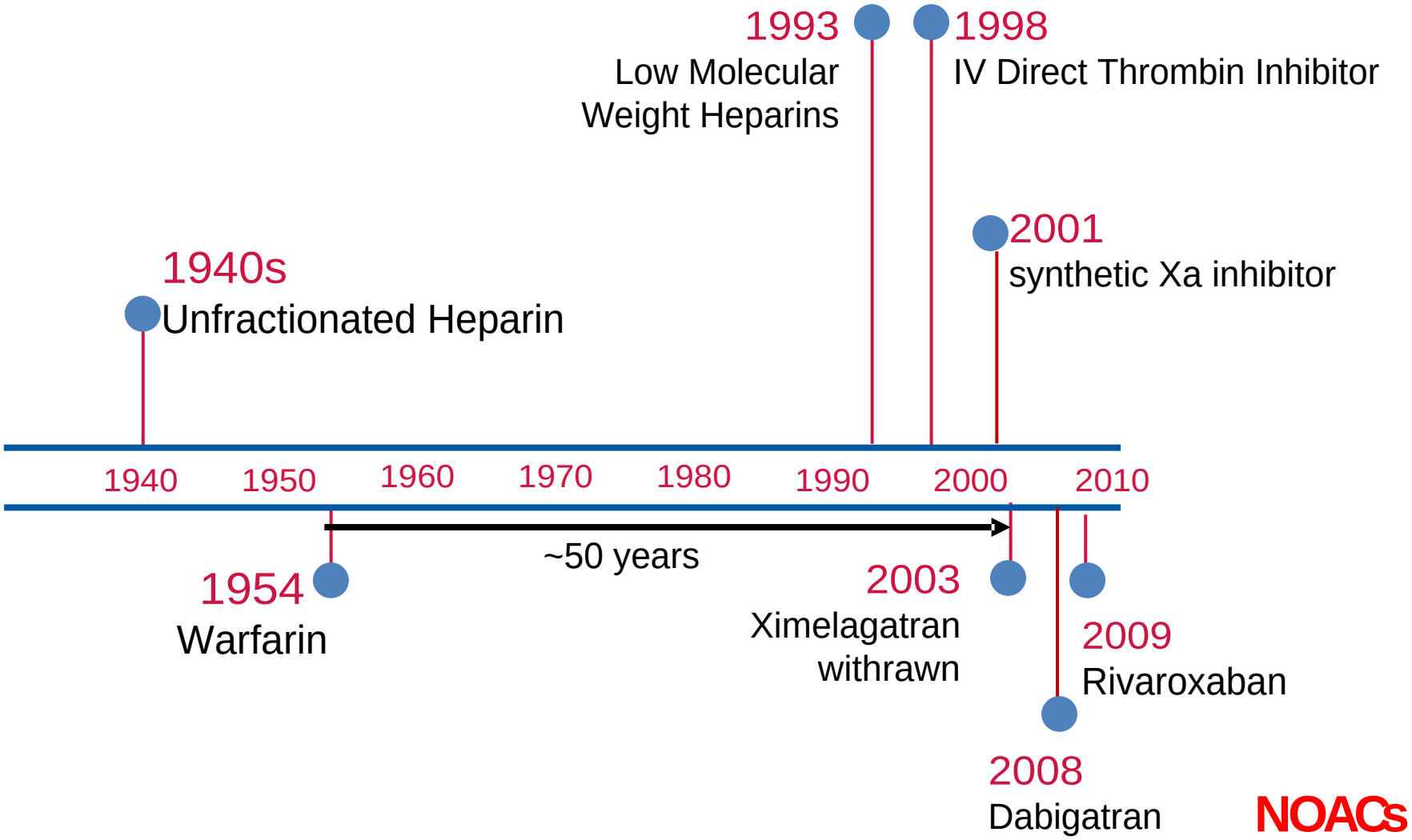
For patients taking warfarin, assess anticoagulation control every visit

Offer an alternative anticoagulant if;

- TTR<65%
- INR>8; INR>5 x 2
- INR<1.5 x 2

Informed discussion with patient about risks/ advantages of DOAC cf. warfarin

Evolution of Anticoagulant Therapy



Characteristics of the ideal anticoagulant

- Effective
- Oral administration
- Rapid onset and offset of action
- Wide therapeutic window
- Predictable response
  - fixed/weight-adjusted dose
  - well defined pharmacokinetics in renal or hepatic impairment
  - no monitoring required
- No food or drug interactions
- Cheap
- Effective antidote available

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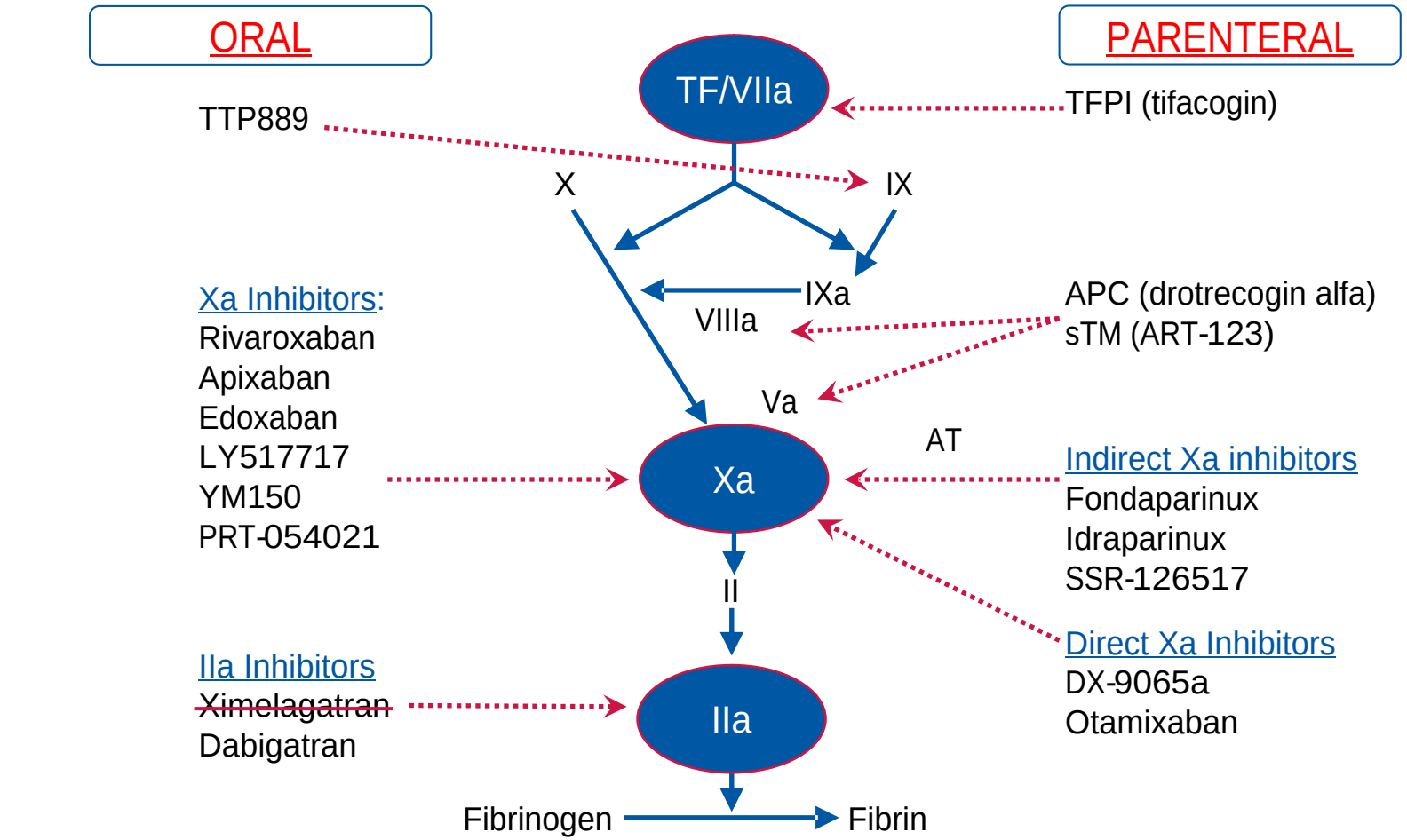
Targets of Direct Anticoagulant Agents



TF=tissue factor

Adapted from Weitz JI et al. *J Thromb Haemost.* 2005;3:1843-1853.

Targets of Direct Anticoagulant Agents

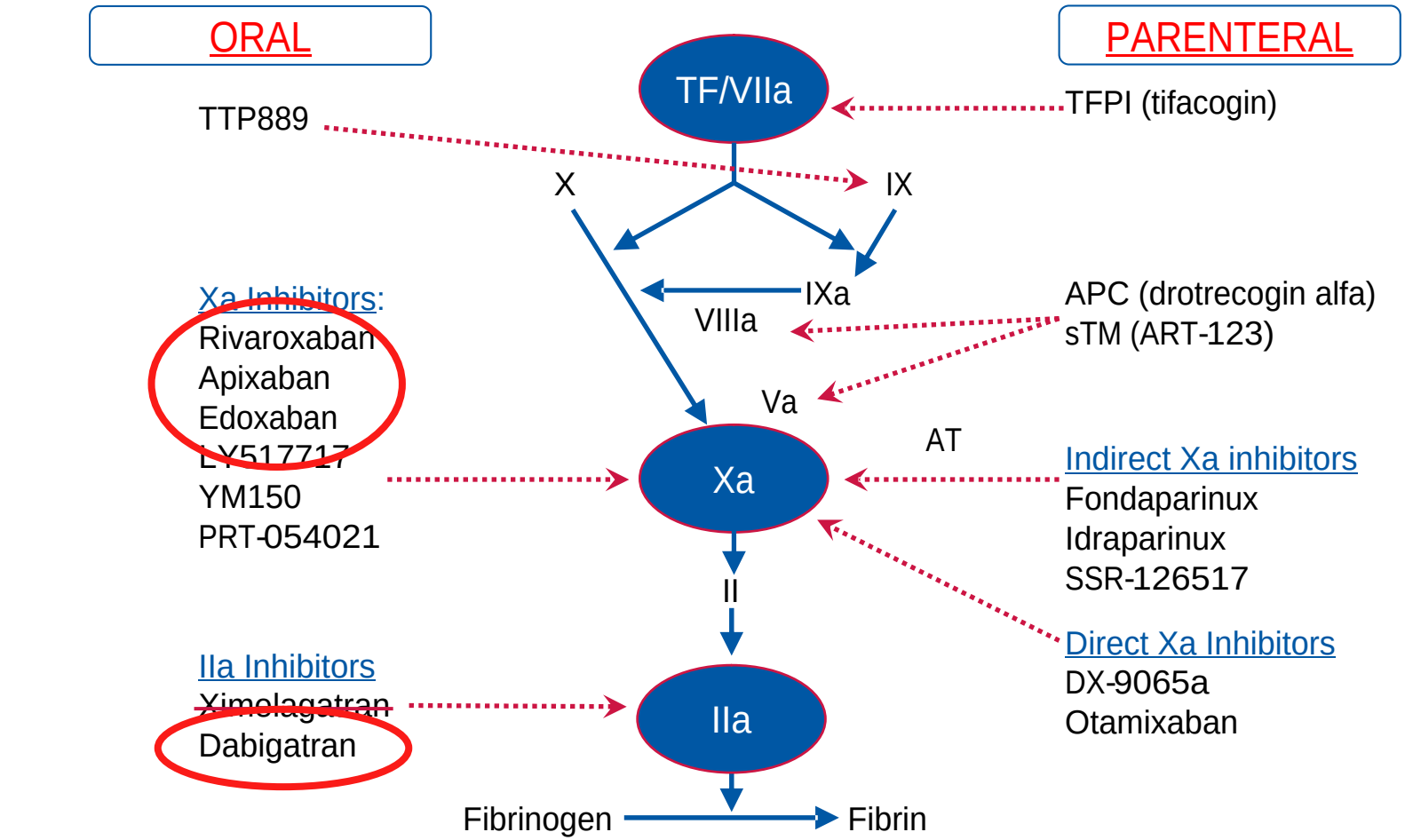


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Table 1: NOACs: Overview and Pharmacology[21,24-26]

	Apixaban[21,24]	Dabigatran[21,25]	Rivaroxaban[21,26]
Drug class	Direct factor Xa inhibitor	Direct factor IIa inhibitor	Direct factor Xa inhibitor
Bioavailability	50%	3%–7%	80%–100% for 10-mg dose 66% for 20-mg dose
Tmax	1–4 hr	1–3 hr	2–4 hr
CYP metabolism	15%–25% CYP3A4	No	30% CYP3A4, CYP2J2
Renal excretion	25%	80%	36%
Half-life	8–15 hr	12–17 hr	5–9 hr
Dosage form	Tablet	Capsule	Tablet
Dosing frequency	BID	BID	Once daily

Apixaban, dabigatran and rivaroxaban have a rapid onset and short half-life.

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Predictable dose-response relationship

➔ No monitoring required

Few drug interactions

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Dose reduction in renal impairment

	Normal renal function/mild renal impairment	Moderate renal impairment (CrCl 30-50ml/min)	Severe renal impairment (CrCl 15-30ml/min)	Hepatic impairment
Dabigatran	Standard dose	Dose ↓	Not recommended	Standard dose
Rivaroxaban	Standard dose	Dose ↓	Dose ↓	Not recommended
Apixaban	Standard dose	Standard dose	Dose ↓	Use with caution

Current licensed indications for DOACs

	Stroke prevention in AF	VTE prevention (THR/ TKR)	VTE treatment (DVT/ PE)
Dabigatran	□	□	□
Rivaroxaban	□	□	□
Apixaban	□	□	□

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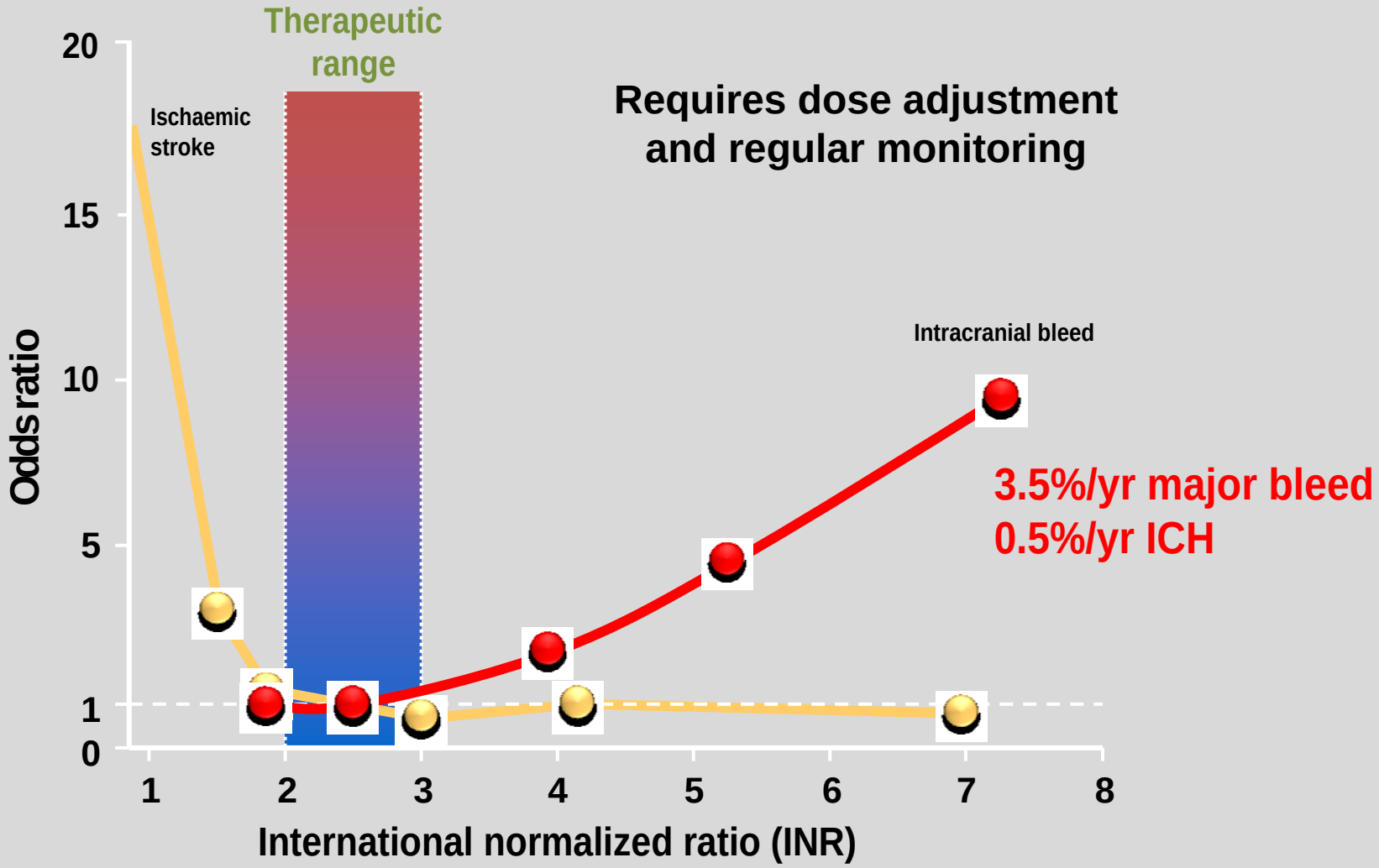
- Cheap
- Effective antidote available

and no bleeding...

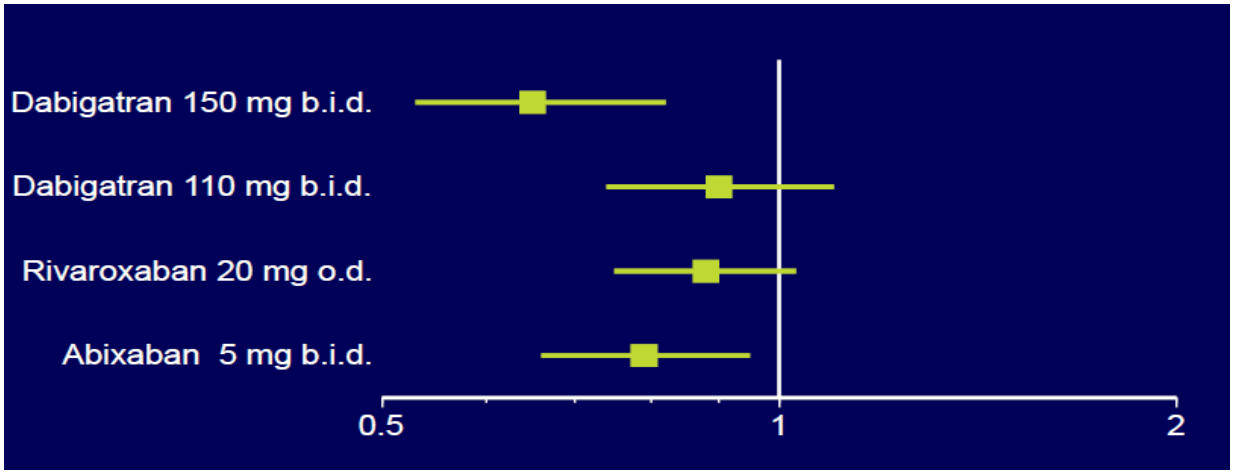
Warfarin and its challenging therapeutic window



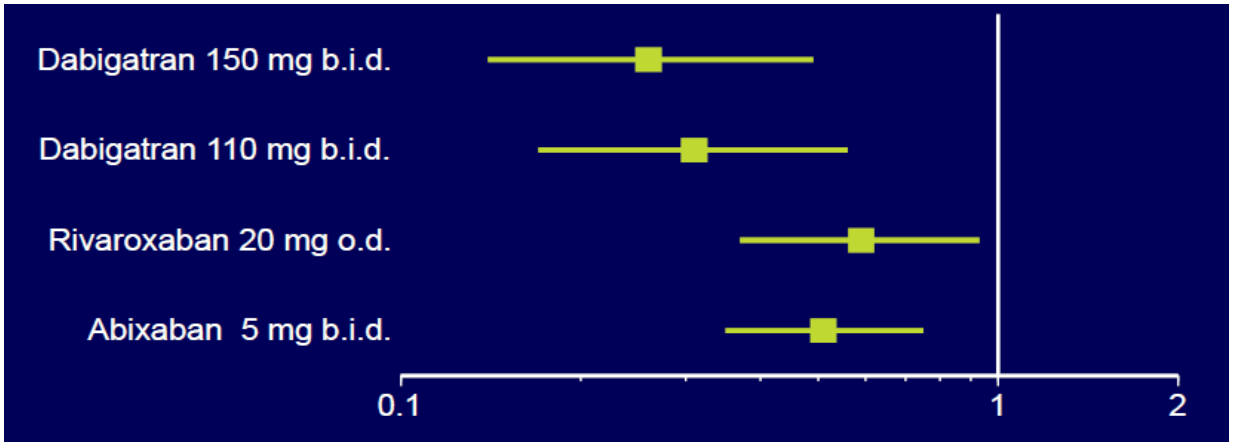
ACC/AHA/ESC guidelines: Fuster V *et al. Circulation* 2006;114:e257–e354.

DOACs vs warfarin for AF

STROKE AND SYSTEMIC EMBOLISM



HAEMORRHAGIC STROKE



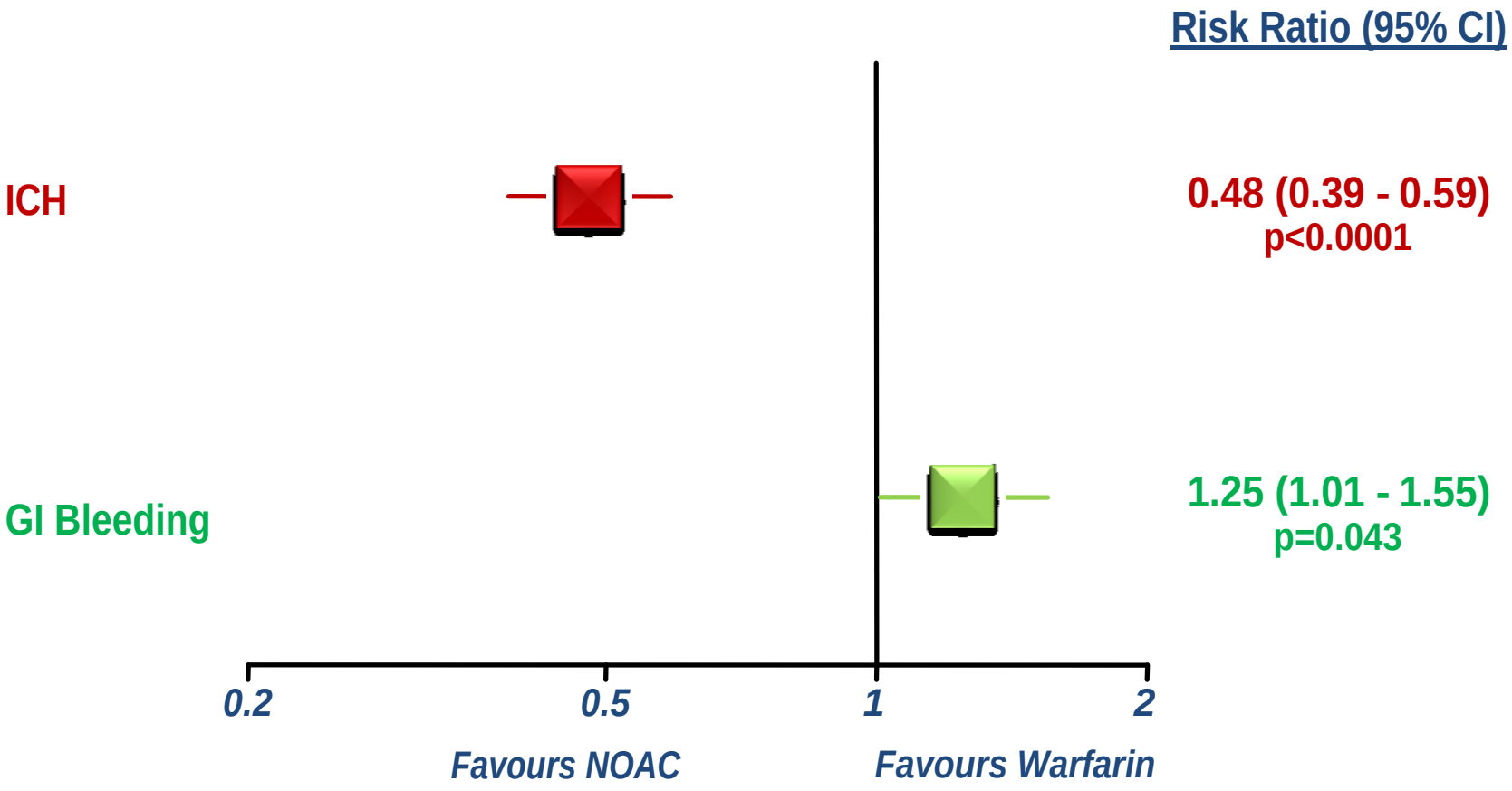
← Favours other treatment

Favours warfarin →

Dabigatran: Adverse events

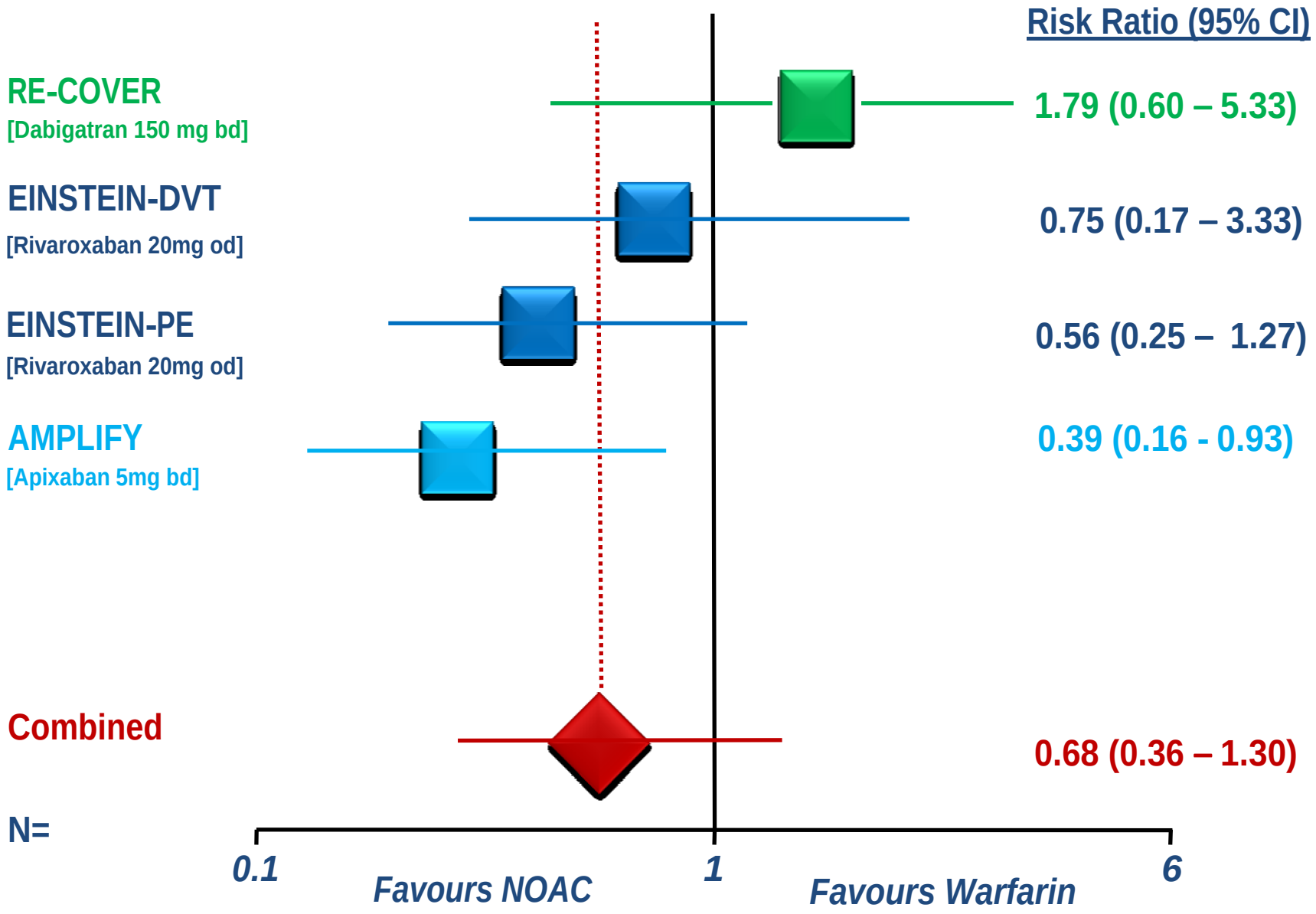
	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Any bleeding	14.74%	16.56%	18.37%
Dyspepsia*	11.8	11.3	5.8
Dyspnoea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral oedema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhoea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

DOACs vs warfarin for AF: Intracranial and GI Bleeding



Dentali F et al *Circulation*. 2012;126:2381-2391.

DOACs vs warfarin for VTE: GI Bleeding



J Thromb Haemost 2014; 12: 320–8.

blood

Prepublished online May 23, 2014;
doi:10.1182/blood-2014-03-563577

Rates, management and outcome of bleeding complications during rivaroxaban therapy in daily care: results from the Dresden NOAC registry

Jan Beyer-Westendorf, Kati Förster, Sven Pannach, Franziska Ebertz, Vera Gelbricht, Christoph Thieme, Franziska Michalski, Christina Köhler, Sebastian Werth, Kurtulus Sahin, Luise Tittl, Ulrike Hänsel and Norbert Weiss

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Atrial Fibrillation

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

Torben Bjerregaard Larsen, MD, PHD,*† Lars Hvilsted Rasmussen, MD, PHD,†
Flemming Skjøth, MSC, PHD,* Karen Margrete Due, MSC,* Torbjörn Callréus, MD, PHD,‡
Mary Rosenzweig, MSC,‡ Gregory Y. H. Lip, MD†§

Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA:
July 2011

Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events

Posted 12/07/2011

MHRA:
December 2011

Drug Safety Update

Latest advice for medicines users

Dabigatran (Pradaxa▼): risk of serious haemorrhage—need for renal function testing

Article date: December 2011

Summary

A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran. Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min)

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- No food or drug interactions
- Cheap
- Effective antidote available

Options for warfarin reversal

Rapid	10 mins	PCC
Fast (Partial)	1-2 hrs	FFP
Prompt	4-6 hrs	IV vitamin K
Slow	24 hrs	Oral vitamin K
Ultra-slow	2-4 days	Omit warfarin

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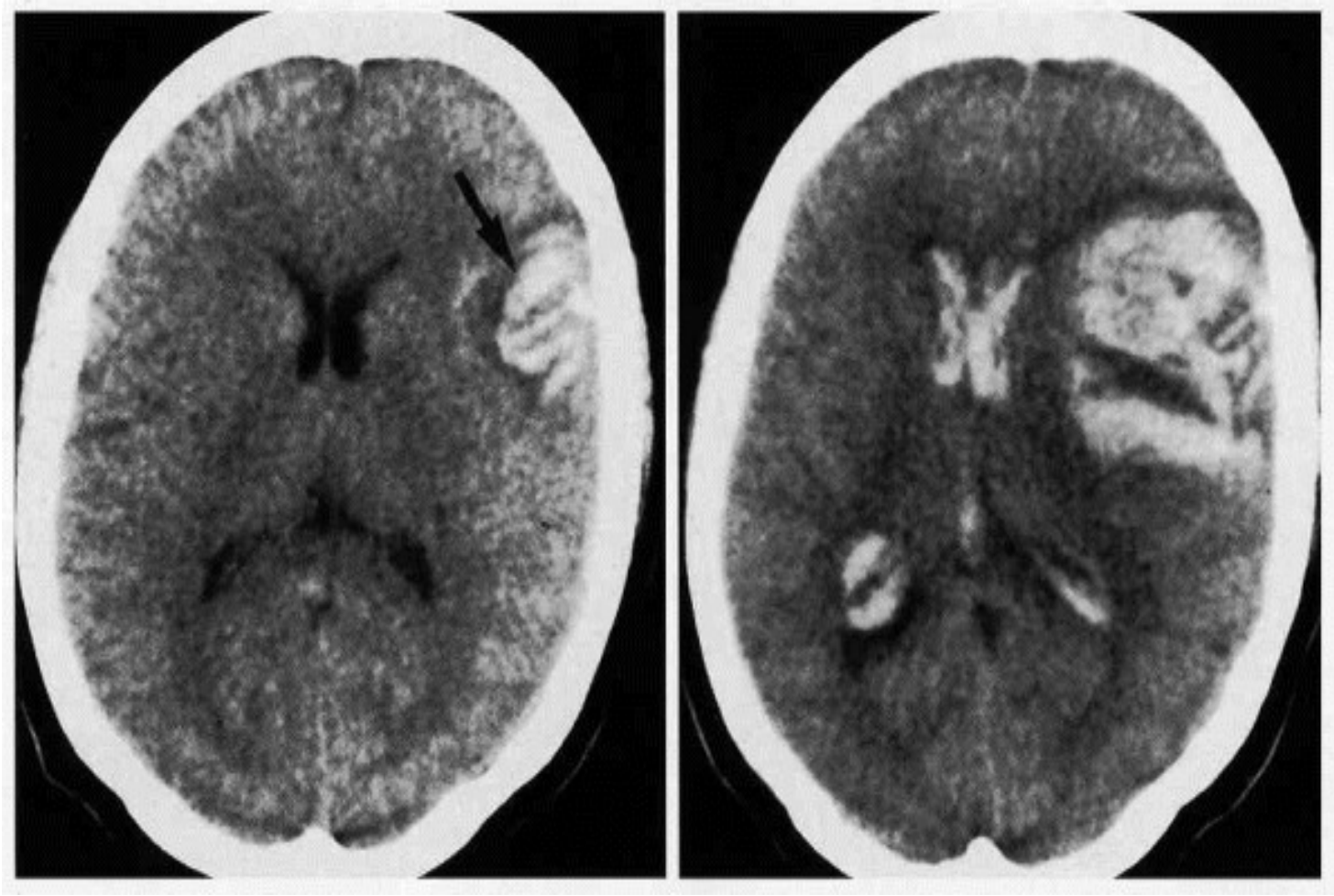
Anticoagulant-associated ICH: Is reversibility important?



Study	n	Lobar	Cerebellar	Mortality, %
Kase et al, 1985[21]	24	6	9 (37%)	63
Franke et al, 1990[15]	79	. . .	1 (1%)	67
Radberg et al, 1991[22]	28	12	4 (14%)	57
Forsting et al, 1991[16]	40	. . .	1 (3%)	50
Fredriksson et al, 1992[23]	29	6	1 (3%)	55
SPAF II Study, 1994[7]	9	3	2 (22%)	67
Staaf et al, 1987[24]	33	. . .	. . .	64
Fogelholm et al, 1992[20]	41	. . .	. . .	54
Hylek and Singer, 1994[13]	77	. . .	. . .	46
ASPECT Study, 1994[6]	17	. . .	. . .	47
Sixty-Plus Study, 1982[19]	4	. . .	. . .	75
Smith et al, 1990[5]	6	. . .	. . .	67
Wintzen et al, 1984[17]	38	. . .	. . .	68
Dawson et al, 1993[14]	18	. . .	. . .	56*
Landefeld and Goldman, 1989[2]	11	. . .	. . .	63*
Aggregate	454	30%	9%†	60%‡

SPAF indicates Stroke Prevention in Atrial Fibrillation; ASPECT, Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis.

*All sites of intracranial bleeds, including subarachnoid and subdural bleeding.

†Cerebellar hemorrhages constitute 5% to 10% of intracerebral hemorrhages in nonanticoagulated patients.

‡In nonanticoagulated patients, approximately 40% (range, 20% to 50%) of intracerebral hemorrhages and 15% of infarcts are fatal by 30 days.

Features of anticoagulant-associated ICH

- Rapid deterioration with first 24-48 hours, increasing ICH volume
- Poor outcome associated with:
  - ICH volume
  - Intraventricular extension of bleeding
- Majority of warfarin-related ICH occurs with INR 2-3.5
- Rapid reversal of anticoagulant effect essential:
  - To prevent haematoma expansion
  - To facilitate appropriate surgical intervention

Sjoblom et al. Stroke (2001), 32, 2567-2574
Management and prognostic features of ICH during anticoagulant therapy: A Swedish Multicenter Study

Reversibility of the DOACs using bypassing agents

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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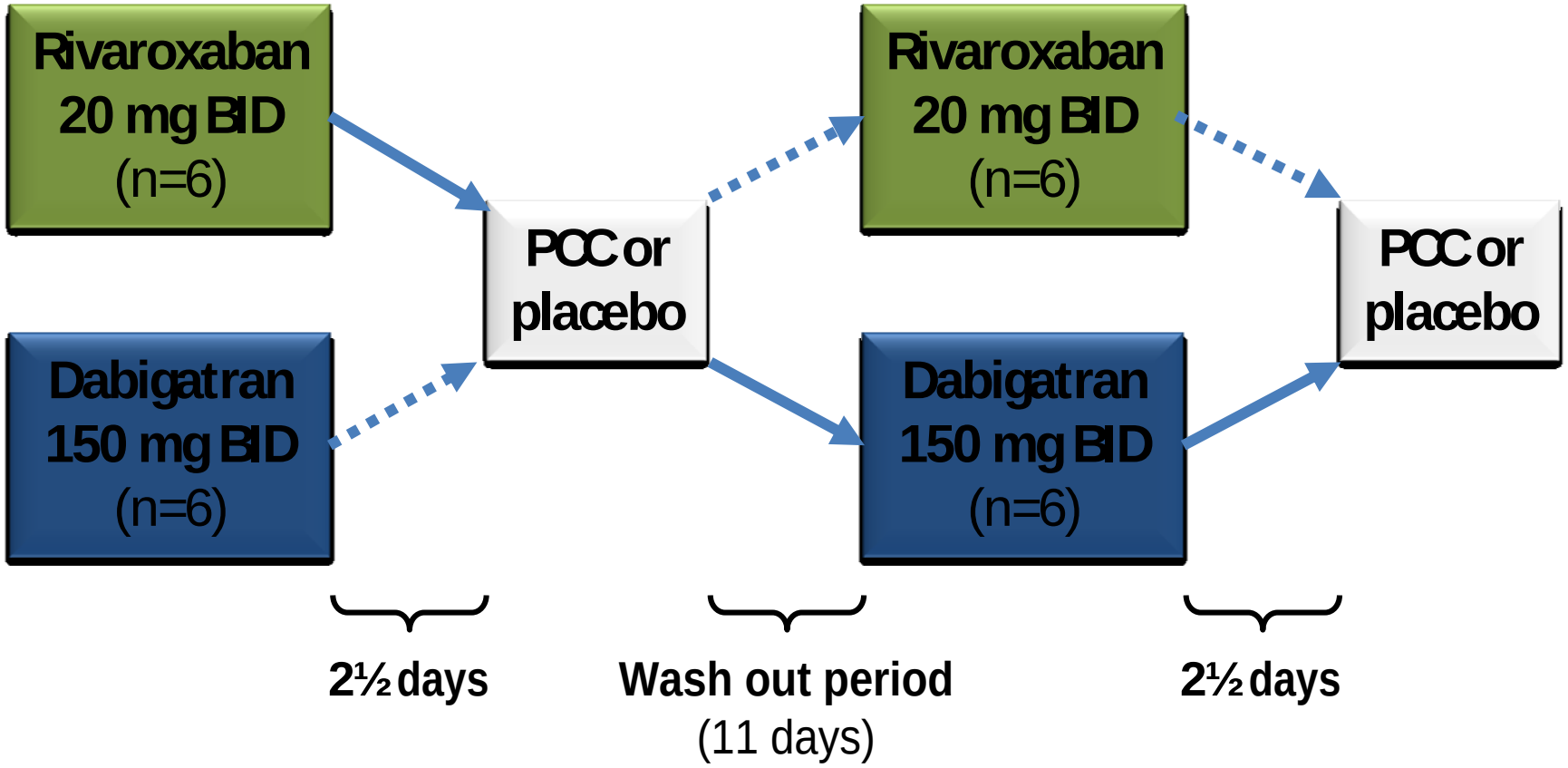
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation published online September 6, 2011
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

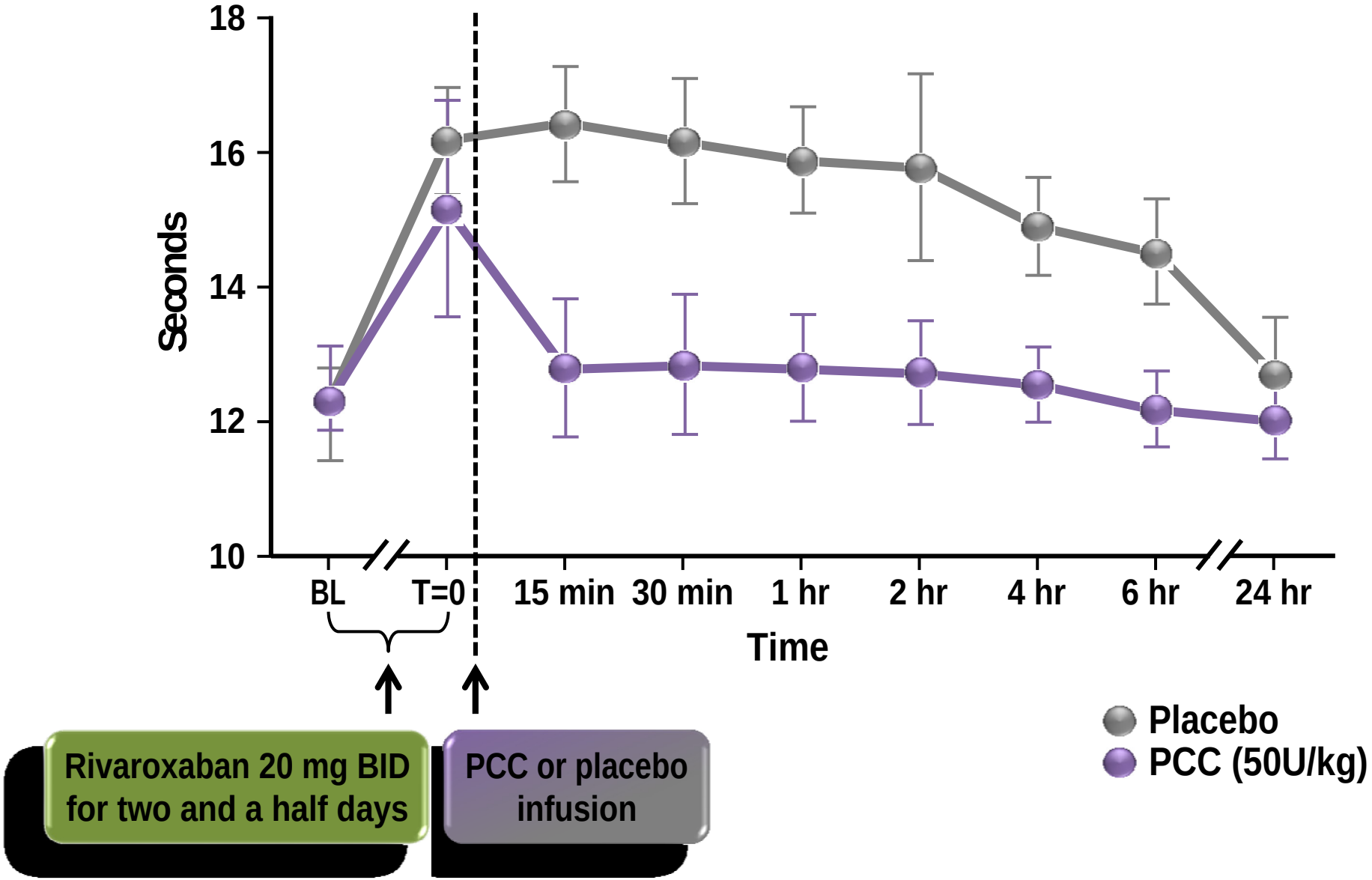
Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate

A randomized, double-blind, placebo-controlled, crossover trial with healthy male subjects (n=12)

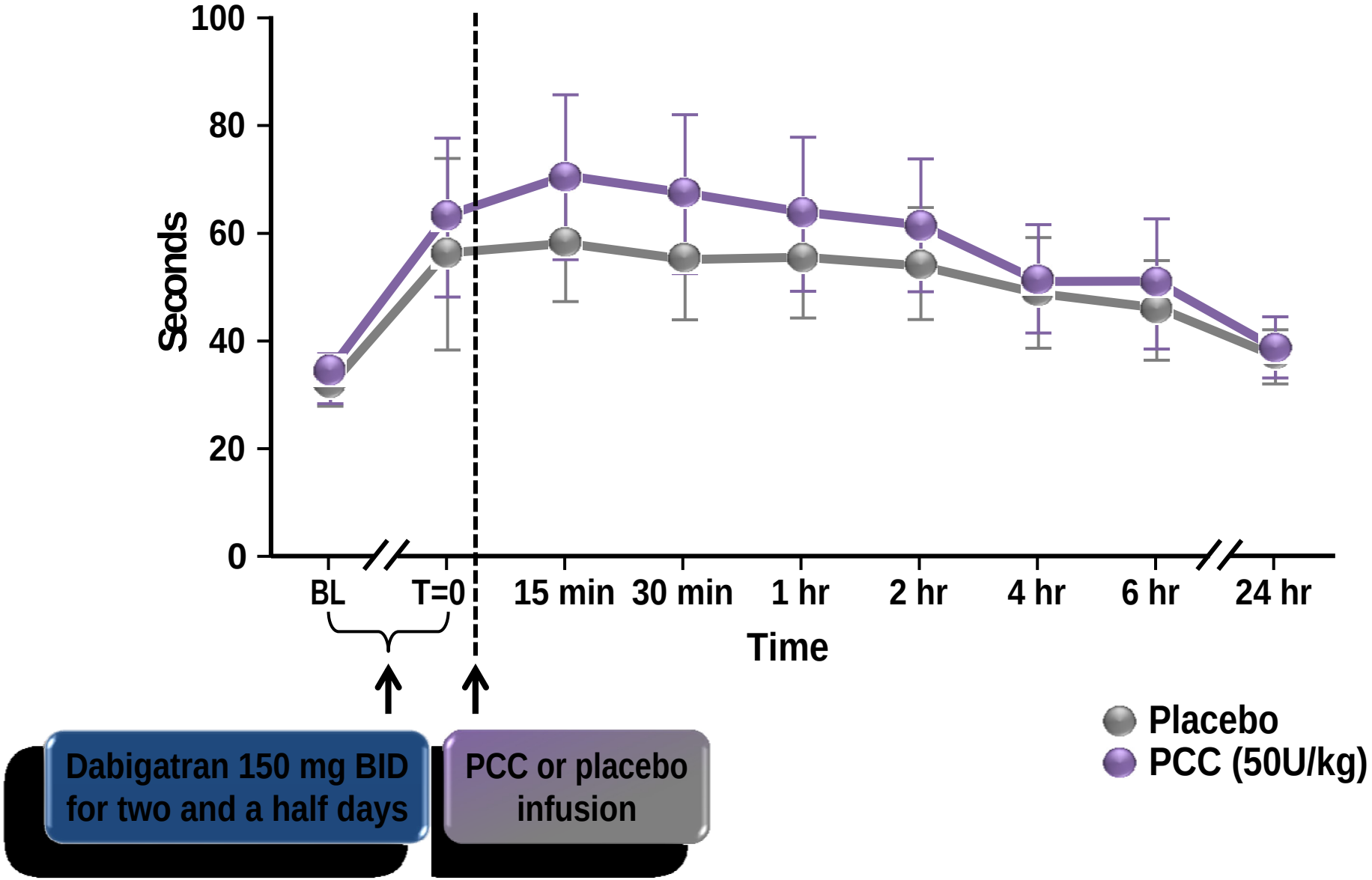


Eerenberg *et al. Circulation* 2011

Reversal of rivaroxaban monitored by PT

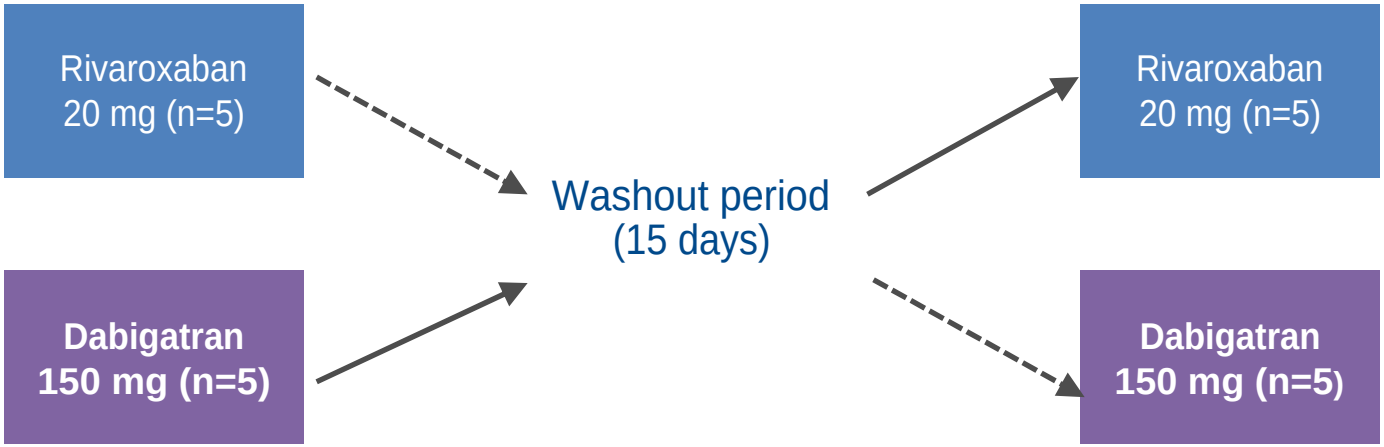


Reversal of dabigatran monitored by aPTT



Reversal of dabigatran and rivaroxaban activity by coagulation factor concentrates

- Randomized, crossover, *ex vivo* study in healthy male volunteers (n=10)
- Blood samples collected immediately before and 2 h after one dose of oral anticoagulant

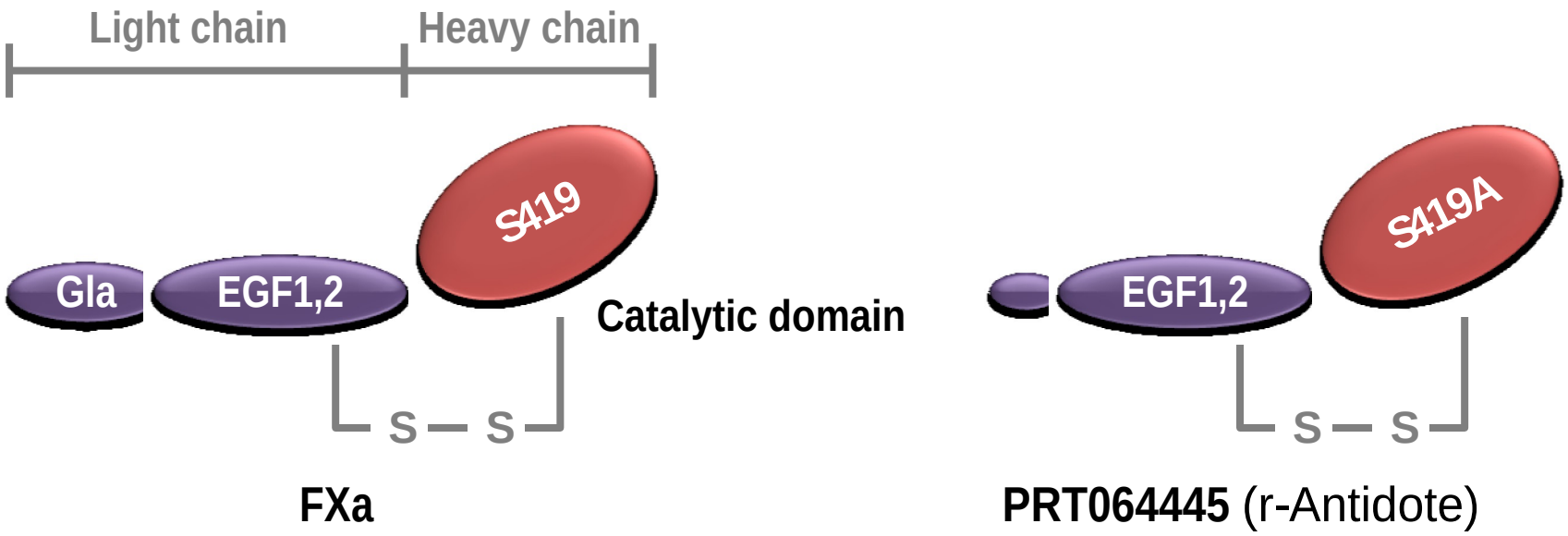


•Haemostatic agents tested *ex vivo*:

PCC (Kanokad: 0.25, 0.5, and 1 U/mL),
rFVIIa (NovoSeven: 0.5, 1.5, and 3 µg/mL),
Activated PCC (FEIBA: 0.25, 0.5, 1, and 2 U/mL)

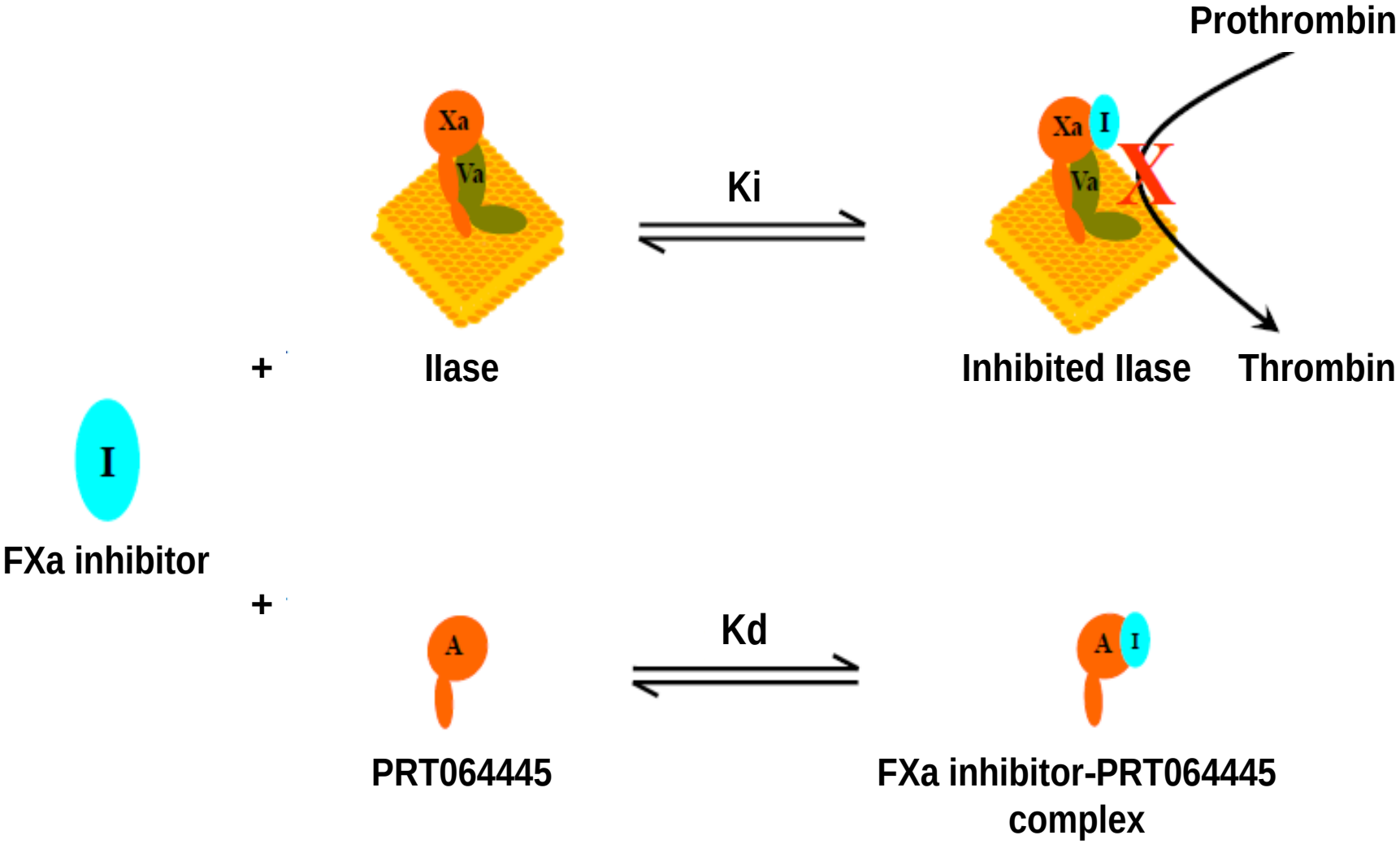
Marlu R et al. Thromb Haemost 2012;108:217–24

PRT064445: recombinant FXa variant

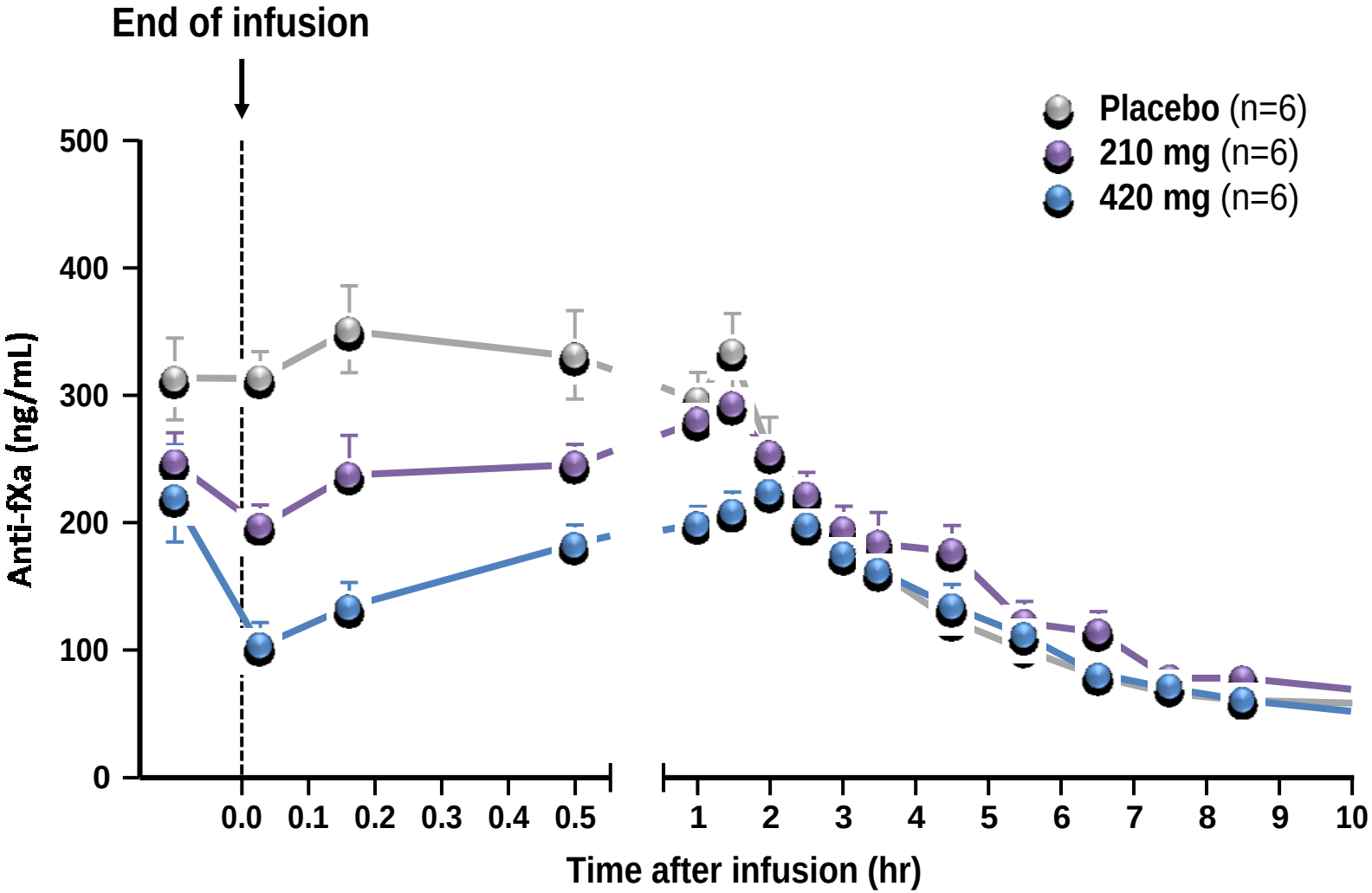


- Two modifications introduced to human fXa
  - Removal of the Gla-domain
  - Mutation at the active site (S419A)
- PRT064445 (r-Antidote)
  - No pro- or anti-coagulant activity
  - Retains binding ability for FXa inhibitors

Mechanism for reversal of oral FXa inhibitor by PRT064445



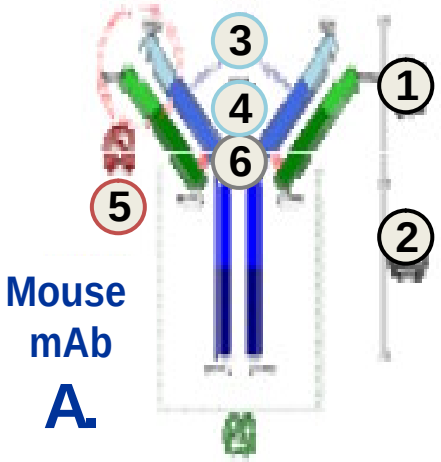
Andexanet Alfa (PRT064445): Phase 2 rivaroxaban induced anticoagulation in healthy subjects



Crowther M. Oral presentation American Society Hematology , New Orleans, Dec 2013

From mouse monoclonal antibody to human antibody fragment (Fab)

A. Monoclonal antibodies were raised in mice immunised with dabigatran hapten coupled to carrier proteins

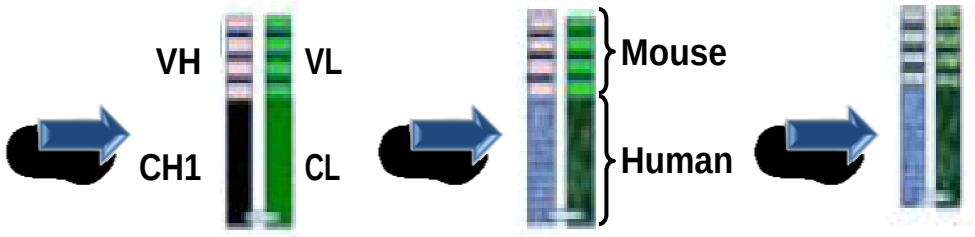


1. Fab
2. Fc
3. Heavy chain (blue)
4. Light chain (green)
5. Antigen binding site
6. Hinge regions

B. Fc portion is removed (Fab)

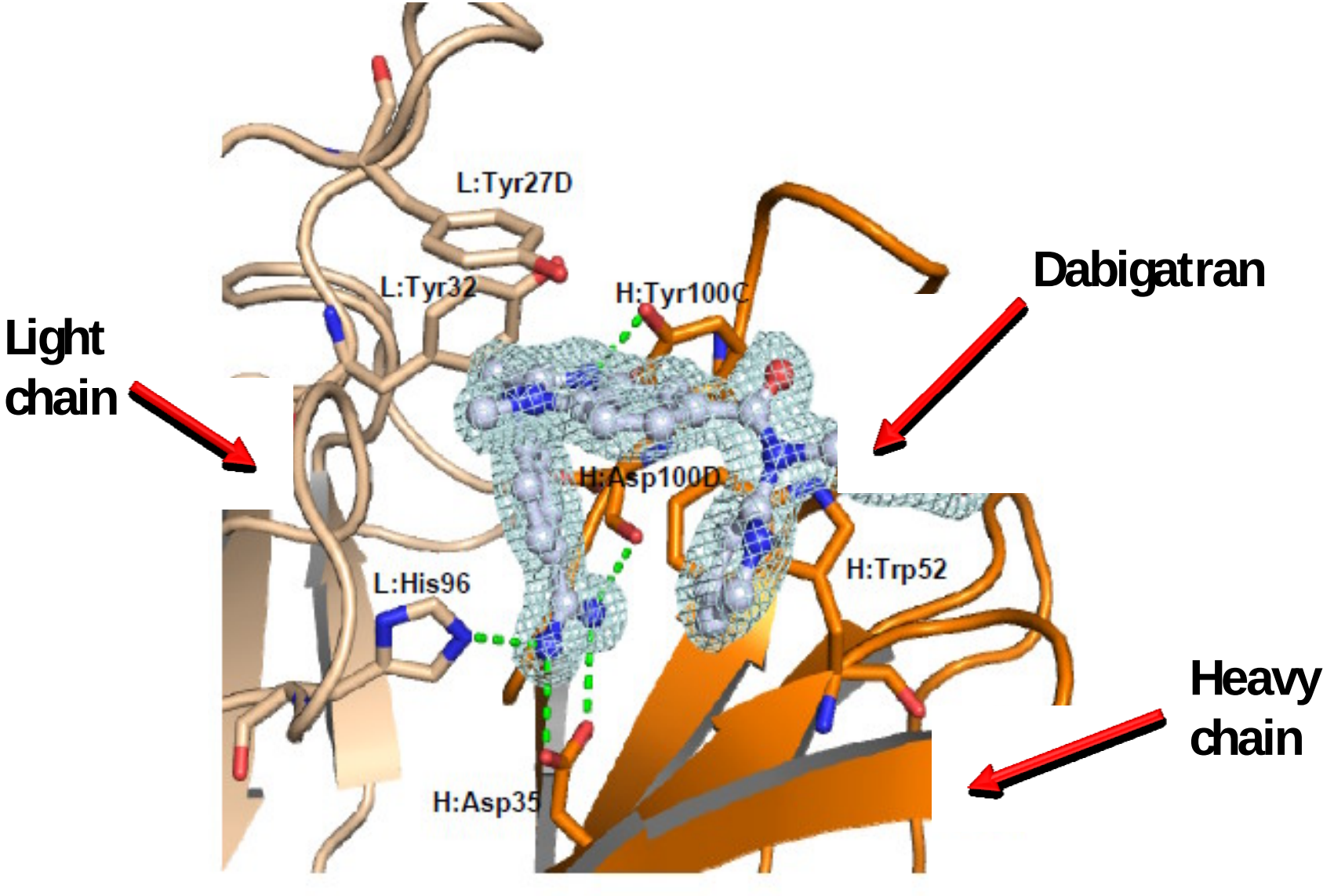
C. Constant regions are replaced with human amino acids (chimeric)

D. Variable regions of Fab humanised



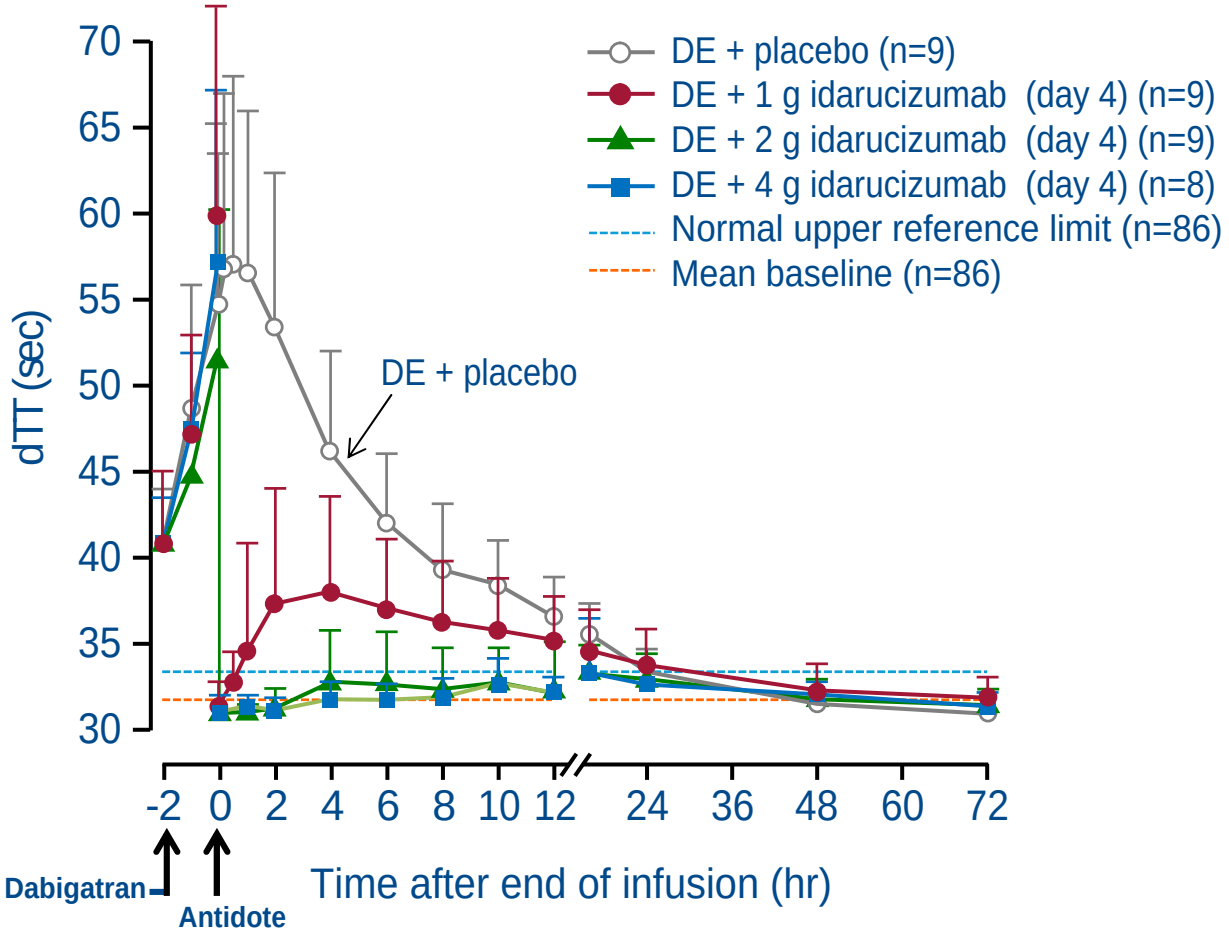
Blood -prepublished online March 8, 2013; DOI 10.1182/blood-2012-11-468207

Dabigatran antidote



Blood -prepublished online March 8, 2013; DOI 10.1182/blood-2012-11-468207

Idarucizumab showed immediate, complete and sustained reversal of dabigatran anticoagulation



DE = dabigatran etexilate

'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

Disclaimer: idarucizumab is not currently licensed for use

DOACs: Management of bleeding or urgent surgery

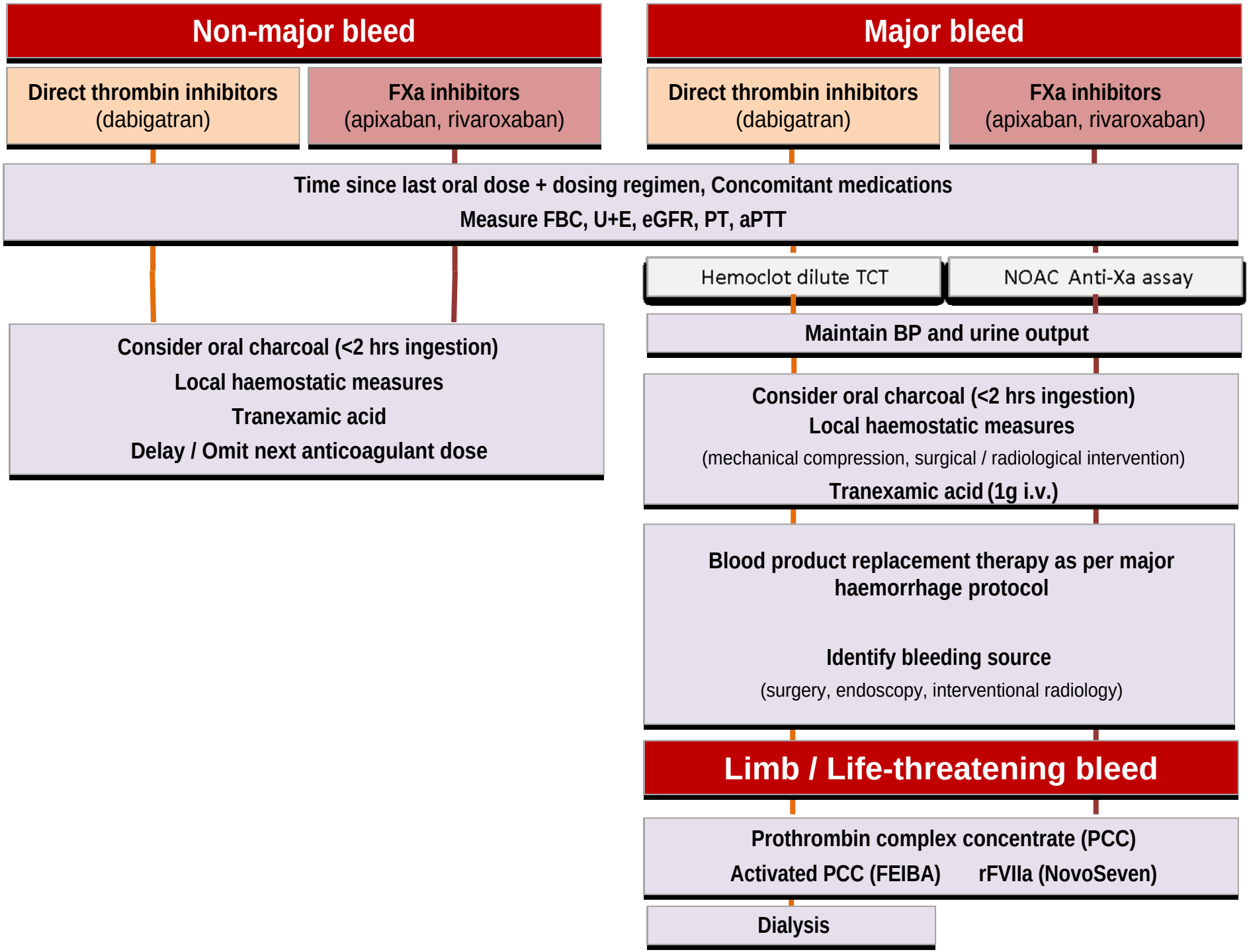
- **General measures:**
  - Stop the drug
  - Document timing of last dose, estimate elimination half-life
  - Check FBC, coagulation screen, creatinine/eGFR, G+S
  - Correct haemodynamic compromise
  - Defer surgery if able
  - Control haemorrhage:
    - Mechanical compression
    - Surgical/radiological intervention

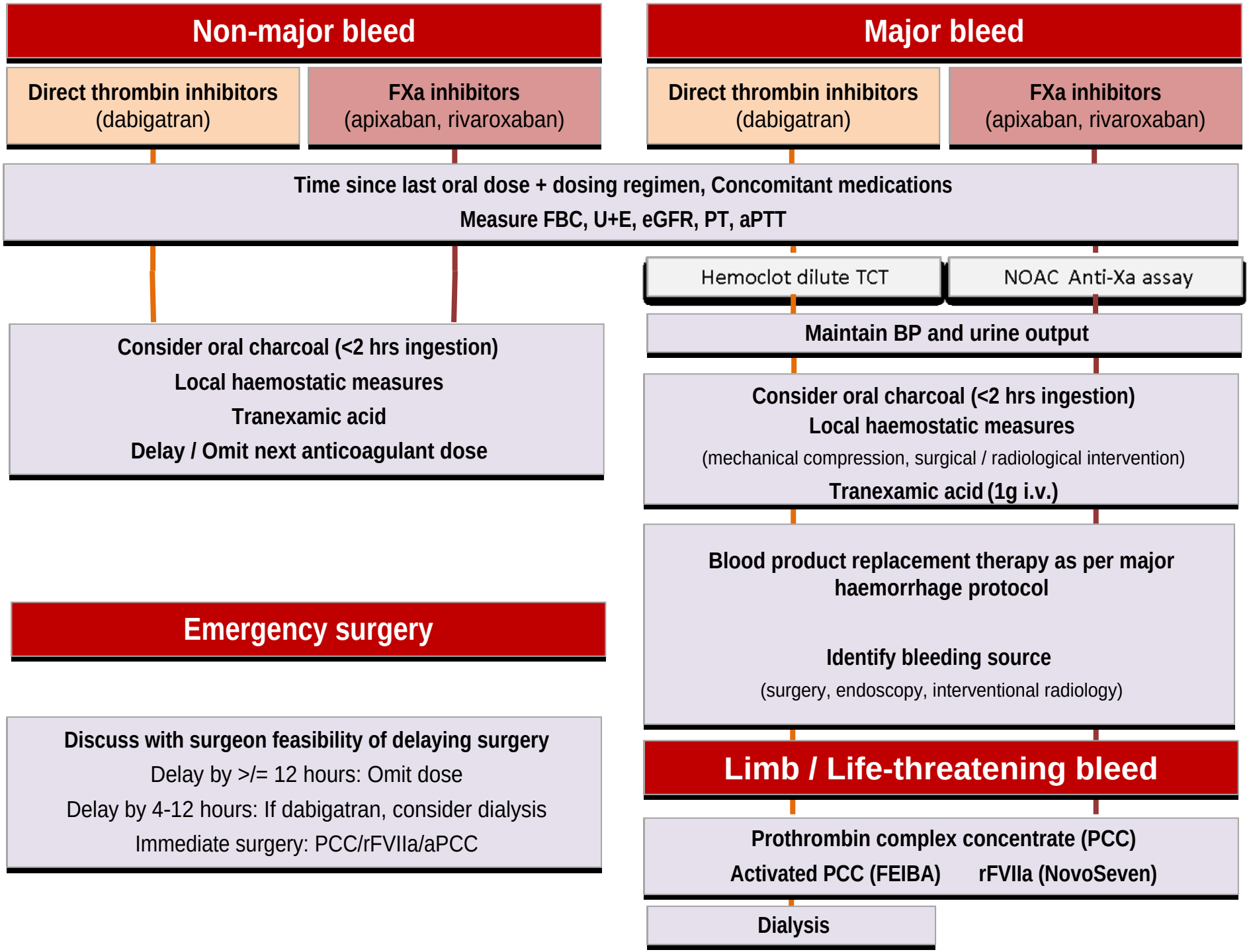
DOACs: Management of bleeding or urgent surgery

- **Specific measures:**
  - Dabigatran
    - Oral activated charcoal if last dose <2 hours previously
    - Consider haemodialysis/haemofiltration (≈60% removed within 2 hours)- guided by normalisation of APTT (although caution re rebound increases in Dabigatran concentration)
  - Rivaroxaban/Apixaban
    - Oral activated charcoal if last dose <2 hours previously
    - Haemodialysis/haemofiltration unhelpful- 95% protein bound

DOACs: Management of bleeding or urgent surgery

- **Pharmacological measures:**
  - Antifibrinolytics- Tranexamic acid, oral/ IV/ topical
  - PCC: Rivaroxaban/ Apixaban, ?not Dabigatran
  - rFVIIa
  - aPCC (FEIBA)


Non-major bleed
Major bleed
Direct thrombin inhibitors (dabigatran)
FXa inhibitors (apixaban, rivaroxaban)
Direct thrombin inhibitors (dabigatran)
FXa inhibitors (apixaban, rivaroxaban)
Time since last oral dose + dosing regimen, Concomitant medications
Measure FBC, U+E, eGFR, PT, aPTT
Hemoclot dilute TCT
NOAC Anti-Xa assay
Consider oral charcoal (<2 hrs ingestion)
Local haemostatic measures
Tranexamic acid
Delay / Omit next anticoagulant dose
Maintain BP and urine output
Consider oral charcoal (<2 hrs ingestion)
Local haemostatic measures
(mechanical compression, surgical / radiological intervention)
Tranexamic acid (1g i.v.)
Blood product replacement therapy as per major haemorrhage protocol
Identify bleeding source
(surgery, endoscopy, interventional radiology)
Limb / Life-threatening bleed
Prothrombin complex concentrate (PCC)
Activated PCC (FEIBA) rFVIIa (NovoSeven)
Dialysis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Measure FBC, U+E, eGFR, PT, aPTT
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Local haemostatic measures
Tranexamic acid
Delay / Omit next anticoagulant dose
Maintain BP and urine output
Consider oral charcoal (<2 hrs ingestion)
Local haemostatic measures
(mechanical compression, surgical / radiological intervention)
Tranexamic acid (1g i.v.)
Blood product replacement therapy as per major haemorrhage protocol
Identify bleeding source
(surgery, endoscopy, interventional radiology)
Emergency surgery
Limb / Life-threatening bleed
Discuss with surgeon feasibility of delaying surgery
Delay by >/= 12 hours: Omit dose
Delay by 4-12 hours: If dabigatran, consider dialysis
Immediate surgery: PCC/rFVIIa/aPCC
Prothrombin complex concentrate (PCC)
Activated PCC (FEIBA)
rFVIIa (NovoSeven)
Dialysis

bjh guideline

Guideline on the management of bleeding in patients on antithrombotic agents

Mike Makris,[1,2] Joost J. Van Veen,[2] Campbell R. Tait,[3] Andrew D. Mumford[4] and Mike Laffan[5] on behalf of the British Committee for Standards in Haematology

[1]Department of Cardiovascular Science, University of Sheffield, Sheffield, [2]Sheffield Haemophilia and Thrombosis Centre, Sheffield Teaching Hospitals NHS Trust, Sheffield, [3]Department of Haematology, Glasgow Royal Infirmary, Glasgow, [4]Bristol Heart Institute, Bristol Royal Infirmary, University of Bristol, Bristol, and [5]Imperial College Academic Health Sciences Centre, Hammersmith Hospital, London, UK

- *There is no specific antidote for dabigatran…general measures…activated charcoal…haemodialysis if rapidly deployable…In situations with ongoing life-threatening bleeding PCC, APCC and rFVIIa should be considered*

- *There is no specific antidote for rivaroxaban…general measures…In situations with ongoing life-threatening bleeding PCC, APCC and rFVIIa*

Oral Anticoagulant agent-associated bleeding (ORANGE) Study

ORANGE study

Oral anticoagulant agent-associated bleeding events reporting system

This hospital is participating in the ORANGE study, a multicentre UK study led by *Barts Health NHS Trust*. The study aims to collect data on the management and outcomes of patients who develop major bleeding whilst on any of the following oral anticoagulant agents – **WARFARIN, DABIGATRAN, RIVAROXABAN, APIXABAN, EDOXABAN and SINTHROME**. The study is ongoing and will run until *31 December 2016*.

Major bleeding is defined as bleeding which requires *hospitalisation* **AND** results in one of the following:

a) Death
b) Transfusion of ≥2 units of red blood cells and/or a drop in Hb of ≥ 2g/dL
c) Transfusion of fresh frozen plasma
d) Administration of PCC, rVIIa, FEIBA or Fibrinogen concentrate (FgC)
e) Symptomatic bleeding in a critical area such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome.

- Retrospective data collection
- Case identification
- No follow up
- No patient consent required

tina.biss@nuth.nhs.uk