The Emerging use of Novel Oral Anticoagulants: Essentials for the Family Physician

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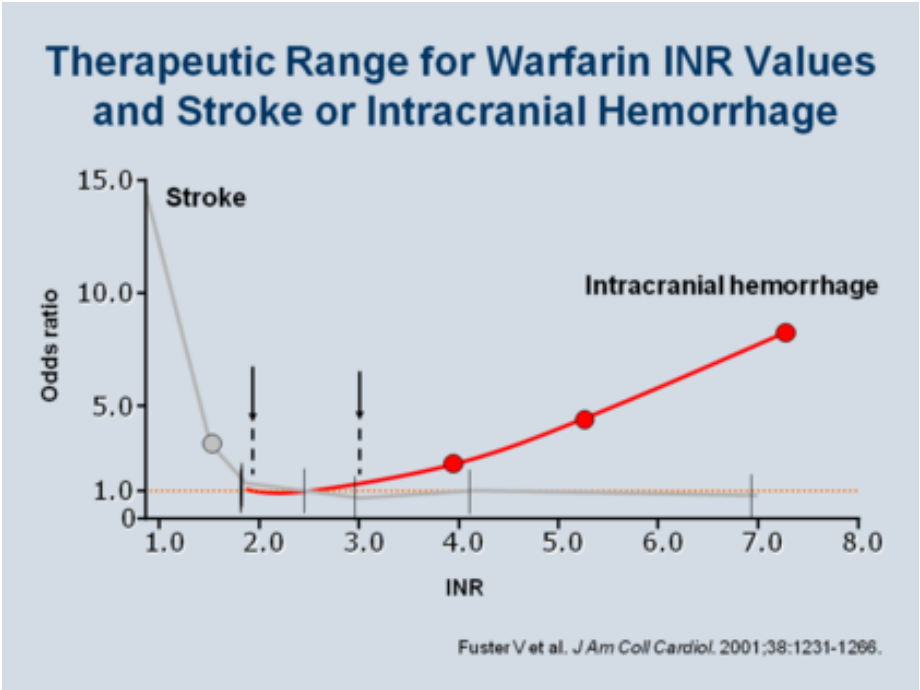
Relevant Disclosures

Educational and Travel Grants	Bayer, Leo, Pfizer
Advisory Boards	Bayer, BMS, Boehringer-Ingelheim, Pfizer, Leo, Covidien
Factor Xa and IIa Inhibitor Clinical Trials – Study Management Committee or Investigator:	VTE Prevention: apixaban (BMS), rivaroxaban (Pfizer) VTE Therapy: apixaban (Pfizer), rivaroxaban (Bayer), edoxaban (Daiichi-Sankyo), dabigatran (Boeringher Ingelheim)
Stocks and Shares	Nil

Oral Anticoagulation

Warfarin -Only approved drug for 60 years

NO RCT



Narrow therapeutic window

Time to reach therapeutic range unpredictable

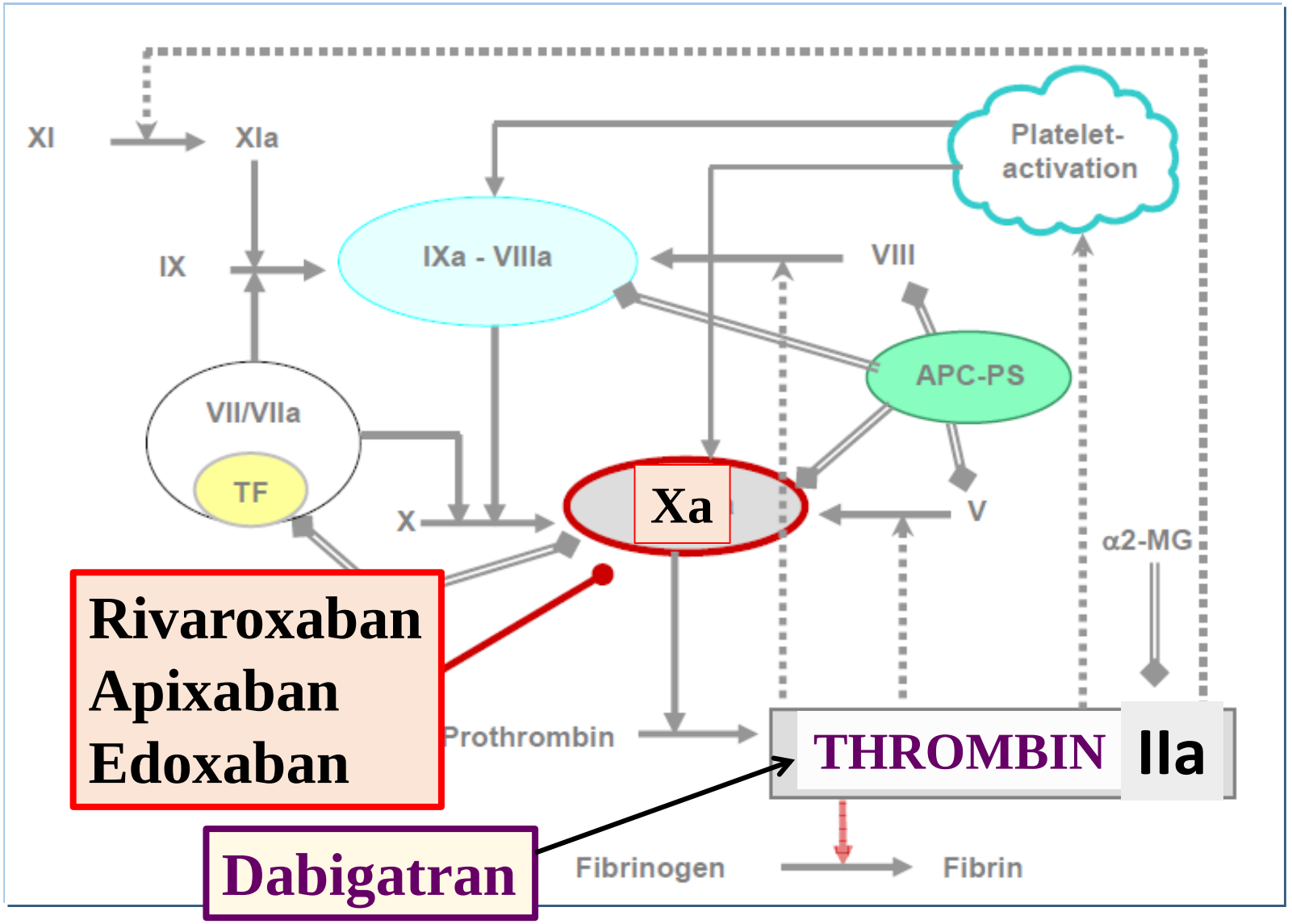
Numerous Factors affecting Maintenance Dosing of Warfarin

Needs close monitoring and dose adjustments

Ideal Anticoagulant

- Oral administration
- Good Efficacy and Safety
- Metabolic Properties with No food and drug interaction
- No need for coagulation monitoring
- Reversal Agent / Antidote available

Non Vitamin K antagonist Oral Anticoagulants



NOACs –
New or Novel
oral anticoagulants

DOACs –
Direct
oral anticoagulants

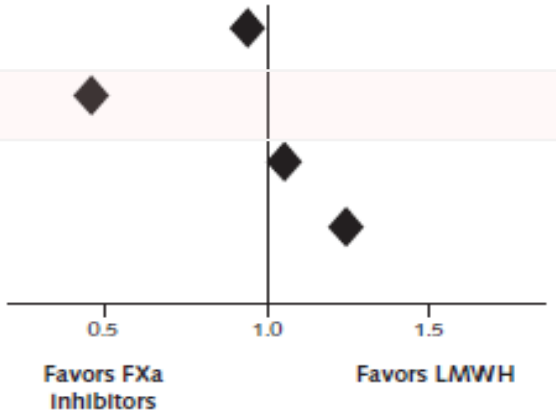
VTE prevention in orthorpaedic surgeries

Drug	Study	Enoxaparin	Efficacy (%)	Bleeding
Apixaban 2.5 mg bd	Advance 1, TKR	30 mg bd	9.0 vs. 8.9 Not non-Inferior	Less in Apixaban
Apixaban 2.5 mg bd	Advance 2, TKR	40 mg od	15 vs 24 P<0.0001	4 vs 5 P=0.09
Rivaroxaban 10 mg od	Records1 THR Record 2 THR Record 3 TKR	40 mg od	Pooled data 0.8 vs 1.6 p<0.001	Pooled data Records 1-4 0.4 vs 0.3 ns
Rivaroxaban 10 mg od	Record 4 TKR	30 mg bd	6.9 vs 10.1 p =0.012	10.5 vs 9.4 ns
Dabigatran 220 mg od	Re-model TKR	40 mg od	2.6 vs 3.5	10 vs 9
Dabigatran 220 mg od	Re-Mobilise TKR	30 mg bd	3.4 vs 2.5	5 vs 12
Dabigatran 220 mg od	Re-novate THR	40 mg od	3.1 vs 3.9	23 vs 18
Dabigatran 220 mg od	Pooled	40-60 mg od	3.0 vs 3.3	38 vs 39
Edoxaban 30 mg od	Stars J5 THR	20 mg od	2.4 vs 6.9 p<0.001	2.6 vs3.7%
Edoxaban 30 mg od	Stars E3 TKR	20 mg od	7.4 vs13.9 P<0.00	6.2 vs 3.7

NOACs vs standard prophylaxis in THR and TKR

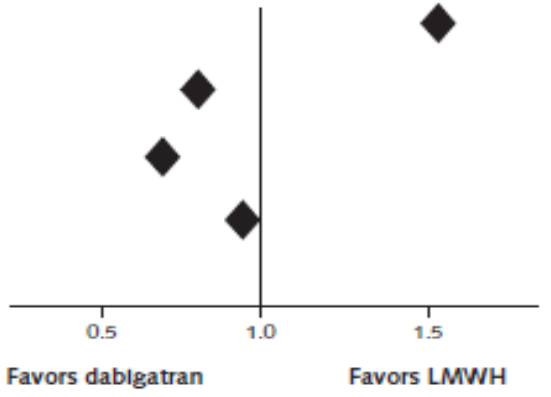
FXa Inhibitors vs. LMWH*

Variable	Total Studies (Patients), *n* (*n*)	Events/Total, *n*/*N* FXa Inhibitors	Events/Total, *n*/*N* LMWH	OR (95% CI)
Mortality†	10 (22 838)	31/12 384	26/10 454	0.95 (0.55–1.63)
Symptomatic DVT	12 (22 877)	41/12 993	57/9884	0.46 (0.3–0.7)
Nonfatal PE	20 (26 998)	44/15 187	29/11 811	1.07 (0.65–1.73)
Major bleeding	21 (31 424)	192/18 307	86/13 117	1.27 (0.98–1.65)



Dabigatran vs. LMWH‡

Variable	Total Studies (Patients), *n* (*n*)	Events/Total, *n*/*N* Dabigatran	Events/Total, *n*/*N* LMWH	RR (95% CI)
Mortality	4 (10 264)	10/6508	2/3756	1.54 (0.38–6.33)
Symptomatic DVT	4 (10 264)	34/6508	18/3756	0.82 (0.17–3.99)
Nonfatal PE	4 (10 264)	14/6508	11/3756	0.69 (0.31–1.54)
Major bleeding	4 (10 264)	81/6508	48/3756	0.94 (0.58–1.52)



These DOACs have never been compared directly with each other

Ann Intern Med. 2013;159:275-284.

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%									47%	35%	33%
3–6	33%									53%	48%	50%
Previous stroke or TIA*	20%									28%	29%	30%
Heart failure†	32%									58%	46%	47%
Diabetes	23%									26%	31%	31%
Hypertension	79%									94%	88%	88%
Prior myocardial infarction	17%									12%	15%	15%
Creatinine clearance‡												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8	2·2	2·2
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)	NA	65 (51–76)

42 411 participants NOACs

vs

29 272 warfarin

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. CHADS$_2$=stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction <40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used VKAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. ¶IQRs not available.

Lancet 2014;383:955-62

Table: **Baseline characteristics of the intention-to-treat populations of the included trials**

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%

Lancet 2014;383:955-62

NOACs for prevention in stroke and arterial emboli in AF

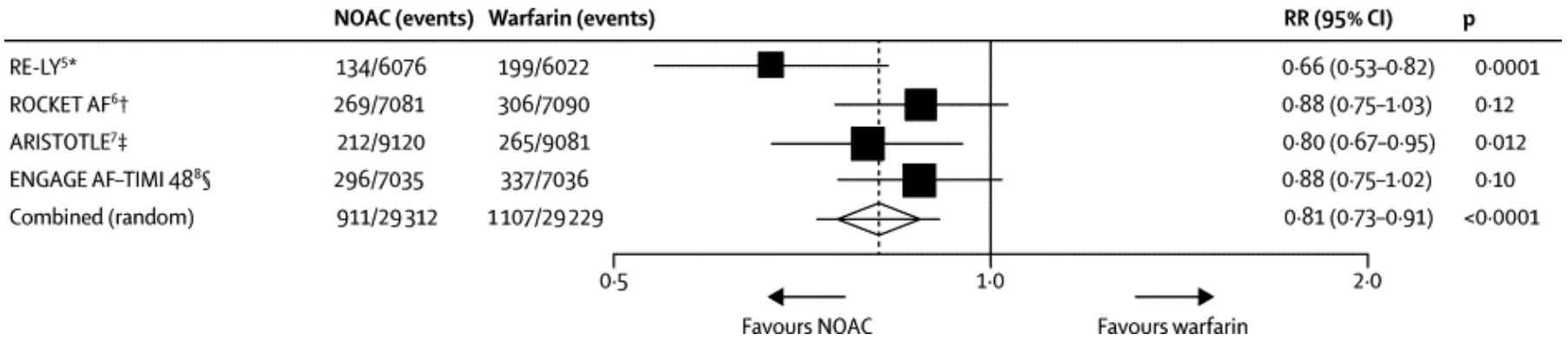


Figure 1. Stroke or systemic embolic eventsData are n/N, unless otherwise indicated. Heterogeneity: I2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban...

These DOACs have never been compared directly with each other

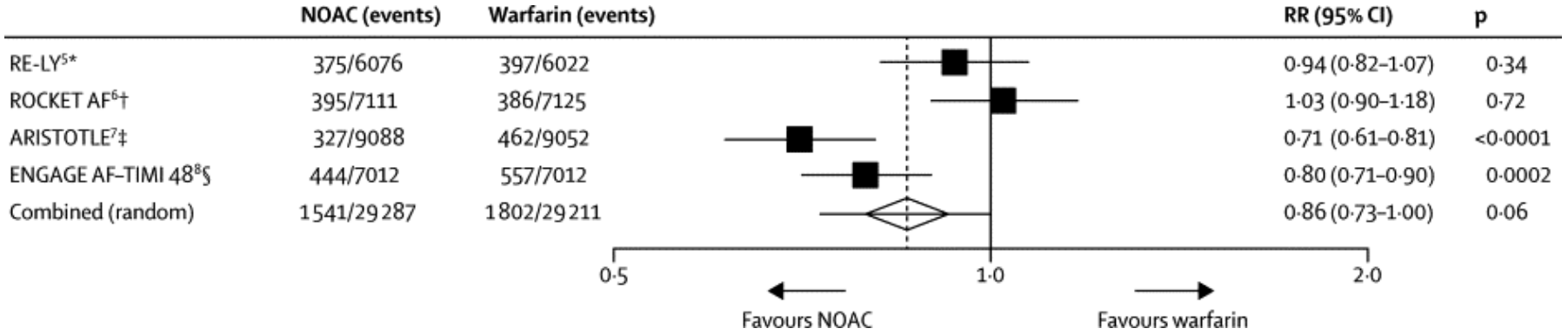


Figure 3. Major bleedingData are n/N, unless otherwise indicated. Heterogeneity: I2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Lancet 2014;383:955-62

Overview of phase III clinical trials NOACs vs VKAs in VTE 27,044 patients

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[293]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[294]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT[295]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[296]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY[297]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Edoxaban	Hokusai-VTE[298]	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

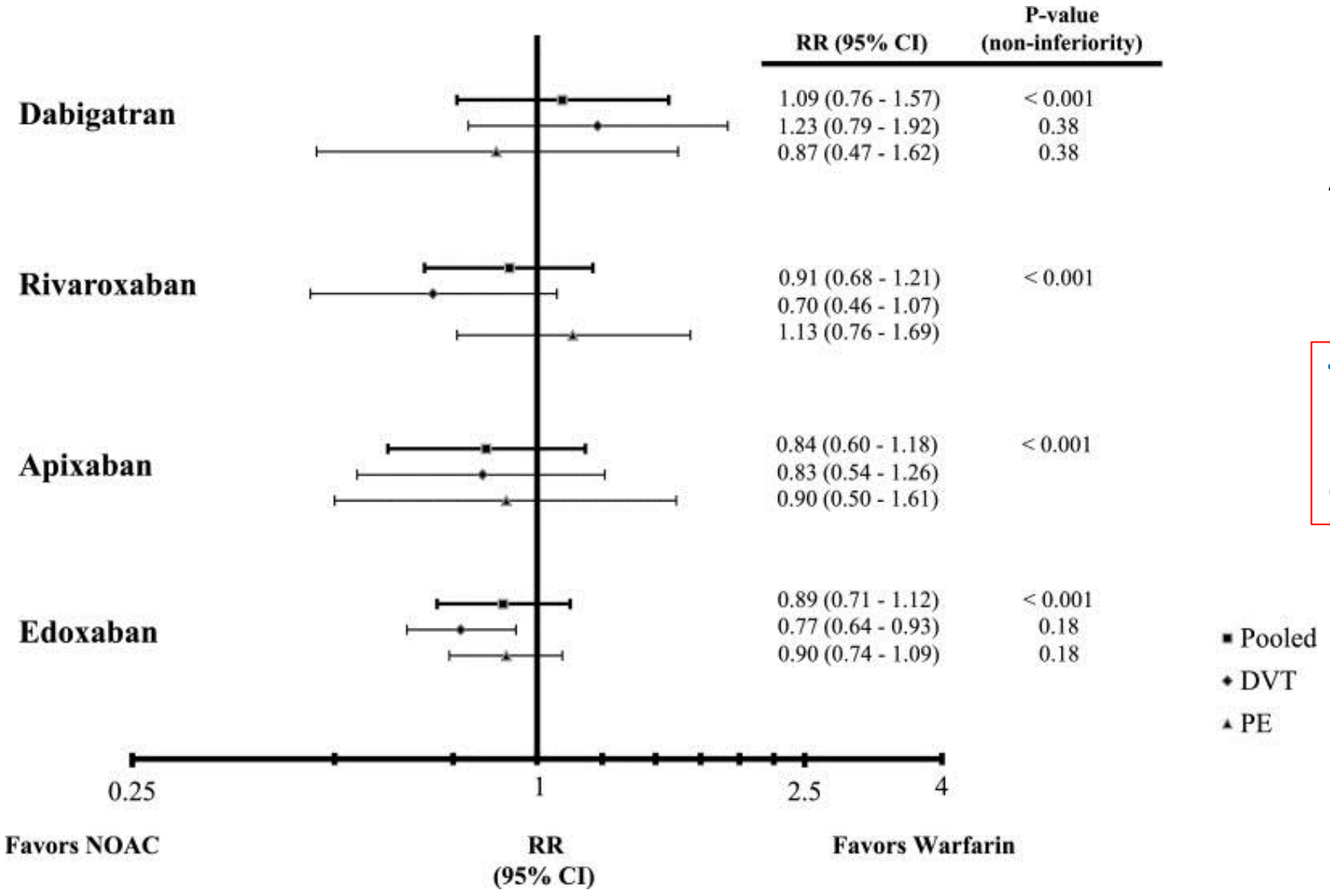
Overview of phase III clinical trials NOACs vs VKAs in VTE

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
Trial	RE-COVER I & II		EINSTEIN DVT	PE	AMPLIFY	Hokusai-VTE
Number of patients	2539	2568	3449	4832	5365	8240
Mean age ± SD (y)	54.9 ± 16.0		56.1 ± 16.4	57.7 ± 7.3	57.0 ± 16.0	55.8 ± 16.3
CrCl <30 mL/min, n (%)	22 (0.4)		15 (0.4)	6 (0.1)	29 (0.5)	n/a
Age ≥75 y, n (%)	529 (10)		440 (13)	843 (17)	768 (14)	1104 (13)
Prior VTE (%)	22		19	20	16	18
Unprovoked VTE (%)	35		62.0	64.5	89.8	65.7
Index event PE ± DVT (%)	31		0.7	100	34	40
Active Cancer (%)	4.8		6.0	4.6	2.7	2.5
Bridge with heparin/LMWH	Yes		No		No	Yes

BLOOD, 14 AUGUST 2014 x VOLUME 124, NUMBER 7

Efficacy of NOACs in VTE Treatment

Hazard ratios (HR) for recurrent VTE and VTE-related death and their 95% confidence intervals (CI) in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment

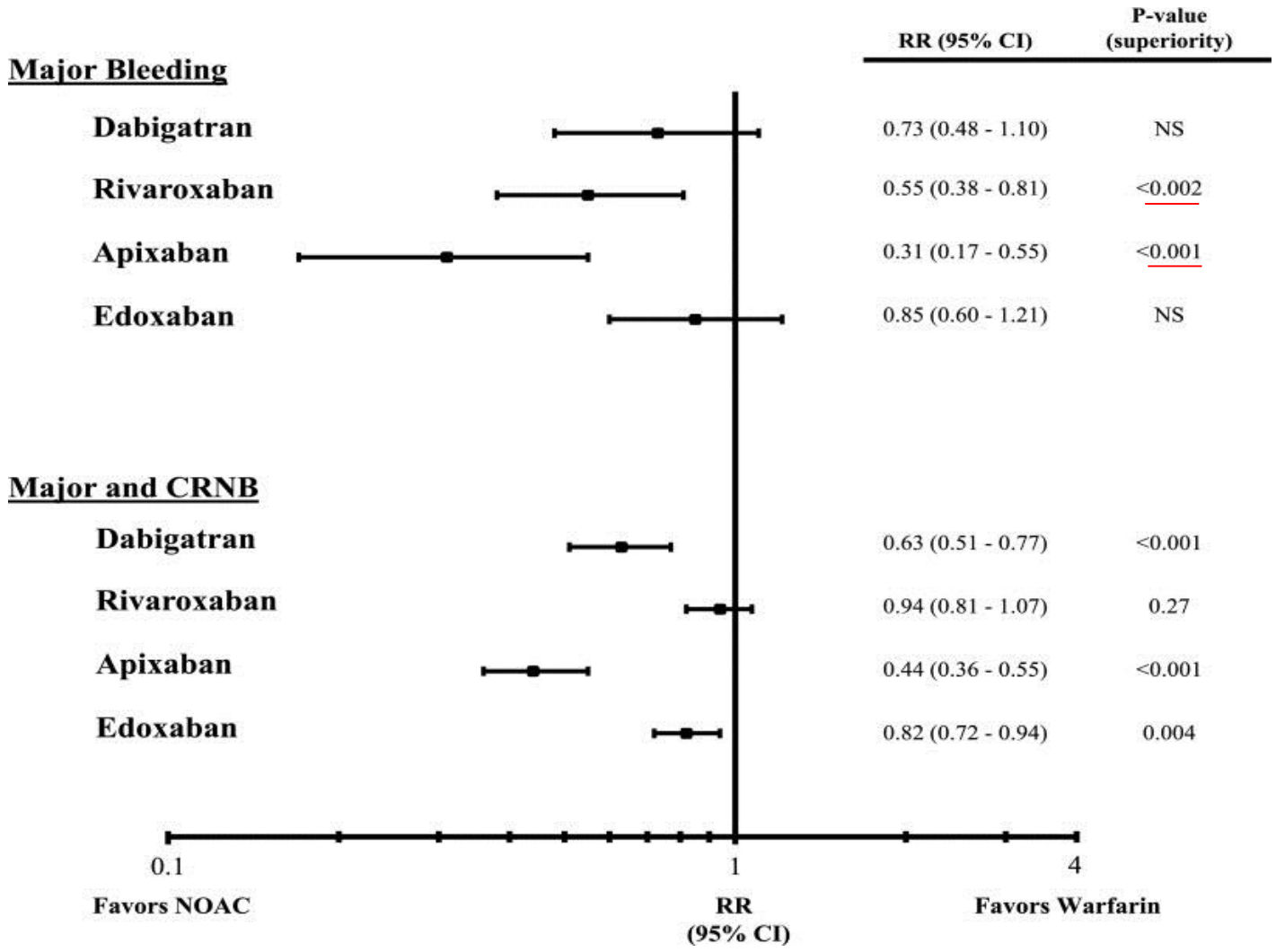


All non inferior to warfarin

These DOACs have never been compared directly with each other

BLOOD, 14 AUGUST 2014 x VOLUME 124, NUMBER 7

Hazard ratios (HR) for major bleeding or major plus clinically relevant nonmajor bleeding (CRNB) in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment



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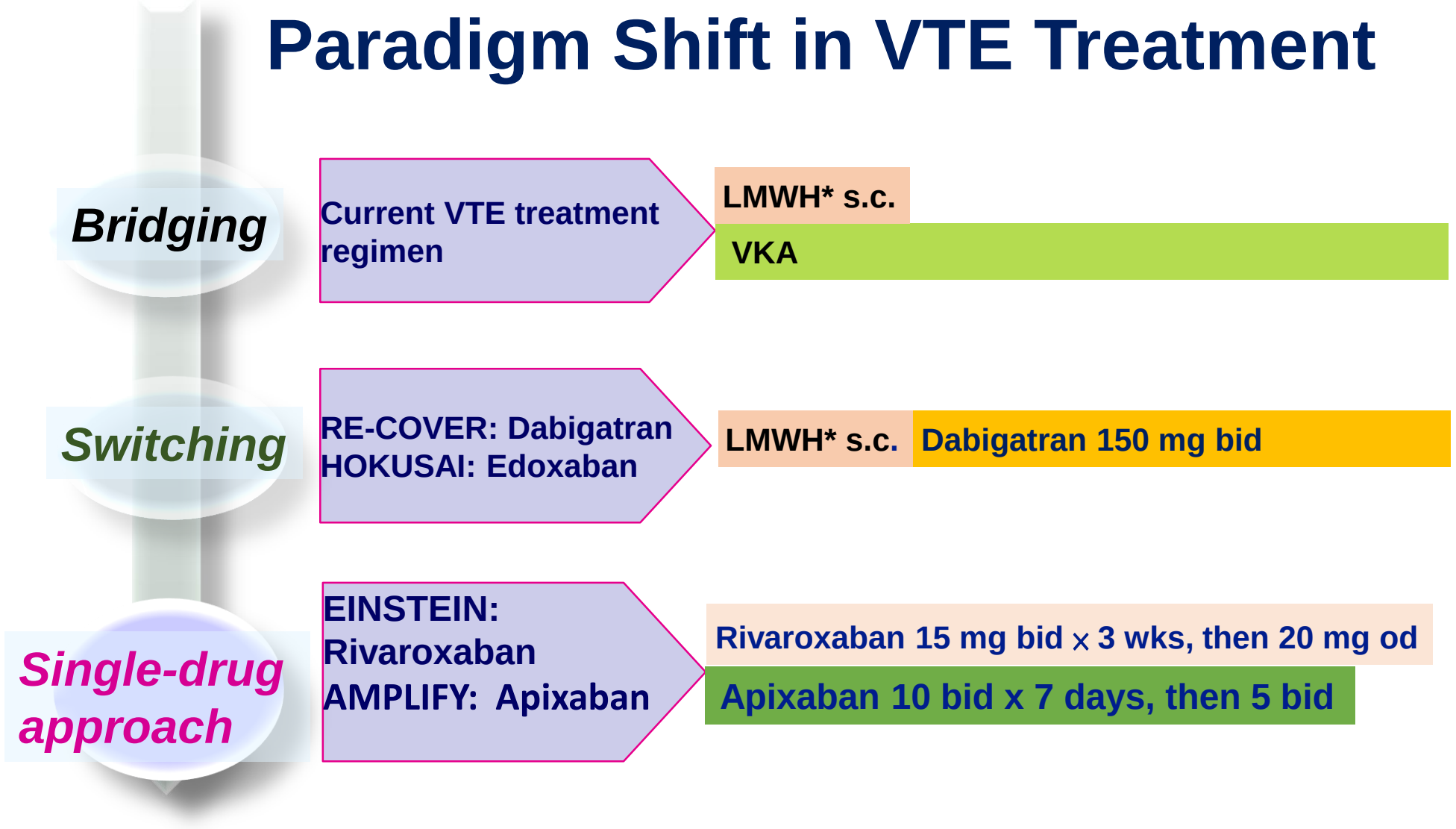
BLOOD, 14 AUGUST 2014 x VOLUME 124, NUMBER 7

Paradigm Shift in VTE Treatment



1. Schulman S *et al*. *N Engl J Med* 2009;361:2342–2352; 2. RE-COVER II. Available at: http://clinicaltrials.gov. Trial ID: NCT00680186. Accessed August 2011;
3. The EINSTEIN Investigators. N Engl J Med 2010;363:2499–2510; 4. The EINSTEIN-PE Investigators. N Engl J Med 2012;366:1287–1297

Limitations of DOACs

- Anti-phospholipid syndrome
- Cancer associated VTE
- Cardiac Intervention when dual antiplatelet drugs indicated
- Mechanical Heart Valves

NOACs / DOACs – Approved use

Dabigatran, Rivaroxaban, Apixaban and Edoxaban

- Prevention of stroke and systemic embolism in atrial fibrillation (AF)
- Venous thromboembolism (VTE) prophylaxis in major orthopaedic surgery
- Treatment of acute VTE and secondary prevention of recurrent VTE
- Prevention of cardiovascular deaths after acute coronary syndrome (Rivaroxaban)

Real World Studies / Data

Phase 4 trials

Registries

Post Authorisation safety/efficacy studies

Prospective/Retrospective Observational studies

Pharmco-economic studies

How well does the drug perform in the real world ?

Outcomes as expected from clinical trials ?

Is the drug being used as recommended ?
Eg indications, dose, duration

Compliance issues ?

Improved QOL ?

Healthcare costs ?

Real-life studies have their inherent weaknesses :

- non-controlled and heterogeneous patient groups
- Physicians' prescribing bias in dosing and choice of patients
- uncontrolled influence of non-compliance, other concomitant medications and co-morbidities

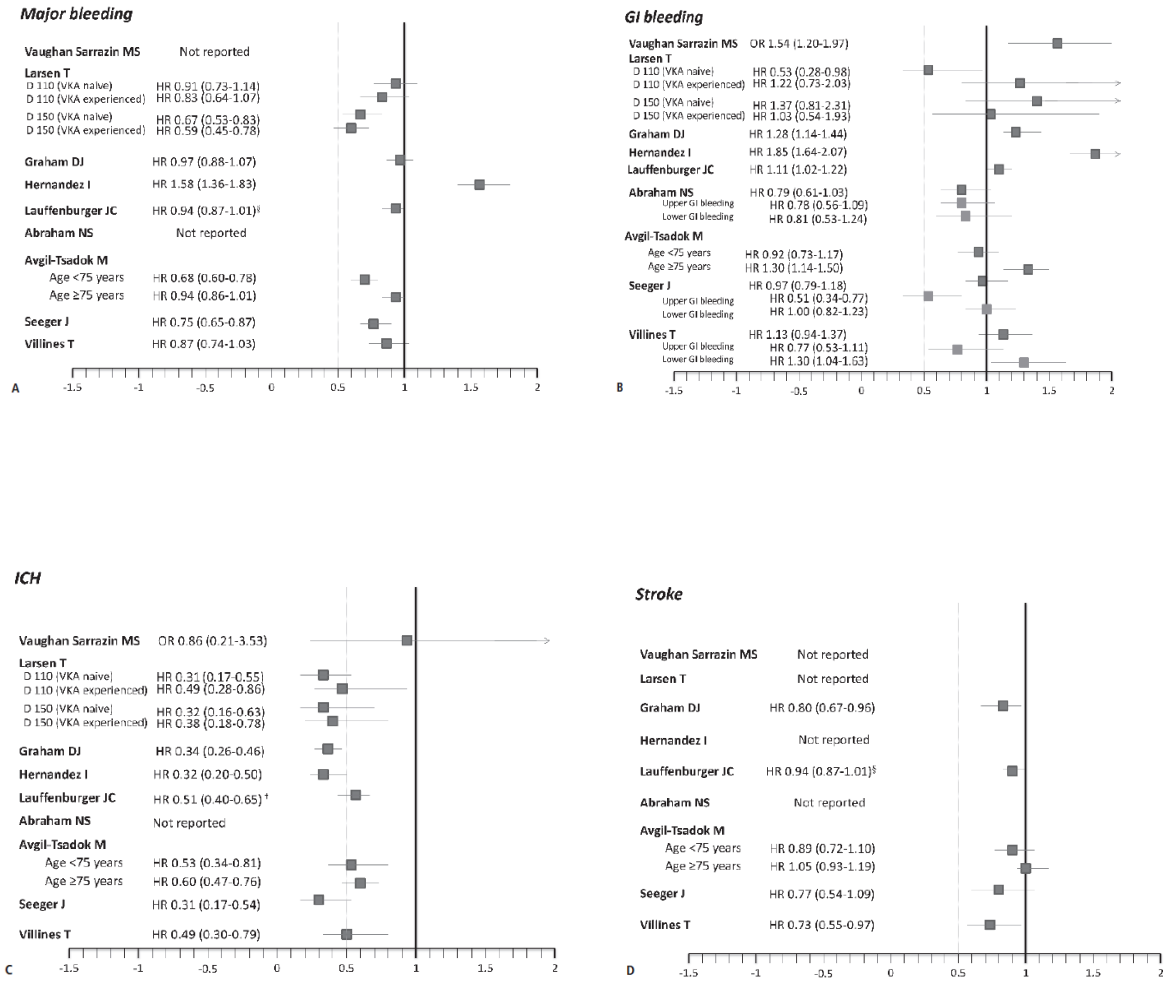
BUT provide a wealth of data and insight into how DOACs are used in the real world

Dabigatran in ‘real-world’ clinical practice for stroke prevention in patients with non-valvular AF

First author, Year of publication	Study period; Database(s)	AF cohort type	Dabigatran bid dose
Sarrazin MS 2014	2010–2012; Veterans Affairs administrative data	VKA experienced	150 mg
Larsen T 2014	2011–2013; Danish National Prescription Registry, National Patient Register, Civil Registration System	OAC naïve or VKA Experienceed	110 mg or 150 mg
Graham DJ 2015	2010–2012; Medicare	OAC naive, Age 65y	150 mg or 75 mg (16% of the cohort)
Hernandez I 2015	2010–2011; Medicare (a 5% random sample)	OAC naive	NR
Lauffenburger JC 2015	2010–2012; Truven Health Market Scan Commercial Claims; Encounters and Medicare SupplementDatabases	OAC naive	150 mg or 75 mg
Abraham NS 2015	2010–2013; Optum Labs Data Warenhouse	OAC naive	150 mg
Avgil-Tsadok 2015	1999 (2011)-2013; Quebec hospital discharge database and Quebec physician and prescription claims database	OAC naive	110 mg or 150 mg
Seeger J 2015	2010–2012; MarketScan, Truven and Cliniformatic, Optum	OAC naive	150 mg or 75 mg (4% of the cohort)
Villines T 2015	2010–2012; The US Department of Defence	OAC naïve or VKA experienced	150 mg or 75 mg (12% of the cohort)

Tatjana S. Potpara[1,2], Thromb Haemost 2015; 114: 1093–1098

Dabigatran in ‘real-world’ clinical practice for stroke prevention in patients with non-valvular AF



Systematic Review 9 Studies
More than 200,000 AF patients

Bleeding when compared to warfarin :

	< 75 yrs	> 75 years
Extra-cranial bleeds	110mg	110mg
	150 mg	150 mg
GIT Bleeds	110 mg	110 mg
	150 mg	150 mg

Tatjana S. Potpara[1,2], Thromb Haemost 2015; 114: 1093–1098

Dabigatran in real-world atrial fibrillation
Meta-analysis of observational comparison studies with vitamin K antagonists

20 studies -711,298 patients, (210,279 dabigatran vs 501,019 VKA)

	Dabigatran / 100 Pt years	VKA/ 100 Pt years	HR	95% CI
Ischaemic Stroke	1.65	2.85	0.86	0.74–0.99
Major Bleeding	3.93	5.61	0.79	0.69–0.89
Risk of mortality			0.73	0.61–0.87
Intracranial Bleed			0.45	0.38–0.52
GIT Bleed			1.13,	1.00–1.28
Myocardial Infarction			0.99,	0.89–1.11

- Lower risk of ischaemic stroke, major bleeding, intracranial bleeding and mortality
- Slightly Higher risk of GI bleeding
- Similar risk of myocardial infarction.

Thromb Haemost 2016; 116: 754–763

Other findings from real world data

(1) **Dabigatran 75 mg dose -**

- not in RE-LY trial but approved in the USA for use in the renal impaired - CrCl 15-30 ml/min.
- Majority renal intact – (33% chronic kidney disease, of which 20% severe renal impairment)
- significantly reduced risk of intracranial haemorrhages
- similar rates of stroke, bleeding and mortality compared to warfarin

(2) **New starters of anticoaulation**

- higher bleeding risk in warfarin new starter

(3) **Higher bleeding rates in the first 90 days** of treatment in elderly new starters of both dabigatran or warfarin

(4) **Higher bleeding risk with renal impairment** in both dabigatran and warfarin

Thromb Haemost 2015; 114: 1093–1098

XANTUS: a real-world, prospective, observational Non Interventional study of patients treated with rivaroxaban for stroke prevention in AF

	Rocket AF	Xantus
Stroke Risks	No CHADs 0 or 1	12.7% CHA2DS2VAS 0 or 1.
Mean CHADs2 score	**3.5%**	**2%**
Previous Stroke/TIA/SE	55%	19%
Annual stroke rates (100 patient-years)	1.7	0.7
Bleeding Incidence (100 patient-years)	**3.6**	**2.1**
Fatal bleeding (100 patient-years)	0.2	0.2
Critical organ bleeding (100 patient-years)	0.8	0.7
ICH (100 patient-years)	0.5	0.4
Major BGIT (100 patient-years)	**2.0**	**0.9**

6784 pts, 311 centres

Europe, Israel, and Canada.

Mean age -71.5 years (range 19–99)

41% female,

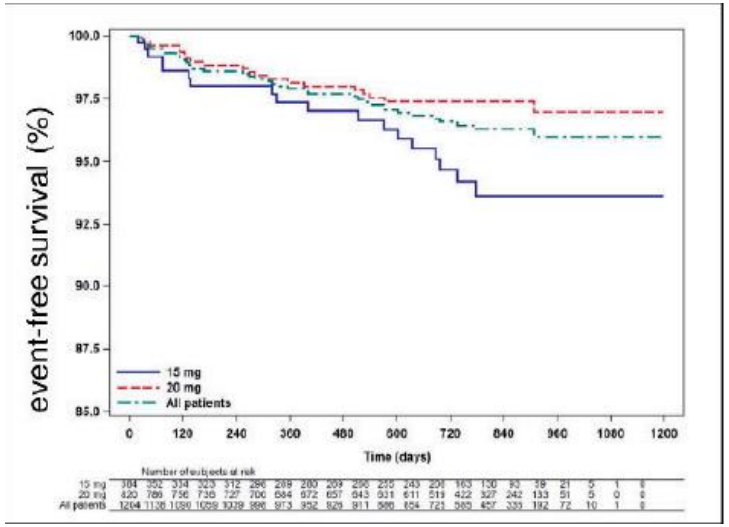
Mean treatment duration 329 days.

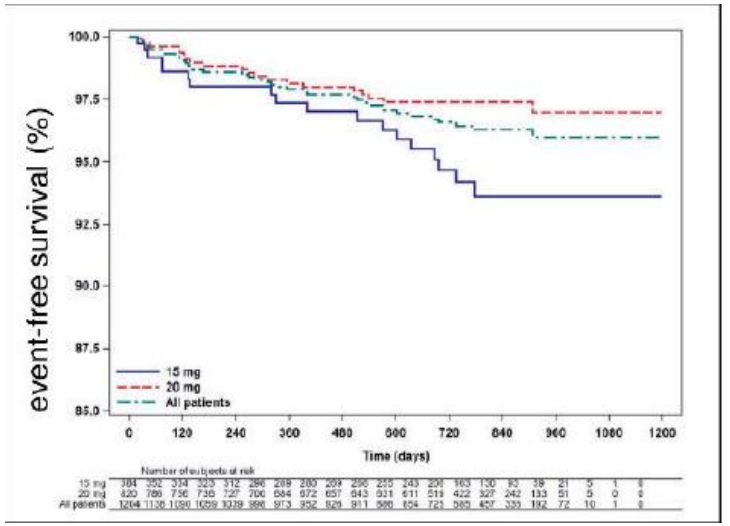
9.4% documented severe or moderate renal impairment (CrCl 50 mL/min)

Persistence with rivaroxaban in XANTUS was 80% at 1 year,

European Heart Journal (2016) 37, 1145–1153

Effectiveness and safety of rivaroxaban therapy in daily-care patients with AF - Results from the Dresden NOAC Registry





	All riva-roxaban SPAF patients (n=1204)	Rivaroxaban 20 mg OD at baseline (n=820)	Rivaroxaban 15 mg OD at baseline (n=384)	P-value 20 mg vs 15 mg OD
Stroke/TIA/systemic embolism	1.7 (1.2–2.3)	1.25 (0.8–1.9)	2.7 (1.6–4.2)	0.0163
All major cardiovascular events	2.0 (1.4–2.6)	1.7 (1.2–2.5)	2.5 (1.5–4.0)	0.2145
ACS	1.1 (0.7–1.6)	0.8 (0.4–1.4)	1.8 (0.9–3.1)	0.0444
Major VTE	0.35 (0.2–0.7)	0.4 (0.1–0.8)	0.3 (0.04–1.1)	0.4752

Values are events/100 patient-years (95 % CI). ACS, acute coronary syndrome; VTE, venous thromboembolism.

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Values are events/100 patient-years (95 % CI). ACS, acute coronary syndrome; VTE, venous thromboembolism.

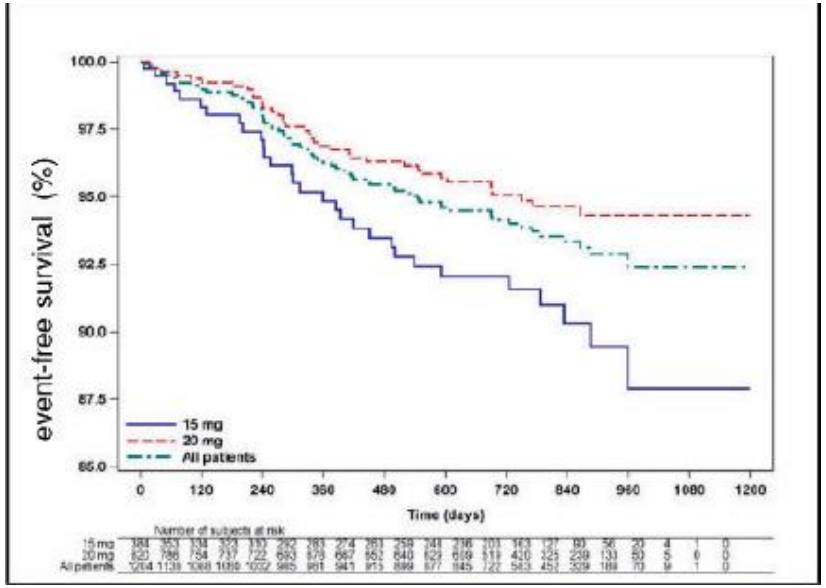
1776/2700 SPAF patients on rivaroxaban

Overall rates of stroke and systemic embolism :

- 2.03/100 pt-yrs in the intention-to-treat analysis
- 1.7/100 pt-yrs in the on-treatment analysis.
- Considerably lower than those in the ROCKET AF trial
- 20 mg OD (1.25/100 pt-yrs)
- 15 mg OD (2.7/100 pt-yrs)

Thromb Haemost 2016; 115: 939–949

Effectiveness and safety of rivaroxaban therapy in daily-care patients with AF - Results from the Dresden NOAC Registry



	All rivaroxaban SPAF patients (n=1204)	Rivaroxaban 20 mg OD at baseline (n=820)	Rivaroxaban 15 mg OD at baseline (n=384)	P-value 20 mg vs 15 mg OD
Major bleeding	3.0 (2.3–3.8)	2.4 (1.7–3.3)	4.5 (3.0–6.5)	0.0073
Any bleeding	61.5 (57.2–66.0)	64.4 (59.1–70.0)	55.5 (48.5–63.2)	0.0593
Minor bleeding	34.9 (32.0–38.0)	37.9 (34.3–41.9)	28.4 (23.9–33.6)	0.0028
NMCR bleeding	22.75 (20.6–25.0)	22.2 (19.7–24.9)	24.0 (20.1–28.4)	0.3668

Values are events/100 patient-years (95 % CI).

Overall major bleeding - 3.0/100 pt-yrs

20 mg OD dose 4.5 /100 py\t-yrs

15 mg OD dose 2.4/100 pt-yrs

Rivaroxaban discontinuation rate - 12.0/100 pt/yrs

Table 6: Overview on the design, mean follow-up and outcomes of the presented analysis in comparison to ROCKET-AF and published "real-world" studies on the effectiveness and safety of NOAC therapy in AF.

Study	Drug	Design and duration of follow-up	Mean $CHADS_2$ score	Effectiveness outcome (stroke/SE ± TIA)	Major bleeding
Dresden NOAC (present data)	*rivaroxaban*	*Prospective cohort study; 796 days*	*2.4*	*2.0/100py (ITT)* *1.7/100py (OT)*	*3.0/100py*
ROCKET-AF (6)	rivaroxaban	RCT; 707 days	3.5	2.1/100py (ITT) 1.7/100py (PP)	3.6/100py
XANTUS (19)	rivaroxaban	Prospective cohort study; 329 days	2.0	1.8/100py	2.1/100py
Laliberté (17)	rivaroxaban	Retrospective database analysis; 83 days	2.0	4.6/100py	3.3/100py
Maura (24)	rivaroxaban	Retrospective database analysis; 80 days	UNK	1.4/100py (stroke/SE)	3.7/100py

2.9 events per 100 patient-years- large US study of electronic medical records of 27,467 patients

Lower major bleed rate than Rocket AF

N Engl J Med 2011; 365:883-891
Clin Cardiol. 2015; 38:63-8.
Blood. 2014;124:955-62.

Rates of major bleeding with rivaroxaban in real-world

- Rates of major bleeding with rivaroxaban in real-world studies of non-valvular AF patients - a meta-analysis 9 studies 51,533 patients

	Major Bleeding	BGIT	ICH
Rocket AF	3.6	3.2	0.5
Overall	3.32 (95% CI¼2.28–4.25)	2.41 (95% CI¼1.25–3.56)	0.40 (95% CI¼0.17–0.74)
5 retrospective claims studies	6.19 (95% CI¼2.29–10.10)	4.21 (95% CI¼2.61–6.02)	0.52 (95% CI¼0.04–1.51)
Prospective claims	**1.98** (95% CI¼1.15–2.82)	**0.61** (95% CI¼0.02–1.19)	**0.32** 95% CI¼0.05–0.84

Real variability and heterogeneity

- clinical presentation patient profiles - CHA2DS2-Vasc and HAS-BLED
- ethnic differences
- doses of rivaroxaban
- concomitant use of the antiplatelet drugs)
- methodological characteristics

CURRENT MEDICAL RESEARCH AND OPINION, 2016

Comparative effectiveness and safety of non-VKAs and warfarin in patients with AF: propensity weighted nationwide cohort study

3 Danish nationwide databases - study population (61 678) :
Warfarin-57%, dabigatran-21%, rivaroxaban-12%, apixaban-10%

- Apixaban and Rivaroxaban - more previous strokes, systemic embolism vascular disease and bleeding
- Dabigatran patients - younger and less renal impaired
- Warfarin – more vascular disease hypertension, renal impairment, COPD and cancer.

Annual rates%	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Iscahemic stroke, Systemic emboli	3.3	2.8 NS	3.0 HR 0.83 (95% CI 0.69-0.99).	4.9 NS
Annual Death Risks	8.2	2.7	7.7 (NS)	5.2
Any Bleeding	5.0	2.4	5.3 (NS)	3.3

All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting

NOT Direct Comparisons

BMJ 2016;353:i3189

The safety and persistence of non-vitamin-K-antagonist oral anticoagulants in atrial fibrillation patients treated in a well structured atrial fibrillation clinic

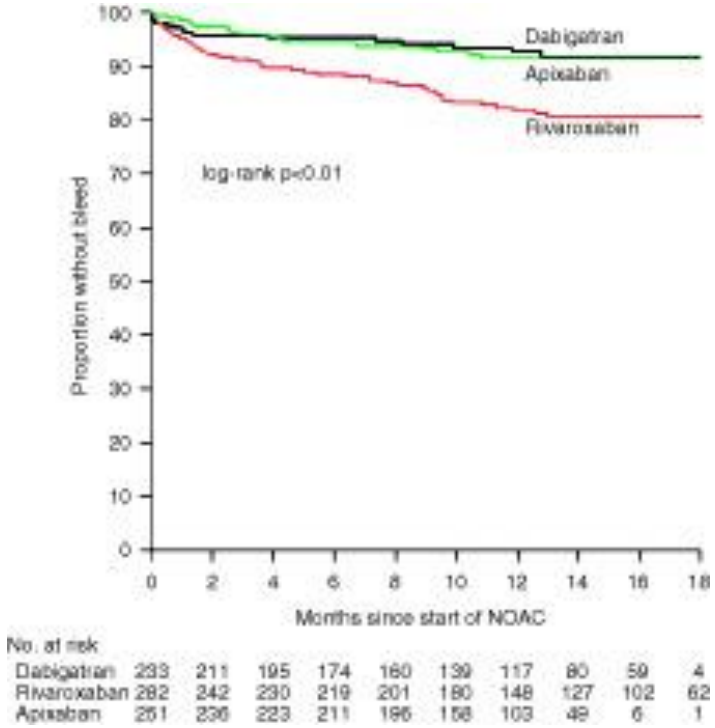


Figure 1. Kaplan–Meier curve for all bleeding events stratified for dabigatran, rivaroxaban and apixaban.

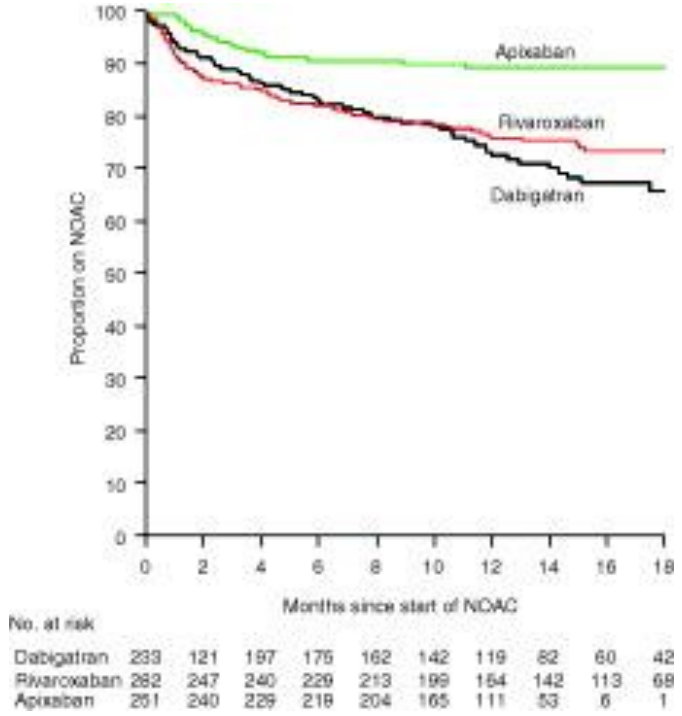


Figure 2. Kaplan–Meier curve for discontinuation events stratified for dabigatran, rivaroxaban and apixaban.

Swedish registry

766 consecutive patients with AF

Initiation of treatment:

- dabigatran (233)
- rivaroxaban (282)
- apixaban (251)

Median age was 74 years (range 36–95)

Comparable pt charateristics

Median FU – 367 days

NOT Direct Comparisons

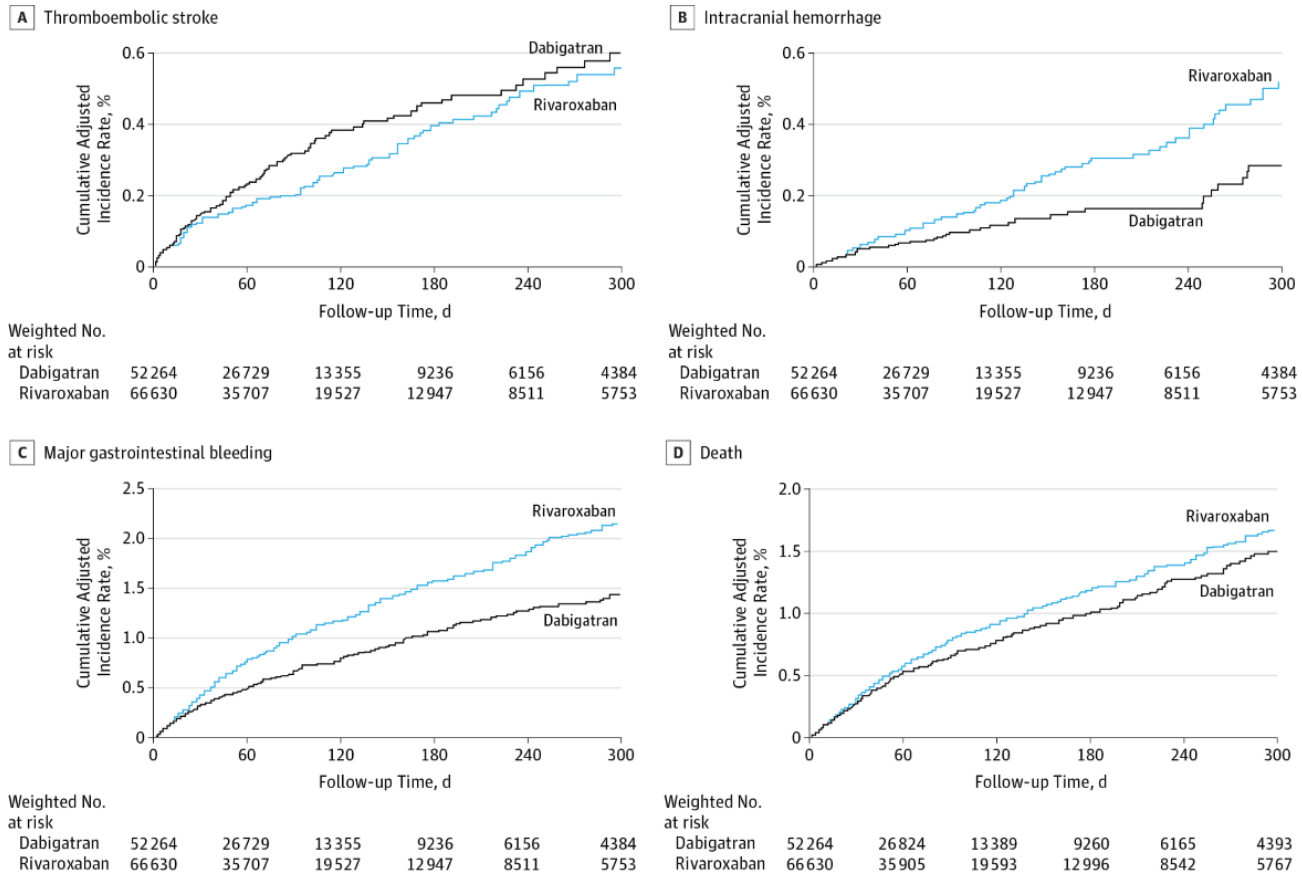
Current Medical Research and Opinion, 32:4, 779-785

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

USA - Retrospective new-user cohort study of **Medicare** 118 891 pts < <65 years or older, mean follow-up 108d (D) and 111d (R)

	Rivaroxaban	Dabigatran
(A) TE events	↓	
	HR, 0.81; 95%CI, 0.65-1.01; *P* = .07	
(B) ICH		↓
	HR, 1.65; 95%CI, 1.20-2.26; *P* = .002	
(C) Major BGIT		↓
	HR, 1.48; 95%CI, 1.32-1.67; *P* < .001	
(D) Cumulative incidence rates		↓
	HR, 1.15; 95%CI, 1.00-1.32; *P* =.051	

<75 years or older or with $CHADS_2$ score < 2, rivaroxaban use was associated with significantly increased mortality compared with dabigatran use.



NOT Direct Comparisons

JAMA Intern Med. 2016;176(11):1662-1671.

Real World Doacs -- Asia AF

Taiwan National Health Insurance Research Database

The HRs (95% CIs) comparing dabigatran with warfarin :

ischemic stroke, 0.62 (0.52–0.73; *P*<0.0001)

Intracranial hemorrhage, 0.44 (0.32–0.60; *P*<0.0001)

All hospitalized major bleeding, 0.58 (0.46– 0.74; *P*<0.0001)

All-cause mortality, 0.45 (0.38–0.53; *P*<0.0001)

myocardial infarction, 0.67 (0.43–1.05; *P*=0.0803)

major GIT bleeding, 0.99 (0.66–1.49; *P*=0.9658)

- Dabigatran did not increase the risk of myocardial infarction or major BGIT in all age groups when compared with warfarin.
- 8772 patients (88%) took a 110-mg dose dabigatran. The magnitude of effect for each outcome of 110-mg was comparable with that of 150-mg dose in the subgroup analysis

A multicenter retrospective cohort study of 241 stroke centers in Japan

Patients with AF treated with a DOAC when compared with those on warfarin, had a lower rates of intracranial haemorrhage (17% vs 26%) and mortality (16% vs 35%)

Stroke. 2016;47:441-9.
Circ J. 2015;79:1018-23.

Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation

Yi-Hsin Chan, et al

Nationwide retrospective cohort study was conducted of consecutive patients with NVAF
Taiwan National Health Insurance Research Database – Feb to Dec, 2013
Rivaroxaban (3,916), dabigatran (5,921), or warfarin (5,251)
The propensity score weighting method was used to balance covariates across study groups.
3,425 (87%) - rivaroxaban (10 to 15 mg once daily)
5,301 (90%) - dabigatran (110 mg twice daily)

Compared with warfarin, both rivaroxaban and dabigatran significantly decreased the risk:

- ischemic stroke or systemic embolism (p 0.0004 and p 0.0006, respectively)
- intracranial hemorrhage (p 0.0007 and p 0.0005, respectively)
- all-cause mortality ($p < 0.0001$ and $p < 0.0001$,)

Comparing Dabigatran and Rivaroxaban (NOT direct comparisons)

- no differences were found regarding risk for ischemic stroke or systemic embolism, intracranial hemorrhage, myocardial infarction, or mortality.
- Rivaroxaban - higher risk for hospitalization for GI bleeding than dabigatran (p 0.0416)
- Rivaroxaban - on-treatment analysis showed that the risk for hospitalized GI bleeding was similar between the 2 drugs (p 0.5783)

JOURNAL OF T H E AMERICAN COL LE GE OF CARD IOLOGY Sept 2016

DOAC - Ideal Anticoagulant ?

- Oral administration
- Good Efficacy and Safety
- Metabolic Properties with ~~No~~ **FEW** food and drug interaction
- No need for coagulation monitoring
- Specific Reversal Agents NOT available (until recently)

Real Life Management Issues

European Heart Journal Advance Access published April 26, 2013

European Heart Journal
doi:10.1093/eurheartj/eht134

EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

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

New Oral Anticoagulant – A practical guide on behalf of the Australasian Society of Thrombosis and Haemostasis (ASTH)

Huyen Tran[1], Joanne Joseph[2], Laura Young[3], Simon McRae[4], Jennifer Curnow[5], Harshal Nandurkar[6], Peter Wood[7], Claire McLintock[8]

Clinical Update

Consensus Recommendations for Preventing and Managing Bleeding Complications Associated with Novel Oral Anticoagulants in Singapore

Heng Joo Ng, [1]*MBBS, MRCP, FRCPath*, Yen Lin Chee, [2]*MBChB, FRCP, FRCPath*, Kuperan Ponnudurai, [3]*MBBS, FRCP, FRCPath*, Lay Cheng Lim, [4]*MBBS, FRCP, FAMS*, Daryl Tan, [5]*MMed, MRCP, FAMS*, Jam Chin Tay, [6]*MBBS, FRCP, FAMS*, Pankaj Kumar Handa, [6]*MBBS, MRCP, FAMS*, Mufeedha Akbar Ali, [1]*BSc*, Lai Heng Lee, [1]*MBBS, MMed, FAMS*
For the Chapter of Haematologist, College of Physicians, Academy of Medicine Singapore

Anticoagulation: a GP primer on the new oral anticoagulants

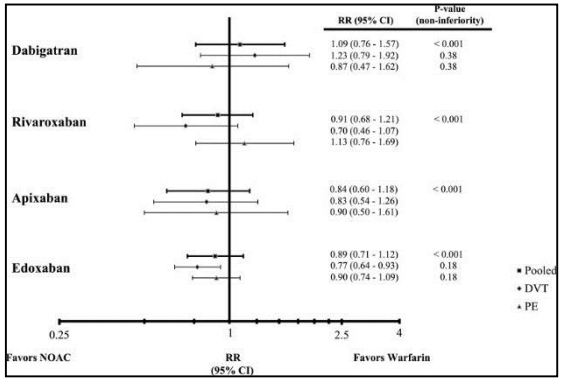
DOACs in Clinical Practice

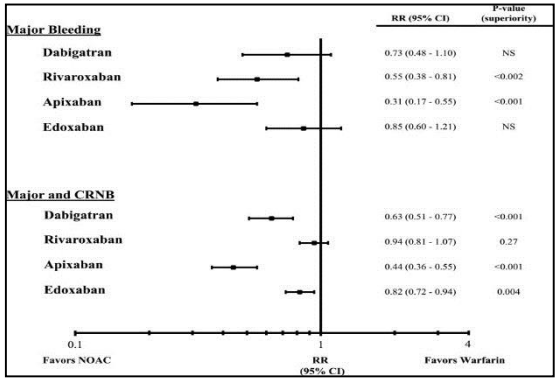
- Important advancement in antithrombotic management
- Careful patient / drug selection
- Monitoring of patients (not INR)
- Limit bleeding events and thrombotic complications
  - Know your Drug
  - Appropriate prescription and dosing
  - Know the high risk situations
  - Ability to handle bleeds

Pharmacological Properties of the DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Half-life (hour)	12-17	5-9	12	6-10
Time to peak effect (hour)	1-3	2-4	1-3	1-2
Dosing in non-valvular AF	150 mg BID	20 mg OD	5 mg BID	60 mg OD
Dosing in VTE treatment	150 mg BID after 5-10 days of parenteral anticoagulation	15 mg BID for 21 days followed by 20 mg OD	10 mg BID for 7 days followed by 5 mg BID	60 mg OD after 5 days of parenteral anticoagulation
Renal clearance as unchanged drug (%)	80	33	27	50
Drug Interactions Pathways	P-gp	3A4/P-gp	3A4/P-gp	3A4/P-gp

Appropriate choice of drug





NOT head to head comparative trials

All comparing with warfarin/LMWH

Does not indicate which NOAC is superior over others

Indications and available data

Co-morbidities – eg renal function, history of BGIT

Other medications

Availability and costs

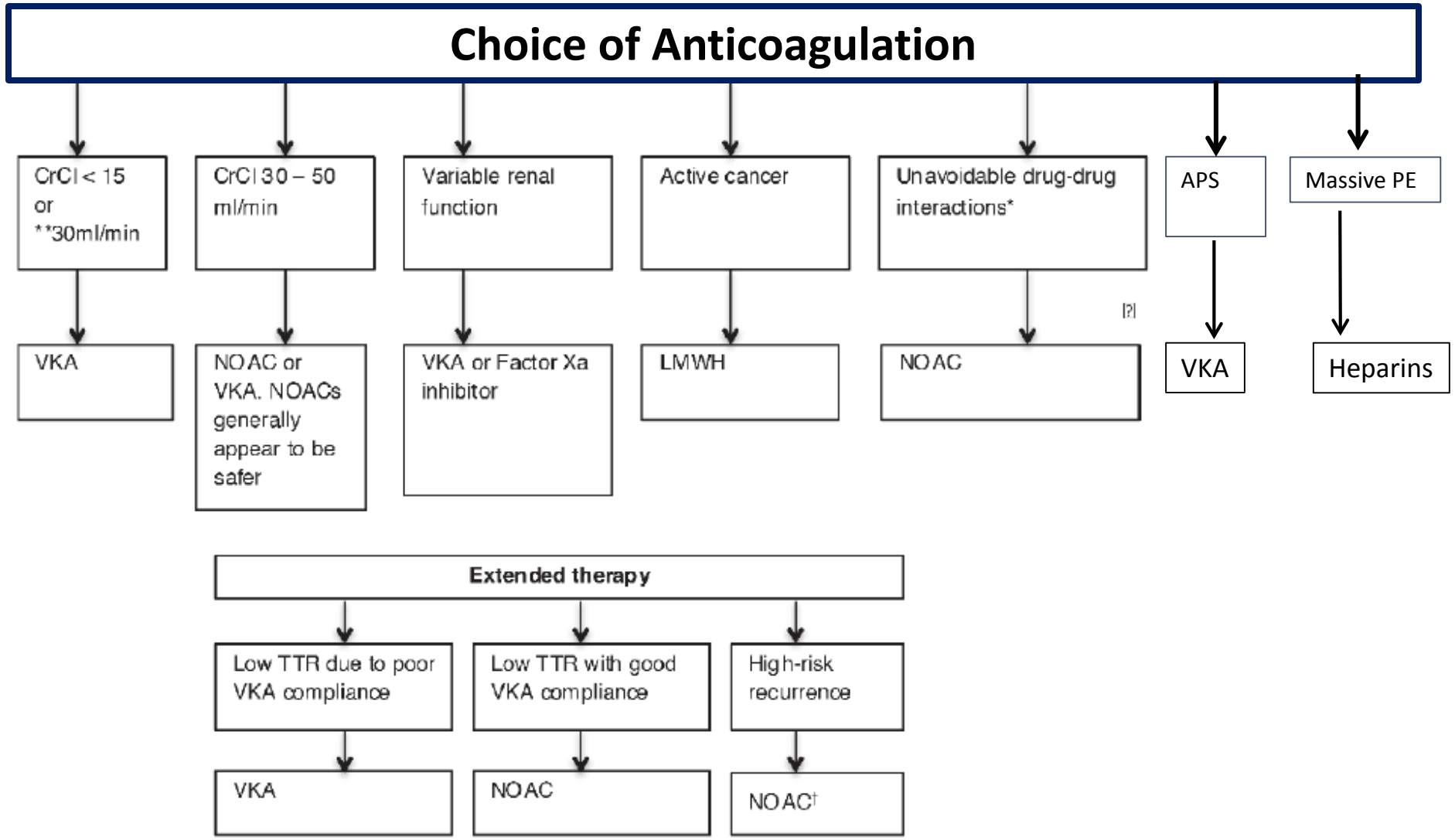
Patient preference

Choice of Anticoagulant

Characteristic	Drug choice	Rationale
All-oral therapy	Rivaroxaban or apixaban	Only NOACs to be evaluated in all-oral regimens
Dyspepsia or upper gastrointestinal symptoms	Rivaroxaban, apixaban, or edoxaban	Dyspepsia in as much as 10% given dabigatran
Recent gastrointestinal bleed	Apixaban	More GI bleeding with dabigatran, rivaroxaban, edoxaban than with warfarin
Recent acute coronary syndrome	Rivaroxaban, apixaban or edoxaban	Small myocardial infarction signal with dabigatran
Poor compliance with long-term twice-daily dosing	Rivaroxaban or edoxaban	OD regimens for long-term use
Unstable INRs despite compliance	NOACs	Unstable INRs predispose to thrombotic and bleeding complications
Limited access to anticoagulation clinic	NOAC	Given in fixed doses without monitoring
Creatinine clearance 30-50 mL/min	Rivaroxaban, apixaban, or edoxaban	Less affected by renal impairment than dabigatran; if edoxaban is chosen, the 30-mg OD dose should be used

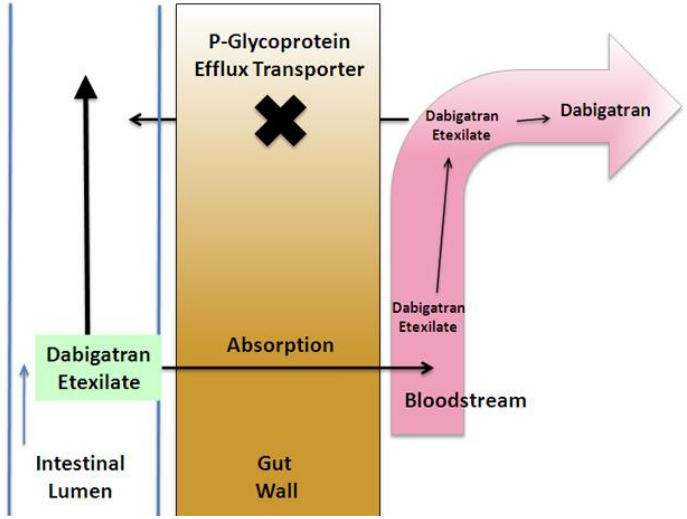
Choice of Anticoagulant -- Patients who should NOT be on NOACs

Characteristic	Drug choice	Rationale
Extensive DVT or massive PE	Heparin	Require advanced therapy and were excluded from trials with the NOACs
High initial risk of bleeding	Heparin	Enables dose titration; rapid offset and availability of protamine as an antidote should bleeding occur
Anti-phospholipid syndrome	Warfarin	Inadequate data for this highly thrombotic diseases
Pregnancy	LMWH	Warfarin and NOACs cross the placenta
Active cancer	LMWH	No trials comparing NOACs with LMWH
Creatinine clearance <30 mL/min	Warfarin	Such patients excluded from trials with NOACs
Creatinine clearance 30-50 mL/min (UNSTABLE)	Warfarin	Avoid overdosage in events of renal deterioration
AF with mitral stenosis, valve abnormalities	Warfarin	No data on efficacy
Mechanical Heart Valves	Warfarin	Clinical Trial failed
CYP3A4 and P-gp strong inducers/inhibitors	Warfarin/LMWH	Under/over exposure


Choice of Anticoagulation
CrCl < 15 or **30ml/min
CrCl 30 – 50 ml/min
Variable renal function
Active cancer
Unavoidable drug-drug interactions*
APS
Massive PE
[?]
VKA
NOAC or VKA. NOACs generally appear to be safer
VKA or Factor Xa inhibitor
LMWH
NOAC
VKA
Heparins
Extended therapy
Low TTR due to poor VKA compliance
Low TTR with good VKA compliance
High-risk recurrence
VKA
NOAC
NOAC†

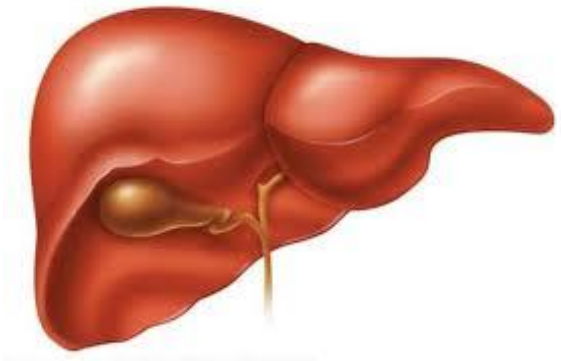
DOAC Metabolism and Drug Interactions

P-Glycoprotein



- P-gp inducers reduces drug level
- P-gp inhibitors increases drug level

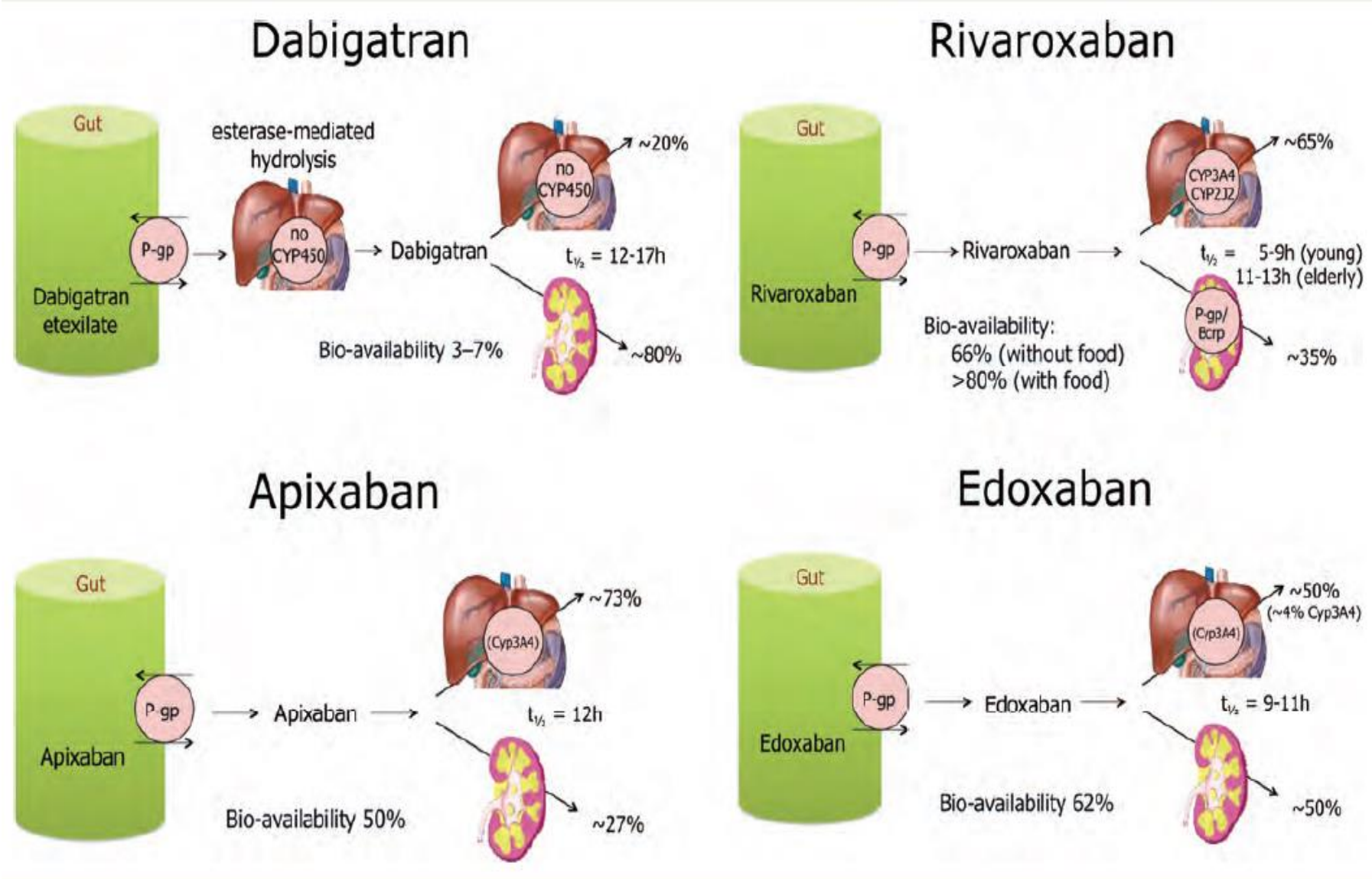
CYP3A4/5 Metabolism



•Strong inducers of CYP3A4/5 decrease exposure of drug

•CYP3A4 Inhibitors increase blood concentrations drug

DOAC Metabolism and Drug Interactions



EHRA Practical Guideline. Europace (2013) 15, 625–651

Table 2. Interactions Between NOACs and Some Commonly Used Drugs

Interacting drug	Class	Anticoagulant effects		
		Dabigatran	Rivaroxaban	Apixaban
Ketoconazole	Anti-fungal	↑↑	↑↑	↑↑
Itraconazole	Anti-fungal	ND	↑↑	↑↑
Voriconazole	Anti-fungal	ND	↑↑	↑↑
Posaconazole	Anti-fungal	ND	↑↑	↑↑
Fluconazole	Anti-fungal	ND	↑	↑
Clarithromycin	Antibiotic	↑	↑	↑
Erythromycin	Antibiotic	ND	↑	↑
Ritonavir	Anti-HIV	ND	↑↑	↑↑
Verapamil	Anti-arrhythmic	↑	↑	↑
Amiodarone	Anti-arrhythmic	↑	↑	↑
Diltiazem	Anti-arrhythmic	ND	↑	↑
Quinidine	Anti-arrhythmic	↑	↑	ND
Rifampicin	Anti-tuberculosis	↓	↓	↓
Phenytoin	Anti-convulsant	ND	↓	↓
Carbamazepine	Anti-convulsant	↓	↓	↓
St John'sWort	Herbal	↓	↓	↓

ND: No data; HIV: human immunodeficiency virus

↑↑: anticoagulant effect likely to be increased; ↑: anticoagulant effect may be increased; ↓: anticoagulant effect may be decreased

StatinDabigatranBleed2016.pdf - Adobe Reader

File Edit View Window Help

Early release, published at www.cmaj.ca on November 21, 2016. Subject to revision.

CMAJ RESEARCH

Association between statin use and ischemic stroke or major hemorrhage in patients taking dabigatran for atrial fibrillation

Tony Antoniou PhD, Erin M. Macdonald MSc, Z
Mina Tadrous PharmD PhD, Muhammad M. Ma
for the Canadian Drug Safety and Effectiveness

Infographic available at www.cmaj.ca/lookup/suppl/doi:10.1

Abstract

Background: Dabigatran etexilate is a prodrug whose absorption is opposed by intestinal P-glycoprotein and which is converted by car-

Possible Drug Interactions ?

StatinDabigatranBleed2016.pdf - Adobe Reader

File Edit View Window Help

Infographic available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160303/-/DC2

Abstract

Background: Dabigatran etexilate is a prodrug whose absorption is opposed by intestinal P-glycoprotein and which is converted by carboxylesterase to its active form, dabigatran. Unlike other statins, simvastatin and lovastatin are potent inhibitors of P-glycoprotein and carboxylesterase, and might either increase the risk of hemorrhage with dabigatran etexilate or decrease its effectiveness.

Methods: We conducted 2 population-based, nested case–control studies involving Ontario residents 66 years of age and older who started dabigatran etexilate between May 1, 2012, and Mar. 31, 2014. In the first study, cases were patients with ischemic stroke; in the second, cases were patients with major hemorrhage. Each case was matched with up to 4 controls by age and sex. All cases and controls received a single statin in the 60 days preceding the index date. We determined the association between each outcome and the use of simvastatin or lovastatin, relative to other statins.

Results: Among 45 991 patients taking dabigatran etexilate, we identified 397 cases with ischemic stroke and 1117 cases with major hemorrhage. After multivariable adjustment, use of simvastatin or lovastatin was not associated with an increased risk of stroke (adjusted odds ratio [OR] 1.33, 95% confidence interval [CI] 0.88 to 2.01). In contrast, use of simvastatin and lovastatin were associated with a higher risk of major hemorrhage (adjusted OR 1.46, 95% CI 1.17 to 1.82).

Interpretation: In patients receiving dabigatran etexilate, simvastatin and lovastatin were associated with a higher risk of major hemorrhage relative to other statins. Preferential use of the other statins should be considered in these patients.

Competing interests: See end of article.

This article has been peer reviewed.

Disclaimer: Muhammad Mamdani is a member of the *CMAJ* Editorial Advisory Board and was not involved in the editorial decision-making process for this article.

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***CMAJ* 2016. DOI:10.1503/cmaj.160303**

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Coagulation Monitoring and Lab Testing

- Routine therapeutic monitoring not indicated
- Lab measurement for residual drug effect:
  - Before surgery or invasive procedure
  - Trauma
  - Suspected overdose - drug interactions, renal impairment
  - The bleeding patient
    - Major Bleeds – access anticoagulation effects of drugs
    - Is bleeding due to high drug levels or other reasons ?

Assays for NOACs testing

	Dabigatran	Rivaroxaban and Apixaban
Qualitative/semiquantitative for high levels	aPTT with a sensitive reagent	PT with a sensitive reagent
Highly sensitive screen	TT	Anti-Xa
Quantitative (using appropriate calibrators)	Diluted TT, factor IIa, Ecarin clotting time	Anti-Xa

Abbreviations: aPTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; PT, prothrombin time; TT, thrombin time.

- **Effects of NOACs on clotting tests are variable**
- **Clotting times do not accurately reflect drug levels / anticoagulant effect**
- **Degree of prolongation is highly dependent on the reagent used for the assay.**
- **Detect peak or supra-therapeutic drug levels**
- **May be normal during low or trough drug levels.**
- **Calibrated assays for quantification of drug levels**
- **Clotting times may be abnormal from other reasons**
- **Does NOT provide an accurate assessment of risk of surgical bleeds**

Table 2. Interference of DOACs With Anti-Xa and Anti-IIa Action Upon Various Coagulation Tests

Test	Assay Principle	Interference	
		Anti-Xa	Anti-IIa
PT/INR	Coagulation	Yes	Yes
APTT	Coagulation	Yes	Yes
Thrombin time	Coagulation	No	Yes
Fibrinogen	Coagulation	No	Yes
Factor II, V, VII, VIII, IX, X, XI, XII	Coagulation	Yes	Yes
Factor XIII	Chromogenic	No	No
Factor VIII chromogenic	Chromogenic	Yes	No
Protein C activity	Chromogenic	No	No
Protein S activity	Coagulation	Yes	Yes
Antithrombin activity	Chromogenic	Yes	Yes
Protein C antigen	Immunoassay	No	No
Protein S antigen	Immunoassay	No	No
Antithrombin antigen	Immunoassay	No	No
Plasminogen activity	Chromogenic	No	No
APC-resistance	Coagulation	Yes	Yes
Lupus anticoagulant	Coagulation	Yes	Yes
D-Dimers	Immunoassay	No	No
Thromboelastometry	Coagulation	Yes	Yes
Reptilase time	Coagulation	No	No

Assays,which do not involve generation of factorXa or IIa, not affected.

D dimers
immunoassays
Reptilase time
Ecarin clotting time

Semin Hematol51:98–101.

Monitoring of patient on DOACs

- NO monitoring of INR
- Need to monitor patients
- Be mindful of the few drug interactions
- Need to monitor renal function

Management of DOAC- associated Bleeding

- **Best Strategy** – **PREVENT** Bleeds
  - Know your Drug and Bleeding risks
  - Patient selection
  - Dose adjustment
- Know what to do when bleeding occurs

Conditions that require attention

- Determinants for Bleeding
  - Combined anticoagulant and antiplatelet treatment
  - The elderly
  - Unstable renal function
- When switching Anticoagulants
- Perioperative Bridging anticoagulation

Determinants of Bleeding

Patient's characteristics

- Age > 75 years
- Uncontrolled hypertension (SBP > 180mm Hg or DBP > 100 mm Hg)
- Comorbidities – Liver disease, Renal Disease
- Alcohol excess, poor drug compliance or clinic attendance
- Bleeding lesions (BGIT, recent ICH)
- Bleeding tendency (coagulation defects, thrombocytopenia)

Anticoagulant Effect

- Intensity of anticoagulation
- Concomitant use of NSAIDs and antibiotics
- Instability of INR control and INR > 3
- Pharmacogenetic factors – P450 CYP2C9
- P-gp induction
- CYP34A inhibition

BMJ VOLUME 325 12 OCTOBER 2002 8th ACCP Guidelines

Switching between DOACs and other anticoagulants

- The rate of clearance of the DOACs.
- Half life of LMWH / Heparin
- The time needed to titrate warfarin to therapeutic range
- The influence of the DOACs on INR measurement
- The need for overlap therapy as determined by the indication for anticoagulation.

When switching anticoagulants

Conversion	Start times recommenced
From VKAs to NOAC	Discontinue VKA and start DOAC when INR<2
From NOAC to parenteral	Start parenteral anticoagulant 12 h after last dose of DOAC
From parenteral to NOAC	Start DOAC at the same time or up to 2 hours before the next parenteral drug dose. For continuous infusions of parenteral drugs, start DOAC at the time of discontinuation of the continuous infusion.
From NOAC to VKAs	Start times for VKAs are based on renal function

BLOOD 2012 119: 3016-3023

When switching anticoagulants - DOAC to VKAs

Calculated creatinine clearance, mL/min	Dabigatran: start day with warfarin	Rivaroxaban : start day with warfarin
>50	Day -3	Day -4
31-50	Day -2	Day -3
15-30	Day -1	Day -2

BLOOD 2012 119: 3016-3023

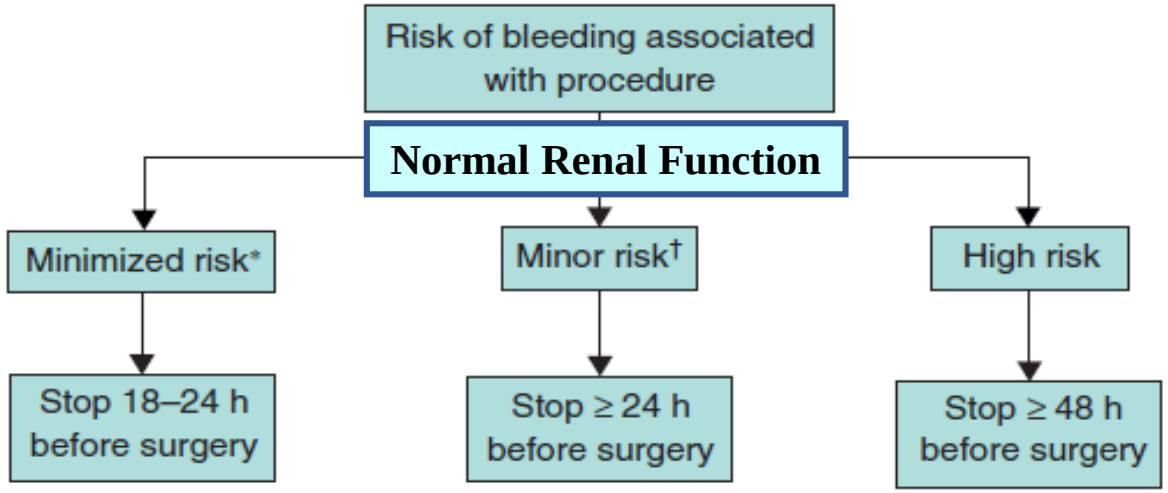
Estimated drug half-lives and effect on area under the curve NOAC plasma concentrations in different stages of chronic kidney disease compared to healthy controls

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I and II	~14 h[48]	No data	~8.6 h[49]	~8.5 h[50] (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h[48]	No data	~9.4 h[49]	~9 h (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h[48]	No data	~16.9 h[49]	~9.5 h (+64%)
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

Europace (2013) 15, 625–651

Peri-surgery Management of DOACs

Check Renal Function before surgery



Creatinine clearance (ml/min)	Risk of bleeding	Suggested interruption (h)		
		Rivaroxaban	Apixaban	Dabigatran
≥ 80	Low	≥ 24	≥ 24	≥ 24
	High	≥ 48	≥ 48	≥ 48
50–79	Low	≥ 24	≥ 24	≥ 36
	High	≥ 48	≥ 48	≥ 72
30–49	Low	≥ 24	≥ 24	≥ 48
	High	≥ 48	≥ 48	≥ 96
15–29	Low	≥ 36	≥ 36	Not indicated
	High	≥ 48	≥ 48	Not indicated
< 15	No indication for any agent			

When Patient Bleeds

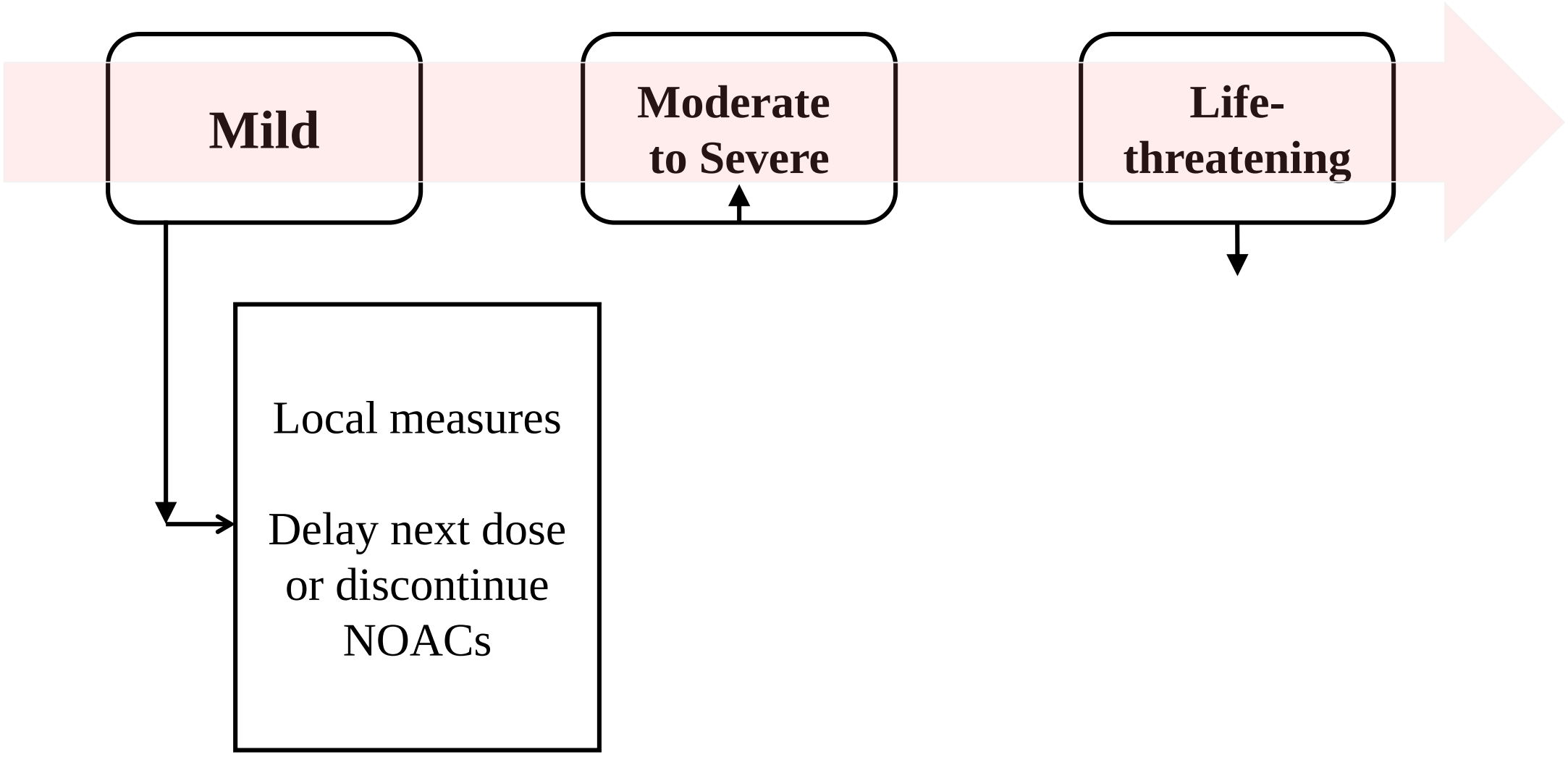
- Anticoagulants do not CREATE bleeds
- Increase the intensity of bleeding[1,2]
- Principles of bleeding management:
  - Are not primarily directed against anticoagulant therapy
  - Are aimed at stopping and controlling the severity of bleeding

1. Ng et al, 2006; 2. Levine et al, 1998; 3. Camm et al, 2012

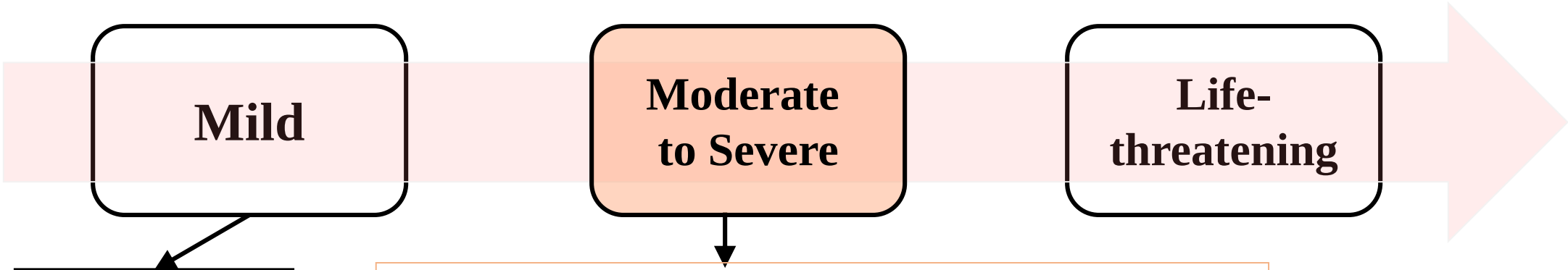
When Patient Bleeds

- **Establish the cause, site and severity for bleed**
- Confirm which anticoagulant was ingested
- Timing of the last ingested dose
- Other contributors to bleed eg. anti-platelet medications
- Use of reversal agents is one of many aspects in management options in severe bleeding
- **Do NOT give vitamin K and FFP for Reversal**

Strategies for bleeding while on DOACs



Strategies for bleeding while on DOACs



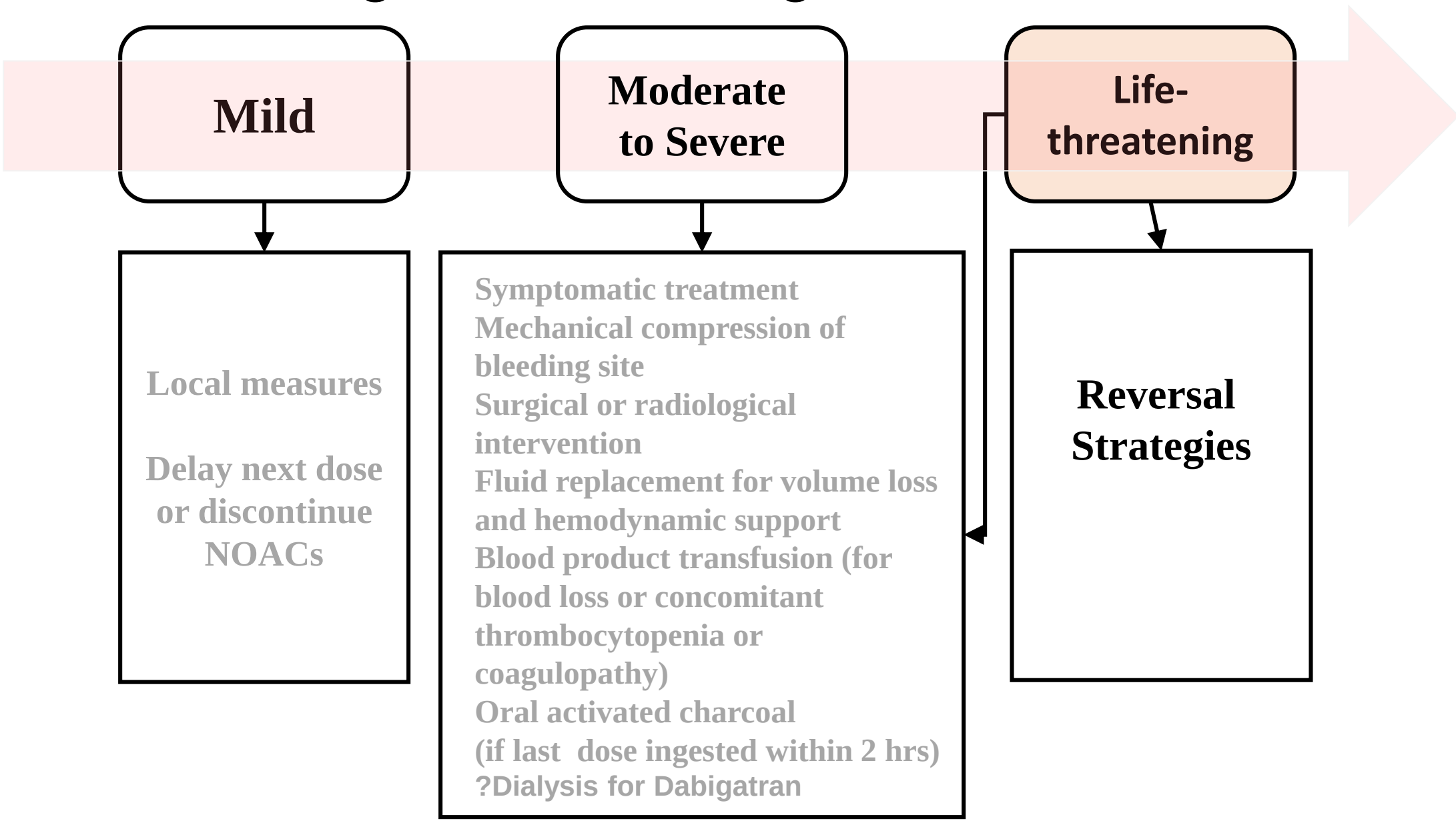
Local measures

Delay next dose or discontinue NOACs

- Symptomatic treatment
- Mechanical compression of bleeding site
- Surgical or radiological intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion (for blood loss or thrombocytopenia or coagulopathy)
- Consider Tranexamic acid
- Oral activated charcoal
- Dialysis for Dabigatran

Anticoagulant effects wear out with time !

Strategies for bleeding while on DOACs



URGENT Reversal of Anticoagulation required:

BLEEDING

Life-threatening bleeding - Intracranial hemorrhage - symptomatic or progressing

Bleeding in a closed space or critical organ - Intra-spinal, intraocular, pericardial, pulmonary, retroperitoneal, intramuscular with compartment syndrome.

Persistent major bleeding despite local hemostatic measures - Esophageal varices

Risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose

EMERGENCY SURGERY / PROCEDURE

- Associated with a high risk of bleeding
- Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery

Journal of Thrombosis and Haemoasis, 14: 623–627

Reversal strategies to restore normal coagulation

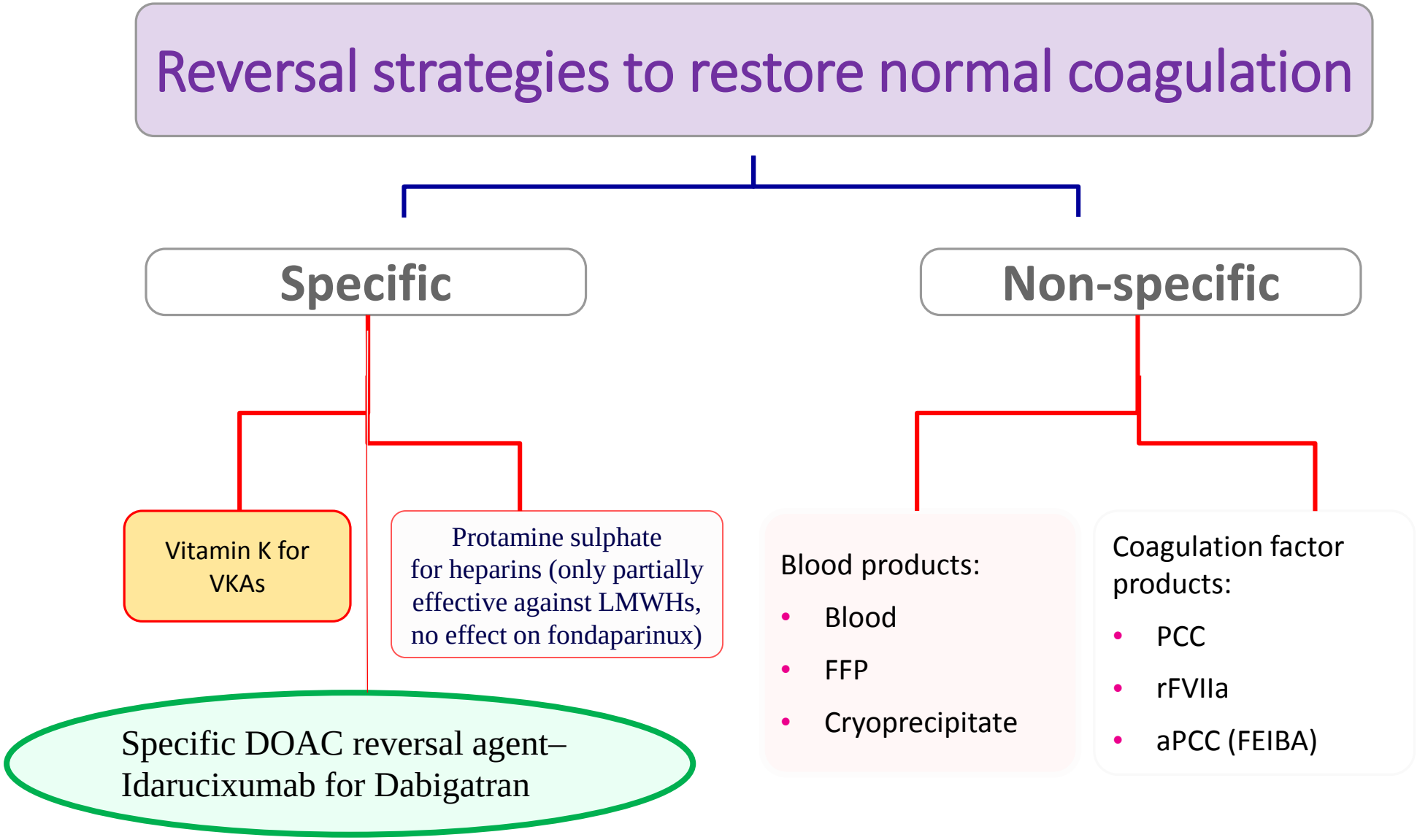


Table 3. Published studies of nonspecific agents for reversal of dabigatran anticoagulant effect in animals and humans

Reversal strategy	Animal studies[23] (dabigatran-treated animals)	Ex vivo studies (dabigatran-treated volunteer or patient plasma)	In vivo human studies (dabigatran-treated healthy volunteers)
PCC	No change in blood loss in mouse tail transection model	Variable effect on TG indices[25,27]	No correction of APTT, ECT, TT[20]
	Reduced intracranial hematoma expansion and 24 hr mortality in mice	Corrected PT, APTT, TT, but not Hemoclot assay[27]	
	Reduced blood loss following kidney incision in rabbits		
	Reduced bleeding time, no effect on coagulation tests in rat tail transection model		
aPCC	No change in blood loss after tail transection in mice	Variable effect on TG indices[25]	
	Reduced bleeding time, no effect on coagulation tests in rat tail transection model	Corrected PT, APTT, but not Hemoclot assay[27]	
rVIIa	No change in blood loss after tail transection in mice	Variable effect on TG indices[25]	
	No change in intracranial hematoma expansion and 24 hr mortality in mice	No correction of PT, APTT and Hemoclot assay[27]	
	Reduced bleeding time, no effect on coagulation tests in rat tail transection model		

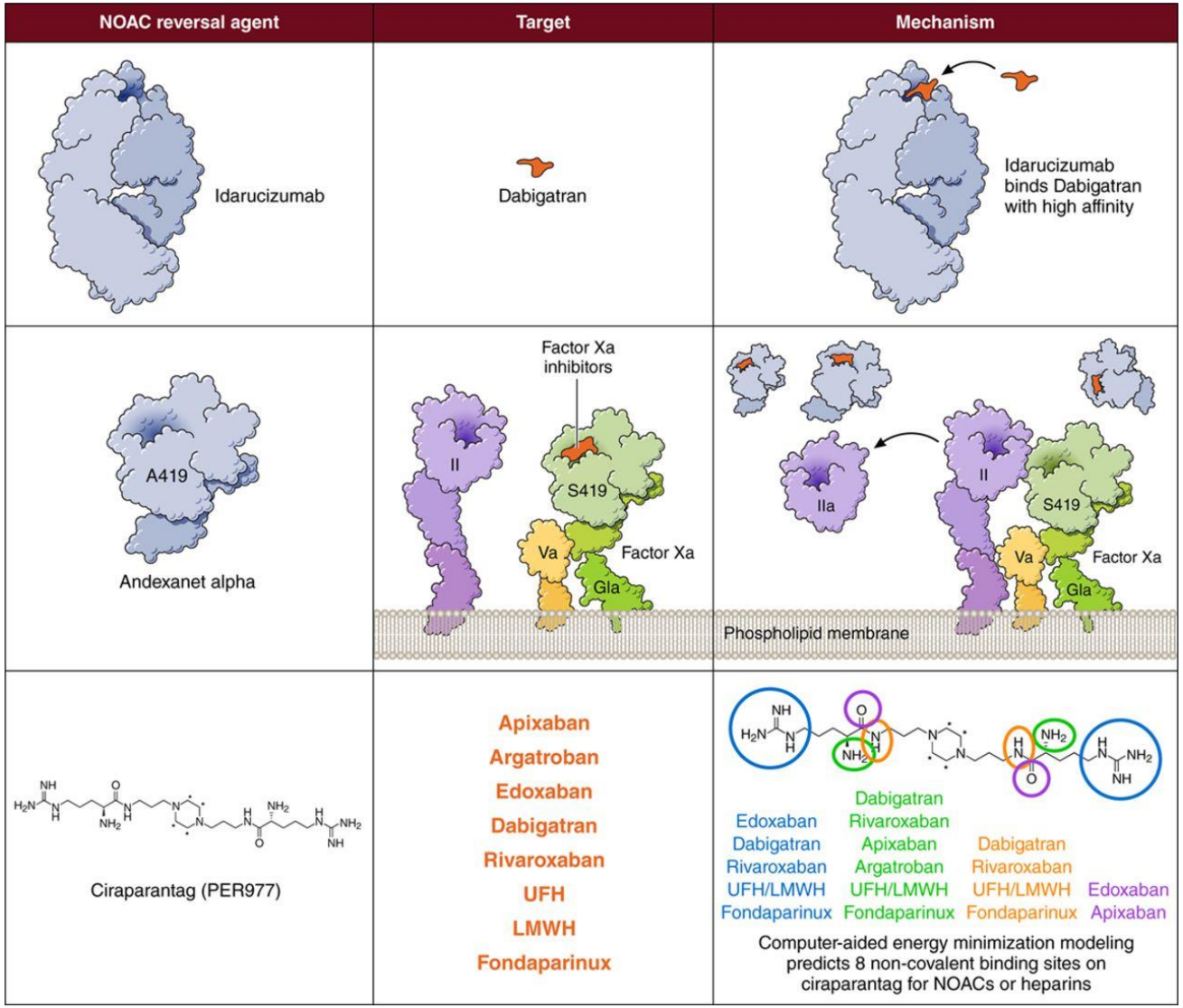
Hematology 2015

Table 4. Published studies of nonspecific agents for reversal of oral factor Xa inhibitor anticoagulant effect in animals and humans

Reversal strategy	Animal studies[23] (factor Xa inhibitor-treated animals)	Ex vivo studies (factor Xa inhibitor-treated volunteer or patient plasma)	In vivo human studies (factor Xa-inhibitor-treated volunteers)
PCC			
Rivaroxaban	Corrected APTT Variable effect on PT	Corrected PT[27] Variable effect on TG indices[25,27]	Corrected PT[20] Partially corrected PT (4-PCC > 3-PCC)[21]
	No reduction of blood loss in rabbits	No correction of anti-Xa activity[27]	Variable effect on TG indices (3-PCC > 4-PCC)[21]
	Reduced bleeding time in rats, but not primates		No correction of APTT, anti-Xa activity[21]
Apixaban	No correction of PT No reduction in hepatosplenic blood loss in rabbits		
Edoxaban	Reduced time to hemostasis and blood loss in rabbit kidney incision model[40]		Reversal of prolonged bleeding duration after punch biopsy (50 IU/kg dose)[22]
aPCC			
Rivaroxaban	Corrected aPTT Variably corrected PT No reduction of blood loss in rabbits Reduced bleeding time in rats and primates	Corrected PT[25] Corrected TG indices[25,27] No correction of anti-Xa activity[27]	
Edoxaban	Reduced bleeding time in rats		
rVIIa			
Rivaroxaban	Corrected PT Reduced bleeding time in rats, but not primates	Corrected PT[27] Variable effect on TG indices[25] No correction of anti-Xa activity[27]	
Apixaban	Corrected PT No reduction in hepatosplenic blood loss in rabbits		
Edoxaban	Reduced bleeding time in rats		

Hematology 2015

Specific DOAC reversal agents.



Christian T. Ruff et al. Circulation. 2016;134:248-261

Idarucizumab (Dabi-Fab) is a humanized Ab fragment that binds to dabigatran, preventing it from binding to thrombin and neutralizing its anticoagulant effect.

Andexanet alfa (And-a) is a modified inactive recombinant FXa that binds circulating FXa inhibitors, allowing native FXa to convert prothrombin to thrombin and restore the coagulation cascade.

Ciraparantag - small synthetic molecule that competitively binds the NOACs, restoring activity of blocked coagulation factors.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

N Engl J Med 2016;375:1131-41.

Thrombosis Research 146 (2016) 113–118

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

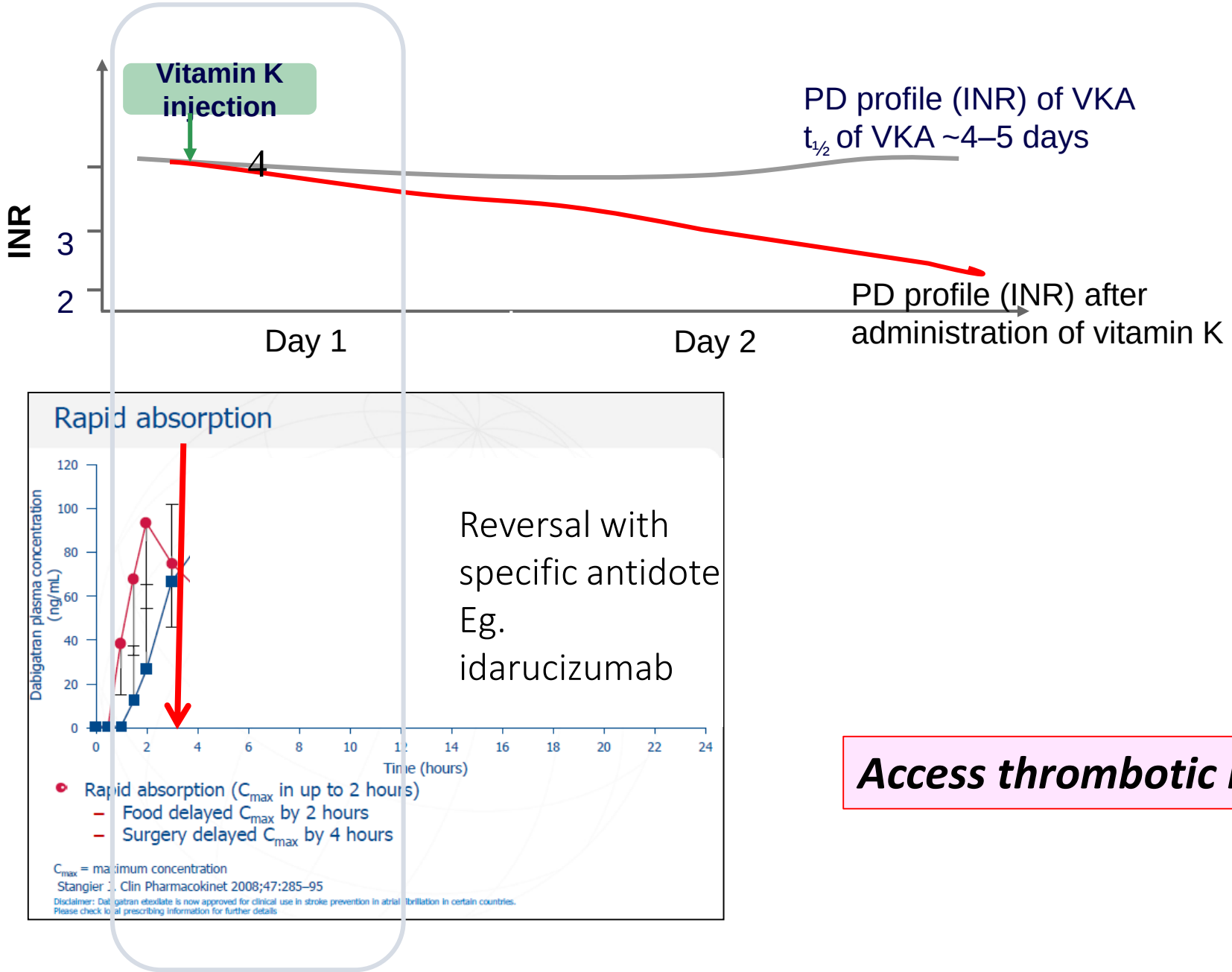
Ciraparantag safely and completely reverses the anticoagulant effects of low molecular weight heparin☆

Jack E. Ansell [a], Bryan E. Laulicht [b], Sasha H. Bakhru [b], Maureane Hoffman [c], Solomon S. Steiner [b], James C. Costin [b,*]

[a] Hofstra North Shore/LIJ School of Medicine, Hempstead, NY, United States
[b] Perosphere Inc., Danbury, CT, United States
[c] Duke University School of Medicine, United States

Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban

TO THE EDITOR: New target-specific oral anticoagulants are limited by the lack of a proven reversal agent. PER977 (Perosphere) is a small, synthetic, water-soluble, cationic molecule that is designed to bind specifically to unfractionated heparin and low-molecular-weight heparin through noncovalent hydrogen bonding and charge–charge interactions (Fig. S1 in the Supplementary Appendix). was used to measure the anticoagulant effect of edoxaban and its reversal by PER977. In clinical trials of PER977, whole-blood clotting time showed low variability (interobserver variation, 3.0%) and high reproducibility (intersubject variation, 3.6%), and correlated well with edoxaban plasma concentrations (Fig. S3 in the Supplementary Appendix).



Reversal with specific antidote Eg. idarucizumab

Access thrombotic risks with Reversal

When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

Indications for use:

- Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage.

- Bleeding in a closed space or critical organ: Intra-spinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome.

- Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose.

- Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance. Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery

Journal of Thrombosis and Haemostasis, 14: 623–627

When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

Potential indication for use

Need for urgent surgery or intervention in patients with acute renal failure

Antidotes should not be used

Elective surgery

Gastrointestinal bleeds that respond to supportive measures

High drug levels or excessive anticoagulation without associated bleeding

Need for surgery or intervention that can be delayed long enough to permit drug clearance

Journal of Thrombosis and Haemostasis, 14: 623–627

Summary – Doacs in real world

- Advances –
  - Real world data reassuring
  - Development of drug specific calibrated assays
  - Development of specific antidotes

- Limitations
  - Lack of data in some disease groups
  - Anti-Xa antidotes not yet available
  - Doctors' familiarity in drug management

Thank you