Coagulation issues and bridging

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“new” oral anticoagulants

NOAC New oral anticoagulants

NOAC Novel oral anticoagulants

NOAC Non vitamin K oral anticoagulants

DOAC Direct oral anticoagulants – ISTH recommended

TSOAC Target specific oral anticoagulants

Overview

- Peri-operative management of
  - Warfarin
  - DOAC’s

- Reversal of anticoagulants

Aim of peri-operative bridging

Risk of thrombosis related to procedure

ATE[1]

- Retrospective cohort study, 30 day rate of stroke.
- 69.202 AF patient vs 2.470.649 non AF patients.
- Absolute risk of stroke
  - 1.8% vs 0.6%
  - Adjusted OR 2.1, highest in neuro or vascular surgery: 3
- Annual risk of stroke in general population of same age 0.7%

VTE[2]

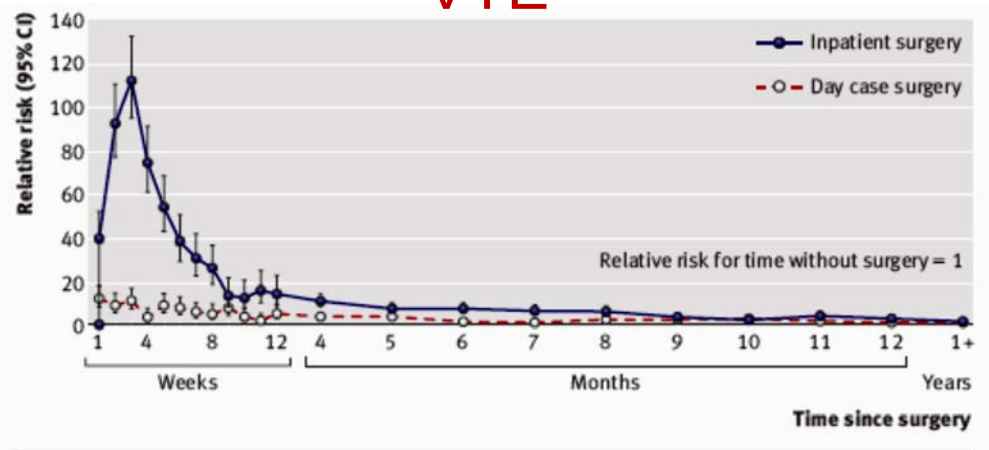


Fig 1 | Relative risk of venous thromboembolism by time since inpatient surgery and since day case surgery

1. Kaatz J Thromb Haemost 2010; 8: 884–90
2. Sweetland et al BMJ 2009;339:b4583

Effectiveness of bridging

Siegal et al Circulation. 2012;126:1630-1639

- 34 papers involving >12000 patients from 2001 – 2010
  - 1 RCT
  - 44% AF, 24% MHV, 22% VTE, 10% other.
  - LMWH 94%, UFH 33%
  - lmwh reinitiation 0 – 24 hrs 55%
- Thromboembolic events
  - 73/7118 bridged patients (0.9%, CI 0-3.4)
  - 32/5160 non bridged (0.6%, CI 0.1.2)
  - 11/1702 non high risk patients (no bridging or prophylaxis 0.6%)
- Bleeding rates
  - Bridging: Overall 13.1% (CI 0 – 45%) and Major 4.2% (0 – 11.3%)
  - Non bridged: 3.4% (1.1 – 5.8%) and 0.9% (0.2 – 1.6%)
- OR 5.40 (CI 3 – 9.7) overall, OR 3.6 (1.5 – 8.5) major.
- Problem: only 1 RCT, observational studies lacking controls, Possibility of systematic bias and bridging may prevent TE events in high risk patients.

Bridge trial

- 934 dalteparin bridging vs 950 no bridging in AF
- 223/235 major surgery
- Mean CHADS2 = 2.3
- 23 patients CHADS2 = 5,
- 3 patients CHADS2 = 6
- 79 previous stroke
- Carotid endartectomy, major cancer surgery, cardiac & neuro surgery not represented.

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

Douketis et al NEJM 2015;373:823-33.

Net benefit of bridging in high risk AF and mechanical heart valves remains unclear

Post op bleeding causes delay in full anticoagulation and thus increased thrombotic risk

Trials

- Periop 2 trial[1]
  - Randomized double blind placebo controlled trial in AF and mechanical heart valves. Dalteparin vs placebo.
  - Primary outcome: thromboembolism
  - 1773 patients, completion date March 2017

1. http://clinicaltrials.gov/ct2/show/study/NCT00432796

Risk stratification BCSH

(Adapted from Keeling Br J Haematol 2011;154:311-324)

	Indication for VKA		
Risk	**Mechanical valve**	**Non valvular AF**	**Venous thrombosis**
High **(consider bridging)**	MVR, old AVR, bileaflet AVR with risk factors	AF with prior stroke/TIA	VTE in last 3 months
Low **(no bridging with therapeutic LMWH)**	Bileaflet AVR without other risk factors	AF without prior stroke/TIA*	VTE > 3 months ago

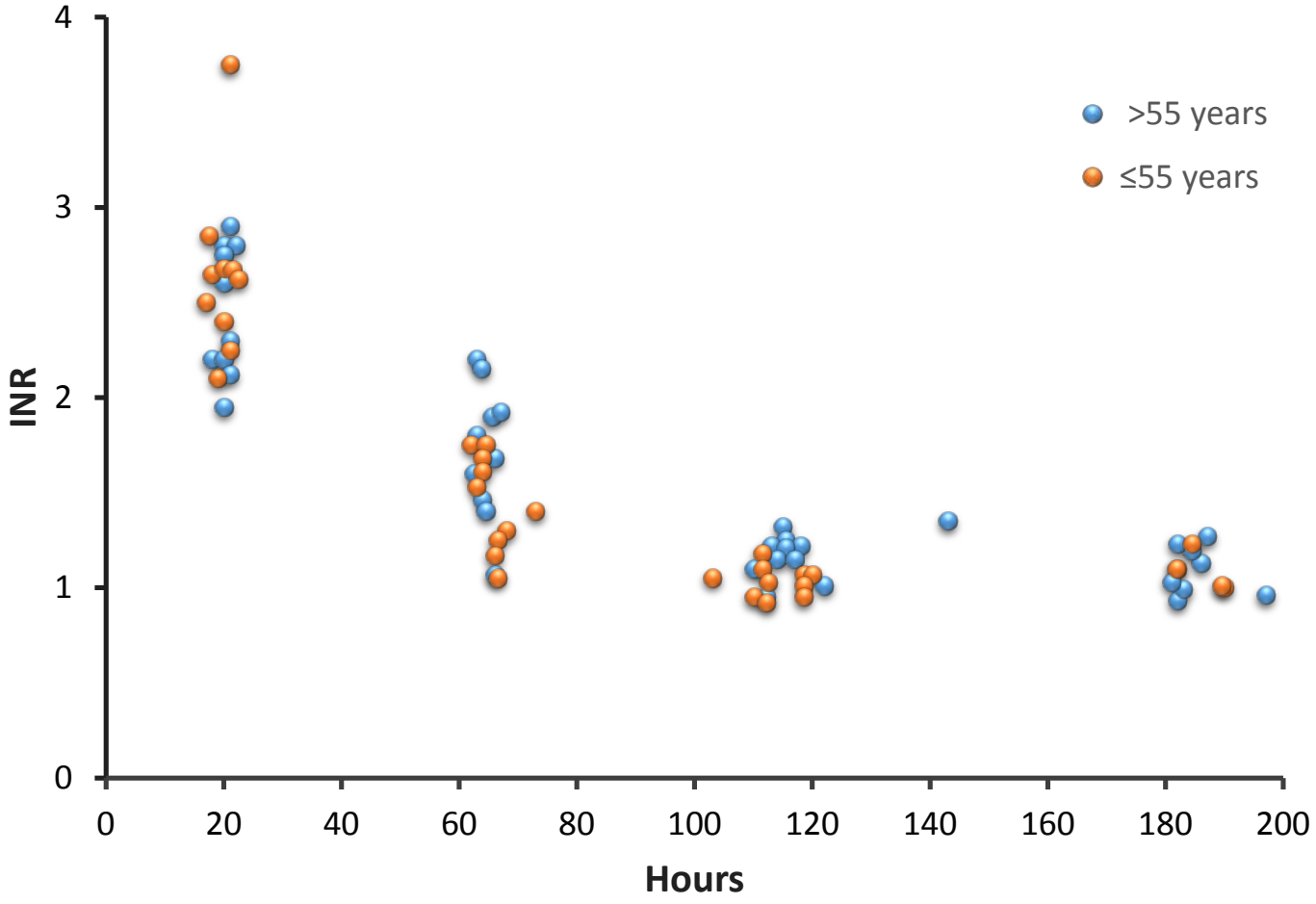
* Consider bridging if multiple risk factors for stroke present

Surgery without interruption or reduction of warfarin

- Dental surgery
  - single or multiple extractions
- Dermatological surgery
- Eye surgery
  - cataract surgery
- Endoscopy with or without biopsy
  - upper or lower gastrointestinal tract
- Joint and soft tissue injections/aspirations
- Coronary angiography and pacemaker insertion

INR following discontinuation of warfarin

White RH et al. Ann Int Med 1995; 122:40-42



All patients had an INR <1.5, five days (120hr) after the last dose

Need 4 clear days without warfarin pre-op

When to start LMWH before surgery?

Avoids delay in surgery with raised INR or blood product usage

INR check
1 mg Vit K if >1.5

-6d	-5d	-4d	-3d	-2d	-1d	Surgery
-144hr	-120hr	-96hr	-72hr	-48hr	-24hr	
Warfarin	Warfarin			LMWH	LMWH	

High thrombotic risk:

Therapeutic LMWH by weight s/c BD, last dose 24 hours pre procedure.

Restarting anticoagulation: high thrombotic risk (Sheffield guidance)

Major surgery prophylactic dalteparin OD 6–8 h post-op	D+1	D+2	D+3	D+4	D+5	D+6
	Warfarin at usual dose Continue prophylactic dalteparin		Warfarin at usual dose Increase prophylactic dalteparin to BID until INR > 2.0		Warfarin at usual dose Increase dalteparin to therapeutic doses until INR > 2.0	

- Provided haemostasis is secure:
  - Continue prophylaxis OD/omit if any concern about bleeding
  - Re-start therapeutic LMWH at earliest at 48–72 hours (ACCP/BCSH guidance[1,2])
  - Consider re-starting therapeutic LMWH at 24 hours after minor procedures[1]

ACCP, American College of Chest Physicians; BCSH, British Committee for Standards in Haematology

1. Douketis *et al. Chest* 2012;141:e326S;
2. Keeling *et al*. *Br J Haematol* 2011;154:311

Discharge

Ensure that usual anticoagulation provider is aware of the bridging plan and happy to review the patient, continue LMWH prescriptions and to stop LMWH when INR ≥ 2

DOACs

	Dabigatran (IIa inhibitor)	Rivaroxaban (Xa inhibitor)	Apixaban (Xa inhibitor)	Edoxaban (Xa inhibitor)
Licensed for	SPAF Treatment and 2nd prevention of VTE	SPAF Treatment and 2nd prevention of VTE	SPAF Treatment and 2nd prevention of VTE	SPAF Treatment and 2nd prevention of VTE
Protein binding	35%	high	high	High
Peak effect, h	0.5–2	2–4	3–4	1–2
Excretion	Renal	Renal/hepatic	Renal/hepatic	Renal/hepatic
$T_{½}$, h	11–14 (27 h CrCl <30 ml/min)	5–13	~12	10–14

Heidbuchel *et al, Europace* doi:10.1093/europace/euv309

Invasive procedures on DOAC's

Beyer-Westendorf et al European Heart Journal doi:10.1093/eurheartj/eht557

- 595 patients with 863 procedures. Dresden prospective NOAC registry.
  - 15.6% minimal, 74.3% minor, 10.1% major.
  - Rivaroxaban 76%, dabigatran 23.5%, apixaban 0.5%
- Peri-operative management
  - DOAC continued in 21.7%
  - Interrupted without heparin 48.6% (median 2 days pre, 1 day post)
  - Interrupted with heparin 7.3% prophylactic, 22.5% therapeutic
    - 74.7% of major, 24.8% minor, 10.4% minimal procedures

Invasive procedures on DOAC's

Beyer-Westendorf et al European Heart Journal doi:10.1093/eurheartj/eht557

- Major cardiovascular events
  - 4.6% major procedures vs 0.8% and 0% minor and minimal
    - Independent of heparin bridging
  - Cardiovascular death 0.3%
- Major bleeding
  - 8% major procedures vs 0.5% and 0% minor and minimal
    - Overall in 2.7% of bridged patients and 0.5% in non bridged patients
    - Heparin not independently associated with bleeding
- All bleeding
  - 16.1% major procedures vs 4.5% minor and 2.2% minimal

Invasive procedures on DOAC's

- Some procedures may be performed without DOAC interruption: ? Same as on VKA but more data needed
- Short interruption probably safe
  - Warfarin stopped 114 hours before procedures, dabigatran 49 hours without differences in major bleeding or thrombotic events[1].
  - Dresden NOAC registry: total interruption 3 days[2].
- Increased bleeding with similar cardiovascular event rate after major procedures with bridging
  - Care needed in re-instituting full anticoagulation after major procedures similar to patients on VKA

1. Healey et al Circulation. 2012. p. 343–8

2. Ebertz et al Eur Heart J. 2014;doi:10.109

Trials

- Perioperative Anticoagulant Use for Surgery Evaluation Study (PAUSE)[1]
  - Prospective observational cohort study
  - to establish a safe, standardized protocol for the perioperative management of patients with atrial fibrillation (AF) who are receiving a novel oral anticoagulant (NOAC) drug, either dabigatran, rivaroxaban or apixaban, and require an elective surgery/procedure.
  - Completion date 2017

1. https://clinicaltrials.gov/ct2/show/study/NCT02228798

Pre-operative management of DOACs: STH advice

Drug	Surgery	CrCl (ml/min)	Day -4	Day -3	Day -2	Day -1	Day 0 (surgery)
Rivaroxaban	Major	>30			Omit →		
		15 – 29.9		Omit →			
	Minor	>30				Omit →	
		15 – 29.9			Omit →		
Dabigatran	Major	>50			Omit →		
		30 - 50		Omit →			
	Minor	>50				Omit →	
		30 - 50			Omit →		
Apixaban	Major	>50			Omit →		
		15 – 50		Omit →			
	Minor	>50				Omit →	
		15 – 50			Omit →		

Adapted from Spyropoulos & Douketis Blood. 2012. p. 2954–62.

Post-operative management of DOAC's

Drug	Surgery	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Rivaroxaban	Major	Prophylactic		Therapeutic ***at earliest*** at 48 – 72 hrs			
	Minor	Prophylactic	Therapeutic ***at earliest*** at 24 hrs				
Dabigatran	Major	Prophylactic		Therapeutic ***at earliest*** at 48 – 72 hrs			
	Minor	Prophylactic	Therapeutic ***at earliest*** at 24 hrs				
Apixaban	Major	Prophylactic		Therapeutic ***at earliest*** at 48 – 72 hrs			
	Minor	Prophylactic	Therapeutic ***at earliest*** at 24 hrs				

- If concern about absorption use LMWH.
- Check U&E/LFT before re-starting.
- No reversal agent.
- Re-start only if no concern about bleeding

DOAC and coagulation tests

- Rivaroxaban prolongs PT > APTT.
  - Cannot be used to determine the drug level.
  - Normal PT makes therapeutic anticoagulation unlikely but does not exclude this. Dependent on reagents used.
  - Drug levels by anti Xa assay
- Dabigatran prolongs APTT > PT
  - Cannot be used to determine the drug level.
  - Normal APTT makes therapeutic anticoagulation unlikely but does not exclude this. Dependent on reagents used.
  - Drug levels by Haemoclot assay
- Apixaban: PT and APTT cannot be used to estimate the presence of therapeutic apixaban
  - Drug levels by anti Xa assay

Emergency surgery on DOACs

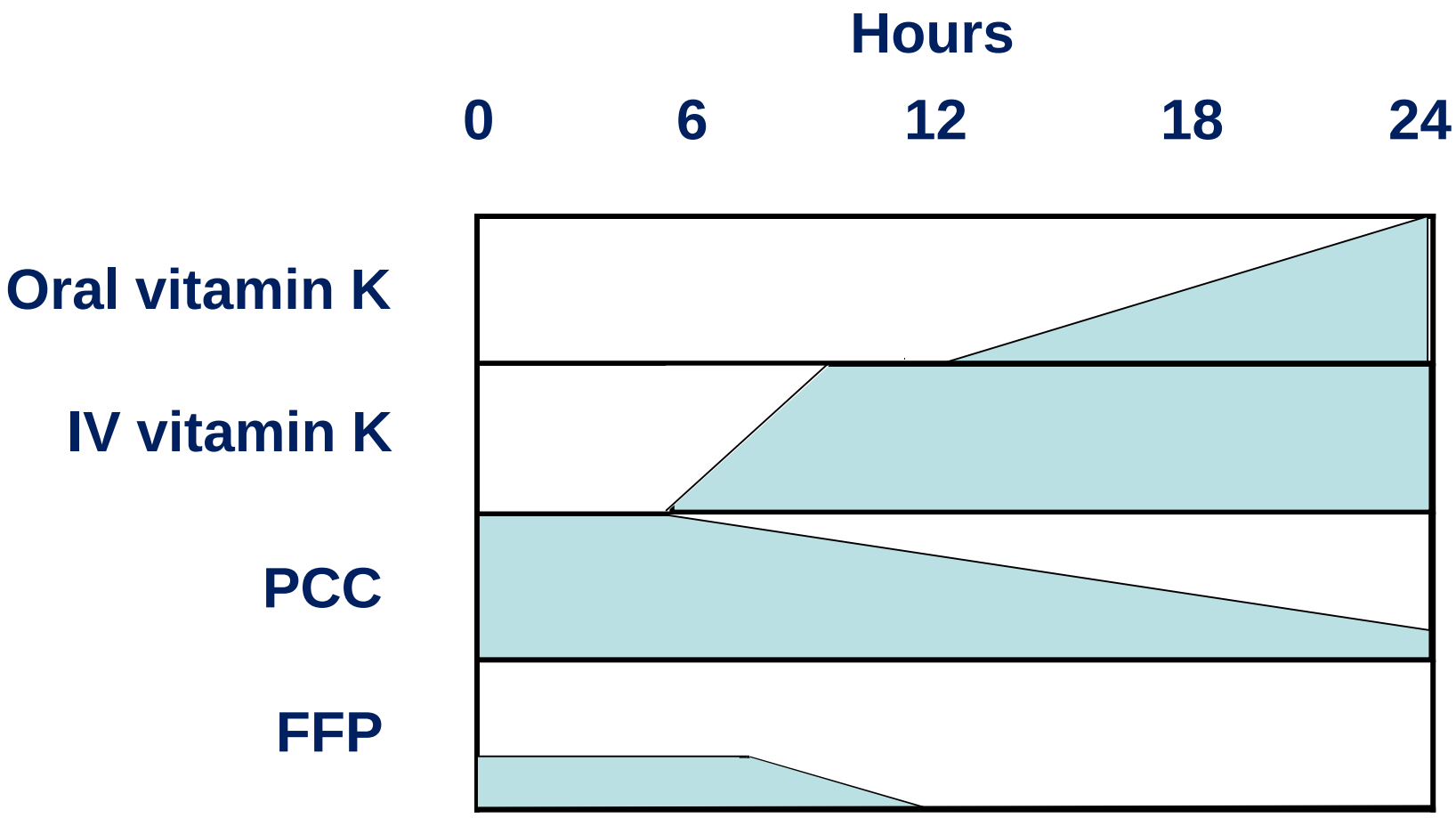
- Establish which drug the patient is taking
- Establish when the last dose was
- PT/APTT/TT *may* be helpful in rivaroxaban and dabigatran
- Specific levels if available
- Wait 1 – 2 half lives if possible
- Avoid epidural/spinal anaesthesia
- Do not use non specific haemostatic agents prophylactically as effectiveness unproven & thrombotic risk
  - rFVIIa, (a)PCC

Bridging anticoagulation - conclusion

- Difficult balance between bleeding and thrombosis.
- Net benefit unproven in high risk AF and mechanical heart valves; await trial data.
  - Risk of bleeding outweighs the risk of thrombosis in low/intermediate risk patients
  - Bridging in DOAC's likely not necessary given short time off anticoagulation
- Consider if continuing oral anticoagulation is an option.
  - Safety of minor procedures with DOACs unproven but anticipated
- Do not start therapeutic doses of any anticoagulant to early.

Reversal of anticoagulants

Reversal of warfarin



Makris et al J Thromb Thrombolysis 2010; 29:171–181

Dabigatran reversal with PCC/aPCC

Reference	Reversal agent	Model	Lab test	Bleeding
Zhou 2011	PCC	Mouse ICH		✓
Pragst 2012	PCC	Rabbit kidney bleeding	✓✗	✓
Hoffman 2012	PCC	Human in vitro	✓	
Van Ryn 2011	PCC	Rat tail cut	✗	✓
Herzog 2013	PCC	Rabbit AV shunt	✓✗	✓
Lambourne 2012	PCC	Mouse tail clip	✗	✗
Eerenberg 2011	PCC	Human volunteers	✗	
Marlu 2012	PCC	Human ex vivo	✓	
Van Ryn 2012	PCC	Rat tail cut	✗	✓
Marlu 2012	aPCC	Human ex vivo	✓	

Rivaroxaban reversal with PCC/aPCC

Reference	Reversal agent	Model	Lab test	Bleeding
Perzborn 2013	PCC	Rat mesenteric bleeding	✓	✓
Zhou 2013	PCC	Mouse ICH	✗	✓
Godier 2012	PCC	Rabbit hepatosplenic bleeding	✓	✗
Eerenberg 2012	PCC	Human volunteers	✓	
Dinkelaar 2013	PCC	Human in vitro	✓	
Marlu 2012	PCC	Human ex vivo	✓	
Marlu 2012	aPCC	Human ex vivo	✓	
Perzborn 2013	aPCC	Rat mesenteric bleeding	✓	✓
Perzborn 2013	aPCC	Baboon mesenteric bleeding	✓	✓
Zahir 2015	PCC	Punch biopsy in humans	✓	✓

Management of bleeding on DOACs[1]

	General measures	Specific reversal agent	Charcoal after ingestion	Haemo-dialysis	rFVIIa/PCC/APCC
Dabigatran	Yes	No	Yes within 2 h	Yes	Consider in ongoing life-threatening bleeding *In vitro* and animal data. Preliminary, inconclusive and contradictory PCC-normalised thrombin generation in healthy volunteers (rivaroxaban, edoxaban)[2,3] Bleeding after punch biopsy (edoxaban)[3]
Rivaroxaban	Yes	No	Yes, can be considered	No	
Apixaban	Yes	No	Yes within 2–6 h	No	
Edoxaban	Yes	No	Yes, can be considered	No	

1. Makris *et al*. *Br J Haematol* 2013;160:34; 2. Eerenberg *et al*. *Circulation* 2011;124:1573;
3. Zahir *et al*. *Circulation* 2015;131:82

Specific reversal agents for DOAC's

- Idarucizumab: Humanised monoclonal antibody fragment against dabigatran.
  - Phase 3 trials done. Applied for license with FDA, EMA, Canadian licensing agency
- Andexanet alpha: Recombinant modified factor Xa.
  - Phase 2 studies completed for: apixaban 5mg BD, rivaroxaban 20 mg OD, enoxaparin 40 mg OD
  - Ongoing edoxaban 60 mg OD, enoxaparin 1 mg/kg and betrixaban 80 mg OD planned
  - Annexa-A and Annexa-R phase 3 studies for reversal of apixaban and rivaroxaban
  - Bolus followed by continuous infusion in 33 subjects
- PER977: Binds all DOACs

Summary

- For warfarin the antidotes are vitamin K and PCC, not FFP
- The DOACs do not have antidotes at present. Management is with supportive care, waiting and possibly PCC.
- Specific DOAC antidotes are likely to be available within the next 1-3 years.