Bridging anticoagulation

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Bridging anticoagulation - conclusion

- Difficult balance between bleeding and thrombosis.
- Net benefit unproven; await trial data.
- Consider if continuing oral anticoagulation is an option.
  - Safety of minor procedures with NOACs unproven but anticipated
- Consider in moderate and high thrombotic risk patients.
- Do not start therapeutic doses to early.
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Aim

- Bridging plan based on LMWH for peri-operative patients on oral coagulants
  - Standardised approach
  - Patients at risk of thrombosis can be treated at home pre-op
  - Avoid cancellation of surgery because of high INR's
  - May allow early discharge in selected patients

Questions

- What is the evidence?
- Does oral anticoagulation need to be stopped and if so when?
- When and at what dose is alternative anticoagulant restarted post operatively?
- New anticoagulants?

Evidence based?

- Quality of published reports poor
- Only 1 randomised controlled trial, mainly observational studies
- Small size reports
- Often no control groups
- Timing of administration and discontinuation of peri-operative anticoagulant often not described
- Duration of follow-up often not stated

Systematic Review

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.

Net benefit of bridging is unclear

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

Trials

- Bridge study[1]
  - Randomized double blind placebo controlled trial in valvular or non valvular AF $CHADS_2 \geq 1$. Dalteparin vs placebo.
  - Primary outcome ATE and major bleeding
  - 1415 patients enrolled so far, completion date March 2015.

- Periop 2 trial[2]
  - Randomized double blind placebo controlled trial in AF and mechanical heart valves. Dalteparin vs placebo.
  - Primary outcome: thromboembolism
  - 1773 patients, completion date March 2013

1. http://clinicaltrials.gov/ct2/show/NCT00786474

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

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

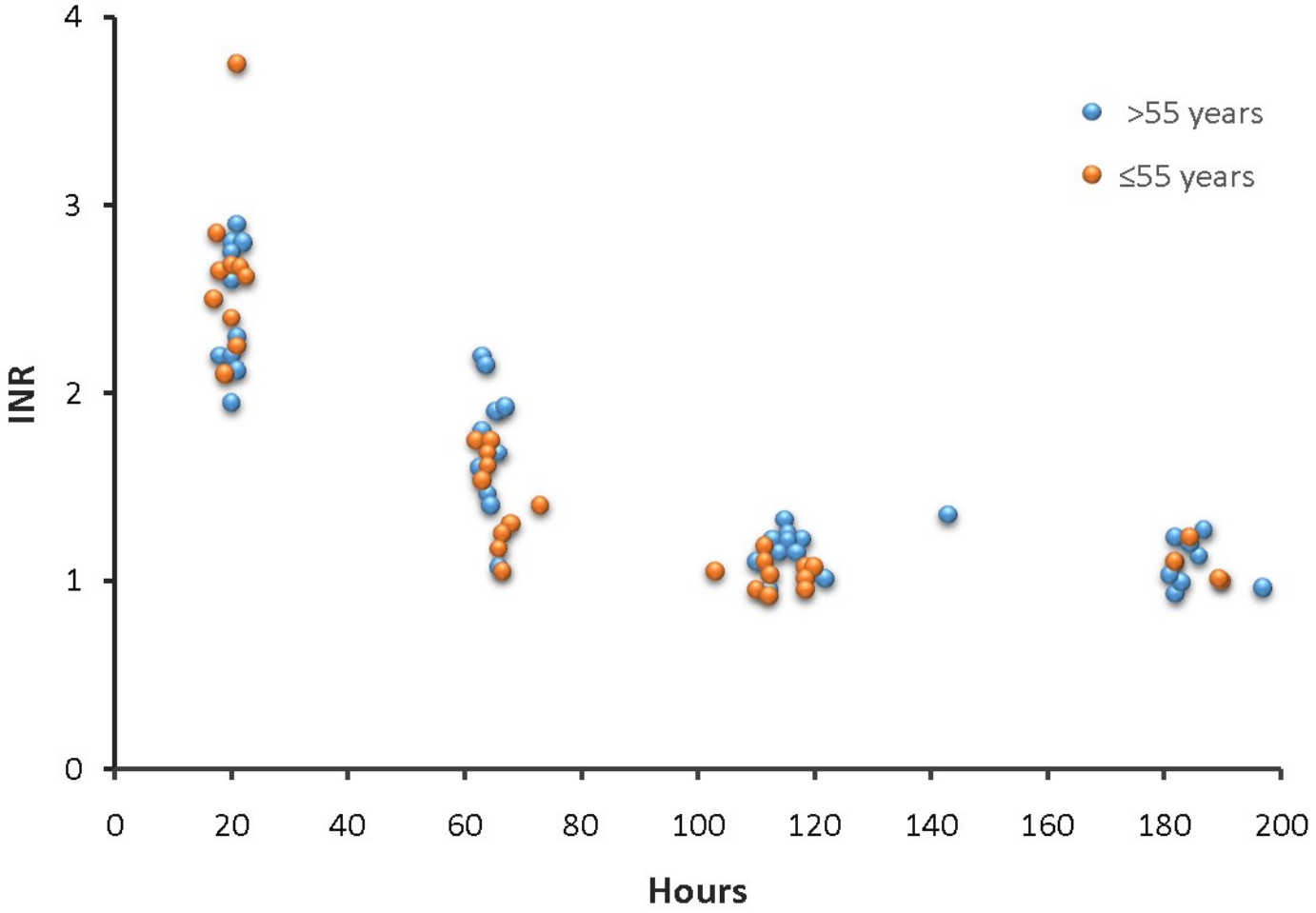
Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation

N Engl J Med 2013. DOI: 10.1056/NEJMoa1302946

Outcome	Heparin bridging (n=338) ≈80% LMWH	Continued warfarin (n=343) Median INR 2.3	RR (95% CI)	P value
Clinically significant Haematoma	54 (16%)	12 (3.5%)	0.19 (0.10-0.36)	<0.001
Haematoma prolonging hospitalisation	16 (4.7%)	4 (1.2%)	0.24 (0.08-0.72)	0.006
Haematoma requiring interruption of anticoagulation	48 (14.2%)	11 (3.2)	0.20 (0.10-0.39)	<0.001
Haematoma requiring evacuation	9 (2.7%)	2 (0.6)	0.21 (0.005-1.00)	0.03
Patient satisfactory score	5.9 +/- 1.8	6.4 +/- 1.5		<0.001

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

When to stop warfarin before surgery?

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

ie 4 clear days without warfarin

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

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.

Risk assessment, vitamin K and dalteparin by pre-assessment clinic.

Last dose LMWH

- **Prophylactic dose** : 18.00hrs on evening before surgery.
- **Therapeutic dose**: 24 hours before surgery
- Both allow for spinal/epidural anaesthesia

Restarting anticoagulation: high thrombotic risk (Sheffield guidance)

Surgery	D +1	D+2	D+3	D+4	D+5	D + 6
Prophylactic dalteparin OD 6 – 8 hrs post op	Warfarin at usual dose Continue prophylactic dalteparin		Warfarin at usual dose Increase prophylactic dalteparin to twice daily 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 hrs: ACCP/BCSH guidance)

Consider re-starting therapeutic LMWH at 24 hours after minor procedures.

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

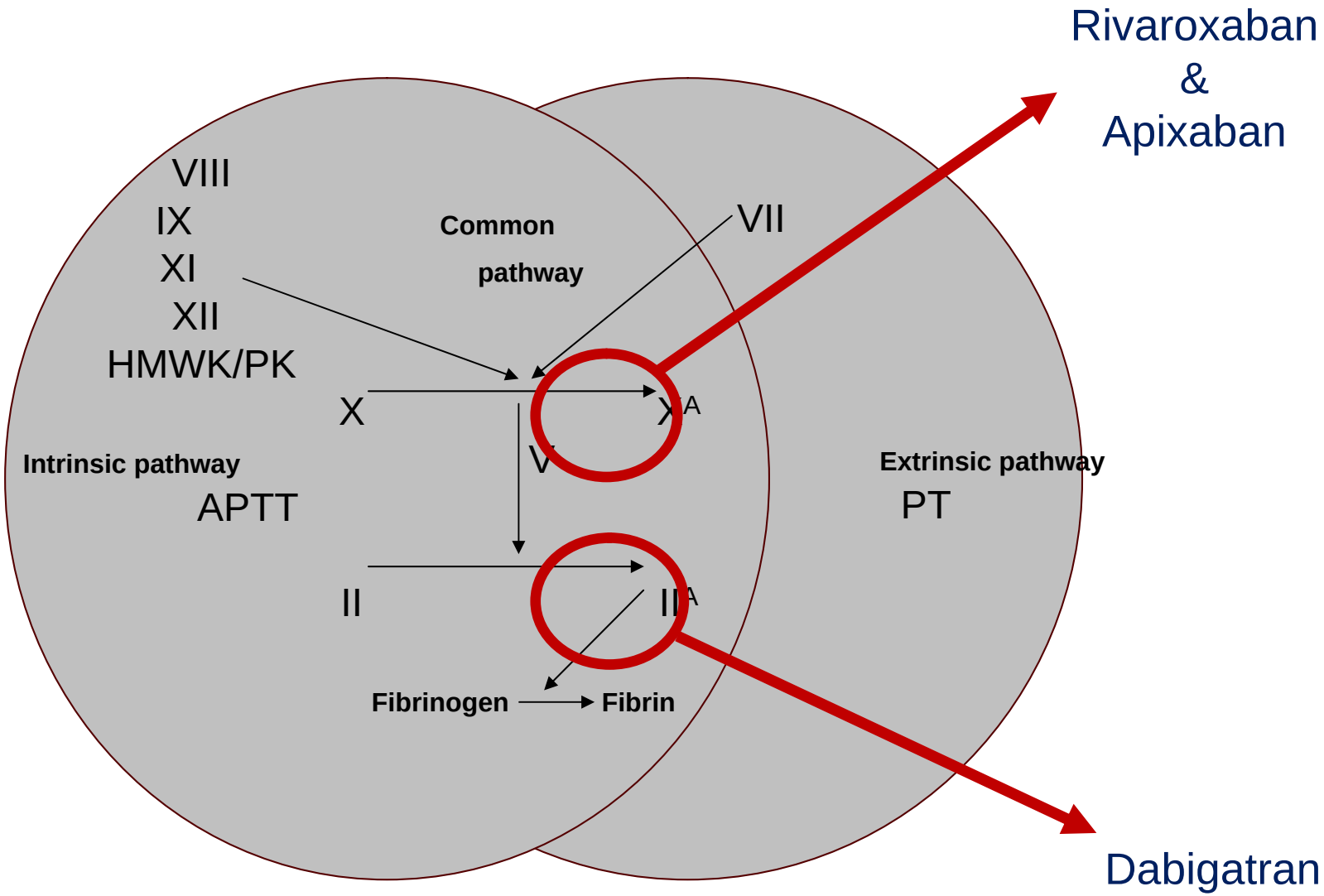
New Oral Anticoagulants

	Dabigatran (IIa inhibitor)	Rivaroxaban (Xa inhibitor)	Apixaban (Xa inhibitor)
Orthopaedic thromboprophylaxis	+	+	+
General thromboprophylaxis	-	-	-
AF	+	+	+
DVT	-	+	-
PE	-	+	-
Peak effect	2 – 3 hours	2 – 3 hours	
Excretion	renal	Renal/hepatic	Renal/hepatic
Half life	13 – 18hours 27 hrs CrCl < 30ml/min	9 – 11 hours	12 hours

Other FXa inhibitors in development:

- Edoxaban (Daiitchi Sankyo) – licensed in Japan for thromboprophylaxis
- Otamixaban (Sanofi Aventis)
- Betrixaban (Portola)

NOAC and coagulation tests



Need calcium and phospholipids

NOAC 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
  - 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
  - Drug levels by Haemoclot assay
- Apixaban: PT and APTT cannot be used to estimate the presence of therapeutic apixaban
  - Levels can not (yet) be measured.

Procedures that can be performed on VKA *may* also be safe on NOACs but no evidence yet

NOAC's – minor procedures that can be done on VKA therapy

Omit the morning dose and re-start post procedure if no concern about bleeding

(Sheffield guidance)

Pre-operative management of NOAC's

Adapted from Spyropoulos Blood 2012;120(15):2954-2962

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

Post-operative management of NOAC'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

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