Association of Anaesthetists

DOACs & Hip Fracture Care

Dr Amy Mayor FRCA
Consultant Anaesthetist

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Declarations

- No financial interests
- Principal Investigator HIP ATTACK trial
- Member of NHS Hip Fracture Perioperative Network
- Member of NHS Yorkshire Hip Fracture Anaesthesia Network
- Author of ratified CHFT #NOF DOAC policy

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Overview

- Putting DOACs into context - anticoagulation and surgery and current established practice
- Dangers of abrupt cessation of these drugs
- Delays to theatre caused by DOACs
- DOACs in detail
- Huddersfield Royal Infirmary's DOAC #NOF protocol
- Evidence of protocol safety and overview of recent publications

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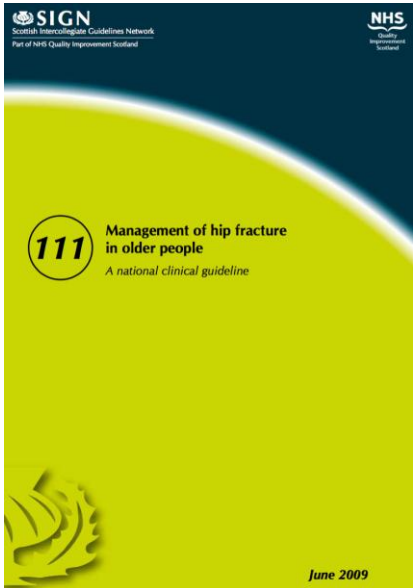
Antiplatelets & Anticoagulation

- Two issues posed by these drugs:
  i. Surgical bleeding
  ii. Vertebral canal haematoma

- Established practice:
  - Aspirin is not a contraindication to CNB
    - (nor should any single antiplatelet inc clopidogrel)
  - Proceed with surgery if INR <2.0 (under GA)
  - Proceed with CNB if INR <1.5



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VERTEBRAL CANAL HAEMATOMA

NAP 3:

- Incidence of VCH = 6 in 707,425 CNBs
- **ALL** in elective epidurals
- **NONE** in 360,000 spinals

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VERTEBRAL CANAL HAEMATOMA

British Journal of Anaesthesia **104 (4):** 429–32 (2010)
doi:10.1093/bja/aeq029 Advance Access publication February 23, 2010

BJA

Epidural analgesia in vascular surgery patients actively taking clopidogrel

W. A. Osta*, H. Akbary and S. F. Fuleihan

Osta et al, BJA 2010

- Series of 306 patients undergoing vascular procedures on clopidogrel +/- heparin
- No VCH

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VCH in a fully anticoagulated patient

- Risk of VCH is increased x 15
- NAP 3
  - 6 in 707425
- Risk x 15 if anticoagulated, so:
  - 6 x 15 = 90 in 707425
  - 1 in 7860
- NHFD
  - 500,000 / 7860 = 64 in 10 years
    - Epidurals, not spinals

- Vigilance is key
  - Back pain
  - Numbness
  - Motor weakness
  - Bowel / bladder incontinence

HIP ATTACK
HIP fracture Accelerated surgical care and TreaTment trACK

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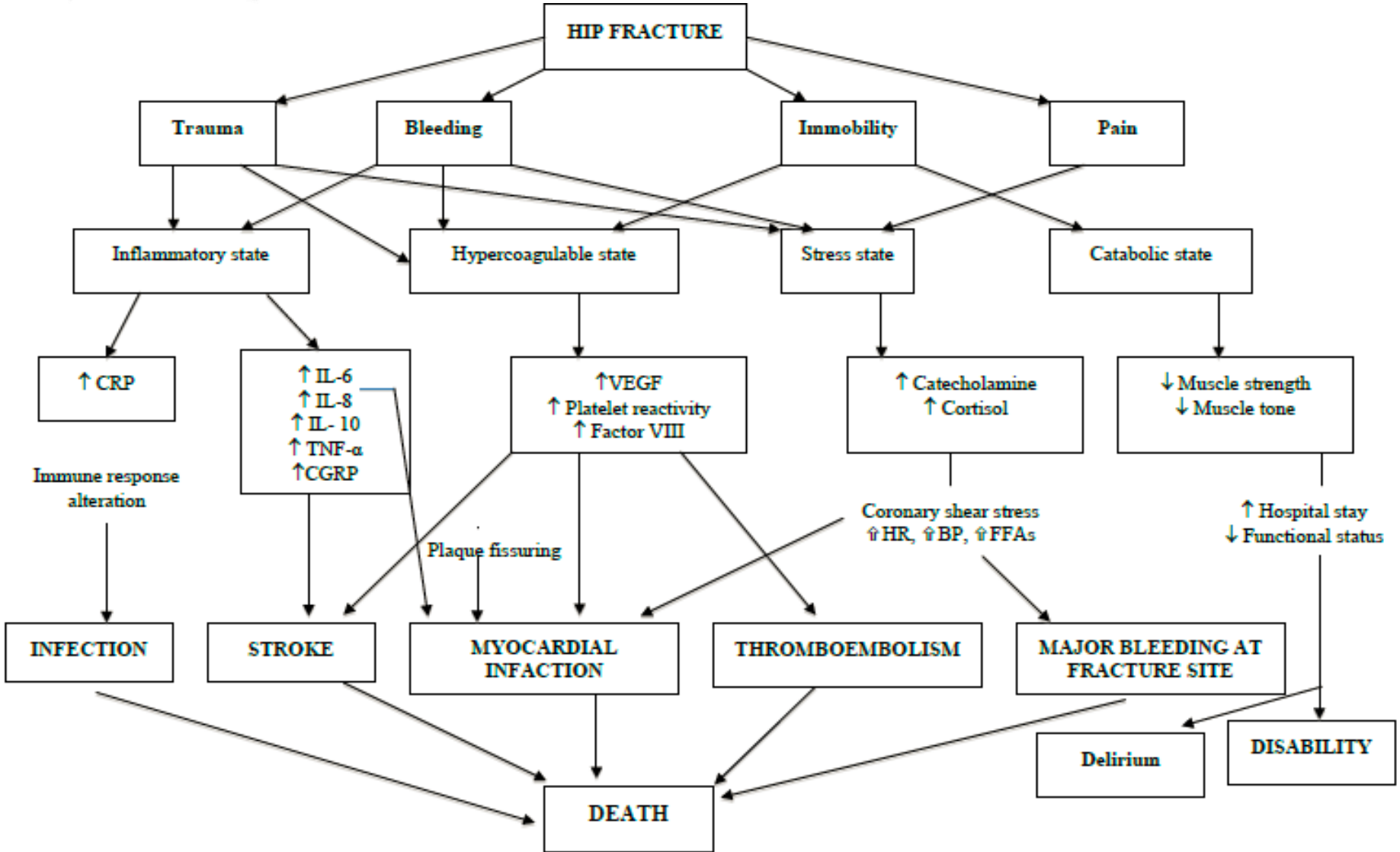
VTE is the real concern



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Abrupt Cessation of Antiplatelets & Anticoagulants

- Abrupt cessation of APM (especially dual-APM) can be detrimental to the patient in terms of cardiovascular, cerebrovascular and vascular pathology.
- Cessation is an independent risk factor for serious events such as stroke and coronary artery stent occlusion, especially in the perioperative period.
- Our #NOF population have risk factors that make thrombosis even more likely
  - Age >65 years, CCF, HTN, DM, PVD, trauma
- **Cessation** of these agents is where the real risk lies

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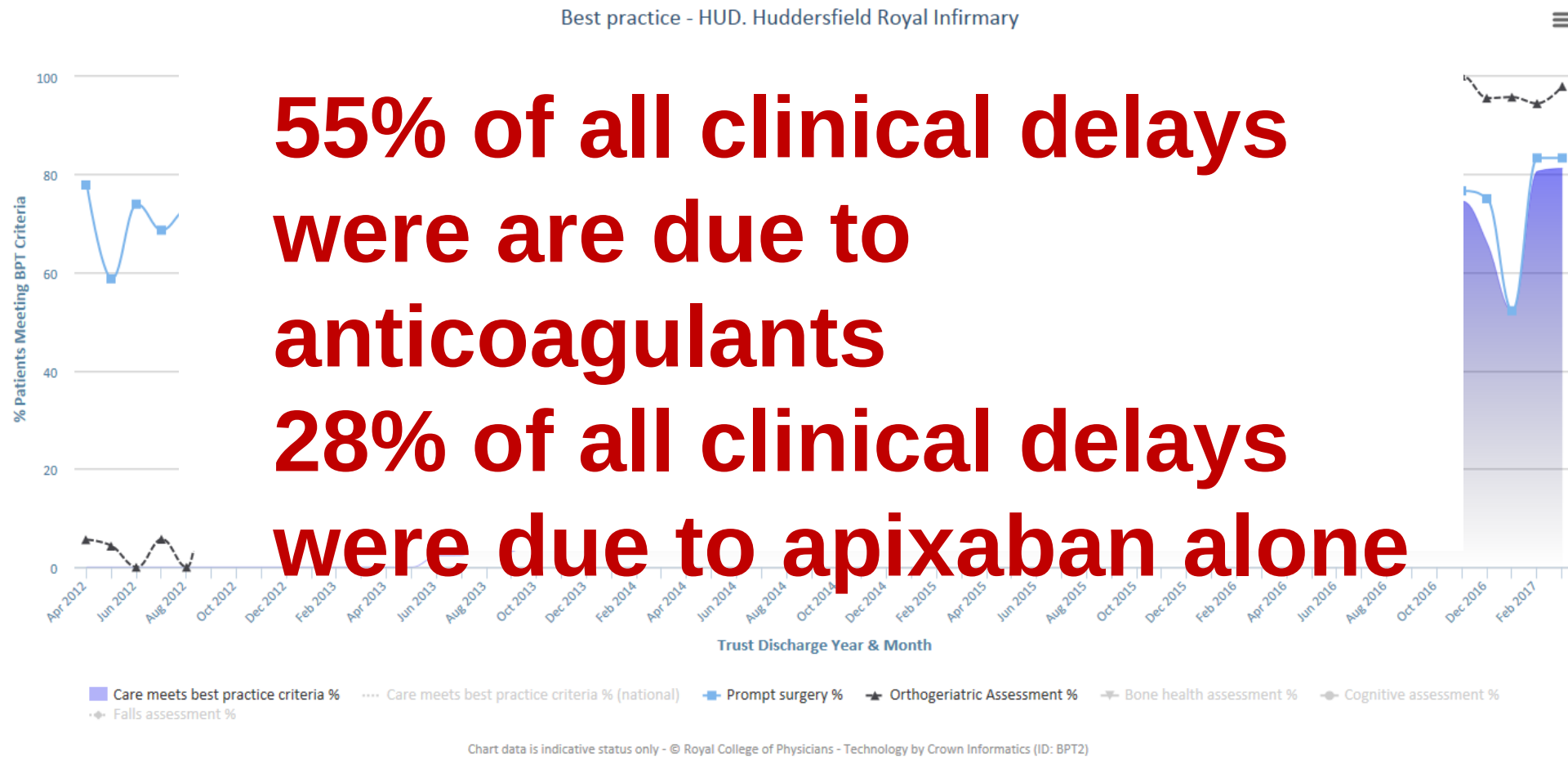

55% of all clinical delays were are due to anticoagulants

28% of all clinical delays were due to apixaban alone

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DOACS in Detail

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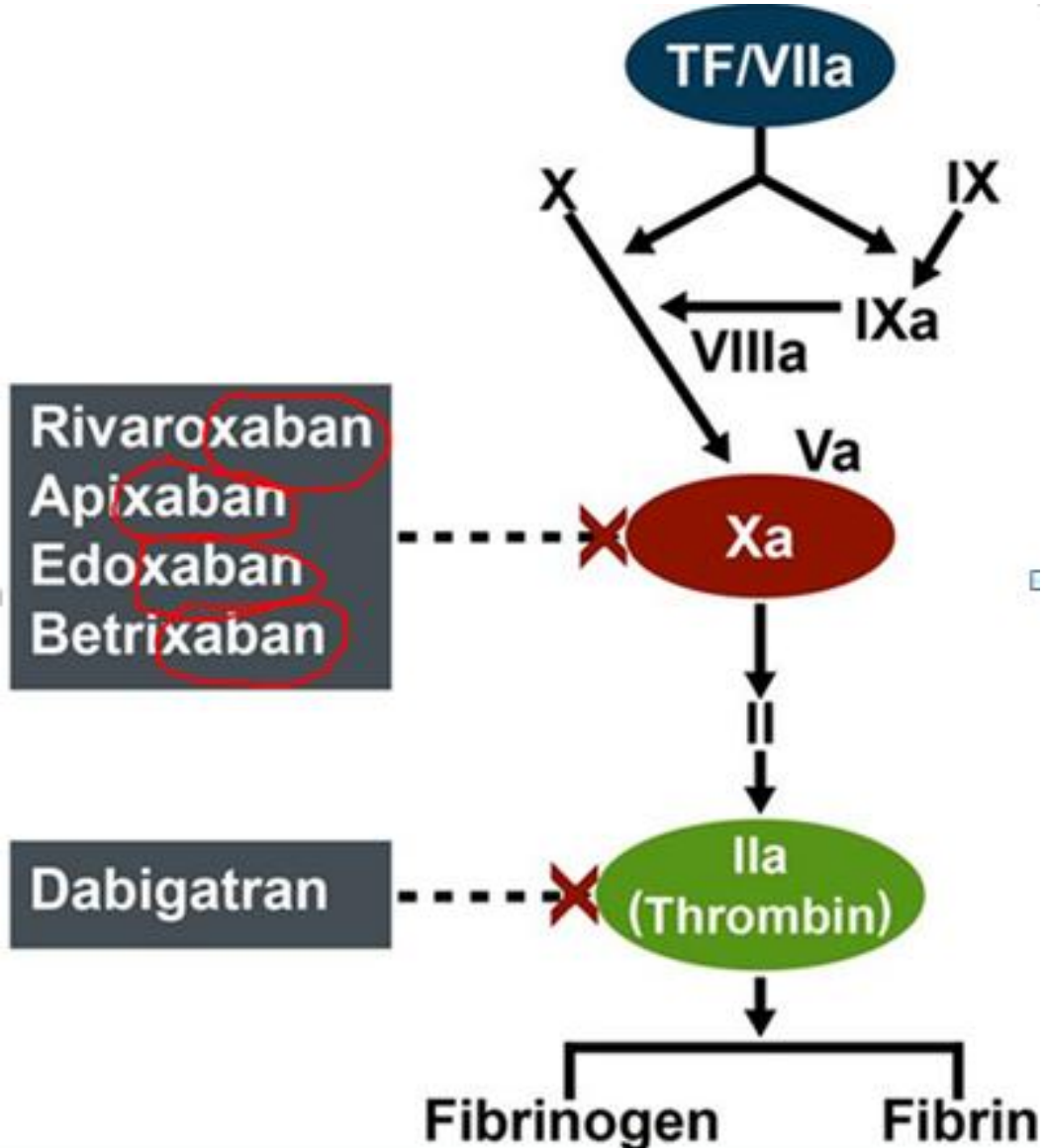

- Prevention of CVA in AF, ACS, VTE treatment and prevention, including after lower limb arthroplasty and #NOF

Apixaban

- Highly specific Xa inhibitor, rapidly absorbed with peak concentrations after 1-2 hours
- Studies show half life of 8.5-9.9 hours, hence BD
- Bioavailability of <50%, eliminated by the gut and kidneys (only around 25%)
- Studies have shown greater reductions in VTE without increasing the rate of major bleeding c.f LMWH
- Specific apixaban assay to monitor clinically

Rivaroxaban

- Direct Xa inhibitor
- Rapid onset, peak 2.5-4 hours
- Half life 5.7-9.2 hours (11-13 hours in elderly/reduced renal function)
- 1/3 eliminated by kidney, 1/3 faecal/biliary, 1/3 unchanged
- Specific assays to monitor clinically

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Dabigatran

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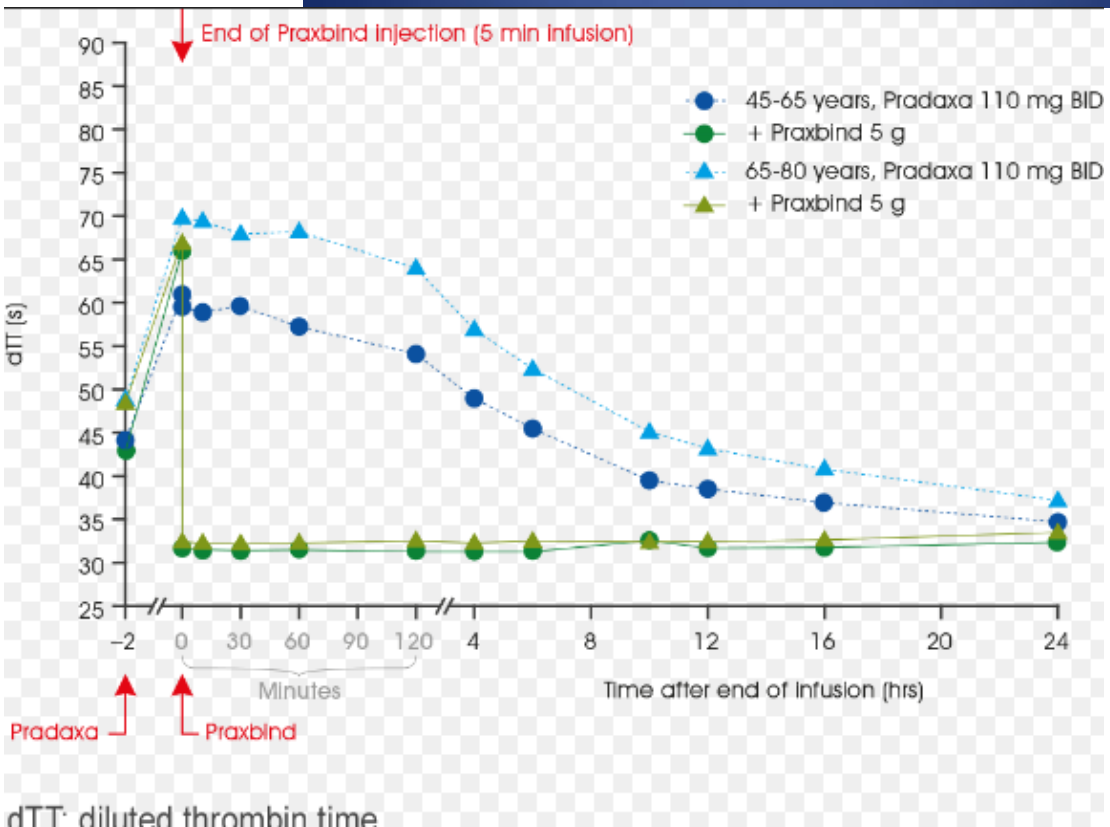
- Prodrug
- Direct thrombin inhibitor
- Half life 14-17 hours
- 80% renally cleared
- Reduced renal function results in “up to a 6 fold increase in plasma concentration and half life”
- Evidence on efficacy and bleeding complications c.f traditional anticoagulants are controversial, hence less popular
- Thrombin time sensitive, now available “in house”

Praxbind®
idarucizumab
INJECTION 5g

- £££ but cost reclaimed from CCG
- Andexanet for Xa inhibitors (licenced for major haemorrhage)
- Aripazine under investigation



dTT: diluted thrombin time

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What do we know and how do we proceed?

- We know stopping these drugs is risky
- We know operating quickly on NOF fractures improves outcomes
- We know DOACs are causing delays to theatre
- Given the lack of RCTs/evidence base how do we decide **when** it's safe to operate?

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GUIDELINES

Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology

Wiebke Gogarten, Erik Vandermeulen, Hugo Van Aken, Sibylle Kozek, Juan V. Llau and Charles M. Samama

Due to the rarity of spinal epidural haematoma, recommendations regarding neuraxial regional anaesthetic procedures with concurrent thromboprophylaxis, are not based on prospective randomised studies, but rather on case reports and expert opinion. The latter is based mainly on knowledge of the pharmacokinetics of the individual agents concerned. A rule of thumb adopted by most national societies puts the time interval between cessation of medication and neuraxial blockade at two times the elimination half-life of the drug. This approach has recently been recommended by others.[5]

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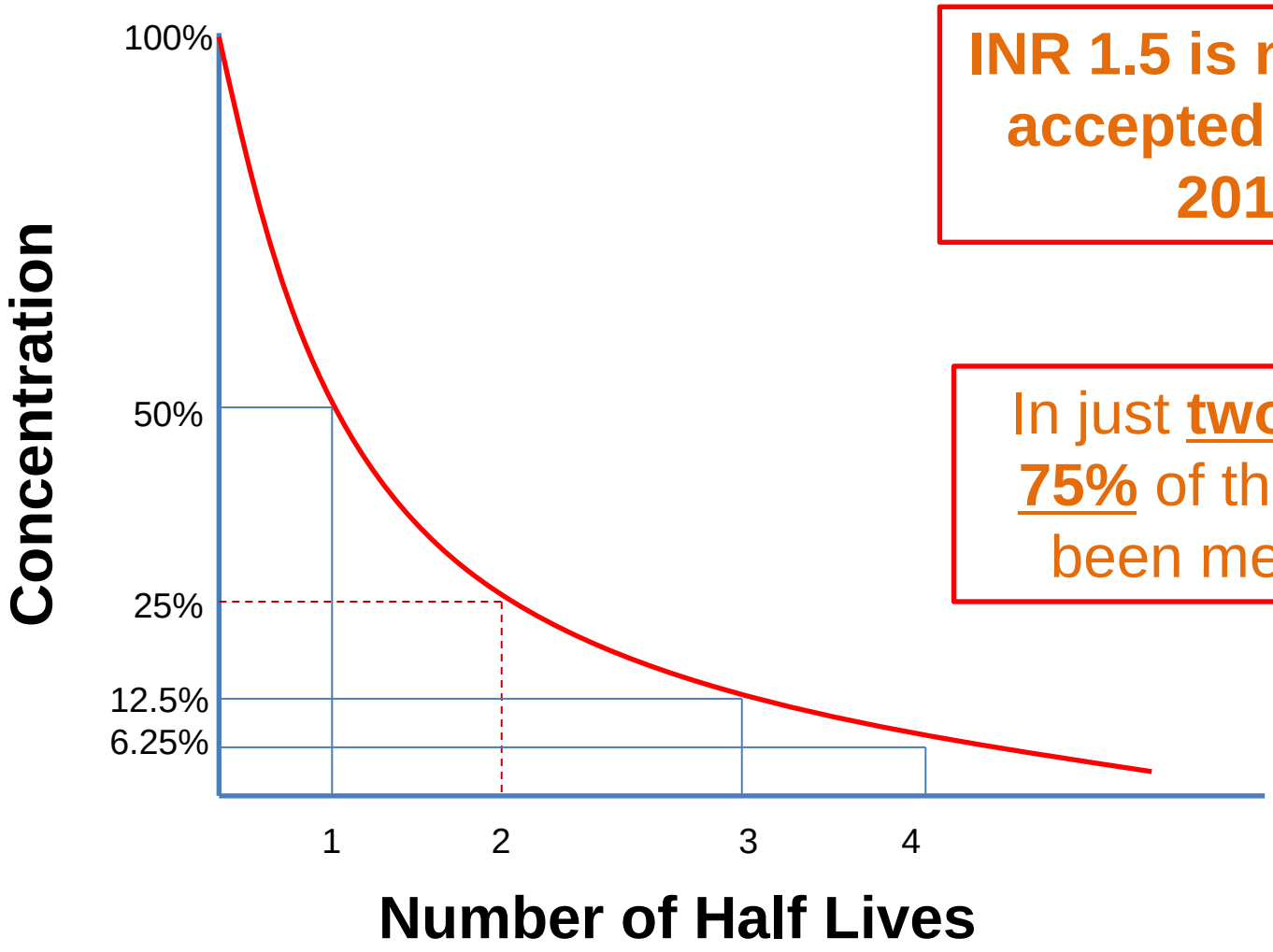

INR 1.5 is nationally accepted (AAGBI 2011)

In just **two half lives** **75%** of the drug has been metabolised

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Huddersfield Royal Infirmary Model

- Weighing the risks and benefits we accepted the passing of two half lives before anaesthesia (RA +/- GA) and surgery
- MDT discussion of proposal (Co-Author; Haematological Lead Consultant for Anticoagulation, Cardiology & Stroke physicians, Orthogeriatricians, Orthopaedic Surgeons, Lead Anticoagulation Pharmacist and EPR representative) and finally MMC ratification

- Two half lives for each drug:
- Apixaban: 20 hours
- Rivaroxaban: 24 hours (unless CrCl < 30)
- Dabigatran: 34 hours (but may be significantly greater as highly renally cleared)

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Pre-operative Anticoagulation Reversal for Emergency Fractured Neck of Femur Surgery

WARFARIN

- Stop warfarin
- Administer **5mg intravenous** vitamin K if INR > 1.5 or INR not known

Recheck INR after 4-6 hours

INR<1.5 → **Proceed to surgery**

INR>1.5 → Contact Haematology Consultant on call for advice regarding administering a further dose of **intravenous** vitamin K or Prothrombin Concentrate Complex. Repeat until INR<1.5 then proceed to surgery

APIXABAN and RIVAROXABAN

- Stop apixaban or rivaroxaban
- Confirm with patient time of last dose
- List for theatre 24 hours after last dose ingested*

*If creatinine clearance <30 ml/min, then consider delaying surgery or sending specific anti Xa assay before proceeding

Creatinine clearance = [f x (140-age) x weight in kg] ÷ serum creatinine

(f = 1.23 for men and 1.04 for women)

DABIGATRAN

- Stop dabigatran
- Confirm with patient time of last dose
- List for next **afternoon** trauma theatre slot
- At 8am on day of surgery, send venous blood for "thrombin time" (TT)

Thrombin time normal → **Proceed to surgery**

Thrombin time prolonged → Contact Haematology Consultant on call for authorisation of Praxbind and prescribe

Inform trauma anaesthetic consultant of the day who will administer pre-op

All patients should be prescribed **5000 units subcutaneous Dalteparin (2500 units if body weight <50kg or EGFR<30 ml/min/1.73m*2)** at **1800** for VTE prophylaxis. Dalteparin **must not** be administered later than 1800 pre-operatively as this may preclude regional anaesthesia and delay surgery

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Edoxaban was added in the 2018 update

APIXABAN and RIVAROXABAN

- Stop apixaban or rivaroxaban
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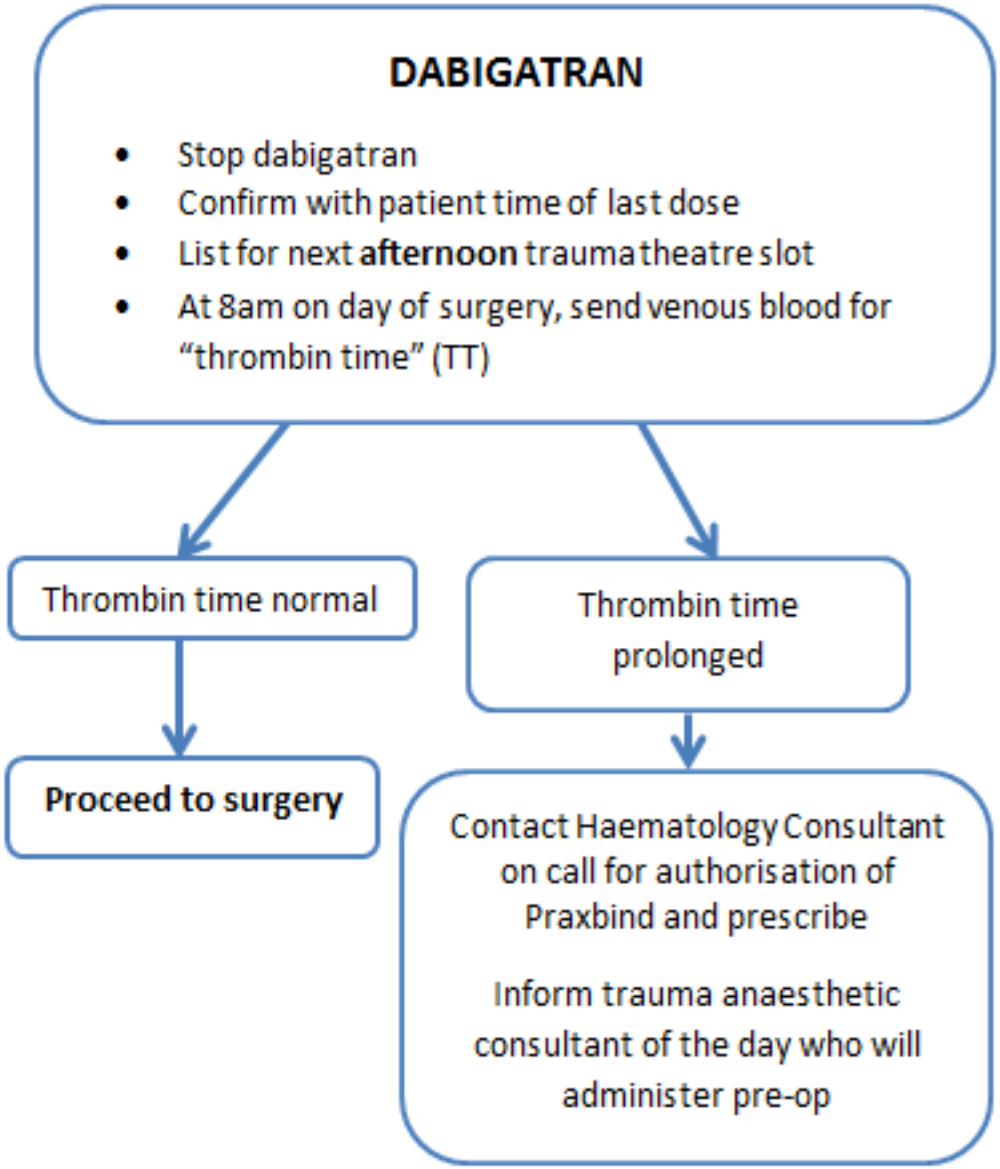

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Guideline for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on RIVAROXABAN or APIXABAN

Rivaroxaban and Apixaban are oral factor Xa inhibitors with a half life of 7-9 hours and 9-14 hours respectively and mostly renal 66% excretion.
There is no licensed reversal agent for direct oral anti-Xa inhibitors.

Rivaroxaban/ Apixaban-related bleeding
Or requirement for urgent reversal in case of need for emergency surgery

↓

STOP rivaroxaban/ Apixaban

↓

- Assess clinical bleeding [1,2] and resuscitate patient as appropriate. May need to act before lab results are back in emergency.
- Check: FBC, G&S, U&E and Clotting screen, PT, APTT, TT, Fibrinogen, d-dimer
- Rivaroxaban and Apixaban prolongs PT – if PT is normal drug levels are low.
- Consider rivaroxaban/ Apixaban plasma level (discuss with haematologist)
- Indicate time of last rivaroxaban dose when requesting test (Citrate sample) and considering management options.

Mild bleeding	Moderate-Severe bleeding	Life-threatening or site critical bleeding
Delay next dose or discontinue treatment as appropriate. With normal renal function level of rivaroxaban/ Apixaban reduces rapidly in 24 hours Monitor clotting screen and PT	Discuss with haematologist on call • Symptomatic treatment • Consider tranexamic acid (avoid in DIC) • Mechanical compression • Surgical intervention/ Endoscopy • Activated charcoal if drug ingestion ≤ 2 hours • Fluid replacement and haemodynamic support- ensure good diuresis • Consider Prothrombin complex concentrate (Octaplex) (50 units/Kg), max 3000 units, IV infusion at 10ml/min • blood product support as indicated • consider role for interventional vascular radiology	Discuss with haematologist on call • Activate massive haemorrhage pathway • Manage as for Moderate-Severe bleeding • Give Prothrombin complex concentrate (Octaplex) (50 units/Kg), max 3000 units, IV infusion at 10ml/min or recombinant FVIIa (90 mcg/kg) Reassess clinically Repeat FBC, U&E, Clotting. Monitor PT (and rivaroxaban/ Apixaban level considered)

[1] **Moderate to Severe bleeding:** - reduction in Hb ≥ 20g/L, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area (i.e. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular or pericardial bleeding).
[2] **Life-threatening bleeding:** – symptomatic intracranial bleed, reduction in Hb ≥ 50g/L, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

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Guideline for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on DABIGATRAN

Dabigatran is a direct thrombin inhibitor with a half- life of 14-17hours.
Dabigatran is renally excreted >80% and the half- life is greatly prolonged in renal impairment.

Dabigatran-related bleeding
Or requirement for urgent reversal in case of need for emergency surgery

↓

STOP dabigatran

↓

- Assess clinical bleeding and resuscitate patient as appropriate. May need to act before lab results are back in emergency
- Check: FBC, Group and save, U&E, Clotting screen, PT, APTT, TT, Fibrinogen, d-dimer
- Dabigatran prolongs APTT (non-linear) and TT (linear but very sensitive) – if APTT and TT are normal then Dabigatran levels are low
- Consider sending dabigatran plasma level- Citrate sample (Discuss with Haematologist)
- Indicate time of last dabigatran dose on requests and in considering management options

Mild bleeding e.g minor epistaxis	Uncontrollable bleeding requiring reversal or emergency surgery/procedure			Life-threatening or CNS bleeding
Delay next dose or discontinue treatment as appropriate. Use local measures to reduce bleeding. With normal renal function level of dabigatran reduces rapidly in 24 hours. In renal impairment can take up to 96 hours	Last dose Dabigatran >24 hours ago	Last dose Dabigatran 12 - 24 hours ago	Last dose Dabigatran <12 hours ago	Local measures to reduce bleeding Give Idarucizumab (PRAXBIND) 5 gram IV bolus (2.5gm in 50ml x2 over 5-10 minutes each given consecutively)
	IF NORMAL renal function unlikely to have significant levels. Check clotting screen (as above) Local measures to reduce bleeding. Discuss with haematology if immediate reversal required.	Local measures to reduce bleeding. Give Idarucizumab (PRAXBIND) 2.5 gram in 50ml IV bolus over 5-10 minutes Consider dabigatran level if abnormal renal function or continued bleeding continues.		Reassess clinically. Repeat FBC, U+E, Clotting, APTT, TT and dabigatran level if bleeding

Note: For advice at any point regarding these guidelines please contact on-call haematology

References
SPC Idarucizumab

Idarucizumab for Dabigatran Reversal; N Engl J Med 2015; 373:511-520

Idaruoizumab fully reverses dabigatran immediately (<5 minutes). It has no effect on other causes of bleeding or on clotting factors. Occasionally 24 hours following idaruoizumab patients can have rebound anticoagulation effects and repeat idaruoizumab can be considered. Remember other things can also cause bleeding.

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Outcome

- **Eliminated** unnecssary clinical delays due to DOACs since June 2017
- No VCH and no complaints from the surgeons!
- Non-inferiority trial to demonstrate safety

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ORIGINAL ARTICLE

Impact of Direct Oral Anticoagulants in Patients With Hip Fractures

Martin Bruckbauer, MD,† Oliver Prexl, MD,*† Wolfgang Voelckel,* Bernhard Ziegler, MD,‡ Oliver Grottke, PhD,§ Marc Maegele,‖ and Herbert Schöchl, MD, PhD*¶*

Delay to theatre (3x longer than non anticoagulated cohort)

But no evidence of higher bleeding rates

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Thrombosis Research 166 (2018) 106–112

Contents lists available at ScienceDirect

Thrombosis Research

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

Full Length Article

Morbidity and mortality after fragility hip fracture surgery in patients receiving vitamin K antagonists and direct oral anticoagulants☆,☆☆

Tal Frenkel Rutenberg[a,*,1], Steven Velkes[a,d,1], Maria Vitenberg[a], Avi Leader[b,d], Yael Halavy[b], Pia Raanani[b,d], Mustafa Yassin[c,d], Galia Spectre[b,d]

[a] Department of Orthopedics, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[b] Institution of Hematology, Coagulation Unit, Rabin Medical Center, Petah-Tikva, Israel
[c] Department of Orthopedics, Hasharon Hospital, Rabin Medical Center, Petah-Tikva, Israel
[d] Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

DOAC patients delayed to theatre

Increased pressure sores and increased readmission rates

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G Model
JINJ 7903 No. of Pages 5

ARTICLE IN PRESS

Injury, Int. J. Care Injured xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Injury

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

Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications

Haggai Schermann*, Ron Gurel, Aviram Gold, Eran Maman, Oleg Dolkart, Ely L. Steinberg, Ofir Chechik

Division of Orthopedics, Tel Aviv Sourasky Medical Center, Affiliated with Tel Aviv University, Tel Aviv, Israel

Increased mortality if DOAC patients are delayed to theatre (27% vs 16%)

Similar transfusion rates and Hb changes

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Original Article

Does Use of Oral Anticoagulants at the Time of Admission Affect Outcomes Following Hip Fracture

Geriatric Orthopaedic Surgery & Rehabilitation
Volume 9: 1-7

DOI: 10.1177/2151459318764151
journals.sagepub.com/home/gos
SAGE

Ariana Lott, BA[1], Jack Haglin, BS[1], Rebekah Belayneh, BA[1], Sanjit R. Konda, MD[1], Philipp Leucht, MD[1], and Kenneth A. Egol, MD[1]

DOACs increased delays to theatre and LOS, 5x increased risk of sepsis

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Original Article

Geriatric Orthopaedic Surgery & Rehabilitation
Volume 9: 1-6

DOI: 10.1177/2151459318764150
journals.sagepub.com/home/gos
SAGE

Use of Anticoagulants Remains a Significant Threat to Timely Hip Fracture Surgery

Razvan Taranu, MRCSEd, MSc[1], Chelsea Redclift, MBChB[1], Patrick Williams, MRCS[2], Marina Diament, MRCSEd[2], Anne Tate, BSc(Hons)[1], Jamie Maddox, MRCP[1], Faye Wilson, MBBS, MSc, MRCP[3], and Will Eardley, MSc, MD[1], Northern Hip Fracture Collaboration

Patients on DOACs were delayed to theatre, had increased LOS and less met BPT

Northern Hip Fracture Collaborative also recommend a protocol of theatre 24 hours post last DOAC dose (GA only) for rivaroxaban, apixaban and dabigatran (if GFR>60)

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Open Access Research

BMJ Open

Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre

Barry Mullins,[1] Harold Akehurst,[1] David Slattery,[2] Tim Chesser[1]

Safe surgery at 19.4 hours

Delaying surgery wasn't shown to reduce per-operative bleeding or mortality

Found no evidence to delay surgery.

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Scientific Research – Falls, Fractures and Trauma

34 **DO ANTICOAGULANTS AFFECT OUTCOME OF HIP FRACTURE SURGERY? A CROSS-SECTIONAL ANALYSIS**

C H Ã Ryck[1], T Ong[2,3], J Chia[2], Y Yap[2], N Weerasuriya[2], O Sahota[2]
[1]*Aarhus University, Denmark*
[2]*Department for Healthcare of Older People, Nottingham University Hospitals NHS Trust*
[3]*Division of Rehabilitation and Ageing, School of Medicine, University of Nottingham*

If time to theatre is similar
(27.1 hours DOAC group vs 24.6 hours control)
then transfusion, LOS and mortality rates are the same between groups

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Osteoporosis International
https://doi.org/10.1007/s00198-018-4786-0

ORIGINAL ARTICLE

Preoperative antithrombotic therapy and risk of blood transfusion and mortality following hip fracture surgery: a Danish nationwide cohort study

C. Daugaard[1] · A.B. Pedersen[1] · N.R. Kristensen[1] · S.P. Johnsen[1,2]

Received: 17 September 2018 / Accepted: 18 November 2018

Operate **within** 24 hours

No increase in mortality

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ORIGINAL ARTICLE

Outcomes of Early Surgical Intervention in Geriatric Proximal Femur Fractures Among Patients Receiving Direct Oral Anticoagulation

Nathan A. Franklin, DO, Ashley H. Ali, MD,† Richard K. Hurley, MD,* Hassan R. Mir, MD,† and Michael J. Beltran, MD**

No difference in transfusion rates, Hb drop, EBL, wound complications or survival with early surgery

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Summary

- Worries with early surgery and increased surgical bleeding, transfusions and wound complications is unfounded and the VCH risk is too tiny to quantify
- The real risk is that these patients are being delayed to theatre and suffering proven increased morbidity and mortality
- Therefore :
  - Xa inhibitors - wait 24 hours from last dose and proceed (if CrCl>30)
  - Dabigatran – wait 24 hours, check thrombin time and proceed either with or without Praxbind
- Liaise with your haematological lead for anticoagulation to get a protocol in place for this high risk group of patients who require urgent surgery