To Doac or not to Doac?

A whistle stop tour!

Lucy Bingham

Emergency Medicine Consultant/ED AEC Lead

New oral anticoagulants:

The hot new drugs or…
A heated discussion?

The arguments in one slide?

- NOACs The Big Three:
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)

- Advantages over warfarin:
  - rapid onset of action
  - no monitoring required
  - reduced risk of bleeding

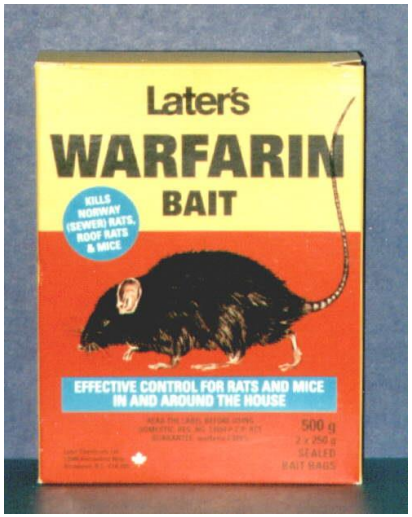
- Disadvantages:
  - lack of monitoring ability
  - lack of antidote (maybe)
  - cost

- Their increased use poses new challenges when bleeding complications occur
- Perioperative management of the NOACs differs from warfarin

	Vitamin K Antagonists	FXa Inhibitors			Direct Thrombin Inhibitors	
	Warfarin	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Dabigatran**	**Ximelagatran**
Mode of action	Inhibition of hepatic synthesis of vitamin K-dependent coagulation factors	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of clot-bound and free thrombin (FIIa)	Direct inhibition of thrombin (FII)
Time to peak effect (hours)	72–96	0.5–3	3	1.5	2–3	1.6–1.9
Half-life hours	20–60	5–9 (9–13 in elderly)	8–13	9–11	14–17	4–5
Bioavailability %	100	80	66	50	6.5	20
Recommended therapeutic dose and frequency	Adjusted-dose based on INR; once daily	20 mg; once daily	5 mg; twice daily	30 mg or 60 mg; once daily	150 mg; twice daily	Not available in the U.S.
Monitoring	Required using INR	Not required In case of hemorrhage or renal impairment, FXa-dependent assays may be used[47]	Not required due to predictable pharmacokinetics In hemorrhage or renal impairment, FXa-dependent assays may be used[47]	Not required due to predictable pharmacokinetics	Not required except in subgroups such as patients with renal impairment [48] Ecarin clotting time can be used if needed[49]	Not required
Renal excretion[39]	1% excreted unchanged in the urine	66% renal elimination	50% renal elimination	45% renal elimination	80% renal elimination	Main route of elimination
Interactions	CYP2C9, CYP1A2, CYP3A4 inhibitors Dietary vitamin K[50]	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors[50]	Potent CYP3A4 inhibitors[50]	P-glycoprotein inhibitors[43]	P-glycoprotein inhibitors Proton pump inhibitors[38]	NA
Drug reversal	Vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant FVIIa[51]	FVIIa partially reverses rivaroxaban anticoagulant effect[52] Prothrombin complex concentrate completely reverses its anticoagulant effect[53]	No available antidote	No available antidote	It is partially dialyzable[54]	NA
Precautions	Severe active bleeding, pregnancy, breast feeding, documented hypersensitivity[55] Severe renal impairment (glomerular filtration rate <30 mL/min/1.73m^2)[39]	Severe active bleeding; severe renal impairment[39]	Severe active bleeding; severe renal impairment	Severe active bleeding; severe renal impairment	Severe active bleeding, severe renal impairment[39]	NA

Is Warfarin becoming obsolete?

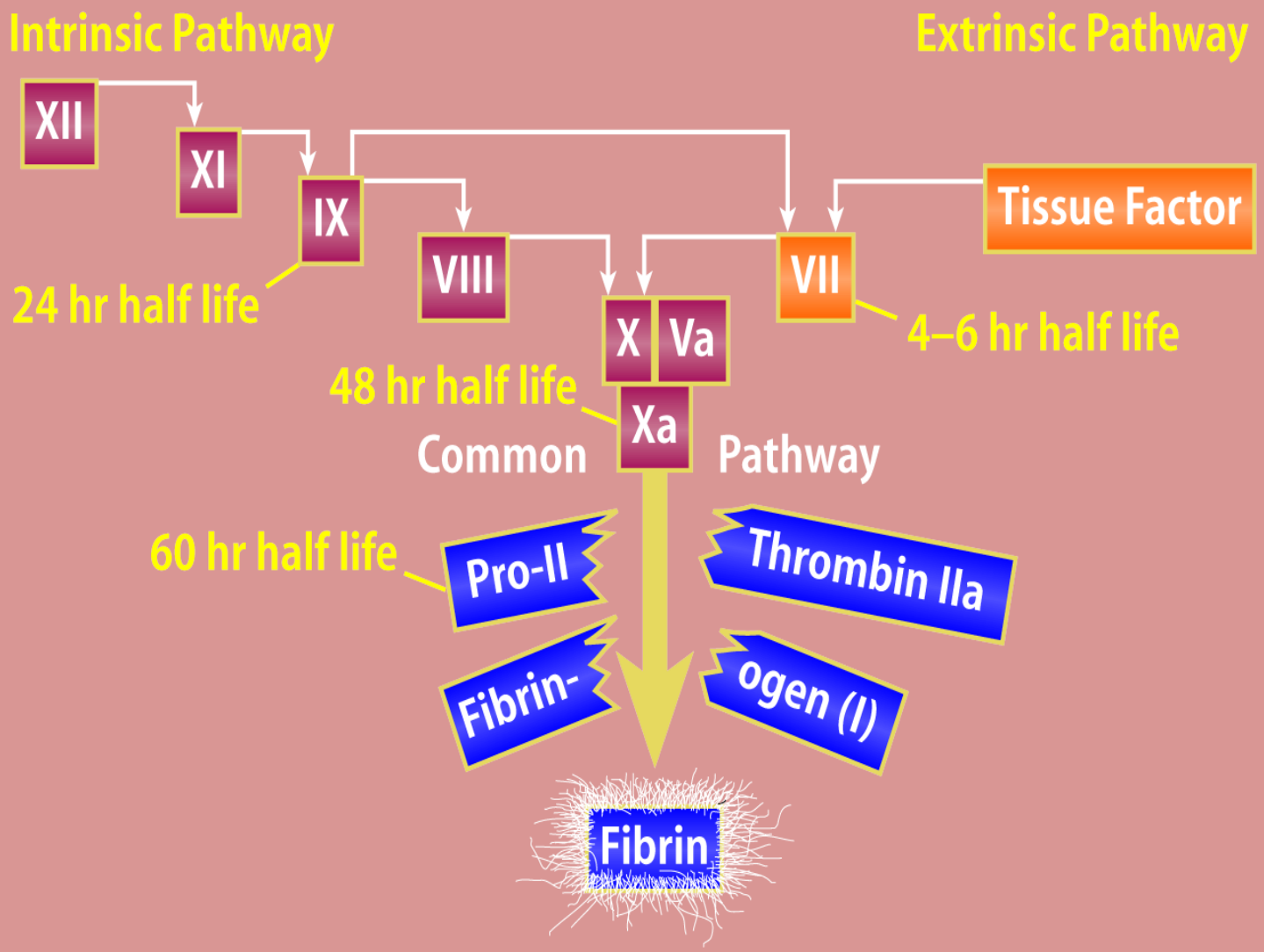
- NO
- Still preferred agent for:
  - mechanical valves
  - rheumatic mitral valve disease
  - advanced renal failure
  - high risk thrombophilias (APAS)
  - cancer patients (if LMWH not used)
- Cost/coverage



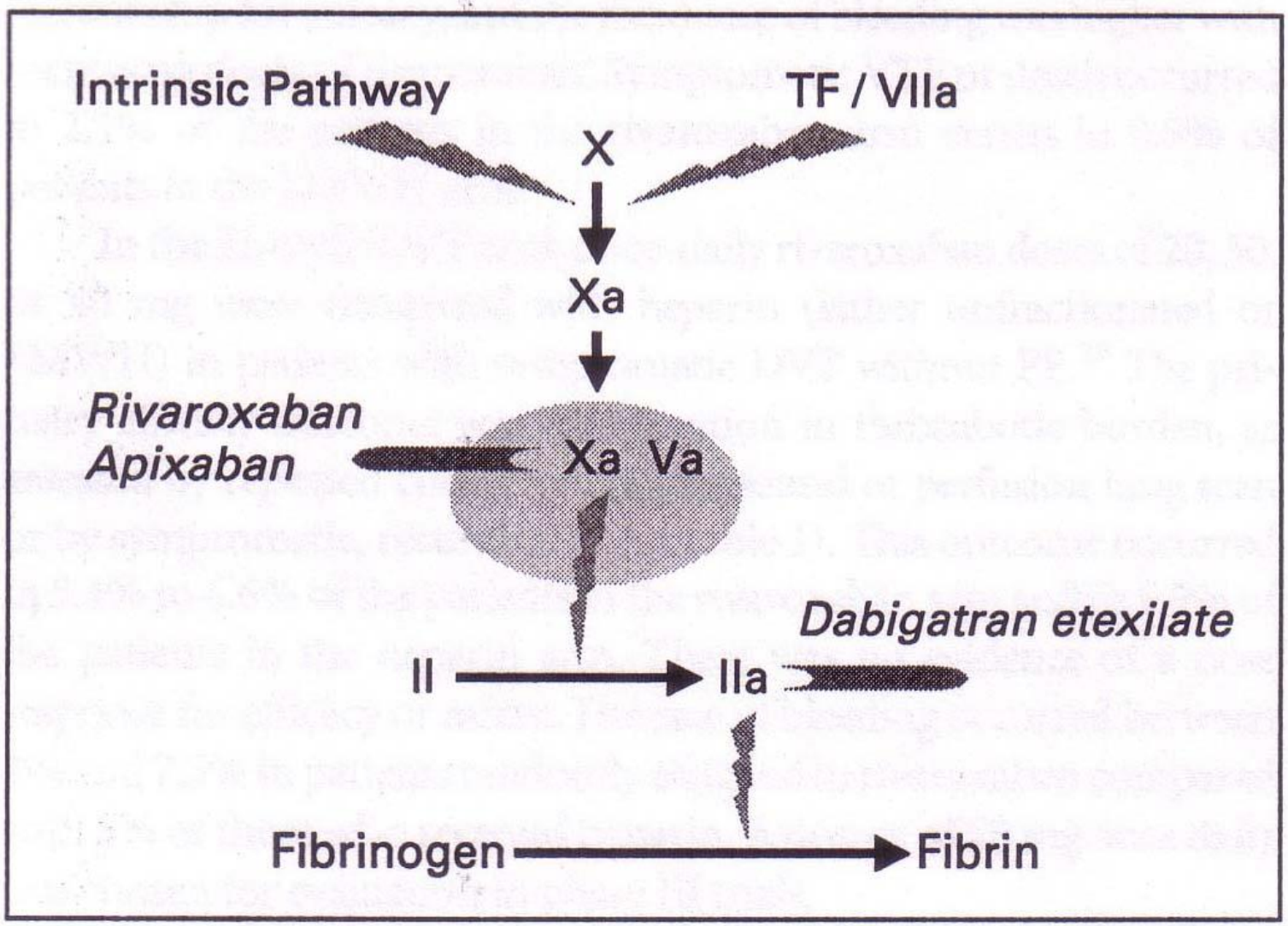
Problems with warfarin

- Variable dose
- INR affected by diet, illness etc
- Drug interactions can be problematic
- Narrow therapeutic index
- BUT – its cheap!
- AND – the INR is a good measure of compliance (or at least their compliance just before clinic)

The clotting cascade



Action of new agents



Novel Oral Anticoagulants – Pharmacological Properties

Characteristic	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Apixaban (Eliquis)
Target	Factor Xa	Factor IIa	Factor Xa
Prodrug	No	Yes	No
Dosing	OD	BID	BID
Bioavailability, %	80-100%*	6.5%	50%
Half-life	5-13h	12-14 h	8-15 h
Renal clearance (unchanged bioavailable drug)	~33%	85%	~27%
Cmax	2-4 h	1-2 h	3-4 h
Drug interactions	Strong inhibitors of both CYP3A4 and P-gp	P-gp inhibitors	Strong inhibitors of both CYP3A4 and P-gp

1. Xarelto® PM, July 18, 2012 ; 2. Pradaxa ® PM November 12, 2012; 3. Eliquis® PM November 27, 2012; 4. Goette Trends Cardiovasc Med. 2013 [Epub ahead of print]

Novel Oral Anticoagulants – Effect on Coagulation Tests

	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Apixaban (Eliquis)
aPTT	↑ or ↔	↑	↑ or ↔
PT/INR	↑ or ↔	↑ or ↔	↑ or ↔
Thrombin Time	Minimal effect	↑	Minimal effect
Hemoclot thombin inhibitor assay	No effect	↑	No effect
Anti Factor Xa	↑	Minimal effect	↑

1. Xarelto® PM, July 18, 2012 ; 2. Pradaxa ® PM November 12, 2012; 3. Eliquis® PM November 27, 2012; 4. Goette Trends Cardiovasc Med. 2013 [Epub ahead of print]

Monitoring NOACs

- None?
- Renal Function/LFT/FBC
- A standard clotting screen has not been validated
- A prothrombin time (using specific reagent neoplastin) or a specific anti Xa
- Counselling: SE, missed doses, procedures
- Check interacting meds (antiplatelets)

Approved Indications

Drug	Apixaban	Dabigatran	Rivaroxaban
Approved Indication	Prophylaxis of DVT/PE in Orthopedic surgery Prevention of stroke in atrial fibrillation Treatment of DVT and PE	Prophylaxis of DVT/PE in Orthopedic surgery Prevention of stroke in atrial fibrillation Treatment of DVT and PE	Prophylaxis of DVT/PE in Orthopedic surgery Prevention of stroke in atrial fibrillation Treatment of DVT and PE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY

- N = 18,113, Follow-up median 2 years, CHADS2 median 2.1, open-label
- Inclusion: Afib on EKG w/in last 6 months, plus at least one: CVA, TIA, LVEF < 40%, NYHA class II or great HF symptoms w/in 6 months and age of at least ≥75 or 65-74 plus DM, HTN, or CAD
- Exclusion: severe heart-valve disorder, stroke w/in 14 days or severe stroke w/in 6 months, increased risk of bleeding, CrCl < 30, liver dx, prenancy
- Randomized to 110 or 150 mg of dabigitran BID vs unblinded warfarin (ASA <100 mg or other antiplatelet agents allowed)
- Primary outcome: stroke or systemic embolization
- Safety outcome: major hemorrhage (reduction of Hgb by 2 g/dL, 2 units of PRBCs, or symptomatic bleeding in critical area)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

ROCKET-AF

- N = 14,264, Follow-up median 1.6 yrs, CHADS2 median 3, double-blind
- Inclusion: Non-valvular Afib by EKG w/ hx of stroke, TIA, or embolism or with at least a CHADS2 ≥ 2
- Randomized to rivaroxaban 20 mg daily or 15 mg daily depending on CrCl vs warfarin
- Primary outcome: stroke and embolism
- Safety end point: major and non-major clinically relevant bleeding

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group*

December 6, 2009

RE-COVER

- N = 2564, Follow-up 6 months, double-blind
- Inclusion: DVT or PE with planned tx for 6 months
- Exclusion: Symptoms longer than 6 months, PE with HD instability or use of TPA, indication for warfarin, unstable heart disease, high risk of bleeding, transaminases, life expectancy < 6 months, CrCl < 30, pregnancy
- Randomized to 150 mg dabigatran BID vs warfarin
- Primary outcome: symptomatic VTE or death 2/2 VTE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

December 2010

EINSTEIN-DVT

- N = 3449, most tx for 6 months, open-label
- Inclusion: DVT w/o PE
- Exclusion: CrCl <30, liver disease, active bleeding or high risk for bleeding, HTN, contraindication to anticoagulation, or received UFH/LMWH for > 48 hrs
- Randomized to rivaroxaban at 15 mg BID for 3 weeks then 20 mg daily for 3, 6, or 12 months vs warfarin
- Primary outcome: symptomatic recurrent VTE

Department of Veterans Affairs
Health Services Research & Development Service

Evidence-based Synthesis Program

QUERI

Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism

April 2012

	All studies (n = 5)		Comparison by Drug Class	
Adverse Effect	**Summary Risk Ratios (95% CI)**	**Tests for Heterogeneity**	**Summary Risk Ratios (95% CI)**	**Test for differences between drug classes**
All-cause mortality	0.88 (0.82 to 0.95)	Q = 1.05, I^2 = 0% p < 0.90	DTI: 0.90 (0.79 to 1.01) FXa: 0.88 (0.80 to 0.96)	p = 0.77
Discontinued due to adverse effects	1.23 (0.94 to 1.61)	Q = 57.96, I^2 = 93% p < 0.001	DTI: 1.61 (1.14 to 2.27) FXa: 1.04 (0.84 to 1.28)	p = 0.03
Major bleeding	0.86 (0.71 to 1.04)	Q = 16.08, I^2 = 75% p = 0.003	DTI: 0.93 (0.82 to 1.06) FXa: 0.83 (0.60 to 1.14)	p = 0.49
Fatal bleeding	0.59 (0.46 to 0.77)	Q = 1.57, I^2 = 0% p = 0.81	DTI: 0.72 (0.45 to 1.16) FXa: 0.55 (0.40 to 0.75)	p = 0.35
Gastrointestinal bleeding	1.30 (1.01 to 1.68)	Q=12.04, I^2 = 75% p = 0.007	DTI: 1.50 (1.24 to 1.80) FXa: 1.14 (0.69 to 1.87)	p = 0.05
Myocardial infarction[a]	1.02 (0.76 to 1.39)	Q = 9.37, I^2 = 57% p = 0.05	DTI: 1.35 (0.99 to 1.85) FXa: 0.86 (0.66 to 1.11)	p = 0.03
Liver dysfunction	0.82 (0.61 to 1.11)	Q = 14.48, I^2 = 72% p = 0.006	DTI: 0.88 (0.72 to 1.09) FXa: 0.76 (0.41 to 1.42)	p = 0.65

Fatal bleeding: 1 fewer death per 1000 pts
GI bleeding: 1 increased bleed per 1000 pts

What does that all mean??

Translating into English…

- Non-inferior for prevention of stroke/embolism in Afib
- Non-inferior for treatment of DVT/PE
- NNT for clinical benefit are large
- Probable reduced hemorrhagic stroke rate
- Reduced rate of fatal bleeding events
- Increased incidence of GI bleeds
- Perhaps increased incidence of MIs with dabigatran
- Cost of drug/year – Lots!

VTE and No Cancer

- Use NOAC – preferred! (Grade 2B)
  - Rivaroxaban, apixaban
    - No bridging needed
  - Dabigatran, edoxaban
    - Start with parenteral anticoagulation x5 days

- If contraindications to NOAC, then use VKA therapy (warfarin) (Grade 2C)
  - Overlap with parenteral anticoagulation x5 days,
  - And INR >2 for 24 hours

Cancer-Associated Thrombosis

- Use LMWH (Grade 2C)
  - Enoxaparin 1 mg/kg/dose BID

Briefly…

Perioperative Management of NOACs

Goals of Perioperative Anticoagulation

- Minimize window of “subtherapeutic” anticoagulation preoperatively
- Normal hemostasis during surgery
- Balance bleeding and thromboembolic risk post-operatively

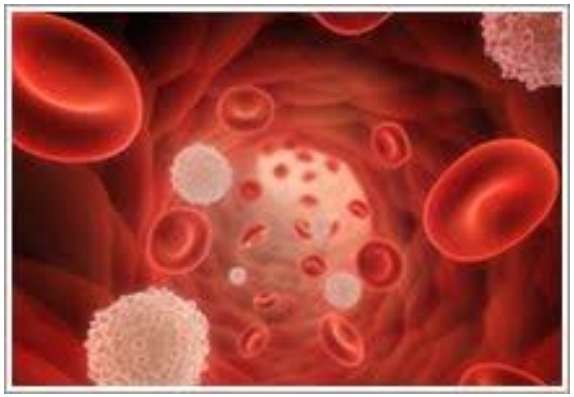
Preoperative Management of Patients taking NOACs

- Influenced by different factors:
  - pharmacokinetics of the drug
  - renal function
  - elective vs urgent surgery
  - bleeding risk of the procedure

Bridging Anticoagulation

- In most circumstances bridging anticoagulation not required with NOACs
- Need for bridging with Warfarin more complex

Bleeding Associated with NOACs



Risk Factors for Bleeding on Anticoagulant Therapy

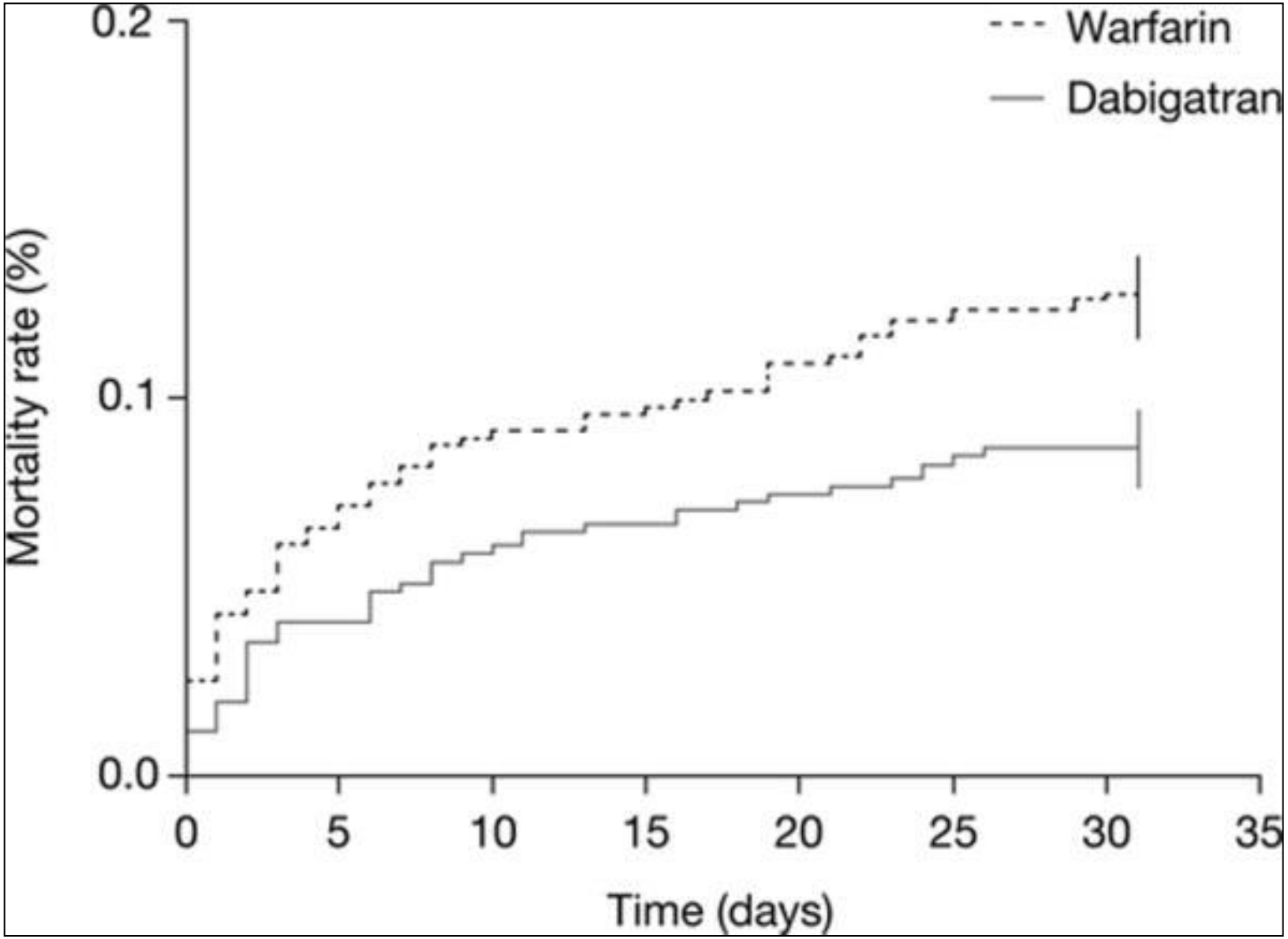
- Age >65
- Age >75
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- NSAID use

Low risk	0 risk factors
Moderate risk	1 risk factor
High risk	≥2 risk factors

Management and Outcomes of Major Bleeding During Treatment with Dabigatran or Warfarin

Circulation. 2013;128:2325-2332

Figure.

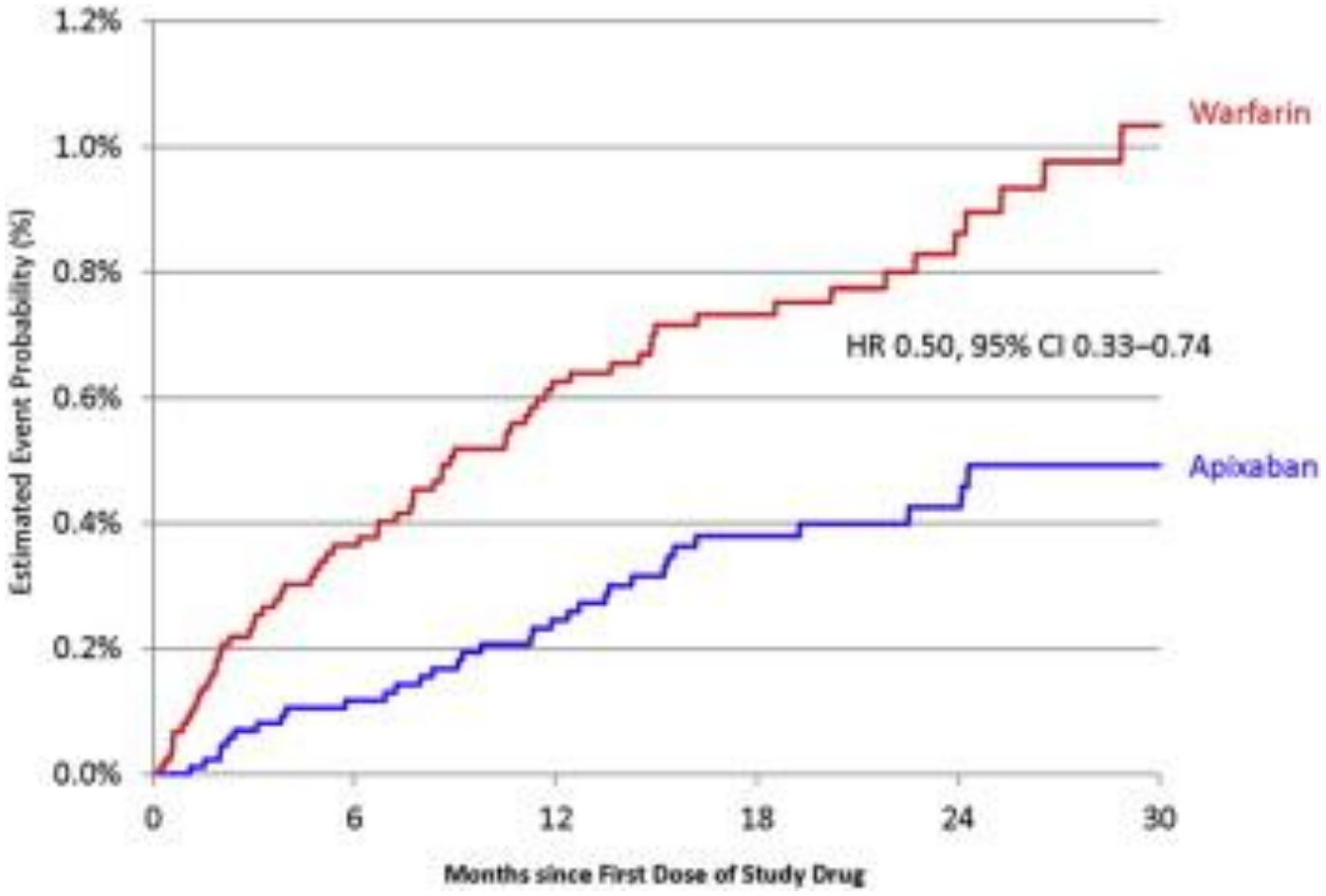


Management of major bleeding events in patients treated with Rivaroxaban vs. Warfarin: results from the ROCKET AF trial

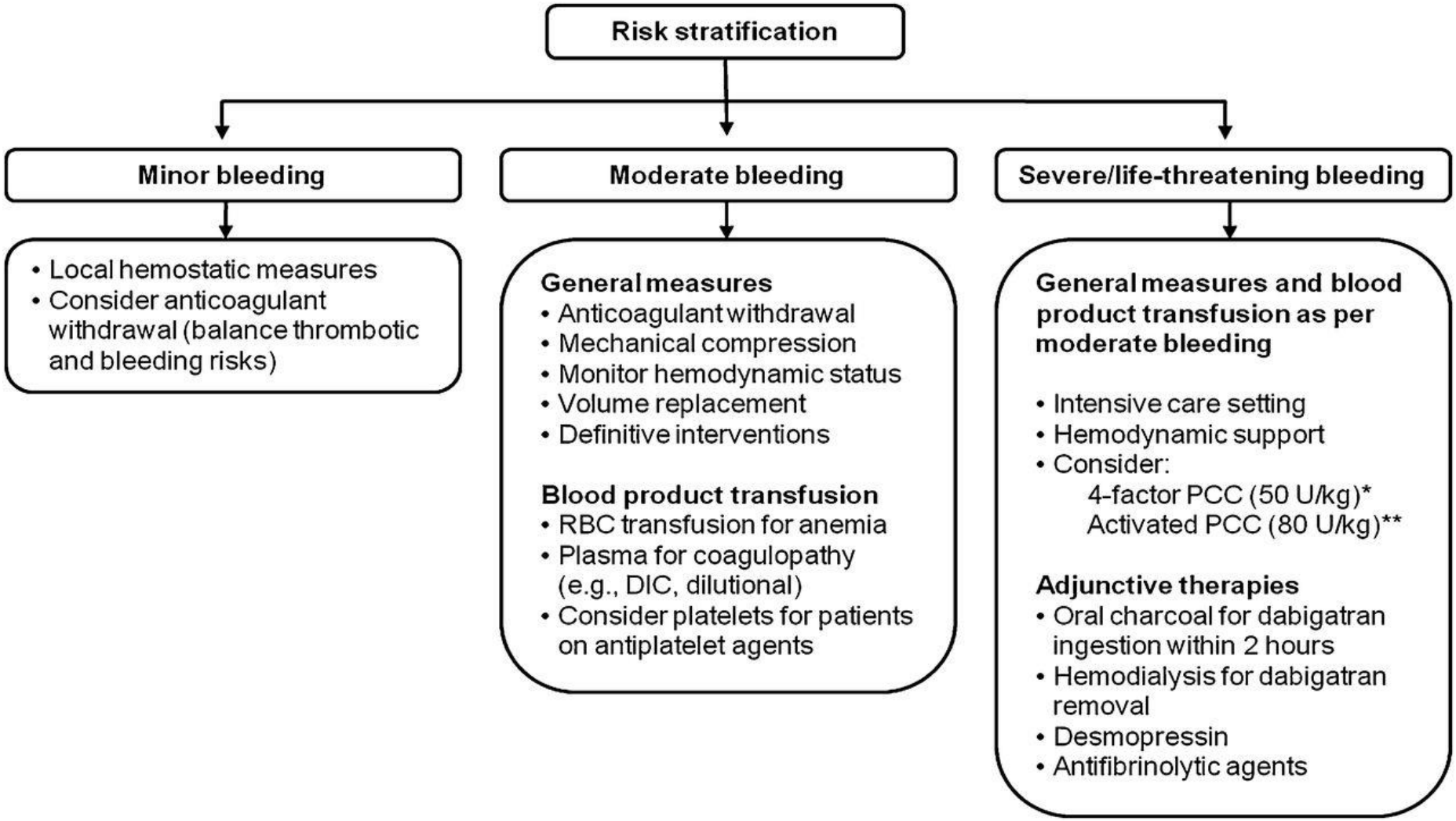
Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors [illegible] al Outcomes

Major bleeding following death within 30 days



Suggested strategy for management of TSOAC-associated bleeding.



Siegal D M et al. Blood 2014;123:1152-1158

blood

Reversal of NOAC anticoagulant effect

- Prothrombin Complex Concentrate (PCC)
  - 3 factor PCC (factors II, IX, X)
  - 4 factor PCC (factors II, VII, IX, X)

Octaplex, *Beriplex*

- No high-quality evidence efficacy and safety of PCC in the bleeding patient
- PCC associated with 1.4% risk of thrombosis when administered to bleeding patients on warfarin

Reversal of NOAC anticoagulant effect

- <u>Activated Prothrombin Complex Concentrate (FEIBA)</u>
  - contains activated factors II, VII, IX, X
  - developed for hemophiliacs with factor inhibitors
  - clinical data in bleeding patients is lacking (1 case report)
  - in vitro data suggests it corrects some abnormal coagulation parameters for all 3 NOACs
  - risk of thrombosis 4-8 events/10$_{0\,000}$ infusions in hemophilia

Reversal of NOAC anticoagulant effect

- Recombinant factor VIIa
  - also developed for hemophilia patients with inhibitors
  - in animal models, rfVIIa failed to ameliorate bleeding following treatment with

Dabigatran or Rivaroxaban

  - variable effect on Rivaroxaban and Apixaban coagulation parameters in vitro
  - twice the risk of thrombotic complications

Reversal of NOAC anticoagulant effect

- Plasma (FFP):

  - not shown to reverse abnormal coagulation tests

  - risks include volume overload, TRALI, allergic reactions, infection

Adjunctive Therapies

- Desmopressin (DDAVP):
  - used for bleeding in context of platelet dysfunction (uremia, VWD)
  - no clinical data
  - watch serum Na
  - in perioperative setting, no increased risk of thrombosis
- Tranexamic Acid:
  - antifibrinolytic
  - can be used as adjunctive therapy for severe bleeding in a variety of circumstances
  - effect in NOAC bleeding unknown
  - no increased risk of thrombosis in perioperative setting

Hemodialysis

- Dabigatran can be removed by hemodialysis
- 49%-68% removed after 4 hours of dialysis in patients with ESRD
- Rivaroxaban and Apixaban are highly protein bound which limits removal with hemodialysis

Appendix 1: Half Life of New Oral Anticoagulants

Creatinine clearance	Elimination half life (hours)		
	Dabigatran	Rivaroxaban	Apixaban
> 80 cc/min	13.8 hr	8.3 hr	15.1 hr
50-79 cc/min	16.6 hr	8.7 hr	14.6 hr
30-49 cc/min	18.7 hr	9.0 hr	17.3 hr
< 30 cc/min	27.5 hr	9.5 hr	17.6 hr

Hr: hours; min: minutes.

* For patients on Dabigatran, hemodialysis can be considered

Specific Antidotes

- Vitamin K (Wafarin)
- Idarucizumab (Dabigatran)
- Andexanet alpha (Fxa inhibitors)

Compliance?

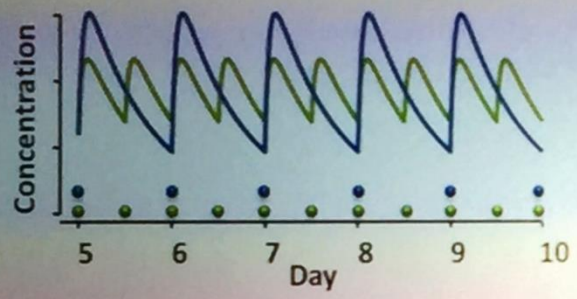
- Warfarin may not be taken in up to 21% of patient days
- Lack of monitioring with NOACs may make adherence to NOACs worse
- Short half-life of NOACs may leave patients at risk if adherence is poor
- Aspirin is NOT a reasonable alternative to anticoagulation for extended therapy… However, aspirin is better than nothing (Grade 2B)

OD or BD – What Would You Choose?

Theoretical pharmacokinetic profiles for OD or BD dosing of a non-NOAC drug with a half-life of ~12 hours and a T_{max} of 3 hours*[1]

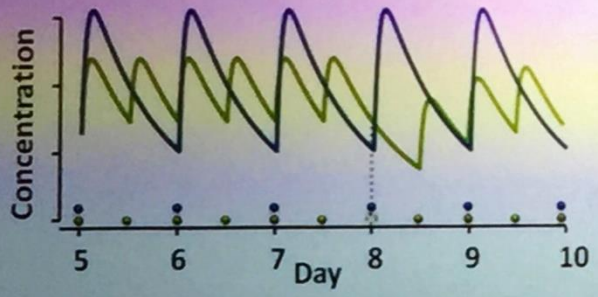
**Based on early pharmacokinetic data, a decision was made to progress the development of apixaban as a twice-a-day regimen rather than a once-a-day regimen. These published modelling data for a non-NOAC drug with a similar pharmacokinetic profile illustrate that this decision was justified*

Steady state

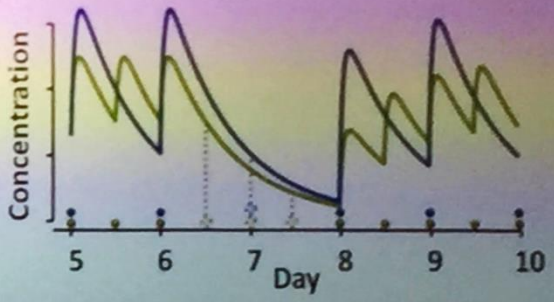


One extra dose

One missed BD dose



One missed OD dose
equals three missed BD doses



Dose X OD
Dose X/2 BD

BD: twice daily: NOAC: non-vitamin K antagonist oral anticoagulant; OD: once daily.

1. Vrijens B, Heidbüchel H. *Europace* 2015;17:514–523.

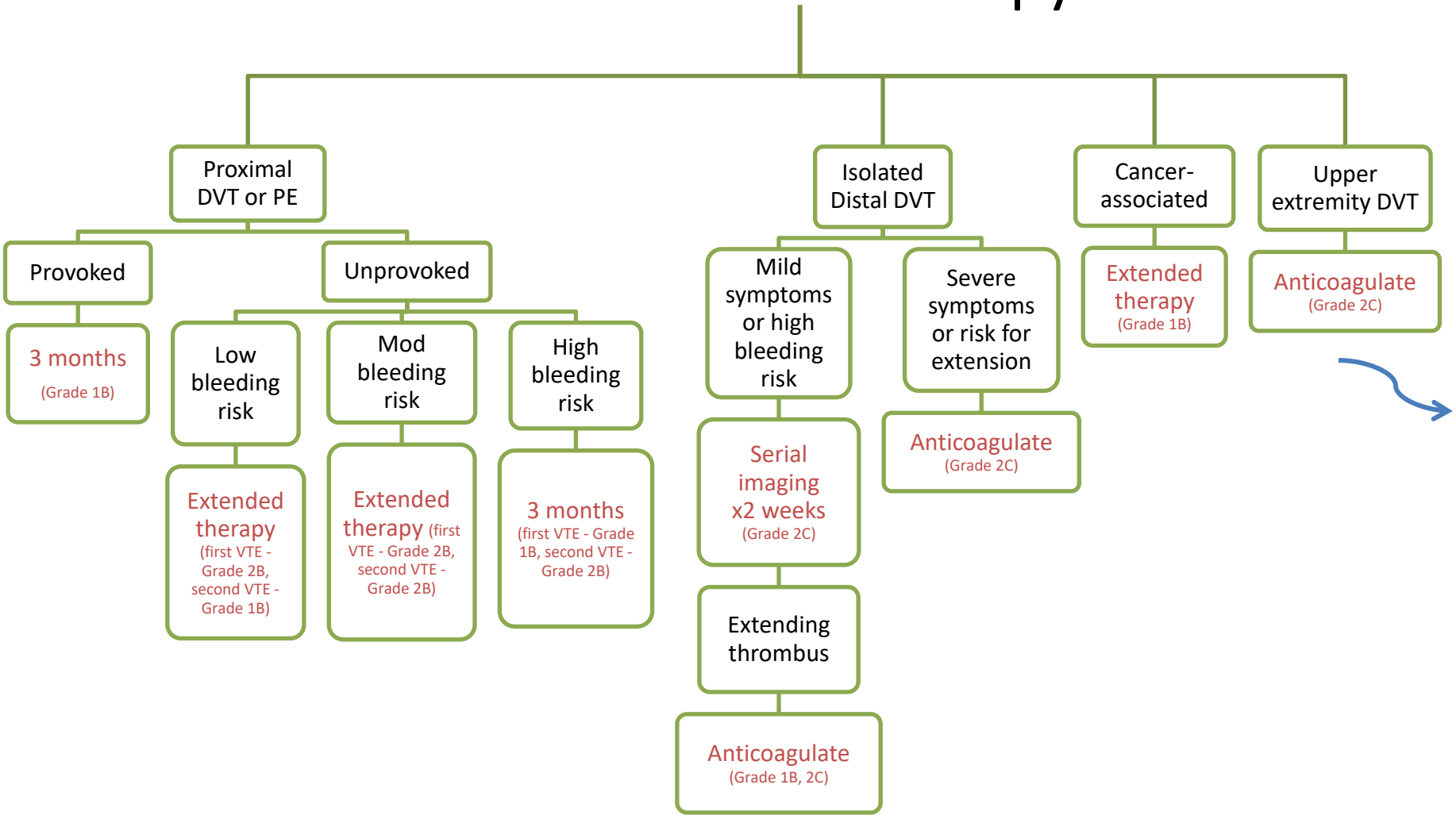
Who would you swap from Warfarin to a NOAC?

- Patients with poorly controlled warfarin levels
- Patients who you are concerned may have a risk of intracranial bleeds
- Patients with contraindications to Warfarin
- Patients who may prefer a NOAC

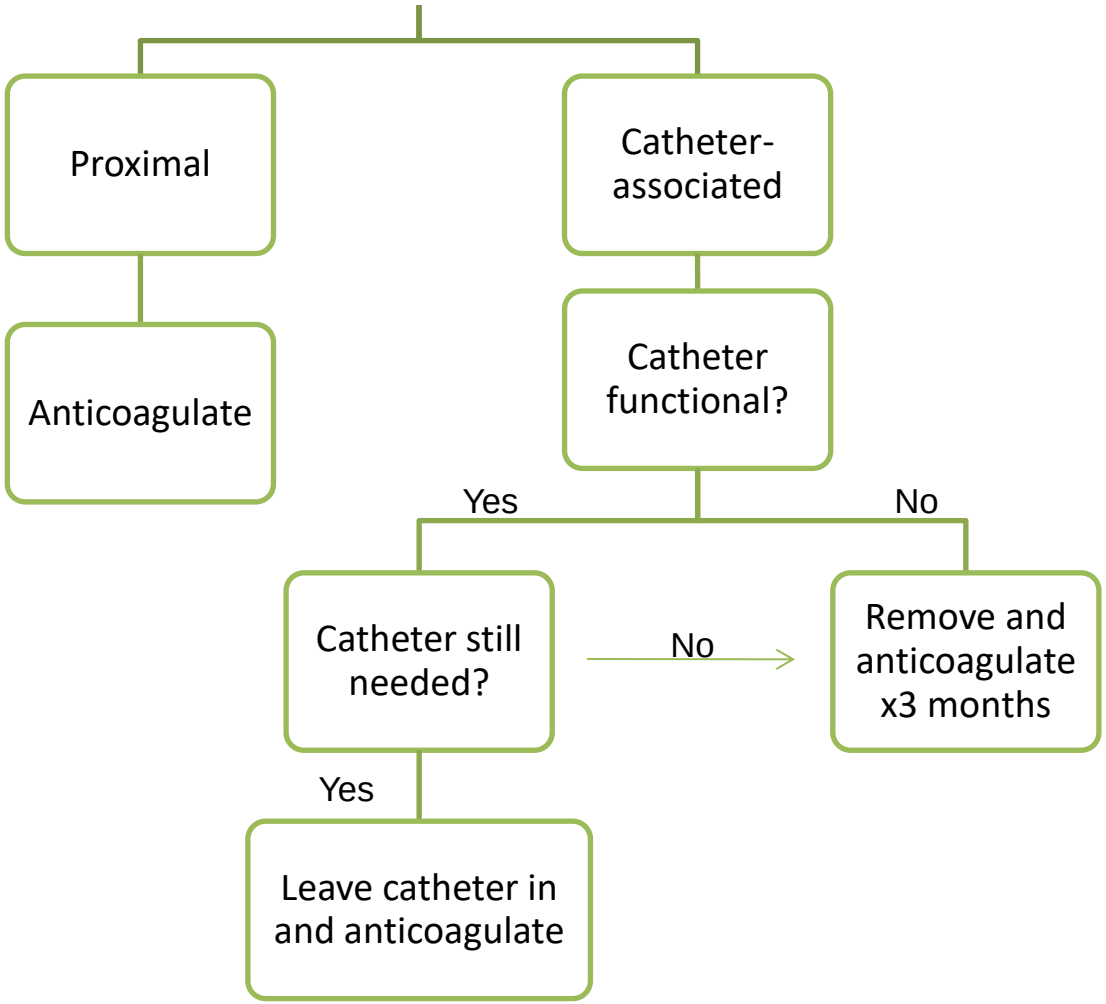
Contraindications to NOACs

- Extreme BMI (>40)
- CrCl <30
- Known hypersentivity to NOACs
- Hepatic Disease
- Significant increased risk of bleeding
- Pregnancy or Breast Feeding
- Concomitant warfarin therapy

Duration of Therapy



Special Considerations for Upper Extremity DVT

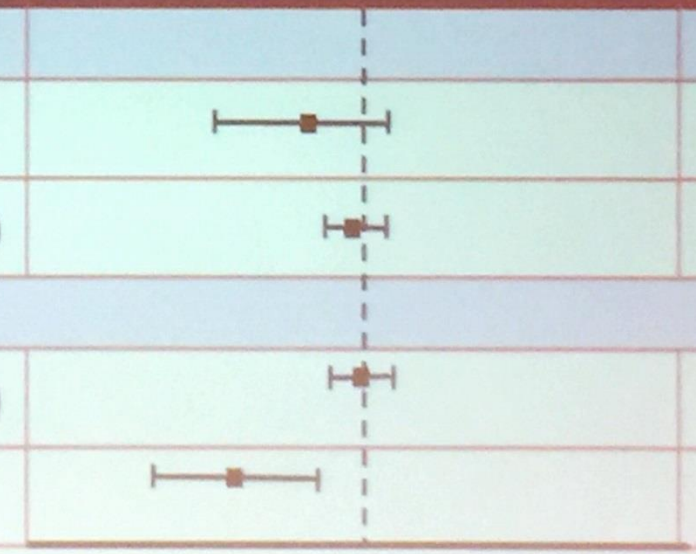


Recurrent DVT on Anticoagulation

- If on therapeutic warfarin or NOAC, then switch to enoxaparin temporarily (minimum 1 month) (Grade 2C)
  - Is this really recurrent VTE?
  - Is my patient compliant with therapy?
  - Is there underlying malignancy?
- If on enoxaparin and compliant, then increase the dose by 25-33% (Grade 2C)

Meta-analysis of relative risk of recurrent VTE or VTE-related death according to age or renal impairment, NOAC versus VKA*

	Pooled NOAC (n/N)	Pooled VKA (n/N)	RR (95% CI)
CrCl (mL/min)			
30–49	26/898 (2.9%)	39/891 (4.4%)	0.70 (0.43–1.15)
≥50	307/12,248 (2.5%)	316/12,282 (2.6%)	0.97 (0.83–1.14)
Age (years)			
<75	296/11,572 (2.6%)	299/11,635 (2.6%)	0.99 (0.85–1.17)
≥75	39/1,858 (2.1%)	68/1,807 (3.8%)	0.56 (0.38–0.82)



Adapted from Van Es et al. 2014[3]

*This meta-analysis included six randomised clinical trials for the following NOACs: dabigatran (RE-COVER and RE-COVER II), rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE studies), apixaban (AMPLIFY study) and edoxaban (Hokusai-VTE study).

CI: confidence interval; CrCl: creatinine clearance; NOAC: non-VKA oral anticoagulant; RR: relative risk; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Which would you choose??

Questions?