Management of DOAC's

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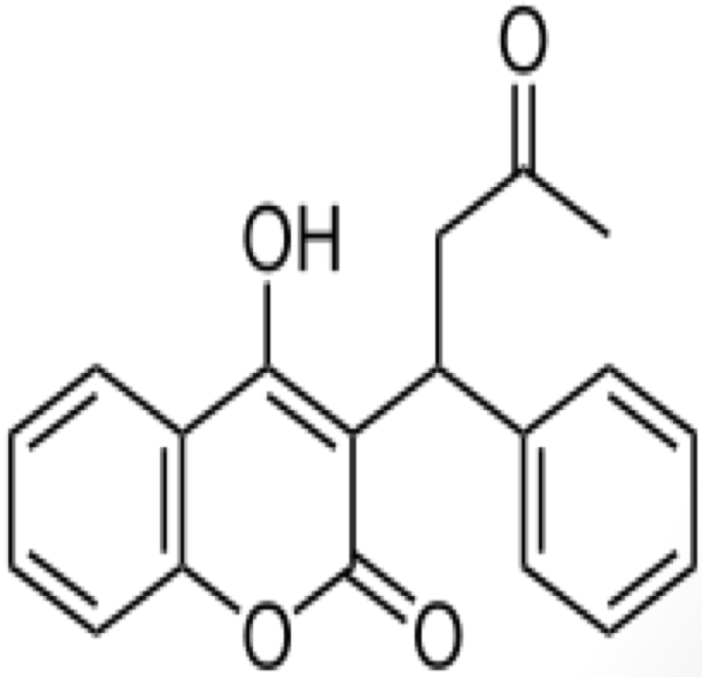
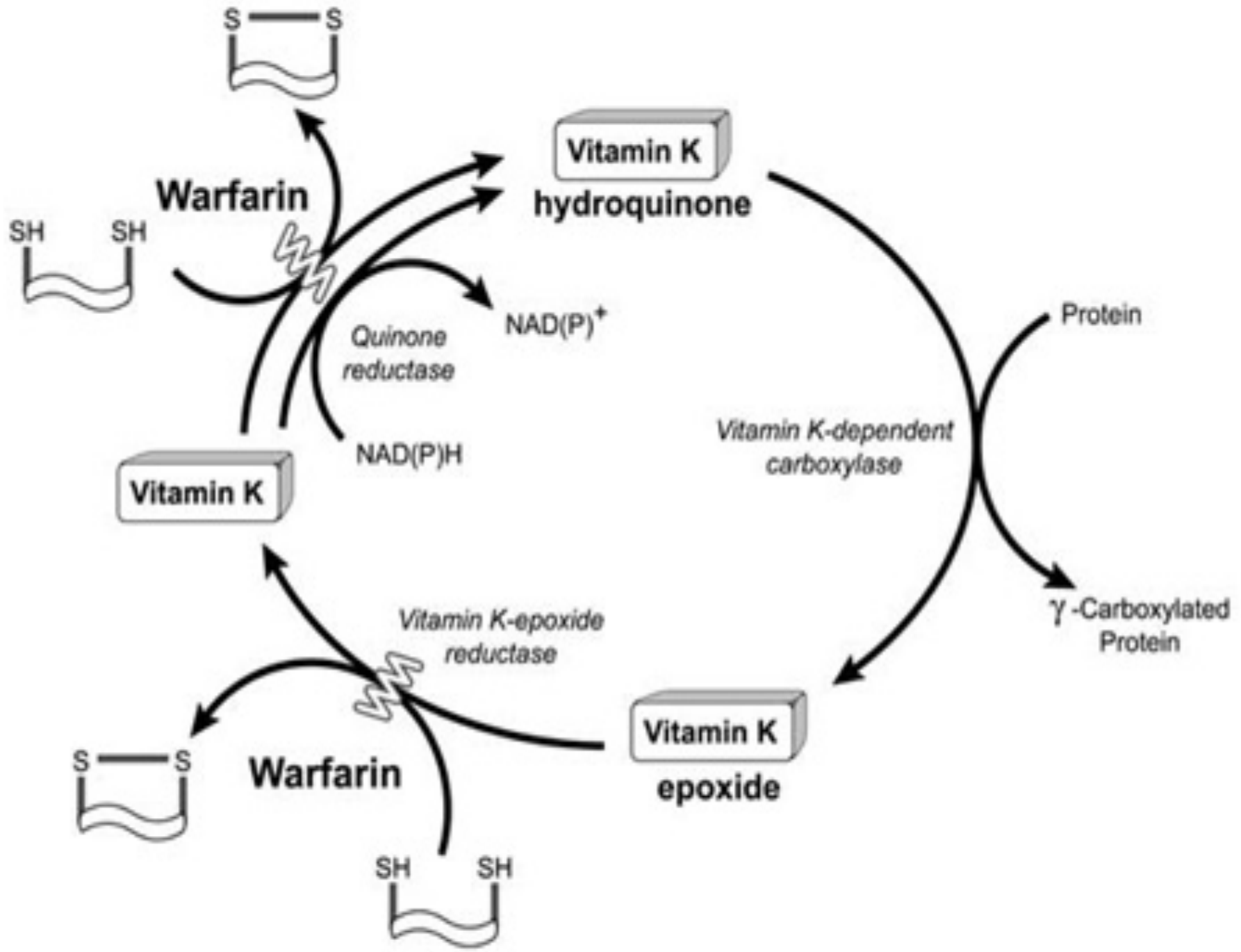
Aims of talk

- Warfarin – how it works and its issues
- What are DOACs/NOACs and how do they work
- Trial data
- NICE guidance
- GMMMG
- How to counsel for these new drugs
- Monitoring
- Pre-op
- Reversal

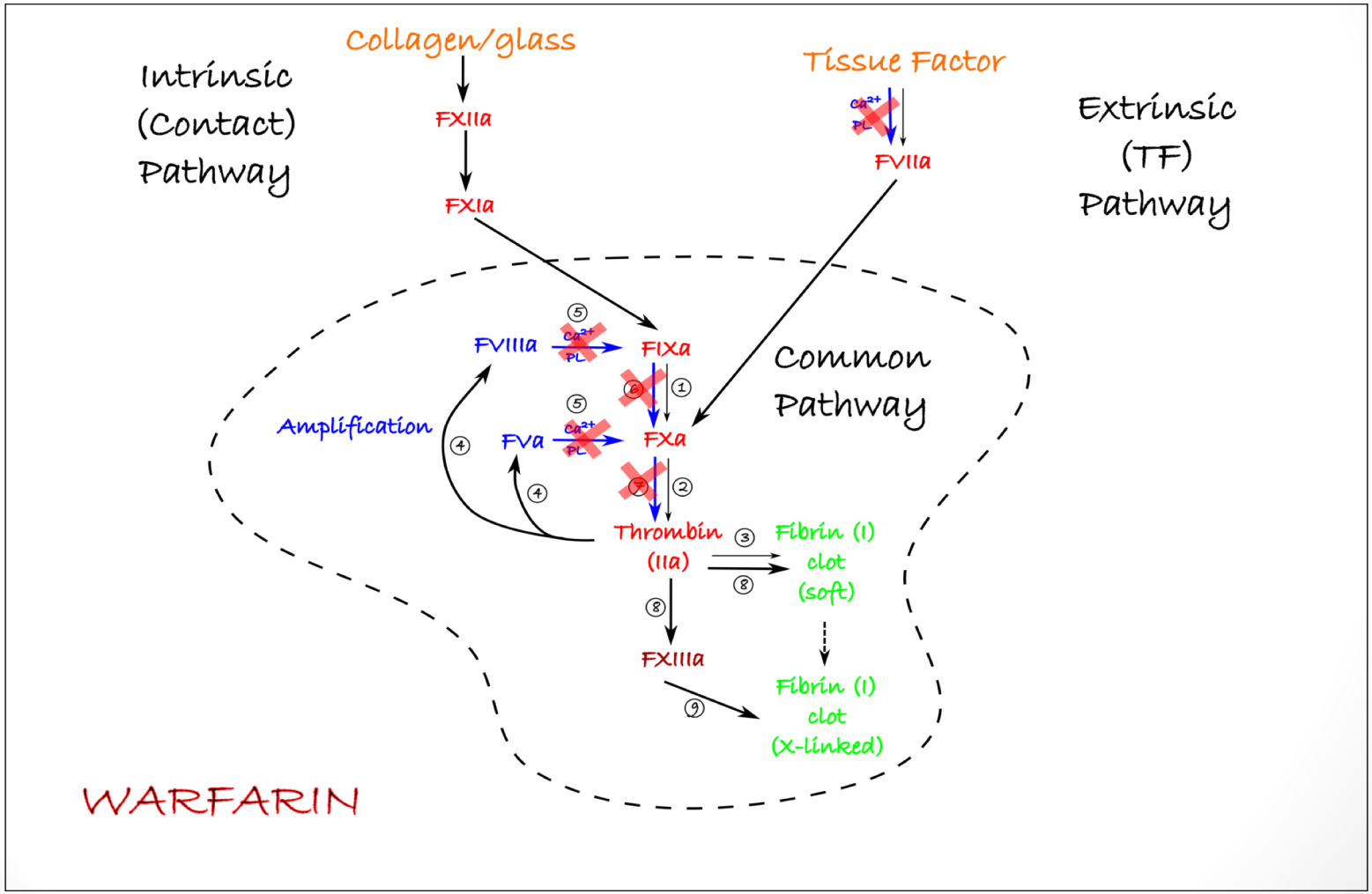
Warfarin

- Discovered by Wisconsin Alumni Research Foundation.
- Licensed since 1954.
- Inhibits vitamin K epoxide reductase, therefore inhibiting factors II, VII, IX, and X.
- Also inhibits Protein C and S




S S
Warfarin
SH SH
Vitamin K
hydroquinone
NAD(P)+
Quinone reductase
NAD(P)H
Protein
Vitamin K-dependent carboxylase
γ -Carboxylated Protein
Vitamin K
Vitamin K-epoxide reductase
Vitamin K
epoxide
S S
Warfarin
SH SH

Warfarin


Collagen/glass
Intrinsic (Contact) Pathway
FXIIa
FXIa
Tissue Factor
FVIIa
Extrinsic (TF) Pathway
FVIIIa
FIXa
Common Pathway
Amplification
FVa
FXa
Thrombin (IIa)
Fibrin (I) clot (soft)
FXIIIa
Fibrin (I) clot (X-linked)
WARFARIN

VKA therapy has several limitations

Narrow therapeutic window (INR range 2–3) → **Risk of stroke**; **Risk of bleeding**

Considerable variability in dose-response (genetic variations)

Interactions with drugs and diet

→ **Convenience not optimal:**
- **Frequent coagulation monitoring**
- **Frequent dose adjustments**

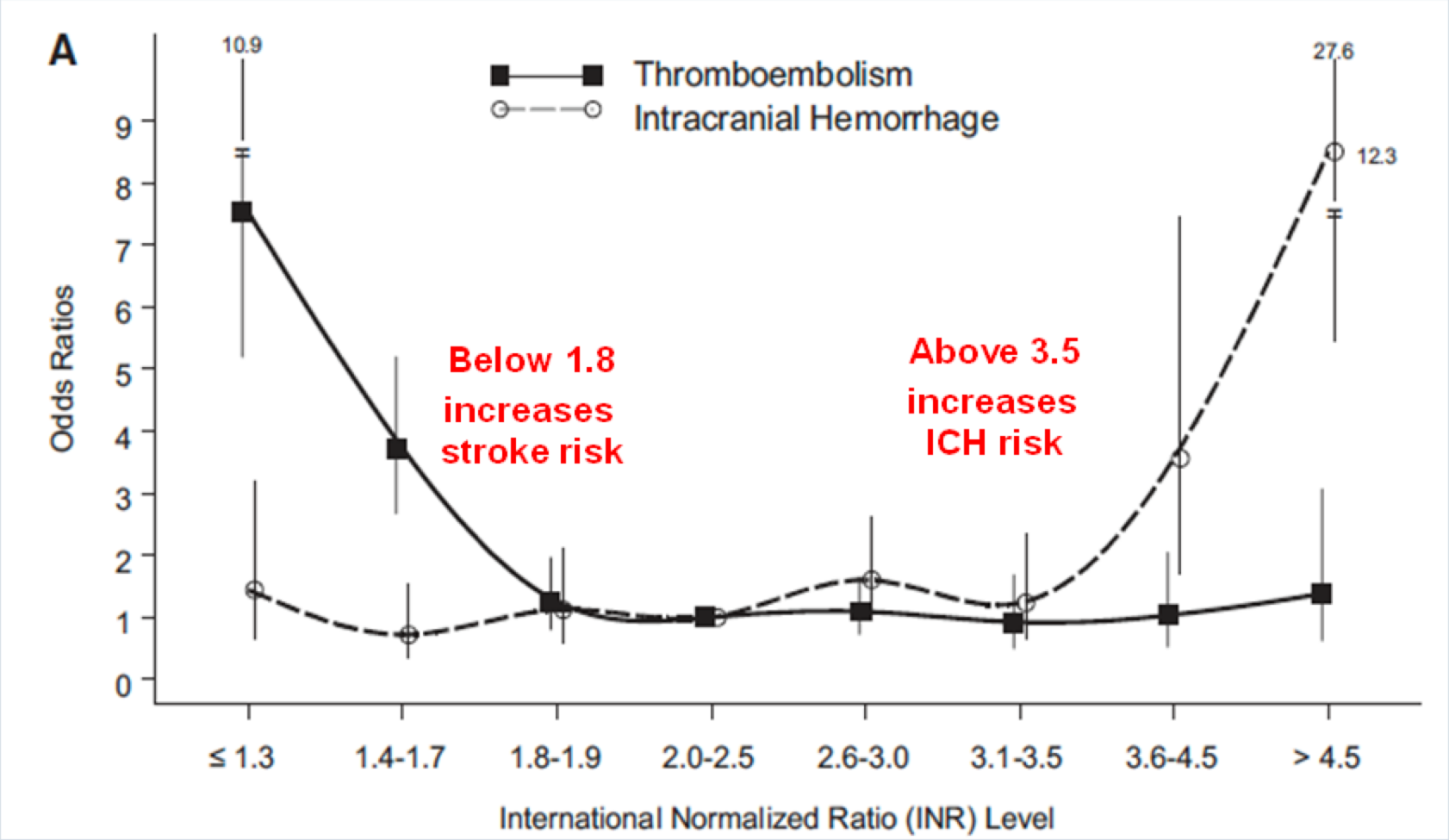
Long half-life

Slow onset and offset of action

→ **Issue in perioperative anticoagulation (bridging)**

VKA, vitamin K antagonist.

Therapeutic Range for Warfarin: Balancing Safety and Efficacy



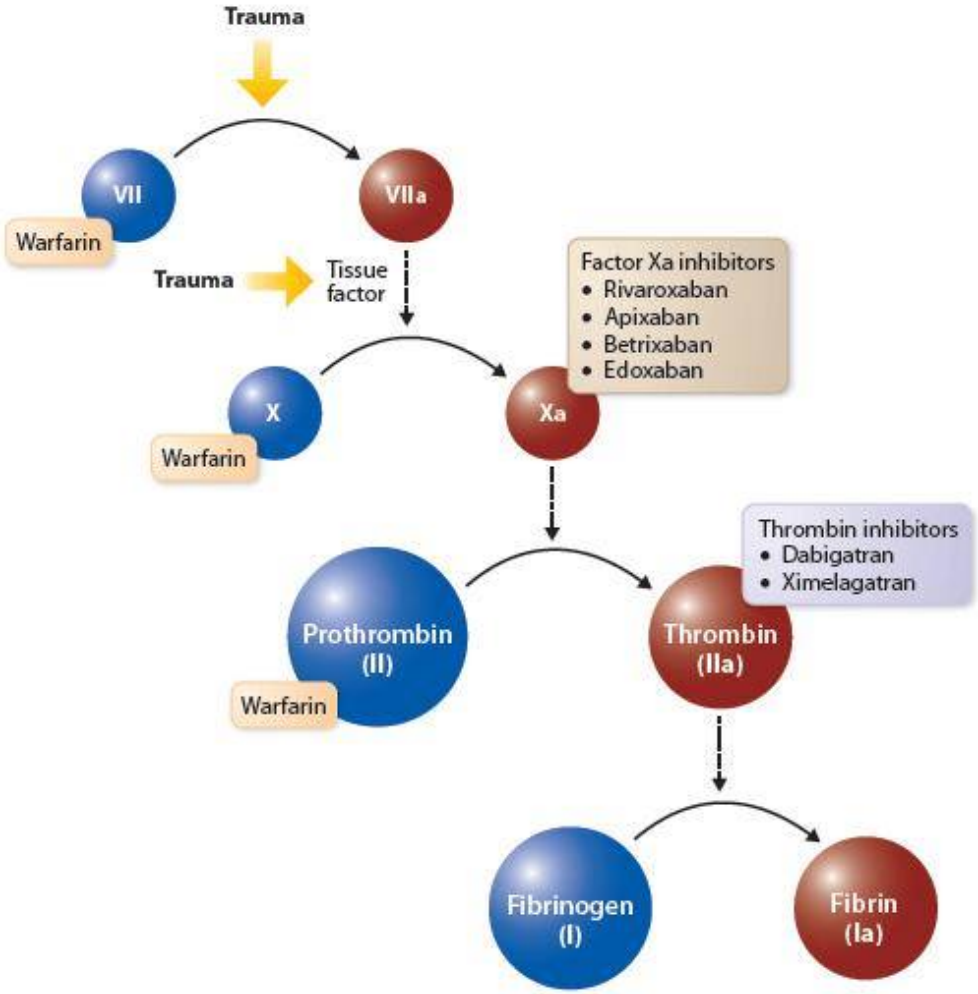
Therapeutic Range for warfarin. Rothman et al. Am J Med 2013

How do we solve a problem like warfarin?

- DOACS/NOACS
  - Direct/New/Noval Oral Anticoagulants

- Dabigatran (Pradaxa) is an orally active direct anti-thrombin inhibitor
- Apixaban (Eliquis)
- Edoxaban (Lixiana)
- Rivaroxaban (Xarelto) are orally active direct Anti-Xa inhibitors

How do they work?



Clinical pharmacology of DOACs

	Apixaban[1,2]	Rivaroxaban[1,3]	Dabigatran[1,4]	Edoxaban[5]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor
Oral bioavailability	~50%	80–100%	~6.5%	~62%
Pro-drug	No	No	Yes	No
Food effect	No	Yes (20 mg and 15 mg doses need to be taken with food)	No	No
Renal clearance	~27%	~33 %*	85%	50%†
Mean half-life ($t_{1/2}$)	12 h	5–9 h (young) 11–13 h (elderly)	12–18 h (patients)‡	10–14 h
T_{max}	3–4 h	2–4 h	0.5–2 h	1–2 h

**Direct renal excretion as unchanged active substance.*
‡ Prolonged in patients with impaired renal function.
† 35% of administered dose

The information in this table is based on the SmPC for apixaban, rivaroxaban, dabigatran and edoxaban.
Please refer to the SmPC for further information.

DOACs versus warfarin for acute VTE

	Apixaban 10 mg BD for 7d, then 5 mg BD[1]	Dabigatran 150 mg BD (pooled I+II[2,3])	Rivaroxaban 15 mg BD for 21d, then 20 mg OD (pooled DVT & PE[4])	Edoxaban 60mg OD (30 mg)[5]*
	Double-blind	Double-blind	Open-label	Double-blind
N (% DVT)	5,395 (65%)	5,107 (69%)	8,281 (42%)	8,240 (60%)
Parenteral required before DOAC?	No	Yes: ≥5d, then dabigatran 150 mg BD	No	Yes: ≥5d then edoxaban 60 mg OD or 30 mg OD*
Recurrent VTE or VTE-related death	RR 0.84 (0.60-1.18)	HR 1.09 (0.76-1.57)	HR 0.89 (0.66-1.19)†	HR 0.89 (0.70-1.13)
Major bleeding	**RR 0.31 (0.17-0.55)**	HR 0.73 (0.48-1.11) / **0.60 (0.36-0.99)‡**	**HR 0.54 (0.37-0.79)**	HR 0.84 (0.59-1.21)
Major + CRNM bleeding	RR 0.44 (0.36-0.55)	HR 0.62 (0.50-0.76) / 0.56 (0.45-0.71)‡	HR 0.93 (0.81-1.06)	HR 0.81 (0.71-0.94)
TTR Duration	61% 6 months	60% / 57%‡ 6 months	62% 3, 6 or 12 months	63% 3-12 months

There are no head-to-head studies between these agents. There are limitations such as differing patient populations, designs and outcomes, and caution should therefore be exercised when interpreting these findings. No conclusions about the relative efficacy or safety of any of these agents should be drawn from these data. Please refer to individual product SmPCs for further information.

** Patients with body weight ≤ 60 kg or a creatinine clearance of 30–50 mlL/min, and patients receiving concomitant treatment with potent P-glycoprotein inhibitors were treated with edoxaban 30 mg once daily.*

† The primary efficacy point in the EINSTEIN study is recurrent VTE.[6]

‡ (From the start of any study drug (single- and double-dummy periods) / (From the start of the oral drug only (double-dummy period only).

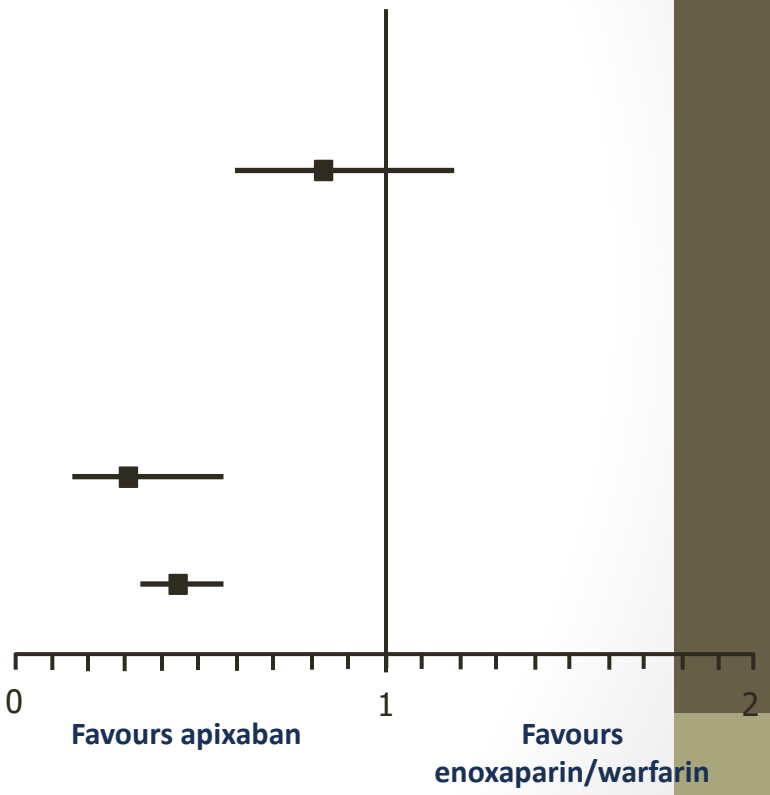
BD: twice daily; DVT: deep vein thrombosis; HR: hazard ratio, OD: once daily; RR: relative risk.

1. Agnelli et al. *N Engl J Med* 2013;369:799–808; 2. Schulman et al. *N Engl J Med* 2009;361:2342–2352;
3. Schulman et al. *Circulation* 2014;129:764–772; 4. Prins et al. *Thrombosis J* 2013, 11:21;
5. Büller et al. *N Engl J Med*2013;369:1406 –1415;
6. The EINSTEIN-PE Investigators. *N Engl J Med* 2012;366:1287–1297.

AMPLIFY: primary efficacy outcome and key safety outcomes

The AMPLIFY trial was a double-blind, randomised trial comparing 6 months of apixaban treatment with enoxaparin bridging to warfarin therapy in patients with acute symptomatic DVT and/or PE

	Apixaban (n=2,609)	Enoxaparin/ warfarin (n=2,635)	RR (95% CI)	*P* Value
Primary efficacy outcome*				
Recurrent VTE or VTE-related death, n (%)	59 (2.3)	71 (2.7)	0.84 (0.60–1.18)	<0.001 Non-inferiority
	Apixaban (n=2,676)	**Enoxaparin/ warfarin (n=2,689)**	**RR (95% CI)**	***P* Value**
Safety outcomes#				
Major bleeding†, n (%)	15 (0.6)	49 (1.8)	0.31 (0.17–0.55)	<0.001
Major or CRNM bleeding, n (%)	115 (4.3)	261 (9.7)	0.44 (0.36–0.55)	<0.001



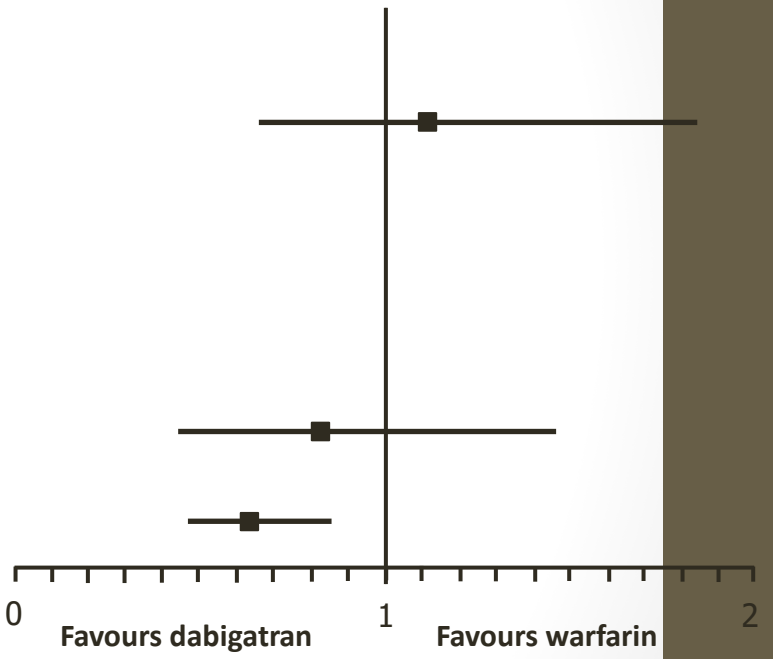
**All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented.*
 # All safety analyses included data obtained from patients during study treatment, defined as the time from administration of the first dose until 48 hours after the last dose was administered.
† Major bleeding was the primary safety endpoint.
HR, hazard ratio.

Agnelli et al. *N Engl J Med* 2013;369:799–808.

RE-COVER: primary efficacy outcome and key safety outcomes

The RE-COVER trial was a double-blind, double-dummy, randomised trial comparing 6 months of dabigatran treatment (150 mg twice daily) with heparin* bridging to dose-adjusted warfarin therapy in patients with acute symptomatic DVT and/or PE

	Dabigatran (n=1,274)	Heparin*/ warfarin (n=1,265)	HR (95% CI)	*P* Value
Primary efficacy outcome#				
Recurrent VTE or VTE-related death, n (%)	30 (2.4)	27 (2.1)	1.10 (0.65–1.84)	<0.001 Non-inferiority
	Dabigatran (n=1,273)	**Heparin*/ warfarin (n=1,266)**	**HR (95% CI)**	***P* Value**
Safety outcomes†				
Major bleeding,‡ n (%)	20 (1.6)	24 (1.9)	0.82 (0.45–1.48)	Data not available from publication
Major‡ or CRNM bleeding, n (%)	71 (5.6)	111 (8.8)	0.63 (0.47–0.84)	0.002



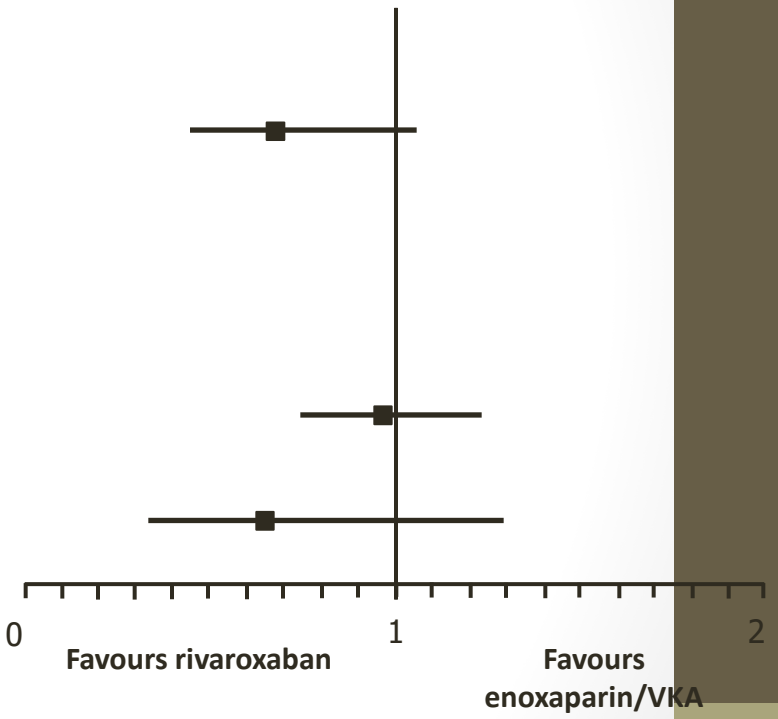
**LMWH, UFH, or fondaparinux.*
 # The efficacy analysis was based on the number of randomly assigned patients who received at least one dose of study drug and who had events during the 6-month treatment period, regardless of early discontinuation of study drug.
†The safety analysis of bleeding events was performed on the basis of the number of patients treated with dabigatran (1,273) or warfarin (1,266), rather than the number assigned to the treatment (1 patient who was assigned to receive dabigatran mistakenly received warfarin instead throughout the study). Events that occurred during the 6-month treatment period plus a 6-day washout period were included.
‡ Major bleeding was the primary safety endpoint.

Schulman et al. *N Engl J Med* 2009;361:2342–2352.

EINSTEIN-DVT: primary efficacy outcome and key safety outcomes

The EINSTEIN-DVT trial was an open-label, randomised trial comparing rivaroxaban treatment (15 mg twice daily for 21d, then 20 mg once daily for 3, 6 or 12 months) with enoxaparin bridging to VKA therapy in patients with acute symptomatic DVT

	Rivaroxaban (n=1,731)	Enoxaparin/VKA (n=1,718)	HR (95% CI)	*P* Value
Primary efficacy outcome* (mean study duration: ~9 months)				
Recurrent VTE, n (%)	36 (2.1)	51 (3.0)	0.68 (0.44–1.04)	<0.001 Non-inferiority
	Rivaroxaban (n=1,718)	**Enoxaparin/VKA (n=1,711)**	**HR (95% CI)**	***P* Value**
Safety outcomes#				
Major or CRNM bleeding†, n (%)	139 (8.1)	138 (8.1)	0.97 (0.76–1.22)	0.77
Major bleeding, n (%)	14 (0.8)	20 (1.2)	0.65 (0.33–1.30)	0.21



**The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The primary efficacy analysis was performed on an intention-to-treat basis with the use of a stratified intended-duration Cox proportional-hazards model, adjusted for the presence of a malignant condition at baseline.*

 # The safety analyses included all patients who received the assigned study drug. Bleeding events were included in the analysis if they occurred during treatment or within 2 days after the last dose of a study drug.

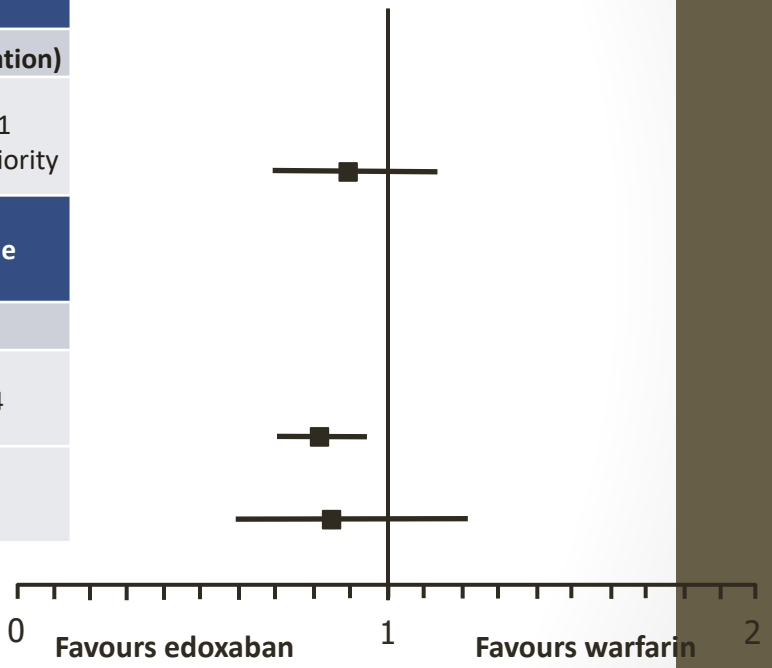
† Major or clinically relevant non-major (CRNM) bleeding was the primary safety endpoint.

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

HOKUSAI-VTE: primary efficacy outcome and key safety outcomes

The HOKUSAI-VTE trial was a randomised, double-blind, non-inferiority trial comparing edoxaban treatment (60 mg once daily for 3 to 12 months)* with warfarin in patients with acute symptomatic DVT or symptomatic PE with or without DVT

	Edoxaban (n=4,118)	Warfarin (n=4,122)	HR (95% CI)	*P* Value
Primary efficacy outcome# (efficacy evaluated at 12 months regardless of treatment duration)				
Recurrent VTE or VTE-related death, n (%)	130 (3.2)	146 (3.5)	0.89 (0.70–1.13)	<0.001 Non-inferiority
	Edoxaban (n=4,118)	**Warfarin (n=4,122)**	**HR (95% CI)**	***P* Value**
Safety outcomes†				
First major or CRNM bleeding‡, n (%)	349 (8.5)	423 (10.3)	0.81 (0.71–0.94)	0.004
Major bleeding, n (%)	56 (1.4)	66 (1.6)	0.84 (0.59–1.21)	0.35



**Patients with body weight ≤ 60 kg or a creatinine clearance of 30–50 mlL/min, and patients receiving concomitant treatment with potent P-glycoprotein inhibitors were treated with edoxaban 30 mg once daily.*

 # All efficacy analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and received at least one dose of the study drug. The primary analysis included all efficacy outcomes from randomization through the end of 12 months or study closure (overall study period), regardless of the duration of the patient's study treatment. the primary efficacy outcome was evaluated for the on-treatment period — the time during which the patients were receiving the study drug or within 3 days after the study drug was stopped or interrupted.

† Analyses of bleeding outcomes included patients who received at least one dose of the study drug (safety population)

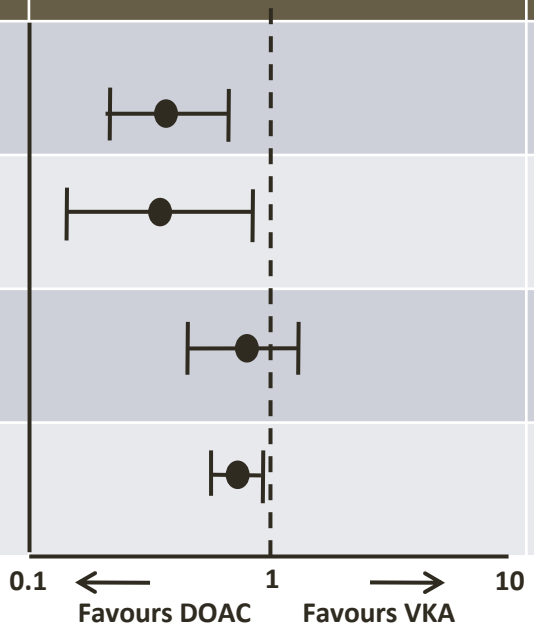
‡ First major or clinically relevant non-major (CRNM) bleeding was the primary safety endpoint.

Büller et al. *N Engl J Med* 2013;369:1406–1415.

Safety analysis of pooled DOAC data vs VKA in VTE treatment[1]

Intracranial, major gastrointestinal, fatal and clinically relevant non-major bleeding

	Pooled DOAC (n/N)	Pooled VKA (n/N)	Risk ratio (95% CI)	P value	ARR (95% CI)
Intracranial bleeding	15/13477 (0.1%)	43/13481 (0.3%)	**0.37 (0.21-0.68)**	0.001	-0.17% (-0.30% to -0.03%)
Fatal bleeding	7/13477 (0.1%)	22/13481 (0.2%)	**0.35 (0.15-0.84)**	0.02	-0.08% (-0.16% to -0.01%)
Major GI bleeding	63/13477 (0.5%)	76/13481 (0.6%)	**0.78 (0.47-1.31)**	0.35	-0.12% (-0.37% to 0.13%)
CRNM bleeding	854/13477 (6.3%)	1103/13481 (8.0%)	**0.73 (0.58-0.93)**	0.01	-1.88% (-3.24% to -0.52%)



Adapted from Van Es et al. 2014.[1]

There are no head-to-head studies between these agents. There are limitations such as differing patient populations, designs and outcomes, and caution should therefore be exercised when interpreting these findings. No conclusions about the relative efficacy or safety of any of these agents should be drawn from these data. Please refer to individual product SmPCs for further information

ARR: absolute risk reduction; CRNM: clinically relevant non major; GI: gastrointestinal;
DOAC: non-VKA oral anticoagulant;
RR: relative risk; VKA: vitamin K antagonist.

1. Van Es et al. *Blood*. 2014:1968–1975.

DOAC dosing regimens across each stage of VTE treatment

	Initial VTE treatment	Ongoing VTE Treatment	Prevention of Recurrent VTE
Apixaban[1]	**10 mg BD** Day 1–7	**5 mg BD** Day 8 onwards for at least 3 months*	**2.5 mg BD** Following completion of 6 months of treatment with apixaban 5 mg BD or another oral anticoagulant
Rivaroxaban[2]	**15 mg BD with food** Day 1–21	**20 mg OD with food** Day 22 onwards for at least 3 months*†	
Dabigatran[3]	**Parenteral anticoagulant** For at least 5 days (not to be taken concomitantly with dabigatran)	**150 mg BD** For at least 3 months*† (Dose adjustments to 110 mg BD in patients ≥80 years, patients on concomitant verapamil, and those at high risk of bleeding)	
Edoxaban[4]	**Parenteral anticoagulant** For at least 5 days (not to be taken concomitantly with edoxaban)	**60 mg OD** For at least 3 months*† (Dose adjustment required to 30 mg OD in patients with CrCl 15–50 ml/min or body weight ≤60 kg or with concomitant use of the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole. Refer to edoxaban SmPC for further information)	

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding

**Short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. Recent surgery, trauma, immobilisation)*

†Longer durations should be based on permanent risk factors of idiopathic DVT or PE.

***Apixaban**: Use with caution in severe renal impairment (CrCl 15–29 mL/min). Not recommended in CrCl <15 mL/min or in patients undergoing dialysis. **Rivaroxaban:** Consider reduction from 20 mg OD to 15 mg OD (after the initial 15 mg BD for 3 weeks) in patients with moderate (CrCl 30–49 mL/min) or severe (CrCl 15–29 mL/min) renal impairment if patient's assessed bleeding risk outweighs risk for recurrent DVT and PE. Use with caution in severe renal impairment. Not recommended in CrCl < 15 mL/min. **Dabigatran**: Contraindicated in CrCl < 30 mL/min. **Edoxaban:** In patients with moderate or severe renal impairment (CrCl 15–50 ml/min) the recommended dose is 30 mg OD. Not recommended in CrCl <15 ml/min or in patients undergoing dialysis.*

CrCl, creatinine clearance; OD, once daily; BD, twice daily.

PP-ELI-GBR-0034

1. Apixaban SmPC. Available at http://www.medicines.org.uk; 2. Rivaroxaban SmPC. Available at http://www.medicines.org.uk;
3. Dabigatran SmPC. Available at http://www.medicines.org.uk; 4. Edoxaban SmPC. Available at http://www.medicines.org.uk.

Current clinical challenges of VTE treatment[1,2]

	Advantages	Disadvantages
VKA	▶ Mainstay of long-term therapy since 1960[1] ▶ Can be used in patients with severe renal impairment[2] ▶ Anticoagulation can be reversed[2]	▶ Slow onset/offset requires bridging[1] ▶ Numerous interactions with other drugs and food[1] ▶ Narrow therapeutic window[1] ▶ Inter-individual variability in dose response[1] ▶ Need for INR monitoring[1,2]
DOACs	▶ Predictable pharmacological profiles[1] ▶ Absence of major interactions with food or other drugs[1] ▶ Do not require routine INR monitoring[1] ▶ May shift practice to longer treatment duration[1]	▶ No readily available monitoring for special circumstances (e.g. major bleeding, urgent procedure) ▶ No long term data ▶ Lack of reversal agent for Anti-Xa inhibitors

1. Van Es J et al. *J Thromb Haemost* 2011;9:265–74;
2. Warfarin SmPC. Available at www.medicines.org.uk.

Counselling

- Need to be aware of risks of bleeding as with warfarin
- No reversal agent for 3 of the drugs AT THE MINUTE
- Lack of long term safety data/unknown interactions
- Pros/cons of the medicines
- What to do if miss a dose
- New drugs/procedures
- Pregnancy
- Annual review
- Outpatient service by anticoag team

NICE technology appraisal guidance on DOACs in VTE

Apixaban

- Recommended as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults[1]
- Recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery[2]

Rivaroxaban

- Recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults[3]
- Recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults[4]
- Recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery[5]

Dabigatran

- Recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery[6]
- Recommended as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults[7]

Edoxaban

- Recommended as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults[8]

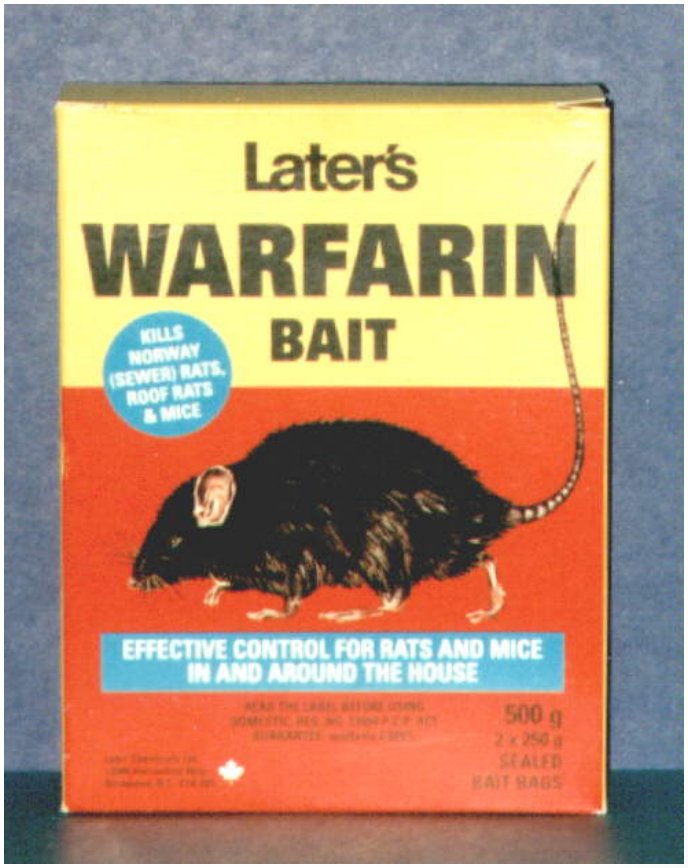
GMMMG

- would prefer to be on a DOAC to their current treatment
- Poor INR control
  - Have a poor time in treatment range (TTR) (<65%)
  - Have had two or more unexplained INR results >5 OR one INR >8 within past 6 months
  - Have had two INR values <1.5 within past 6 months.
- There are insurmountable difficulties with safe compliance of INR monitoring and dose adjustments, e.g. due to cognitive impairment or poor venous access.
- Side effects/intolerance to warfarin other than bleeding (i.e. alopecia, rash)

Greater Manchester Medicine Management Group. Prescriber Decision Support, NOACs. November 2015

When not to start a DOAC...

- Warfarin is the preferred option in patients with eGFR <15
- Patients with a baseline eGFR of 15-50 are at risk of progressive/acute renal dysfunction and the potential risks of bleeding with a DOAC should be weighed on an individual basis.
- DOACs are not licensed for valvular AF/Cancer associated VTE/under 18's/pregnant women/breastfeeding women
- Non-compliance is not a reason to switch to DOACs.



Discontinuation time

Renal Function CrCl ml/min	Low bleeding risk	High bleeding risk
Dabigatran		
>80	24 hours	48 hours
>50 to <80	24-48 hours	48-72 hours
>30 to <50	48-72 hours	96 hours
Anti-Xa direct inhibitors		
>30	24 hours	48 hours
<30	48 hours	72 hours

Peri-operative management of anticoagulation and antiplatelet therapy. Keeling et al. BJH. 175 (4). Nov 2016 p602-613

Bridging

- Minor/low risk procedure with low bleeding risk patient restart 6-12 hours post op
- High risk procedure or high bleeding risk or if bleeding unacceptable – 48 hours post op
- If thrombotic risk – prophylactic LMWH

Peri-operative management of anticoagulation and antiplatelet therapy. Keeling et al. BJH. 175 (4). Nov 2016 p602-613

Managing bleeding on DOACs

- Stop the drug!
- Need to know renal/liver function and time/dose of last dose=estimate half-life of drug
- FBC/Coag screen inc fibrinogen/creatinine/Drug levels
- Assess bleeding source and correct haemodynamic compromise
- Tranexamic acid

Guideline on the management of bleeding in patients on antithrombotic agents. Makris et al. BJH. 160(1). Jan 2013, p35-46.

Reversal

- Dabigatran within 2 hrs activated charcoal
- Dabigatran is reversible with haemofiltration
- Dabigatran – idarucizumab (Praxbind)
- PCC/aPCC/rFVIIa

Peri-operative management of anticoagulation and antiplatelet therapy. Keeling et al. BJH. 175 (4). Nov 2016 p602-613

THANKYOU

ANY QUESTIONS?