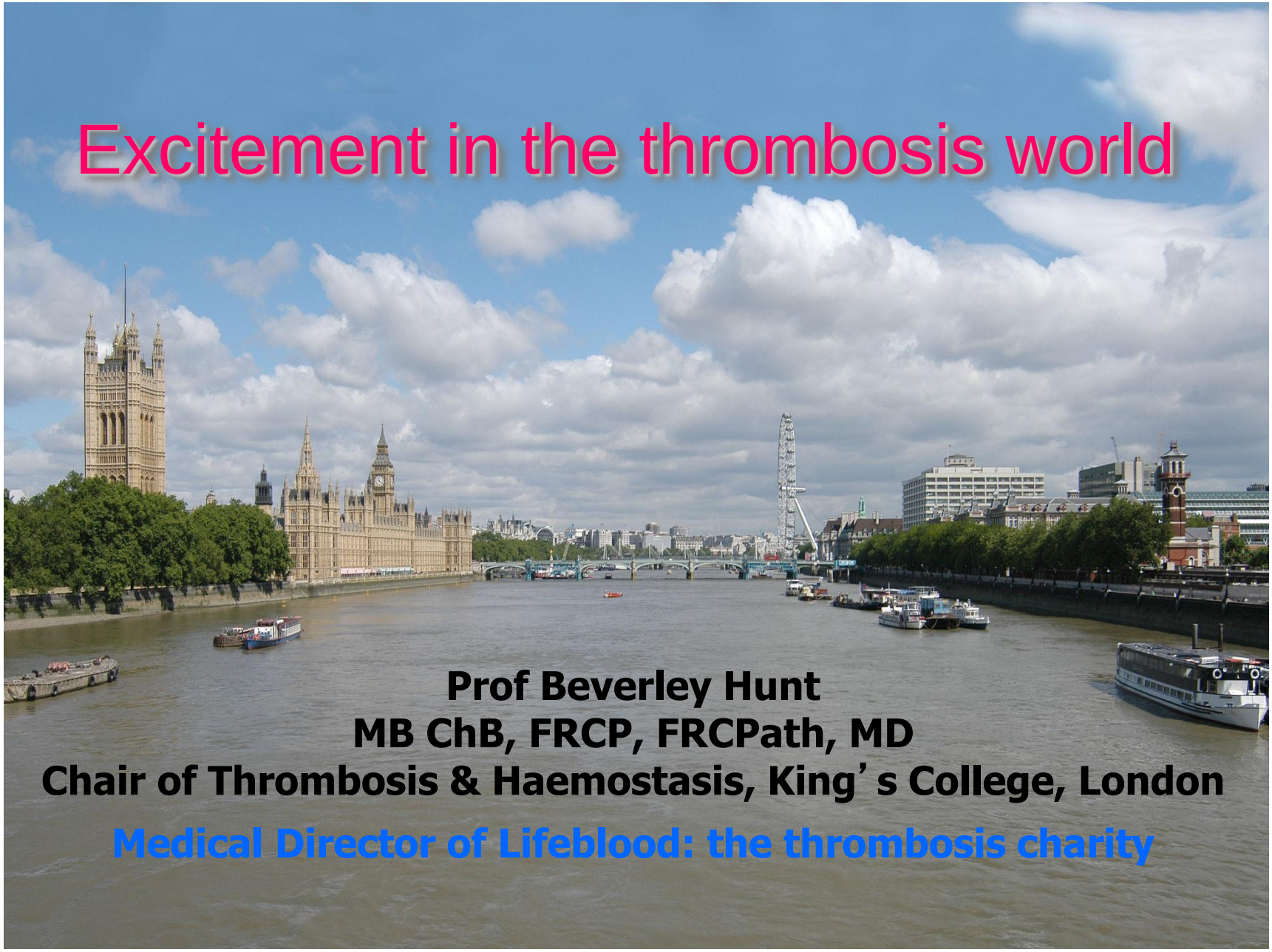
Excitement in the thrombosis world



Prof Beverley Hunt
MB ChB, FRCP, FRCPath, MD
Chair of Thrombosis & Haemostasis, King's College, London
Medical Director of Lifeblood: the thrombosis charity

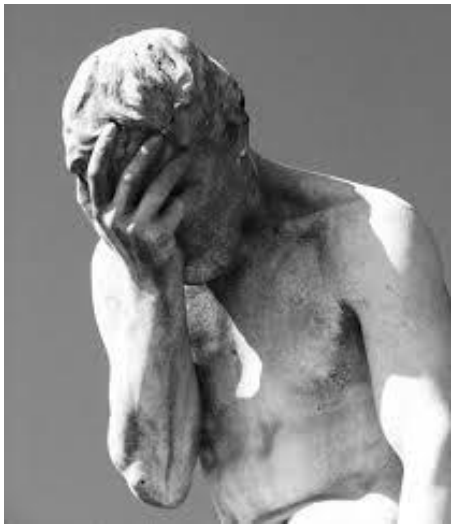
Conflicts of interest

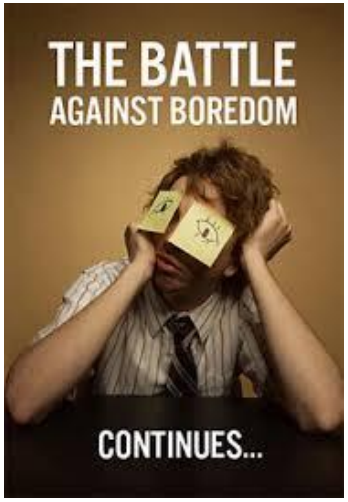
None

I have not taken any personal funding from pharmaceutical companies producing anticoagulant drugs since 2010

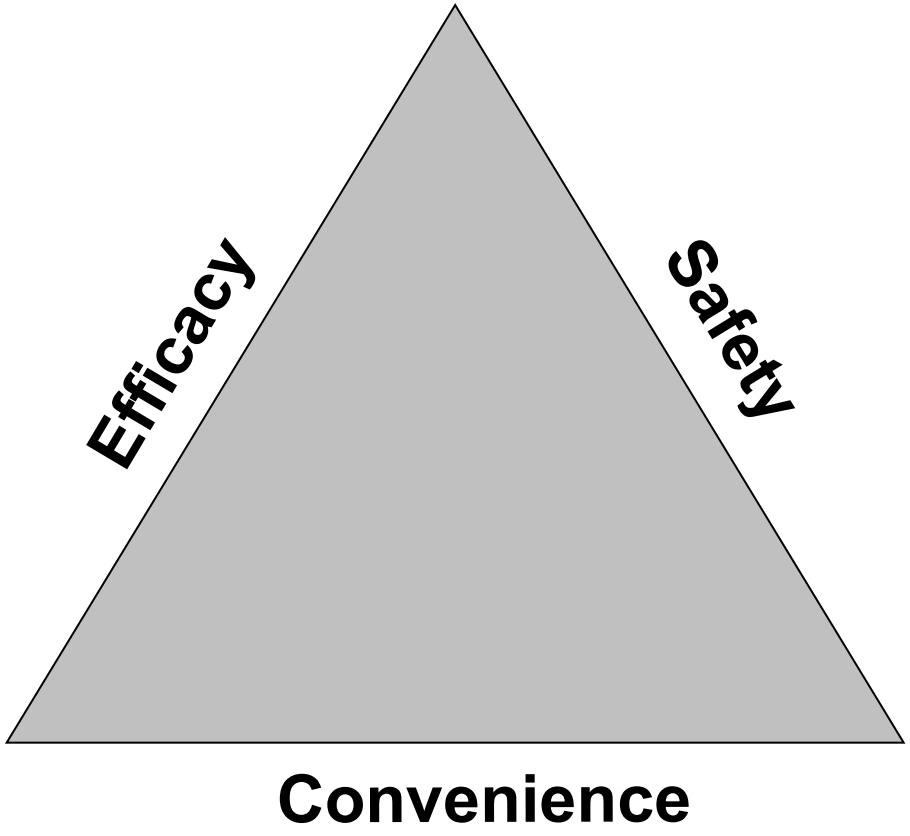
Lifeblood will no longer take any funding from big pharma

How it used to be:



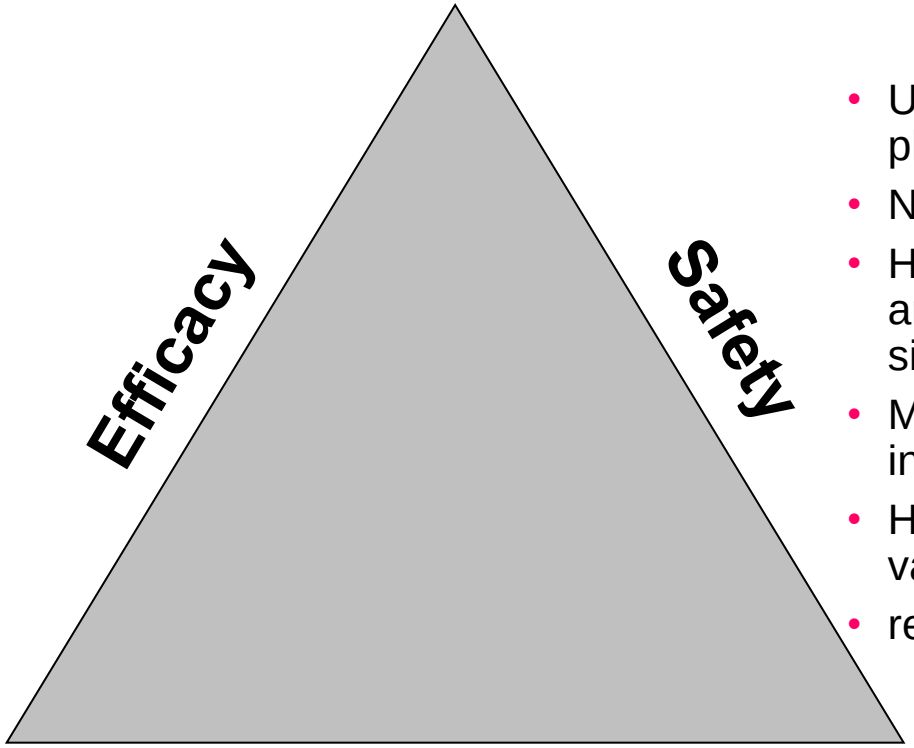


The Ideal Oral Anti-thrombotic



Coumarins- discovered 1930s

Yes



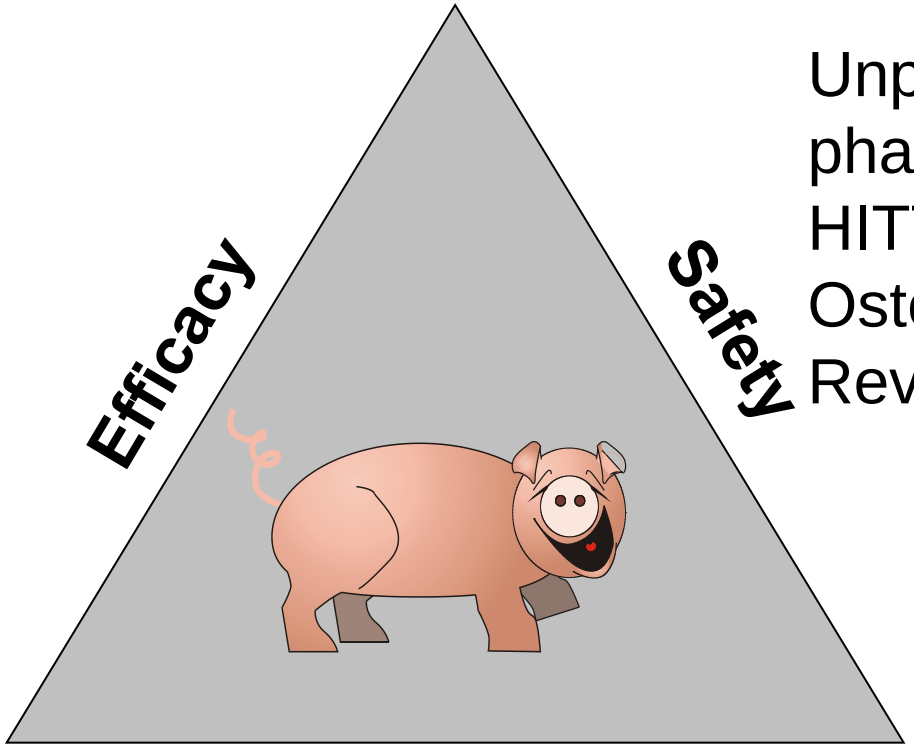
- Unpredictable pharmacokinetics
- Narrow therapeutic window
- High perception of incidence and severity of bleeding and side effects
- Many food and drug interactions
- High inter and intra patient variability
- reversible

Convenience

- Dose adjustment required
- Slow on-set and off-set of action
- Routine coagulation monitoring required

UF heparin

Yes



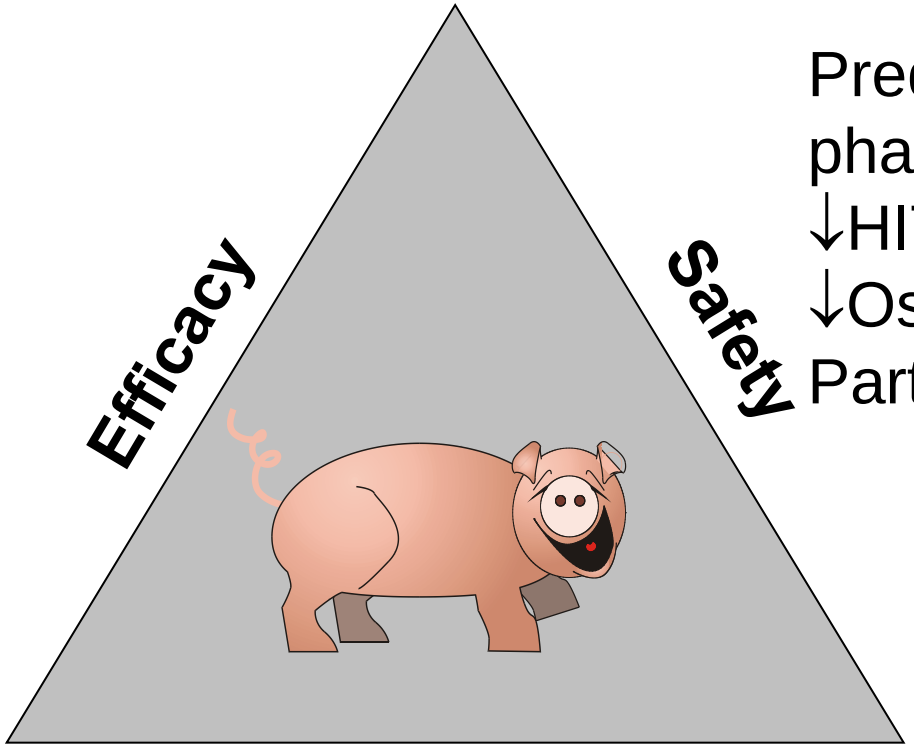
Unpredictable pharmacokinetics
HITT
Osteoporosis
Reversible

Convenience

No oral form
Needs monitoring
*Supply problems

LMW heparin

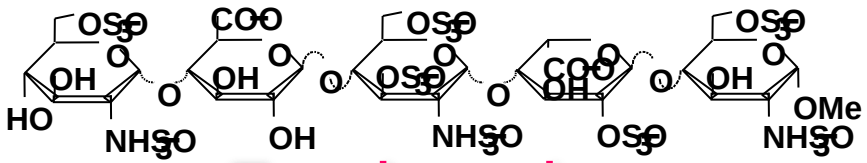
Yes



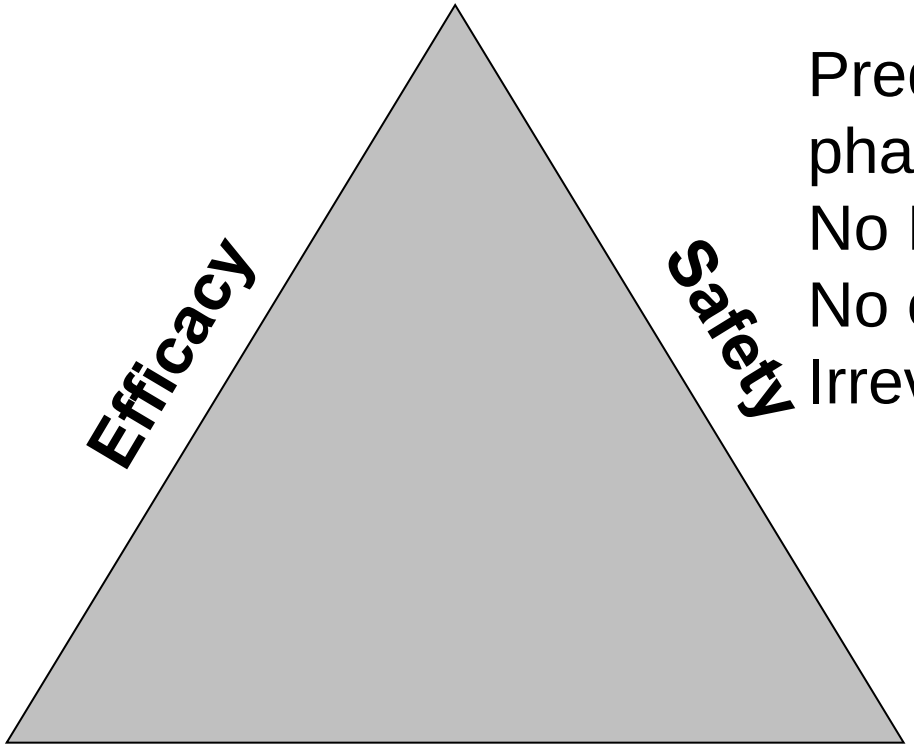
Predictable pharmacokinetics!
↓HITT
↓Osteoporosis
Partially reversible

Convenience

No oral form
No monitoring unless BMI or renal failure
*Supply problems



Fondaparinux



Yes

Predictable pharmacokinetics!
No HITT
No osteoporosis
Irreversible

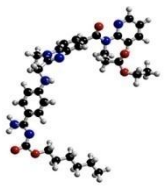
No oral form
No monitoring unless BMI or renal failure
No supply problems but thromboprophylaxis is costly

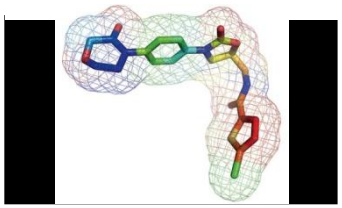
The essence of maintaining a stable INR

- Warfarin is a vitamin K antagonist
- Therefore have a consistent intake of vitamin K
- In a “normal” British diet = same amount of green vegetables (+cauliflower) EVERY day
- Check INR 3 days after changing medication if using a drug that may affect warfarin

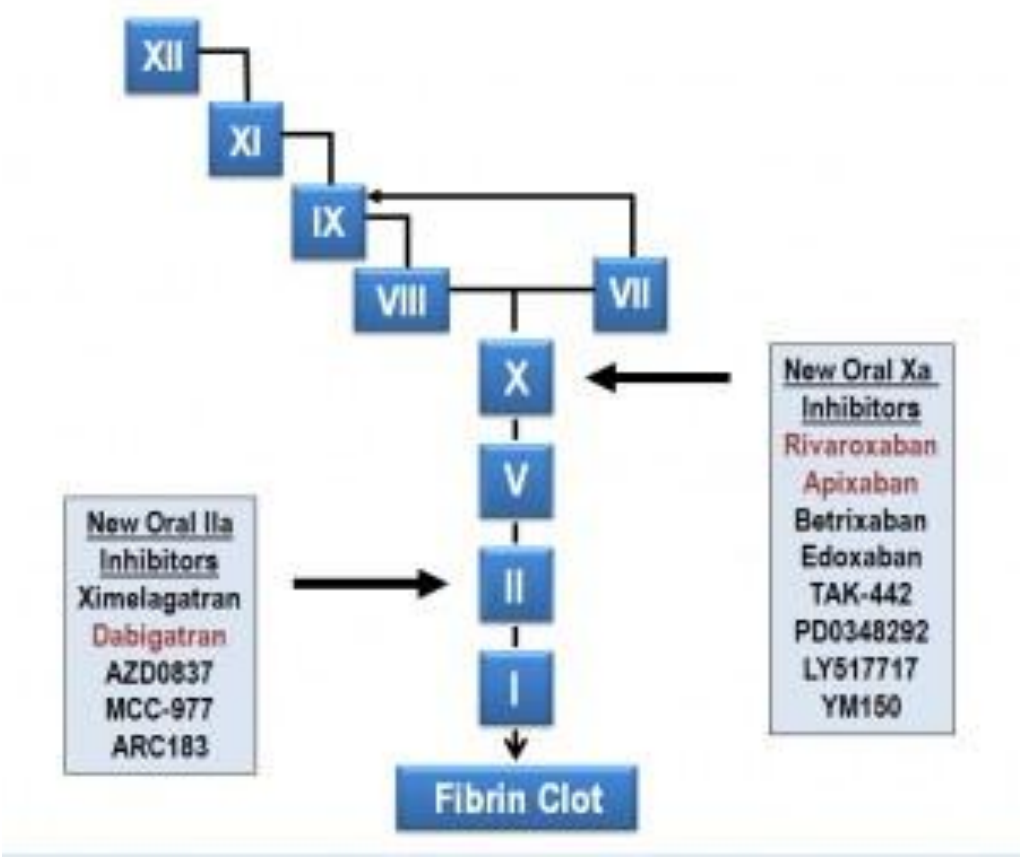
NOACs

- **predictable dose response**
- **no need for routine monitoring**
- **reduced need for dose adjustment**
- **no food interactions**
- **limited drug interactions**



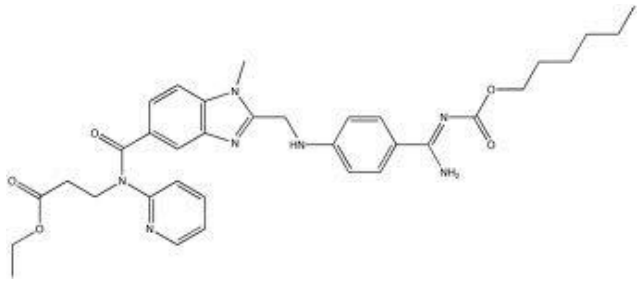


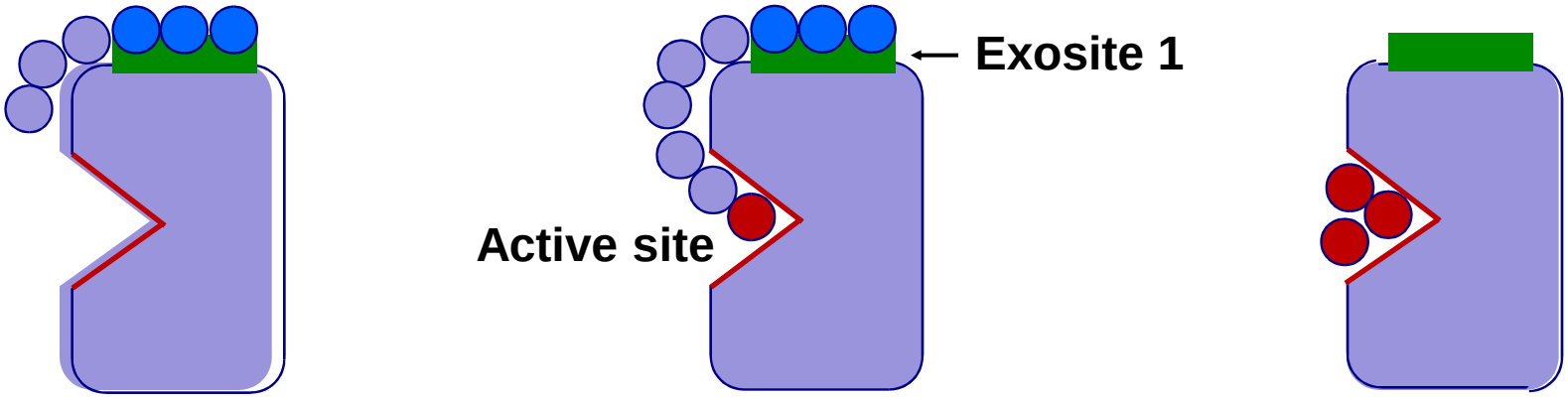
The new oral anticoagulants



Dabigatran –a direct thrombin inhibitors

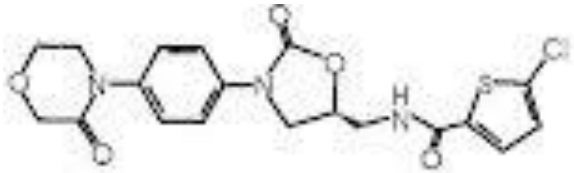
- **Dabigatran etexilate is an oral direct thrombin inhibitor**
  - Predictable anticoagulant effect
  - Fixed dose
  - No need for monitoring



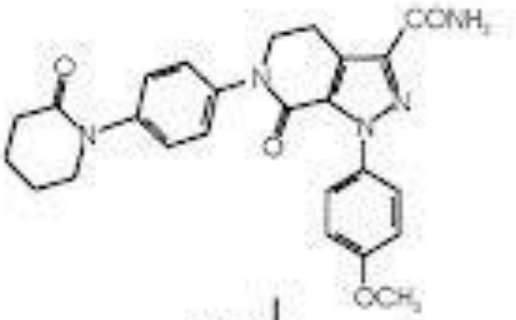


It is the pro-drug of the active compound dabigatran, which binds directly to thrombin with a high affinity and specificity

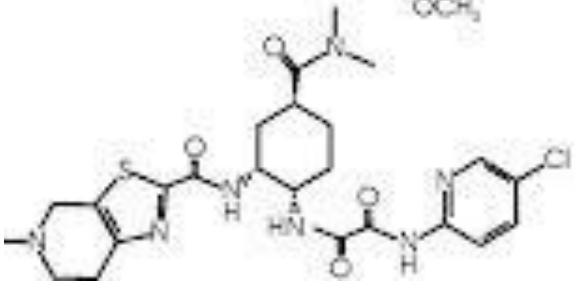
The new direct anti-Xa agents



Rivaroxaban



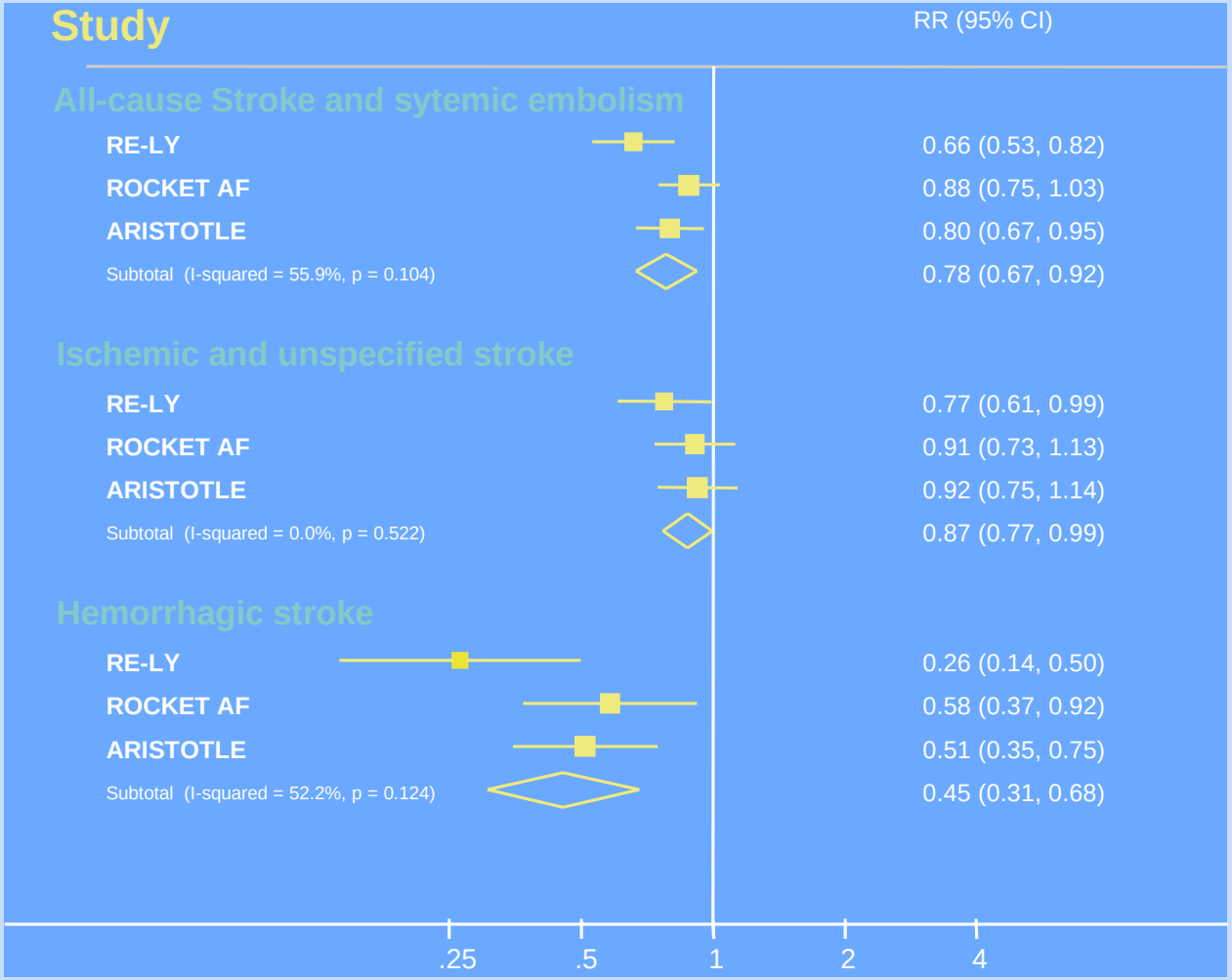
Apixaban



Edoxaban

- Predictable anticoagulant effect
- Fixed dose
- No need for monitoring

New oral coagulants versus warfarin in patients with AF



RE-LY: dabigatran;
ROCKET AF: rivaroxaban
ARISTOTLE: apixaban

Miller SC et al. April 27,Am J Cardiol 2012

Pharmacodynamics of new oral direct inhibitors

	Apixaban	Dabigatran	Rivaroxaban
Direct factor inhibition	Xa	IIa	Xa
Bioavailability (F_{rel})	80%	6%	80%
Peak action (t_{max})	1–3 hr	1–3 hr	1–3 hr
Protein binding	84%	35%	92–95%
Renal clearance	25%	80%	33%
Elimination half life with creatinine clearance > 80 ml/min	15.1 hr	13.8 hr	8.3 hr
Elimination half life with creatinine clearance 50–79 ml/min	14.6 hr	16.6 hr	8.7 hr
Elimination half life with creatinine clearance 30–49 ml/min	17.6 hr	18.7 hr	9.0 hr
Elimination half life with creatinine clearance < 30 ml/min	17.3 hr	27.5 hr	9.5 hr

Taken from Kaatz *et al* Am J Hematol 2012;S141

Anticoagulants for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Drug use and dosing based on kidney function estimation (estimated creatinine clearance [eCrCl])

CrCl >50 ml/min	**Any anticoagulant** – no dose adjustment needed based on kidney function
CrCl 30–49 ml/min	**Apixaban** 5 mg twice daily or 2.5 mg twice daily if serum creatinine (SCr) ≥133 μmol/L with age ≥80 years or body weight ≤60 kg **Dabigatran** 110 mg twice daily if high risk of bleeding (suggest use of HAS-BLED score to assess risk); otherwise 150 mg twice daily **Rivaroxaban** 15 mg once daily **Warfarin** International normalised ratio (INR) dependent dose adjustment
CrCl 15–29 ml/min	**Apixaban** 2.5 mg twice daily **Dabigatran** contraindicated **Rivaroxaban** 15 mg once daily but caution – plasma concentrations significantly increased (average 1.6-fold), which may increase bleeding risk **Warfarin** INR dependent dose adjustment under expert advice and review
CrCl <15 ml/min	No anticoagulant use recommended in general use, take expert advice

SCr (μmol/L)	Women ≥60 kg* eCrCl (ml/min) (NB do not use table if weight <60 kg – see below)													Men ≥70 kg* eCrCl (ml/min) (NB do not use table if weight <70 kg – see below)											
	Age (years)													Age (years)											
	40	45	50	55	60	65	70	75	80	85	90	95	100	40	45	50	55	60	65	70	75	80	85	90	95	100
50	120	114	108	102	96	90	84	78	72	66	60	54	48	168	160	151	143	134	126	118	109	101	92	84	76	67
60	100	95	90	85	80	75	70	65	60	55	50	45	40	140	133	126	119	112	105	98	91	84	77	70	63	56
70	86	81	77	73	69	64	60	56	51	47	43	39	34	120	114	108	102	96	90	84	78	72	66	60	54	48
80	75	71	68	64	60	56	53	49	45	41	38	34	30	105	100	95	89	84	79	74	68	63	58	53	47	42
90	67	63	60	57	53	50	47	43	40	37	33	30	27	93	89	84	79	75	70	65	61	56	51	47	42	37
100	60	57	54	51	48	45	42	39	36	33	30	27	24	84	80	76	71	67	63	59	55	50	46	42	38	34
110	55	52	49	46	44	41	38	35	33	30	27	25	22	76	73	69	65	61	57	53	50	46	42	38	34	31
120	50	48	45	43	40	38	35	33	30	28	25	23	20	70	67	63	60	56	53	49	46	42	39	35	32	28
130	46	44	42	39	37	35	32	30	28	25	23	21	18	65	61	58	55	52	48	45	42	39	36	32	29	26
140	43	41	39	36	34	32	30	28	26	24	21	19	17	60	57	54	51	48	45	42	39	36	33	30	27	24
150	40	38	36	34	32	30	28	26	24	22	20	18	16	56	53	50	48	45	42	39	36	34	31	28	25	22
160	38	36	34	32	30	28	26	24	23	21	19	17	15	53	50	47	45	42	39	37	34	32	29	26	24	21
170	35	34	32	30	28	26	25	23	21	19	18	16	14	49	47	44	42	40	37	35	32	30	27	25	22	20
180	33	32	30	28	27	25	23	22	20	18	17	15	13	47	44	42	40	37	35	33	30	28	26	23	21	19
190	32	30	28	27	25	24	22	21	19	17	16	14	13	44	42	40	38	35	33	31	29	27	24	22	20	18
200	30	29	27	26	24	23	21	20	18	17	15	14	12	42	40	38	36	34	32	29	27	25	23	21	19	17

Current evidence suggests that an absolute CrCl (Cockcroft & Gault), as used in drug licence dosing studies, should be used for dosing decisions, not normalised estimated glomerular filtration rate (eGFR), especially for older patients and for narrow therapeutic index and high-risk drugs.

The tables should not be used for patients in acute renal impairment, who are dehydrated or if under the stated weights when eCrCl should be calculated individually (manually using the Cockcroft & Gault equation in **Box 2** or on e.g. SystmOne>clinical tools>renal calculations) *Average ideal body weight.

Based on data taken from the current Summaries of Product Characteristics (SmPCs). Available from: www.medicines.org.uk/emc/

Development status of the new oral anticoagulants in Europe[1]

- Licensed indication
- Phase III study completed
- Phase III study in progress
- No study ongoing

	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
VTE prevention in orthopaedic surgery	**RECORD 1 - 4**	**RE-NOVATE RE-MODEL**	**ADVANCE 1 - 3**	**Licensed in Japan**
Stroke prevention in AF	**ROCKET AF**	**RE-LY**	**AVERROES**	**Nov 2013**
			ARISTOTLE	
VTE treatment	**EINSTEIN DVT**	**RE-COVER**	**AMPLIFY**	**HOKSAI**
	EINSTEIN PE			

1.www.clinicaltrials.gov

Guideline for Management of Acute Deep Vein Thrombosis in Non Pregnant Patients

Guy's and St Thomas' NHS
NHS Foundation Trust

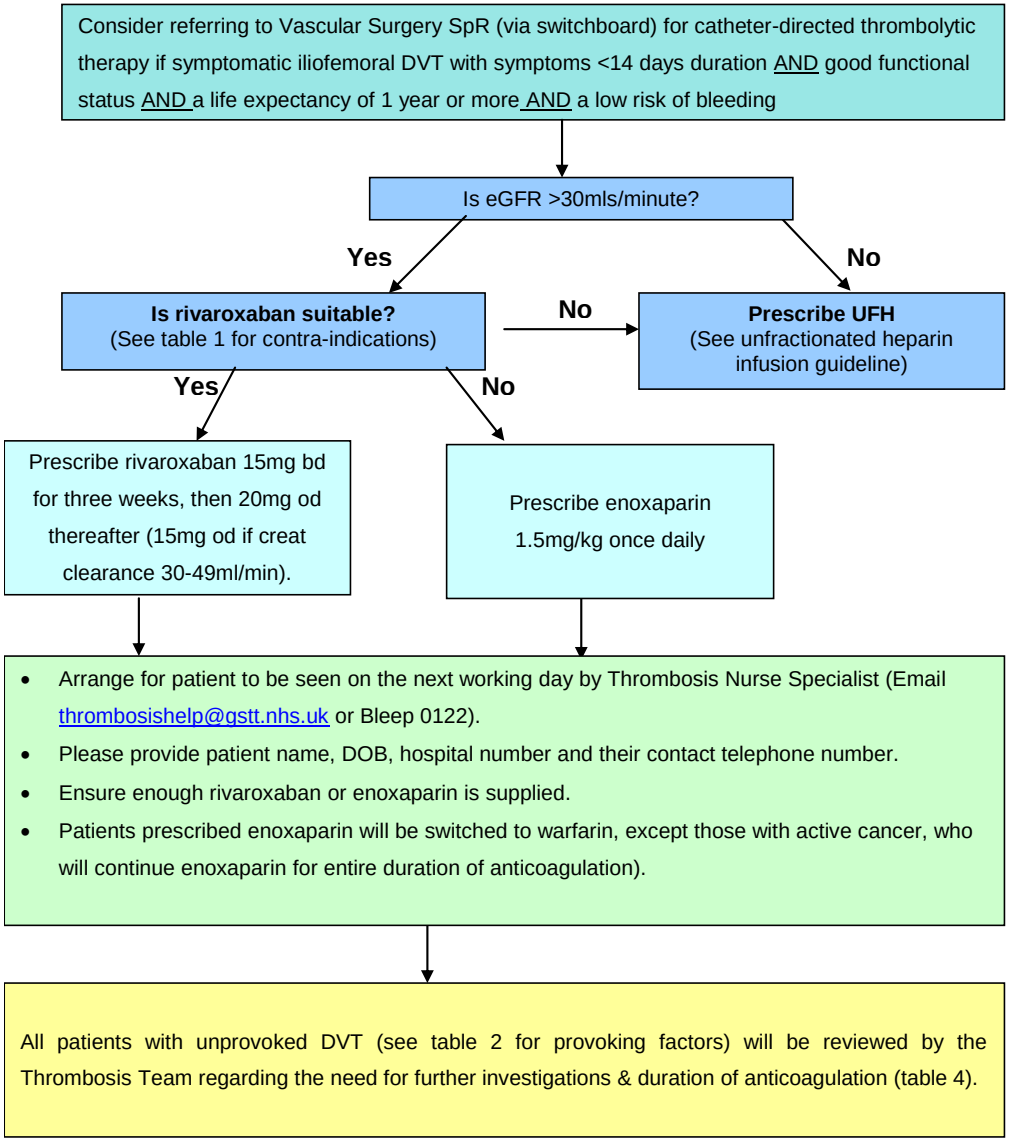


Table 1: Contra-indications to Rivaroxaban

Significant liver disease
Pregnancy of Breastfeeding
Creatinine clearance <30mls/min
Concomitant use of cytochrome P-450 3A4 inhibitors: eg fluconazole, anti-retrovirals
Currently not recommended in active cancer – patients should receive enoxaparin or UFH

Table 2: Provoking factors for DVT

Any of the following are considered to be transient risk factors within 3 months of DVT:
Surgery
Trauma
Acute medical illness
Long haul flight (>4 hours)
Significant immobility
Pregnancy or post partum
Hormonal therapy (OCP or HRT)

Table 3: Are further investigations needed?

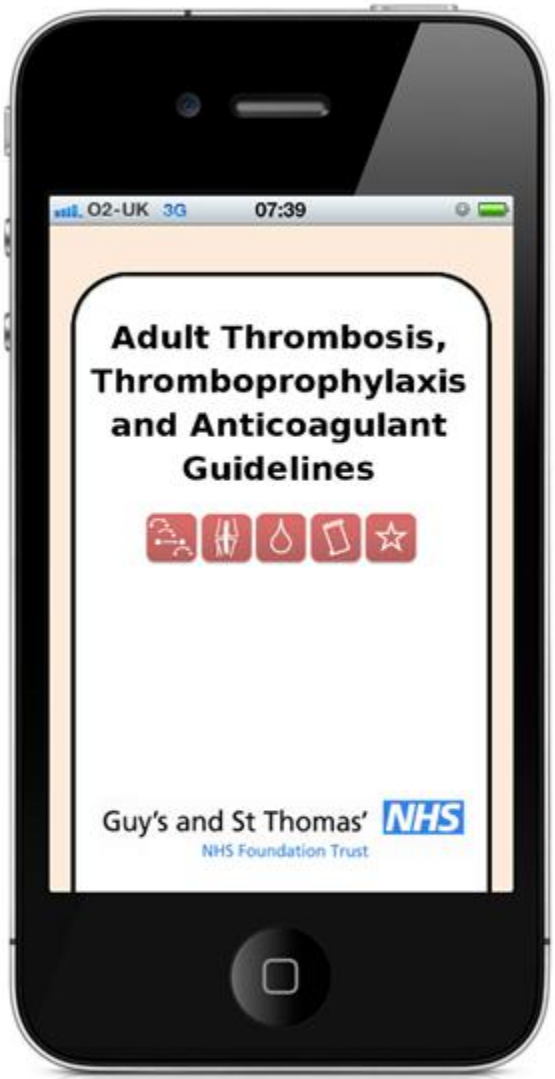
- Those with provoked DVT do not require further investigation. **- For unprovoked DVT consider:**
1: Investigations for cancer If patient is >40 years old: perform history, full physical examination, chest X-ray,FBC, liver function tests, calcium and urinalysis. (CT Abdo/pelvis and mammogram if above normal).
2: Thrombophilia testing There is no role for thrombophilia screening if it is not planned to stop anticoagulation. If it is planned to stop treatment, screen for antiphospholipid antibodies. Screen for hereditary thrombophilia if patients have a first degree relative with previous VTE.

Table 4: Duration of anticoagulation

Provoked: Three months if first calf or proximal lower limb DVT. At least 6 months if proximal DVT and cancer is provoking factor for DVT
Unprovoked: Three months if calf DVT. At least 6 months treatment if first proximal lower limb DVT, and indefinite depending on risk of recurrence

DTC ref 12035q. Review by Mar 2014

Guy's and St Thomas' NHS
NHS Foundation Trust



- Up to 1:1000 people are affected by VTE in the UK each year and up to 1:10 people who suffer a PE will die if not treated.
- Venous thromboembolism is the most common cause of preventable hospital deaths in the UK.

Download the new GSTT Thrombosis App today!

Available on the App Store

Cranworth medical

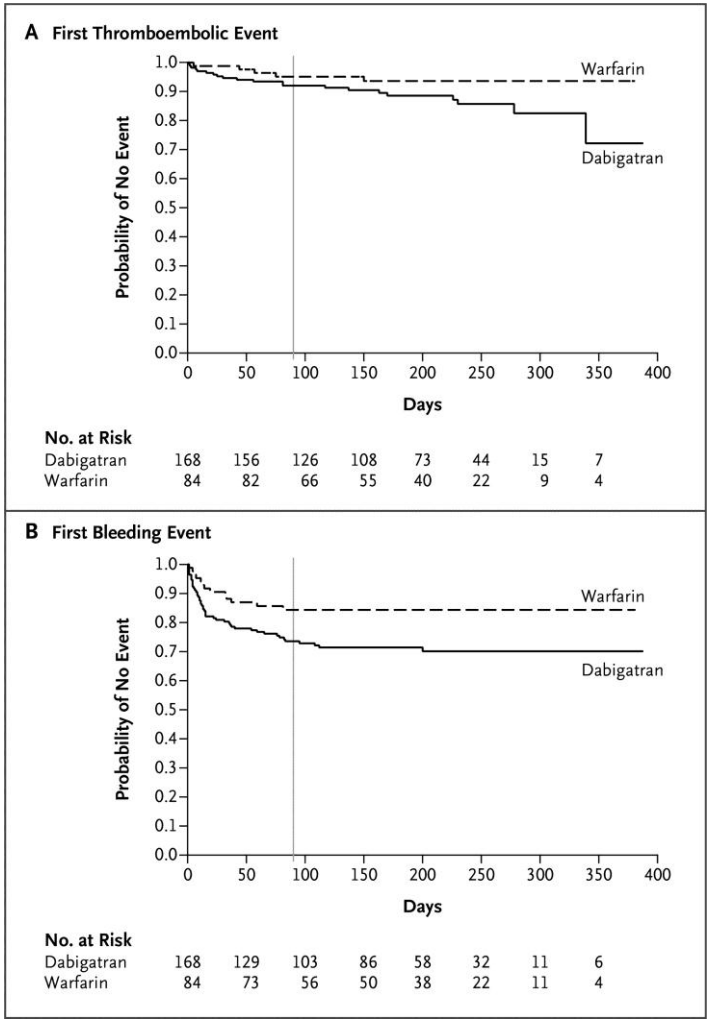
NICE's Incremental Cost-effectiveness Ratios (ICER) for rivaroxaban in secondary prevention of venous thromboembolism

Patient group	ICER (£/QALY)	Meaning
3 months anticoagulation	RIV dominates	Rivaroxaban is cost saving and more effective than standard of care
6 months anticoagulation	£3,200	Rivaroxaban cost-effective
12 months anticoagulation	£14,900	Rivaroxaban cost-effective
Long term	£19,400	Rivaroxaban cost-effective
Cancer	N/A	N/A

NICE. Technology appraisal guidance 261. July 2012

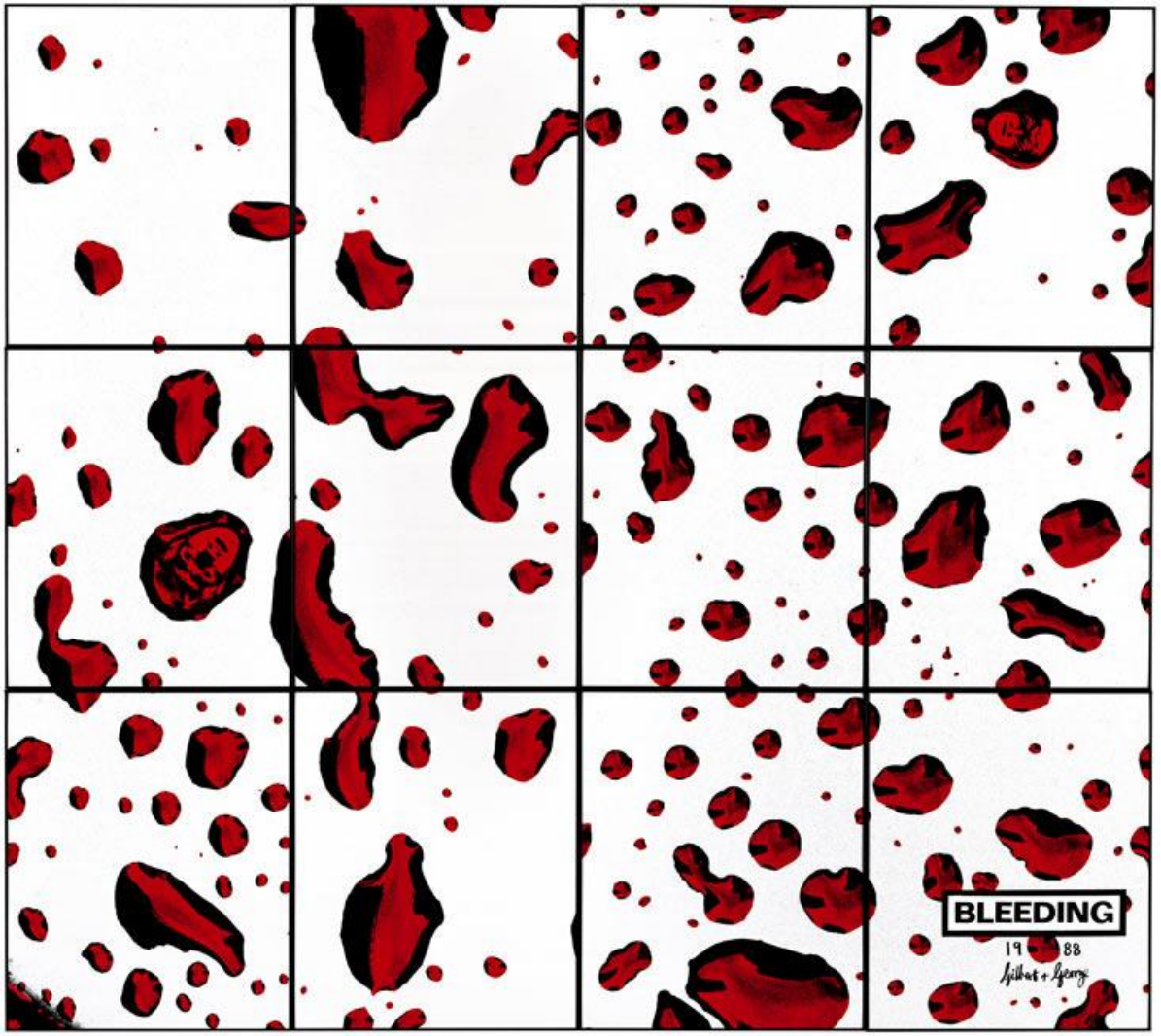
Other areas to explore?

- All successful studies in patients normally with INR target of 2-3
- SELECT-D looking at riva vs LMWH in cancer patients with VTE
- RAPS study – rivaroxaban in APS patients with previous DVT or PE & INR target of 2-3



- In a phase 2 trial, patients with mechanical heart valves were randomly assigned to receive either dabigatran or warfarin for anticoagulation.
- Dabigatran was associated with higher rates of ischemic stroke (5%, vs. 0% with warfarin) and major bleeding (4% vs. 2%).
- Eikelboom J et al New Engl J Med 2013

Reversing bleeding……



Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking ODIs

When to measure anticoagulant effect?

when a patient has
- bleeding,
- overdose,
- renal failure
- pre emergency op
- thrombosis on treatment

(?failure of therapy or lack of adherence).

1 which ODI
2 dose
3 when last taken
4 expected T1/2
5 factors influencing pharmacokinetics

Measurement oral direct inhibitors of thrombin and factor Xa: A recommendation from the Subcommittee on Control of Anticoagulation

- Semi-quantitative: readily available, easily performed urgent / emergency situation – sub, therapeutic, supra-therapeutic level

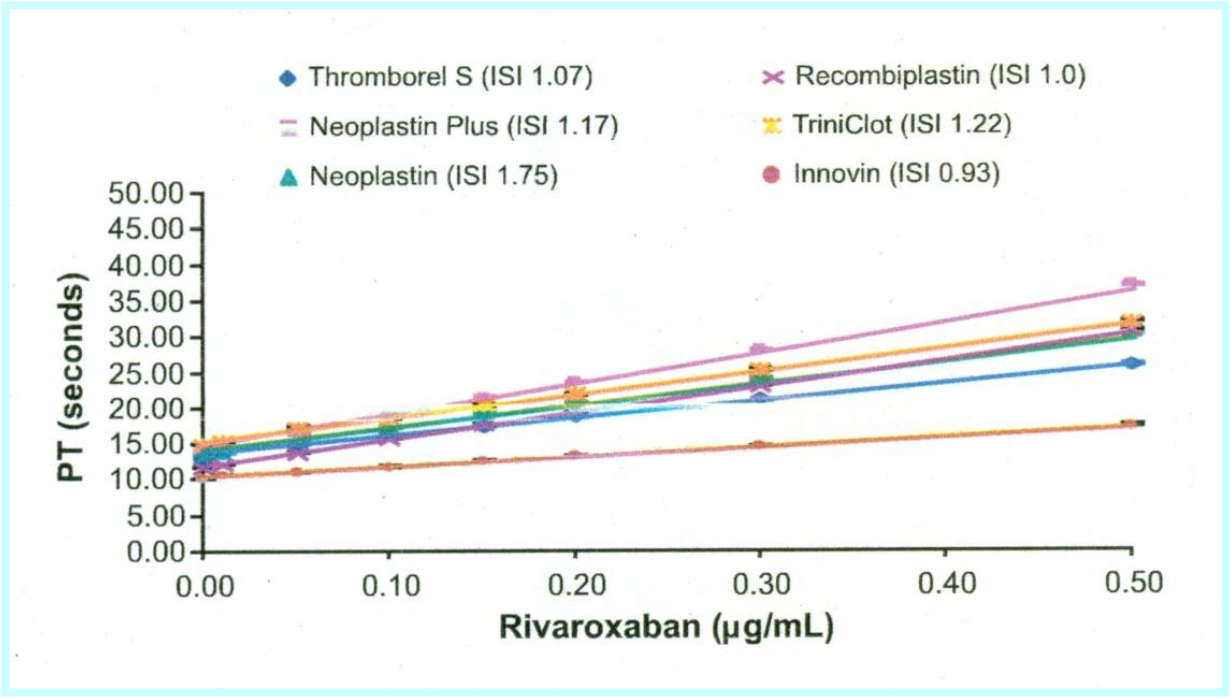
  Prothrombin Time / Activated Partial Thromboplastin Time

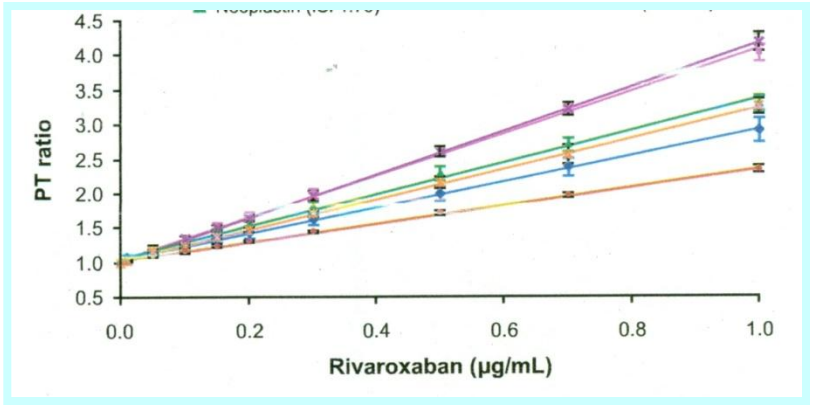
  Each laboratory should be aware of the sensitivity of their PT / APTT to each thrombin and factor Xa inhibitor

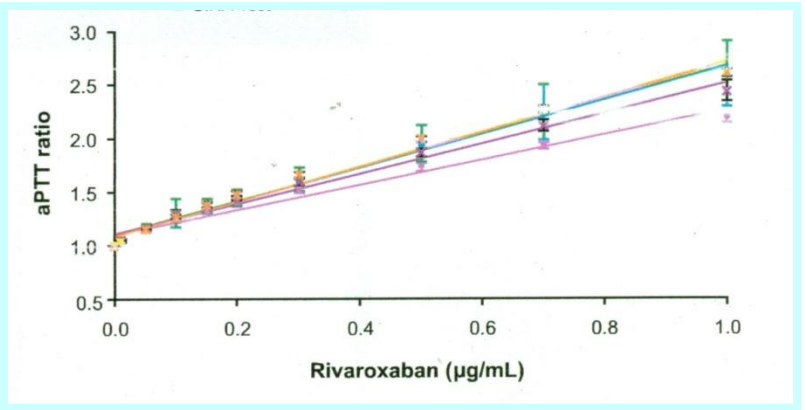
- Quantitative – drug level

J Thromb Haemostas 2013;11:1

Effect of rivaroxaban on coagulation assays

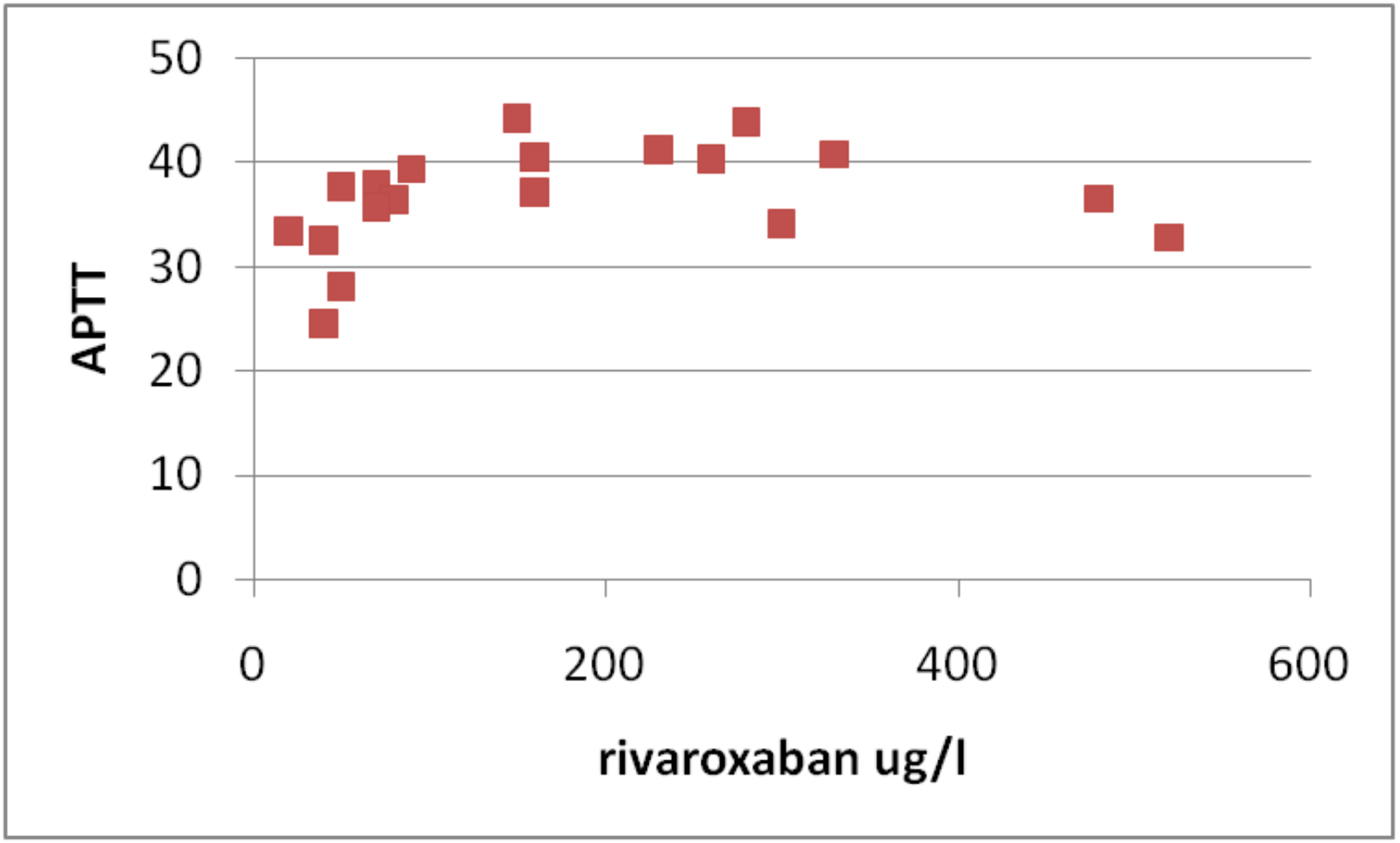






Samama *et al* Thromb Haemostas 2010;103:815

Measurement of rivaroxaban in routine laboratory practice



APTT – SynthASil – IL TOPS D

BIOPHEN DiXal rivaroxaban kit with BIOPHEN calibrators

Impact of rivaroxaban and dabigatran on commonly used coagulation tests.

	PT (INR)	APTT	Fibrinogen	Thrombin T	Ecarin clotting
Dabigatran	↑	↑	↓/no change*	↑↑↑	↑↑↑
Rivaroxaban	↑↑	↑↑	No change	No change	No change

Effect dependent on dose, time since Rx and renal function

“Standard’ effect of dabigatran is APTT 2-3…….
24 hours after stopping APTT 1.5……..

*Thrombin-based fibrinogen assays can yield falsely low fibrinogen levels in the presence of high concentrations of direct thrombin inhibitors.

Bleeding in patients taking new oral anticoagulants

1) Management depends on the severity of bleeding

2) The time of last dose of ODI should be determined and the half-life
should be estimated from measurement of serum creatinine and calculation of CrCl

3) The anticoagulant activity of the ODI should be determined by the most
appropriate laboratory assay

4) When bleeding is not severe temporary drug withdrawal may be the only requirement.

Principals of management of novel anticoagulant associated bleeding

Assess and monitor vital signs – intervene as required with life-saving therapies
"Consider transfer to intensive care setting"
Alert other health care professionals including radiology, endoscopy, surgery, as required
Measure the coagulation cascade and blood count – reassess if bleeding continues
Withdraw the anticoagulant
Address mechanical causes of bleeding using interventional procedures
Consider activated charcoal with recent ingestion of dabigatran
Consider administration of non-specific prohemostatic agents
rFVIIa
Activated prothrombin complex concentrates
Consider modalities that may remove the anticoagulant
Hemodialysis
Hemoperfusion
Plasmapheresis

Bleeding with dabigatran

Case reports of bleeding and difficulty of reversal
In multiple journals

Cotton BA,MacCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. New Engl J Med 2011; 365: 2039-40.

Eikelboom JW, Weitz JI. More on acutely injured patients receiving dabigatran. New Engl J Med 2012; 366: 9

Reversing dabigatran & rivaroxaban

12 healthy men - rivaroxaban 20mg BD
- dabigatran 150mg BD for 2.5 days each
Given a single bolus of 50iu/Kg PCC

Rivaroxaban PT prolonged (15 sec vs baseline 12)
Completely reversed by PCC
Normalised thrombin potential

Dabigatran APTT, ecarin clotting time & thrombin time prolonged
Not restored by PCC
Eerenberg ES et al. Circulation 2011; 124: 1573-9.

Dabigatran and post marketing reports of bleeding

Southworth et al, Editorial New Engl J Med 14th March 2013

- FDA reviewed the Adverse Events Reporting System (FAERS)
- Dabigatran being used “on license” appropriately
- Few cases of renal impairment where dose not reduced
- ? greater likelihood of bleeding events on dabigatran being reported due to its novelty or a true increased bleeding risk relative to warfarin in the post marketing setting?
- FDA therefore compare bleeding rates for dabigatran and warfarin using insurance claim data and the FDA Mini-Sentinel database

Bleeding rates in new users of dabigatran and warfarin Oct 2010-Dec 2011 (Mini Sentinel database)

Southworth et al, Editorial New Engl J Med 14th March 2013

Dabigatran				Warfarin		
Analysis	Patients	Event	Incidence per 100,00	Patients	Event	100,000
GI haemorrhage with AF	10,599	16	1.6	43,541	160	3.5
Intracranial haemorrhage	10,589	8	0.8	43,594	109	2.4

Reassuringly similar rates to RE-LY

Reversal of VKAs

a major cause of iatrogenic admission

Nearly 1 million UK individuals receiving a vitamin K antagonist

- **Stop warfarin**
- **Give vitamin K 1-2mgs orally/IV (takes 6 hours)**

IMMEDIATE REVERSAL

- **Prothrombin complex concentrates (Factor II, VII, IX and X)**
- **Fresh frozen plasma (but need to give large volumes)**

Bleeding in patients taking new oral anticoagulants

Vitamin K and protamine sulphate have no effect

Beneficial effect of DDAVP & tranexamic acid unknown

FFP does not reverse effect of ODIs

Specific antidotes not yet available for clinical practice

aDabi-Fab

PRT4445

Bleeding in patients taking new oral anticoagulants

For more severe bleeding general treatment measures may be required and consideration should be given to:

1 mechanical compression (e.g. for epistaxis or superficial wounds);
2 surgical haemostasis (sutures and cautery);
3 fluid replacement;
4 correction of anaemia by transfusion of red cells;
5 correction of additional coagulopathy (e.g. dilutional coagulopathy) with platelet transfusion and appropriate blood products.

Future reversal of anti Xa agents

- No Fxa inhibitor has an effective antidote (rivaroxaban, apixaban, edoxaban)
- Fondaparinux has no effective antidote
- LMWH can only be partially reversed by protamine

- R- antidote = PRT064445 (Portola) is a potential universal antidote
- It is a modified FXa molecule, with modification in the Gla domain and active site, with no pro or anticoagulant effect

-has been shown to reverse LMWH and fondaparinux

-potential to reverse rivaroxaban

Summary

- It is the dawning of a new age for convenient anticoagulation
- Current perception: despite their advantages, the difficulties in reversing “new” make “old” anticoagulants look more attractive to some……

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