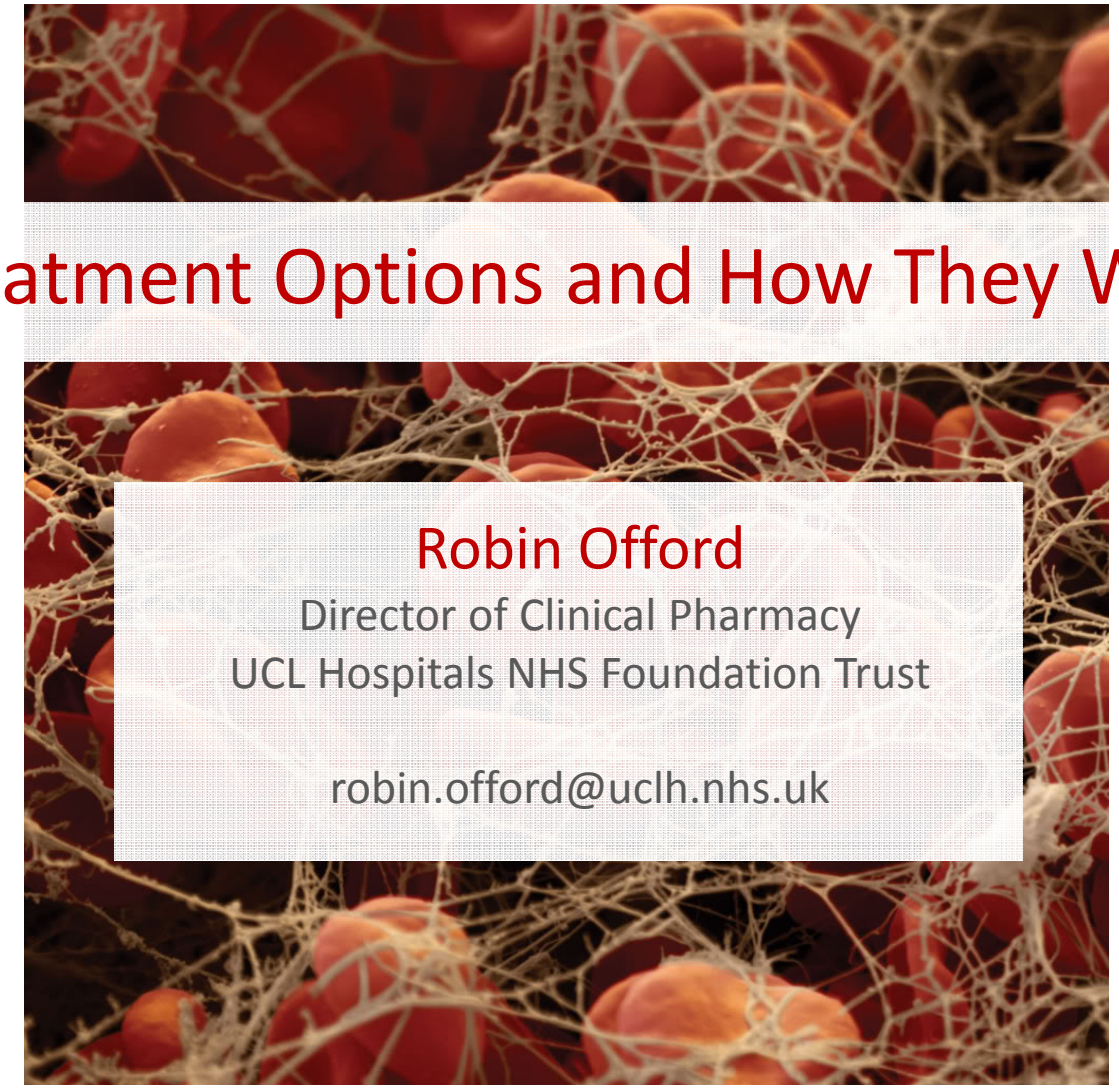

Treatment Options and How They Work

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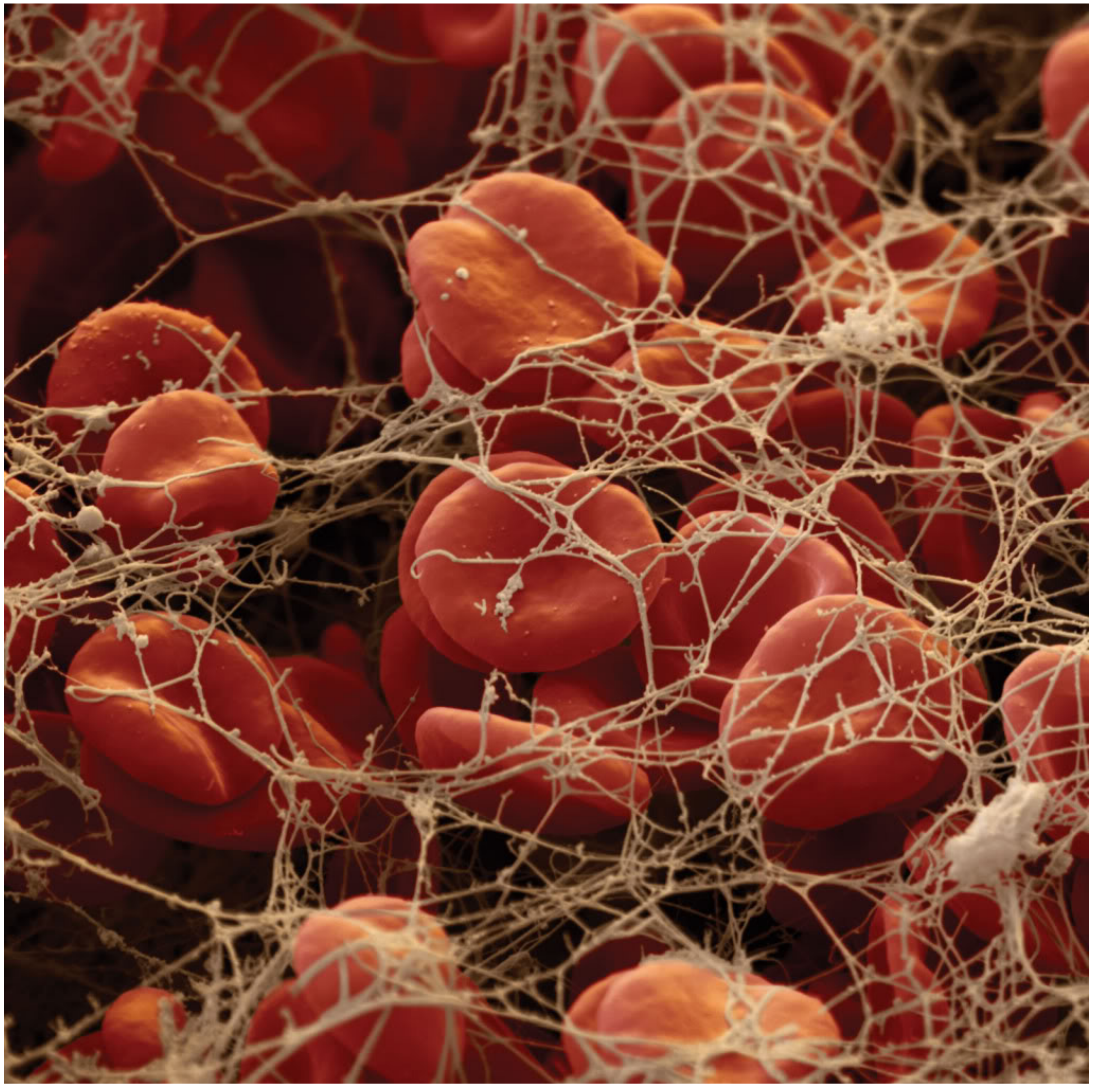

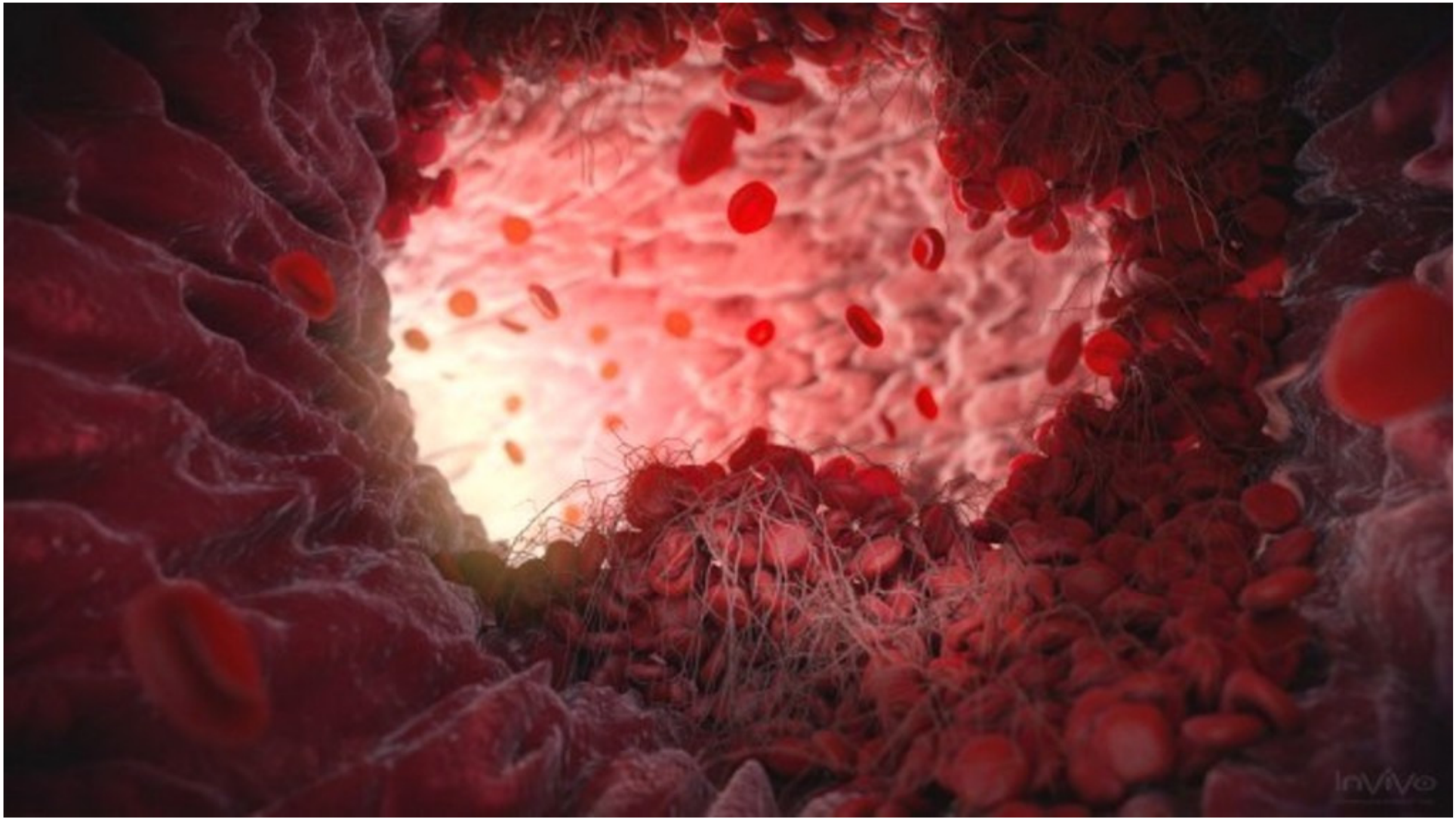
InVivo

Introducing the term anticoagulant . . .

- What they do –
  - Inhibit the effect of the body's own procoagulant clotting proteins
  - Reduce the risk of clot growth or embolism
    - Embolism = Fragments of clot breaking off and lodging elsewhere
  - Allow the body's clot lysis (breakdown) process to take effect

- What they don't do –
  - Dissolve a clot that already exists

Treatment of venous thromboembolism (VTE)

- May start with an injectable agent (usually a heparin; occasionally an alternative)
  - For rapid onset of effect
- Once stable, typically convert to an oral agent (warfarin or a DOAC)
  - For longer-term convenience

- Historically patients would be treated in hospitals
- Now routinely managed in the community (at home)
  - Occasional outpatient attendances

Heparin (unfractionated heparin, or UFH)

- Discovered by a second year medical student in 1916
- Originally derived from canine liver tissue – Hence the name
- First clinical trials did not take place until 1935

- Works as a catalyst for a natural anticoagulant - Antithrombin
- Effect can be monitored using a test, called aPTT
- Can also be reversed using a substance called protamine

Difficulties with heparin (UFH) treatment

- Needs to be given by infusion or regular subcutaneous injections
  - Short half-life
- Unpredictable effect, requiring frequent aPTT tests
  - Binds to and interacts with various circulating proteins
  - Cleared from the body via a number of mechanisms
- Rare but very significant side effects
  - Heparin-induced thrombocytopenia

Low Molecular Weight Heparins (LMWH)

- Significant advantages over UFH
  - Once or twice daily subcutaneous injections
  - Predictable response – No need for monitoring
  - Lower risk of HIT
- Some disadvantages
  - Requires dose alteration in kidney disease
  - Longer half-life may prolong bleeding, if it occurs
  - Only partially reversed by protamine
  - Still relatively expensive (outside hospitals)

LMWHs

- Enoxaparin (Clexane®)
- Dalteparin (Fragmin®)
- Tinzaparin (Innohep®)

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Warfarin

- Derived from a chemical found in clover and many other plants
- Originally used in the late 1940s as a pesticide – ‘Rat poison’
- Developed for medical use by the University of Wisconsin
  - Work funded by the **Wisconsin Alumni Research Foundation**
- Licensed as a medicine for human use in 1954

- Prevents the formation of vitamin K dependent clotting factors
  - Factors II, XVII, IX and X
  - Also some natural anticoagulants – Proteins C and S

Warfarin – Pros and Cons

Pros	Cons
More than sixty years of experience	Unpredictable Dose response varies between people
Licensed in a wide range of indications	Narrow therapeutic index
It works!! (with caveats)	Lots of drug and food interactions
INR correlates with effect Can be used in patients with different risks	Frequent blood monitoring (INR tests)
Effective reversal agent (Vitamin K)	Slow onset of action
Relatively few non-bleeding side effects	Long duration of action

Where we are …

The potential of the Direct Oral Anticoagulants (DOACs)

Properties of an ideal anticoagulant

- Safe at a wide range of doses
- Predictable response, without laboratory monitoring
- Can be given by mouth or via a vein
- Works quickly after a dose
- Safe antidote available
- No non-anticoagulant side effects
- No interactions with other drugs

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Hirsh J, *et al*. Blood 2005; **105**: 453-463
King CS, *et al*. Chest 2013; **143**(4): 1106–1116

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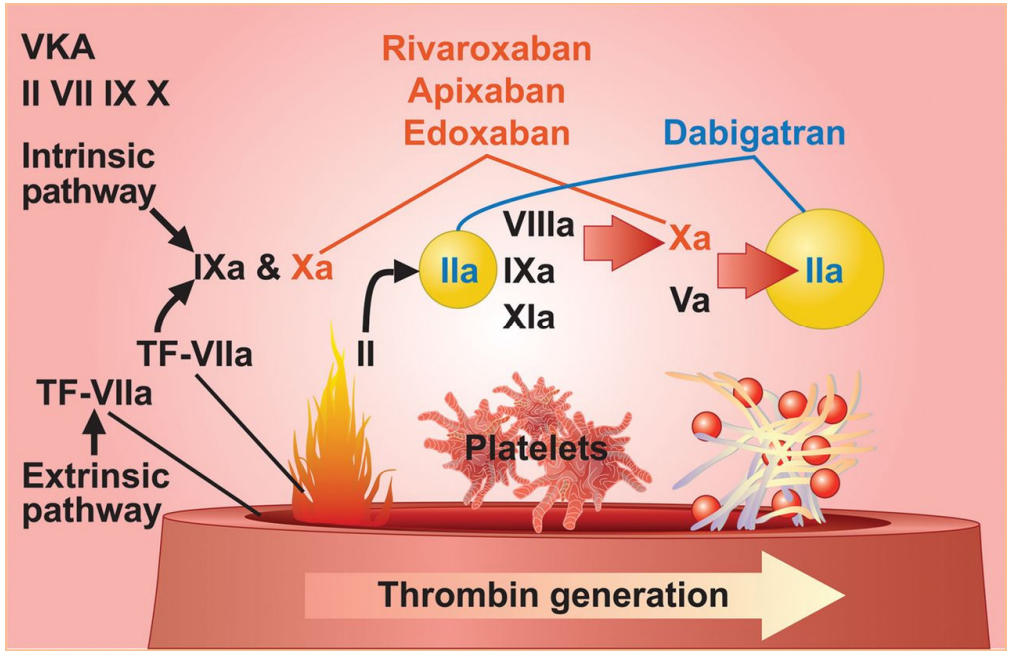
DOACs – Direct Oral Anticoagulants



DOACs

- Dabigatran (Pradaxa®)
- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)
- Edoxaban (Lixiana®)

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Warfarin v DOACs

As effective as warfarin in reducing VTE recurrence, with potential benefits:

	Warfarin	DOACs
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food interactions	Yes	Rivaroxaban only
Drug interactions	Many	Few(-ish)
Monitoring required	Yes	No
Offset	Long	Shorter
Reversal	Straightforward	Complex

Factors taken into account when prescribing an anticoagulant

Factors	Options
Cancer	low molecular weight heparin
Parenteral therapy to be avoided	rivaroxaban, apixaban
Once daily therapy preferred	rivaroxaban, edoxaban, warfarin
Liver disease and coagulopathy	LMWH
Kidney disease and creatinine clearance <30 mL/min	Warfarin
Coronary artery disease	warfarin, rivaroxaban, apixaban, edoxaban
Dyspepsia or history of GI bleeding	warfarin, apixaban
Poor compliance	warfarin (perhaps)
Thrombolytic therapy use	Heparin infusion
Reversal agent needed	warfarin or heparin
Pregnancy or pregnancy risk	low molecular weight heparin
Range of licensed indications	Favours older products

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Chest 2016; **149**(2): 315-352

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Pharmacokinetics of the DOACs

Adapted from: EHRA Practical Guide – NOACs in NVAF
Europace (2013); **15**: 625–651

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	3-7 %	66 % without food Almost 100 % with food	50 %	62 %
Pro-drug?	Yes	No	No	No
Renal clearance of absorbed dose (normal renal function)	80 %	35 % 36 % Unchanged – Remainder inactive metabolites	27 % Mostly unchanged	50 % Almost entirely unchanged
Liver metabolism	No	Yes (partly CYP3A4)	Yes (CYP3A4 major contributor)	Minimal (<4 %)
Substrate of CYP3A4?	No	Yes	Yes	No
Substrate of P-glycoprotein (P-gp)?	Yes	Yes	Yes	Yes
Protein binding	35 % (active dabigatran)	92-95 %	87 %	55 %
Absorption with food	No effect	+ 39 %	No effect	+ 6-22 %
Intake with food recommended?	No	Mandatory	No	No
Absorption with H_2B/PPI	- 12-30 %	No effect	No effect	No effect
Asian ethnicity	+ 25 %	No effect	No effect	No effect
GI tolerability	Dyspepsia 5-10 %	No problem	No problem	No problem
Elimination half-life	12-17 h	5-9 h (young); 11-13 h (elderly)	12 h	9-11 h

Aspirin

- Possible role in patients with:
  - First unprovoked VTE who did not have an increased risk of bleeding
  - Completed 3 to 18 months of anticoagulant therapy
- Reduces recurrent VTE by about one-third
- However, DOACs in the same patient group reduce recurrence by 80%
  - Similar bleeding risk in extended therapy

WARFASA. *N Engl J Med* 2012; **366**(21): 1959-1967
ASPIRE. *N Engl J Med* 2012; **367**(21): 1979-1987
INSPIRE. *Circulation* 2014; **130**(13): 1062-1071

Treatment Duration

Type of VTE	Recommendation
Provoked proximal DVT of leg or PE	3 months
Provoked isolated distal DVT of leg	3 months
Unprovoked isolated DVT of leg or PE	At least 3 months
First unprovoked proximal DVT of leg or PE and low to moderate bleeding risk	Extended
First unprovoked proximal DVT of leg or PE and high bleeding risk	3 months
Second unprovoked VTE and low to moderate bleeding risk	Extended
Second unprovoked VTE and high bleeding risk	3 months
VTE and active cancer	Extended

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