Endorsed by:

The Management of Venous Thromboembolism

Thursday 3rd May 2018

The NOWGEN Centre, Grafton Street, Manchester, M13 9WU

This conference has been awarded 6 CPD Points by the Royal College of Pathologists

Time	Presentation	Speaker
10:00 – 10:30	**Registration – Refreshments and access to exhibition**	
10:30 – 10:45	Introduction & House keeping	**Anticoagulation Specialist Nurses** MFT - Central
10:45 – 11:30	Medico-Legal issues in VTE Diagnosis and Management	**Professor Charles Hay** Consultant Haematologist, MFT - Central
11:30 – 12:15	Diagnosing and Living with Thrombosis – A Patient's Perspective	**Clare Reynolds** Project Development Officer, Thrombosis UK
12:15 – 12:45	Anticoagulation in Renal Impairment	**Dr Jecko Thachil** Clinical Haematologist, MFT – Central
12:45 – 13:30	Lunch and refreshments	

Notes

13:30 – 14:00	Management of DOACs	**Dr Rachel Brown** Clinical Haematologist, MFT – Central/TGH
14:00 – 14:30	Laboratory Testing of DOACs – When, Why & how	**Lynne Keighley** Chief BMS for Anticoagulation, MFT - Central
14:30 – 14:45	Refreshments	

Notes

14:45 – 15:15	Managing Anticoagulation / Thromboprophylaxis in extremes of weight	**Dr Jayne Peters** SpR, MFT - Central
15:15 – 15:45	Unprovoked VTE – To screen or not to screen	**Dr Martin Scott** SpR Haematology, MFT - Central
15:45 – 16:30	VTE and Cancer	**Dr Simon Watt** Consultant Haematologist, MFT - Wythenshawe
16:30 – 17:00	Evaluation, Thanks and Close	

This meeting has kindly been supported by device, pharmaceutical and healthcare companies. Some companies, including pharmaceutical companies, have purchased exhibition space and will have a presence of an exhibition stand in the exhibition area.

BMS are sponsoring stand sponsorship only

Diagnosing and Living with Thrombosis

A patients perspective

Thrombosis UK

About Me

My name is Clare Reynolds, I am 39 years and I am the Project Development Officer for Thrombosis UK. I am a mum of two and live in Liverpool with my partner. I am also a chronic thrombosis patient, I have antiphospholipid syndrome and have had more blood clots than I can currently recall. The most recent was five weeks ago when I had multiple PE's in the left half of my lung despite anticoagulation of Fragmin 7500iu three times a day. Over the years I have had DVT's in the leg's, arms, groin, lung and brain. I hope my experiences as a patient but also from my work in Thrombosis UK can give you all an insight into the patient journey and what it is like to live with Thrombosis.

Firstly if I can ask you all to look at the picture on the right hand side of this slide.

This was taken three days before I presented with TIA's at the Royal Liverpool Hospital last October. Apart from a slight facial droop on the day I did not look much different. I would like you all to remember this as this is the face of Thrombosis – which I think you will all agree looks pretty much the same as the average person walking past you on the street.

Diagnosis

The issues currently affecting patients can be no more accurately described then me recounting a phonecall I had for the charity just hours before me typing this presentation.

The tale of patient A

Patient A was 6 weeks post DVT diagnosis and because she couldn't get a doctors appointment for 3 weeks she called us to ask if her leg swelling and discolouration was normal.

During the course of the conversation it was established that like many other patients the following issues had arisen:

- Clear lack of explanation as to what has happened and what to expect.
- Incorrect information given at diagnosis.
- Although follow up was given at an anticoagulation service the patient felt alone and uninformed.
- Patient felt that she had learned more in a 10 minute conversation with myself than she had done in the whole process.

Diagnosis - Cont

Whilst my previous slide may sound like a very negative take on the patient experience it is not an uncommon occurrence - As a charity we are currently receiving increasing numbers of calls similar to this one on a weekly basis. At Thrombosis UK we are not medically trained so quite often we cannot help these people all we can do is redirect them back to a GP or A and E.

My aim today is not to slam the NHS or its services but to ask you as front line people who have an interest in Thrombosis to think of ways you may be able to improve things in your trusts, clinics and surgery's to stop this from happening. Our Let's Talk Clot's Events go some way to promoting awareness and this doesn't and shouldn't stop after the one event or the three week period we are currently running it for. The NHS has grown very good in prevention and diagnosing but work still needs to be done to help us prepare and give patients the ability to be able to live and deal both mentally and physically with what a Thrombosis diagnosis can bring.

Create a patient charter

Give newly diagnosed patients Thrombosis UK as a resource

Try mystery shopping the DVT diagnosis pathway

Speak to your patients

Living With Thrombosis

This subject is something I could do a whole one week conference on. But for today I am going to concentrate on two main areas:

- Psychology of Thrombosis Patients.
- Living with Thrombosis as a chronic condition and its impact on life.

Quick question: How many of you in here deal with long term Thrombosis patients or as I am one myself repeat offenders? So not necessarily on the initial diagnosis side more the management of the condition.

How many patients in general post diagnosis, have you felt are either highly anxious, panicky, worried over every little itch?

Am I going to die?

No one is listening to me

I feel so alone!

I don't have anyone who understands

Psychology

What's going on inside the patients head?

Quite often as explained in diagnosis there are a number of issues that lead to patients with Thrombosis becoming anxious.

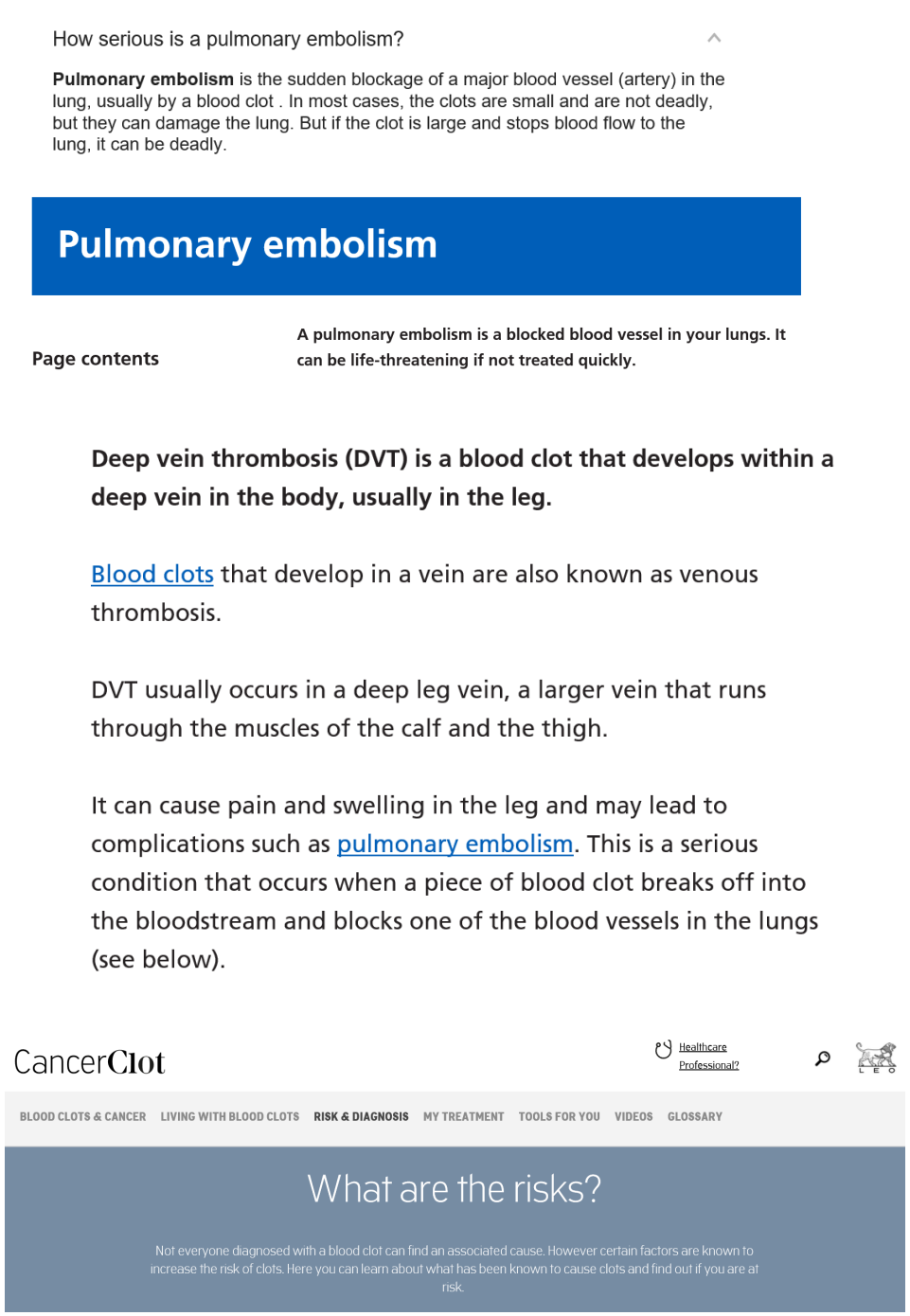
Imagine you have just been diagnosed with an illness you know very little if anything at all about, you go home with little or no information, whilst you are receiving the diagnosis you aren't thinking about what you need to ask, so you go home with unanswered questions. You then realise that there's no one to ask until a follow up appointment is arranged which in some cases can be weeks! Within a week, the symptoms you first experienced either aren't getting any better or in some cases are worse – as you are not sure what to expect you think it is happening all over again. In some cases there have been one or several episodes of misdiagnosis so you begin to wonder if it is another will it be picked up or will you die?

If we look at the above scenario you can start to see where anxiety starts to build – A lot of the time when these patients call up they have worked themselves up so much they are in a high state of anxiety and the first 10 - 15 minutes of a conversation can be spent just literally calming them down.

Psychology - Cont

This pattern can plague patients for months and years if not managed correctly. With the growing dependence on the internet and social media patients believe they are more informed than ever. From experience they tend to trust Google more than medically trained staff or new found friends they have found on Facebook with their condition. Sadly if not used correctly these tools just do not help and increase the anxiety even more. The doctors waiting room is no longer confined to bricks and mortar!

How do you tackle this? For me it has to start as soon diagnosis is confirmed. There is no re inventing the wheel here, all I'm asking is that you remember the scenario I described and place yourself in that position. Talk to your patients and gain knowledge of their experience and tailor your approach accordingly. It may not resolve it but it will go a long way to helping



Living With Thrombosis as a Chronic Condition

The last part of my talk today is an issue that is very close to home. There is no point me standing here telling you all how to live with it, so I would just like you all to know the impact is has and why if I ever pop up in a clinic or an A and E department of yours why I am like I am.

Thrombosis, impacts every single part of my life, from my job, to my children right down to when I go to bed and when I wake up. Now I am standing before you, and admittedly I am the extreme end of the Thrombosis patient scale – I clot through anticoagulants, I also bleed because of the level of anticoagulation I am on.

I am extremely fortunate as a patient that the team of doctors and nurses I have supporting me are fantastic – none more so than my consultant Vanessa Martlew. My journey hasn't always been smooth or problem free but my experiences have made me who I am today and the patient I am today.

Admittedly I am not now or never have been the easiest patient to deal with! It is in my nature to want to know and question every little thing especially about my condition. This not only mentally ensures I can deal with the diagnosis I have been dealt but also so that issues that have arisen in the past don't tend to raise their ugly head again.

Living With Thrombosis as a Chronic Condition - Cont

So what issues affect me?

- I do not look like I am ill even when I am ill!
- The impact repeat diagnosis' have had on my family.
- The impact of my condition on daily living, travel, work!
- The impact of my condition on other investigations and diagnosis'

.

All in Thrombosis is a part of me but hopefully it doesn't control me and I hope that my experience can be used to help others in my position lead a better life.

Finally……

How can Thrombosis UK help your help patients:

We are looking for medics to help us arrange patient days where patients like yours can access talks and information and meet others in a safe environment. We need a local medical lead for each one though where your help comes in. Our supporters our crying out for them. In terms of support these are invaluable especially with the time pressures there are currently within the NHS.

If any of you want to discuss this further please contact me on Clare@thrombosisuk.org.

If time is not on your side and you feel patients need more time, information or just someone to talk to please direct them to us, we have a brand new website www.thrombosisuk.org with tonnes of downloadable resources and ways to access help. We also have a non medical advice helpline 0300 772 9603.

I hope this helps.

Any questions

ANTICOAGULATION IN EXTREMES OF BODY WEIGHT

DR JAYNE PETERS
ST7 HAEMATOLOGY
PENNINE ACUTE FOUNDATION TRUST
THURSDAY 4TH MAY 2018

OVERVIEW

- LMWH and DOACs
- Treatment and prophylaxis
- Dosing
- Monitoring

What is not covered?

- Extended discussion of anticoagulation indications
- Discussion regarding dose reduction with other indications (renal/hepatic function)
- Dosing of LMWH in pregnancy
- Unfractionated heparin

BBC NEWS

Home

Health

TV Radio

HOUSE OF COMMONS
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BRIEFING PAPER

Number 3336, 20 March 2018

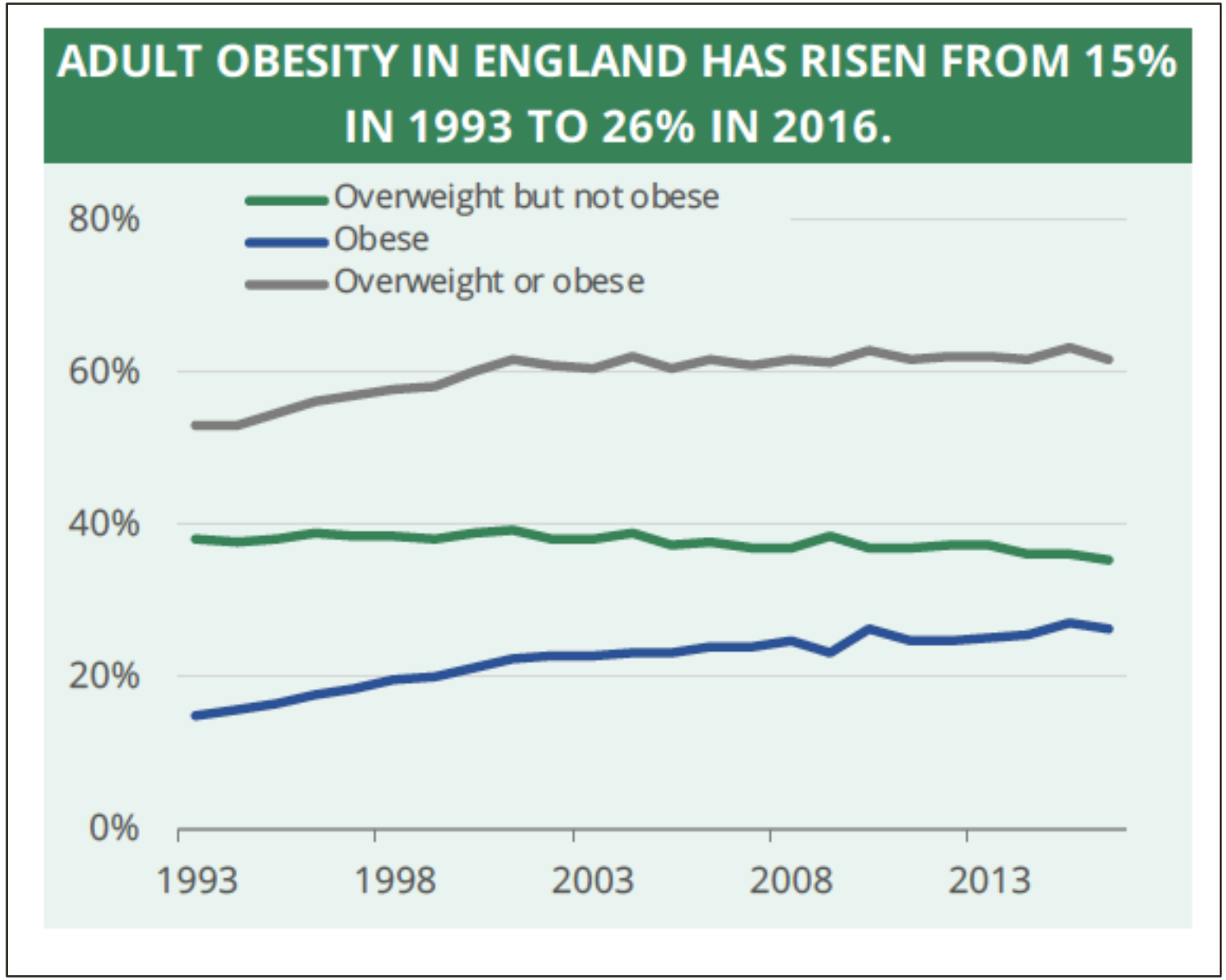
Obesity Statistics

By Carl Baker

DEFINING OBESITY

$$\text{BMI (Metric)} = \frac{\text{Weight (kg)}}{\text{Height x Height (m)}}$$

Classification	BMI
Underweight	< 18.5
Normal weight	18.5 - 24.9
Overweight	25.0 - 29.9
Obese: Class I	30.0 - 34.9
Obese: Class II	35.0 - 39.9
Obese: Class III	40.0+


ADULT OBESITY IN ENGLAND HAS RISEN FROM 15% IN 1993 TO 26% IN 2016.
Overweight but not obese
Obese
Overweight or obese
80%
60%
40%
20%
0%
1993
1998
2003
2008
2013

PROBLEMS

Obesity = BMI ≥ 30

BMI ≥ 30 ≠ obesity

Weight ≥ 100kg ≠ obesity

- Lack of information/weight
- Lack of evidence
- No universally agreed strategy
- Should we cap?
- Under-dosing just as dangerous as overdosing
- Be ‘pragmatic’

FACTORS INFLUENCING DRUG CONCENTRATION

Absorption/route

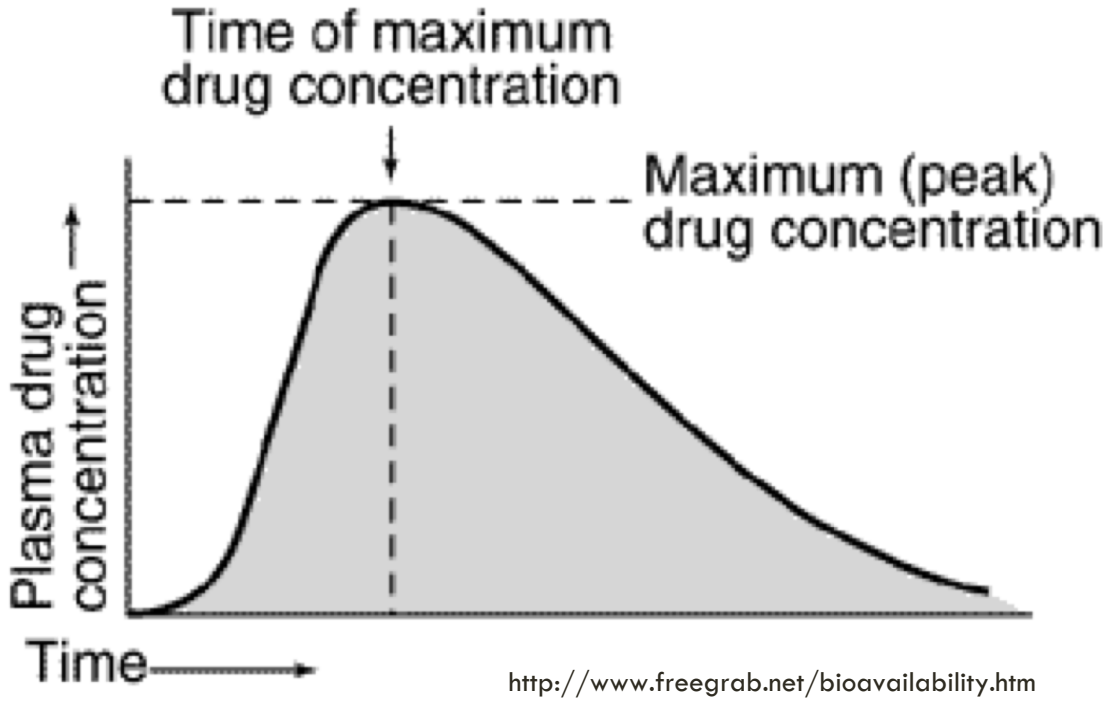
Volume of distribution

- Size of molecule
- Ionization
- Lipid solubility
- Ability to cross membranes

Drug clearance

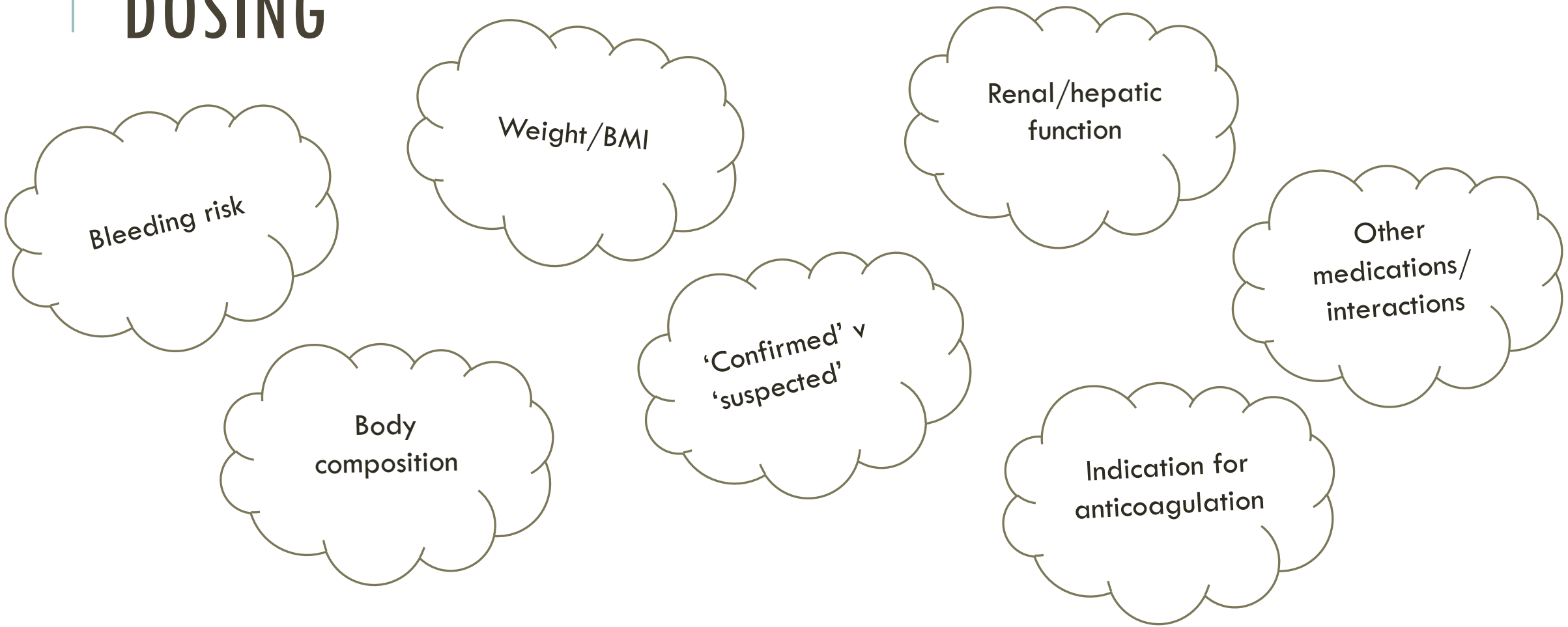
- Renal function
- Hepatic metabolism/P450 pathway

Area under the curve (AUC)



http://www.freegrab.net/bioavailability.htm

FACTORS INFLUENCING ANTICOAGULATION DOSING



WHEN SHOULD WE MEASURE DEGREE OF ANTICOAGULATION?

Kitchen S, Gray E, Mackie I, Baglin T, Makris M; BCSH committee. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014 Sep;166(6):830-41. doi: 10.1111/bjh.12975.

Table II. Circumstances when measurement of anticoagulant concentration may be useful.

- In the presence of spontaneous or traumatic haemorrhage
- Following suspected overdose
- When patients are taking another interacting drug
- To monitor efficacy in patients presenting with new thrombosis whilst on the anticoagulant
- When emergency surgery is required
- In patients due to have neuraxial anesthesia for elective or emergency procedures or surgery
- In patients requiring elective surgery and in whom the drug may still be present
- In patients with renal impairment
- When bridging from one anticoagulant to another
- To assess compliance
- At the extremes of body weight
- In subjects with prior intestinal surgery where it is unclear if absorption will be affected
- Trough levels may be useful to assess potential accumulation in very elderly patients

LMWH: DOSING AND MONITORING

LMWH – PROPHYLACTIC DOSING

NHS

Medicines Q&As

UKCPA | HAT
HAEMOSTASIS, ANTICOAGULATION AND THROMBOSIS

Q&A 326.2

What doses of thromboprophylaxis are appropriate for adult patients at extremes of body weight?

Prepared by the HAT Committee of the UK Clinical Pharmacy Association for NHS healthcare professionals
Before using this Q&A, read the disclaimer at www.ukmi.nhs.uk/activities/medicinesQAs/default.asp
Date Prepared: June 2015

LMWH – PROPHYLACTIC DOSING

	<50kg	50-100kg	100-150kg	>150kg
Enoxaparin	20mg daily*	40mg daily	40mg twice daily*	**60mg twice daily***
Dalteparin	2500 units daily*	5000 units daily	5000 units twice daily*	**7500 units twice daily***
Tinzaparin	**3500 units daily***	**4500 units daily**	**4500 units twice daily***	**6750 units twice daily***

Table 1: Suggested doses of LMWH for thromboprophylaxis in adult patients
* 'off-licence' dose

'Some UK centres (e.g. King's College Hospital, London), use once daily dosing of enoxaparin in obese patients, particularly for ease of use if extended prophylaxis is prescribed, e.g. for patients weighing 100 to 150kg: 80mg once daily, and for patients weighing more than 150kg: 120mg once daily. These doses are 'off-licence'.'

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ENOXAPARIN – TREATMENT DOSING (VTE)

	Standard dosing	Notes
Enoxaparin Clexane	1.5mg/kg OD (150 IU/kg) 1.0mg/kg BD (100 IU/kg)	'After repeated SC 150 IU/kg (1.5 mg/kg) once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while maximum plasma anti-Xa activity level is not increased. **Bazinet et al (2005)** – no dose adjustments required Bazinet, A., Almanric, K., Brunet, C., Turcotte, I., Martineau, J., Caron, S., Blais, N. & Lalonde, L. (2005) Dosage of enoxaparin among obese and renal impairment patients. Thrombosis Research, 116, 41–50. **Green and Duffull (2003)** – '1mg/kg every 8 hours based on LBW' Green, B. & Duffull, S.B. (2003) Developing a dosing strategy for enoxaparin in obese patients. British Journal of Clinical Pharmacology, 56, 96–103.
https://www.medicines.org.uk/emc/product/1695/smpc		

DALTEPARIN – TREATMENT DOSE (VTE)

	Standard dosing	**Notes**
Dalteparin Fragmin	200 IU/kg OD	'*Singl*e daily doses' 100mg/kg BD dosing
https://www.medicines.org.uk/emc/product/4245/smpc		

DALTEPARIN – TREATMENT DOSE (VTE)

	Standard dosing	Notes
Dalteparin Fragmin	200 IU/kg OD	'*Single* daily doses' 100mg/kg BD dosing
https://www.medicines.org.uk/emc/product/4245/smpc		

Weight (kg)	Dose
< 46	7,500 IU
46-56	10,000 IU
57-68	12,500 IU
69-82	15,000 IU
83 and over	18,000 IU

Abbreviations: IU = International Unit

The single daily dose should not exceed 18,000 IU.

DALTEPARIN – TREATMENT DOSE (VTE)

	Notes
Dalteparin Fragmin	'In cancer patients with body weight < 40kg at time of venous thromboembolic event, Fragmin should not be used for extended treatment of symptomatic VTE and prevention of its recurrences due to lack of data' **Yee and Duffull (2000)** – Base dose on total or adjusted body weight, not LBW Yee, J.Y.V. & Duffull, S.B. (2000) The effect of body weight on dalteparin pharmacokinetics. European Journal of Clinical Pharmacology, 56, 293–297. **Wilson et al (2001)** – No capping Wilson, S.J.-A., Wilbur, K., Burton, E. & Anderson, D.R. (2001) Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low molecular weight heparin for the treatment of venous thromboembolism. Haemostasis, 31, 42–48. **Al-Yaseen et al (2005)** – No capping Al-Yaseen, E., Wells, P.S., Anderson, J., Martin, J. & Kovacs, M.J. (2005) The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. Journal of Thrombosis and Haemostasis, 3, 100–102. Conclude cap at 18,000IU unjustified
https://www.medicines.org.uk/emc/product/4245/smpc	

TINZAPARIN – TREATMENT DOSE (VTE)

	Standard dosing	Notes
Tinzaparin Innohep	175 IU/kg OD	**Hainer et al (2002)** – no capping required Hainer, J.W., Barrett, J.S., Assaid, C.A., Fossler, M.J., Cox, D.S., Leathers, T. & Leese, P.T. (2002) Dosing in heavy-weight / obese patients with the LMWH, Tinzaparin: a pharmacodynamic study. Thrombosis Haemostasis, 87, 817–823. **Barrett et al (2001)** – no capping required Barrett, J.S., Gibiansky, E., Hull, R.D., Plane`s, A., Pentikis, H., Hainer, J.W., Hua, T.A. & Gastonguay, M. (2001) Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. International Journal of Clinical Pharmacology and Therapeutics, 39, 431–446. **Diepstraten et al (2009)** – Advise to cap in morbid obesity with an upper limit of 28 000 IU/day for 160kg person used Diepstraten, J., van Kralingen, S., Snijder, R.J., Hackeng, C.M., Ramshorst, B.V. & Knibbe, C.A.J. (2009) Treatment of pulmonrary embolism in an extremley obese patient – case report. Obesity Surgery, 19, 1186–1189.
https://www.medicines.org.uk/emc/product/3632/smpc		

DOACS: DOSING AND MONITORING

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Dabigatran Pradaxa	• No dose adjustment is necessary • close clinical surveillance is recommended in patients with a body weight < 50 kg • Weight <50kg 'minor' risk for elevation of plasma dabigatran levels
https://www.medicines.org.uk/emc/product/4703/smpc	

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Rivaroxaban Xarelto	• No dose adjustment • Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary
https://www.medicines.org.uk/emc/product/6402/smpc	

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Apixaban Eliquis	• VTEt - No dose adjustment required • NVAF - No dose adjustment required, unless criteria for dose reduction are met • Low body weight (< 60 kg) may increase haemorrhagic risk • Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30% lower exposure and body weight < 50 kg was associated with approximately 30% higher exposure
https://www.medicines.org.uk/emc/product/2878/smpc	

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Edoxaban Lixiana	• For patients with body weight ≤ 60 kg, the recommended dose is 30 mg Lixiana once daily • In Phase 3 clinical studies (both NVAF and VTE indications) patients with body weight ≤ 60 kg had a 50% edoxaban dose reduction and had similar efficacy and less bleeding when compared to warfarin
https://www.medicines.org.uk/emc/product/6906/smpc	

USE OF THE DIRECT ORAL ANTICOAGULANTS IN OBESE PATIENTS: GUIDANCE FROM THE SSC OF THE ISTH

J THROMB HAEMOST. 2016 JUNE ; 14(6): 1308–1313. DOI:10.1111/JTH.13323

Guidance statements

We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m^2 and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF.

We suggest that DOACs should not be used in patients with a BMI of > 40 kg m^2 or a weight of > 120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about underdosing in the population at the extreme of weight.

If DOACs are used in a patient with a BMI of > 40 kg m^2 or a weight of > 120 kg, we suggest checking a drug-specific peak and trough level (anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs). If the level falls within the expected range, continuation of the DOAC seems reasonable. However, if the drug-specific level is found to be below the expected range (Table S1) [17,24,26–29], we suggest changing to a VKA rather than adjusting the dose of the DOAC.

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Guidance statements

We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m^2 and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF.

We suggest that DOACs should not be used in patients with a BMI of > 40 kg m^2 or a weight of > 120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about underdosing in the population at the extreme of weight.

If DOACs are used in a patient with a BMI of > 40 kg m^2 or a weight of > 120 kg, we suggest checking a drug-specific peak and trough level (anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs). If the level falls within the expected range, continuation of the DOAC seems reasonable. However, if the drug-specific level is found to be below the expected range (Table S1) [17,24,26–29], we suggest changing to a VKA rather than adjusting the dose of the DOAC.

MEASURING DOAC LEVELS

1. When to take DOAC level? 2-3 hours after dose
2. Which bottle to take sample in?
3. Inform laboratory if urgent
4. How to interpret results?

INTERPRETATION OF DOAC ASSAYS

Table III. Expected plasma concentrations of Oral Direct Inhibitors.

Drug	Dose	Peak levels mean and range	Trough levels mean and range	References
Apixaban	2·5 mg bd	0·062 mg/l (CV 37%)	0·021 mg/l (CV 17%)	Frost *et al* (2013)
Apixaban	5 mg bd	0·128 mg/l (CV 10%)	0·050 mg/l (CV 20%)	Frost *et al* (2013)
Dabigatran	150 mg bd	0·184 mg/l (95% CI 0·064–0·443)	0·090 mg/l (0·031–0·225)	Van Ryn *et al* (2010)
Rivaroxaban	10 mg od	0·125 mg/l (0·091–0·195)	0·009 mg/l (0·001–0·038)	Mueck *et al* (2008)
Rivaroxaban	20 mg od	0·223 mg/l (0·16–0·36)	0·022 mg/l (0·004–0·096)	Mueck *et al* (2008)

CV, coefficient of variation; 95% CI, 95% confidence interval.

Kitchen S, Gray E, Mackie I, Baglin T, Makris M; BCSH committee. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014 Sep;166(6):830-41. doi: 10.1111/bjh.12975.

MEASURING ANTI-XA LEVELS

1. When to take anti-Xa level?
   - Pre and 4 hours post (Trust – 2 hours)
   - After third dose
2. Which bottle to take sample in?
3. Inform laboratory if urgent
4. How to interpret results?
   - 'Pre' (trough) once daily dosing <0.2 IU/ml
   - 'Prophylaxis' 0.2 – 0.4 IU/ml
   - 'Post' (peak) 0.5-1.0 IU/ml

CONCLUSION

- No universally agreed dosing strategy
- Follow Trust guidance and discuss cases
- Should we be adopting a Trust wide weight adjusted prophylaxis protocol?
- Pragmatic dosing of treatment dose LMWH in obesity with monitoring
- DOAC monitoring in extremes of weight (discussion with haemostasis team regarding target levels)

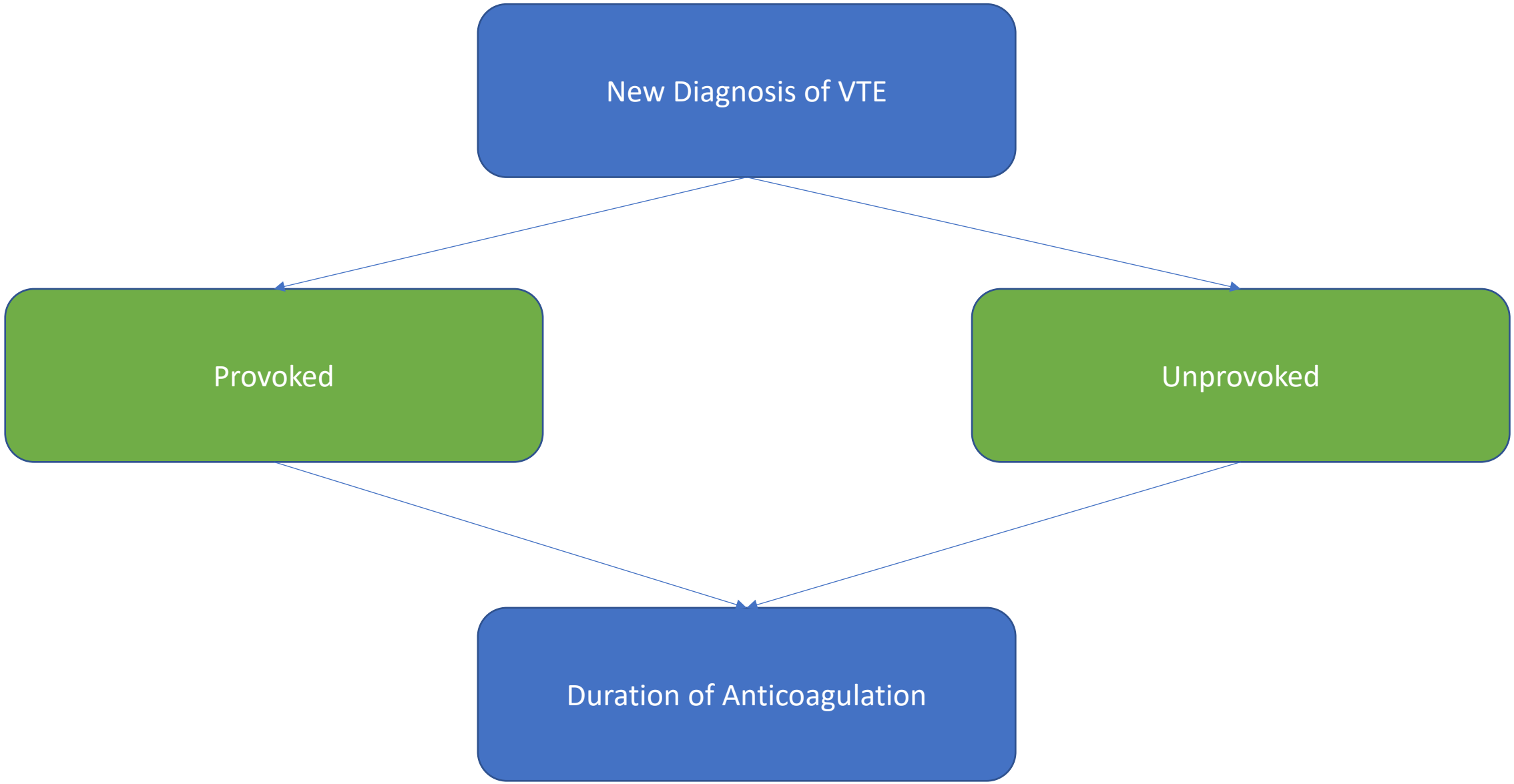
THANK YOU FOR LISTENING

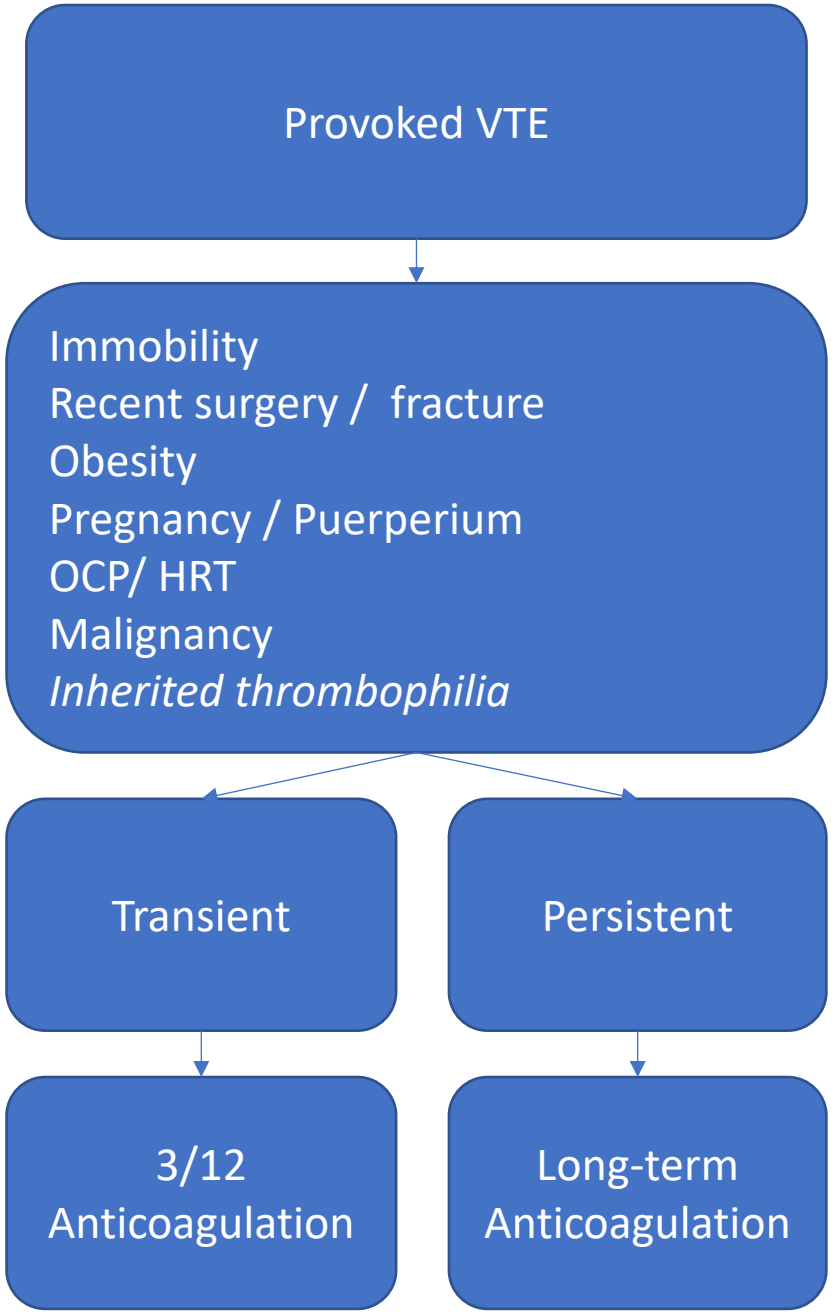
ANY QUESTIONS?

Unprovoked VTE: to screen or not to screen

VTE Study Day

3rd May 2018


New Diagnosis of VTE
Provoked
Unprovoked
Duration of Anticoagulation



Dehydration
Cancer treatments
Infection/ Sepsis
Hyopalbuminaemia / Nephrotic syndrome
HIT – Heparin Induced Thrombocytopenia
DIC - Disseminated Intravascular Coagulation
PNH -Paroxysmal Nocturnal Haemoglobinuria
MPD – Myeloproliferative Disorders

History/ Clinical context

Blood / Screening Tests

~~Immobility~~
~~Recent surgery / fracture~~
~~Obesity~~
~~Pregnancy / Puerperium~~
~~OCP/ HRT~~
~~Malignancy~~
Inherited thrombophilia
~~Dehydration~~
~~Infection~~

~~Occult malignancy~~
Inherited thrombophilia
~~Hypoalbuminaemia / Nephrotic syndrome~~
~~HIT – Heparin Induced Thrombocytopenia~~
~~DIC - Disseminated Intravascular Coagulation~~
~~PNH -Paroxysmal Nocturnal Haemoglobinuria~~
~~MPD – Myeloproliferative Disorders~~

Full Blood Count
Biochemistry
Coagulation

NICE (2012)

Serum Calcium
Liver Function Tests
CxR
Urinalysis

Cancer in VTE

- 15 – 20% of VTE patients have overt cancer at diagnosis
- ≈ 4% have occult malignancy
- Approx 10% will develop over following 5 - 10 years
  - 1 – 2% annual risk after diagnosis
  - Risk uniform over time
  - > 2-fold higher annual risk in those with unprovoked VTE (0.83 vs 1.76%)
- Risk factors
  - Unprovoked event (HR 1.86)
  - Advancing age (HR 1.32)

Douketis, J et al. The long-term risk of cancer in patients with a first episode of venous thromboembolism. Journal of Thrombosis and Haemostasis, 7: 546–551
Carrier, M et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. N Engl J Med 2015; 373:697-704

Exclusion of Malignancy

- NICE (2012)
  - Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer:

1. Physical examination/ Full history
2. Chest X-ray
3. Blood tests (full blood count, serum calcium and liver function tests)
4. Urinalysis.

- Consider **abdomino-pelvic CT scan** (and a mammogram for women)
  - All patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation

Is extensive screening for malignancy necessary?

SOMIT Study (2004) - Screening for Occult Malignancy in Thrombosis

- 201 patients with idiopathic VTE with no initial signs/ symptoms of malignancy
- Random allocation
  - Extensive screening vs no further testing
  - 2 years follow-up
- Screening group: 14 malignancies (13 during screening, 1 during follow-up)
  - 10/13 detected by CT-AP alone
  - Control group: 10 malignancies during follow-up
  - Relative Risk 9.7 ($p<0.001$)
- Cancer related mortality:
  - 2.0% (screening) vs 3.9% - Not significant

Piccioli A et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism. J Thromb Haemost. 2004 Jun;2(6):884-9

Is a CT necessary?

- Carrier et al (2015)
  - Multicentre, randomised trial
  - Limited screening vs limited screening + CT
    - CT included virtual colonoscopy, gastroscopy and pancreatography
  - 1 year follow-up
    - Primary end-point: New cancers missed during screening
- 854 patients
  - Mean age: 54 years
  - 33 new diagnoses of cancer during f/u
    - 14 (3.2%) in limited screening – 4 missed (29%)
    - 19 (4.5%) in limited + CT – 5 missed (26%)
    - No difference in time to diagnosis or mortality

Carrier, M et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. N Engl J Med 2015; 373:697-704

Is a CT necessary?

- Hildyard (2016)
  - 16 month audit all patients referred to VTE service
  - 239 patients with confirmed DVT (190 malignancy free)
    - 164 over 40 years of age
      - 139 with unprovoked VTE
  - 62 agreed to CTAP
  - 28 (45%) abnormal scans
  - Only 1 malignancy diagnosed

Hildyard, C et al. Is there a benefit in computed tomography screening for cancer in patients with unprovoked proximal deep venous thrombosis? A cohort study in the Oxford University Hospitals NHS Trust. Br J Haematol. 2016 Mar;172(6):978-9

Is extensive screening for malignancy necessary?

- Addition of CT-Abdo/pelvis
  - Does not increase screening sensitivity
  - No mortality benefit
    - Although, cancer may be detected earlier

- Is this true in an older population?
    - Mean age (Carrier et al) = 54 years
    - Prandoni (2016)
      - 195 patients, mean age 69 years, 2 years follow-up
      - Randomised to limited * screening vs limited + CT-TAP
      - Cancers detected in 10% vs 8%
      - 2 cancers developed in each group during follow-up

Prandoni P et al. Extensive computed tomography versus limited screening for detection of occult cancer in unprovoked venous thromboembolism: a multicenter, controlled, randomized clinical trial. Semin Thromb Hemost2016;356:884-90

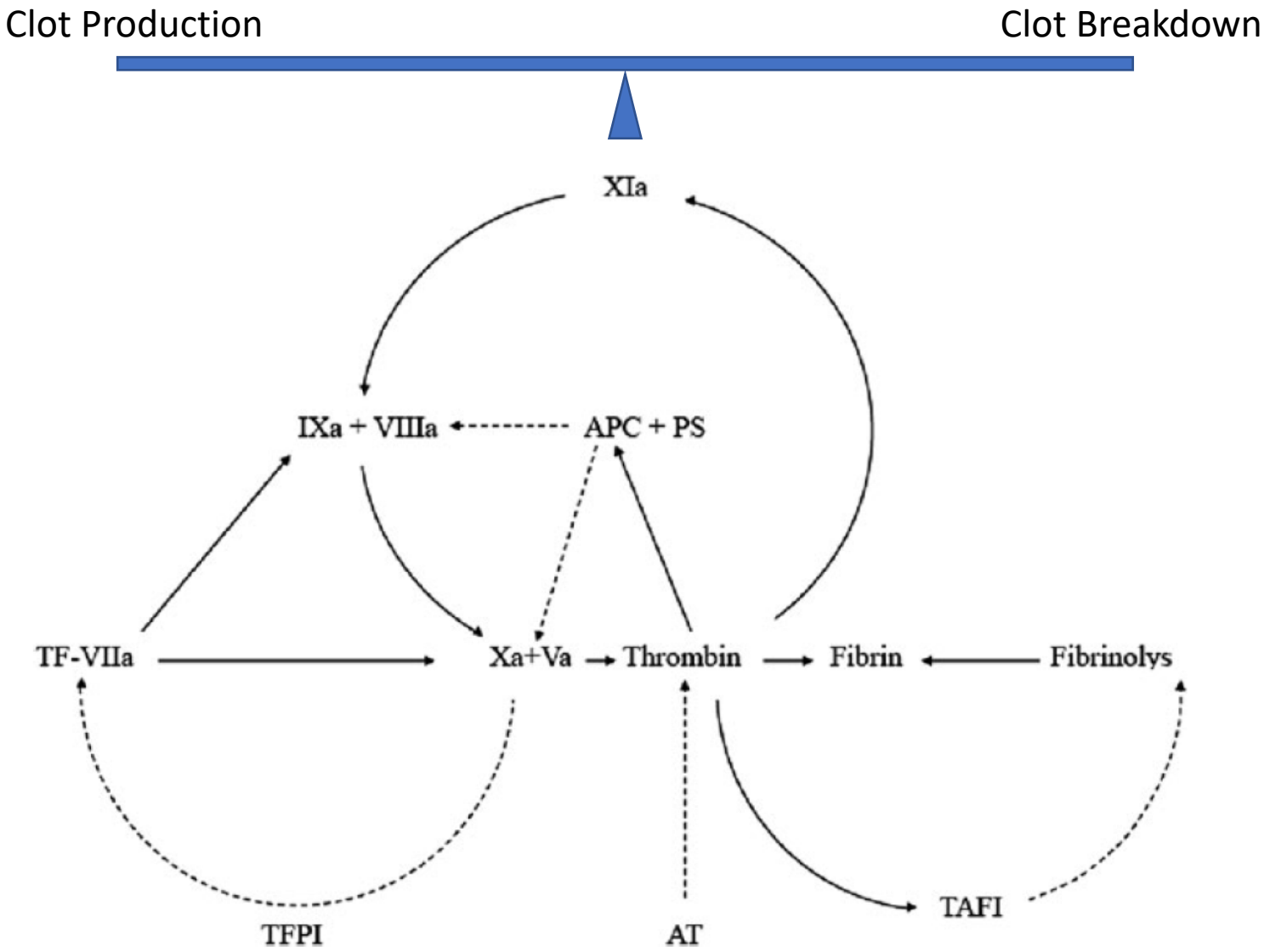
What to conclude?

- “Limited” screening may be as effective as extensive
  - Uncertain, even good quality studies limited:
    - Underpowered to detect differences in cancer-related mortality
    - Wide confidence intervals – low numbers of occult cancers detected

- How limited is limited?
  - Variation in protocols between studies
    - Carrier (2015): FBC, Biochemistry, LFTs, CxR, PAP-Smear, Mammography, Prostate exam/ PSA
    - Prandoni (2016): Any test at physicians discretion other than CT-TAP

(Who) Should we screen for inherited thrombophilia?

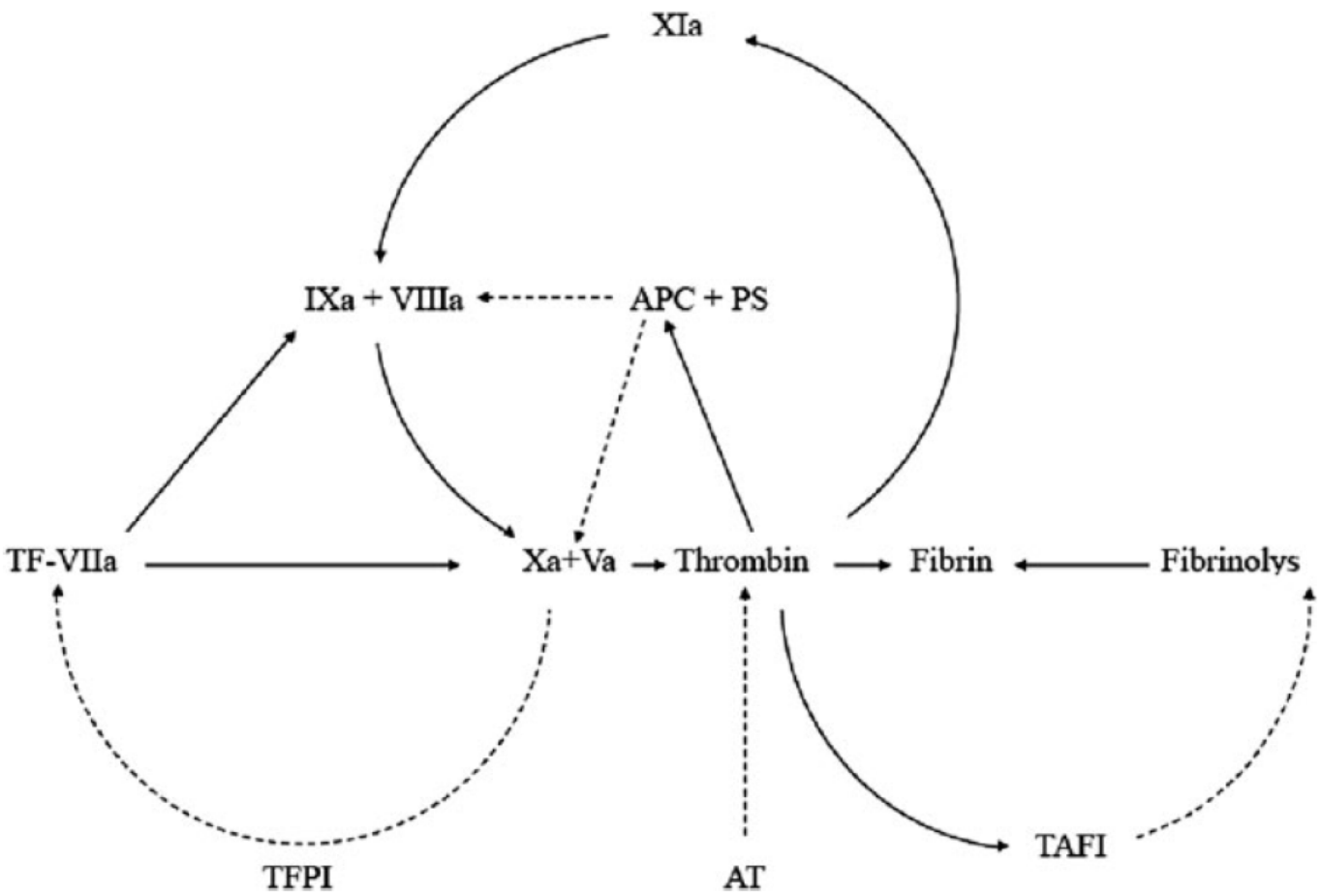
Normal Haemostasis

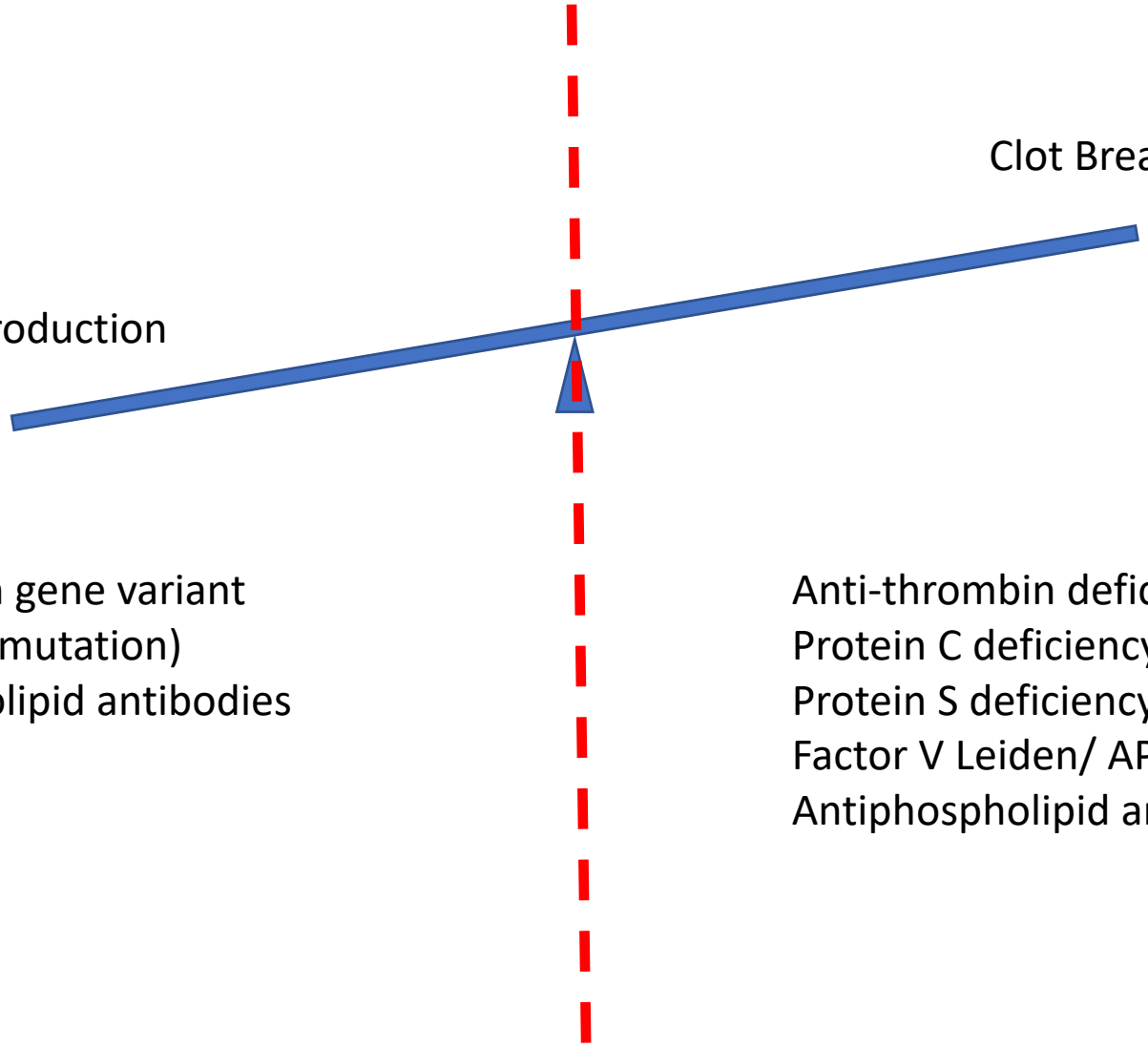


Thrombophilia

Clot Breakdown

Clot Production





Prothrombin gene variant
(PG 20210A mutation)
Antiphospholipid antibodies

Anti-thrombin deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden/ APC resistance
Antiphospholipid antibodies

Who Should be tested?

- BCSH guidelines (2010)
  - Complicated and confusing
- Hardly ever recommended
  - Results will not change management of index case or relatives
- Most patients are tested at the wrong time

When to test

- Can be done anytime:
  - Genotypic tests: FVL, PGV
  - APS antibodies: β-2-glycoprotein, aCL antibodies
- After 3 months & off anticoagulation
  - Protein C, S, Antithrombin, lupus anticoagulant

- Results will never influence initial treatment
  - ie first 3/12 of anticoagulation
- Potential for inappropriate anticoagulant management

Why test for inherited thrombophilias?

- ~~Intensity of anticoagulation~~
- ~~Duration of anticoagulation~~
- ~~Predict risk of recurrence~~
- Predict risk in asymptomatic relatives

Duration of Anticoagulation

- ACCP (2016) and ESC (2014) consensus guidelines
  - Initial anticoagulation should be for 3 months duration
  - “Suggest anticoagulants should be continued indefinitely in unprovoked VTE patients with non-high bleeding risk” (GRADE 2B- Weak recommendation)
- Risk scores
  - DASH, HERDOO2, Vienna
  - None identified inherited thrombophilia as a risk

Predicting risk of recurrence

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation	Lupus anticoagulant*	Anti-cardiolipin antibodies*	Anti-β2 GPI antibodies
Prevalence in the general population	0.02%	0.2%	0.03%-0.13%	3-7%	0.7%-4%	1%-8 %	5	3.4
Relative risk for a first venous thrombosis	5-10	4-6.5	1-10	3-5	2-3	3-10	0.7	2.4
Relative risk for recurrent venous thrombosis	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4	2-6	1-6	
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9	10	1.5-10	
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3	No consistent data	No consistent data	

Who (not) to Test – NICE 2015

- Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
- Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.
- Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

- **Consider** testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.
- **Consider** testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.

Appendix I: Obstetric thromboprophylaxis risk assessment and management

Antenatal assessment and management (to be assessed at booking and repeated if admitted)

- Any previous VTE except a single event related to major surgery → **HIGH RISK**: Requires antenatal prophylaxis with LMWH; Refer to trust-nominated thrombosis in pregnancy expert/team
- Hospital admission
- Single previous VTE related to major surgery
- High-risk thrombophilia + no VTE
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
- Any surgical procedure e.g. appendicectomy
- OHSS (first trimester only)

→ **INTERMEDIATE RISK**: Consider antenatal prophylaxis with LMWH

- Obesity (BMI > 30 kg/m²)
- Age > 35
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current pre-eclampsia
- Immobility, e.g. paraplegia, PGP
- Family history of unprovoked or estrogen-provoked VTE in first-degree relative
- Low-risk thrombophilia
- Multiple pregnancy
- IVF/ART

→ **Four or more risk factors**: prophylaxis from first trimester

Three risk factors: prophylaxis from 28 weeks

Fewer than three risk factors → **LOWER RISK**: Mobilisation and avoidance of dehydration

Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel

Postnatal assessment and management (to be assessed on delivery suite)

- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx

→ **HIGH RISK**: At least 6 weeks' postnatal prophylactic LMWH

- Caesarean section in labour
- BMI ≥ 40 kg/m²
- Readmission or prolonged admission (≥ 3 days) in the puerperium
- Any surgical procedure in the puerperium except immediate repair of the perineum
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU

→ **INTERMEDIATE RISK**: At least 10 days' postnatal prophylactic LMWH

NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

- Age > 35 years
- Obesity (BMI ≥ 30 kg/m²)
- Parity ≥ 3
- Smoker
- Elective caesarean section
- Family history of VTE
- Low-risk thrombophilia
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, PGP, long-distance travel
- Current pre-eclampsia
- Multiple pregnancy
- Preterm delivery in this pregnancy (< 37+0 weeks)
- Stillbirth in this pregnancy
- Mid-cavity rotational or operative delivery
- Prolonged labour (> 24 hours)
- PPH > 1 litre or blood transfusion

Two or more risk factors → **INTERMEDIATE RISK** (as above)

Fewer than two risk factors → **LOWER RISK**: Early mobilisation and avoidance of dehydration

Antenatal and postnatal prophylactic dose of LMWH

Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily
Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily
Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily
Weight 131–170 kg = 80 mg enoxaparin/10000 units dalteparin/9000 units tinzaparin daily
Weight > 170 kg = 0.6 mg/kg/day enoxaparin/ 75 u/kg/day dalteparin/ 75 u/kg/day tinzaparin

APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β_2-glycoprotein 1 antibodies); ART = assisted reproductive technology; BMI based on booking weight; DM = diabetes mellitus; FHx = family history; gross varicose veins = symptomatic, above knee or associated with phlebitis/oedema/skin changes; high-risk thrombophilia = antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD = inflammatory bowel disease; immobility = ≥ 3 days; IVDU = intravenous drug user; IVF = in vitro fertilisation; LMWH = low-molecular-weight heparin; long-distance travel = > 4 hours; low-risk thrombophilia = heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS = ovarian hyperstimulation syndrome; PGP = pelvic girdle pain with reduced mobility; PPH = postpartum haemorrhage; thrombophilia = inherited or acquired; VTE = venous thromboembolism.

Who do we Test?

- Pregnancy
  - Asymptomatic patients with 1st degree relative with VTE and known thrombophilic defect
- Unprovoked VTE
  - Only those wishing to stop after 3/12
- Family history
  - Screen asymptomatic relatives if very strong history
  - Ie Multiple events in multiple 1st degree relatives with known thromphophilic defect

Management of DOAC's

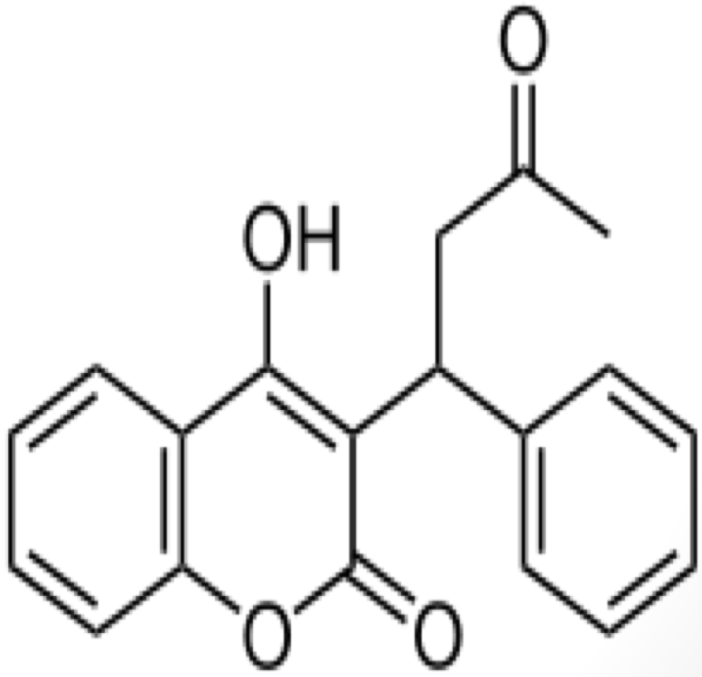
Dr Rachel Brown
Haematology Consultant, MFT

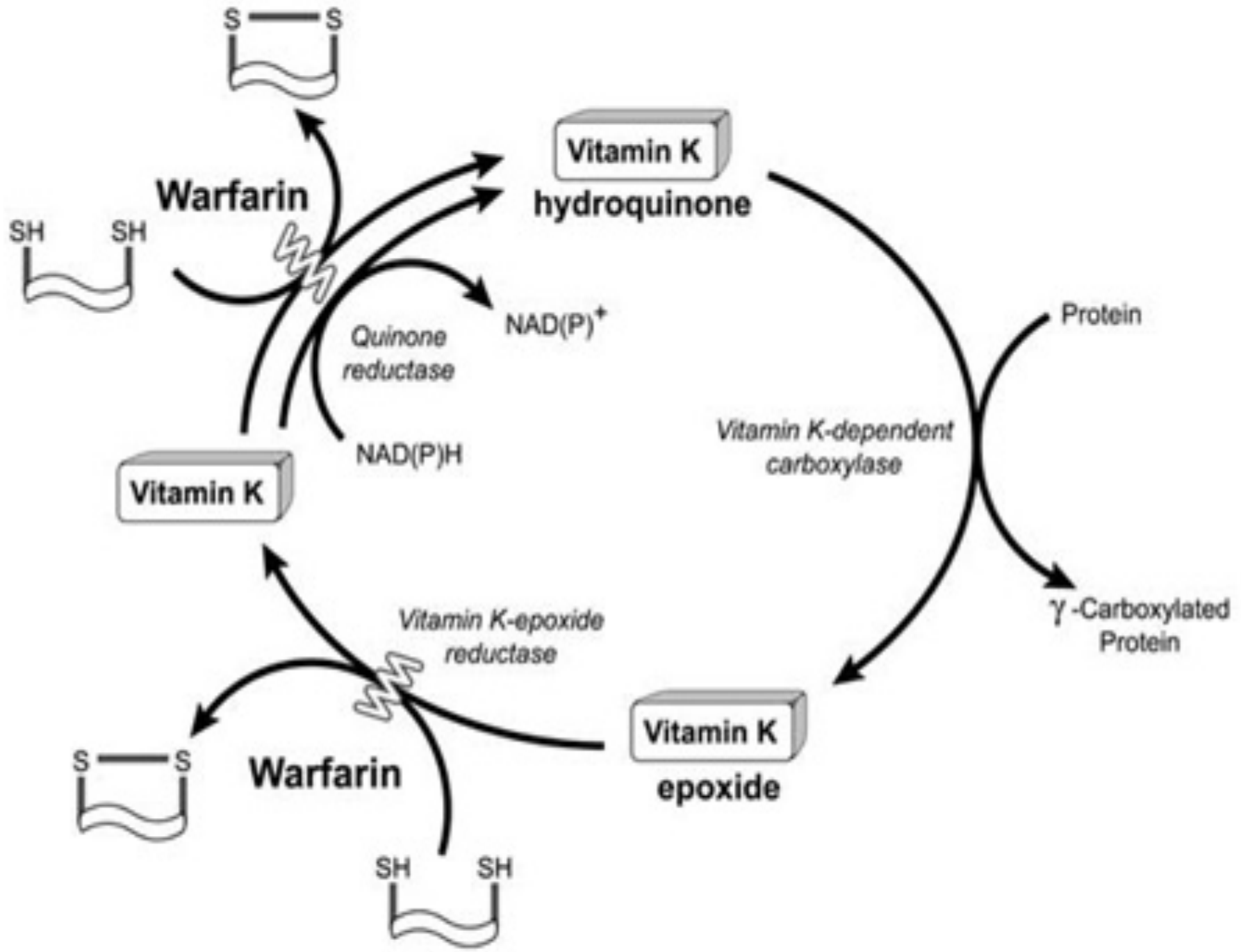
Aims of talk

- 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

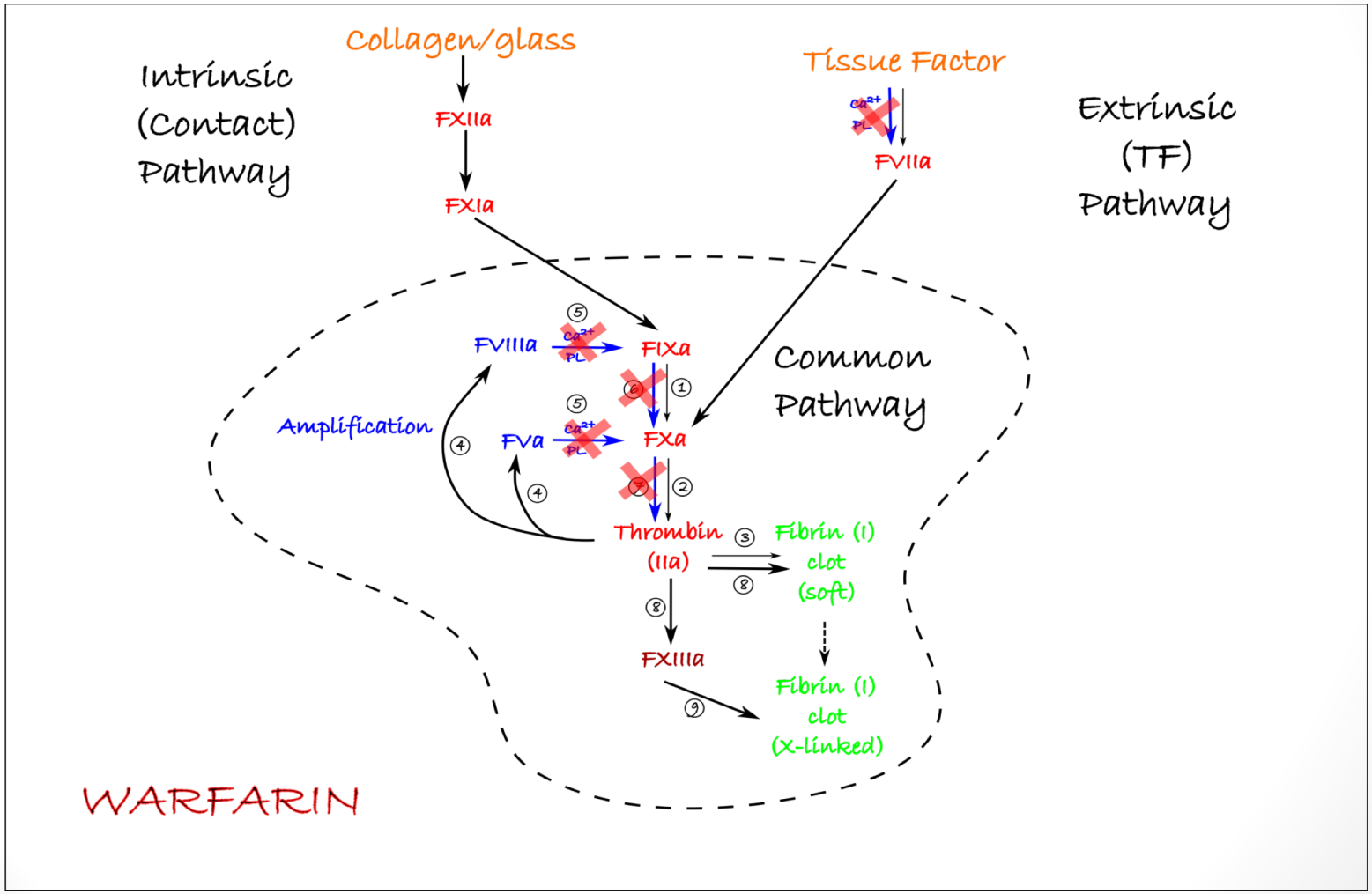
Warfarin

- 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**

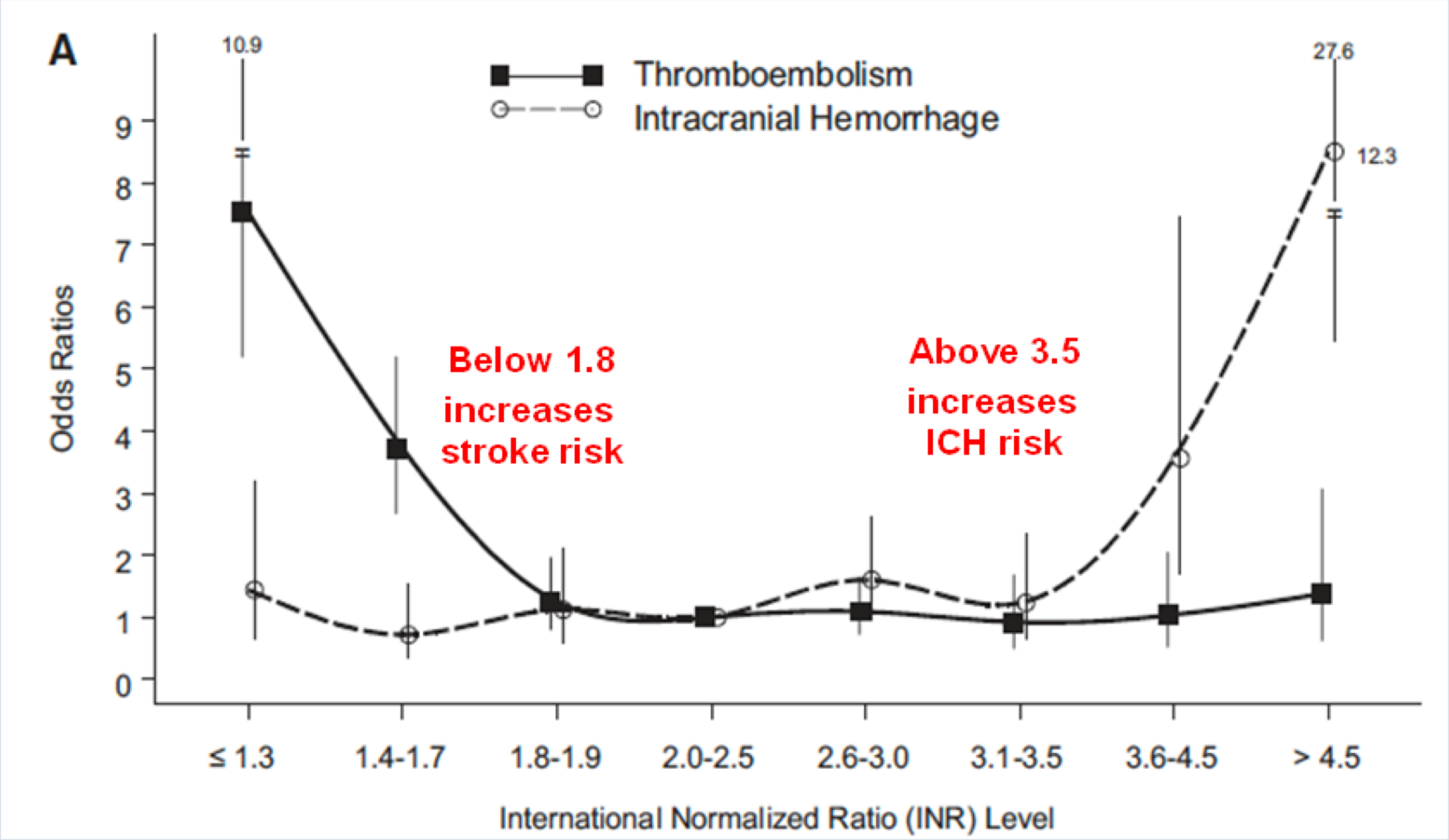
Long half-life

Slow onset and offset of action

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

VKA, vitamin K antagonist.

Therapeutic Range for Warfarin: Balancing Safety and Efficacy



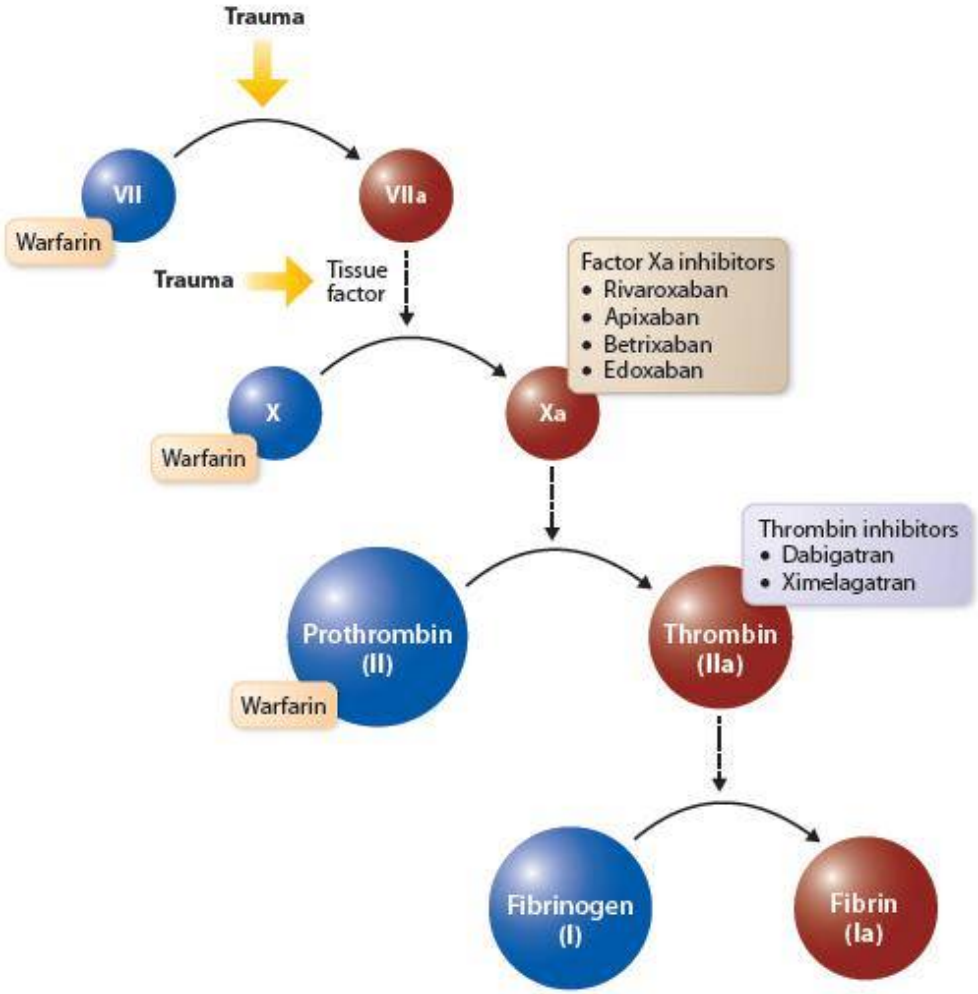
Therapeutic Range for warfarin. Rothman et al. Am J Med 2013

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).

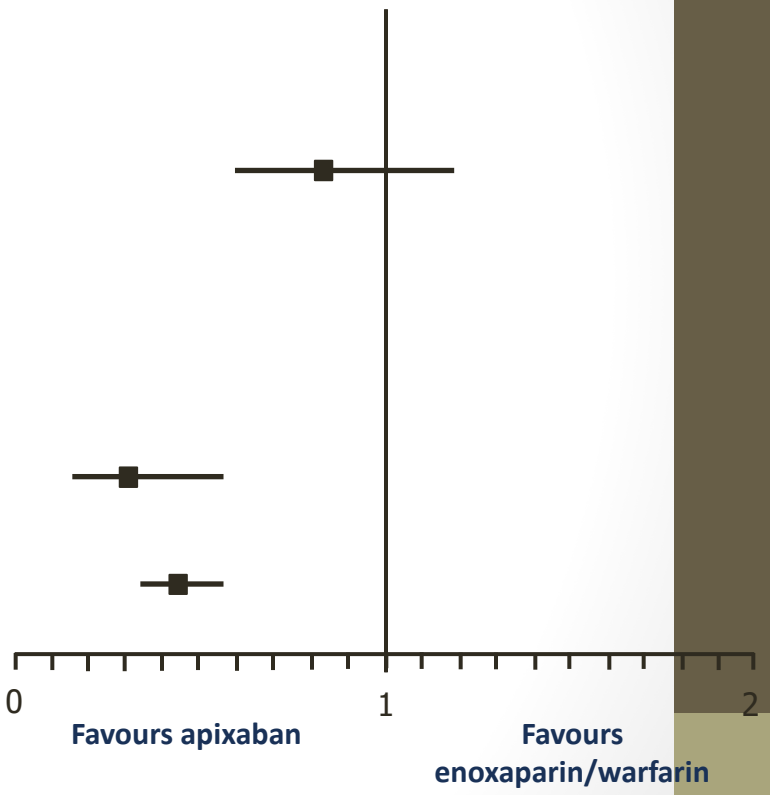
BD: twice daily; DVT: deep vein thrombosis; HR: hazard ratio, OD: once daily; RR: relative risk.

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



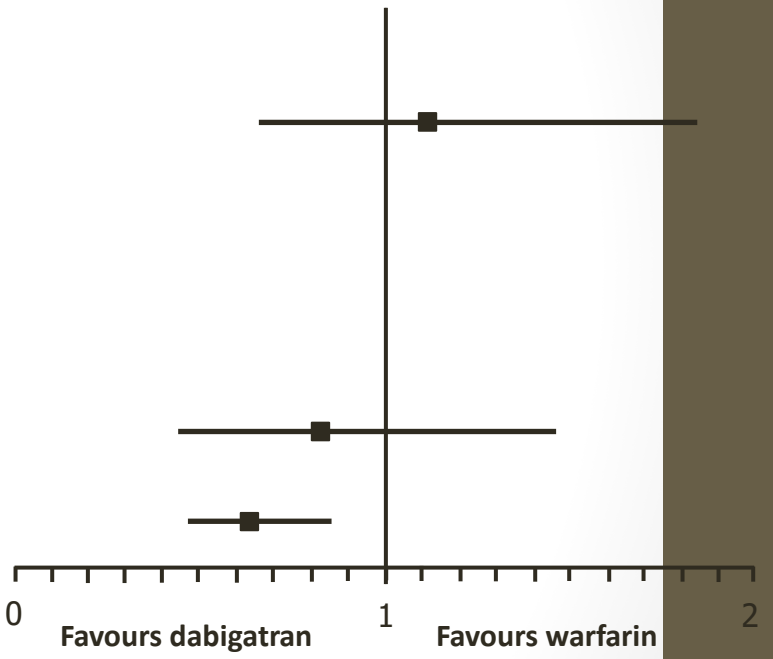
**All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented.*
 # All safety analyses included data obtained from patients during study treatment, defined as the time from administration of the first dose until 48 hours 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



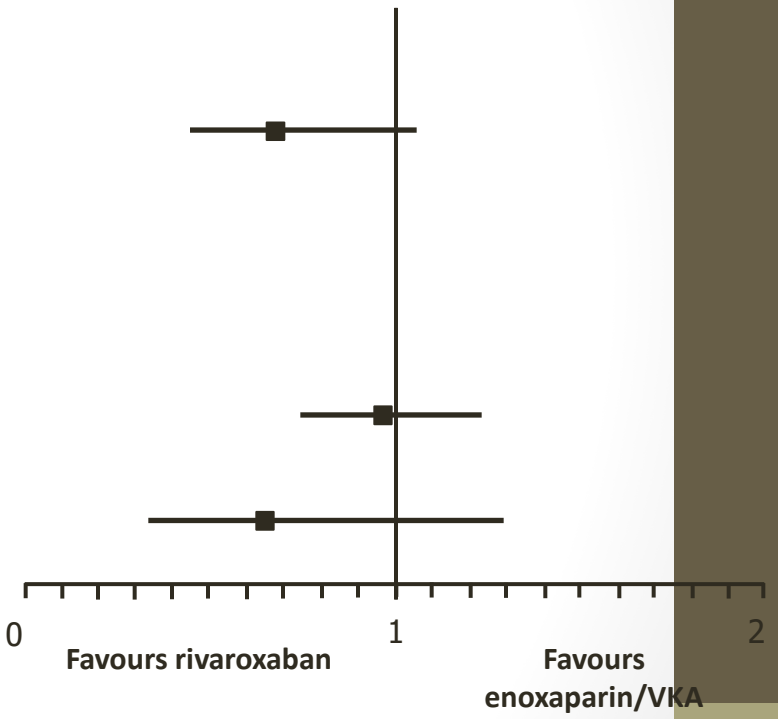
**LMWH, UFH, or fondaparinux.*
 # The efficacy analysis was based on the number of randomly assigned patients who received at least one dose of study drug and who had events during the 6-month treatment period, regardless of early discontinuation of study drug.
†The safety analysis of bleeding events 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.

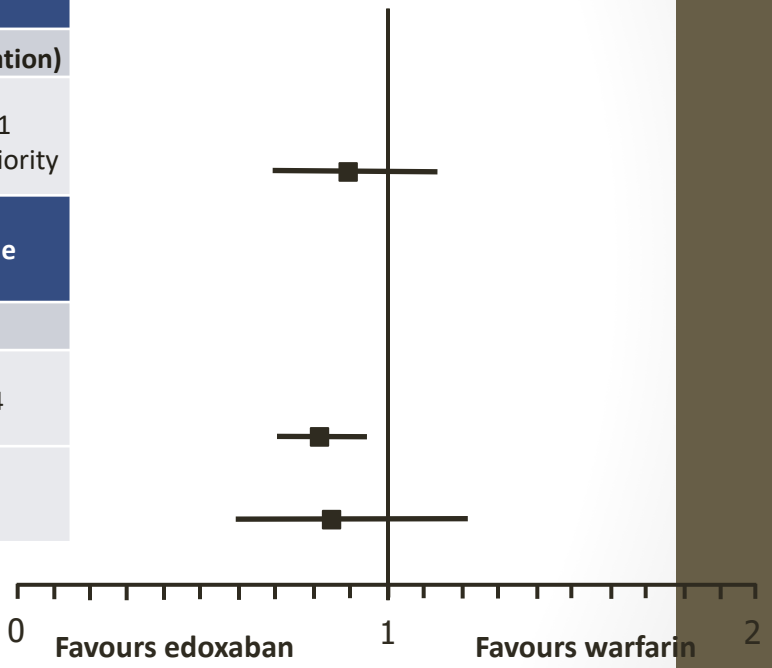
† Major or clinically relevant non-major (CRNM) bleeding was the primary safety endpoint.

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)

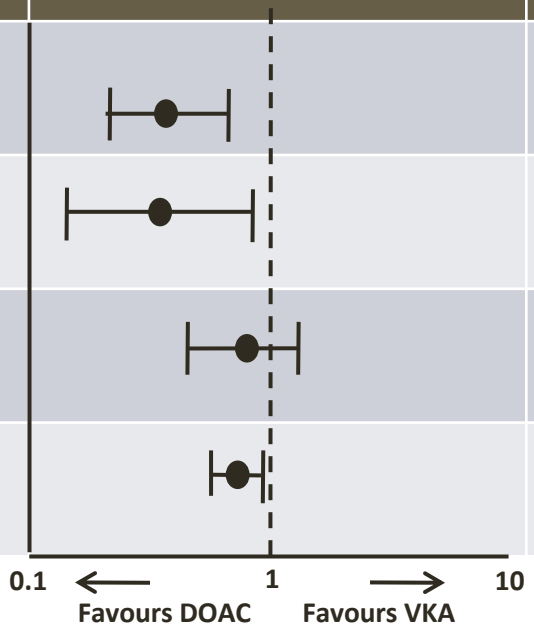
‡ First major or clinically relevant non-major (CRNM) bleeding was the primary safety endpoint.

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]

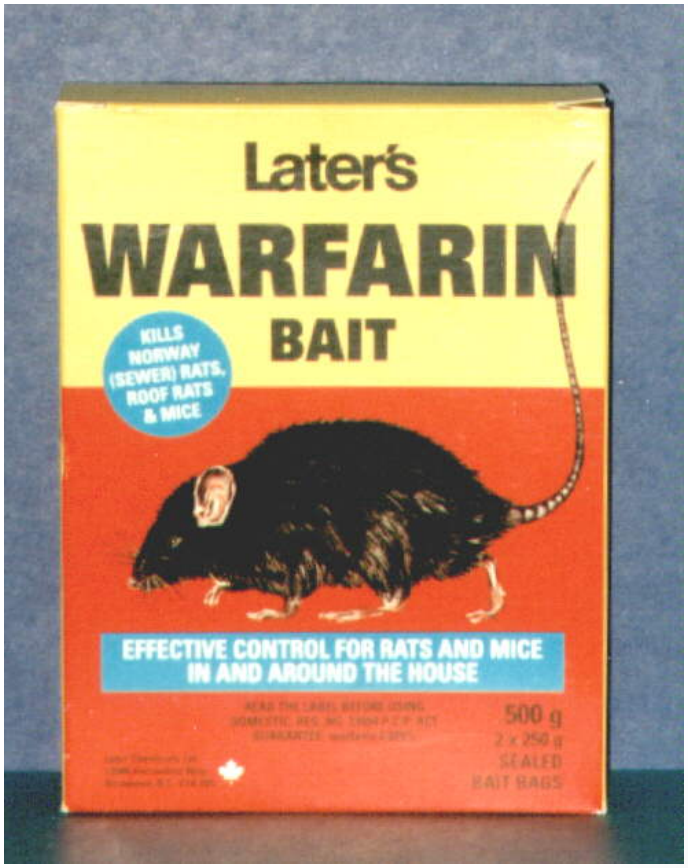
GMMMG

- 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?

Thrombosis and Treatment in Oncology

Simon Watt

- Epidemiology
- Causes of thrombosis and relevance to cancer
- Specific problems in malignancies
- In VTE who might have cancer?
- Treatment of VTE
- NOACS and the relevance in malignancy

VTE and Cancer: Epidemiology

- Of all cases of VTE:
  - About 20% occur in cancer patients
  - Patients with spontaneous VTE have a 4x risk of being diagnosed with cancer
- Of all cancer patients:
  - 15% will have symptomatic VTE
  - As many as 50% have VTE at autopsy
- Compared to patients without cancer:
  - Higher risk of first and recurrent VTE
  - Higher risk of bleeding on anticoagulants
  - Higher risk of dying

Lee AY, Levine MN. *Circulation*. 2003;107:23 Suppl 1:I17-I21

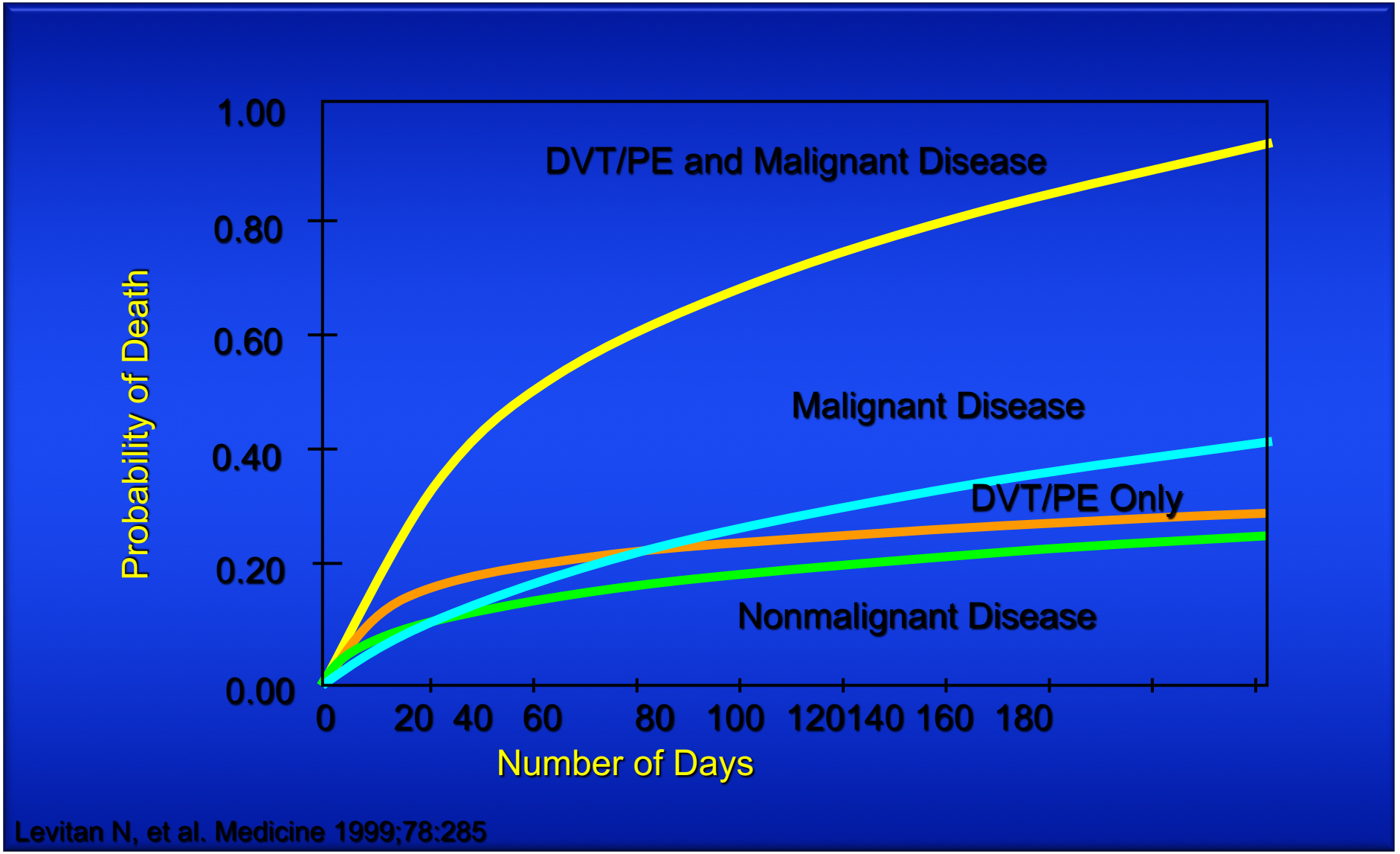
Clinical Features of VTE in Cancer

- VTE has significant negative impact on quality of life

- VTE may be the presenting sign of occult malignancy
  - 10% with idiopathic VTE develop cancer within 2 years
  - 20% have recurrent idiopathic VTE
  - 25% have bilateral DVT

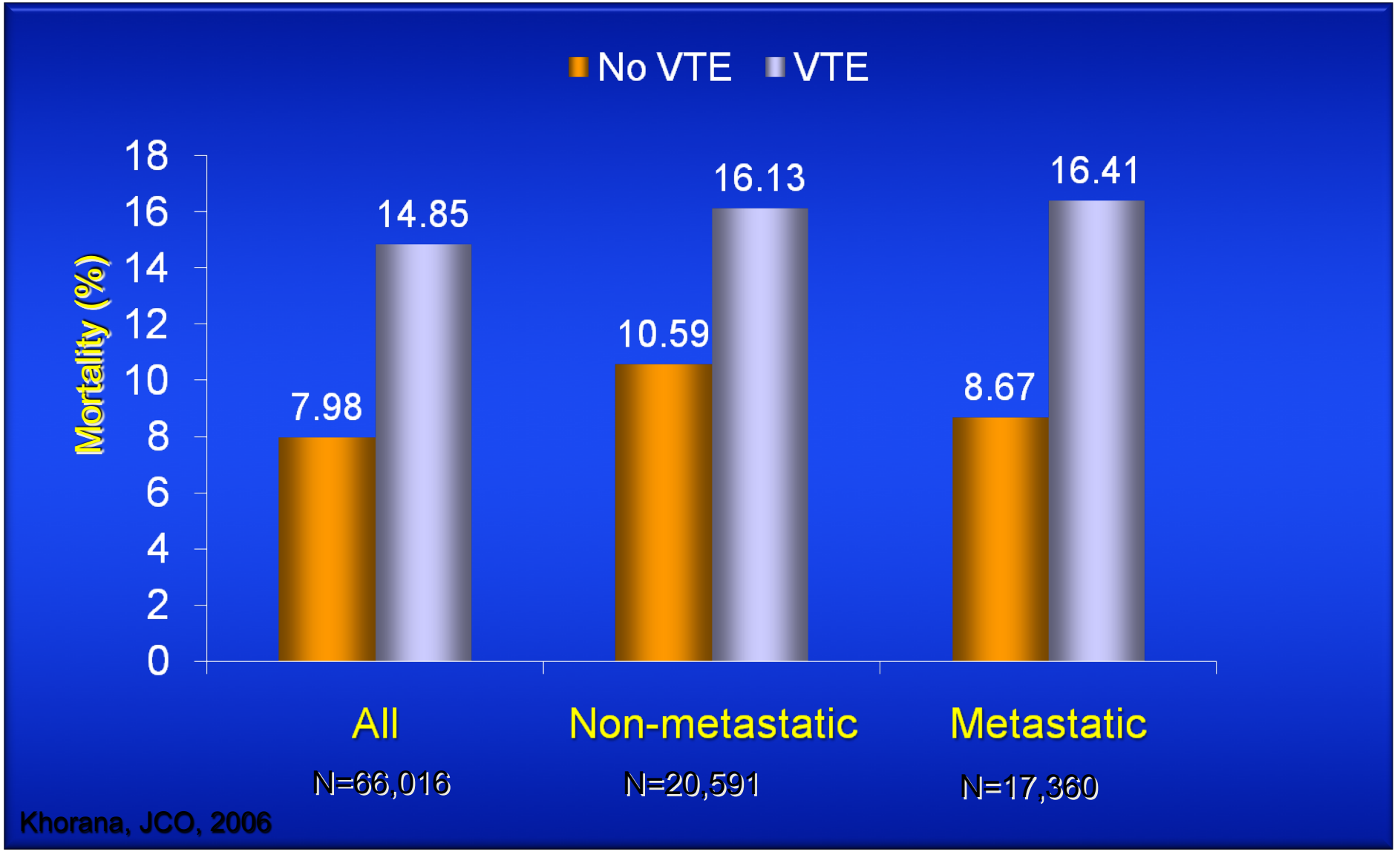
Bura *et. al., J Thromb Haemost* 2004;2:445-51

Likelihood of Death After Hospitalization



Levitan N, et al. Medicine 1999;78:285

Hospital Mortality With or Without VTE



WHAT CAUSES VTE ?

Three main components were identified by Rudolph Virchow,19th century German pathologist

- **A change in blood flow** due to immobility/paralysis resulting in **stasis**
- **Hypercoaguability** causing the blood to clot more readily, e.g. hormone replacement, clotting disorders or thrombophilias
- **Injury to the vessel wall,** e.g. trauma or infection

Risk factors for first thrombosis

- Age
- Active cancer/cancer treatment-20%
- Critical care admission
- Surgery
- Thrombophilia
- Family/personal history of VTE
- Obesity
- HRT/oestrogen-containing contraceptive pill
- Pregnancy/given birth within 6 weeks

Risk factors for recurrent thrombosis

- Previous thrombosis
- Spontaneous
- Male sex
- Antiphospholipid syndrome
- Active cancer

Natural History of DVT

Rare under 16 years

Annual incidence 30/100,000 40 years

Annual incidence 90/100,000 60 years

Annual incidence 260/100,000 80 years

Thrombophilia

Factor V Leiden (V resistant to cleavage by Protein C)

Prothrombin gene G20210A variant (high II)

Protein C

Protein S

Low Antithrombin

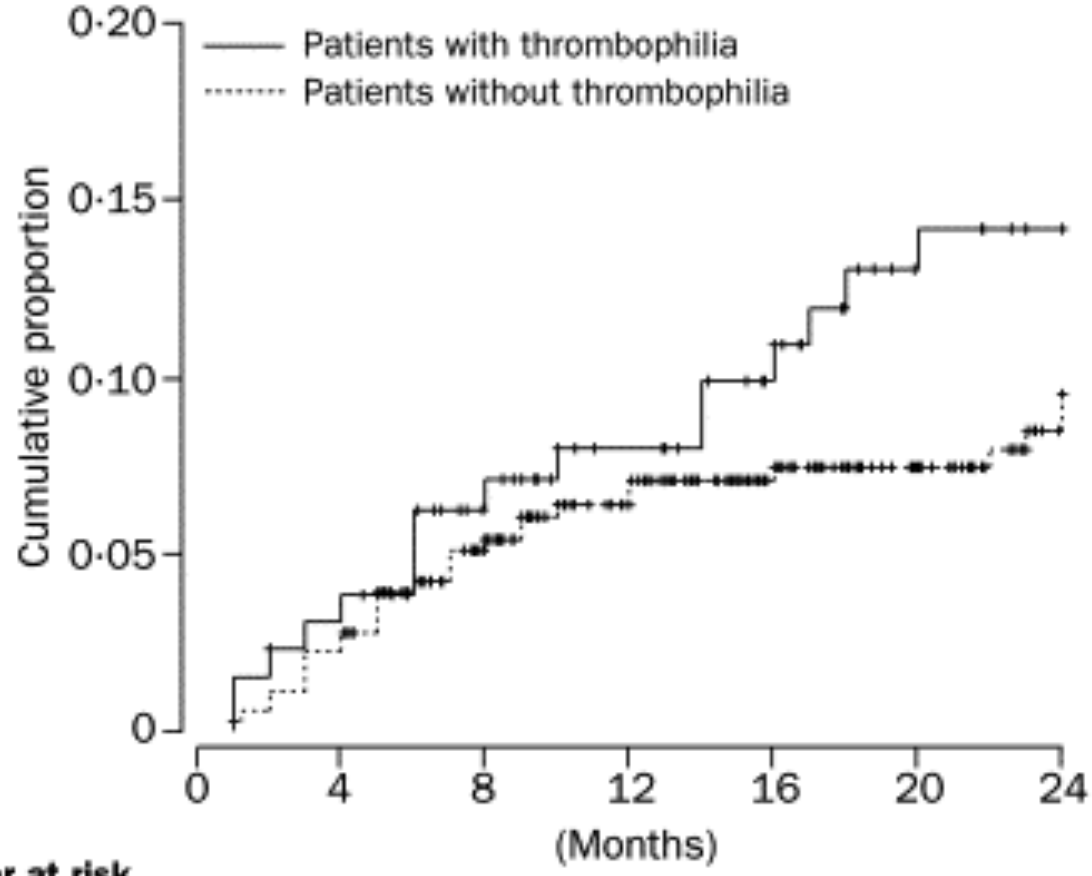
Thrombophilia

- Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia(1B).
- Decisions regarding duration of anticoagulation in unselected patients should be made with reference to whether or not a first episode of venous thrombosis was provoked or not, other risk factors, and risk of anticoagulant therapy-related bleeding, regardless of whether a heritable thrombophilia is known (1B)

Thrombophilia

- Adults who develop skin necrosis in association with oral VKAs should be tested for protein C and S deficiency when VKA treatment is withdrawn (2B).

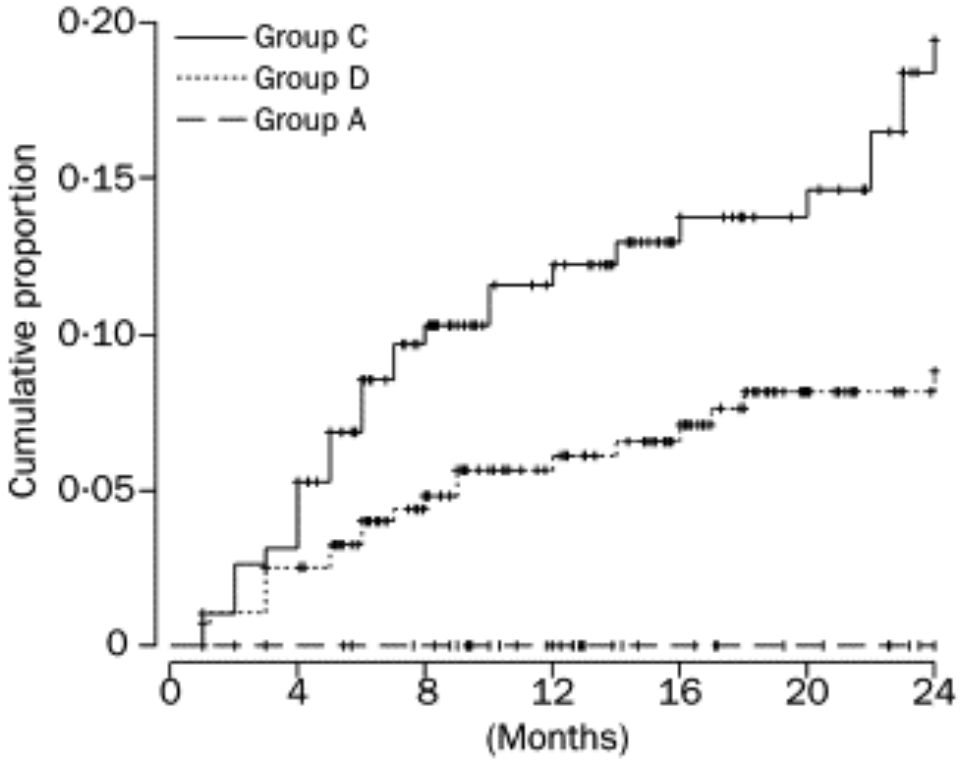
Thrombophilia?



Number at risk

Patients with thrombophilia	130	125	111	100	90	76	71
Patients without thrombophilia	359	350	308	272	230	201	174

Recurrence



Number at risk

Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

Figure 1: **Cumulative proportions of recurrent thrombosis after cessation of anticoagulant therapy**

Data for group B are not included because it was a small group with no recurrences.

Thrombophilia screening- Acquired

Antiphospholipid antibodies

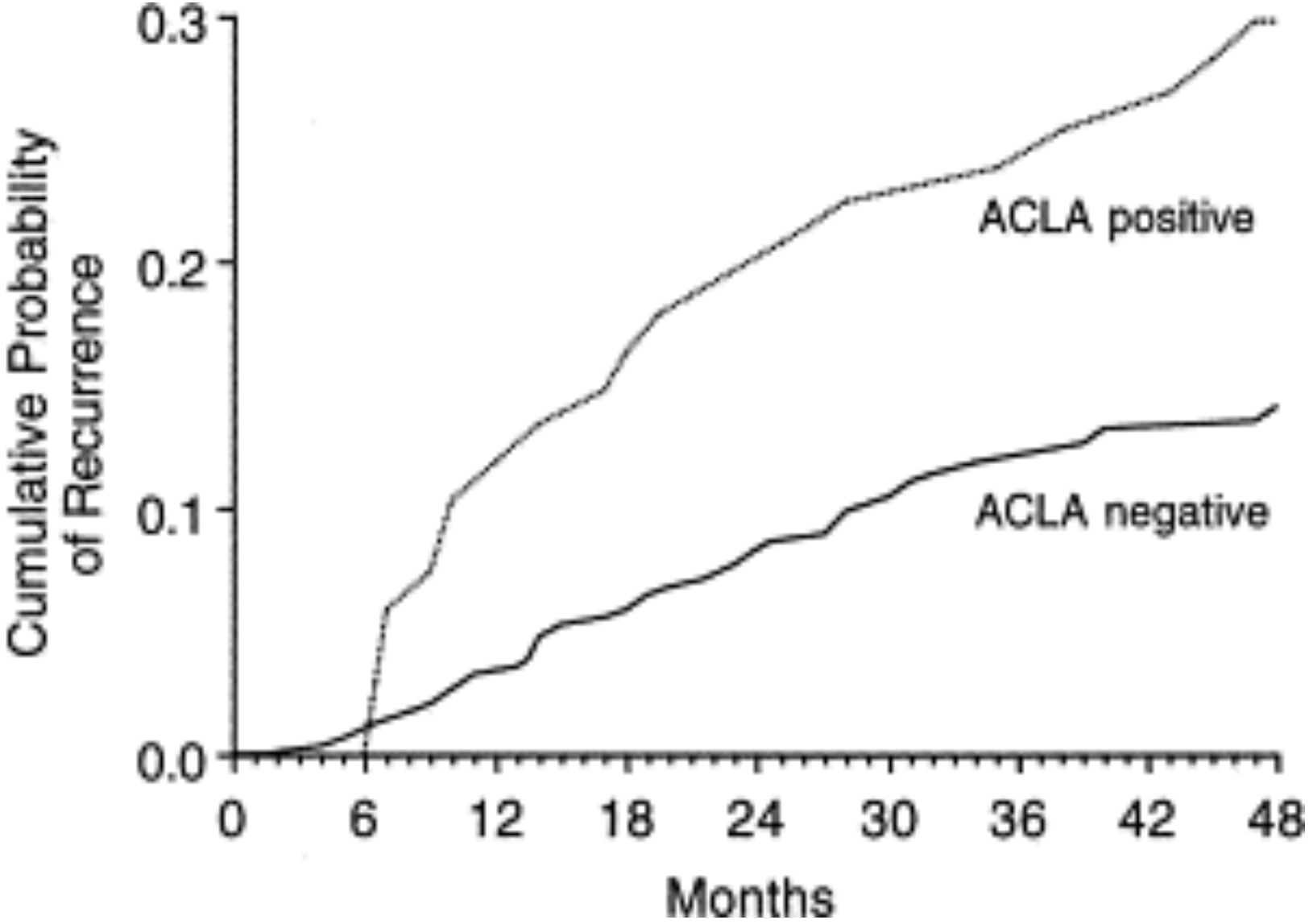
Anticardiolipin antibodies

Lupus anticoagulant

Anti-Beta2 glycoprotein I antibodies

High homocysteine

Schulman et al AJM 1998



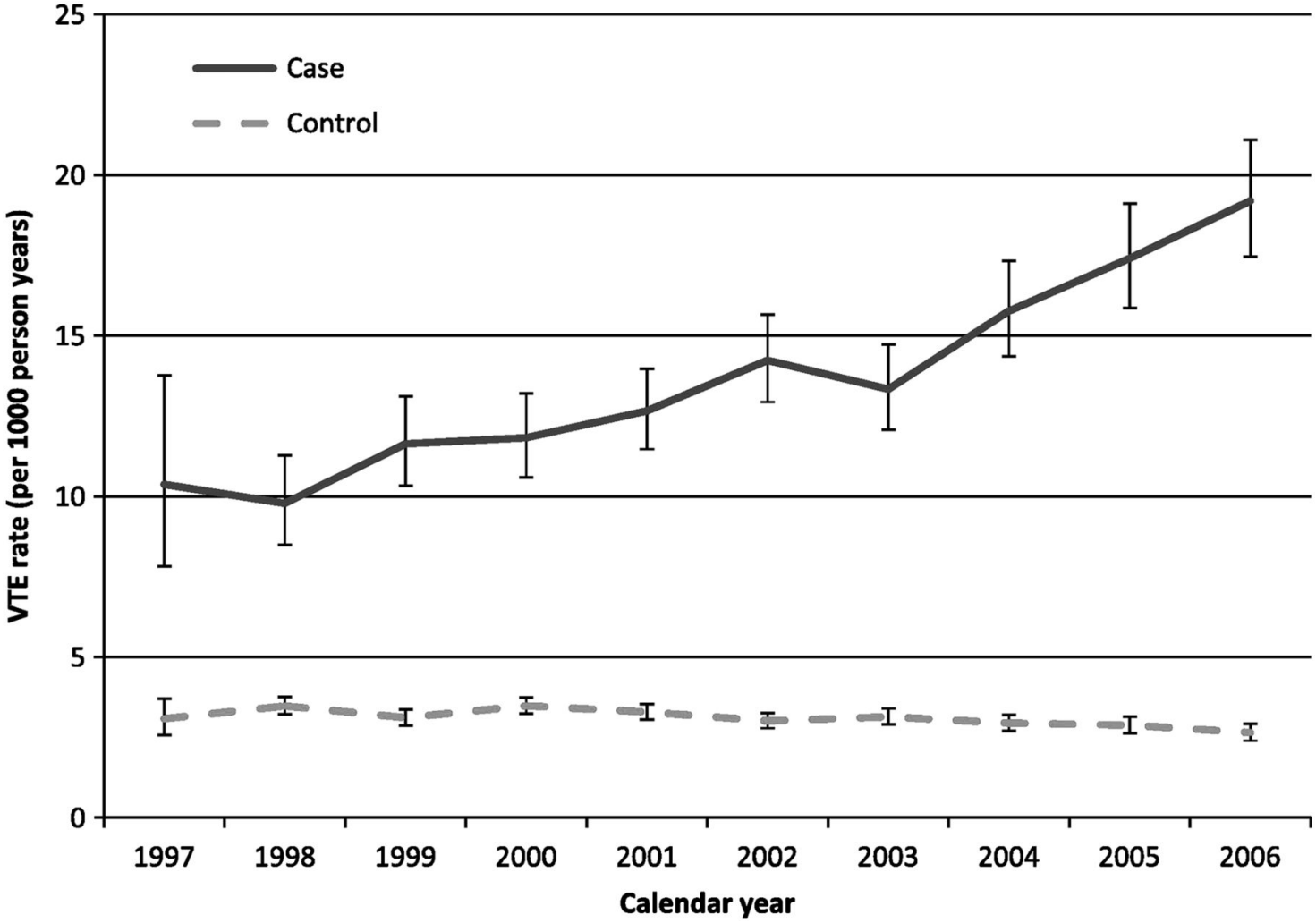
Cancer-Associated VTE

Elyamany G, et al. *Clin Med Insights Oncol*. 2014;8:129-137.

Risk factors in cancer

- Site
- Stage
- Aggressiveness
- Direct/mass effects of tumour
- Chemotherapy
- Central catheters
- Surgery
- Immobility

Absolute rates of venous thrombosis (per 1000 person-years) for individual calendar years between 1997 and 2006.



Jasmijn F. Timp et al. Blood 2013;122:1712-1723

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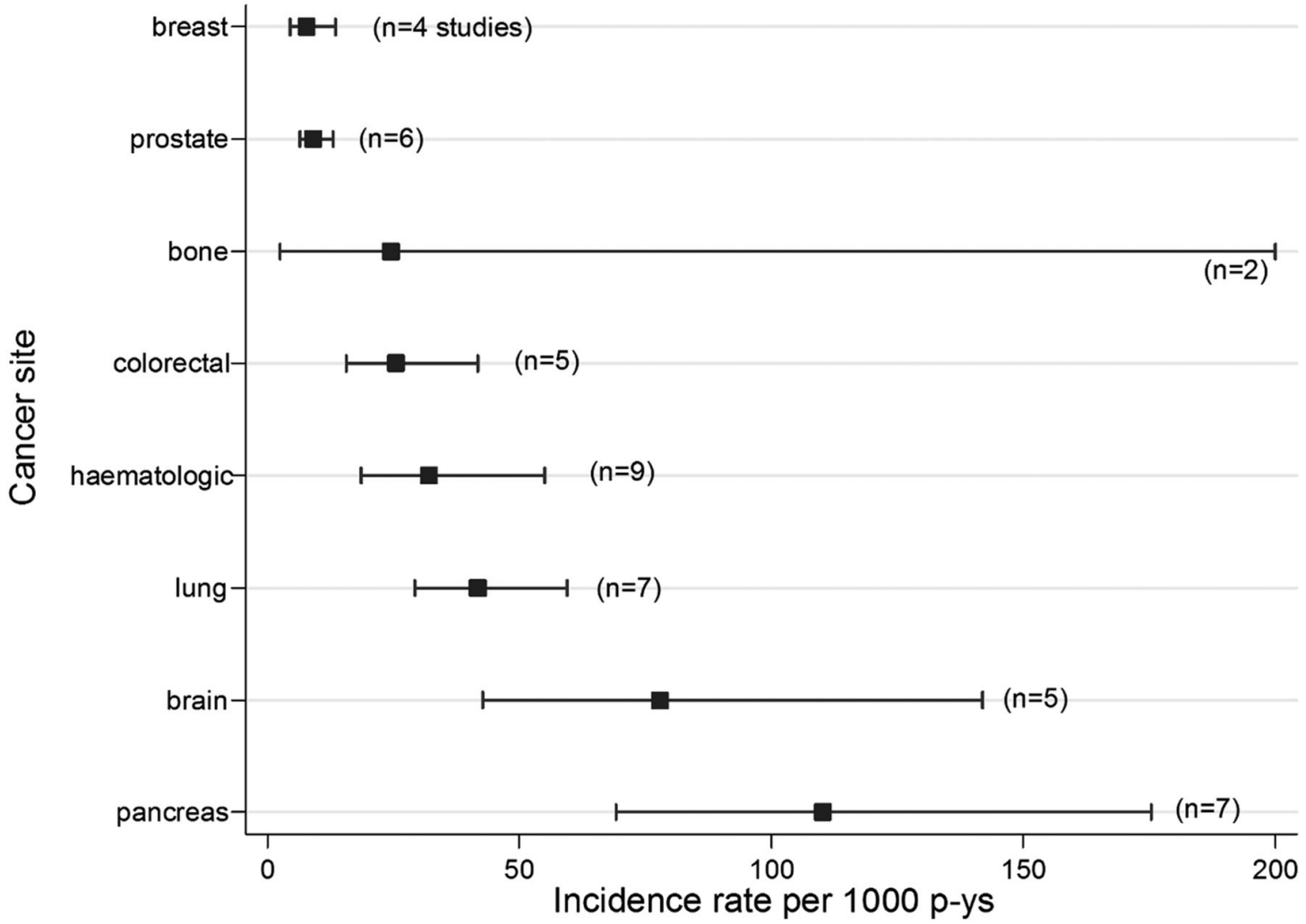
Pooled incidence rates (per 1000 person-years) of venous thrombosis per type of cancer.



Jasmijn F. Timp et al. Blood 2013;122:1712-1723

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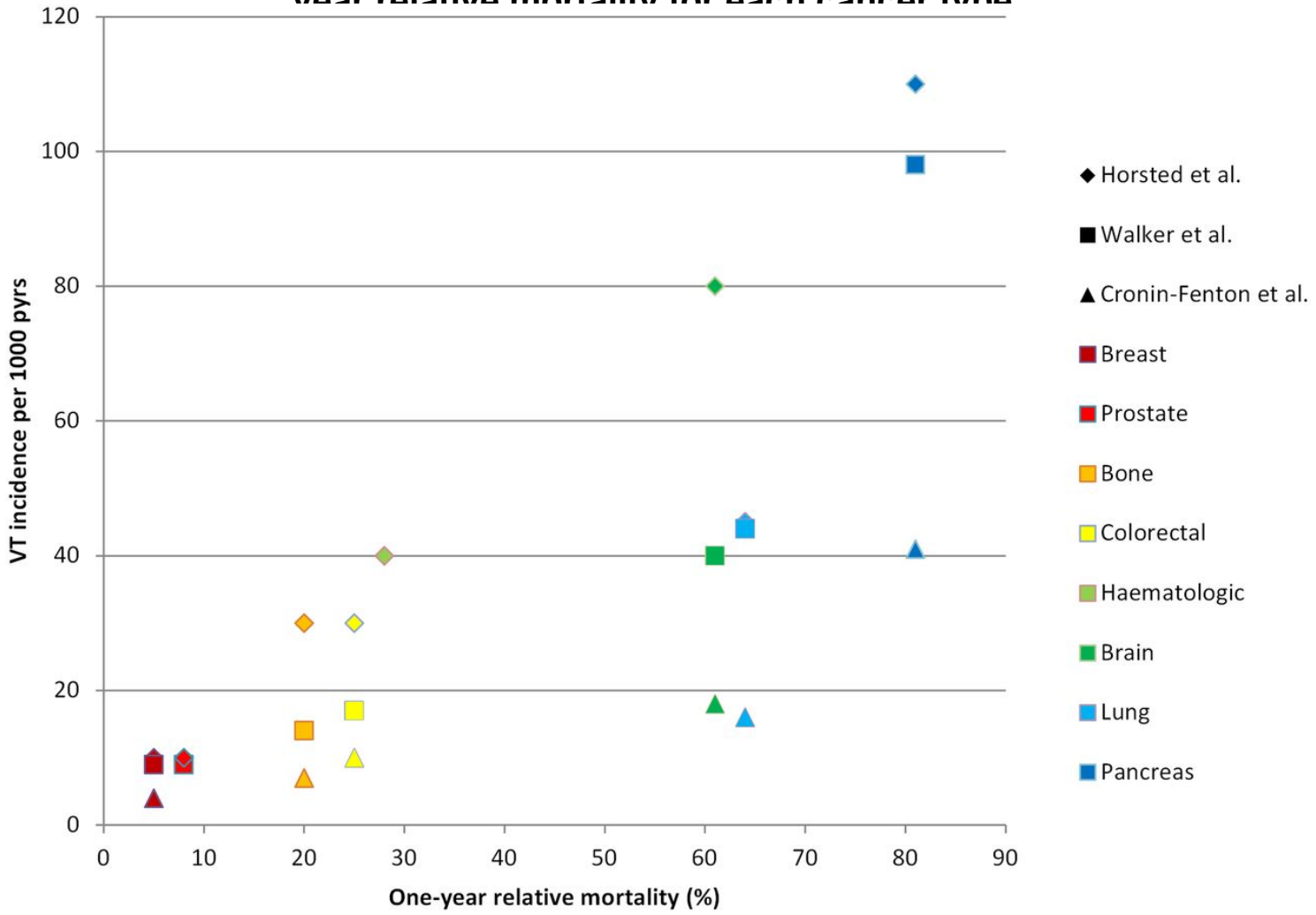
Incidence rates of venous thrombosis (VT) (per 1000 person-years) per type of cancer (according to Horsted et al,17 Walker et al,13 and Cronin-Fenton et al11) plotted against the 1-year relative mortality for each cancer type



Jasmijn F. Timp et al. Blood 2013;122:1712-1723

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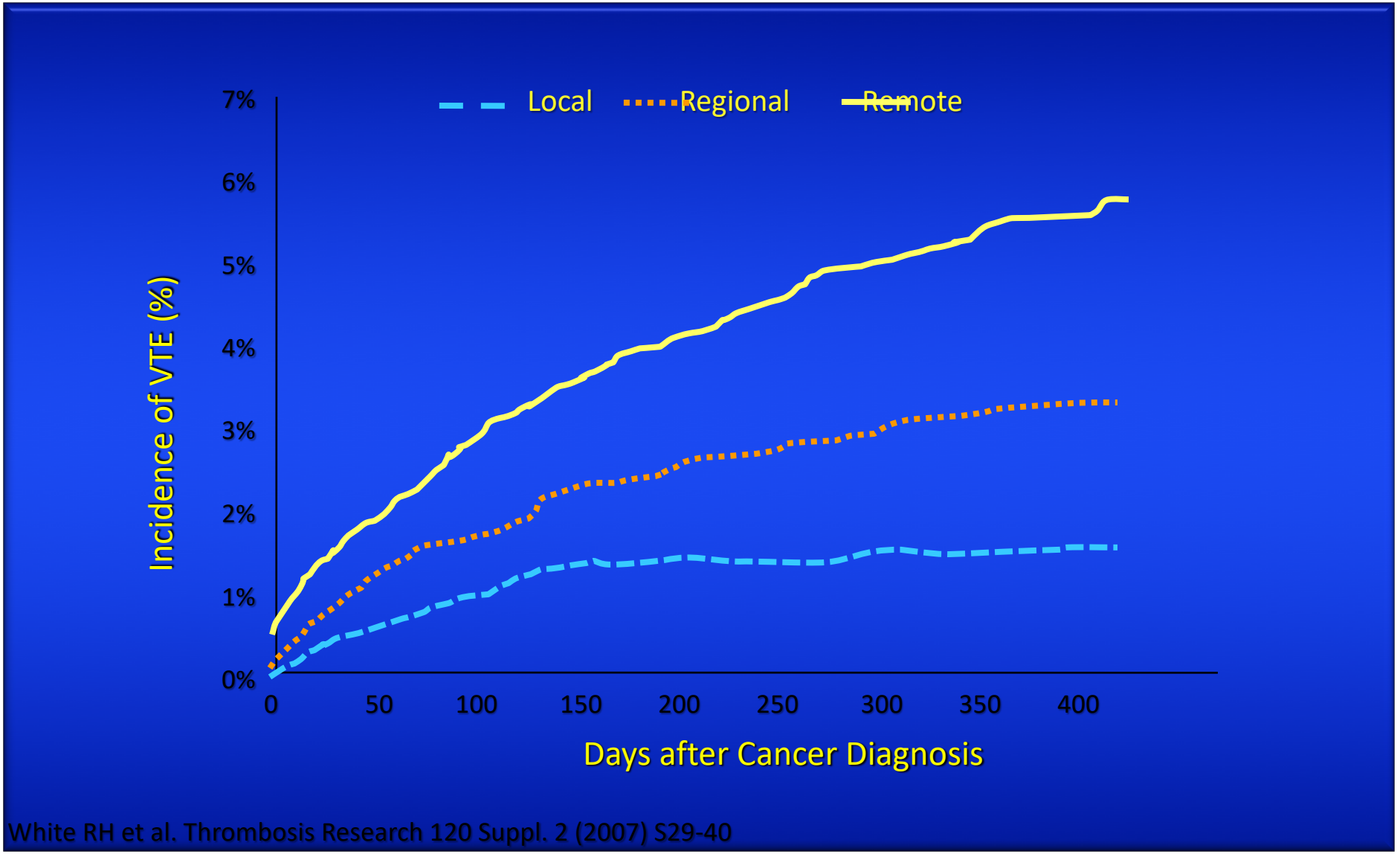
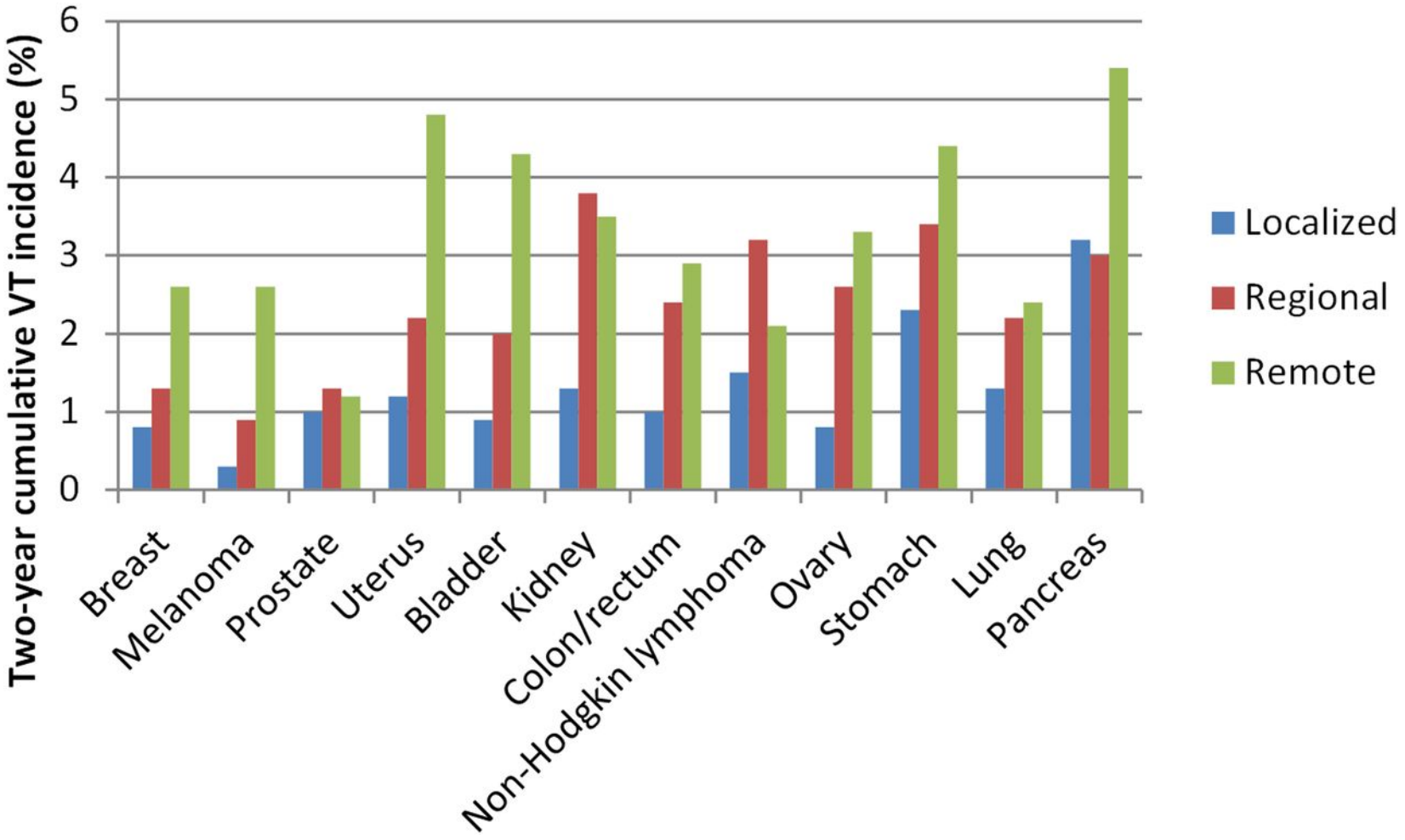
Incidence of VTE and Colon Cancer Stage



White RH et al. Thrombosis Research 120 Suppl. 2 (2007) S29-40

Two-year cumulative incidence (%) of venous thrombosis per type and stage of cancer.



Jasmijn F. Timp et al. Blood 2013;122:1712-1723

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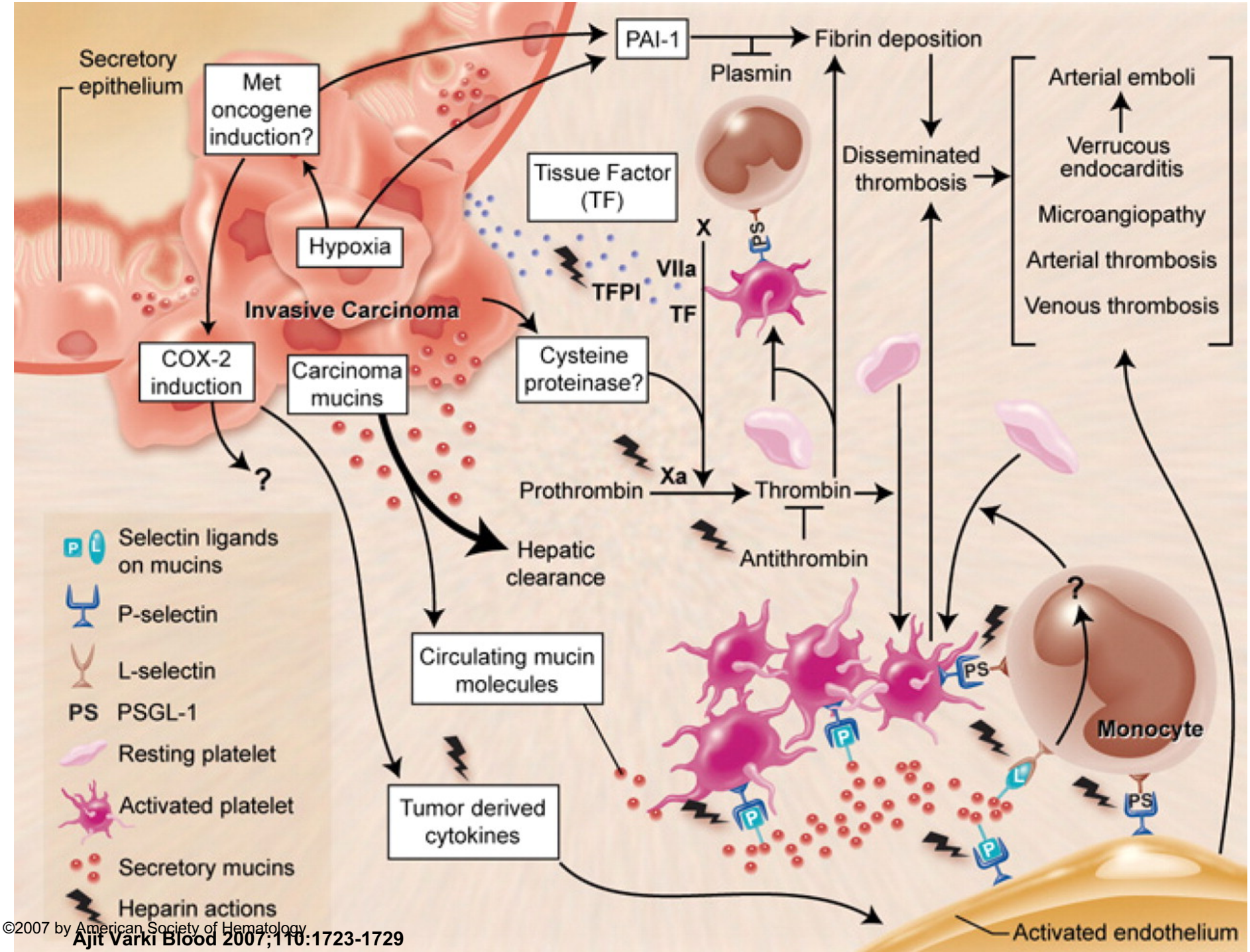


©2007 by American Society of Hematology
Ajit Varki Blood 2007;110:1723-1729

Thalidomide and Lenalidomide

- In myeloma increased thrombosis
- Rates 3% as single agent
- Up to 17% as combination treatment
- ?worse with anthracyclines

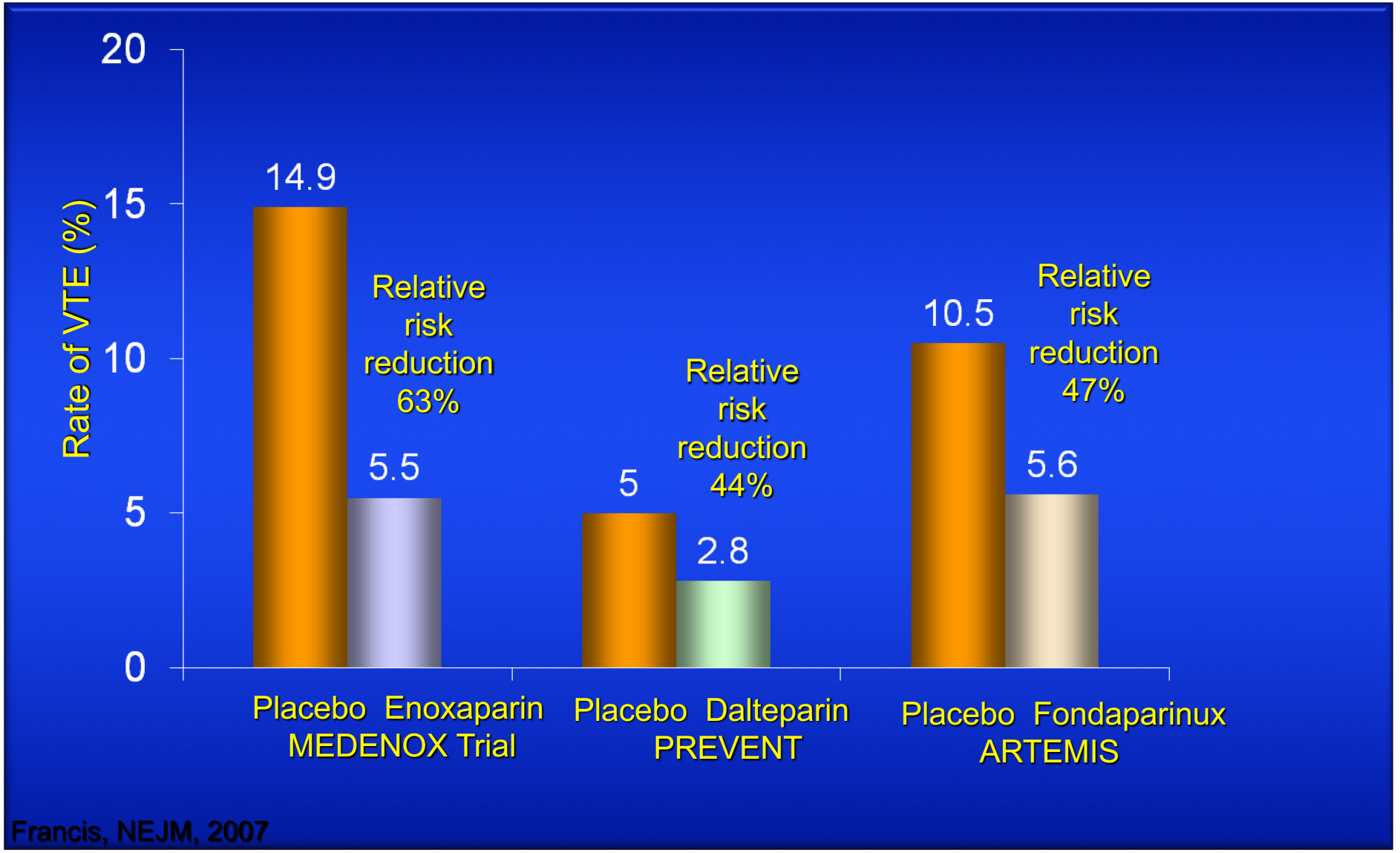
Thalidomide and Lenalidomide

- Increased tissue factor and vascular endothelial growth factor
- Downregulate thrombospondin causing cytokine-mediated, activated protein C resistance.
- Increase the levels von Willebrand factor and factor VIII.
- Regulates the level of the prothrombotic factor COX-2

Prevention

- Treatment of choice -LMWH
- Aspirin?
- Warfarin?

Prophylaxis Studies in Medical Patients



Francis, NEJM, 2007

Thromboprophylaxis

- For hospitalised medical or surgical patients
- No specific cancer patient trials for inpatients
- Not for outpatients unless assessed as high risk
- Cochrane review of 9 RCTs
- relative risk (RR) 0.66
- However, this analysis identified that 60 patients needed to be treated to prevent 1 episode of thrombosis
- Not for CV catheter patients- no proven benefit

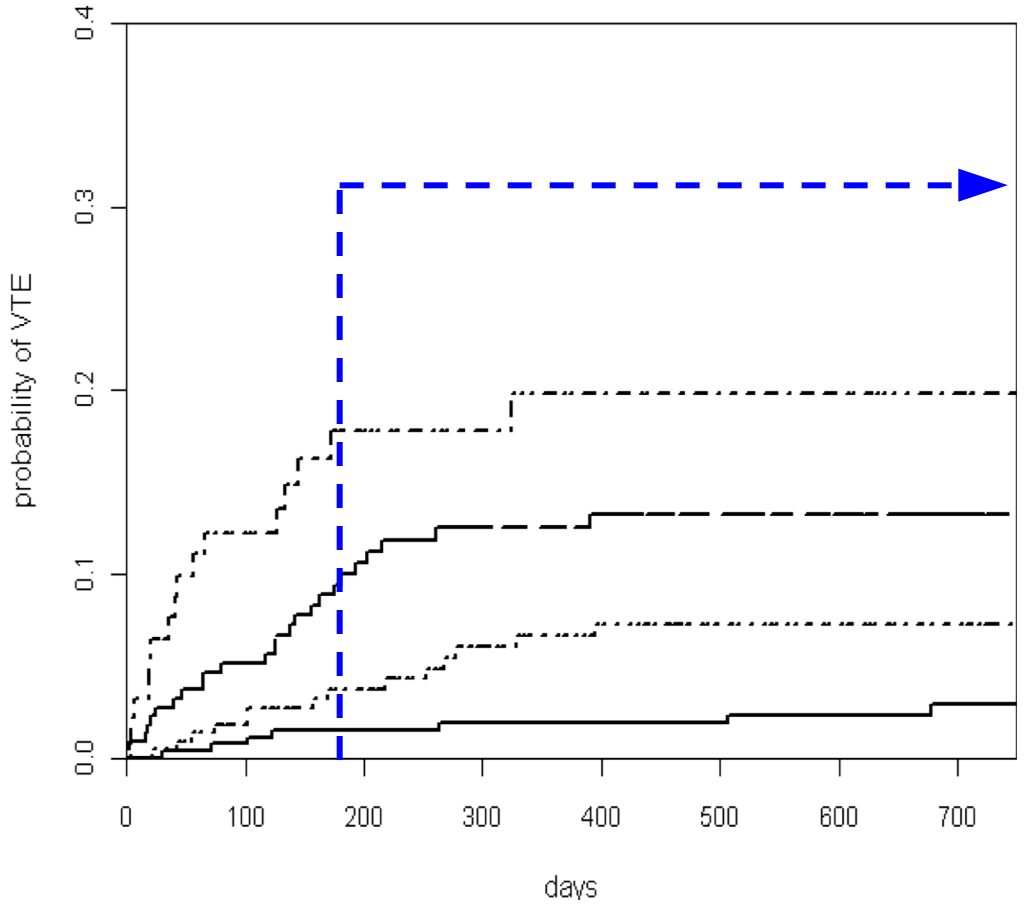
Khorana Model for Outpatients

Patient Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Pre-chemotherapy platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Prechemotherapy leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

Khorana et al. Blood 2008.

Khorana Model Validation

- Prospective follow up of 819 patients
- Median observation time/follow-up: 656 days



6-mo cumulative VTE rates:

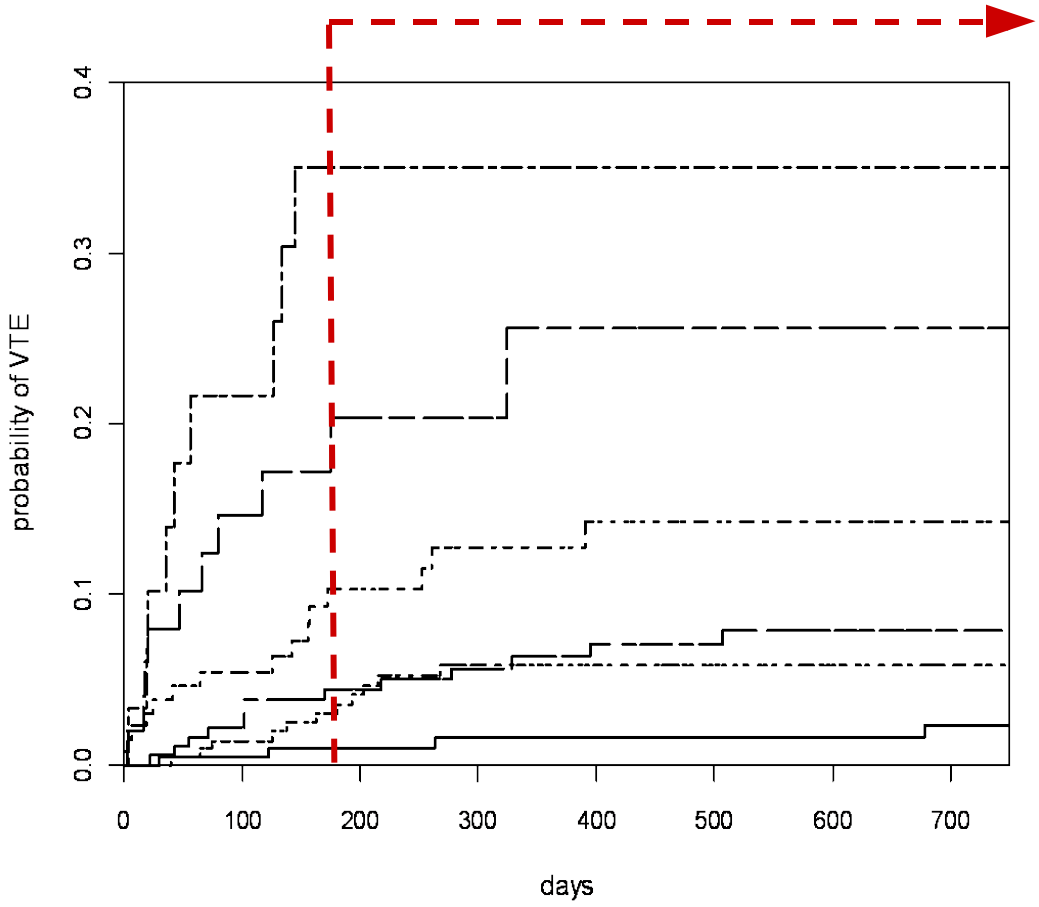
	Patients n	Events %
Score ≥3	93	17.7%
Score 2	221	9.6%
Score 1	229	3.8%
Score 0	276	1.5%

CANCERANDTHROMBOSISSTUDY

Ay et al Blood 2010.

Ay Model for Outpatients

- Addition of D-dimer and soluble P-selectin to Khorana model:



6-mo cumulative VTE rates:

	Patients, n	Events, %
Score ≥5	30	35%
Score 4	51	20.3%
Score 3	130	10.3%
Score 2	218	3.5%
Score 1	190	4.4%
Score 0	200	1.0%

CANCERANDTHROMBOSISSTUDY

Validation of score

- PROTECHT high risk patients were 11.1 % in the placebo arm and 4.5 %
- SAVE-ONCO, NNT was 25 for high-risk patients but 333 in low risk patients

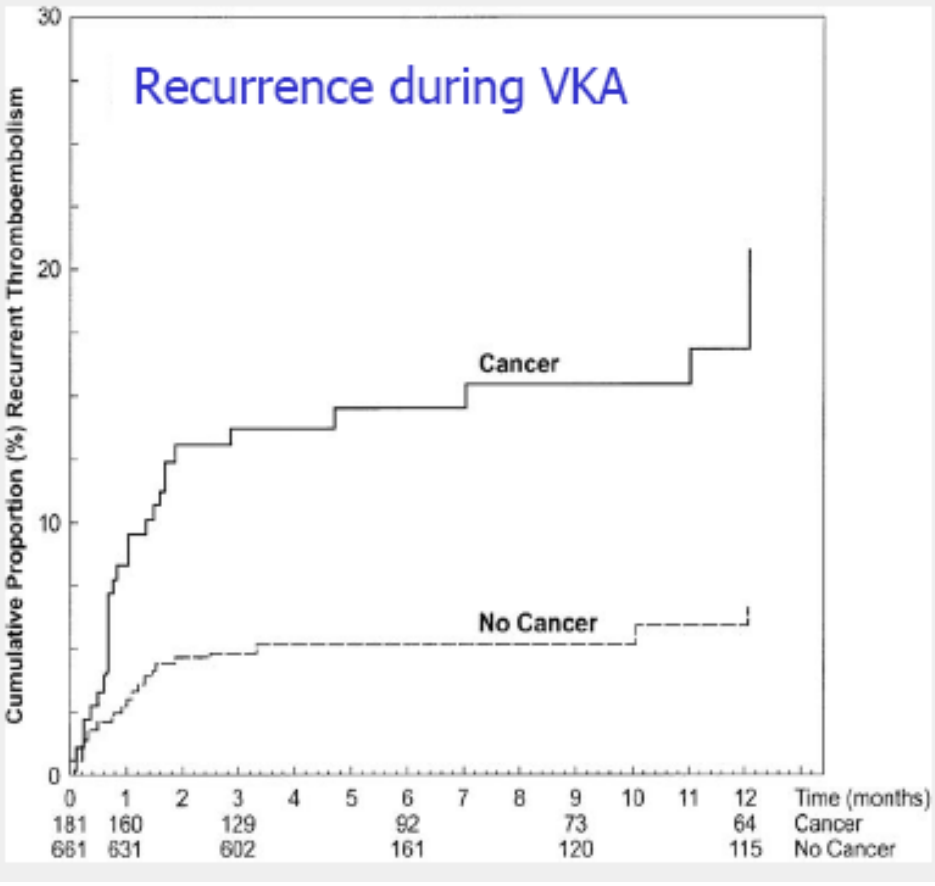
Treatment

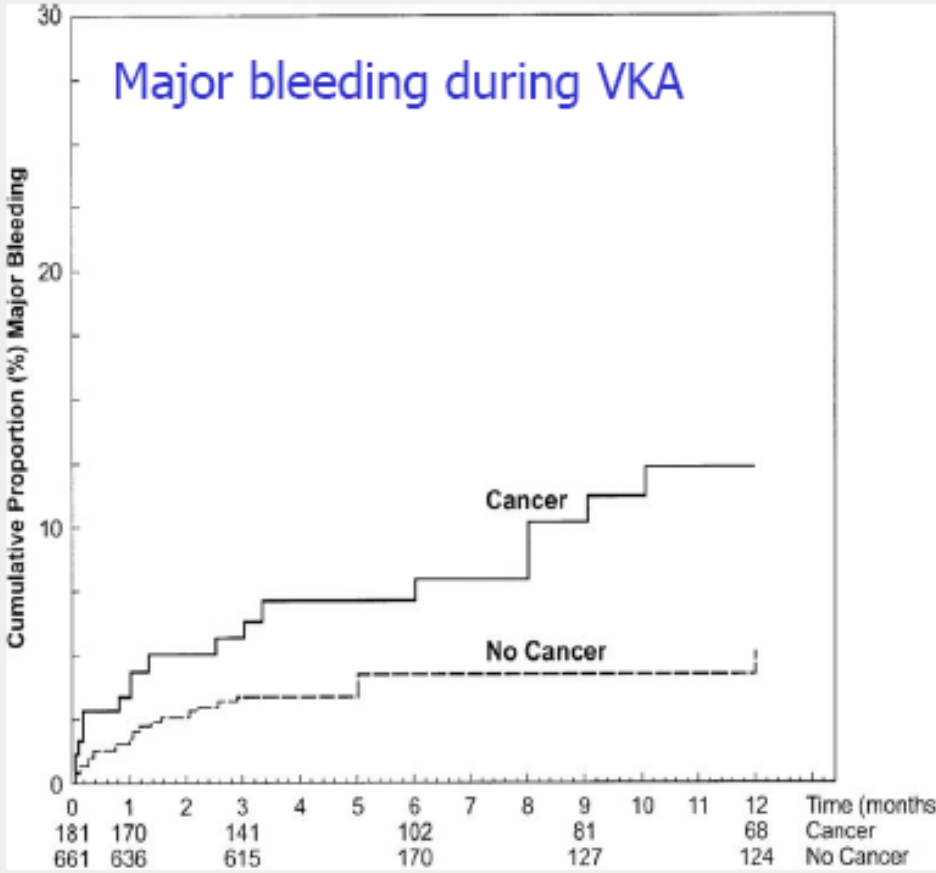
- American College of Chest Physicians (ACCP)
- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Network (NCCN)
- European Society for Medical Oncology (ESMO)
- International Clinical Practice Guidelines
- **Guidelines**Management and treatment of VTE* in cancer patients
- BSH

Warfarin

- Warfarin therapy is complicated by:
  - Difficulty maintaining tight therapeutic control, due to anorexia, vomiting, drug interactions, etc.
  - Frequent interruptions for thrombocytopenia and procedures
  - Difficulty in venous access for monitoring
  - Increased risk of both recurrence and bleeding

Warfarin


Recurrence during VKA
Cumulative Proportion (%) Recurrent Thromboembolism
30
20
10
0
Cancer
No Cancer
0 1 2 3 4 5 6 7 8 9 10 11 12 Time (months)
181 160 129 92 73 64 Cancer
661 631 602 161 120 115 No Cancer


Major bleeding during VKA
Cumulative Proportion (%) Major Bleeding
30
20
10
0
Cancer
No Cancer
0 1 2 3 4 5 6 7 8 9 10 11 12 Time (months
181 170 141 102 81 68 Cancer
661 636 615 170 127 124 No Cancer

Treatment of Cancer-Associated VTE-LMWH

Study	Design	Length of Therapy (Months)	N	Recurrent VTE (%)		Major Bleeding (%)		Death (%)	
CLOT Trial (Lee 2003)	Dalteparin OAC	6	336 336	9 17	0.002	6 4	NS	39 41	NS
CANTHENOX (Meyer 2002)	Enoxaparin OAC	3	67 71	11 21	0.09	7 16	0.09	11 23	0.03
LITE (Hull ISTH 2003)	Tinzaparin OAC	3	80 87	6 11	0.03	6 8	NS	23 22	NS
ONCENOX (Deitcher ISTH 2003)	Enox (Low) Enox (High) OAC	6	32 36 34	3.4 3.1 6.7	NS		NS		NR

LMWH

- In recurrence 90% response to increasing LMWH dose by 25-50%
- LMWH dose reduction is effective in patients with thrombocytopenia ($< 50 \times 10^9/L$)
  - consider platelet transfusion if VTE is acute
  - reduce dose to 50% if count $20 – 50 \times 10^9/L$
  - prophylactic or withhold dose if count $<20 \times 10^9/L$

IVC filters

- Not recommended in initial treatment of DVT or PE
- Routine insertion of filters in patients who are also anticoagulated does not alter the frequency of recurrent VTE or total mortality
- Venous thrombosis at the site of filter insertion sites is common- 10%
- If anticoagulant therapy contra-indicated, insert temporary filter and anticoagulate when contra-indication over

IVC filters

- Recurrence- Should only be considered after increasing the target INR/LMWH in recurrence on anti-coagulation
- Can be considered if surgery required within a month of VTE

BRIDGE study

- AF Bridging v no bridging with LMWH in surgery
- No increase in thrombosis in those not given LMWH
- Increase in bleeding 3.2 v 1.3%

What about the reverse?

- Should we be looking for cancer in those with VTE?
- Evidence is weak, guidance varies
- NICE says to consider an abdo pelvis CT and mammography
- No trials have shown a mortality benefit
- Simple lab tests CXR and clinical examination may be as good as more extensive investigations
- Expense, radiation, anxiety, low yield and unnecessary investigations should be considered

NOACS/OACS/DOACS

Novel/Direct/non Vitamin K oral anticoagulants

Current licensed drugs

- Direct thrombin inhibitors
- Dabigatran
- Xa inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

Current position

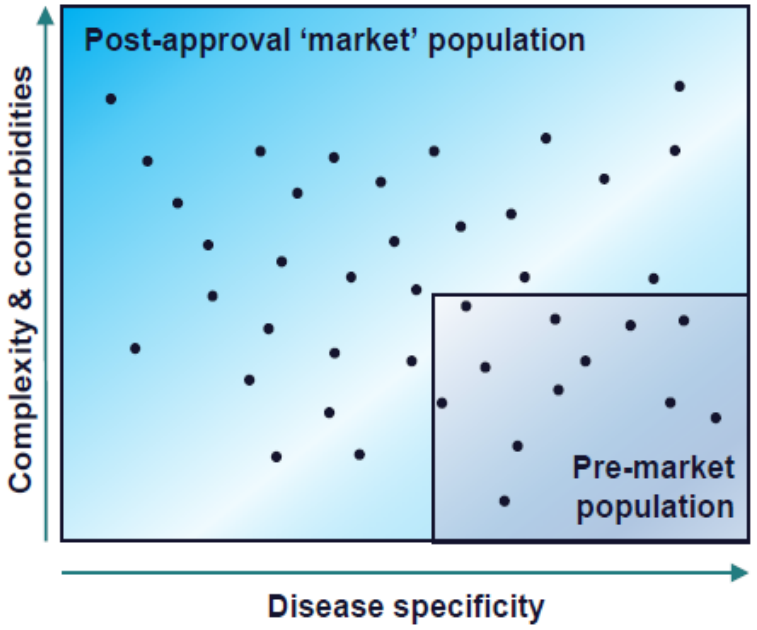
- Apixaban Dabigatran and Rivaroxaban licensed for THR and TKR, AF and VTE
- Edoxaban AF and VTE
- Rivaroxaban-licence for ACS reduction in stent thrombosis and cardiovascular death
- Apixaban failed to show benefit in ACS or medical admissions

DVT

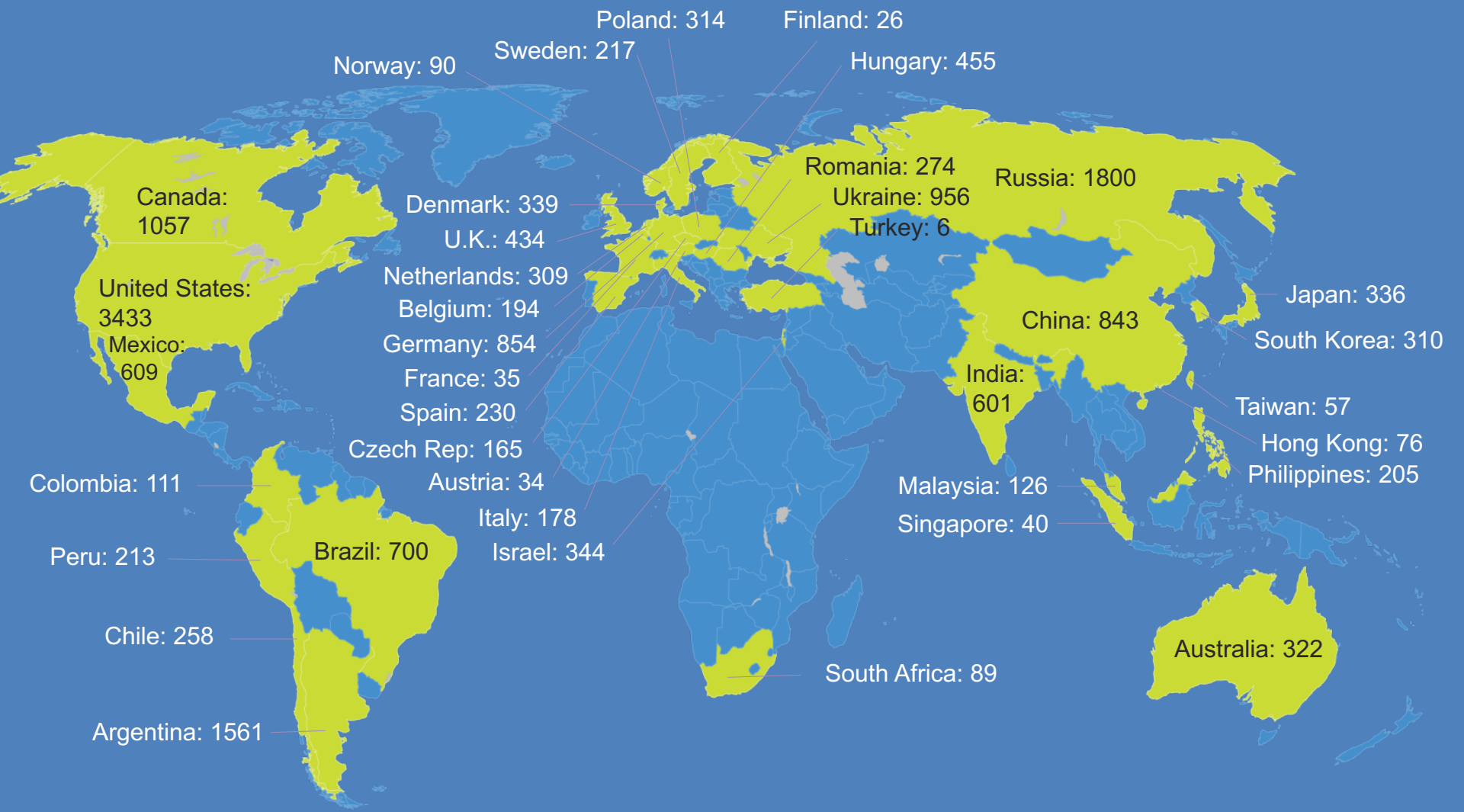
- Warfarin v NOAC
- Numbers comparible. Possibly slightly less bleeding

Challenges today:
Targeting innovative therapies at appropriate patients

- Patient populations vary greatly within disease groups, and this diversity is not always reflected in controlled clinical trials
- Innovative therapies should be assessed in representative sub-groups before implementation in diverse populations
- Understanding and targeting patients at greatest risk is necessary to reduce overall burden of disease most efficiently



Enrollment
18,201 patients, 1034 sites, 39 countries



Precautions

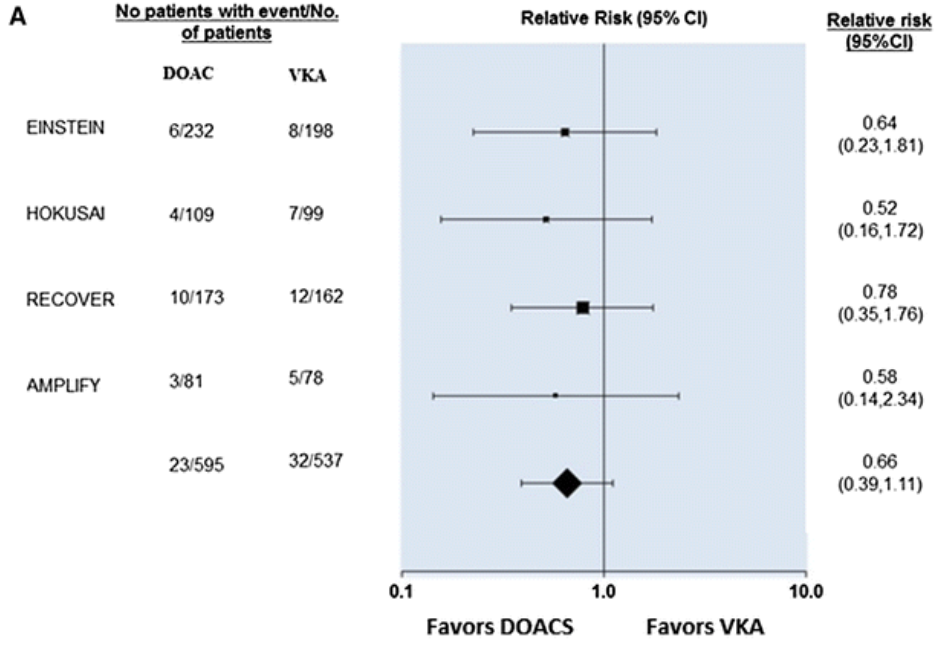
- Renal impairment CC<30ml/min
- Limited data on subgroups eg anti-phospholipids
- Not licensed for heart valves
- Apixaban, Rivaroxaban study didn’t show to LMWH equivalence in medical patients

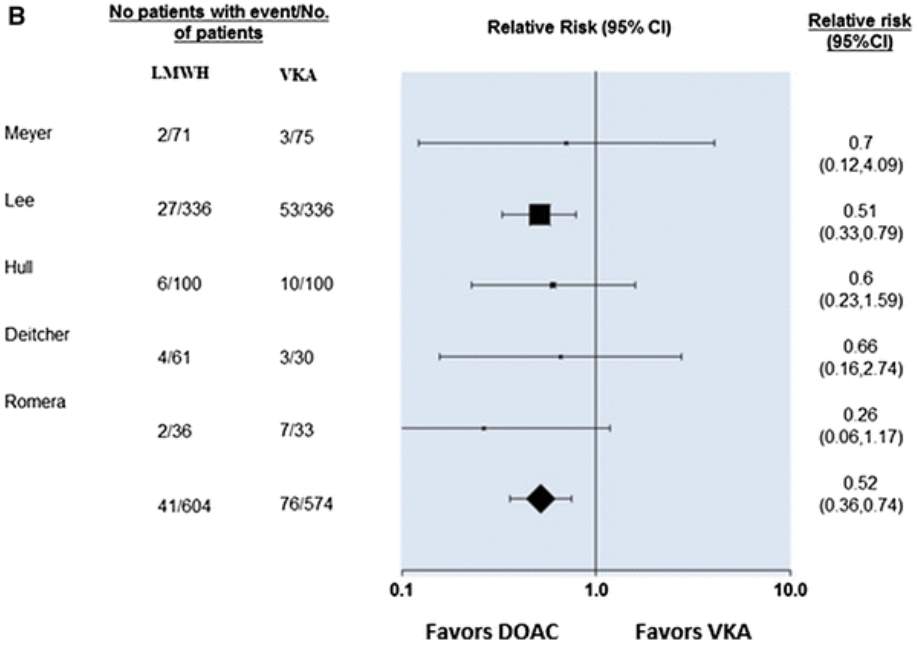
Reversal

- Relatively short half lives
- Only dabigatran has a specific reversal agent
- Idarucizumab
- For surgery, consult SPCs, consider renal function

In cancer

- Apixaban appears safe for primary prophylaxis in a phase 2 study- Not clear how this could be taken forward as no standard therapy for this group
- Phase 3 trial with apixaban- oral presentation, but not yet published

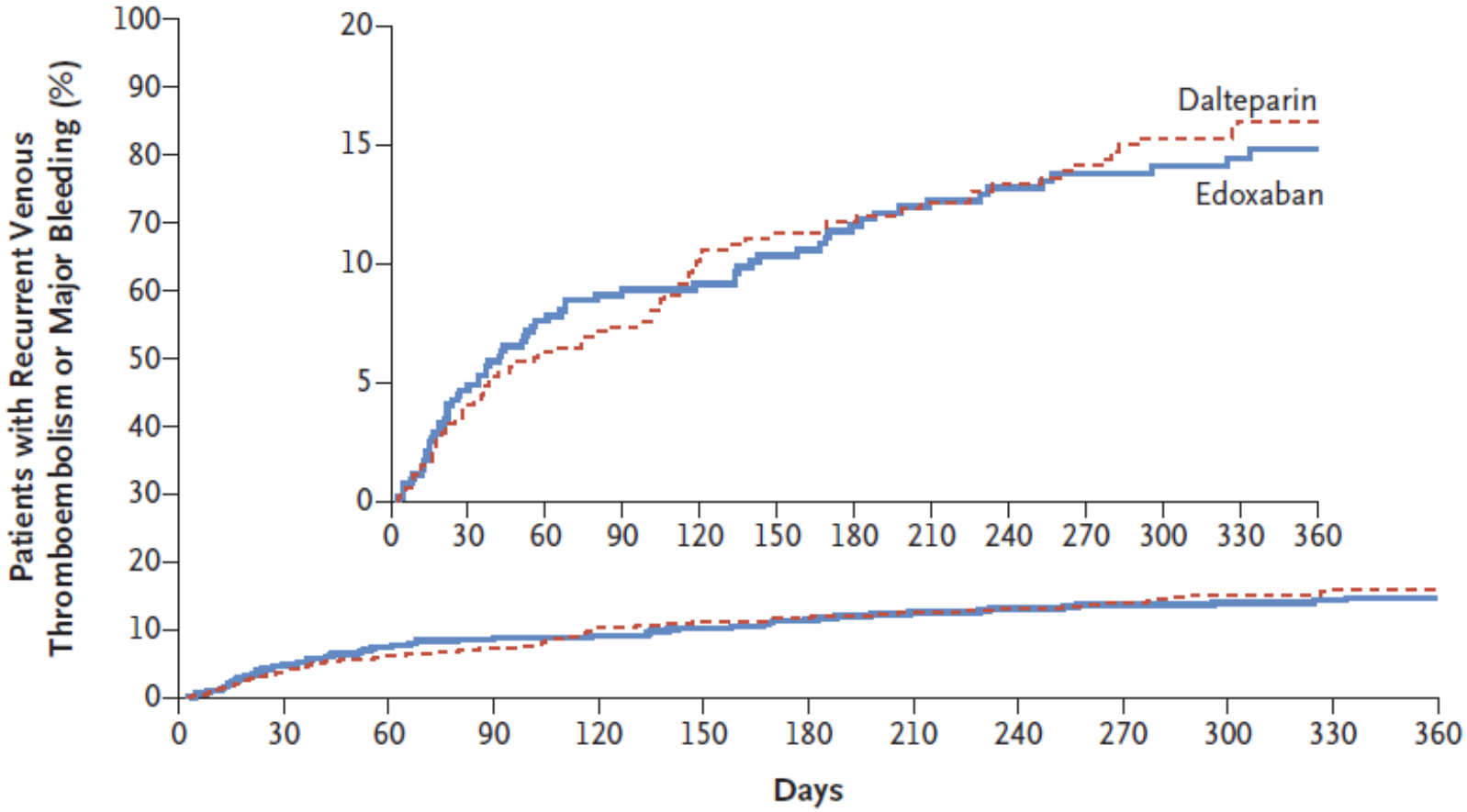

A
No patients with event/No. of patients
DOAC
VKA
Relative Risk (95% CI)
Relative risk (95%CI)
EINSTEIN
6/232
8/198
0.64 (0.23,1.81)
HOKUSAI
4/109
7/99
0.52 (0.16,1.72)
RECOVER
10/173
12/162
0.78 (0.35,1.76)
AMPLIFY
3/81
5/78
0.58 (0.14,2.34)
23/595
32/537
0.66 (0.39,1.11)
0.1
1.0
10.0
Favors DOACS
Favors VKA

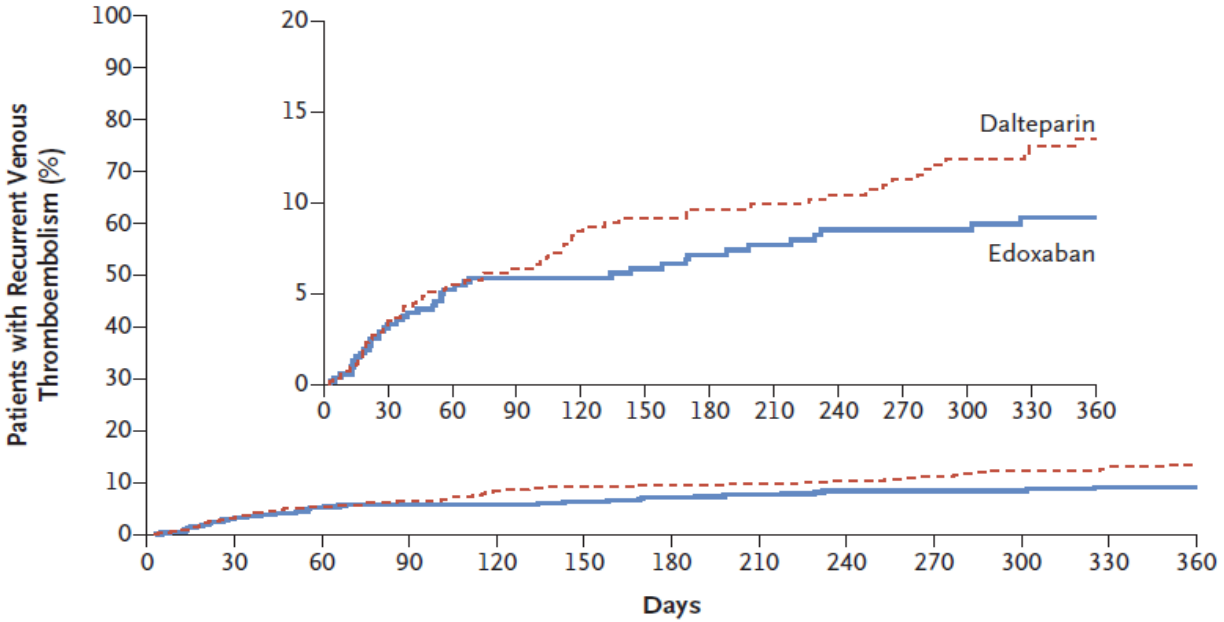

B
No patients with event/No. of patients
LMWH
VKA
Relative Risk (95% CI)
Relative risk (95%CI)
Meyer
2/71
3/75
0.7 (0.12,4.09)
Lee
27/336
53/336
0.51 (0.33,0.79)
Hull
6/100
10/100
0.6 (0.23,1.59)
Deitcher
4/61
3/30
0.66 (0.16,2.74)
Romera
2/36
7/33
0.26 (0.06,1.17)
41/604
76/574
0.52 (0.36,0.74)
0.1
1.0
10.0
Favors DOAC
Favors VKA

Meta-analysis of subgroups v VKA with cancer

- Trend towards less bleeding
- Similar recurrence rates
- BUT, not compared with standard of care in UK LMWH

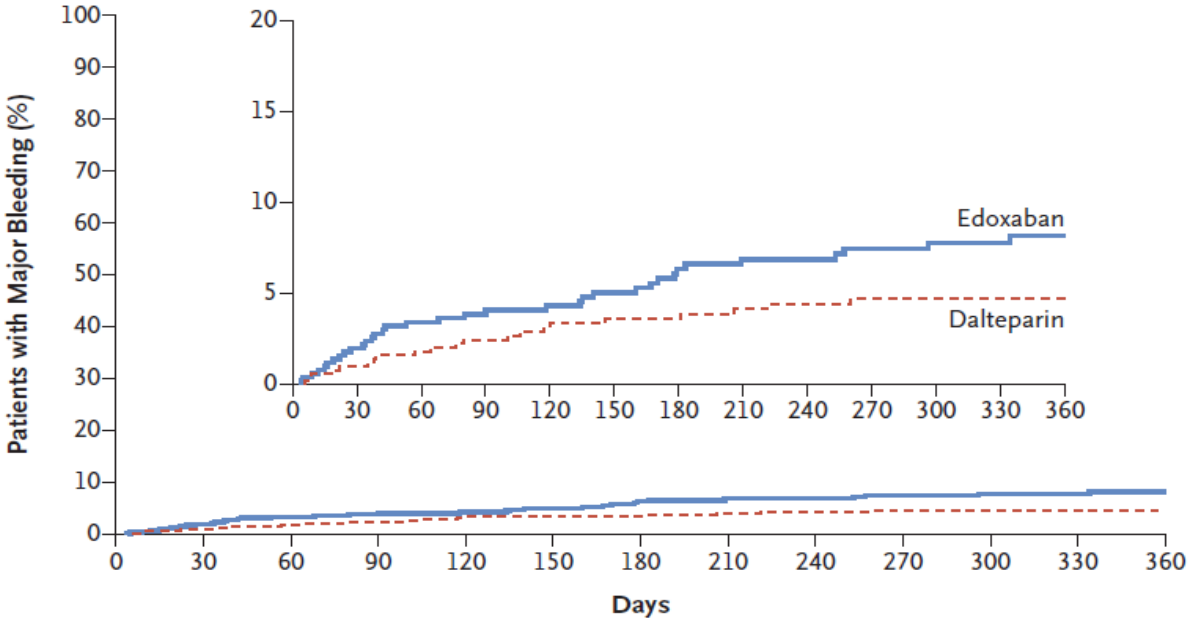
Edoxaban


Patients with Recurrent Venous Thromboembolism or Major Bleeding (%)
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
210
240
270
300
330
360
Days
20
15
10
5
0
Dalteparin
Edoxaban



o. at Risk

doxaban	522	480	437	415	395	370	356	340	320	307	281	245	168
alteparin	524	488	452	423	389	370	358	348	333	321	282	246	174



Current position with NOACS

- Not standard of care
- Could be considered where LMWH not appropriate
- Consider renal function and absorption
- Increased GI bleeding in trials, but decreased CNS bleeding
- Potential interaction with various chemo/drugs
- No routine monitoring of levels
- Further significant trials unlikely in view of going off patent 2019-20

Patients with AF and cancer

Both are common!

CH A_2DS_2 VASC

- Heart failure/LV dysfunction
- Hypertension
- Age >65 1 >75 2
- Diabetes
- Stroke/TIA/thromboembolism 2
- Vascular disease
- Female

Risk of stroke

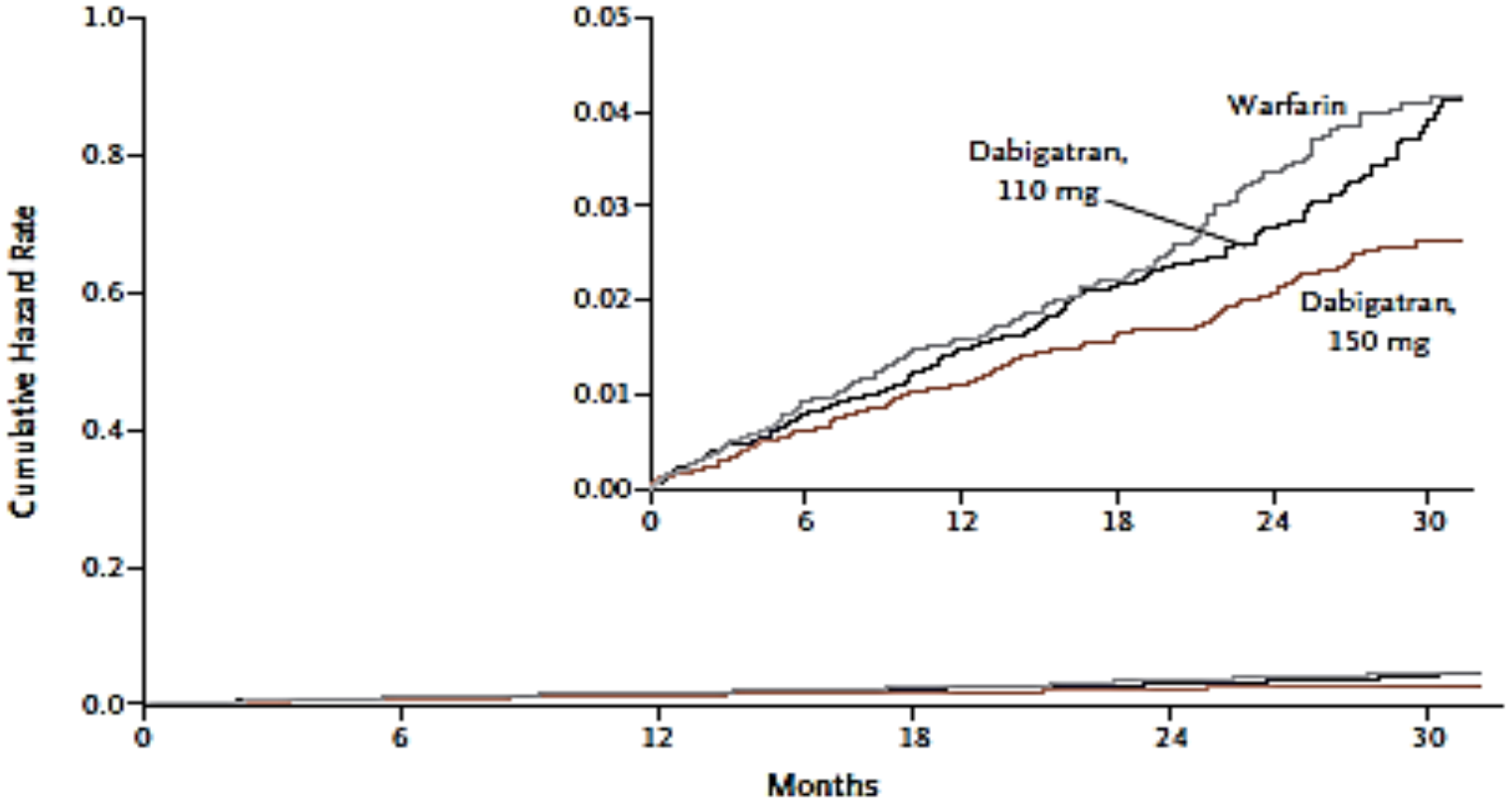
Score	% / yr
0	0
1	1.2
2	2.2
3	3.2
4	4
5	6.7
6	9.8

HAS-BLED score

Table 2. Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

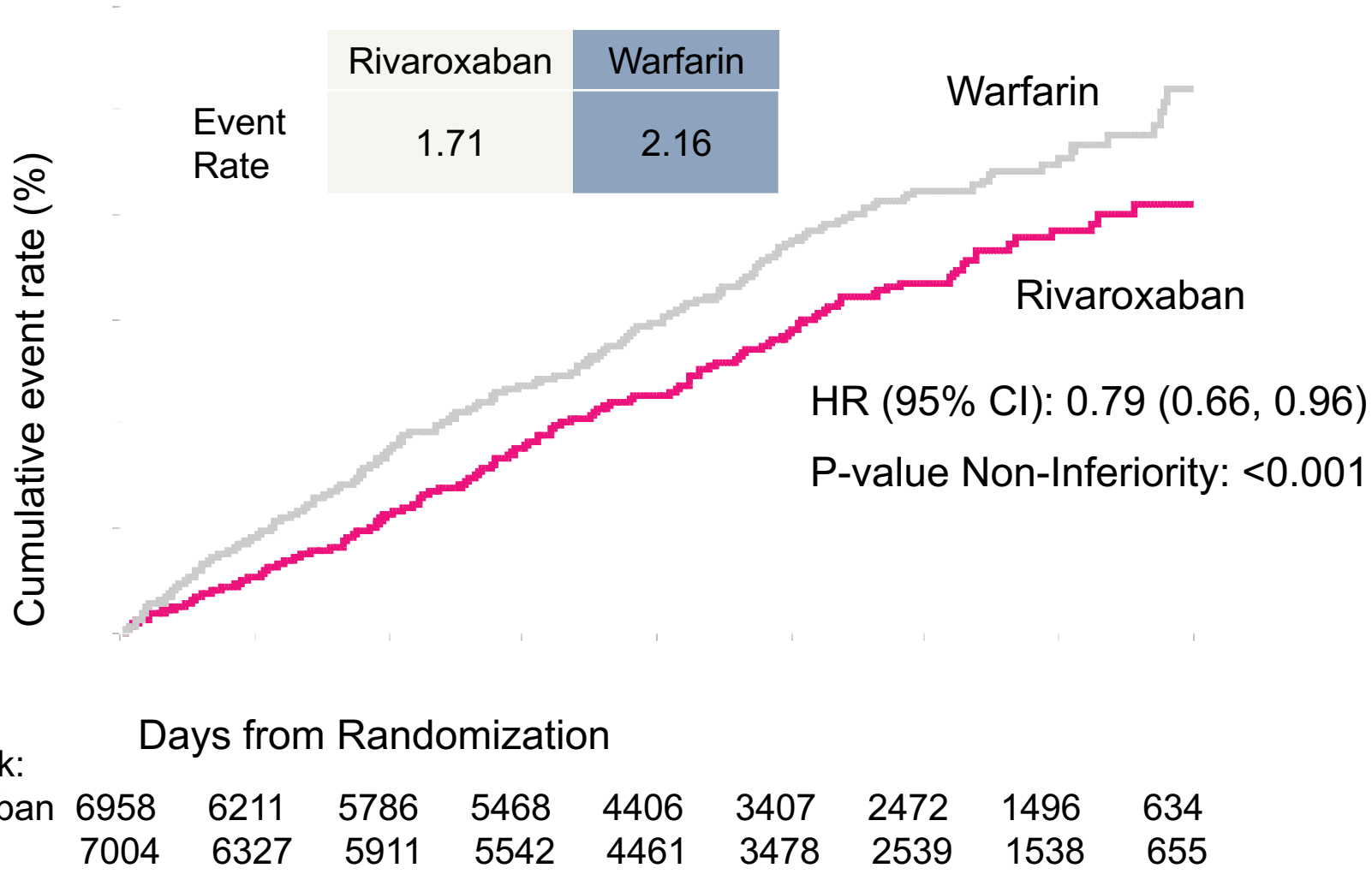
Dabigatran



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Rivaroxaban



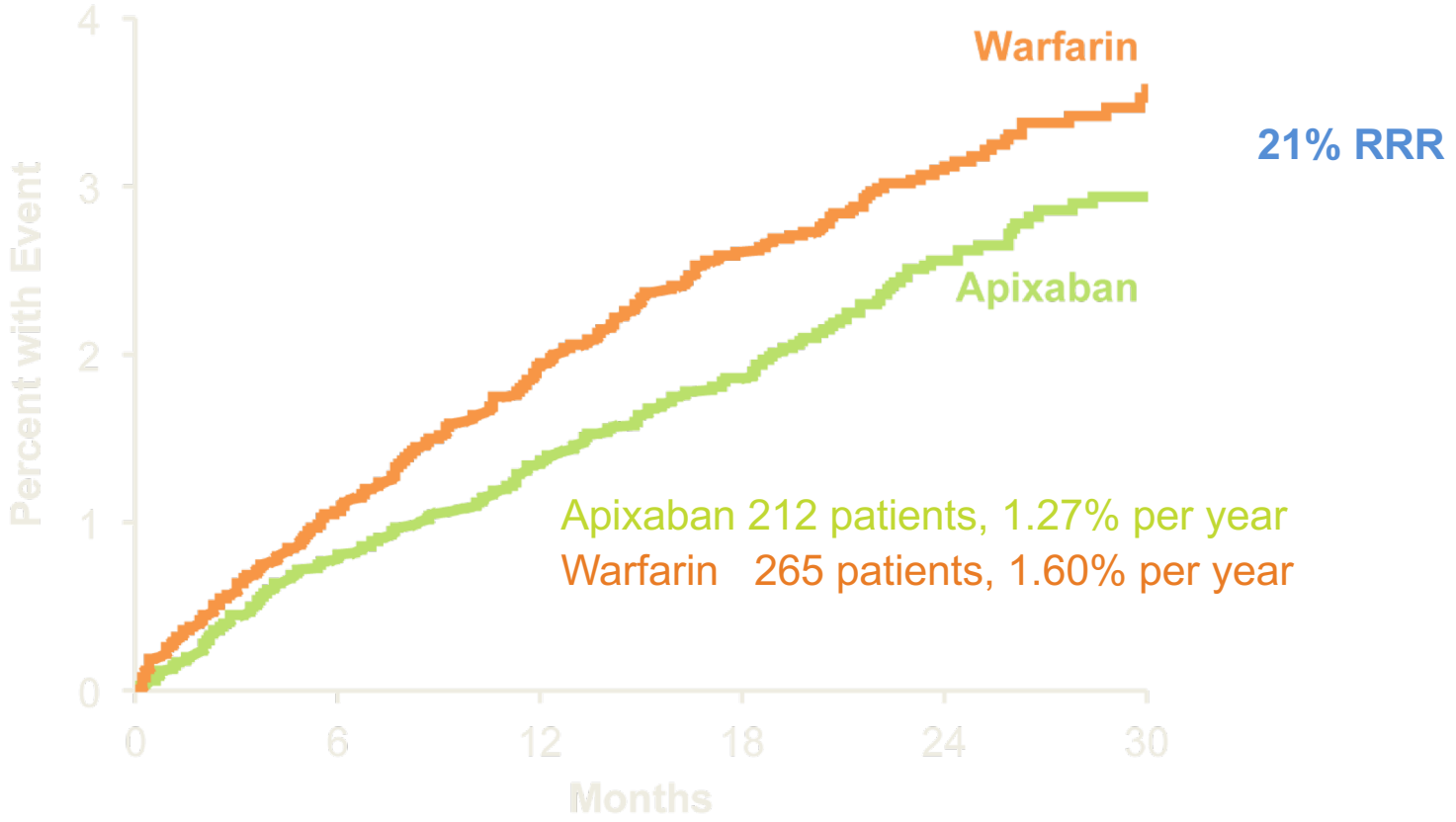
No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Apixaban

Stroke (ischemic or hemorrhagic) or systemic embolism



Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Thoughts?

- Individualised decisions
- Consider thrombosis risk, bleeding risk and overall prognosis
- Less evidence for LMWH
- ? Effect on cancer and risk of embolus

Thrombosis in Cancer

- VTE is a very common complication that increase morbidity and mortality in cancer patients
- Should we be using a risk model to estimate risk of VTE in ambulatory patients with new or progressive disease?
- Selected cancer patients benefit from extended prophylaxis after surgery
- Prophylaxis in hospitalized patients is a patient safety priority
- LMWH is the “best” agent available for prevention and treatment

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Laboratory Testing of DOAC's When, Why & How.

Directorate of Laboratory Medicine

Lynne Keighley

Introduction

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- The new/noval oral anti-coagulants have now been in use for a number of years.
- They are called DOACs Direct oral anticoagulants as they act directly on the coagulation factors unlike warfarin which reduces the production of vitamin K.
- However as heparin has been used since 1930's and warfarin since 1960's many of us still think of them as new.

How they work

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There are two types of DOAC

- Those which act directly on factor II Direct Thrombin Inhibitor. – Dabigatran (brand name Pradaxa)
- Those which act directly on factor X – Rivaroxaban, apixaban and edoxaban (brand names Xarelto, Eliquis and Savaysa)
- These are licensed for the treatment of AF and VTE, they are contra indicated in patients with mechanical heart valve replacement due to adverse events during trials.

Why do we need them

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- Warfarin is long lasting, can be given orally and reversed with vitamin K but requires regular monitoring
- Heparin is short acting and can only be given by intravenous or intramuscular injection.
- The new anticoagulants can be given orally and do not require monitoring but occasionally require measuring.

When would we measure levels?

- In cases of prolonged or life threatening bleeding .
- Before emergency surgery when the patient has taken the drug in the last 24hrs or has reduced creatinine clearance
- Assessment of compliance
- Other drug interaction
- Extremes of body weight
- Deteriorating renal function
- Overdose

Why do we need specific assays?

Direct Thrombin Inhibitor

- PT is variable in its response to dabigatran.
- aPTT can be used to determine the degree of anticoagulation due to dabigatran but not the drug level.
- Thrombin time is too sensitive to determine degree of anticoagulation but a normal TT excludes the presence of dabigatran

Factor X inhibitors

- PT or aPTT can be used to determine the degree of anticoagulation due to rivaroxaban/apixaban/edoxaban but is inconsistent.
- PT is usually more sensitive but varies with reagents.
- No effect on the Thrombin time .

Dabigatran

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- Back in Sept 2011 we were tasked with setting up an assay for dabigatran measurement.
- Dabigatran is a direct thrombin inhibitor with a half life of 14-17 hours, it is renally excreted and its half life is prolonged in renal impairment.
- The recommended method is a calibrated dilute thrombin time.
- We chose the Hyphen Biomed Direct Thrombin Inhibitor assay with dabigatran calibrators and controls.

How the assay works

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- The Dabigatran in a sample inhibits the function of factor II to such a degree that a thrombin time will be >240secs at therapeutic levels of dabigatran.
- To overcome this the calibrator, control or patient plasmas are diluted.
- The diluted sample to be measured is mixed with normal pooled plasma and we measure the inhibitory affect of the dabigatran in the sample to prolong the thrombin time of the pooled plasma.
- Comparing control and patient clotting times to a calibration plasma gives us the level of circulating drug.

Case study 1 Patient AM

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- A 73yr old female with a new diagnosis of AF started on dabigatran
- She is seen in A&E with a diagnosis of unwell and abnormal clotting results, we queried the results and suggested repeat samples.
- Presents four days later with an acute GI bleed.

	29/11	4/12	5/12	6/12	7/12	11/12	18/12
PT secs	45.2	36.5	23.2	18.8	19.3	15.3	
APTT secs	90.4	74.8	60.5	46.9	35.9	32.1	
TT secs		>240	184.6	149.6	102.7	26.2	16.9
Dabig level ng/ml		317	157		10.6		
Red cells		3 units	2 units				
Plats		1 unit	1 unit				
PCC		3000iu	3000iu				

Rivoroxaban, Apixaban, Edoxaban

- These are a factor X inhibitors with a half life of 10-12hrs. In elderly patients, this may be prolonged. They are measured using an anti Xa method.
- Specific calibrators and controls are required but we use our “Hyphen Biomed liquid Xa kit”
- As this is on board our analysers 24/7 we are easily able to perform Rivaroxaban levels urgently.

How the assay works

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- The heparin anti-Xa assay is a chromogenic assay for the determination of anti-Xa activity in human plasma.
- The method is a one-step reaction based on a principle of competition; as soon as factor Xa is added to the plasma-substrate mixture, two reactions take place simultaneously, namely:
- – hydrolysis of the substrate by factor Xa
- – inhibition of factor Xa by rivaroxaban, apixaban or endoxaban.
- After the necessary period of time for the competitive reaction to reach equilibrium, the quantity of paranitroaniline (chomogenic substrate) that is released is inversely proportional to the concentration of anti-coagulant present in the sample or control.
- Specific calibrators are used to produce a calibration curve.

Patients

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- We have done a number of patients on rivaroxaban and there is no consistency in PT and APTT results. Hence the need for specific assays.

	Patient 1 pre (Lupus)	Patient 1 post (Lupus)	Patient 2 pre (VTE)	Patient 2 post (VTE)	Patient 3 pre (AF)	Patient 3 post (AF)
PT secs	17.2	33.9	14.0	39.0	14.1	18.8
APTT secs	47.6	81.3	23.8	30.5	34.6	46.9
Rivaroxaban ng/ml	37.5	249.8	40.7	698	34.0	229.2
Factor VIII			440u/dl			

Laboratory Medicine.

Case study 2
Patient AL

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- A 91yr old female with a diagnosis of AF on Rivaroxaban
- Admitted following a fall and needing to go to theatre # NOF.
- Readmitted 3 months later with further fracture.

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Patient AL	14/7	15/7	17/7		14/10	15/10 am	15/10 pm	16/10
PT secs	16.4	13.7	12.8		18.3			
APTT secs	29.4	31.6	31.7		41.2			
Rivaroxaban ng/ml	65.2	47.9	18		447.9	154.1	119.6	48.3
Creatinine umol/L	146	317	157		140	156		139

Laboratory testing of DOACs. When, Why & How. Directorate of Laboratory Medicine.

Further information

- Due to renal impairment and recurrent fractures/falls the patient anti-coagulation was changed to warfarin.

Case study 3
Patient KM

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NHS Foundation Trust

- 78yrs old female patient started on Apixaban following a DVT in February.
- Presented in May with a further query DVT.
- One week later admitted with GI bleeding.

Patient KM	22/5	24/5	25/5
PT secs	13.5	10.7	10.9
APTT secs	25.3	19.6	18.8
Apixaban ng/ml	>800		81.6
Creatinine umol/L	123	128	127
PCC	3000iu		

Case study 4
Patient MA

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NHS Foundation Trust

- 91yrs old female patient on Rivaroxaban.
- Presented with a large haematoma and a haemoglobin of 44g/L

Patient MA	11/8	12/8	15/8
PT secs	13.6		10.5
APTT secs	40.7		23.9
Rivoroxaban ng/ml	443.8	46.4	12.4
Creatinine umol/L	163	156	
PCC	3000iu		
Red cell	5 units		

Laboratory testing of DOACs. When, Why & How. Directorate of Laboratory Medicine.

Follow up

- Converted to LMWH
- Diagnosed with new DVT on 23/8
- Warfarin commenced.

The future of DOACs

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- There are more “new” anticoagulants awaiting approval and we may have to provide assays for them all!
- Some patient groups will remain on warfarin eg valve replacements.