VTE

The evolution of anticoagulation in primary care

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Objectives

1. Identify and assess DVTs
   - Know when to treat
   - Know when to refer
   - Understand the treatment goals
   - Assess risk of recurrence
2. Treatment decisions

How many deaths are related to VTE annually in Australia?

a. 500

b. 1000

c. 2000

d. 5000

e. 50,000

How many deaths are related to DVT or PE annually in Australia?

a. 500

b. 1000

c. 2000

d. >5000

e. 50,000

VTE – Burden of disease

- Over 14,000 cases of DVT/PE in Australia every year, resulting in more than 5000 DVT/P-related deaths
- Risk increase with age – 1% annual incidence in those over the age of 60
- Despite adequate treatment, VTE often recurs with estimated recurrence rate of 13% annually

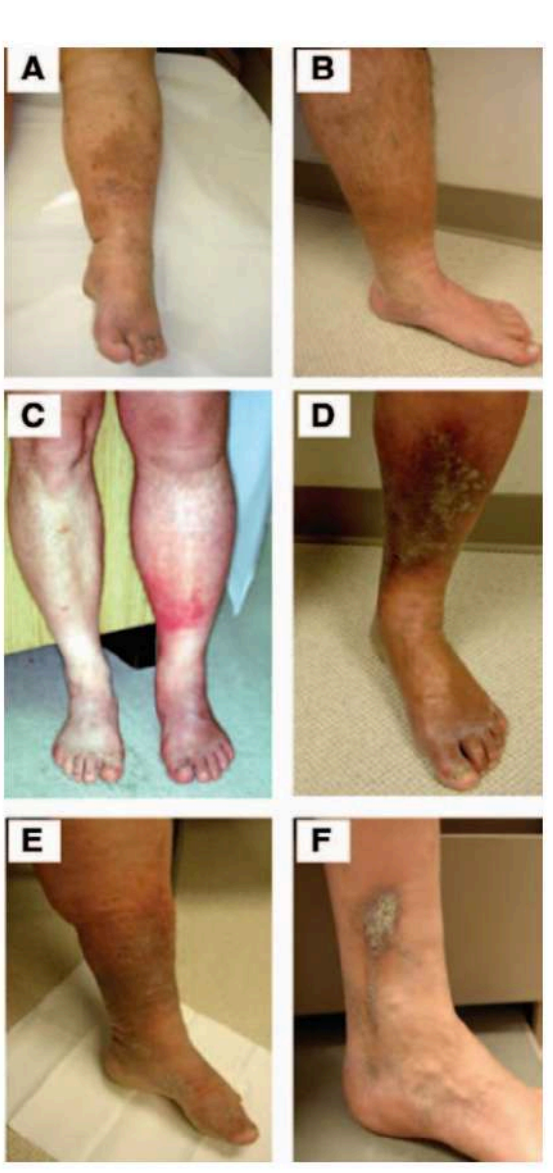
References: 1. Access Economics. The burden of venous thromboembolism in Australia, 2008. 2. Ho WK *et al. Med J Aust* 2008; **189:** 144-47. 3. Ho WK *et al. Med J Aust* 2005; **182:** 476-481.

VTE – Burden of disease

Post Thrombotic Syndrome

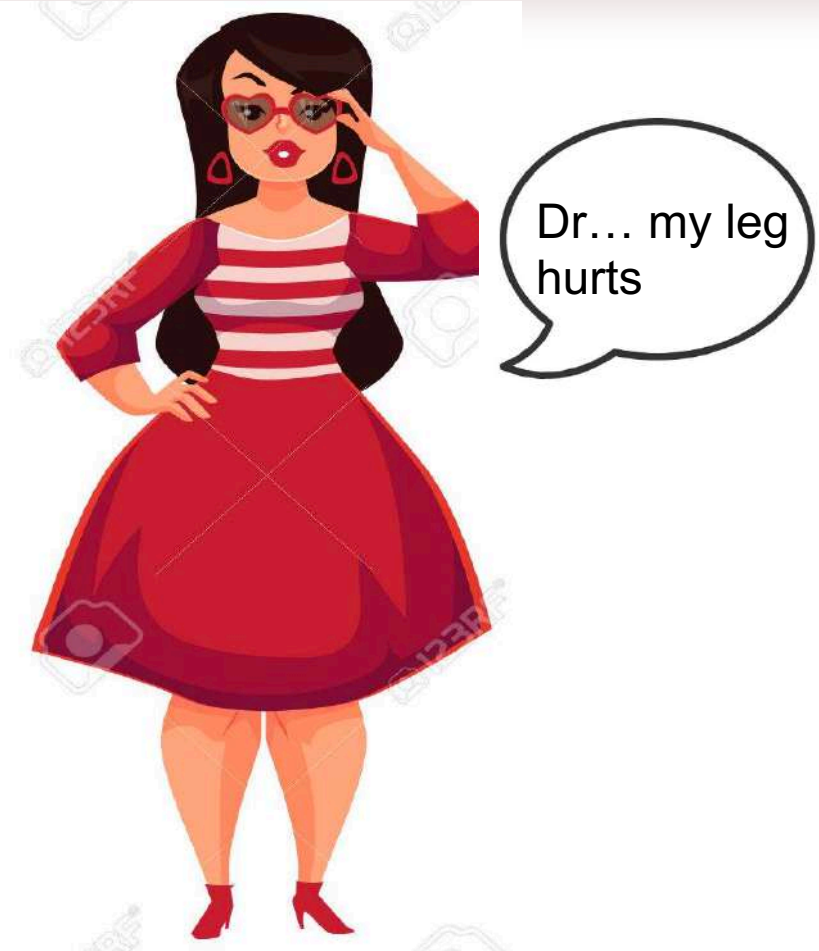
Table 2. Clinical Characteristics of PTS

Symptoms	Clinical Signs
Pain	Edema
Sensation of swelling	Telangiectasia
Cramps	Venous dilatation/ectasia
Heaviness	Varicose veins
Fatigue	Redness
Itching	Cyanosis
Pruritis	Hyperpigmentation
Paresthesia	Eczema
Bursting pain	Pain during calf compression
Venous claudication	Lipodermatosclerosis
	Atrophie blanche
	Open or healed ulcers



Pulmonary hypertension

Ms Vivien Leiden



Age: 43

History: G2P2, cholecystectomy in 2014

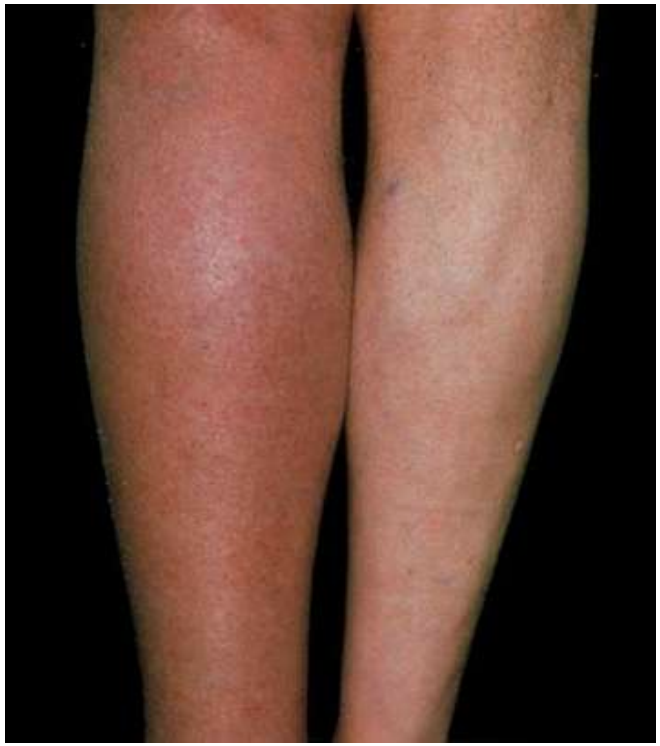
Weight 89kg, BMI 32

Smoker; 20 daily, ~20 yrs

Additional history:

- No personal history of VTE
- Mother died of a PE post surgery
- Factor V Leiden homozygote
- No OCP/HRT

Ms Leiden



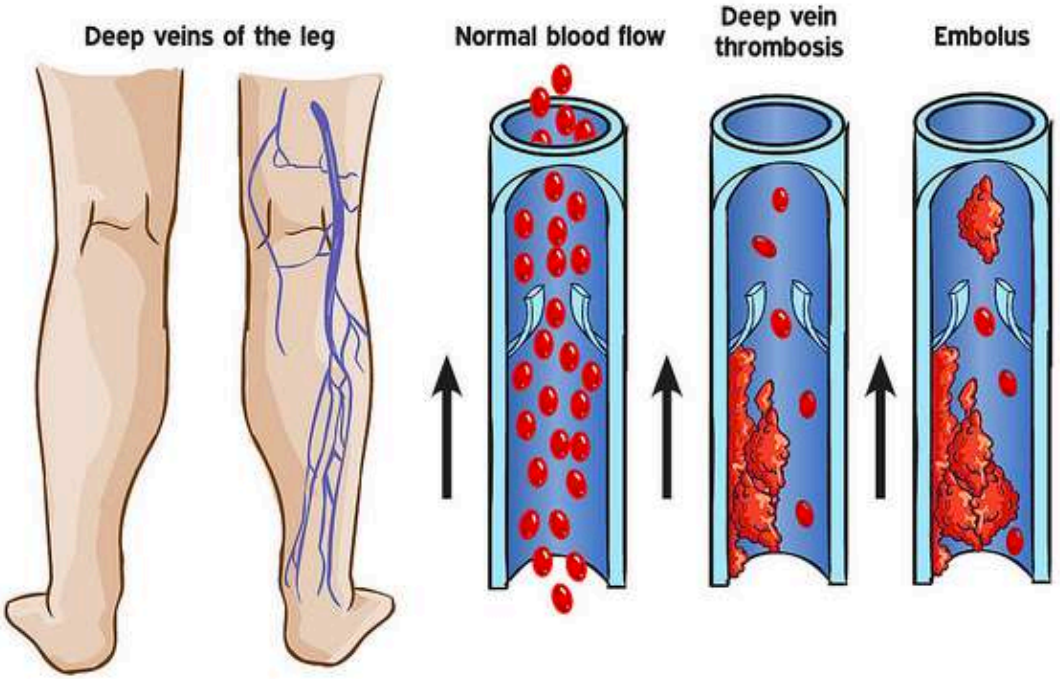
Examination:

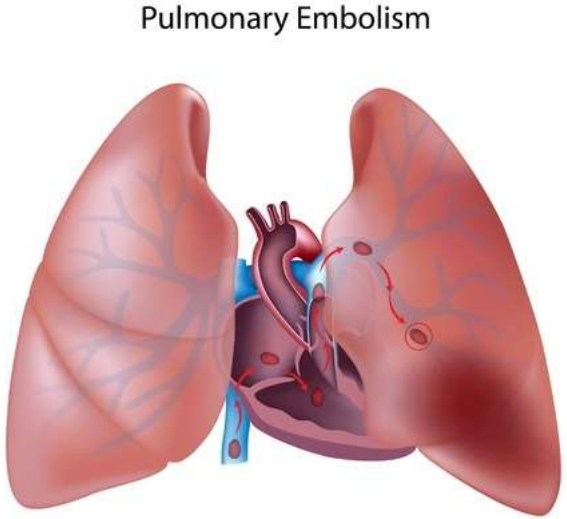
- Tender and warm R) calf
- 2cm increase in R) calf circumference
- No varicosities

Additional history:

- No recent surgery, immobilisation or long-distance travel
- No personal history of VTE
- Factor V Leiden heterozygote
- No OCP/HRT

VTE:


Deep veins of the leg
Normal blood flow
Deep vein thrombosis
Embolus


Pulmonary Embolism

VTE: Signs and Symptoms

DVT

- Swelling
- Pain
- Erythema
- Heaviness
- Skin changes

PE

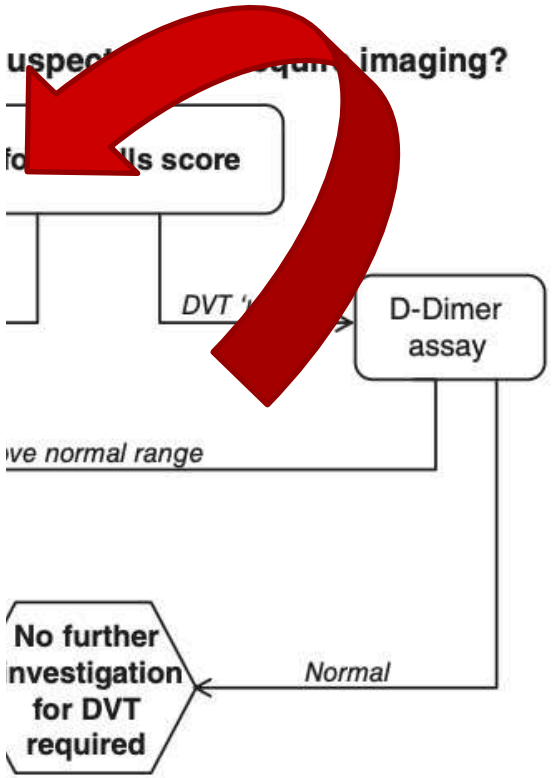
- Shortness of breath
- Chest pain (pleuritic)
- Pre-syncopal / syncopal
- Palpitations
- Hemoptysis
- Hypoxia / tachycardia / tachypnoea

VTE Diagnosis

Table 3 Wells score for deep vein thrombosis (DVT)

Factors	Points awarded
Active malignancy	+1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring regional or general anaesthesia	+1
Localised tenderness along the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling at least 3 cm larger than that on the asymptomatic side	+1
Pitting oedema confined to the symptomatic leg	+1
Collateral superficial veins (non-varicose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	−2
Clinical probability of DVT	Total score
Unlikely	<2
Likely	≥2

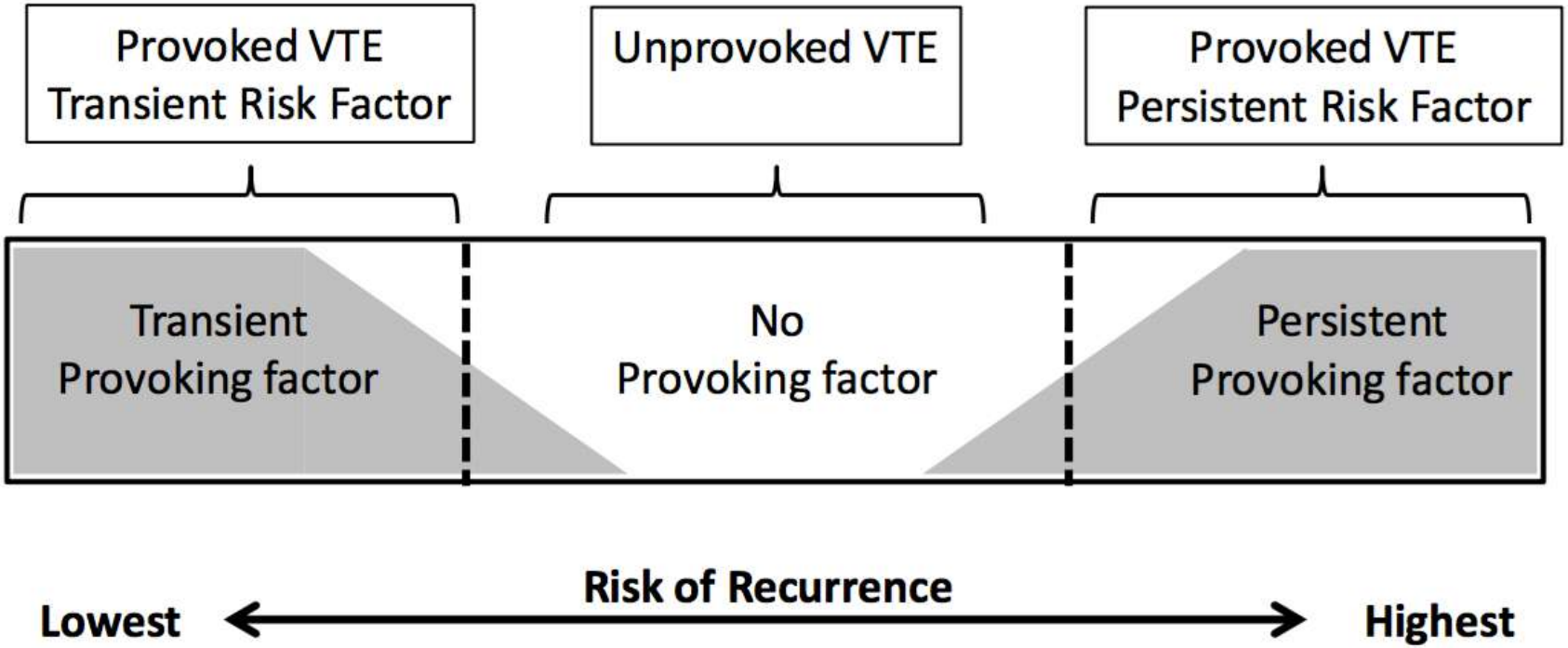
Adapted from Goergen *et al.*[20]



for suspected deep vein thrombosis.

Why categorise VTE?

Distal DVT → Proximal DVT → PE



Kearon C *et al. J Thromb Haemost* 2016; **14**: 1480-3

Categorising DVT appropriately

- **Provoked** by an acquired (environmental) risk factor 60%-70%
  - **Transient Provoking factors**
    - Major: surgery >30 min, hospitalisation >3 days, c-section
    - Minor: surgery <30 min, hospitalisation <3 days, leg injury, travel (>8hr), hormonal (OCP, pregnancy, HRT)
  - **Persistent Provoking factors**
    - Active cancer, APS, paralysis
    - Inflammatory bowel disease, Autoimmune disease
  - **Other environmental risk factors to consider**
    - Older age, gender, obesity, thrombophilia, paralysis
- **Unprovoked** 20%-30%

Kearon C *et al. J Thromb Haemost* 2016; **14**: 1480-3

Risk factors for VTE

TABLE 1. Risk Factors for VTE[10]

Strong	Moderate	Weak
• Fracture of pelvis, hip, or long bones of leg • Hip or knee arthroplasty • Major general surgery • Major trauma • Spinal cord injury	• Arthroscopic knee surgery • Central venous lines • Congestive heart failure • Estrogen therapy • Malignancy • Paralytic stroke • Pregnancy/postpartum • Genetic thrombophilia	• Bed rest >3 days • Prolonged immobility • Age • Laparoscopic surgery • Obesity • Varicose veins

Adapted from Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation.* 2003;107(23 suppl 1):I9-I16. doi: 10.1161/01.CIR.0000078469.07362.E6.

Ms Leiden – Audience discussion

What would you do next?

a. DVT is quite unlikely - treat as cellulitis

b. DVT is quite likely. Order CUS, FBC, Coag and EUC, LFT, D-dimer and follow up later in the day

c. DVT is quite likely. Initiate LMWH and order CUS

d. Commence NOAC while waiting for CUS

e. Manage conservatively with compression stockings, NSAID and rest

Ms Leiden

CUS report: consistent with an occlusive **popliteal DVT**

Categorising DVT appropriately - location

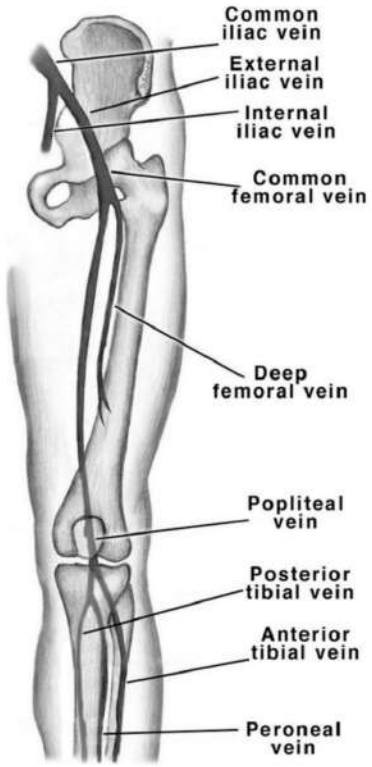
Proximal

- 'above the knee' DVT
- located in the **popliteal**, femoral, or iliac veins

Distal

- 'below the knee' or calf DVT, has no proximal component
- confined to peroneal, posterior, anterior tibial and muscular veins

The (superficial) femoral vein is a deep vein and not part of the superficial venous system[1]



Ms Leiden - discussion

How would you manage Mr Leiden?

a. Continue/initiate LMWH, ensure all baseline blood tests are performed, reviewed, discussed then refer to a specialist

b. Refer to ED immediately

c. Commence treatment with a DOAC and make follow up arrangements

d. Send home to rest and elevate leg, request repeat CUS in 3 days

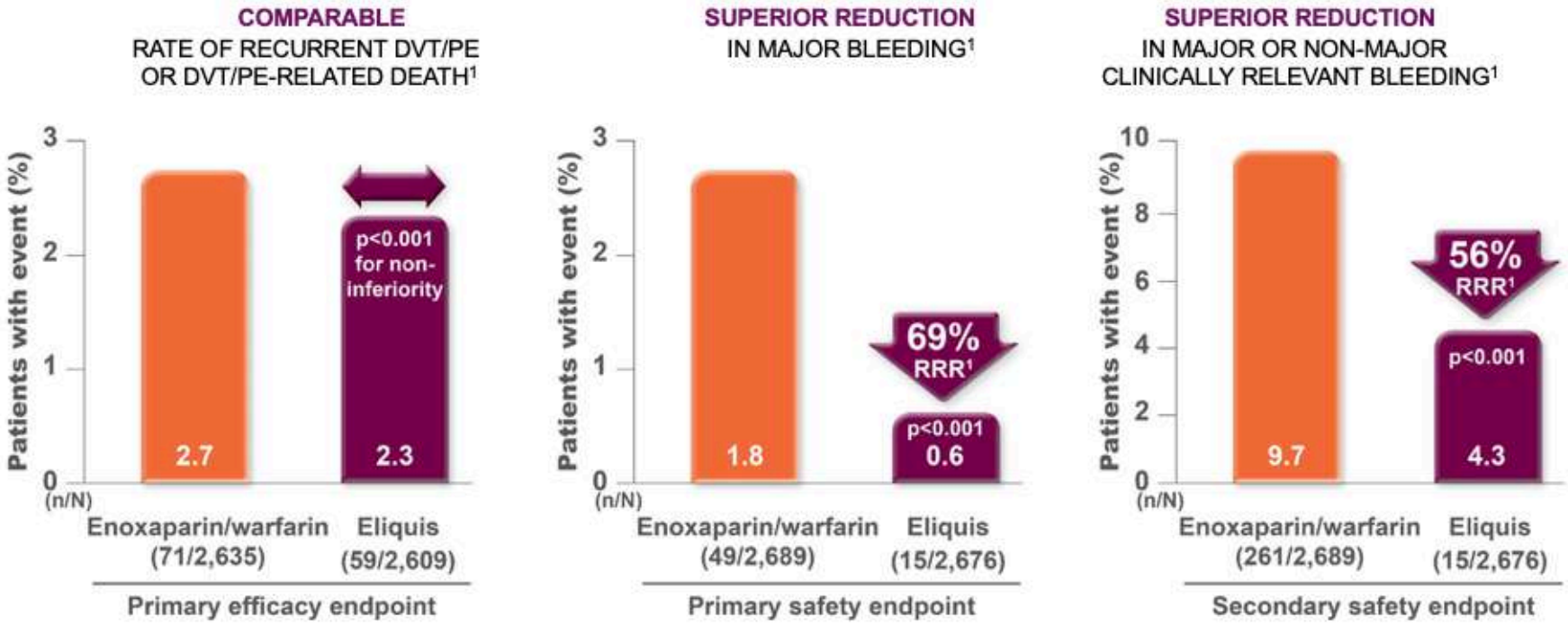
Options for anticoagulation

	Warfarin	Rivaroxaban	Apixaban	LMWH	Dabigatran	Edoxaban
Mechanism of Action	Vit K antagonist	Direct Xa inhibitor	Direct Xa inhibitor	Indirect Xa inhibition	Direct thrombin inhibitor	Direct Xa inhibitor
Excretion		33% renal, 66% hepatic	27% renal, remainder faeces	renal	80% renal	35% renal, 70% unchanged
Dosing	INR guided	15mg BD 21/7 then 20mg Daily	10mg BD 7/7 then 5mg BD	1mg/kg BD S/C	150mg BD	60mg D
Monitoring	Yes – INR (target 2-3)	No	No	No	No	No
Use in renal impairment	Yes	No if CrCl<30ml/min	No if CrCl <25ml/min *	DR if CrCl<30ml/min	No	No if CrCl <30ml/min

DOACs in VTE

Apixaban, compared with enoxaparin/warfarin, demonstrated comparable efficacy, with a significant 69% relative risk reduction in major bleeding[1,2]

AMPLIFY



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

Ms Leiden - discussion

- **Unprovoked proximal DVT**
- **Low bleeding risk**
- **No cancer**

Apixaban 10mg BD for 7 days then reduced to 5mg BD to complete 3 months treatment

Ms Leiden – Goals of care

Goals of treatment

- Prevent extension of DVT or PE
- Prevent mortality associated with PE
- Reduce risk of post-thrombotic syndrome

Approximately 50% of proximal DVTs will be associated with a PE

Hirsh J *et al. Circulation* 1996; **93**: 2212-45

VTE - When to refer

Refer to specialist	Send to ED immediately
• Possible iliofemoral DVT (e.g. unexplained swelling of the entire leg)	• Significant cardiovascular or pulmonary comorbidity
• Suspected thromboses of the deep veins in the upper limbs and 'unusual sites', such as mesenteric veins	• Contraindications to anticoagulation
• Familial or inherited disorder of coagulation	• Familial bleeding disorder
• Morbid obesity (>120 kg),[3] BMI 40 kg/m2	• Pregnancy
• Consideration of long-term therapy	• Renal failure (creatinine clearance <25 mL/min)

VTE - Treatment Duration

Guideline summary

New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism

Treatment of VTE		
	Distal DVT caused by a major provoking factor that is no longer present requires OACs for 6 weeks	Stro
	Distal DVT that has been unprovoked or with persisting risk factors requires OACs for 3 months	Stro
	Proximal DVT or PE caused by major surgery or trauma that is no longer present requires OACs for 3 months	Stro
	Proximal DVT or PE that is unprovoked or associated with a transient (non-surgical) risk factor requires OACs for 3–6 months	Stro
	For DVT or PE that is provoked by active cancer, treat with therapeutic LMWH for at least 6 months	Stro
	For patients continuing with extended anticoagulation, either therapeutic or low dose DOAC is preferred over warfarin in the absence of contraindications	Stro
	Aspirin should be avoided unless anticoagulation cannot be used	Stro

Ms Leiden - Duration of anticoagulation?

- **Patients with unprovoked proximal DVT should be managed with anticoagulation for a minimum of 3 months, unless contraindicated**
- Reassess after 3 months and consider any **ongoing risk factors** and **risk of recurrence**
- Ongoing treatment may be recommended after assessing patients' response to and tolerance of initial 3 months anticoagulation and any individual risk factors for recurrent DVT or bleeding risk
- Repeat Doppler ultrasound at 3-6 months – this will be a new baseline

NICE (2015). www.nice.org.uk/guidance/ta34
Kearon C *et al. Chest* 2016; **149**: 315-52.

Ms Leiden – What is her risk of recurrence risk at 5 yrs?

a. 5%

b. 15%

c. 30%

d. 40%

e. 70%

Ms Leiden – What is her risk of recurrence risk at 5 yrs?

a. 5%

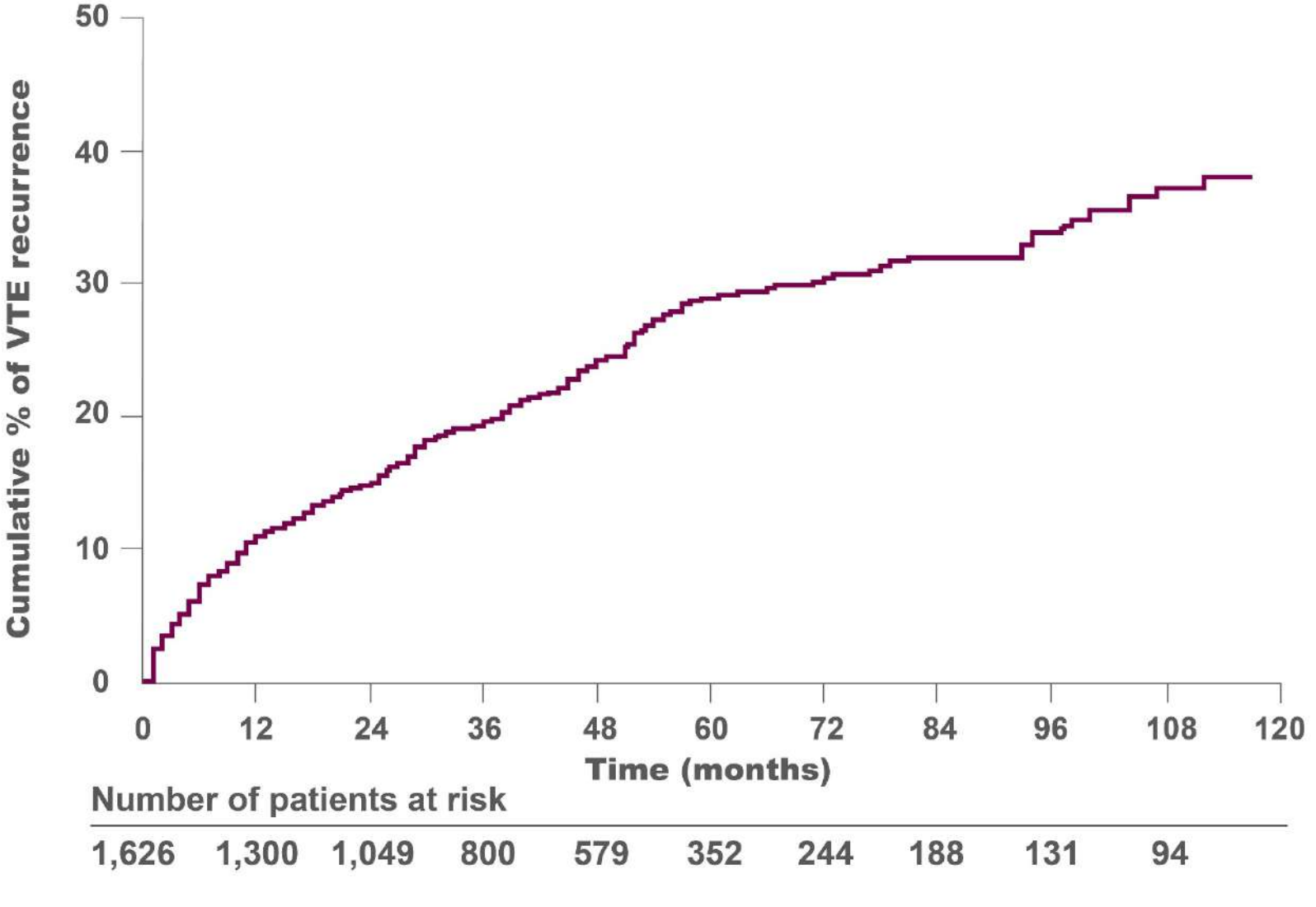
b. 15%

c. 30%

d. 40%

e. 70%

Recurrence risk in unprovoked VTE



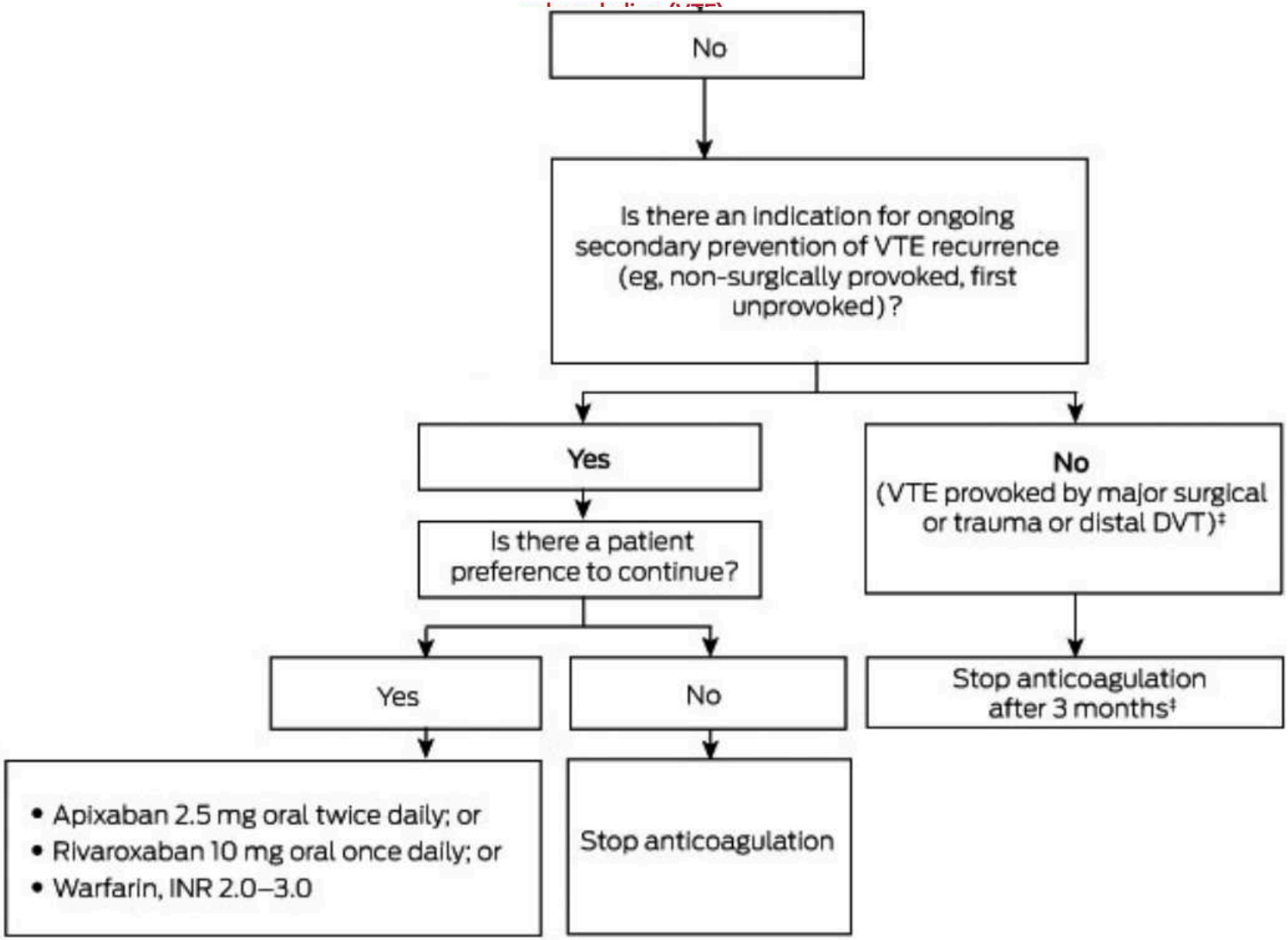
Prandoni P *et al. Haematologica* 2007; **92:** 199-205.

Risk factors for recurrence

10 Risk factors for recurrent venous thromboembolism (VTE)[5,30–33]

	Risk factor
Strong risk factors for recurrence	• Unprovoked VTE • Prior VTE • PE or proximal DVT • Persistent risk factor (eg, active cancer, antiphospholipid syndrome) • Antithrombin, protein C or S deficiency
Moderate risk factors for recurrence	• VTE provoked by non-surgical risk factor • Male sex • Elevated D-dimer level after cessation of anticoagulation
Factors that have little or no effect on recurrence	• Factor V Leiden or prothrombin gene heterozygosity • Residual thrombus on imaging

Tran, MJA, 2019



ome. DVT = deep vein thrombosis. INR = international normalised ratio. LMWH = low molecular weight heparin. PE = pulmonary embolism. * Refer t
.[24] ‡ For distal DVT without persisting risk, anticoagulation can stop after 6 weeks. ◆

APS = antiphospholipid syndrome. DVT = deep vein thrombosis. INR = international normalised ratio. LMWH = low molecular weight heparin. PE = pulmonary embolism. * Refer to Box 8.
† Warfarin is preferred in APS.[24] ‡ For distal DVT without persisting risk, anticoagulation can stop after 6 weeks. ◆

Ms Leiden - discussion

Would you screen Ms Leiden for malignancy?

YES

NO

Screening for occult malignancy in unprovoked VTE

- Prevalence of occult malignancy is low amongst patients with first unprovoked VTE (~3.9%)

- Limited occult-cancer screening is suggested
  - Basic bloods including iron studies
  - Chest xray
  - Breast screen
  - Pap smears
  - PSA
  - FOBT

- The addition of CT abdo/pelvis was not shown to improve the rate of occult-cancer detection

Carrier M *et al. NEJM* 2015; **373**: 697-704

Cancer-associated VTE

If Ms Leiden's DVT was cancer- associated would this change your management?

Cancer and VTE: Prospective Randomized DOAC Trials				
Completed				
Trial Name	**New Drug**	**Comparator**	**N**	
HOKUSAI	Edoxaban	Dalteparin	1,046	Raskob GE et al
SELECT-D	Rivaroxaban	Dalteparin	406	Young AM et al
ADAM	Apixaban	Dalteparin	300	McBan RD et al (full publication peding)
Ongoing				
Trial Name	**New Drug**	**Comparator**	**N**	
CARAVAGGIO	Apixaban	Dalteparin	1,168*	Study ongoing. First results expected at the end of 2019.

Raskob, *NEJM, 2018, 378: 615-624*
Yong et al. *J Clin Oncol* 2018; 36: 2017-23

Isolated distal DVT

If Ms Leiden's DVT was distal would this change your management?

Treatment of VTE	Distal DVT caused by a major provoking factor that is no longer present requires OACs for 6 weeks	Strong
	Distal DVT that has been unprovoked or with persisting risk factors requires OACs for 3 months	Strong
	Proximal DVT or PE caused by major surgery or trauma that is no longer present requires OACs for 3 months	Strong
	Proximal DVT or PE that is unprovoked or associated with a transient (non-surgical) risk factor requires OACs for 3–6 months	Strong
	For DVT or PE that is provoked by active cancer, treat with therapeutic LMWH for at least 6 months	Strong
	For patients continuing with extended anticoagulation, either therapeutic or low dose DOAC is preferred over warfarin in the absence of contraindications	Strong
	Aspirin should be avoided unless anticoagulation cannot be used	Strong

Kearon C *et al. Chest* 2016; **149**: 315-52
Tran, MJA, 2019

Pulmonary Embolism

If Ms Leiden's DVT was complicated by PE, would this alter your management?

Treatment of VTE	Distal DVT caused by a major provoking factor that is no longer present requires OACs for 6 weeks	Strong
	Distal DVT that has been unprovoked or with persisting risk factors requires OACs for 3 months	Strong
	Proximal DVT or PE caused by major surgery or trauma that is no longer present requires OACs for 3 months	Strong
	Proximal DVT or PE that is unprovoked or associated with a transient (non-surgical) risk factor requires OACs for 3–6 months	Strong
	For DVT or PE that is provoked by active cancer, treat with therapeutic LMWH for at least 6 months	Strong
	For patients continuing with extended anticoagulation, either therapeutic or low dose DOAC is preferred over warfarin in the absence of contraindications	Strong
	Aspirin should be avoided unless anticoagulation cannot be used	Strong

Kearon C *et al. Chest* 2016; **149**: 315-52
Tran, MJA, 2019

Summary

- DVT is best managed when quickly delineated into **provoked vs unprovoked** and **distal vs proximal**
- Assess each individual patient's risk of
  1.) recurrent VTE
  2.) bleeding
- Phone a haematology colleague if in doubt… or refer them to our clinic

Questions….

Thrombophilia testing

- **Hereditary:**
  - **Protein C or S deficiency**, **anti-thrombin deficiency**,
  - FVL(het vs **homo**), prothrombin gene G20210A mutation (het vs **homo vs compound het**)

- **Acquired:** Lupus anticoagulant, anticardiolipin Ab, B2 glycoprotein

- FVL and prothrombin gene mutation heterozygosity is **common** (3% and 5% respectively), however, seldom influence treatment decisions

- Test after careful counselling in **young** patients with **unprovoked** VTE (and a strong **family history**) particularly when cessation of anticoagulation is being considered

- Consider APS testing in all patients with unprovoked VTE

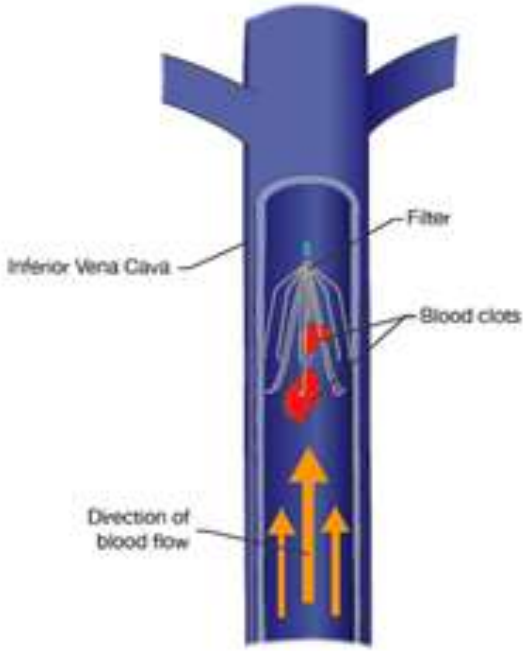
Carrier M *et al. NEJM* 2015; **373**: 697-704

Reversal agents

- Yes…
- Dabigatran:
  - **Idarucizumab**
  - Available in Australia
- Direct Xa inhibitors ie apixaban and rivaroxaban:
  - No routinely available reversal agent
  - Two agents in late stages of clinical trials – **andexenet** alpha and ciraparantag
- Does the capacity to reverse the agent improve patient outcome?

Carrier M *et al. NEJM* 2015; **373**: 697-704

IVC filters

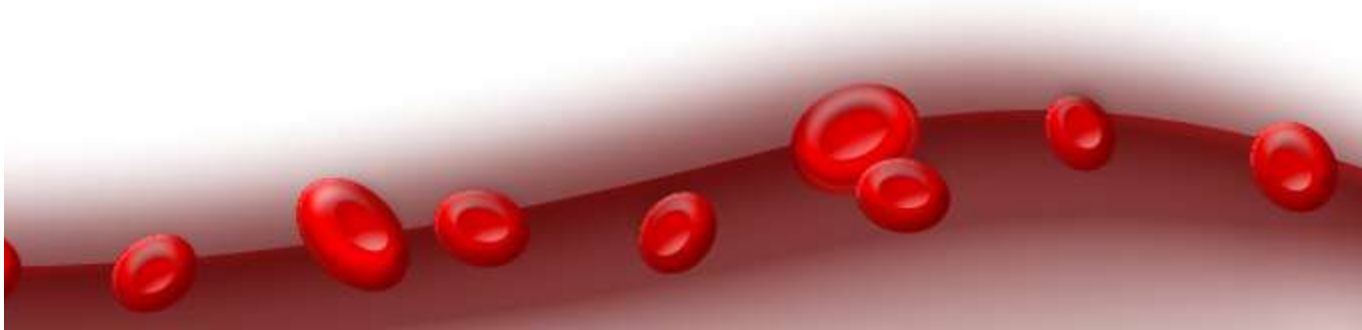


Indications

- Contraindication to therapeutic anticoagulation
- Failure of anticoagulation (rare)

Consider

- Large free-floating iliocaval thrombus
- Limited cardiopulmonary reserve
- ?Poor compliance
- ?Falls



Superficial vein thrombosis

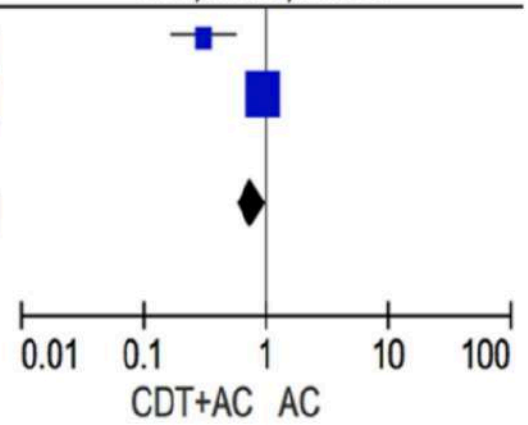
Carrier M *et al. NEJM* 2015; **373**: 697-704

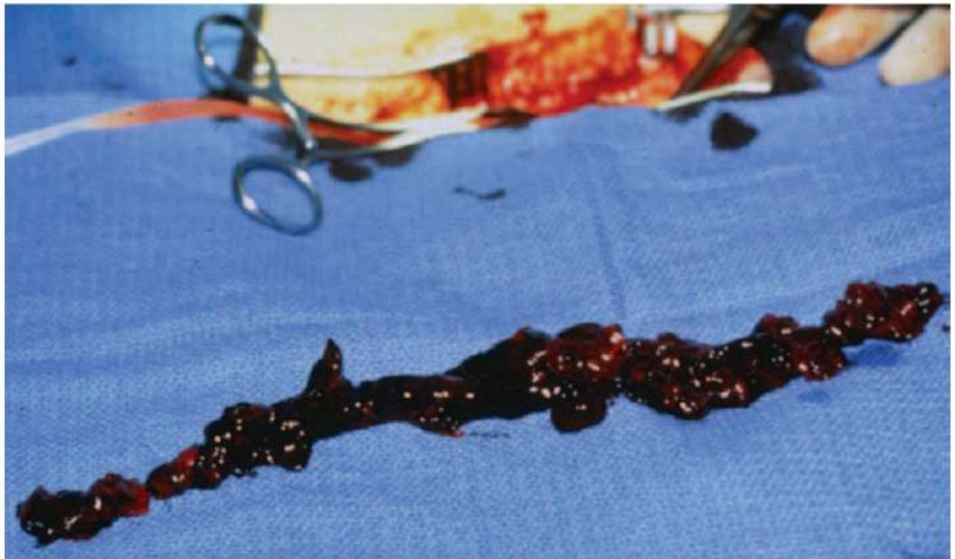
Catheter Directed thrombolysis

Study or Subgroup	CDT+AC Events	CDT+AC Total	AC Events	AC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Haig (CaVenT) 2016	37	87	63	89	28.7%	0.31 [0.16, 0.57]
Vendantham (ATTRACT) 2017	157	337	171	355	71.3%	0.94 [0.70, 1.27]
Total (95% CI)		**424**		**444**	**100.0%**	**0.76 [0.58, 0.99]**
Total events	194		234			

Heterogeneity: $Chi^2 = 10.12$, df = 1 (P = 0.001); $I^2 = 90\%$

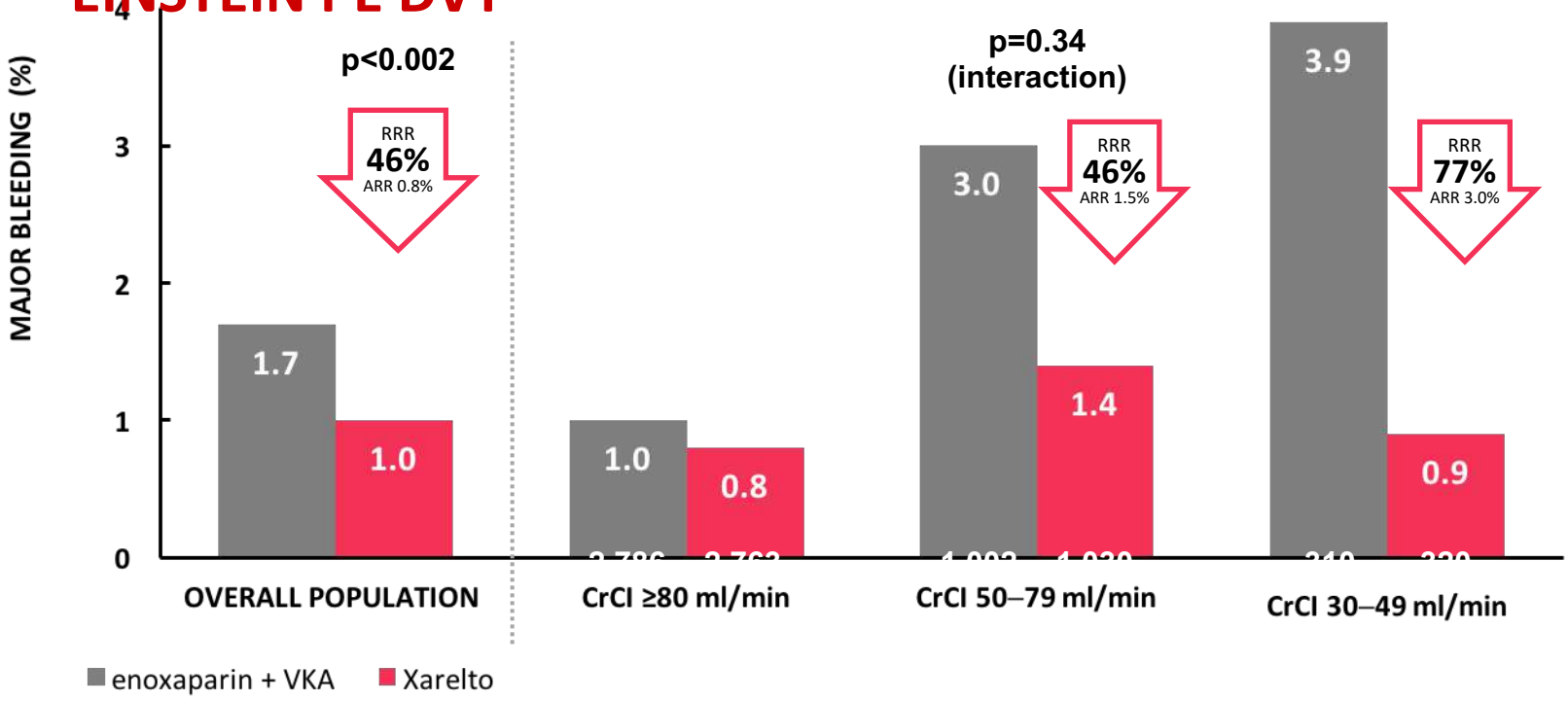
Test for overall effect: Z = 2.05 (P = 0.04)





Alhazmi et al.Cureus, 2019

- **EINSTEIN PE DVT**



Adapted from the EINSTEIN Investigators 2010 and Bauersachs et al 2014.[1,2]

‡Includes data from a post-hoc subgroup analysis.

Study design: a pre-specified pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies comparing the efficacy and safety of Xarelto (15 mg daily twice-daily for 21 days, followed by 20 mg once-daily) with standard-therapy (enoxaparin 1.0 mg/kg twice-daily and warfarin or acenocoumarol). Patients were treated for 3, 6, or 12 months and followed for suspected recurrent VTE and bleeding. The pre-specified non-inferiority margin was 1.75.[2])

1. Bauersachs RM *et al. Thrombosis J* 2014;12:25. 2. EINSTEIN DVT Investigators. *N Engl J Med* 2010;363:2499–510.

3 Types of venous thromboembolism (VTE) and associated VTE recurrence rates[5]

Type of VTE	Recurrence rate at one year after stopping anticoagulation	Recurrence rate at 5 years after stopping anticoagulation
First VTE provoked by major surgery or major trauma	1%	3%
First VTE provoked by transient risk factor (non-surgical)	5%	15%
Provoked VTE with persistent risk factors (eg, active cancer)	15%	45%
First unprovoked distal DVT	5%	15%
First unprovoked proximal DVT or PE	10%	30%
Second episode of unprovoked VTE	15%	45%

DVT = deep vein thrombosis. PE = pulmonary embolism. ◆