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Friday, August 09, 2019 (Room 6)

16:30 - 17:25 WS #51: Venous Thromboembolism and Issues Around Anticoagulation

17:35 - 18:30 WS #61: Venous Thromboembolism and Issues Around Anticoagulation (Repeated)

Venous thromboembolism and issues around anticoagulation

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On behalf of Dr Mark Smith, Haematologist

Conflicts of Interest

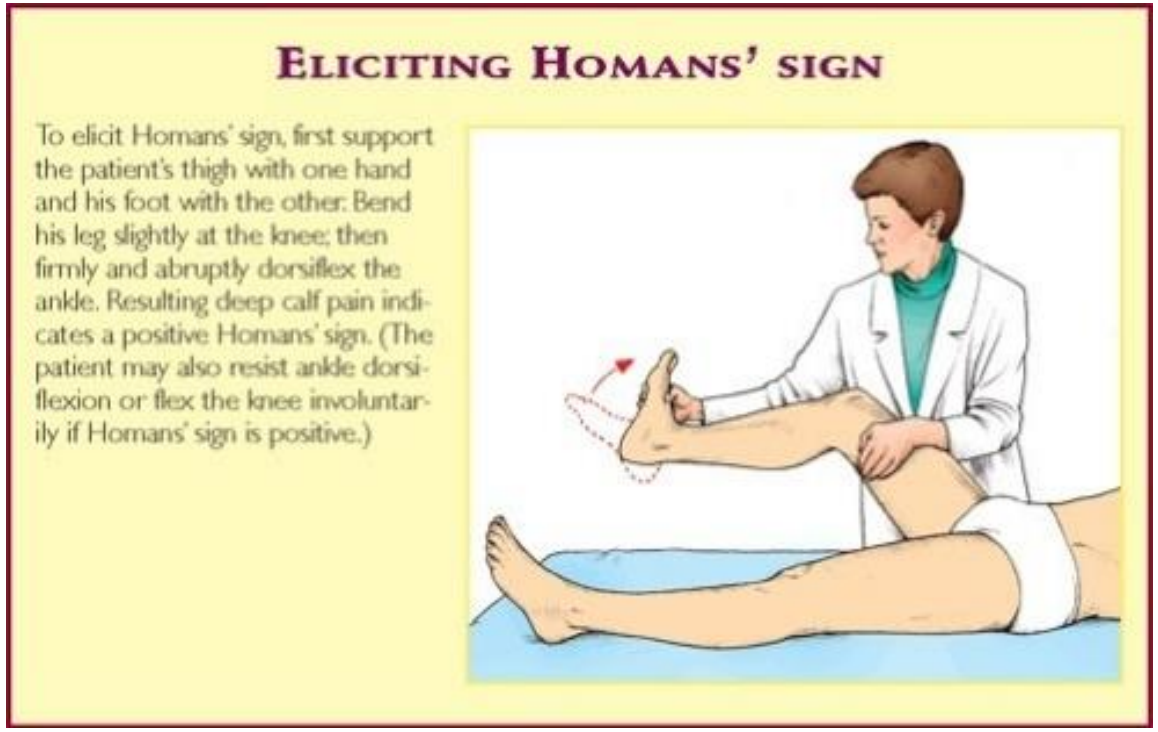
- None

Introduction

- VTE is a common and serious problem
- The signs and symptoms are non-specific and high clinical suspicion is needed
- The field of VTE is constantly evolving, with constant progress made into risk stratification and increasing treatment options
- We will cover several scenarios regarding the diagnosis and management of venous thromboembolism in various challenging situations
  - Case-based discussion

Case #1 - Sam

- Sam is a 60 year old engineer who presents with mild swelling and discomfort in the left lower limb. His PMH includes HTN on cilazapril only. He has no personal or family history of VTE. He is an ex-smoker of 20 pack years. He had a minor fall off his bike a week prior.
- Examination
  - Normal vital signs
  - Left calf mildly tender along deep veins,
  - Left calf swollen ~3cm compared to right
  - Pitting oedema in left calf only
  - Collapsed superficial veins below the knee
- Would you do Homans' sign?
  - **No** – Sensitivity 33%, Specificity 50%
- You calculate Well's score of 4
- What would you do?
  A. Watch and wait
  B. D-dimer
  C. Ultrasound
- You decide to do USS – which of these would you elect?
  A. Ultrasound whole left leg
  B. Compression ultrasound of the proximal leg



Well's score for DVT

- Validated and reproducible
  - Low probability – risk of DVT 3%
  - Intermediate probability – 17%
  - High probability – 17-53%
- Does not trump clinical gestalt
  - If clinically strongly suspicious regardless of Well Score → ultrasound

Table Wells Model for DVT Assessment

Clinical Parameter Score	Score
Active cancer (treatment ongoing, or within 6 months or palliative)	+1
Paralysis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for >3 days or major surgery <4 weeks	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling >3 cm compared with the asymptomatic leg	+1
Pitting edema (greater in the symptomatic leg)	+1
Previous DVT documented	+1
Collateral superficial veins (non-varicose)	+1
Alternative diagnosis (as likely or greater than that of DVT)	-2
Total Score	

High probability	>3
Moderate probability	1 or 2
Low probability	<0

Source: Adapted from: Wells PS, et al. *JAMA* 2006;295:199-207.

Take home points

#1 – Homans sign should be discarded (low sensitivity and specificity)[1]

#2 – For DVT with high clinical suspicion or high Well score (i.e. high pre-test probability), do NOT do a D-dimer. Organise an Ultrasound.

- NPV for D-dimer in **low-moderate** risk is 99.6%[2]
- A negative D-dimer in the presence of HIGH clinical suspicion/High Well score may miss up to 20% clots

#3 – Whole leg ultrasound is preferred over proximal compression only ultrasound as it picks up more distal DVTs[3]

[1]Ambesh P, Obiagwu C. Indian Heart Journal. 2017;69:418–419

[2]Bates SM, Kearon C, Crowther M, et al. Ann Intern Med. 2003;138:787-94

[3]Needleman L, et al. Circulation. 2018;137:1505–1515.

Case #1 – Sam (Cont'd)

- Ultrasound: "3 cm DVT in the left posterior tibial vein. There is no extension into the popliteal vein".
- You propose to Sam commencing anticoagulation.
- Sam says "My mother died of a blood thinner overdose. I'd rather not take a blood thinner if I don't have to. Are there any other options?"
- **What do you say?**

Below-knee (infrapopliteal) DVT

- The risk of embolization is ~4%
- About one third will propagate proximally – usually within the first 2 weeks
- The risk of post-thrombotic syndrome is *thought to be* lower with BKDVT and tends to be milder
- Not all patients with isolated BKDVT need anticoagulation
- However anticoagulation will hasten the resolution, reduce the risk of propagation (OR 0.29), and reduce risk of recurrence (OR 0.5) without increased risk of bleeding [meta-analyses of low-quality trials[4,5]]
- One approach:
  - If severely symptomatic – anticoagulate
  - If no or mild symptoms or patient preference not to anticoagulated, **repeat USS in 2 weeks** to ensure no progression
  - Risk factors for progression:
    - Unprovoked DVT
    - D-dimer >500 ng/mL
    - Extensive thrombosis involving multiple veins (eg, >5 cm in length, >7 mm in diameter)
    - Thrombosis close to the proximal veins
    - Persistent/irreversible risk factors such as active cancer
    - Prior DVT or PE
    - Prolonged immobility
    - Inpatient status

[4]Martino RR, Wallaert JB, Rossi AP et al. J Vasc Surg. 2012;56(1):228.
[5]Franco L< Giustozzi M, Agnelli G et al. J Thromb Haemost. 2017;15(6):1142.

Case #1 - Sam

- Sam opts for active surveillance. His USS two weeks later reveals no propagation and so anticoagulation is not initiated.

Take home point

#4 – Below knee DVT could be managed with active surveillance

- TWISTER study approach (ANZ data) – if low-risk, 2 weeks of enoxaparin or rivaroxaban then repeat USS and stop if **no proximal extension** and **symptom-free**
- Otherwise continue for 6-12 weeks total

Case #2 - Maggie

- Maggie is a 50 year old who presents with right leg swelling. She has known varicose veins and raised BMI. She takes oral HRT.
- No past or family hx of VTE
- O/E:
  - Bilateral gross varicosities with venous eczema
  - R leg has mild swelling, there is a tender palpable cord in the great saphenous vein territory going up to groin, with mild erythema
- You suspect R great saphenous vein thrombosis
- **What would you do next?**
- **How would you treat?**

Superficial vein thrombosis

- Large heterogeneous group of disorders
  - Varicose vein related (V-SVT) – occurs in 10-20% of those with VV.
  - Unrelated to varicose veins (N-SVT)
  - IV cannula/infusion related
- More common that DVT
- Same risk factors as other venous thromboses
- Previously thought to be benign and self-limiting. However:
  - Similar pathophysiology to VTE
  - Can be associated with DVT (5-20%) or PE at time of diagnosis (up to 4%)
  - OR for DVT is **6.3**, for PE is **3.9** in those with SVT
  - 5 year risk of VTE is increased
  - V-SVT is less associated with VTE than N-SVT

Superficial vein thrombosis

- Diagnosis:
  - Clinical
  - D-dimer – no role in SVT
  - Ultrasound recommended to look for DVT – some guidelines suggest bilateral lower limb full leg ultrasound as 5-10% of concurrent DVTs occur in the contralateral leg
  - Clinical assessment for PE
- Treatment:
  - No consensus
  - Analgesia (topical NSAIDs favoured), compression stockings (Grade 2+)
  - Mobilisation > rest. When sitting down, leg elevation
  - Antibiotics are **not recommended** unless clear evidence of infection
  - Active treatment results in lower VTE and faster resolution than no treatment

Superficial vein thrombosis – Who to anticoagulate?

- Peripheral cannula-related thrombosis – conservative management
- SVT – anticoagulate if:
  - ≥5cm in length **AND** EITHER
    - Within 3 cm of a junction with deep venous system, OR
    - One or more of the following risk factors:
      - 65 or older, Male, Previous VTE (or previous idiopathic SVT), Medical risk factors (pregnancy, cancer, prolonged immobility, chronic inflammation)
- What do you use and how long?
  - **Enoxaparin** intermediate dose (1mg/kg daily seems to be better than prophylactic dose), **rivaroxaban** 10mg daily (SURPRISE trial, but not in pregnancy)
  - Treat for **6 weeks**
- If not anticoagulating, clinic review within 7-10 days
  - Low threshold for rescanning if symptoms worsen
- Surgery – not a primary treatment. For GSV, ligation should be considered if V-SVT to prevent recurrence

Case #2 Maggie (Cont'd)

- Maggie has no history of cancer, autoimmune disease or previous VTE.
- USS shows no DVT but a "6cm superficial thrombus in the right great saphenous vein terminating close to saphenofemoral junction"
- She agrees to 10mg Rivaroxaban for 6 weeks and seeks private referral for venous ligation

Take Home points

#5 – Superficial vein thrombosis is not as benign as previously thought and forms part of VTE. They are a strong risk factor with concurrent and future DVT and PE[6]

#6 – USS assessment is indicated even with clinically palpable SVT[6,7]

#7 – Treat **high-risk** superficial vein thromboses with intermediate dose enoxaparin (1mg/kg/day) or rivaroxaban 10mg daily for 45 days, along with topical NSAIDs and compression stockings[6-9]

[6]Kitchens CS. Blood 2011 117:39-44

[7]Kalodiki E, Stvrtinova V, Allegra C et al. Int Angiol 2012;31:203-16

[8]The superficial Thrombophlebitis Treated by Enoxaparin Study Group. Arch Intern Med 2003;163:1657-53

[9]Beyer-Westendorf J, Schellong SM, Gerlach H et al. Lancet Haematol. 2017 Mar;4(3):e105-e113.

Case #3 - Jim

- Jim is a 50 year old farmer. He comes to see with a few weeks of dry cough and mild exertional dyspnea. He mentions unintentional weight loss of 10kg and left pleuritic chest pain.
- He is a smoker of 30 pack years
- He has no fever or sputum. He denies calf tenderness
- Exam – looks well
  - HR 110, Sats 93% RA, RR 20/min
  - No clubbing or cyanosis
  - Stony dull Left base with reduced breath sound
- A CXR shows a unilateral pleural effusion and a 2cm lesion suggestive of primary lung cancer
- You liaise with respiratory physician and a CT chest is organized –
  - This confirms a Left sided solitary mass consistent with primary lung cancer
  - Left pleural effusion
  - **An incidental left lower lobe pulmonary embolism**
- Blood show mild normocytic anaemia, normal liver and renal function and calcium.
- While awaiting respiratory review – **what treatment would you offer for the PE?**

Cancer-associated thrombosis

- Cancer patients make up 10-20% of VTE
- Treatment is different
  - Standard of care is enoxaparin 1.5mg/kg daily or 1mg/kg BD
  - Duration – minimum 3 months but continue as long as the malignancy is active
  - **Warfarin is less efficacious than LMWH (40% more clots)** and associated with higher rates of bleeding (4 RCTs - CANTHANOX, LITE, CLOT, CATCH) – should not be used
- What about DOACs?
  - No evidence for Dabigatran
  - Rivaroxaban showed **non-inferiority** to LMWH in a recent small RCT (SELECT-D study) in terms of preventing VTE, however there was increase in major bleeding (by 83%) and clinically relevant non-major bleeds (3-4x)
  - Rivaroxaban particularly not favoured in GI cancers as they are higher risk of bleeding

What about screening unprovoked VTE patients for cancer?

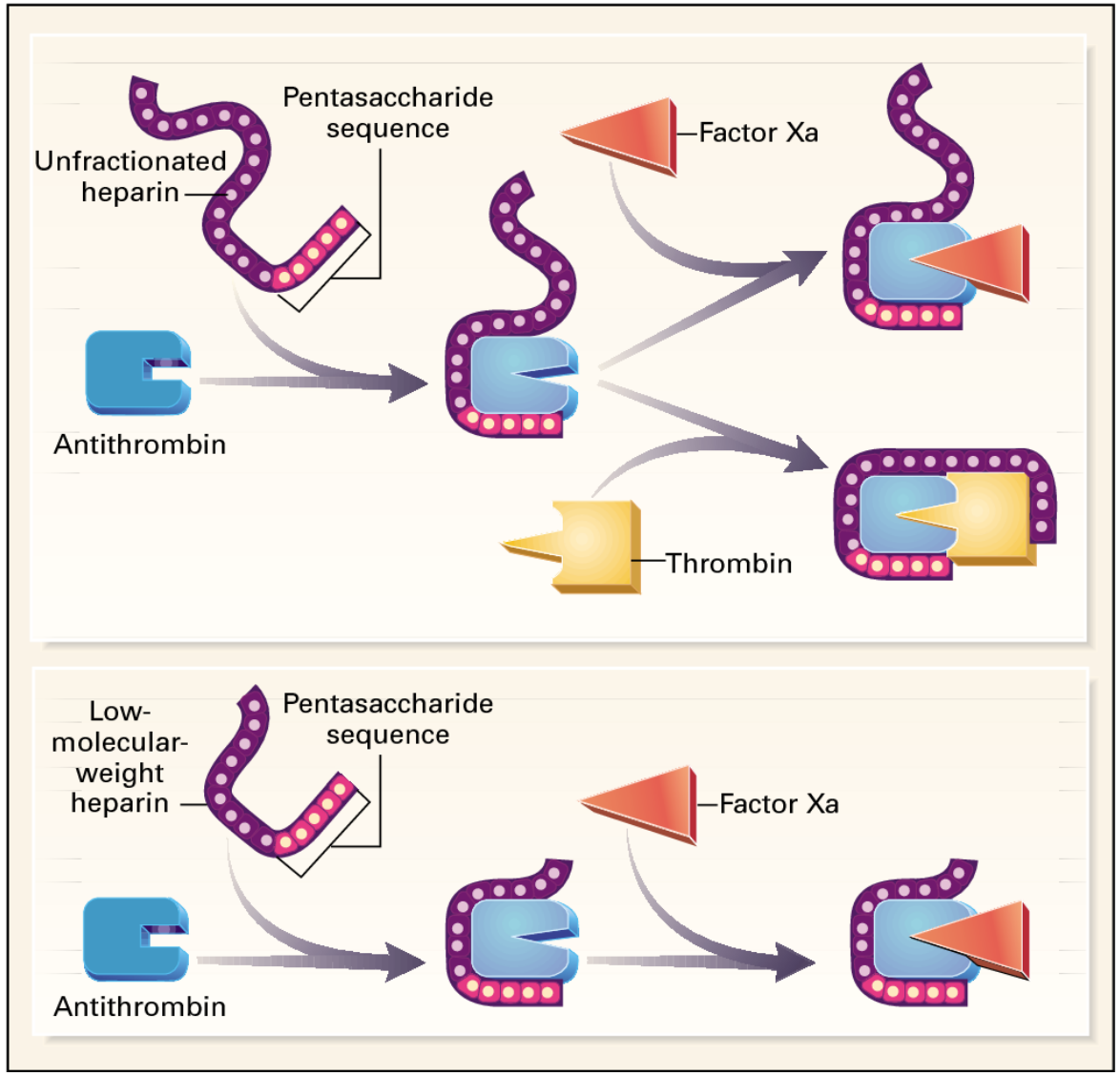
- VTE can be the first sign of an occult malignancy
  - In general, ~4-5% of all patients with unprovoked VTE are diagnosed with malignancy within 12 months of presentation
- SOME trial (NEJM 2015) – compared standard screening (history, exam, basic blood tests, CXR and age-appropriate screening) to standard screening + CT scan and found no mortality benefit, increased cancer detection or reduced time to cancer diagnosis with addition of CT
  - Results confirmed in Cochrane review in 2018
- It is recommended that all patients with unprovoked VTE undergo discretionary evaluation for malignancy
  - History and physical exam
  - CBC, U&E, LFTs, Calcium, urinalysis
  - CXR
  - Age-appropriate standard cancer screening (e.g. cervical screening, mammography, colorectal, prostate)
- Patients who have recurrent VTE despite therapeutic coagulation with no clear provoking factor should be considered for **more aggressive cancer screening e.g. CT chest & abdomen** (expert consensus)

Case #3 – Jim (Cont'd)

- You review Jim and commence him on enoxaparin
- Jim weighs 120kg (Ht 180cm) and has creatinine clearance of 80ml/min – a 1.5mg/kg/day dose would result in a dose of 180mg daily – **is that ok?**
  - With patients weighing >100kg, 1mg/kg BD dosing leads to more accurate dosing
  - Use real body weight (120mg BD in Jim's case) up to max 150mg BD
  - With patients who are underweight, use ideal body weight
- You commence Jim on 120mg BD of enoxaparin, **how would you monitor?**
  - Clinically
  - Anti-Xa Levels

LMWH – mechanism of action and monitoring

- Anti-Xa levels (citrate tube) should be monitored in LMWH in the following situations:
  - Extremes of body weight (<50 or >120)
  - Renal impairment (especially CrCL <30ml/min)
  - Pregnancy
  - Use of LMWH for >7 days
- Anti-Xa levels are measured **4 hours** after 3rd or 4th dose



LMWH is partially cleared through the kidneys

- Dose is adjusted based on Creatinine clearance
- Enoxaparin – 1.5mg/kg/day for daily dosing or 1mg/kg BD
- Data is scarce on use of LMWH at CrCL <30ml/min – generally avoid
- Community Health Pathways suggest the following:

Enoxaparin dosage in renal impairment	
CrCl (mL/min)	Recommended dose
More than 60	full dose
50 to 60	70% of full dose
40 to 50	60% of full dose
30 to 40	50% of full dose
Less than 30	Seek acute haematology advice

Take Home points

#8 – In cancer-related thrombosis, standard of care treatment is LMWH, with some evidence supporting rivaroxaban (but increased bleeding risk)

#9 – Screen all patients with unprovoked VTE for malignancy using history, physical examination, basic blood and urine tests, CXR and age/sex-appropriate cancer screening

#10 – Use real body weight for enoxaparin dosing

#11 – Enoxaparin dose needs renal adjustment especially with CrCL <50ml/min and should generally be avoided at CrCL <30ml/min

#12 – Anti-Xa levels can be used to monitor LMWH in select situations (extremes of body weight, renal impairment, pregnancy and prolonged use >7days)

Case #4 - Tony

- Tony is a 40 year old man who presents with low-grade fever, mild shortness of breath and cough. He has recently returned from LA.
- He has no personal or family history of VTE, is a non-smoker. No history of malignancy.
- Physical exam
  - RR 18, Sats 96% RA, HR 90, BP 140/80, Temp 37.6^{o}C
  - Chest clear
  - No calf tenderness or swelling
- You decide he is low risk with a Well score for PE of Zero
- **What do you do now?**

PERC criteria

- If PERC negative, D-dimer is **not** needed
  - PE risk is <2%
- Only use in low-risk situation, and does **not** replace clinical gestalt

Pulmonary Embolism Rule-Out Criteria

Variable
Age <50 years
Pulse <100 beats per minute
SaO_2 ≥95% on room air
No hemoptysis
No exogenous estrogen use
No prior venous thromboembolism
No surgery or trauma requiring hospitalization within the past 4 weeks
No unilateral leg swelling

Journal WATCH

Take Home point

#13 – In low-risk patients, PE can be ruled out if all PERC criteria are met without a D-dimer[13]

[13]Freund Y, Cachanado M, Aubry A et al. JAMA 2018;319(6):559-66.

Case #5 - Sarah

- Sarah is a 42 year old lady. You had referred her to hospital a week earlier with acute SOB and was found to have bilateral pulmonary emboli with right heart strain. She was started on enoxaparin 1.5mg/kg/day for 5 days and then switched to warfarin.
- You find out Sarah has no personal history of VTE, no features of malignancy, and no recent surgery, trauma or immobility. A pregnancy test was negative as inpatient
- Sarah's mother had a blood clot in her 60s after a minor illness
- Sarah is not a fan of warfarin and wants to know about her anticoagulation options – **what can you tell her?**

Oral anticoagulants in NZ

	Warfarin	Dabigatran	Rivaroxaban
Mechanism of action	Vitamin K epoxide reductase inhibitor	Factor II inhibitor	Factor X inhibitor
Half-life	20 to 60 hours	12-17 hours	5-9 h (up to 12h in elderly)
Dosing frequency	Once daily	Twice daily	Once daily (twice daily initially for 3 weeks in VTE treatment)
Renally cleared?	No	Yes (80%)	Yes (36%)
Potential for drug interacitons	Yes (metabolized by CYP2C9)	Few (P-glycoprotein)	Yes (metabolized by CYP3A4)
Antidote available in NZ?	Yes	Yes	No
Needs lead-in phase with LMWH on commencement	Yes	Yes (local experts disagree)	No
Risk of bleeding compared to warfarin	Same	Lower CNS Higher GI	Lower CNS Higher GI
Monitoring	INR	TCT (sensitive), APTT	Not available to most

Case #5 – Sarah (Cont’d)

- Sarah elects to go on Dabigatran. You switch her.
- Sarah asks about thrombophilia testing – **what do you advise her?**

Thrombophilia testing in VTE

- A thrombophilia screen includes:
  - Factor V leiden
  - Prothrombin gene mutation (G20210A mutation)
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Antiphospholipid Syndrome (lupus anticoagulant, anticardiolipin, anti-beta-2-glycoprotein antibodies)

Common but weak (usually heterozygotes)

Less common, but higher risk

Acquired, rare, very strong risk factor

- Do not test for thrombophilia in acute phase of VTE (not reliable, *does not change management*)
- Do not test for thrombophilia if VTE is clearly provoked by a strong factor (cancer/surgery)
- Do not test for thrombophilia while on anticoagulation (interferes with tests)
- The presence or absence of a thrombophilia does not dictate duration of anticoagulation after VTE – this is dictated by whether it was provoked or unprovoked
  - (except for antiphospholipid syndrome)

Thrombophilia testing in VTE

- Remember –
  - Most people with thrombophilia do not develop VTE
  - Most people with thrombophilia who develop VTE do so in the presence of an acquired factor
  - Having a strong family history of VTE is a big risk factor even if thrombophilia testing is negative
- Who to screen?
  1. Patient with unprovoked VTE aged <45
     - Weak provoking factor e.g. long haul travel should also be considered
  2. Patients with VTE who have strong family history (at least one first degree relative with young/unprovoked VTE)
  3. Unaffected patient with a first-degree relative with a **confirmed specific thrombophilia**
  4. 3 unexplained consecutive miscarriages or late-term pregnancy loss without clear cause
  5. Warfarin induced skin necrosis (proteins C & S)
  6. Neonates with purpura fulminans
  7. Patients with thrombosis at unusual sites (cerebral and splanchnic circulation)
- If not sure, please consult haematology rather than test
  - Thrombophilia testing is **rarely urgent**

Thrombosis at unusual sites

- Cerebral veins, renal veins, portal vein, mesenteric veins
- Ensure there is no clear provoking factor e.g. manipulation during surgery, cirrhosis (associated with portal vein clots), pancreatitis (associated with splenic vein clots), trauma
- In addition to usual thrombophilia testing – test for:
  - Myeloproliferative disorders even if CBC normal (JAK2 mutation)
  - Paroxysmal Noctural haemoglobinuria (PNH screen – 1x EDTA required)

Case #5 - Sarah (Cont’d)

- After 3 months of anticoagulation, Sarah comes back and asks if she could come off blood thinners
- Remember she had unprovoked significant PE
- She wants to know about her risk and if there is any way her personal risk could be evaluated
- **What do you tell her?**

VTE recurrence

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. ◆

THANZ 2019, MJA

Predicting recurrence after first unprovoked VTE

- Risk is high
  - Lifelong anticoagulation is generally recommended after one unprovoked VTE
- This is unacceptable to many, and sometimes the bleeding risk is too high
- Elevated D-dimer ~1 month after **cessation** of anticoagulation is strongly associated with increased VTE recurrence **(PROLONG study, NEJM 2006;355:1780-9)**

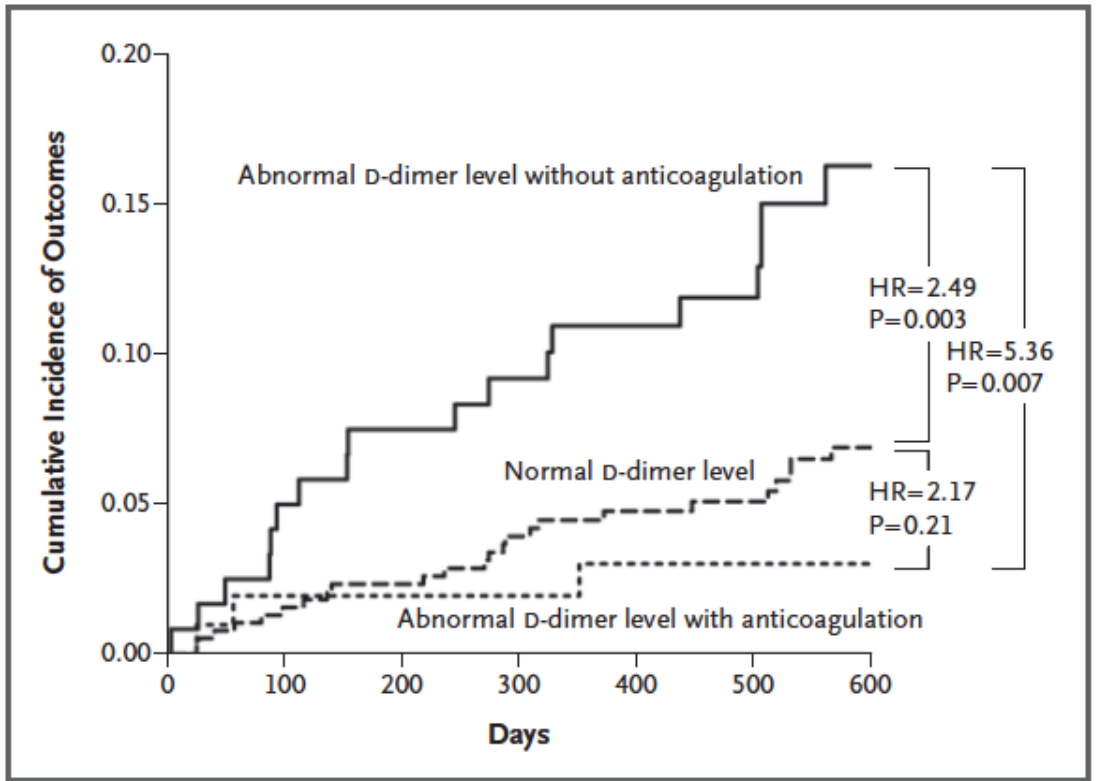


Figure 2. Cumulative Incidence of and Hazard Ratios (HRs) for Main Outcomes.
The graph compares the outcomes among patients who had a normal D-dimer level with those among patients who had an abnormal level and either resumed or stopped anticoagulation therapy.

Predicting recurrence after first unprovoked VTE

- Several scores have been developed to aid decision making

DASH Prediction Score for Recurrent VTE

☆

Predicts likelihood of recurrence of first VTE.

INSTRUCTIONS
Do NOT use in patients with active hemorrhage or signs/symptoms of VTE.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

D-dimer abnormal Measured ~1 month after stopping anticoagulation	**No 0**	Yes +2
Age ≤50 years	**No 0**	Yes +1
Male patient	**No 0**	Yes +1
Hormone use at VTE onset (if female) If male patient, select "No"	**No 0**	Yes -2

Scoring using the HERDOO2 rule

validated only for women

	Risk predictor	Value
H	**H**yperpigmentation,	1 point
E	**E**dema, or	1 point
R	**R**edness in either leg	1 point
D	**D**-dimer test positive at 250 mcg/L or more	1 point
O	**O**besity, with a BMI of 30 kg/m^2 or more	1 point
O	**O**lder age (65 years or greater)	1 point
2	2 or more points place a woman at high risk of recurrent VTE if she is off anticoagulant therapy	

Case #5 – Sarah (Cont'd)

- Based on this information, Sarah comes off anticoagulation for one month
  - Her D-dimer is low so she elects to remain off
- Sarah undergoes thrombophilia testing and this shows presence of antiphospholipid antibodies
- Sarah recalls history of 3 miscarriages prior to her only daughter, Olivia
- **Can she now be labelled as having antiphospholipid syndrome?**
  - Not quite – need repeat antibody testing 3 months apart for confirmation
  - Antiphospholipid antibodies (esp lupus anticoagulant) can appear and disappear in infection and randomly and on their own do not make a diagnosis of APLS or require anticoagulation – they often interfere with APTT
- Repeat testing is positive – **recommendation?**
  - Lifelong anticoagulation with warfarin (DOACs not validated) – INR 2-3

Case #5 - Sarah (Cont'd)

- Sarah's daughter, Olivia, is 18 and wants to go on the COCP. How do you counsel her?
  - Avoid given family history
- She wants to know if she should get tested for antiphospholipid antibodies
  - No – APLS is generally not hereditary. And if positive, anticoagulation is not required until she gets symptoms.
  - However, studies demonstrate that family history of VTE is still associated with high risk of VTE so still recommend against COCP
- What if Sarah had Antithrombin deficiency – would you screen Olivia?
  - Yes – but need to counsel her
  - Avoid false reassurance with negative testing in the presence of a strong family history

Take Home points

#14 – There are multiple options for oral anticoagulation in NZ (warfarin, dabigatran, rivaroxaban)

#15 – Thrombophilia testing is not recommended during acute phase or while on anticoagulation, and does not influence duration of anticoagulation (except antiphospholipid syndrome)

#16 – There are only a few and very specific indications for thrombophilia testing. Discuss with haematology if ordering outside of these

#17 – Unprovoked VTE should be treated with life-long anticoagulation. If this is undesirable, there are scores that allow prediction of VTE recurrence and may aid decision making

- One emerging option is using **low dose rivaroxaban** (10mg daily) after 6 months in those who have unprovoked VTE or recurrent VTE requiring lifelong anticoagulation – EISNTEIN CHOICE study (NEJM 2017; 376:1211-22)
- Avoid this approach in males with unprovoked VTE

Take Home points

#18 – Do not test for thrombophilia in patients requesting COCP – if strong family history then **avoid**, and if strong family history with specific thrombophilia consider selective testing

#19 – Thrombosis at unusual site (gut, brain, renal)? – consider JAK2 and PNH screen

#20 – Antiphospholipid antibodies ≠ Antiphospholipid syndrome

Case #6 - Rawiri

- Rawiri is a 74 year old man who presents with 2 day history acute SOB and cough. He has had a previous PE 10 years ago after a hip replacement but is no longer on anticoagulation. He is an ex-smoker of 40 pack years
- O/E:
  - Alert, RR 24, Sats 92% on air, afebrile
  - Hyperinflated chest
  - Mild accessory muscle use
  - Widespread rhonchi
- Your colleague thinks Rawiri has a non-infective exac of probable COPD. He is not keen on going to hospital. They decide to add a D-dimer to some bloods given his past history
- D-Dimer comes back as 650 (normal <500), CRP 10 (normal <3), WCC normal
  - It is handsed over to you as they finish early on Friday and you have to chase it up
- **What do you do now?**

Case #6 – Rawiri (Cont'd)

- What do you do?
  - IGNORE IT
  - Firstly it's far more likely he has COPD exacerbation
  - Secondly – it's negative if **age-adjusted**
    - **ADJUST-PE** study (JAMA 2014;311(11):1117-24) and many others
    - ULN of D-dimer above 50 is **age x 10** (if for Rawiri it's 740 - so 650 is negative)
- What about post-op D-dimer?
  - D-dimer elevated with surgical trauma
  - If minor surgery – do not do for 7-10 days
  - If major surgery – maybe raised for up to 6 weeks

Take Home points

#21 – Age adjusting D-dimer (ULN = age x10) above 50 years when used to rule out VTE

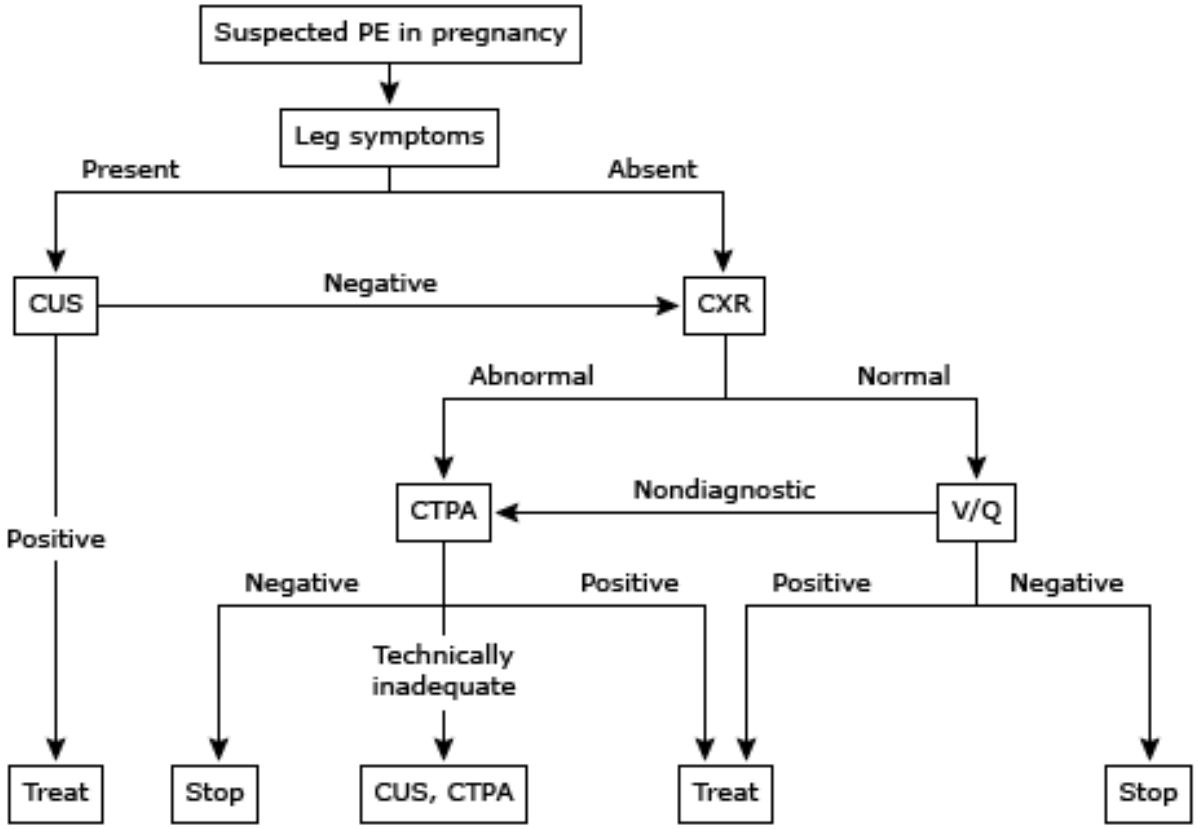
#22 – Avoid postop D-dimer – if needed, do not do within 7-10 days of minor surgery OR within 6 weeks of major surgery

Case #7 – Amy

- Amy is a 25 year old lady who is 30 weeks pregnant. She presents with acute breathlessness and palpitations
- Uneventful singleton pregnancy so far. No PHx or FHx of VTE. No Hx pulmonary disease
- She has no infective symptoms
- O/E:
  - RR 20, Sats 95% RA, HR 110, BP 110/60
  - Chest clear
- You suspect PE – what do you do?

VTE in pregnancy - diagnosis

- Common, major cause of maternal morbidity and mortality
- Risk is increased throughout pregnancy and 6 weeks postpartum
- D-dimer should not be used (not validated)
- CTPA results in irradiation to breasts (10% increase in Ca breast later on), both V/Q and CTPA have very small irradiation doses for foetus
- CXR is considered safe with foetal shielding



Algorithm from UpToDate

Case #7 – Amy (Cont'd)

- Amy has no signs or symptoms for DVT clinically
- You refer to acute GM registrar
  - CXR is NAD
  - No clear alternative diagnosis
- Perfusion only scan done to minimize radiation – this shows small filling defects consistent with bilateral PE
- Amy is discharged on enoxaparin 1.5mg/kg/day
- Amy asks you if she could have oral treatment instead - what do you say?

Case #7 – Amy (Cont'd)

- Warfarin is teratogenic but safe in breastfeeding
- There is **insufficient** data about DOACs in pregnancy or breastfeeding
- Hence the mainstay of treatment of VTE in pregnancy is LMWH
- Duration
  - 3-6 months
  - I would continue until end of postpartum period
  - It's clearly provoked – therefore thrombophilia testing is not required
  - Anti-Xa monitoring is suggested
- VTE prophylaxis is recommended with future pregnancies for Amy
  - The dose is not standardized – **ACOG recommends enoxaparin 1mg/kg daily** (intermediate dose); others use 40mg SC BD or once daily
  - Anti-Xa is suggested as well

Take Home points

#23 – VTE is common in pregnancy. D-dimer is not validated and the specified algorithm should be followed. Referral for inpatient workup, or discussion with acute obstetrics or haematology is advised.

 # 24– Treatment of VTE in pregnancy is with LMWH. Warfarin and DOACs are contraindicated (warfarin may be used in breastfeeding women).

#25 – Pregnant women should be offered VTE prophylaxis if:

- previous unprovoked or estrogen related VTE
- Strong thrombophilia (protein C, S, ATIII, homozygous for fVL or prothrombin gene mutation OR compound heterozygous – APLS should be given treatment dose + aspirin)
- Weak thrombophilia + VTE (or strong family history of VTE – this is debatable)

ACOG Practice Bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018; 132:e18-34.

Final message

- There are a lot of grey areas in VTE diagnosis and management
- RISK STRATIFICATION is “the name of the game”
- Patient preference should be taken into account
- A fully informed patient may accept more risk than us despite the guidelines. By the same token we should not offer tests that would not change management and may cause unnecessary anxiety, over-investigation and overtreatment

Thank you

Any Questions?