Controversies in thrombosis

The clot thickens..

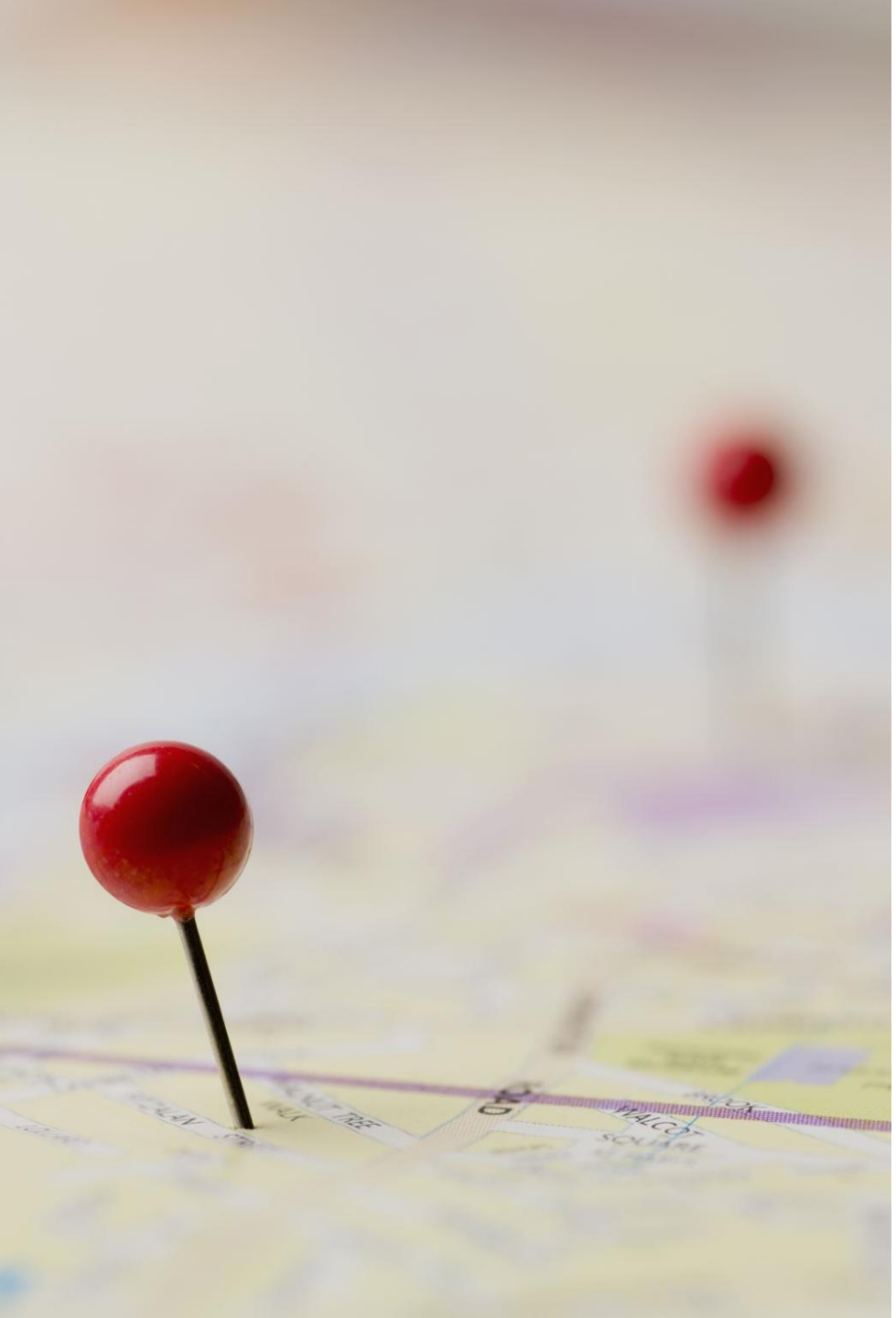
Carolyne Elbaz, MDCM, MScCH

Hematology, St Mary's Hospital

Associate Professor, McGill University

Disclosures

- None



Good resources – check platform

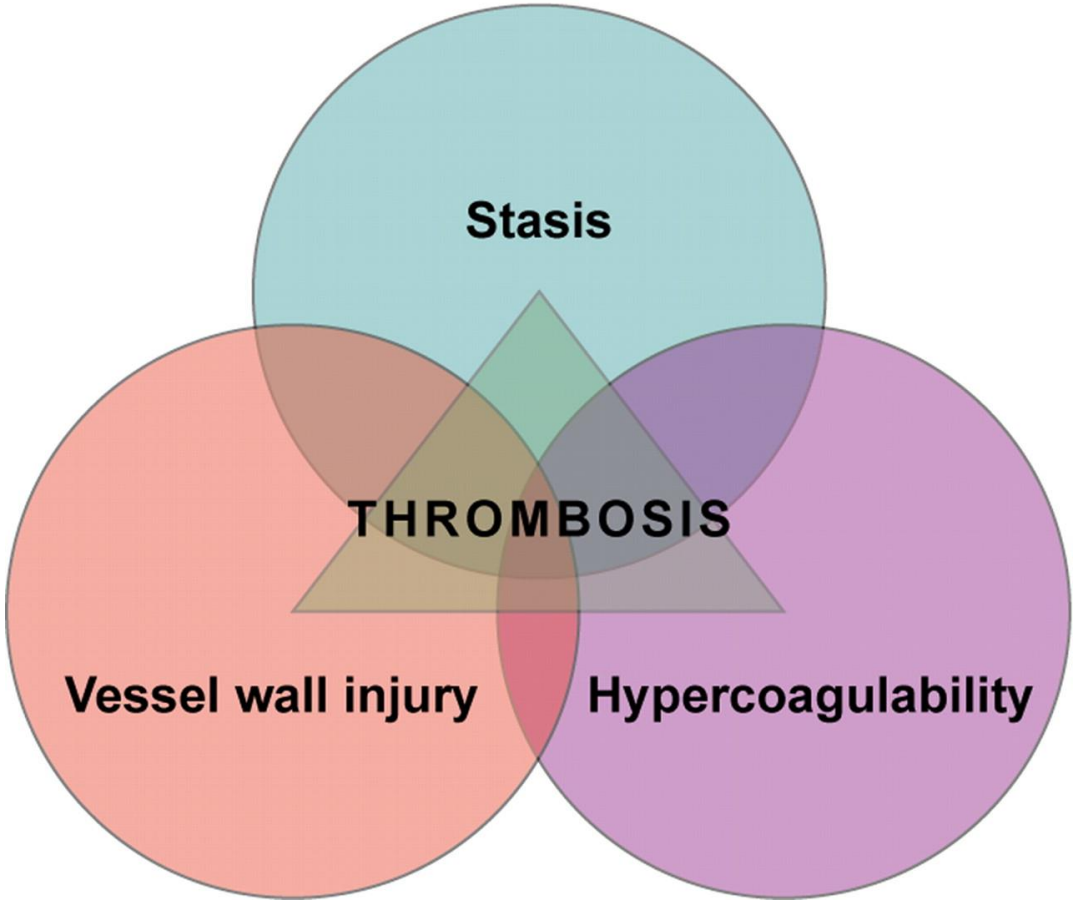
- https://thrombosiscanada.ca/clinicalguides/
- https://thrombosiscanada.ca/tools/
- https://transfusionontario.org/wp-content/uploads/2020/06/ORBCON-EN-BE_Coagulation_02259.pdf

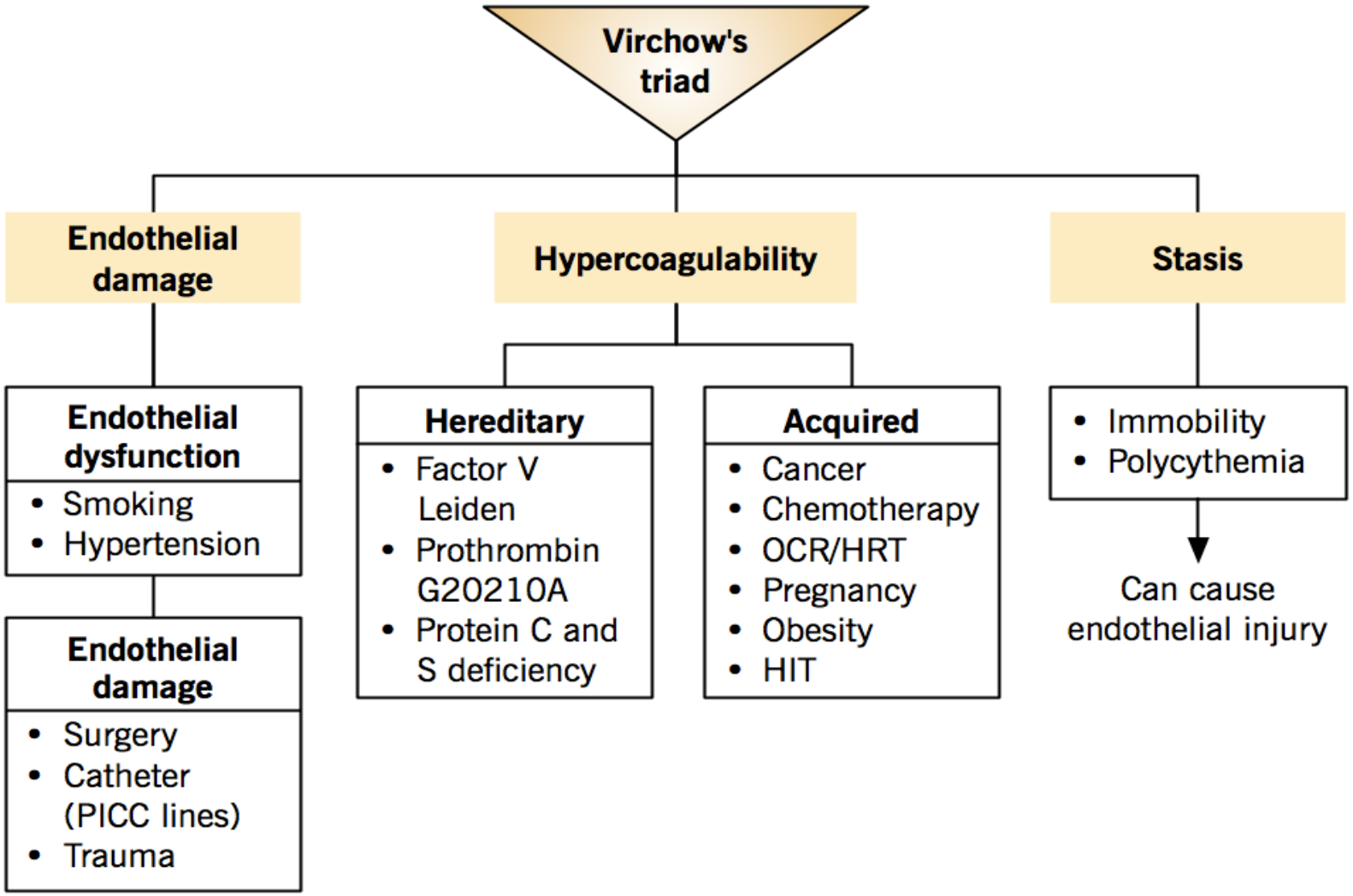
Objectives

- Review the management of estrogen-associated VTE
- Review the management of superficial venous thrombosis
- Describe the indications for thrombophilia testing

Brief review

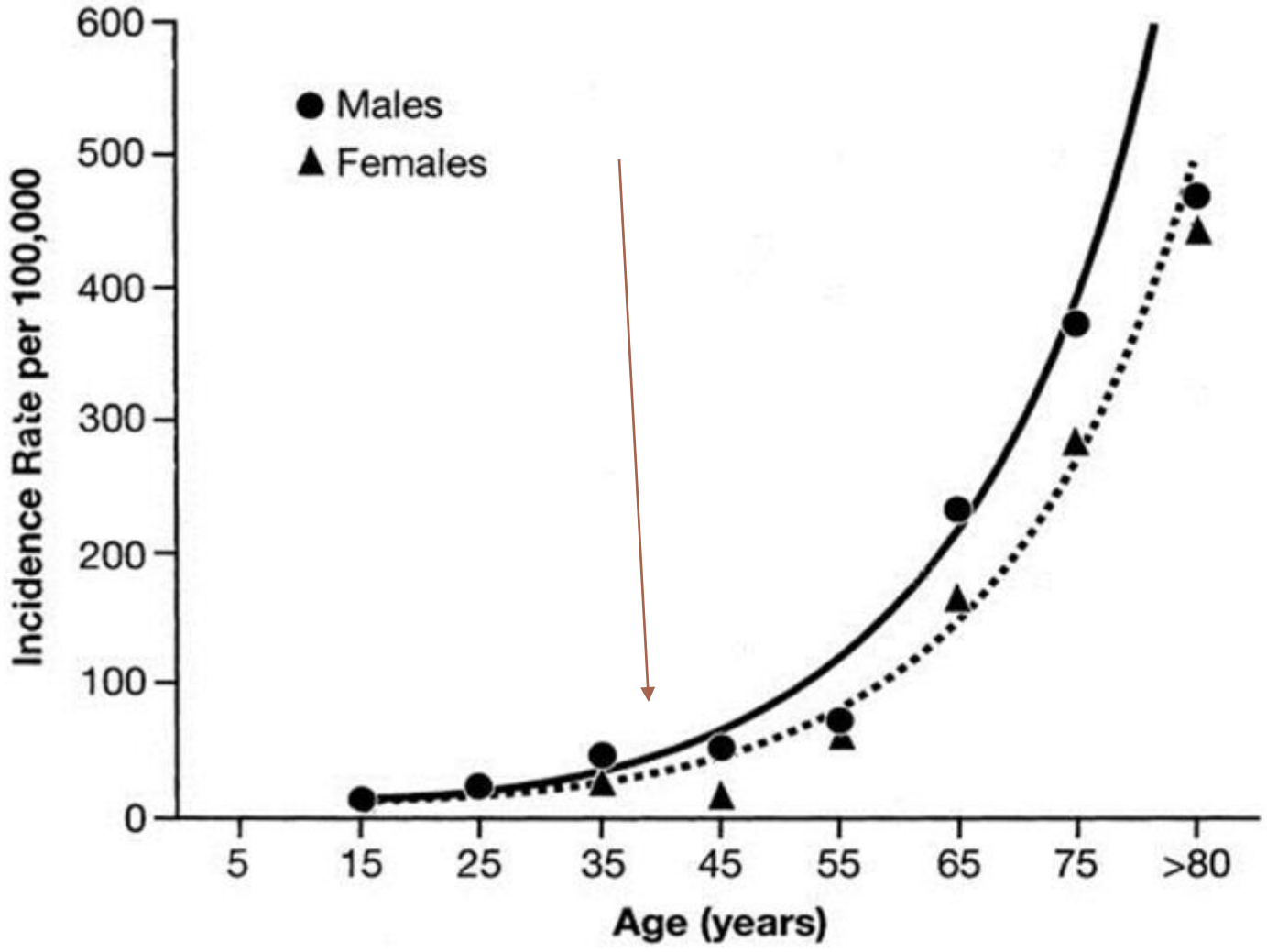
Risk factors for VTE





http://www.pathophys.org/wp-content/uploads/2013/01/PE-Virchow.png

Age as an independent risk factor

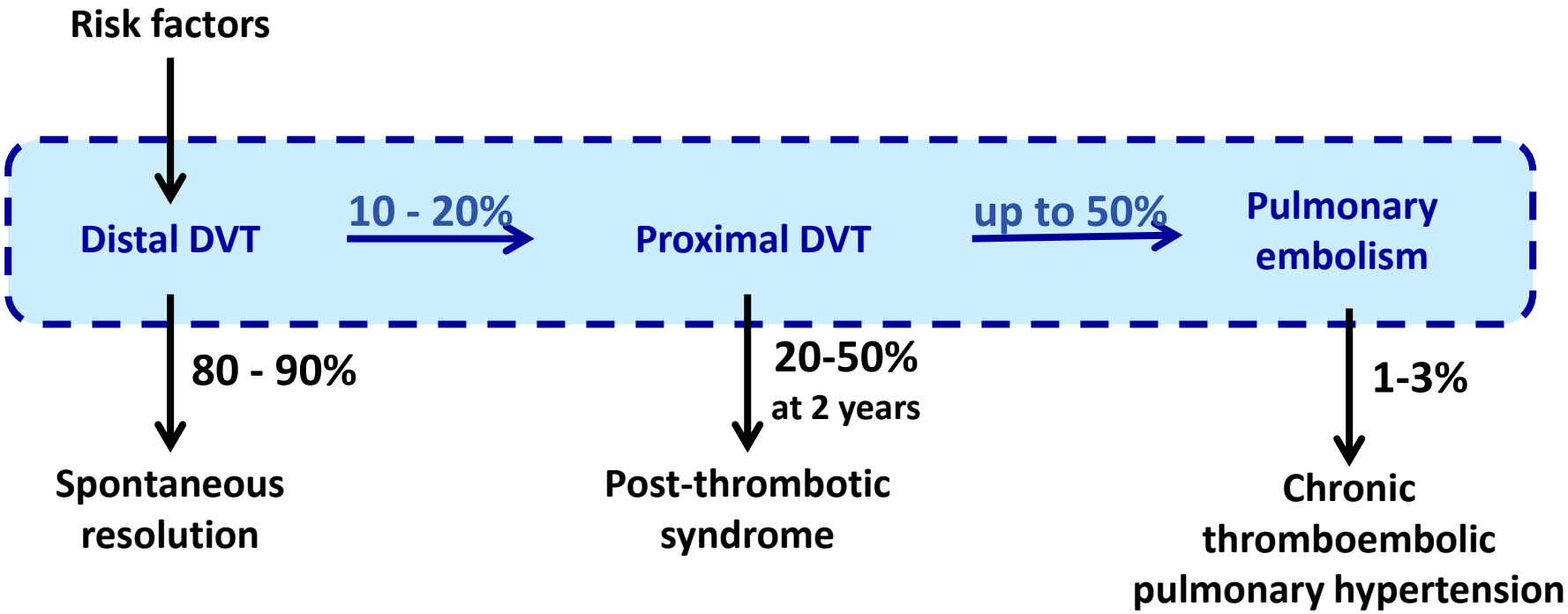


Anderson FA, et al. Arch Intern Med 1991;151:933

VTE is Common

- VTE occurs in 1/1000 of the population annually
- 50-60% of symptomatic VTE occurs in patients who are hospitalized or who have recently been in hospital
- VTE is a common preventable cause of hospital death (5-10% of hospital deaths)

Natural history of VTEs

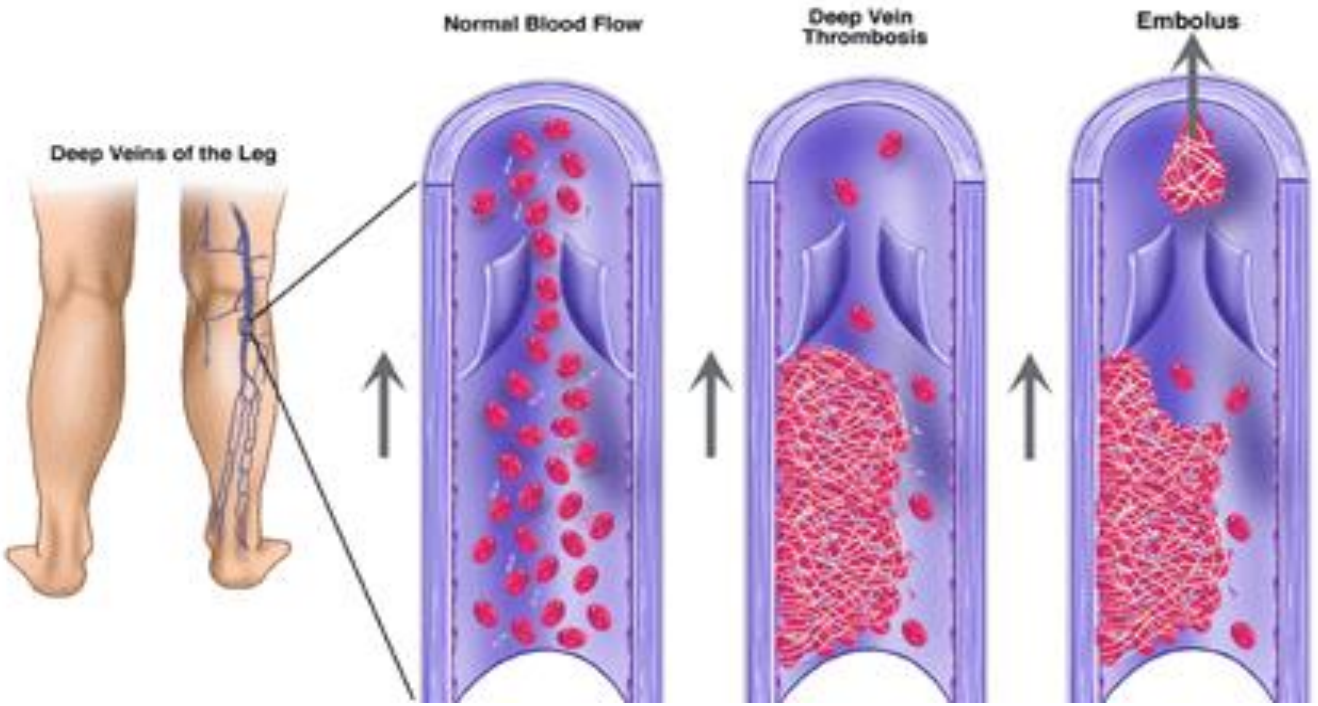


VTE Classification

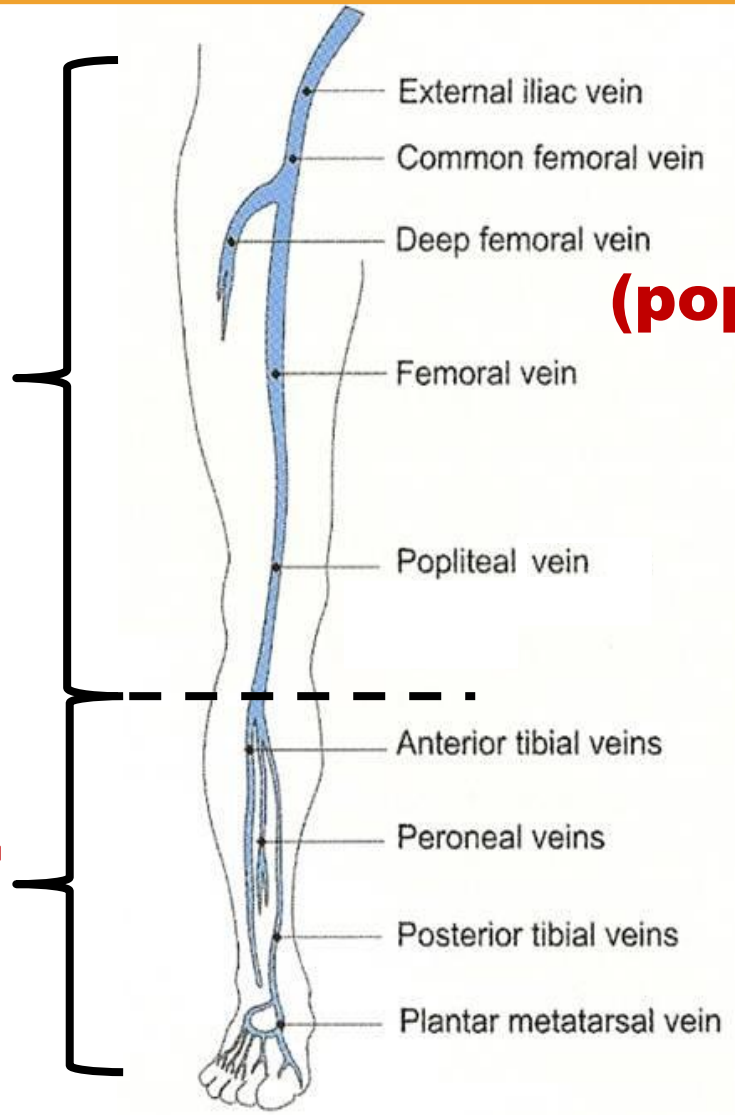
1. Deep Vein Thrombosis (DVT)
2. Pulmonary Embolism (PE)

Deep Vein Thrombosis (DVT)

- **Thrombus in one or more deep veins**
  - **Occurs in the legs much more often than the arms**
  - **Can also occur in other veins: abdominal, pelvic or cerebral veins, inferior vena cava, etc.**



Distal DVT vs Proximal DVT



Proximal DVT
(popliteal vein and higher)

Distal DVT
(below the popliteal vein)

http://venacure-evlt.com/endovenous-laser-vein-treatment/procedure/venous-anatomy/

Investigation of VTE

- Risk factors
- History
- Physical Exam
- D-dimer
- Doppler ultrasound
- CT pulmonary angiography

Pretest probability

Pretest Probability: Wells Score

Wells Score for DVT	
Previous VTE	1
Active Cancer (≤6 months)	1
Paresis OR Recent Plaster Cast	1
Bedridden > 3 days OR Major Surgery < 4 weeks	1
Tender Along Deep Vein System	1
Whole Leg Swelling	1
Calf swelling > 3 cm	1
Pitting Edema (in affected leg)	1
Collateral Veins	1
Alternate Diagnosis at Least as Likely	-2

0 = DVT unlikely (incidence 5%)

1 - 2 = moderate DVT risk (incidence 17%)

> 2 = DVT likely (incidence 17 - 53 %)

Wells Score for PE	
Previous VTE	1.5
Active Cancer (≤6 months)	1
Bedridden > 3 days OR Major Surgery < 4 weeks	1.5
Symptoms and signs of DVT	3
PE is Most Likely Diagnosis	3
Hemoptysis	1
HR > 100	1.5

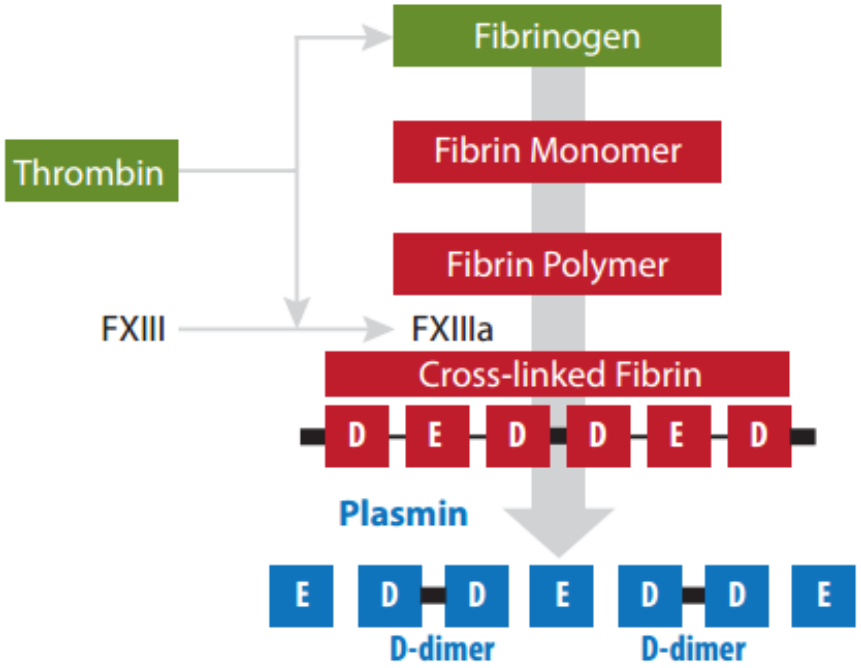
≤ 4 = PE unlikely (3% incidence)

> 4 = PE likely (28% incidence)

Don't use in inpatients!

D-dimer

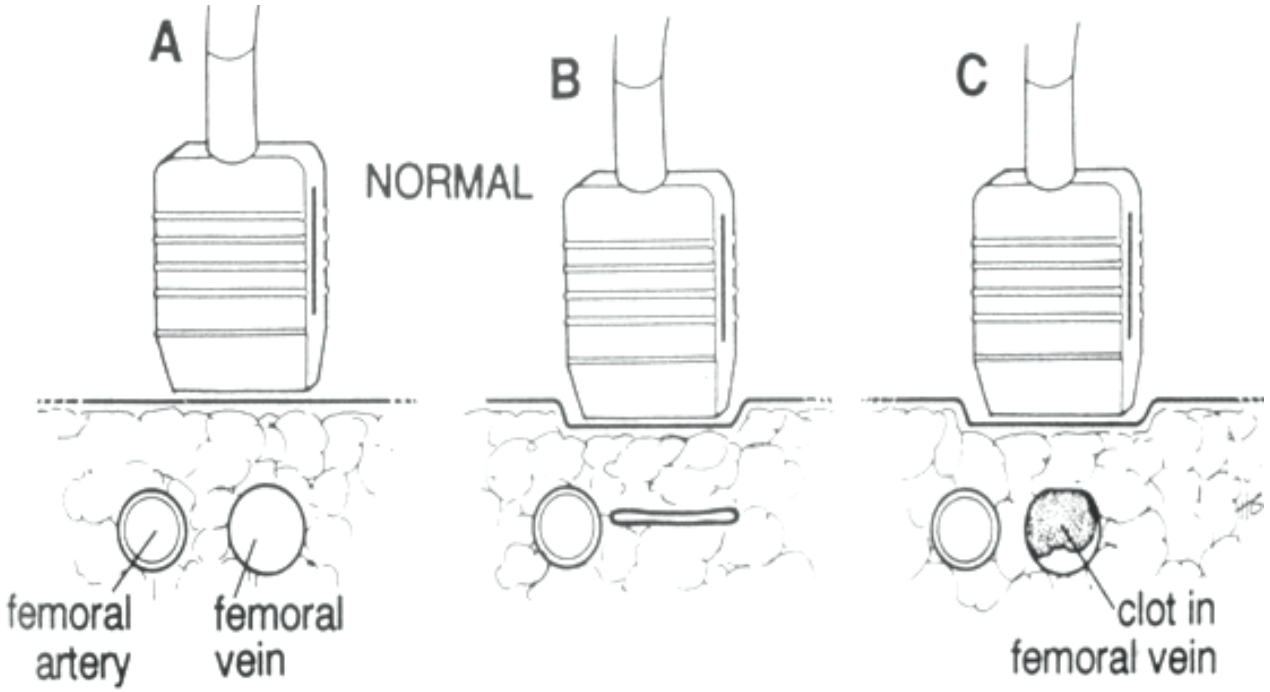
- Formed by the effect of plasmin on fibrin
- Increased in acute VTE
  - Also increased after surgery, trauma, in cancer, sepsis, inflammation, healthy elderly, pregnancy, etc.
- Only useful when normal
- Normal D-dimer = helps rule out acute VTE
- Positive D-dimer = not diagnostic for VTE



Investigation of Suspected DVT

Doppler ultrasonography (DUS)

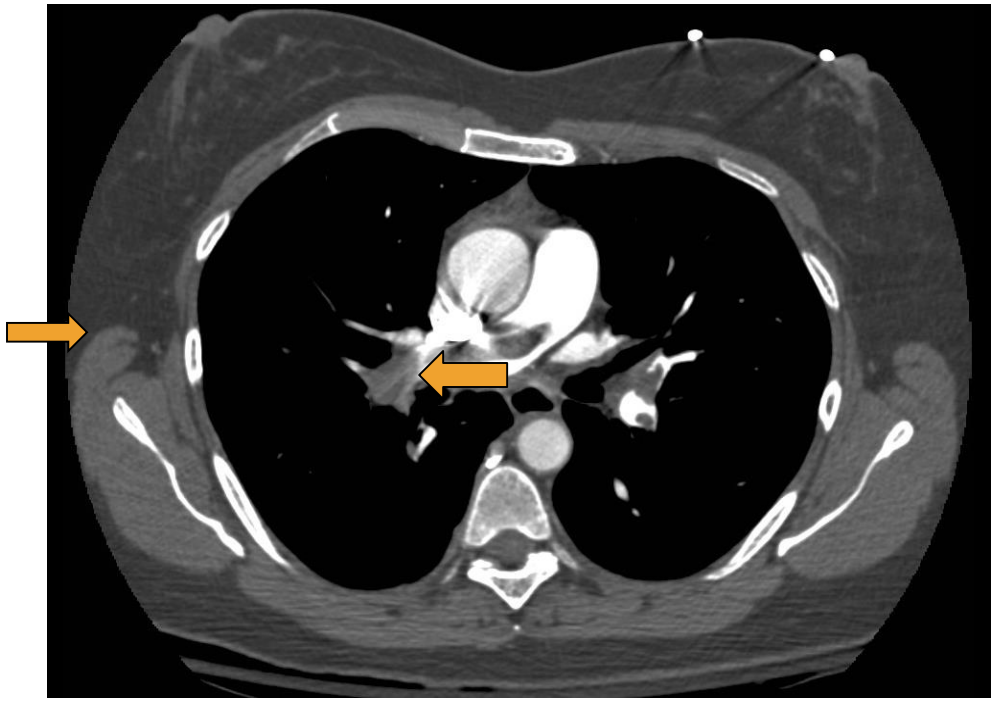
- Very accurate for proximal DVT
- Less accurate for pelvic and calf DVT



Investigation of Suspected PE

CT pulmonary angiogram (CTPA)

- Very accurate for PE
- Test of choice for most patients
- Requires IV contrast (kidneys)
- Radiation exposure = ~ 300-600 CXRs



Treatment principles

If high suspicion, treat **ASAP** unless compression ultrasound is readily available

Treatment should have immediate anticoagulant effect

Outpatient management is preferred

Consider patient’s bleeding risk

3 Treatment Options for VTE

LMWH injections

Generally once daily

1

warfarin (INR 2.0-3.0)

5-7 days

- APLAS, metallic valve..

2

Low molecular weight heparin injections

- pregnancy, some VTE in cancer, high bleeding risk

3

Direct oral anticoagulant (DOAC)

- rivaroxaban, apixaban

Balance

Risk of recurrence	Risk of bleed
• Provoked • Unprovoked • Cancer	• Age • Concomitant meds • Hx of bleeding

Risk of recurrent thrombosis

VTE type	First year	5 year risk
First episode of unprovoked VTE	10%	30% (5-6%/year)
First VTE provoked by non surgical risk factor	5%	15% (3%/year)
First VTE provoked by surgery	1%	3% (0.5%/year)
Cancer	15%	-

Approach to VTE

- Does this patient need anticoagulation?
- If so, how long?
- Which is the preferred agent?
- Additional considerations

Case 1

Case 1 : Luiza

- 23 F nurse
- On Alesse (levonorgestrel and ethinyl estradiol) x 1 year for contraception
- No other pmhx
- No family hx of VTE
- Presents with a few weeks of SOBOE, found to have bilateral PE.

Questions – Luiza

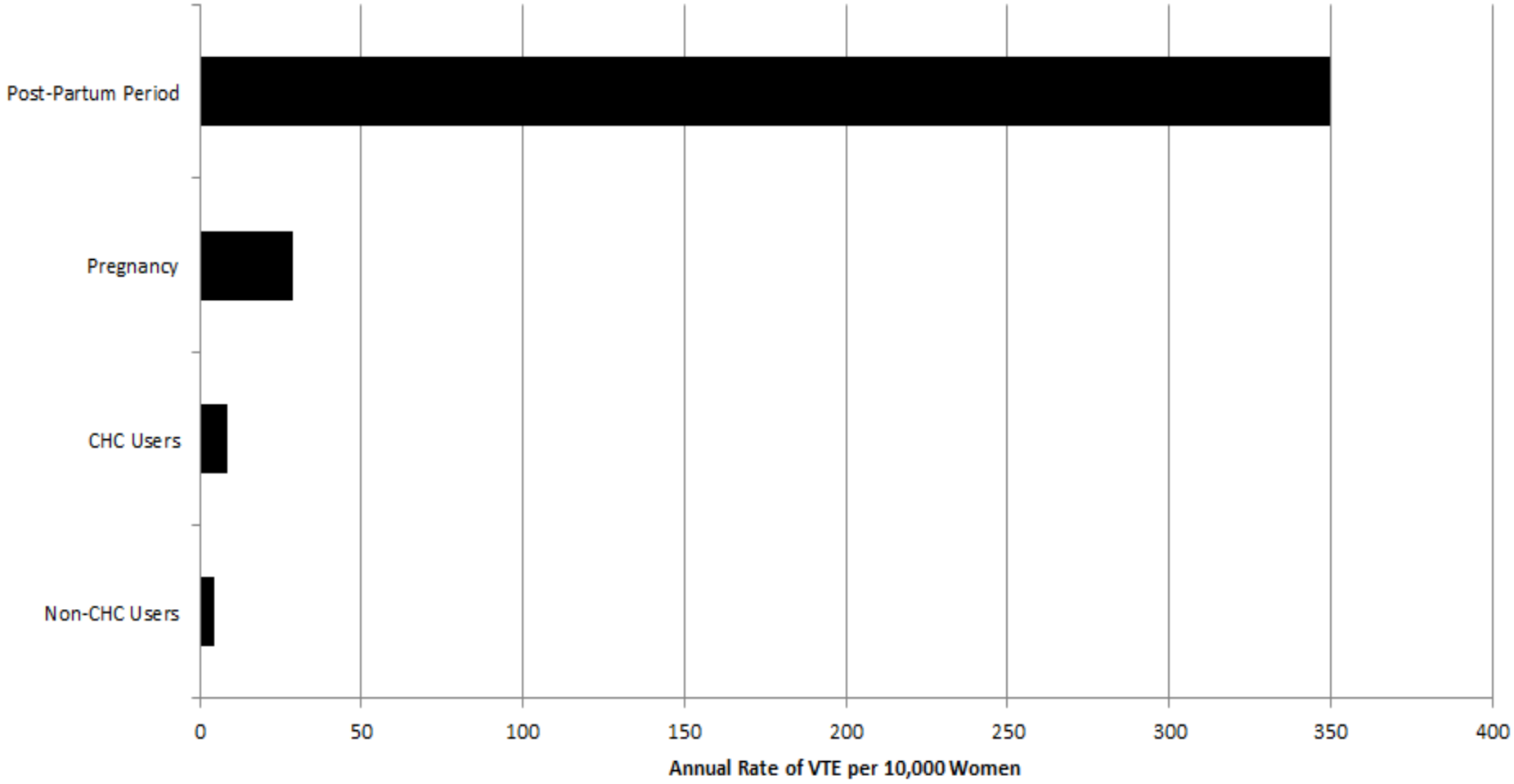
- Does she need anticoagulation?
- If so, which agent?
- How long should she receive anticoagulation?
- Additional considerations
  - What should we do about her OCP?
  - Does she need another contraceptive method?
  - How do we manage a pregnancy ?

Estrogen and pregnancy

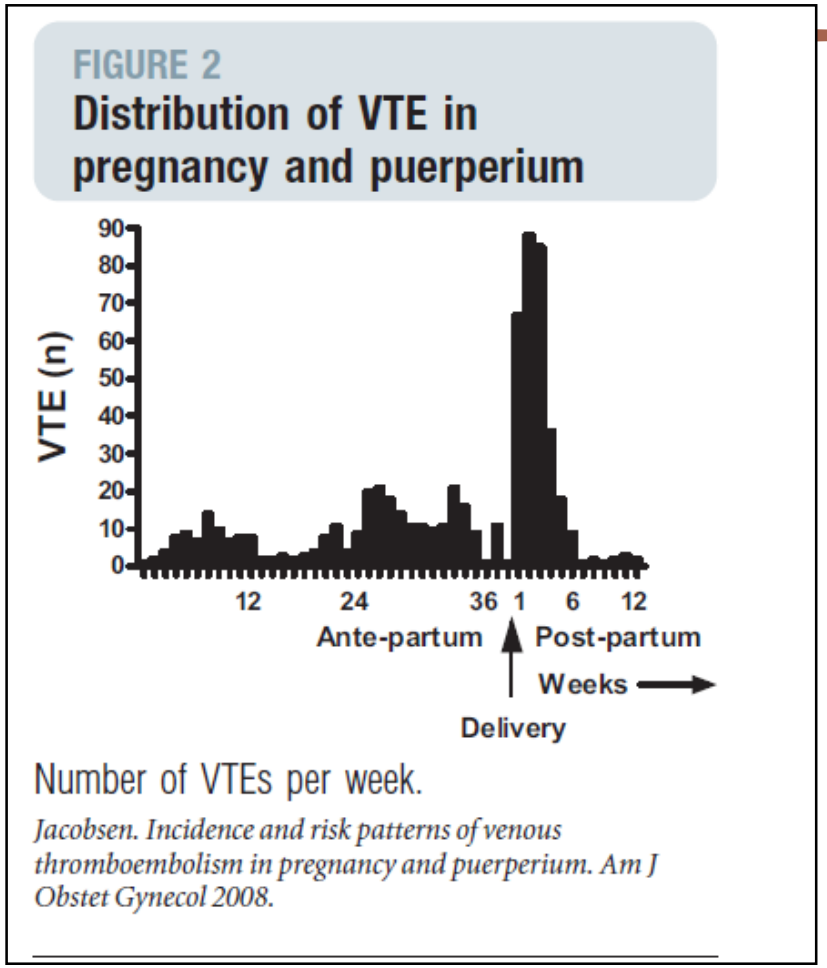
Combined hormonal oral contraceptives (CHC)	• **4-fold increased risk of VTE**
	• **Risk depends on:**
	  • **Dose of estrogen**
	  • **The specific progestin**
	  • **Patient age**
	  • **Other risk factors (e.g. smoking, obesity, family history of VTE)**

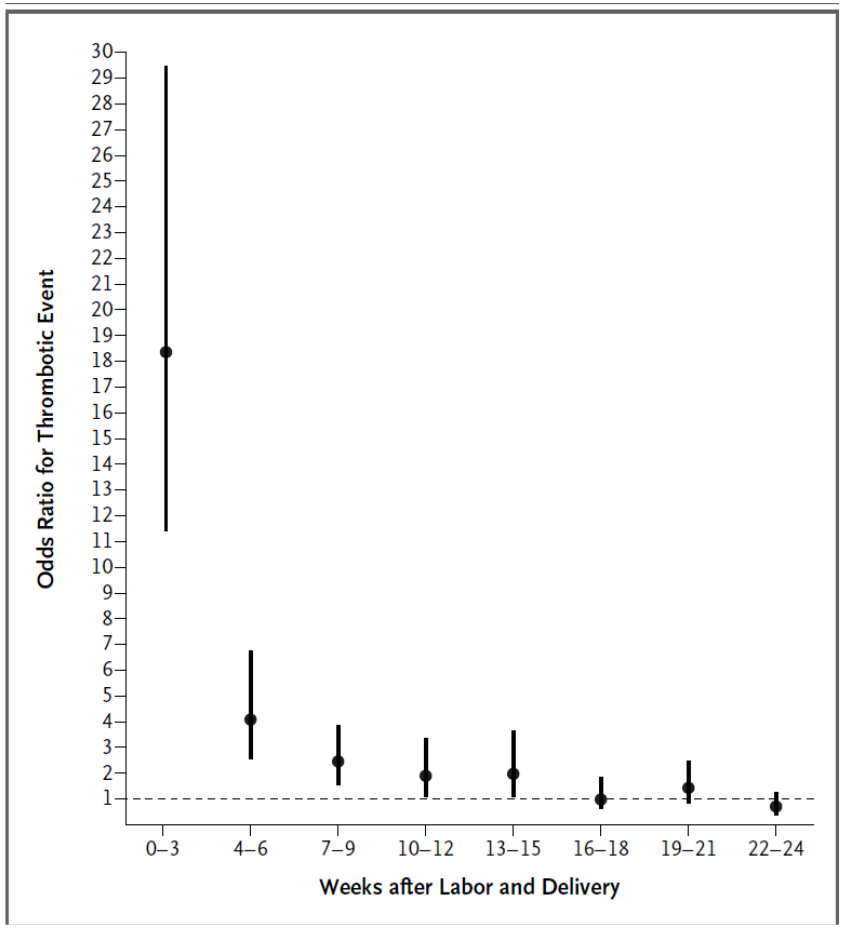
Hormone replacement therapy (HRT)	• 4-fold increased risk of VTE • Absolute risk higher than CHC because population risk greater at older age
Pregnancy	• 4-fold increased risk of VTE
Postpartum	• 8-fold increased risk of VTE

Estrogen and pregnancy



Epidemiology of post partum VTE





Jacobsen, A. F et al. *Am. J. Obstet.* Gynecol. 2008

Kamel, H. et al. N. Engl. J. Med. 2014

Estrogen associated VTE : controversial definition

- Although the American Society of Hematology guidelines define the use of estrogen-containing contraceptives as a minor transient risk factor, others consider estrogen-containing contraceptive related VTE to be unprovoked.

- The duration of treatment in patients with a minor transient risk factor is, however, debatable.

Hormone preparations	Progesterone	Estrogen (mcg) (multiple numbers indicate multiphasic/extended formulations)	Effectiveness*	VTE risk
Progestin only pills	Norethindrone	None	93.0%	No increased risk
	Drospirenone	None		
LNG IUD	Levonorgestrel	None	99.7%	No increased risk
Implant†	Etonogestrel	None	99.9%	No increased risk
Injectable ("Depo")	Medroxyprogesterone	None	96.0%	OR 2.2 (1.3-4.0)‡
Vaginal ring	Segesterone	Ethinyl estradiol (13 mcg/day)	93.0%	6.5-fold (4.7-8.9) increased risk compared to non hormone users (mixed data compared to oral preparations)§
	Etonogestrel	Ethinyl estradiol (15 mcg/day)		
Transdermal patch¶	Levonorgestrel	Ethinyl estradiol (30 mcg/day)	93.0%	7.9-fold (3.5-17.7) increased risk compared to non hormone users (mixed data compared to oral preparations)§
	Norelgestromin	Ethinyl estradiol (30 mcg/day)		
4th Generation Progesterone COC	Dienogest	Estradiol valerate (3,2,2,1 mg)	93.0%	Similar/improved risk as 2nd generation progesterone COC

LeVasseur et al, 2021.

2nd Generation Progesterone COC	Levonorgestrel	Ethinyl estradiol (20, 10)	93.0%	OR 2.38 (2.18-2.59)**
		Ethinyl estradiol (20)		
		Ethinyl estadiol (30)		
		Ethinyl estradiol (20, 25, 30,10)		
		Ethinyl estradiol (30, 10)		
1st Generation Progesterone COC	Norethindrone acetate	Ethinyl estradiol (10,10)	93.0%	No data comparing 1st and 2nd generation, recommend lowest dose of estrogen for lowest risk of VTE
		Ethinyl estradiol (20)		
		Ethinyl estradiol (30)		
		Ethinyl estradiol (20,30,35)		
	Norethisterone††	-		
	Norethindrone	Ethinyl estradiol (35)		
	Ethynodiol diacetate	Ethinyl estradiol (35)		
		Ethinyl estradiol (50)††		
	Norgestrel	Ethinyl estradiol (30)		
		Ethinyl estradiol (50)††		
	Medroxyprogesterone††	-		
3rd Generation Progesterone COC	Norgestimate	Ethinyl estradiol (35)	93.0%	OR 2.53 (2.17-2.96)**
	Desogestrel	Ethinyl estradiol (20,0,10)	93.0%	OR 3.64 (3.00-4.43)**
		Ethinyl estadiol (30)		
	Gestodene†	-		OR 4.28 (3.66-5.01)**
4th Generation Progesterone COC	Drospirenone	Ethinyl estradiol (20)	93.0%	Similar risk as 3rd generation progesterone COC
		Ethinyl estradiol (30)		
		Estetrol (14.2 mg)		

Alesse

Lolo

Freya

YAZ

Highest risk

LeVasseur et al, 2021.

Anticoagulants may increase menstrual bleeding

Incidence of Major or Clinically Relevant Nonmajor Uterine Bleeds in Randomized Controlled Trials of Direct Oral Anticoagulants[7,8]

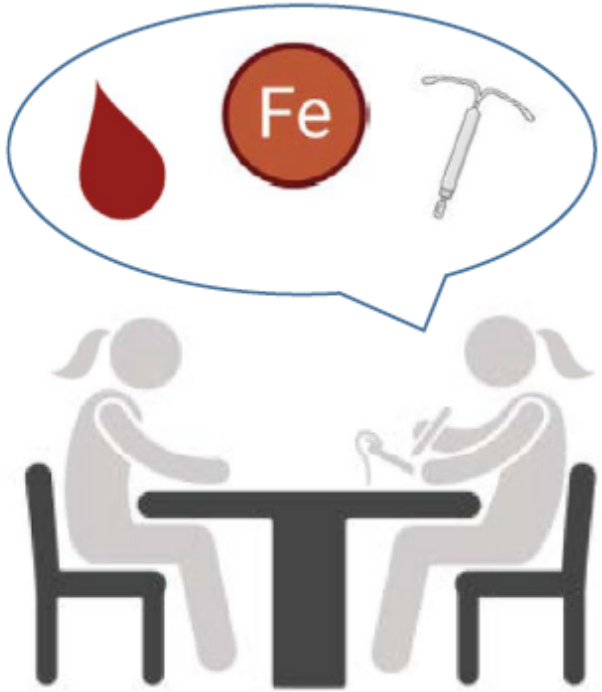
Drug	Incidence	OR (vs warfarin)
Rivaroxaban	9.5%	2.1
Edoxaban	9.0%	1.26
Apixaban	5.4%	1.18
Dabigatran	5.9%	0.59

Proportion of Women Requiring Medical or Surgical Therapy for Uterine Bleeding Within Six Months of Anticoagulant Initiation[9]

Samuelson Bannow BT, et al. *Thromb Res*. 2021;

Starting, Monitoring and Stopping Anticoagulation in Menstruating People

Have a low index of suspicion



When starting:

Ask about:

- History of heavy or abnormal bleeding
- History of iron deficiency

Check:

- CBC & ferritin

Counsel on:

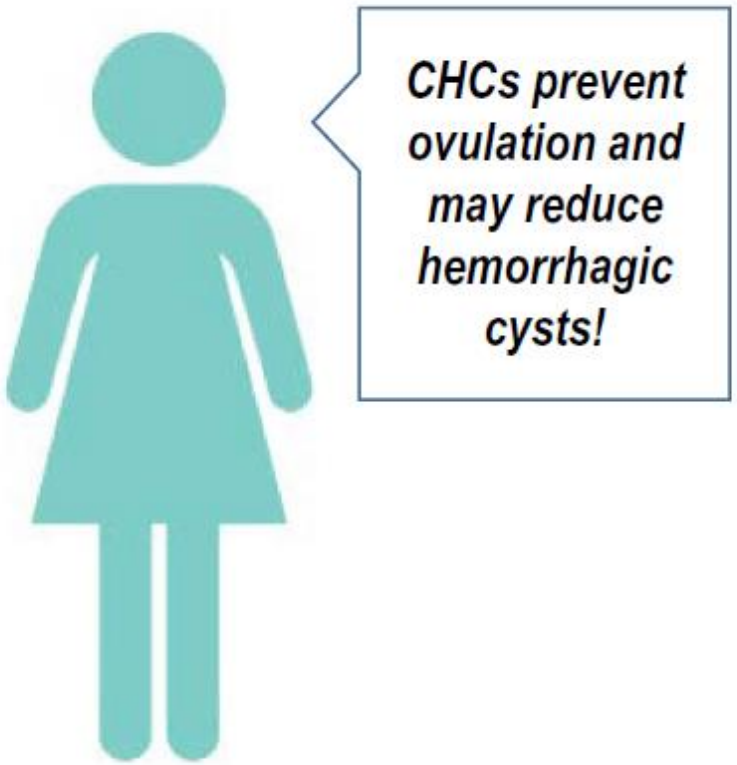
- Anticoagulant options & risk of HMB
- Signs and symptoms of HMB
- Contraception

Did you know?

You **do not have to stop oral contraceptives** in therapeutically anticoagulated patients. Anticoagulation prevents VTE and continuing OCPs may prevent HMB.[10]

Risk of VTE in Anticoagulated Women on Hormonal Therapies[10]

Hormonal Therapy	VTE Risk (%/year)
None	4.7
Estrogen-containing	3.7
Progestin-only	3.8
Any therapy	3.7



Martinelli I., *Blood*. 2016

Follow up

At future visits

Ask about:

- Changes in periods
- Symptoms of anemia

Check:

- CBC & ferritin at least every 6 months

Discuss:

- Plan for stopping anticoagulation
- Possible need to transition from combined contraceptives to progesterone-only options

When stopping

Discontinue:

- Estrogen therapies 1 month in advance

Offer:

- Effective, estrogen-free contraception

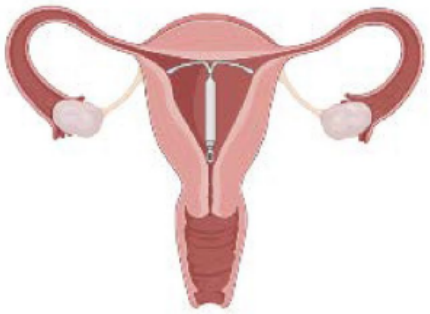
Discuss:

- Planning for future pregnancies if desired, including preconception counseling with obstetrics or perinatology

Progestin-only Contraceptives for Menstrual Management

Changes in VTE Risk with Addition of Progestin Only Contraceptives

Levonorgestrel IUS	Subdermal Implant	Progestin Pills	Depot - medroxyprogesterone
⟷	⟷	⟷	↑↑



The levonorgestrel intrauterine system (LNG-IUS) is associated with:

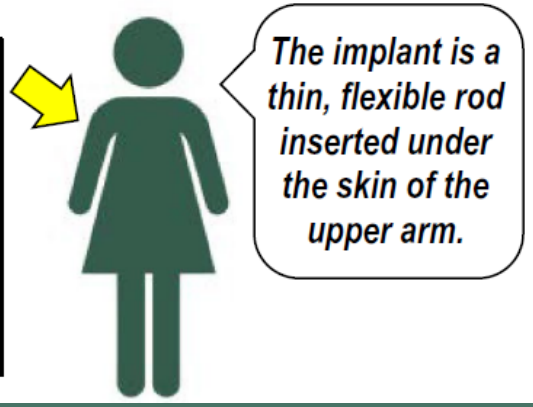
- 86% reduction in blood loss at 3 months
- 97% reduction at 12 months[14]
- High rates (>20%) of amenorrhea
- >99% effective for prevention of pregnancy[12]

Mirena

Nexplanon

The etonogestrel subdermal implant is associated with:

- Amenorrhea in 22%
- Infrequent bleeding in 34%
- Prolonged 9 (17.7%) or frequent (6.7%) bleeding/spotting [15]
- >99% effective for prevention of pregnancy



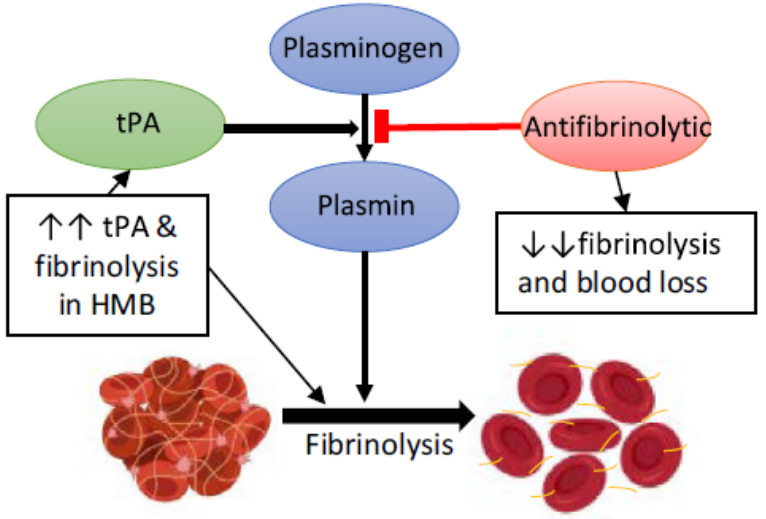
The implant is a thin, flexible rod inserted under the skin of the upper arm.

Additional Approaches to Menstrual Management

Tranexamic acid is effective for the treatment of HMB

- 40% reduction in menstrual blood loss
- Improved quality of life
- Contraindicated in the setting of acute thrombosis
- Not studied in women on anticoagulation or with a history of VTE

Fibrinolysis and Menstrual Bleeding



Holding or discontinuing anticoagulation early

- Increases the risk of recurrent VTE
- Is not proven to reduce menstrual blood loss
- Is not recommended

Lukes A,. *J et al. Obstet Gynecol.*

Management of Iron Deficiency in HMB + Anticoagulation

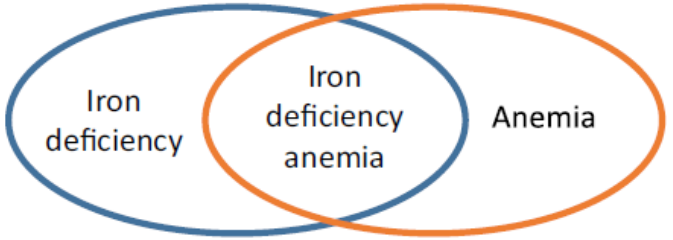
Beware of collateral damage

- Iron deficiency effects up to 48% of reproductive age women
- Pregnancy and menstrual bleeding are contributing factors
- Risk of iron deficiency increases significantly with HMB

Iron deficiency is associated with:

- Fatigue
- Loss of concentration
- Headaches
- Easy bruising
- Restless legs
- Hair loss
- Pica

Ferritin is the best measure of iron stores. Serum iron levels vary with many factors including recent food intake and time of day.



Did you know?
Patients may be symptomatic from iron deficiency without anemia. Ferritin should always be checked in addition to the CBC in menstruating individuals.

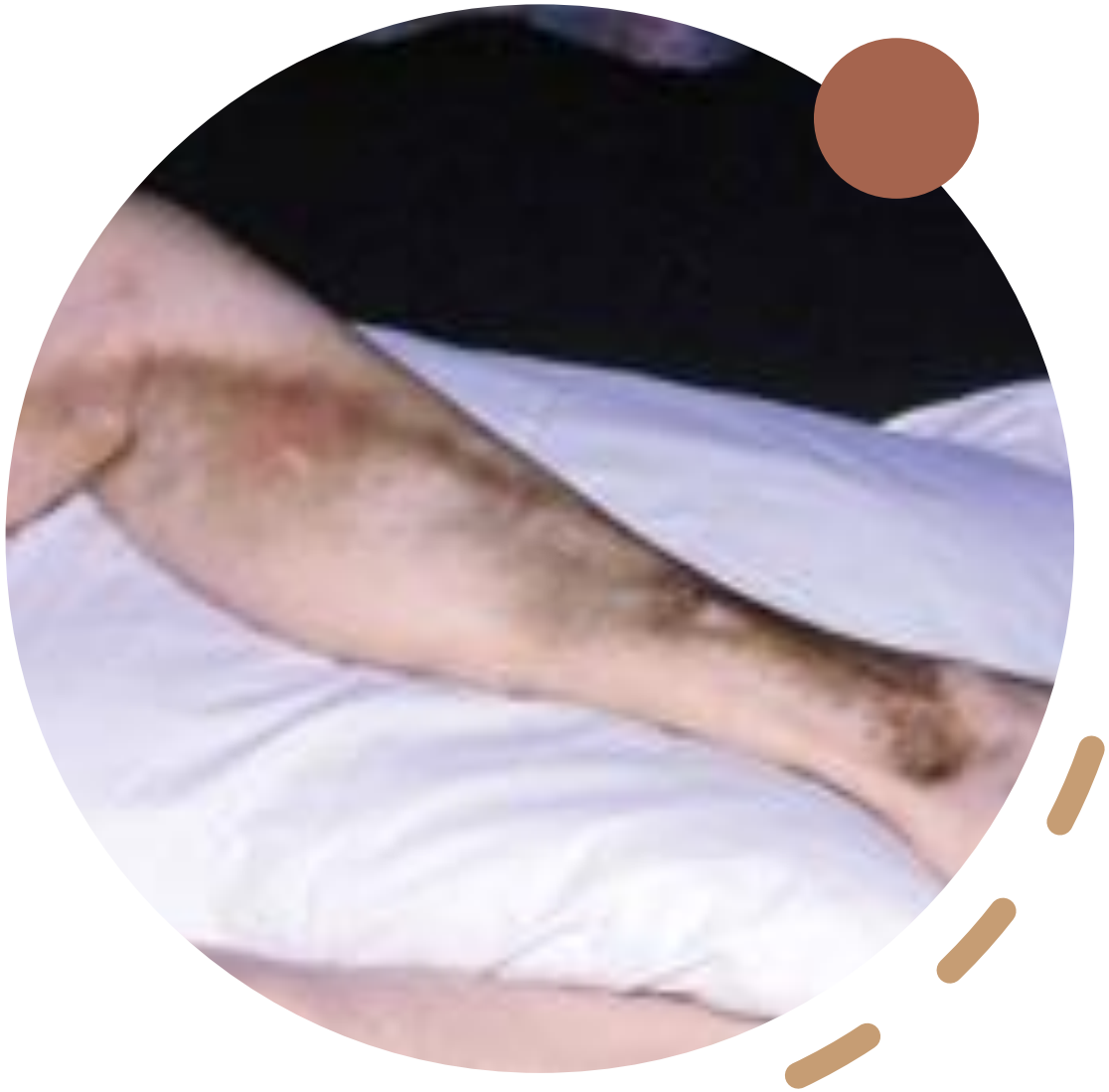
Questions – Luiza

- Does she need anticoagulation?
  - Yes
- If so, which agent?
  - DOAC, ?Eliquis for minimal menstrual bleeding
- How long should she receive anticoagulation?
  - Minimum 3-6 months
- Additional considerations
  - What should we do about her OCP?
    - Ok to continue but eventually needs another contraceptive method if AC stopped and DOAC teratogenic
  - How do we manage a pregnancy ?
    - Antepartum and postpartum prophylaxis

Case 2

Mr C

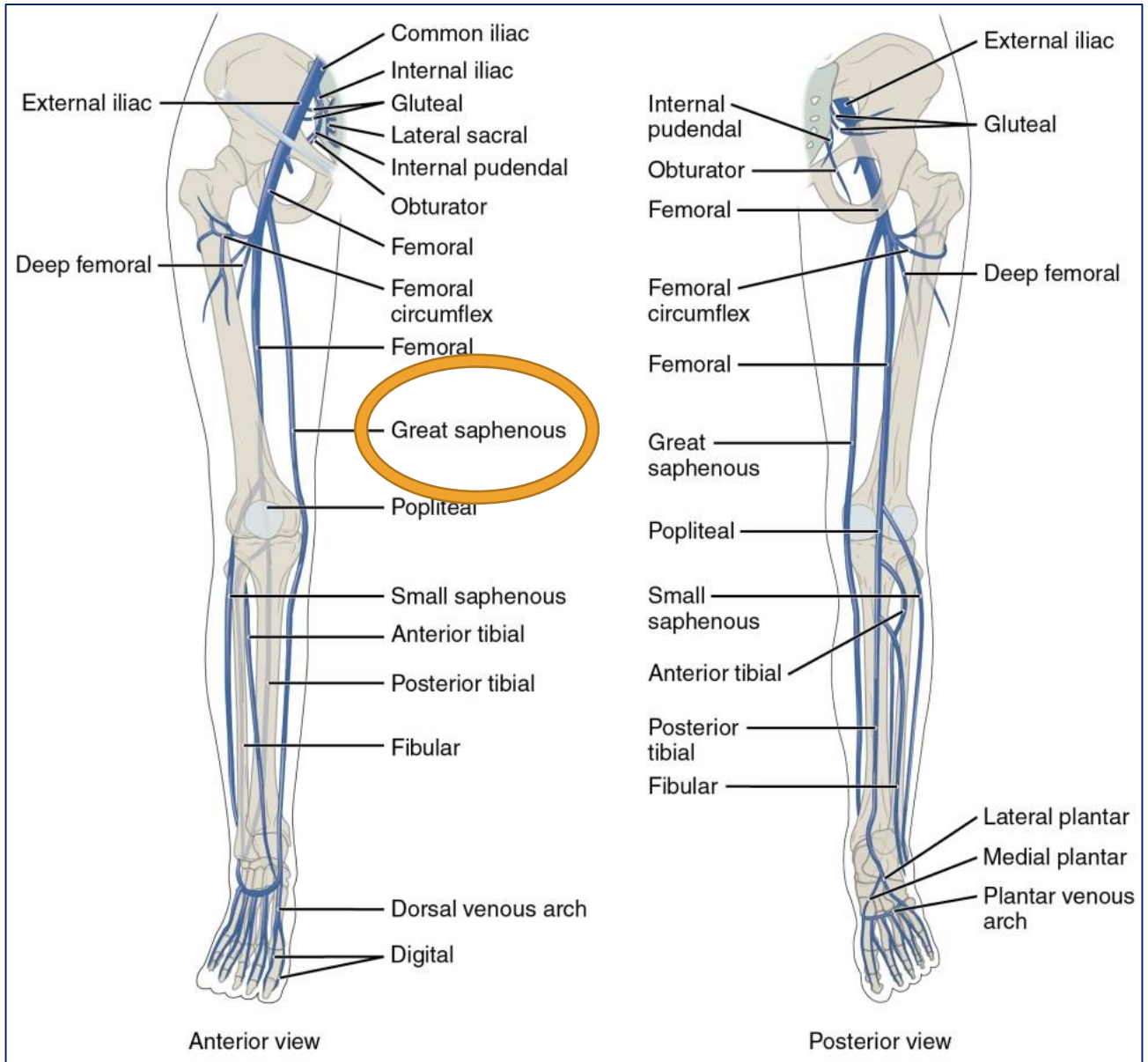
- 71 M
- PMHX : HTN, DLP
- Presents with pain at right medial thigh
- Physical exam shows a tender palpable cord from mid calf to mid thigh



Questions – Mr. C

- Does he need anticoagulation?
- If so, which agent?
- How long should he receive anticoagulation?
- Additional considerations
  - Should I send him for an ultrasound?

Review



- **Proximal veins**
  - **Common iliac**
  - **Internal iliac**
  - **External iliac**
  - **Superficial femoral**
  - **Popliteal**
- **Distal veins**
  - **Peroneal**
  - **Posterior tibial**
  - **Anterior tibial**
- Superficial veins
  - Greater saphenous
  - Lesser saphenous

Superficial vein thrombosis

- Common condition
  - incidence of 0.3 to 1.5 per 1000 person-years in older patients.
- SVT can occur in every vascular region, including the arm (often as a result of trauma, blood sampling or intravenous injections, or indwelling catheters), chest, or abdominal veins, but the most common manifestation is in the superficial vein system of the lower extremities.

Decousus H. et al, Annals of Internal Medicine, 2010

Does he need a Doppler ultrasound?

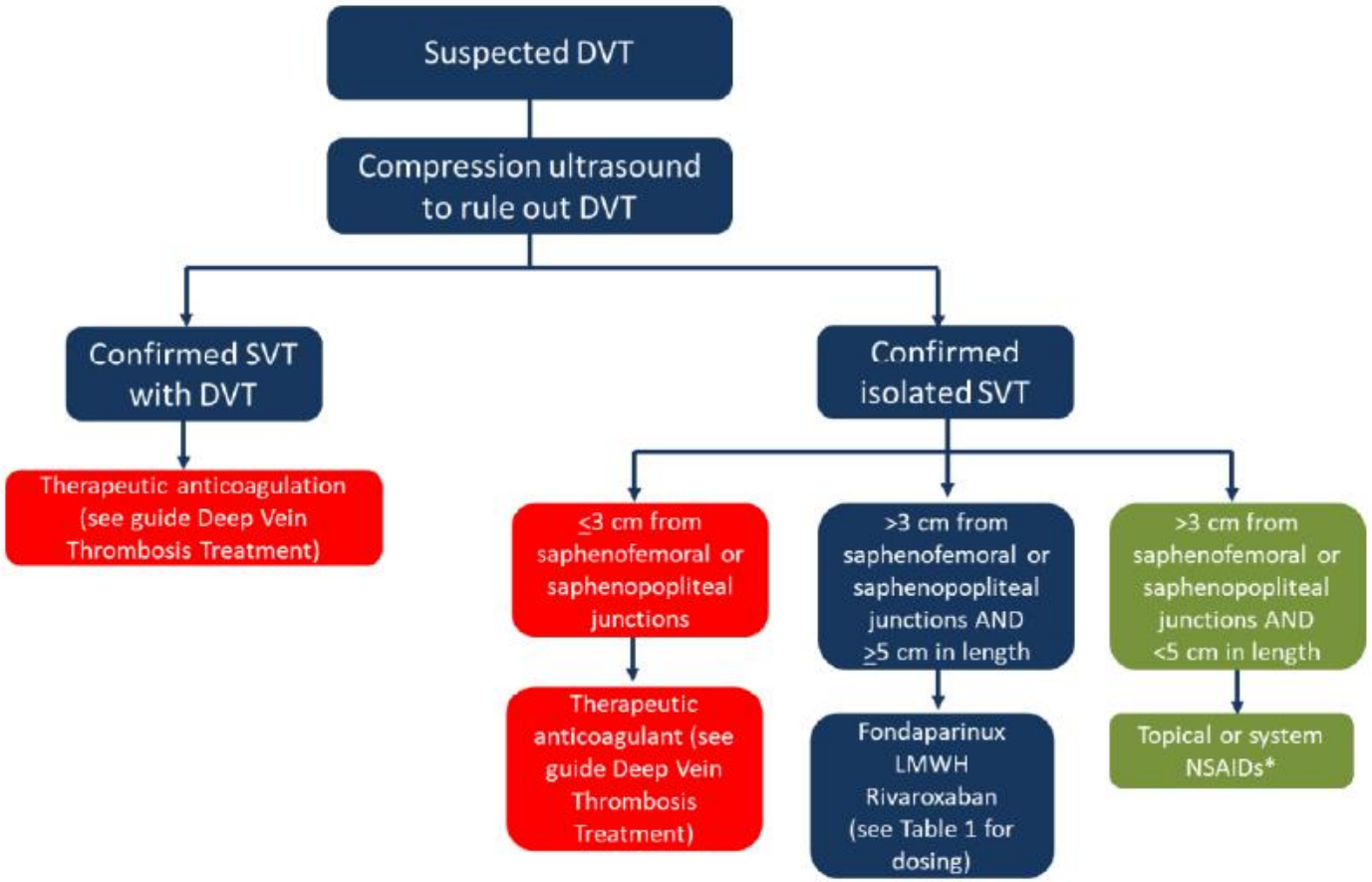
- In the Prospective Observational Superficial Thrombophlebitis (POST) The prevalence of isolated SVT, concomitant DVT, and PE without DVT was 75.1%, 23.5%, and 1.1%, respectively.
- Importantly, 17.2% of patients presented with concomitant DVT in the contralateral leg.
- DVT was significantly more common in patients in whom SVT affected the trunk of the greater saphenous vein, extended close to the saphenofemoral/popliteal junctions, or affected perforating veins concomitantly.

Decousus H. et al, Annals of Internal Medicine, 2010

Management

- In patients with SVT who have a high risk of thromboembolic complications, a bilateral ultrasound may be considered.
  - Patients with below the knee SVT restricted to a varicose vein without additional VTE risk factors may not require CUS assessment
- Furthermore, every patient with SVT should be assessed for symptoms and signs suggestive of PE, because the superficial vein thrombus may have progressed into the deep vein system.
  - Patients with symptoms of PE should undergo objective testing.
- If patients with SVT are diagnosed with concomitant DVT and/or PE, the type, intensity, and duration of anticoagulant therapy should be guided by the DVT and/or PE.

FIGURE 1: APPROACH TO MANAGEMENT OF SVT



* Prophylactic/intermediate dosing anticoagulation is reasonable for severe symptoms or with risk factors. If not treating or if using topical NSAIDs, monitor for extension with serial U/S

DVT, deep vein thrombosis; **NSAID**, non-steroidal anti-inflammatory; **LMWH**, low molecular weight heparin

Management principles

1. Patients in whom a **concomitant DVT/PE** is identified should be managed with **therapeutic anticoagulation x 3 months**
2. Isolated SVT which extends to **within 3 cm of the SFJ or SPJ** is associated with a high risk of progression into the deep venous system. These patients should also receive **therapeutic anticoagulation** for 3 months
3. Isolated SVT **≥5 cm in length** located >3 cm from the SFJ should receive **prophylactic doses of fondaparinux or rivaroxaban or LMWH** for 45 days.
    I. Patients can also receive topical (NSAIDs) and/or compression therapy for symptomatic relief in conjunction with anticoagulation.
4. Isolated SVT **<5 cm in length located >3 cm from the SFJ/SPJ** can be treated with oral or topical NSAIDs, compresses (warm or cool), and elevation for symptomatic relief. Compression stockings of appropriate length and tension can be considered
    1. In patients with isolated SVT <5 cm in length located >3 cm from the deep system with **severe symptoms or risk factors for extension** (prior history of DVT/PE or SVT, cancer, pregnancy, hormonal therapy, recent surgery or trauma), treatment with prophylactic fondaparinux, rivaroxaban (10 mg PO daily) LMWH for up to 45 days can be considered.
5. SVT associated with IV cannulation is **not generally treated** with anticoagulation. Supportive measures such as warm compresses and topical NSAIDs can be considered for symptom relief.

Table 1: Treatment Options for SVT*

Drug Class	Suggested dosing	Duration of treatment
LMWH	Dalteparin 5,000-10,000 units SC daily Enoxaparin 40-80 mg SC daily Nadroparin 2,850-5,700 units SC daily Tinzaparin 4,500-10,000 units SC daily	45 days
Fondaparinux	2.5 mg SC daily	45 days
Rivaroxaban	10 mg PO daily	45 days
Oral NSAIDs	Ibuprofen 400 mg PO TID Naproxen 500 mg PO BID	7-14 days
Topical NSAIDs	Topical diclofenac [Voltaren Emugel®] apply 2 to 4 g to affected area 3 or 4 times daily	7-14 days

Take home points

- Superficial venous thrombosis do not need to be treated every time.
- Consider Doppler ultrasound to r/o DVT.
- Duration of treatment is short and prophylactic doses are used.
- Criteria for treatment :
  - Concomitant deep thrombus (DVT/PE)
  - Size
  - Proximity to SFJ/SPJ

Case 3

Eli

- 31 M
- Hashimoto thyroiditis on Synthroid
- Presents with left calf and thigh swelling
- Doppler US shoes DVT of popliteal vein, common femoral vein and superficial femoral veins.
- No preceding immobilization, fracture, surgery.
- No family history of venous thromboembolism

Questions

- Should we test Eli for inherited thrombophilias?

Thrombophilia testing

Do I need to test my patient with an unprovoked VTE for genetic thrombophilias?

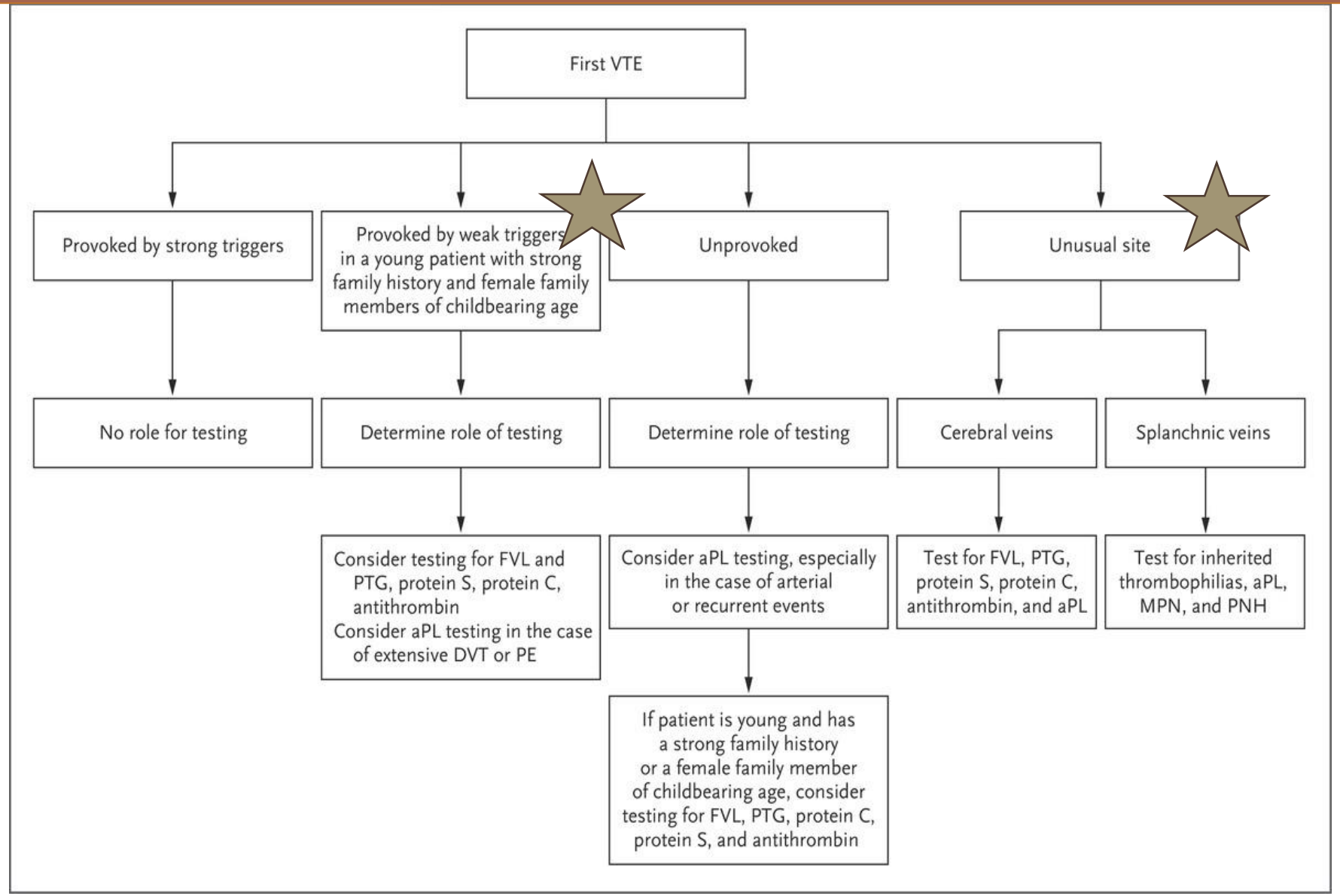
Genetic thrombophilias

Inherited thrombophilias	Acquired thrombophilias
Examples : • Antithrombin deficiency • Protein C deficiency • Protein S deficiency • Factor V Leiden • Prothrombin Gene mutation	Examples : • Antiphospholipid antibodies • JAK 2 mutation • Heparin induced thrombocytopenia • Paroxysmal nocturnal hemoglobinuria

Common conditions lead to inaccurate testing for inherited thrombophilias

Test	Common acquired causes of spurious results
Antithrombin activity	DIC, liver disease, nephrotic syndrome, L-asparaginase, recent thrombosis
Protein C activity	DIC, liver disease, warfarin, recent thrombosis
Free protein S antigen	DIC, liver disease, warfarin, pregnancy, estrogen tx, recent thrombosis
Factor V Leiden genotype	Unaffected
PGM genotype	Unaffected

Algorithm for Selecting Patients with a First Venous Thromboembolism (VTE) for Thrombophilia Testing



Consider referral

The NEW ENGLAND JOURNAL of MEDICINE

Connors JM. N Engl J Med 2017.

Received: 9 March 2022 | Accepted: 26 April 2022

DOI: 10.1111/bjh.18239

GUIDELINE

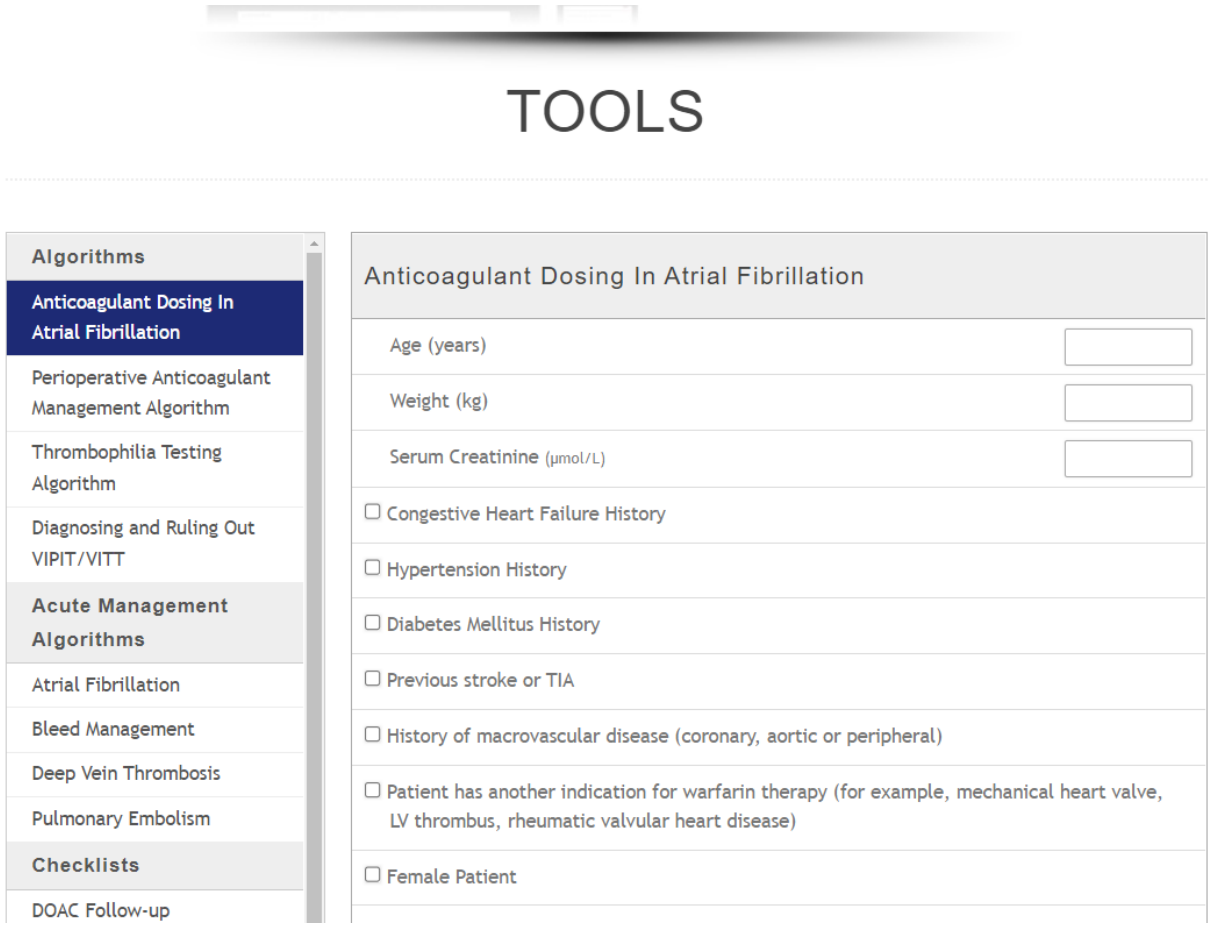
Thrombophilia testing: A British Society for Haematology guideline

- Testing for heritable thrombophilic traits after a venous thrombotic event is **not recommended** as a routine to guide management decisions (Grade 2B).
- We do **not recommend** offering routine thrombophilia testing to **first-degree relatives** of people with a history of VTE (Grade 2B).
- We suggest **selective testing** of asymptomatic first-degree relatives of probands with protein C, protein S and antithrombin deficiency where this may inf luence the management and life choices depending on personal cir-cumstances (Grade 2B).
- Genetic testing for variants in genes (e.g., MTHFR, SERPINE1variants (PAI-1plasma level)) without a clinically significant link to thrombosis is **not recommended** (Grade 2C).

- We do not recommend testing for heritable thrombo-philia in patients with thrombosis if the only indication is thrombosis at an unusual site because the association is weak, and management would not be changed by their presence (Grade 2B).
- We recommend testing with MPN panel in patients with thrombosis at unusual sites with full blood count ab-normalities suggestive of a myeloproliferative neoplasm (Grade 1C).
- We suggest genetic testing with JAK2 mutation in patients with splanchnic vein thrombosis or CVST in the absence of clear provoking factors and a normal FBC (Grade 2C).
- We recommend testing for antiphospholipid antibodies in patients with thrombosis at unusual sites in the absence of clear provoking factors as the type and duration of antico-agulation are affected by the presence of these antibodies (Grade 1A).

Why test for inherited disorders?

Thrombosis Canada Thrombophilia tool



Acquired thrombophilias

WHEN TO TEST FOR ANTIPHOSPHOLIPID ANTIBODIES

- unprovoked VTE
- recurrent VTE despite adequate anticoagulant therapy
- autoimmune disease (e.g., SLE)
- recurrent pregnancy loss

WHEN TO TEST FOR MYELOPROLIFERATIVE NEOPLASM

(consider referral)

- elevated platelets, hematocrit and/or white count
- unexplained hepatosplenomegaly
- blood film abnormalities including teardrop cells, nucleated red blood cells, and/or pancytopenia

Case 3 : Take home points

- Judicious use of genetic thrombophilia testing → will it make a difference in the management?
- Consider referral for thrombophilia testing evaluation
  - Unprovoked thrombosis
  - Unusual site
  - Recurrent with/without anticoagulation
  - Reproductive age

Objectives

- Review the management of estrogen-associated VTE
- Review the management of superficial venous thrombosis
- Describe the indications for thrombophilia testing

Thank you

References

1. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, Maccallum P, Laffan M. Thrombophilia testing : A British Society for Haematology guideline. 2022;(April):443–58.

2. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016 Jan 1;41(1):92–128.

3. Beyer-Westendorf J, Tittl L, Bistervels I, Middeldorp S, Schaefer C, Paulus W, et al. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study. Lancet Haematol. 2020;7(12):e884–91.

4. Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. Pulmonary embolism in pregnancy. Lancet [Internet]. 2010;375(9713):500–12. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60996-X

5. Connors JM. Thrombophilia Testing and Venous Thrombosis. N Engl J Med. 2017;1177–87.

6. Ragni M V. Case-based discussion on the implications of exogenous estrogens in hemostasis and thrombosis: The hematologist's view. Hematol (United States). 2019;2019(1):152–7.

7. Relke N, Chornenki NLJ, Sholzberg M. Tranexamic acid evidence and controversies: An illustrated review. Res Pract Thromb Haemost. 2021;5(5):1–14.

8. Samuelson Bannow BT, Chi V, Sochacki P, McCarty OJT, Baldwin MK, Edelman AB. Heavy menstrual bleeding in women on oral anticoagulants. Thromb Res [Internet]. 2021;197(November 2020):114–9. Available from: https://doi.org/10.1016/j.thromres.2020.11.014

9. Speed V, Roberts LN, Patel JP, Arya R. Venous thromboembolism and women's health. Br J Haematol. 2018;183(3):346–63.

10. Wiegers HMG, Knijp J, van Es N, Coppens M, Moll S, Klok FA, et al. Risk of recurrence in women with venous thromboembolism related to estrogen-containing contraceptives: Systematic review and meta-analysis. J Thromb Haemost. 2022;20(5):1158–65.