CancerCare Manitoba
ActionCancerManitoba

Blood Disorders Day 2018

FOR Health Professionals

Venous thromboembolism in 2018

Best evidence and Best practices

Vi Dao, MD FRCPC

May 4th, 2018

University of Manitoba

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Presenter Disclosure

- Faculty / Speaker's name: Vi Dao

- Relationships with commercial interests:
  - Grants/Research Support: none
  - Speakers Bureau/Honoraria: Celgene, Pfizer, Jansen
  - Consulting Fees: none

Mitigating Potential Bias

- All honoraria received had been forwarded to professional development fund or CancerCare Manitoba Foundation
- No off label use of drugs will be discussed in this talk

Learning Objectives

1. Recognize the different subgroups of venous thromboembolism
   - ***Proximal*** versus ***distal*** *clot*
   - ***Unprovoked*** versus ***provoked*** by various risk factors
2. Select the appropriate ***choice of anticoagulants*** as well as the appropriate ***duration for anticoagulation*** for the various VTE subgroups

Referral to Hematology

Question to Consultant

Please provide specific clinical question for consult below

See attachments: ☑ History ☐ Labs ☐ Diagnostic Imaging ☐ Other

70 y/o ♀ c̄ recurrent PE's shortly after being taken off her NSAIDs for same. PMHx: HTN, GERD, arthritis

Why do we treat VTE?

- Untreated PE can be fatal
  - historical estimate risk of death is 26% (Barritt et al, Lancet 1960)
  - Even with treatment, 2% die at 30 days and 9% at 1 year
    3 patients needed to be treated to prevent 1 death
- Mortality rate from VTE in the modern era is lower compared to historical cohort

Kelly et al, J Int Med 2003

Risk of treating VTE: bleeding

- Anticoagulation increases the risk of bleeding
  - Major bleed in the first 3 month with LMWH/warfarin: 2.1%
  - 0.4% result in death (4 per 1000 patient)
- Clinicians need to ensure that the risk of untreated VTE is higher than the risk of treating the VTE

Linkins et al, Ann Int Med 2003

Impact of clot location & clot burden

- Location of clot matters (PE vs DVT)
  - Mortality is 2-3x higher for PE when compared to DVT
  - Despite having the same risk of recurrence (~20%), patients with PE is more likely to recur with PE (10% vs 3%)
- Size of clot matters (proximal vs distal)
  - Smaller clot burden such as distal DVT or PE in subsegmental vessels (SSPE) has no impact on mortality

Baglin et al, J Thromb Haem 2010

Case 1

- A 30 year old man presents with moderate calf pain and swelling for 5 days after he was kicked playing soccer. Ultrasound shows DVT in the *posterior tibial vein*. Does he need anticoagulation?
  - ❑ Yes
  - ❑ No

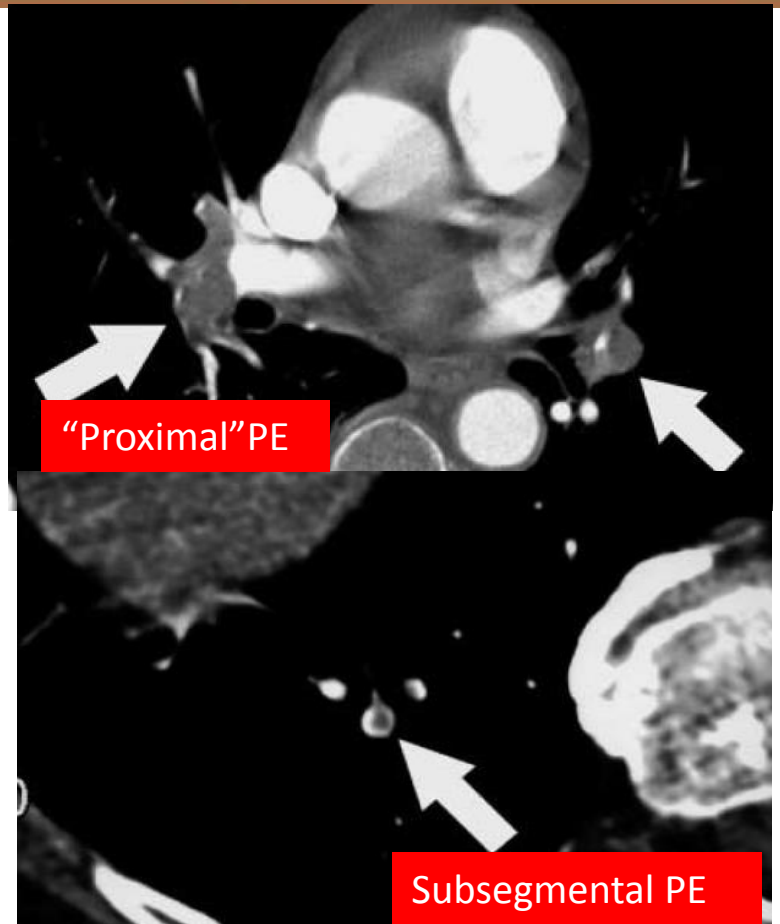
Distal DVT

- Leg US have lower sensitivity and specificity to detect clot in smaller vessels
- Difficult to know if the reported "DVT" is a *new* clot or *residual* thrombosis (scarring)
- Indirect evidence suggests treating *distal* DVT does not further reduce the 3 month VTE risk → 0.3% rec VTE
- Therefore, selected patients may not benefit from anticoagulation

Righini et al, Curr Opin Pulm Med 2008

Subsegmental PE (SSPE)

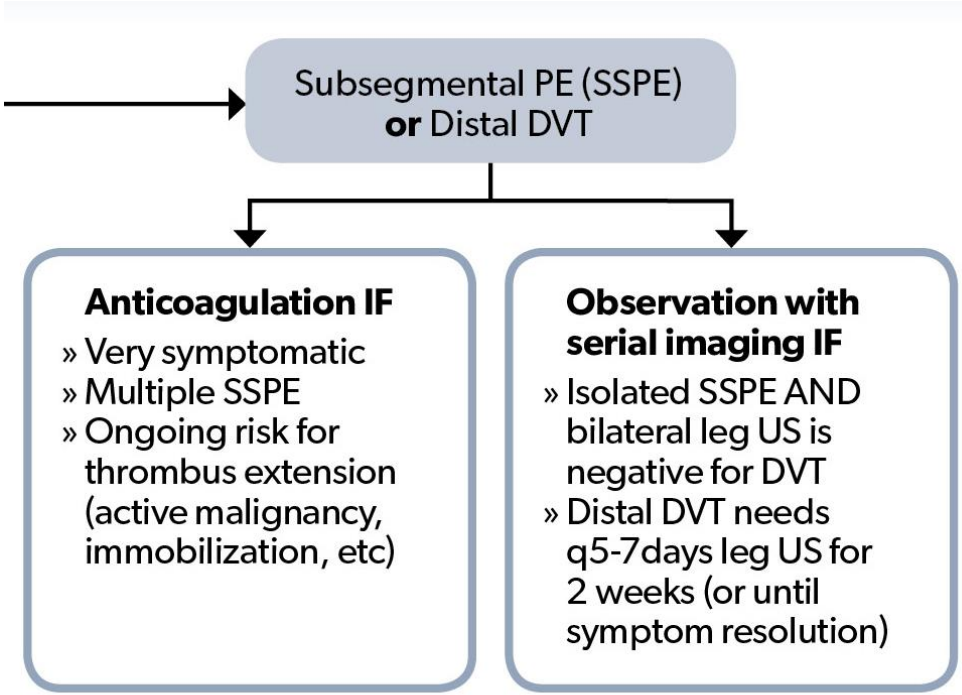
- Is a common incidental finding (5-10% of all PE)
- Can be false positive (low inter-observer agreement)
- Some patients may not need to be treated (0% recurrent at 3 month)



Which patients do not require anticoagulation?

1. Patients with **small** clot burden (distal DVT or SSPE with no DVT)
2. Adequate cardiopulmonary reserve (absent of: syncope, tachyarrhythmias, abnormal spirometry, hypoxia, SBP<90)
3. A major risk factor for VTE that is no longer present
4. Compliant and trustworthy patient who would return for serial noninvasive leg imaging

Approach to the patient with small clot burden



Initial management of VTE

1. Start *empiric* anticoagulation while waiting for imaging
2. Review history/exam including vitals, weight
3. Review medications
4. Baseline investigations
    1. CBC, reticulocytes (?platelet, myeloproliferative d/o, cancer)
    2. Creatinine (to estimate GFR)
    3. Liver enzymes, INR (to help estimate bleeding risk)
    4. Urinalysis (to rule out hematuria) and urine albumin/creatinine (rule out nephrotic syndrome)

Simplified Pulmonary Embolus Severity

1. Age >80
2. History of cancer
3. COPD
4. HR >110
5. SBP <100mmHg
6. O_2 saturation <90% on room air

High risk if >1 point: **11% 30 day mortality**

Low risk if ≤1: **1% 30 day mortality**

Jimenez et al, Arch Int Med 2010

Initial VTE management in first 3 months

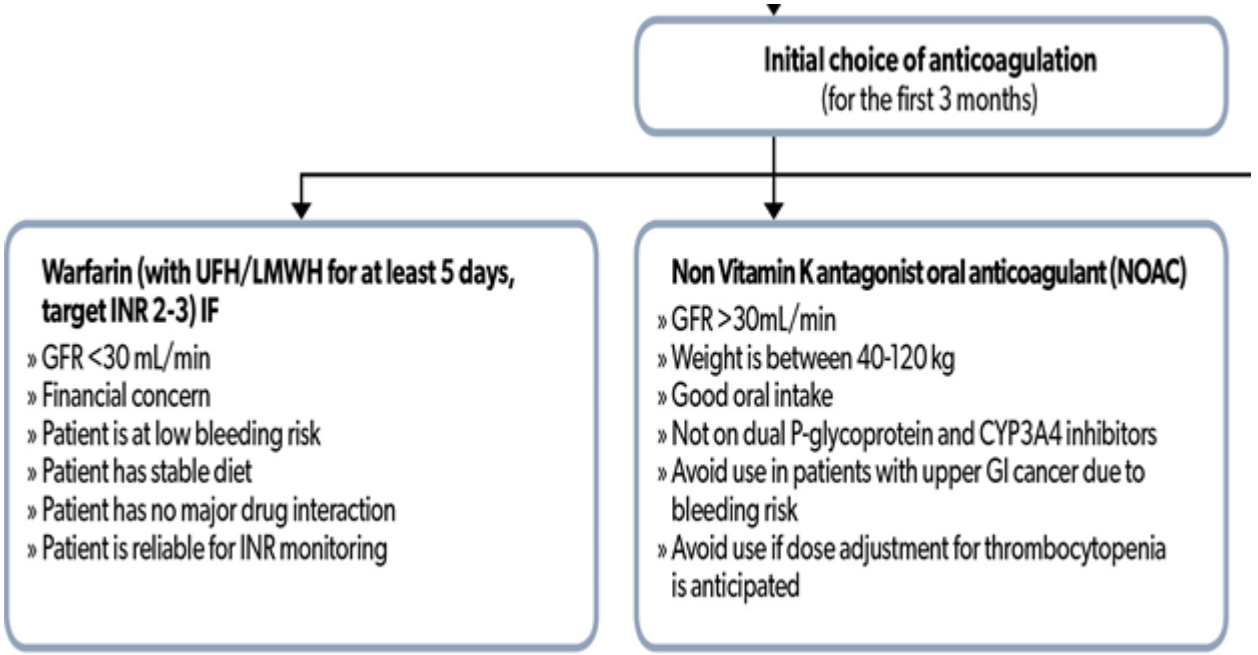
- In patients with DVT or PE *without* active cancer
  - NOAC are preferred over warfarin (Grade 2B)
- Common themes with NOAC
  - All are given in fixed doses
  - None has significant dietary interactions (though rivaroxaban should be taken with food)
  - Drug interactions with CYP 3A4 and P-glycoprotein modulators
  - Contraindicated in patients with poor renal function (CrCl <30ml/min)

Kearon et al, CHEST Guideline, Chest 2016

NOAC versus warfarin

Trials	EINSTEIN DVT/PE	AMPLIFY	RECOVER I/II	HOKUSAI VTE
Regimen	Rivaroxaban 15 mg BID x 21 days then 20 mg OD	Apixaban 10mg BID x 7 days then 5 mg BID	LMWH/UFH x 5 days then dabigatran 150 mg BID	LMWH/UFH x 5-12 days then edoxaban 60 mg OD
Efficacy	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Major Bleed	Less	Less	Non-inferior (or less)	Non-inferior
*CRNMB	Non-inferior	Less	Less	Less

*clinically relevant non major bleed


Initial choice of anticoagulation
(for the first 3 months)
Warfarin (with UFH/LMWH for at least 5 days, target INR 2-3) IF
» GFR <30 mL/min
» Financial concern
» Patient is at low bleeding risk
» Patient has stable diet
» Patient has no major drug interaction
» Patient is reliable for INR monitoring
Non Vitamin K antagonist oral anticoagulant (NOAC)
» GFR >30mL/min
» Weight is between 40-120 kg
» Good oral intake
» Not on dual P-glycoprotein and CYP3A4 inhibitors
» Avoid use in patients with upper GI cancer due to bleeding risk
» Avoid use if dose adjustment for thrombocytopenia is anticipated

Case 2

- 68 M with stage 4 NHL on chemotherapy, now with a symptomatic PE

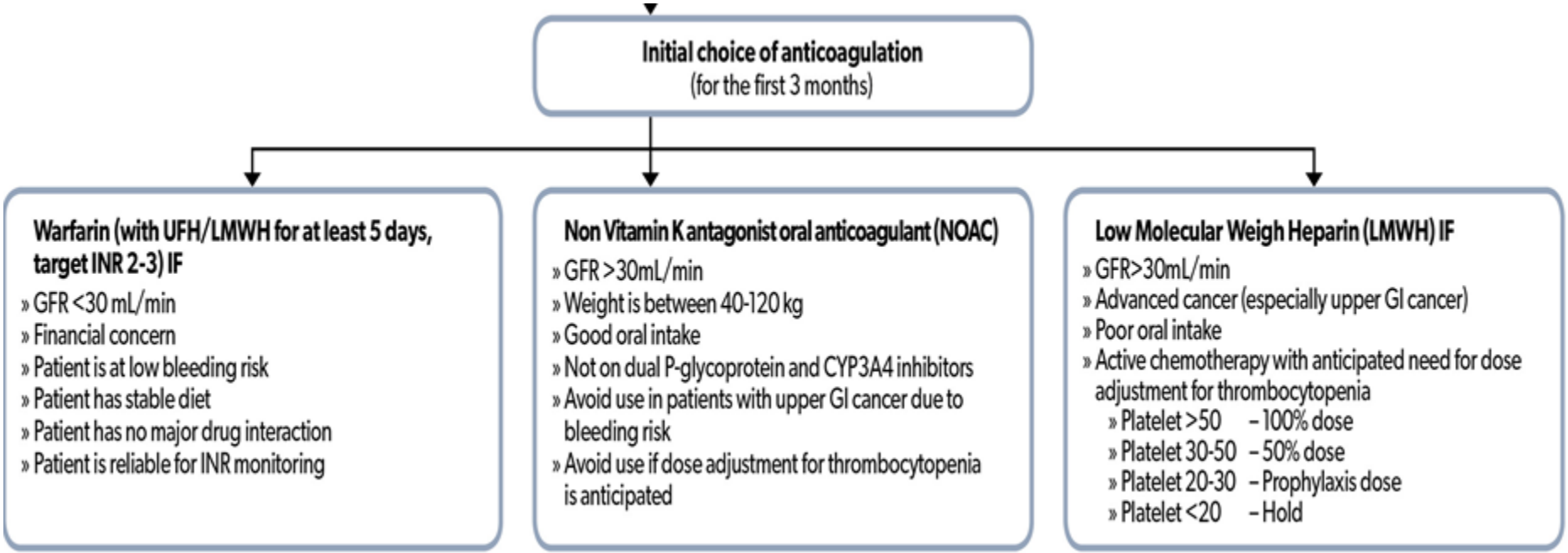
❑ How should he be treated?

A. LMWH x 6 month
B. NOAC x 6 month
C. LMWH and transition to warfarin x 6 month

Initial VTE management in the patient ***with cancer***

- NOAC is an *option* in patients with cancer associated thrombosis
- Similar rate of recurrent VTE compared to dalteparin
- Higher rate of clinically relevant bleeding
  - Particularly in patients with GI malignancy
- Other limitations of NOACs
  - Oral route (poor oral intake, absorption issues)
  - Drug interactions with modulators of P-glycoprotein and CYP3A4 function

Cancer associated VTE



Case 2 continued

- 68 M with stage 4 NHL and cancer associated PE. He was treated with 6 months of NOAC.
- He is completed chemotherapy and is in remission. When can he stop the NOAC?

Deciding when to stop anticoagulation?

- All patients should be treated for a minimum of 6 months
- Who are good candidates to stop?
  1. If cured or in remission from their cancer and is not receiving active treatment → risk of rec VTE 3.2 per 100 patient year (most had recurrent of their cancer)
  2. High bleeding risk that is not controlled
  3. Reaching the end of the cancer journey

Van der Hulle et al, Chest 2016

Case 3

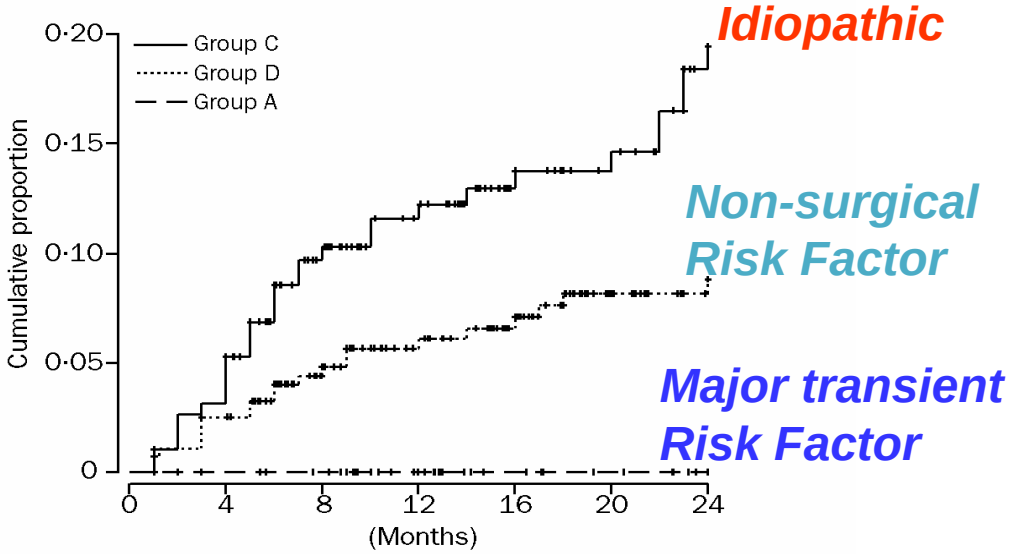
- 30F with unprovoked PE. Treated for 3 months with NOAC and recovering well. She asks if she can stop her NOAC and what is her risk of recurrent clot?
  - ❑ She needs to complete 6 months of anticoagulation and stop
  - ❑ High risk (>10%) and no, she should not stop
  - ❑ Risk unclear. She needs a thrombophilia work up to determine risk of recurrent

Duration of anticoagulation

- All patients should be treated for minimum of 3 months
- Factors to consider when deciding on duration of treatment:
  1. What is the risk of VTE recurrence after stopping treatment?
  2. What is the risk of bleeding when treatment is continued?
  3. What is the patients' values and preferences?

Predicting risk of VTE recurrence

1. "Weak" thrombophilia status did NOT influence risk of VTE recurrence
2. The protective benefit is lost when a patient stops anticoagulation



Baglin et al, Lancet 2003

Who should stop anticoagulation?

- Patients with low risk (<5%) for VTE recurrence
  - Patients with small clot burden (distal DVT or SSPE without DVT)
  - Patients with VTE provoked by major risk factors that are no longer present
- These patients should receive VTE prophylaxis when they encounter VTE risk period in the future

Kearon et al, Blood 2005

Unprovoked VTE: higher VTE recurrence

- About ½ of all patients will fall into this group
- Risk of VTE recurrence is comparable to other high risk thrombophilias (antiphospholipid syndrome, antithrombin, protein C or S deficiency or compound defects)
- Risk of VTE recurrence estimate varies widely (~5-10% recurrence in the first year)

Kearon et al, Blood 2005

Can we identify a “low” risk patient?

- All men are considered high risk
- For women: 4 risk factors
  1. Hyperpigmentation, Edema, or Redness in either leg (“HER”)
  2. D-dimer ≥250 µg/L during treatment
  3. Obesity (BMI ≥30)
  4. Older age (Age ≥65)
  - ➢ Low risk: 0 or 1 risk factor
  - ➢ High risk: 2 or more risk factors

Rodger et al, BMJ 2017

HERDOO2 can identify a “low” risk women

- Women at low risk
  - Can stop anticoagulation after 6 months with acceptable risk of VTE recurrence (3% at 1 year)
- For the remainder high risk patients
  - If anticoagulation is discontinued → higher risk of VTE recurrence (8% at 1 year)
  - If anticoagulation is continued → treatment is effective with 2% VTE recurrence

Rodger et al, BMJ 2017

Extended anticoagulation

- Patients who continue active treatment (compared to observation or placebo) has less VTE *during the treatment phase* (3% vs 10%, p<0.001)
- *The case fatality for recurrent VTE AND bleeding is in favour of NOAC for extended treatment*

Marik et al, Plos ONE 2015

Can we lower the dose of NOAC?

- Apixaban or rivaroxaban at prophylactic dose is effective at reducing risk of VTE recurrence without increase in major bleeding
- Unclear if we can apply this to all patients
  - Higher risk patients may not have been included (those with anticoagulation failure, severe thrombophilias)

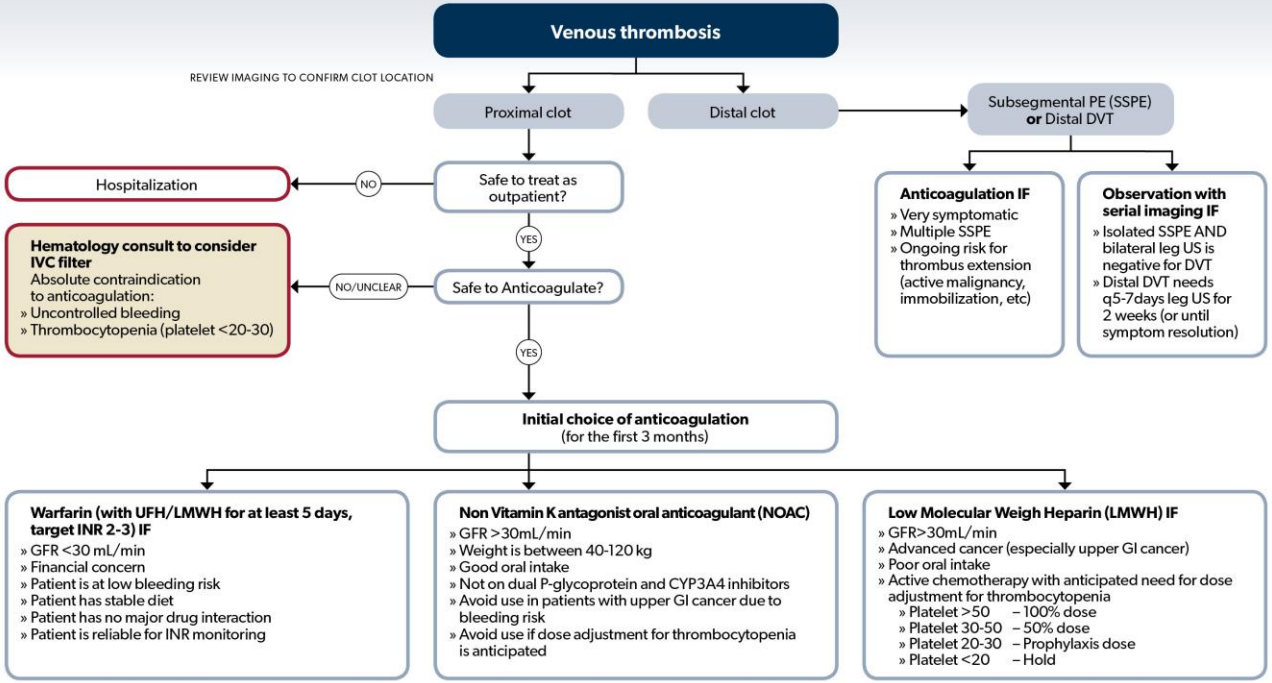
Take home messages

1. Not all clots require anticoagulation → review imaging to confirm the clot location/burden to decide if anticoagulation is required
2. If treatment is required → treat for a minimum of 3 months
3. At 3 months, assess the risk of VTE recurrence, risk of bleeding as well as patient's preference to determine if extended prophylaxis is warranted

→ Re-evaluate this decision annually (for bleeding risk, CBC, renal function) to decide if extended prophylaxis is still appropriate

Blood Disorders Day

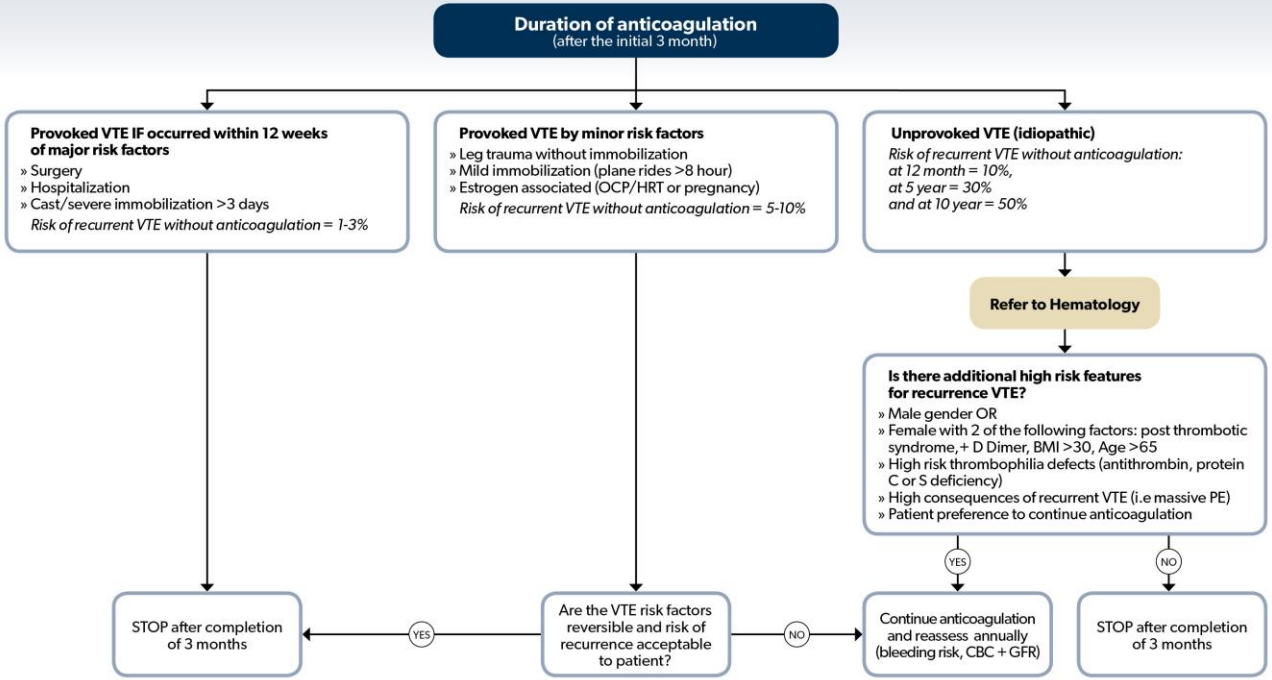
Venous Thromboembolism



CONTINUED »

Blood Disorders Day

Venous Thromboembolism



Pathways are subject to clinical judgement and actual practice patterns may not always follow the proposed steps in this pathway.

CancerCare Manitoba
ActionCancerManitoba

Thank you

vdao@cancercare.mb.ca

University of Manitoba

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM