Management of DVT & PE- the silent killers

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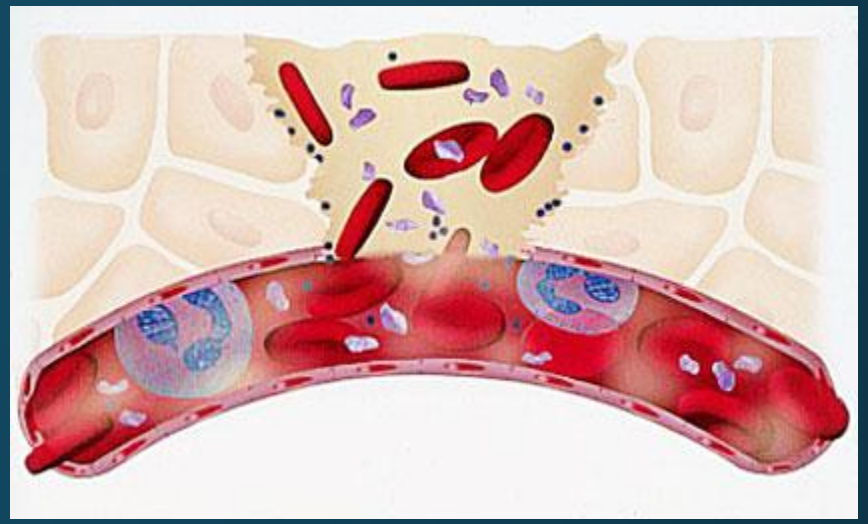
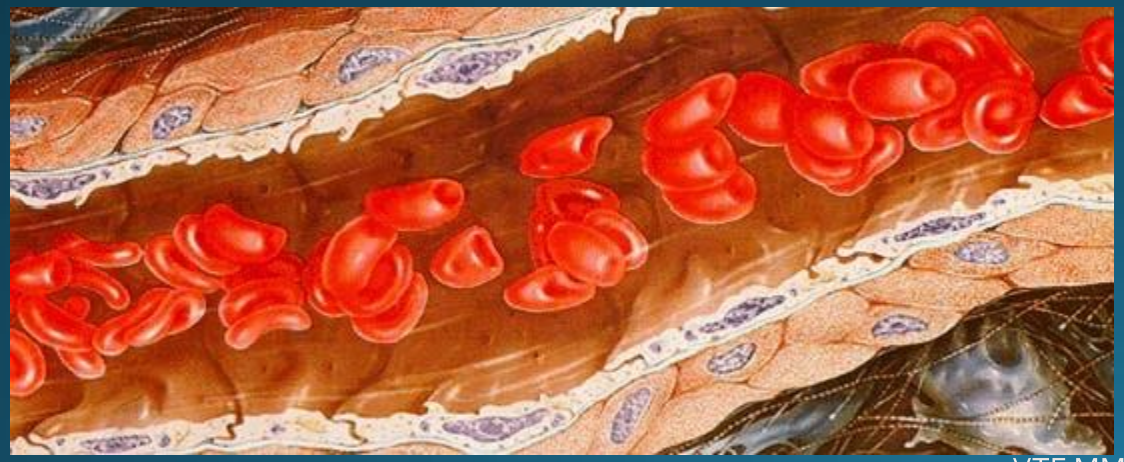
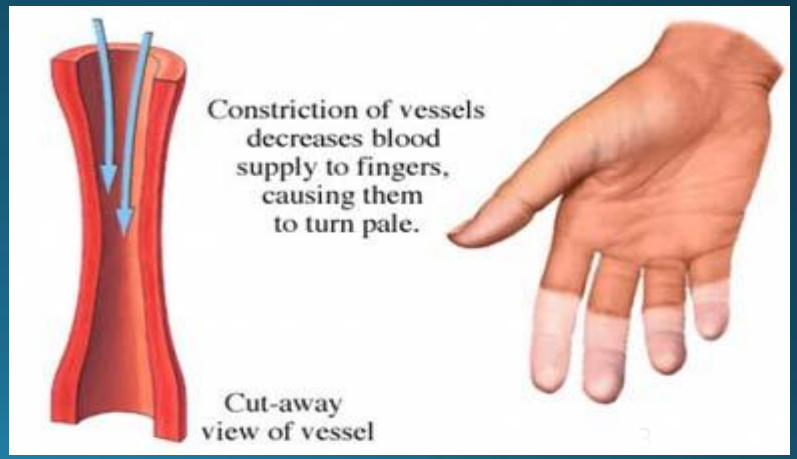
Basic facts

Virchow's Triad

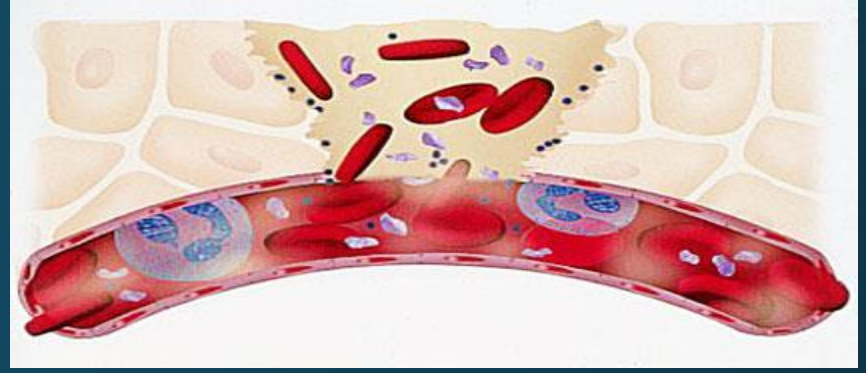
- Vessel Damage
- Vascular Constriction
- Blood Viscosity





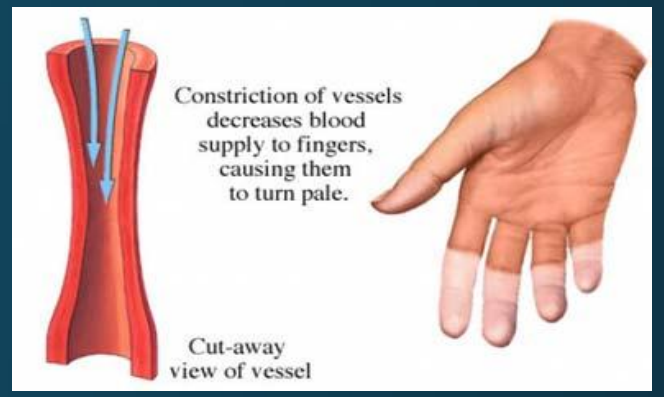


Vessel Damage

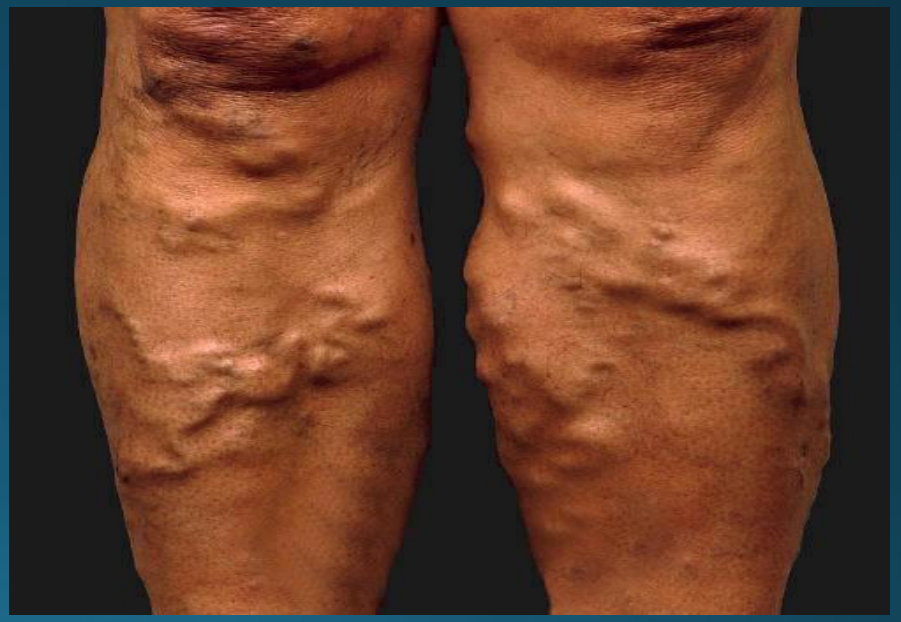


- Endothelial cells allow blood to flow with ease through vessels.
- Factor VIII or von Willibrand's Factor
- Conditions/lifestyles that damage vessel walls:
  - Past VTE
  - Smoking
  - High Cholesterol
  - Varicose Veins
  - Pressure Ulcers
  - Cellulites

Vascular Constriction

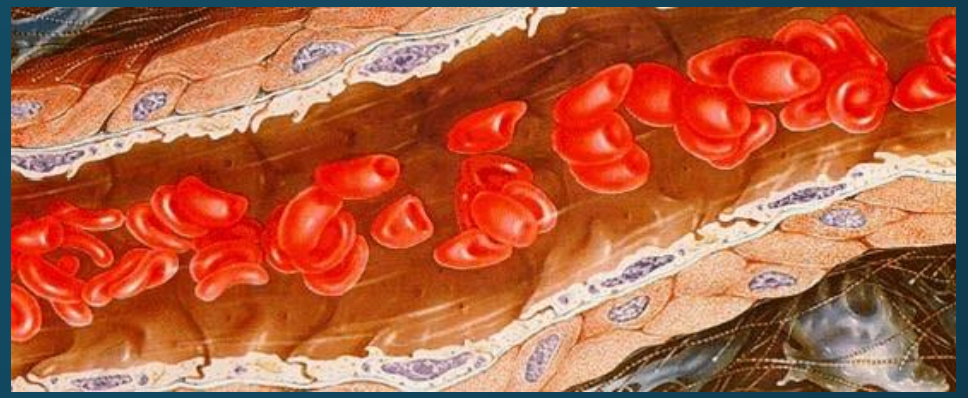


- Trauma
- Surgery
- Insertion of central line
- Varicose Veins
- Restricted Mobility
- Sepsis
- Induction
- MI
- HF
- Stroke



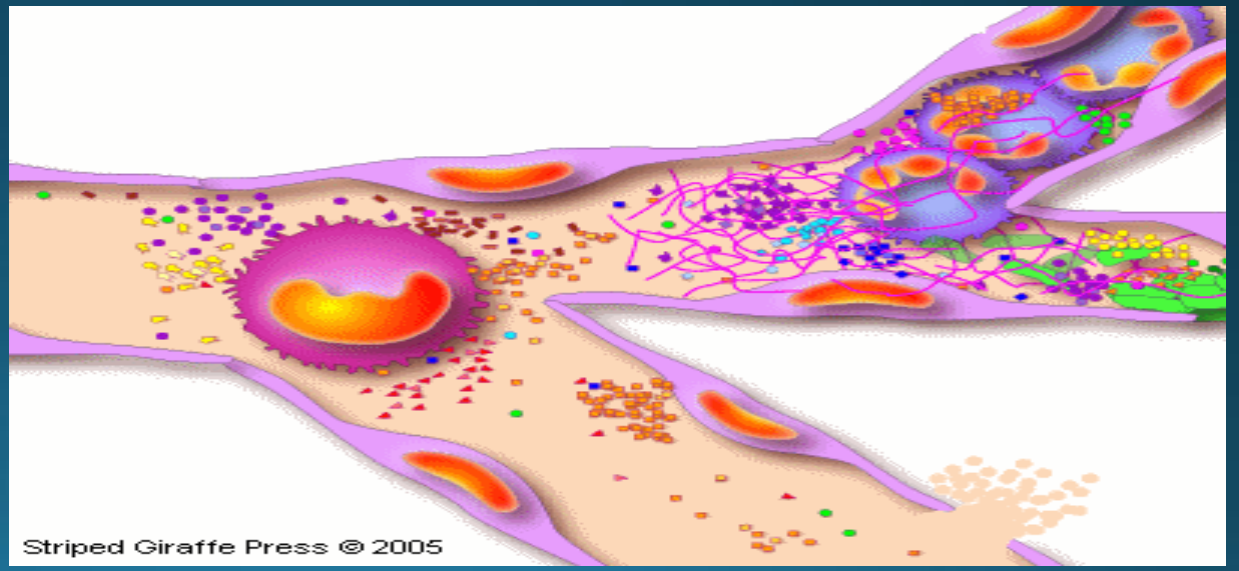
Any external force that cause damage to the vascular system can cause slow blood flow

Blood Viscosity



- Dehydrating
- Birth Control Pills
- High estrogen states
  - Pregnancy
  - Postpartum
- Cancer
- Sepsis
- Blood transfusions
- Obesity

- IBS
- Hematologic Disorders
- Elevated Blood Sugar
- Platelet Aggregation



Outline

- Subgroups of VTE
- Medications for VTE anticoagulation
- Guidelines for duration of therapy
- Differences in therapy based on type of VTE with case scenarios

Subgroups of VTE

- Cancer-associated vs No cancer
- Provoked vs Unprovoked
- Proximal vs Distal DVT
- Upper extremity vs Lower extremity DVT

Definitions

- Provoked DVT or PE: DVT or PE in patients with recent occurrence of major clinical risk factor for VTE
- Unprovoked DVT or PE: DVT or PE in patients with no recently occurring major clinical risk factors for VTE or patients with active cancer, thrombophilia or family history of DVT (these are risks, but they are constant)
- Proximal DVT: DVT in popliteal vein or above
- Wells score: clinical prediction rules for estimating probability of DVT and PE

Provoking Transient Risk Factors for VTE

- Surgery
- Estrogen therapy
- Pregnancy
- Leg injury
- Flight >8h

Location of VTE

- Lower extremity DVT
  - Proximal – Popliteal or more proximal veins
  - Distal – Calf veins
- Upper extremity DVT
  - Proximal – Axillary or more proximal veins
  - Catheter-associated

Risk Factors for Extension of Distal DVT

- Positive D-dimer
- Extensive thrombus
  - >5cm long, involves multiple veins, >7mm diameter
- Thrombus close to proximal veins
- No reversible provoking factor
- Active cancer
- History of VTE
- Inpatient status

Risk Factors for Bleeding on Anticoagulant Therapy

- Age >75
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- NSAID use

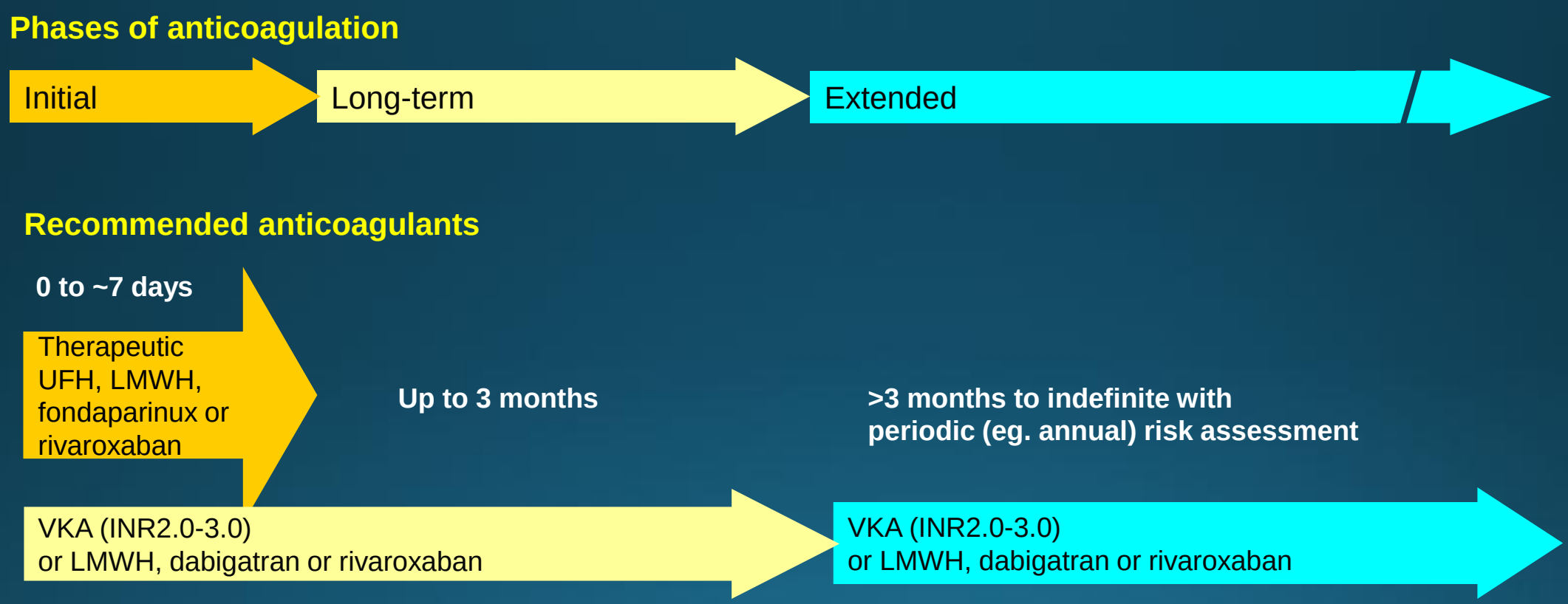
Low risk	0 risk factors
Moderate risk	1 risk factor
High risk	≥2 risk factors

Summary of 2016 ACCP guidelines: duration of anticoagulant treatment

Condition	ACCP recommendation	Grade of recommendation
First provoked DVT or PE	Therapy for 3 months	1B 2B (nonsurgical risk factor and low or moderate bleeding risk)
First unprovoked proximal DVT or PE with low to moderate risk for bleeding	Extended treatment	2B
First unprovoked proximal DVT or PE with high risk for bleeding	Therapy for 3 months	1B
First unprovoked proximal DVT or PE in cancer patients	extended therapy	1B 2B (high bleeding risk)
	with LMWH over VKA	2B
Second unprovoked VTE	extended therapy in low to moderate bleeding risk	1B (2B moderate bleeding risk)
	3 months therapy in high bleeding risk	2B
Choice of agent	VKA or LMWH over dabigatran or rivaroxaban	2B
Extended therapy	Reassessed at periodic intervals (eg, annually)	

Kearon C *et al*. *Chest* 2012

2012 ACCP guidelines: recommended agents for VTEx



Kearon C *et al*. *Chest* 2012

Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional 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 asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	−2
Clinical probability simplified score	
DVT *likely*	2 points or more
DVT *unlikely*	1 point or less

[a] Adapted with permission from Wells PS et al. (2003) Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. New England Journal of Medicine 349: 1227–35

Return to slide 8
'Diagnostic investigations (1)'

Two-level PE Wells score

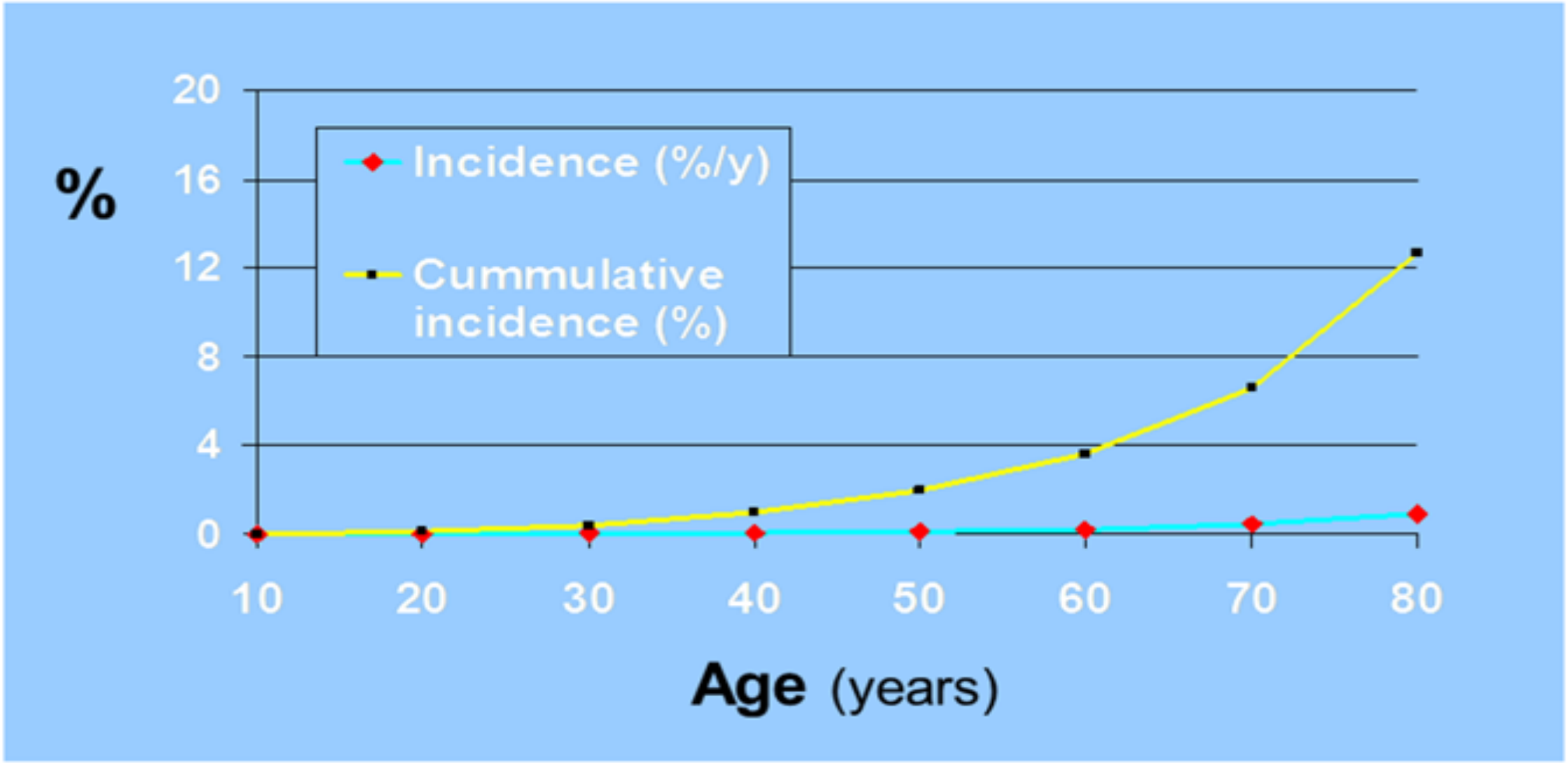
Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation more than 3 days/surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment/treated in the past 6 months/palliative)	1
Clinical probability simplified scores	
PE **likely**	More than 4
PE **unlikely**	4 or less

[a] Adapted with permission from Wells PS et al. (2000) Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thrombosis and Haemostasis 83: 416–20

Objectives of Treatment of DVT

- To prevent pulmonary embolism (PE)
- To reduce morbidity, and
- To prevent or minimize the risk of developing the postthrombotic syndrome (PTS)

Age-specific incidence of VTE



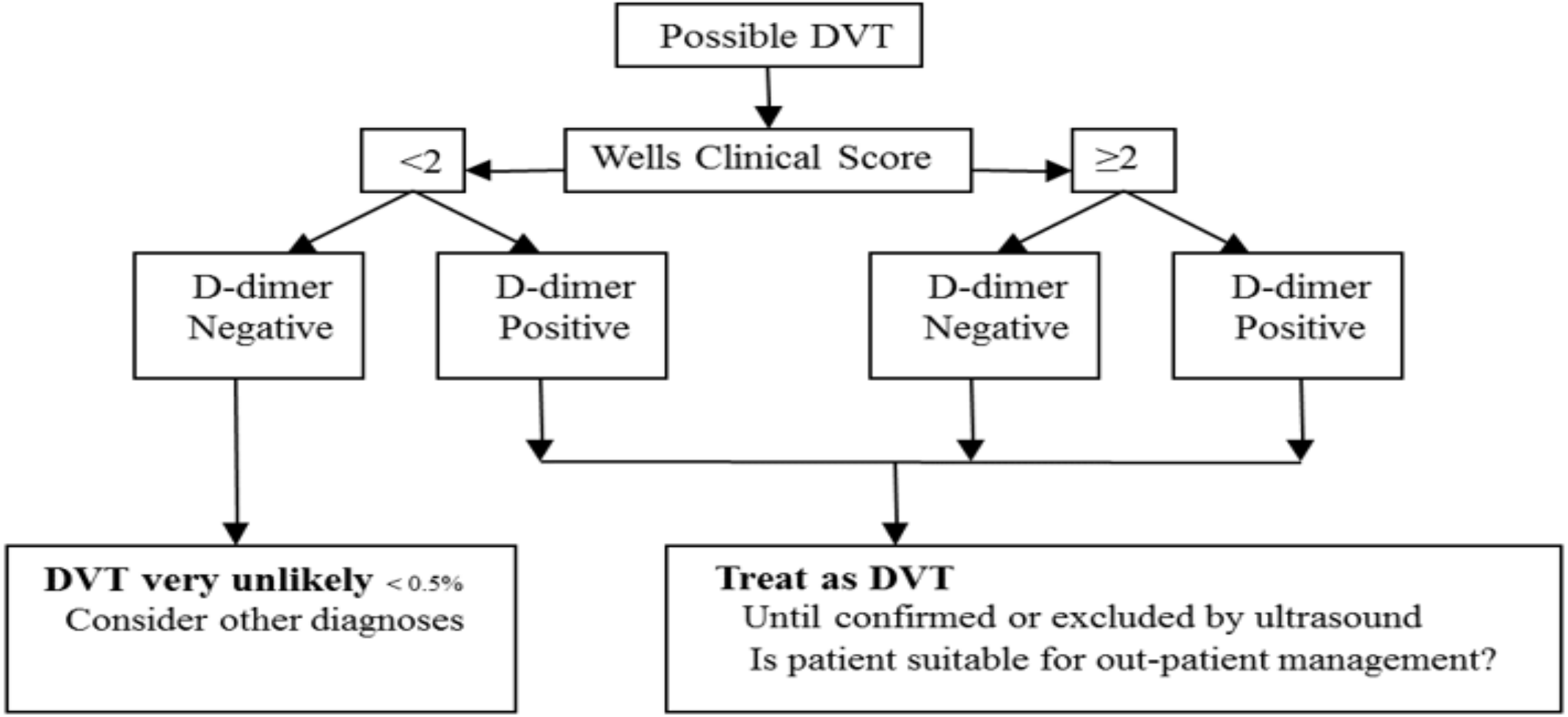
Average incidence = 1.5/1,000 population per year

45% will be DVT

VTE – some Key Facts

- 45% DVT , 45% PE, 10% other sites
- 10% cancer associated VTE
- 50-60% provoked VTE
  (surgery, C-OCP/HRT, pregnancy, immobilising condition)
- ~40% unprovoked [~ 20% recurrent VTE]
- If 1st VTE is a PE, then recurrence more likely to be a PE (than if 1st event was a DVT)
- Case fatality rate for recurrent PE is ~5%

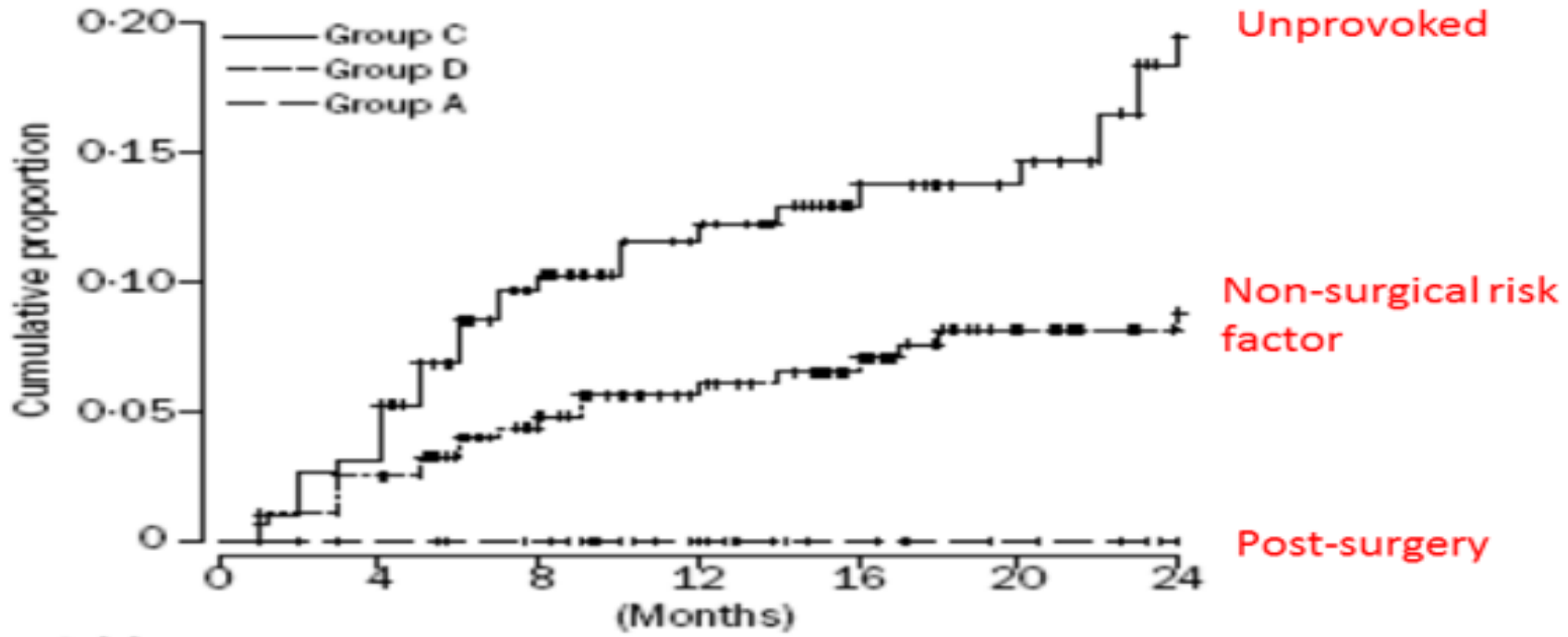
DVT Diagnosis Decision Algorithm



Cancer and VTE

- 10% VTE associated with cancer
  - 6% at diagnosis
  - 4% cancer diagnosis over coming 12m
- VTE common incidental finding on cancer staging CT
- Cancer + VTE = poor prognosis
- VTE + cancer = high recurrent VTE rate
- NICE suggest consider screening for occult cancer if unprovoked VTE >40y of age

Risk of recurrent thrombosis based on presence or absence of known risk factors at first thrombosis

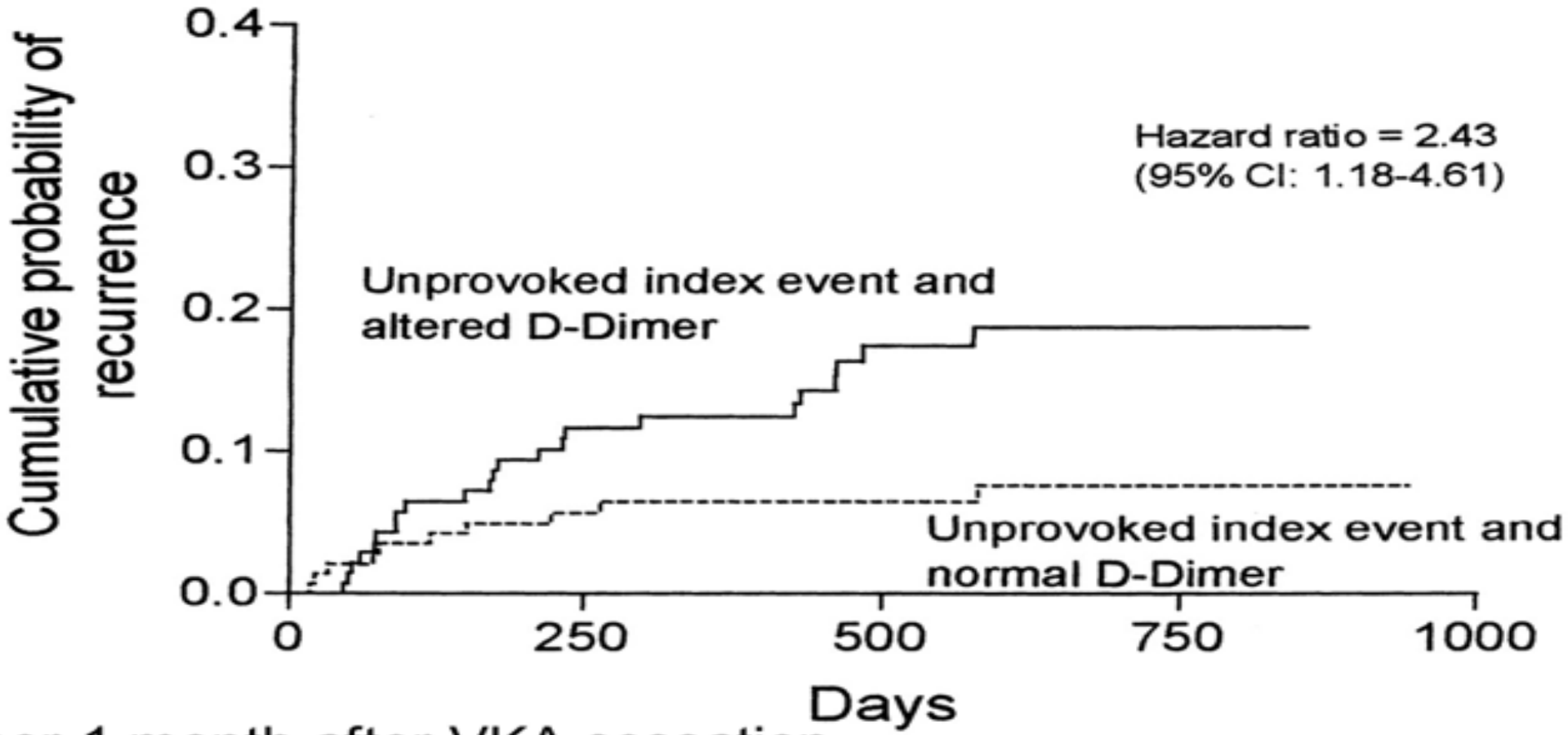


Adapted from Baglin et al *Lancet* 2003; 362: 523–26

Factors influencing risk of recurrent VTE

- site of initial VTE
  - PE & proximal leg DVT > distal leg DVT & UEDVT & CVT
- circumstances around initial VTE
  - idiopathic > transient/reversible risk factor
- initial anticoagulant treatment
  - early therapeutic anticoagulation
- age and sex
  - young > old
  - male > female
- presence of a continuing risk factor
  - cancer, major thrombophilia, paralysis

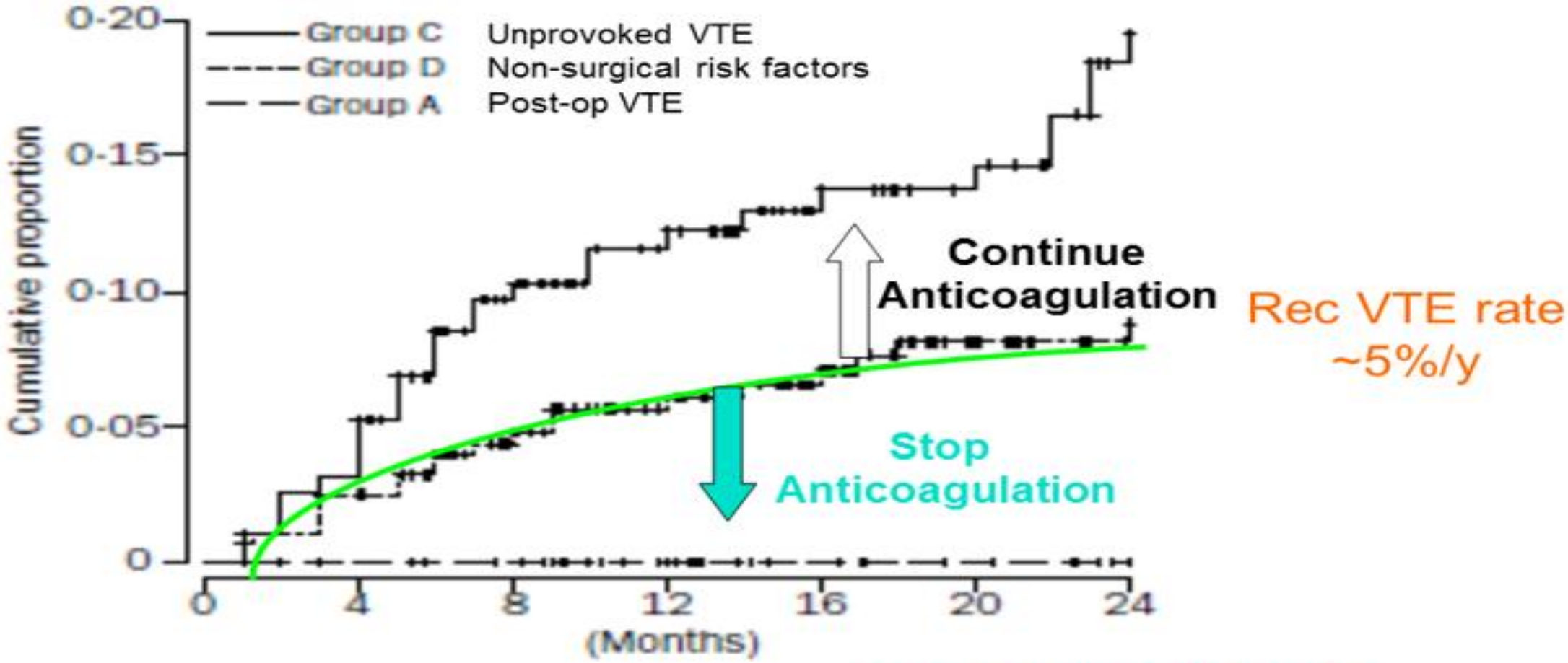
D-dimer predicts Recurrent VTE



D-dimer 1 month after VKA cessation

G Palareti et al. (2003) Circulation 108:313-8

Clinical equipoise for benefit v risk of long term warfarin



Baglin, T et al. Lancet 2003; 362:523-26

Case scenario 1

Case 1

- 75-year old man, John
- recent (4 weeks ago) admission to hospital for hip replacement under GA
- During admission, John received VTE prophylaxis with anti-embolism stockings and pharmacological VTE prophylaxis
- John reported that his right leg has been swollen for over 2 weeks
- He presented to his GP and the GP has referred him to your accident and emergency (A&E) department.

- general medical history and a physical examination to exclude other causes.

- had a DVT 20 years ago and has osteoarthritis.
- On admission, he is apyrexial with a temperature of 37°C and his right calf and ankle are red, blotchy and swollen with pitting oedema.
- His heart rate is 80/min, respiratory rate 15/min, BP: 136/80 mmHg and SpO_2 96% in air.

two-level DVT Wells score to estimate the clinical probability of DVT.

Wells score is 3 (DVT likely):

- Major surgery within 12 weeks requiring general or regional anaesthesia = 1.
- Pitting oedema confined to symptomatic leg = 1.
- Previously documented DVT = 1.

- Organise a **proximal leg vein ultrasound scan**.
- Unfortunately, in your organisation, this scan is not available within 4 hours of being requested.
- **D-dimer test**,
- an interim 24-hour dose of a parenteral anticoagulant
- a proximal leg vein ultrasound scan carried out within 24 hours
- The D-dimer test is positive and the proximal leg vein ultrasound scan is also positive.

- Diagnosed DVT and start treatment with low molecular weight heparin (LMWH) as soon as possible and continue it for at least 5 days or until the INR is 2 or above for at least 24 hours, whichever is longer.
- Also start Warfarin within 24 hours of diagnosing DVT
- outpatient clinic in 3 months to assess whether to continue VKA.

- A week after diagnosis, or when swelling is reduced sufficiently, John should be offered **below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg,** if there are no contraindications.
- worn for at least 2 years and are replaced 2 or 3 times a year or in line with the manufacturer's instructions.

- Verbal and written information about his anticoagulant treatment, including monitoring, side effects, interactions and lifestyle impacts
- Provide him with an anticoagulant information booklet and an anticoagulant alert card
- Advise him to carry the anticoagulant alert card at all times

Case scenario 2

Presentation

- Gary is a 52-year old man who is an endurance cyclist. He presents to your A&E department after referral from his GP.
- He reports shortness of breath at rest and chest pain.
- On direct questioning, he admits to pain in the right calf for a month, which he put down to muscle sprain.

- On admission Gary's SpO_2 is 93% in air, heart rate is 102 beats/min, respiratory rate 17 breaths/min, BP 110/70 mmHg, temperature 37°C.

the two-level PE Wells score to be 7.5 (PE likely):

- Clinical signs and symptoms of DVT = 3.
- Alternative diagnosis less likely than PE = 3.
- Heart rate >100 beats per minute = 1.5.

- Offer immediate CTPA
- The CTPA is positive showing several pulmonary emboli

- Offer LMWH immediately and continue this for at least 5 days or until the INR is ≥2 for at least 24 hours (whichever is longer)
- Start VKA within 24 hours of diagnosis of the PE and continue this for 3 months
- In 3 months' time, assess benefits and risks of continuing the VKA

- The anticoagulation treatment for pulmonary embolism is very similar to that for DVT.

- Apply graduated compression stocking to prevent the development of post thrombotic limb.

- In addition to the LMWH and VKA, a week after diagnosis or when swelling is reduced sufficiently, below-knee graduated compression stockings should be offered with an ankle pressure >23 mmHg, if there are no contraindications.

- the stockings are worn for at least 2 years, are replaced 2 or 3 times a year and are worn in line with the manufacturer's instructions.

- Verbal and written information about his anticoagulant treatment including monitoring, side effects, interactions and lifestyle impacts
- Provide him with an anticoagulant information booklet and an anticoagulant alert card
- Advise him to carry the anticoagulant alert card at all times.

- investigations for cancer: a physical examination (guided by his full history) and a chest X-ray and blood tests (FBC, Serum Ca, LFTs) and urinalysis.
- abdomino-pelvic CT scan for cancer.
- If active cancer is identified, it may be necessary to re-assess PE and DVT treatment plan.
- If the plan is to stop anticoagulant treatment, you should also consider thrombophilia testing.

Case scenario 3

Presentation

- Jane is a 65-year old woman with inoperable ovarian cancer and poor functional status.
- She presents to your A&E department after a referral from the oncology outpatient clinic.
- She complains of pain along the length of her left leg with her left calf feeling particularly painful.
- She also reports that her left calf feels hot.

- She has no other significant past medical history.
- Her heart rate is 90 beats/min, respiratory rate 13 breaths/min, BP 135/60 mmHg, temperature 37.5°C, SpO_2 96% in air.
- two-level DVT Wells score to estimate the clinical probability of DVT.

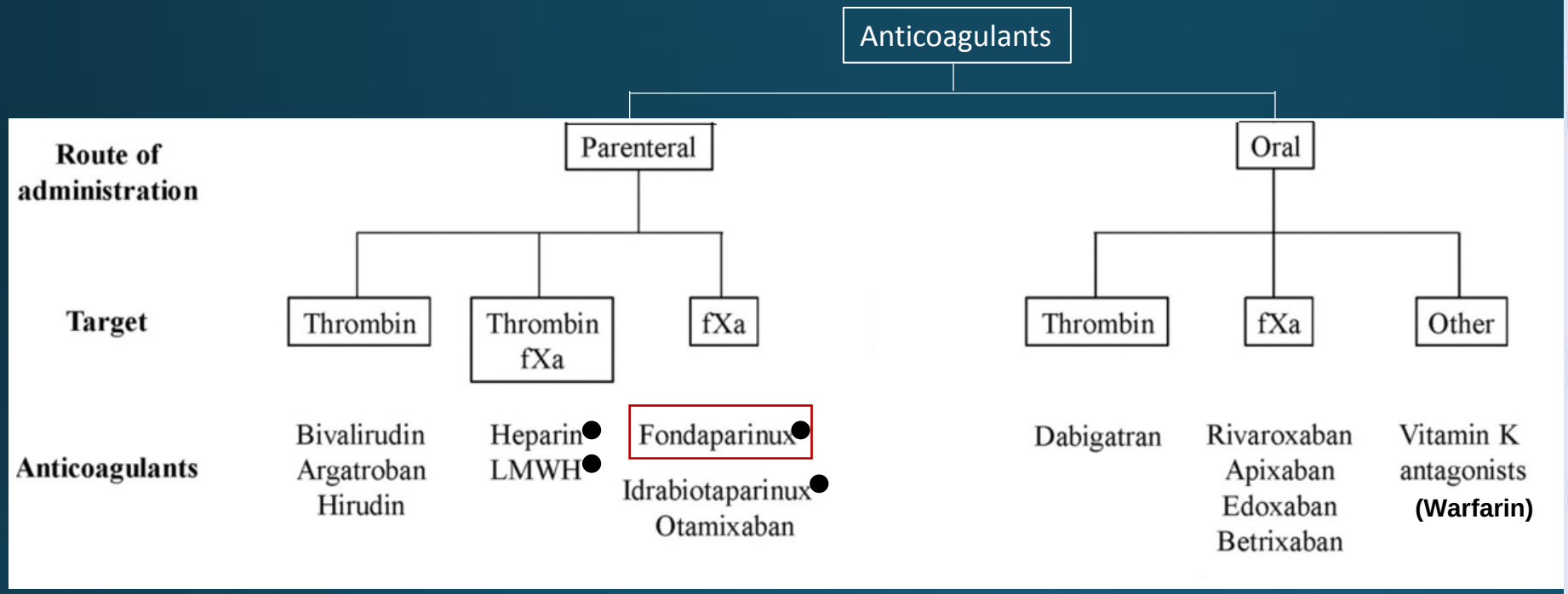
- Jane's two-level DVT Wells score is 2 (DVT likely):
- Active cancer = 1.
- Localised tenderness along the distribution of the deep venous system = 1

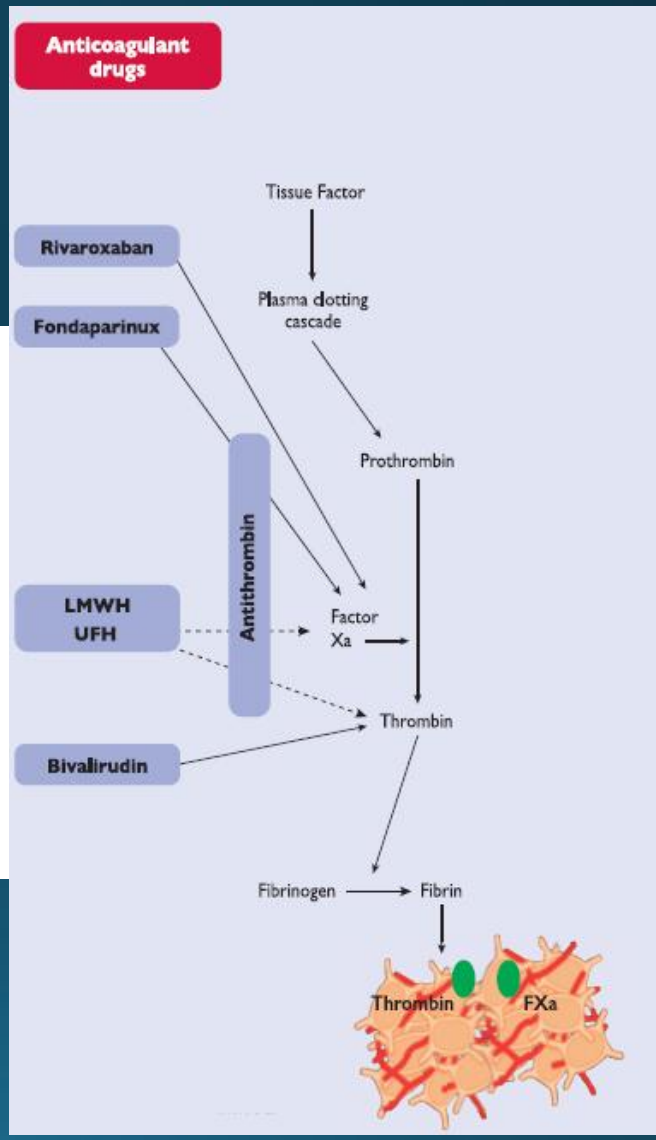
- The proximal leg vein ultrasound scan identifies a DVT.

- Diagnose DVT and start treatment with LMWH for 6 months.
- Follow her up at 6 months' time to assess the risks and benefits of continuing anticoagulation.
- Current international guidelines and UK clinical practice recommend continuing anticoagulation lifelong in patients with active cancer, based on expert clinical experience, case series and opinion, in the absence of randomised controlled trials.

- Offer Jane verbal and written information about her anticoagulant treatment, including monitoring, side effects, interactions and lifestyle impacts.
- Provide her with an anticoagulant information booklet and an anticoagulant alert card.
- Advise her to carry the anticoagulant alert card at all time

Anticoagulants Classification





Anticoagulants

- **Warfarin**
  - Warfarin inhibits the vitamin K-dependent synthesis of biologically active forms of the calcium-dependent clotting factors II, VII, IX and X
  - Warfarin requires dose modification and INR monitoring (determine the clotting tendency of blood)

- **Heparin and derivative substances - Heparin**
  - Heparin is a biological substance, usually made from pig intestines
  - It works by activating antithrombin III, which blocks thrombin from clotting blood.

- **Low molecular weight heparin – Enoxaparin (Clexane)**
  - Low molecular weight heparin, a more highly processed product, is useful as it does not require monitoring of the APTT coagulation parameter
  - It has more predictable plasma levels and has fewer side effects.

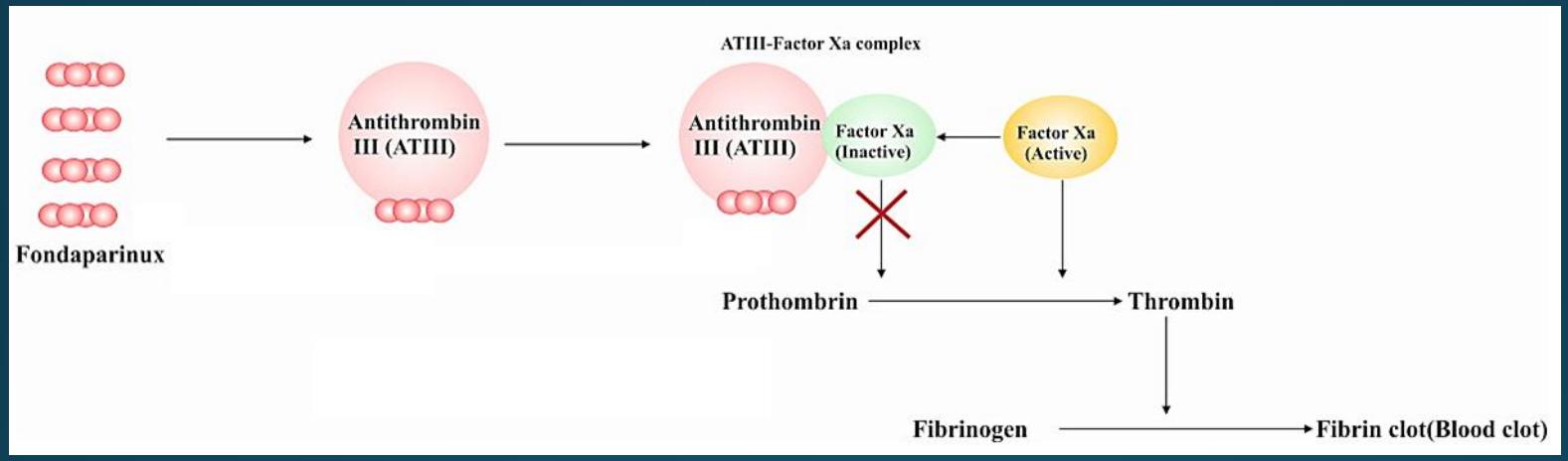
INR, international normalized ratio

Anticoagulants

- **Synthetic pentasaccharide inhibitors of factor Xa - Fondaparinux**
  - Fondaparinux is a synthetic sugar composed of the five sugars (pentasaccharide) in heparin that bind to antithrombin
  - It is a smaller molecule than low molecular weight heparin
- **Direct factor Xa inhibitors**
  - Drugs such as rivaroxaban and apixaban work by inhibiting factor Xa directly
- **Direct thrombin inhibitors**
  - Include the bivalent drugs hirudin, lepirudin, and bivalirudin; and the monovalent drugs argatroban and dabigatran

Fondaparinux

- Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor
- First selective factor Xa inhibitor approved by the FDA (2001)



Mechanism

- The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa
- **By binding selectively to ATIII, Fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII**
- Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development
- Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets

Indications and dosage

Indication	Duration	Dosage
Prevention of Venous Thromboembolic Events (VTE)		
Major orthopaedic surgery	5 to 9 days	2.5 mg OD SC
Abdominal surgery who are judged to be at high risk of thromboembolic complications (abdominal cancer surgery).		
High risk for VTE (immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease).	6-14 days	
Treatment of		
Unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)	Max of 8 days or until hospital discharge if that occurs earlier	2.5 mg OD SC
ST segment elevation myocardial infarction (STEMI)		2.5 mg OD. First dose IV, subsequent SC
Acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs	Min of 30 days and up to a max of 45 days	2.5 mg OD SC

Anticoagulant Treatment for VTE

Initial anticoagulation → **Long-term anticoagulation**

First 10 days

- Anticoagulation should be started immediately
- Heparin agents and **Fondaparinux** are typically preferred over factor Xa and direct thrombin inhibitors because of the longer clinical experience
- Heparin or Fondaparinux are typically administered for at least 5 days together with warfarin; the warfarin dose is adjusted until INR is therapeutic at 2 to 3 (target 2.5) for a minimum of two consecutive days, at which point heparin can be discontinued

10 days to three months

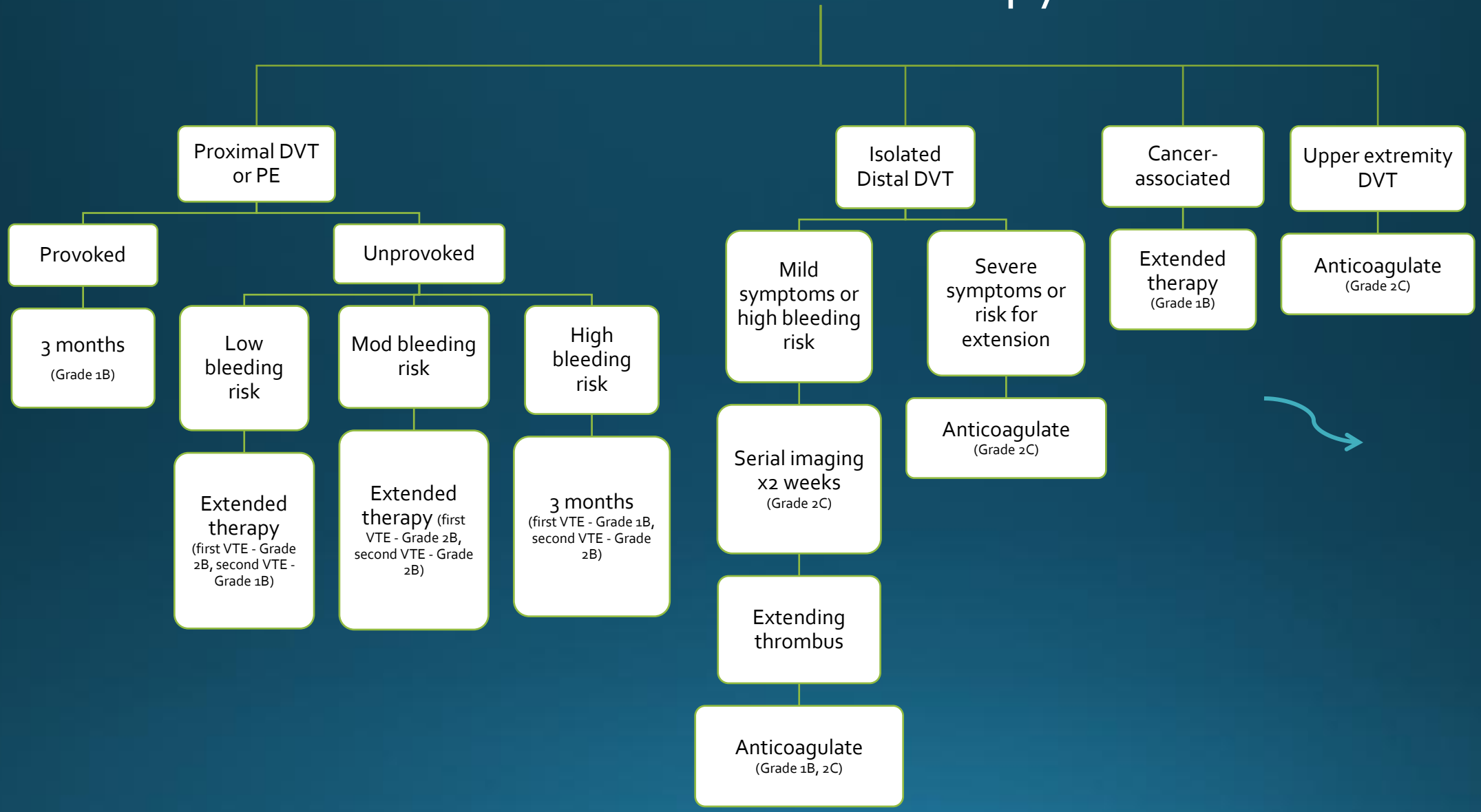
- **Warfarin** adjusted to an INR range (2 to 3; target 2.5)
- LMW heparin and Fondaparinux are acceptable alternatives for patients who wish to avoid the burden of INR monitoring and are willing to accept daily injections
- Similarly, **factor Xa and direct thrombin inhibitors** can be considered in patients who also wish to avoid the burden of INR monitoring and daily injections

Summary of 2016 ACCP guidelines: duration of anticoagulant treatment

Condition	ACCP recommendation	Grade of recommendation
First provoked DVT or PE	Therapy for 3 months	1B 2B (nonsurgical risk factor and low or moderate bleeding risk)
First unprovoked proximal DVT or PE with low to moderate risk for bleeding	Extended treatment	2B
First unprovoked proximal DVT or PE with high risk for bleeding	Therapy for 3 months	1B
First unprovoked proximal DVT or PE in cancer patients	extended therapy	1B 2B (high bleeding risk)
	with LMWH over VKA	2B
Second unprovoked VTE	extended therapy in low to moderate bleeding risk	1B (2B moderate bleeding risk)
	3 months therapy in high bleeding risk	2B
Choice of agent	VKA or LMWH over dabigatran or rivaroxaban	2B
Extended therapy	Reassessed at periodic intervals (eg, annually)	

Kearon C *et al*. *Chest* 2012

Duration of Therapy

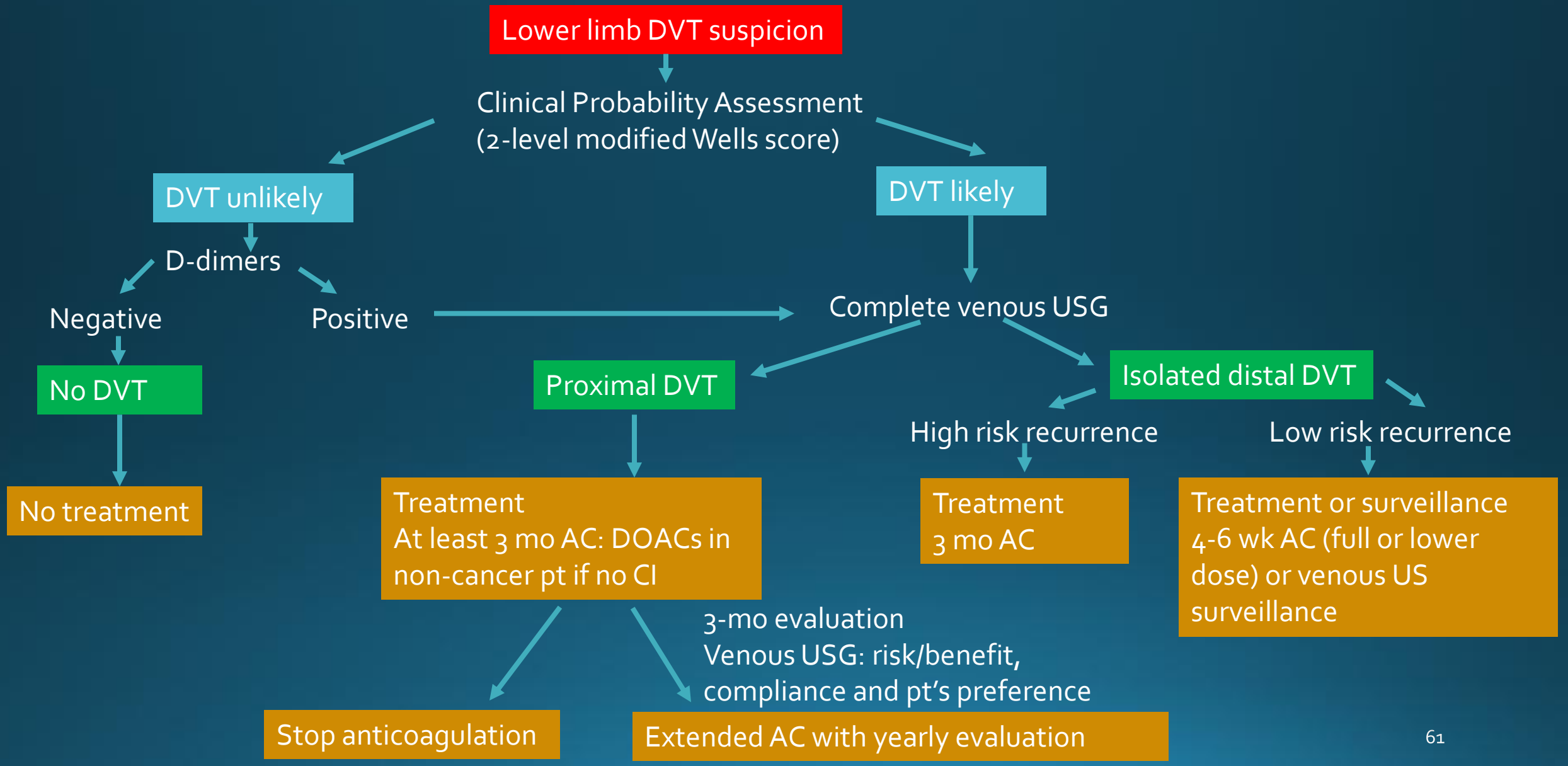


Risk Factors for Bleeding on Anticoagulant Therapy

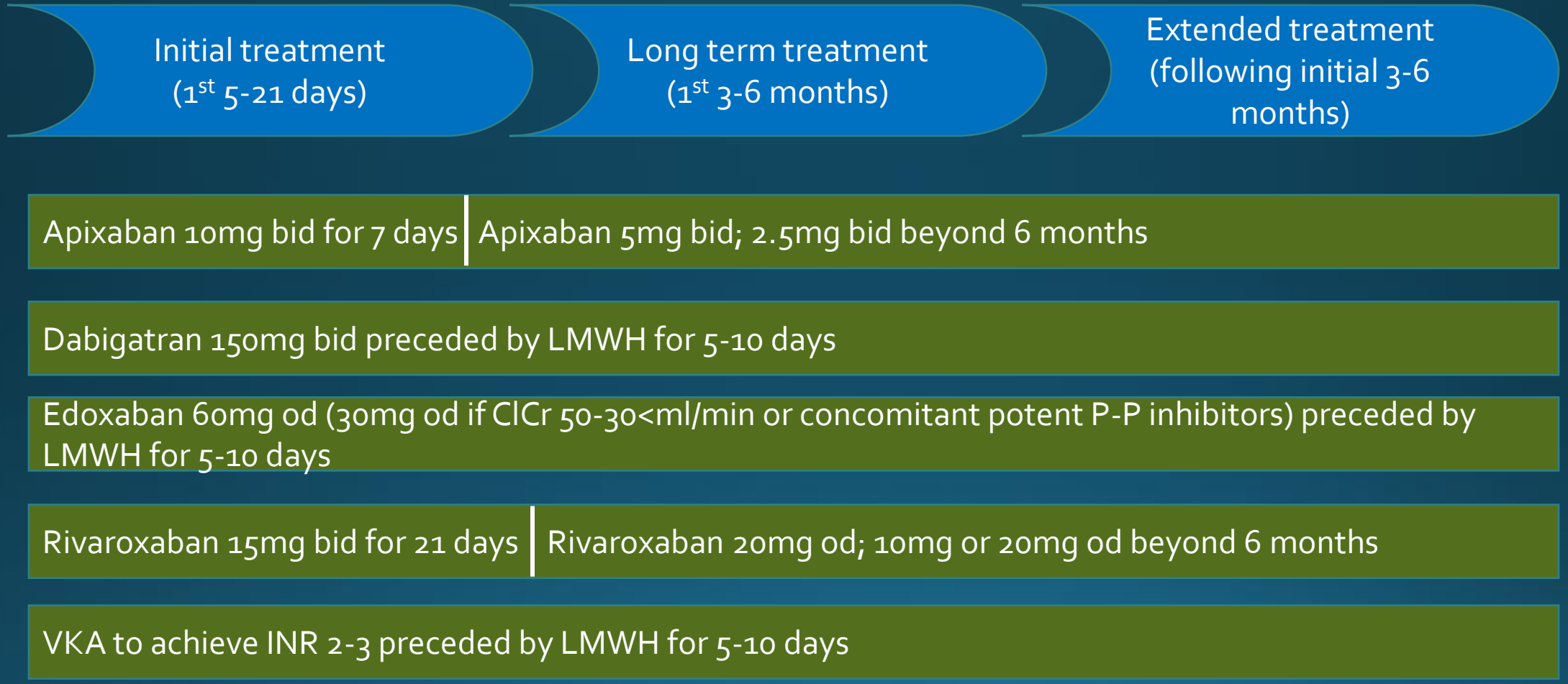
- Age >65
- Age >75
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- NSAID use

Low risk	0 risk factors
Moderate risk	1 risk factor
High risk	≥2 risk factors

Proposed DVT diagnostic and management algorithm



DVT Treatment Phases



Mazzolai L et al. EHJ 2017;00:1-14

Questions/Comments