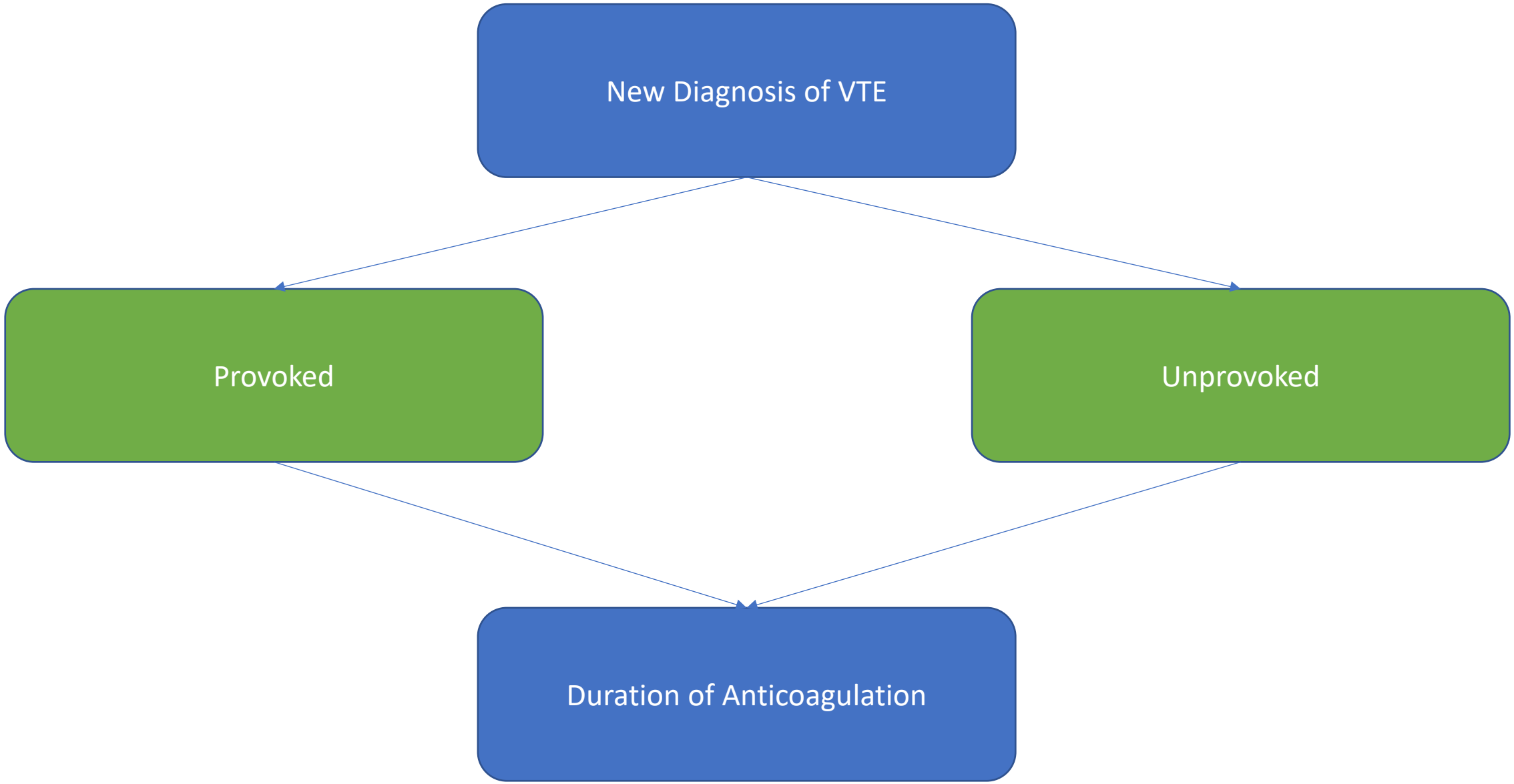
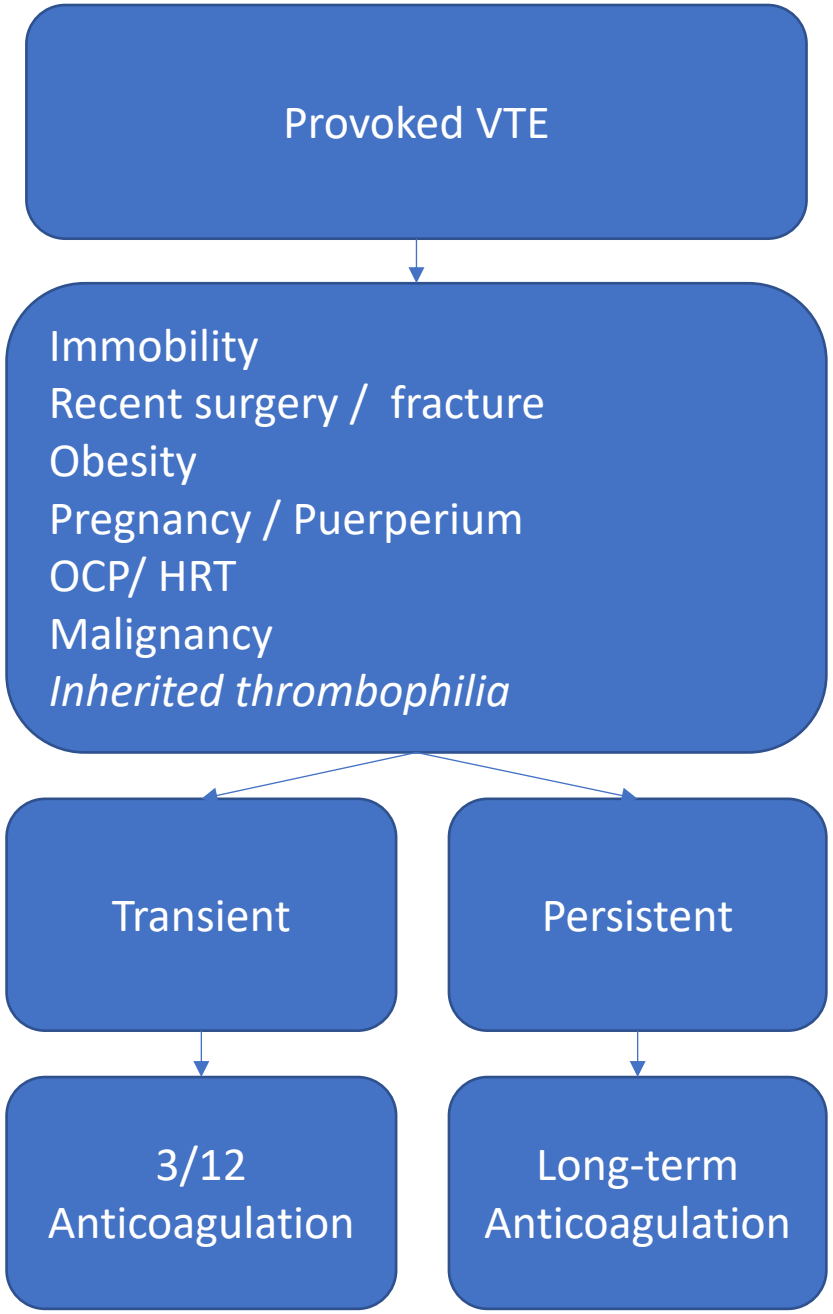
Unprovoked VTE: to screen or not to screen

VTE Study Day

3rd May 2018


New Diagnosis of VTE
Provoked
Unprovoked
Duration of Anticoagulation



Dehydration
Cancer treatments
Infection/ Sepsis
Hyopalbuminaemia / Nephrotic syndrome
HIT – Heparin Induced Thrombocytopenia
DIC - Disseminated Intravascular Coagulation
PNH -Paroxysmal Nocturnal Haemoglobinuria
MPD – Myeloproliferative Disorders

History/ Clinical context

Blood / Screening Tests

~~Immobility~~
~~Recent surgery / fracture~~
~~Obesity~~
~~Pregnancy / Puerperium~~
~~OCP/ HRT~~
~~Malignancy~~
Inherited thrombophilia
~~Dehydration~~
~~Infection~~

~~Occult malignancy~~
Inherited thrombophilia
~~Hypoalbuminaemia / Nephrotic syndrome~~
~~HIT – Heparin Induced Thrombocytopenia~~
~~DIC - Disseminated Intravascular Coagulation~~
~~PNH -Paroxysmal Nocturnal Haemoglobinuria~~
~~MPD – Myeloproliferative Disorders~~

Full Blood Count
Biochemistry
Coagulation

NICE (2012)

Serum Calcium
Liver Function Tests
CxR
Urinalysis

Cancer in VTE

- 15 – 20% of VTE patients have overt cancer at diagnosis
- ≈ 4% have occult malignancy
- Approx 10% will develop over following 5 - 10 years
  - 1 – 2% annual risk after diagnosis
  - Risk uniform over time
  - > 2-fold higher annual risk in those with unprovoked VTE (0.83 vs 1.76%)
- Risk factors
  - Unprovoked event (HR 1.86)
  - Advancing age (HR 1.32)

Douketis, J et al. The long-term risk of cancer in patients with a first episode of venous thromboembolism. Journal of Thrombosis and Haemostasis, 7: 546–551
Carrier, M et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. N Engl J Med 2015; 373:697-704

Exclusion of Malignancy

- NICE (2012)
  - Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer:

1. Physical examination/ Full history
2. Chest X-ray
3. Blood tests (full blood count, serum calcium and liver function tests)
4. Urinalysis.

- Consider **abdomino-pelvic CT scan** (and a mammogram for women)
  - All patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation

Is extensive screening for malignancy necessary?

SOMIT Study (2004) - Screening for Occult Malignancy in Thrombosis

- 201 patients with idiopathic VTE with no initial signs/ symptoms of malignancy
- Random allocation
  - Extensive screening vs no further testing
  - 2 years follow-up
- Screening group: 14 malignancies (13 during screening, 1 during follow-up)
  - 10/13 detected by CT-AP alone
  - Control group: 10 malignancies during follow-up
  - Relative Risk 9.7 ($p<0.001$)
- Cancer related mortality:
  - 2.0% (screening) vs 3.9% - Not significant

Piccioli A et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism. J Thromb Haemost. 2004 Jun;2(6):884-9

Is a CT necessary?

- Carrier et al (2015)
  - Multicentre, randomised trial
  - Limited screening vs limited screening + CT
    - CT included virtual colonoscopy, gastroscopy and pancreatography
  - 1 year follow-up
    - Primary end-point: New cancers missed during screening
- 854 patients
  - Mean age: 54 years
  - 33 new diagnoses of cancer during f/u
    - 14 (3.2%) in limited screening – 4 missed (29%)
    - 19 (4.5%) in limited + CT – 5 missed (26%)
    - No difference in time to diagnosis or mortality

Carrier, M et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. N Engl J Med 2015; 373:697-704

Is a CT necessary?

- Hildyard (2016)
  - 16 month audit all patients referred to VTE service
  - 239 patients with confirmed DVT (190 malignancy free)
    - 164 over 40 years of age
      - 139 with unprovoked VTE
  - 62 agreed to CTAP
  - 28 (45%) abnormal scans
  - Only 1 malignancy diagnosed

Hildyard, C et al. Is there a benefit in computed tomography screening for cancer in patients with unprovoked proximal deep venous thrombosis? A cohort study in the Oxford University Hospitals NHS Trust. Br J Haematol. 2016 Mar;172(6):978-9

Is extensive screening for malignancy necessary?

- Addition of CT-Abdo/pelvis
  - Does not increase screening sensitivity
  - No mortality benefit
    - Although, cancer may be detected earlier

- Is this true in an older population?
    - Mean age (Carrier et al) = 54 years
    - Prandoni (2016)
      - 195 patients, mean age 69 years, 2 years follow-up
      - Randomised to limited * screening vs limited + CT-TAP
      - Cancers detected in 10% vs 8%
      - 2 cancers developed in each group during follow-up

Prandoni P et al. Extensive computed tomography versus limited screening for detection of occult cancer in unprovoked venous thromboembolism: a multicenter, controlled, randomized clinical trial. Semin Thromb Hemost2016;356:884-90

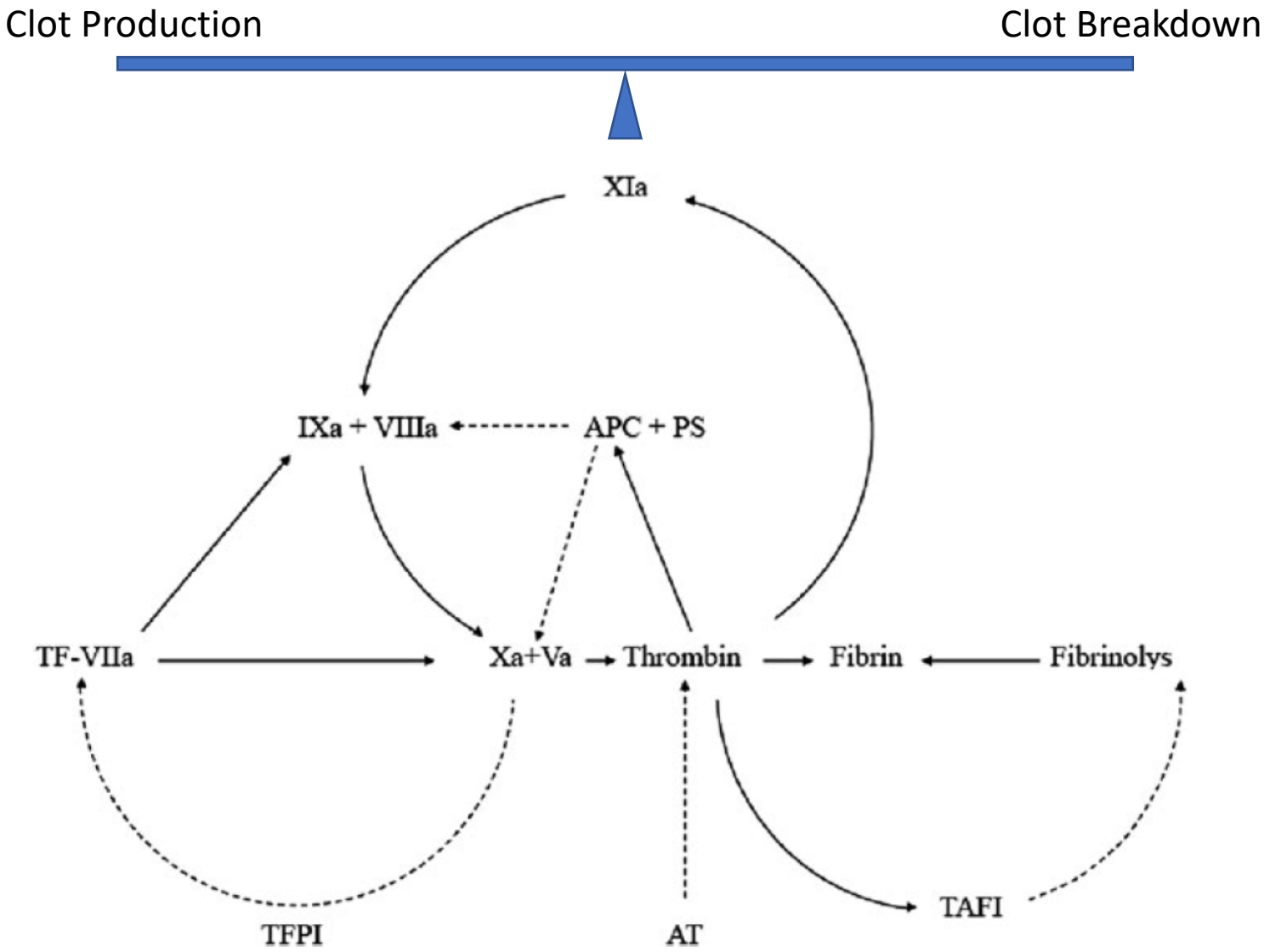
What to conclude?

- “Limited” screening may be as effective as extensive
  - Uncertain, even good quality studies limited:
    - Underpowered to detect differences in cancer-related mortality
    - Wide confidence intervals – low numbers of occult cancers detected

- How limited is limited?
  - Variation in protocols between studies
    - Carrier (2015): FBC, Biochemistry, LFTs, CxR, PAP-Smear, Mammography, Prostate exam/ PSA
    - Prandoni (2016): Any test at physicians discretion other than CT-TAP

(Who) Should we screen for inherited thrombophilia?

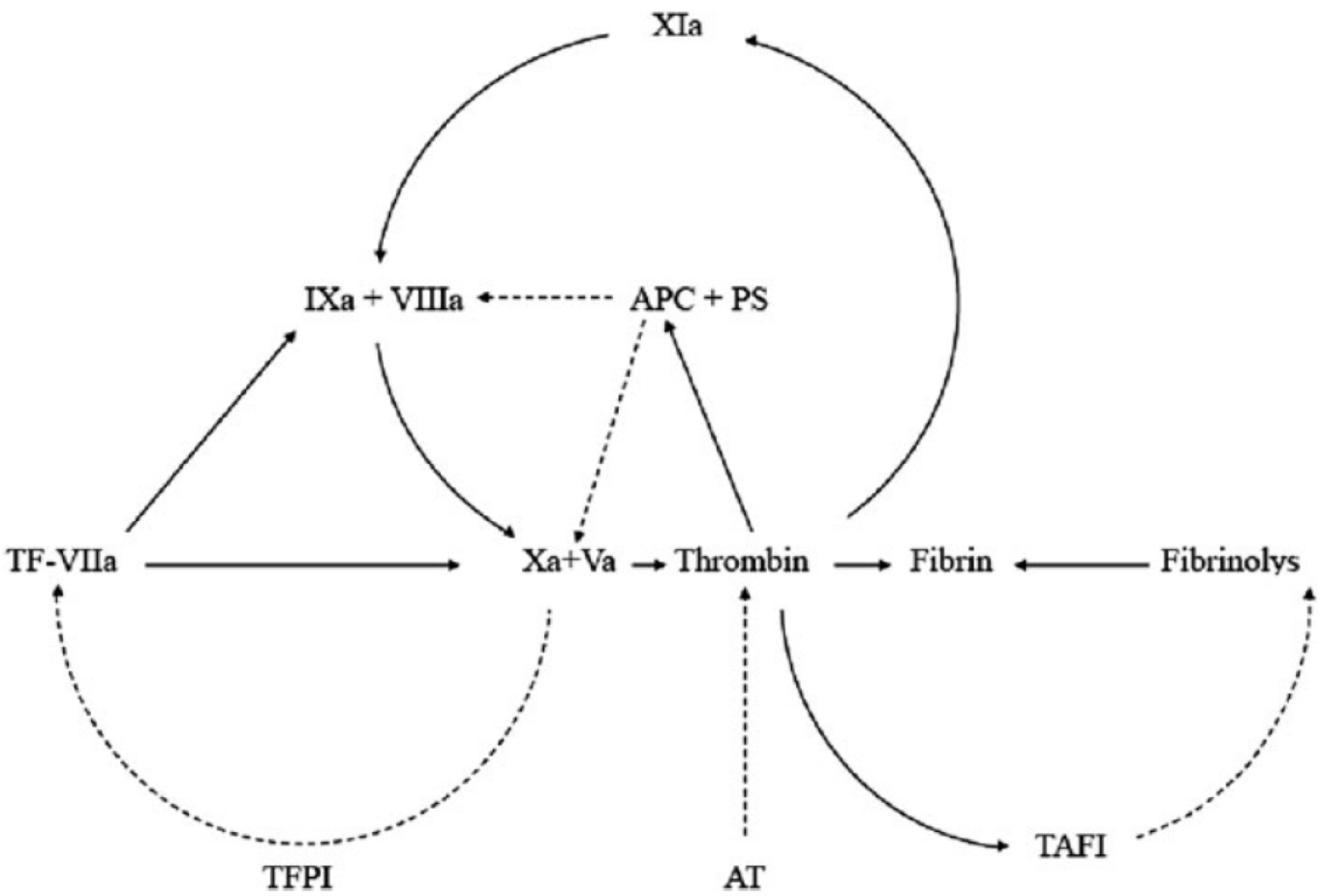
Normal Haemostasis

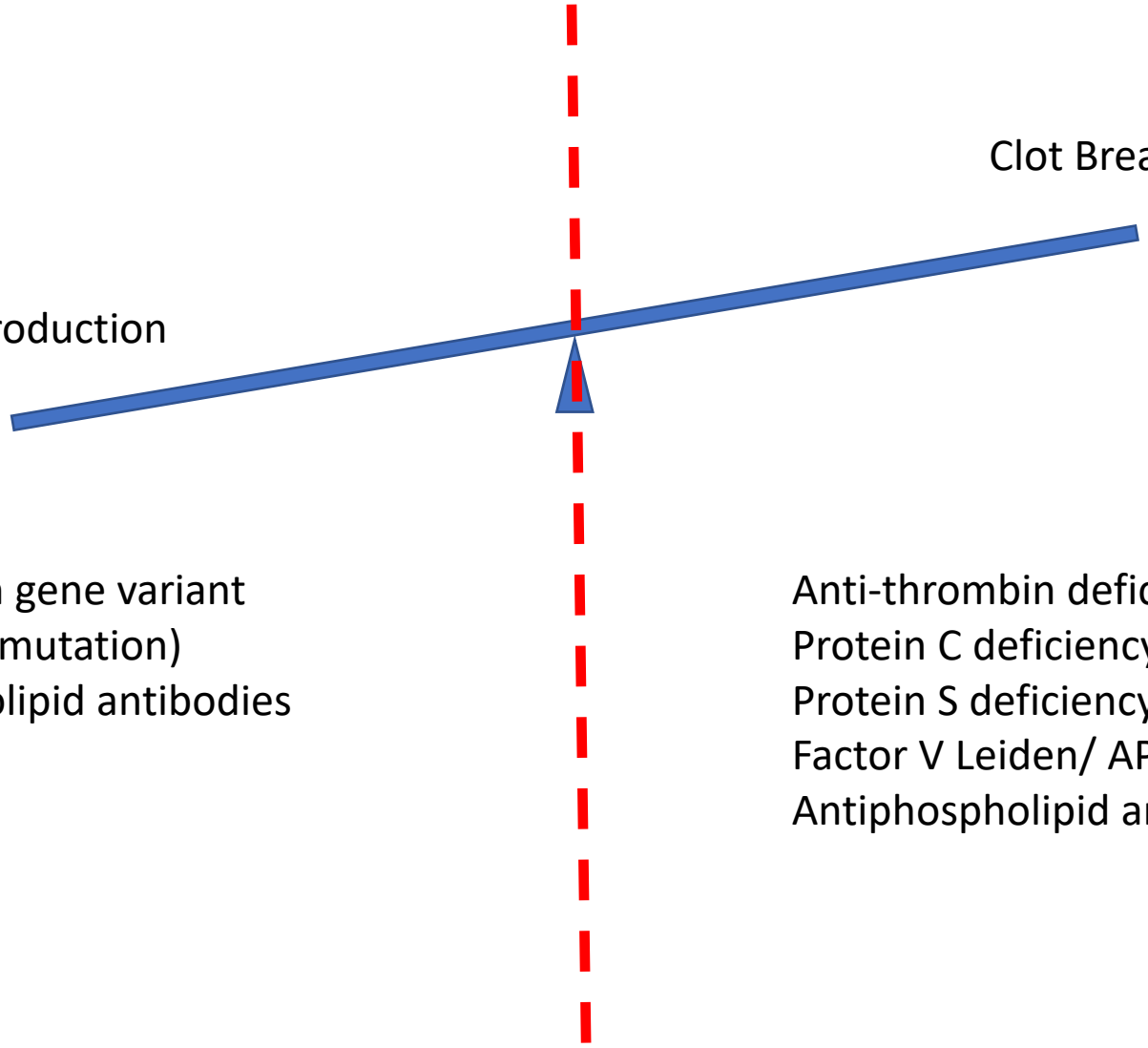


Thrombophilia

Clot Breakdown

Clot Production





Prothrombin gene variant
(PG 20210A mutation)
Antiphospholipid antibodies

Anti-thrombin deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden/ APC resistance
Antiphospholipid antibodies

Who Should be tested?

- BCSH guidelines (2010)
  - Complicated and confusing
- Hardly ever recommended
  - Results will not change management of index case or relatives
- Most patients are tested at the wrong time

When to test

- Can be done anytime:
  - Genotypic tests: FVL, PGV
  - APS antibodies: β-2-glycoprotein, aCL antibodies
- After 3 months & off anticoagulation
  - Protein C, S, Antithrombin, lupus anticoagulant

- Results will never influence initial treatment
  - ie first 3/12 of anticoagulation
- Potential for inappropriate anticoagulant management

Why test for inherited thrombophilias?

- ~~Intensity of anticoagulation~~
- ~~Duration of anticoagulation~~
- ~~Predict risk of recurrence~~
- Predict risk in asymptomatic relatives

Duration of Anticoagulation

- ACCP (2016) and ESC (2014) consensus guidelines
  - Initial anticoagulation should be for 3 months duration
  - “Suggest anticoagulants should be continued indefinitely in unprovoked VTE patients with non-high bleeding risk” (GRADE 2B- Weak recommendation)
- Risk scores
  - DASH, HERDOO2, Vienna
  - None identified inherited thrombophilia as a risk

Predicting risk of recurrence

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation	Lupus anticoagulant*	Anti-cardiolipin antibodies*	Anti-β2 GPI antibodies
Prevalence in the general population	0.02%	0.2%	0.03%-0.13%	3-7%	0.7%-4%	1%-8 %	5	3.4
Relative risk for a first venous thrombosis	5-10	4-6.5	1-10	3-5	2-3	3-10	0.7	2.4
Relative risk for recurrent venous thrombosis	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4	2-6	1-6	
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9	10	1.5-10	
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3	No consistent data	No consistent data	

Who (not) to Test – NICE 2015

- Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
- Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.
- Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

- **Consider** testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.
- **Consider** testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.

Appendix I: Obstetric thromboprophylaxis risk assessment and management

Antenatal assessment and management (to be assessed at booking and repeated if admitted)

- Any previous VTE except a single event related to major surgery → **HIGH RISK**: Requires antenatal prophylaxis with LMWH; Refer to trust-nominated thrombosis in pregnancy expert/team
- Hospital admission
- Single previous VTE related to major surgery
- High-risk thrombophilia + no VTE
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
- Any surgical procedure e.g. appendicectomy
- OHSS (first trimester only)

→ **INTERMEDIATE RISK**: Consider antenatal prophylaxis with LMWH

- Obesity (BMI > 30 kg/m²)
- Age > 35
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current pre-eclampsia
- Immobility, e.g. paraplegia, PGP
- Family history of unprovoked or estrogen-provoked VTE in first-degree relative
- Low-risk thrombophilia
- Multiple pregnancy
- IVF/ART

→ **Four or more risk factors**: prophylaxis from first trimester

Three risk factors: prophylaxis from 28 weeks

Fewer than three risk factors → **LOWER RISK**: Mobilisation and avoidance of dehydration

Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel

Postnatal assessment and management (to be assessed on delivery suite)

- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx

→ **HIGH RISK**: At least 6 weeks' postnatal prophylactic LMWH

- Caesarean section in labour
- BMI ≥ 40 kg/m²
- Readmission or prolonged admission (≥ 3 days) in the puerperium
- Any surgical procedure in the puerperium except immediate repair of the perineum
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU

→ **INTERMEDIATE RISK**: At least 10 days' postnatal prophylactic LMWH

NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

- Age > 35 years
- Obesity (BMI ≥ 30 kg/m²)
- Parity ≥ 3
- Smoker
- Elective caesarean section
- Family history of VTE
- Low-risk thrombophilia
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, PGP, long-distance travel
- Current pre-eclampsia
- Multiple pregnancy
- Preterm delivery in this pregnancy (< 37+0 weeks)
- Stillbirth in this pregnancy
- Mid-cavity rotational or operative delivery
- Prolonged labour (> 24 hours)
- PPH > 1 litre or blood transfusion

Two or more risk factors → **INTERMEDIATE RISK** (as above)

Fewer than two risk factors → **LOWER RISK**: Early mobilisation and avoidance of dehydration

Antenatal and postnatal prophylactic dose of LMWH

Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily
Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily
Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily
Weight 131–170 kg = 80 mg enoxaparin/10000 units dalteparin/9000 units tinzaparin daily
Weight > 170 kg = 0.6 mg/kg/day enoxaparin/ 75 u/kg/day dalteparin/ 75 u/kg/day tinzaparin

APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β_2-glycoprotein 1 antibodies); ART = assisted reproductive technology; BMI based on booking weight; DM = diabetes mellitus; FHx = family history; gross varicose veins = symptomatic, above knee or associated with phlebitis/oedema/skin changes; high-risk thrombophilia = antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD = inflammatory bowel disease; immobility = ≥ 3 days; IVDU = intravenous drug user; IVF = in vitro fertilisation; LMWH = low-molecular-weight heparin; long-distance travel = > 4 hours; low-risk thrombophilia = heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS = ovarian hyperstimulation syndrome; PGP = pelvic girdle pain with reduced mobility; PPH = postpartum haemorrhage; thrombophilia = inherited or acquired; VTE = venous thromboembolism.

Who do we Test?

- Pregnancy
  - Asymptomatic patients with 1st degree relative with VTE and known thrombophilic defect
- Unprovoked VTE
  - Only those wishing to stop after 3/12
- Family history
  - Screen asymptomatic relatives if very strong history
  - Ie Multiple events in multiple 1st degree relatives with known thromphophilic defect