Approach to Thrombosis

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Approach to Thrombosis

- Thrombosis: *" thrombus formation at any parts of cardiovascular system including veins, arteries, heart and microcirculation."*
- In 1806, Virchow Rudolf proposed a *triad* of factors to explain the pathogenesis of thrombosis

Approach to Thrombosis

Virchow's triad

- blood vessel (vasculitis, atherosclerosis)
- blood flow (stasis)
- blood component

- thrombophilia or
- hypercoagulable state

Approach to Thrombosis

Thrombosis

- Diagnosis
  - clinical
  - image
  - thrombophilic workup
- Treatment
  - medication: antithrombotic
  - duration: 6 months or life-long
- Prevention
  - primary prophylaxis
  - secondary prophylaxis

Deep Vein Thrombosis (DVT)

Diagnosis

- symptoms and signs
  - unilateral leg pain
  - unilateral leg edema
  - femoral triangle tenderness
  - Homans sign positive
- laboratory
  - venography, venous sonography
  - biomarker: d-dimer

Deep Vein Thrombosis (DVT)

	Advantage	Disadvantage
▪ clinical	easy to recognize	insensitive
▪ venography	reference, standard	invasive
▪ venous sonography	accurate for proximal vein	insensitive for calf vein thrombosis limitation for iliac vein thrombosis
▪ D-dimer	easy to perform used to excluded VTE	insensitive

Deep Vein Thrombosis (DVT)

Wells score	
▪ active cancer	1
▪ bedridden recently > 3 days or major surgery within 4 months	1
▪ calf swelling > 3 cm compared to the other leg	1
▪ collateral (nonvaricose) superficial veins present	1
▪ entire leg swollen	1
▪ localized tenderness along the deep venous system	1
▪ pitting edema confined to symptomatic leg	1
▪ paralysis, paresis or recent plaster immobilization of the lower extremity	1
▪ previously documented DVT	1
▪ alternative diagnosis to DVT as likely or more likely	-2

≤ 1 LOW PROBABILITY; ≥ 2 HIGH PROBABILITY

JAMA.2006;295:199-207.

Pulmonary Embolism (PE)

Diagnosis

- symptoms and signs
  - sudden dyspnea
  - desaturation
- laboratory
  - EKG, chest X-ray, arterial blood gas analysis
  - pulmonary angiography
  - ventilation/perfusion scan
  - helical CT scan of chest

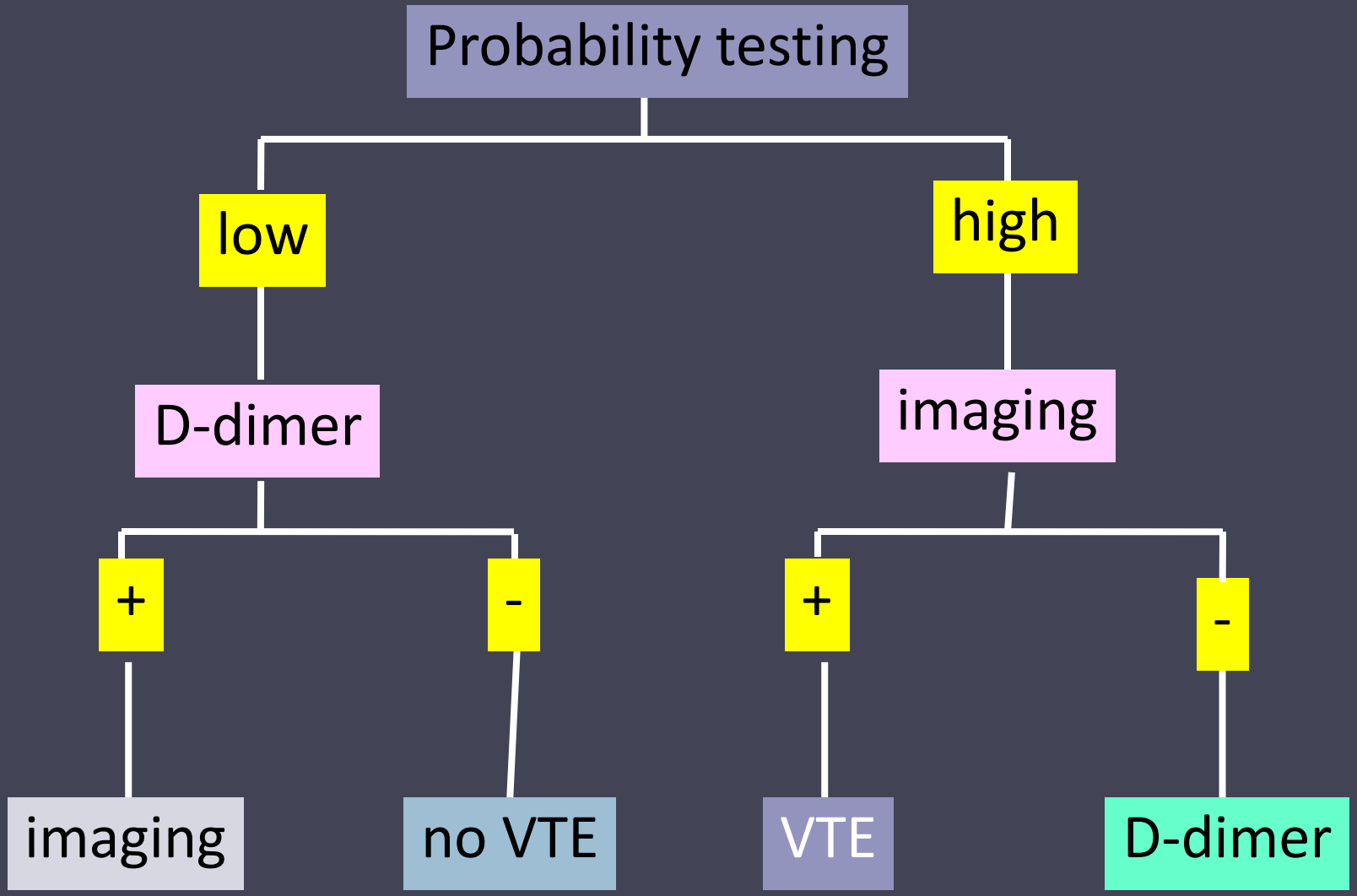
Pulmonary Embolism (PE)

	Advantage	Disadvantage
▪ clinical	easy to recognize	insensitive
▪ pulmonary angiography	reference, standard	invasive serious complications
▪ V/P lung scan	90% sensitivity in high probability	not available in all institute
▪ helical CT scan	non invasive	insensitive for peripheral PE
▪ D-dimer	easy to perform	insensitive

Pulmonary Embolism (PE)

Well's score	
clinical DVT	3
heart rate >100/minute	1.5
immobilization (prolonged bed rest > 3 consecutive days, surgery within 4 weeks)	1.5
previous DVT or PE	1.5
hemoptysis	1
malignancies	1

<4 LOW PROBABILITY; ≥ 4 HIGH PROBABILITY


Probability testing
low
high
D-dimer
imaging
+
-
+
-
imaging
no VTE
VTE
D-dimer

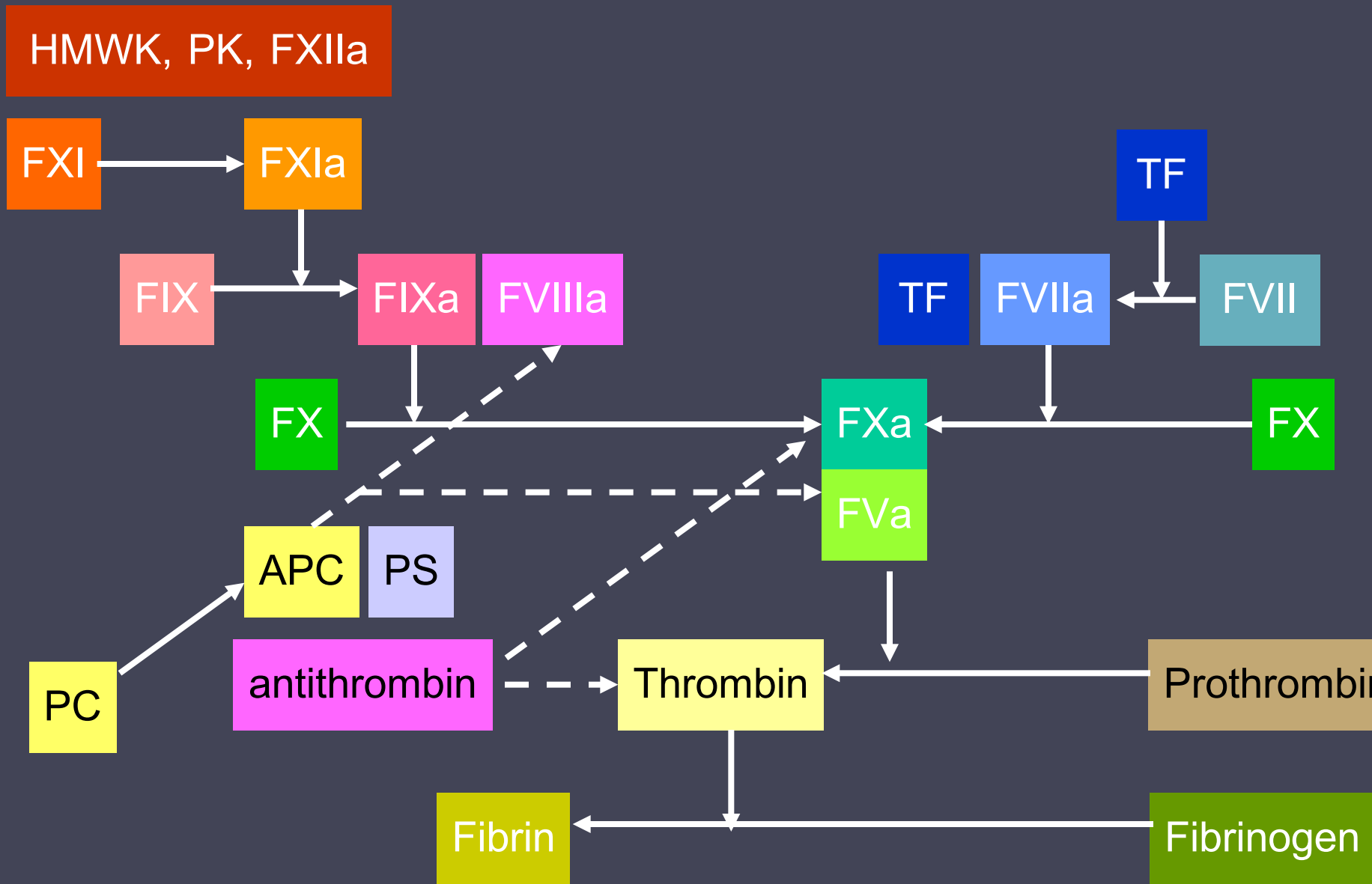
Thrombophilic risks

Normal hemostasis

- blood vessel
- platelet
- coagulation proteins
- fibrinolytic system
- natural anticoagulants

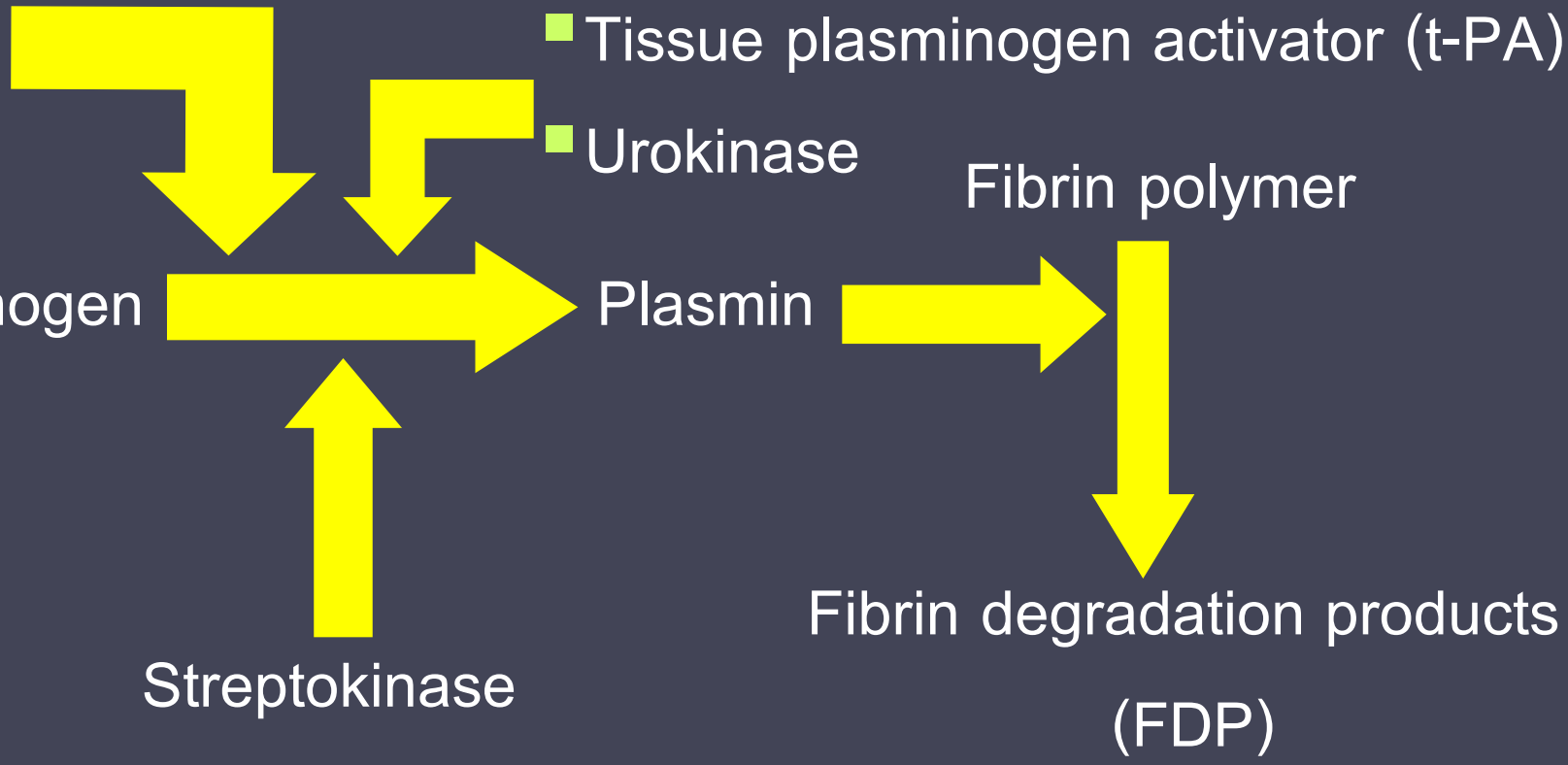
Normal Hemostasis

Normal Hemostasis

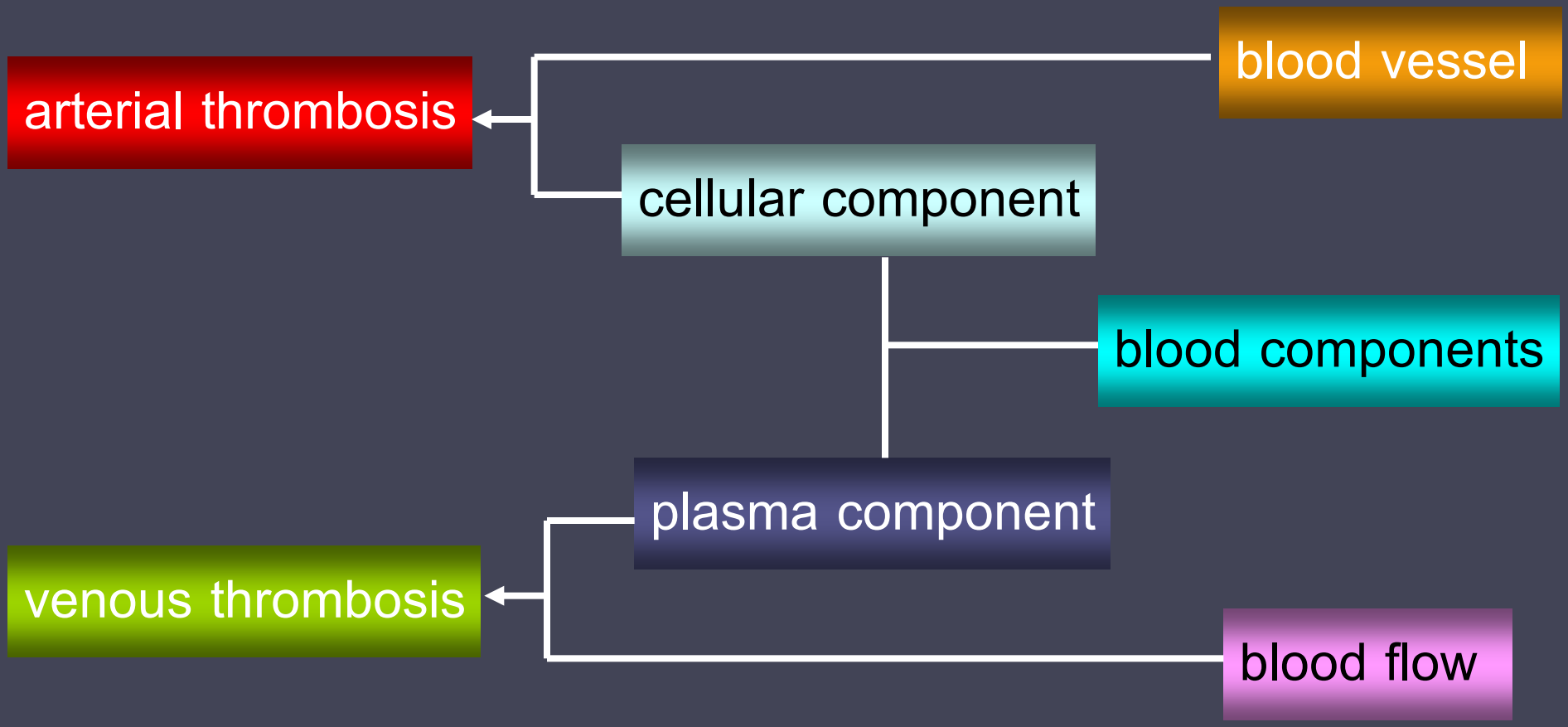


Normal Hemostasis

- High Molecular Weight Kininogen (HMWK)
- Prekallekrein (PK)
- F.XII



Thrombophilic Workup



Clues for Thrombophilic Investigation

Bleeding disorders	Thrombophilia
▪ multiple sites of bleeding at the same period	▪ multiple sites of occlusion
▪ familial history of bleeding	▪ familial history of thrombosis
▪ onset at the early year of life	▪ onset at the early year of life
▪ inappropriate with injuries	▪ unprovoked
	▪ unusual sites of thrombosis
	▪ repeated thrombosis or abortion

Thrombophilic risks

- Hereditary defects
- Acquired conditions
  - transient
  - ongoing
- Combination

Thrombophilic risks

Hereditary

- antithrombin deficiency
- protein C deficiency
- protein S deficiency
- factor V Leiden mutation
- prothrombin G20210A polymorphism
- homocysteinemia (rare)

Acquired

- transient
- ongoing

Thrombophilic risks

Acquired conditions

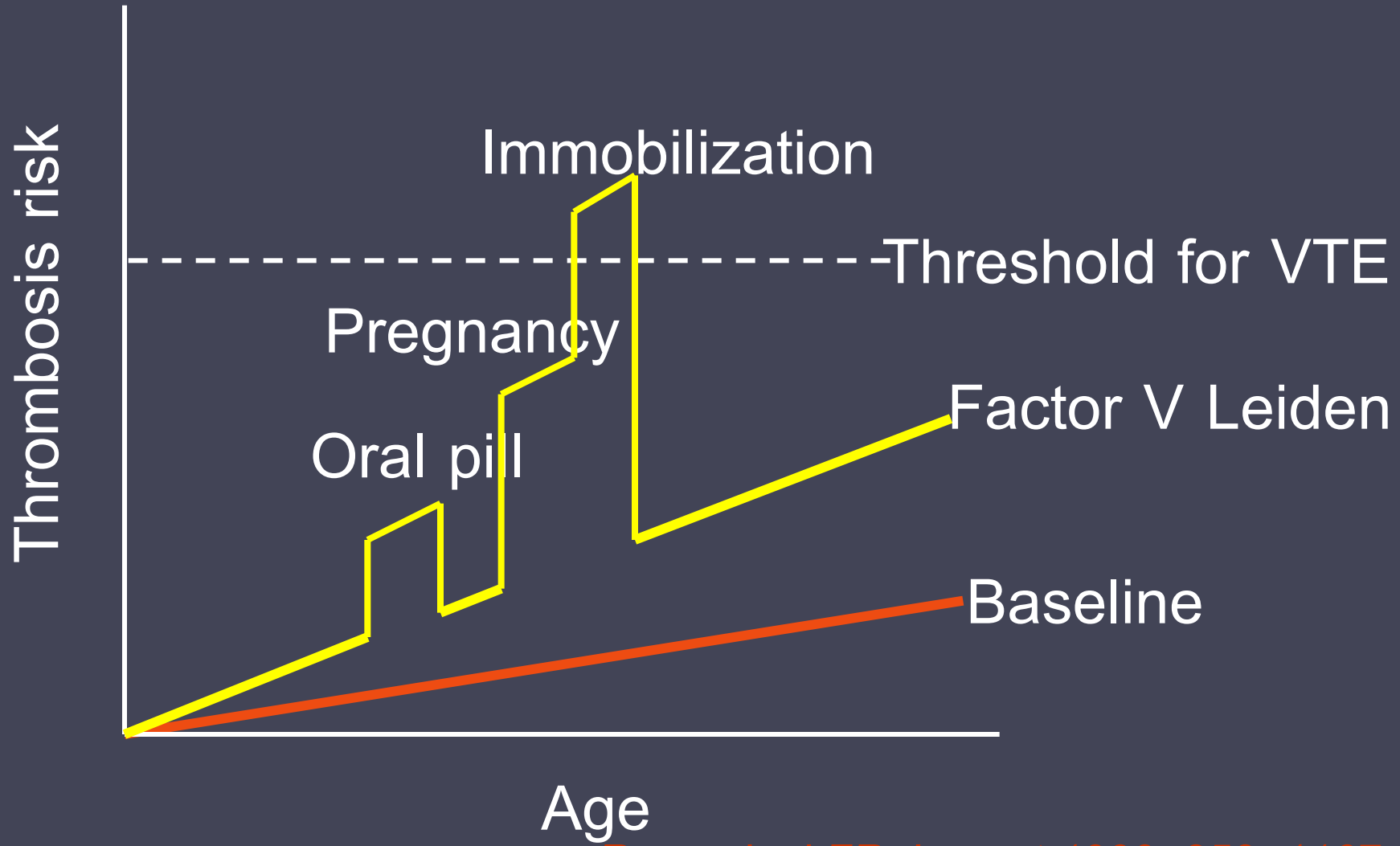
- transient risks (provoked thrombosis)
  - immobilization
  - recent surgery
  - heparin-induced thrombocytopenia/thrombosis (HIT/T)
  - pregnancy or puerperium
  - oral contraceptive pills

Thrombophilic risks

Acquired conditions

- ongoing risks
  - aging
  - malignancy
  - antiphospholipid syndrome (APS)
  - disseminated intravascular coagulation (DIC), chronic
  - paroxysmal nocturnal hemoglobinuria (PNH)
  - nephrotic syndrome

Thrombophilic risks



Rosendaal FR. Lancet 1999; 353: 1167.

Thrombophilic investigation

hereditary

First line

- antithrombin
- protein C
- protein S
- factor V Leiden mutation
- prothrombin G20210A polymorphism
- Ham's test
- urine hemosiderin
- CBC
- JAK 2 mutation
- lupus anticoagulant
- anticardiolipin
- β_2-glycoprotein I

PNH, PV, ET

APS

Second line

- plasminogen level
- tissue plasminogen activator (PA)
- plasminogen activator inhibitor (PAI)
- factor XII
- prekallekrein
- high molecular weight kininogen
- dysfibrinogenemia

Isolated aPTT

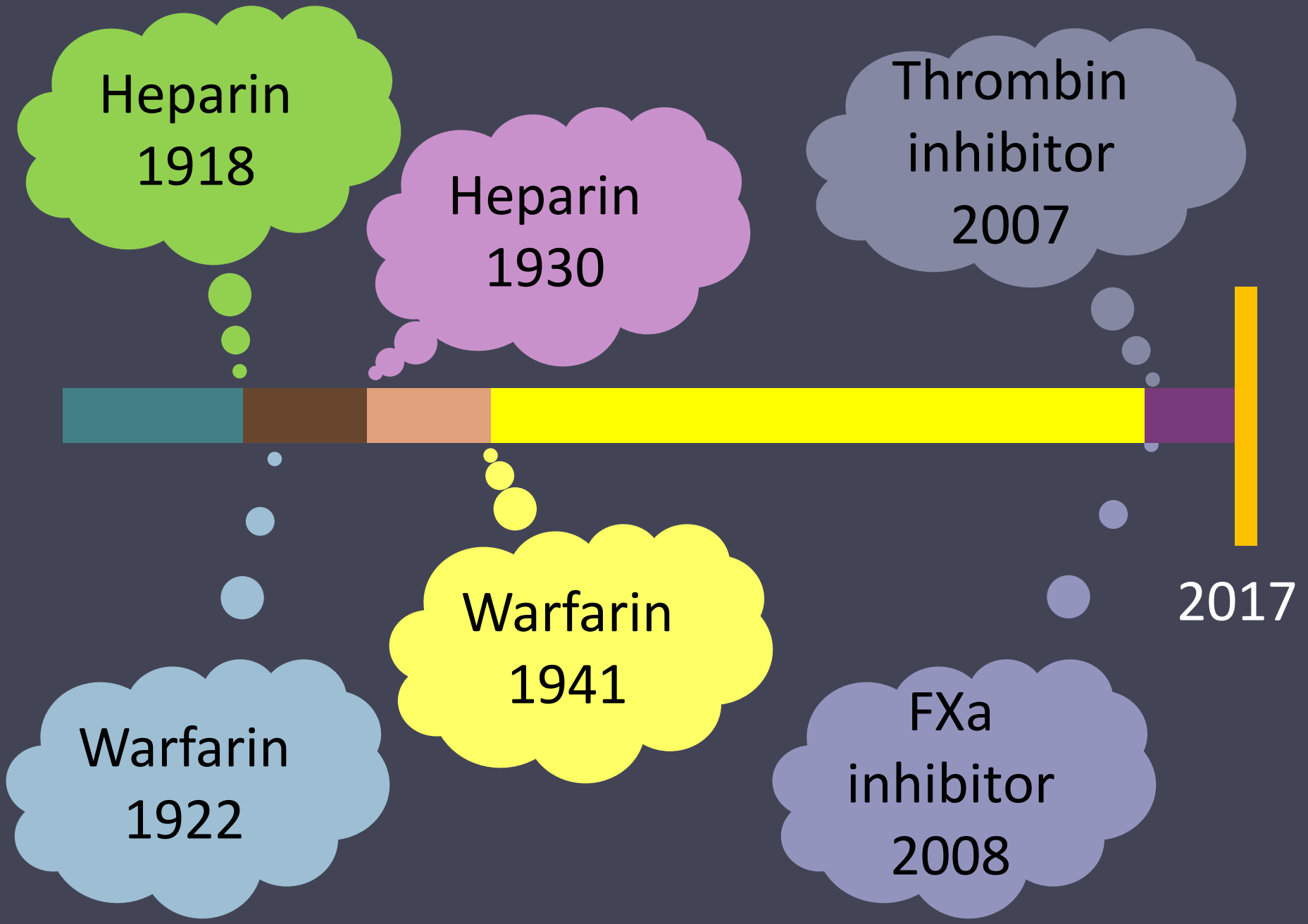
Thrombophilic investigation

Investigation

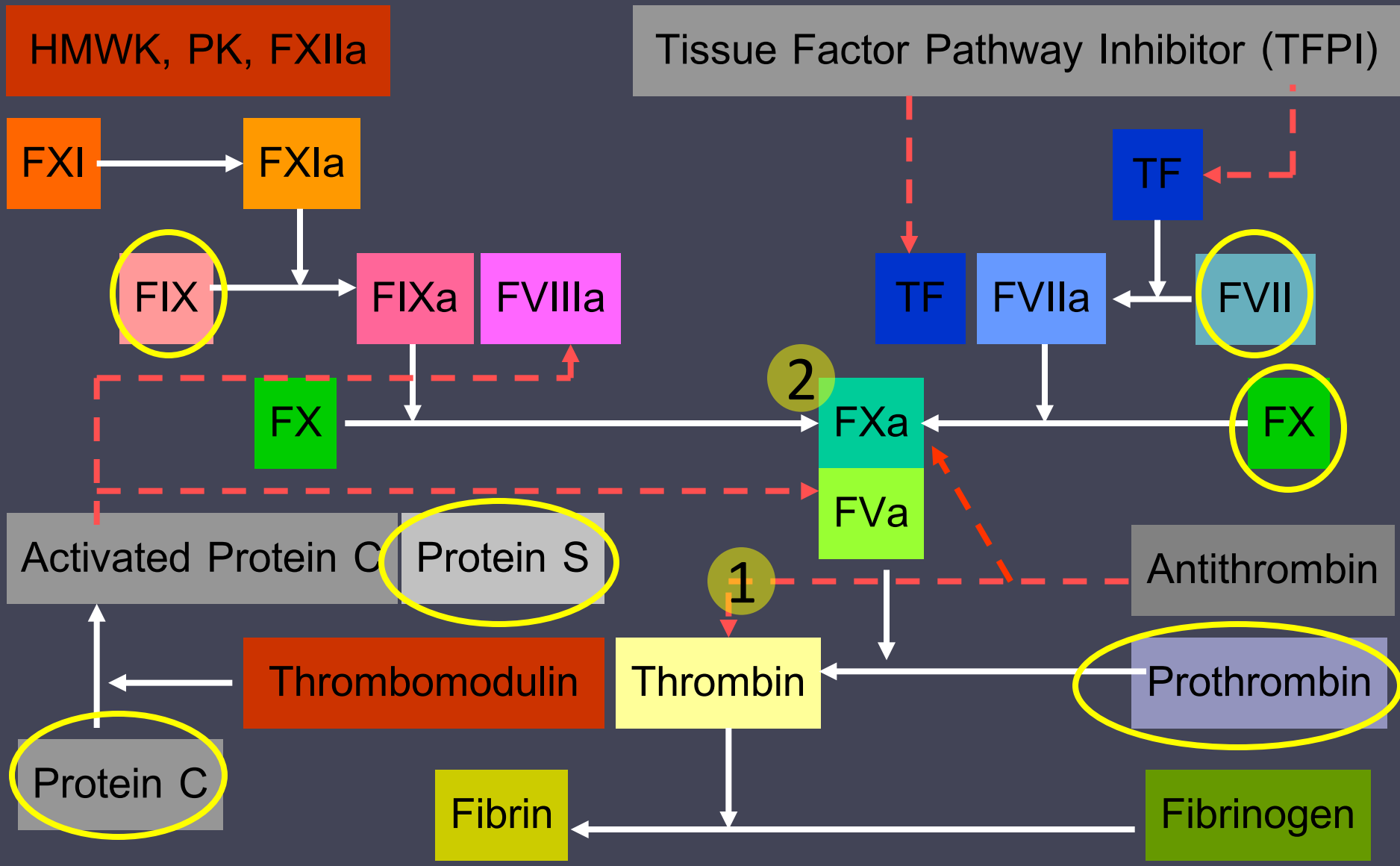
- functional assay
  - antithrombin , protein C, protein S, lupus anticoagulant, homocysteine,
  - should perform 2 weeks after cessation of antithrombotic agents
- genetic analysis or antigenic assays
  - factor V Leiden, prothrombin polymorphism, anticardiolipin antibodies IgG, anti β_2-glycoprotein I, IgG
  - can be tested at any times

Management

- type of antithrombotics
- duration of treatment


Heparin
1918
Heparin
1930
Thrombin
inhibitor
2007
2017
Warfarin
1941
Warfarin
1922
FXa
inhibitor
2008

Anticoagulants



Type of Anticoagulants

- Heparin
  - unfractionated
  - low molecular weight
  - pentasaccharides
- Vitamin K antagonist
- Direct oral anticoagulants

Step of Treatment

	Day	Drugs
▪ acute	5-7	UFH, LMWH, pentasaccharides, DOACs
▪ long term	>7 (1 week)	warfarin, DOACs
▪ extended	>90 (12 weeks)	warfarin

Management

- *acute management:* no difference between those with or without thrombophilic risks
- *long-term management:*
  - life-long?
  - prophylaxis?

Management

Treatment-summary

- anticoagulants as conventional style
  - unfractionated heparin
  - low molecular weight heparin
  - warfarin
  - direct oral anticoagulants
- duration
  - 3-6 months
  - life long treatment ??

Management

Antithrombotics

- acute: UFH, LMWH, Pentasaccharides
- long term: oral anticoagulants
  - warfarin: target INR = 2-3
  - direct FXa inhibitor
  - direct thrombin inhibitor

Direct Oral Anticoagulants (DOACs)

Direct thrombin inhibitor

- dabigatran etixilate (Pradaxa®) 75 , 110 mg

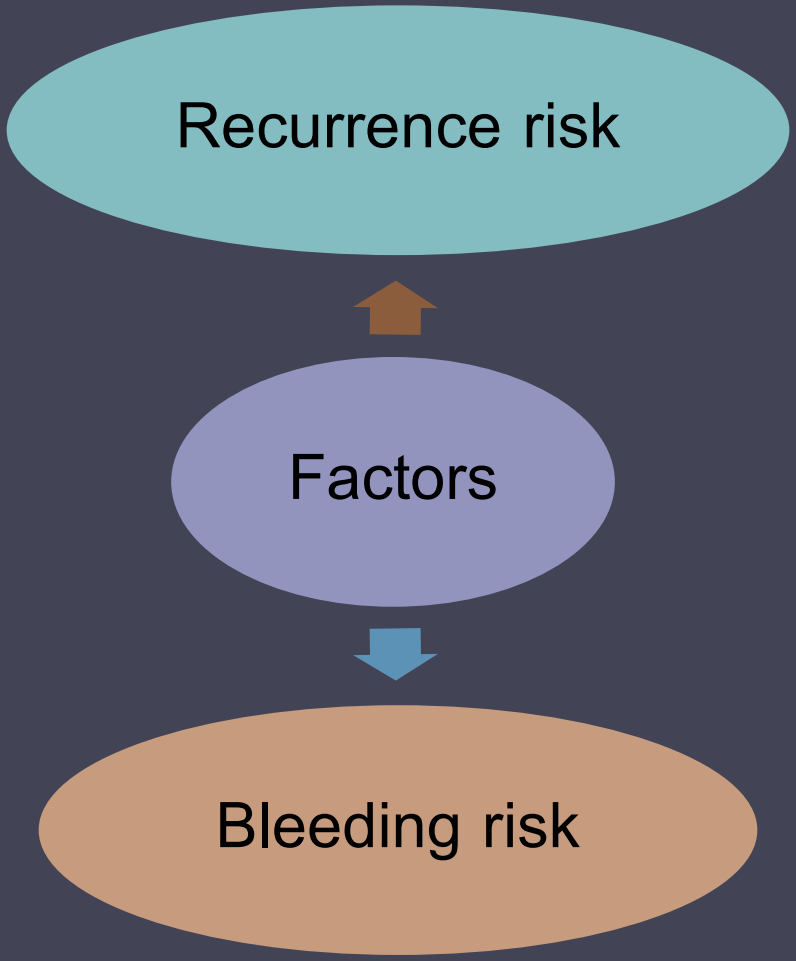
Direct FXa inhibitor

- rivaroxaban (Xarelto®)

  10, 15, 20 mg
- apixaban (Eliquis®)

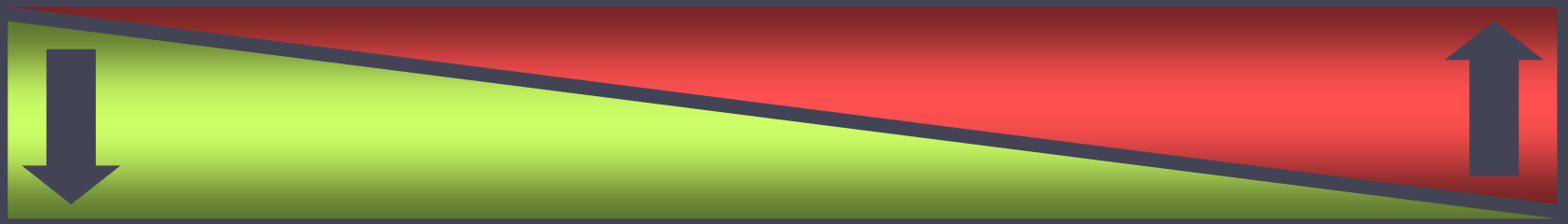
  2.5 mg
- edoxaban (Lixeana®)

Management



Management

- Hemorrhagic complication: 2%/year



- Recurrence rate of thrombosis:
  - incidence: varied 10% at the first 2 years , 3%/year afterward
  - depend on thrombophilic risks
    - Acquired
    - Hereditary

Carrier M et al. Ann Intern Med. 2010; 152: 578–589.

Management

Estimated relative risks for a first episode of VTE in individuals with a thrombophilic defect as compared to individuals without a defect

Defect	Relative risk	references
Antithrombin deficiency	8-10	*1, 2*
Protein C deficiency	7-10	*1, 2*
Protein S deficiency	8-10	*1, 2*
Factor V Leiden/ APC resistance	3-7	*3,4*
Prothrombin 20210 mutation	3	*Blood1996;88:3698-3703*

1) Blood 1998;92: 2353-8.

2) Thromb Haemost 1999; 81: 198-202.

3) Ann Int Med 1998; 128: 15-20.

4) Lancet 1993; 342: 1503-6.

Management

Estimated relative risks for a first episode of VTE in individuals with a thrombophilic defect as compared to individuals without a defect

Defect	Relative risk	references
Elevated Factor VIII:C	2-11	*1*
Elevated Factor IX:C	2-3	*2*
Elevated Factor XI:C	2	*3*
Anticardiolipin (high titer)	3.2	*4*
Lupus anticoagulant	11	*4*

1) Thromb Haemost 2000; 83: 5-9

2) Blood 2000; 95: 3678-82.

3) NEJM 2000; 342: 696-701.

4) Lupus 1998; 7: 15-22.

Management

Estimated relative risks for recurrent VTE in individuals with a thrombophilic defect as compared to individuals without a defect

Defect	Relative risk	references
Antithrombin deficiency	2.5	*1, 2*
Protein C deficiency	2.5	*1, 2*
Protein S deficiency	2.5	*1, 2*
Factor V Leiden/ APC resistance	1.4	*3,4*
Prothrombin 20210 mutation	1.4	*3*

1) Arch Int Med 1997;157: 2227-32.

2) Thromb Haemost 1999; 82: 1583-7.

3) Thromb Haemost 1999; 81: 684-9.

4) Circulation 2003; 108: 313-8.

Management

Duration

Patients with first episode of VTE	Drugs	Duration (months)	Comments
▪ with transient risk	VKA	3	both proximal and distal DVT
▪ Idiopathic or unprovoked	VKA	6-12	
▪ with cancer	LMWH	3-6	indefinite?
▪ with one hereditary risk	VKA	6-12	indefinite?
▪ with two or more hereditary risks or with APS	VKA	12	indefinite?

Management

Indication for *indefinite* anticoagulation (target INR 2-3)

- one spontaneous thrombosis with
  - life threatening thrombosis
  - unusual site of thrombosis
  - heterozygous antithrombin deficiency or lupus anticoagulant - positive
  - ≥ 1 genetic defects (heterozygous = 1 defect)
- more than two spontaneous thrombosis

Bauer KA. Ann Int Med 2001; 135: 367-73.

Follow up

Compression doppler ultrasound

- The association with positive residual thrombus and recurrence rate of VTE is controversy.
- The standardization of the method and definition is not established.
- Not recommended to use the compression doppler ultrasound to extended the duration of treatment.
- Use to perform for baseline after stop treatment.

Follow up

D-dimer

- Test at the end of treatment and one month later

	D-dimer (ng/ml)	
Recurrence rate (%/year)	< 500	≥ 500
	3.5	8.9

Palareti G et al. N Engl J Med. 2006;355:1780 –1789.

Verhovsek M et al. Intern Med. 2008;149:481– 490.