

Hypercoagulability

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Disclosures

GSK – Speaker (fondaparinux)

**Bayer Healthcare/J&J – Consultant
(rivaroxaban)**

Agenda

- **Overview of risk factors for thrombosis**
- **Acquired risk factors**
- **Genetic risk factors**
- **Management of venous thromboembolism**
 - **impact of thrombophilia**

Case Presentation

- 19 year old female developed right proximal DVT 3 weeks following initiation of oral contraception; no family history of VTE
- Treatment: LMWH followed by warfarin
- Lab Evaluation: Homozygous for Factor V Leiden mutation, (homozygous for MTHFR C677T polymorphism, normal homocysteine)
- Duration of anticoagulation: ? lifelong

Risk Factors For Venous Thrombosis

ACQUIRED

Advancing Age

Prior Thrombosis

Immobilization

Major Surgery

Malignancy

**Estrogens/Pregnancy
(OCP, HRT, SERMs)**

Antiphospholipid
antibody syndrome

Myeloproliferative
disorders

IBD, Nephrotic syndrome, AAV

Heparin-induced
thrombocytopenia

Obesity

Prolonged Air Travel

Male Sex

INHERITED

Antithrombin Deficiency

Protein C Deficiency

Protein S Deficiency

Factor V Leiden (FVL)

Prothrombin G20210A

MIXED/UNKNOWN

↑ Homocysteine

↑ Factor VIII

APC resistance
in the absence
of FVL

↑ Factor IX

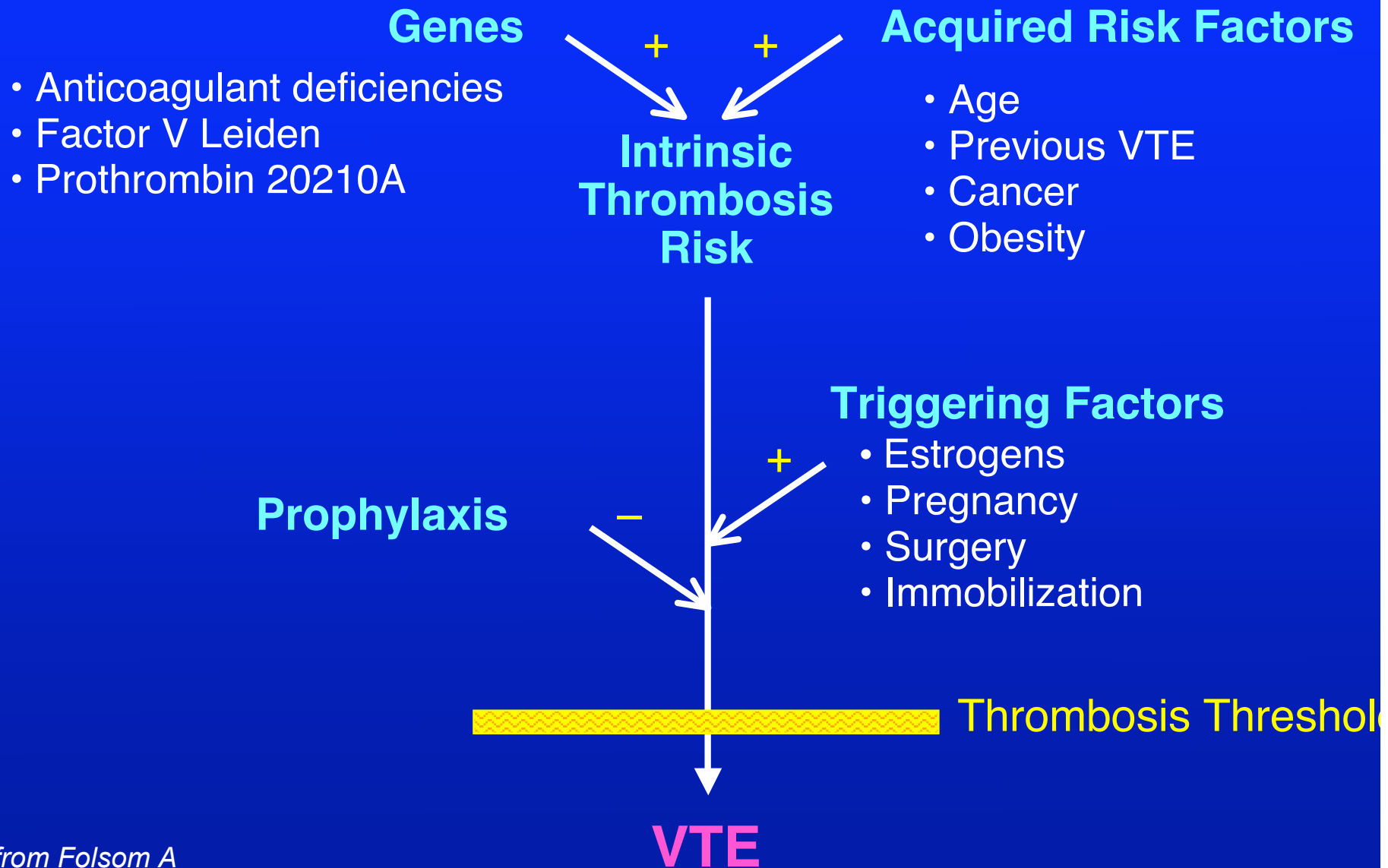
↑ Factor XI

↑ TAFI

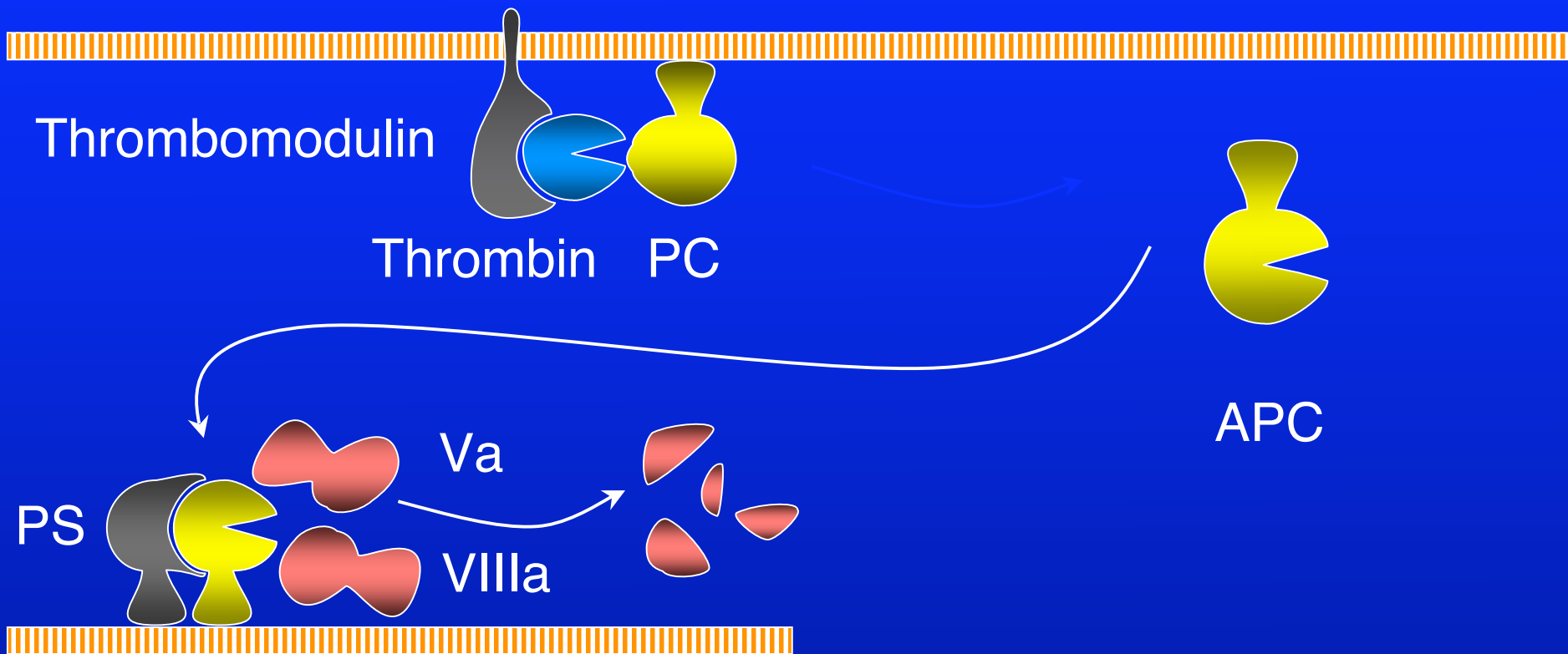
↓ Free TFPI

↓ fibrinolytic activity

VTE Risk Factor Model



Activated Protein C: Mechanism of Action as a Natural Anticoagulant



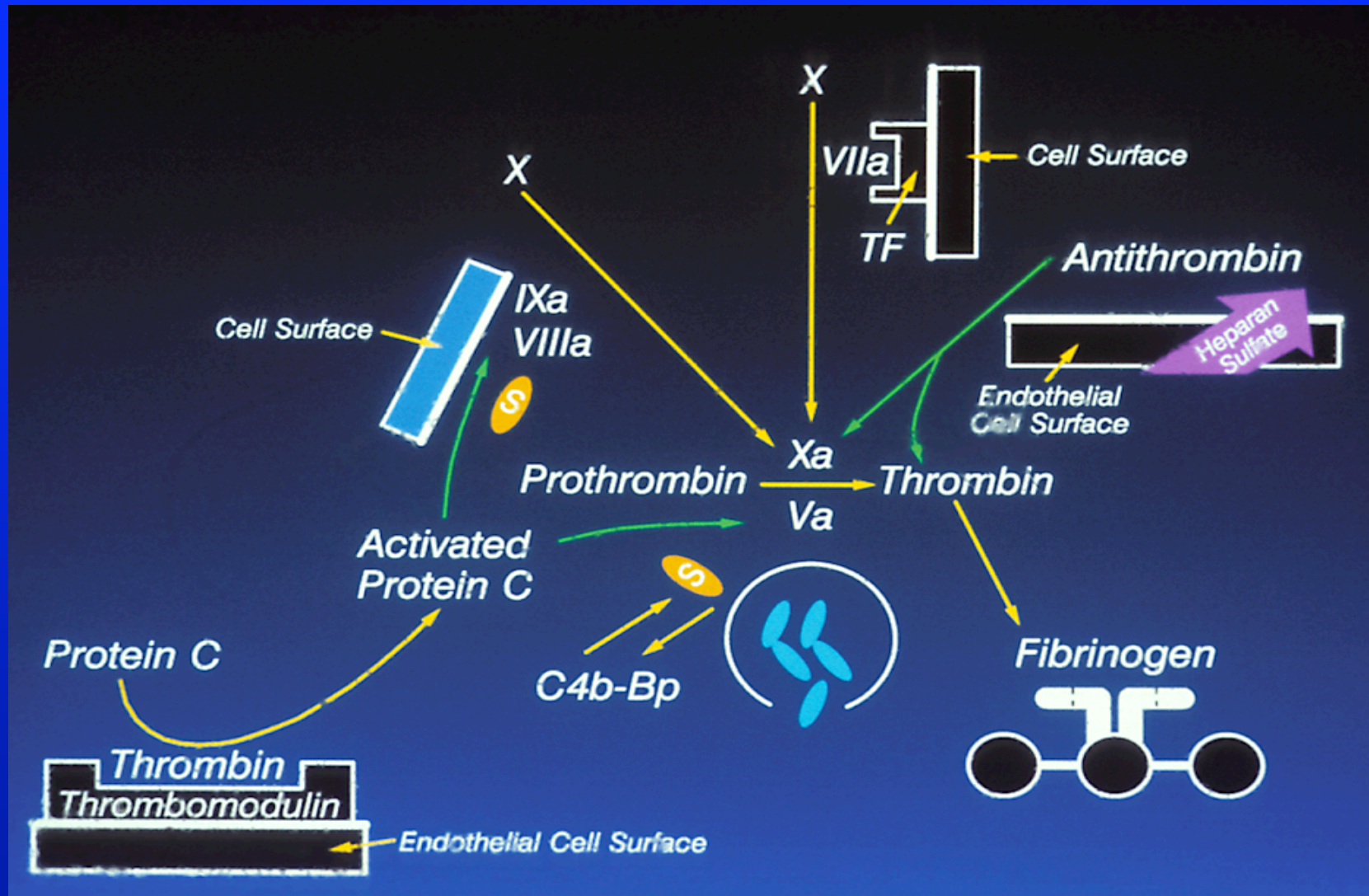
from Weiler H

Prothrombin Gene Mutation G ⇒ A Mutation at Position 20210 in 3'-UT Region

<u>GENOTYPE</u>	<u>PROTHROMBIN</u>	<u>RANGE</u>
20210 AG	132%	95-178
20210 GG	105%	55-156

From Poort et al, Blood 1996

Mutation leads to increased efficiency of prothrombin mRNA 3'-end formation and increased prothrombin biosynthesis without affecting the rate of transcription.



The “Hypercoagulable Workup”

- Tests for Antiphospholipid Antibody Syndrome
- Genetic test for Factor V Leiden mutation or coagulation assay for Activated Protein C Resistance (if abnormal, confirm genetically)
- Genetic test for Prothrombin G20210A mutation
- Functional assay of Antithrombin*
- Functional assay of Protein C*
- Protein S assays*
 - Functional assay
 - Measurements of total and free Protein S

Antiphospholipid Antibody Syndrome (APLS)

- Definition: thrombotic event (venous or arterial thrombosis, recurrent fetal loss) in association with a **persistent** LA in specialized clotting assays or **persistently** elevated titers of cardiolipin (IgG or IgM) or β_2 -glycoprotein I antibodies
- Clinical manifestations include thrombocytopenia and livedo reticularis.
- \uparrow β_2 -glycoprotein I antibodies **rarely** found in absence of a LA or \uparrow cardiolipin IgG/IgM levels

Antiphospholipid Antibody Syndrome (APLS)

- Associated with SLE, cancer, infections, drugs, idiopathic
- LA result from the presence of immunoglobulins which bind to phospholipids and plasma proteins (β 2-glycoprotein 1, prothrombin) in vitro and prolong clotting times (critically dependent on the amount of phospholipid in assay). LA do not cause bleeding.
- 1st unprovoked thrombotic event in association with persistent LA \Rightarrow **high** risk for recurrent thrombosis \Rightarrow long-term anticoagulation indicated
- Two randomized trials have shown that an INR of 2-3 is adequate in patients with venous thrombosis and APLS.

Lowering homocysteine levels with B-vitamins does not lower risk of recurrent thrombosis

- Arterial Thrombosis
 - NORVIT Trial (N Eng J Med 2006)
 - 3,479 patients with acute MI
 - Trend toward increased risk with combined B vitamin treatment
 - HOPE 2 Investigators (N Eng J Med 2006)
 - 5,522 patients > age 55 with vascular disease or diabetes
- Venous Thrombosis
 - HOPE 2 Investigators (Ann Int Med 2007)
 - VITRO Study (Blood 2007)
 - Patients ages 20-80 with unprovoked proximal DVT or PE
 - Recurrences: 43/348 vitamins, 50/353 placebo

⇒ **No** reason to measure homocysteine levels

⇒ **Never** test for MTHFR polymorphisms (C677T, A1298C)

Prevalence of Hereditary Defects in Patients with Venous Thrombosis

APC Resistance (Factor V Leiden)	12-40%
Prothrombin Gene Mutation	6-18%
Deficiencies of AT, Protein C, Protein S	5-15%

Sites of Thrombosis

<u>ABNORMALITY</u>	<u>ARTERIAL</u>	<u>VENOUS</u>
Factor V Leiden	-	+
Prothrombin 20210A	-	+
AT Deficiency	-	+
Protein C Deficiency	-	+
Protein S Deficiency	-	+
Lupus Anticoagulant	+	+

Acquired Deficiencies in Antithrombin, Protein C, or Protein S

ANTITHROMBIN

Pregnancy
Liver Disease
DIC
Nephrotic syndrome
Major surgery
Acute thrombosis

Heparin
Estrogens

PROTEIN C

Liver Disease
DIC

Acute thrombosis

Warfarin

PROTEIN S

Pregnancy
Liver Disease
DIC

Inflammation
Acute thrombosis

Warfarin
Estrogens

Caveats:

1. Don't draw these tests when patients present with VTE or are receiving anticoagulants.
2. Abnormal results drawn at presentation with VTE must be confirmed. Draw protein C and S after discontinuing warfarin for several weeks.

Prevalence of the Factor V Leiden (FVL) and Prothrombin G20210A Mutations

<u>POPULATION</u>	<u>FVL (%)</u>	<u>G20210A (%)</u>
European		
Northern	5-10	1.7
Southern	2-3	3
African	EXTREMELY RARE	
Asian		

Leiden Thrombophilia Study: A Population Based Study **Koster T et al, *Lancet* 1993**

- **Patients: Inclusion Criteria**
 - **Consecutive outpatients < age 70 referred for warfarin treatment to thrombosis centers with a first DVT**
 - **Laboratory evaluation > 3 months after discontinuation of oral anticoagulants**
- **Patients: Exclusion Criteria**
 - **Malignancy**
- **Controls: Healthy matched unrelated subjects**

First Episode of Deep Venous Thrombosis (Leiden Thrombophilia Study)

	<u>RISK</u>
Normal	1
Prothrombin 20210A heterozygotes	2.8 ↑
Oral contraceptives	4x ↑
Factor V Leiden heterozygotes	7x ↑
Oral contraceptives + Factor V Leiden	35x ↑
Factor V Leiden Homozygotes	80x ↑

First Episode of Deep Venous Thrombosis (Leiden Thrombophilia Study)

	<u>INCIDENCE/YEAR (%)</u>
Normal	0.008
Oral contraceptives	0.03
Factor V Leiden heterozygotes	0.06
Oral contraceptives + Factor V Leiden	0.3
Factor V Leiden Homozygotes	0.5 - 1

Should we screen women for factor V Leiden prior to starting OCPs?

- If all women with factor V Leiden did not take OCPs, their risk of VTE would decrease from 30 to 6 VTE events per 10,000 women/year.
- \Rightarrow prevent 1 event per 417 women
- To find 417 women with factor V Leiden, you would have to screen 6,770 women given a prevalence of 6%.
- Costs of screening exceed benefits.

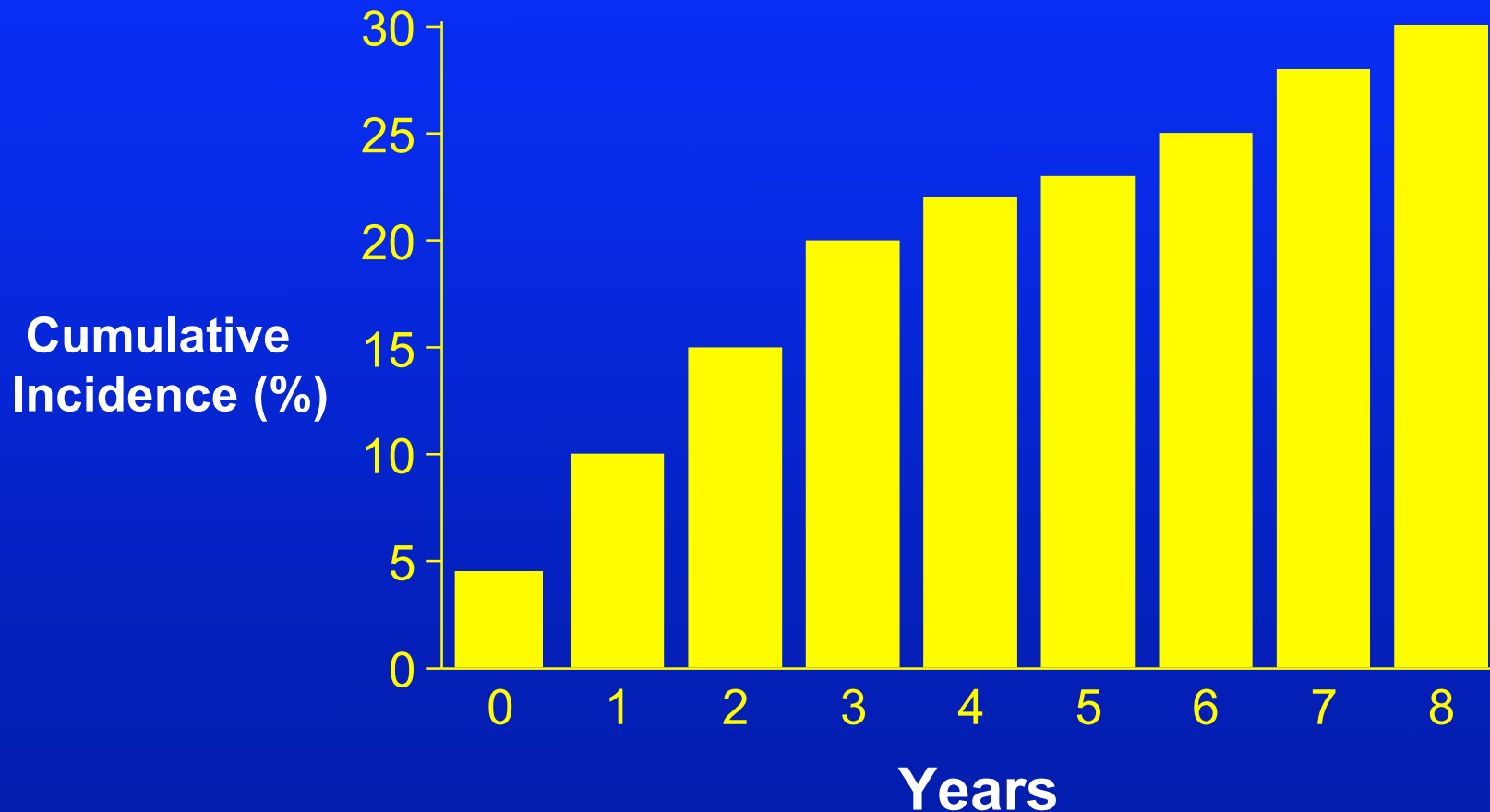
Hereditary Thrombophilia and Obstetric Complications

- Increased risk for second and 3rd trimester fetal loss (~3-fold ↑)
- No association with other obstetric complications (preeclampsia, IUGR) and likely 1st trimester losses
- 1 positive randomized trial of LMWH therapy to prevent recurrent fetal loss > 10 weeks - 86% vs 29% live birth rate in control (ASA) arm (Gris 2004)
- Retrospective case-control study: relatively favorable prognosis for women with thrombophilia and a first pregnancy loss without treatment - live birth rate 74% (Coppens 2007)

Treatment of DVT/PE

- **Heparin**
 - Unfractionated or Low Molecular Weight Heparin or Fondaparinux for at least 5 days
- **Warfarin**
 - Start on day 1 to achieve INR of 2-3, treat for 3 months

Recurrent Venous Thrombosis Following a First Episode of Symptomatic DVT



Prandoni et al, Ann Intern Med 1996;125:1-7

SUMMARY

ACCP 2008 (Chest 2008; 133:454S-545S)

The presence of hereditary thrombophilia has **not** been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of recurrence.

Risk of Recurrent Venous Thrombosis in Patients with Hereditary Thrombophilia

- **Heterozygosity for Factor V Leiden (FVL) or Prothrombin (PT) G20210A do not increase risk.**
- **Higher in heterozygotes with both FVL and PT G20210A (retrospective studies); probably higher in homozygotes with FVL**
- **Antithrombin, Protein C, Protein S Deficiency**
 - **High in selected kindreds with strong clinical penetrance (retrospective studies)**
 - **Less data in unselected patients**

Factors Influencing Duration of Anticoagulation Following 1st Unprovoked VTE

- **Recurrent VTE**

- Risk (% / year) ~10% (5-15%)
- Consequences (case fatality) 0.3-1.0%

- **Bleeding**

- Risk (% / year) ~1-2%
- Consequences (case fatality) 0.2-0.6%

⇒ A recurrent VTE rate of <5% per year is considered **”acceptable”** (risk of anticoagulation > benefit).

Guidelines on Duration of Anticoagulant Therapy

- **First event with reversible or time limited risk factor**
 - **3 months at INR 2-3**
- **Unprovoked VTE, first or second event**
 - **3-6 months at target INR, then consider indefinite anticoagulation at INR 2-3**
- **First (unprovoked) event in high risk thrombophilias**
thrombophilias - indefinite anticoagulation
 - **Cancer until remission (consider chronic LMWH)**
 - **Antiphospholipid antibody syndrome**
 - **Antithrombin deficiency or multiple genetic defects**

Guidelines on Anticoagulant Therapy

- **1 VTE episode with a clear precipitant that is no longer present or asymptomatic with acquired or inherited thrombophilia**
 - **Ensure thromboprophylaxis in high-risk settings**

Considerations: Long-Term OAC in Patients following 1st Unprovoked VTE

- Resolution of triggering risk factor
- Sites and severity of thrombosis
- Bleeding risk
- Identification of a prothrombotic defect coupled with family's thrombotic history
- **PATIENT VALUES AND PREFERENCE** (includes lifestyle and occupational considerations)
⇒ **An individualized decision**

Who should be considered for evaluation for hereditary thrombophilia?

Yes

VTE at age <50 with positive family history (1st degree relatives)

Cerebral venous thrombosis

Portal/mesenteric vein thrombosis (r/o MPD, PNH)

Pregnancy loss (2nd and 3rd trimester)

Reasonable

VTE in association with OCPs/HRT or pregnancy

Patients > 50 with first spontaneous VTE

No

Arterial thrombosis (save for paradoxical emboli)

Asymptomatic patients with no personal or familial hx of VTE

Women going on OCPs or HRT

VTE in patients with active cancer

Elderly patients with postoperative VTE

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After Initial Anticoagulation

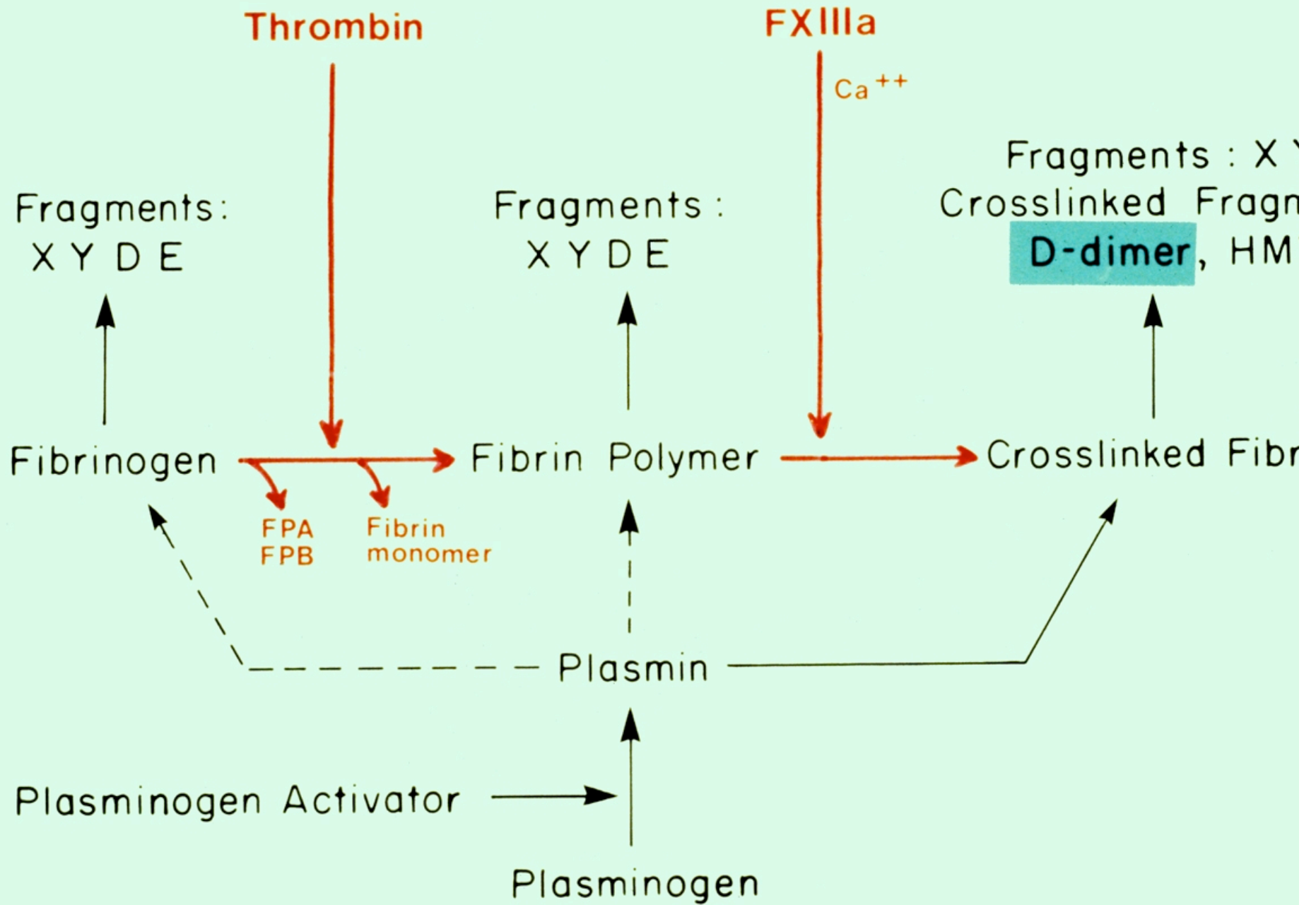
Accept the risk
of recurrence

Extend in
high-risk
patients

6 months

Extend
with new
strategies

Extend in
all patients



Recurrent VTE in patients with a 1st unprovoked VTE according to whether D-dimer levels were higher or lower after stopping treatment

Study (D-dimer assay)	D-dimer Level (ng/mL)	Recurrent VTE rate (/100 pt-yr)	Hazard Ratio (95% CI)
Palareti 2003 (Vidas)	≤ 500	4.8	2.43 (1.18-4.6)
	> 500	11.4	
Eichinger 2003 (Asserachrom)	< 250	2.4	0.4 (0.2-0.8)
	≥ 250	5.0	
Shrivastava 2006 (Liatest)	< 500	2.9	3.2 (1.3-8.0)
	≥ 500	10.9	
Palareti 2006 (Simplify)	Negative	4.4	2.49 (1.35-4.5)
	Positive	10.9	

Should D-dimer be used to determine the need for long-term anticoagulation in patients with a 1st unprovoked VTE?

NOT QUITE YET

- 1) Only useful in patients with a 1st unprovoked VTE.
- 2) Less useful in patients over age 75 as D-dimer increases with age (need for a higher cut-point).
- 3) Separation between high and low risk groups < 2.5 fold.

BMJ 2007; 334:674-681: "Further large, well designed studies are needed to establish the optimum duration of anticoagulation in various subgroups, including more studies of the value of D-dimer testing in determining duration."