Hypercoagulable States

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Risk Factors for Venous Thrombosis

Acquired	Inherited	Unknown
Prior Thrombosis	**Antithrombin deficiency**	↑ **Homocysteine**
Advancing Age	**Protein C deficiency**	↑ Factor VIII
Obesity	**Protein S deficiency**	APC resistance in
Immobilization	**Factor V Leiden(FVL)**	absence of FVL
Major surgery	**Prothrombin G20210A**	↑ Factor IX
Estrogens(OCP's HRT, SERMs)	Dysfibrinogenemias(rare)	↑ Factor XI
Malignancy		↑ TAFI levels
Prolonged Air travel		↓ Free TFPI
Antiphospholipid Syndrome		↓ fibrinolysis
MPDs, PNH		
IBD, nephrotic syndrome		
HIT		
Trauma		

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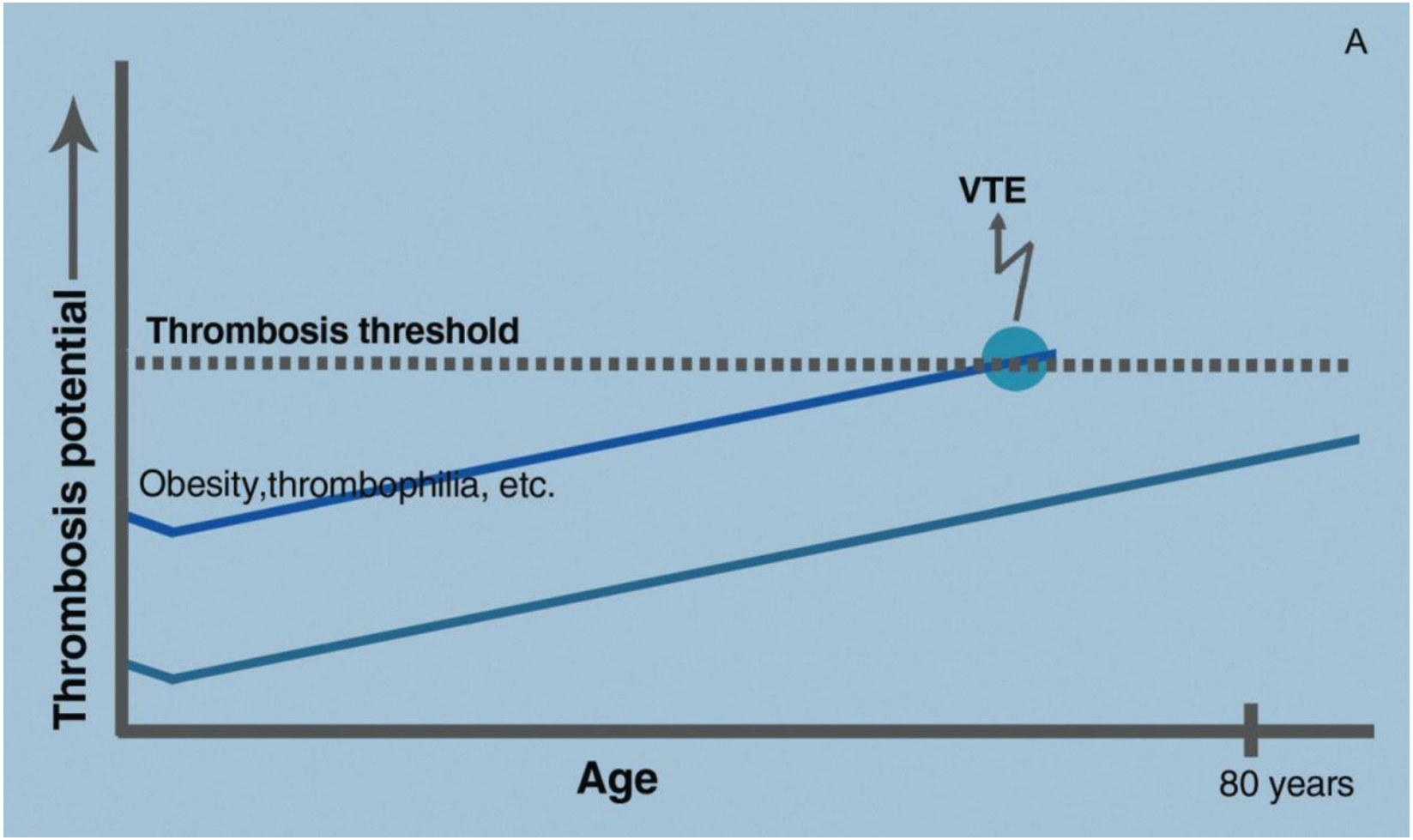
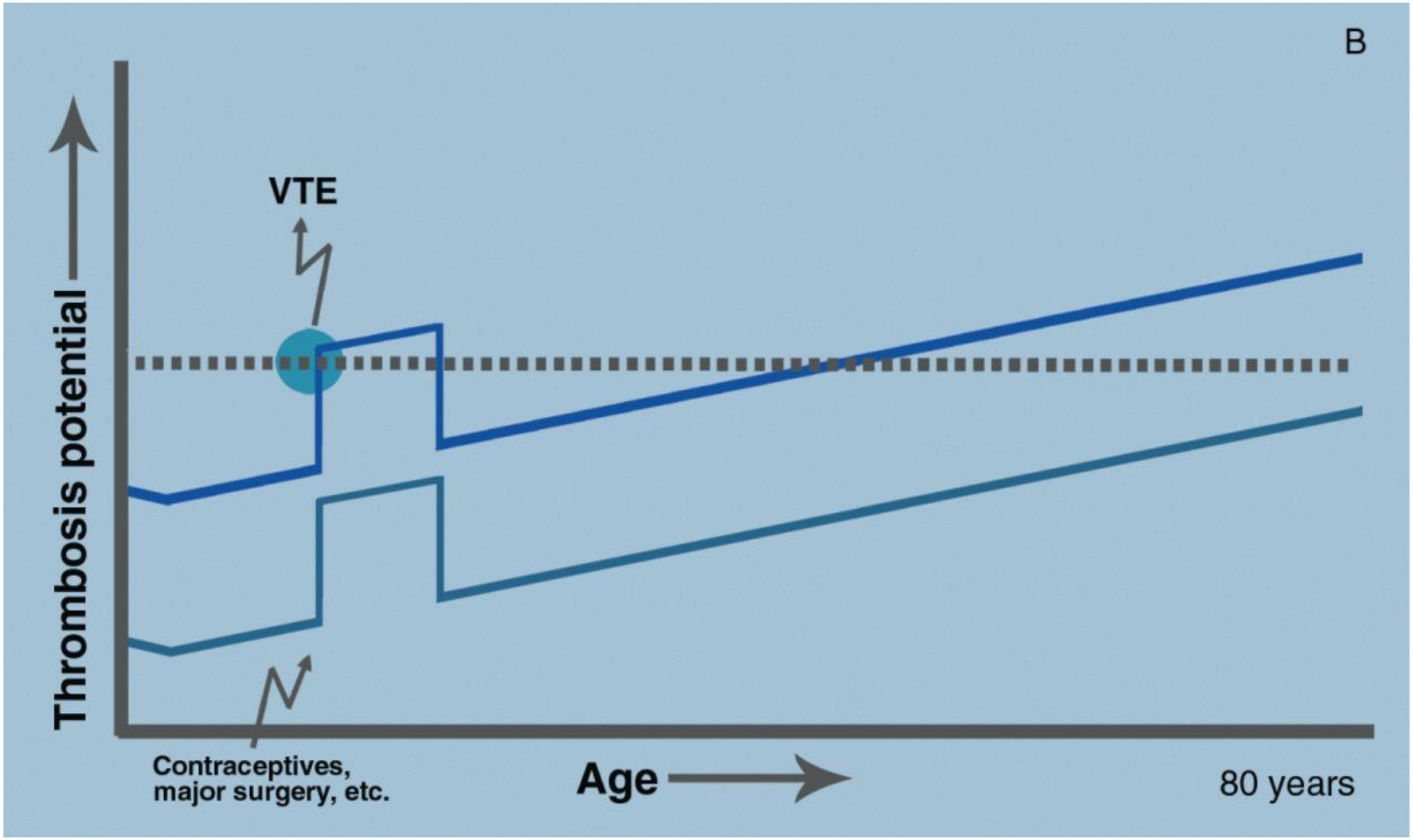
Threshold model of thrombosis risk.



Moll S et al. ASH 2013;2013:169-207

Threshold model of thrombosis risk.



Moll S et al. ASH 2013;2013:169-207

Sites of Thrombosis

Abnormality	Arterial	Venous
Factor V Leiden	-	+
Prothrombin 20210	-	+
AT Deficiency	-	+
Protein C deficiency	-	+
Protein S deficiency	-	+
Homocysteine	+	+
Lupus Anticoagulant	+	+

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Risk Factors for arterial thrombosis

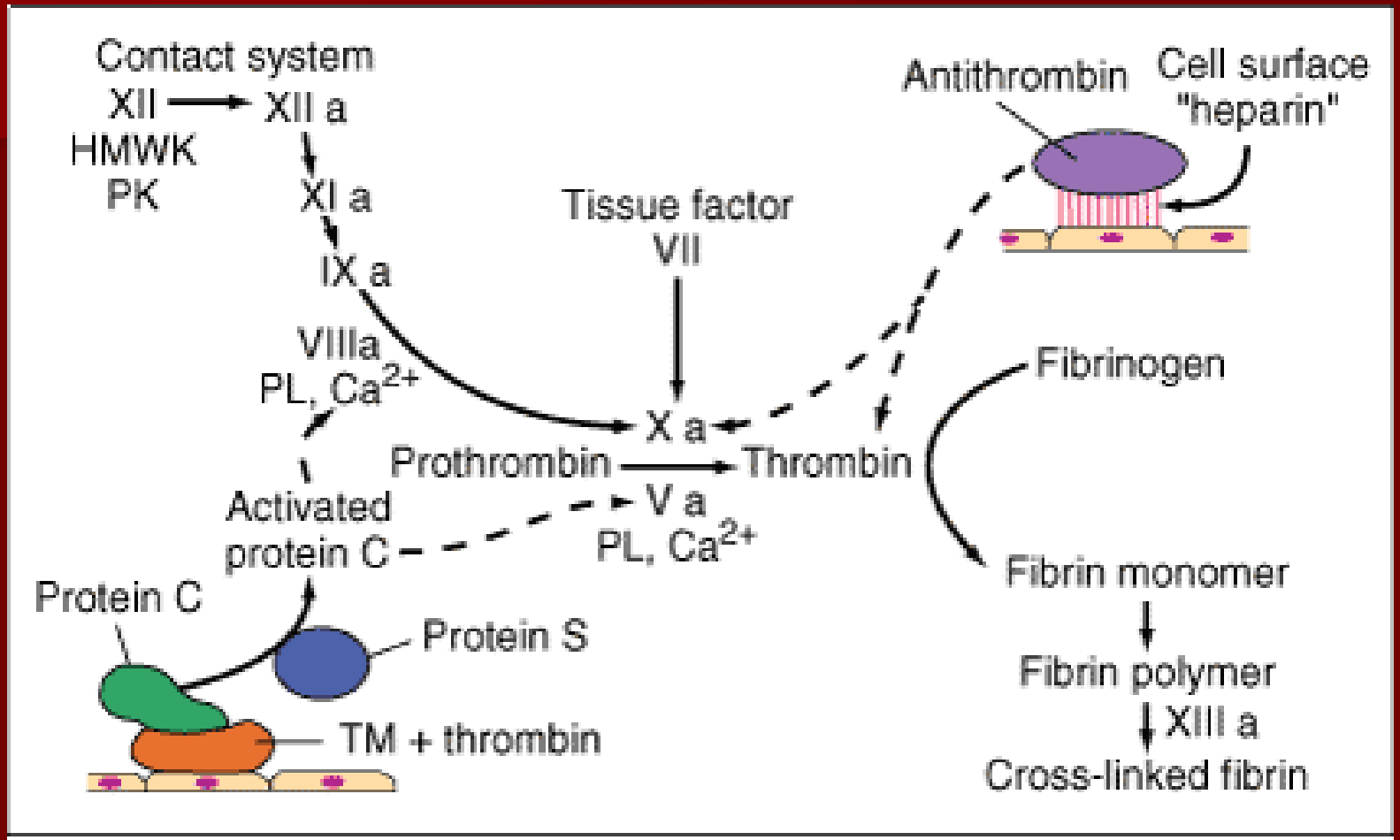
- Age
- Diabetes
- Hypertension
- Hypercholesterolemia
- Smoking
- Estrogens

Hypercoagulable States

- **Natural anticoagulant deficiencies**
  - **Antithrombin (III) deficiency**
  - **Protein C deficiency**
  - **Protein S deficiency**
- **Factor V Leiden**
- **Prothrombin 20210 mutation**

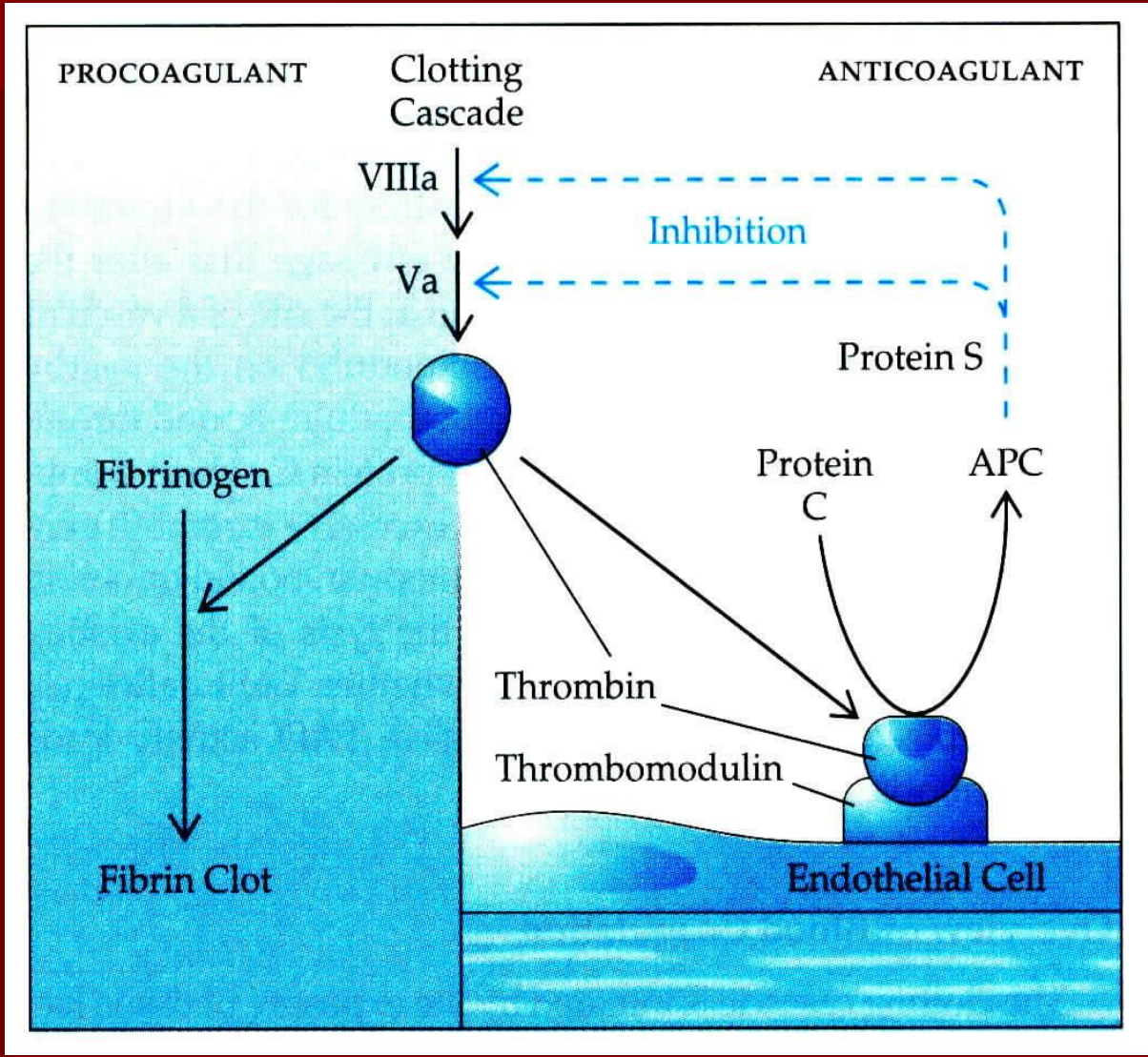
- **Hyperhomocysteinemia**
- **Antiphospholipid syndrome**
- **Malignancy**

Natural Anticoagulants

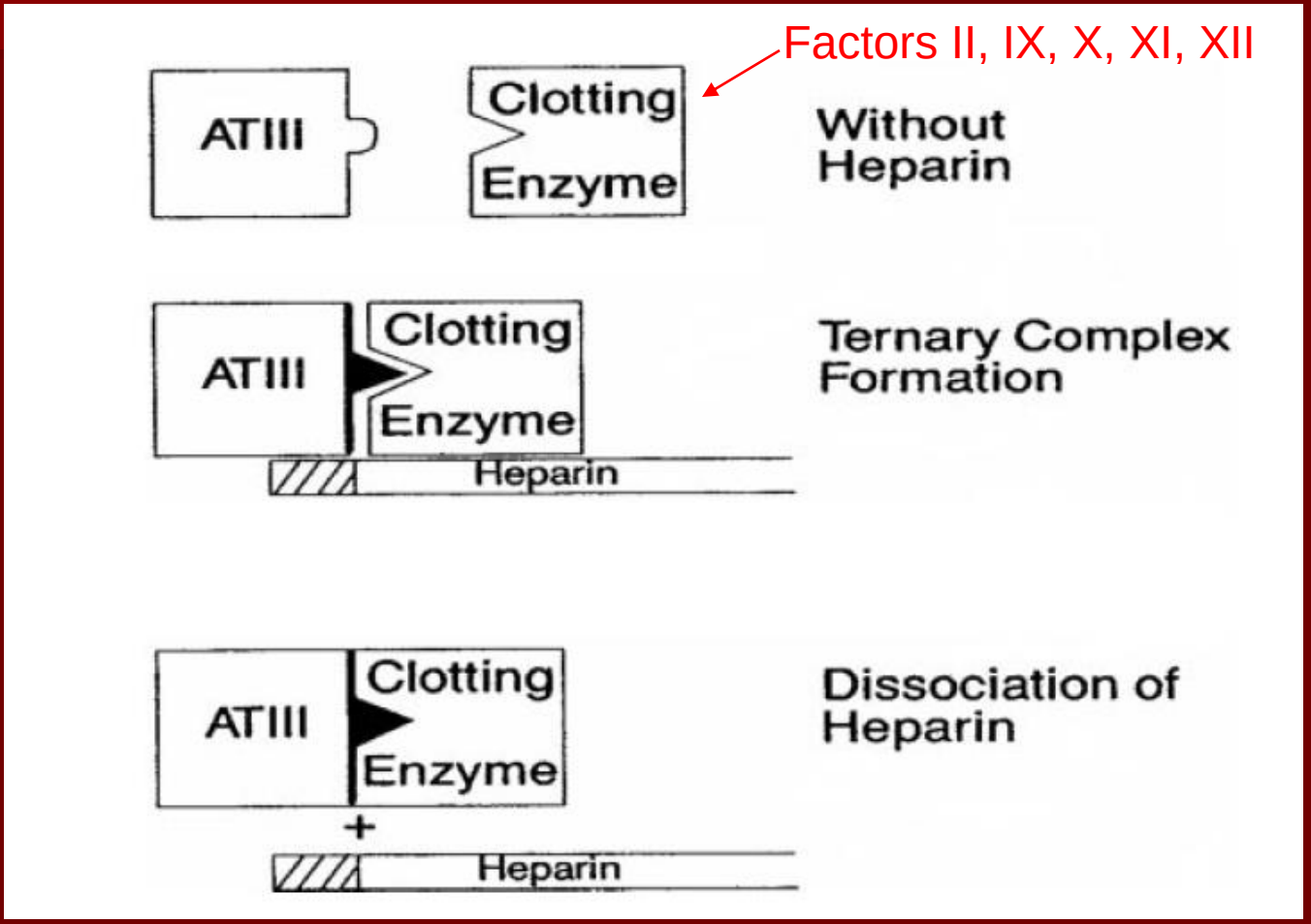


Protein C & Protein S

- Vitamin K dependent
- Protein S: cofactor for Protein C
- Activated Protein C inactivates VIIIa and Va



Natural Anticoagulants: Anti-thrombin



The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy
Chest 126, supplement 2004

Aquired Deficiencies in Antithrombin, Protein C, and Protein S

ANTITHROMBIN	PROTEIN C	PROTEIN S
Pregnancy		Pregnancy
Liver Disease	Liver Disease	Liver Disease
DIC	DIC	DIC
Nephrotic Syndrome		
Major surgery		Inflammation
Acute Thrombosis	Acute Thrombosis	Acute Thrombosis
TREATMENT WITH:		
Heparin	Warfarin	Warfarin
Estrogens		Estrogens

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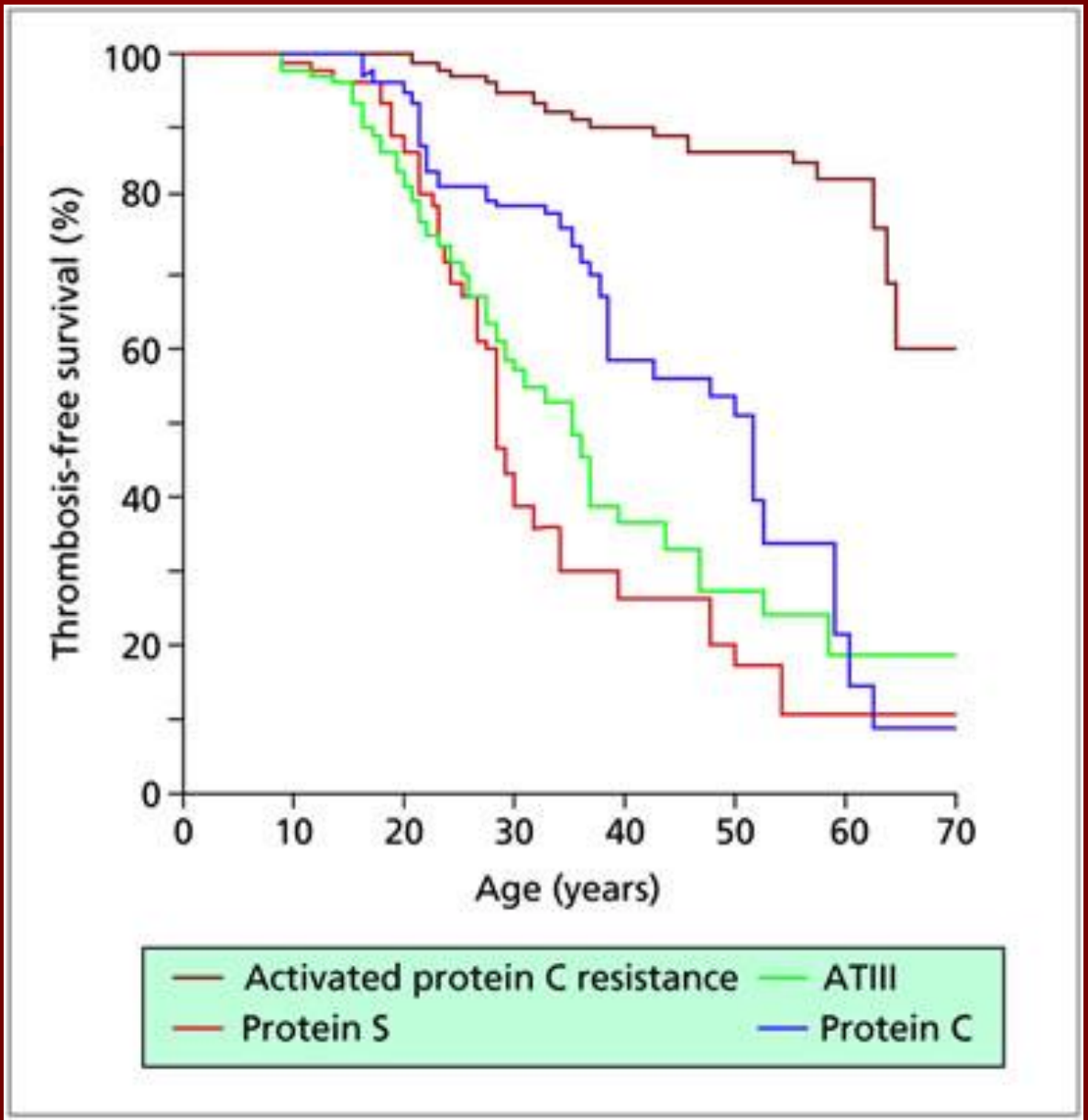
Thrombosis-free Survival



ASH SAP 3rd edition

Protein C deficiency

- Incidence is 1:500, but less than 1:1000 will have thrombosis.
- Coumadin skin necrosis
  - can be seen when starting coumadin secondary to dropping protein C levels acutely, causing a prothrombotic state
- Falsely low activity levels with high levels of factor VIII, and with lupus anticoagulants
- Risk of recurrence 37% over 5 years

ASH SAP Fifth edition

Protein S

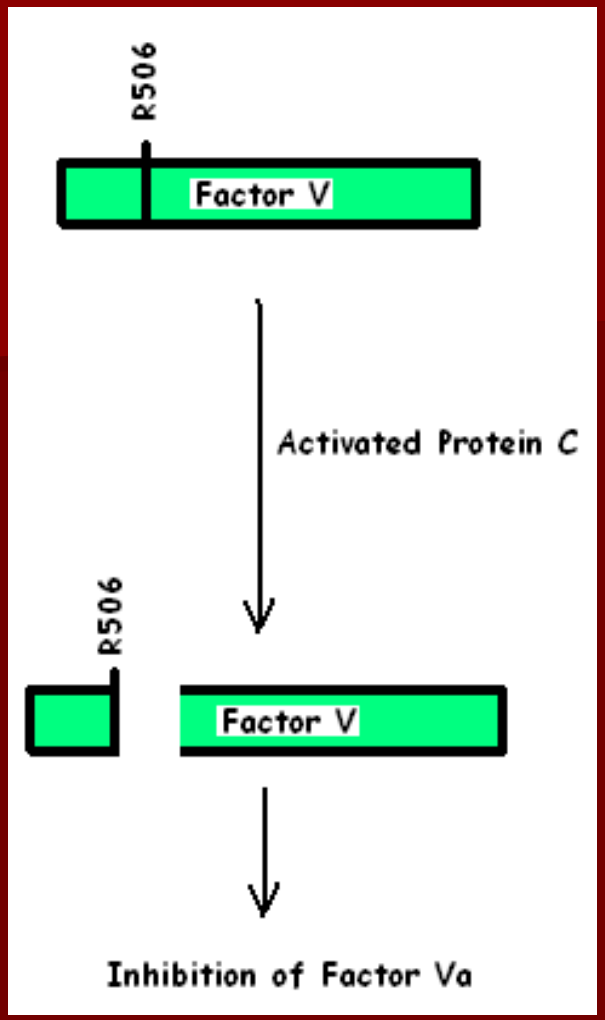
- Incidence thought to be 1:800-3,000
- Bound to C4b Binding protein(C4BBP).
- May have unusual presentations – mesenteric vein thrombosis. Migraines
- 50% will have thrombosis by age 35
- Risk of recurrence 44% at 5 years

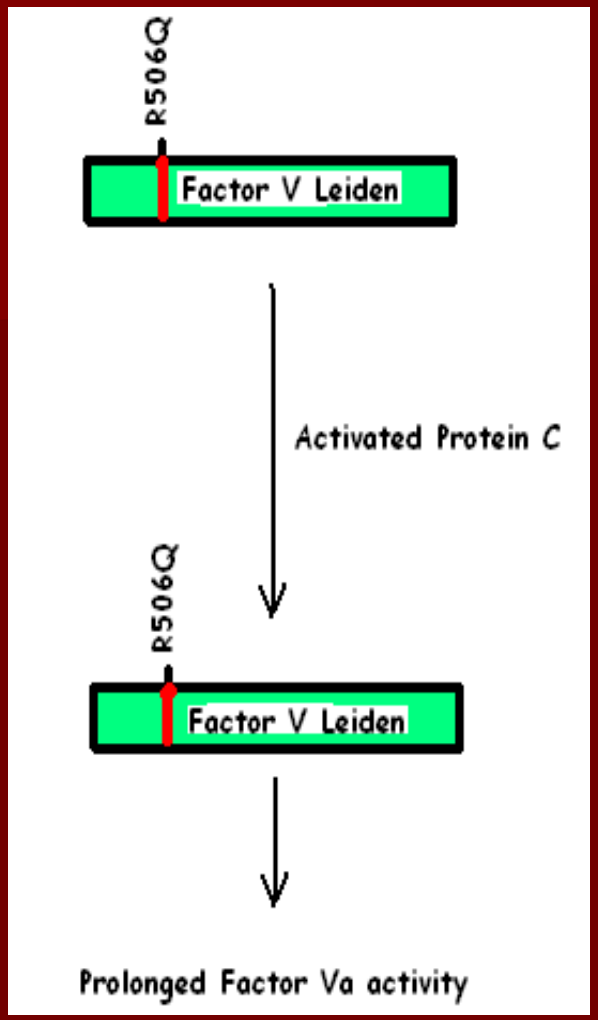
ASH SAP Fifth edition

Antithrombin III

- Autosomal Dominant
- deficiency incidence is 1:2000-5000
- 30% will have a thrombosis by age 30.
- May need to give Antithrombin III concentrates during surgery or childbirth to prevent clotting.
- Homozygote incompatible with life
- 10-17%/year risk of relapse

ASH SAP Fifth edition



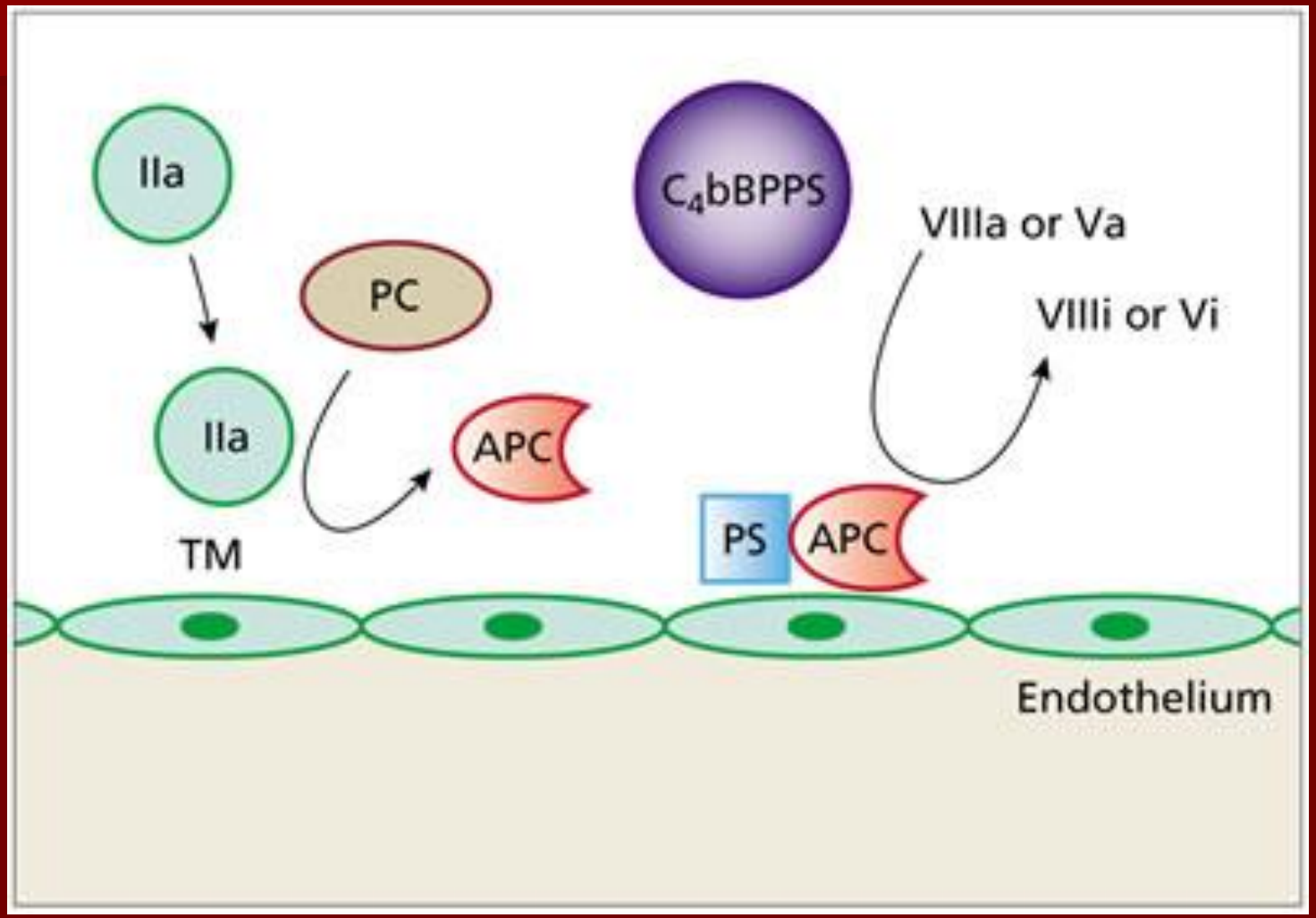


"Factor V Leiden"= point mutation in factor V that leads to Activated Protein C Resistance (APC-R)

APC: normally inactivates Va (a natural anticoagulant)

Resistance to APC → Unopposed clotting

F V Leiden


IIa
C4bBPPS
VIIIa or Va
PC
VIIIi or Vi
IIa
APC
TM
PS
APC
Endothelium

Factor V Leiden

- Mutation results in resistance to Activated Protein C
- Common in caucasians.
- Rare in Asians and African non-whites
- Only 1% of African Americans
- Heterozygote is a relatively weak risk factor.
- 90% of persons with FVL will never have a clot.
- 50% of homozygotes will have clot by 50.
- Cohort study of men>40, no association of factor V Leiden with arterial thrombi(MI/CVA).
- May screen for APC resistance, then if + check gene mutation

Prothrombin Gene Mutation

- G to A Mutation at position 20210
- Similar population distribution as FVL

GENOTYPE	PROTHROMBIN	RANGE
20210 AG	132%	95-178%
20210 GG	105%	55-156%

Poort et al, Blood 1996

- Check Gene Mutation, Prothrombin levels are variable.

MTHFR

- MTHFR commonly tested for 1 or 2 mutations:
  - C677T –"thermolabile"-
    - 35% of caucasians heterozygous, 12% homozygous
  - A1298C
- Higher levels of homocysteine may be seen in homozygous C677T or double hetero for C677T/A1298C
- in metaanalyses these polymorhisms **ARE NOT** a risk factor for Venous or Arterial thromboembolism.
- Increasing evidence suggests that VTE and ischemic Cardiovascular disease may lead to elevated HCY levels rather than vice versa.

HCY lowering by B-vitamin supplements DO NOT lower risk of recurrent thrombosis

- Arterial Thrombosis
  - NORVIT trial(NEJM 2006)
    - 3,479 pts with acute MI
    - Trend towards increase risk with combined B vit Rx
  - HOPE 2 Trial(NEJM 2006)
    - 5,522 pts> age 55 with vascular diz or DM
- Venous Thrombosis
  - VITRO Study(Blood 2007)
    - Pts age 20-80 with unprovoked proximal DVT or PE
    - Recurrences: 43/348 vitamins, 50/353 placebo

Lupus Anticoagulant

- Seen often in autoimmune diseases, such as SLE, or malignancy.
- Pt presents with clotting, but found paradoxically to have an elevated PTT.
- Therefore not truly an anticoagulant, but an artifact of the invitro assay secondary to antibodies against the phospholipids used in the assay.

Antiphospholipid Syndrome "*Clinico-Pathologic Syndrome*"

"CLINICAL"

- Thrombosis(arterial or venous
- Spontaneous Pregnancy loss
- Thrombocytopenia
- Livedo Reticularis

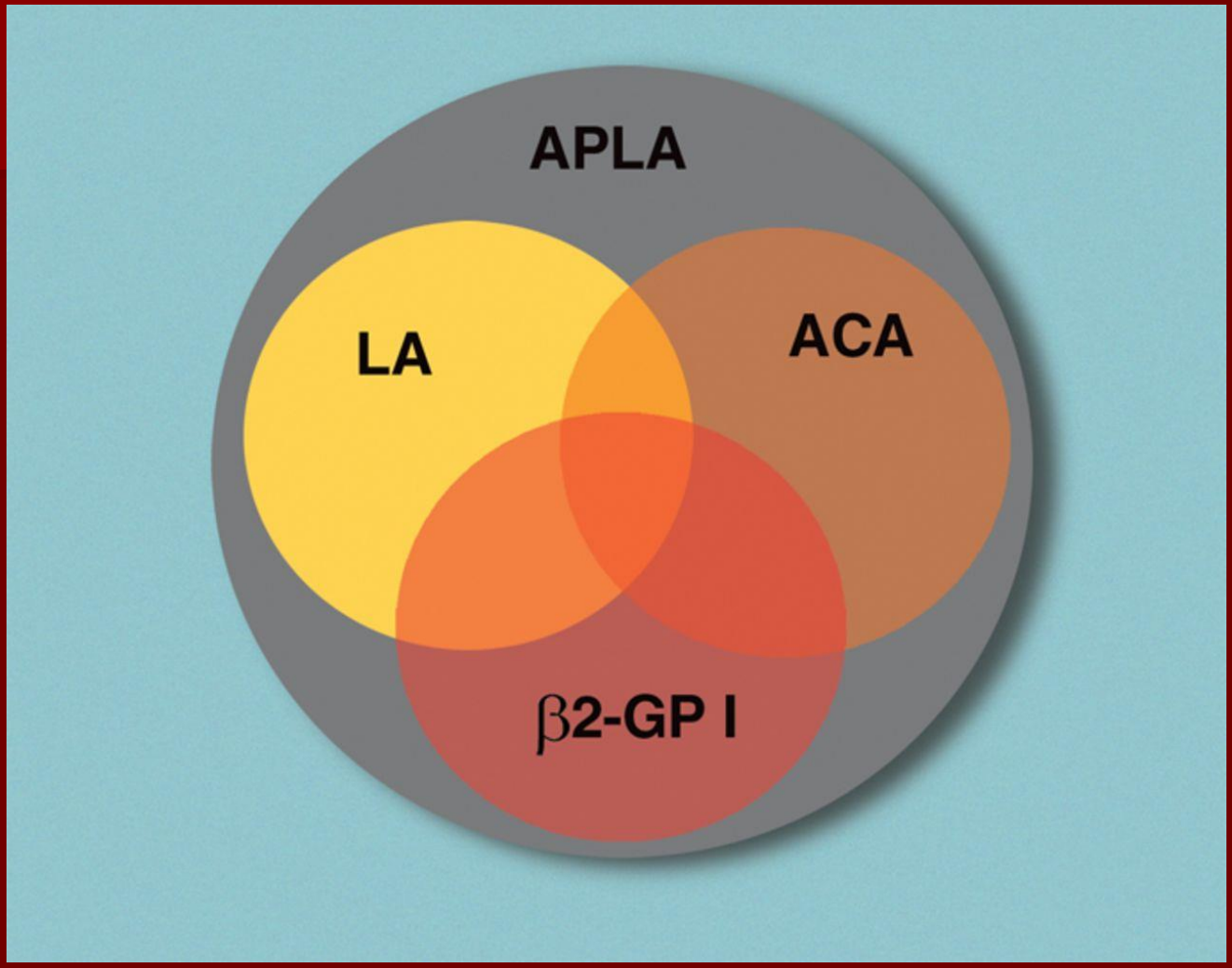
"PATHOLOGIC"

- Lupus Anticoagulant
- Anticardiolipin Antibody IgG, IgM
- Anti Beta 2 Glycoprotein I antibodies(IgG, IgM)

– Repeated at 3 months

Sapporo Criteria, 2006

Antiphospholipid antibodies (APLAs) with their different subtypes.

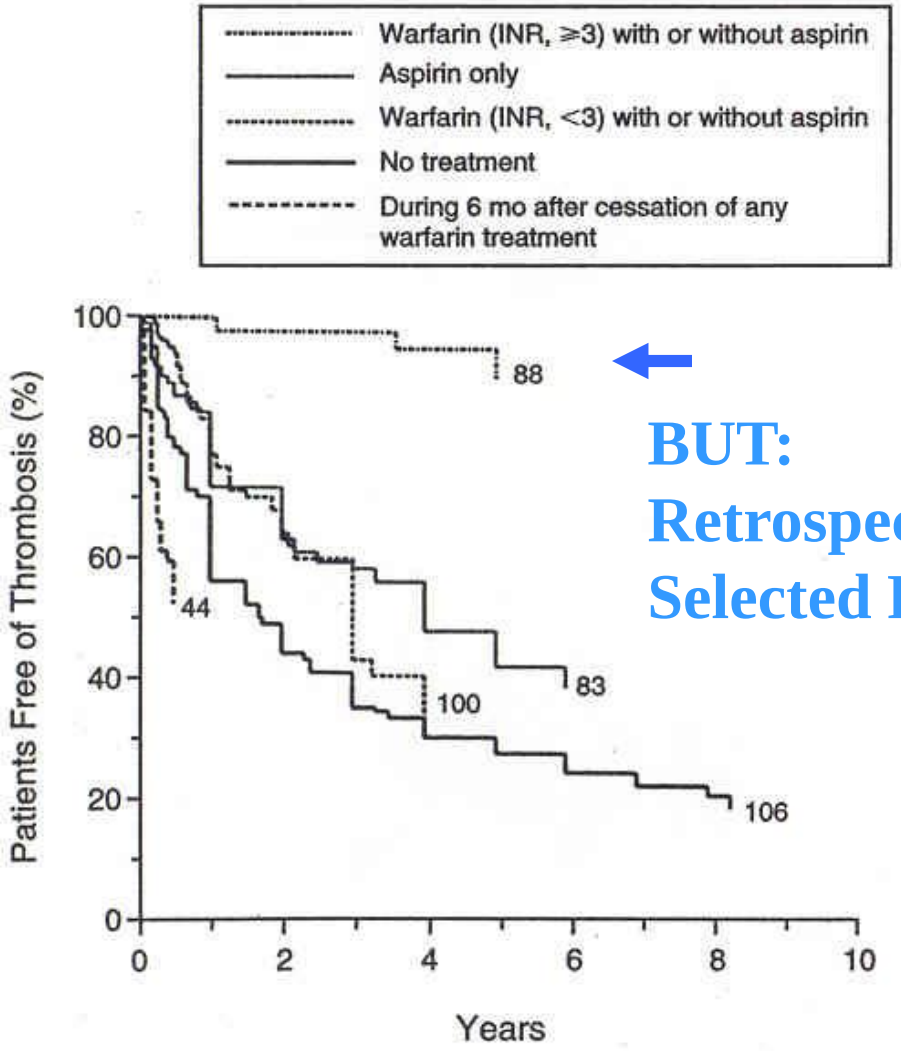


Moll S et al. ASH 2013;2013:169-207

ash-sap

Antiphospholipid Antibody Syndrome(APLS)

- Triple positives have more significant disease
- Antiphospholipid antibodies found in 50% of patients with SLE, and only 1-5% of general population
- Nearly 40% of patients with SLE will meet diagnostic criteria of APLS
- Titers can be low or transiently positive during thrombotic event
- No clear indication to test for other antiphospholipid antibodies



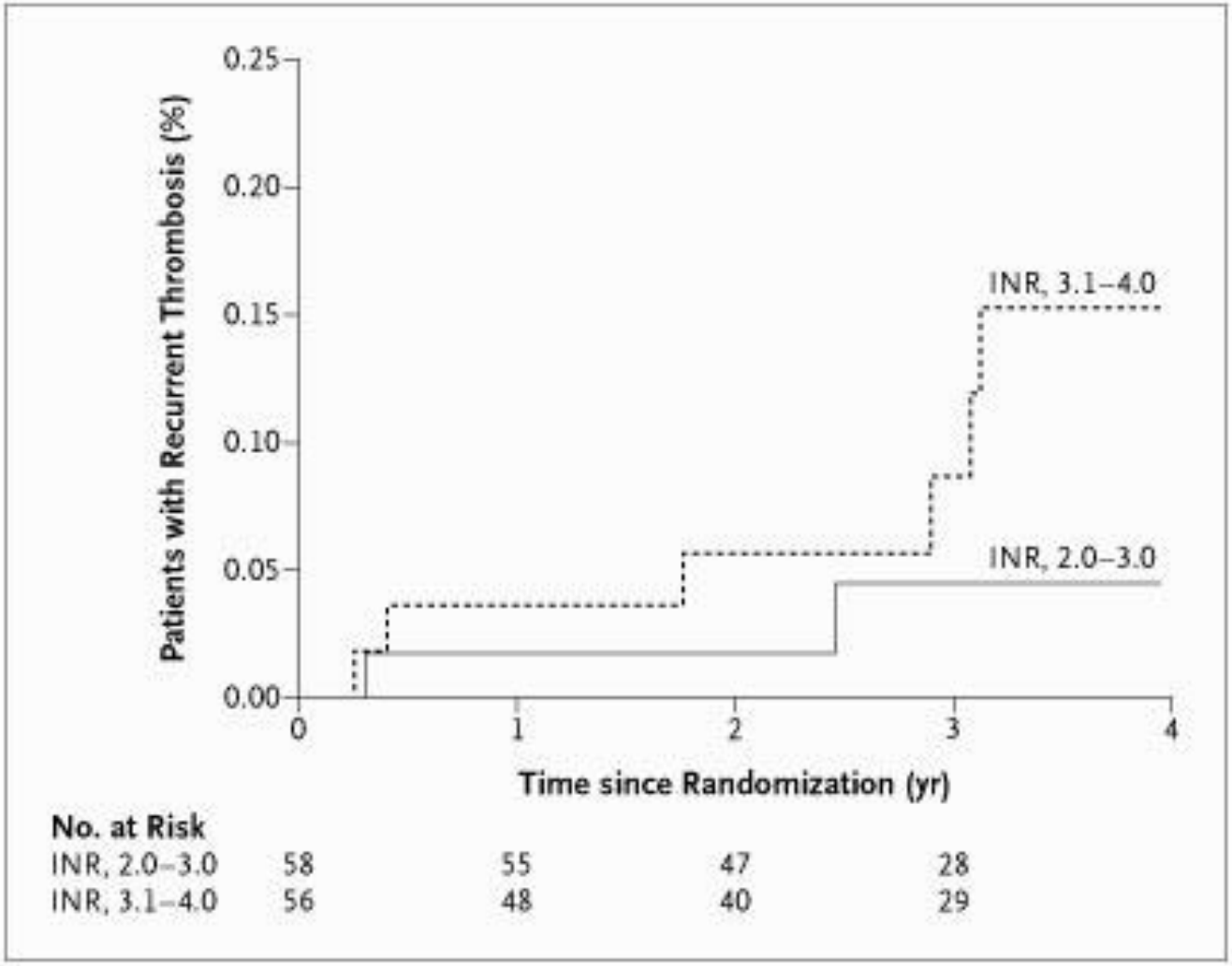
BUT:
Retrospective Study
Selected Patient Population

Figure 1. Kaplan–Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.

The total number of such intervals for the patients while they were receiving each treatment is shown after each curve. INR denotes international normalized ratio.

Khamashta NEJM 4/13/95

Time to First Recurrent Thrombosis for All Patients (114) Enrolled in the Study



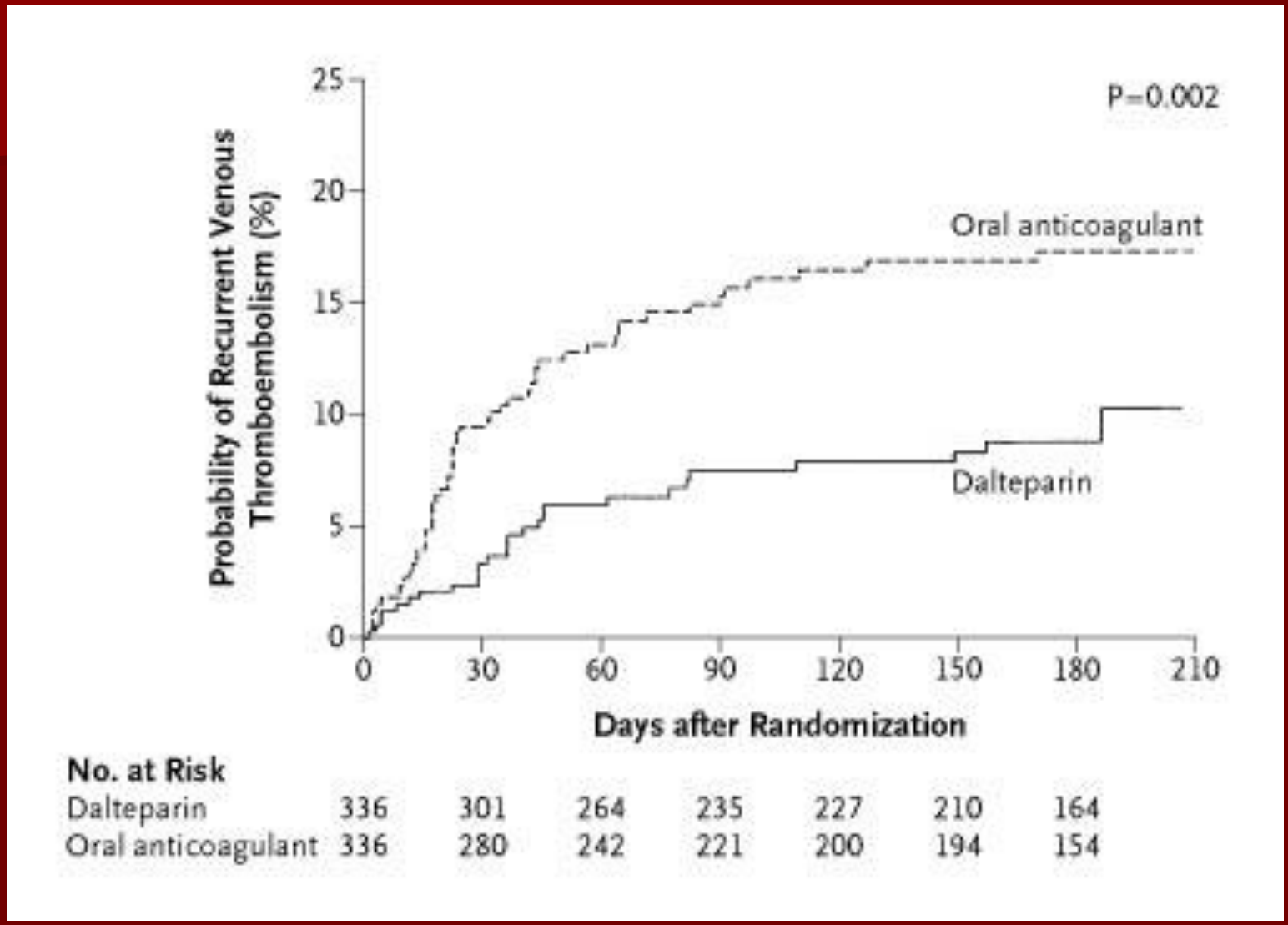
Crowther M et al. N Engl J Med 2003;349:1133-1138

The NEW ENGLAND JOURNAL of MEDICINE

Clots and Cancer

- ~20 % of pts with symptomatic VTE
- Increased risk of recurrent VTE despite warfarin therapy
- Increased risk of bleeding on coumadin
  - Anorexia, vomitting, drug interactions.
- Mucin may trigger activation of platelets/neutrophils which is blocked by heparin(mouse model).
- ? Pan scan for malignancy

CLOT Trial



Lee A et al. N Engl J Med 2003;349:146-153

The NEW ENGLAND JOURNAL of MEDICINE

CLOT – Bleeding Events

	LMWH (n=338)	OAC (n=335)	P-value*
Major Bleed	19(5.6%)	12(3.6%)	0.27
Any Bleed	46(13.6%)	62(18.5%)	0.093

* Fisher's exact test

Overall Mortality data?
Mets vs no mets?

Relative Risk of first episode of VTE

Baseline Risk (increases with age)	**2-3/1000/yr**
Factor V Leiden (heterozygous)	**3 - 7**
Hyperhomo-cysteinemia	**2.5**
Protein C or S Deficiency	**7 - 10**
Anticardiolipin AB All / High titers only	**1.6 / 3.2**
Elevated Factor VIII:c	**2 - 11**
Oral contraceptives (OCP)	**4**
Factor V Leiden + OCP	**35**
Factor V Leiden (homozygous)	**80**

Screening

- No
  - with inciting factors, such as surgery, malignancy, myeloproliferative disorders
  - Patients >50 with first spontaneous VTE
  - Retinal vein thrombosis
  - Women going on OCP's

Screening

- Yes
  - under age of 50 with positive family history(1st degree)
  - with clotting in unusual sites (hepatic, mesenteric, cerebral veins)
  - with recurrent thrombosis
  - ? VTE with OCP, Pregnancy
  - ? Late Pregnancy loss

ACCP for testing

- 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.

  Chest 2008 and 2012

Risk for Recurrent VTE

- After first Unprovoked DVT following 6 months of warfarin
  - 5-15% at 1 year
  - Almost 25% by 5 years.
- Heterozygosity for FVL or Prothrombin (PT) mutation increases risk only slightly above controls

Risk for Recurrent VTE

- Higher in heterozygotes with both FVL and PT mutations; probably higher in Homozygotes for FVL. (Retrospective study showed that not significantly higher(Lijfering WM Circulation 2010)
- AT III, Protein C/S deficiency
  - High in selected kindreds with strong penetrance

High Risk of Recurrence

- two or more spontaneous thromboses;
- one spontaneous thrombosis in the case of antithrombin deficiency or the antiphospholipid antibody syndrome;
- one spontaneous life-threatening thrombosis (e.g. near-fatal PE)
- one spontaneous thrombosis at an unusual site (e.g. mesenteric or cerebral vein);
- one spontaneous thrombosis in the presence of more than a single genetic defect predisposing to a thromboembolic event.
- Cancer – until resolved(consider LMWH)

USUALLY WARRANTS LIFE LONG AC

Moderate Risk

- 1 event with a stimulus
- Asymptomatic VTE

CONSIDER PROPHYLAXIS IN HIGH-RISK SETTINGS.

Patient Discussion

- NO MORTALITY BENEFIT FROM LONG-TERM ANTICOAGUALTION
  - Weigh case fatality with recurrent risk, vs. risk of bleed
- Factors that go into decision for AC
  - Recurrence risk
  - Patient preference
  - Alternatives
  - Bleeding risk
  - Location(PE recurs as PE), Severity

PREVENT Trial(NEJM 2006)

- D- dimer and recurrent DVT.
- Abnormal d-dimer(greater than 0.5) on coumadin vs observation after completing 6 months of coumadin
- positive D-dimer assay after 6 months of anticoagulant therapy may predict a higher risk of recurrent thrombosis, thus perhaps justifying prolonged anticoagulant therapy
- negative D-dimer in patients with suspected recurrent VTE may predict a low risk of subsequent clinical recurrence, thus justifying withholding of anticoagulants

Post Hoc

- Women, Negative D Dimer –
  - < 65 - rate 0.4%/ year
  - > 65 - Rate 6.6%
- Men, negative D Dimer
  - >65 - 8.1%/year risk
  - < 65 - 5.1%/year

Cosmi B, et al. J Thromb Haemost. 2010; epub.

WARFASA Trial

- Aspirin(100mg) vs. Placebo for preventing Recurrence of VTE
- 42% risk reduction (on coumadin 90+% risk reduction)
- 6% recurrence rate in 1 year, down from 11%
- Study median 2 years

N Engl J Med. 2012 May 24;366(21):1959-67.

ASPIRE Trial

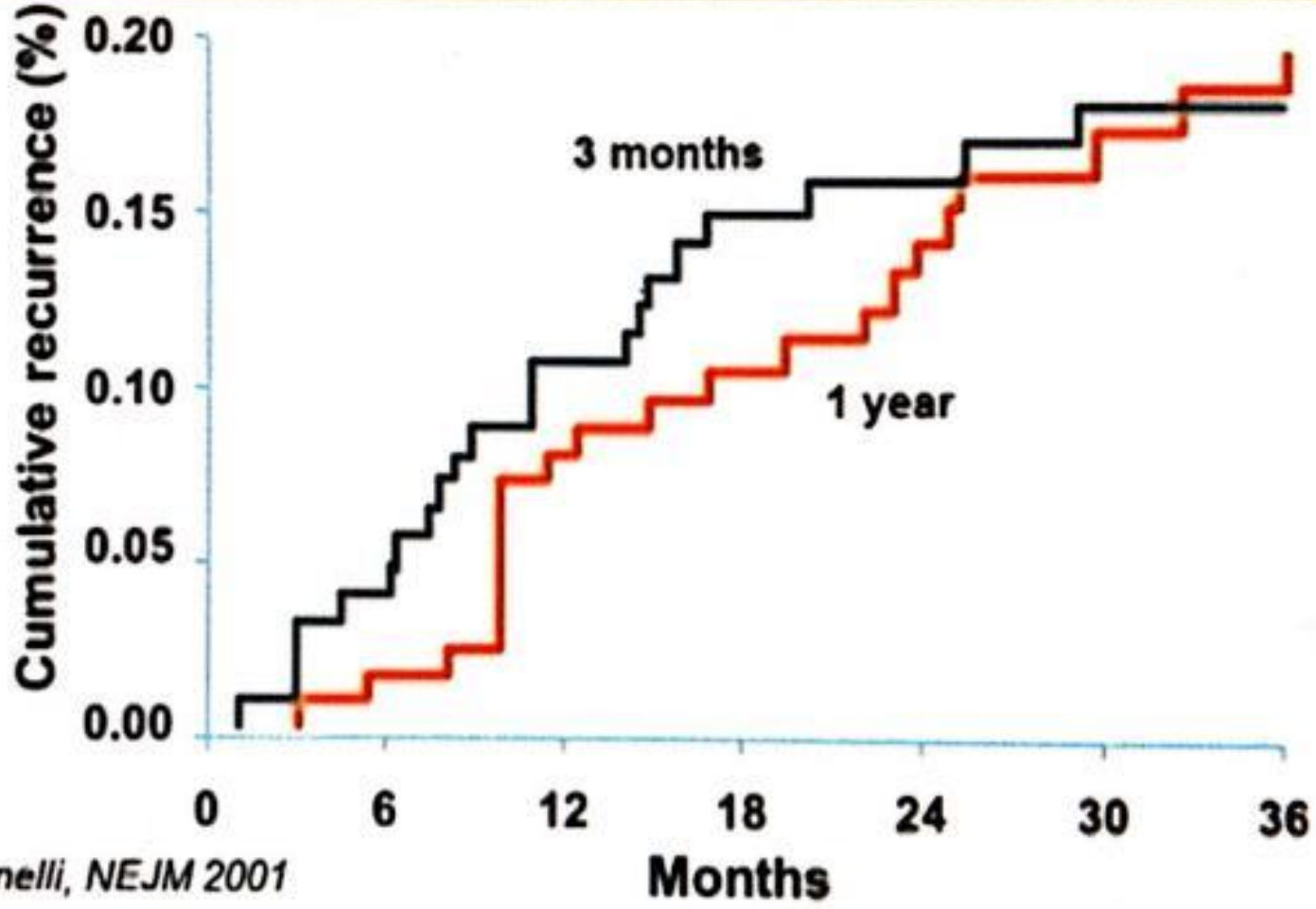
- Aspirin did not significantly lower the risk of recurrence of DVT or PE
- statistically significant benefit in reducing the overall risk of major vascular events (arterial and venous event together)
- Metaanalysis – showed risk reduction and decreased risk of major vascular events with aspirin, with no increased bleeding risk

N Engl J Med. 2012 Nov 22;367(21):1979-87.

Guidelines for Duration of Anticoagulant Therapy

- 3 months is equivalent to 6 months
- Extending anticoagulation treatment is highly effective(>90% risk reduction), but only as long as treatment is continued, and is associated with more bleeds
- Recurrence risk is highest during the two first years
- Unprovoked DVT/PE is associated with a significantly higher risk of recurrence after discontinuation of AC

3 Months vs 1 Year of Anticoagulation for Idiopathic DVT



Agnelli, NEJM 2001

ACCP Guidelines - 2012

Distal leg DVT

- a) *Severe symptoms:* Treat with anticoagulants. Length of treatment: 3 months (no matter whether DVT was associated with a transient risk factor (surgery, hospitalization, estrogen therapy, etc.) or was unprovoked.

ACCP Guidelines - 2012

b) *No, mild or moderate symptoms* and no risk factors for clot extension

- positive D-dimer,
- DVT that is extensive or close to the proximal veins,
- no reversible provoking factor for DVT present,
- active cancer,
- previous history of blood clots,
- inpatient status

ACCP Guidelines - 2012

- No anticoagulation needed
- Physician to obtain several (‘serial”) Doppler ultrasound leg examinations over the next 2 weeks to make sure the DVT has not extended (which it does in about 15 % of patients).
- If DVT has extended: treat with anticoagulants for 3 months.

- If extension of clot has not occurred within the first 2 weeks, it is unlikely to occur subsequently

ACCP Guidelines - 2012

Incidentally discovered (asymptomatic) DVT or PE

- DVT (of the leg, arm, pelvis or abdominal/splanchnic) or PE that was asymptomatic and was discovered incidentally, for example because CT scans were done for other reasons:
  - a) *Leg, pelvic or IVC DVT:* Treat with blood thinners. Length: same as discussed in proximal and distal DVT section (discussed above).

ACCP Guidelines - 2012

- *b) Abdominal DVT (portal, splenic, mesenteric or hepatic vein thrombosis)*: Do not treat with blood thinners.
- *c) PE:* The CT should be reviewed with a good radiologist to determine whether the reported PE is really a PE. If there is uncertainty, then additional studies should be done (such as D-dimer, Doppler ultrasound of the legs, VQ scan, etc). If the conclusion is that the patient does, indeed, have a PE: Treat with anticoagulants. Length: same as discussed in the PE section below.

ACCP Guidelines - 2012

- ***Upper extremity DVT associated with a central venous catheter***:
  - Suggestion is to not remove the catheter if it is functional and there is an ongoing need for the catheter. Anticoagulation should be given as long as the catheter is in place.
  - If the catheter is removed, anticoagulation should continue for 3 months thereafter.

ACCP Guidelines - 2012

Superficial thrombophlebitis

- In patients with superficial thrombophlebitis of the leg of at least 5 cm in length, the suggestion is to give prophylactic dose of fondaparinux (preferred) or LMWH for 45 days, rather than no anticoagulation.

ACCP Guidelines - 2012

Compression stockings

- Wear for at least 2 years (to prevent or minimize the occurrence of postthrombotic syndrome.
- If at 2 years the patient has bothersome symptoms of postthrombotic syndrome (swelling, pain), continue to wear stockings for symptoms relief.

SOX trial

- Multicenter, randomized, placebo-controlled trial in patients with acute first episode of proximal DVT. Patients wore either 30-40 mm Hg graduated elastic compressions stockings or "placebo stockings" with identical appearance but less than 5 mm Hg compression at the ankle.
- The follow-up period was 2 years.
- 806 patients were enrolled
- PTS (as assessed by the so-called "Ginsberg's criteria") developed in 14.2 % in the active stocking group, and in 12.7 % in the placebo stocking group
- *Conclusion:* Elastic compression stockings did not prevent PTS after a first proximal DVT.

Kahn S et al. Lancet Dec 6, 2013

ACCP Guidelines - 2012

Vena cava filter (=IVC filter)

- Should only be placed in the patient with an acute DVT who cannot tolerate blood thinners because of active bleeding or a high risk for bleeding.
- "We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation".

ASH Choosing Wisely Campaign

- Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).
- Don't use inferior vena cava (IVC) filters routinely in patients with acute venous thromboembolism (VTE).(75% of retrievable filters never removed)
- Don't administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e. outside of the setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).