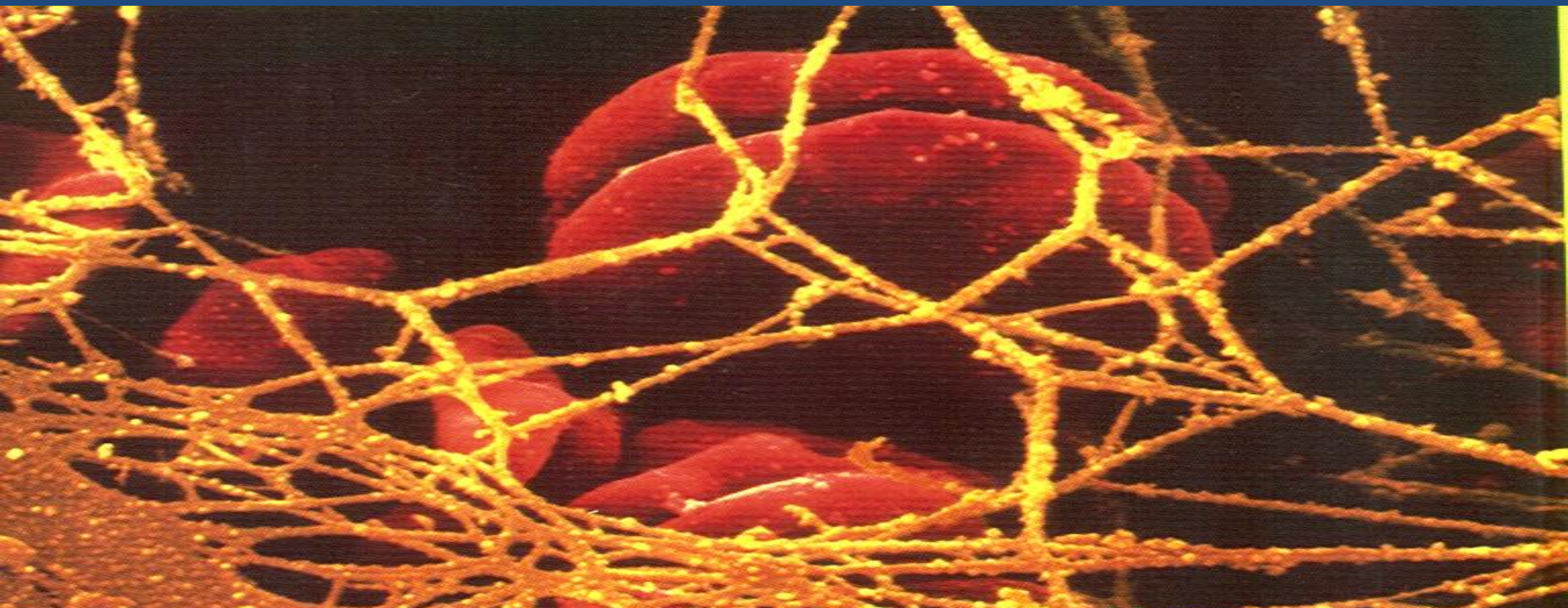
Thrombophila and venous thromboembolism

Jan Kvasnička, Prague,CZ

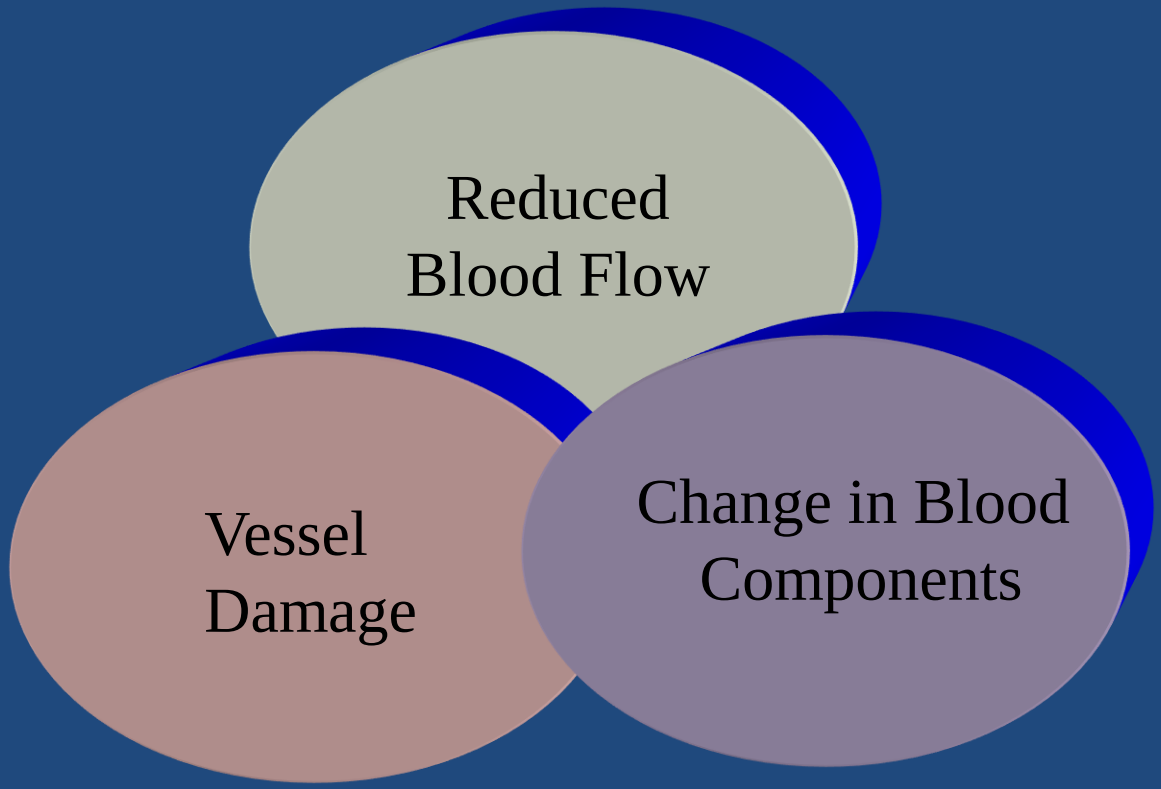


Introduction

- Venous thrombosis is a multifactorial disease and analysis of the interactions between acquired and inherited risk factors is an extremely interesting field of investigation

VENOUS THROMBOEMBOLISM

Virchow's triad for venous thromboembolism:



Annual Incidence of Venous Thromboembolism

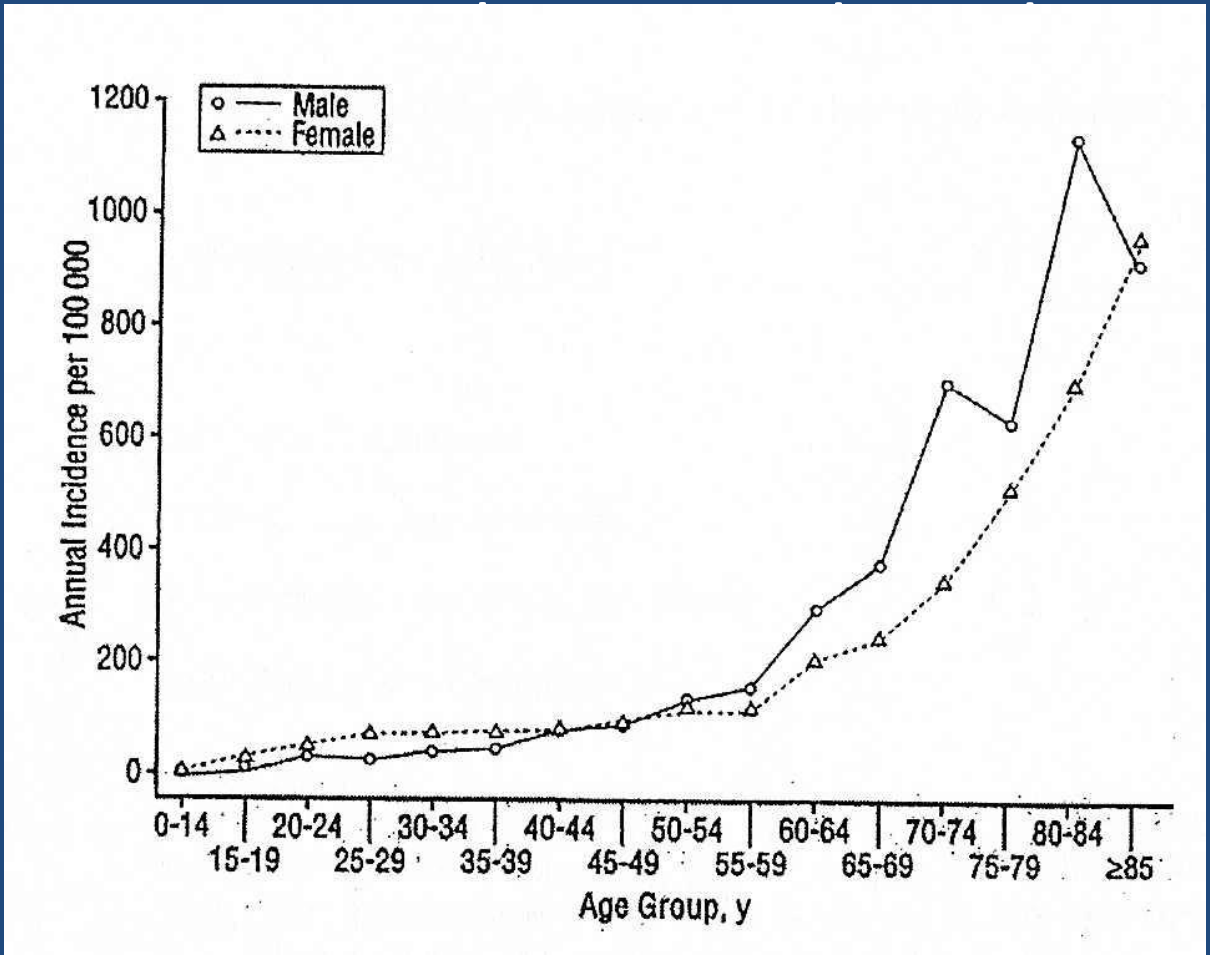
- Symptomatic, objectively confirmed and population based

F. Anderson et al. 1991, *Arch Intern Med*	VTE: 1.07 per 1000 - 66% first episode - DVT : PE = 2 : 1
M. Nordstrom et al. 1992, *J Intern Med*	DVT: 1.6 per 1000
M. Silverstein et al. 1998, *Arch Int Med*	First VTE: 1.17 per 1000

→ **2 per 1000 per year**

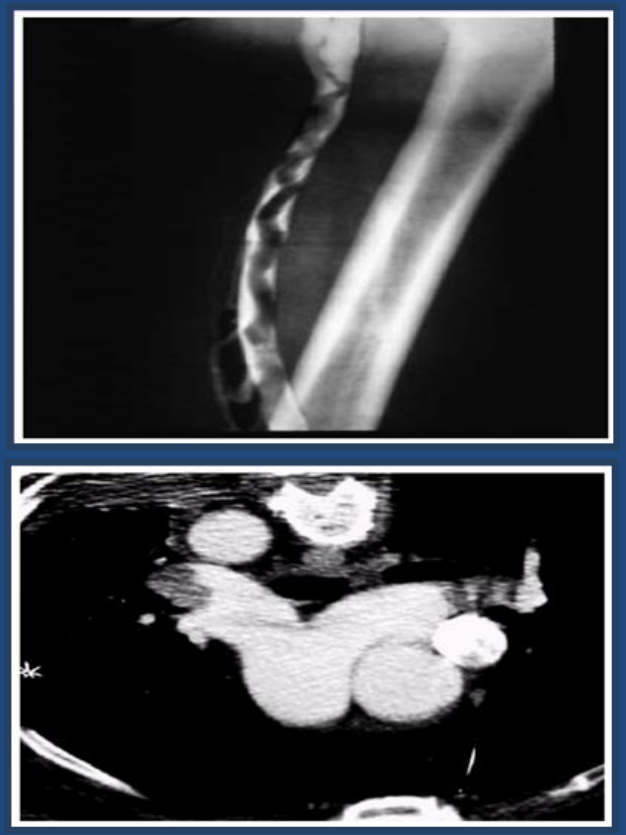
DVT = deep vein thrombosis; VTE = venous thromboembolism

Annual incidence of venous thromboembolism among Olmsted County, Minnesota residents,



Venous Thromboembolism

- Third most common vascular disease
- PE is leading preventable cause of death[1, 2]
- > 500,000 deaths from VTE annualy in EU (25 states)



PE = pulmonary embolism, VTE = venous thromboembolism

[1] **Cohen AT et al.** *Thromb Haemost*. 2007; 98(4): 756-764

[2] **Hirsh J, Hoak J.** *Circulation*. 1996; 83(12): 2212-2245

A Silent Killer:
VTE

Etiology

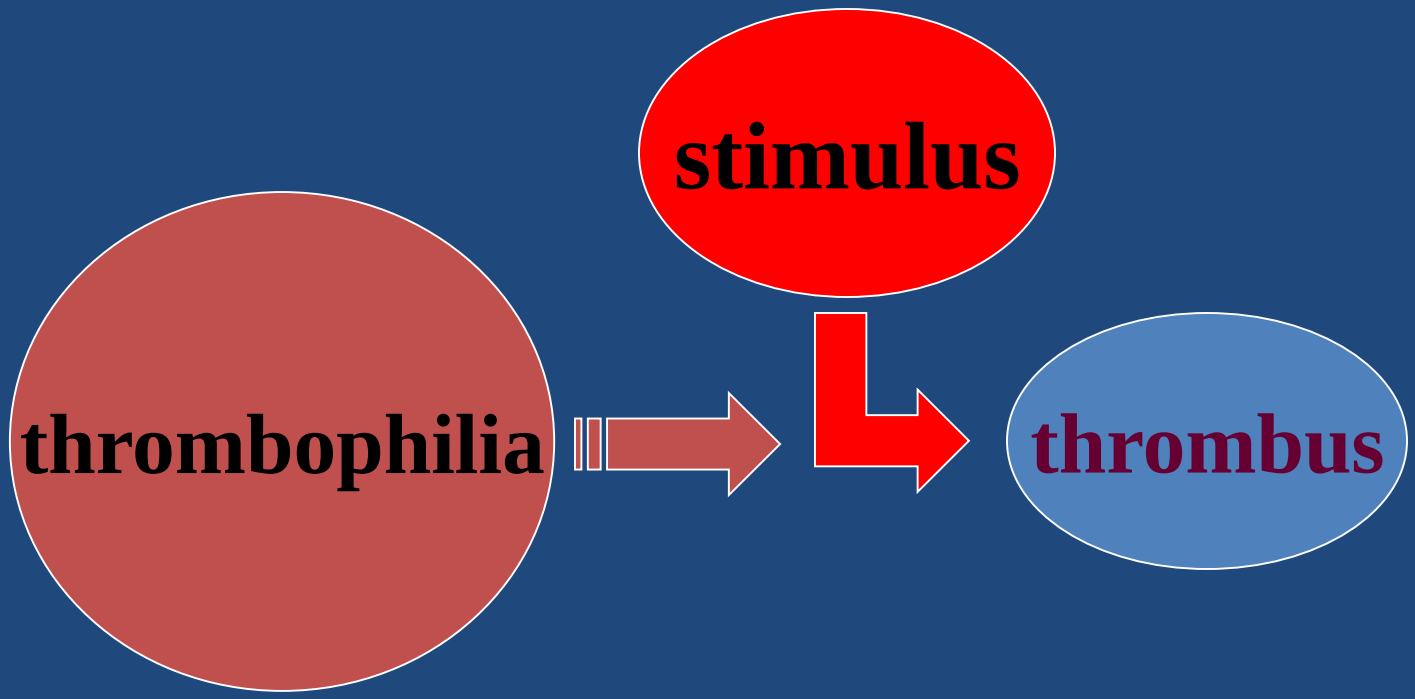
- In approximately 70% of VTE patients a thrombophilic abnormality can be detected
- Gene-environment interaction essential for clinical expression

THROMBOPHILIA

- (synonymum hypercoagulable state)
  - has been referred to as hereditary and / or acquired tendency to thrombosis.
- therefore the people with hereditary thrombophilia are at constant, lifelong risk of thrombosis.

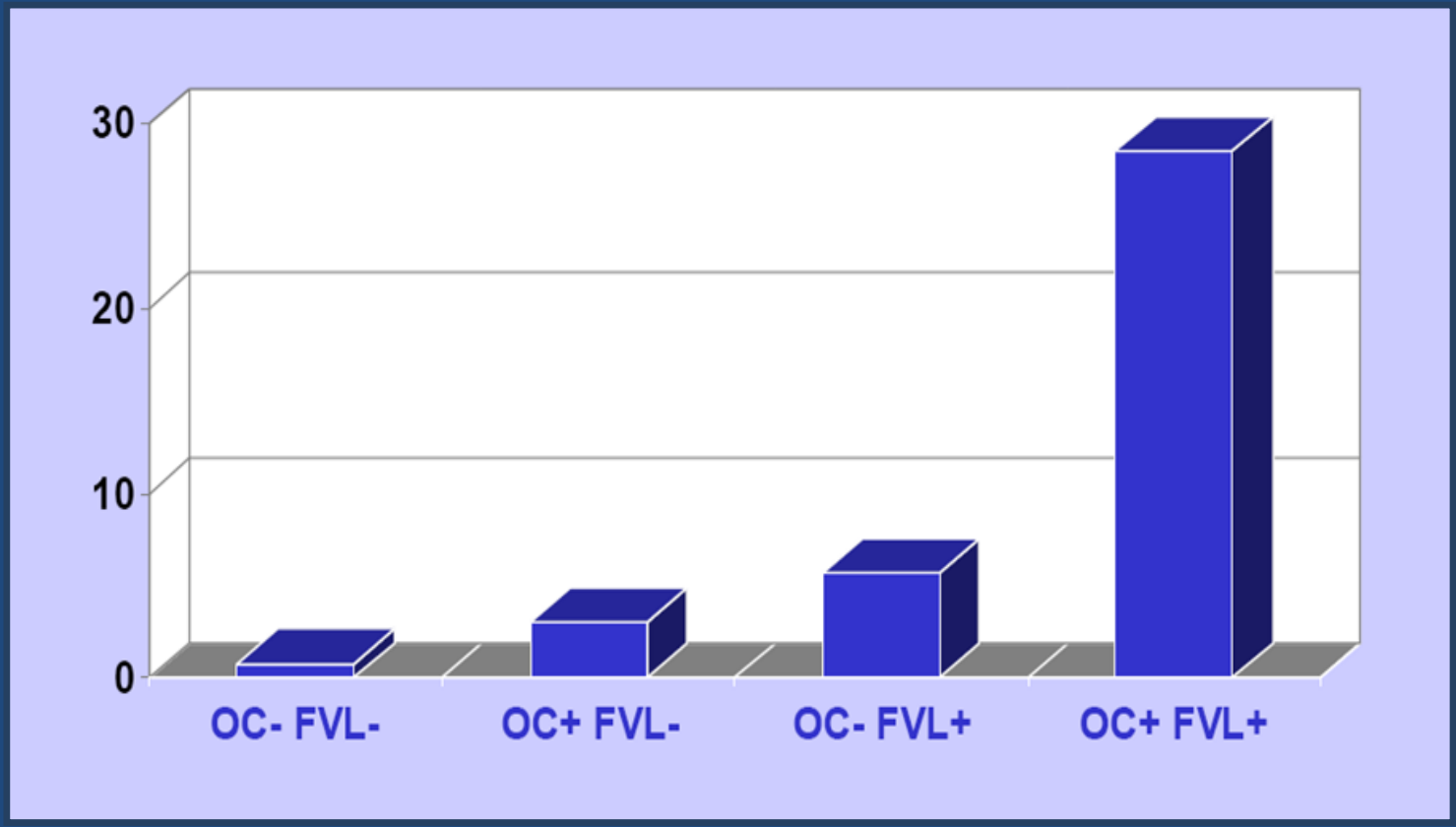
Thrombogenesis

A.I.Schafer (Lancet,1994,344:1739)



VT is multifactorial disease, presence of different factors raises the risk :
e.g. - risk of VT while thrombophilia FVL is approx. 2 -3x,
but risk of VT while FVL and O.C. is 30x higher than in persons without these.

Interaction Factor V Leiden and Oral Contraceptives



Vandenbroucke JP et al. *Lancet*. 1994; 344(8935): 1453-1457

Hereditary thrombophilia

Antithrombin, Protein C, Protein S Deficiencies

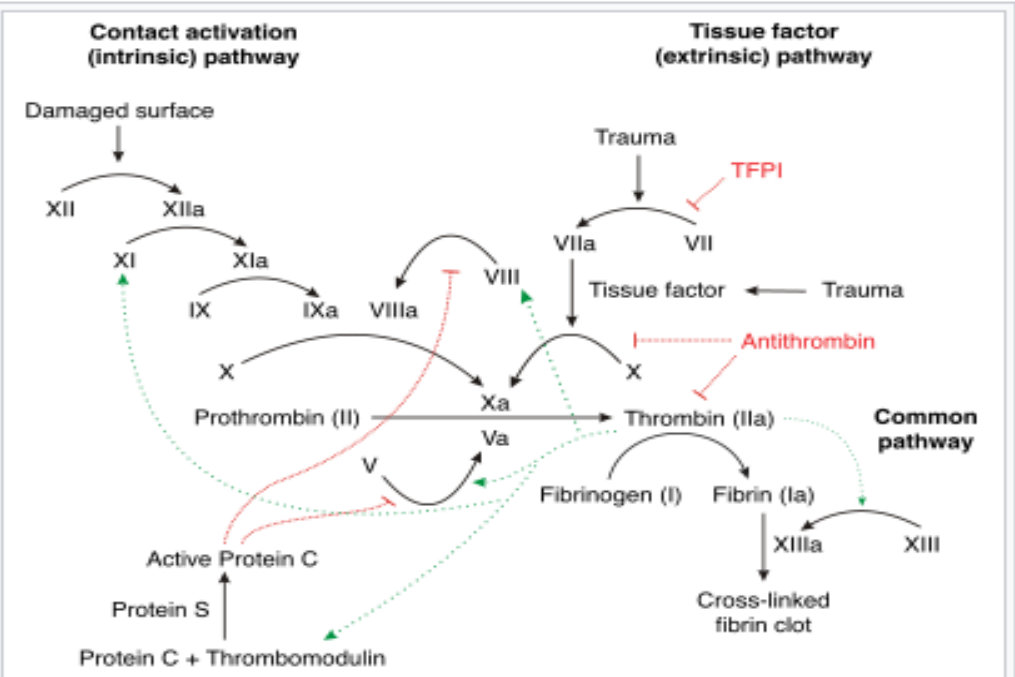
- Loss-of-Function Abnormalities
- Deficiencies of AT, PC, and PS are most commonly seen in the heterozygous state
- Levels are about 30 – 60% of normal
- Risk potential of each of these deficiencies is 10 – 25 fold
- Individuals with AT, PC, or PS deficiencies typically have a thrombotic event at young age
- Their prevalence – 0.2% till 1.0 % only

Genetic studies

- More than 40 genetic polymorphisms were described in over 25 hemostasis - related genes,

  but only 2 of these polymorphisms have been consistently associated with thrombosis:
- mutation FV-Leiden 1691 G→A,
- mutation FII 20210 G→A.

ACP resistence – FV Leiden



The coagulation cascade.

Prof. Rogier M. **Bertina (1994 FVL)**
Hemostasis and Thrombosis Research Center, **Leiden** University

Prothrombin G20210A mutation

- Prevalence in normal population approximately 3%
- G $\rightarrow$ A translation at nucleotide 20210 in prothrombin gene
  - Leads to an increase in Factor II (prothrombin) levels
- Increased risk of venous thrombosis

Faktor V Leiden (1691G>A) a Faktor II (20210G>A)

- výskyt v české populaci (Kvasnička T et al. Physiol Res. 2014;63:245).

FVL (1691 G>A)	Počet 2637	%
HET		8,15 %
HOM		0,11 %
Neg (wild type)		91,73 %
F II (20210G >A)		%
HET		2,24 %
HOM		0,04 %
Neg (wild type)		97,72 %

Laboratory Evaluation of Thrombophilia

- Genetic test for Factor V – Arg506Gln (Factor – V Leiden)
- Genetic test for prothrombin G20210A mutation
- Functional assay of antithrombin III (activity 80-120%)
- Function assay of protein C (activity 80-120%)
- Function assay of protein S along with immunological assays of total and free protein S
- Clotting assay for lupus anticoagulant/ELISA for cardiolipin antibodies (IgG and IgM)
- Meassurment of fasting total plasma homocysteine levels

Prevalence of Biologic Defects in Patients with Venous Thrombosis

- Activated Protein C Resistance (Factor V Leiden) 12 - 40%
- Prothrombin G20210A Mutation 6 - 18%
- Deficiencies of Antithrombin III, PC, PS 5 - 15%
- Hyperhomocysteinemia (Hcy >15,0 umol/l) 10 - 20%
- Antiphospholid Antibody Syndrome 5 - 10%

Acquired thrombophilia

Acquired risk factors for VTE

- Age > 65,
- surgery,
- neoplasm,
- reduced mobility (3 days) or paresis,
- among women - estrogen hormonal status
  (oral contraceptive, hormone replacement therapy, pregnancy)
- antiphospholipid sy

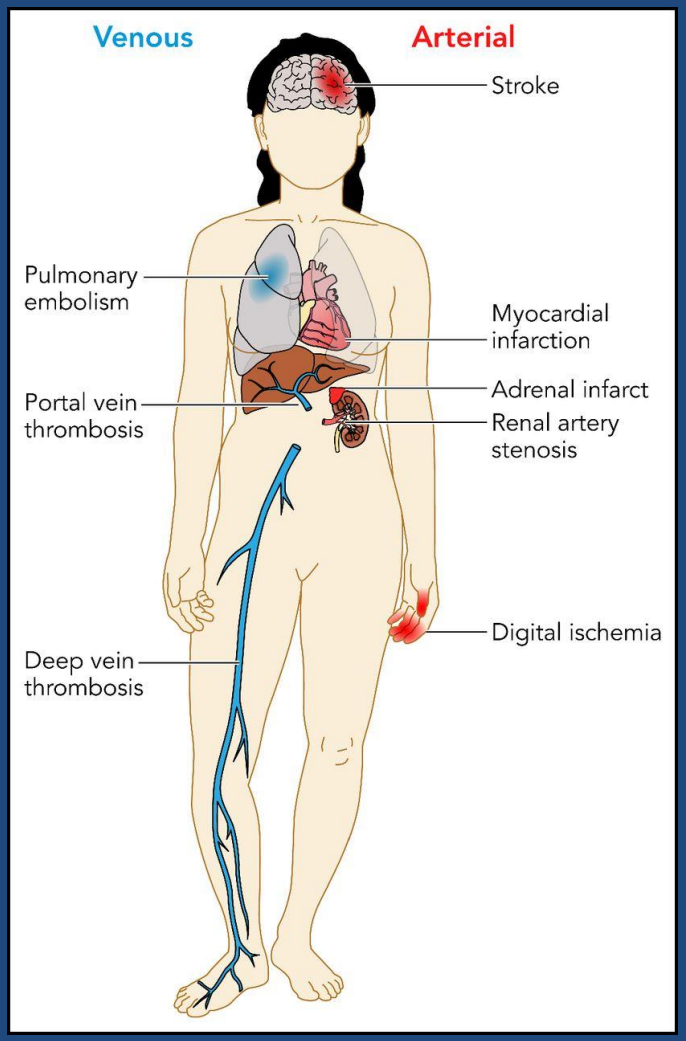
? controversial impact of other factors : obesity, tobacco use and varicose veins.

Oger E. et al. *Ann Cardiol Angiol (Paris).* 2002 Jun;51(3):124-8.

Lupus Anticoagulant / Anti-Phospholipid Syndrome (APS)

- Auto-antibodies against phospholipids or phospholipid-binding proteins
- Also known as Lupus Anticoagulant
- Major risk for recurrent miscarriage
- Major risk factor for venous thrombosis
  - Presence of antiphospholipid antibodies increases risk 9-fold
  - Thrombotic event in about 30% of patients with aPS

Patients with APS can experience a variety of thrombotic complications, both arterial and venous.



Marissa Laureano, and Mark A. Crowther Blood 2018;132:1357-1358

Disease Associations

Primary diagnosis requiring admission or bedrest in patients >40 years

- **Evidence-based**
  - cardiac disease (acute MI/acute heart failure – NYHA III/IV)
  - infectious disease/sepsis
  - active cancer requiring therapy
  - respiratory diseases (respiratory failure with/without mechanical ventilation; exacerbation of chronic respiratory disease)
  - rheumatic disease (including acute arthritis of lower extremities, vertebral compression, and acute back disorders)
  - neurological disorders (stroke, paraplegia)
- **Consensus-based**
  - inflammatory disorders with immobility
  - inflammatory bowel disease

MI = myocardial infarction
NYHA = New York Heart Association

Cohen AT et al. *J Thromb Haemost* 2003;1 Suppl 1:OC437

Risk Factors for VTE (1)

- Strong risk factors (odds ratio >10)
  - fracture (hip or leg)
  - hip or knee replacement
  - major general surgery
  - major trauma
  - spinal cord injury

Anderson F & Spencer F. *Circulation* 2003;107:I09-I16

Risk Factors for VTE (2)

- Moderate risk factors (odds ratio 2–9)
  - arthroscopic knee surgery
  - central venous line
  - chemotherapy
  - CHF/respiratory failure
  - HRT/oral contraceptive therapy
  - Malignancy -cancer could induce a generalized hypercoagulable state
  - previous VTE
  - paralytic stroke
  - pregnancy/post-partum
  - thrombophilia

CHF = congestive heart failure
HRT = hormone replacement therapy

Anderson F & Spencer F. *Circulation* 2003;107:I09-I16

Prof.Armand Trousseau

(1860)Trousseau's Syndrome – VTE can be an early sign of gastric or pancreatic Ca

Risk Factors for VTE (3)

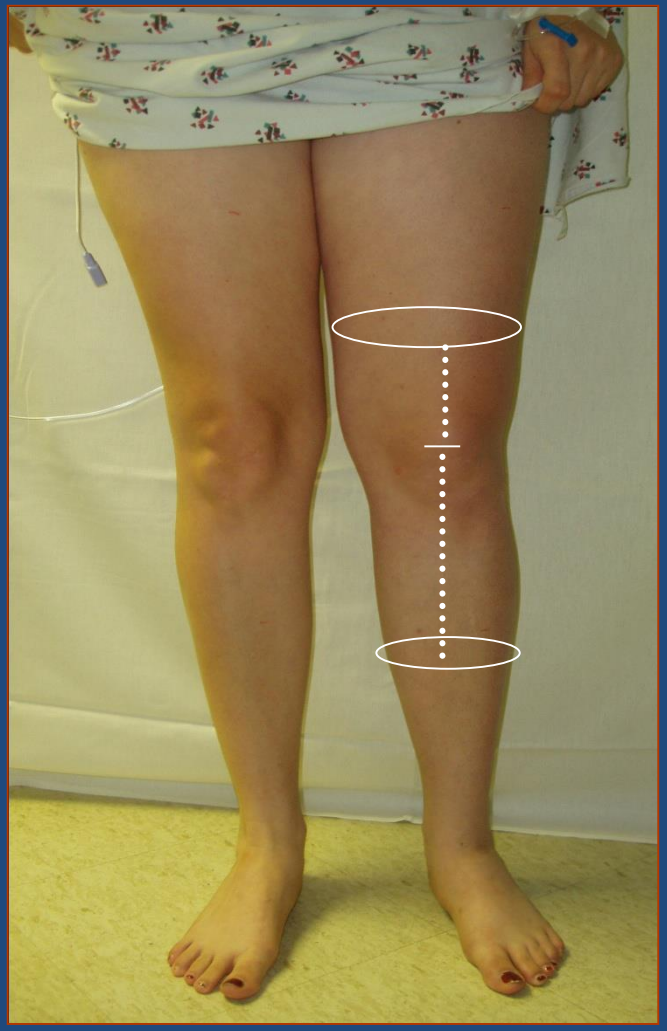
- Weak risk factors (odds ratio <2)
  - bedrest >3 days
  - sitting for prolonged periods, e.g. >8 hours of air travel
  - increased age
  - laparoscopic surgery
  - Obesity ≥ 35 BMI
  - pregnancy/postpartum
  - varicose veins

Anderson F & Spencer F. *Circulation* 2003;107:I09-I16

Diagnosis

- Deep vein thrombosis
  - clinical observation
  - D-dimer test
  - ultrasound

A simple test - measure the circumference of thighs and calves



L > P o 4 cm

L > P o 3 cm

Clinical decision rule

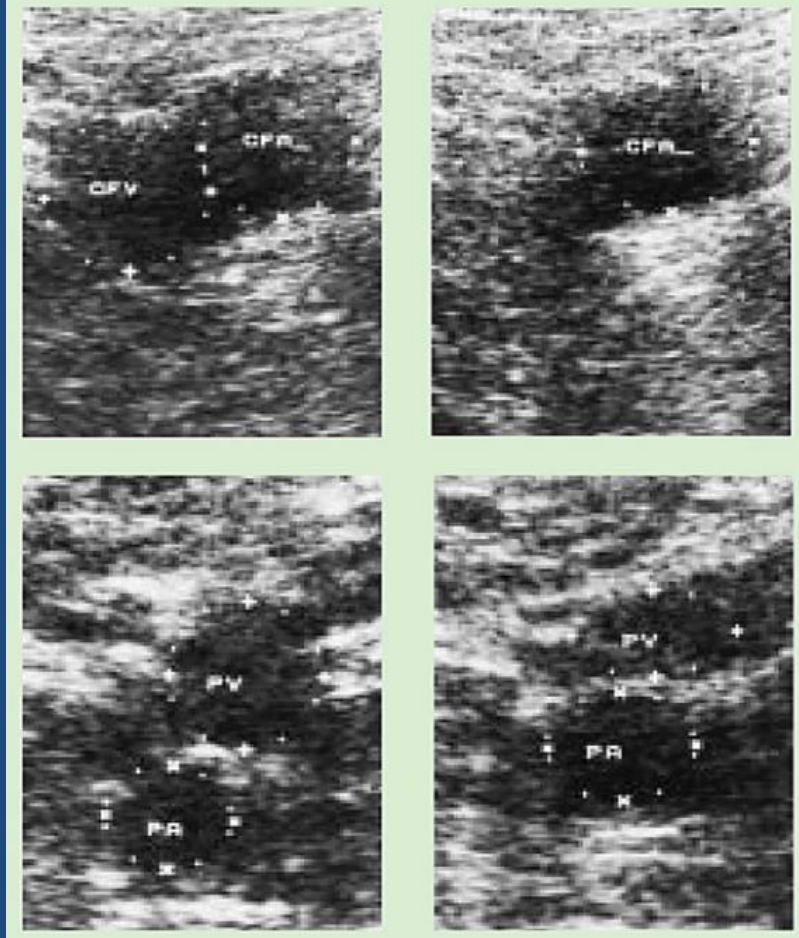
Deep vein thrombosis –Wells score

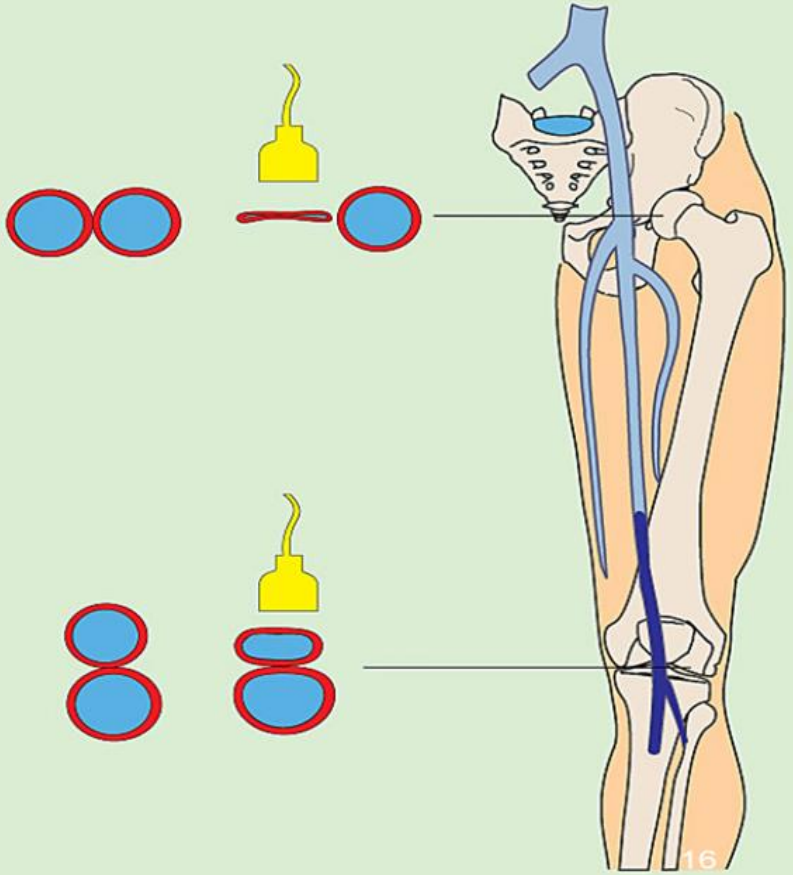
	Points
Active cancer (treatment ongoing or within previous 6 months palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden > 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non varicose)	1
Alternative diagnosis as likely or greater than DVT	-2

Score ≤ 2 : DVT unlikely
Score > 2 : DVT likely

Low 0
Moderate 1-2
High > 3

Wells PS et al. *Lancet*. 1997; 350(9094): 1795-1798


CFA
CFV
CFA
PV
PA
PV
PA



Recommendations for diagnosis (3)

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Recommendations	Class	Level
D-dimer		
Plasma D-dimer measurement, preferably using a highly sensitive assay, is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or PE-unlikely, to reduce the need for unnecessary imaging and irradiation.	I	A
As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an age-adjusted cut-off (age x 10 µg/L, in patients >50 years) should be considered for excluding PE in patients with low or intermediate clinical probability, or PE-unlikely.	IIa	B

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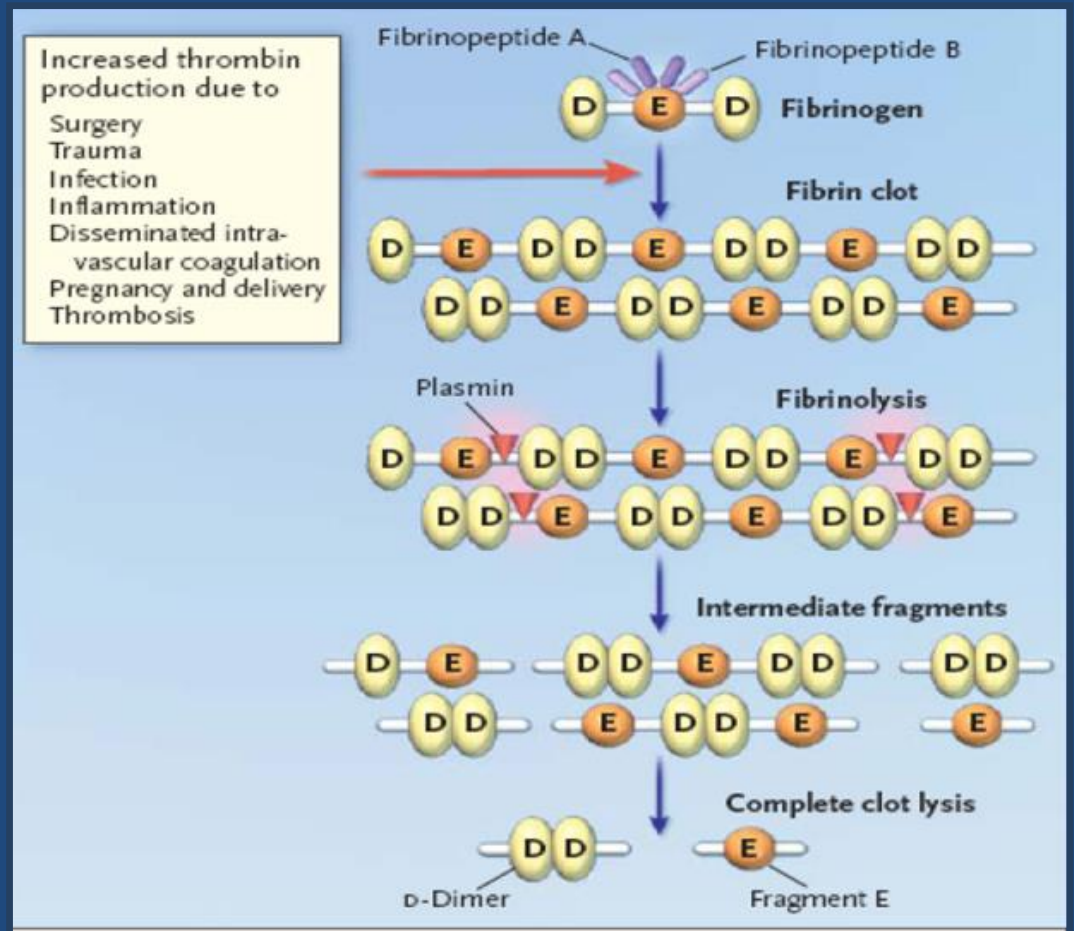
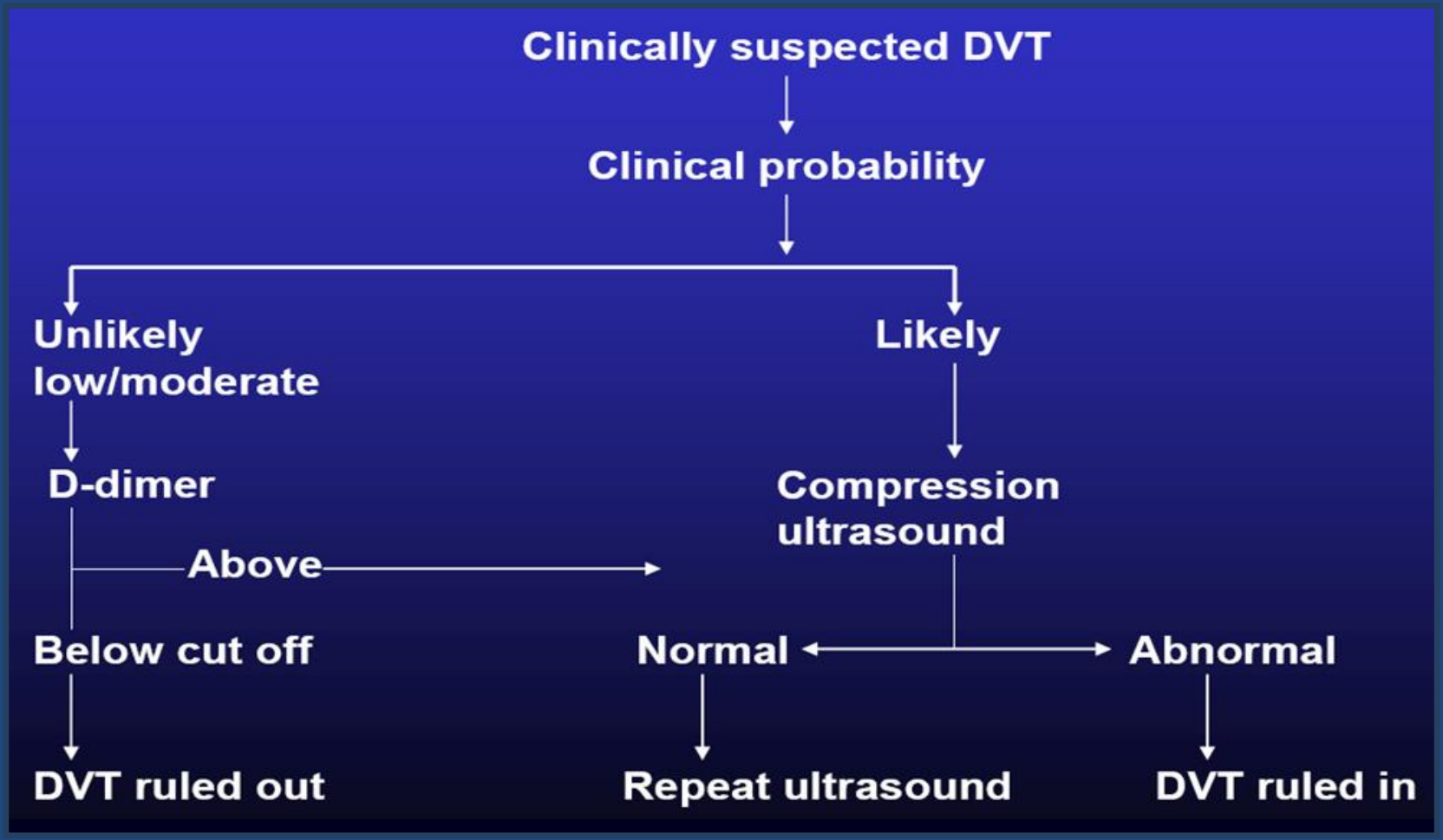
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

D-dimer Test



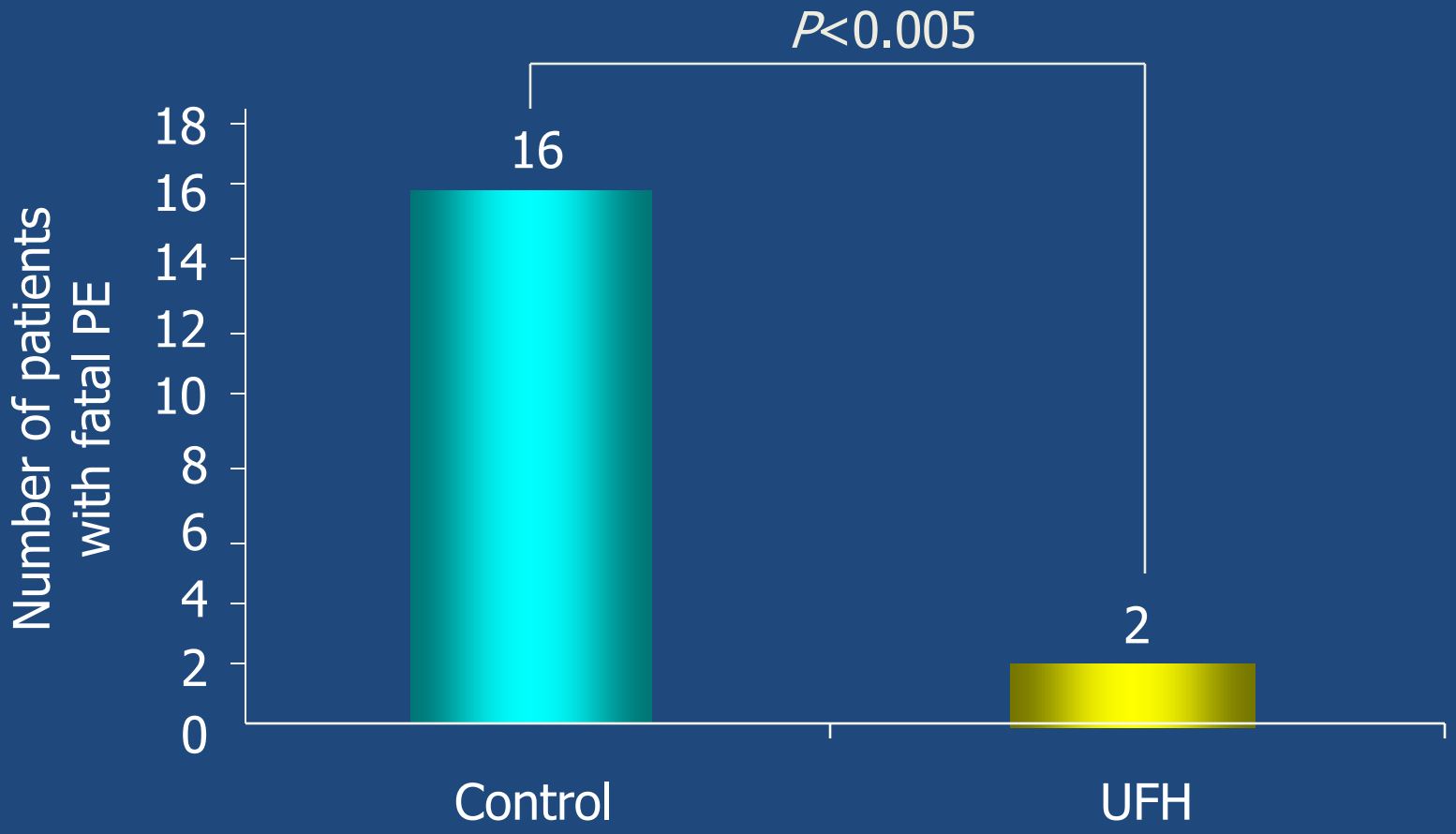
Plasmin Degradation of a Fibrin Clot.

Validated Diagnostic Strategy for Deep Vein Thrombosis



Prophylaxis and treatment of VTE

Surgery : Prophylaxis of Fatal, Postoperative PE with Low-dose UFH (2x5000j s.c./24 h)



Low-dose UFH saves 7 lives for every 1,000 operated patients

Lancet 1975;2:45-51

LMW Heparin

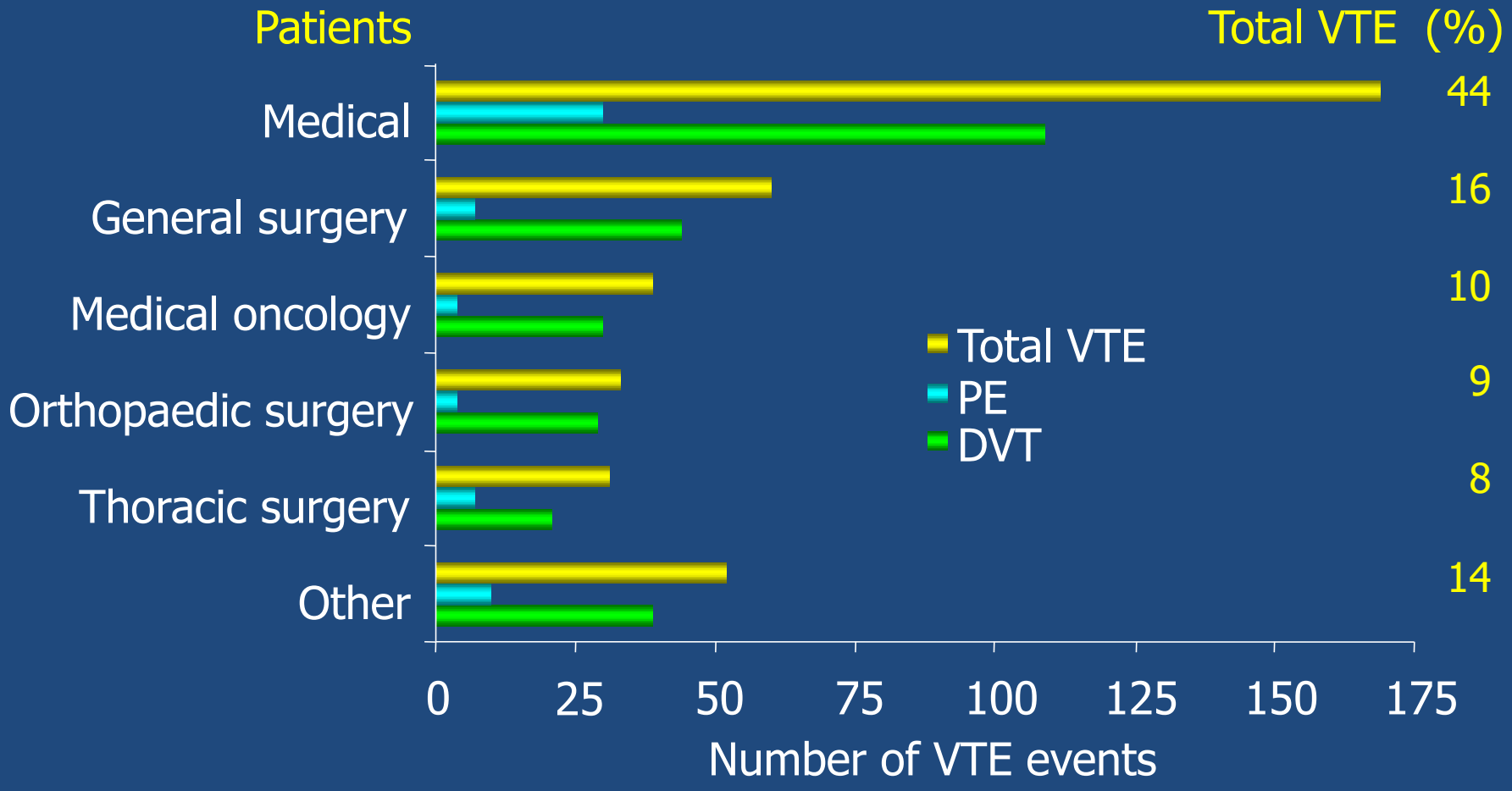
- Low Molecular Weight Heparin (LMWH) s.c. has been shown as effective as UFH in preventing recurrent VTE and cause less bleeding
- Generally LMWH does not need monitoring
- When monitoring is required, a chromogenic anti-Xa assay is required
- Prophylaxis of VTE : 0.2-0.4 IU/ml anti FXa
- Treatment of VTE : 0.6-1.0 IU/ ml anti FXa

Now : LMWH

	Median molecular weight	Anti-Xa IU/mg	Anti-IIa IU/mg	Xa/IIa ratio
Enoxaparin	4,500	104	32	3.3
Dalteparin	5,000	122	60	2.0
Nadroparin	4,500	94	31	3.0
Tinzaparin	6,500	90	50	1.8
Reviparin	3,900	130	40	3.3

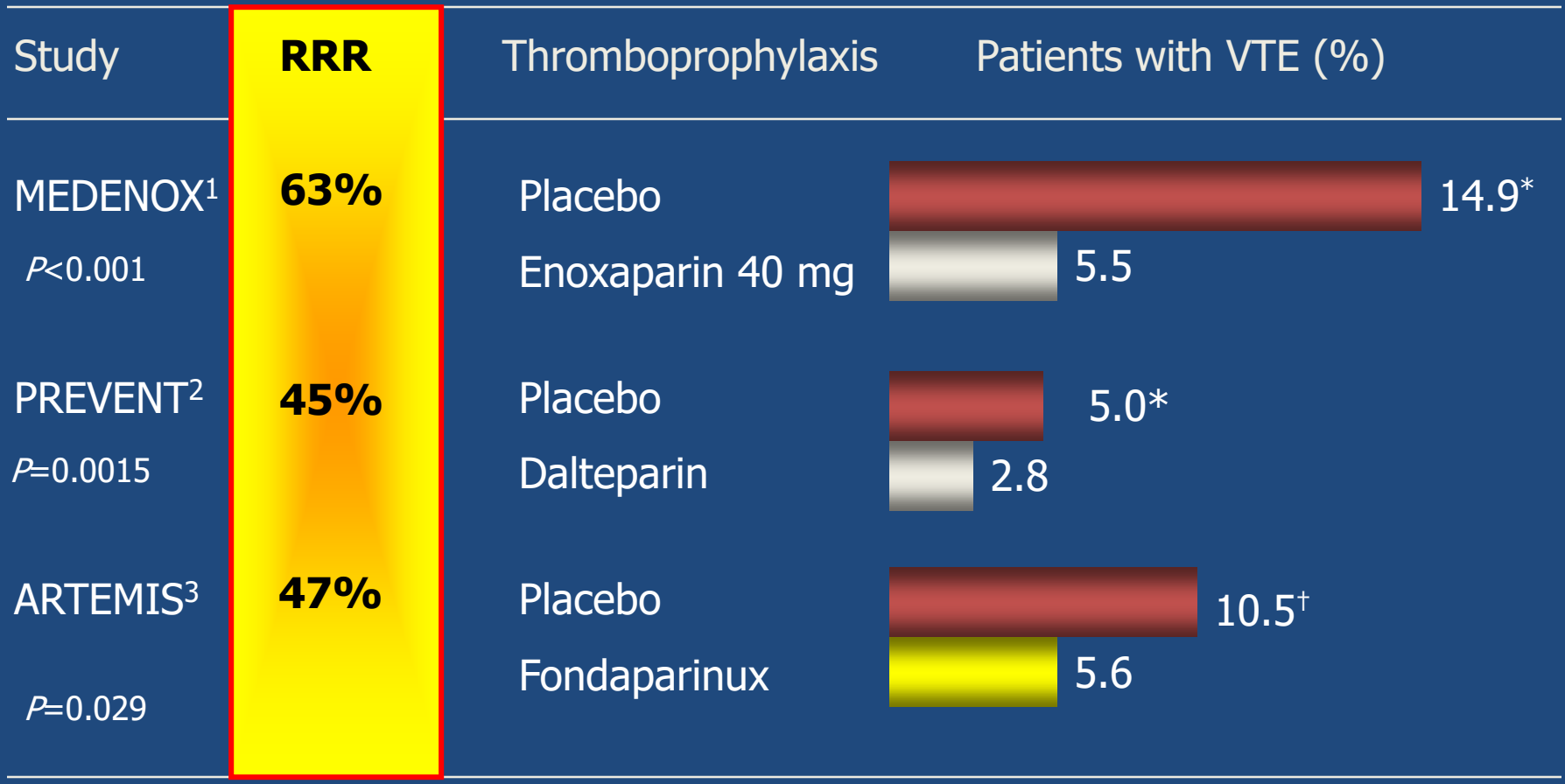
Drug prescribing information

State of the DVT prophylaxis in hospital today



Goldhaber SZ et al. *Chest* 2000; 118: 1680-4

Clear Benefits of Thromboprophylaxis over Placebo (Medical Patients)

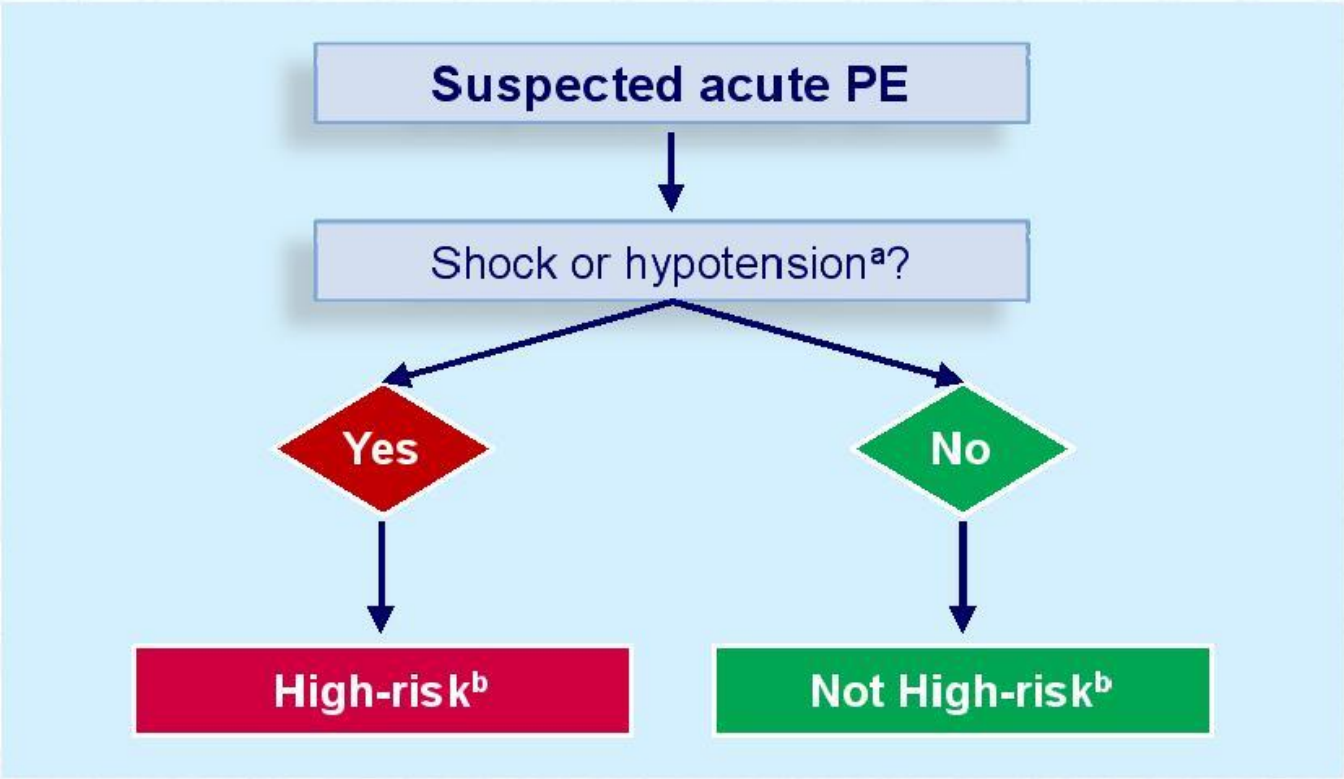


*VTE at day 14; †VTE at day 15.

RRR = relative risk reduction

[1]**Samama MM et al.** *N Engl J Med* 1999;341:793-800
[2]**Leizorovicz A et al.** *Circulation* 2004;110:874-9
[3]**Cohen AT et al.** *J Thromb Haemost* 2003;1 (Suppl 1):P2046

Initial risk stratification of acute PE



[a] Defined as systolic blood pressure <90 mmHg, or a systolic pressure drop by ≥40 mmHg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.
[b] Based on the estimated PE-related in-hospital or 30-day mortality.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

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Recommendations for acute-phase treatment of high-risk PE[a] (1)

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Recommendations	Class	Level
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.[a]	I	C
Systemic thrombolytic therapy is recommended for high- risk PE.	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.	I	C

[a] After haemodynamic stabilization of the patient, continue anticoagulation as in intermediate- or low-risk PE.
UFH = unfractionated heparin.

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Table 12 Thrombolytic doses and contraindications (1)

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Molecule	Regimen	Contraindications to fibrinolysis
Recombinant tissue-type plasminogen activator (rtPA)	100 mg over 2 h	**Absolute** • History of haemorrhagic stroke or stroke of unknown origin • Ischaemic stroke in previous 6 months • Central nervous system neoplasm • Major trauma, surgery, or head injury in previous 3 weeks • Bleeding diathesis • Active bleeding
	0.6 mg/kg over 15 min (maximum dose 50 mg)	
Streptokinase	250,000 IU as a loading dose over 30 min, followed by 100,000 IU/h over 12–24 h	
	Accelerated regimen: 1.5 million IU over 2 h	

Recommendations for acute-phase treatment of intermediate- or low- risk PE (1)

ESC European Society of Cardiology

Recommendations	Class	Level
Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, while diagnostic work-up is in progress.	I	C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.	I	A
Oral anticoagulants		
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA.	I	A

NOAC = non-vitamin K antagonist oral anticoagulant; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; UFH = unfractionated heparin.

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Recommendations for acute-phase treatment of intermediate- or low- risk PE (2)

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Recommendations	Class	Level
Oral anticoagulants		
When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2.0–3.0) is reached.	I	A
NOACs are not recommended in patients with severe renal impairment, during pregnancy and lactation, and in patients with the antiphospholipid antibody syndrome.	III	C

INR = International Normalized Ratio; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); VKA = vitamin K antagonist.

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Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (1)

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Recommendations	Class	Level
Therapeutic anticoagulation for at least 3 months is recommended for all patients with PE.	I	A
Patients in whom discontinuation of anticoagulation after 3 months is recommended		
For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months.	I	B

VTE = venous thromboembolism.

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (4)

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Recommendations	Class	Level
NOAC dose in extended anticoagulation		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg *b.i.d.*) or rivaroxaban (10 mg *o.d.*) should be considered after 6 months of therapeutic anticoagulation.	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis.	IIb	B

NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); VTE = venous thromboembolism.

Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (2)

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Recommendations	Class	Level
Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor.	I	B
Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with the antiphospholipid antibody syndrome.	I	B

DVT = deep vein thrombosis; VKA = vitamin K antagonist.

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (4)

ESC European Society of Cardiology

Recommendations	Class	Level
NOAC dose in extended anticoagulation		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg *b.i.d.*) or rivaroxaban (10 mg *o.d.*) should be considered after 6 months of therapeutic anticoagulation.	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis.	IIb	B

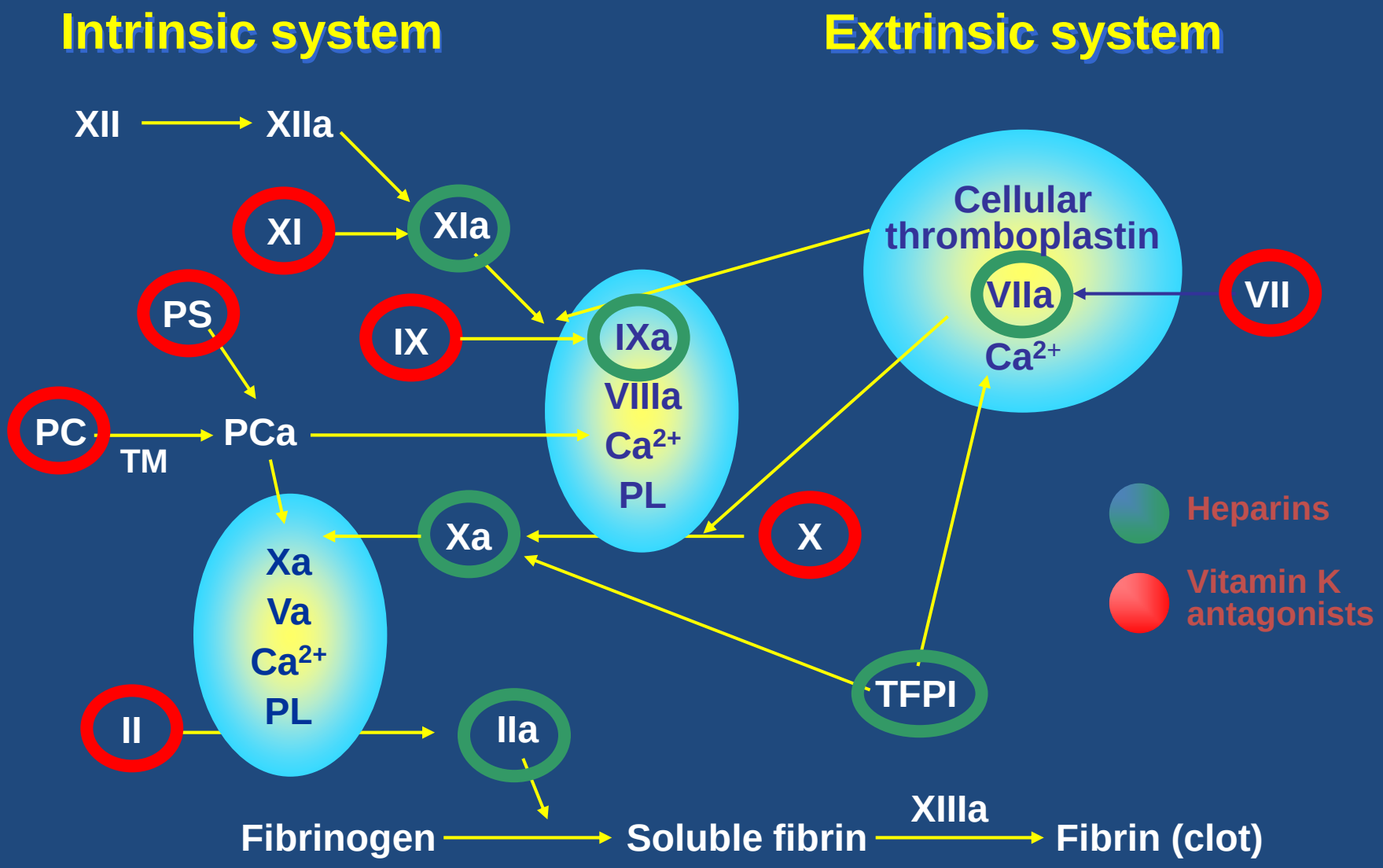
NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); VTE = venous thromboembolism.

Anticoagulant drug

Main Characteristics of "Old" Anticoagulant Drugs

	Unfractionated Heparin	**LMW**	**Fondaparinux**	**VKA**
Mechanism	Fast acting Antithrombin-mediated IIa & Xa inhibitor	Fast acting Antithrombin-mediated Xa inhibitor	Fast acting Antithrombin-mediated Xa Inhibitor	Slow acting carboxylation -mediated reduction of VII, IX, X, II, PC, PS
Administration	IV	SC	SC	Oral
Lab monitoring for dose-adjustment	YES APTT (2xnorm)	Anti FXa (in general NO)	Anti F Xa (in general No)	YES PT (INR 2,0-3,0

An „old“ antithrombotic agents:

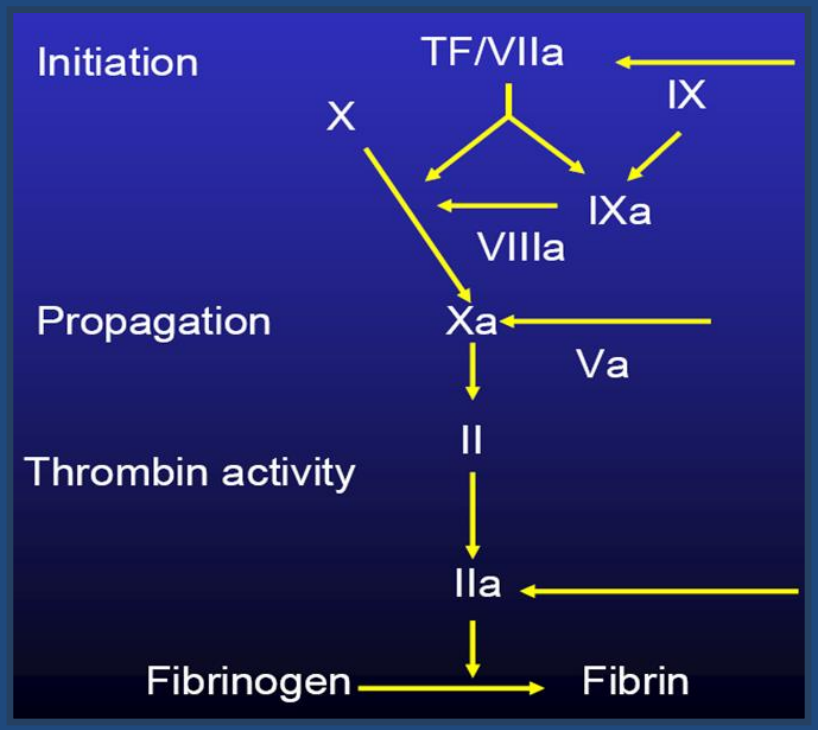


Boneu B, et al. *Sang Thrombose Vaisseaux* 1998; **10**:291–313.

New Anticoagulants (DOACs/NOACs)

Drug

Coagulation cascade



- Direct Factor Xa Inhibitors

  Apixaban Edoxaban Rivaroxaban

- Indirect Factor Xa Inhibitors
- LMWH , Fondaparinux

- **Dabigatran**

DOAC Characteristics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Commercial name	Pradaxa®	Xarelto®	Eliquis®	Lixiana®
Mechanism of action	Direct Thrombin-Inhibitor	Direct factor Xa Inhibitor		
Dosing frequency	bid	od	bid	od
Bioavailability	6%	80%	66%	45%
Prodrug	yes	no	no	no
Half-life	12-14 h	7-10 h	8-15 h	9-10 h
Tmax	2 h	1,5-4 h	3 h	1-3 h
Drug interaction(s)	P-gp	CYP3A4 P-gp	CYP3A4 P-gp	P-gp
Renal elimination	>80%	66% (33% as the active substance)	25%	33%

DOAC Efficacy

In the pivotal trials, DOAC proved to be either superior or non-inferior to warfarin for:

- Prevention of stroke and systemic embolism in atrial fibrillation
- Prevention of VTE in orthopedic surgery
- Treatment and secondary prevention of VTE

NOACs for acute phase VTE treatment

Trial	Drug	Design Dose	Initial treatment
RE-COVER (Schulman NEJM 2009) RE-COVER II (same design)	Dabigatran (Pradaxa) Anti-IIa	Double-blind 150 mg BID	Parenteral ACs in first 5-7 d; then dabigatran
EINSTEIN DVT (Bauersachs NEJM 2010) EINSTEIN PE (Buller NEJM 2012)	Rivaroxaban (Xarelto) anti-Xa	Open-label 15 mg BID for the first 3 weeks followed by 20 mg OID	Single drug
AMPLIFY (Agnelli NEJM 2013)	Apixaban (Eliquis) anti-Xa	Double-blind 10 mg BID for the first 7 d. followed by 5 mg BID	Single drug
HOKUSAI (Buller NEJM 2013)	Edoxaban anti-Xa	60 mg OID (30 mg in high risk pts)	Parenteral ACs in first 5-7 d; then edoxaban

DOAC Safety

- *Major bleeding*
- At least not inferior to VKA
- *Intracranial bleeding*
- Superior to VKA

DOAC
Advantages & Disadvantages

- *Advantages*
- Direct and quick onset of anticoagulant effect
- Quick offset of anticoagulant effect
- Fixed dosage: no dose-adjustment
- *Disadvantages*
- Variable effect: renal and/or liver function
- Price !
- Compliance

The Laboratory & Oral anticoagulation

- ***Monitoring***

– dosage adjustment based on test results (VKA, unfractionated heparin)

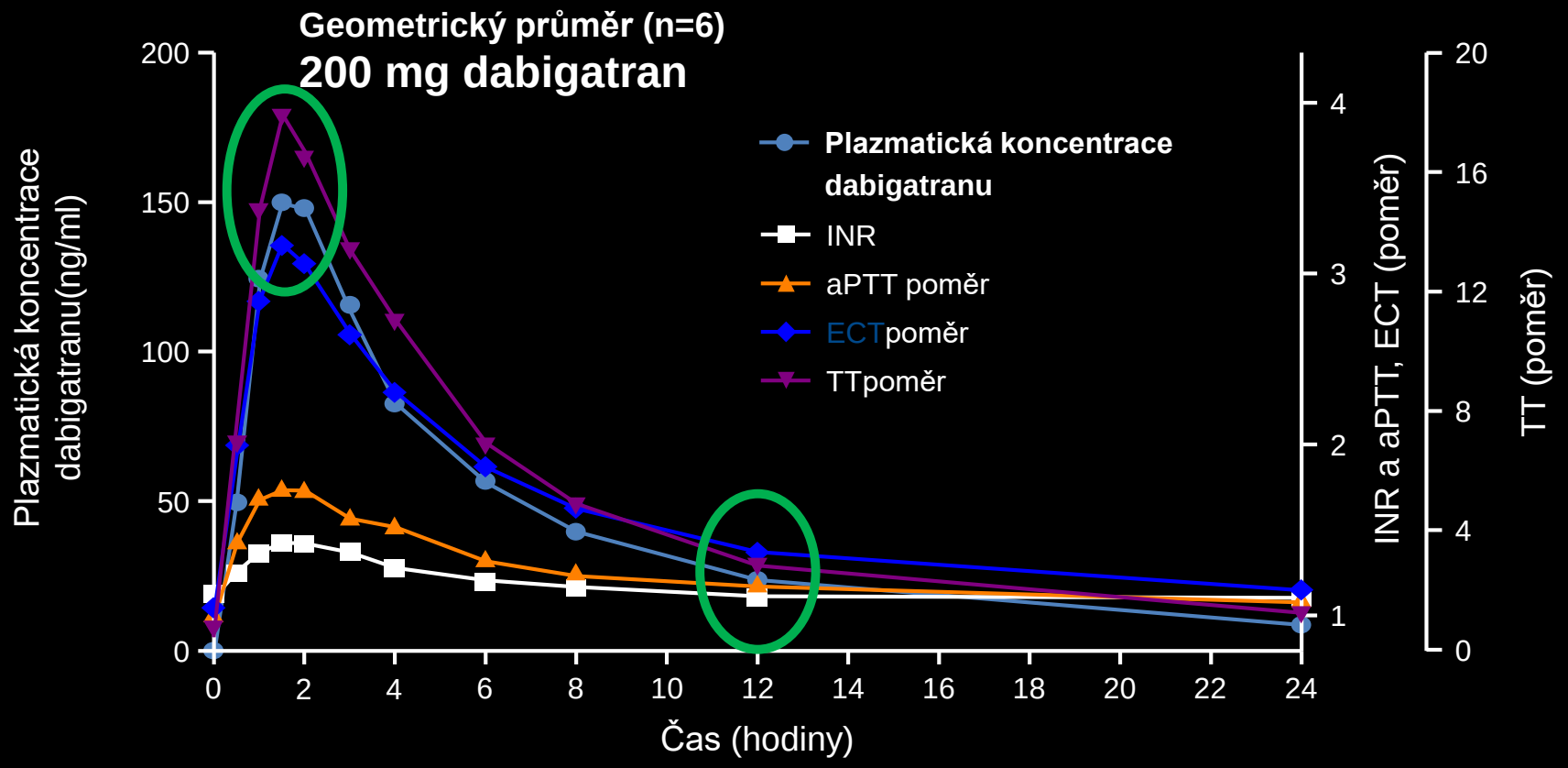
- ***Measuring***

– determining the anticoagulant effect (DOAC)

Laboratory & DOAC
When to measure

- DOAC reach *Cmax* approximately 2h after ingestion
- DOAC minimum *C* approximately 12h (bid) or 24h (od) after ingestion
- Timing of blood draw is essential for results interpretation

NOACs – C max after 2 h and Cmin before next dose



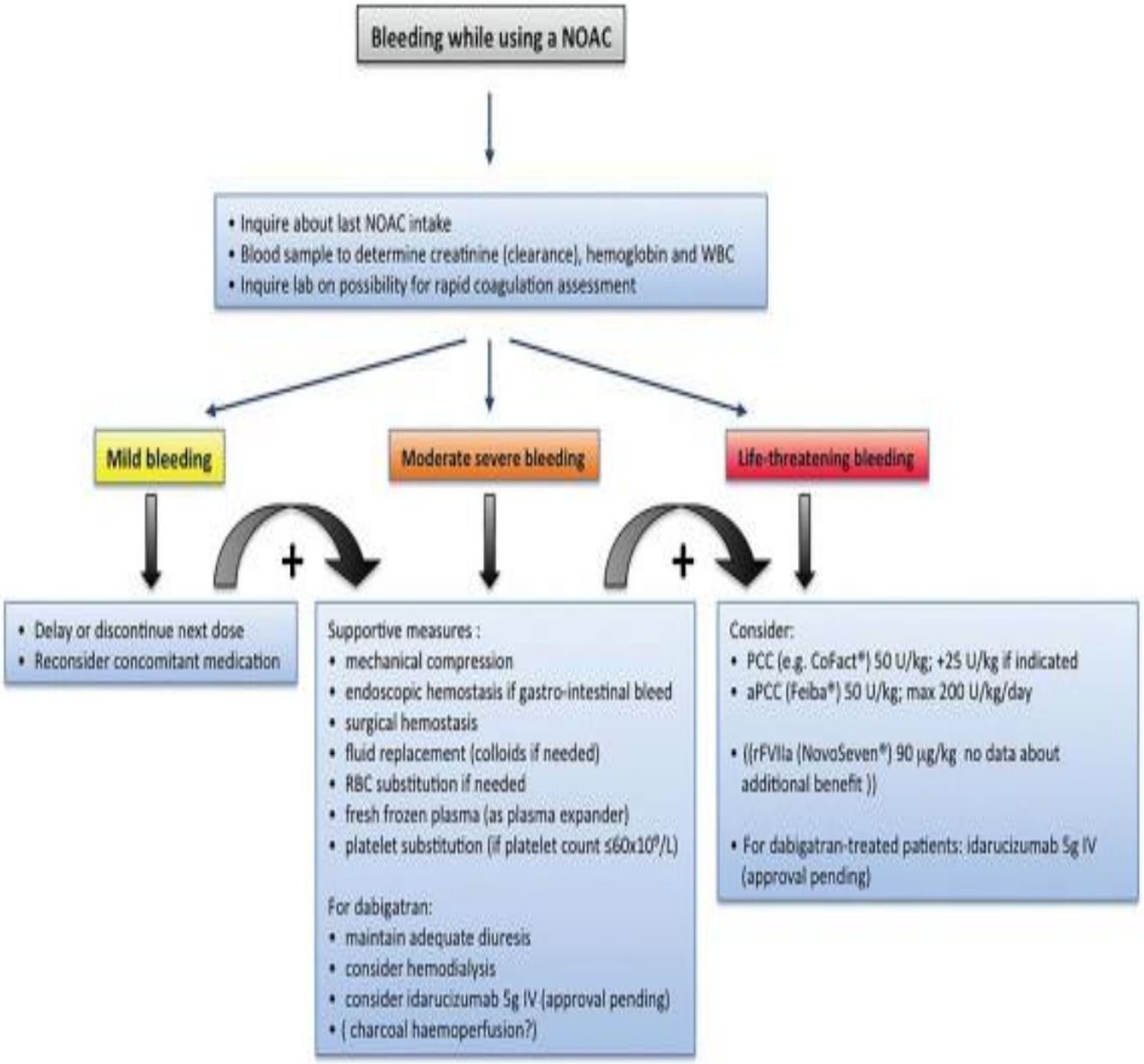
Stangier J et al. Br J Clin Pharmacol 2007;64:292–303

Which Test for Dabigatran

- APTT
- Thrombin Time (TT)
- Ecarin clotting time (ECT)
- Anti-FIIa activity (HEMOCLOT)

Which test for rivaroxaban,edoxaban and apixaban ?

- Anti-Xa
- (PT)


Bleeding while using a NOAC
• Inquire about last NOAC intake
• Blood sample to determine creatinine (clearance), hemoglobin and WBC
• Inquire lab on possibility for rapid coagulation assessment
Mild bleeding
Moderate severe bleeding
Life-threatening bleeding
+
+
• Delay or discontinue next dose
• Reconsider concomitant medication
Supportive measures :
• mechanical compression
• endoscopic hemostasis if gastro-intestinal bleed
• surgical hemostasis
• fluid replacement (colloids if needed)
• RBC substitution if needed
• fresh frozen plasma (as plasma expander)
• platelet substitution (if platelet count ≤60x10⁹/L)
For dabigatran:
• maintain adequate diuresis
• consider hemodialysis
• consider idarucizumab 5g IV (approval pending)
• (charcoal haemoperfusion?)
Consider:
• PCC (e.g. CoFact®) 50 U/kg; +25 U/kg if indicated
• aPCC (Feiba®) 50 U/kg; max 200 U/kg/day
• ((rFVIIa (NovoSeven®) 90 µg/kg no data about additional benefit))
• For dabigatran-treated patients: idarucizumab 5g IV (approval pending)

Conclusion I

- It is known that the majority of VTE may be considered to be preventable, but the patients at increased risk must be firstly identified.
- In contrary to this fact, the laboratory testing of inherited thrombophilia was not recommended for its screening on the costbenefit basis till now.

Conclusion II

- We suggest , the next investigation of thrombophilic states for prevention of VTE at increased risk conditions (e.g.before starting of O.C.) will be very efficient after adopting new research tools in our practice , such as non-expensive genetic testing in the near future.