Venous Thromboembolism: Pathophysiology & Management

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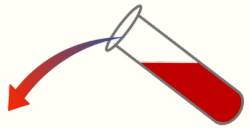
Disclosures

- Research Support (Past 5 years):
  - Amgen
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
- Advisory Boards (Past 5 years)
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Sanofi
  - Novartis
  - Agios Pharmaceuticals.



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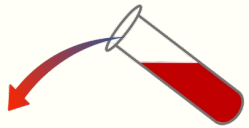
1. Scope of the Problem
2. Vascular Anatomy
3. Thrombosis: Arterial versus Venous
4. Post-Thrombotic Syndrome
5. Pathophysiology of Venous Thromboembolism
6. Pathophysiology of Venous Thromboembolism: Acquired Thrombophilias
7. Thrombophilia: Prevalence, Evaluation, and Impact
8. Treatment of Venous Thromboembolism: Historical Perspective
9. Treatment of Venous Thromboembolism: Direct Oral Anticoagulant (DOAC)
10. Reversal of Anticoagulant Effect of DOAC
11. How Long To Treat With Anticoagulation After VTE?

Not covering:

- Antiphospholipid Antibody Syndrome
- Thrombolysis In Pulmonary Embolism



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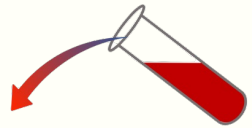
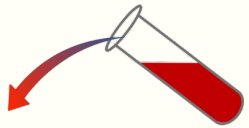


Venous Thromboembolism (1)

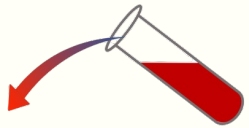
- Approximately 1 to 2 per 1,000 each year in the United States.
- "Venous thromboembolism (VTE), defined as deep vein thrombosis, pulmonary embolism, or both, affects an estimated 300,000-600,000 individuals in the U.S. each year."
- Estimates suggest that 60,000-100,000 Americans die of VTE.
  - 10 to 30% of people will die within one month of diagnosis.
- Incidence strongly correlates with demographics and risk factors.

- https://www.cdc.gov/ncbddd/dvt/data.html
- Beckman et al. Am J Prev Med. 2010 Apr;38(4 Suppl):S495-501. doi: 10.1016/j.amepre.2009.12.017.

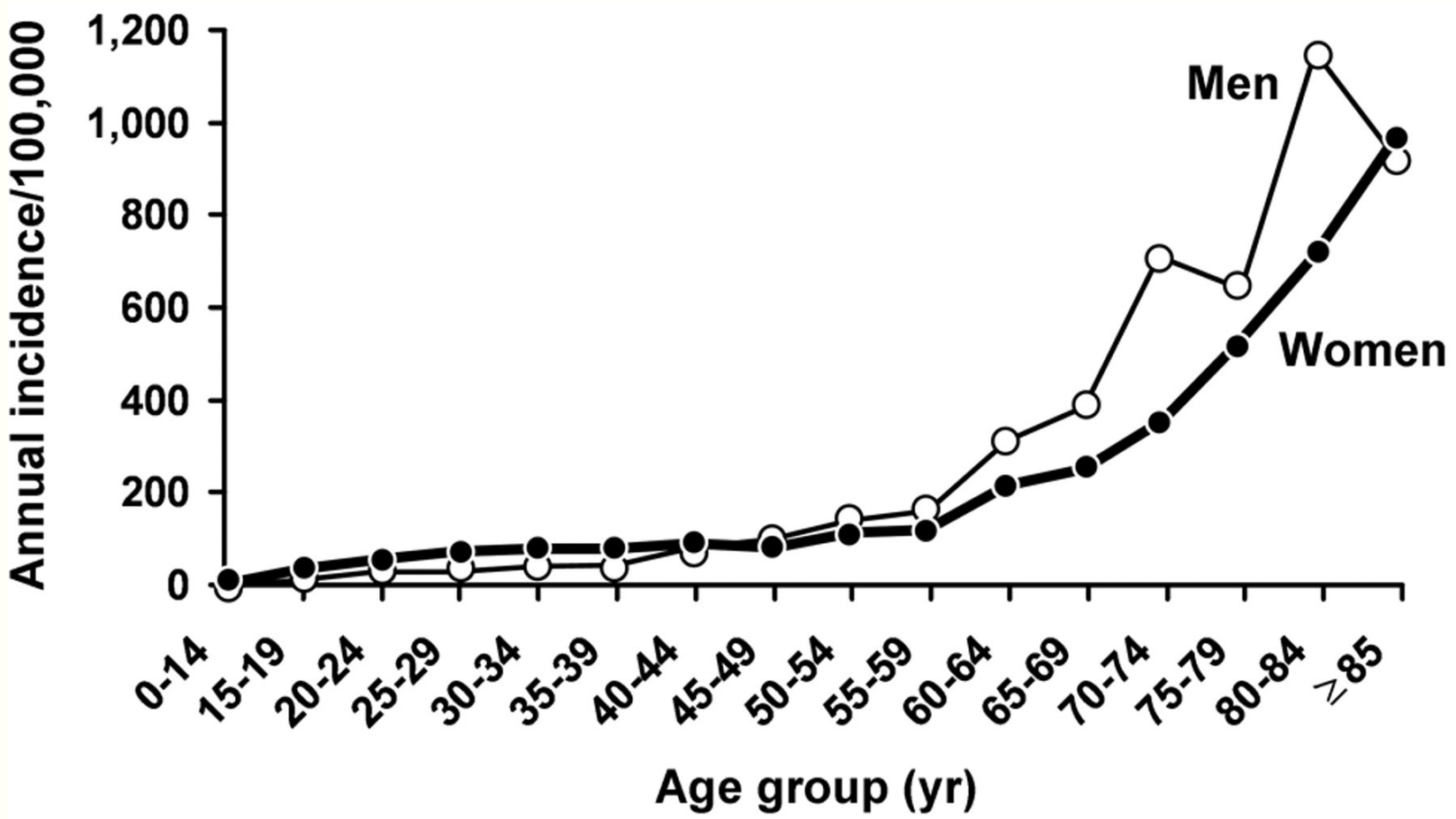


Venous Thromboembolism (2)

- Among people who have had a DVT, one third to one half will have long-term complications (post-thrombotic syndrome) such as swelling, pain, discoloration, and scaling in the affected limb.
- One-third (about 33%) of people with DVT/PE will have a recurrence within 10 years.
- Approximately 5 to 8% of the U.S. population has one of several inherited thrombophilias in which a genetic defect can be identified that increases the risk for thrombosis.
  - https://www.cdc.gov/ncbddd/dvt/data.html
  - Beckman et al. Am J Prev Med. 2010 Apr;38(4 Suppl):S495-501. doi: 10.1016/j.amepre.2009.12.017.



Annual Incidence of Venous Thromboembolism By Age and Sex



Heit JA, Hematology 2007:127-135

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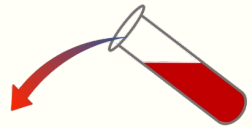
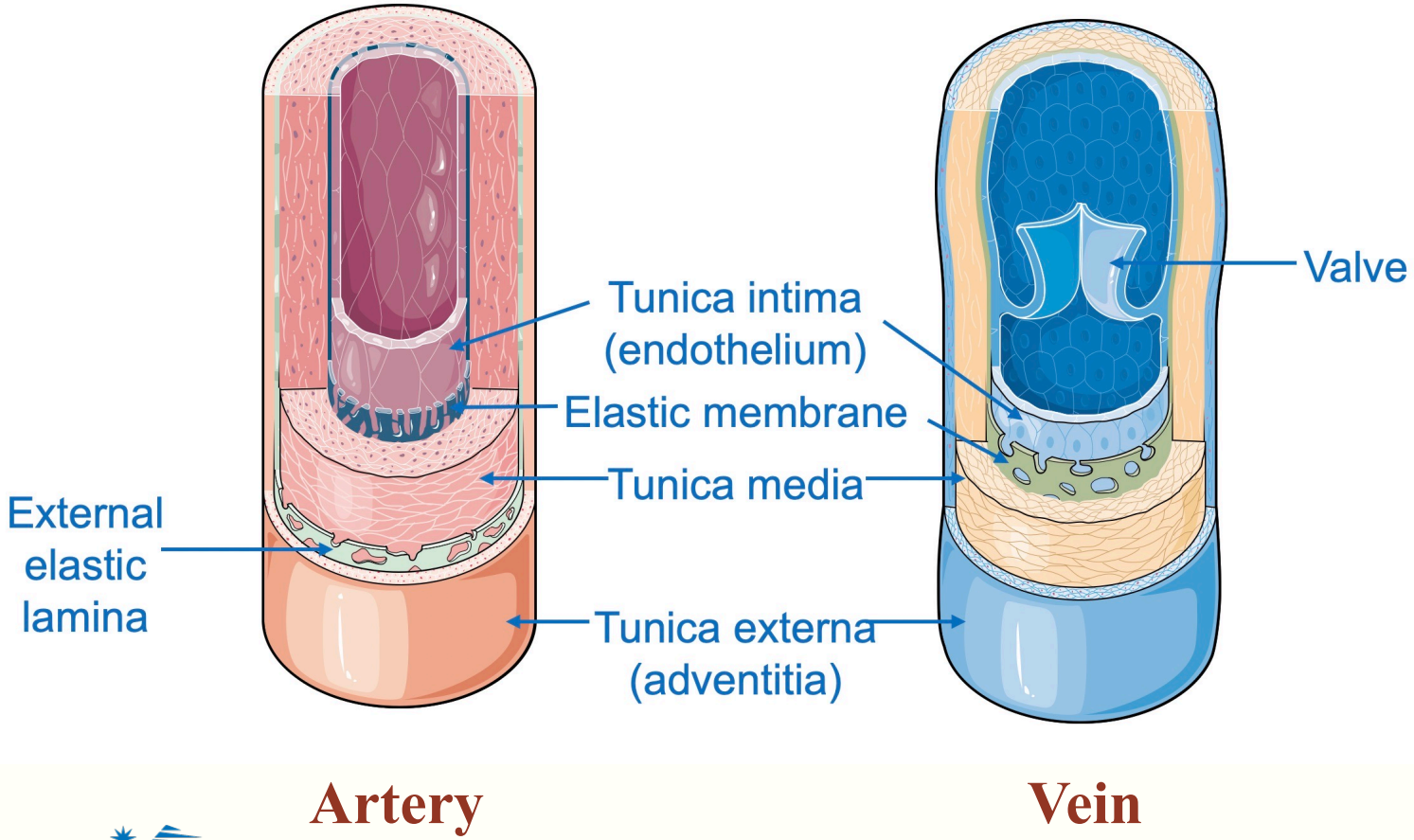
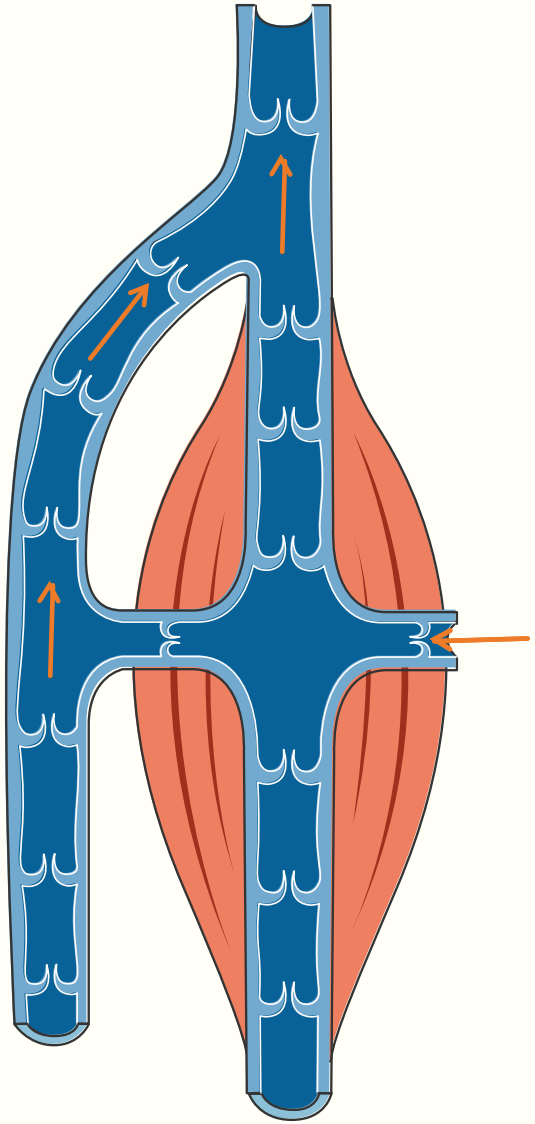


Structure of Normal Blood Vessels



Artery **Vein**

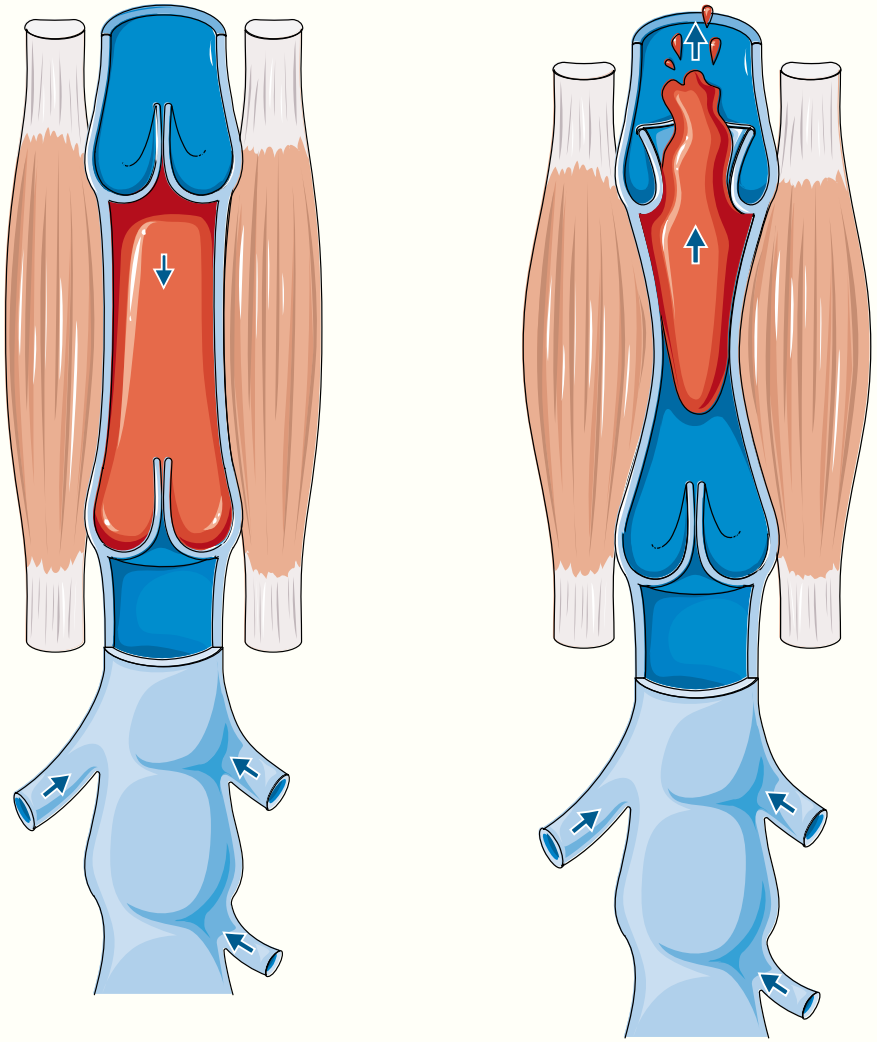
- Arteries pump blood by peristaltic motion.
- Veins pump blood by external compression, with series of one-way valves directing blood towards the heart.

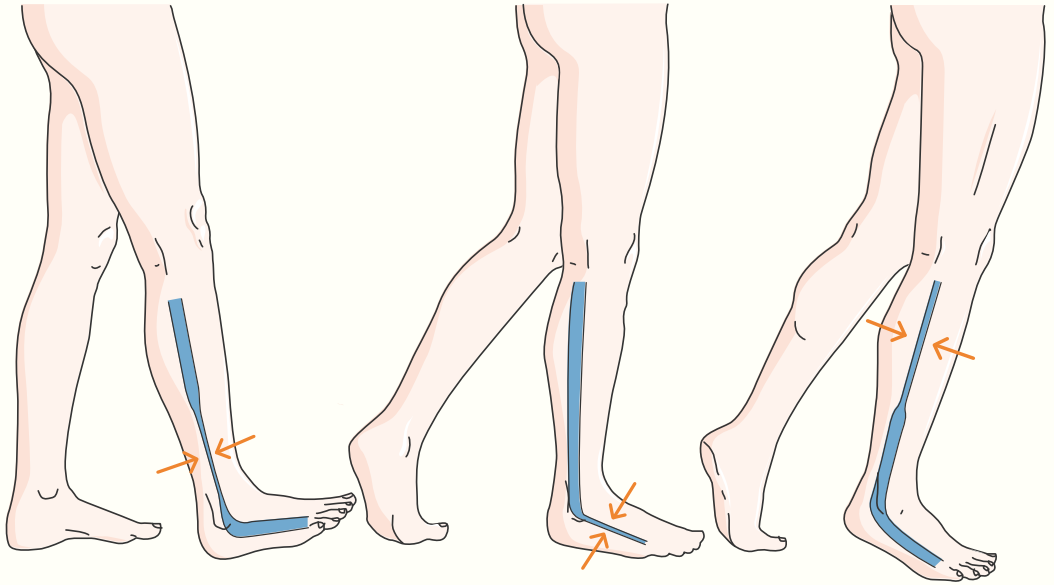


Venous Return: Superficial and Deep Veins

- Deep veins are intramuscular
- Blood flows from superficial to deep veins through perforating veins.
- Blood flow “pumped” by contraction of deep muscles.
- Flow directed by series of one-way valves.

Intramuscular/Deep Vein Function





Contraction/Relaxation of leg muscles pumps blood through deep veins.

Prolonged Bedrest/Immobility Reduces Venous Return

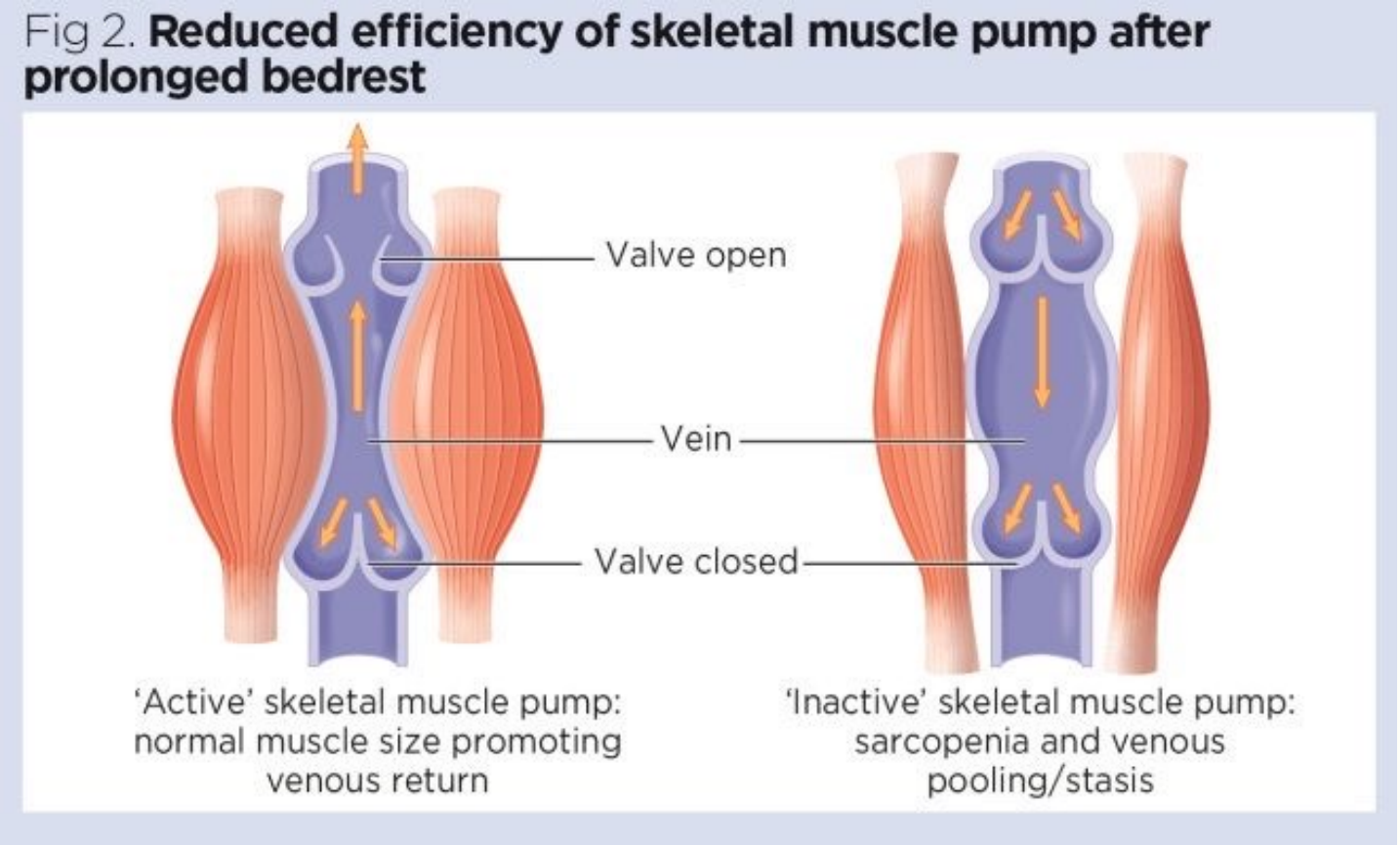


Image Source: *Source: Peter Lamb*
https://www.nursingtimes.net/clinical-archive/cardiovascular-clinical-archive/effects-of-bedrest-1-introduction-and-the-cardiovascular-system-26-11-2018/

https://www.grunge.com/1010307/the-british-military-guards-must-follow-proper-protocol-even-while-fainting/

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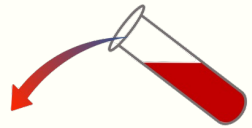
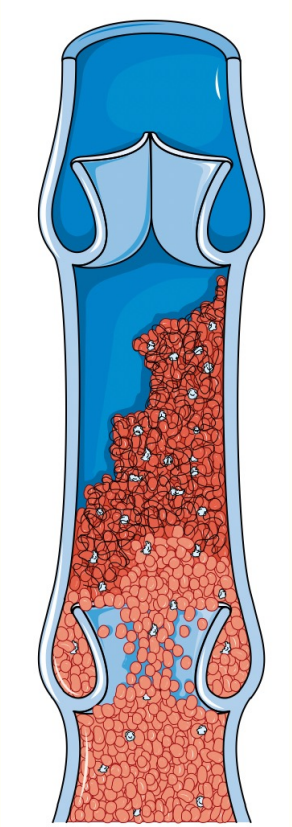


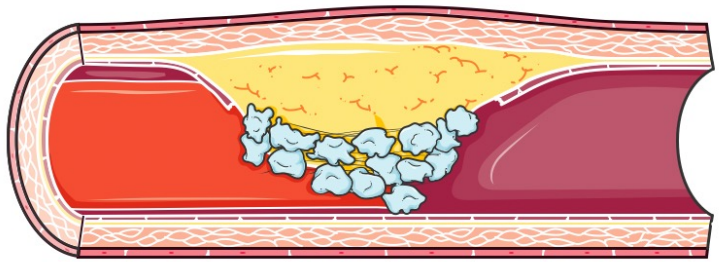
Venous Thrombosis

- "Red Clot"
- Abundant trapped red cells
- Tend to involve venous valves



Arterial Thrombosis

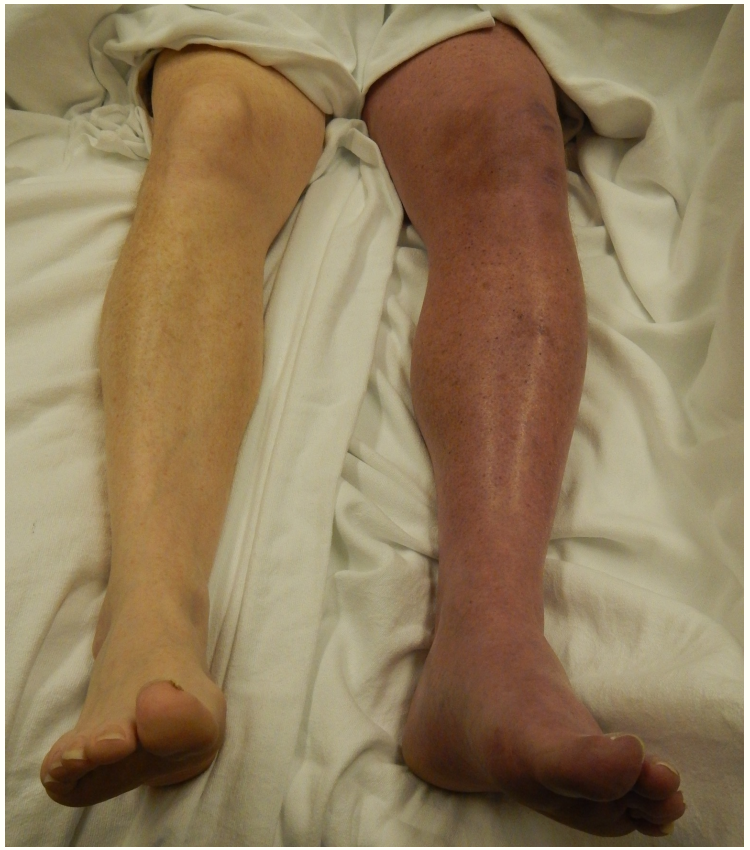
- "White Clot"
- Few red cells
- Tend to form on atherosclerotic plaque, especially following plaque rupture.
- Risk factors ~ risks of atherosclerotic Disease.



Deep Vein Thrombosis: 5 Signs of Inflammation of Galen

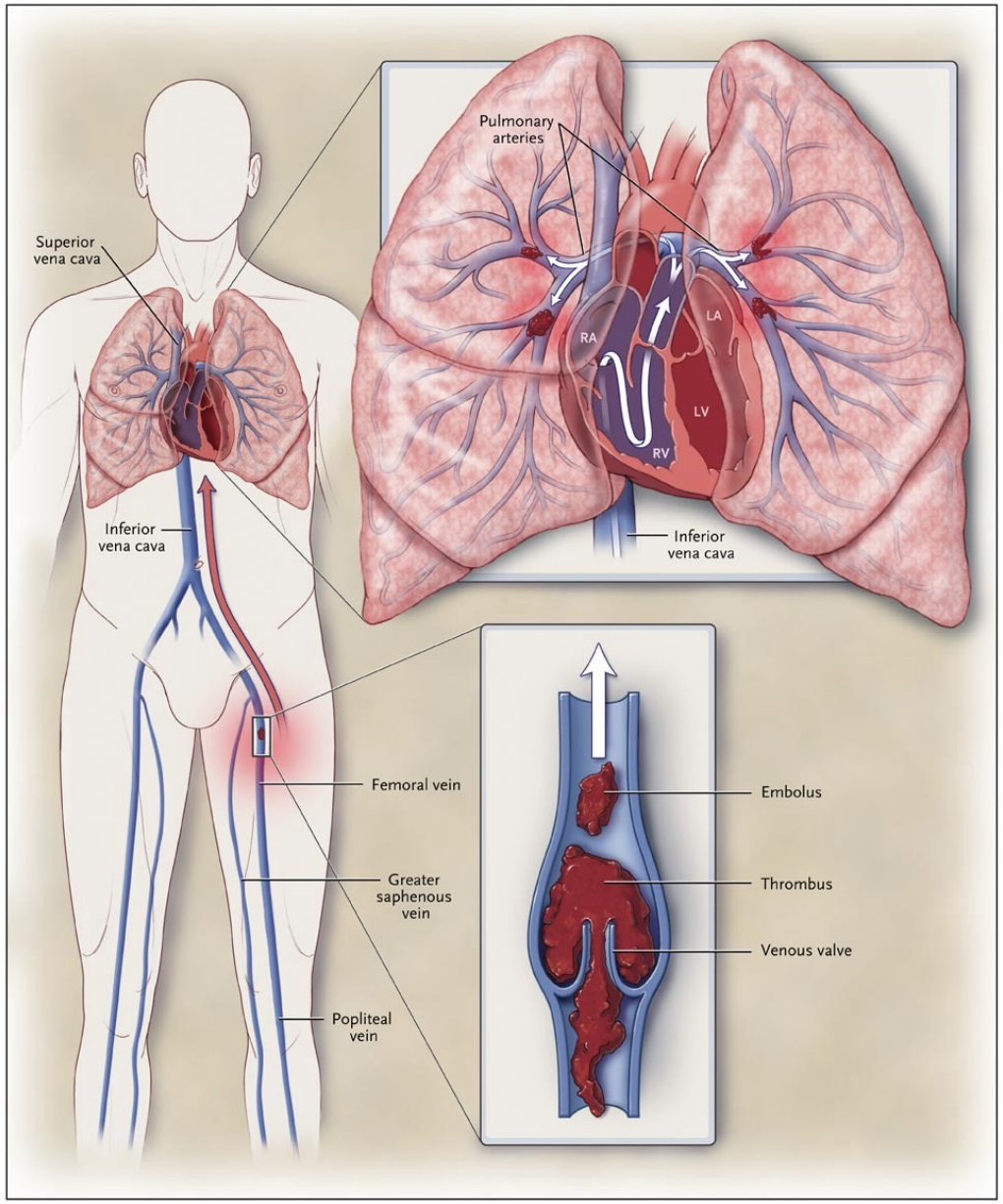
1. Rubor: Erythema
2. Tumor: Edema
3. Calor: Warmth
4. Dolor: Pain
5. Functio Laesa: loss of function

- However, many patients have minimal or no symptoms.
- High index of suspicion is essential in high-risk settings.



- https://commons.wikimedia.org/wiki/File:PCD2016.jpg
- James Heilman, MD, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons

Pulmonary Embolism



- Pulmonary embolism usually originates from the deep veins of the legs or pelvis.
- Venous thrombi predominantly originate in venous valve pockets and at other sites of presumed venous stasis (inset, bottom).
- If a clot propagates to the knee vein or above, or if it originates above the knee, the risk of embolism increases.
- Thromboemboli travel through the right side of the heart to reach the lungs.
  - Tapson VF. NEJM 2008;358:1037-1052.
- Sudden death is the first symptom in about one-quarter (25%) of people who have a PE.

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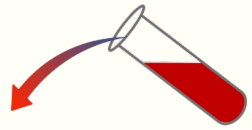
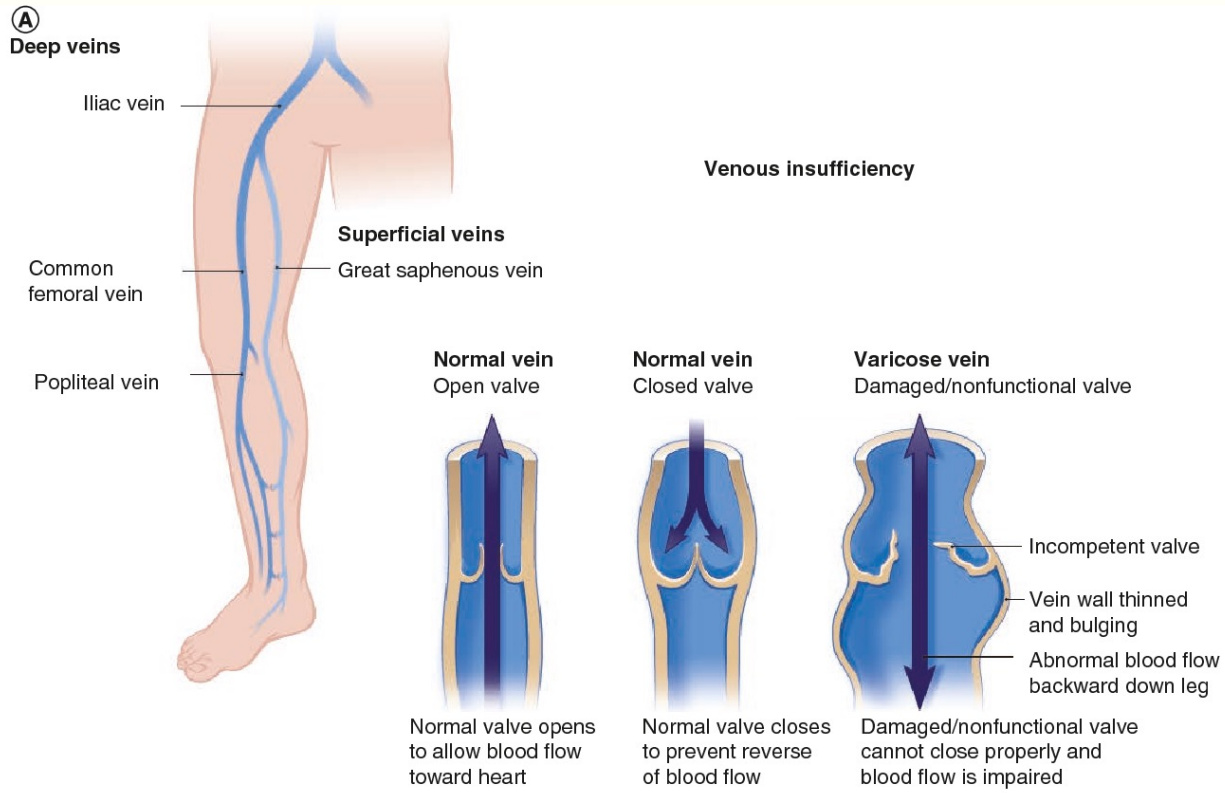


Post-Thrombotic Syndrome

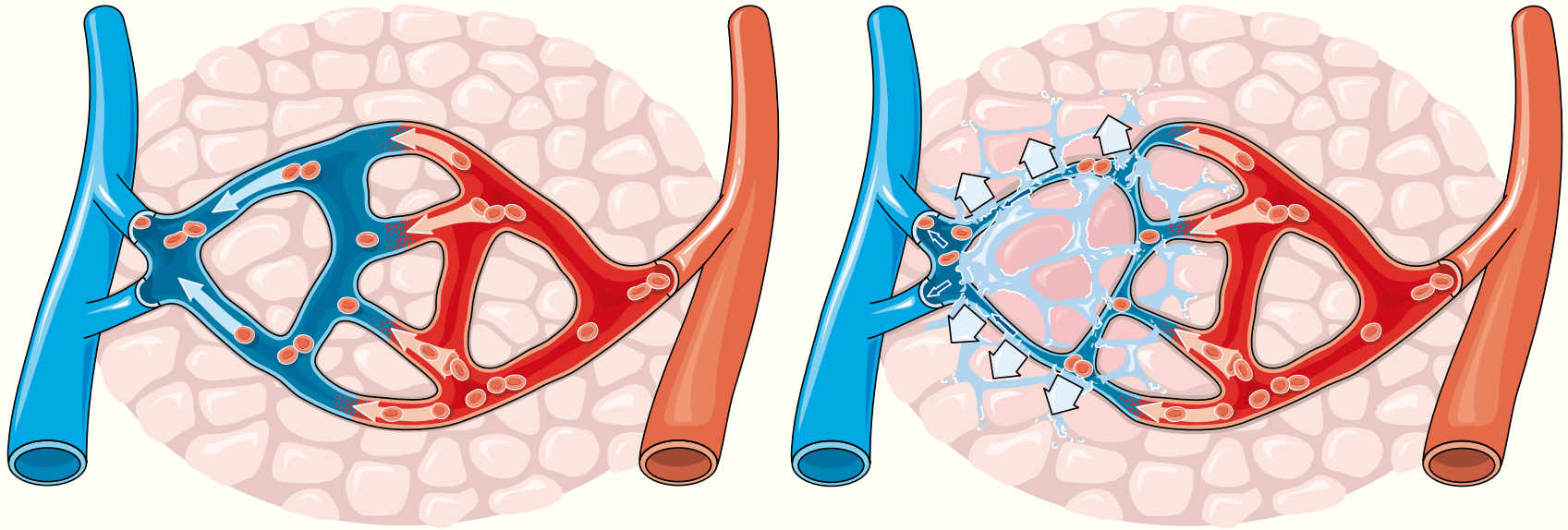
- Venous incompetence (Varicose veins)
- Due to destruction of venous valves associated with DVT.
- Decreased venous return increases extravascular pressure and decreased capillary blood flow, leading to tissue ischemia and venous ulcers.
- As much as half of patients will develop PTS after initial DVT.
- **Increased risk of recurrent VTE.**



https://www.semanticscholar.org/paper/Varicose-veins%3A-evaluating-modern-treatments%2C-with-Vandy-Wakefield/6c1e53cb135bc601e10ab15879d64bfd56418ecb

Tissue Breakdown From Post-Thrombotic Syndrome

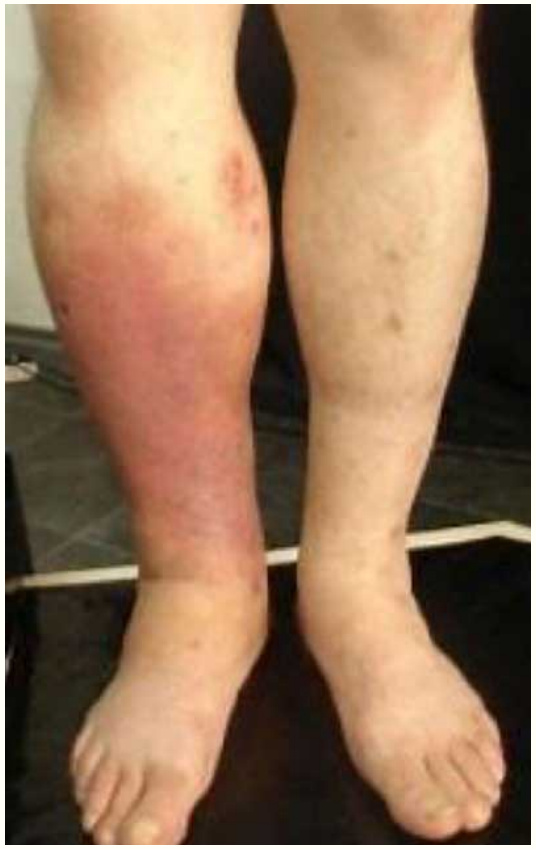
- Reduced venous return leads to tissue edema.
- Edema reduces capillary blood flow, reduced oxygen delivery.
- Tissue breakdown.



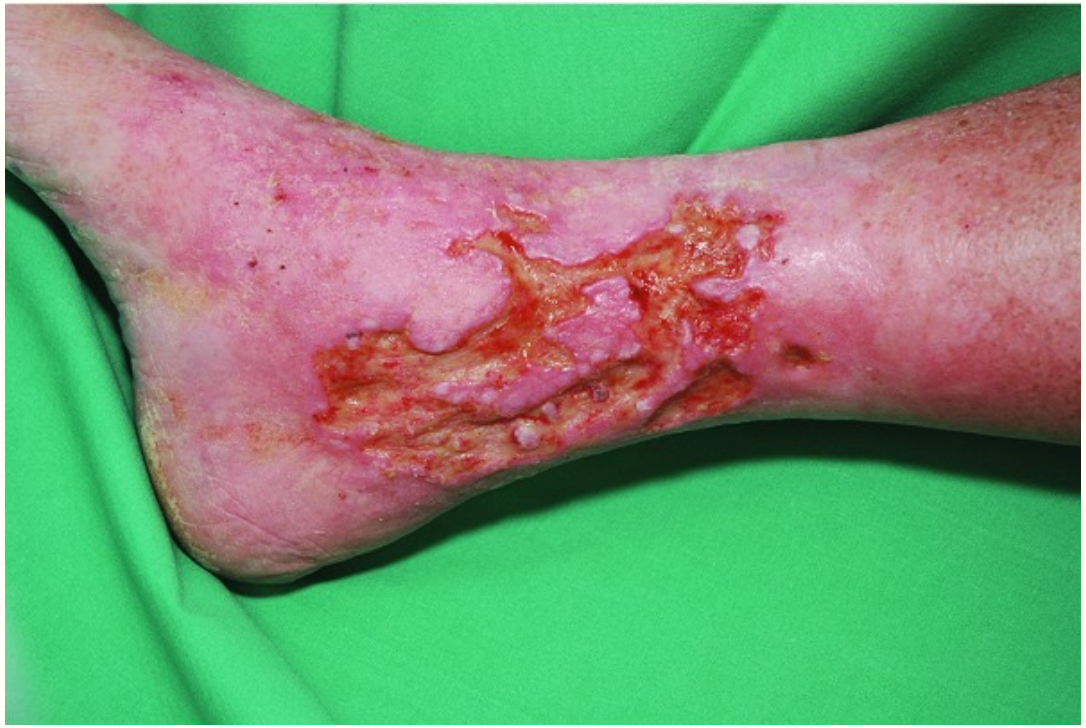
Normal capillaries

Edema formation

Post-Thrombotic Syndrome: Chronic Venous Insufficiency/Ulcers



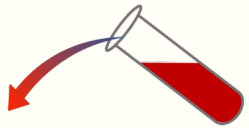
https://vasocare.com/conditions/post-thrombotic-syndrome/



JDDG: Journal der Deutschen Dermatologischen Gesellschaft, Volume: 15, Issue: 5, Pages: 538-556, First published: 09 May 2017, DOI: (10.1111/ddg.13242)

Compression therapy for prevention of post-thrombotic syndrome

- Overall, use of elastic compression stockings led to a clinically significant reduction in the incidence of PTS (risk ratio (RR) 0.62, 95% confidence interval (CI) 0.38 to 1.01; P = 0.05.
- "Low-quality evidence" suggests that compression stockings may reduce the occurrence of PTS after DVT.
  - Appelen et al, Compression therapy for prevention of post-thrombotic syndrome (Review)



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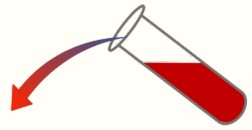
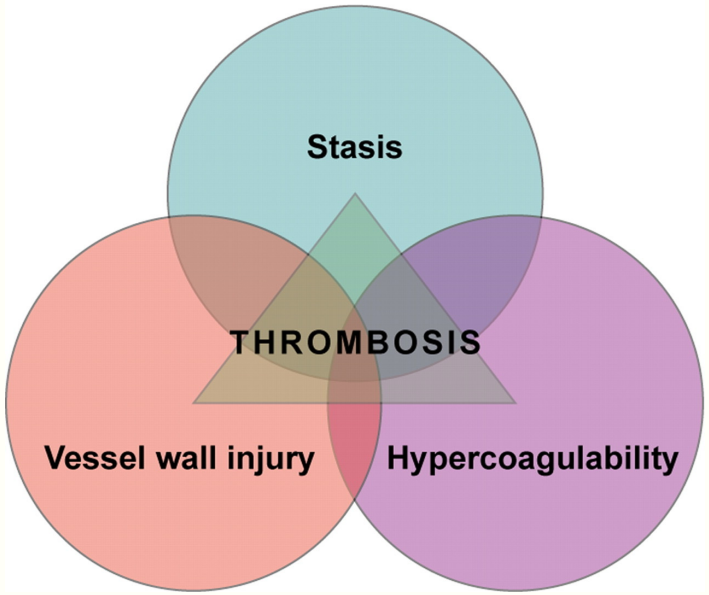


Virchow's Triad: Factors Contributing to Thrombosis

Rudolf Virchow
October 13, 1821 –
September 5, 1902

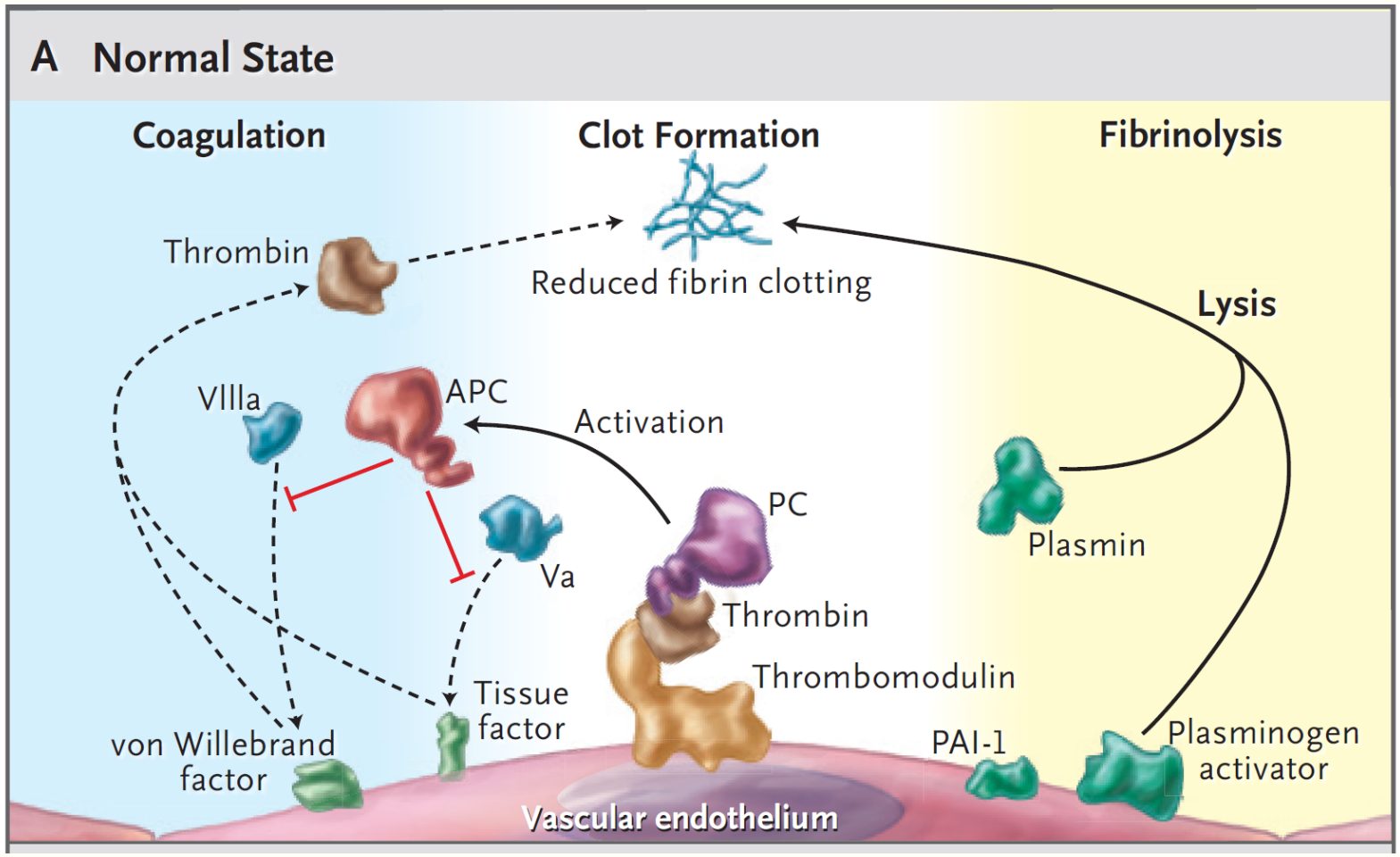
- **Altered Blood Flow/Venous stasis**
  - Immobilization
  - Obesity
  - Heart disease
- **Vessel wall damage**
  - Accidental trauma
  - Surgical trauma
  - Prior history of DVT
  - Advanced Age
- **Increase In Blood "Coagulability"**
  - Increase in tissue factor
  - Presence of activated factors
  - Decrease in coagulation inhibitors



Kyrle & Eichinger. Blood, 2009

WORLD THROMBOSIS DAY
OCTOBER 13

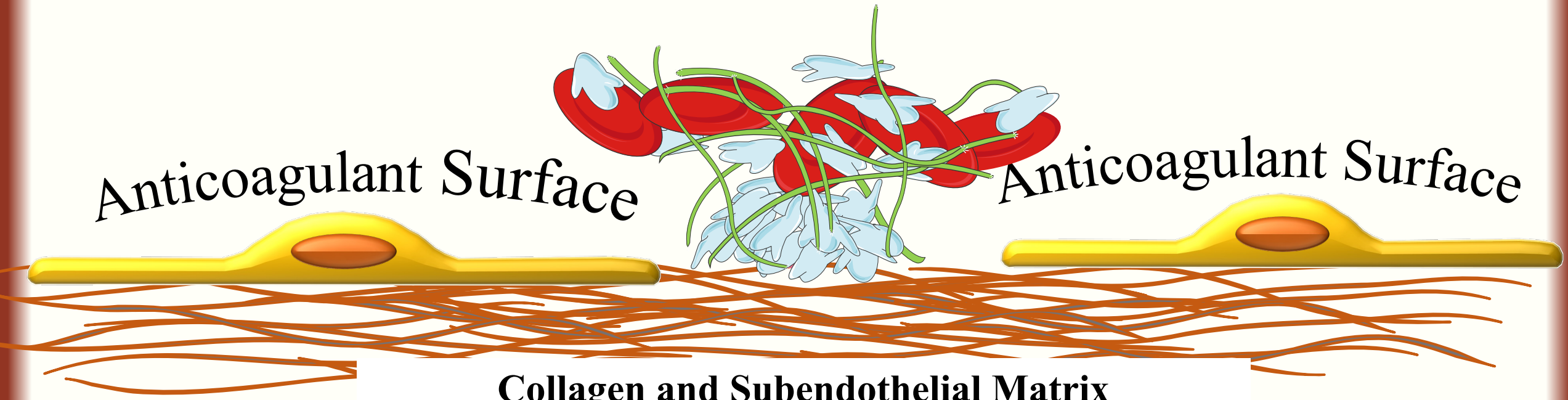
Normal Hemostatic Balance



N ENGL J MED 361;27 NEJM.ORG DECEMBER 31, 2009

Thrombophilia

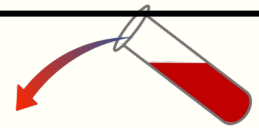
- Vascular endothelial cells present anticoagulant surface.
- Disruption of endothelial surface exposes blood to Collagen and Subendothelial Matrix (procoagulants) leading to activation of coagulation.
- Deficiency of physiologic anticoagulants leads to activation of coagulation.



Collagen and Subendothelial Matrix

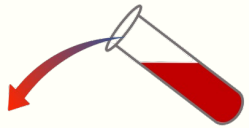
Physiologic Anticoagulation Processes on Endothelial Cells

Pathway	Activity	Effect
CD39-Ecto ADPase	Degrades ADP	Reduced ADP, reduced platelet activation
NO Synthase	Synthesis of Nitric Oxide	Relaxes smooth muscle and inhibits platelet activation
Cyclooxygenase 2	Synthesis of Prostacyclin (PGI2)	Relaxes smooth muscle and inhibits platelet activation
Heparan Sulfate (Glycosaminoglycan)	Heparan binds Antithrombin	Heparan:AT complex neutralizes coagulation enzymes
Thrombomodulin & Endothelial Protein C Receptor	Thrombomodulin binds Thrombin EPCR binds protein C	Thrombin:TM complex has reduced procoagulant activity. Activates protein C which inactivates Cofactors (FVa, FVIIIa)
Tissue Factor Pathway Inhibitor	TFPI inhibits direct activation of Factor X by TF:VIIa complex	



Inherited Thrombophilias

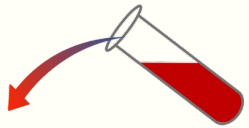
- Approximately 5 to 8% of the U.S. population has one of several genetic risk factors, also known as inherited thrombophilia, in which a genetic defect can be identified that increases the risk for thrombosis
- Most common are Factor V:Leiden and Prothrombin G20210A.
- Other hereditary thrombophilias are rare.
  - https://www.cdc.gov/ncbddd/dvt/data.html
  - Beckman et al. Am J Prev Med. 2010 Apr;38(4 Suppl):S495-501. doi: 10.1016/j.amepre.2009.12.017.



Established Inherited Thrombophilias: Mutations/Polymorphisms Create Coagulation Imbalance:

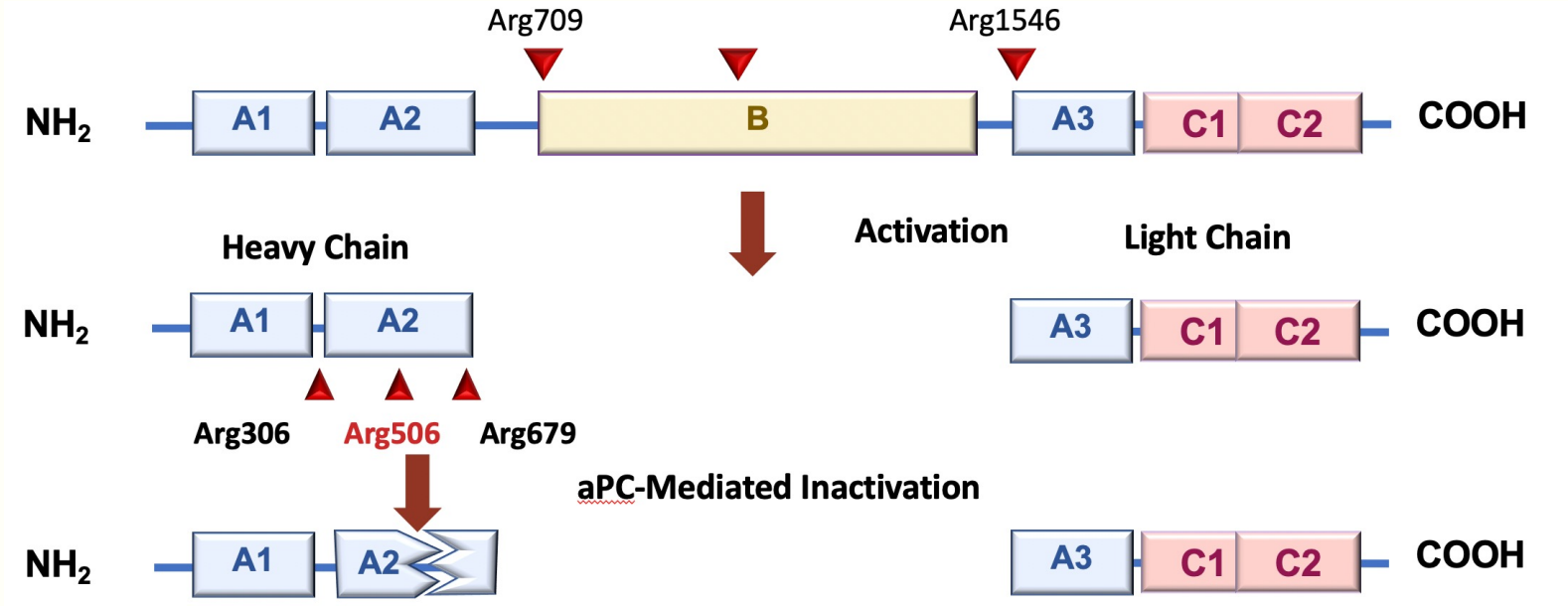
Increased procoagulant activity	Decreased anticoagulant activity

➢ **Factor V Leiden** polymorphism
  ➢ APC "resistance"
➢ **Prothrombin gene G20210A** polymorphism
  ➢ Increased prothrombin levels
	➢ **Protein C**: inactivates FVIII and FV
	➢ **Protein S**: cofactor for protein C
	➢ **Antithrombin**: inactivates thrombin, Xa, and other enzymes of the coagulation system.
	➢ Multiple mutations lead to decreased level or altered function (quantitative vs qualitative).



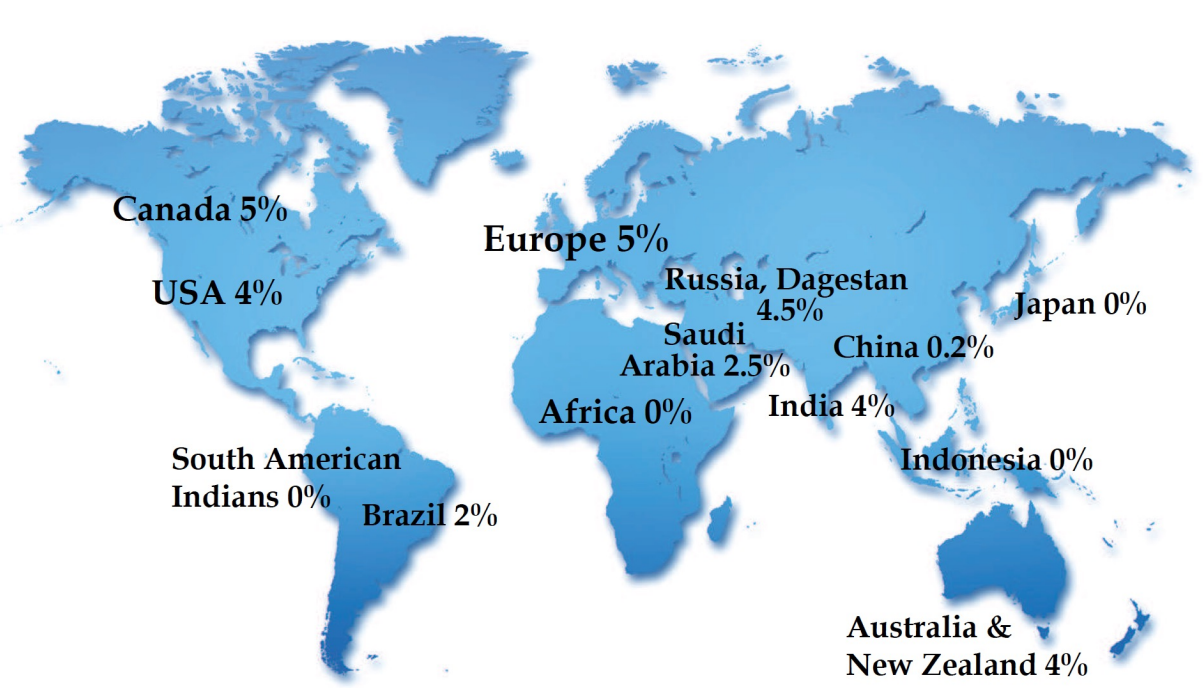
Factor V:Leiden: Activated Protein C Resistance

- Inactivation of Factor Va involves four sequential cleavages of the membrane-bound procofactor at Arg306, Arg506, Arg679, and Lys994.
- **Factor V:Leiden polymorphism (G1691A) (R506Q)** is associated with activated protein C resistance, prolonged/enhanced activity of Factor Va, and thrombotic tendency.



Factor V:Leiden: Activated Protein C Resistance

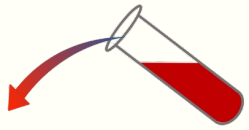
- Found predominantly in European populations (~7-8%), with ~1% in Indian subcontinent and Arabs.
- Heterozygotes (in isolation); ~5-fold increase risk in thrombosis.
- Homozygotes; ~ 50-fold increase in thrombotic risk.



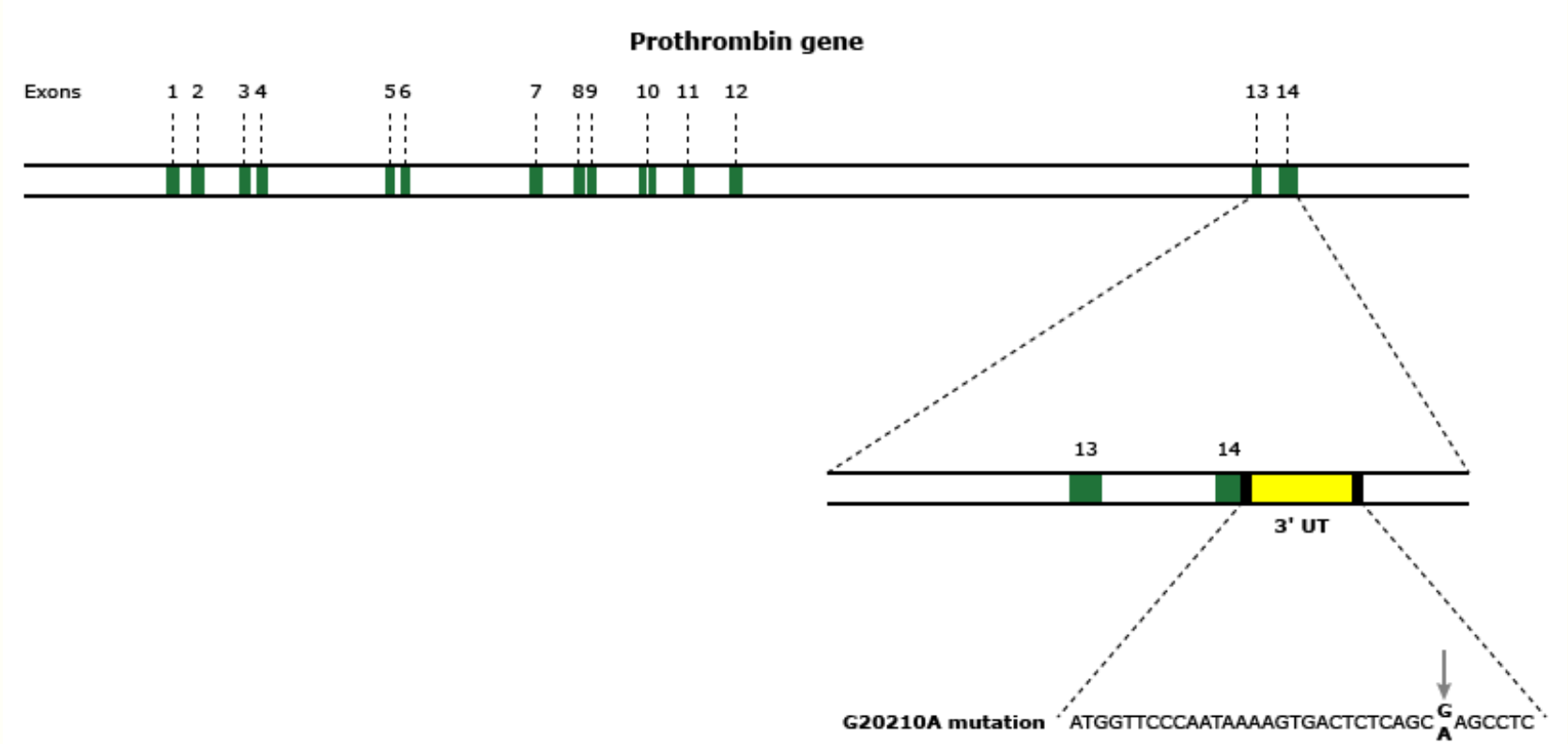
Jorine S. Koenderman and Pieter H. Reitsma (November 9th 2011). Inherited Thrombophilia: Past, Present, and Future Research, Thrombophilia, Andrea Luigi Tranquilli, IntechOpen, DOI: 10.5772/26050. Available from: https://www.intechopen.com/books/thrombophilia/inherited-thrombophilia-past-present-and-future-research

Prothrombin Gene Mutation: (Prothrombin G20210A)

- G → A point mutation at position 20210 in the 3' untranslated region of the prothrombin (factor II) gene.
- Genetic polymorphism associated with increased mRNA half-life and Prothrombin levels.
- ~ 3-fold increased risk of thrombosis.
  - Poort et al Blood. 1996;88(10):3698.
- ~1.7-3% % of population in Europe and European ancestry.
  - Rosendaal, F. R. et al. Thromb. Haemost. 79: 706-708, 1998.
- Arose approximately 24,000 years ago.
  - Zivelin et al. Blood 107: 4666-4668, 2006



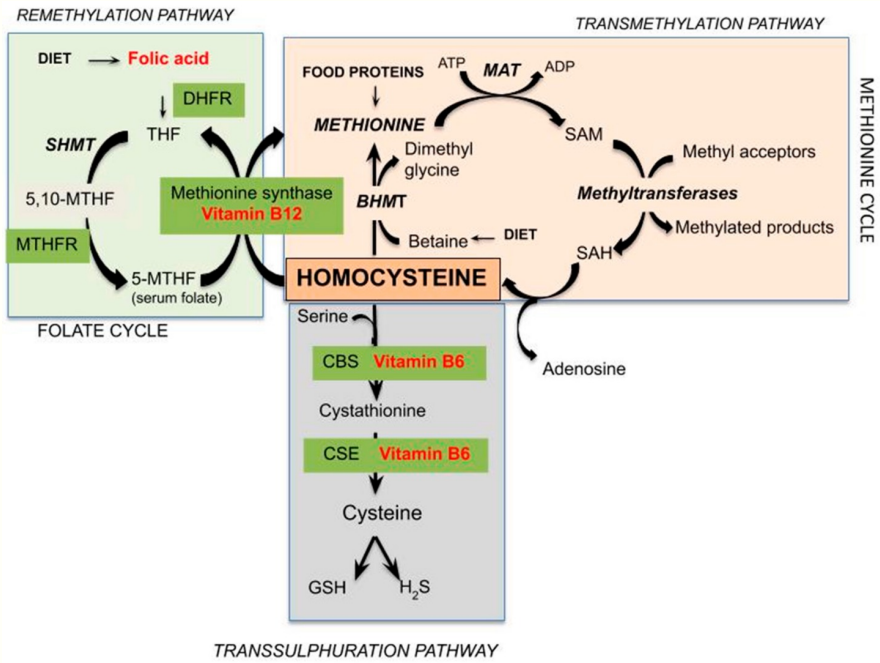
Prothrombin G20210A



The prothrombin G20210A mutation is a single G-to-A point mutation at position 20210 in the 3' untranslated region of the prothrombin (factor II) gene. The mutation does not affect the protein-coding region (exons) of the gene.
Dahlback B. Advances in understanding pathogenic mechanisms of thrombophilic disorders. Blood 2008; 112:19.

Homocysteine Metabolism

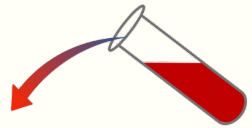
- Elevated Homocysteine levels associated with increased incidence of both arterial and venous thrombosis.
- **Cystathionine Beta Synthase(CBS) deficiency**. (Homocysteinuria)
  - Autosomal recessive, Severe congenital
  - Connective tissue, muscles, central nervous system (CNS), and cardiovascular system.
- **Methylene Tetrahydrofolate Reductase (MTHFR)**
  - Autosomal recessive. Milder form
  - Homocysteine (Hcy) levels only increased with concomitant deficiency of folic acid and other B-vitamins.
  - Hcy levels decreased with folic acid or combination vitamin therapy.
  - den Heijer et al. Arterioscler Thromb Vasc Biol. 18:356, 1998.



Azzini et al. Int. J. Mol. Sci. 2020, 21(4), 1421; https://doi.org/10.3390/ijms21041421

MTHFR/Homocysteine Association with VTE?

- It remains unresolved if there is an association of MTHFR homozygosity or mild to moderate homocysteine elevation and increased risk of VTE.
- Most contemporary guidance documents do not recommend testing for MTHFR or serum homocysteine levels in evaluation for hypercoagulability.
  - Bezemer, Arch Int Med 2007
  - Naess, BJH 2008

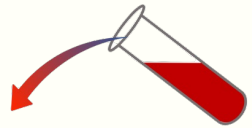


Coagulation Abnormalities Causing Inherited Thrombophilia and Associated RR of VTE.

Causes	Prevalence (%)	Relative risk of first venous thrombosis
Antithrombin deficiency	0.02	5–10
Protein C deficiency	0.2	4–6.5
Protein S deficiency	0.03–0.13	1–10
Factor V Leiden	3.0–7.0	3–5
Prothrombin G20210A	0.7–4.0	2–3

- **These are dominant traits.**
- **50% levels or heterozygous state is associated with thrombotic tendency.**

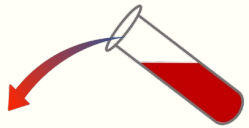
Middeldorp S. *Hematology Am Soc Hematol Educ Program* (2016) 2016 (1): 1–9 https://doi.org/10.1182/asheducation-2016.1.1



"Non-O Blood Type Is an Important Genetic Risk Factor for VTE"

- Non-O blood group, Odds Ratio of VTE: 2.1 – 2.5
  - Dentali et al. *Semin Thromb Hemost* 2012;38:535–548.
  - Franchini & Makris. *Blood Transfus*. 2013 Apr; 11(2): 164–165.

- ABO is associated with von Willebrand Factor (VWF) and coagulation Factor VIII plasma levels.
- While ABO Blood type is associated with thrombotic risk, it is not routinely considered in hypercoagulable workup, or impact on VTE management.



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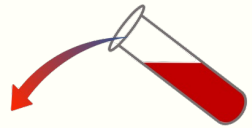
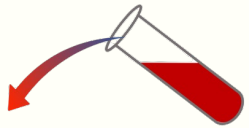


Acquired Thrombophilias

Disease-Based	Situational
➢ Antiphospholipid Syndrome * ➢ Malignancy * ➢ Myeloproliferative neoplasms ➢ Nephrotic syndrome ➢ Paroxysmal nocturnal hemoglobinuria	➢ Pregnancy * ➢ Obesity ➢ Exogenous estrogen ➢ Prior VTE ➢ Major Surgery ➢ Trauma ➢ Immobilization ➢ Venous catheters

* To be discussed in future presentations.

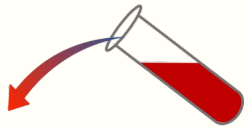


Multiplicative Effect of Risk Factors For Thrombosis

	Odds Ratio (95% CI)
Normal genotype without oral contraceptives	1 (Reference)
Normal genotype with oral contraceptives	4.6 (2.6–8.0)
Factor II:A20210 without oral contraceptives	2.7 (0.6–12.7)
Factor V:A1691 without oral contraceptives	2.4 (0.4–15.1)
Factor II:A20210 with oral contraceptives	16.3 (3.4–79.1)
Factor V:A1691 with oral contraceptives	20.0 (4.2–94.3)

- The Multiplicative Effect or synergy of risk factors holds true with acquired and hereditary factors.
- i.e. Oral contraceptives, pregnancy, surgery, medical illnesses, etc.

- Martinelli et al. Arteriosclerosis, Thrombosis, and Vascular Biology Volume 19, Issue 3, March 1999; Pages 700-703. https://doi.org/10.1161/01.ATV.19.3.700



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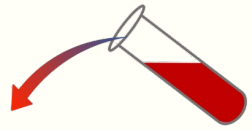


Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE)

Table 1. Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

Thrombosis at a young age (<50 yr), especially in association with weak provoking factors (minor surgery, combination oral contraceptives, or immobility) or unprovoked VTE
Strong family history of VTE (first-degree family members affected at a young age)
Recurrent VTE events, especially at a young age*
VTE in unusual sites such as splanchnic or cerebral veins†

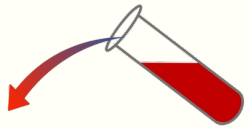
* The antiphospholipid syndrome must also be considered, but it is not inherited.
† Patients with splanchnic-vein VTE should be assessed for myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria.

Connors JM. N Engl J Med 2017;377:1177-1187

Molecular/Biochemical Risk Factors Of Thromboembolic Disease

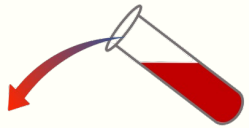
- **Common**
  - G1691A mutation in the factor V gene (**factor V Leiden**)
  - G20210A mutation in the prothrombin (**factor II) gene**
  - **Antiphospholipid Antibody Syndrome**
- **Rare**
  - **Antithrombin deficiency**
  - **Protein C deficiency**
  - **Protein S deficiency**
- **Very rare**
  - Dysfibrinogenemia/Alterations in fibrinolysis.

- Except for DNA analysis, do not work-up during acute event, pregnancy, oral contraceptives, acute medical/surgical illness.



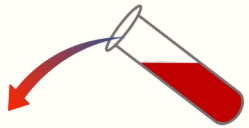
Thrombophilia Testing and Venous Thrombosis

- "After full-intensity anticoagulant therapy has been started, the next step in the management of VTE is to determine the duration of anticoagulation. **The role that thrombophilia status plays in this decision-making process is limited**…
- For patients with VTE who are found to have an inherited thrombophilia, it is the provoked or unprovoked nature of the VTE, not the thrombophilia, that drives decisions about the duration of anticoagulant therapy."
  - Connors. NEJM 2017; 377:1177-1187 DOI: 10.1056/NEJMra1700365
- **Identification of Antiphospholipid Antibody Syndrome may impact management.**



Acquired Protein S Deficiency

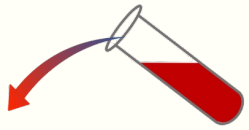
- Protein S circulates as free (~40%) and bound to C4b-binding protein (C4BP) (~60).
  - Free protein S is functionally active. Bound protein S is inactive.
- Estrogen and pregnancy increase levels of C4BP and therefore reduce levels of free protein S.



Thrombophilia Associated With About 50% Increased Risk of Recurrent VTE.

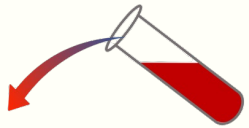
- Pooling all high-quality epidemiological data, the risk of recurrent VTE was increased by 46% in patients with heterozygous FVL mutation.
  - Eppenberger D. Et al. Front. Cardiovasc. Med., 07 April 2022, https://doi.org/10.3389/fcvm.2022.883986

- In a prospective cohort study following unselected patients with a first VTE, 85% of whom underwent inherited thrombophilia screening, VTE recurrence rates were not significantly different in those with or without inherited thrombophilia (HR, 1.50; 95% CI, 0.82-2.77).
  - Baglin, T. et al. Lancet 362, 523-526, 2003.



Antiphospholipid Antibody Syndrome

To be discussed in future lecture!



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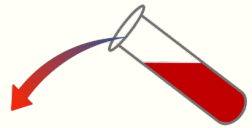
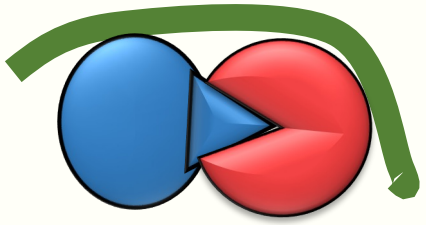
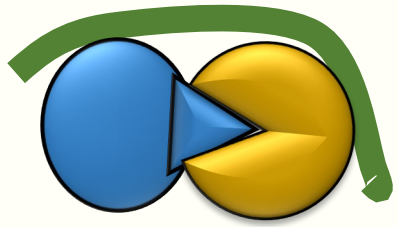


Heparin: "An Indirect Anticoagulant" Dependent of Antithrombin

Unfractionated Heparin

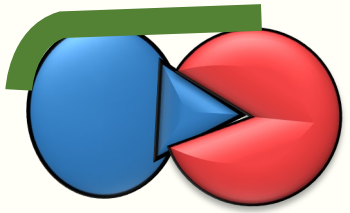


Factor Xa

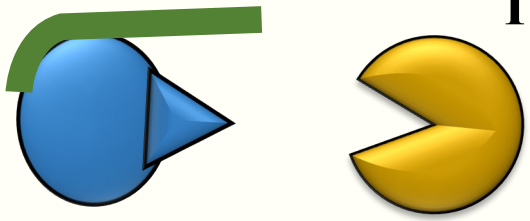


Thrombin

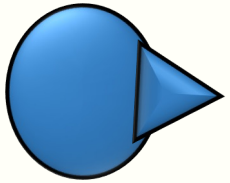
LMWH



Factor Xa



Thrombin

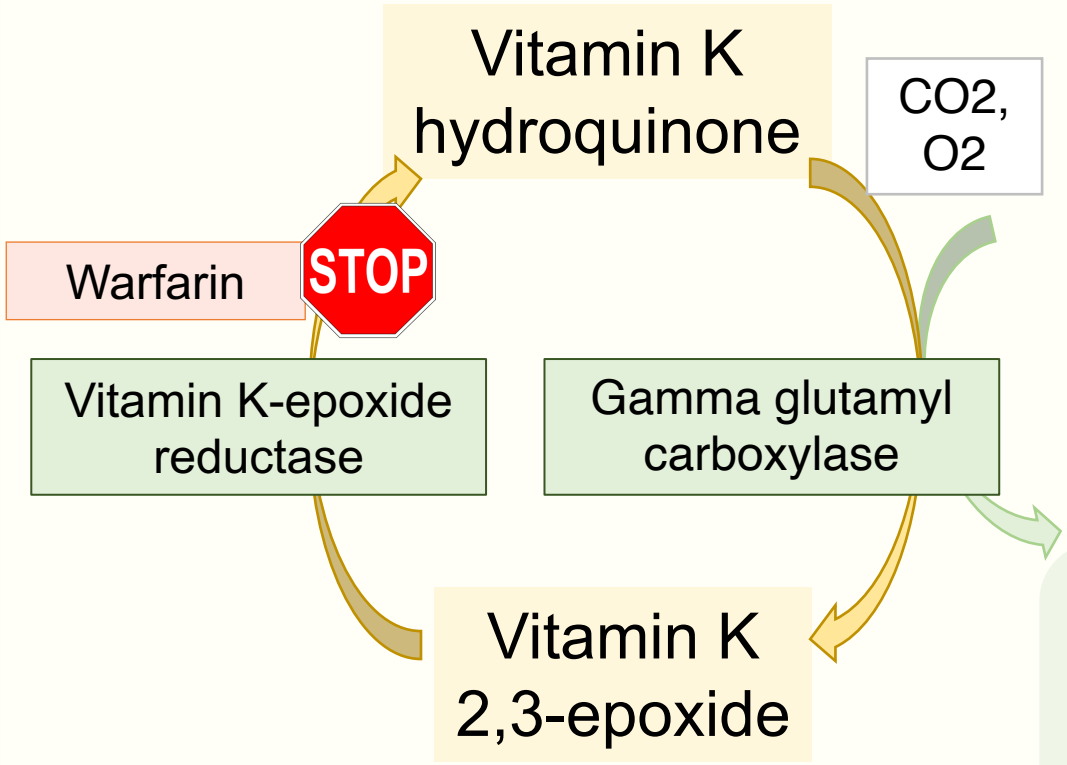


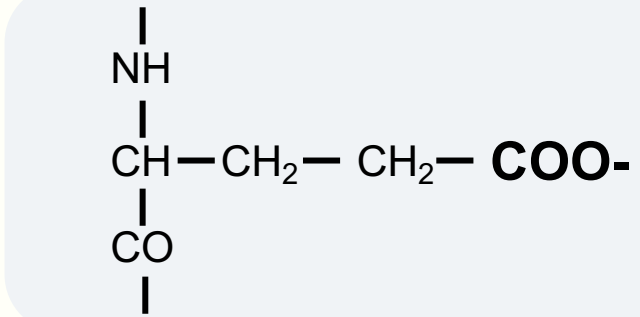
Antithrombin

Factor Xa

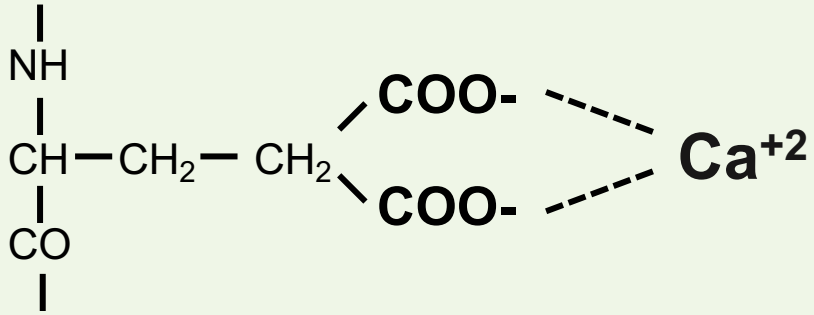
Thrombin

Vitamin K Mediated γ-Carboxylation of Glutamic Acid





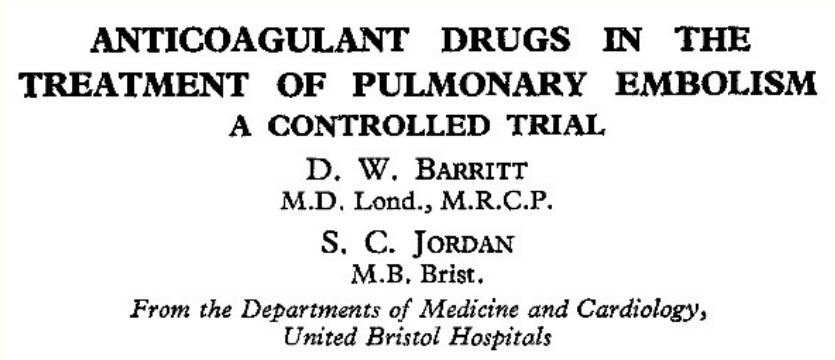
Glutamic Acid: Single negative charge



- **Vitamin K Antagonists reduce synthesis of coagulation factors (II, VII, IX, X, C, S), but does not "inhibit" function.**

Gamma-Carboxyglutamic Acid (Gla): Divalent negative charge. Can bind calcium

Management of Venous Thromboembolic Disease

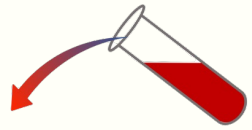


ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM
A CONTROLLED TRIAL

D. W. BARRITT
M.D. Lond., M.R.C.P.
S. C. JORDAN
M.B. Brist.
From the Departments of Medicine and Cardiology, United Bristol Hospitals

Lancet 1(7138): 1309-1312, 1960.

- Randomized, controlled study of anticoagulation versus no treatment.
- Med/Surg. patients with PE (based on history, physical exam, pulmonary infarction on CXR, and right heart strain on EKG).
- Treatment:
  - Heparin 10,000 units q 6 hours, for 6 doses without laboratory control.
  - Acenocoumarol (VKA) adjusted for Prothrombin Time
- *Established the paradigm of initial use of heparin (low molecular weight heparin) followed by vitamin K antagonist.*

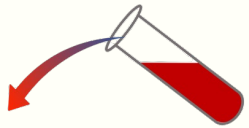


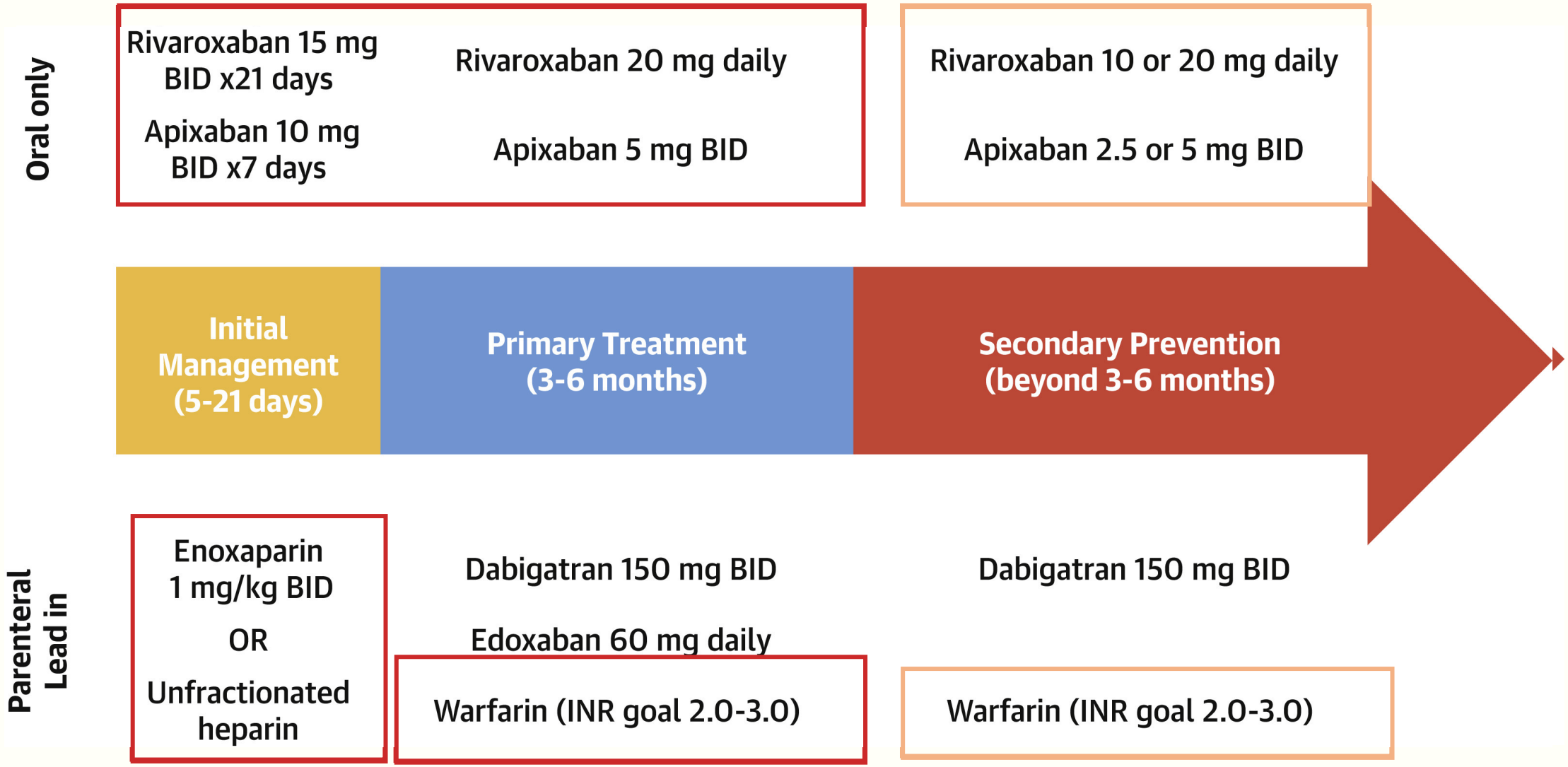
Management of Venous Thromboembolic Disease: Heparin/Warfarin

- Initial:
  - Unfractionated Heparin
    - Titrate to aPTT or anti-Actor Xa level
  - Low Molecular Weight Heparin: Enoxaparin
    - 1 mg/kg twice daily
    - 1.5 mg/kg once daily
  - Continue 5-7 days, until warfarin is therapeutic.

- Maintenance
  - Warfarin
  - Target INR of 2.0-3.0
    - (INR is derived from the Prothrombin Time)
  - May have transient hypercoagulable state when first started, due to suppression of Protein C prior to full anticoagulant effect.

Had not changed much in 50 years!





Elizabeth Renner, Geoffrey D. Barnes, Journal of the American College of Cardiology, Volume 76, Issue 18, 2020, Pages 2142-2154, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2020.07.070.

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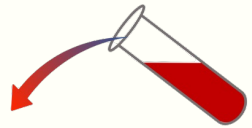
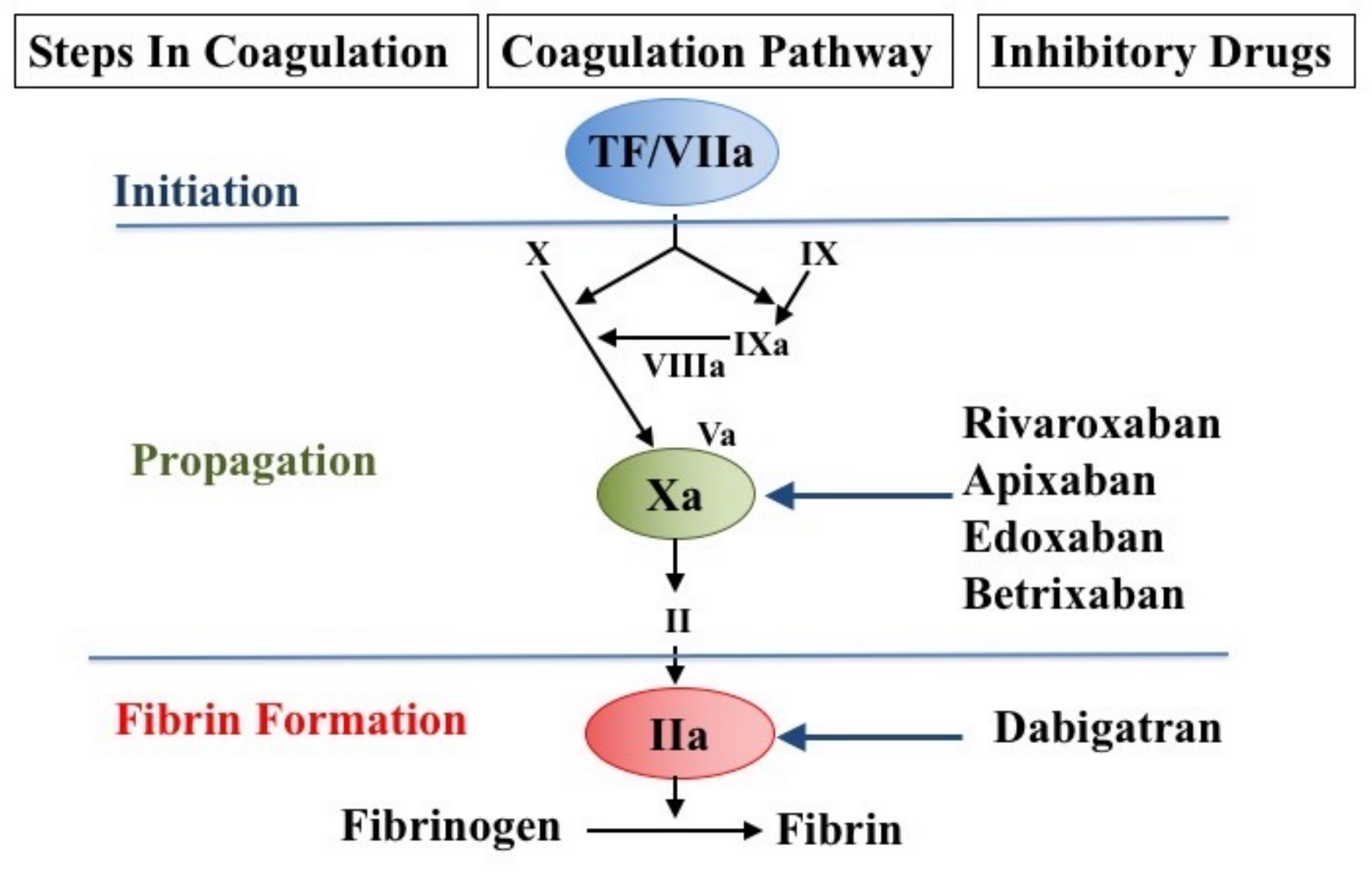
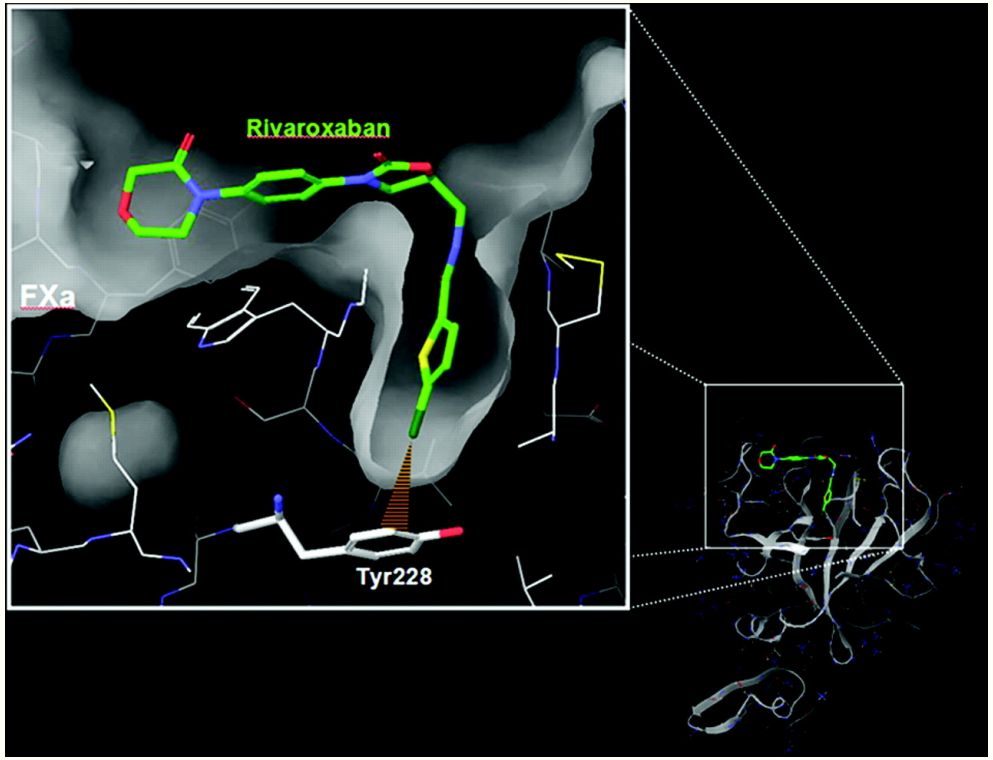




Adapted from Soff, Arteriosclerosis, Thrombosis, and Vascular Biology 2012, 32:569-574.

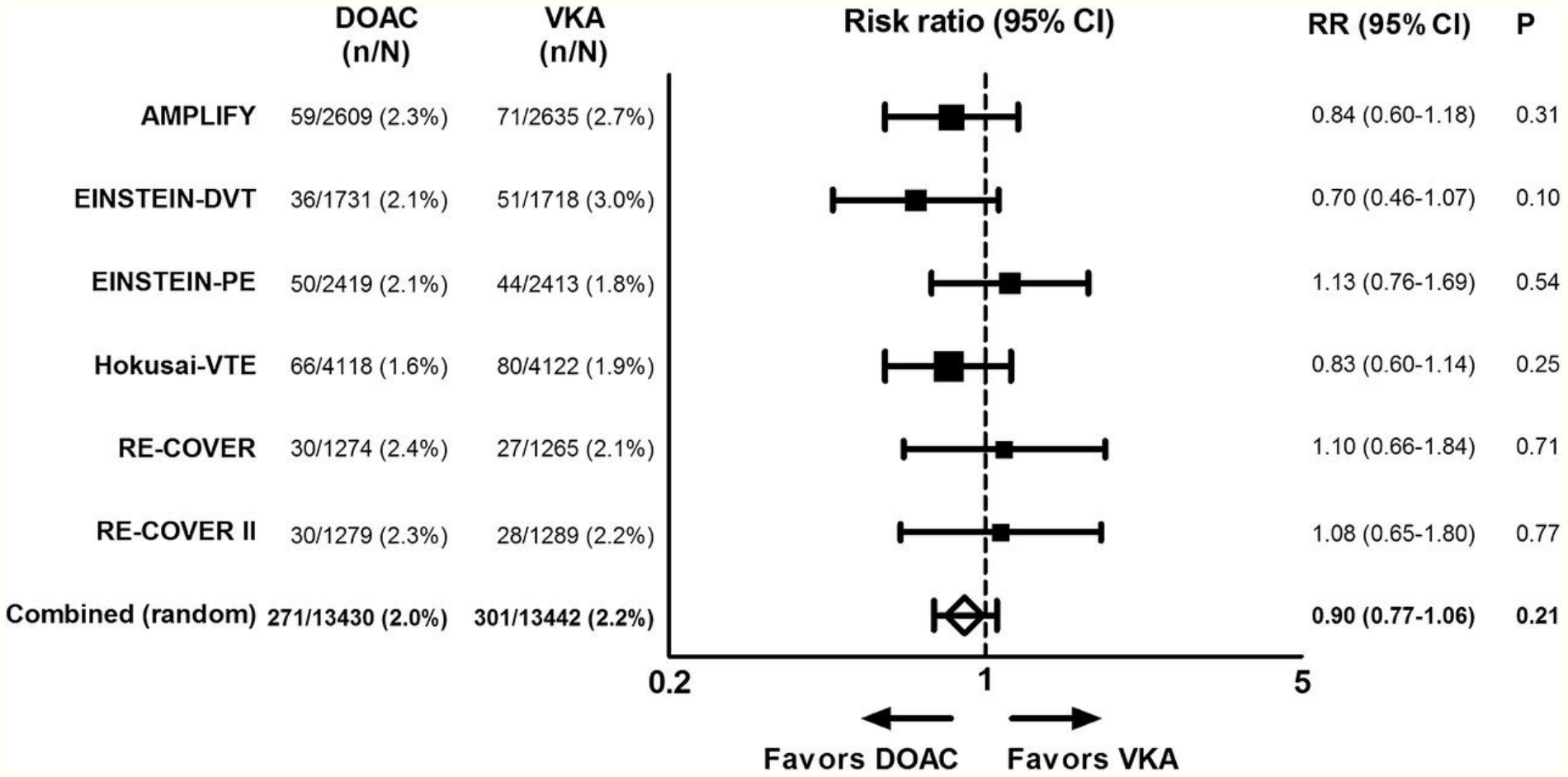
Direct Oral Anticoagulant (DOAC)

- Small molecules targeting the active site of a specific enzyme (Xa or IIa).
- Not dependent on a cofactor.
- Readily absorbed orally
- "Direct" anticoagulants in that they do not require the presence of a cofactor, such as antithrombin, for function.
  - Soff. Arterioscler Thromb Vasc Biol 2012, 32:569-574. doi: 10.1161/ATVBAHA.111.242834



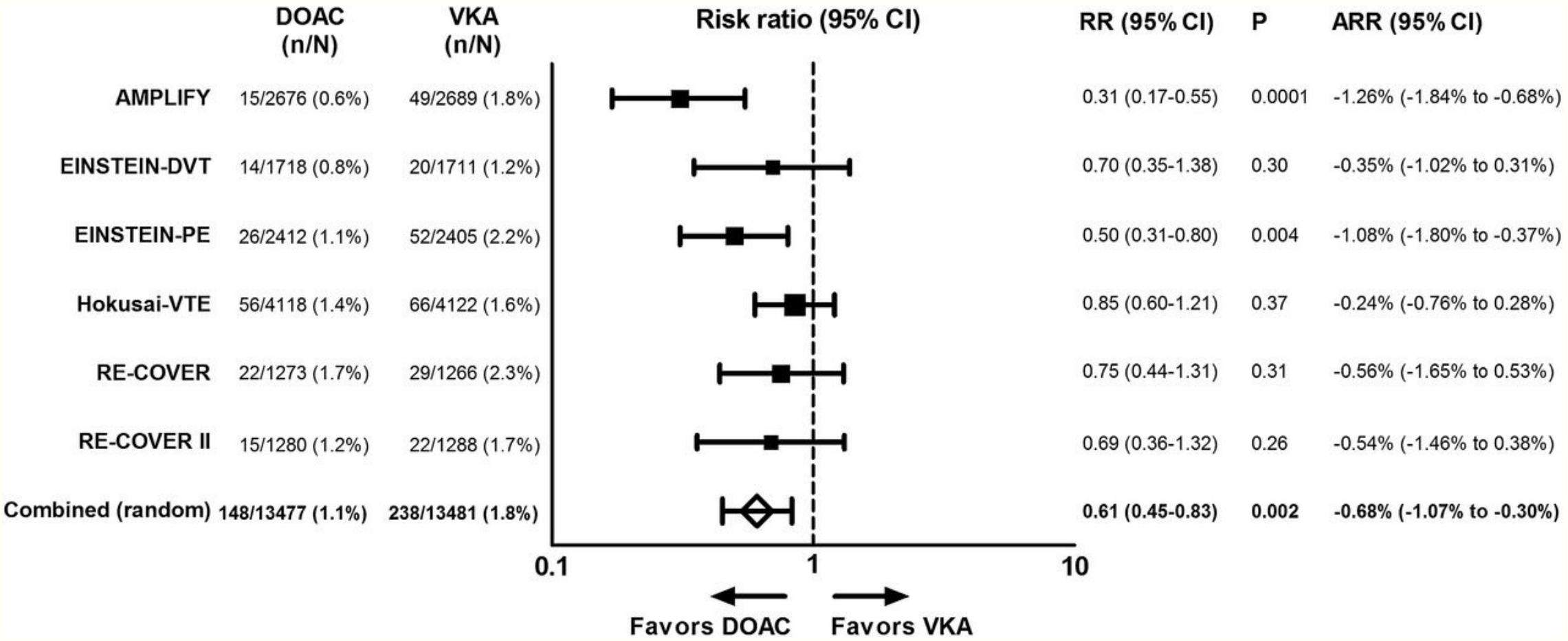
Perzborn E et al. Arterioscler Thromb Vasc Biol. 2010;30:376-381

First Recurrent VTE or VTE-Related Death



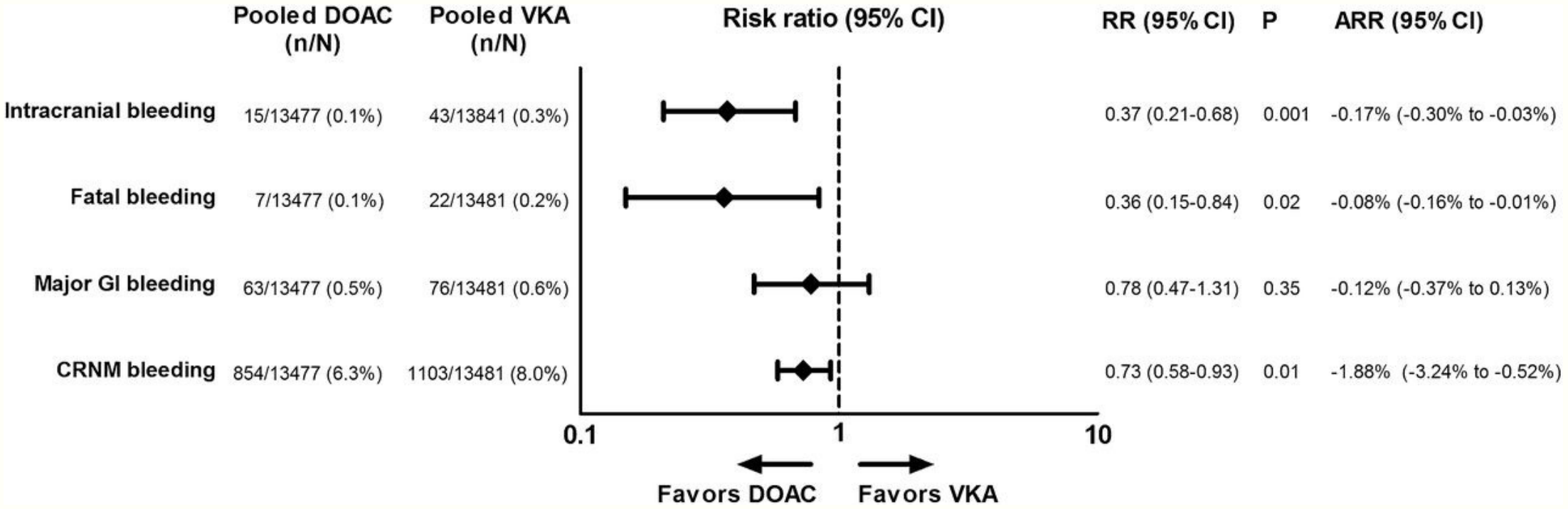
- Nick van Es et al. Blood 2014;124:1968-1975

Major Bleeding



- Nick van Es et al. Blood 2014;124:1968-1975

Intracranial, Major Gastrointestinal, Fatal, And Clinically Relevant Nonmajor Bleeding.



- Nick van Es et al. Blood 2014;124:1968-1975

- ***Mostly based on cancer literature, use of DOACs in patients with underlying GI or GU luminal pathology is associated with increased bleeding. Warfarin or maintenance LMWH may be preferable in those settings.***

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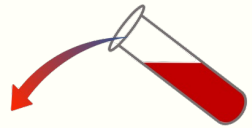
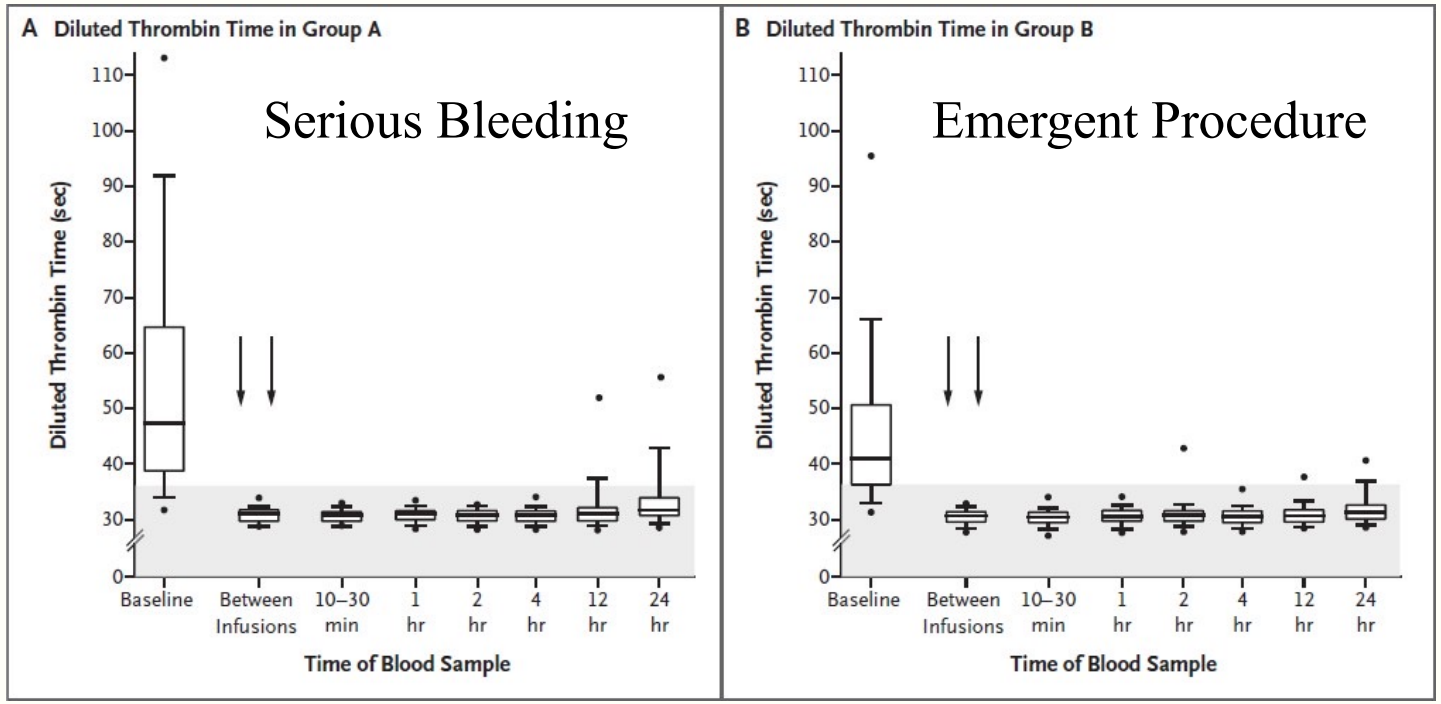
10. **Reversal of Anticoagulant Effect of DOAC**
11. How Long To Treat With Anticoagulation After VTE?

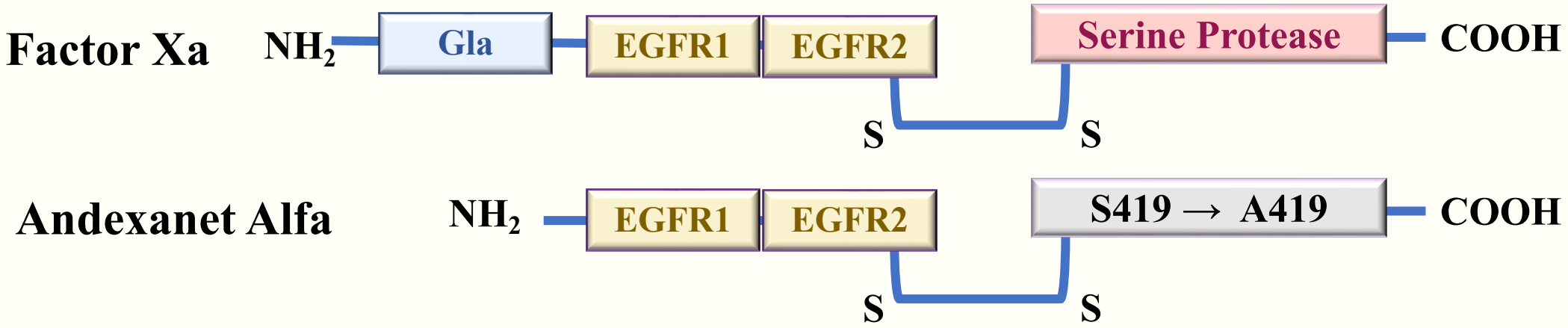


Idarucizumab for Dabigatran Reversal



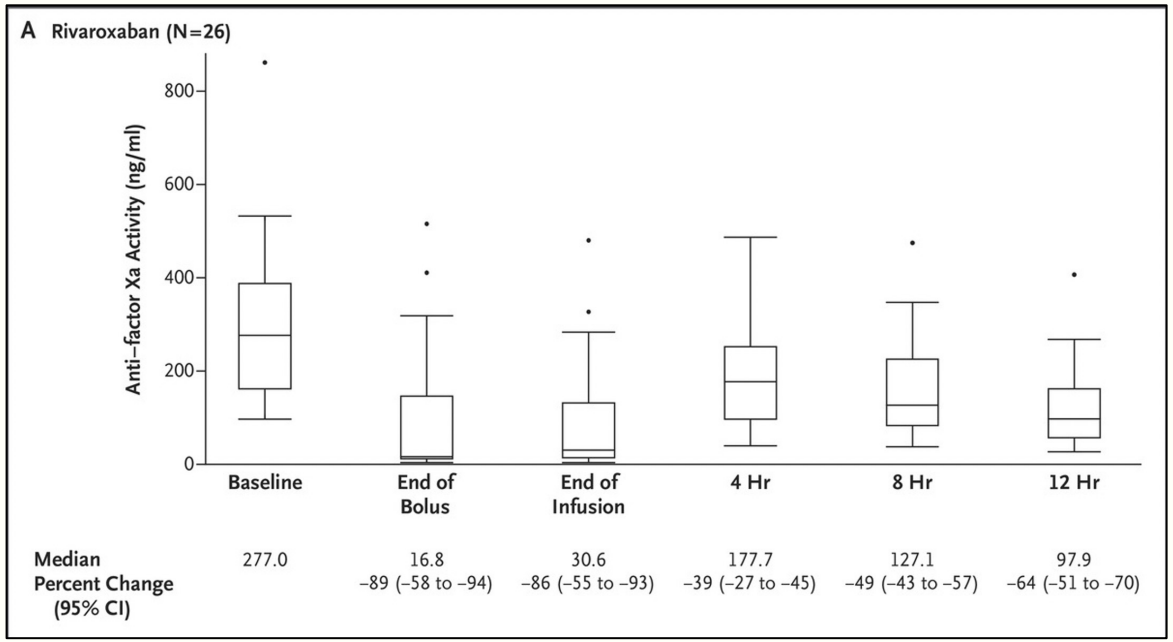
- Humanized anti-dabigatran FAb fragment.
- Two separate boluses of 2.5 g given no more than 15 min apart.
  - Pollack CV *et al*, N Engl J Med 2017.

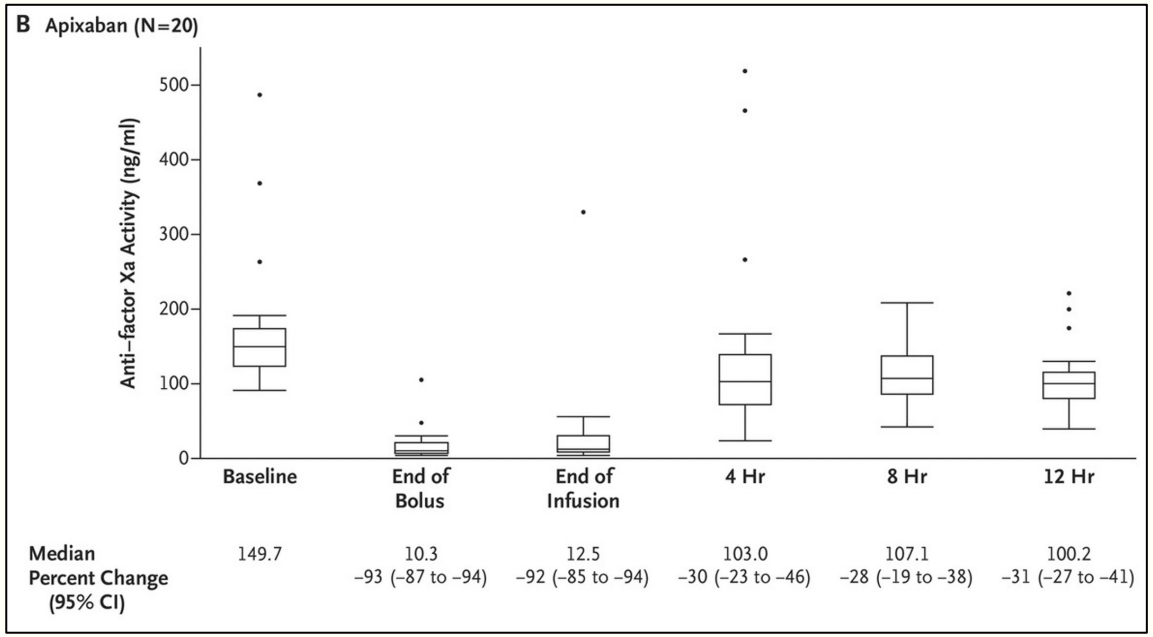
Andexanet Alfa: Reversal of Xa-DOACs



- Xa Decoy (Andexanet Alfa)
- "Decoy" Xa drug neutralizes the effect of anti-Xa agents
  - Inactive mimetic binds the anticoagulant
  - Serine, the active site of FXa, was substituted with alanine
  - The Gla domain of FXa was removed to prevent its assembly into the prothrombinase complex.

Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban





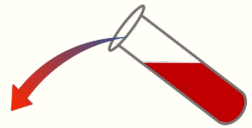
Connolly SJ et al. N Engl J Med 2016;375:1131-1141.

Recommend all patients on a DOAC wear medical alert bracelet!

Andexanet Versus Prothrombin Complex Concentrates

- In vitro studies indicate that Andexanet is more effective than 4-Factor prothrombin complex concentrate (KCentra ®) in reversing DOAC anticoagulation.
  - Lu et al. Res Pract Thromb Haemost. 2020;00:1–13.

- Advantage of PCC is cost.



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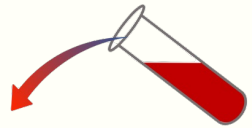
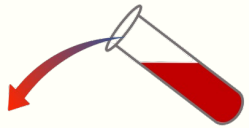


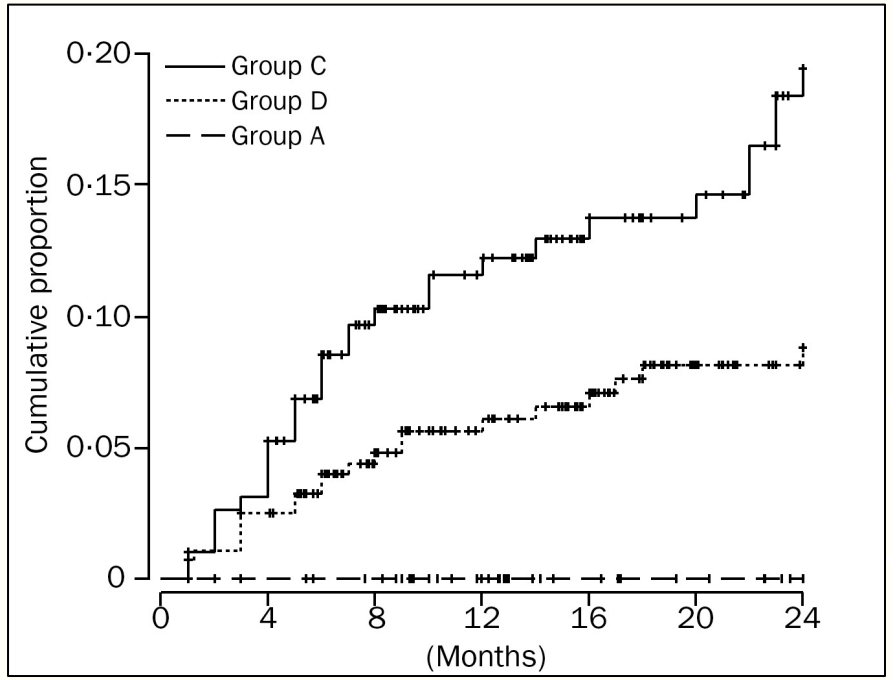
Risks for Recurrent VTE After Initial Unprovoked VTE:

- Post-Thrombotic Syndrome
- Obesity, BMI $\geq$ 30
- Older Age, Different studies, $\geq$ 50 Yr., $\geq$65 Yr.,
- Male

- Not routinely used:
  - Residual vein thrombosis. (Probably a surrogate for Post-Thrombotic Syndrome.)
  - Positive D-Dimer, one month after discontinuation of warfarin.



VTE Recurrence Rate as a Function of Provoking Factors



Unprovoked

Non-Surgical Provoked

Post-Operative Provoked

- Post-operative thrombosis have very low recurrence rate. (Removal of risk)
- Non-surgical triggers (Reduced risk)
- Unprovoked: No reduction in risk factors, presumably hereditary.
- Baglin et al. The Lancet. 362: 523-526, 2003.

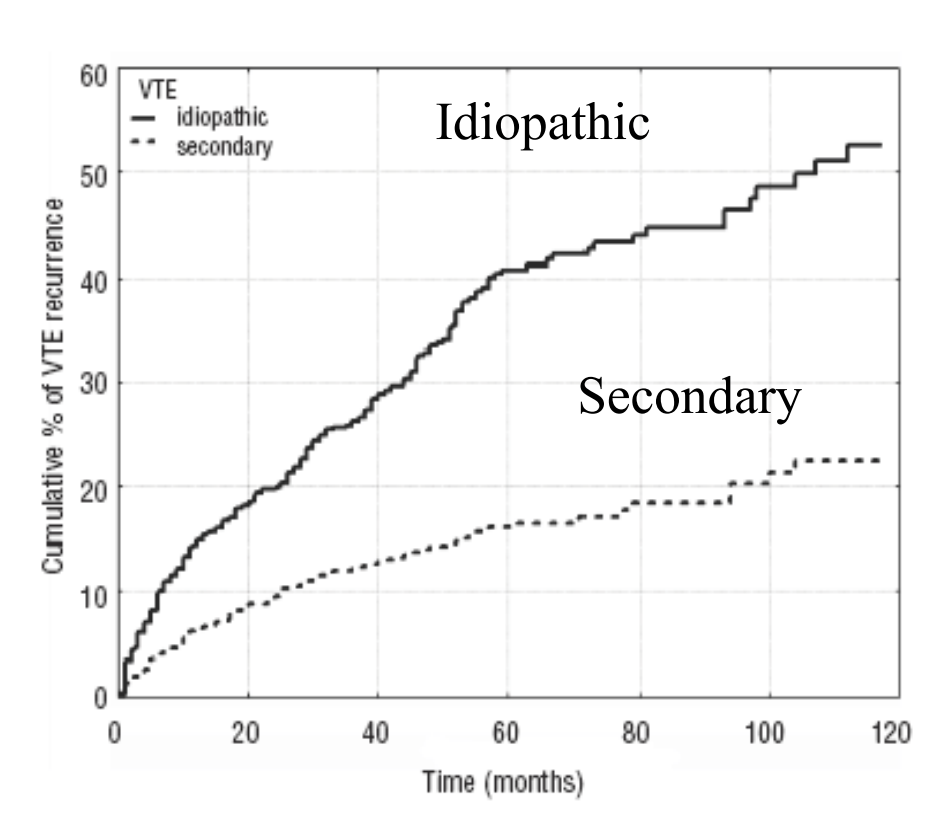
Duration of Anticoagulation

Provoked

- 3 months may be sufficient if risk factor has resolved.
- 1% risk per year of recurrence, not changed by 3 vs 6 months

Idiopathic

- Recurrence rate highest in first 2 years, but persists indefinitely.
  - 10% per year in 1st 2 years
  - 40% at 5 years



Prandoni *Haematologica* 2007

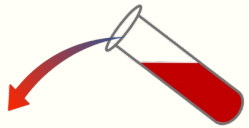
Duration of Anticoagulation

- Treatment duration is more difficult to determine in patients with VTE that don't fall neatly into the provoked or unprovoked category or occur in patients with continually present/non-modifiable VTE risk factors.

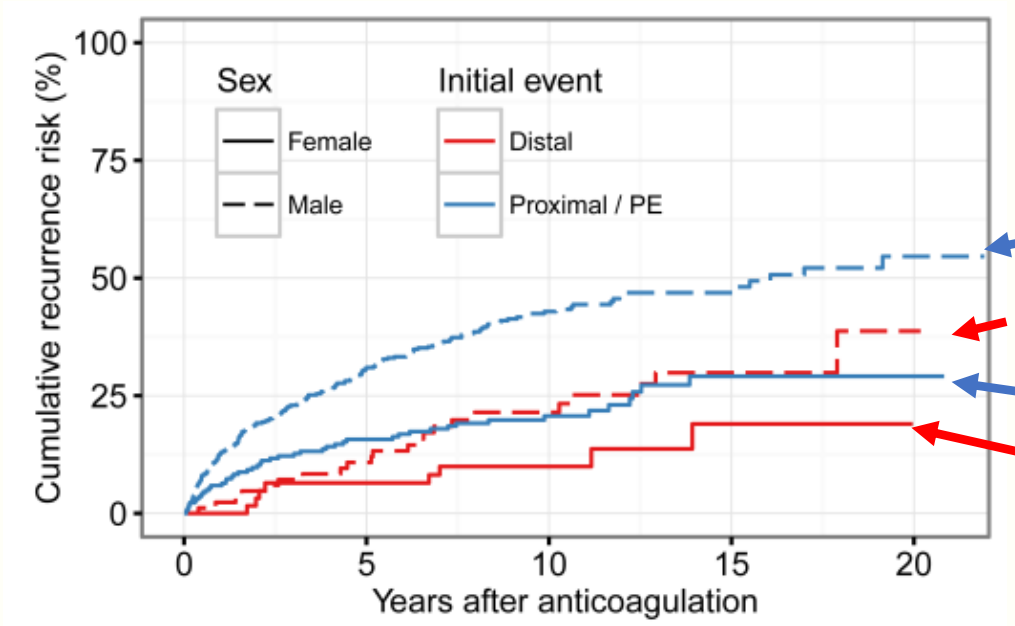
- 2019 ESC PE Guidelines:

"Terminology such as 'provoked' vs. 'unprovoked' PE/ VTE is no longer supported by the Guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation."

(European Heart Journal 2019)



Recurrence of VTE According to Site of First Event and Sex



Male, PE or proximal DVT

Male, Distal DVT

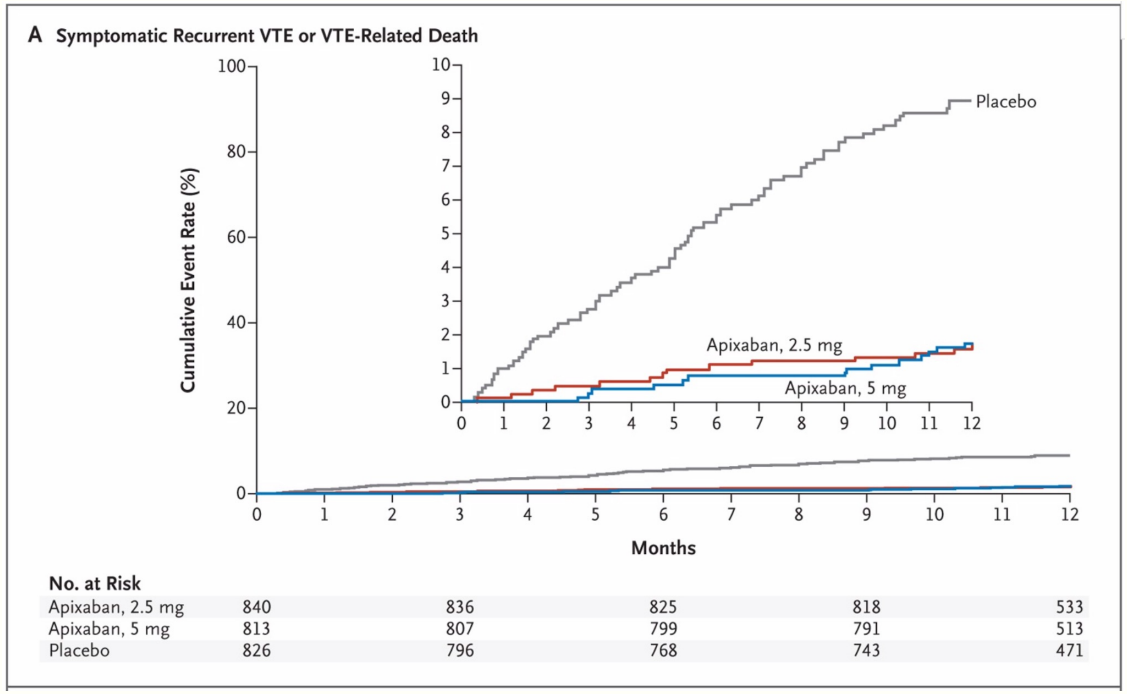
Female, PE or proximal DVT

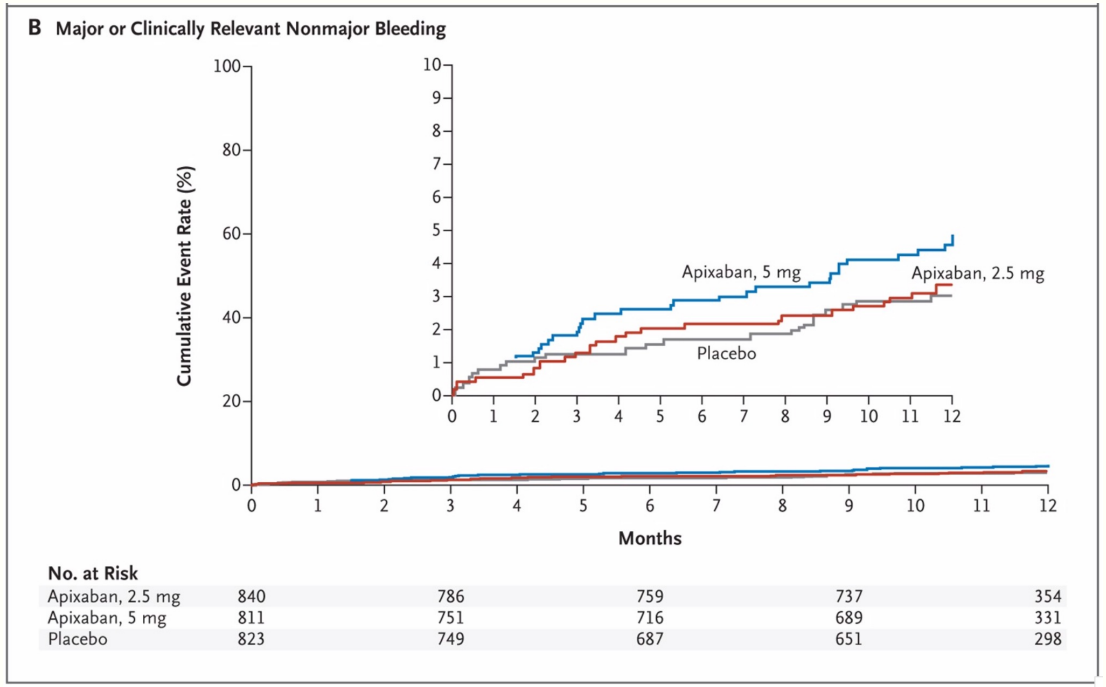
Female, Distal DVT

Kyrle, JTH, 2017

Extended Prophylaxis: Apixaban

- Compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy.





Agnelli G et al. NEJM 2013;368:699-708.

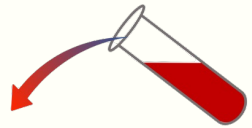
Rivaroxaban versus Aspirin For Extended Thrombosis Secondary Prophylaxis

- Patients with VTE, completed 6-12 months of anticoagulation.
- Randomized to:
- Rivaroxaban 20 mg daily
- Rivaroxaban 10 mg daily
- ASA 100 mg daily

	Riva 20 mg	Riva 10 mg	ASA
Symptomatic recurrent VTE	**1.5% ***	**1.2% ***	**4.4%**
Major Bleeding	**0.5%**	**0.4%**	**0.3%**
CRNMB	**2.7%**	**2.0%**	**1.8%**

*** P<0.001**

Weitz et al, NEJM 2017;376:1211-22.



EINSTEIN-CHOICE

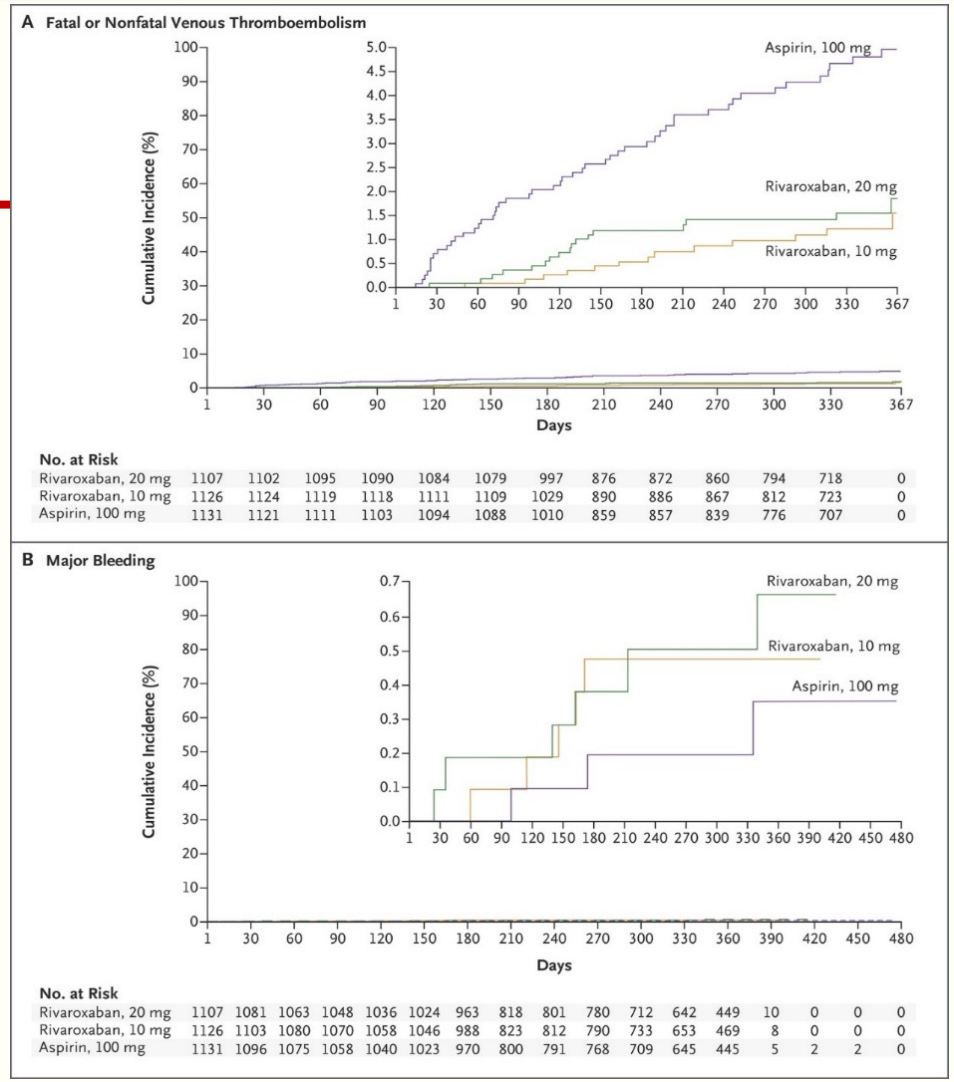
EINSTEIN Choice

3,364 participants

60% provoked

40% unprovoked

Patients in equipoise for need to continue anticoagulation.

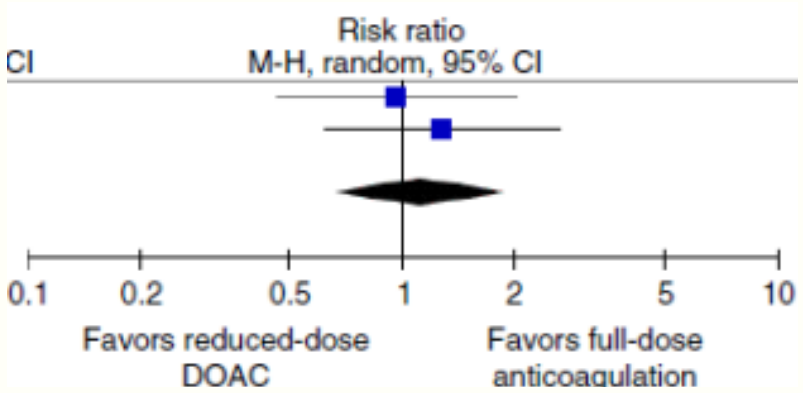


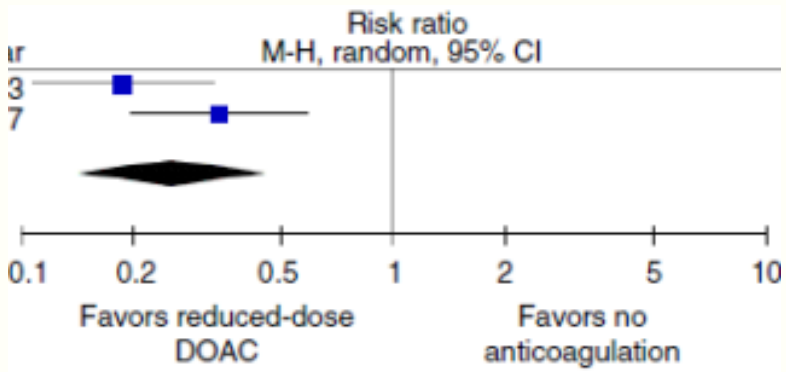
Kaplan–Meier Cumulative Event Rates

Weitz NEJM 2017

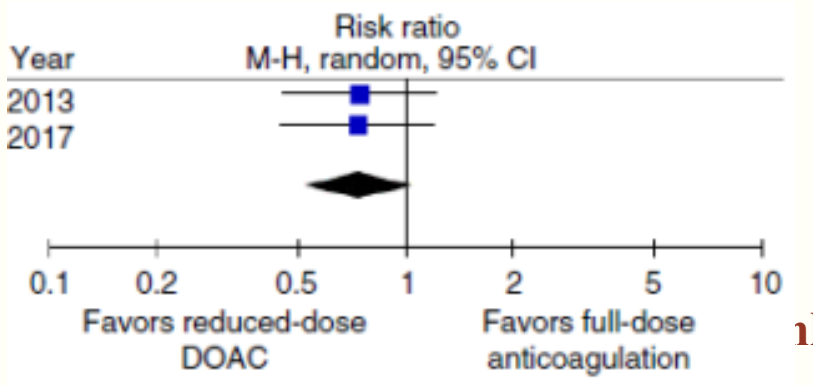
Meta-analysis: which is more important for your patient?

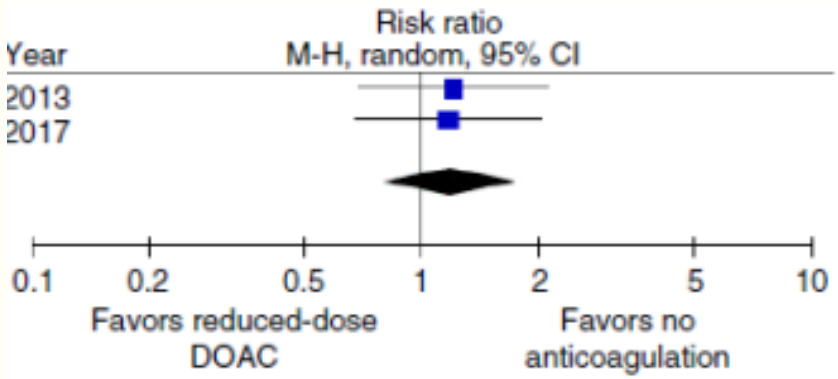
Preventing recurrent VTE?





Preventing major and CRNM Bleeding?





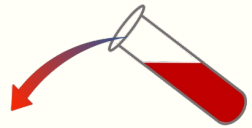
Vasanthamohan
JTH 2018

Extended Duration Anticoagulation

- **After full intensity anticoagulation for unprovoked VTE consider change to reduced dose apixaban or rivaroxaban.**

- **For provoked VTE with persistent risks and for patients in equipoise, switch to reduced dose apixaban or rivaroxaban**
  - Unclear provoking factors
  - Post thrombotic syndrome or significant persistent residual vein thrombosis
  - Obesity, heart failure, immobile
  - No contraindication to DOAC use

- **Patients who should not be on reduced dose**
  - Antiphospholipid syndrome
  - Mechanical heart valves (should not be on a DOAC)
  - Atrial fibrillation
  - Cancer? Trials of reduced dose apixaban in progress




"That's all Folks!"