Heparin vs DOACs in the Management of PE

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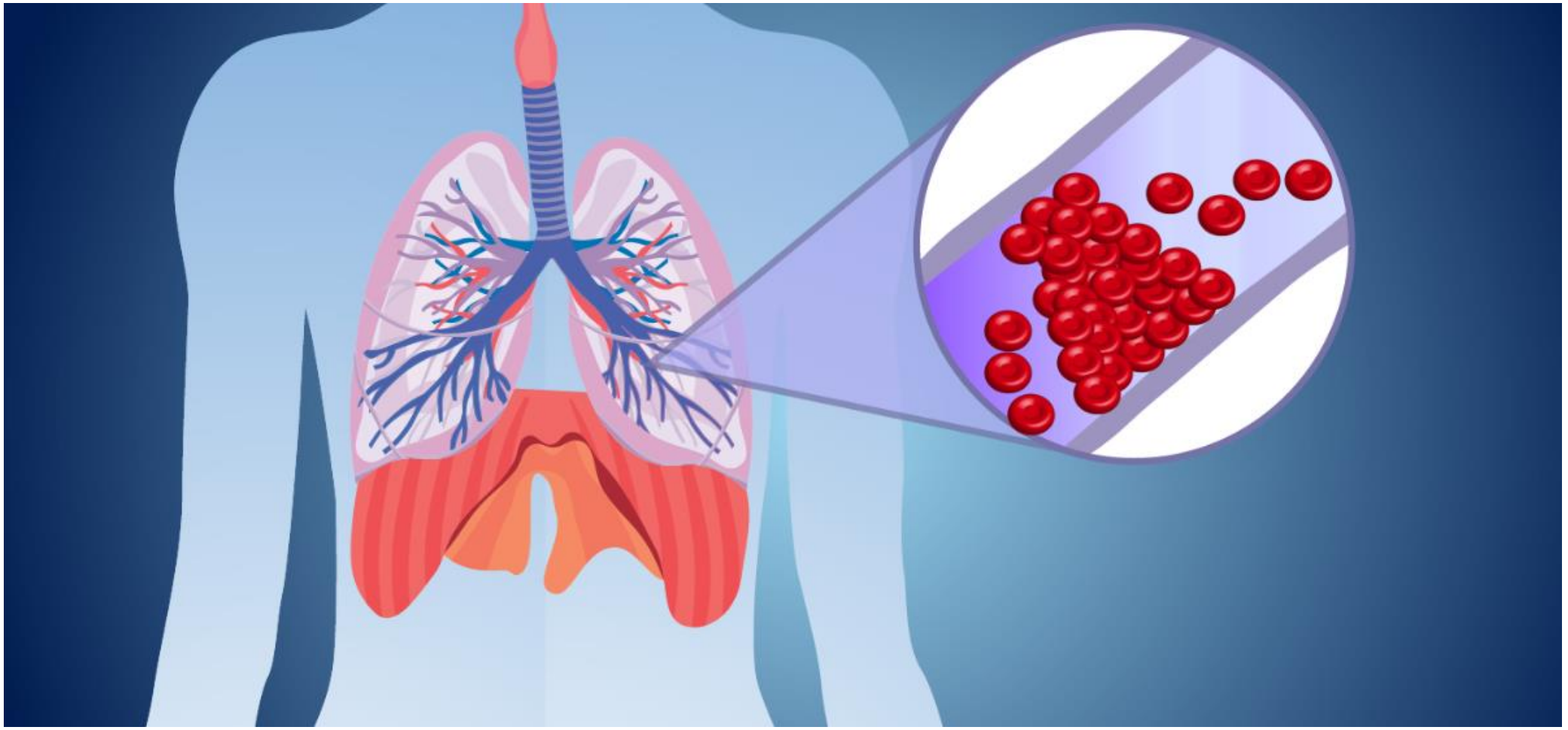
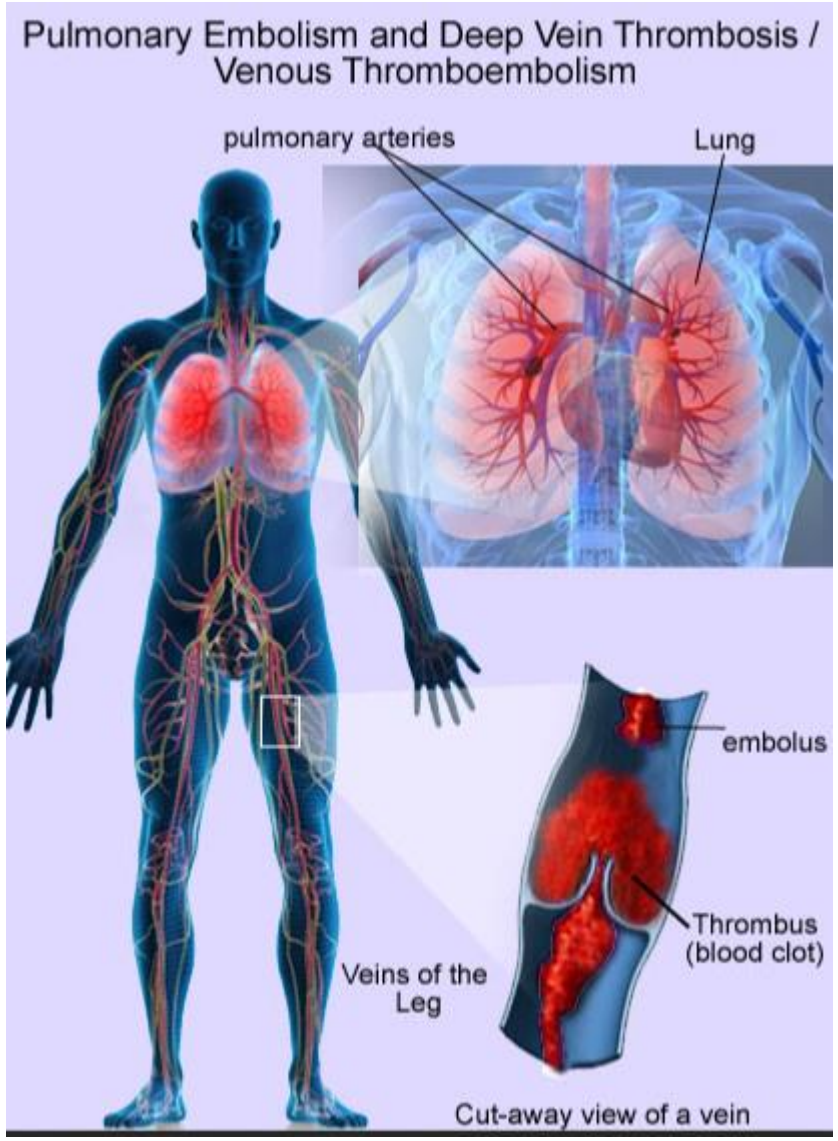
VTE and Pulmonary Embolism



- Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, prevalence is 1-2 per thousand per year.
- This corresponds to 300,000 – 600,000 events in the US annually.

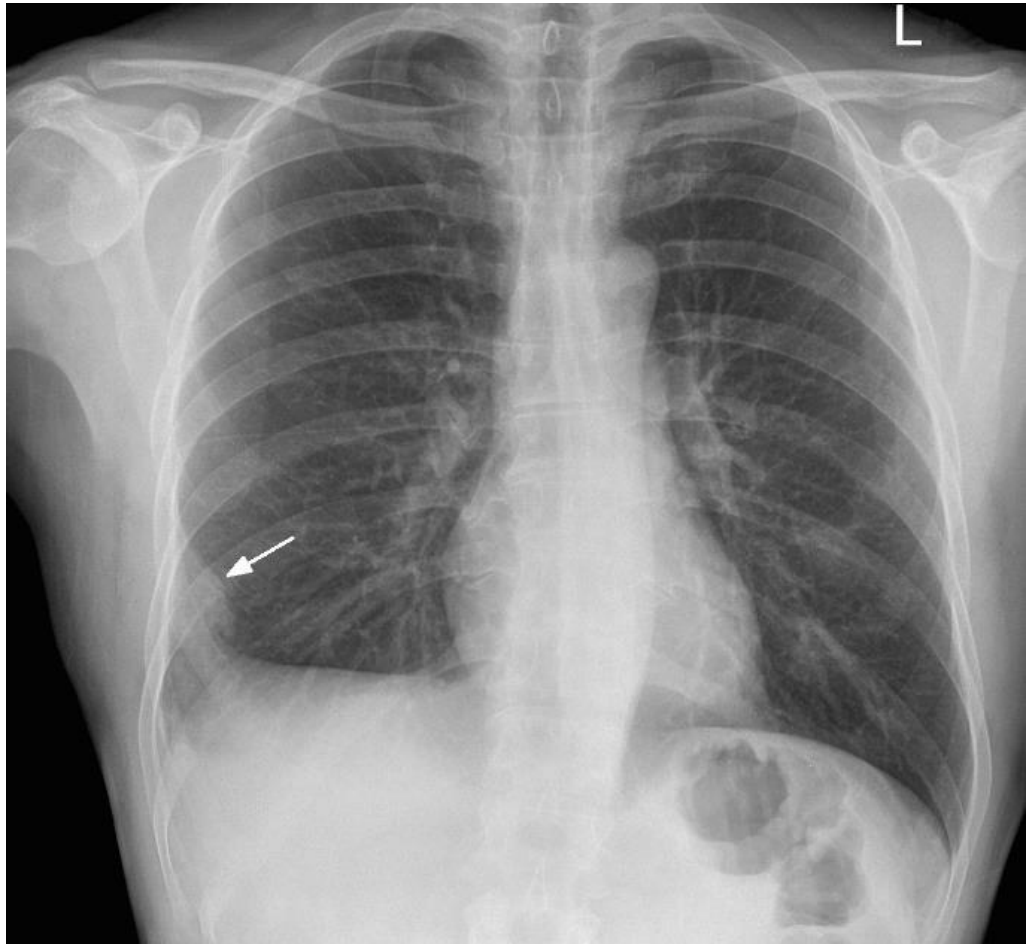
Pulmonary Embolism



- Blood clot occludes an artery in the lungs, thereby blocking the blood flow to part of the lung.
- Blood clots usually start in the legs and travel up through the right side of the heart and into the lungs.

Symptoms of Pulmonary Embolism

- Shortness of breath
- Chest pain
- Cough

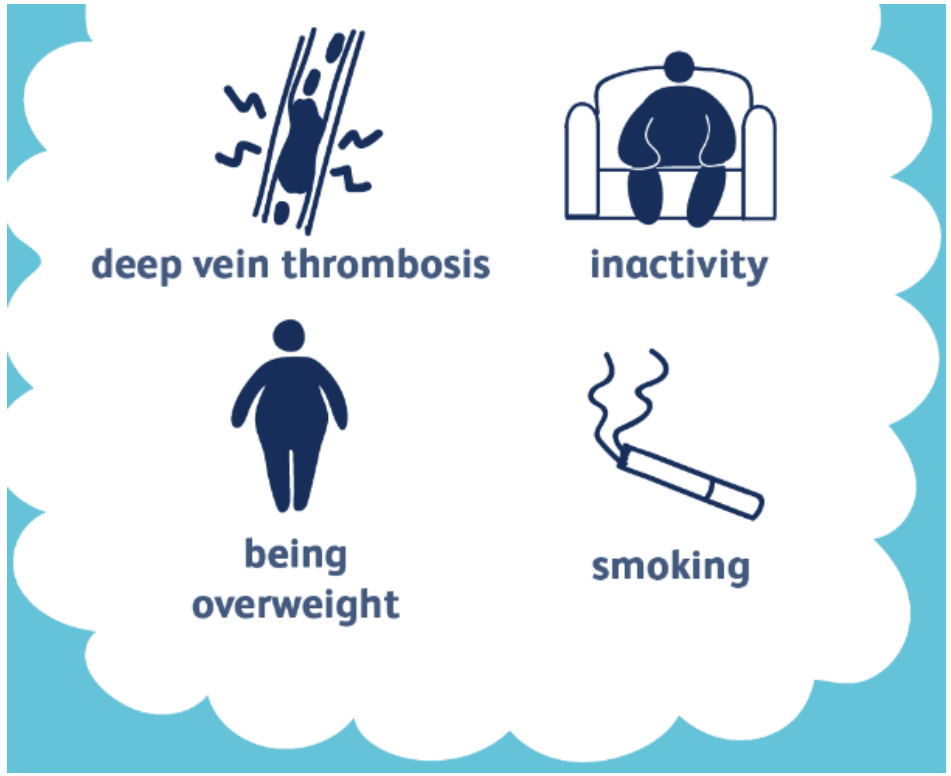


Treatment of Pulmonary Embolism

- Dissolution of clot (thrombolytic drugs)
- Anticoagulation (heparins, oral anticoagulants)
- Compression stockings

Risk for Pulmonary Embolism

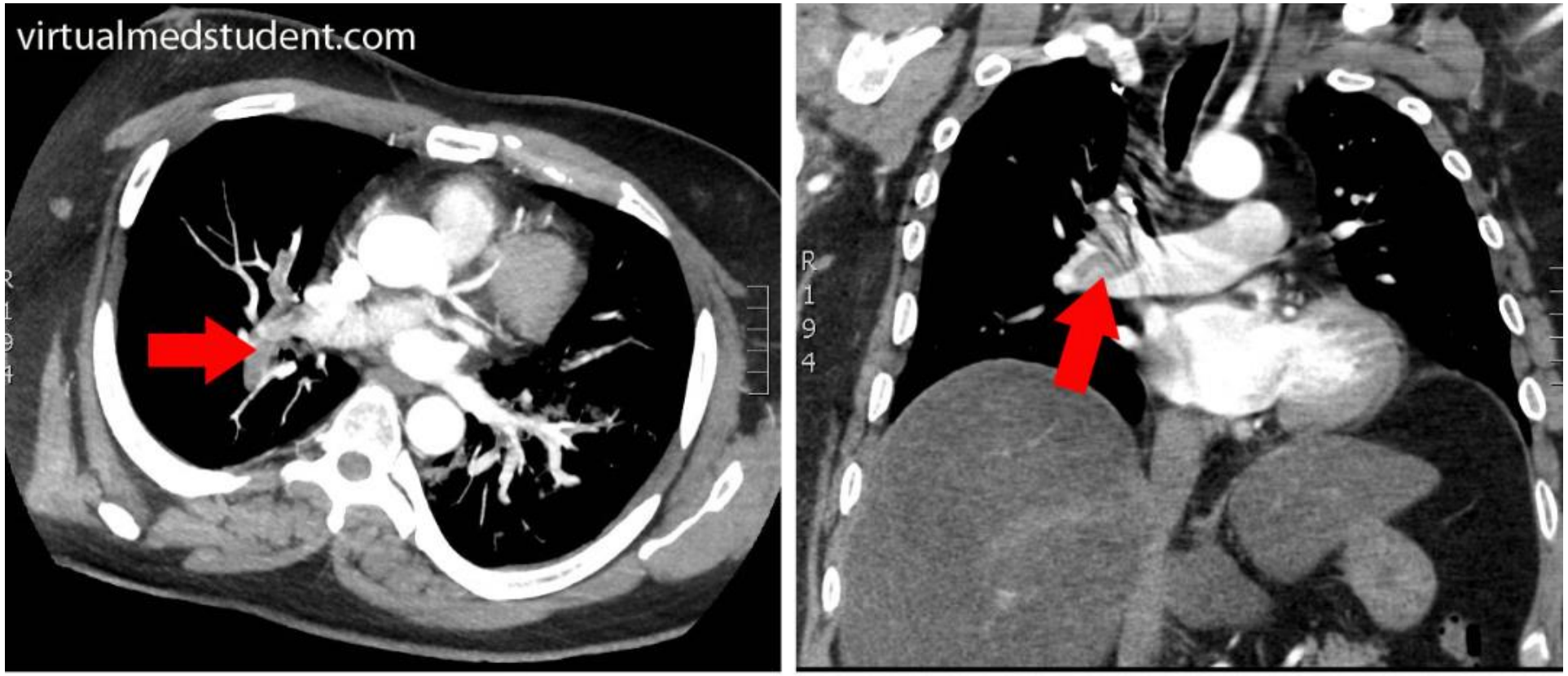
- Clot in the legs
- Stasis (immobility)
- Recent surgery or trauma
- Medication including birth control pills
- Smoking
- Heart failure
- Overweight
- Pregnancy
- Central venous catheter



Diagnosis of pulmonary embolism

- D-dimer
- X-ray, computed tomography
- Ultrasound of legs
- Ventilation perfusion scan

CT Scan of Pulmonary Embolism



The areas at the tip of the arrowheads are slightly "darker" than normal indicating a decreased ability for contrast dye to enter the pulmonary artery and its branches. This is indicative of a pulmonary embolism (ie: a blood "clot" in the blood vessels of the lung).

Treatment Options for Pulmonary Embolism

- In-hospitalization management
- Anticoagulation
- Clot lysis (Thrombolysis)
- Surgery (Thrombectomy)

Anticoagulants for Treating Pulmonary Embolism

During Hospitalization

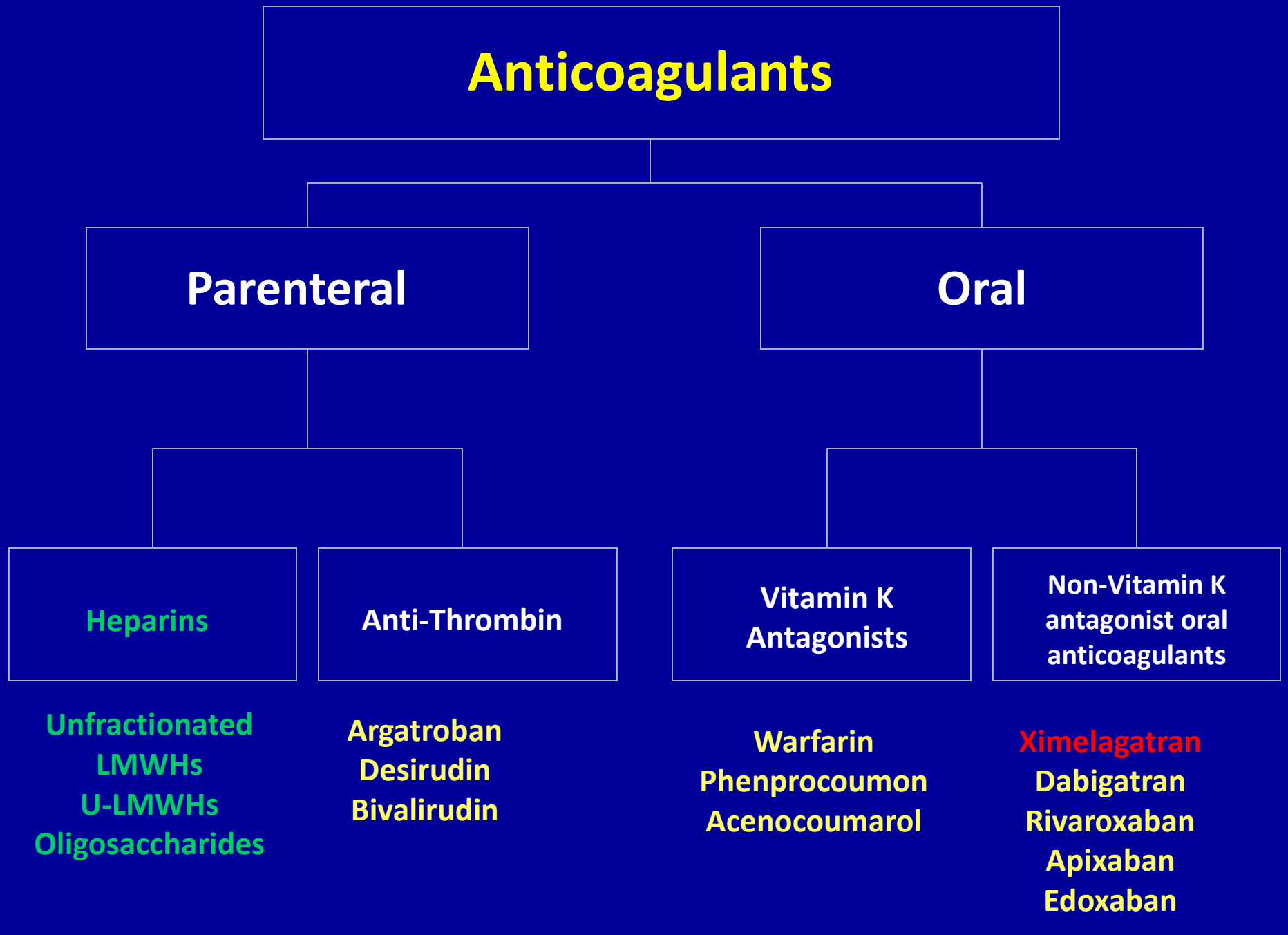
- Unfractionated heparin (IV)

Outpatient

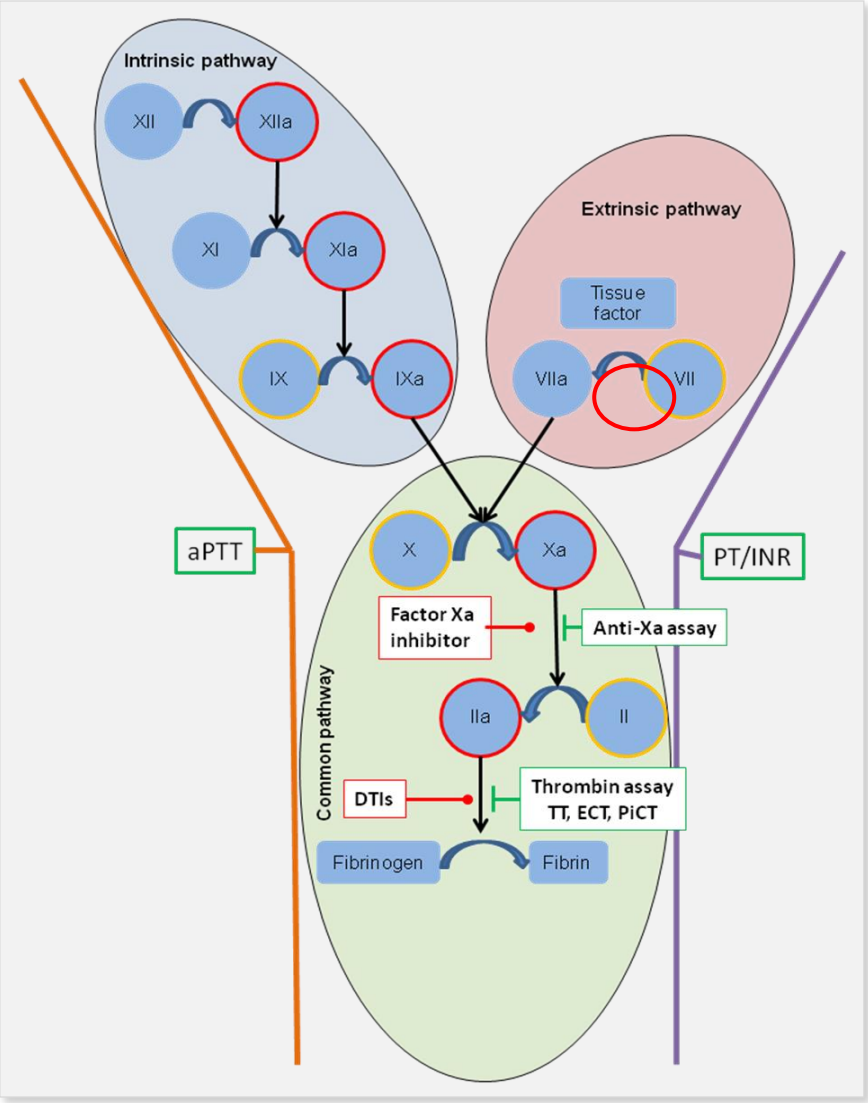
- Unfractionated heparin (SC)
- LMW heparin (SC)
- Warfarin (Oral)
- Anti-Xa agents (Oral)
  - Rivaroxaban
  - Apixaban

Outpatient Management of Pulmonary Embolism

- After 3 – 10 days of hospitalization
- Anticoagulation for 3 – 6 months
- With either Warfarin or direct oral anticoagulant drugs
- Low dose aspirin
- Heparins can only be used initially and during the bridging period in combination with other anticoagulants following the guidelines


Anticoagulants
Parenteral
Oral
Heparins
Anti-Thrombin
Vitamin K Antagonists
Non-Vitamin K antagonist oral anticoagulants
Unfractionated
LMWHs
U-LMWHs
Oligosaccharides
Argatroban
Desirudin
Bivalirudin
Warfarin
Phenprocoumon
Acenocoumarol
Ximelagatran
Dabigatran
Rivaroxaban
Apixaban
Edoxaban

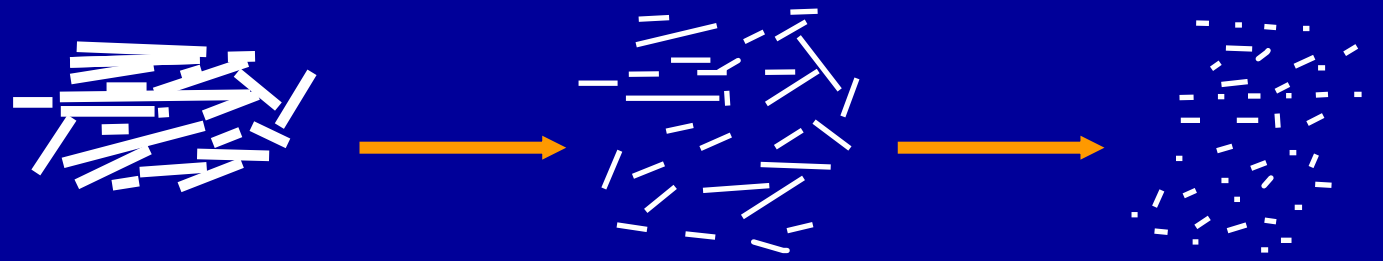
Mechanism of Action of Current Anticoagulant Drugs



Legend	Class	Example	Mechanism of Action
#	**Vitamin K antagonists (VKA)**	Warfarin	Inhibit synthesis of II, VII, IX, X
#	**Heparins**	UFH	Indirectly inhibit Xa, IIa via AT; indirectly inhibit VIIa via TFPI release
		LMWH	
	Pentasaccharide	Fondaparinux	Indirectly inhibit Xa via AT
	Direct acting thrombin inhibitors (DTI)	Argatroban	Inhibit II
		Bivalirudin	
		Dabigatran	
	Direct acting Xa inhibitors	Apixaban	Inhibit Xa
		Rivaroxaban	
		Edoxaban	
		Betrixaban	

From Heparin to Heparin Fractions

Unfractionated Heparin (UFH)



UFH

15 kDa

Anti-Xa/IIa = 1.0

Low Molecular Weight Heparin

~3-7 kDa

Anti-Xa/IIa = 2-8

Ultra LMWH

1-3 kDa

Anti-Xa/IIa = 10-50

Synthetic Oligosaccharides

Pentasaccharide

<2 kDa

Pure Anti-Xa

Only 20% of heparin components are anticoagulants; the other 80% exhibit multiple pharmacological actions which at not yet fully understood

Non-Vitamin K Oral Anticoagulants

* Betrixaban (Portola) is in clinical development

Heparin Versus DOACs for Outpatient Management of Pulmonary Embolism

	Heparins	DOAC's
Dosing	Fixed dosing for heparin at 7,500 sc / bid. For LMWH, 30 mg per day sc	Only oral use once or twice
Laboratory Monitoring	Not needed however recommended in compromised patients	Needed in patients with low weight and kidney disease
Diet	No interactions	No major interactions
Drug Interactions	Significant drug interactions	Limited data – no major interactions
Use in renal patients	Only LMWHs	No data available
Use in pregnant patients	Can be used	Pass placental barrier, contraindicated
Bleeding complications	Yes	Yes
Antidote	Yes	Available but very expensive
Cost	Relatively cheap	Relatively expensive
Compliance	Moderate	Good

A Comparison of Anticoagulants in the Outpatient Management of PE

Population	Warfarin	Low molecular weight heparin (LMWH)	Direct oral anticoagulants (DOACs) [1]
General adult population	**Yes** Given *concurrently* with LMWH for first 5 days until two consecutive INR test results between 2.0 and 3.0.	Only if contraindications to warfarin and DOACs.	**Yes** Rivaroxaban [2] OR Dabigatran, *preceded* by at least 5 days of LMWH
Pregnant adults	No [3]	**Yes**	No [4]
Adults with active cancer	No	**Yes**	Yes [5]
CrCl < 30 ml/min	**Yes**	Shared decision-making [6]	No [5]

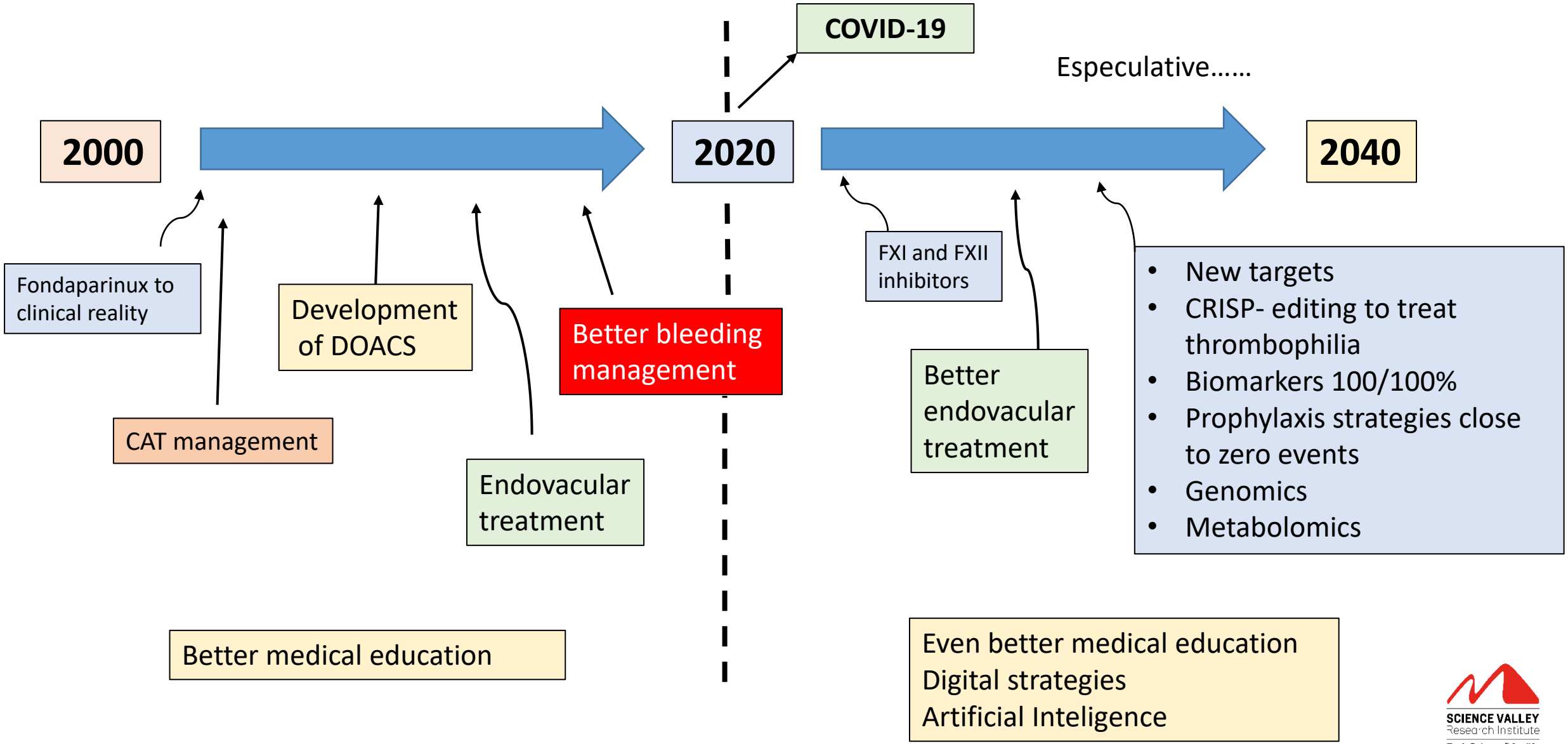
1 DOACs are contraindicated for patients with mechanical heart valves.
2 Prior authorization required.
3 Warfarin can be started immediately post-delivery.
4 DOAC can be started immediately post-delivery **if not breastfeeding.**
5 Rivaroxaban should be avoided in gastrointestinal and genitourinary cancers, high bleeding risk situations, and active brain metastasis, or when chemotherapy will cause significant thrombocytopenia. Apixaban (nonformulary DOAC) can be considered in cancer-associated VTE patients with CrCl < 30 mL/min. Dabigatran has not been adequately studied in cancer-associated VTE.
6 Shared decision-making: Hospitalization with heparin may be preferred treatment if CrCl < 15 mL/min.

Comparison: warfarin versus DOACs		
	Warfarin (Coumadin)	**DOACs**
Years on market	In use for many years. Known long-term side effects. Most common anticoagulant.	Research lacking on • Long-term side effects, and • Relative effectiveness of one DOAC against another.
Dosing	Taken once a day in the evening. Dose might change based on lab test results.	Taken one or two times per day. Dose might change based on lab test results.
Lab tests/monitoring	Protime/INR blood tests as needed to maintain target range.	Annual labs (CrCl, CBC, LFTs). If indicated, CrCl may be repeated quarterly.
Diet	Requires consistent intake of foods containing vitamin K.	No specific dietary restrictions.
Drug interactions	Interacts with many drugs.	Fewer drug interactions. DOACs should be avoided with P-gp inducers and 3A4 inducers such as carbamazepine and phenytoin.
Use in patients with reduced renal function	Can be used no matter what the renal function.	DOACs have only been studied in patients with CrCl > 30.
Intervention to stop dangerous bleeding	Vitamin K.	General measures to control bleeding can be used. Reversal agents are available on a limited basis.
Cost	Low cost; generic available.	More expensive; dabigatran generic is anticipated in 2023.

Summary

- Unfractionated heparin remains the first line anticoagulant after the initial diagnosis of PE. Neither low molecular weight heparin nor DOACs can be used in the initial stages of PE
- LMWHs can be used after the hospitalization for the initial stages and during the bridging with either warfarin or DOACs
- LMWHs and DOACs are not used for intravenous indications
- DOACs such as rivaroxaban and apixaban can be used for extended therapy up to 6 months for the anticoagulation of PE patients following the guidelines and recommendations of ASH, ACCP and other groups.

Progress in the last two decades and projections for the next two decades



Thank You