Personalized Anticoagulation for VTE Patients: Selection, Dosing, and Duration

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Case: 25/F DVT with PTE

- **Chief complain: Rt. Leg swelling with pain (3 days)**

- **P. M. Hx: cerebral sinus thrombosis**

- V/S : 141/110 mmHg - 130/min - 20/min – 36.0°C - 99%
- Lab.: CBC 8700-13.6-256000

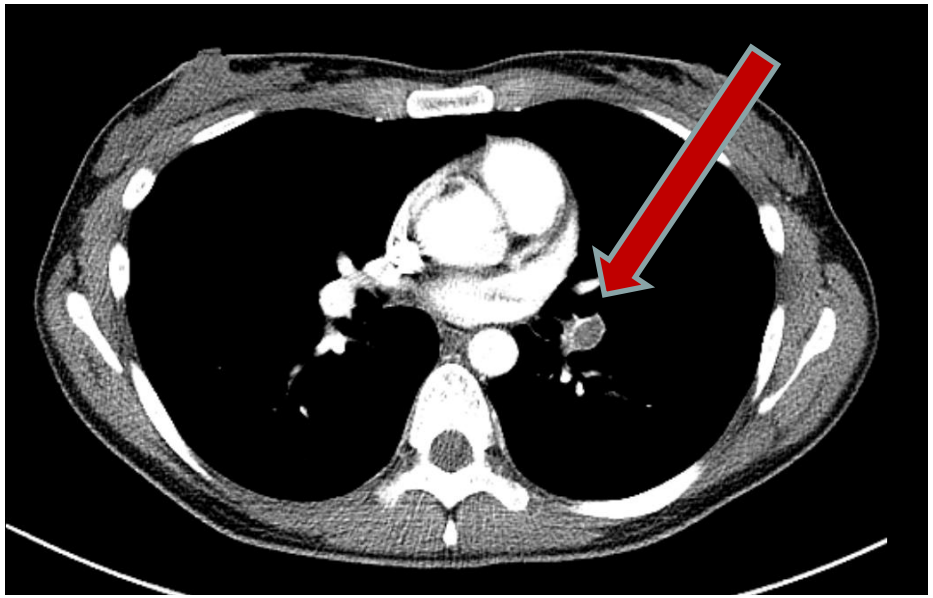
  AST/ALT 27/10 IU/L Protein/albumin 8.7/4.9 mg/DL, total bilirubin 1/3 mg/dL

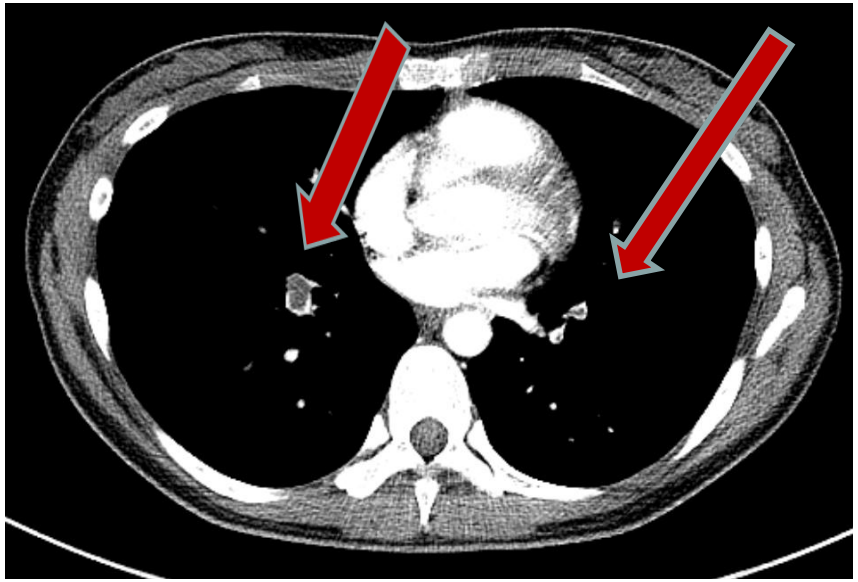
  BUN/cr 11/0.79 mg/dL

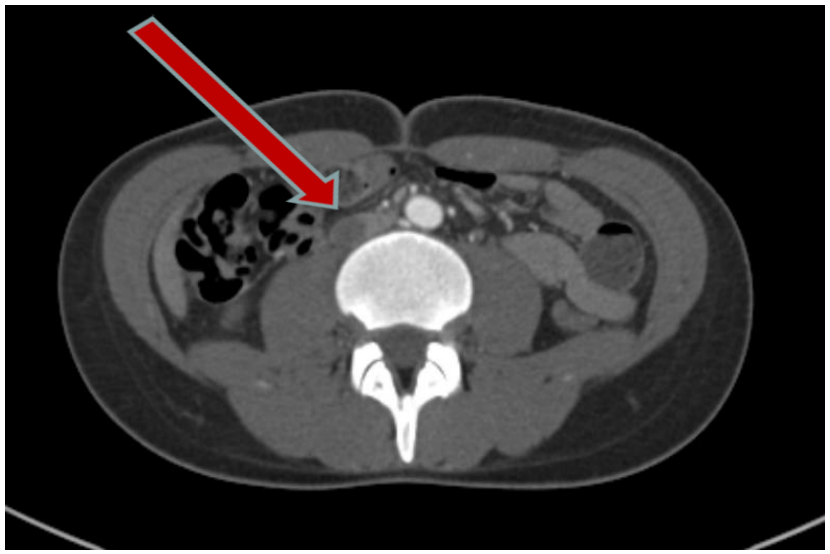
  D-dimer 10.94 ug/mL FEU

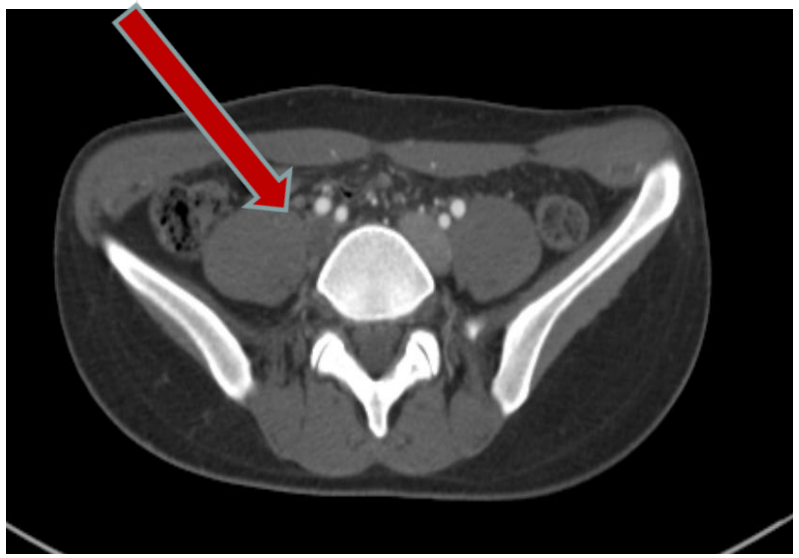
  CK-MB/TnI 0.8/0.006 ng/ML

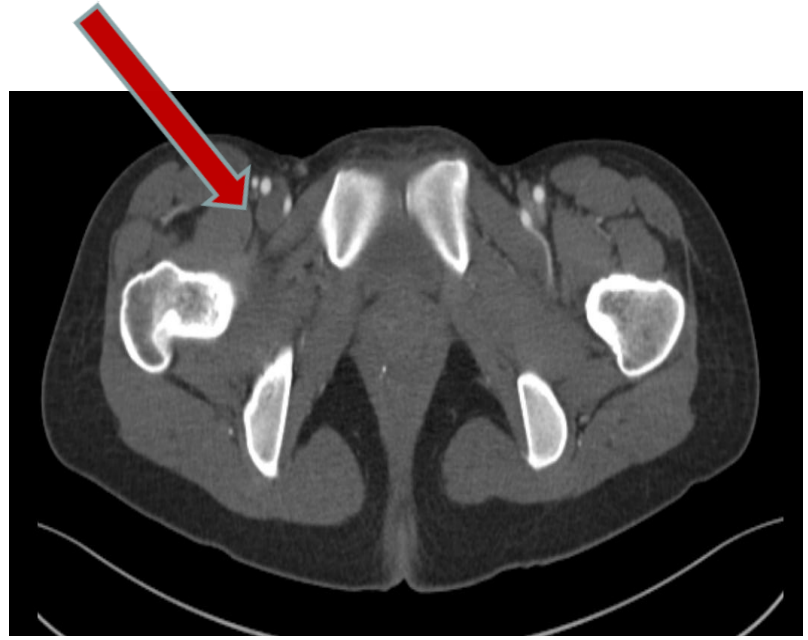
  ABGA pH 7.40, pCO2 25.7, PO2 82.4, Bicarbonate 15.9, SaO2 96%











Which anticoagulant would you select for the initial anticoagulation therapy ?

1. IV unfractionated heparin
2. SC Low molecular weight heparin
3. Rivaroxaban
4. Apixaban

Classification of anticoagulants

Route	Class	Mechanism	Generic names
Parenteral	**Unfractionated heparin (UFH)**	**Activates antithrombin III;** inhibits Thrombin (IIa) & Factor Xa	**Heparin**
	Low molecular weight heparin (LMWH)	**Activates antithrombin III;** inhibits Factor Xa > Thrombin (IIa)	**Enoxaparin, Dalteparin**
	Synthetic pentasaccharide	**Activates antithrombin III;** Selective Factor Xa inhibition	**Fondaparinux**
	Direct Thrombin Inhibitors	Directly binds to and inhibits thrombin (IIa)	**Argatroban**
Oral	Vitamin K antagonists (VKA)	Inhibits vitamin K epoxide reductase (Factors II, VII, IX, X)	Warfarin
	Direct oral anticoagulants (DOACs)	Direct Xa inhibition	**Rivaroxaban, Apixaban, Edoxaban**
		Direct IIa inhibition	**Dabigatran**

Timeline for VTE Treatment

	Initial (0-21 days)	Long-term (~3 months)	Extension (>3 months)
Thrombosis burden	Highest clot propagation and embolism risk	Clot stabilization Endogenous fibrinolysis	Resolved or organized clot
Treatment goal	Stop clot propagation Prevent PE	Treat index VTE Prevent early recurrence	Prevent recurrence
Anticoagulation intensity	High intensity	Standard therapeutic dose	Prophylactic dose
Typical therapy	IV UFH/SC LMWH Loading dose DOAC	Warfarin INR 2-3 Standard dose DOAC	Warfarin INR 2-3 Reduced dose DOAC

Anticoagulation in VTE treatment

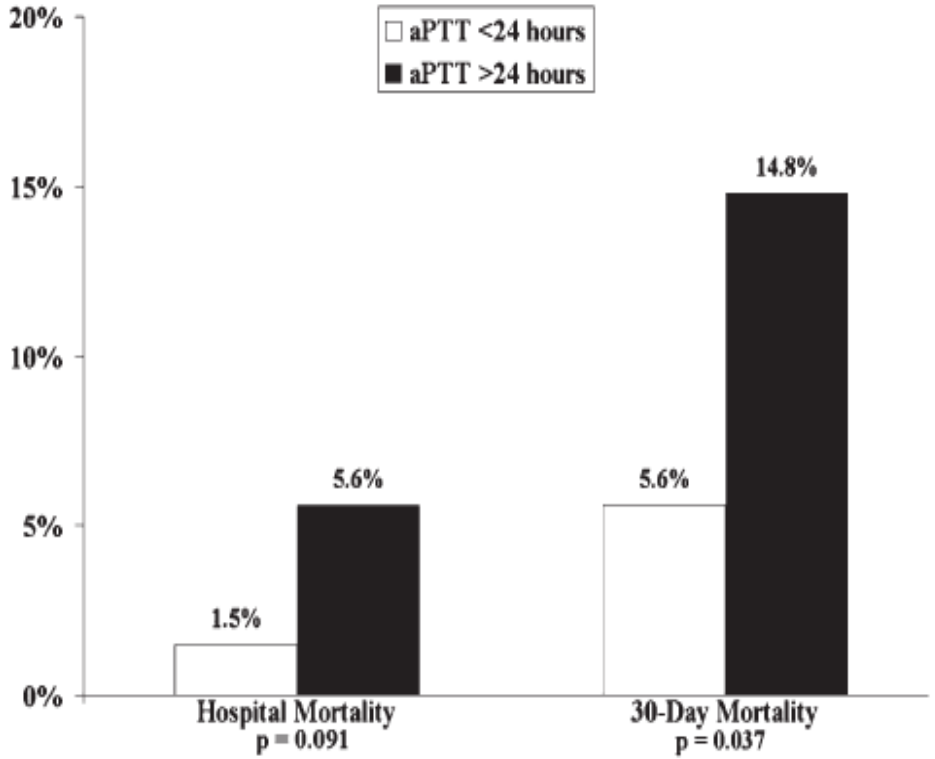
	Initial (0-21 days)	Long-term (~3 months)	Extension (>3 months)
Conventional	IV or SC UFH or SC LMWH SC fondaparinux	VKA with PT monitoring	
Mono-therapy	Rivaroxaban 15mg bid (3weeks)	Rivaroxaban 20mg qd	Rivaroxaban 10mg qd
	Apixaban 10mg bid (1 week)	Apixaban 5mg bid	Apixaban 2.5mg bid
Switch Therapy	IV UFH or SC LMWH (1 week)	Dabigatran 150mg bid	
		Edoxaban 60mg qd (30mg qd if Ccr 30-50 ml/m or body weight < 60kg)	

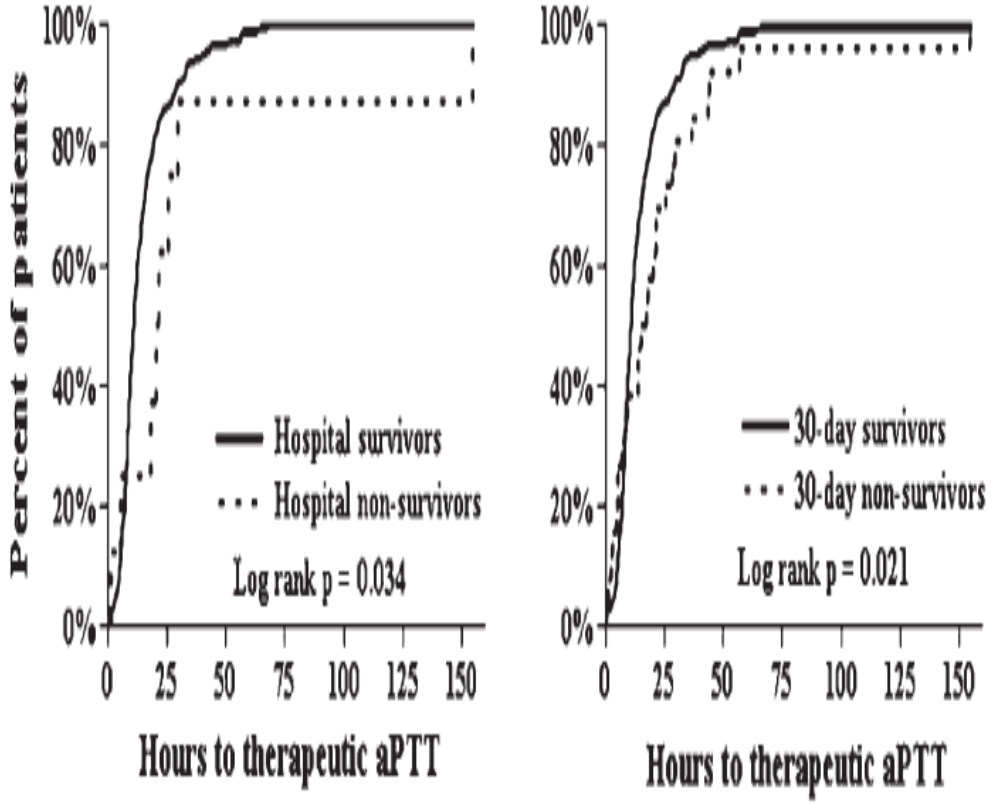
Acute phase treatment of high-risk PE

Recommendations	Class[b]	Level[c]
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE. [282]	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[d] [281]	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[d]	IIa	C

ESC guidelines. Eur heart J 2019

Early anticoagulation for acute PE





CHEST 2010; 137(6):1382-1390

Acute-phase treatment of intermediate-or low-risk PE

LMWH > UFH
DOAC > warfarin

Initiation of		
Initiation of ar without delay mediate clinic nostic workup		C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.[262,309–311]	I	A
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.[260,261,312–314]	I	A
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.[315,316]	I	A
NOACs are not recommended in patients with severe renal impairment,[d] during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome.[260,261,312–314]	III	C

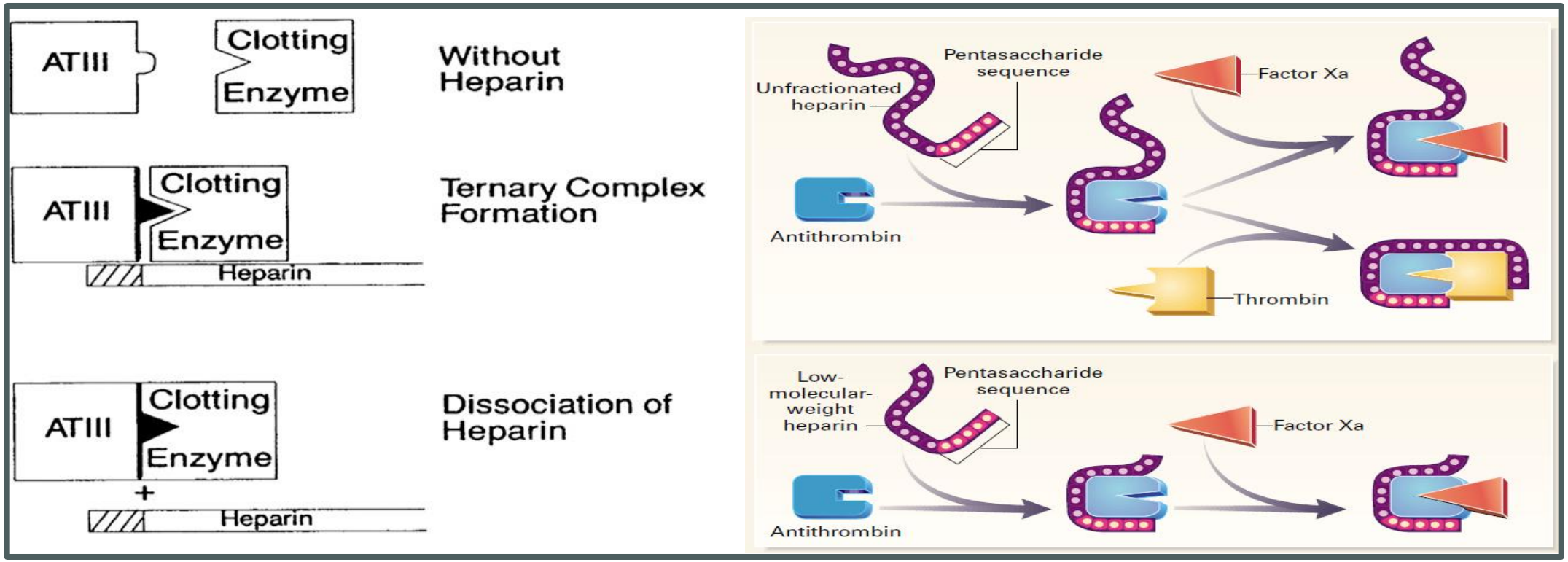
ESC guidelines. Eur heart J 2019

LMWH vs UFH for initial anticoagulation of acute VTE

Outcomes	No. of participants (studies)	Relative risk (95% CI)	Absolute risk difference
All-cause mortality	7908 (17 studies)	**0.79 (0.66-0.95)**	10 fewer per 1,000
Recurrent VTE	7976 (17 studies)	**0.72** (0.58-0.89)	15 fewer per 1,000
Major bleeding	6910 (20 studies)	**0.67 (0.45-1)**	5 fewer per 1000

Kearon et al., ACCP 9th Guideline. Chest 2012;141(2)(Suppl):e419S-3494S

Anticoagulant effects of heparin



Binds to AT and catalyzes the inactivation of factors IIa, Xa, IXa, XIa and XIIa	**Major mechanism for anticoagulant effect, produced by only one-third of heparin molecules (those containing the unique AT-binding pentasaccharide)**
Binds to **Heparin cofactor II** and catalyzes inactivation of factor IIa	Requires high concentrations of heparin and is independent of the pentasaccharide
Binds to **factor IXa** and inhibits factor X Activation	Requires very high concentration of heparin and is AT- and HCII-independent

Theoretical advantage of UFH

- **Inactivation of Factor IIa, Xa, IXa, XIa, and XIIa**
- **Heparin inhibit thrombin, thereby interrupting thrombin-induced platelet activation**, which may reduce the release of platelet-derived vasoconstrictors.
- **Heparin may cause modest endothelium-dependent vasodilation.**

Gurewich V et al. Am Heart J 1968;76;784;794
Tangphao O et al. Clin Pharmacol Ther 1999;66:232-238
Sternberg WC et al. J Vasc Surg 1993; 17:318-327.

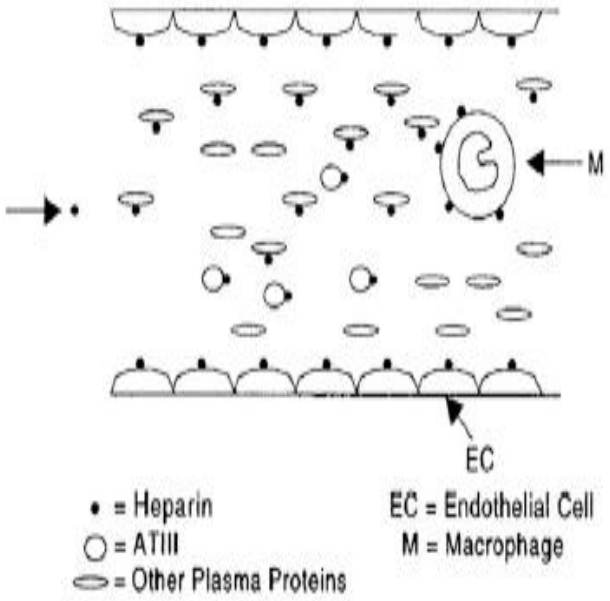
Theoretical disadvantage of UFH

- **Variability of anticoagulant response**

  = Heterogeneity of pentasaccharide

  +

  Binding to other protein & cells



*** The Phenomenon of heparin resistance**

*** Non-hemorrhagic side effects : HIT**

UFH vs LMWH

	UFH	LMWH
Mechanism	**Inhibits IIa & Xa (Ratio 1:1)**	**Mainly inhibits Xa (Ratio 1:2 to 1:4)**
Half-life	**Short (1–2 hours)**	**Long (3–6 hours)**
Bioavailability	**Low & Variable**	**High & Predictable**
Monitoring	**aPTT (Required)**	**Not required (Anti-Xa if needed)**
Renal Impairment	**Safe (Hepatic metabolism)**	**Use with caution (Renal clearance)**
Heparin induced thrombocytopenia	Higher risk	Lower risk
Reversibility	**Fully reversed by Protamine**	**Partially reversed by Protamine**

UFH recommendations

- **Check total body weight, CBC, PT/aPTT prior to initiating heparin therapy.**
- **Heparin efficacy is related to dose regardless of route.**
- **The initial dose is more important than the aPTT in predicting efficacy.**
- **Achieve aPTT ratio > 1.5 within 24 hours.**
- Although optimal initial dosing for bolus and continuous infusion remain uncertain, u**se a protocol (fixed dose vs. weight based)**

Monitoring of heparin treatment

	aPTT	Anti-Xa Assay
Principle	Measures clotting time of intrinsic + common pathways	Measures inhibition of factor Xa by heparin
What it reflects	Multiple coagulation factors (VIII, IX, XI, XII, etc.)	Direct heparin activity (anti-Xa level)
Therapeutic range	Typically 1.5–2.5 × control	UFH: 0.3–0.7 IU/mL
Variability	High (affected by patient factors)	Lower (more stable)
Key influencing factors	Factor deficiencies, inflammation, liver disease, lupus anticoagulant	Anti-thrombin level
Effect of lupus anticoagulant	Prolonged (false elevation)	Minimal effect
Effect of high factor VIII	Shortened → underestimates heparin effect	Minimal effect
Accuracy in critical illness	Reduced	Better
Best use cases	Routine UFH monitoring	Heparin resistance, unreliable aPTT, ICU patients

aPTT: therapeutic range

324 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 17, 1972

A PROSPECTIVE STUDY OF THE VALUE OF MONITORING HEPARIN TREATMENT WITH THE ACTIVATED PARTIAL THROMBOPLASTIN TIME

DILIP BASU, M.D., ALEXANDER GALLUS, M.B., M.R.A.C.P., JACK HIRSH, M.D., F.R.A.C.P., AND JOHN CADE, M.D., PH.D., M.R.A.C.P.

Abstract Two hundred and thirty-four patients treated with continuous intravenous infusions of heparin were studied prospectively to seek a relation between the activated partial thromboplastin time (APTT) and recurrent venous thromboembolism or bleeding during treatment. One hundred and sixty-two patients were treated for venous thromboembolism and the remaining 72 for other diseases. The heparin dose was adjusted to keep the APTT between 1½ and 2½ times control levels. The five patients with venous thromboembolism in whom recurrence developed had a significantly lower APTT than patients without recurrence even

bolism during heparin treatment appears to be rare if the APTT is prolonged to 1½ times or more control values at all times.

162 VTE patients
- 5 recurrence in lower aPTT level
- aPTT 1.5-2.5 times control:
no recurrent VTE

These data provided the foundation for an empiric aPTT therapeutic range of 1.5–2.5 times control.

Recommended dosing for UFH in VTE treatment

Route		Bolus dose	Maintenance dose
Continuous IV infusion	**Fixed dose**	**5,000 units**	**1,250-1280 units/h**
	Weight based	**80 units/kg**	**18 units/kg/h**
Subcutaneous	**Fixed dose**	333 units/kg	250 units/kg q12h
	Adjusted dose	5000 units	17500 units q12h adjusted to aPTT

- Optimal initial dosing for bolus and continuous infusion remain uncertain.
- Monitoring is optional in those receiving SC weight based heparin therapy.

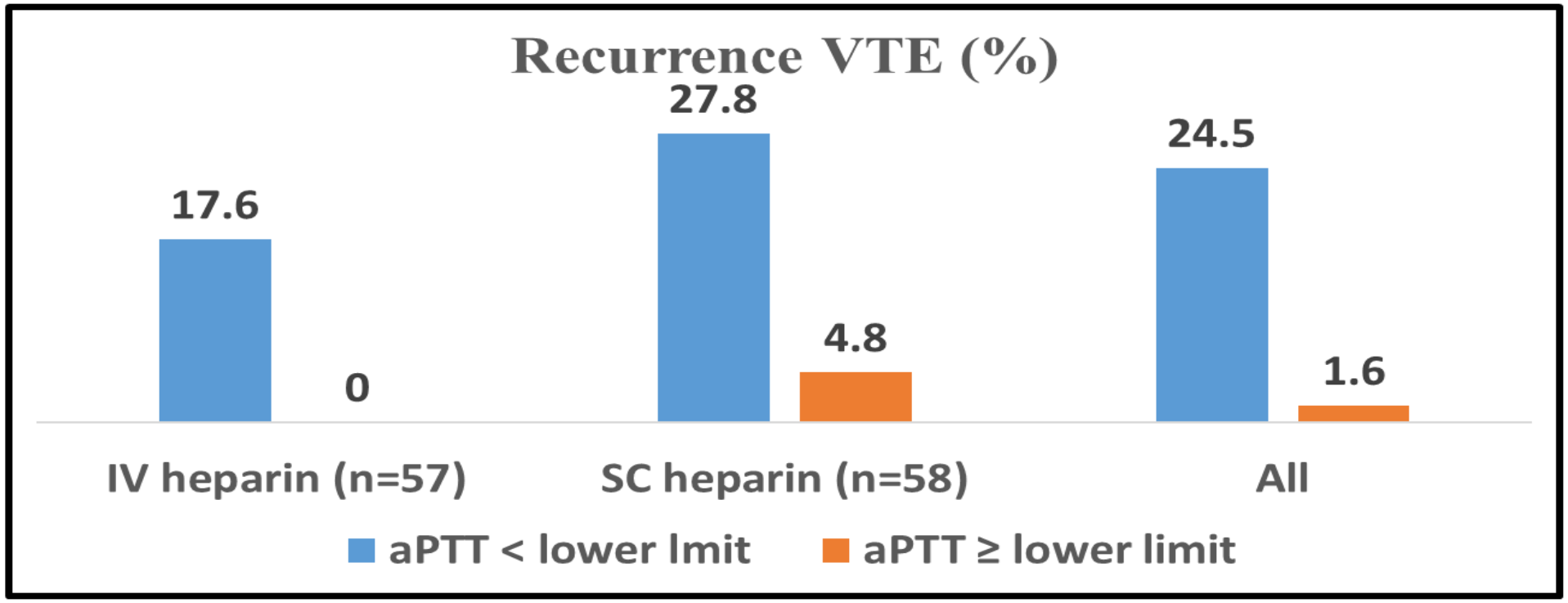
J Thromb Thrombolysis 2016;41:165–186

Continuous IV vs intermittent SC heparin

- Randomized, DB trial in the initial treatment of 115 patients with proximal DVT.
- **IV heparin bolus of 5000 IU**

  → IV heparin (29,760/24 hr) vs SC heparin (15,000 q12hr)

High recurrence in SC heparin and sub-therapeutic aPTT



Hull RD, et al. N Engl J Med 1986;315:1109-1114

The Weight-based Heparin Dosing Nomogram Compared with a "Standard Care" Nomogram

- Patients were randomized to the **weight-based nomogram (starting dose, 80 units/kg body weight bolus, 18 units/kg per hour infusion)** or the **standard care nomogram (starting dose, 5000-unit bolus, 1000 units per hour infusion)**

	Standard	Weigh-based	p value
First aPTT* on therapy >1.5 times control, %	32	86	<0.001
aPTT >1.5 times control within 24 hours, %	77	97	0.002
aPTT in therapeutic range within 24 hours, %	75	89	0.08
Recurrent VTE, n of n (%)	8/32(25)	2/41(5)	0.02

Raschke RA, et al. Ann Intern Med. 1993;119:874-881.

Heparin dosing normogram

The ACCP recommend that each institution define its own therapeutic aPTT range based upon the responsiveness of the aPTT reagent and coagulometer in use.

aPTT	DOSE (IU/kg)
Initial dose	80 bolus, then 18/hr
<35 sec (<1.2×)*	80 bolus, then 4/hr
35-45 sec (1.2-1.5×)	40 bolus, then 2/hr
46-70 sec (1.5-2.3×)	No change
71-90 sec (2.3-3×)	Decrease infusion rate by 2/hr
>90 sec (>3×)	Hold infusion 1 hr, then decrease infusion rate by 3/hr

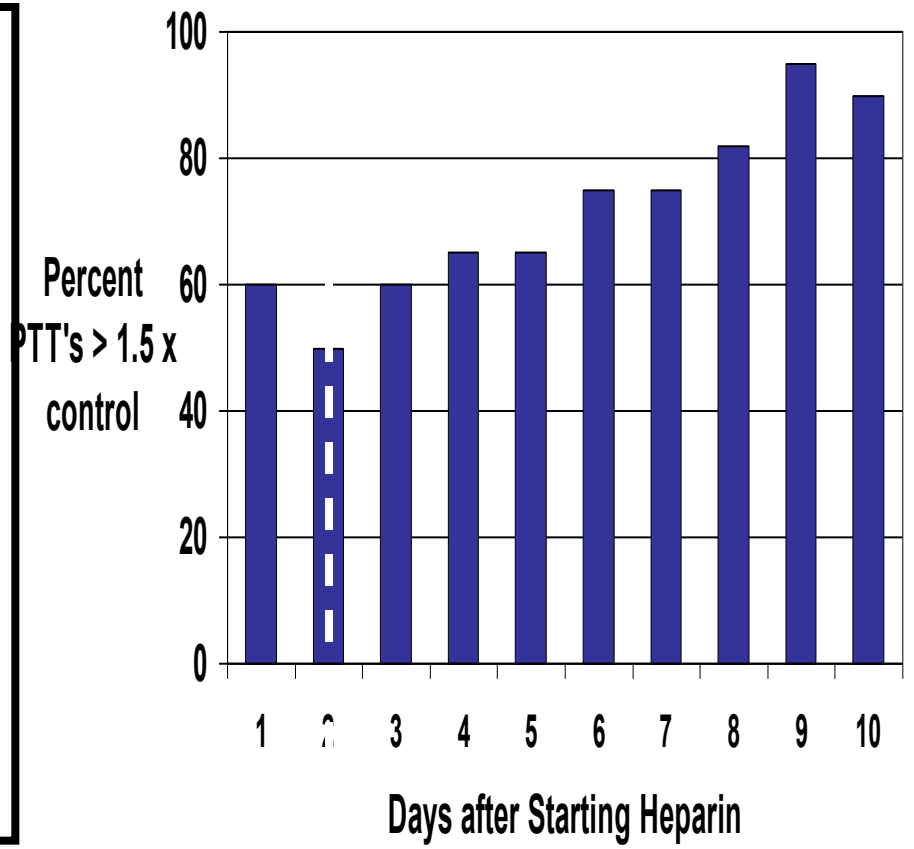
Goldman-Cecil textbook of medicine

[Standard dose Heparin]		
aPTT(sec)	주입 속도	F/U aPTT
<40	5,000iu (XV-HEPA 25KU 1cc) IV bolus 후 3cc/hr(120iu/hr) 증량	6시간 후
40≤ <50	2cc/hr(80iu/hr) 증량	6시간 후
50≤ <75	현재속도 유지(no change)	24시간 후
75≤ <85	1cc/hr(40iu/hr) 감량	6시간 후
85≤ <110	30분간 주입 중지 후 2cc/hr(80iu/hr) 감량	6시간 후
110≤	60분간 주입 중지 후 3cc/hr(120iu/hr)감량	6시간 후

Asan Medical center protocol

Challenges in using IV UFH

- **Delayed heparin initiation and aPTT monitoring**
- **Inappropriate dose adjustments** (insufficient escalation for low aPTT and excessive, prolonged reduction for high aPTT) led to sub-therapeutic anticoagulation.



Wheeler Arch Int Med 1988;148:1321

Heparin resistance

- Common operational definitions:

  Failure to reach target aPTT despite ≥ 35,000 units/day of UFH

- **Causes :**

  1) **anti-thrombin deficiency**; congenital, acquired (sepsis, surgery, ECMO, etc.)

  2) **Increased heparin-biding proteins: acute phase reactant** (inflammation, trauma, etc)

  3) **Elevated factor VIII/fibrinogen : aPTT shortening -> pseudo-resistance**

  4) Increased heparin clearance: obesity, hyperdynamic circulation

- **Management: Check anti-Xa to differentiate true or pseudo-resistance**

  Replace anti-thrombin if anti-thrombin deficiency

  Switch to direct thrombin inhibitor (Argatroban)

Recommended dosing for LMWH in VTE

	Prophylaxis Dose	Intermediate Dose	Treatment Dose
Enoxaparin	**40 mg SC qd or 30 mg SC q12h**	**40 mg SC q12h or ~0.5 mg/kg SC q12h**	**1 mg/kg SC q12h or 1.5 mg/kg SC qd**
Dalteparin	**5,000 IU SC qd**	**5,000 IU SC q12h (selected pts)**	**200 IU/kg SC qd or 100 IU/kg SC q12h**
Tinzaparin	4,500 IU SC qd	Limited data (not routinely used)	175 IU/kg SC qd
Nadroparin	2,850–3,800 IU qd	~3,800 IU SC q12h (practice-based)	86 IU/kg SC q12h
Bemiparin	3,500 IU SC qd	Limited data	115 IU/kg SC qd

LMWH Use by GFR

GFR (mL/min)	Recommendation	Clinical Notes
≥ 60	Standard dosing	No adjustment needed
30–59	Standard dosing (caution)	Consider monitoring in high-risk patients
< 30	**Dose reduction or UFH**	Drug accumulation → ↑ bleeding risk
< 15 or dialysis	**❌ Avoid LMWH**	**UFH**

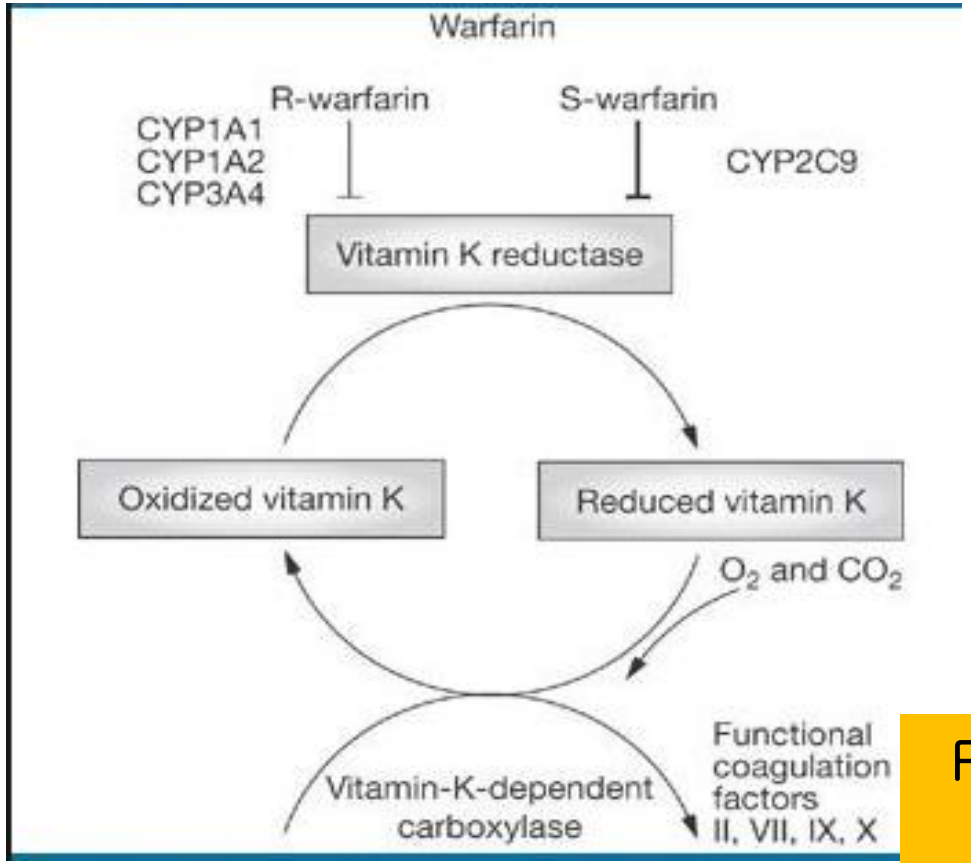
Indication	Normal Renal Function	GFR < 30 mL/min
Prophylaxis (enoxaparin)	**40 mg SC once daily**	**30 mg SC once daily**
Treatment (enoxaparin)	**1 mg/kg SC q12h**	**1 mg/kg SC once daily**

Monitoring of LMWH

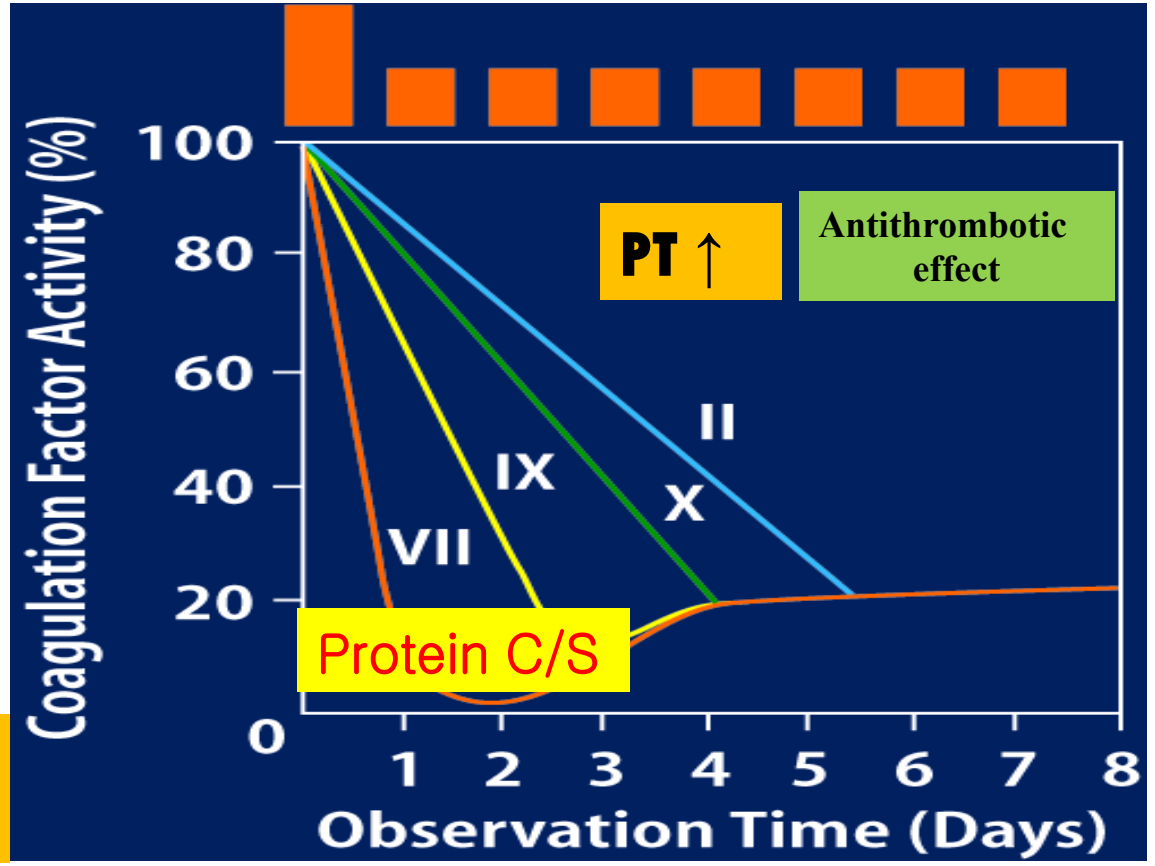
- **Routine monitoring of LMWH is generally not required**; however, **Anti-Xa assay is strongly recommended** for specific patient populations, including those with **renal impairment (CrCl <30 mL/min), extreme body weights (<40 kg or >140-150 kg), pregnancy, and pediatrics**.
- **Prophylactic dosing: 0.2 – 0.5 IU/mL**
- **Twice-daily (BID) dosing: 0.6 – 1.0 IU/mL**
- **Once-daily (QD) dosing: 1.0 – 2.0 IU/mL**

- Blood samples should be drawn at the **peak concentration**, typically **3 to 5 hours after the subcutaneous dose**, once the drug has reached a steady state (usually after the 3rd or 4th dose).

Warfarin Mechanism of Action



Protein C,S



Since decreased factor II levels are most important for clinical efficacy, warfarin's benefits are delayed for several days after it is initiated.

Conversion from Heparin to Warfarin

- We recommend **early initiation of VKA (eg, same day as parenteral therapy is started)** over delayed initiation, and **continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h** (Grade 1B).

- **Time to peak antithrombotic effect of warfarin is delayed 96 hours (despite INR)**

1. ACHIEVING A THERAPEUTIC RANGE

DAY	INR	RECOMMENDED DOSE (MG)
1		5
2		5
3	<1.5	10
	1.5-1.9	5
	2.0-3.0	2.5
	>3.0	0
4	<1.5	10
	1.5-1.9	7.5
	2.0-3.0	5
	3.0-4.0	2.5
	>4.0	0
5	<1.5	10
	1.5-1.9	7.5
	2.0-3.0	5
	3.0-4.0	2.5
	>4.0	0
6	<1.5	12.5
	1.5-1.9	10
	2.0-3.0	5
	3.0-4.0	2.5

2. INR-INTERNATIONAL NORMALIZED RATIO GOAL

2 to 3	target 2.5	Venous thromboembolism (treatment and prevention), atrial fibrillation, bioprosthetic heart valve
2.5 to 3.5	target 3.0	Mechanical prosthetic heart valve (except low-risk patients with bileaflet aortic valves) Anti-phospholipid syndrome with recurrent thromboembolism

Goldman-Cecil textbook of medicine

Warfarin induced skin necrosis

- **A rare (0.01-0.1%) but life-threatening complication (mortality 15-20%)**, typically occurring within **3 to 10 days of starting warfarin therapy.**

- Pathogenesis: **Protein C/S deficiency creates a temporary "pro-thrombotic" window**, leading to small vessel thrombosis

- **Prevention: Heparin bridging**

  avoid high initial "loading dose" of warfarin

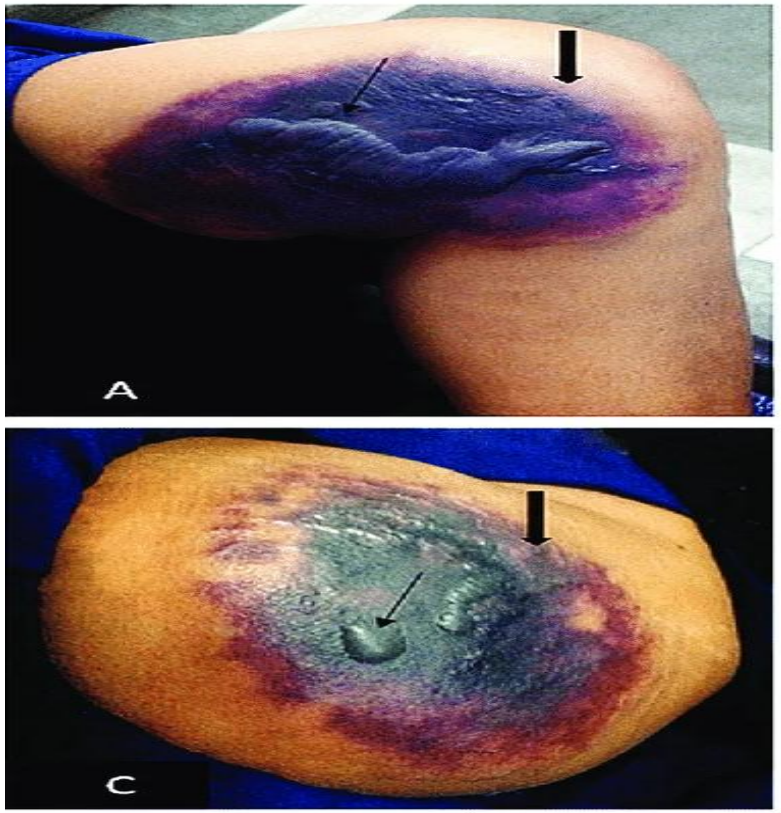
- Treatment: **Immediate discontinuation of warfarin,**

  vitamin K/FFP, activated protein C

  switch to heparin

- About 40% of survivors require surgical debridement or skin grafts.

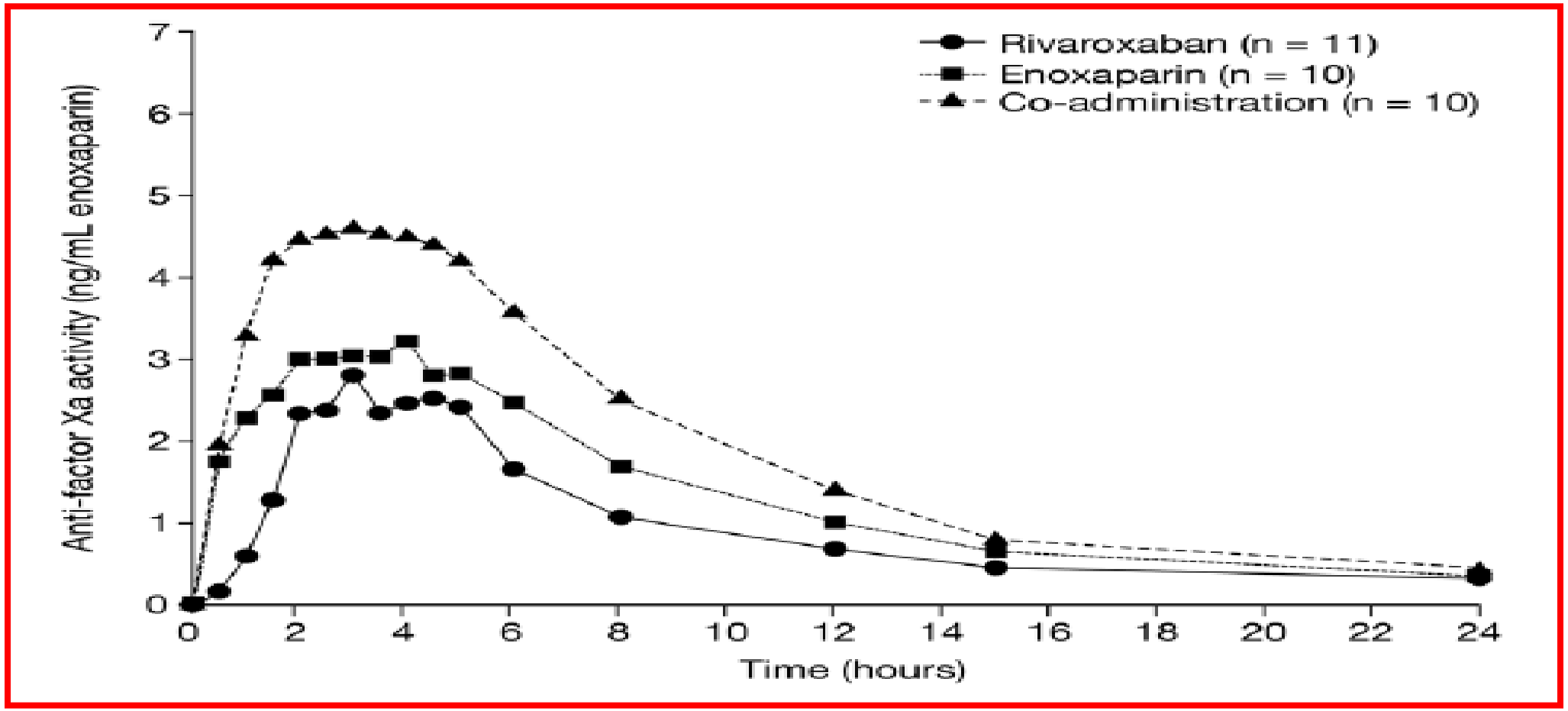
painful, hemorrhagic skin lesions that can rapidly progress to full-thickness tissue necrosis



Warfarin vs DOACs

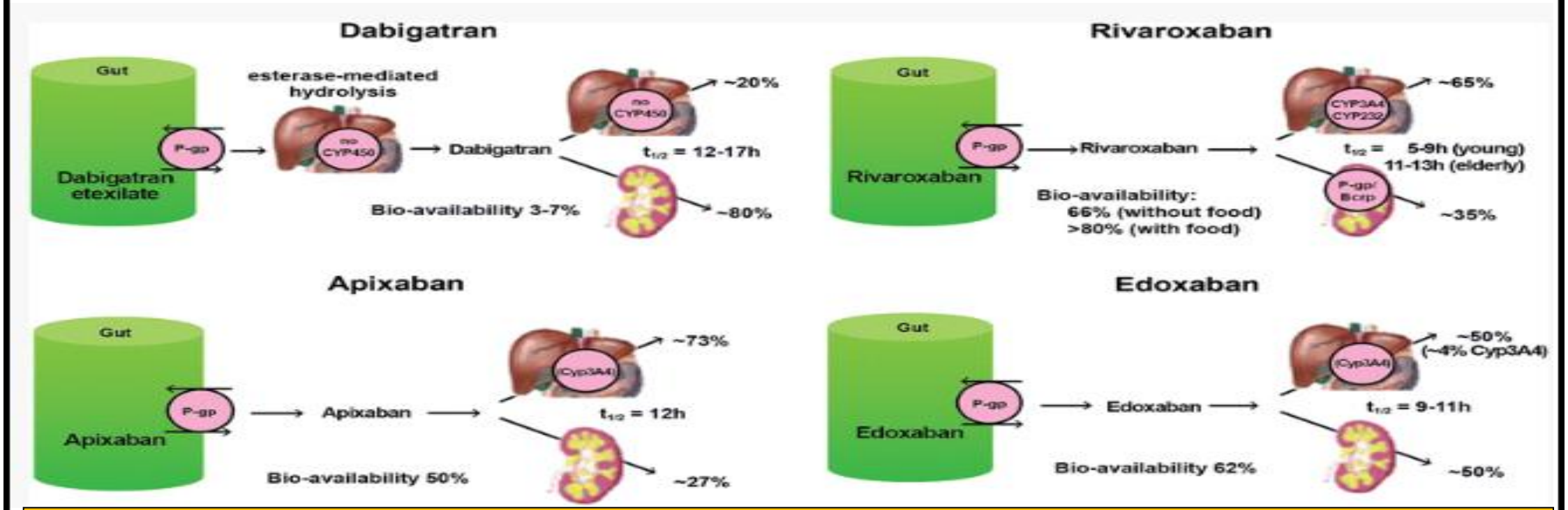
	Warfarin (VKA)	DOACs
Mechanism	Inhibits Vitamin K epoxide reductase	Direct Factor Xa or Thrombin (IIa) inhibition
Onset of Action	**Slow (3–5 days)**	**Rapid (1–4 hours)**
Dosing	Variable (Adjusted by INR)	Fixed (Once or twice daily)
Monitoring	Required (Routine INR tests)	Not required (Routine)
Dietary Interaction	High (Vitamin K intake)	Minimal to None
Drug Interaction	Extensive (Multiple pathways)	Fewer (P-gp/CYP3A4 mediated)
Renal Impairment	**Preferred in severe CKD/ Dialysis**	**Dose adjustment or avoid (Drug-specific)**
Reversibility	Vitamin K, PCC, FFP	Specific agents (Idarucizumab, Andexanet alfa)
Bleeding Risk	**Higher risk of Intracranial Bleed**	**Lower risk of Intracranial Bleed**

Anti-factor Xa activity : rivaroxaban vs enoxaparin



Kubitza D et al. Br J Clin Pharmacol 2010;70-703-712

The pharmacokinetic properties of DOACs



Rivaroxaban and edoxaban: pH-dependent absorption

Apixaban: pH-independent absorption

distal small bowel and ascending colon (55%)

Drug interaction of DOACs

X	Rivaroxaban RifAMPin (Inducers of CYP3A4 (Strong) and P-glycoprotein)
X	Apixaban RifAMPin (Inducers of CYP3A4 (Strong) and P-glycoprotein)
X	Edoxaban RifAMPin
X	Dabigatran Etexilate RifAMPin (P-glycoprotein/ABCB1 Inducers)
X	Itraconazole (Inhibitors of CYP3A4 (Strong) and P-glycoprotein) Rivaroxaban
D	Itraconazole (Inhibitors of CYP3A4 (Strong) and P-glycoprotein) Apixaban

B	Rivaroxaban Rifabutin (CYP3A4 Inducers (Moderate))
B	Apixaban Rifabutin (CYP3A4 Inducers (Moderate))

No interactions of Risk Level A or greater identified.

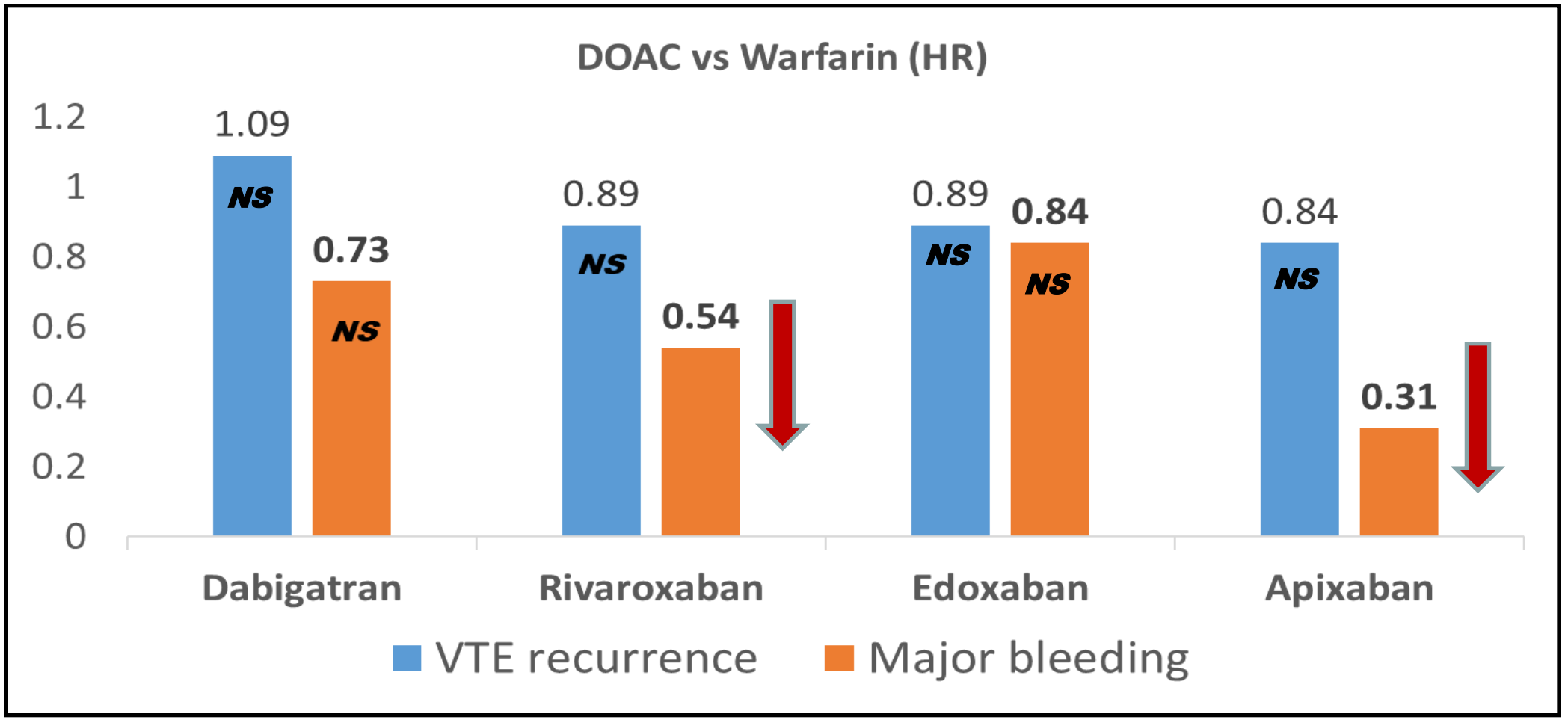
No interactions of Risk Level A or greater identified.

C	Voriconazole (CYP3A4 Inhibitors (Strong)) Rivaroxaban
C	Voriconazole (CYP3A4 Inhibitors (Strong)) Apixaban

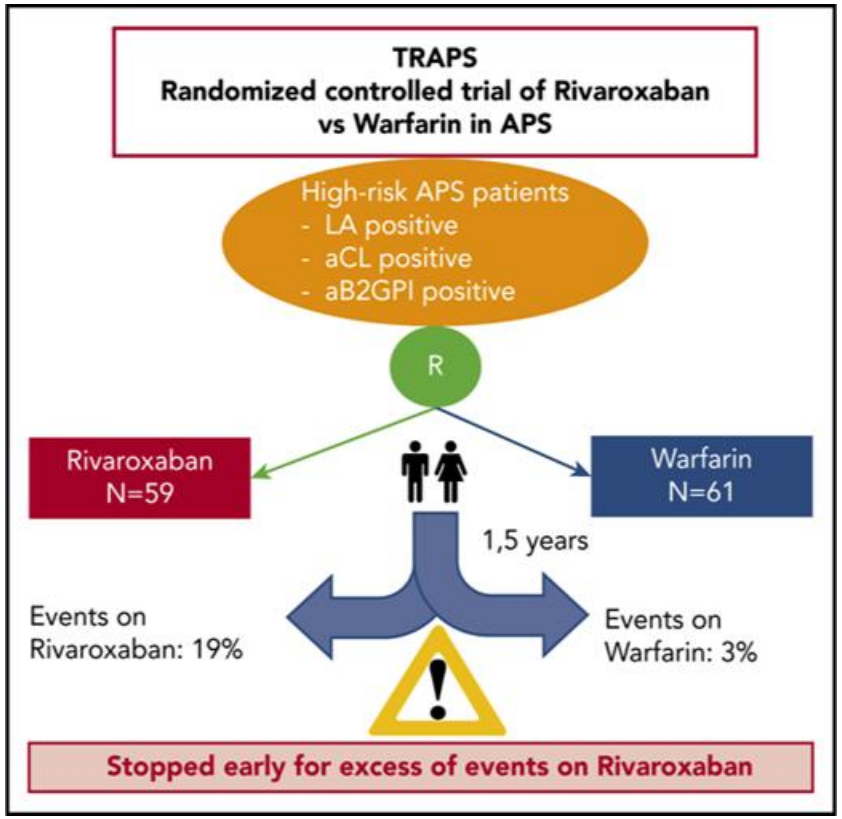
X	Avoid combination	C	Monitor therapy	A	No known interaction
D	Consider therapy modification	B	No action needed	*More about Risk Ratings*	▼

Drug Interactions – UpToDate

DOAC vs warfarin in VTE



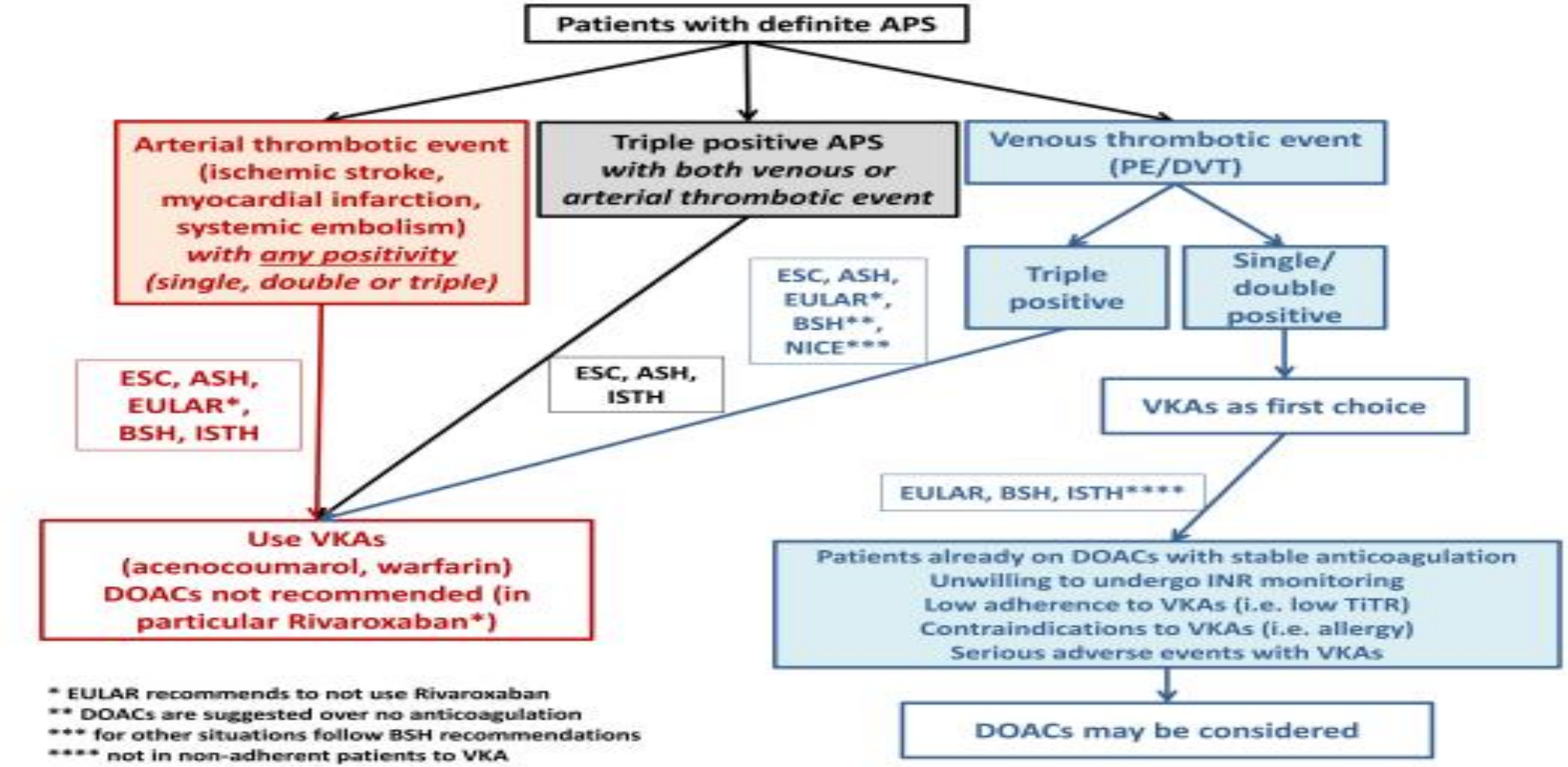
Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome



Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis	7 (12)	0	–	–	7 (12)	0	–	–
Ischemic stroke	4 (7)	0			4 (7)	0		
Myocardial infarction	3 (5)	0			3 (5)	0		
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	–	–	1 (2)	0	–	–

Pengo V et al. Blood (2018) 132 (13): 1365–1371.

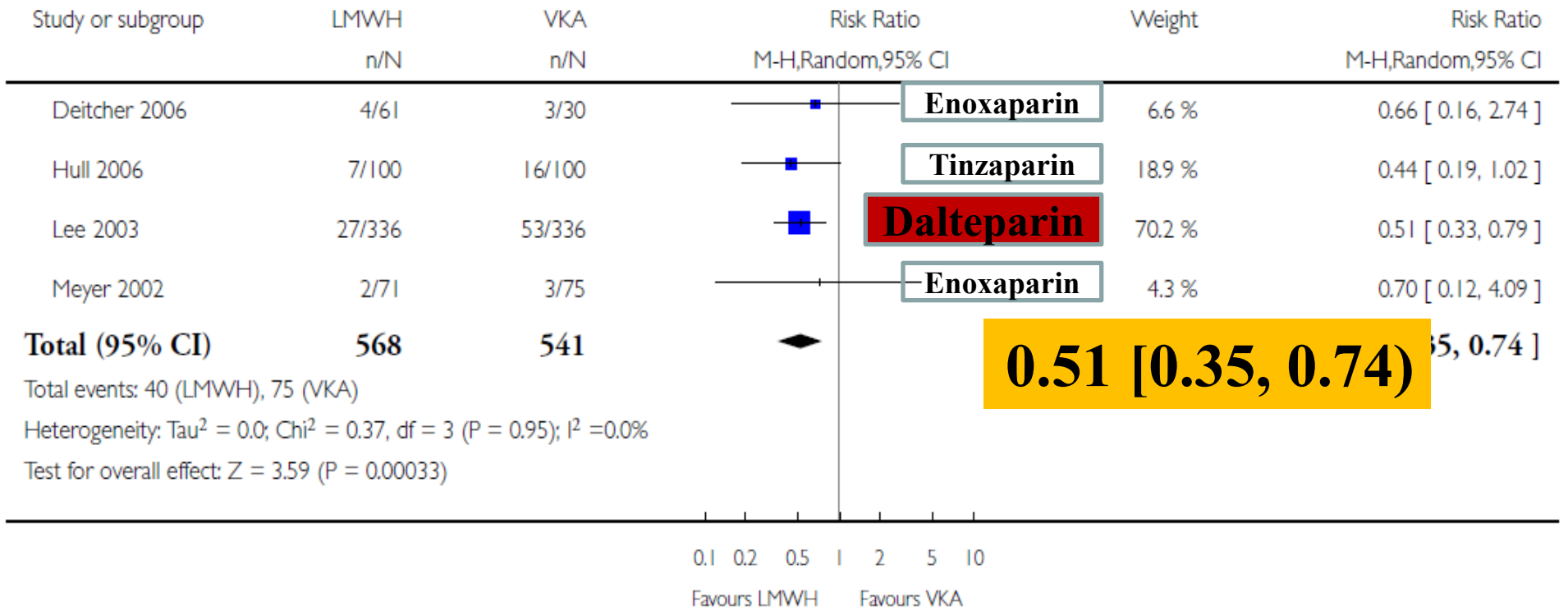
Anticoagulation in patients with antiphospholipid antibody syndrome



Pastori D, et al. Front. Cardiovasc. Med. 2021 8:715878

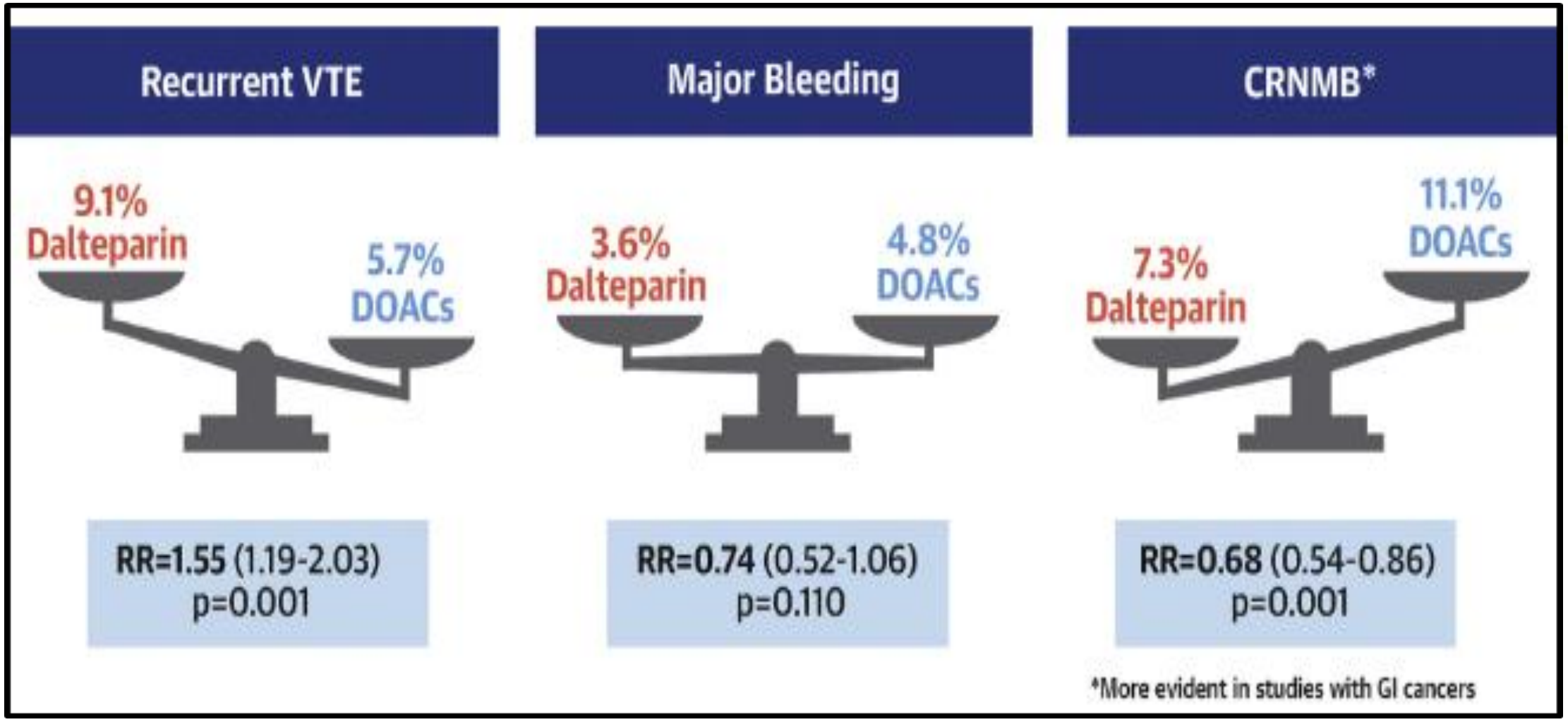
LMWH vs warfarin in patients with cancer-VTE

Recurrent VTE



Akl EA et al. Cochrane Database Syst Rev 2011

DOAC vs LMWH in patients with cancer-VTE



Sabatino, J. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):428–40

Risk of recurrence and extended anticoagulation

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

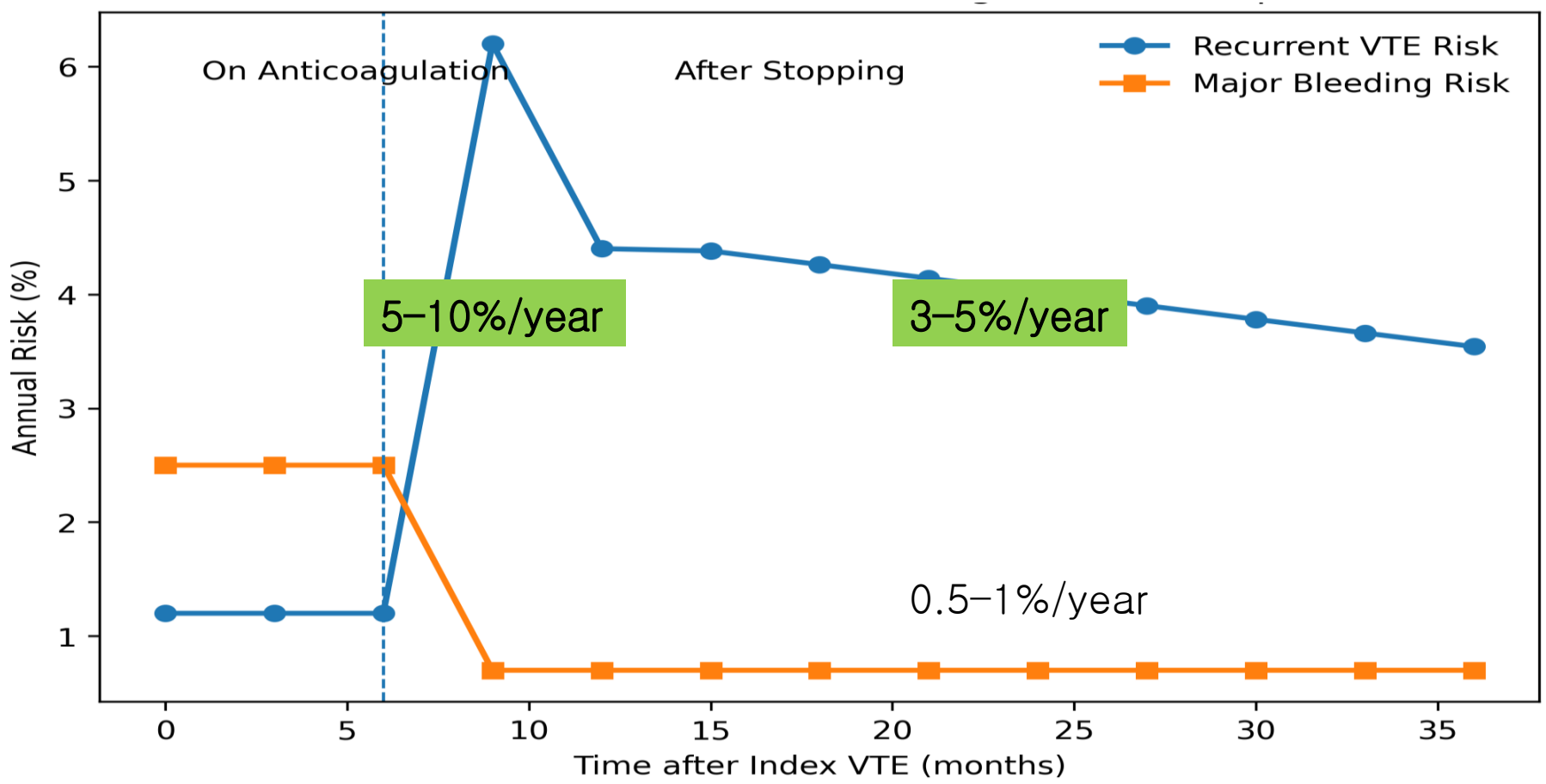
Indefinite treatment with a VKA is recommended for patients with antiphospholipid antibody syndrome.	I
Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event.	IIa
Extended anticoagulation should be considered for patients with a persistent risk factor other than anti-phospholipid antibody syndrome.	IIa
Extended anticoagulation should be considered for patients with a minor transient/reversible risk factor for the index PE event.	IIa
A reduced dose of apixaban or rivaroxaban should be considered after the first 6 months.	IIa

ESC guidelines. Eur heart J 2019

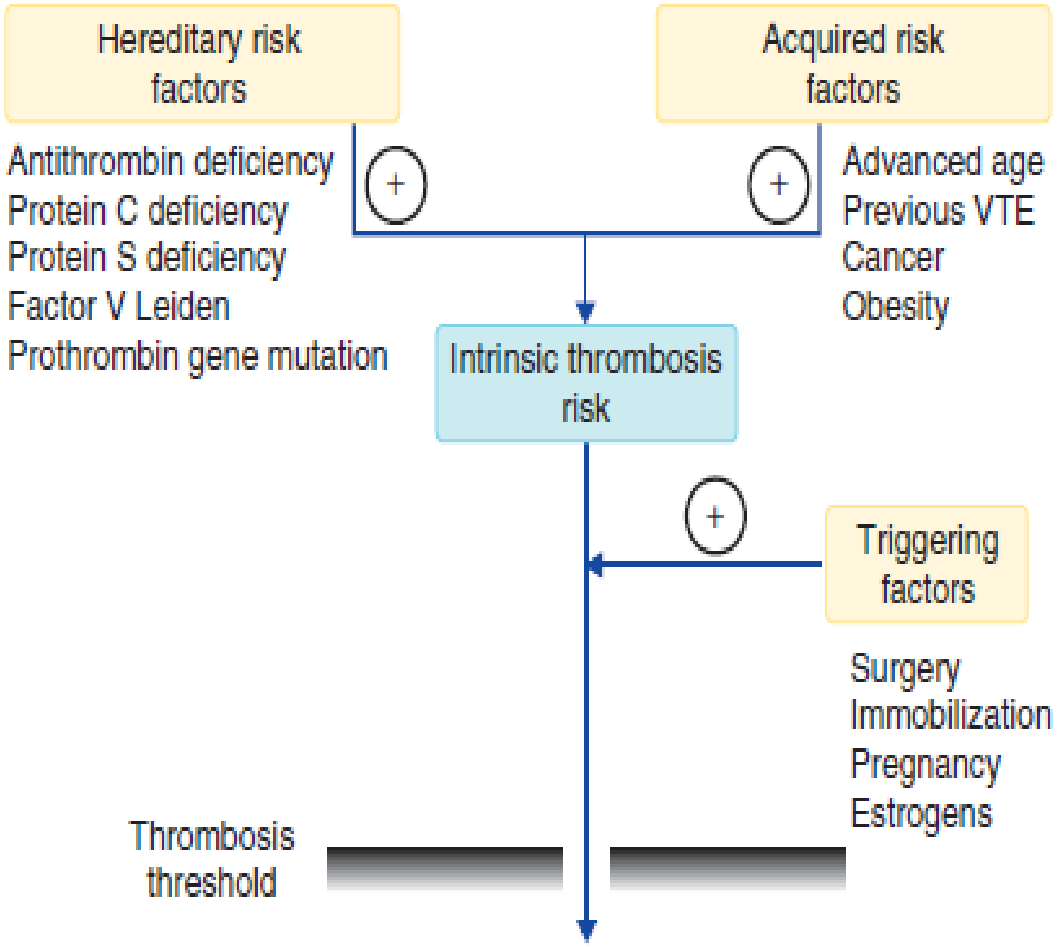
Recommendations for anticoagulation therapy by recurrence risk

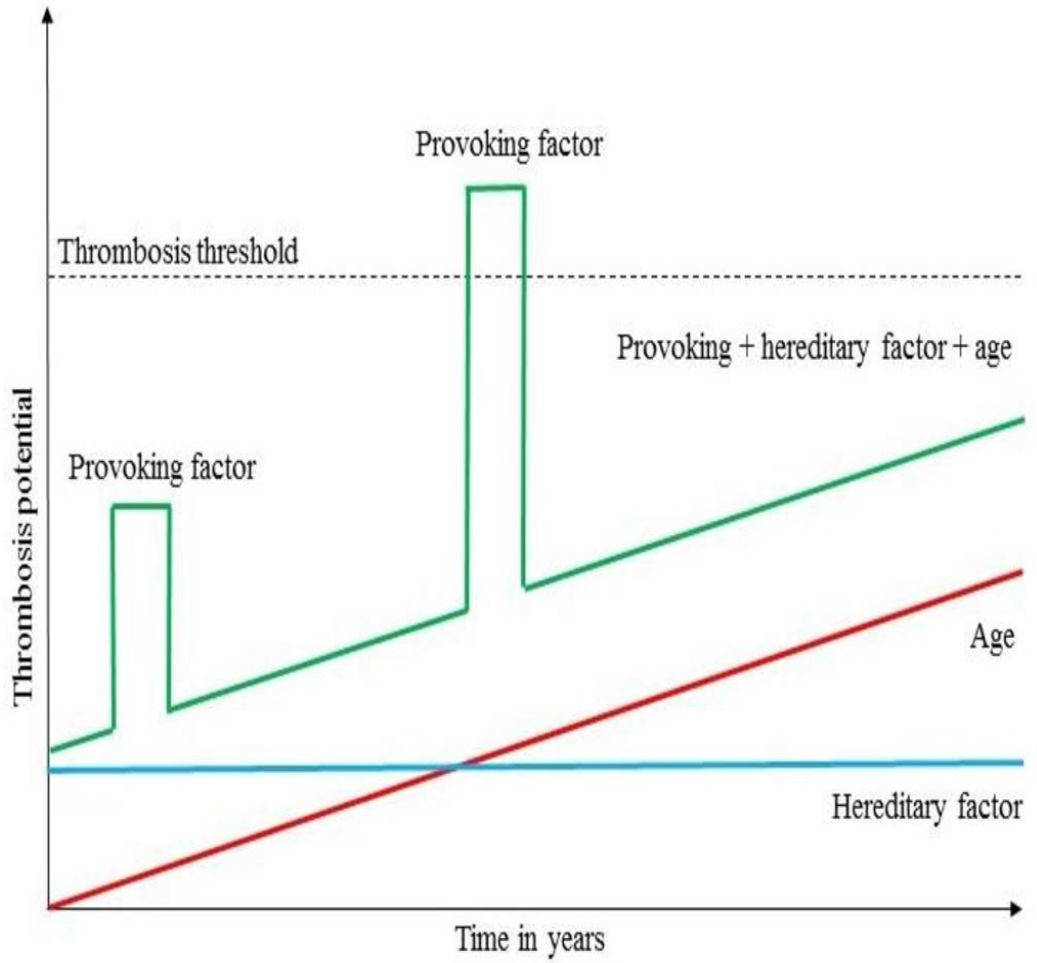
	Transient or reversible	Persistent
Major	• **Major surgery** (General anesthesia >30 mins) • **Major trauma** with fractures • **Hospitalization** (≥3 days) with while confined to hospital bed	• **Active cancer** (Metastatic or undergoing treatment) • **Antiphospholipid Syndrome** (APS) • **Chronic paralysis** or limb paresis
Minor	• Minor surgery (GA <30 mins) • Pregnancy or postpartum period • Hormonal therapy (Oral contraceptives, HRT) • Long-distance travel (e.g., >8 hours) • Minor leg injury with reduced mobility	• Congestive heart failure • Obesity (BMI >30 kg/m²) • **Inherited thrombophilia** • Inflammatory Bowel Disease (IBD)

Two-Phase VTE Risk Model (Unprovoked VTE)



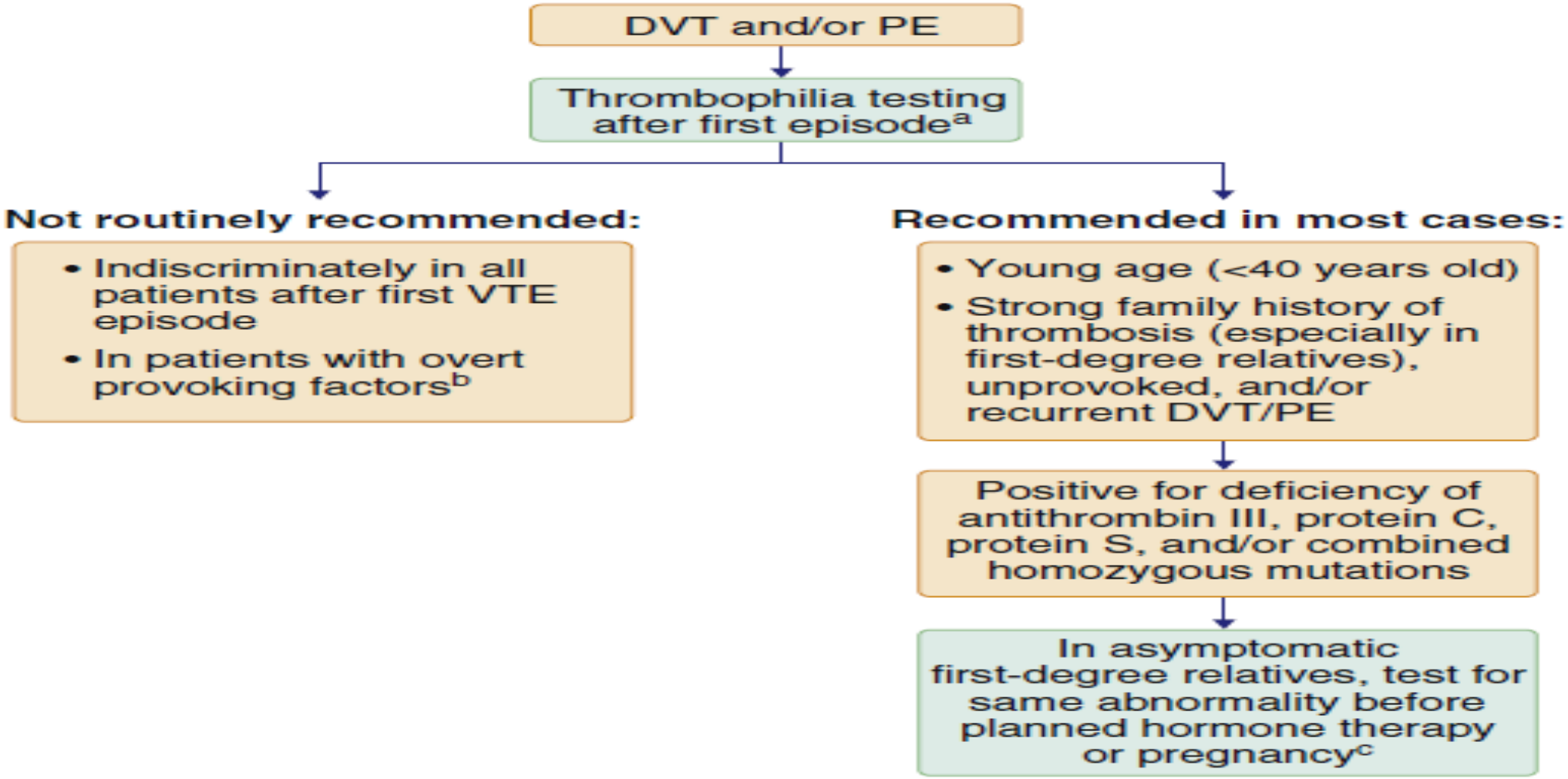
Thrombosis potential model





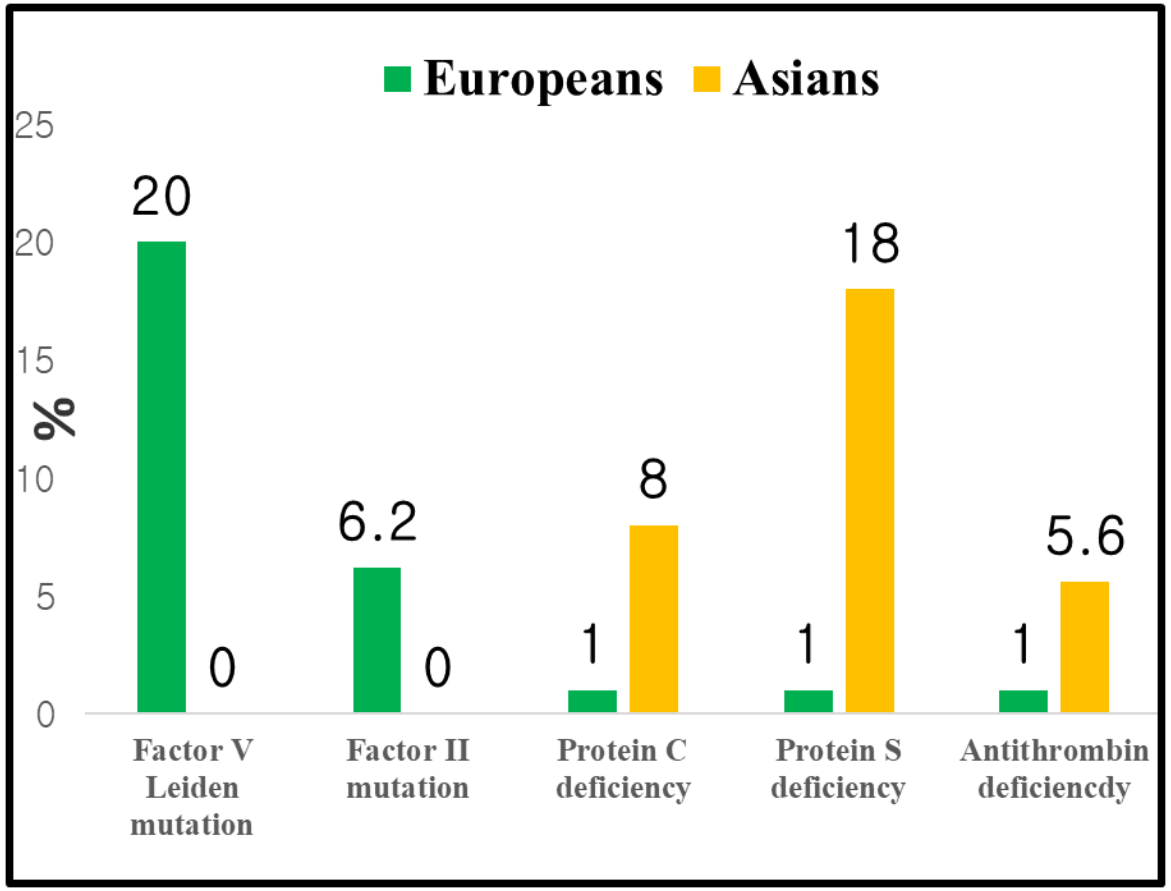
Rosendaal, F.R. Lancet 1999; 353: 1167–1173

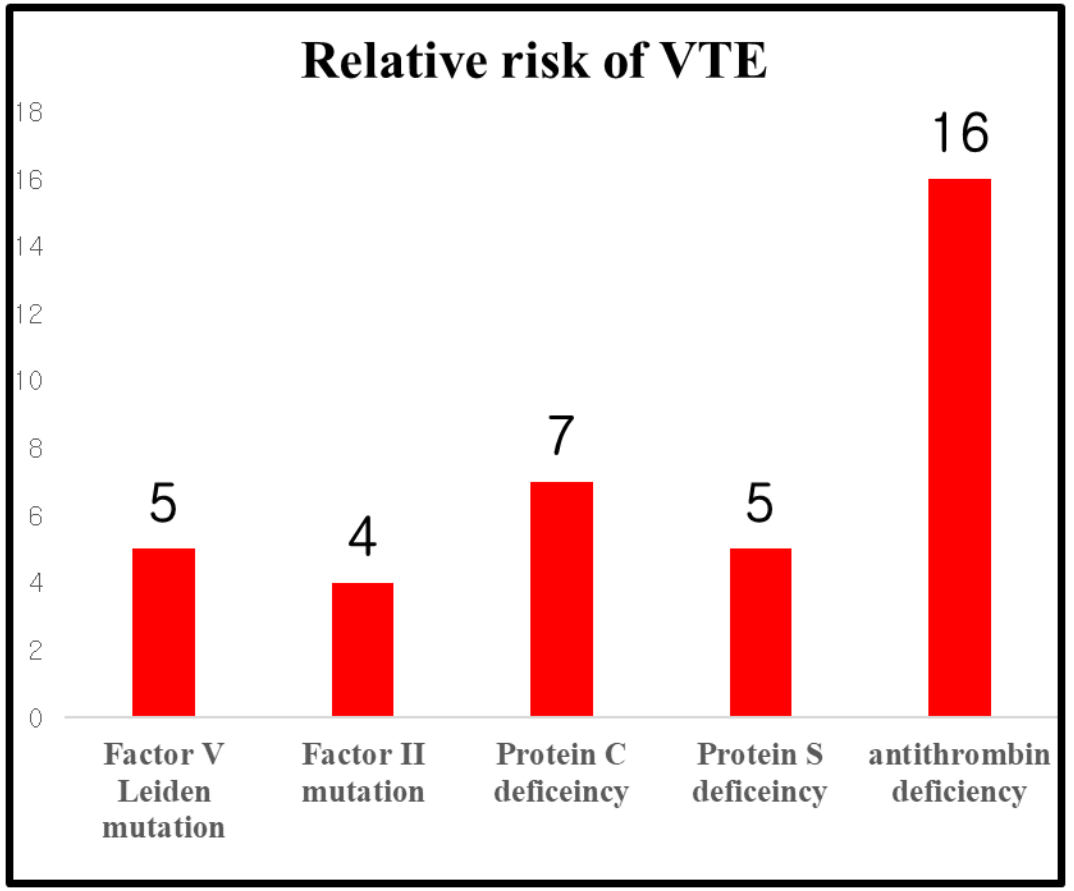
Thrombophilia testing: who



Goldman-Cecil Medicine

Prevalence of hereditary thrombophilia and VTE risk





Thrombophilia testing: when

- Optimally, it should be performed **in clinically stable patients after completion of oral anticoagulation** following a thrombotic episode.
- **Warfarin can elevate anti-thrombin levels** into the normal range in patients who do have an inherited deficiency state.
- **The direct oral anticoagulants can interfere with testing for lupus anticoagulant**.
- Blood should be drawn **at least 2 weeks after stopping warfarin and at least 48 to 72 hours after stopping a direct oral anticoagulant.**

Case: 25/F DVT with PTE

혈액응고검사 2020-12-14 09:08:16

AB0011	Protein C (Qn)[ChemR-I],Blood	92	70	140	%
AB0015	Factor II (Qn)[ChemR-I],Blood	119	79	131	%
AB0016	Factor V (Qn)[ChemR-I],Blood	89	62	139	%
AB0020	Factor VIII (Qn)[ChemR-I],Blo...	63	50	150	%
AB0024	Protein S(Function) (Qn)[Che...	89	65	140	%
AB0035	Antithrombin III (Qn)[ChemR...	53	80	120	%
AB0041	ACA IgG (Ql),Blood	Negative		Ne...	U/mL
AB0042	ACA IgM (Ql),Blood	Negative		Ne...	U/mL
AB0055	β2-GPI-IgG (Ql),Blood	Negative		Ne...	U/mL
AB0057	β2-GPI-IgM (Ql),Blood	Negative		Ne...	U/mL

21 혈액응고검사 2021-02-01 09:25:00

AB0035	Antithrombin III (Qn)[ChemR...	47	80	120	%

혈액응고검사 2020-12-14 09:05:12

AB0037	Lupus anticoagulant screeni...	Positive
AB0039	Lupus anticoagulant screeni...	Positive

혈액응고검사 2021-02-01 13:53:36

AB0037	Lupus anticoagulant screeni...	Negative
AB0039	Lupus anticoagulant screeni...	Negative

Case: 25/F genetic study

산정특례;극희귀질환 등록

RESULT :

Mutations of SERPINC1 gene: Detected (Positive)

Genetic Variations Observed

Base Change	AA Change	Designation	Mutation/Polymorphism
c.981A>G	p.Val327=	Homozygous	Polymorphism (rs5877)
c.1011A>G	p.Gln337=	Homozygous	Polymorphism (rs5878)
c.377C>A	p.Ala126Asp	Heterozygous	Known

* Nucleotide number는 cDNA를 기준으로 하였습니다(GenBank Accession No. NM_000488.3).
Known mutation의 여부는 Web-based database인 HGMD (The Human Gene Mutation Database, <http://www.hgmd.cf.ac.uk>)를 참고하였습니다.

INTERPRETATION :

환자의 임상상(antithrombin deficiency)과 연관성이 있을 것으로 예상되는 돌연변이가 관찰되었습니다.

SERPINC1 유전자의 exon 2의 염기순서를 분석한 결과 뉴클레오타이드 377번 C가 A로 치환되어, Alanine 이 Aspartate 로 치환되는 missense mutation 이 관찰되었습니다. 이는 국내에서도 보고된 적이 있는 돌연변이 입니다(Haematologica
. 2014 Mar;99(3):561-9.).

Case: 25/F 1st pregnant state

- 2025.10 임신 계획: 임신시 apixaban -> dalteparin 10000 IU SQ QD
- 2026.01 임신 확인: dalteparin 10000 IU SQ QD

- 2026.03.03 D-dimer 9.47 (←0.27) anti-thrombin 40%, anti-Xa activity 0.37 (0.3-0.6)

  dalteparin 12500 IU SQ QD
- 2026.03.10 D-dimer 12.03, anti-Xa activity 0.55 IU/mL

  dalteparin 15000 IU 증량

2026.03.16 dyspnea D-dimer > 35.2, anti-Xa activity 0.44 IU/mL

anti-thrombin 3000 IU (주 1회), enoxaparin 80mg bid

2026.03.25 D-dimer 2.5, anti-thrombin 79%, anti-Xa activity 0.77

2026.04.07 D-dimer 0.75 anti-thrombin 46% anti-Xa acitivty 0.57

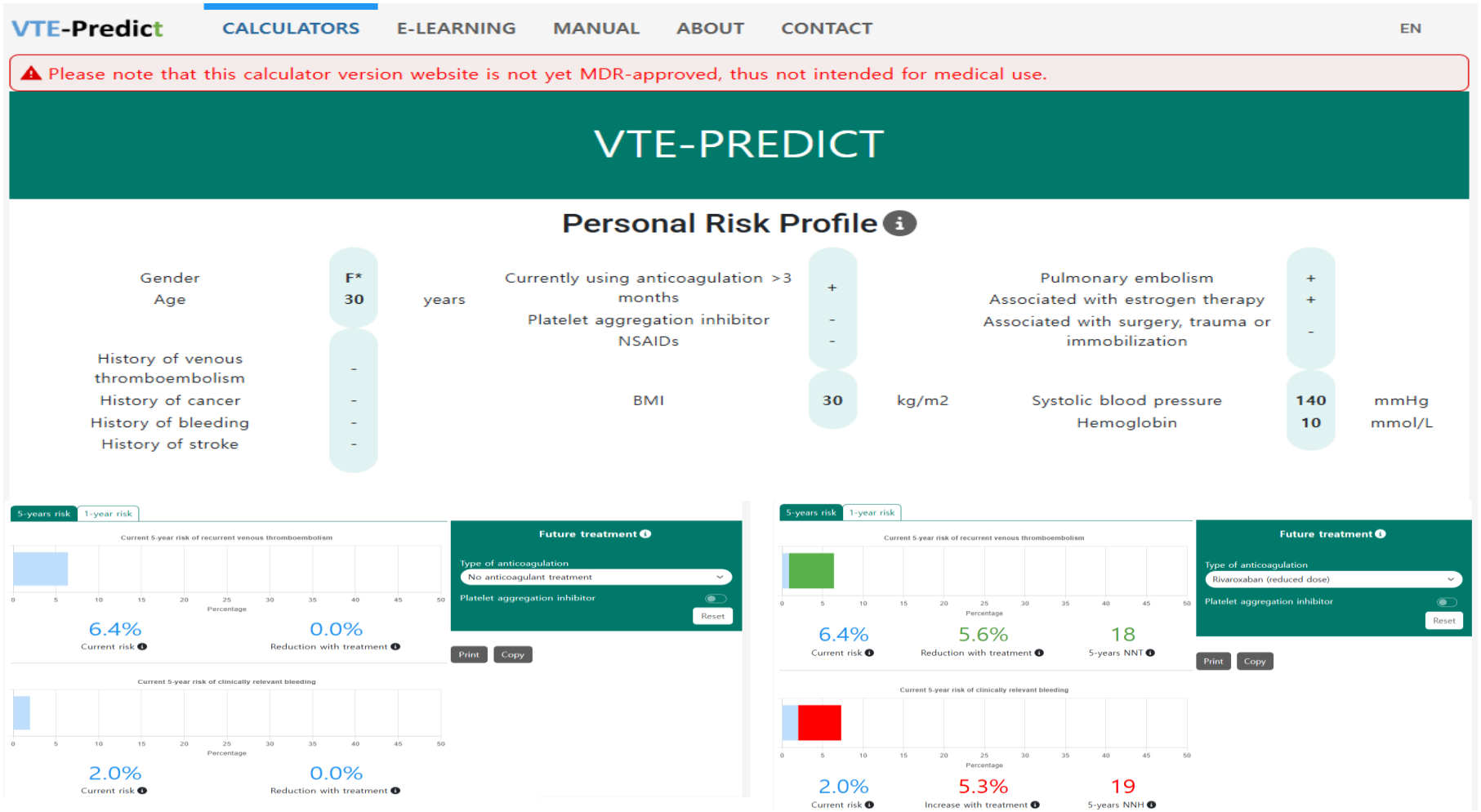
VTE recurrence prediction model performance

Model	Target Population	C-statistic (Range)	Clinical Utility
HERDOO2	Women (Unprovoked)	**0.61 (0.54-0.68)**	**Best for identifying low-risk women (<3%/yr)**
DASH Score	Men & Women	**0.60 (0.53-0.72)**	**Accuracy drops significantly in elderly (65+)**
Vienna (VPM)	Men & Women	**0.58 ~ 0.61**	**Good for 1-year risk; may underestimate long-term**
Vienna CAT	Cancer Patients	**0.68 ~ 0.69**	**Reliable performance in cancer-specific VTE**
VTE-PREDICT	General VTE	**0.70 ~ 0.73**	**High discrimination; considers bleeding risk**

Bleeding prediction model

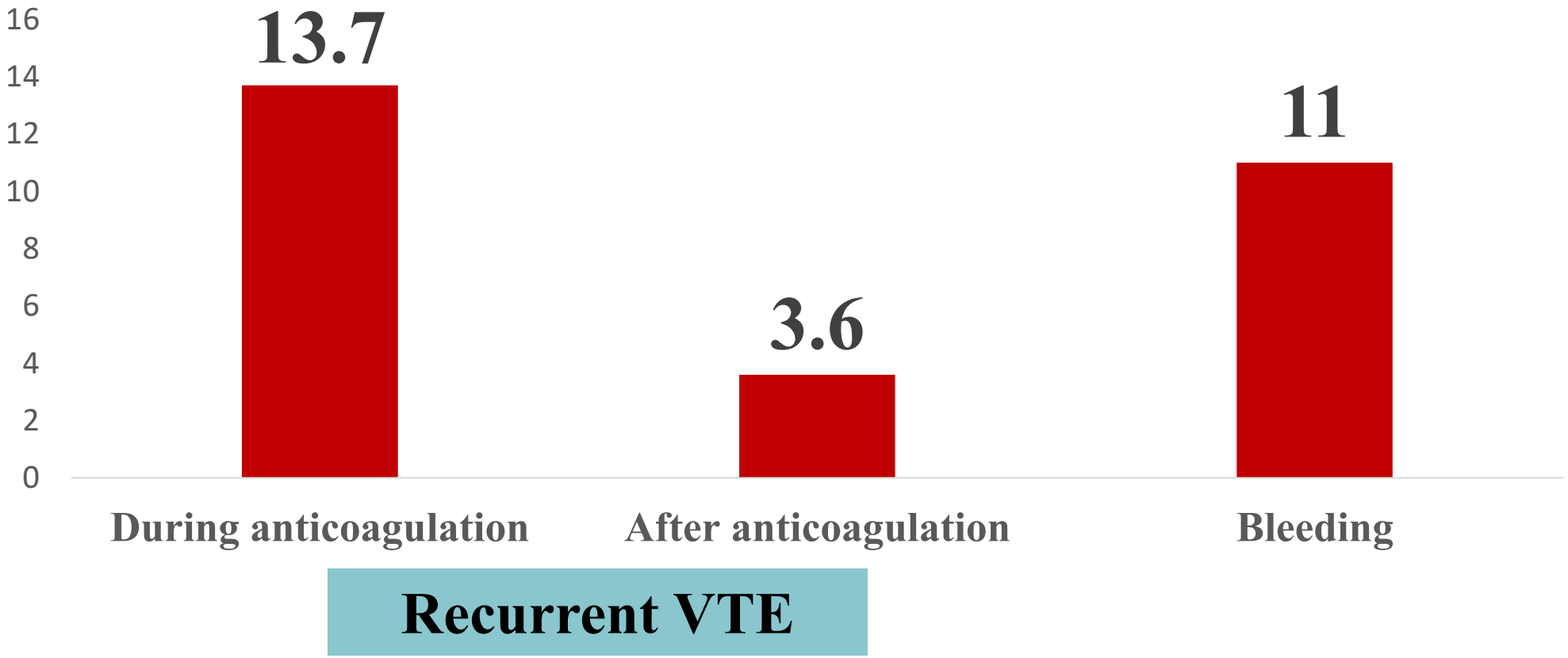
Model	Target Population	Key Predictors (Score)	High-Risk Threshold
VTE-BLEED	Stable VTE Patients	Active Cancer (+2), HTN (Male +1), Anemia (+1.5), Hx of Bleeding (+1.5), Age ≥60 (+1.5), Renal Failure (+1.5)	**≥ 2 Points** (Major Bleeding ~12%)
HAS-BLED	General (Commonly AF)	HTN, Renal/Liver dz, Stroke, Bleeding Hx, L abile INR, Elderly, Drugs/Alcohol (+1 each)	**≥ 3 Points**
IMPROVE	Inpatients (Pro phylaxis)	Ulcer (+4.5), Bleeding Hx (+4), Low Platelets (+4), Renal/Liver failure (+2.5)	**≥ 7 Points** (Risk ~7.9%)

Integrated Approach (VTE-PREDICT Model)



Case fatality of recurrent VTE and major bleeding

Systematic review



Carrier M, et al. Ann Intern Med. 2010;152:578-589.

Recommendations for anticoagulation therapy by recurrence risk

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with a first acute PE and no major reversible risk factor, continuing anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase* is beneficial to prevent recurrent VTE.[1-4]
1	B-NR	2. In patients with a first acute PE due to a major reversible risk factor, stopping anticoagulation at the end of the initial treatment phase (3-6 months) is recommended over continuing anticoagulation into the extended treatment phase in order to optimize the net clinical benefit of recurrent VTE versus bleeding.[5]
1	C-LD	3. In patients with a first PE due to a persistent risk factor, continuing anticoagulation at the initial treatment phase (3-6 months) into the extended treatment phase is reasonable in order to prevent recurrent VTE.[6]

2a	B-NR	8. In patients with a first acute PE due to a minor reversible risk factor, shared decision-making about stopping anticoagulation at the end of the initial treatment phase (3-6 months) versus continuing anti-coagulation into the extended treatment phase is reasonable in order to optimize the net clinical benefit of recurrent VTE versus bleeding.[3]

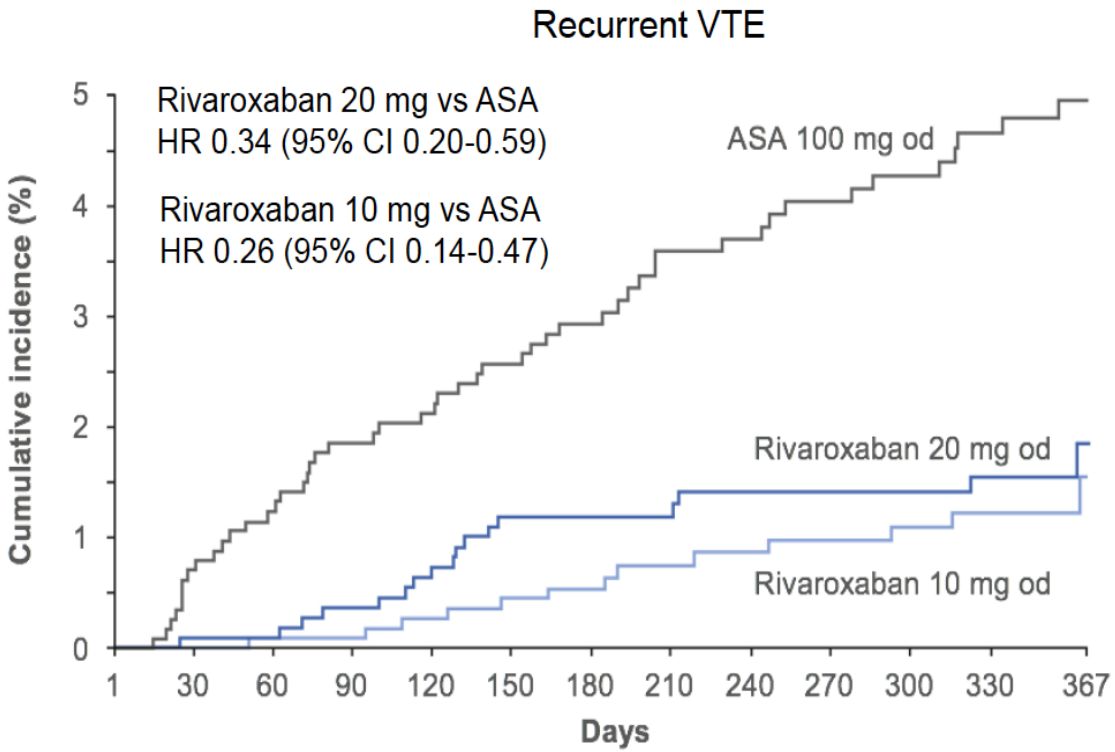
2026 AHA/ACC/ACCP Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults

Recommendations for extended anticoagulation therapy

COR	LOE	RECOMMENDATIONS
1	A	4. For patients with a PE who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, treatment with a DOAC, unless contraindicated, is recommended over a VKA to reduce the risk of bleeding.[7-9]
1	A	5. For patients with a PE and with cancer who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, either a DOAC or LMWH is recommended over VKA to reduce the risk of recurrent VTE.[10-15]
1	B-R	6. For patients with a PE and without cancer offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, but have a contraindication to DOAC, VKA is recommended over aspirin or no therapy to reduce the risk of recurrent VTE.[16-18]
1	A	7. For patients with a PE who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, treatment with half-dose apixaban or rivaroxaban is recommended to reduce the risk of bleeding.[8,9,19,20]

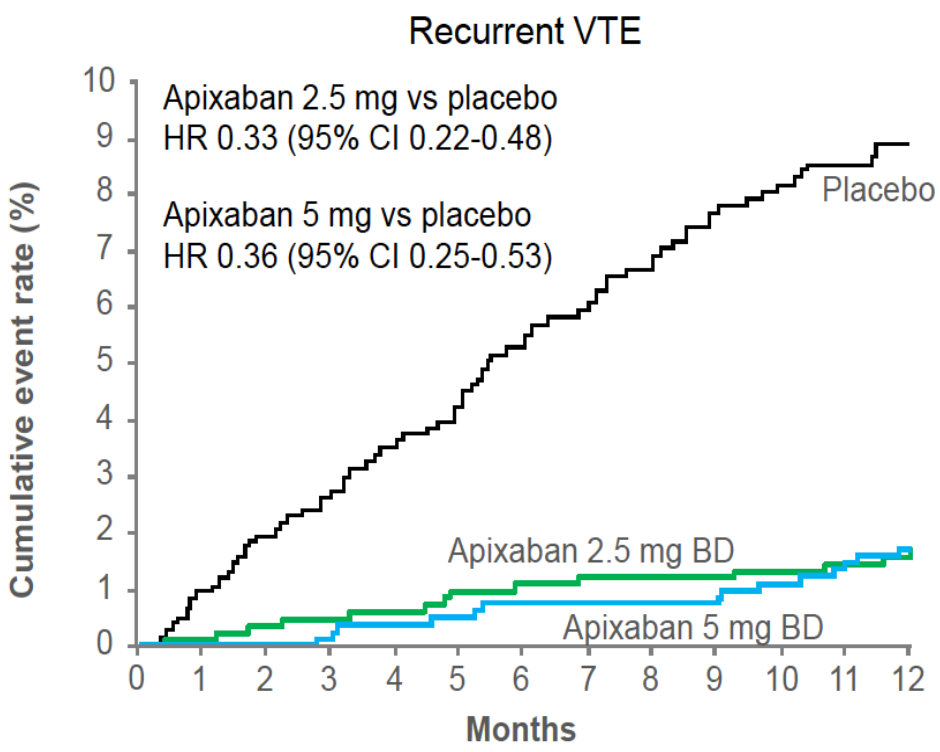
2026 AHA/ACC/ACCP Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults

Reduced doses of DOACs for extended treatment: recurrent VTE



EINSTEIN CHOICE

Weitz JI et al, N Engl J Med 2017; 376:1211-1222.

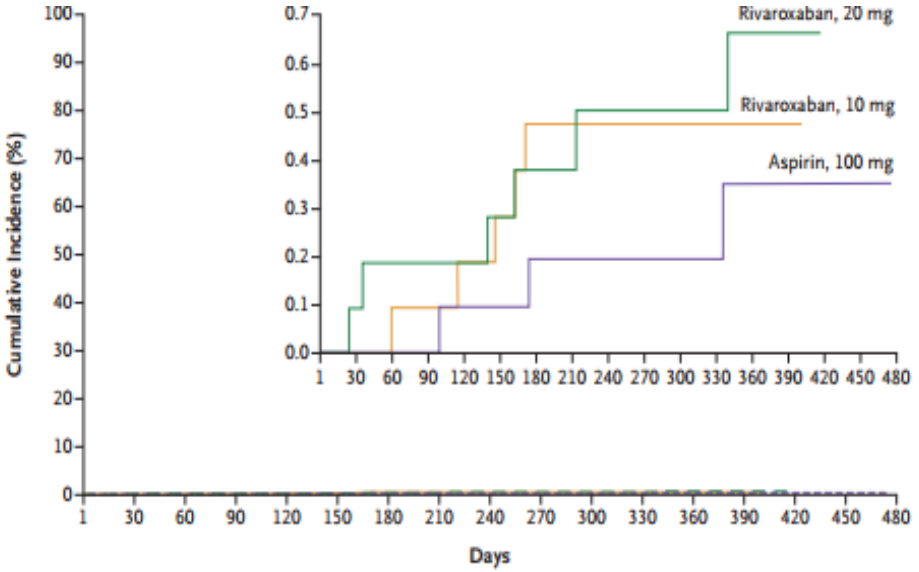


AMPLIFY-EXT

Agnelli G et al. N Engl J Med 2013; 368: 699-708.

Reduced doses of DOACs for extended treatment: Bleeding

Major Bleeding

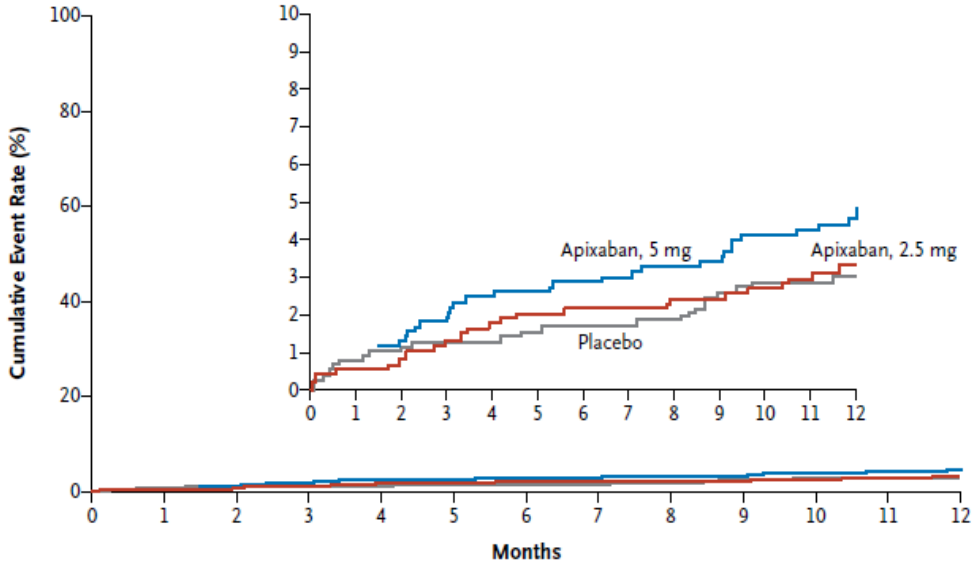


No. at Risk																
Rivaroxaban, 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

EINSTEIN-CHOICE

Weitz JI et al, N Engl J Med 2017; 376:1211-1222.

Major or Clinically Relevant Non-major Bleeding



No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

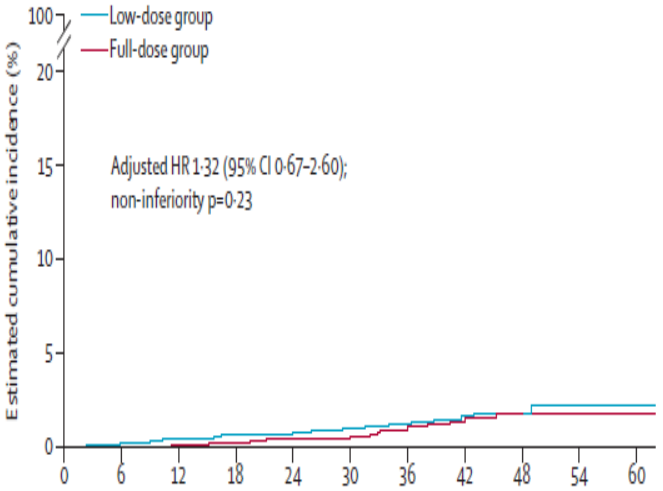
AMPLIFY-EXT

Agnelli G et al. N Engl J Med 2013; 368: 699-708.

Extended treatment of VTE with reduced-dose versus full-dose DOACs in patients at high risk of recurrence

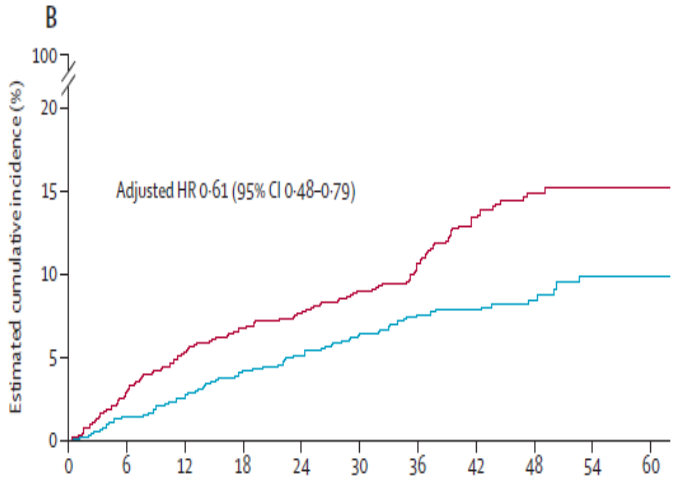
- **RENOVE was a non-inferiority, investigator-initiated, multicentre, randomised, open-label, blinded endpoint trial done in 47 hospitals in France.**

Symptomatic recurrent VTE



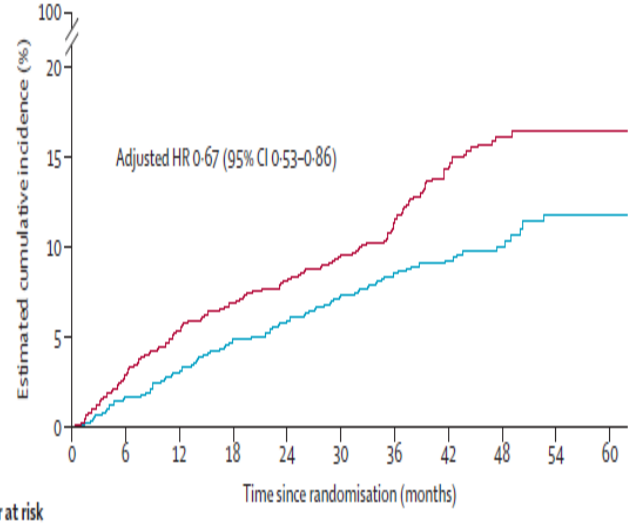
Number at risk (number censored)											
Low-dose group	1383 (0)	1357 (23)	1284 (93)	1154 (220)	1040 (333)	897 (474)	726 (643)	586 (780)	387 (978)	207 (1157)	60 (1304)
Full-dose group	1385 (0)	1365 (20)	1290 (93)	1161 (221)	1027 (352)	897 (481)	733 (595)	595 (777)	384 (986)	213 (1157)	71 (1299)

Major or Clinically Relevant Non-major Bleeding



Number at risk (number censored)											
Low-dose group	1383 (0)	1341 (22)	1254 (94)	1114 (214)	994 (324)	848 (458)	679 (617)	545 (749)	360 (931)	187 (1100)	53 (1234)
Full-dose group	1385 (0)	1327 (17)	1225 (88)	1087 (208)	953 (332)	826 (446)	665 (594)	529 (711)	334 (898)	184 (1047)	63 (1168)

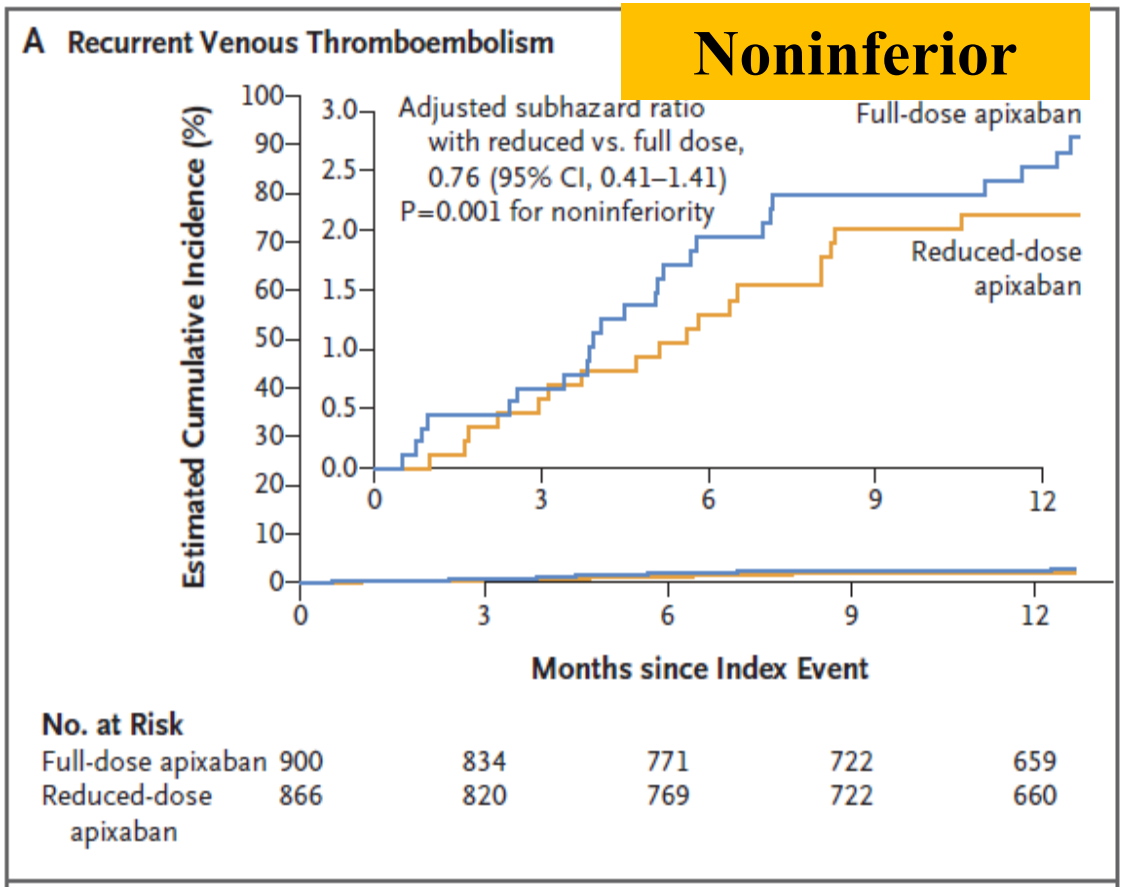
Net clinical benefit



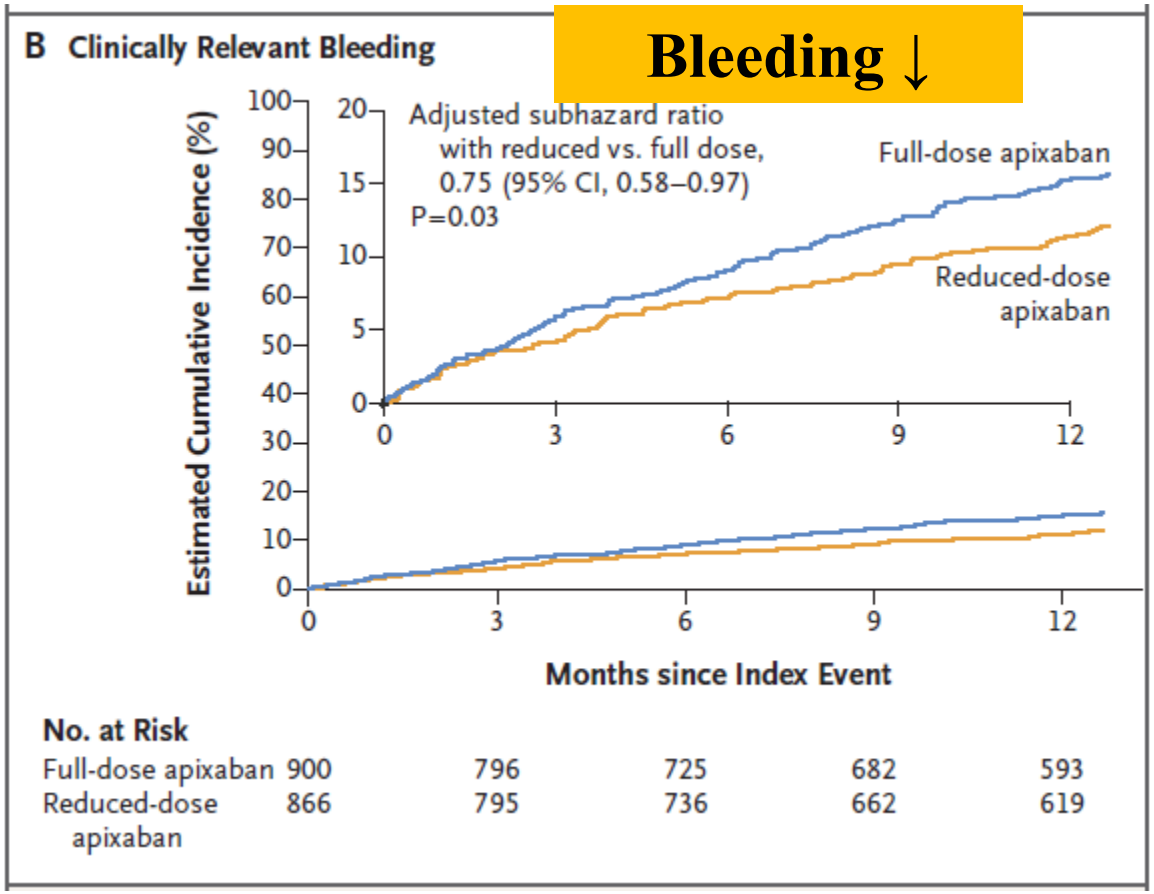
Number at risk number censored)											
Low-dose group	1383 (0)	1338 (22)	1250 (92)	1107 (212)	987 (321)	843 (452)	674 (610)	539 (740)	355 (920)	183 (1087)	53 (1217)
Full-dose group	1385 (0)	1327 (17)	1223 (88)	1086 (206)	951 (328)	823 (442)	660 (590)	525 (705)	331 (889)	183 (1036)	62 (1157)

Extended Reduced-Dose Apixaban for Cancer-Associated VTE: API-CAT trial

Noninferior



Bleeding ↓

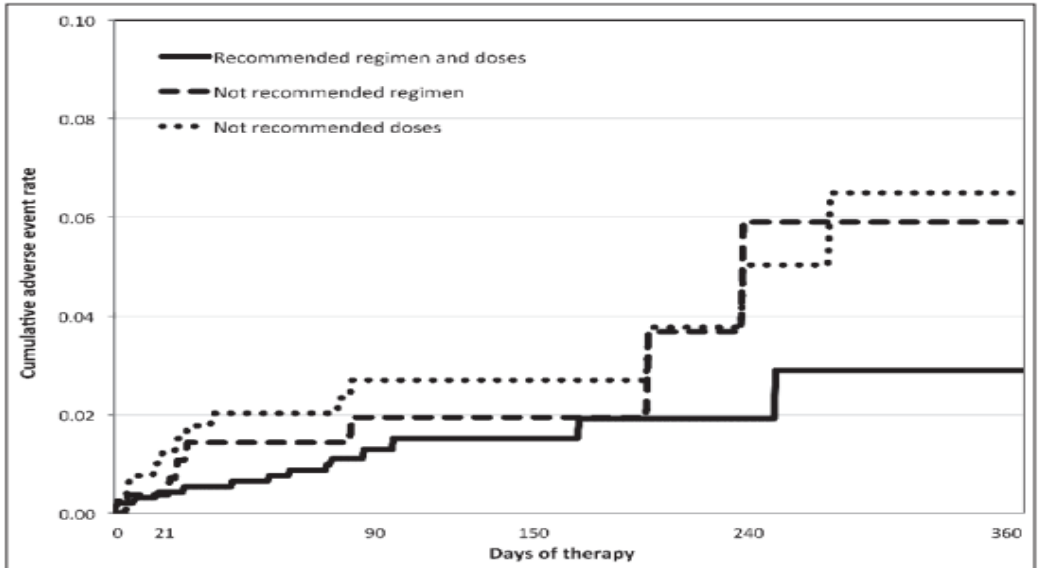


Mahe I, et al. N Engl J Med 2025;392:1363–73.

Real-life treatment of VTE with DOACs: The influence of recommended dosing and regimens

- **The RIETE registry to compare the outcomes in patients with VTE receiving DOACs**

Patients receiving DOACs at **non-recommended doses and/or regimens experienced a higher rate of VTE recurrences (adjusted HR: 10.5; 95 %CI: 1.28–85.9)** and **a similar rate of major bleeding** (adjusted HR: 1.04; 95 %CI: 0.36–3.03) or death (adjusted HR: 1.41; 95 %CI: 0.46–4.29) than those receiving the recommended doses and regimens.



Days of therapy	0	21	90	150	240	360
Recommended doses and regimens	963	920	763	364	133	51
	0	4 (0.4 %)	10 (1.0 %)	12 (1.2 %)	13 (1.3 %)	14 (1.5 %)
Not recommended regimens	282	279	226	127	45	21
	0	1 (0.4 %)	4 (1.4 %)	5 (1.8 %)	6 (2.1 %)	7 (2.5 %)
Not recommended doses	416	391	313	188	79	37
	0	5 (1.2 %)	8 (1.9 %)	10 (2.4 %)	11 (2.6 %)	13 (3.1 %)

Trujillo-Santos J, et al. Thromb Haemost 2017; 117: 382–389

Recurrent VTE

- **Cancer, APS, non-adherence, Off-label sub-therapeutic DOAC**
- vasculitis, inflammatory conditions, paroxysmal nocturnal hemoglobinuria, pregnancy, and vascular compression or other vascular abnormalities, HIT, anti-thrombin deficiency, sub-theraeputic drug levels

- Management option:

  Reduced dose DOAC -> full-dose DOAC

  Increasing the dose of LMWH by 20-25%

  Alternate anticoagulant regimen

  adding a vena cava filter to LMWH

2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults

Take home messages

	Selection	Dosing
DOACs	Most patients without contra-indications(severe renal impair ment, during pregnancy and la ctation)	Rivaroxaban 15mg bid →20mg qd →10mg qd Apixaban 10mg bid → 5mg bid → 2.5mg bid
UFH	Only for high risk PE CKD (GFR < 15) or ESRD on HD	aPTT 1.5-2.5 times control within 24hr Dose: 30000 IU/day
Warfarin	Triple positive APS CKD (GFR < 15) or ESRD on HD	Early initiation and a minimum of 5 days and until the INR is 2.0 or above for at least 24 h

"VTE recurrence risk is not static; it evolves over time and should be periodically reassessed"

"Prediction is difficult—response is essential in VTE management. "