PULMONER TROMBOEMBOLİDE SÜRESİZ-UZATILMIŞ TEDAVİ

Dr. Nuri Tutar

ERCİYES ÜNİVERSİTESİ TIP FAKÜLTESİ GÖĞÜS HASTALIKLARI ANABİLİM DALI

ESC
European Society of Cardiology

European Heart Journal (2019) **00**, 1–61
doi:10.1093/eurheartj/ehz405

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)

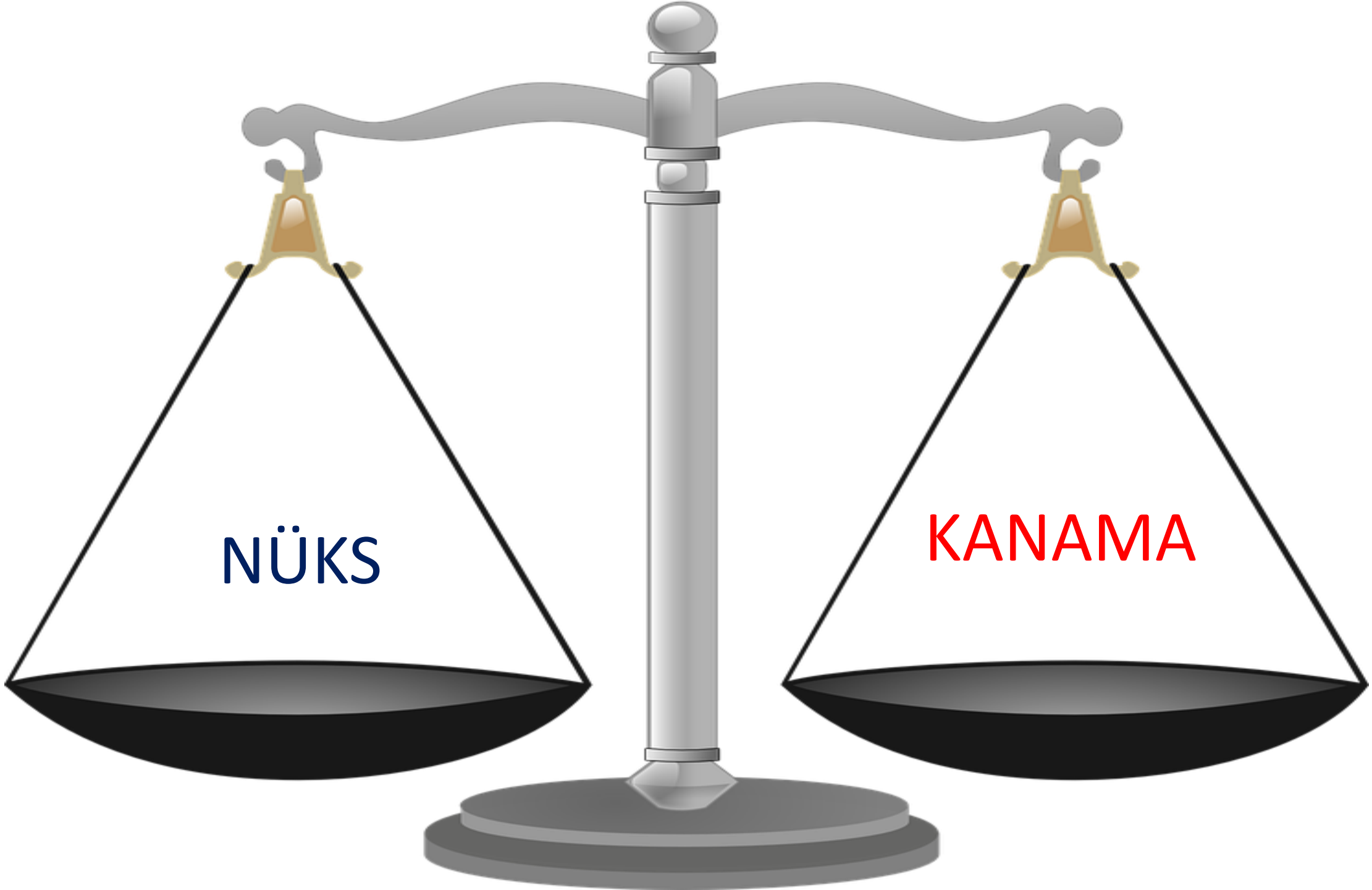
The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)

Authors/Task Force Members: Stavros V. Konstantinides* (Chairperson) (Germany/Greece), Guy Meyer* (Co-Chairperson) (France), Cecilia Becattini (Italy), Héctor

- Akut PTE tedavisinden sonraki süreç **akut episodun tedavisini tamamlamak** ve **uzun dönemde VTE rekürrensini önlemektir.**
- İlk atak **PTE** olarak geçirilirse bir sonraki **PTE** şeklinde, **DVT** olarak geçirilerse **DVT** olarak nüks ediyor.

- Oral antikoagülanlar tedavi esnasında VTE nüksünün önlenmesinde oldukça etkili ilaçlar **(%90 dan fazla**)
- Fakat tedavi süresi bitip ilaçlar kesildikten sonra **koruyucuulukları bitiyor.**
- Unprovoke VTE'si olan tüm hastalarda birkaç yıllık antikoagülasyondan sonra, antikoagülasyonda kalırken ki **kanama riskinin**, antikoagülasyon kesildikten sonra **tekrarlayan VTE riskini yakalaması ve sonunda aşması beklenmektedir**.
- Bu nedenle akut PTE geçiren hastalarda uzun süreli tedavi **nüksün önlenmesi ve kanama riski arasındaki dengeye** göre planlanmalıdır.

Couturaud F. Presse Med 53 (2024) 104245


NÜKS
KANAMA

Rekürrens Riski

- Antikoagülan tedavi kesildikten sonra gelişecek VTE rekürrensi, ilk geçirilen VTE esnasındaki özellikler ile ilişkilidir.
- PTE hastalarının ilk ataktan sonra geçici risk faktörü olan hastalarda tedavi kesilmesinden sonraki nüks riski **%2.5 yıl** iken, kanser-bilinen trombofilisi ve geçici risk faktörü olmayan hastalarda ise nüks riski **%4.5 yıldır.**

Journal of Thrombosis and Haemostasis, **14**: 2402–2409 DOI: 10.1111/jth.13524

ORIGINAL ARTICLE

The long-term recurrence risk of patients with unprovoked venous thromboembolism: an observational cohort study

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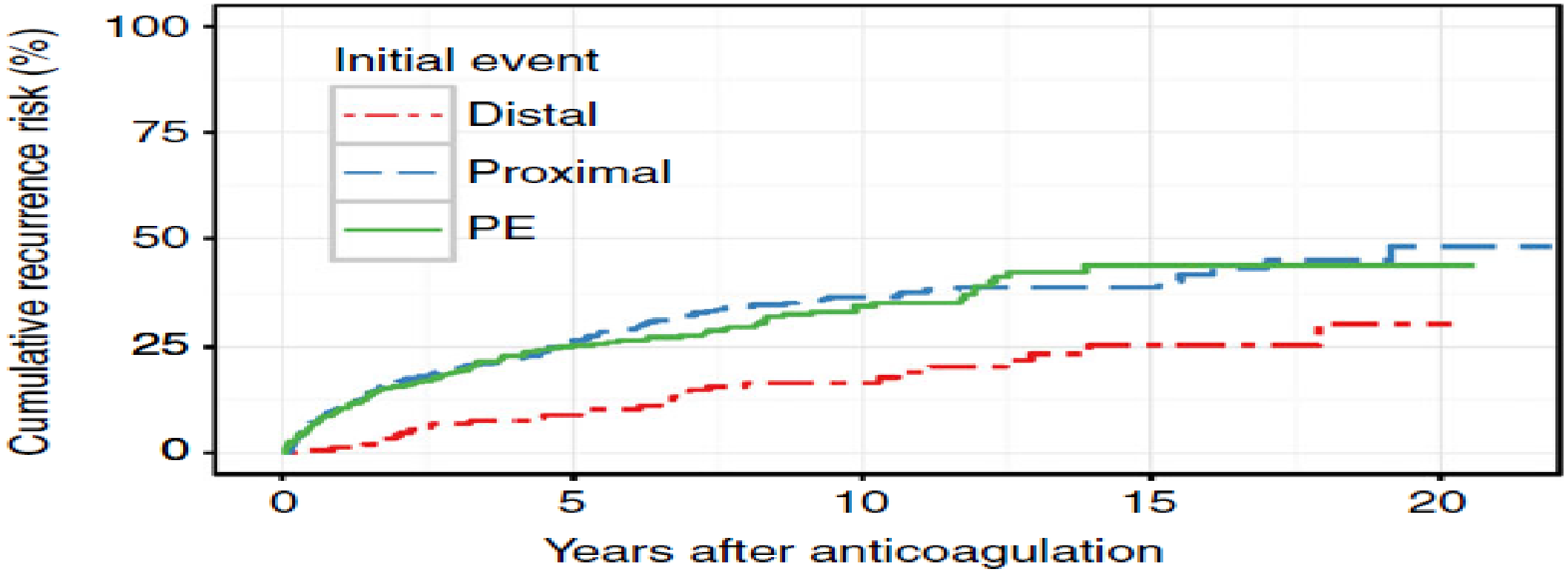
Volume 14, Issue 12, December 2016, Pages 2402-2409

Ameliyat, travma, gebelik veya hormon kullanımıyla ilişkili VTE'si olan; antitrombin, protein C veya protein S eksikliği olan; lupus antikoagülanı olan; kanser hastası olan; faktör (F) V Leiden ve/veya FII G20210A mutasyonu için çift heterozigot veya homozigot olan veya VTE dışındaki nedenlerle antitrombotik bir ilaçla uzun süreli tedavi alacak olan hastalar **hariç tutulmuştur.**

Table 1 Baseline characteristics of 839 patients with first unprovoked VTE

Age at time of VTE, years	53 ± 14
Sex, *n* (%)	
Men	550 (66)
Women	289 (34)
Site of first VTE, *n* (%)	
Distal DVT	154 (18)
Proximal DVT	349 (42)
PE	336 (40)
BMI	28 ± 5
Duration of anticoagulation, months	7 ± 3
Follow-up, years	7.7 (3.3, 11.4)

- Toplam 263 **(%31)** hastada semptomatik tekrarlayan VTE vardı.
- Nüks 232 hastada **(%88) provoke edilmemiş** ve 31 hastada (%12) geçici bir risk durumu ile ilişkilendirilmiştir.
- Yüz on altı hastada (%44) nüks PE, 97 hastada (%37) proksimal DVT, 46 hastada (%18) distal DVT ve dört hastada (%1) başka bir bölgede trombüs vardı (iki hastada üst ekstremite DVT'si, iki hastada splanknik ven trombozu).



Patients at risk

Distal	154	106	47	18	1
Proximal	349	160	66	20	3
PE	336	146	54	9	2

Fig. 2. Cumulative risk of recurrence according to site of first thrombosis (distal DVT vs. proximal DVT vs. PE). DVT, deep vein thrombosis; PE, pulmonary embolism. [Color figure can be viewed at

- ESC rehberi artık provoke-unprovoke teriminin kullanılmamasını önermemektedir.
- Hastaları
  - Major geçici veya reverzibl risk faktörü olanlar
  - Minör geçici veya reverzibl risk faktörü veya non-malign persistan risk fakötürü olanlar veya risk faktörü saptanamayanlar
  - Aktif kanseri olan veya antifosfollipid antikor sendromu gibi protrombotik risk faktörü olanlar

    olarak ayrılmasını önermektedir.

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

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
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	

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
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

- NÜKS ORANI İÇİN GELİŞTİRİLMİŞ SKALALAR

Supplementary Table 13 Validated prediction models for quantification of the risk of recurrent venous thromboembolism

Prediction model	Parameters	Points	Categories of recurrence risk	Risk group (for VTE recurrence) studied	Type of studies	Number of PE patients included	Remarks
Vienna prediction model[33–35]	• Male sex • Proximal DVT • Pulmonary embolism • D-dimer (continuous value)	n.a.	Continuous (nomogram)	Unprovoked VTE	Cohorts database (derivation, validation)	Derivation study: 438 (47% of cohort) Validation study: 291 (32%)	
HERDOO2[36,37]	• Hyperpigmentation, oedema or leg redness • D-dimer ≥250 µg/L (on VKAs) • Body mass index ≥30 kg/m^2 • Age ≥65 years	1 1 1 1	0–1 points: low risk; ≥2 points: high risk	Unprovoked VTE (derivation); unprovoked VTE, or with minor risk factors (validation)	Management study (derivation, internal validation)	Derivation study: 327 (49%) Management study: 1634 (59%)	Only applicable in women
DASH tool[38,39]	• D-dimer (post-VKA; normal or abnormal) • Age <50 years • Male sex • Hormonal therapy	2 1 1 −2	≤1 points: low risk; ≥2 points: high risk	Unprovoked VTE, or minor risk factors	Cohorts database (derivation, external validation)	Not reported	
DAMOVES[40,41]	• Age (continuous) • Sex • Obesity • Abnormal D-dimer • Factor VIII (continuous) • Genetic thrombophilia • Varicose veins	n.a.	Continuous (nomogram)	Unprovoked VTE	Prospective cohort (derivation) Retrospective cohort (external validation)	Derivation study: 270 (68%) Validation study: not reported	

HERDOO2

HERDOO2 Rule

	Predictor	Scoring
H	Hyperpigmentation	1 point total, if any one of these criteria is present
E	Edema	
R	Redness of either leg	
D	D-dimer ≥ 250 µg/L while anticoagulated	1
O	Obesity with BMI ≥ 30 kg/m^2	1
O	Older age, ie, ≥ 65 years	1

Decision Making:		
Women:	0-1	Discontinue anticoagulation
	≥2	Continue anticoagulation
All men		Continue long-term anticoagulation

Rodger MA, et al. *BMJ*. 2017;356:j1065.

Risk Assessment Tool	Factors	Points	Total Score	Annual Risk of Recurrence
HERDOO2[5,6]	Post-thrombotic signs (hyperpigmentation, edema or redness of either leg)	1	0–4	Men: 8.4-13.7%
	D-dimer level >250 µg/L (during anticoagulation)	1		Women with score <2: 1.6-3.0%
	Body mass index ≥30 kg/m2	1		Women with score 2: 7.4-14.1%
	Age ≥65 years	1		

DASH Prediction Score for Recurrent VTE

D-dimer abnormal Measured ~1 month after stopping anticoagulation	**No 0**	Yes +2
Age ≤50 years	**No 0**	Yes +1
Male patient	**No 0**	Yes +1
Hormone use at VTE onset (if female) If male patient, select "No"	**No 0**	Yes -2

MANAGEMENT

In a patient with previously diagnosed VTE who has completed a 3-6 month course of anticoagulation:

- DASH ≤1:
  - Consider **discontinuing** anticoagulation, as this group has an annual recurrence risk of 3.1%.
- DASH ≥2:
  - Consider **continuing** anticoagulation, as this group has an annual recurrence risk of 9.3%.

DASH[7,8]	D-dimer level abnormal 1 month after stopping anticoagulation	2	-2 to 4	Score 1: 0.5-5.3%
	Age ≤50 years	1		Score 2: 6.4-6.7%
	Male	1		Score 3: 6.8-12.3%
	Hormone use at VTE onset (female only)	-2		

Antikoagülasyon ilişkili kanama

- VKA (warfarin) yıllık kanama riski **%3**
- YOAK larda bu oranın %40 daha düşük olduğu ve Faz 3 klinik çalışmalarda yaklaşık yıllık **%1** olduğu saptanmıştır.
- Bununla beraber günlük pratikte daha fazla olacağı tahmin edilmektedir.

J Thromb Thrombolysis. 2017 Aug;44(2):169-178. doi: 10.1007/s11239-017-1519-8.

Effectiveness and safety of apixaban therapy in daily-care patients with atrial fibrillation: results from the Dresden NOAC Registry.

Helmert S[1], Marten S[1], Mizera H[1], Reitter A[1], Sahin K[2], Tittl L[1], Beyer-Westendorf J[3,4].

Author information

Abstract

The effectiveness and safety of apixaban for stroke prevention in atrial fibrillation (SPAF) demonstrated in ARISTOTLE needs to be confirmed in daily care. To evaluate effectiveness and safety of apixaban therapy in SPAF patients in daily care, we used data from an ongoing, prospective, non-interventional registry of more than 3000 patients on novel oral anticoagulants in daily care. Between 1 December 2012 and 31 August 2015, 514 patients receiving apixaban were enrolled. During a mean follow-up of 803.5 ± 228.9 days, the combined endpoint of stroke/transient ischaemic attack/systemic embolism occurred at a rate of 2.4/100 patient-years in the intention-to-treat analysis (95% confidence interval [CI] 1.5-3.5) and at 1.8/100 patient-years (95% CI 1.0-2.8) in the on-treatment analysis (events within 3 days after last intake). On-treatment rates were numerically lower for patients selected for 5 mg apixaban (n = 404) twice daily [BID] compared with the 110 patients selected for 2.5 mg BID [1.6 (95% CI 0.8 to 2.7) vs. 2.6/100 patient-years (95% CI 0.8-6.1)]. On treatment, major bleeding occurred at a rate of 2.8/100 patient-years and significantly more often in patients receiving the 2.5 mg BID dose compared with the 5 mg BID dose (5.3 vs. 2.2/100 patient-years). Apixaban treatment discontinuation occurred in a total of 122 patients during follow-up (12.5/100 patient-years in Kaplan-Meier analysis). Our data contribute to the confirmation of effectiveness and relative safety of apixaban in daily-care patients. Furthermore, apixaban discontinuation rates were considerably lower than those reported for vitamin K antagonists.

Blood. 2014 Aug 7;124(6):955-62. doi: 10.1182/blood-2014-03-563577. Epub 2014 May 23.

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry.

Beyer-Westendorf J[1], Förster K[1], Pannach S[2], Ebertz F[1], Gelbricht V[1], Thieme C[1], Michalski F[1], Köhler C[1], Werth S[1], Sahin K[3], Tittl L[1], Hänsel U[1], Weiss N[1].

Author information

Abstract

Worldwide, rivaroxaban is increasingly used for stroke prevention in atrial fibrillation and treatment of venous thromboembolism, but little is known about rivaroxaban-related bleeding complications in daily care. Using data from a prospective, noninterventional oral anticoagulation registry of daily care patients (Dresden NOAC registry), we analyzed rates, management, and outcome of rivaroxaban-related bleeding. Between October 1, 2011, and December 31, 2013, 1776 rivaroxaban patients were enrolled. So far, 762 patients (42.9%) reported 1082 bleeding events during/within 3 days after last intake of rivaroxaban (58.9% minor, 35.0% of nonmajor clinically relevant, and 6.1% major bleeding according to International Society on Thrombosis and Haemostasis definition). In case of major bleeding, surgical or interventional treatment was needed in 37.8% and prothrombin complex concentrate in 9.1%. In the time-to-first-event analysis, 100-patient-year rates of major bleeding were 3.1 (95% confidence interval 2.2-4.3) for stroke prevention in atrial fibrillation and 4.1 (95% confidence interval 2.5-6.4) for venous thromboembolism patients, respectively. In the as-treated analysis, case fatality rates of bleeding leading to hospitalizations were 5.1% and 6.3% at days 30 and 90 after bleeding, respectively. Our data indicate that, in real life, rates of rivaroxaban-related major bleeding may be lower and that the outcome may at least not be worse than that of major vitamin K antagonist bleeding, and probably better. This trial was registered at www.clinicaltrials.gov as identifier #NCT01588119.

Multicenter Study > Int J Cardiol. 2020 Feb 15:301:167-172. doi: 10.1016/j.ijcard.2019.11.105. Epub 2019 Nov 17.

Prediction of major bleeding in patients receiving DOACs for venous thromboembolism: A prospective cohort study

Maria Cristina Vedovati [1], Alessandra Mancuso [2], Lucia Pierpaoli [3], Ugo Paliani [4], Serenella Conti [5], Alessandra Ascani [6], Giulia Galeotti [4], Francesco Di Filippo [3], Carla Caponi [4], Giancarlo Agnelli [2], Cecilia Becattini [2]

Affiliations + expand

PMID: 31761402 DOI: 10.1016/j.ijcard.2019.11.105

Abstract

Background: In the direct oral anticoagulants (DOACs) era, extended anticoagulation is an attractive strategy after venous thromboembolism (VTE). The role of currently available bleeding risk scores for VTE patients treated with DOACs in clinical practice is undefined.

Methods: Consecutive patients with VTE were included in a prospective multicenter cohort at the initiation of treatment with DOACs. The role of ATRIA, HAS-BLED, Kuijer, ORBIT, RIETE and VTE-BLEED scores in predicting major bleeding (ISTH definition) while on DOAC treatment was assessed.

Results: Overall, 1034 patients were included and followed for one year or until the end of treatment or the occurrence of major bleeding. During study period, 26 major bleedings occurred in 25 patients (2.8% patient-year). Anemia, bleeding history and creatinine clearance <60 ml/min were significant predictors of major bleedings. The predictive value of bleeding risk scores was modest. In the 12-month study period, ORBIT (HR intermediate-high vs. low risk patients 3.62, 95% CI 1.65-7.94 and c-statistics 0.645, 95% CI 0.523-0.767) and VTE-BLEED (HR high vs. low 16.11, 95% CI 2.18-119.09 and c-statistics 0.674, 95% CI 0.593-0.755) score significantly predicted major bleeding. The lowest incidence of major bleeding (0.3%) was observed in the low-risk category of VTE-BLEED, while the highest (7.1%) in the high-risk category of ORBIT.

- KANAMA ORANI TAHMİNİ İÇİN GELİŞTİRİLMİŞ SKALALAR

Supplementary Table 14 **Prediction models for quantifying bleeding risk**

Prediction model	Parameters	Points	Categories of bleeding risk	Validation status
OBRI[44]	Age ≥65 years	1	0: low	Validation showed modest accuracy in VKA cohorts (reviewed in Klok *et al*[45])
	History of stroke	1	1–2: intermediate	
	History of gastrointestinal bleeding	1	3–4: high	
	Recent myocardial infarction, renal insufficiency, diabetes, or anaemia	1		No data in patients treated with NOACs
Kuijer *et al*[46]	Age ≥60 years	1.6	0: low	
	Female sex	1.3	1–3: intermediate	
	Malignancy	2.2	>3: high	
RIETE[47]	Age >75 years	1	0: low	
	Recent bleeding	2	1–4: intermediate	
	Cancer	1	>4: high	
	Creatinine >1.2 mg/dL	1.5		
	Anaemia	1.5		
	PE (vs. DVT) index event	1		
HAS-BLED[48,49]	Uncontrolled hypertension	1	0–2: low	
	Abnormal liver/renal function	1	≥3: high	
	Previous stroke	1		
	Bleeding history or predisposition	1		
	Labile INR (time in therapeutic range <60%)	1		
	Age >65 years	1		
	Concomitant drugs or alcohol	1		
VTE-BLEED[50]	Active cancer	1.5	0–1: low	Validated in *post hoc* analysis of RCTs testing NOACs vs. VKAs after initial LMWH treatment[50,51]
	Male patient with uncontrolled hypertension	2	≥2: high	
	Anaemia	1		
	History of bleeding	1.5		
	Age ≥60 years	1.5		
	Renal dysfunction (CrCl 30–60 mL/min)	1.5		

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

Risk Factors[b]
Age >65 y[184-193]
Age >75 y[184-188,190,192,194-202]
Previous bleeding[185,191-193,198,201-204]
Cancer[187,191,195,198,205]
Metastatic cancer[181,204]
Renal failure[185,191-193,196,199,201,206]
Liver failure[186,189,195,196]
Thrombocytopenia[195,204]
Previous stroke[185,192,195,207]
Diabetes[185,186,196,200,202]
Anaemia[185,189,195,198,202]
Antiplatelet therapy[186,195,196,202,208]
Poor anticoagulant control[189,196,203]
Comorbidity and reduced functional capacity[191,196,204]
Recent surgery[189,209,c]
Frequent falls[195]
Alcohol abuse[191,192,195,202]
Nonsteroidal anti-inflammatory drug[210]

Categorization of Risk of Bleeding[d]			
	Estimated Absolute Risk of Major Bleeding		
	Low Risk[e] (0 Risk Factors)	Moderate Risk[e] (1 Risk Factor)	High Risk[e] (≥2 Risk Factors)
Anticoagulation 0-3 mo[f]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[g]	3.2	12.8[h]
Anticoagulation after first 3 mo[f]			
Baseline risk (%/y)	0.3[i]	0.6	≥2.5
Increased risk (%/y)	0.5	1.0	≥4.0
Total risk (%/y)	0.8[j]	1.6[j]	≥6.5

VTE BLEED SCORE
(Valide edilmiş (doğrulanmış))

Factor	Score
Active cancer[a]	2
Male with uncontrolled arterial hypertension[b]	1
Anaemia[c]	1.5
History of bleeding[d]	1.5
Age ≥60 years old	1.5
Renal dysfunction[e]	1.5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

UZUN SÜRELİ TEDAVİ ÇALIŞMALARI

Supplementary Table 15 Trials on extended anticoagulant treatment

Active[a]	Study	Comparison	Design	No. patients enrolled	Patients with index PE	Treatment duration	VTE rate in control group	Risk reduction for recurrent VTE (HR; 95% CI)	Major or CRNM bleeding in active[a] group (HR; 95% CI)
Dabigatran	RE-SONATE[52]	Placebo vs. D 150 mg b.i.d.	Superiority	1343	33%	6 months	5.6%	92% (0.08; 0.02–0.25)	5.3% (2.92; 1.52 - 5.60)
	RE-MEDY[52]	Warfarin (INR 2–3) D 150 mg b.i.d.	Non-inferiority	2856	35%	18–36 months	1.3%	Risk difference, 0.38% vs. VKA (1.44; 0.78–2.64)	5.6% (0.54; 0.41 - 0.71)
Rivaroxaban	EINSTEIN Extension[23]	Placebo R 20 mg o.d.	Superiority	1196	38%	6–12 months	7.1%	82% (0.18; 0.09–0.39)	6.0% (5.19; 2.3 - 11.7)
	EINSTEIN Choice[53]	Aspirin 100 mg o.d. R 20 mg o.d. R 10 mg o.d.	Superiority	3365	49%	12 months	4.4%	66% (0.34; 0.20–0.59; R 20 mg vs. aspirin)	3.3% (1.59; 0.94 - 2.69)
								74% (0.26; 0.14–0.47; R 10 mg vs. aspirin)	2.4% (1.16; 0.67 - 2.03)
Apixaban[b]	AMPLIFY Extension[54]	Placebo vs. A 5 mg b.i.d. vs. A 2.5 mg b.i.d.[b]	Superiority	2486	35%	12 months	8.8%	80%[d] (0.36; 0.25–0.53; A 5 mg vs. placebo)	4.3% (1.62; 0.96 - 2.73)
								81% (0.33; 0.22–0.48; A 2.5 mg vs. placebo)	3.2% (1.20; 0.69 - 2.10)
Aspirin	WARFASA[55]	Placebo vs. ASA 100 mg daily	Superiority	402	40%	≥24 months	11.2%[c]	40% (0.58; 0.36–0.93)	1.0% (0.98; 0.24–3.96)
	ASPIRE[56]	Placebo vs. ASA 100 mg daily	Superiority	822	30%	Between 2 and 4 years (actual, 27 months)	6.5%[c]	26% (0.74; 0.52 - 1.05)	1.1%
Sulodexide	SURVET[57]	Placebo vs. S 2 cp 250 mg b.i.d.	Superiority	617	8%	24 months	9.7%	51% (0.49; 0.27 - 0.92)	0.6% (0.97; 0.14 - 6.88)

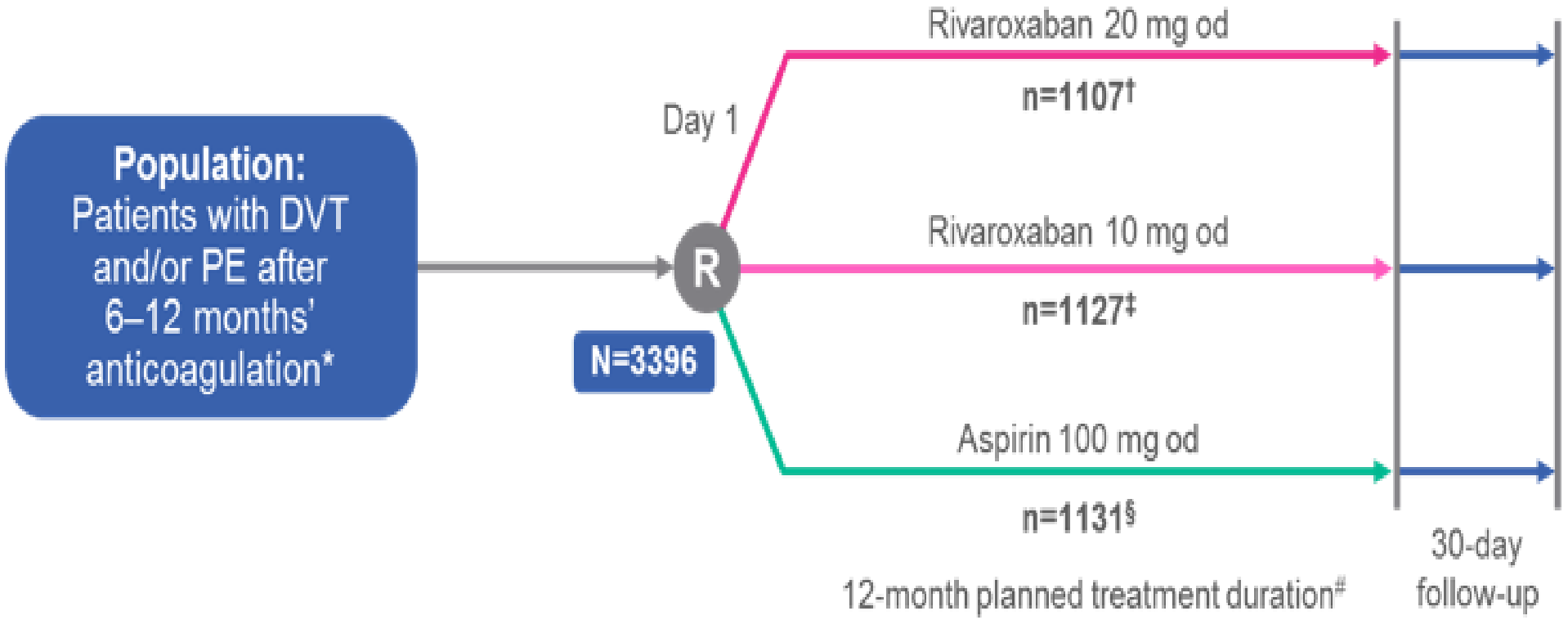
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mart 2017

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf,



Supplemental Table S2. Annualized incidence rates of all pre-specified study outcomes.

Outcome	Rivaroxaban 20 mg (N=1107)		Rivaroxaban 10 mg (N=1127)		Aspirin 100 mg (N=1131)	
	Events (n)	% per person year	Events (n)	% per person year	Events (n)	% per person year
Primary efficacy outcome	17	1.8	13	1.4	50	5.3
Other efficacy outcomes						
Primary efficacy outcome, myocardial infarction, ischemic stroke, or systemic embolism	19	2.0	18	1.9	56	6.0
All-cause mortality	8	0.8	2	0.2	7	0.7
Primary efficacy outcome or all-cause mortality	23	2.4	15	1.6	55	5.8
Primary efficacy outcome or venous thrombosis in other locations	20	2.1	16	1.7	57	6.1
Primary efficacy outcome, myocardial infarction, ischemic stroke, systemic embolism or venous thrombosis in other locations	22	2.3	21	2.2	63	6.7
Principal safety outcome						
Major bleeding (ISTH)	6	0.7	5	0.5	3	0.3

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Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

AMPLIFY-EXT[1]

- Phase III, randomised, double-blind trial
- 2,482 patients with DVT or PE who completed 6 to 12 months of anticoagulation therapy
- Duration: 12 months

ELIQUIS® prophylactic dose arm
2.5mg BD
N=840

ELIQUIS® treatment dose arm
5mg* BD
N=813

Placebo arm
N=829

Only ELIQUIS® 2.5mg BD* is licensed for extended treatment

Table 2. Clinical Outcomes in the Intention-to-Treat Population during the Intended Active Study Period.*

Outcome	Apixaban, 2.5 mg (N=840)	Apixaban, 5 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI)		
				Apixaban, 2.5 mg, vs. Placebo	Apixaban, 5 mg, vs. Placebo	Apixaban, 2.5 mg vs. 5 mg
	number (percent)					
Recurrent VTE or death from any cause — primary efficacy outcome†	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22–0.48)	0.36 (0.25–0.53)	NA
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11–0.33)	0.20 (0.11–0.34)	0.97 (0.46–2.02)
Non–VTE-related cardiovascular death, myocardial infarction, or stroke	4 (0.5)	5 (0.6)	11 (1.3)	0.36 (0.11–1.12)	0.47(0.16–1.33)	0.77 (0.21–2.88)
Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13–0.35)	0.23 (0.14–0.38)	0.92 (0.48–1.74)
Major bleeding	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09–2.64)	0.25 (0.03–2.24)	1.93 (0.18–21.25)
Clinically relevant nonmajor bleeding	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72–2.33)	1.82 (1.05–3.18)	0.71 (0.43–1.18)
Major or clinically relevant nonmajor bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69–2.10)	1.62 (0.96–2.73)	0.74 (0.46–1.22)

Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism
The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD;

JAMA. 2015;314(1):31-40. doi:10.1001/jama.2015.7046

MAIN OUTCOMES AND MEASURES The primary outcome was the composite of recurrent venous thromboembolism or major bleeding at 18 months after randomization. Secondary outcomes were the composite at 42 months (treatment period plus 24-month follow-up), as well as each component of the composite, and death unrelated to pulmonary embolism or major bleeding, at 18 and 42 months.

MUHTEŞEM PLANLANMIŞ ÇALIŞMA, ilk atak unprovoke emboli
6+12
6+PLASEBO
+24 AY İLAÇSIZ GÖZLEM

	No. (%) of Patients With Events[a]			
	Warfarin (n = 184)	Placebo (n = 187)	Hazard Ratio (95% CI)[a]	*P* Value[a]
Person-years	593.5	612.6		
During the 18-mo study treatment period				
Primary composite outcome[b]	6 (3.3)	25 (13.5)	0.22 (0.09-0.55)	.001
Recurrent venous thromboembolism	3 (1.7)[c]	25 (13.5)	0.15 (0.05-0.43)	<.001
Fatal pulmonary embolism	0	0		
Symptomatic nonfatal pulmonary embolism	2	21		
Symptomatic proximal deep-vein thrombosis	1	4		
Major bleeding	4 (2.2)[d]	1 (0.5)[e]	3.96 (0.44-35.89)	.22
Fatal	0	0		
Nonfatal	4	1		
Death from causes other than venous thromboembolism or major bleeding	2 (1.1)	2 (1.1)	1.32 (0.19-9.35)	.78
During the entire study period (median, 41 mo)				
Composite outcome	33 (20.8)	42 (24.0)	0.75 (0.47-1.18)	.22
Recurrent venous thromboembolism	28 (17.9)	39 (22.1)	0.69 (0.42-1.12)	.14
Fatal pulmonary embolism[f]	4	0		
Symptomatic nonfatal pulmonary embolism	17	31		

Extended treatment of venous thromboembolism with reduced-dose versus full-dose direct oral anticoagulants in patients at high risk of recurrence: a non-inferiority, multicentre, randomised, open-label, blinded endpoint trial

*Francis Couturaud, Jeannot Schmidt, Olivier Sanchez, Alice Ballerie, Marie-Antoinette Sevestre, Nicolas Meneveau, Laurent Bertoletti, Jérôme Connault, Ygal Benhamou, Joël Constans, Thomas Quemeneur, François-Xavier Lapébie, Gilles Pernod, Gaël Picart, Antoine Elias, Caroline Doutrelon, Claire Neveux, Lina Khider, Pierre-Marie Roy, Stéphane Zuily, Nicolas Falvo, Philippe Lacroix, Joseph Emmerich, Isabelle Mahé, Julien Boileau, Azzedine Yaici, Sylvain Le Jeune, Dominique Stéphan, Pierre Plissonneau-Duquene, Valérie Ray, Marc Danguy des Déserts, Rafik Belhadj-Chaidi, Bouchra Lamia, Yves Gruel, Emilie Presles, Philippe Girard, Cécile Tromeur, Farès Moustafa, Vincent Rothstein, Karine Lacut, Solen Melac, Sophie Barillot, Patrick Mismetti, Silvy Laporte, Dominique Mottier, Guy Meyer, Christophe Leroyer, for the RENOVE Investigators**

Summary

Background In patients with venous thromboembolism at high risk of recurrence for whom extended treatment with direct oral anticoagulants has been indicated, the optimal dose is unknown. We aimed to assess efficacy and safety of reduced-dose versus full-dose direct oral anticoagulants in patients in whom extended anticoagulation has been indicated.

Lancet 2025; 405: 725–35

See **Comment** page 676

*The RENOVE Investigators are listed in the appendix (pp 2–5)

Metod: 6-24 ay tedavi alan hastalar ortalama 37.1 ay takip edilen PTE veya Proximal DVT hastaları.
Amaç: Uzun süreli antikoagülasyon gerektiren tekrarlayan venöz tromboembolizm riski yüksek olan hastalarda azaltılmış doz antikoagülasyonun (rivaroxaban 10 mgr veya apixaban 2x2.5 mgr) tam doz antikoagülasyona (rivaroxaban 20 mgr veya apixaban 2x5 mgr) göre etkinlik açısından üstün olup olmadığını değerlendirme amaçlanmış.

- **Dahil edilme kriterleri**
- - 18 yaşından büyük hastalar
- - Venöz tromboembolizm (VTE) (yani semptomatik pulmoner emboli [PE] veya proksimal derin ven trombozu [DVT]) sonrası uzun süreli antikoagülasyon endikasyonu olan ve başlangıçta 6 (-15 gün) ila 24 ay (+3 ay) arasında tedavi edilen hastalar:
- - Birden fazla VTE atağı geçiren hastalar veya
- - İlk kez provoke edilmemiş* VTE atağı geçiren hastalar
- - Kalıcı risk faktörü† ile ilişkili VTE'si olan hastalar veya
- - Klinisyenlerin süresiz antikoagülasyonun gerekli olduğunu düşündüğü hastalar‡
- - Sosyal güvenlik ilişkisi.

**Ameliyat, alt ekstremite travması, son üç ay içinde uzun süreli immobilizasyon, östrojen içeren doğum kontrol hapı veya hormonal replasman tedavisi, 3 aydan kısa süreli gebelik veya doğum gibi majör geri döndürülebilir risk faktörlerinin yokluğunda ve kalıcı risk faktörlerinin yokluğunda VTE meydana gelmişse VTE provoke olmamış olarak tanımlanır (aşağıya bakınız).*

†Kalıcı risk faktörleri (kapsamlı liste değildir):

- *- kronik enflamatuar hastalıklar (örneğin, kronik enflamatuar bağırsak hastalıkları, romatoid artrit, vb.),*
- *- kalıcı veya sürekli hareketsizlik (örn. nörolojik hastalıklar veya diğer nedenler),*
- *- majör trombofili, örneğin: doğrulanmış protein C, S veya antitrombin eksiklikleri, kombine trombofili, homozigot Faktör V Leiden veya homozigot protrombin gen varyantı,*
- *- hormonal tedavi (örn. meme ve prostat kanseri için) veya kanser için diğer protrombotik tedavi, dahil edilmeden önce 6 aydan fazla bir süre boyunca kontrol altındadır.*

‡Akut fazda ölüm riski yüksek PE, ilio-vena kava DVT, ailede ölümcül PE öyküsü gibi özel durumlar.

Hariç bırakma kriterleri

- - Rivaroksaban ve apiksabana karşı bilinen alerji, yardımcı maddelerden herhangi birine karşı alerji
- - Terapötik doz antikoagülan tedavi endikasyonu
- **- İzole distal DVT**
- **- HERDOO2 skoru ≤ 1**
- - DVT veya PE dışında antikoagülasyon endikasyonu (örn. atriyal fibrilasyon, mekanik kapakçıklar)
- - Dahil edilmeden önce 14 gün veya daha uzun süre antikoagülasyona ara verilmesi
- - Kronik karaciğer hastalığı veya kronik hepatit
- - Yüksek kanama riski altında olduğu düşünülen hasta (örn. son üçay içinde geçirilmiş gastrointestinal sistem kanaması, kontrolsüz hipertansiyon, vb.)
- - Cockcroft ve Gault formülüne göre kreatinin <25 mL/dakika olan böbrek yetmezliği
- **- Antifosfolipid sendromu**
- - İkili antiplatelet tedavi veya günde >100 mg dozda aspirin
- - Güçlü bir sitokrom P-450 3A4 (CYP3A4) inhibitörünün birlikte kullanımı
- **- 6 aydan kısa süreli aktif kanser**
- - Aktif gebelik veya beklenen gebelik
- - 12 aydan kısa yaşam beklentisi

	Reduced-dose group (n=1383)	Full-dose group (n=1385)	Hazard ratio (95% CI)	p value
Primary outcome				
Symptomatic recurrent venous thromboembolism	19 (2·2% [1·1–3·3])*	15 (1·8% [0·8–2·7])†	1·32 (0·67–2·60)	0·23‡
Symptomatic recurrent pulmonary embolism	11 (1·5% [0·5–2·4])§	13 (1·5% [0·7–2·4])¶	..	..
Fatal pulmonary embolism‖	3 (0·3% [0·0–0·6])	3 (0·3% [0·0–0·7])	..	..
Symptomatic non-fatal pulmonary embolism	8 (1·2% [0·3–2·1])	11 (1·3% [0·5–2·1])	..	..
Symptomatic proximal deep vein thrombosis	9 (1·1% [0·2–2·1])§	2 (0·2% [0·0–0·6])	..	..
Key secondary outcomes				
Clinically relevant non-major bleeding and major bleeding	96 (9·9% [7·7–12·1])	154 (15·2% [12·8–17·6])	0·61 (0·48–0·79)	..
Major bleeding	15 (2·1% [0·7–3·5])**	38 (4·0% [2·7–5·3])††	0·40 (0·22–0·72)	..
Fatal bleeding	2 (0·5% [0·0–1·2])	3 (0·2% [0·0–0·5])	..	..
Non-fatal bleeding	13 (1·7% [0·5–2·9])	35 (3·8% [2·5–5·1])	..	..
Clinically relevant non-major bleeding	84 (8·6% [6·6–10·7])	118 (11·5% [9·3–13·6])	0·70 (0·53–0·93)	..
Net clinical benefit (symptomatic recurrent venous thromboembolism, or major bleeding, or clinically relevant non-major bleeding)	113 (11·8% [9·4–14·3])	166 (16·5% [14·0–19·0])	0·67 (0·53–0·86)	..
Other secondary and safety outcomes				
All-cause death	35 (4·3% [2·6–6·0])‡‡	54 (6·1% [4·3–8·0])	0·67 (0·44–1·03)	..
Death from causes other than venous thromboembolism or major bleeding	30 (3·6% [2·1–5·1])	48 (5·6% [3·9–7·4])	0·64 (0·41–1·02)	..
Symptomatic pulmonary embolism, proximal or distal deep vein thrombosis, or venous thrombosis in other location	33 (3·4% [2·1–4·7])	20 (2·2% [1·2–3·3])	1·70 (0·98–2·97)	..
Arterial cardiovascular events	78/1249 (6·2% [5·0–7·7])§§	69/1252 (5·5% [4·3–6·9])¶¶	..	..
Chronic thromboembolic pulmonary hypertension	3/1242 (0·24% [0·05–0·70])	4/1242 (0·34% [0·09–0·82])	..	..
Newly diagnosed cancer	91/1261 (7·2% [5·9–8·8])	99/1269 (7·8% [6·4–9·4])	..	..

- **Sonuç:**
- Uzatılmış antikoagülasyon gerektiren venöz tromboembolizmli hastalarda, doğrudan oral antikoagülan dozunun azaltılması **non-inferiorite kriterlerini karşılamamıştır.**
- Bununla birlikte, her iki gruptaki düşük nüks oranları ve **azaltılmış dozla klinik olarak anlamlı kanamanın önemli ölçüde azalması**, bu rejimi bir seçenek olarak destekleyebilir.

The NEW ENGLAND JOURNAL of MEDICINE

29 Mart 2025

ORIGINAL ARTICLE

Extended Reduced-Dose Apixaban for Cancer-Associated Venous Thromboembolism

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Metod: 6 ay tedavi alan hastalar ortalama 11.8 ay takip edilen PTE veya Proximal DVT hastaları

Amaç: Kanser hastalarında 2.5 mgr 2x1 apixabanın 5 mgr 2x1 apixabana karşı rekürren VTE açısından non inferior olup olmadığının araştırılması.

Table 2. Clinical Outcomes during the Trial Period.*

Outcome	Reduced-Dose Apixaban (N=866)	Full-Dose Apixaban (N=900)	Treatment Effect (95% CI)	P Value
	number (percent)			
Primary efficacy outcome: recurrent venous thromboembolism†	18 (2.1)	24 (2.8)	0.76 (0.41–1.41)	0.001
Recurrent symptomatic venous thromboembolism	17 (2.0)	18 (2.1)	0.97 (0.50–1.88)	—
Lower-limb deep-vein thrombosis‡	8 (0.9)	6 (0.7)	—	
Pulmonary embolism	9 (1.1)	10 (1.2)	—	
Fatal pulmonary embolism	0	0	—	
Unexplained sudden death§	3 (0.4)	2 (0.3)	—	
Upper-limb deep-vein thrombosis	1 (0.1)	3 (0.4)	—	
Central venous catheter–related thrombosis	1 (0.1)	2 (0.2)	—	
Incidental venous thromboembolism¶	1 (0.1)	6 (0.7)	—	
Recurrent major venous thromboembolism‖	17 (2.0)	21 (2.4)	0.83 (0.44–1.57)	—
Key secondary safety outcome: major or clinically relevant non-major bleeding**	102 (12.1)	136 (15.6)	0.75 (0.58–0.97)	0.03
Major bleeding	24 (2.9)	37 (4.3)	0.66 (0.40–1.10)	—
Fatal bleeding	2 (0.2)	2 (0.2)	—	
Major gastrointestinal bleeding	12 (1.4)	25 (2.9)	—	
Upper gastrointestinal bleeding	6 (0.7)	13 (1.5)	—	
Lower gastrointestinal bleeding	7 (0.8)	13 (1.5)	—	
Clinically relevant nonmajor bleeding	84 (10.0)	107 (12.3)	0.79 (0.59–1.05)	
Other secondary outcomes				
Death from any cause	148 (17.7)	168 (19.6)	0.96 (0.86–1.06)	—
Recurrent symptomatic venous thromboembolism, major bleeding, or death from any cause††	167 (19.9)	191 (22.1)	0.96 (0.87–1.07)	—
Major venous thromboembolism or major bleeding‡‡	41 (5.2)	55 (6.8)	0.96 (0.87–1.06)	—

8.4 Recommendations for the regimen and duration of anticoagulation after pulmonary embolism in patients without cancer

Recommendations	Class[a]	Level[b]
Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE.[347]	I	A
Patients in whom discontinuation of anticoagulation after 3 months is recommended		
For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months.[331,340,341]	I	B
Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor.[358]	I	B
Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with antiphospholipid antibody syndrome.[359]	I	B
Patients in whom extension of anticoagulation beyond 3 months should be considered[c,d]		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor.[330,331,347,351–353]	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome.[330,352,353]	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor.[330,331,352]	IIa	C

NOAC dose in extended anticoagulation[e]		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered after 6 months of therapeutic anticoagulation.[352,353]	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis.[355–357]	IIb	B
Follow-up of the patient under anticoagulation		
In patients who receive extended anticoagulation, it is recommended that their drug tolerance and adherence, hepatic and renal[f] function, and bleeding risk be reassessed at regular intervals.[259]	I	C

Bunlar önerilir (recommended)

- Major veya geri döndürülebilir bir risk faktörü olmadan geçirilen **iki VTE atağında sınırsız süre** (indefinite) antikoagülan öneriliyor (Kanıt düzeyi **IB**).
- Antifosfolipit sendromu olanlarda **WARFARİN ile sınırsız süre** antikoagülan öneriyor (Kanıt düzeyi **IB**).

Save

Diagnostic criteria of ANTIPHOSPHOLIPID SYNDROME

≥1 clinical criteria + ≥1 laboratory criteria

CLINICAL CRITERIA:

1. ≥1 arterial, venous, or small-vessel thrombosis event of any organ (excluding superficial venous thrombosis)

2. Pregnancy morbidity (A, B or C):

   A. ≥1 unexplained fetal death of a morphologically normal fetus at ≥10 weeks' gestation

   B. ≥1 premature birth before 34 weeks' gestation due to eclampsia, severe pre-eclampsia, or placental insufficiency

   C. ≥3 consecutive spontaneous abortions before the 10th week of gestation (in the absence of anatomic, hormonal, or chromosomal causes)

LABORATORY CRITERIA:

1. Lupus anticoagulant positivity on ≥2 occasions ≥12 weeks apart

2. IgG or IgM anticardiolipin antibodies in moderate or high titers (>40 GPL units or >99th percentile) measured by standard ELISA on ≥2 occasions ≥12 weeks apart

3. IgG or IgM anti-beta-2-glycoprotein I antibody in moderate or high titers (>99th percentile) measured by standard ELISA on ≥2 occasions ≥2 weeks apart

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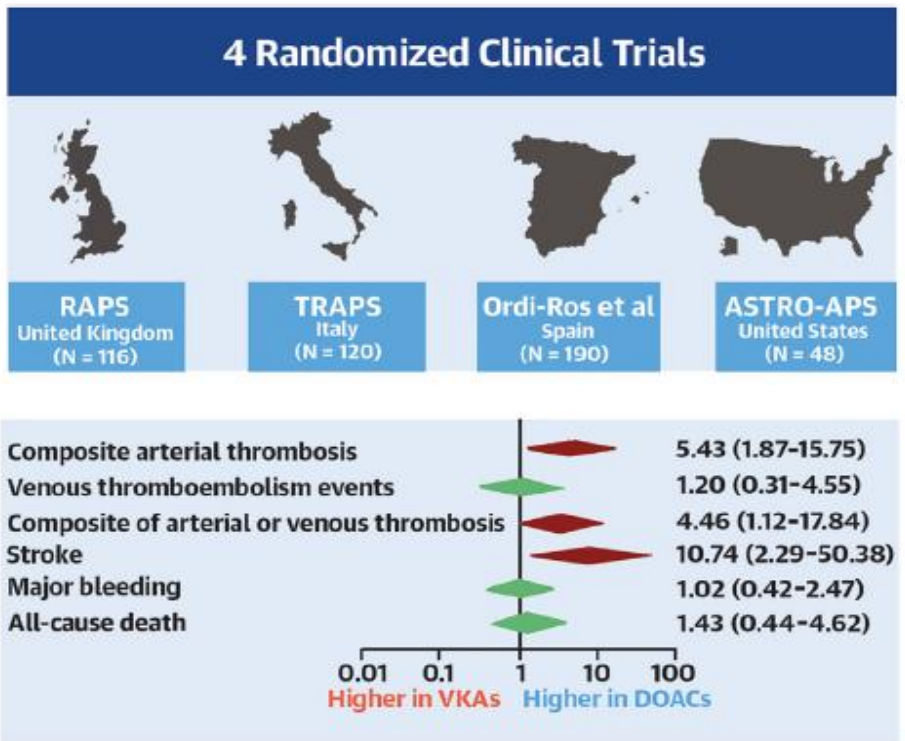
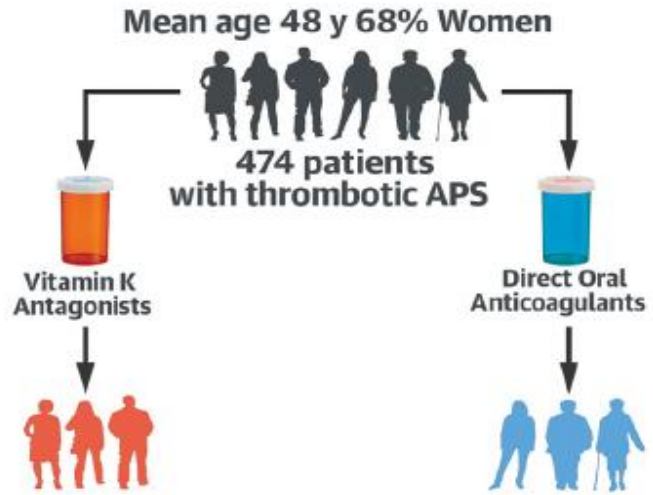
Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Antiphospholipid Syndromes

Meta-Analysis of Randomized Trials

CENTRAL ILLUSTRATION Use of Direct Oral Anticoagulants vs Vitamin K Antagonists in Thrombotic Antiphospholipid Syndrome





Use of DOACs Compared With VKAs Was Associated With:

- Increased odds of arterial thrombotic events, especially stroke
- No change in the odds of VTE or major bleeding

Results were consistent within subgroups

Khairani CD, et al. J Am Coll Cardiol. 2023;81(1):16-30.

Bunlar düşünülür (considered)

- **Sınırsız süreli antikoagülasyon**
  - Nedeni saptanmayan ilk atakta düşünülebilir (Kanıt düzeyi **IIaA**).
  - Antifosfolipid antikor sendromu dışında kalıcı risk faktörü varsa ilk atakta düşünülebilir (Kanıt düzeyi **IIaC**).
  - Minor - geçici veya reverzibl risk faktörü sonucu VTE oluşmuşsa ilk atakta düşünülebilir (Kanıt düzeyi **IIaC**).

Bunlar düşünülür (considered)

- Eğer kanser hastası dışında bir hastada uzun süreli antikoagülasyon öneriliyor ise, 6 aylık tedaviden sonra azaltılmış dozda **apixaban 2x2.5** mgr veya **rivaroxaban 1x10 mgr** düşünülebilir (Kanıt düzeyi IIaA).
- Uzatılmış süreli antikoagülasyon alan tüm hastalarda KCFT, BFT ve kanama riski belli aralıklarla değerlendirilmelidir.

Akut PTE sonrası takip hastasında öneriler

- **1-** 3-6 aylık tedavi süresi sonunda rutin **klinik değerlendirme** önerilir. [Bunlar rekürrens semptomları, kanama, malignite ve persistan veya yeni ortaya çıkan dispne (mMRC) sorgulanmalı ve tedavi uzatılmasının gerekliliğine karar verilmelidir.] (Kanıt 1B).
- **2-** 3 aylık tedaviden sonra **hala semptomatik** ve **V/P dengesizliği olan** hastalar, EKO ve natriüretik peptid düzeyi ile değerlendirilerek PAH/KTEPH merkezine yönlendirilmelidir (Kanıt 1C).
- **3-** Asemptomatik olsa da **risk faktörü olan** hastalar gösterildiği gibi ileri tetkiklerle incelenmelidir (Kanıt 2bC).

Rehberlerde Üzerinde Durulmayan İki Durum

RPVO

Risk factors for recurrent venous thromboembolism after unprovoked pulmonary embolism: the PADIS-PE randomised trial Eur Respir J 2017; 51: 1701202

ABSTRACT We aimed to identify risk factors for recurrent venous thromboembolism (VTE) after unprovoked pulmonary embolism.

Analyses were based on the double-blind randomised PADIS-PE trial, which included 371 patients with a first unprovoked pulmonary embolism initially treated during 6 months who were randomised to receive an additional 18 months of warfarin or placebo and followed up for 2 years after study treatment discontinuation. All patients had ventilation/perfusion lung scan at inclusion (*i.e.* at 6 months of anticoagulation).

During a median follow-up of 41 months, recurrent VTE occurred in 67 out of 371 patients (6.8 events per 100 person-years). In main multivariate analysis, the hazard ratio for recurrence was 3.65 (95% CI 1.33–9.99) for age 50–65 years, 4.70 (95% CI 1.78–12.40) for age >65 years, 2.06 (95% CI 1.14–3.72) for patients with pulmonary vascular obstruction index (PVOI) ⩾5% at 6 months and 2.38 (95% CI 1.15–4.89) for patients with antiphospholipid antibodies. When considering that PVOI at 6 months would not be available in practice, PVOI ⩾40% at pulmonary embolism diagnosis (present in 40% of patients) was also associated with a 2-fold increased risk of recurrence.

After a first unprovoked pulmonary embolism, age, PVOI at pulmonary embolism diagnosis or after 6 months of anticoagulation and antiphospholipid antibodies were found to be independent predictors for recurrence.

41 aylık takipte çoklu analize göre nüks için risk faktörleri

1- 50-65 yaş arası 3.65 kat

2- 65 yaş üstü 4.7 kat

3- **Tedavinin 6. ayında saptanan PVOI ≥%5 olanlar** 2.06 kat

4- Antifosfolipit antikor sendromu olanlar 2.38 kat daha fazla nükse sahip.

5- **Eğer tedavinin 6. ayında PVOI olmasa da PTE tanısı aldığında %40 dan fazla PVOI** varsa 2 kat fazla nüks oranına sahip.

MANUSCRIPT ID : ERJ-01202-2017, FIRST REVISION (CLEANED)

Risk Factors for Recurrent Venous Thromboembolism after Unprovoked Pulmonary Embolism.
Results from the PADIS-PE randomized clinical trial.*

Cécile Tromeur, Olivier Sanchez, Emilie Presles, Gilles Pernod, Laurent Bertoletti, Patrick Jego, Elisabeth Duhamel, Karine Provost, Florence Parent, Philippe Robin, Lucile Deloire, Florent Leven, Fanny Mingant, Luc Bressollette, Pierre-Yves Le Roux, Pierre-Yves Salaun, Michel Nonent, Benjamin Planquette, Brigitte Pan-Petesch, Philippe Girard, Karine Lacut, Solen Melac, Patrick Mismetti, Silvy Laporte, Guy Meyer, Dominique Mottier, Christophe Leroyer, and Francis Couturaud, for the PADIS-PE Investigators.*

Online supplemental content

Pulmonary Vascular Obstruction Index

PVOI at the diagnosis of PE and at inclusion (i.e.; at 6 months of anticoagulation) were calculated using scores having been validated and correlated with the Miller index.[1]

For PVOI measured on V/Q lung scan, each perfusion scan was scored as described by Meyer *et al.*: (i) each lobe was assigned a weight based on the regional distribution of pulmonary blood flow in the supine position (right lower lobe 25%, right middle lobe 12%, right upper lobe 18%, left lower lobe 20%, lingula 12% and left upper lobe 13%); (ii) for each lobe, a semi-quantitative perfusion score (0, 0.25, 0.5, 0.75 or 1) was estimated from the film density in the anterior, posterior and oblique views by comparison with the photodensity of an apparently normally perfused area; (iii) each lobar perfusion score was then calculated by multiplying the weight by perfusion score; and (iiii) the overall perfusion score was determined by summing the six separate lobar perfusion scores and the percentage of vascular obstruction was then calculated.[2]

For PVOI measured on CTPA, each lung was divided in 10 segmental arteries (3 to the upper lobes, 2 to the middle lobe and to the lingula and 5 to the lower lobes) as previously described by Qanadli *et al.*: (i) the presence of an embolus in a segmental artery was scored 1 point and emboli in the most proximal arterial level were scored a value equal to the number of segmental arteries arising distally; (ii) to evaluate the residual perfusion distal to the embolus, a weighting factor was assigned to each value, depending on the degree of vascular obstruction (factor equal to zero when no embolus was observed or 1 with partially occlusive embolus or 2 with complete occlusion); and (iii) the maximal pulmonary vascular obstruction score was 40 per patient and results were expressed as percentage of vascular obstruction.[3]

Masif PTE sonrası tedavi süresi

Should oral anticoagulation be discontinued after 3 months in the setting of a first high-risk pulmonary embolism secondary to a major transient/reversible risk factor?

To the Editor:

Should oral anticoagulation be discontinued after 3 months in the setting of a first high-risk pulmonary embolism event secondary to a major transient/reversible risk factor?

Hans Slabbynck, Johan Clukers and Daniella Galdermans
Dept of Respiratory Medicine, ZNA Middelheim, Antwerp, Belgium.

Eur Respir J 2020; 55: 1902028

severity of the index episode [5]. We do acknowledge that, in clinical practice, when a high-risk, life-threatening PE has been suffered, this results in persisting uncertainty and fears for the patients and their families, and that the wish of some of these patients to prolong anticoagulation needs to be taken into account in the decision. In such cases, the questionable benefits of continuing anticoagulation should be explained to the patient along with the bleeding risk of prolonging this treatment.

Guy Meyer[1] and Stavros Konstantinides[2,3]

CEVAP BEKLEYEN SORULAR

- 1- Hastanın ilk geçirdiği emboli tipine göre tedavi süresi (örnek major geçici risk faktörü olan ve masif PTE gelişen hastalarda emboli süresi).
- 2- Rezidüel pulmoner vasküler obstrüksiyon tedavi süresini etkilemeli mi (Özellikle V/P sintigrafisi) (Rehbere girmeli?)
- 3- Trombus yükü ve tedavi süresi

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Quarterly Medical Review - Venous thromboembolic disease: a tribute to Professor Guy Meyer

Duration of anticoagulation of venous thromboembolism

Francis Couturaud[a,b,c,*], Nicolas Meneveau[d,e], Marie Antoinette Sevestre[f], Pierre-Emmanuel Morange[g], David Jimenez[h,i,j]

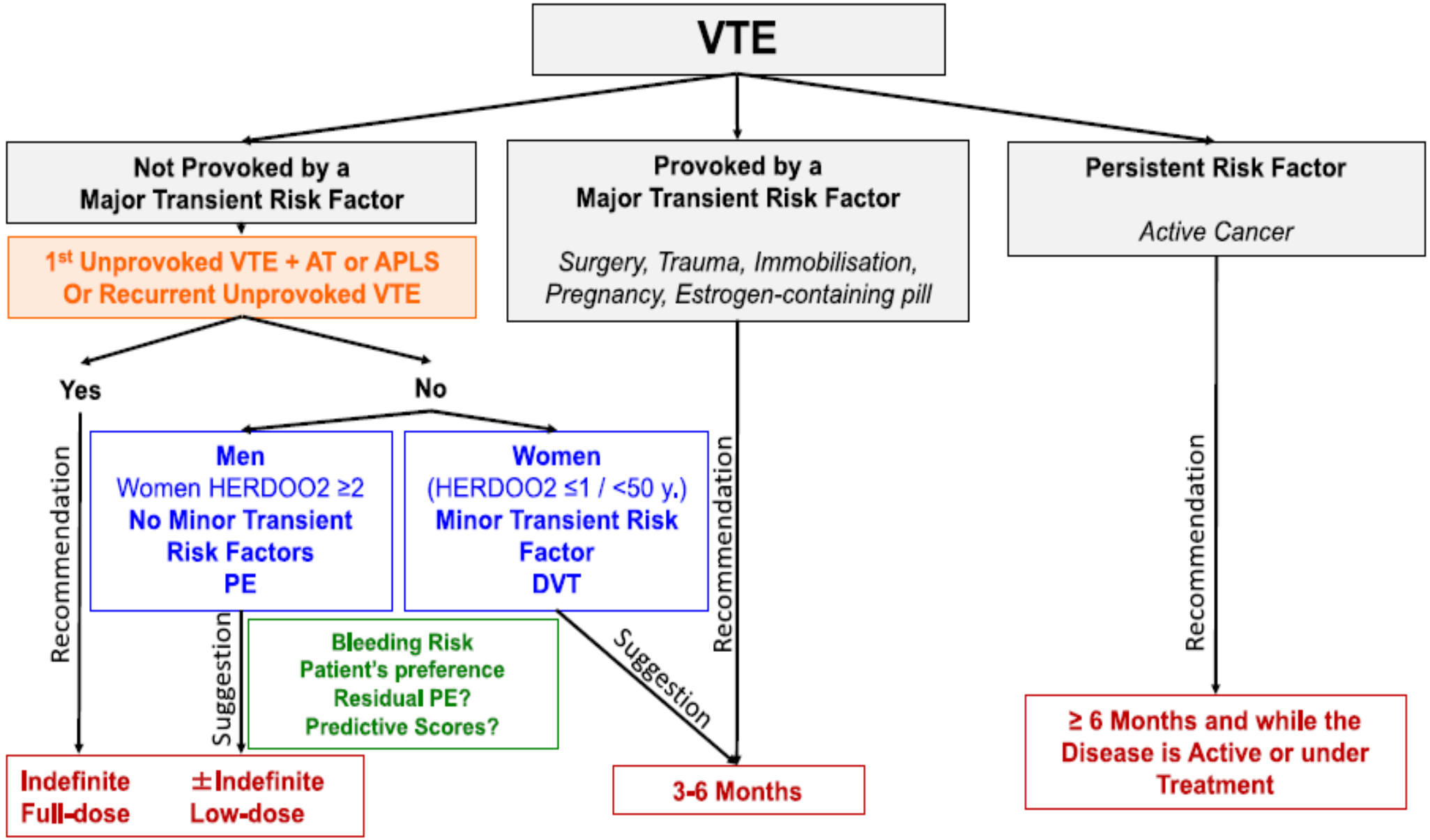


Fig. 2. Synthesis of guidelines on optimal duration of anticoagulation*
VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.
* Based on references 4,5,6,7.

BİZİ NE TÜR GELİŞMELER BEKLİYOR

nature reviews cardiology

https://doi.org/10.1038/s41569-025-01144-z

Review article

Check for updates

Factor XI inhibitors for the prevention and treatment of venous and arterial thromboembolism

Davide Capodanno[1], John H. Alexander[2], M. Cecilia Bahit[3,4], John W. Eikelboom[5,6], C. Michael Gibson[7], Shaun G. Goodman[8,9,10], Vijay Kunadian[11], Gregory Y. H. Lip[12,13,14,15], Renato D. Lopes[2], Roxana Mehran[16], Shamir R. Mehta[5,6], Manesh R. Patel[2], Jonathan P. Piccini[2], Sunil V. Rao[17], Christian T. Ruff[18,19], P. Gabriel Steg[20,21], Jeffrey I. Weitz[5,6] & Dominick J. Angiolillo[22]

- Faktör Xa ve trombin mekanizmasıyla karşılaştırıldığında FXI, **pıhtı oluşumunda rol aldığı** ancak **hemostazı etkilemediği** bilinmektedir.
- **Kalıtsal FXI eksikliği olan hastalarda**, spontan kanama komplikasyonu olmaksızın VTE ve kardiyovasküler olayların görülme sıklığında azalma vardır
- Bu bulgular, FXI'nin pıhtılaşma kaskadında yalnızca mütevazı bir rol oynadığını, çünkü FXI'nin başlatmaya değil, trombüsün stabilizasyonuna ve genişlemesine katkıda bulunduğunu göstermektedir. Bu durum, kanama riski olmaksızın benzer tromboembolik faydalardan yararlanma umuduyla FXI ve/veya XIa'yı spesifik olarak inhibe eden ilaçların geliştirilmesine yol açmıştır

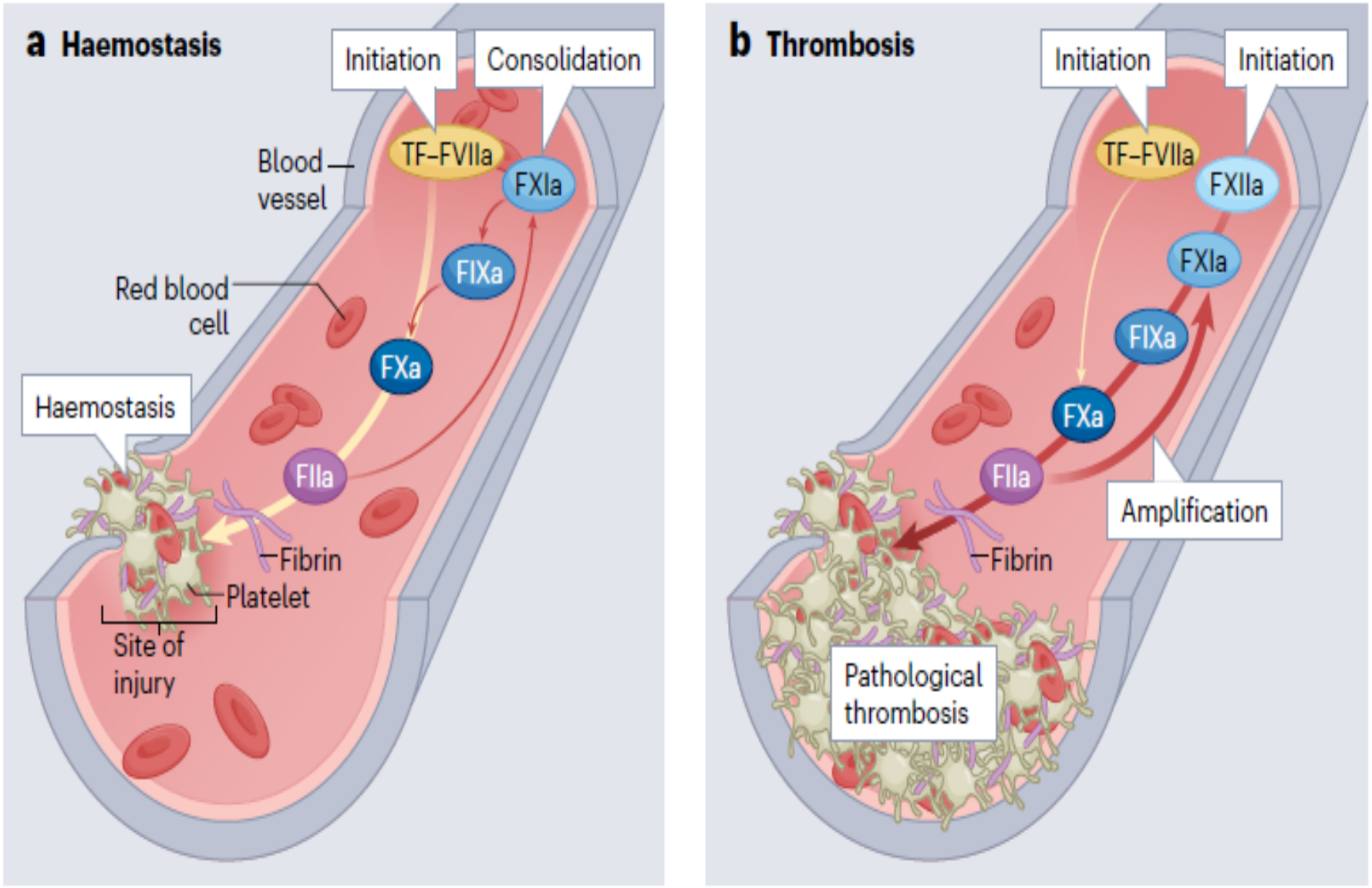
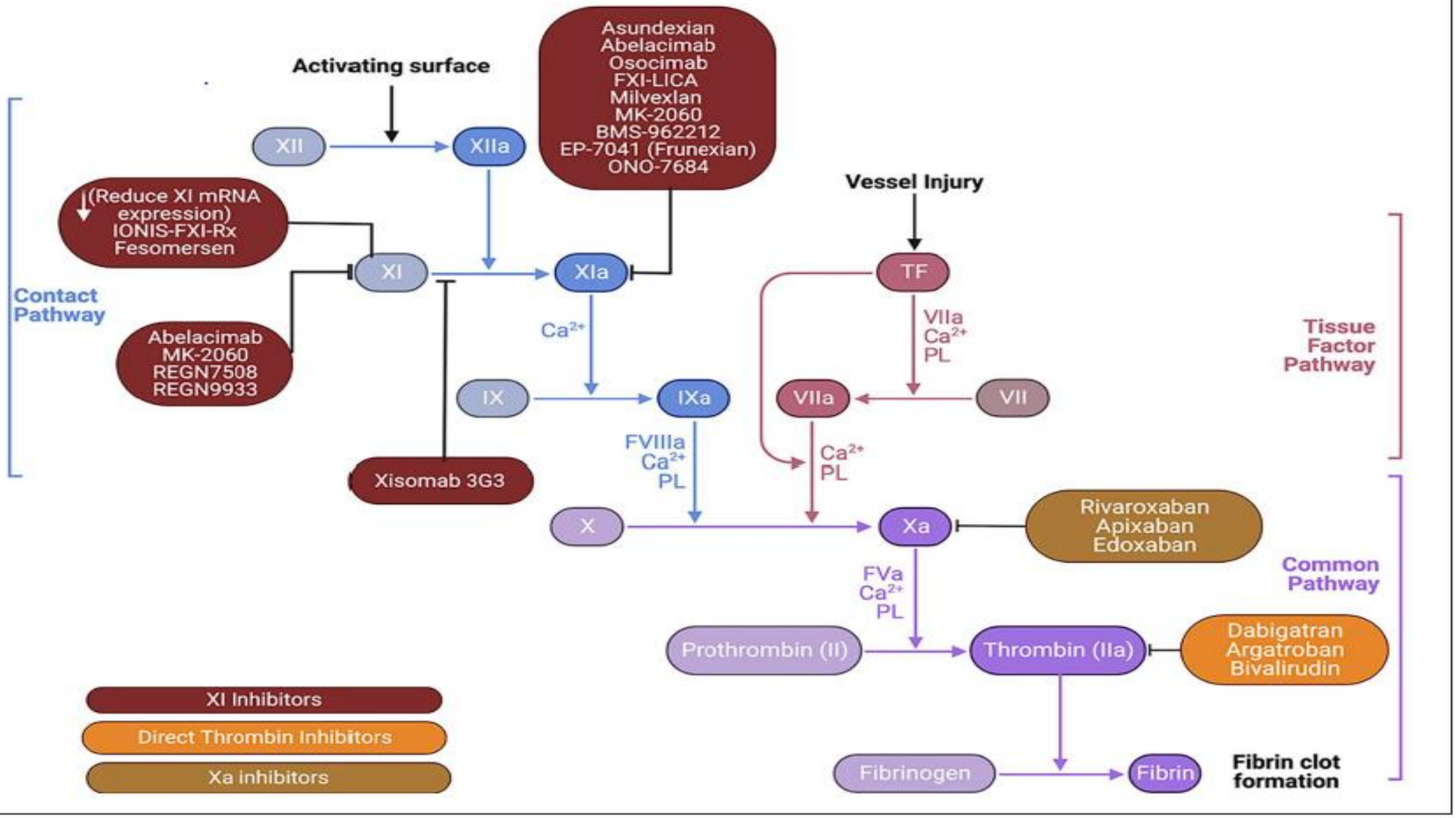


Fig. 1 | Contribution of factor XI to haemostasis and thrombosis. Two related but distinct processes of coagulation are depicted. Haemostasis is characterized by clot formation to seal vessel wall injuries (panel **a**). By contrast, in thrombosis, intraluminal clot formation obstructs blood flow (panel **b**). Tissue factor (TF) bound to activated factor VII (FVIIa) initiates both processes, with activated factor XI (FXIa) having a minor role in haemostasis (that is, consolidation) but a crucial role in thrombosis (that is, thrombus propagation). For details on these processes, see Box 1. FIIa, activated factor II (thrombin); FIXa, activated factor IX; FXa, activated factor X; FXIIa, activated factor XII.


Activating surface
Asundexian
Abelacimab
Osocimab
FXI-LICA
Milvexlan
MK-2060
BMS-962212
EP-7041 (Frunexian)
ONO-7684
XII
XIIa
(Reduce XI mRNA expression)
IONIS-FXI-Rx
Fesomersen
XI
XIa
Contact Pathway
Abelacimab
MK-2060
REGN7508
REGN9933
Ca2+
IX
IXa
FVIIIa
Ca2+
PL
Xisomab 3G3
Vessel Injury
TF
VIIa
Ca2+
PL
Tissue Factor Pathway
VIIa
VII
Ca2+
PL
X
Xa
Rivaroxaban
Apixaban
Edoxaban
FVa
Ca2+
PL
Common Pathway
Prothrombin (II)
Thrombin (IIa)
Dabigatran
Argatroban
Bivalirudin
Fibrinogen
Fibrin
Fibrin clot formation
XI Inhibitors
Direct Thrombin Inhibitors
Xa inhibitors

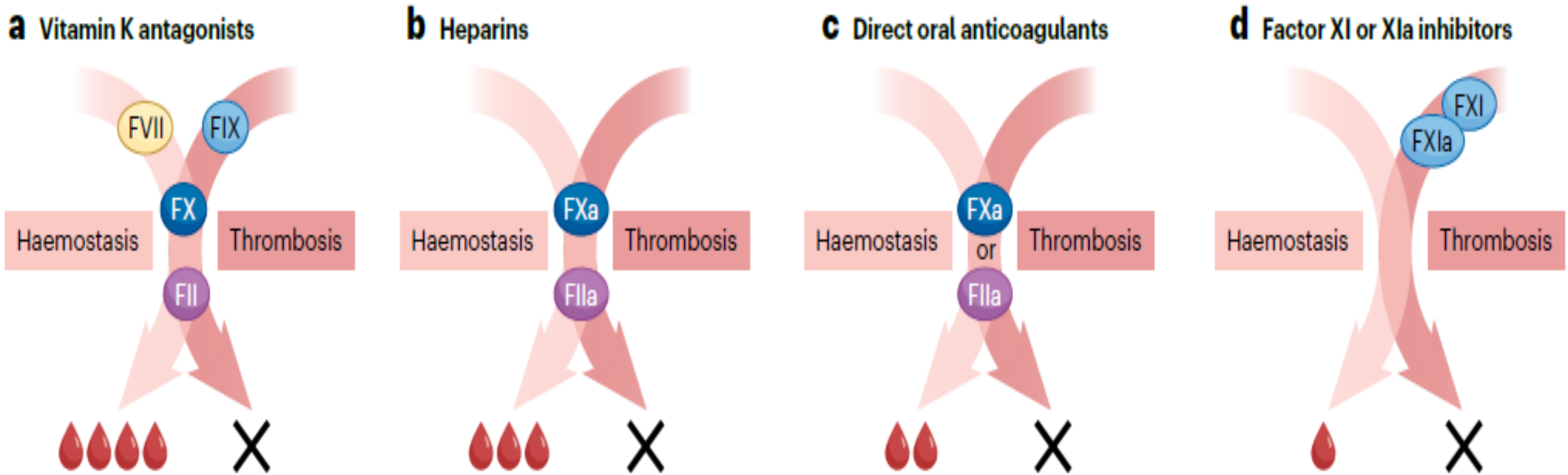


Fig. 2 | Mechanisms of action of anticoagulant drugs. a, Vitamin K antagonists reduce the synthesis of coagulation factor precursor molecules, leading to a reduction in the levels of factor VII (FVII), factor IX (FIX), factor X (FX) and factor II (FII). **b**, Heparins enhance antithrombin III activity to inhibit activated FX (FXa) and activated FII (FIIa). **c**, Direct oral anticoagulants selectively inhibit either FXa or FIIa. Vitamin K antagonists, heparins and direct oral anticoagulants all reduce thrombosis but can compromise haemostasis, leading to bleeding. **d**, Novel inhibitors that selectively target factor XI (FXI), activated factor XI (FXIa) or both are undergoing clinical trials. The predominant role of FXI in thrombosis rather than haemostasis suggests a potential for haemostasis-sparing anticoagulation.

SONUÇ

- Akut PTE nüksü önlemek için uzun süreli düşük doz mevcut DOAK ları çalışmalar tam desteklemese de öneriliyor
- Ulaşılmak istenen hedef nokta kanama yapmayan ve nüksü önleyen bir ajana ihtiyaç var
- Gelecekte FXI inhibitörlerinden bu konuda ciddi bir beklenti var.

TEŞEKKÜRLER

Özet

- Nüks açısından düşük riskli, emboli açısından major risk içeren durumlarda **3 aylık** tedavi verilmeli.
- Aktif kanser veya inflamatuar barsak hastalığı olanlarda en az 6 ay ve hastalık kontrol altına alınana kadar **uzun süreli** antikoagülasyon verilmeli.
- Major veya geri döndürülebilir bir risk faktörü olmadan geçirilen iki VTE atağında **uzun süreli** antikoagülan öneriliyor.

- Yukarıda bahsedilen bu iki grupta değil ise ve **Minor - geçici veya reverzibl risk faktörü var** ya da **sebebi bulunamamış** ise 3-6 aylık tedavi sonrası HERDOO2 veya DASH skoru ile nüksü hesaplayın, VTE-BLEED skoru ile kanama riskini hesaplayın,
  - Nüks riski yüksek ve kanama riski düşük ise tedaviye devam edin ve hastayı belli aralıklarla tekrar değerlendirerek tedavi sürdürme veya kesmeyi değerlendirin.
  - Nüks riski düşük ve kanama riski yüksek olan hastalarda hasta ile görüşerek tedaviyi sonlandırmayı düşünün.
  - Her iki riski yüksek olan hastalar ile konuşarak hasta tercihini sorun ve beraber tedavi planı yapın.

- Antifosfolipit sendromu olanlarda **WARFARİN ile sınırsız süre** antikoagülan verilmeli.
- Diğer trombofililerden **antitrombin, protein C** veya **protein S eksikliği** doğrulanmış olanlar, **homozigot faktör V Leiden** veya **homozigot protrombin G20210A mutasyonu** olan hastalarda, ilk PE epizodundan sonra uzun süreli antikoagulan tedavisi için plan yapın, yıllık kanama riskini değerlendirin, kanama riski düşük olduğu sürece tedaviye devam edin.

- Eğer kanser hastası dışında bir hastada uzun süreli antikoagülasyon planladınız ise, 6 aylık tedaviden sonra azaltılmış dozda **apixaban 2x2.5** mgr veya **rivaroxaban 1x10 mgr** (Antifosfolipid antikor sendromu, rekürrent VTE, trombofilide veya KTEPH hastalarında dozu azaltmayı düşünmeyin!)
- Uzatılmış süreli antikoagülasyon alan **tüm hastalarda KCFT, BFT ve kanama riski belli aralıklarla değerlendirin**.

- **3 aylık tedaviden sonra hala semptomatik** ve V/P dengesizliği olan hastalar, EKO ve natriüretik peptid düzeyi ile değerlendirilerek PAH/KTEPH merkezine yönlendirilmelidir.

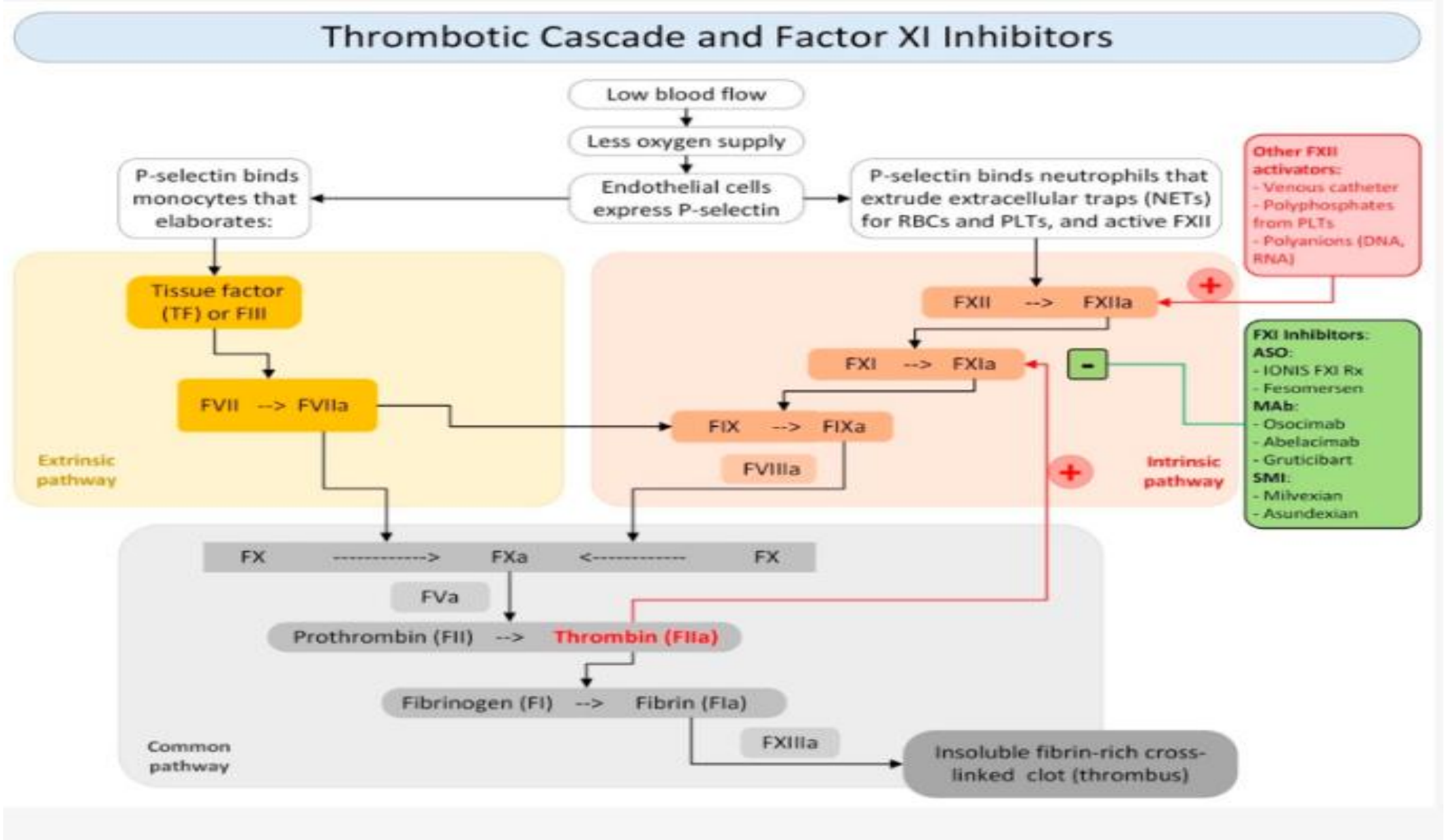

Thrombotic Cascade and Factor XI Inhibitors
Low blood flow
Less oxygen supply
Endothelial cells express P-selectin
P-selectin binds monocytes that elaborates:
P-selectin binds neutrophils that extrude extracellular traps (NETs) for RBCs and PLTs, and active FXII
Other FXII activators:
- Venous catheter
- Polyphosphates from PLTs
- Polyanions (DNA, RNA)
Tissue factor (TF) or FIII
FVII --> FVIIa
Extrinsic pathway
FXII --> FXIIa
FXI --> FXIa
FIX --> FIXa
FVIIIa
Intrinsic pathway
FXI Inhibitors:
ASO:
- IONIS FXI Rx
- Fesomersen
MAb:
- Osocimab
- Abelacimab
- Gruticibart
SMI:
- Milvexian
- Asundexian
FX ----------> FXa <---------- FX
FVa
Prothrombin (FII) --> Thrombin (FIIa)
Fibrinogen (FI) --> Fibrin (FIa)
FXIIIa
Common pathway
Insoluble fibrin-rich cross-linked clot (thrombus)

FIGURE 1 The Coagulation Cascade and Mechanisms of Different Anticoagulants