Embolia polmonare

Lugano, 17.10.2025

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Treatment of pulmonary embolism (PE)

- From Heparin to LWMH, VKA and DOACS
- Treatment in the acute phase
- Follow-up of patients post-PE

Treatment with heparin

ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM
A CONTROLLED TRIAL

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TABLE III—RESULTS IN COMPLETE SERIES OF 73 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	54	0	1	2

Barritt et al. Lancet. 1960;1:1309-12

Treatment with warfarin

SAFETY AND EFFICACY OF WARFARIN STARTED EARLY AFTER SUBMASSIVE VENOUS THROMBOSIS OR PULMONARY EMBOLISM ☆

TABLE III—RATES OF RECURRENT VTE, BLEEDING, AND MORTALITY

—	Completed trial		Withdrawn		Excluded (n = 78*)
	L (n = 127)	S (n = 139)	L (n = 10)	S (n = 3)	
Symptoms of recurrent VTE:					
Confirmed	4 (3·1%)	3 (2·2%)	0	0	6 (7·7%)
Probable	2 (1·6%)	1 (0·7%)	0	0	0
Possible	0	1 (0·7%)	0	0	2 (2·6%)
Total VTE†	6 (4·7%)	5 (3·6%)	0	0	8 (10·3%)
VTE refuted	6 (4·7%)	11 (7·9%)	0	1	0
Bleeding:					
Major	2 (1·6%)	3 (3·9%)	0	0	6† (7·7%)
Minor	31 (24%)	19 (14%)	1	1	4 (5%)
Death¶	3 (2·4%)	5 (3·6%)	0	0	5 (6·4%)

Early warfarin treatment significantly shortened hospital stay by an average of 3.9 days (30%)

Gallus et al. Lancet. 1986;2:1293-6

Treatment with warfarin

Oral Anticoagulants

Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range

Table 1—*Recommended Therapeutic Range for Oral Anticoagulant Therapy*

Indication	INR
Prophylaxis of venous thrombosis (high-risk surgery)	
Treatment of venous thrombosis	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	2.0–3.0
AMI (to prevent systemic embolism)*	
Valvular heart disease	
Atrial fibrillation	
Mechanical prosthetic valves (high risk)	2.5–3.5
Bileaflet mechanical valve in aortic position	2.0–3.0

Low-dose coumarins same efficacy as high-dose coumarins

Less bleeding

Introduction of INR monitoring

Hirsch et al. CHEST 1998; 114:445S-469S

Treatment with LMWH

Treatment of Venous Thrombosis with Intravenous Unfractionated Heparin Administered in the Hospital as Compared with Subcutaneous Low-Molecular-Weight Heparin Administered at Home

Table 4. Recurrent Venous Thromboembolism, Major Bleeding, and Death in the Study Patients According to Treatment Group.*

Event and Time of Occurrence	Standard Heparin (N = 198)	Low-Molecular-Weight Heparin (N = 202)
Recurrent venous thromboembolism — no. of patients (%)		
Days 0–14	5	4
Days 15–84	5	4
Day 85 to end of follow-up	7	6
All	17 (8.6)	14 (6.9)
	Difference, 1.7 percentage points (95% CI, −3.6 to 6.9)	
Major bleeding — no. of patients (%)		
Days 0–14	2	1
Days 15–84	2	0
All	4 (2.0)	1 (0.5)
	Difference, 1.5 percentage points (95% CI, −0.7 to 2.7)	
Death — no. of patients (%)		
Days 0–14	0	0
Days 15–84	7	4
Day 85 to end of follow-up	9	10
All	16 (8.1)	14 (6.9)
	Difference, 1.2 percentage points (95% CI, −4.0 to 6.3)	

LMWH vs. standard heparin

Same efficacy

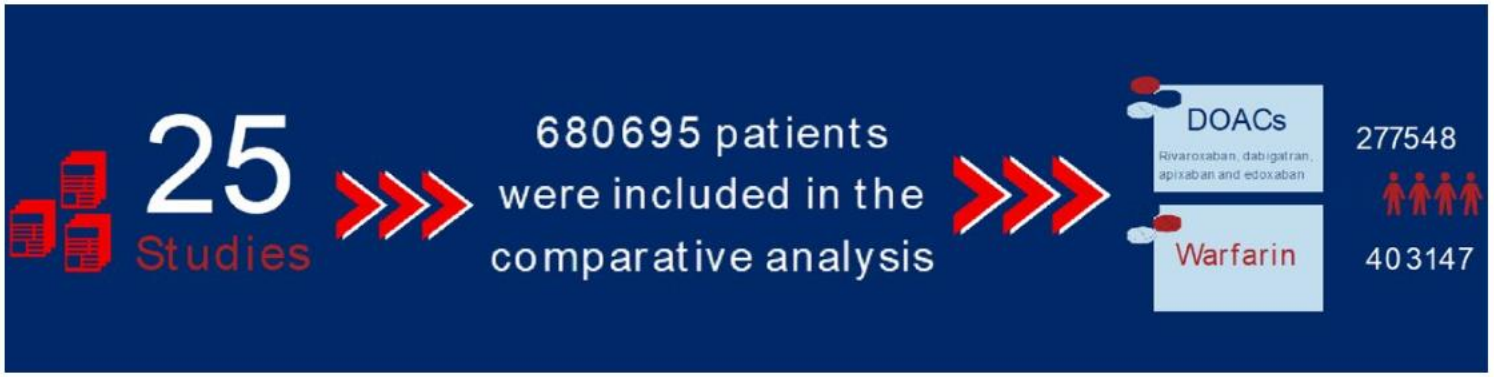
No increase in bleeding

Reduced length of hospital stay

Home therapy

Koopman et al. N Engl J Med 1996; 334:682-687

Treatment with DOAC



Carrier et al. European Heart Journal 2024; 45:54-56

Bed rest or early ambulation?

PLOS ONE | Management of Deep Vein Thrombosis, Bed Rest or Early Ambulation?

Study or Subgroup	early ambulation Events	Total	bed rest Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Schellong 1999	14	63	10	59	3.8%	0.05 [-0.09, 0.19]	1999
Aschwanden 2001	10	69	6	60	4.0%	0.04 [-0.07, 0.16]	2001
Blattler 2003	6	27	4	10	0.9%	-0.18 [-0.52, 0.16]	2003
Trujillo-santos 2005	4	988	7	1050	63.2%	-0.00 [-0.01, 0.00]	2005
Junger 2006	7	53	14	50	3.2%	-0.15 [-0.30, 0.01]	2006
Romera 2006	2	79	2	67	4.5%	-0.00 [-0.06, 0.05]	2006
Isma 2007	0	32	0	35	2.1%	0.00 [-0.06, 0.06]	2007
Manganaro 2008	18	172	43	80	6.8%	-0.43 [-0.55, -0.31]	2008
Romera 2008	3	114	2	105	6.8%	0.01 [-0.03, 0.05]	2008
Rahman 2009	0	12	0	12	0.7%	0.00 [-0.15, 0.15]	2009
Huang 2010	0	20	0	20	1.2%	0.00 [-0.09, 0.09]	2010
Feng 2011	1	15	1	17	1.0%	0.01 [-0.16, 0.18]	2011
Liu 2013	0	30	0	30	1.9%	0.00 [-0.06, 0.06]	2013
Total (95% CI)		**1674**		**1595**	**100.0%**	**-0.03 [-0.05, -0.02]**	
Total events	65		89				

Heterogeneity: $Chi^2 = 148.16$, $df = 12$ ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 4.79$ ($P < 0.00001$)

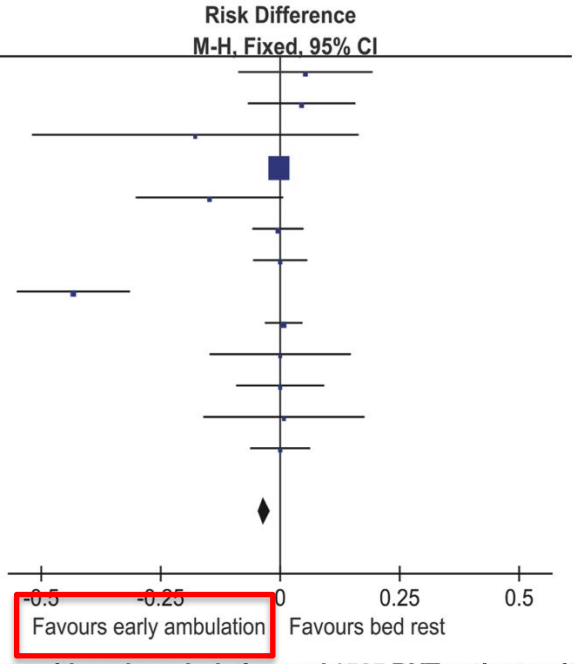


Fig 5. Meta-analysis of the incidence of primary end events among 1674 DVT patients with early ambulation and 1595 DVT patients with bed rest.

doi:10.1371/journal.pone.0121388.g005

sPESI score: PE cohort with a lower clinical and economic burden

Parameter	Simplified version[218]
Age	1 point (if age >80 years)
Male sex	–
Cancer	1 point
Chronic heart failure	1 point
Chronic pulmonary disease	
Pulse rate ≥110 b.p.m.	1 point
Systolic blood pressure <100 mm Hg	1 point
Respiratory rate >30 breaths per minute	–
Temperature <36 °C	–
Altered mental status	–
Arterial oxyhaemoglobin saturation <90%	1 point

30-day mortality: 0 points: 1%

≥ 1 point: 10.9%

P. Wells et al. Thromb Thrombolysis 2019;48(1):149

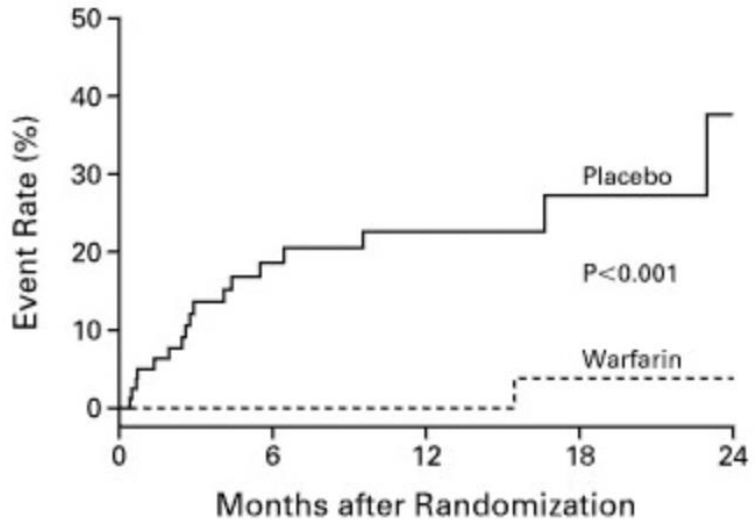
Treatment of the acute PE

- **Most patients with PE can be safely managed with anticoagulation (NOAC)**
- **PE with hemodynamic instability: reperfusion with thrombolysis**
- **Intermediate-high risk PE**
  - **In the absence of hemodynamic compromise, the evidence of interventional approach to PE management is weak**

Duration of anticoagulant treatment

Duration of anticoagulant treatment

A Comparison of Three Months of Anticoagulation with Extended Anticoagulation for a First Episode of Idiopathic Venous Thromboembolism



Patients at Risk					
Placebo	83	44	25	14	4
Warfarin	79	57	36	21	11

Patients with a first episode of idiopathic venous thromboembolism should be treated for longer than three months

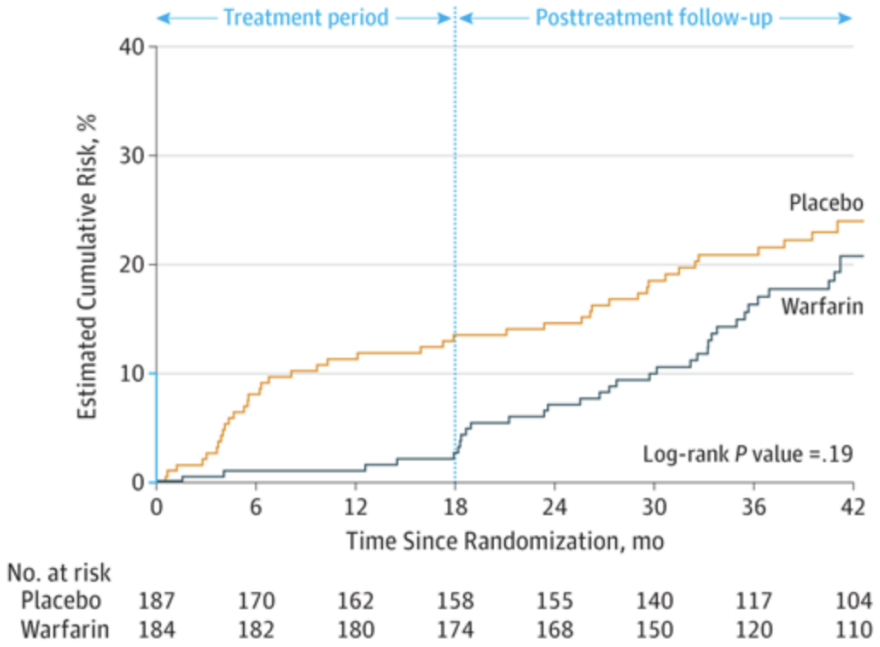
Kearon et al. NEJM 1999; 114:445S-469S

Duration of anticoagulant treatment

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Figure 2. Probability of the Composite Outcome of Recurrent Venous Thromboembolism and Major Bleeding Throughout the Study Period



The risk is low as long as treatment is continued

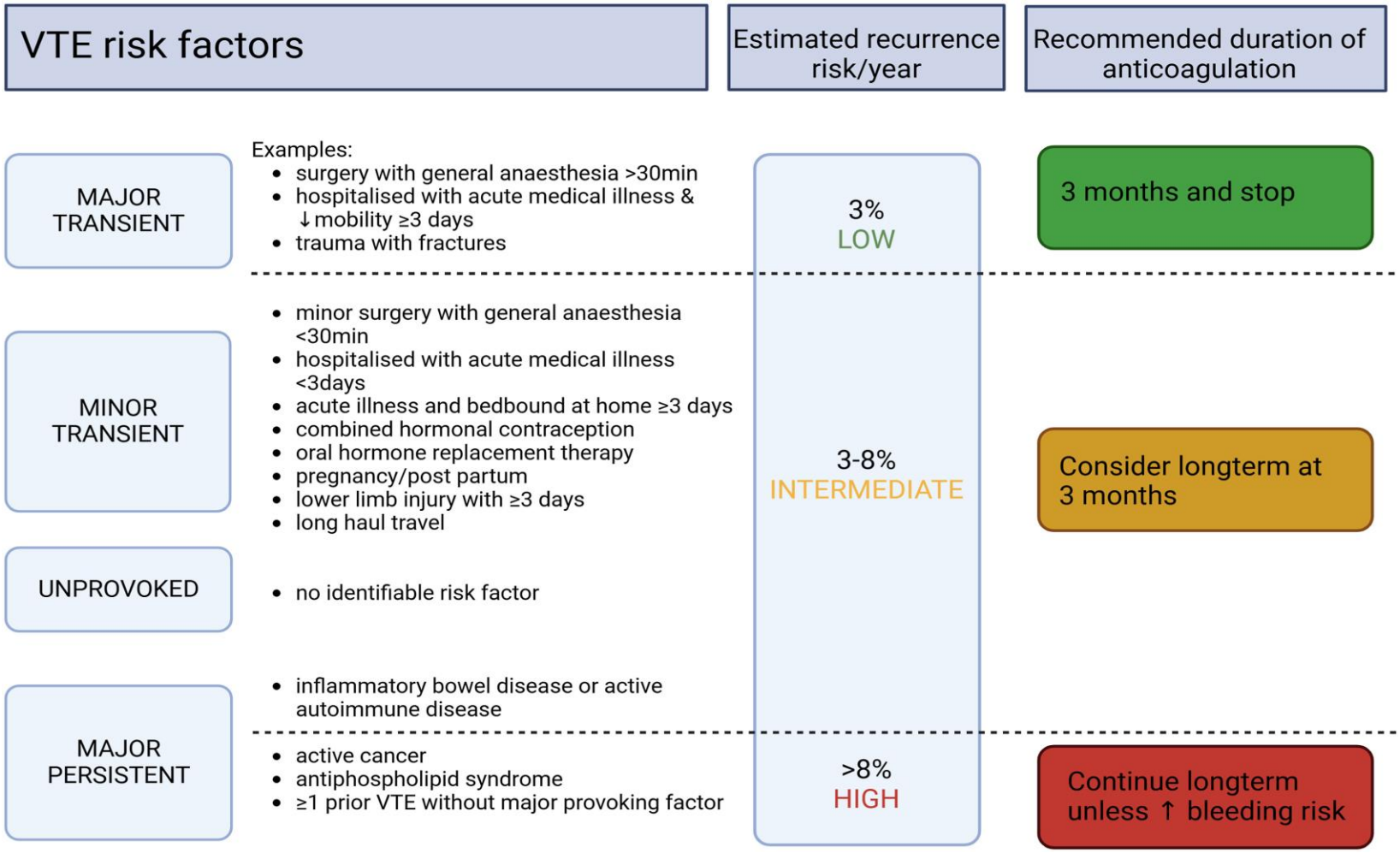
Longer durations of treatment do not reduce the risk of long-term recurrent VTE at discontinuation

Couturaud et al. JAMA 2015; 114:314:31-40

Duration of treatment: terminology

- Terminology such as «provoked» vs. «non-provoked» is not helpful for decision-making regarding the duration of anticoagulation
- Separate VTE events into four categories based on risk factors
  - Major persistent
  - Major transient
  - Minor persistent
  - Minor transient

Duration of anticoagulant treatment



Cox et al. J Thromb Haemost 2025; 23:1185-1202

Duration of anticoagulant treatment

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

Konstantinides et al. European Heart Journal 2020; 41:543-603

Duration of anticoagulant treatment

Discontinue after 3 months (major transient RF)

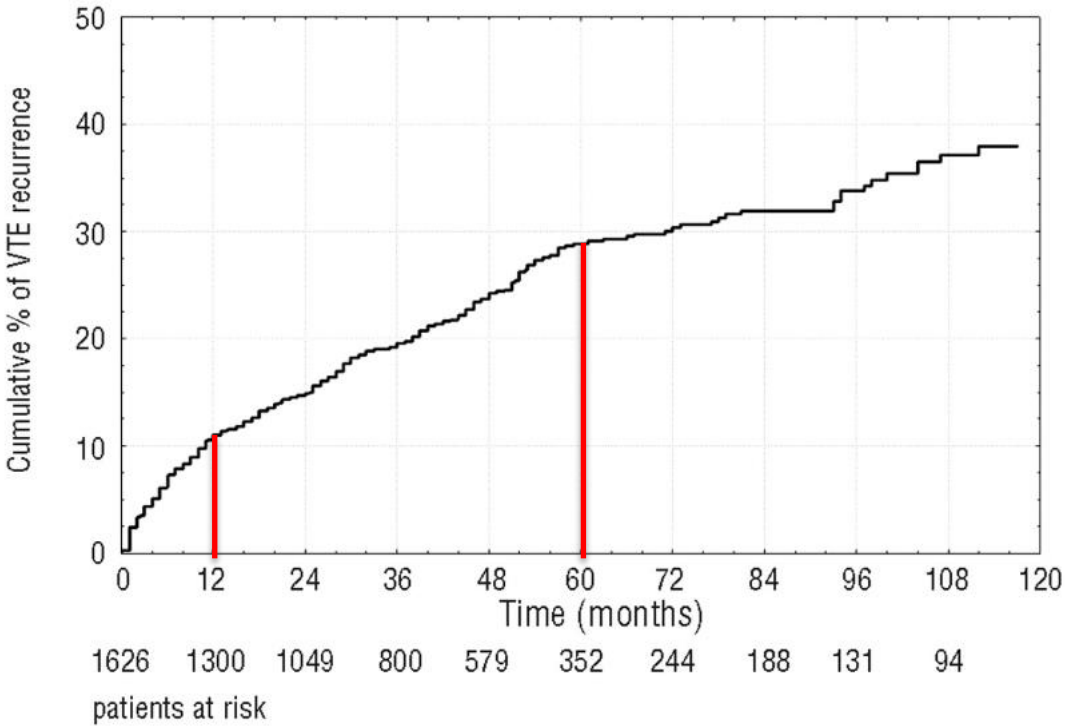
- Surgery with general anesthesia > 30 min
- Trauma with fractures
- Hospitalization with acute medical > 3 days with prolonged bed rest

Continue long-term (major persistent RF)

- Active cancer
- Prior unprovoked VTE
- Antiphospholipid syndrome

Duration of anticoagulant treatment

The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients



After 1 year: 10%

After 5 years: 2% per year

Prandoni et al. Haematologica 2007; 92:199-205

Duration of anticoagulant treatment

OFFICIAL COMMUNICATION OF THE SSC

Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting

International Society on Thrombosis and Haemostasis

Stop anticoagulants if the risk of recurrent VTE is less than 5% at one year after discontinuing treatment (<15% at 5 years)

Kearon et al. J Thromb Haemost 2010; 8:2313-2315

Duration of anticoagulant treatment

Recurrence scores

Recurrence scores must be able to detect patients with a low recurrence rate for VTE

- **HERDOO2 prediction model (only women)**
  - More appropriate to use in older woman
- **DASH prediction score**
  - More suited to use in younger patients
- **Vienna prediction model**

Duration of anticoagulant treatment

HERDOO2 prediction model

HERDOO2 score determination based on risk factors		
Factor	**Yes**	**No**
Post-thrombotic signs (eg, hyperpigmentation, oedema or redness on either leg)	+1	0
D-dimer level ≥250 µg/L	+1	0
BMI ≥30 kg/m^2	+1	0
Age ≥65 years	+1	0

Risk of recurrence by HERDOO2 score in learning and validation data sets		
HERDOO2 score	Risk of major* VTE recurrence per 100 patient years, % (95% CI)	
	Learning data set[46]	Validation data set[47]
0 or 1	1.6 (0.3 to 4.6)	3.0 (1.8 to 4.8)
2–4	14.1 (10.9 to 17.3)	7.4 (3.0 to 15.2)

*Proximal deep vein thrombosis and segmental or greater pulmonary embolism.
BMI, body mass index; HERDOO2, Hyperpigmentation, Edema, Redness, D-dimer, Obesity, Older age; VTE, venous thromboembolism.

Man continue

and

HERDOO2

(her do too)

Rodger et al. Can Med Assoc J 2008;179:417–26

Duration of anticoagulant treatment

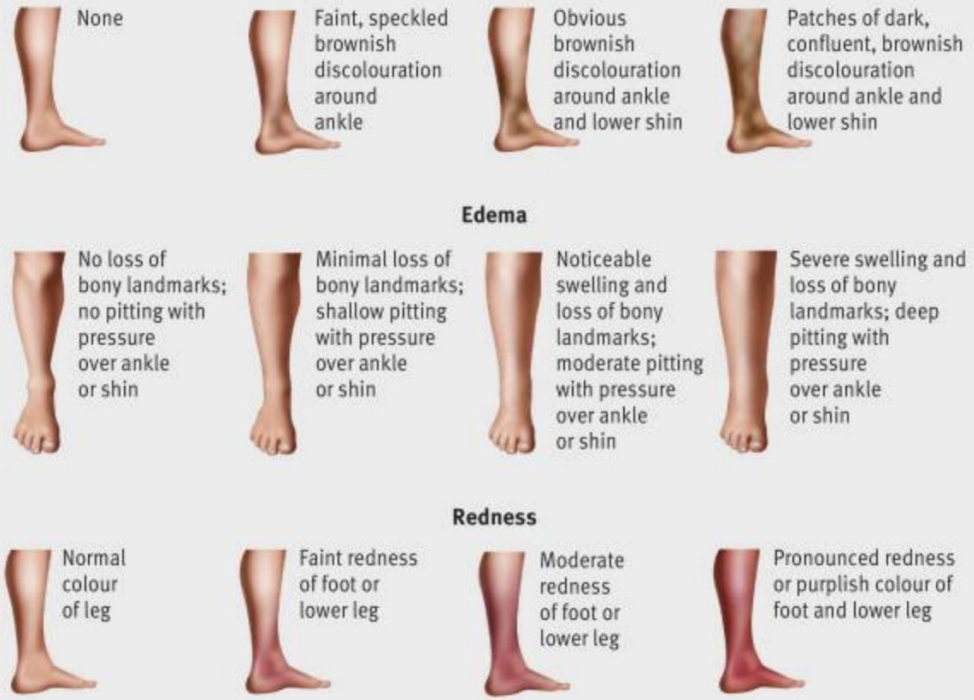
HERDOO2 prediction model

HER: any Hyperpigmentation, Edema, or Redness in either leg (ie, mild, moderate, or severe).
Assign 1 point for HER (ie, see visual guide below) — 1 point
VIDAS D-dimer ≥250 µg/L — 1 point
Obesity (body mass index ≥30) — 1 point
Older age (≥65 years) — 1 point

TOTAL=

Low risk: 0 or 1 point
High risk: ≥2 points

Visual guide:
Note: Signs may be less apparent in patients with brown or black skin



Rodger et al. BMJ 2017;356:j1065

Duration of anticoagulant treatment

DASH prediction score

DASH score determination based on risk factors		
Factor	**Yes**	**No**
D-dimer abnormal (measured 1 month after stopping anticoagulation)	+2	0
Age ≤50 years	+1	0
Male patient	+1	0
Hormone use at VTE onset (if female; select 'No' if male)	−2	0

Risk of recurrence of VTE as by DASH score in learning and validation data sets[50]		
DASH score	Annualised risk of recurrence (95% CI)	
	Learning data set (used to derive the DASH score)	Validation data set
≤−1	1.2 (1.1 to 1.3)	0.5 (0.4 to 0.6)
0	2.4 (1.4 to 4.2)	3.9 (3.6 to 4.2)
1	3.9 (2.9 to 5.3)	5.3 (5.1 to 5.4)
2	6.4 (5.0 to 8.1)	6.7 (6.5 to 7.0)
3	10.8 (8.7 to 13.4)	6.8 (6.5 to 7.2)
4	19.9 (13.9 to 28.2)	12.1 (10.9 to 13.3)

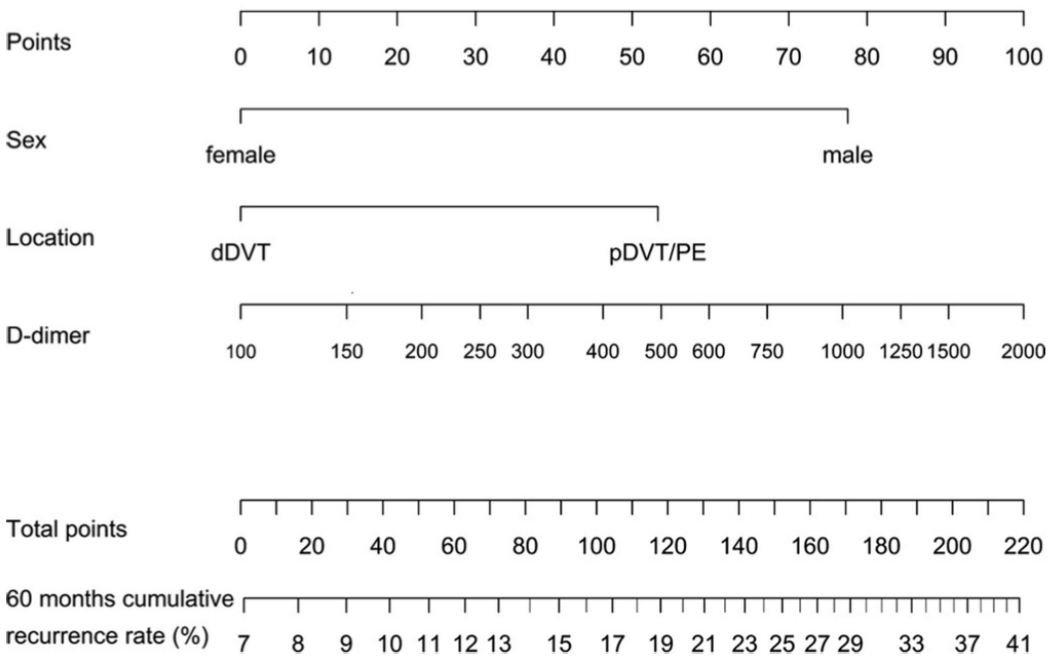
CI, confidence interval; DASH, D-dimer, age, sex, hormonal therapy; VTE, venous thromboembolism.

Caution with older patients

Tosetto et al. J Thromb Haemost 2012;10:1019

Duration of anticoagulant treatment

Vienna prediction model

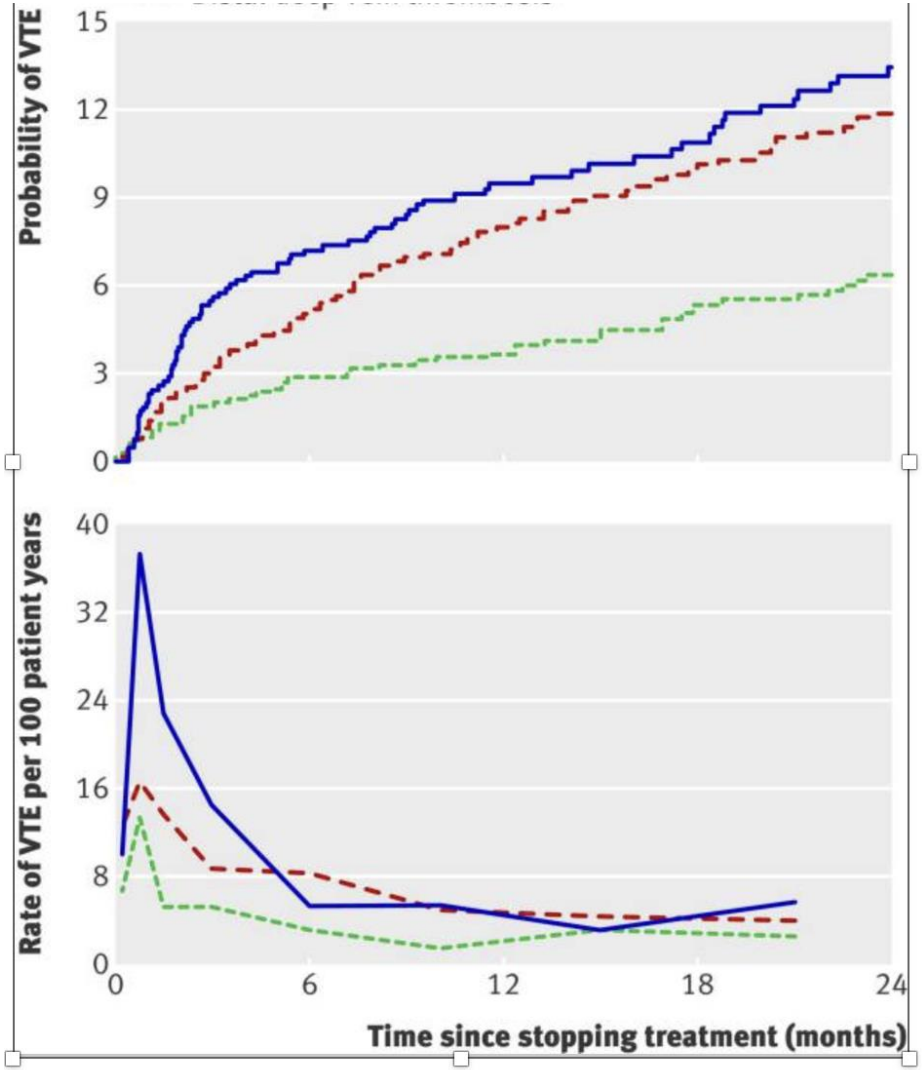


Vienna prediction model

Eichinger et al. Circulation 2010;121:1630

Duration of anticoagulant treatment

Recurrent VTE after VKA withdrawal

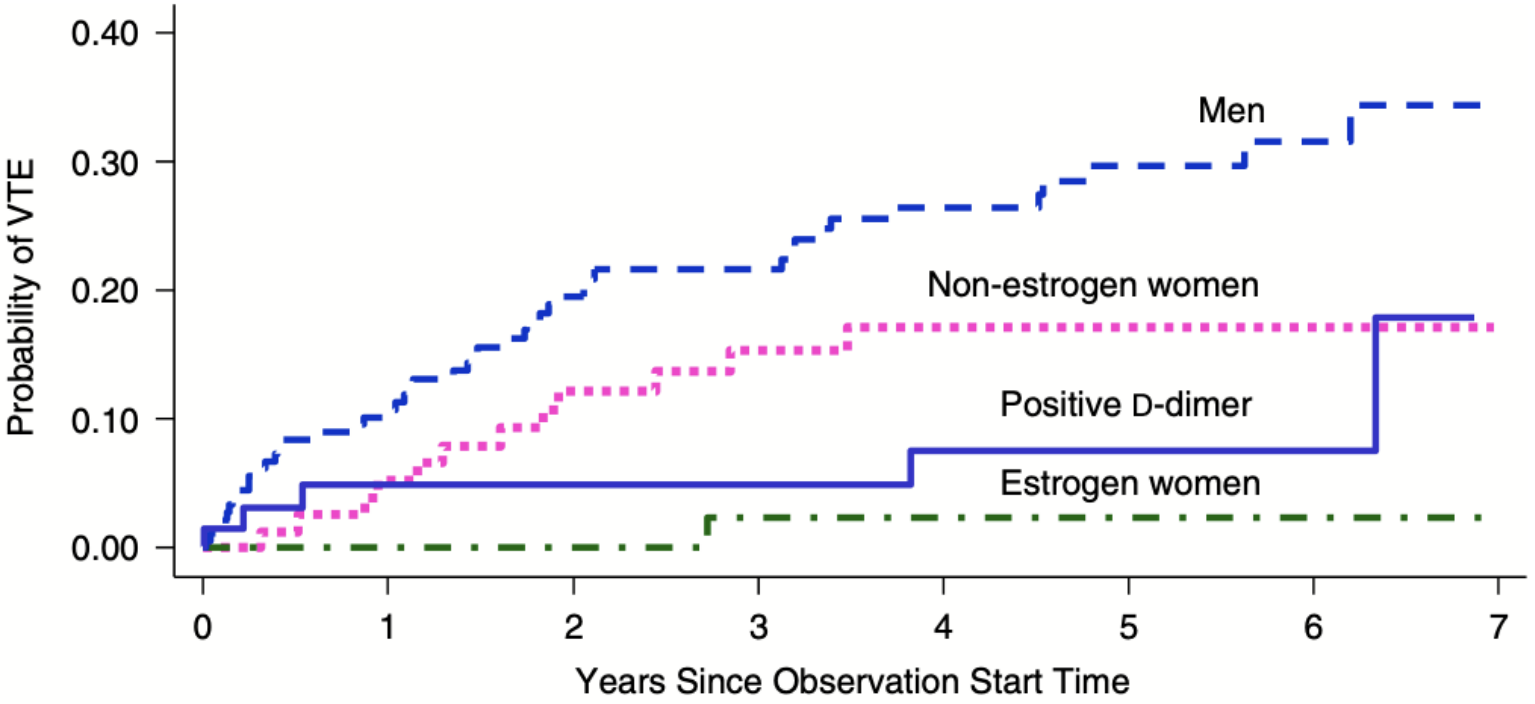


Location of initial VTE

- Pulmonary embolism
- Proximal deep vein thrombosis
- Distal deep vein thrombosis

Boutitie et al. BMJ 2011; 24:342

Duration of anticoagulant treatment



Kearon et al. J Thromb Haemost. 2019;17:1144

Continuing Anticoagulation after Unprovoked VTE?

Benefits

Less VTE

Risks

More bleeding

Patient preferences?

Carrier et al. European Heart Journal (2024) 45, 54–56

Duration of anticoagulant treatment

Risk of VTE recurrence

- 1 in 10 in the first year
- Rising to 1 in 3, in over 5-19 years once anticoagulation is stopped
- PE > DVT

Overall risk of major bleeding

- Case-fatality of bleeding > VTE recurrence
- 1-2 cases per year (2-3% initial 3-6 months)
  - 1.7 per 100 person-years for VKA
  - 1.0 per 100 person-years for DOAC

Extended-phase anticoagulant therapy

Reduce modifiable risk factors

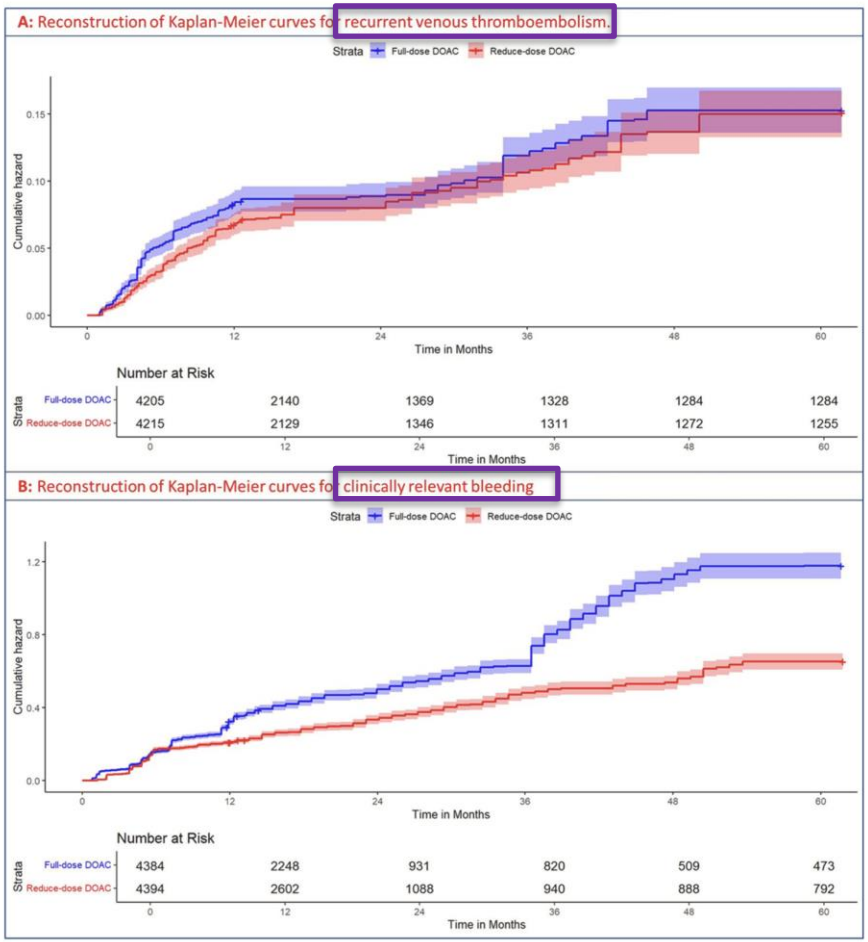
- Stop antiplatelets and NSAIDs if possible
- Reduce alcohol intake, prevent falls
- Control of hypertension, interacting medications

Choice of anticoagulant medication

- Reduced-dose DOAC (apixaban, rivaroxaban)

Extended-phase anticoagulant therapy

Efficacy and safety of reduced-dose versus full-dose direct oral anticoagulants for extended treatment of venous thromboembolism: A meta-analysis with trial sequential analysis and reconstructed time-to-event data



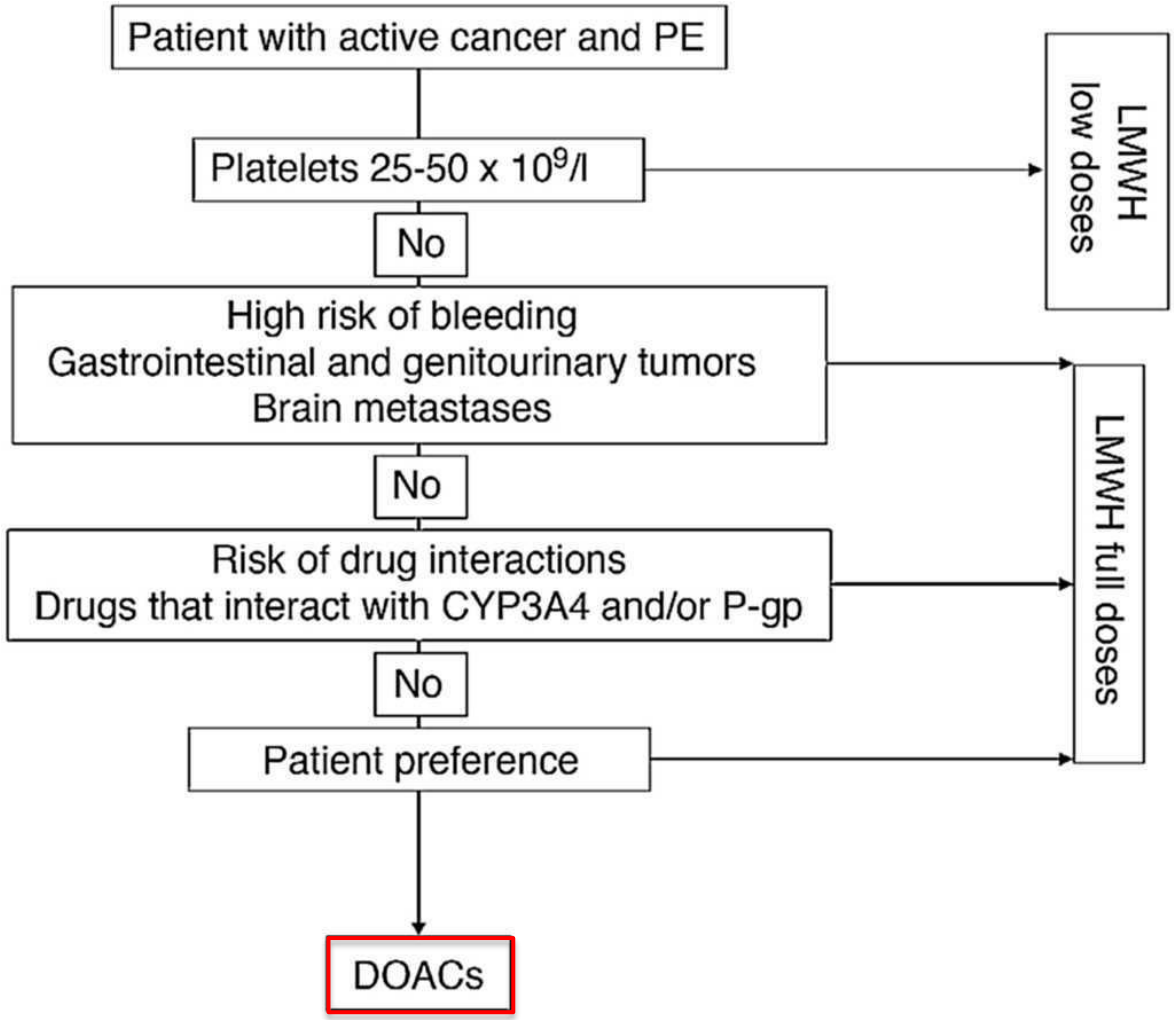
Reduced-dose

Apixaban (2x2.5 mg)

Rivaroxaban (1x10 mg)

Ibrahim et al. Thrombosis Research. Online 11 Sept 2025

Anticoagulant therapy in cancer patients



LMWH

Arch Bronconeumol. 2022;58:T246–T254

Extended-phase anticoagulant therapy

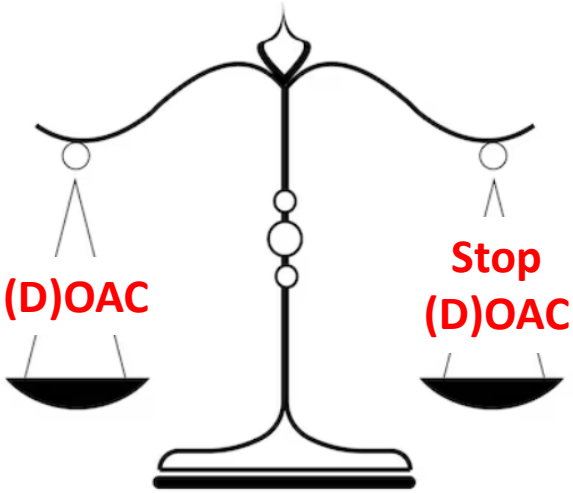
Reduced dose (after 6 months)

- HERDOO2 ≥2 (women)
- Unprovoked TEV in men
- Minor persistent/transient RF (obesity, renal impairment, CHF, . . .)

Major persistent RF

- Active neoplasia
- Second episode of TEV
- Antiphospholipid antibody syndrome

Normal dose



Bleeding risk > recurrence

- Recent/active major bleeding
- Neoplasm with a high risk of bleeding

Major transient RF

- Surgery with general anesthesia > 30 min
- Trauma with fractures
- Hospitalization with acute medical > 3 days with prolonged bed rest

HERDOO2 ≤1 (women)

Adapted from: Picariello et al. G Ital Cardiol 2023;24(4):275