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Hypercoagulable Work Up, Thrombophilia Testing, And Duration Of Anticoagulation

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VEITH 2023

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Disclosures

Rachel P. Rosovsky, MD, MPH

- Institutional Research Support:
  - BMS, Janssen
- Advisory/Consultant:
  - Abbott, BMS, Boston Scientific, Dova, Inari, Inquis, Janssen, Penumbra
- National Lead Investigator, *Storm-PE*, Penumbra
- Immediate Past President, The PERT Consortium™

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Thrombophilia Testing

- Will testing change management?
  - Effect duration of anticoagulation
  - Predict recurrence
  - Guide thromboprophylaxis?
  - Identify family members at risk
    - Avoid estrogen
- Will it cause harm?
- Is it accurate?
- How much does it cost?

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Inherited Thrombophilia

Table 2 Prevalence of inherited thrombophilic disorders and relative risk estimates for first and recurrent VTE[a]

Disorder	Affected gene	Prevalence in the general population[b]	Prevalence in patients with VTE	Relative risk for first VTE	Relative risk for recurrent VTE
Factor V Leiden heterozygote	F5	5–12%	12–20%	3–6	1.1–1.8
Factor V Leiden homozygote		0.004–0.25%	0.01–1.5%	6–20	1.2–2.6
Prothrombin G20210A heterozygote	F2	0.7–4%	5–8%	2–4	0.7–2.3
Prothrombin G20210A homozygote		Rare	Rare	10–20	Insufficient data
Antithrombin deficiency	SERPINC1	0.02–0.2%	0.5–2%	5–30	1.9–2.6
Protein C deficiency	PROC	0.2–0.5%	2–5%	4–24	1.4–2.5
Protein S deficiency	PROS1	0.03–0.7%	1–3%	5–30	1–2.5

50%

Abbreviation: VTE, venous thromboembolism.
[a]Relative risks are compared with persons without thrombophilia. Prevalence and risk estimates have wide ranges as they are taken from multiple studies and may differ based on how calculations were derived, and what populations were included.[1,28,32,35,40–42,51,57,58,65,66,98–107]
[b]Rates apply to Caucasian populations; prevalence is much lower in other groups.

Is thrombophilia testing useful?

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Whom should we test?

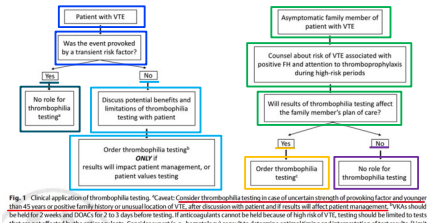
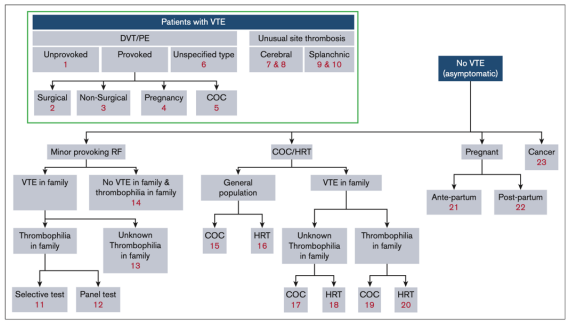


Fig. 1 Clinical application of thrombophilia testing. [a]Caveat: Consider thrombophilia testing in case of uncertain strength of provoking factor and younger (<45 years or positive family history or unusual location of VTE, after discussion with patient and if results will affect patient management. [b]VKAs should be held for 2 weeks and DOACs for 2 to 3 days before testing. If anticoagulants cannot be held because of high risk of VTE, testing should be limited to tests that are not affected by the anticoagulants. Consider expert (e.g., hematology) consult to determine optimal timing and interpretation of test results. [c]Limit testing to the thrombophilia identified in the affected family member, if known. VKAs, vitamin K antagonists; VTE, venous thromboembolism.

Gaddh, Rosovsky, Semin Resp Crit Care Med 2021



Duration of Anticoagulation

- Aim of long-term anticoagulation after VTE is to prevent recurrent VTE over time.
- Evidence suggests that risk of recurrence after stopping therapy is largely determined by:
  - whether acute episode of VTE has been effectively treated.
  - patient's intrinsic risk of having new episode of VTE (individual risk of recurrence).

VTE = venous thromboembolism

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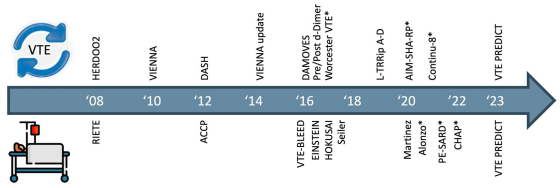
Table 11 Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

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 5/10-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

ESC 2019

VTE Prediction Models



Burggraaf JLI, et al. Pol Arch Intern Med 2023; 133(5): 16492 de Winter MA, et al. Thrombosis Research 2021; 199: 85-96

*No external validation

Courtesy of Allison Burnett, President AC Forum

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Prediction Risk Scores

ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–14 https://doi.org/10.1093/eurheartj/ehac776

CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Recurrent venous thromboembolism and bleeding with extended anticoagulation: the VTE-PREDICT risk score

Maria A. de Winter[1], Harry R. Büller[2], Marc Carrier[3], Alexander T. Cohen[4], John-Bjarne Hansen[5], Karin A.H. Kaasjager[1], Ajay K. Kakkar[6], Saskia Middeldorp[7], Gary E. Raskob[8], Henrik T. Sørensen[9], Frank L.J. Visseren[10], Philip S. Wells[3], Jannick A.N. Dorresteijn[10†], Mathilde Nijkeuter[1†‡], and the VTE-PREDICT study group

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Received 9 May 2022; revised 23 October 2022; accepted 7 December 2022

VTE-Predict Risk Score

VTE-PREDICT to predict risks of recurrent VTE, bleeding and individual benefits, and harms of extended anticoagulation

Development

Competing risk-adjusted models for
- Recurrent VTE
- Clinically relevant bleeding

were derived in combined individual patient data (n = 15,141)

Bleeding Risk Study, Hokusai-VTE, RE-MEDY, RE-SONATE, PREFER in VTE Registry

Validation

External validation (n = 59,257) showed agreement between predicted and observed risks up to 5 years

Danish VTE Cohort, EINSTEIN-CHOICE, GARFIELD-VTE, Tromsø study, MEGA study

Key features of the VTE-PREDICT risk score

- Suitable for all adult patients with VTE without active cancer for whom the decision to stop or continue anticoagulation is yet to be made
- Uses 14 simple, readily available patient characteristics
- Available worldwide through https://vtepredict.com

Individual patient example

Healthy male patient
60 years old
Unprovoked DVT
BMI 29.8 kg/m2
Hb 15 g/dL
SBP 135 mmHg

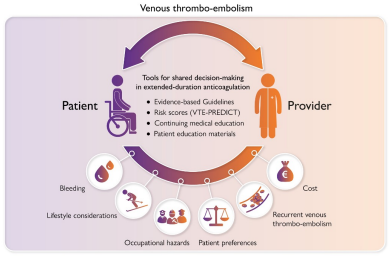
	1.6%	9.8%
VKA		
DOAC (full dose)	2.8%	5.2%
DOAC (reduced)	2.3%	2.3%
Aspirin	7.5%	2.9%

5-year risk with extended treatment

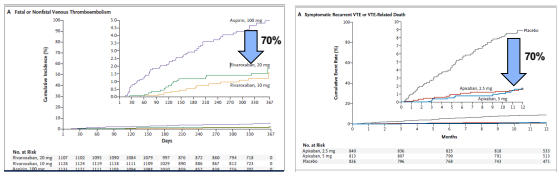
10.3% 2.0%

5-year risk without extended treatment

The Balance of Shared Decision Making in Determining the Optimal Duration of Anticoagulation After VTE



Dose Reductions



Rivaroxaban and Apixaban reduced the risk of recurrent VTE compared to aspirin, placebo, respectively, without increasing rate of major bleeding

Weitz et al. NEJM. 3017

How do I apply these results to my patients?

- Who do I consider for long term anticoagulation?
  - No identifiable risk factor (unprovoked)
  - Identifiable risk factor but with persistent risk factors (cancer)
  - Recurrent VTE
  - "high risk thrombophilia" or APLS
- Reduce dose at 6-12 months
- Reassess

APLS: antiphospholipid antibody syndrome

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Closing Reflections

- Duration of Anticoagulation will depend on patient
  - risk of recurrent VTE off AC
  - risk bleeding risk on AC
  - Preference
- Patients who had a VTE without an identifiable risk or identifiable risk but with persistent risk factors AND a low risk of bleeding AND whose preference is to continue AC should be offered long term AC.

VTE: venous thromboembolism
AC: anticoagulation

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Thank you

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