Testing For Cancer And Other Hypercoagulable States In PE: Why, When, And What Tests

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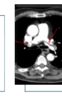
Thrombophilias: Why Test

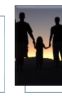

Guide clinical management


Predict VTE recurrence risk


Inform family planning and pregnancy management


Evaluate VTE risk before initiating hormone therapy


Need for thromboprophylaxis


Identify family members are risk for VTE

Blood Advances 7, no. 22 (2023): 7101–7138; *Am Fam Physician*. **2022;105(4):377-38**

Thrombophilia's: Prevalence and Clinical Implications

Thrombophilia's	RR for VTE recurrence
FVL homozygous	2.10
FVL heterozygous	1.36
PGM	1.34
Antithrombin (AT) deficiency	2.07
Protein C (PC) deficiency	2.13
Protein S (PS) deficiency	1.30
Antiphospholipid Antibody Syndrome	1.92

Conventional risk factors are far more common than hereditary thrombophilias.

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Risk of VTE Recurrence

Estimated Annual Risk of Recurrent VTE	Risk Category	Scenarios
LOW (<3%)	Major Transient Risk Factors (>10x increase risk of VTE)	• Major Surgery • Trauma • Confined to hospital bed > 3 days
INTERMEDIATE (3-8%)	Transient risk factors with <10x increased risk of VTE	• Pregnancy/ contraception • Long-haul flight • Leg injury without fracture
HIGH (> 8%)		• Strong thrombophilia's • Recurrent unprovoked VTE • Active cancer

European Heart Journal (2020) 41, 543603

Other High-Risk Thrombotic States

- Cancer
- Myeloproliferative disorders
- Heparin-induced thrombocytopenia
- Vasculitis/ autoimmune conditions
- Inflammatory conditions: IBD
- Nephrotic syndrome
- Paroxysmal nocturnal hemoglobinuria
- Splenectomy
- Certain medications

What I do not test!

- MTHFR polymorphisms
- <u>Minimal or uncertain significance:</u>
  - PAI-1 4G/ 5G polymorphisms
  - Factor XIII polymorphisms
  - Heparin co-factor II deficiency
  - Plasminogen deficiency
  - TAFI polymorphism
  - TFPI deficiency
  - Increased FXI activity
  - Protein Z deficiency
- <u>Elevated FVIII</u>
  - Considerable variation between individuals
  - Many conditions lead to elevation (e.g., acute thrombosis, acute illness, normal aging, pregnancy, African Americans, non-O type blood, cirrhosis)
  - No definite cutoff that defines this disorder but levels >234 IU/dL associated with higher VTE risk

<u>I do not generally test for this.</u>

Reed, et al. Thrombophilia. Consultative Hemostasis and Thrombosis. 4th ed.
Tsai, et al. Coagulation factors, inflammation markers, and venous thromboembolism: LITD. Am J Med. 2002.

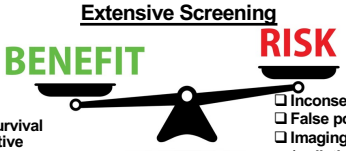
Scenario with PE	Testing	Notes
Unprovoked PE	Not recommended Patient may want to know	• Often does not alter treatment—special consideration for APS • May impact the care of family members • Recurrent VTE despite therapeutic anticoagulation

Blood Advances 7, no. 22 (2023): 7101–7134.

Occult Cancer Screening after VTE

- Important acquired cause of VTE
- Marker of poor prognosis (higher mortality and recurrent VTE events)
- RIETE registry: 2 years from VTE event: 8%
- Higher rates of cancer detection in unprovoked (7.6%) vs. provoked VTE (1.9%)

Extensive Screening

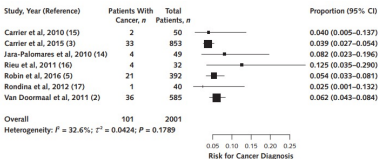


❑ Improve survival
❑ Cost-effective

❑ Inconsequential findings
❑ False positive results
❑ Imaging modality (radiation, contrast, cost)

Extensive Screening for Occult Cancer in VTE

Prevalence of cancer in the first 12 months of follow-up



- Occult cancer: 1 in 20 patients within a year of unprovoked VTE
- At 12 months, extensive screening vs. limited screening (OR, 1.4; 0.89 to 2.1)
- Cancer rates: 7x higher in older patients (age> 50).
  - Age <50 (1%) vs. age >50 (7%)

Ann Intern Med. 2017;167:410-417

Extensive Screening for Occult Cancer in VTE

Procedure (on top a routine screening based on history and physical exam, basic laboratory, chest X-ray, and age- and sex-directed cancer screening)	Finding and reference
CT of the abdomen and pelvis, including virtual colonoscopy and gastroscopy	Not useful[9]
Whole-body ^{18}F-FDG PET-CT	Possibly useful
CT of the chest, abdomen, and pelvis with fecal occult blood test	Not useful[11]

- French MVTEP study: 394 unprovoked VTE
  - (limited screening vs. 18F-FDG PET-CT)
  - At 2 years: PET-CT detected more cancer (5.2% vs. 2%), p=0.07

Hämostaseologie 2021;41:42–47; Lancet Oncol 2016;17(02):193–199

Risk Assessment Models

RIETE model
Male sex [+1]
Age >70 y [+2]
Chronic lung disease [+1]
Anemia [+2][a]
Platelet count >350 G/L [+1]
Postsurgery VTE [−2]
Previous VTE [−1]
Low risk ≤2
High risk ≥3

	RIETE	SOME
High risk	5.9%	5%
Low risk	2.9%	3.8%

SOME model
Age ≥60 y [+1]
Current smoking [+1]
Previous VTE [+1]
Low risk ≤1
High risk ≥2

	RIETE	SOME
HOKUSAI-VTE	2.7% vs. 2.9%	1.7% vs. 1.8%

Chest 2017;151(03):564–571, N Engl J Med 2015;373(08):697–704

What do the Guidelines say

- **ISTH** (2017): Limited Cancer Screening for unprovoked VTE
  - H&P, labs(CBC, calcium, UA, LFTs), age and gender-specific cancer screening

- **National Institute for Health and Care Excellence** (2020): Unprovoked VTE
  - H & P, basic labs & age and gender-specific cancer screening . No further investigations unless relevant clinical symptoms or signs.

Thromb Haemost 2017;15 (10):2076–2079.; November 2020:1–47

Clinical Scenarios with High Cancer Risk

- Advanced age
- Extensive thrombosis with bilateral proximal DVT
  - 2 French cohorts: occult cancer detected in 10 and 26% of patients
- Recurrent VTE despite therapeutic anticoagulation
- Recurrent superficial vein thrombosis in non-varicose veins
- Concurrent arterial and venous thrombosis
- Splanchnic vein thrombosis / Budd-Chiari syndrome
  - Seen in hepatocellular carcinoma
  - Colon, pancreas, and gastric tumors and myeloproliferative disorders

Summary

- Thrombophilia testing is often given prime importance in clinical practice; however, traditional clinical risk factors are far more prevalent!
  - Do not let pursuing hereditary thrombophilia testing distract from more important clinical risk factors in decision-making
- Negative thrombophilia labs ≠ no thrombophilic tendency
- Hypercoagulable testing is nuanced. Involve patients in decision-making!

- Extensive cancer screening is yet to show improved clinical outcomes
- PET scans are promising but not ready for prime time!
- Role of RNA profiling of platelets and other biomarkers?
- Need to learn more on appropriate patient selection who benefit from extensive screening and correct detection modality