POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

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Should Patients Be Tested for Thrombophilia?

April 2025

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Saskia Middeldorp, MD, PhD Arielle Langer, MD, MPH

Hereditary and acquired thrombophilia are risk factors for venous thromboembolism (VTE). Experts question whether testing should be used to guide management decisions. Screening for inherited thrombophilic conditions is controversial because studies haven't consistently shown an increased risk of recurrent VTE in patients with these conditions, even though they are

- **Who needs to be tested for thrombophilia?**
- **What are the benefits of testing? The drawbacks?**
- **Does the timing of the test matter?**
- **Which thrombophilias should physicians test for?**
- **How does provoked versus unprovoked VTE affect the decision whether to test?**
- **How does the possibility of a recurrence of VTE affect a decision to test or not test?**
- **If a test comes back positive, what is the next step?**
- **If you don't test, what do you watch for?**

DEBATE ORLANDO 2025

What stands for thrombophilia testing?

Thrombophilia markers	
Accepted	**Not accepted**
• Factor V Leiden • Prothrombin mutation G20210A • Antithrombin • Protein C • Protein S • Homocysteine (high values) • Anti-phospholipid antibodies • Factor VIII:C (acute phase reactant protein) • Non-O blood type group (ancillary risk factor)	• Plasminogen deficiency • High PAI-1 levels • Lipoprotein (a) • FXIII Leu34Val polymorphism • MTHFR C677T and A1298C polymorphisms • High coagulation factor levels (FV, FVII, FX) • Thrombomodulin polymorphisms • ACE polymorphisms • PZ/ZPI polymorphisms • High TAFI plasma levels

Marongiu F and Barcellona D, Blood Transfus 2025

When to perform thrombophilia testing?

Table 1. Timing considerations for thrombophilia testing

Aspect	Recommendation
Timing of testing	• *Genetic assays* (FVL, Prothrombin G20210A) can be performed at any time, as results are unaffected by anticoagulants or acute illness • *Functional assays* (AT, PC, PS) should be postponed until recovery and after discontinuation of anticoagulant therapy • *APS* (*aPL*) *testing* may be performed during anticoagulation; however, results must be confirmed ≥12 weeks apart to establish persistent positivity according to APS classification criteria
Guideline timing recommendations	• NICE / BSH: ≥6 weeks after stopping therapy • ASH: 2–4 weeks • ACCP: 4–6 weeks after discontinuation • All recommend delaying ≥2 weeks after full recovery from acute illness
Pre-testing assessment	Always determine whether a provoking factor (surgery, trauma, immobilization, estrogen exposure) is present; in provoked DVT, thrombophilia testing offers limited diagnostic or therapeutic value

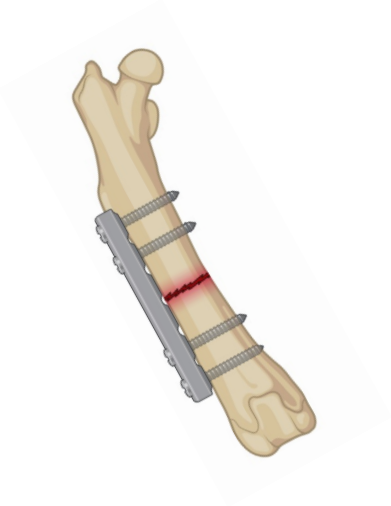
Shin J et al. Ann Phlebology 2025

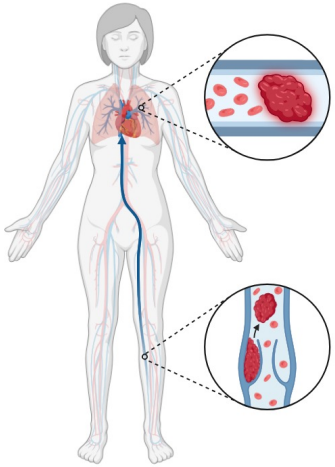
Who needs to be tested for thrombophilia?

Thrombophilia testing should be reserved for carefully selected patients in whom the results are likely to influence clinical decision-making….

…..nevertheless, it's sometimes easier to say who doesn't need to be tested

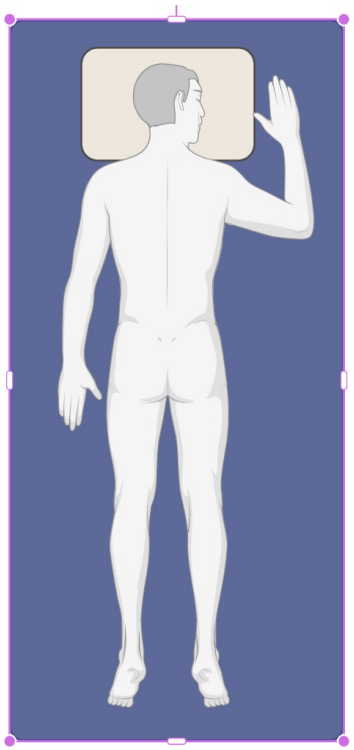
MAJOR SURGICAL PROVOKED = short-term anticoagulation

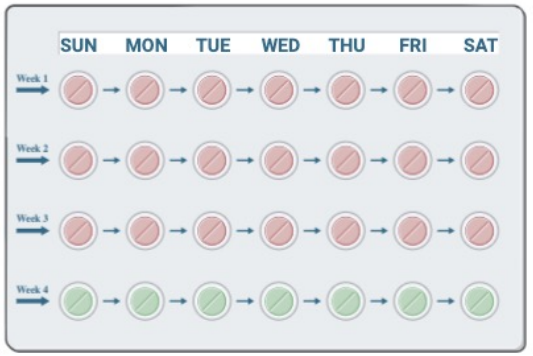


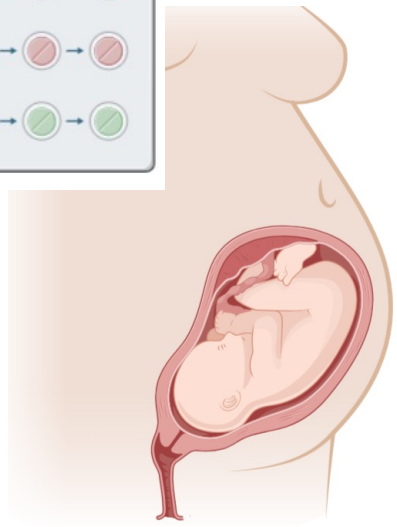


UNPROVOKED = long-life anticoagulation

What to do in intermediate-risk factor risks?



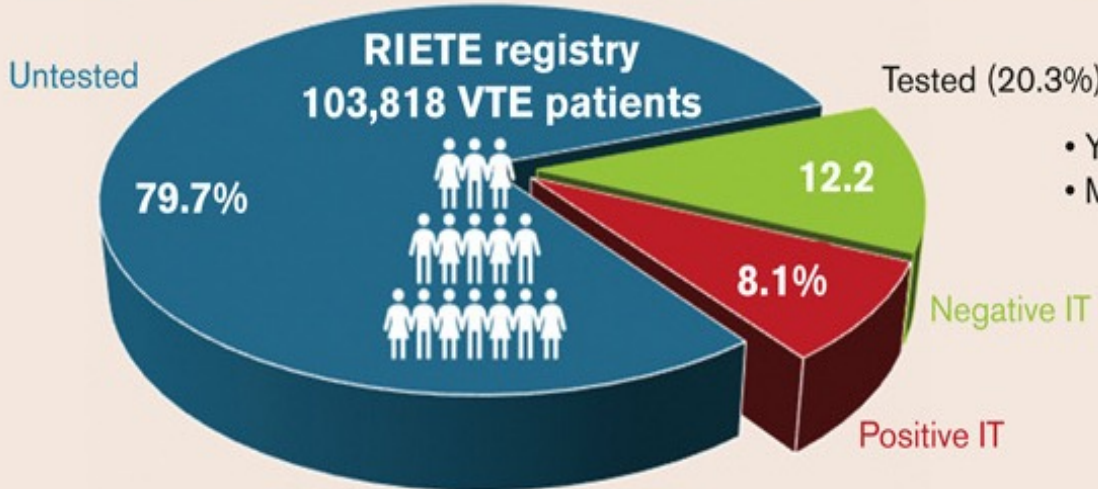




Thrombophilia testing: the RIETE trial

Venous Thromboembolism Characteristics and Outcomes
Among RIETE Patients Tested & Untested for Inherited Thrombophilia

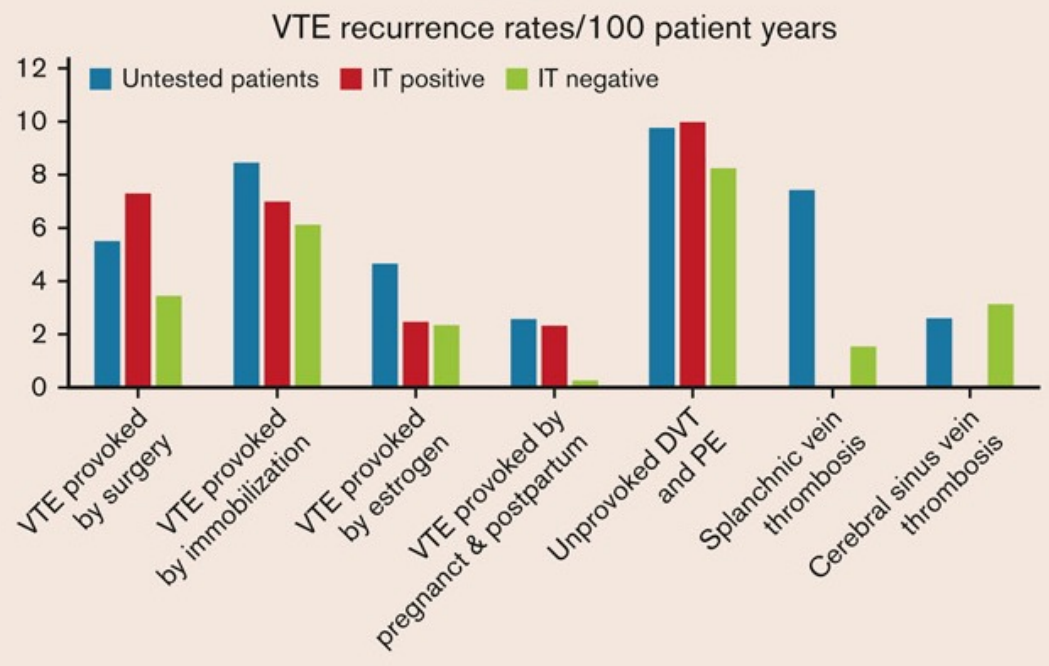
- Older, mean age 68 (± 16)
- Less testing with in VTE patients with pro-thrombotic risk-factors:
  - Recent surgery
  - Immobilization
  - Cancer-associated VTE



- Younger, mean age 55 (± 18)
- More testing in patients with:
  - Unusual site thrombosis
  - Prior VTE events
  - Estrogen exposure, pregnancy & post-partum VTE
  - Unprovoked VTE

Cohen O et al. Blood Adv 2024

Thrombophilia testing: the RIETE trial



Cohen O et al. Blood Adv 2024

During anticoagulant therapy, untested patients showed higher VTE recurrence rates (3.46 [95% confidence interval, 3.31-3.62]) than those tested for IT (2.58 [2.38- 2.80]), regardless of IT status (P < .001). They also exhibited higher rates of major bleeding (4.44 [4.27-4.61]), all-cause mortality (16.2 [15.9-16.5]), PE-related mortality (1.32 [1.23-1.41]), and bleeding related mortality (0.65 [0.58-0.71]) than tested patients (P < .001). Major bleeding and all-cause mortality rates were the lowest in patients with FVL and PT G20210A mutations.

Anticoagulant treatment was discontinued in 36 097 patients, of whom 10 048 (27.8%) were tested for IT, and 3488 were positive. Untested patients continued to exhibit higher incidences of VTE recurrence (8.69 [8.35-9.05]), major bleeding (1.14 [1.03-1.27]), and all-cause mortality (13.1 [12.7-13.5]), PE-related mortality (0.17 [0.13-0.22]), and bleeding-related mortality (0.62 [0.54-0.72]) than tested patients (P < .001).

What are the benefits of testing?

1. If your preference as a patient is to not discontinue anticoagulant, then perhaps thrombophilia testing may help to justify continuing
2. If your preference as a patient is to discontinue anticoagulant, then perhaps negative thrombophilia testing may help to justify discontinuing

Middledorp S and Langer A, ASH Clinical News; Shin J et al. Ann Phlebology 2025

What are the disadvantages of testing?

1. Mainly in acute phase, tests can be difficult to be interpreted
2. Negative testing may give someone false reassurance after a clearly unprovoked high-risk clot, and clinicians try to take the patient off anticoagulation because the test is negative
3. Family-members can be cared in ways that are inappropriate (?)

Middledorp S and Langer A, ASH Clinical News; Shin J et al. Ann Phlebology 2025

Controversial

1. Massive family testing or guided family counseling?
2. Can testing help us to decide on long-term prophylaxis dosage?

Middledorp S and Langer A, ASH Clinical News

Non è vero ma ci credo ?

Abstract Title : Prevalence and outcomes of inherited and acquired thrombophilia in pediatric patients with venous thromboembolism: Findings from an institutional prospective inception cohort study.

Wooley E at al. Johns Hopkins All Children Hospital, St Petersburg, United States

A total of 177 children were included. The median age was 7 years, 53% were female, and 75% were white. The prevalence of at least one **thrombophilia was 20%** (n=36), while multiple thrombophilia traits were present in 6% of children (n=10).

Among those diagnosed with thrombophilia, antiphospholipid syndrome (APS) and FVL mutations were the most common diagnoses (50% and 31%, respectively), while AT deficiency and F2 mutations were the least common (6% and 3%, respectively).

Children with thrombophilia compared to children without:

- were older (median age 5.5 vs. 12.9 years, p=0.011), and more frequently female (49% vs. 69%, p=0.038);
- had a higher frequency of pulmonary embolism (17% vs. 7%) and lower extremity deep venous thrombosis (DVT) (42% vs. 28%)
- higher rates of unprovoked (31% vs. 8%, p<0.001) and drug-related VTE (28% vs. 12%, p=0.034), and lower rates of central venous catheter (CVC)-associated DVT (39% vs. 67%, p=0.004)
- had a higher rate of recurrent VTE compared to those without (28% vs. 11%, p=0.014).

Pediatric Data – Key Messages

- Testing rarely changes acute management
- Catheter-related VTE predominant cause
- Inherited thrombophilia modestly influences recurrence
- Avoid routine broad panels

CLINICAL GUIDELINES

blood advances

American Society of Hematology/International Society on Thrombosis and Haemostasis 2024 updated guidelines for treatment of venous thromboembolism in pediatric patients

Recommendation 2. For pediatric patients with **clinically unsuspected** (previously termed asymptomatic) DVT or PE, the ASH/ISTH guideline panel suggests either using anticoagulation or no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⨁○○○). **Remarks:** The natural history of clinically unsuspected DVT or PE in pediatric patients appears to carry a lower risk (compared with symptomatic DVT or PE) of acute and long-term sequelae, especially in certain pediatric subpopulations. The recommendation is based on studies that report outcomes for pediatric patients with clinically unsuspected DVT or PE. Single institution, observational, and retrospective studies in select subpopulations of pediatric patients suggest that not using anticoagulation for clinically unsuspected DVT or PE does not lead to severe outcomes. The benefits or harms of anticoagulation or no anticoagulation vary for different populations including neonates, pediatric patients who are critically ill, patients with cardiac disease, or patients who have experienced trauma. **However, if clinically unsuspected DVT or PE is detected, the decision to treat or not treat should be individualized.** Research to better understand the natural history of clinically unsuspected DVT or PE, benefits, and harms of treatment in a variety of subgroups and clinical settings in pediatrics is a high priority.

Monagle P et al. Blood Adv 2024

Thrombophilia testing to better evaluation of unsuspected thrombosis ?

Abstract Title: Thrombophilia testing and thrombotic risk evaluation in beta-thalassemia: A cohort analysis from a hub regional center

Raso S at al. Haematology and Rare Disease University Unit, PO "Cervello", Palermo, Italy

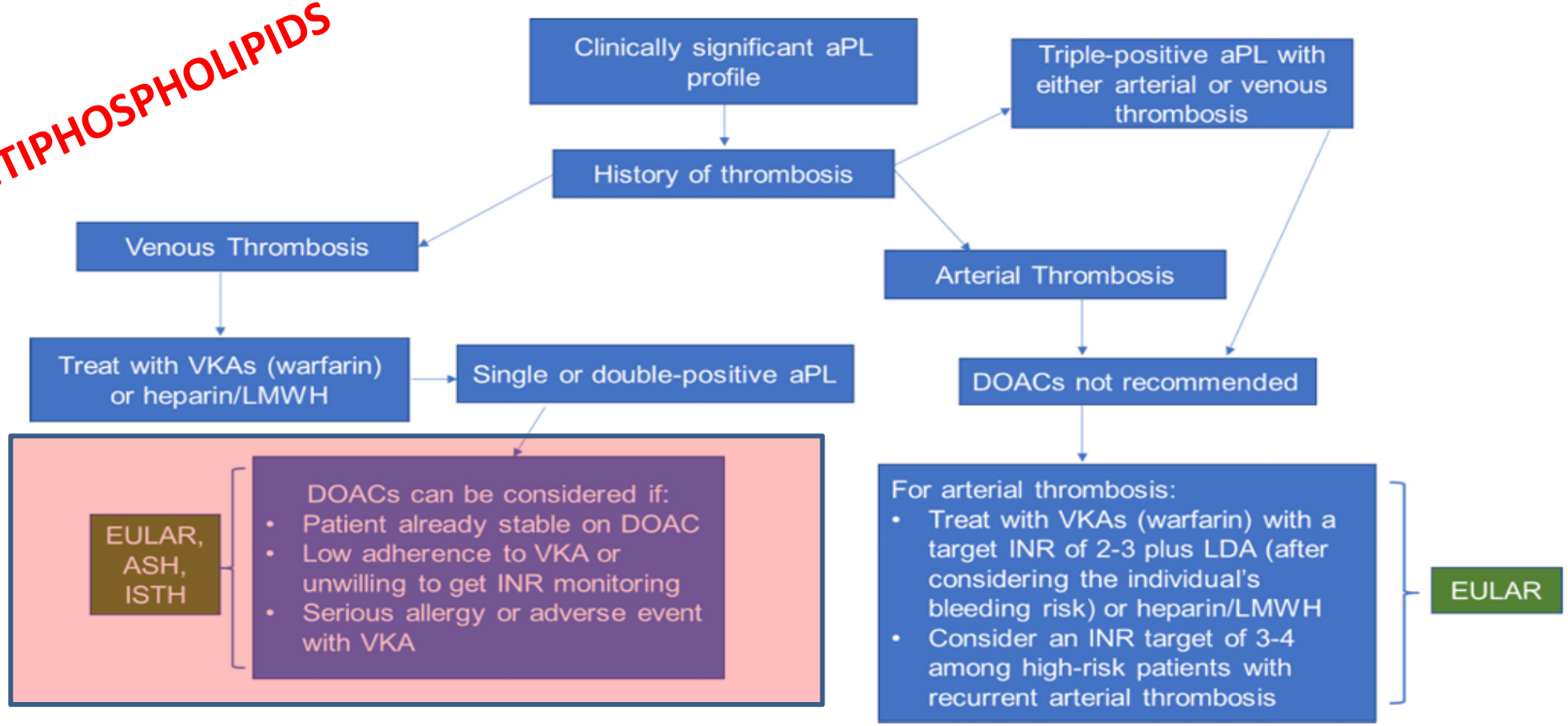
Sixty-four βT patients underwent thrombophilia screening: 34 males, 31 females, with a mean age of 44 years (range 35-53). Eighteen patients underwent a complete thrombophilia screening, while 34/64 and 38/64 patients had a genetic and functional screening, respectively .
Complete thrombophilia screening was mostly indicated by splenectomy (56%) and a personal history of VTE (100%).

Thrombotic complications occurred in **17** subjects over five years:**12 patient with thrombophilia** had one VTE episode, 5 experienced a TEE due to atrial fibrillation.

One patient (2.9%) was heterozygous for FII (G20210A) and three (4%) for FV Leiden. **Elevated aCL and anti-β2GPI were detected in 7.5 % of patients.**

Hemopathies and thrombophilia

ANTIPHOSPHOLIPIDS



Franco-Moreno A et al. Drug Discoveries & Therapeutics 2024

Abstract Title: Real-world outcomes of direct oral anticoagulants versus warfarin in patients with single-positive antiphospholipid antibody syndrome: A trinetx cohort analysis

Khan F et al. Buffalo Roswell Comprehensive Cancer Center, Buffalo, NY, United States

Authors performed three parallel, retrospective cohort studies using the TriNetX global network. Adult patients (≥18 years) with APS and isolated positivity for aCL, LAC, or B2GP1 antibodies were identified.

In the aCL-positive cohort, DOACs were associated with a higher risk of myocardial infarction (MI) (HR 2.48, 95% CI 1.01–6.09, p=0.040) and a lower risk of hospitalization (HR 0.378, 95% CI 0.175–0.817, p=0.010) compared to warfarin.

In the LAC-positive cohort, DOAC therapy was associated with significantly lower risks for GI bleed (HR 0.72, 95% CI 0.58–0.88, p=0.001), hemoperitoneum (HR 0.18, 95% CI 0.06–0.53, p<0.001), ICH (HR 0.50,95% CI 0.32–0.77, p=0.001), blood transfusion (HR 0.76, 95% CI 0.57–1.00, p=0.049), ischemic stroke (HR 0.50, 95% CI 0.37–0.67, p<0.001), peripheral arterial thrombosis (HR 0.59, 95% CI 0.43–0.80, p=0.001),DVT (HR 0.79, 95% CI 0.69–0.91, p=0.001), hospitalization (HR 0.75, 95% CI 0.66–0.86, p<0.001), and all-cause mortality (HR 0.61, 95% CI 0.53–0.71, p<0.001), compared to warfarin. Iron deficiency anemia was more frequent with DOACs (HR 1.22, 95% CI 1.05–1.42, p=0.010).

In the B2GP1 ab–positive cohort, DOACs were associated with a lower risk of ischemic stroke (HR 0.21, 95% CI 0.06–0.74, p=0.007).

Antiphospholipid Syndrome (APS)

- Triple positive APS → VKAs remain standard (INR 2–3)
- Higher arterial events with DOACs in RCTs
- Single-positive APS: individualized decision
- Ongoing debate discussed at ASH 2025

Why this topic still matters

- Up to 40–50% of VTE patients undergo thrombophilia testing
- In most cases, results do NOT change duration of anticoagulation
- Growing DOAC use reshaping management
- Need for cost-effective and selective testing

When Does Testing Change Management?

- Suspected APS
- Antithrombin deficiency
- Strong family history + young patient
- Counseling in women considering pregnancy
- NOT routine unprovoked VTE in older adults

TAKE HOME MESSAGES ORLANDO 2025

•Thrombophilia testing retains a role in the management of thrombotic events when the decision to continue or discontinue **anticoagulation is uncertain**.

•In the **pediatric setting**, thrombophilia evaluation may support decision-making regarding the treatment of asymptomatic thrombosis.

•A thrombophilia workup can help clarify the underlying **etiology of thrombosis**, addressing patients' need for an explanation.

•Family screening: prevention of further thrombotic events in relatives VS overestimation of risks in **asymptomatic carriers**?

•The identification of **antiphospholipid antibodies** is crucial in guiding the choice of the most appropriate anticoagulant therapy.