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Review

Thrombophilia testing in venous thromboembolism: When, who and why it matters. A practical review

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ABSTRACT

Thrombophilia encompasses inherited and acquired biological abnormalities that predispose to venous thromboembolism (VTE). Although thrombophilia testing has been available for decades, routine screening of all patients presenting with deep vein thrombosis or pulmonary embolism is neither recommended nor cost-effective. Current international guidelines support testing for clinical scenarios where results may meaningfully inform recurrence risk and thereby influence therapeutic decisions regarding anticoagulation duration, anticoagulant choice, contraceptive counselling or pregnancy management. This narrative review provides a practical, evidence-based framework for thrombophilia investigation. We address testing indications stratified by clinical context, including unprovoked VTE in young patients, hormone-associated thrombosis and unusual-site thrombosis. Practical considerations for testing timing and anticoagulant interference are detailed, including recent expert guidance on charcoal-based direct oral anticoagulant neutralization strategies. Therapeutic implications are examined across specific populations: women requiring hormonal contraception or menopause hormone therapy, cancer-associated thrombosis and chronic thromboembolic pulmonary hypertension. Thrombophilia results should be interpreted within the broader clinical context. A clinical decision algorithm synthesizing current evidence and recommendations is proposed to guide selective testing.

1. Abbreviations

aβ2GPI anti-β2-glycoprotein I antibodies
aCL anticardiolipin antibodies
aPL antiphospholipid antibodies
APS antiphospholipid syndrome
aPS/PT anti-phosphatidylserine/prothrombin antibodies
ASH American Society of Hematology
AT antithrombin
BSH British Society for Haematology
COC combined oral contraceptives
CTEPH chronic thromboembolic pulmonary hypertension
DOAC direct oral anticoagulant
dRVVT dilute Russell viper venom time
ELISA enzyme-linked immunosorbent assay
ESVS European Society for Vascular Surgery
F2 factor 2 (prothrombin)
FIIa factor IIa
FVL factor V Leiden
FXa factor Xa
HbAS sickle cell trait
HbSS sickle cell anaemia
IgA immunoglobulin A
IgG immunoglobulin G
IgM immunoglobulin M
INR international normalized ratio
JAK2 Janus kinase 2
LA lupus anticoagulant
LMWH low-molecular-weight heparin
MHT menopause hormone therapy
PC protein C
PS protein S
SFMV Société Française de Médecine Vasculaire (French Vascular Medicine Society)

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VKA vitamin K antagonist
VTE venous thromboembolism

2. Introduction

Venous thromboembolism (VTE) is a multifactorial disease arising from the interplay of genetic predisposition, acquired conditions and environmental exposures [1]. The thrombophilia concept emerged with Egeberg's description of antithrombin (AT) deficiency in 1965, subsequently expanding to include protein C (PC) and protein S (PS) deficiencies (1981–1984) and the more prevalent factor V Leiden (FVL) and prothrombin (factor 2 [F2]) G20210A mutations (1994–1996) [2–7]. These discoveries initially fostered optimism that identifying prothrombotic states would improve outcomes through personalized anticoagulation strategies. However, decades of clinical experience have revealed a gap between the detection of thrombophilic abnormalities and the demonstration of clinical benefit [8,9].

Inherited thrombophilias vary substantially in prevalence and thrombogenicity. FVL, present in 2–15% of Europeans but rare in Asian and African populations, confers a 3–7-fold increased first VTE risk in heterozygotes [7,10]. The F2 G20210A mutation, found in 1–3% of Europeans, carries a similar risk magnitude (odds ratio [OR] 2–4). In contrast, deficiencies of natural anticoagulants, AT, PC and PS are considerably rarer (0.02–0.7% prevalence) yet more thrombogenic [7,10]. Meta-analyses demonstrate relative risks ranging from 4 to 16 for PC and PS deficiencies, while AT deficiency confers the highest risk with ORs of 10–50 depending on deficiency subtype [11,12]. Antiphospholipid syndrome (APS) represents a distinct entity among acquired thrombophilias, characterized by persistent antiphospholipid antibodies (aPL) in association with vascular thrombosis or pregnancy morbidity [13,14].

Contemporary international guidelines from the Société Française de Médecine Vasculaire (SFMV; French Vascular Medicine Society), European Society for Vascular Surgery (ESVS), British Society for Haematology (BSH) and American Society of Hematology (ASH) have converged on a principle of selective testing [3–6]. The rationale is straightforward: thrombophilia testing should be performed only when results may influence management decisions. In practice, however, testing patterns often deviate from this principle: overtesting occurs in low-yield scenarios while potentially informative contexts remain undertested [15–17]. This review synthesizes current evidence to provide clinicians with a practical framework for thrombophilia testing indications, anticoagulant interference management and therapeutic implications across specific populations. A decisional framework integrating the major international guideline recommendations is proposed in the Central Illustration, which articulates three sequential clinical questions: when to test, how to test and how to interpret results to guide management.

3. Indications for thrombophilia testing

Thrombophilia testing is clinically justified when its result may modify the estimated risk of recurrent VTE, thereby informing the decision to continue or discontinue anticoagulation, guide anticoagulant choice or direct management in specific clinical contexts such as pregnancy and hormonal therapy. Two related but distinct risk estimates underpin this framework: the risk of a first VTE event associated with a given thrombophilia and the risk of VTE recurrence after anticoagulation discontinuation (Table 1 and Table A.1) [11,12,18–21].

3.1. Unprovoked VTE

Unprovoked VTE occurring at a young age has traditionally been considered the classic indication for thrombophilia testing. Guidelines vary in their age thresholds: SFMV and ASH suggest < 50 years, ESVS < 45 years and BSH < 40 years (Table 2) [3–6]. Regarding family history, two distinct situations should be differentiated: (1) a family history of VTE without known thrombophilia in the index case represents a form of clinical thrombophilia that increases recurrence risk but does not direct targeted laboratory testing and (2) a documented heritable thrombophilia–particularly AT, PC or PS deficiency–in a first-degree relative justifies targeted testing in the proband, as results would directly influence treatment decisions. The 2023 ASH guidelines provide conditional recommendations against routine thrombophilia testing in patients with unprovoked VTE [6]. The rationale is that unprovoked VTE already justifies extended anticoagulation based on the elevated risk of recurrence (approximately 30% at 10 years after treatment discontinuation), regardless of thrombophilia status [22,23]. When thrombophilia is identified, recurrence risk after anticoagulation discontinuation varies substantially by type (Table 1): low for heterozygous FVL or F2 G20210A, moderate for PC or PS deficiency, high for AT deficiency as demonstrated in prospective family cohort studies with systematic thrombophilia ascertainment [11,12,19,24,25]. This risk stratification, rather than the detection of thrombophilia per se, informs the decision on anticoagulation duration.

3.2. VTE provoked by hormonal context

In contrast to unprovoked VTE, the ASH guidelines conditionally recommend thrombophilia testing in patients whose VTE was provoked by hormonal factors (combined oral contraceptives (COC), hormone replacement therapy, pregnancy or postpartum period), in settings where anticoagulation would otherwise be discontinued [6]. These patients face future re-exposure to similar hormonal contexts, and thrombophilia status informs both recurrence risk upon anticoagulation discontinuation and future hormone-related decisions.

Real-world data from the RIETE registry revealed that approximately 50% of women with oestrogen-associated or pregnancy-related VTE who were tested harboured inherited thrombophilia, and those who tested negative had 10-fold lower recurrence rates after anticoagulation discontinuation than those who tested positive [15].

Conversely, thrombophilia testing provides limited clinical utility in patients whose VTE was clearly provoked by major transient surgical risk factors with low recurrence rates after anticoagulation discontinuation regardless of thrombophilia status [9].

3.3. Unusual-site thrombosis

Guidelines conditionally recommend thrombophilia testing in patients presenting with unusual-site thrombosis (cerebral venous sinuses, splanchnic veins or upper-extremity veins in the absence of a catheter) when anticoagulation would otherwise be discontinued [3–6,26]. For example, the prevalence of natural anticoagulant deficiencies is elevated in portal vein thrombosis compared with healthy controls (AT deficiency: OR 8.89, 95% confidence interval [CI] 2.34–33.72); PC deficiency: OR 17.63, 95% CI 1.97–158.21; PS deficiency: OR 8.00, 95% CI 1.61–39.86) [26]. However, the recurrence risk associated with heritable thrombophilia in unusual-site thrombosis appears higher than for limb VTE, and anticoagulation is often continued long term based on site rather than thrombophilia status alone. Beyond inherited thrombophilia, aPL testing is particularly important for these locations, as the presence of APS directly influences anticoagulant choice and treatment duration [3,5,26]. For unusual-site thrombosis, the diagnostic workup extends beyond classical inherited thrombophilia to include evaluation for myeloproliferative neoplasms and paroxysmal nocturnal haemoglobinuria. In splanchnic vein thrombosis and cerebral venous sinus thrombosis without clear provoking factors, Janus kinase 2 (JAK2) V617F mutation testing is recommended even in patients with normal complete blood count, as 2.6–5.6% harbour this mutation [5,26,27].

Table 1
Anticoagulation duration guidance by thrombophilia type following VTE.

Thrombophilia	Recurrence risk	Annual rate[a]	Duration guidance[b]
FVL or F2 G20210A heterozygous	Low	~ 3–4%	Standard duration; no prolongation for isolated provoked VTE
Isolated aCL/aβ2GPI at low/medium titres	Low	Variable	Standard duration; reassess if persistent positivity at 12 weeks
PC deficiency	Moderate	5–6%	Consider extended therapy if unprovoked or recurrent
PS deficiency	Moderate to high	6–8%	Consider extended therapy if unprovoked or recurrent
FVL homozygous, double heterozygous (FVL + F2), or F2 G20210A homozygous[c]	High	Limited data	Consider extended therapy if unprovoked or recurrent
Antithrombin deficiency	High	8–10%	Extended/indefinite therapy strongly favoured
APS meeting classification criteria	High/very high	No data	Indefinite anticoagulation with VKA (INR 2–3); DOACs contraindicated in triple-positive APS

aβ2GPI: anti-β2-glycoprotein I antibodies; aCL: anticardiolipin antibodies; APS: antiphospholipid syndrome; DOAC: direct oral anticoagulant; FVL: factor V Leiden; F2: factor 2 (prothrombin) gene; INR: international normalized ratio; PC: protein C; PS: protein S; VKA: vitamin K antagonist; VTE: venous thromboembolism.

[a] Annual recurrence rates after discontinuation of anticoagulation, derived from prospective cohort studies with systematic thrombophilia ascertainment [24,25].

[b] All recommendations should be individualized based on bleeding risk assessment.

[c] Classification as 'high risk' is based on first VTE risk in heterozygous FVL/F2 combined or homozygous carriers (RR ≈ 10); however, recurrence risk data for F2 G20210A homozygous carriers are limited and may not differ significantly from heterozygous carriers.

Table 2
Clinical scenarios and thrombophilia testing recommendations.

Clinical scenario/guidelines	SFMV 2019	ESVS 2021	BSH 2022	ASH 2023
First unprovoked VTE	Consider if age < 50 years + 1st degree family history	Recommended if age < 45 years	Recommended if age < 40 years	Conditional AGAINST (extended AC already indicated) otherwise age < 50 years (suggested)
Recurrent unprovoked VTE	Recommended	Recommended	Recommended	Conditional AGAINST
VTE provoked by hormonal factors (COC, MHT, pregnancy)	Recommended	Recommended	aPL testing recommended	Conditional FOR (if AC would be discontinued)
VTE provoked by major surgery (> 30 min GA)	NOT recommended	NOT recommended	NOT recommended	Conditional AGAINST
VTE provoked by immobilization (> 3 days)	NOT recommended	NOT recommended	NOT recommended	Conditional AGAINST
Unusual-site VTE (cerebral, splanchnic)	Recommended + JAK2	Recommended + JAK2/MPN screen	Recommended + JAK2	Conditional FOR (if AC would be discontinued)
Cancer-associated VTE	NOT recommended	NOT recommended	NOT recommended	NOT addressed
Recurrent pregnancy loss (≥ 3 early or ≥ 1 late)	Inherited: NOT recommended	Inherited: limited evidence; aPL: recommended	Inherited: NOT recommended; aPL: recommended	Inherited: NOT addressed; aPL: recommended
Routine family screening (asymptomatic relatives)	NOT recommended	NOT recommended	Selective: AT/PC/PS in women of childbearing age	NOT recommended
Before starting COC (no personal/family VTE history)	NOT recommended	NOT recommended	NOT recommended (discuss family history)	NOT recommended

AC: anticoagulation; aPL: antiphospholipid antibodies; ASH: American Society of Hematology; AT: antithrombin; BSH: British Society for Haematology; COC: combined oral contraceptives; ESVS: European Society for Vascular Surgery; GA: general anaesthesia; JAK2: Janus kinase 2; MHT: menopause hormone therapy; MPN: myeloproliferative neoplasm; PC: protein C; PS: protein S; SFMV: Société Française de Médecine Vasculaire (French Vascular Medicine Society); VTE: venous thromboembolism.

3.4. Obstetric complications

Women with recurrent pregnancy loss (≥ 3 consecutive early losses or ≥ 1 late foetal death) or other obstetric complications represent a specific population where aPL testing is clearly indicated, given both diagnostic and therapeutic implications [5,6,14]. The clinical rationale is that APS identification carries direct recurrence risk implications: untreated obstetric APS is associated with pregnancy loss rates exceeding 80% in subsequent pregnancies, which is substantially reduced by low-dose aspirin and/or prophylactic anticoagulation [14]. For inherited thrombophilia, testing in women with pregnancy morbidity remains more controversial. While associations between inherited thrombophilia and adverse pregnancy outcomes have been reported, evidence supporting thromboprophylaxis based on thrombophilia status alone (without prior VTE) is limited and guidelines do not recommend routine testing in this context unless additional indications are present [5].

4. Laboratory assessment

Following the clinical indications outlined above, laboratory evaluation must be interpreted in light of both biological validity and clinical relevance.

4.1. Inherited thrombophilia

4.1.1. First-line markers: natural anticoagulant deficiencies and genetic variants

The core thrombophilia panel targets abnormalities with established associations with VTE and reasonable prevalence to justify testing costs. Natural anticoagulant assessment (AT, PC and PS) forms the backbone of inherited thrombophilia screening, complemented by genetic testing for FVL and prothrombin G20210A mutations (Table A.1) [3–6].

AT deficiency, though exceedingly rare (approximately 0.02–0.04% in the general population, 0.5–1.0% in VTE cohorts), carries the highest thrombotic risk among inherited thrombophilias (relative risk of 10–30 for first VTE) [11,12,28]. Testing relies on functional assays; both quantitative (type I) and qualitative (type II) deficiencies exist, the latter showing normal antigen levels with reduced activity [12,28].

PC and PS deficiencies are somewhat more common (0.1–0.5% general population prevalence, 1–5% in VTE cohorts) and confer relative risks of 8–16 in heterozygous carriers [11,12]. PC homozygous or compound heterozygous states cause neonatal purpura fulminans [29]. PC assessment should include both antigenic and functional assays, while PS evaluation requires free antigen measurement alongside functional testing to detect all deficiency subtypes. For PC, type I (quantitative) deficiency predominates over type II (qualitative).

FVL and prothrombin G20210A mutations occupy a different clinical niche. Their high prevalence in European populations (3–8% and 1–3%, respectively) means they are frequently detected, yet their associated thrombotic risks are considerably more modest (OR 3–8 for heterozygous FVL, OR 2–4 for prothrombin G20210A) [7,10,11]. Homozygosity dramatically amplifies risk (approximately 50–80-fold for FVL homozygotes), as does compound heterozygosity for both mutations [4,30]. FVL demonstrates a preferential association with deep vein thrombosis over pulmonary embolism, the so-called 'FVL paradox', with reported ORs of 4.5 for deep vein thrombosis versus 1.7 for pulmonary embolism, whereas prothrombin G20210A does not exhibit a consistent differential effect between these two VTE manifestations [10,31]. Beyond these common European variants, sickle haemoglobin variants are associated with an increased thrombotic risk across genotypes: while symptomatic sickle cell disease–including homozygous sickle cell anaemia (HbSS) and compound heterozygous forms such as haemoglobin S/β-thalassemia–carries the highest thrombotic burden, sickle cell trait (HbAS) also confers a modest but real increase in VTE risk (OR ~ 1.45) [32–35].

4.1.2. Molecular genetics of natural anticoagulant deficiencies

Genetic testing to identify causative variants should be performed after phenotypic confirmation when it will impact clinical management. Testing of first-degree relatives may be reasonable when results would alter management, particularly in women of childbearing age with highly penetrant deficiencies of AT, PC or PS [5]. In AT deficiency specifically, diagnosis enables access to AT concentrate therapy and facilitates interpretation of heparin monitoring.

For AT, molecular analysis of *SERPINC1* (chromosome 1q25.1) detects causative mutations in 77–82% of functional deficiency cases [36]. Over 300 loss-of-function variants have been identified [18,36]. Type I (quantitative) deficiency typically confers severe thrombosis risk, while type II variants show heterogeneity depending on the affected domain: reactive site mutations may exceed type I severity, whereas heparin-binding site variants range from benign to highly thrombogenic [28,37].

For PC (*PROC*, chromosome 2q13-q14), over 360 mutations have been reported, without consistent genotype-phenotype correlation [18,38–40].

For PS (*PROS1*, chromosome 3q11.2), over 200 variants have been identified [41,42]. Loss-of-function *PROS1* variants are rare (~ 1 in 10,000) but carry high VTE risk (OR 14.01, 95% CI 6.98–27.14), with plasma PS levels approximately 48% of normal in carriers [43]. Notably, germline variants explain < 0.3% of plasma PS variance; acquired factors, including lower age, lower body mass index and oral contraceptive use predominate [6,44].

4.1.3. Markers of uncertain significance

A marker is generally considered clinically relevant when associated with an OR ≥ 2 for developing VTE; most additional inherited markers fall below this threshold, limiting their utility in routine clinical decision-making [45,46]. MTHFR polymorphisms (C677 T, A1298 C) should not be included in thrombophilia workup. Meta-analyses show no association with VTE in European populations, likely due to folate fortification of food [10,47–49]. In contrast, elevated plasma homocysteine levels–with prevalence increasing from 5–10% in the general population to 15–25% in patients with VTE–demonstrate stronger association with VTE (OR 2.95, 95% CI 2.08–4.17), though lowering homocysteine has not shown benefit in arterial thrombosis, and evidence for VTE is lacking [50,51]. Elevated factor VIII (> 150%) has demonstrated associations with VTE in epidemiological studies (OR 2–5), but incorporation into routine testing panels remains debated due to its role as an acute-phase reactant [4–6,45]. At present, none of these markers adds significantly to routine thrombophilia testing, and their identification may generate more confusion than clinical benefit (Table A.2).

4.2. Acquired thrombophilia: APS

4.2.1. Classification criteria

APS occupies a unique position among thrombophilic disorders, being both an acquired condition and a systemic autoimmune disease with implications extending beyond thrombosis to include pregnancy morbidity and diverse non-thrombotic manifestations [13,14].

The 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria have refined the diagnostic framework from the 2006 revised Sapporo criteria, introducing a weighted scoring system that better stratifies risk (99% specificity, 84% sensitivity for thrombotic APS) according to antibody profiles and clinical manifestations of APS [14]. Laboratory diagnosis is based on the detection of three categories of aPL (Table A.3). Lupus anticoagulant (LA), identified through functional coagulation assays using dilute Russell viper venom time (dRVVT) and activated partial thromboplastin time, paradoxically prolongs clotting times in vitro while conferring thrombotic risk in vivo. Anticardiolipin antibodies (aCL) and anti-β2-glycoprotein I antibodies (aβ2GPI), measured by enzyme-linked immunosorbent assay (ELISA), complete the diagnostic triad [14,52]. The 2023 criteria mandate confirmation of positivity ≥ 12 weeks apart, with ≥ 1 positive test occurring within 3 years of the clinical criterion.

4.2.2. Antibody profiles and risk stratification

Antibody profile-based risk stratification now guides APS management. Triple positivity–concurrent positivity for LA, aCL and aβ2GPI with concordant immunoglobulin G (IgG) isotype–identifies patients at highest thrombotic and obstetric risk [14,53]. This profile warrants the most intensive monitoring and therapeutic intervention. Double positivity for aCL and aβ2GPI IgG carries elevated but somewhat lower risk, while isolated LA positivity demonstrates intermediate risk with particular relevance in obstetric contexts. Isolated immunoglobulin M (IgM) antibody positivity, conversely, has limited predictive value for thrombosis, especially outside pregnancy [14,52].

The 2023 criteria introduced semiquantitative thresholds, defining moderate positivity as 40–79 units and high positivity as ≥ 80 units for aCL and aβ2GPI ELISA assays [14]. Higher titres receive greater diagnostic weight, reflecting the established dose–response relationship between antibody levels and clinical risk. Second-line testing with anti-phosphatidylserine/prothrombin antibodies (aPS/PT) may assist when LA results are uninterpretable or discordant, while anti-domain I β2GPI antibodies can help confirm high-risk profiles [52].

4.2.3. Non-criteria antiphospholipid antibodies

Beyond the classification criteria, several non-criteria aPL such as aPS/PT, aβ2GPI Domain I, anti-annexin A5 or immunoglobulin A (IgA) isotypes of aCL and aβ2GPI have demonstrated clinical relevance and may provide diagnostic value in specific situations [52,54–57]. aPS/PT, targeting prothrombin bound to phosphatidylserine, appear most clinically valuable and show strong correlation with LA positivity [54,57,58]. A systematic review has reported aPS/PT prevalence of approximately 65% in patients with APS, with both IgG and IgM isotypes showing comparable frequencies (50% and 45%, respectively). In triple-positive patients, aPS/PT positivity reaches 84%, and these antibodies demonstrate 95% prevalence among patients who meet full classification criteria [54]. Importantly, aPS/PT antibodies should be distinguished from anti-prothrombin antibodies: aPS/PT target prothrombin in complex with phosphatidylserine, whereas anti-prothrombin target prothrombin bound to solid phase directly. This distinction matters clinically, as aPS/PT demonstrate stronger correlation with thrombotic events [54,58]. The primary utility of aPS/PT testing lies in two scenarios: (1) when LA testing is unreliable due to anticoagulant interference, aPS/PT may serve as a useful surrogate marker and (2) in seronegative APS, where 6–17% of patients with clinical features of APS but negative standard testing are positive for aPS/PT [59].

4.3. Practical considerations for testing

4.3.1. Timing of thrombophilia testing

The optimal window for thrombophilia testing is 3–6 months after the acute thrombotic event, when acute-phase responses have subsided and anticoagulation decisions are being reconsidered [3–6,60]. Testing during hospitalization for acute VTE is generally inadvisable, as acute thrombosis itself transiently depletes natural anticoagulants and may generate transient aPL positivity. Genetic tests for FVL and prothrombin mutations constitute the exception, remaining reliable regardless of clinical timing or anticoagulation status.

4.3.2. Anticoagulant interference and management strategies

Anticoagulant interference represents a significant practical challenge, particularly in the era of widespread direct oral anticoagulant (DOAC) use [18,60,61]. Vitamin K antagonists (VKAs) reduce vitamin K-dependent factors including proteins C and S, potentially masking true deficiencies or creating false impressions of deficiency. For LA testing, VKA can produce both false negatives and false positives [52]. Testing should be deferred until ≥ 2 weeks after VKA discontinuation, or antigenic assays employed where functional results appear discordant (Table 3) [40].

DOACs can interfere with thrombophilia testing even at concentrations below the lower limit of quantification of specific anti-Xa and anti-IIa assays [52,61]. Factor Xa inhibitors overestimate AT activity in Xa-based assays and may falsely elevate PC and PS functional levels, potentially masking genuine deficiencies. Rivaroxaban shows the highest false-positive rates with dRVVT. Direct thrombin inhibitors affect thrombin-based assays similarly [18,60,61]. LA testing is particularly vulnerable, with DOACs capable of producing both false-positive and false-negative results depending on drug concentration and assay methodology [60]. Several strategies can mitigate DOAC interference. Treatment discontinuation for ≥ 4 days allows drug clearance, although this approach carries theoretical thrombotic risk and may not fully eliminate interference in highly sensitive assays [18,60]. Activated charcoal-based adsorbents offer ex vivo drug neutralization, enabling testing without treatment interruption. However, complete neutralization cannot be guaranteed, particularly for LA testing. Negative LA screen results are reliable in samples treated with activated charcoal provided adequate DOAC removal has been confirmed by residual drug level measurement; in such cases, no confirmatory tests should be performed. Conversely, when screen results remain positive after charcoal treatment, formal DOAC discontinuation followed by repeat testing is preferred [18,60,61]. Alternative assays may circumvent some interferences: for AT, choosing the appropriate assay (factor Xa [FXa]- or factor IIa [FIIa]-based) according to the DOAC used is recommended over charcoal neutralization; chromogenic PC activity and free PS antigen measurements are unaffected by DOACs and reliably detect quantitative deficiencies [40,60]. When uncertainty persists, confirmatory testing after formal anticoagulation discontinuation remains the gold standard.

5. Therapeutic implications

Beyond diagnosis, the clinical value of thrombophilia testing lies in its potential to refine management decisions. Anticoagulation duration and intensity must integrate thrombophilia type, clinical context, recurrence risk and bleeding risk [3–6,62].

5.1. Anticoagulation duration by thrombophilia type

For low-risk thrombophilias (heterozygous FVL or F2 G20210A mutations), detection does not independently justify prolonged anticoagulation after a first provoked VTE. These patients should receive standard-duration therapy dictated by clinical circumstances, with thrombophilia status informing counselling about modifiable risk factors and situational thromboprophylaxis [3–6].

High-risk thrombophilias warrant consideration of extended anticoagulation. AT deficiency, homozygous FVL and combined FVL/F2 heterozygous mutations carry the highest recurrence risk favouring indefinite anticoagulation following unprovoked VTE. PC and PS deficiency confer moderate-to-high recurrence risk and warrant consideration of extended therapy (Table 1). Even in these contexts, the decision should incorporate patient preferences, bleeding risk and quality-of-life considerations [3–6].

5.2. Anticoagulant choice

For inherited thrombophilia, DOACs are acceptable alternatives to VKA in most patients with VTE, consistent with general VTE management guidelines [3,5]. Available data, though limited to subgroup analyses, suggest comparable efficacy and safety, but nuances apply to severe thrombophilias. A 2024 International Society on Thrombosis and Haemostasis Scientific and Standardization Committee communication synthesizing cohort data from over 5000 patients found comparable efficacy between full-dose DOACs and VKA in severe thrombophilia, although all estimates were underpowered and none reached statistical significance [63]. However, caution is warranted in two specific settings: (1) PS deficiency with very low PS levels (< 20%), where cases of DOAC failure under direct FXa inhibitors have been reported and (2) homozygous AT Budapest 3 deficiency, where thrombotic events under apixaban have been documented. In both situations, VKA may be preferable. Reduced-dose DOACs cannot currently be recommended for secondary prevention in severe thrombophilia due to lack of evidence as these populations were excluded from extension studies [20,63–65].

APS represents the key exception. VKA therapy with an international normalized ratio (INR) target of 2–3 remains the standard of care for thrombotic APS [5,14]. For triple-positive APS or patients experiencing recurrence despite standard anticoagulation, intensification to INR

Table 3
Anticoagulant interference with thrombophilia testing and alternative strategies.

Test	Assay type	VKA	Heparin	DOAC	Alternatives/discontinuation	Washout VKA	Washout DOAC
Antithrombin	Cofactor activity	↔	↑ (UFH > LMWH)	↑	• Antigenic assay if available • FIIa-based assay if on anti-Xa DOAC; FXa-based assay if on dabigatran • Charcoal adsorbents[a]	NA	≥ 4 days
PC	Functional activity	↓	↔	↑	• Chromogenic PC (unaffected) • Charcoal adsorbents[a]	≥ 2 weeks	≥ 4 days
PS	Free Ag or activity	↓	↔	↑	• Free PS antigen (unaffected) • Charcoal adsorbents[a]	≥ 2 weeks	≥ 4 days
Lupus anticoagulant	Functional (dRVVT, APTT)	↓↑	↔ (if anti-Xa therapeutic[b])	↑ (false +)	• TSVT/ET if available • Charcoal adsorbents[a] (screen only) • aPS/PT if LA unreliable	≥ 2 weeks	≥ 4 days
aCL, aβ2GPI	ELISA	↔	↔	↔	• Unaffected	None	None
FVL, F2 G20210A	Genetic testing	↔	↔	↔	• Unaffected	None	None

↑ = overestimation/false positive; ↓ = underestimation/false negative; ↔ = no significant interference. aβ2GPI: anti-β2-glycoprotein I antibodies; aCL: anticardiolipin antibodies; Ag: antigen; APPT: activated partial thromboplastin time; aPS/PT: anti-phosphatidylserine/prothrombin antibodies; DOAC: direct oral anticoagulant; dRVVT: dilute Russell viper venom time; ELISA: enzyme-linked immunosorbent assay; F2: factor 2 (prothrombin); FVL: factor V Leiden; FXa: factor Xa; LA: lupus anticoagulant; LMWH: low-molecular-weight heparin; NA: not applicable; PC: protein C; PS: protein S; TSVT/ET: Taipan Snake Venom Time/Ecarin Time; UFH: unfractionated heparin; VKA: vitamin K antagonist.

[a] Charcoal adsorbents (DOAC-Stop®, DOAC-Remove®, DOAC-Filter®).

[b] dRVVT interpretable if anti-Xa within therapeutic range (reagents neutralize heparin up to 1 IU/mL).

3–4 or addition of low-dose aspirin may be considered, although evidence supporting these approaches remains limited [5,14]. The TRAPS and ASTRO-APS trials showed increased arterial thrombosis with rivaroxaban compared with warfarin in triple-positive APS, contraindicating DOACs in this population [5,66]. For lower-risk APS profiles (single or double positive, LA-negative, first venous event only), DOACs may be considered (at full therapeutic dose only) in patients with documented VKA intolerance or persistently erratic INR, and following careful shared decision-making [5,14,66].

5.3. Management of asymptomatic carriers

Asymptomatic thrombophilia carriers may be identified through three distinct clinical pathways:

- targeted family screening following identification of a severe inherited thrombophilia, particularly AT, PC or PS deficiency, in a symptomatic index case;
- pre-contraceptive or pre-pregnancy evaluation in women with a first-degree relative carrying a high-risk thrombophilia;
- or incidental discovery during an unrelated workup. The clinical implications and management intensity differ substantially across these contexts, and the discovery pathway should inform subsequent counselling.

Isolated thrombophilia detection without clinical thrombotic events does not indicate therapeutic anticoagulation. However, identification of a heritable thrombophilic trait in an asymptomatic individual carries implications for risk awareness, situational prophylaxis, lifestyle counselling and reproductive planning.

Routine thrombophilia screening of first-degree relatives is not recommended [5,6]. However, testing may be reasonable for women of childbearing age with a first-degree relative harbouring AT, PC or PS deficiency, as results may influence contraceptive choices and pregnancy management (see Section 6.1) [5,18]. Routine FVL screening is not required prior to initiating oestrogen-containing contraception in women with affected relatives but no personal VTE history; however, the influence of family history and thrombophilia-related risks should be discussed to inform therapy choices [5,6].

Asymptomatic carriers warrant risk-stratified thromboprophylaxis during high-risk situations, with intensified regimens for severe thrombophilias [5,6]. Major transient risks warranting pharmacological prophylaxis include hospitalization with immobilization ≥ 3 days, major surgery and significant trauma [3,4]. Asymptomatic triple-positive aPL carriers face approximately 5% annual thrombosis incidence, justifying consideration of low-dose aspirin for primary prevention [5]. Carriers should be counselled regarding modifiable risk factors: weight management (obesity compounds genetic risk), smoking cessation, avoiding prolonged immobility and precautions during long-distance travel (≥ 8 hours) including hydration, ambulation and compression stockings [3,14]. Education on VTE symptoms enables prompt medical evaluation.

6. Special populations

Specific patient populations require tailored interpretation of thrombophilia results.

6.1. Thrombophilia in women: hormonal context

Hormonal influences significantly affect both thrombophilia test interpretation and clinical management decisions. Understanding these interactions is essential for accurate diagnosis and optimal care of women with, or at risk for, thrombophilia.

6.1.1. Contraception in women with thrombophilia

The clinical approach to contraception in women with thrombophilia must be informed by the context in which the thrombophilia was identified: (1) discovery following a prior VTE event, in which both thrombophilia status and personal VTE history contribute to the overall risk assessment or (2) discovery through family screening in the absence of prior VTE, in which risk stratification is based on thrombophilia type and severity alone.

Women with established thrombophilia face contraindications to COC, which synergistically amplifies thrombotic risk [5,6,67]. This applies regardless of personal VTE history, although women with both thrombophilia and prior VTE face the highest absolute risks. Acceptable alternatives include progestin-only methods (oral, implant or hormonal intrauterine device), copper intrauterine device and barrier methods. Of note, COC reduces PS levels; when PS testing is indicated, it should follow ≥ 4 weeks of COC discontinuation [3,5,6].

Contraceptive counselling should be individualized, incorporating thrombophilia severity, family history and patient preferences (Table A.4).

6.1.2. Pregnancy

Pregnancy is an acquired hypercoagulable state with VTE incidence around 1 in 1000, a 5–10-fold increase relative to age-matched non-pregnant women, rising further in the first 6 weeks postpartum to a 20–80-fold increase [5]. Pregnancy induces physiological changes in haemostatic parameters that can confound thrombophilia testing [3,5,6,67]. AT levels decrease during normal pregnancy, while PS undergoes substantial reduction that may mimic deficiency states. Testing performed during pregnancy or the early postpartum period risks false-positive deficiency diagnoses. Lupus anticoagulant testing may yield false-positive results due to pregnancy-associated inflammation. Accordingly, testing should ideally be deferred until ≥ 6 weeks postpartum, with genetic tests for FVL and F2 G20210A being the exception, as they are unaffected by pregnancy or anticoagulation [5]. Women with AT, PC or PS deficiency or homozygous FVL face a sufficiently elevated absolute risk to warrant thromboprophylaxis in pregnancy and puerperium (Table A.4). In contrast, women with heterozygous FVL, heterozygous prothrombin G20210A or compound heterozygosity for both mutations should generally not receive thromboprophylaxis based on thrombophilia and family history alone (Table 4) [5,6,67,68].

AT deficiency confers the greatest absolute risk even in the absence of prior VTE and warrants prophylactic low-molecular-weight heparin (LMWH) throughout pregnancy and for 6 weeks postpartum [68]. The peripartum period, in particular, carries the highest absolute thrombotic risk, requiring systematic multidisciplinary planning. AT concentrate substitution at the time of delivery is recommended in type I deficiency and type II reactive site variants. A loading dose of 50 IU/kg is administered when anticoagulant therapy is withheld, with AT level monitoring, in conjunction with LMWH resumed postpartum [69].

Women with prior VTE and any thrombophilia who are not on long-term anticoagulation should receive prophylactic LMWH throughout pregnancy and the puerperium [5,6,68].

APS requires specific obstetric management. Women with thrombotic APS should receive therapeutic LMWH combined with low-dose aspirin throughout pregnancy [14,68]. Obstetric APS (pregnancy morbidity without thrombosis) warrants prophylactic LMWH plus aspirin. Women with high-risk aPL profiles but no prior clinical events may benefit from aspirin with or without prophylactic LMWH, although evidence guiding management in this subgroup remains limited. The Highlow trial demonstrated no superiority of intermediate-dose over standard prophylactic-dose LMWH in pregnant women with prior VTE, simplifying prophylactic regimen selection [70].

6.1.3. Menopause hormone therapy

Evidence demonstrates that VTE risk with menopause hormone therapy (MHT) depends strongly on oestrogen administration route and progestogen type. Transdermal oestrogen shows no significant VTE risk increase across thrombophilia subtypes, while oral preparations confer a 2–17-fold increased risk [71]. This differential reflects first-pass hepatic effects of oral oestrogens on coagulation factor synthesis. Micronized progesterone appears neutral or protective, whereas synthetic progestogens, particularly norpregnane derivatives, may amplify oestrogen-associated prothrombotic effects [71–73]. In women with prior VTE, transdermal MHT was not associated with increased recurrence risk; in carriers of FVL or F2 G20210A mutations, transdermal preparations conferred minimal to no increased VTE risk [72]. The British, European and North American Menopause Societies now recognize transdermal oestrogen as the preferred route for women with VTE risk factors or inherited thrombophilia [71–73]. Thrombophilia screening before MHT initiation is not routinely recommended but may be considered in women with a strong family history of VTE at a young age or multiple affected relatives.

6.2. Cancer-associated thrombosis

Cancer patients face a 9-fold higher risk of VTE than the general population, raising the question of whether inherited thrombophilia further amplifies this baseline risk [74,75]. A meta-analysis of 37 studies provided compelling evidence that inherited thrombophilia remains clinically relevant even in the context of malignancy-associated hypercoagulability [74]. Among heterozygous carriers, FVL conferred a 2.28–fold (95% CI 1.51–3.48) and heterozygous prothrombin G20210A a 2.14-fold (95% CI 1.14–4.03) increased risk of a first VTE event in patients with cancer, magnitudes comparable to non-cancer populations [74]. These estimates were derived predominantly from studies of heterozygous carriers; homozygous data in the cancer context are too limited for reliable quantification. Available data address incident VTE risk only; recurrence risk in patients with cancer and inherited thrombophilia remains poorly characterized, and no prospective trial has demonstrated that genotype-guided management reduces recurrence in this population.

These findings suggest genetic variables could enhance VTE risk prediction beyond clinical scores such as the Khorana score [76]. Notably, a prospective cohort of ambulatory patients with cancer and Khorana score ≥ 2 demonstrated even stronger associations, with an adjusted OR of 5.24 for FVL [74]. However, routine thrombophilia screening in unselected patients with cancer is not currently recommended, given that cancer itself represents a powerful acquired hypercoagulable state that supersedes most inherited risk factors and the absence of prospective trials demonstrating that genotype-guided thromboprophylaxis improves outcomes. In patients with active cancer and VTE, current guidelines recommend therapeutic anticoagulation with DOAC(s) (full therapeutic dose or reduced-dose) or LMWH for the duration of cancer treatment, irrespective of inherited thrombophilia status [77]. This recommendation applies regardless of whether thrombophilia testing was performed, further limiting the practical utility of routine thrombophilia screening in this setting.

6.3. Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) develops in approximately 2.7% of patients following acute pulmonary embolism [78,79]. Up to 25% of patients with CTEPH lack a documented history of symptomatic acute pulmonary embolism, suggesting that

Table 4
Thromboprophylaxis during pregnancy and postpartum according to thrombophilia and clinical history based on guideline consensus.

Clinical situation	Antenatal management	Postpartum (6 weeks)
Antithrombin deficiency, no prior VTE	Prophylactic LMWH[a]	Prophylactic LMWH
Other severe thrombophilia, no prior VTE	Consider if additional risk factors	Prophylactic LMWH
Low-risk thrombophilia, no prior VTE	Not routinely indicated	Consider if additional risk factors
Any thrombophilia + prior VTE (not on long-term AC)	Prophylactic LMWH	Prophylactic LMWH
Thrombotic APS	Therapeutic LMWH + aspirin	Therapeutic LMWH or transition to VKA
Obstetric APS	Prophylactic LMWH + aspirin	Prophylactic LMWH

AC: anticoagulation; APS: antiphospholipid syndrome; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist; VTE: venous thromboembolism.
[a] Decision to anticoagulate in absence of family history requires individualized assessment in expert centre.

silent or subclinical embolic events may initiate the disease process in a substantial minority [80].

The relationship between inherited thrombophilia and CTEPH shows ethnic variability. In an Asian cohort (n = 367), inherited thrombophilia was identified in 9.8%, predominantly PS deficiency (5.2%), PC deficiency (3.5%) and AT deficiency (1.1%); FVL and prothrombin mutations were absent, consistent with their rarity in Asian populations [81]. Patients with thrombophilia more frequently presented with proximal pulmonary artery lesions and documented VTE history [81]. European data suggest prothrombin G20210A may be overrepresented (OR 4.5), while FVL shows no association [82].

aPL appear particularly relevant, with a prevalence of approximately 12% among patients with CTEPH, associated with younger age and proximal arterial involvement [83]. These observations parallel findings in general VTE populations and suggest that APS-associated CTEPH may represent a distinct clinical entity warranting specific therapeutic considerations.

From a practical standpoint, thrombophilia testing merits consideration in patients with CTEPH without documented prior pulmonary embolism, young patients and those with features suggestive of APS. Identification of APS favours VKA over DOACs and may influence pulmonary thromboendarterectomy eligibility [84].

7. Synthesis and future perspectives

Thrombophilia testing in unselected populations rarely modifies management and has not been shown to improve clinical outcomes when applied indiscriminately. Benefit accrues when results meaningfully inform therapeutic decisions regarding anticoagulation duration, anticoagulant choice, family counselling or management during future high-risk situations.

Testing should target patients in whom results may influence management: young patients with unprovoked or recurrent VTE, unusual-site thrombosis, VTE provoked by hormonal factors and women requiring contraceptive or pregnancy counselling. Appropriate timing and awareness of anticoagulant interference are essential, an increasingly important consideration in the DOAC era, now addressed by recent expert guidance on charcoal-based neutralization strategies. Results should be integrated within comprehensive clinical assessment rather than dictating management in isolation. The identification of heterozygous FVL in a patient with surgery-provoked VTE carries different implications than AT deficiency in a young patient with unprovoked recurrent thrombosis.

Key areas requiring further investigation include validation of DOAC neutralization protocols for reliable LA testing, dedicated trials comparing standard versus reduced-dose DOACs in severe thrombophilia populations and integration of genetic risk scores into clinical algorithms. Until such evidence emerges, selective testing guided by clinical context–identifying patients most likely to benefit from results–remains the cornerstone of rational thrombophilia evaluation (Central illustration).

Central Illustration. Age thresholds: ASH/SFMV < 50 years, ESVS < 45 years, BSH < 40 years.

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Data availability

All data are available in the tables and appendix materials.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Claude AI and ChatGPT in order to improve language and readability of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2026.04.004.

Disclosure of interest

The authors declare that they have no competing interest.

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