Prothrombotic disorders combine with environmental risk factors to increase the risk of venous thromboembolism (VTE). For example, heterozygous factor V Leiden, present in about 5% of whites, increases the incidence rate of VTE in young women from 1 in 10 000 annually to about 4–7 in 10 000. If a young woman with factor V Leiden is obese, the incidence becomes 8–14 in 10 000 (1). If she is taking oral contraceptives, incidence is 34 in 10 000 (2). Among middle-aged women, VTE incidence is higher since VTE risk rises with age. Women in their 50s with factor V Leiden have about a 4 in 1000 annual risk of VTE, which rises to about 1% annually with use of postmenopausal estrogen plus progestin (3) and about 3% if there is a family history of thrombosis (4).

There are unanswered questions on how to utilize knowledge of prothrombotic conditions to manage both men and women. Most experts agree that indiscriminate testing has limited clinical value. For patients with VTE, there are no large-scale studies of the clinical impact of testing (5), yet the epidemiologic literature allows us to devise a rational approach. Key topics to consider include the definition of thrombophilia testing, the rationale for testing, and how to test in a clinically useful way.

Thrombophilia testing refers to laboratory testing performed to identify propensity to thrombosis. In our practice, we use a panel of assays to detect conditions associated with first or recurrent VTE: genetic tests for factor V Leiden and prothrombin 20210A; activity assays for protein C, protein S, antithrombin, factor VIII coagulant activity, and D-dimer; and assessment for antiphospholipid syndrome using the dilute viper venom time, partial thromboplastin time, and cardiolipin antibody serology (6).

Among VTE patients, we developed a 4-component strategy for thrombophilia testing to assist with medical decision-making, the 4 P’s:

- Patient selection;
- Pretest counseling;
- Proper lab test interpretation; and
- Provision of education and advice.

### Patient Selection

VTE events are classified as unprovoked (spontaneous) or provoked (occurring in the presence of major triggers; surgery, trauma, immobilization, cancer, or central venous catheters). Patients with unprovoked VTE are anticoagulated for 3–6 months, then risk stratification and decision-making is done regarding use of long-term anticoagulation. Non–cancer-provoked VTE requires treatment with only 3 months of anticoagulation, and cancer patients are treated as long as the cancer is active; thus patients with provoked VTE will not benefit from thrombophilia testing.

Most available guidelines on the use of thrombophilia testing to predict recurrent VTE agree that testing is useful in patients with unprovoked VTE (7). Some suggest testing only in those with a family history of VTE. However, information on family history is often unreliable, and a positive family history of VTE does not predict discovery of thrombophilia (8). In our practice, we recommend thrombophilia testing in any patient with unprovoked VTE who desires testing.

### Pretest Counseling

Among patients with first unprovoked VTE, once anticoagulation is stable, we discuss the role of thrombophilia testing in clinical decision-making to establish the patient’s desire for testing. We review the implications of a genetic diagnosis to the patient and family. If a patient desires long-term anticoagulation regardless of his or her level of risk, testing is not performed, although this is uncommon.

### Proper Lab Test Interpretation

Pre-analytic, analytic, and clinical factors influence the interpretation of results of thrombophilia testing (9, 10). Full discussion is beyond the scope of this paper, but a few factors are reviewed:
• The panel of tests is drawn 2 or more weeks after stopping anticoagulation, while the patient is in stable health. Anticoagulant treatments and acute illness alter many of the test results.
• For D dimer testing, different thresholds must be used for result interpretation if D dimer is measured during or after stopping warfarin treatment (11, 12).
• Mass assays do not rule out anticoagulant factor deficiencies; these are used to classify deficiency detected by activity assays.
• Liver and kidney disease can cause acquired factor deficiencies.
• Diagnosis of antiphospholipid syndrome requires test results to be outside the reference interval on repeated determinations at least 12 weeks apart.

Provision of Education and Advice

Among patients with unprovoked VTE, thrombophilia test results are used with other patient factors to identify a low-risk group who might not require ongoing anticoagulation. We consider sex (men have twice the recurrence risk as women), obesity (it doubles the risk of recurrence), bleeding risk (it is evaluated by use of medical history and stability of initial anticoagulation), and patient preferences for the outcomes of recurrent thrombosis, inconvenience of treatment, and bleeding complications. Although prediction tools for absolute risk of recurrent VTE are available (11, 13, 14), none is clinically validated. Furthermore, patients with high-risk thrombophilias were excluded from those studies, so it is difficult to integrate this information into decision-making.

After considering patient factors, we consider laboratory results. When D dimer is increased or there is an anticoagulant factor deficiency, double disorder, or antiphospholipid syndrome, we usually recommend long-term anticoagulation. This is based on the approximate 2-fold or higher increased risk of recurrent VTE with each of these conditions.

Conveying results of thrombophilia testing to patients is complex. Discussion should include information on the nature of the defect and its role as a risk factor. Reassurance is provided that these disorders usually do not shorten lifespan. If there is a genetic disorder, counseling is offered, as many patients want to explain their diagnosis to their families and discuss the role of testing for their relatives. Provision of written educational information is helpful (15). The complexity of the information provided often requires a subsequent clinic visit to reinforce the education. Some have argued that testing causes psychological harm, but this not been demonstrated (16, 17).

Special Circumstances for Women

Women often present to our clinic after VTE related to exogenous hormone treatments. This type of VTE does not fit well into the classification of provoked versus unprovoked VTE, as it is mildly provoked.

In women with contraceptive-related thrombosis, alternative contraception that does not increase thrombosis risk must be discussed. Although there are no trials available for definitive guidance, acceptable treatment options include the levonorgestrel or copper intrauterine device or progestin-only oral medications (18).

After 3 months of treatment for contraceptive-related thrombosis, the short-term risk of recurrent VTE is low, assuming no re-exposure to hormones (18), therefore we do not recommend long-term anticoagulation. However, the lifetime risk of recurrence after contraceptive-related VTE is unclear, so we do offer thrombophilia testing to allow us to counsel the patient on her disorder and emphasize the potential for future thrombosis in her medical record.

Among women with pregnancy-related VTE and VTE related to postmenopausal hormone use, we apply evaluation pathways similar to those for contraceptive-related VTE.

Asymptomatic women who are considering oral contraceptive use but are related to VTE patients with thrombophilic disorders may desire testing to determine their individual VTE risk. In their clinical evaluation, it is important to know whether the proband was tested for multiple thrombophilic disorders, as presence of more than 1 defect is associated with higher VTE risk. Figure 1 illustrates the expected incidence of VTE in women with different thrombophilias, with and without use of oral contraceptives (19). Each woman needs to consider these absolute risks against the need to prevent pregnancy (a condition that also increases VTE risk). Body weight should also be taken into account; risk estimates in Fig. 1 can be doubled for obese women. For example, the estimated 10-year VTE incidence in an asymptomatic obese woman with factor V Leiden using oral contraceptives is about 10%. Discussing this information with patients offers an opportunity for lifestyle counseling on weight loss.

For women choosing combined hormonal contraceptives, we recommend they avoid high-risk contraceptives such as those containing third-generation progestins with estrogen (18); maintain normal weight; understand signs and symptoms of VTE to promote early diagnosis; receive VTE prophylaxis (and perhaps interrupt the contraceptive) in high-risk settings; and have periodic follow-up in some cases.

Postmenopausal hormone therapy also increases the risk of VTE among women with thrombophilia and...
no prior VTE. Therefore we often recommend transdermal hormones when indicated, since these do not appear to increase VTE risk (20).

In conclusion, as our understanding of VTE risk factors has changed, so has our approach to patient care in the last few decades. Further outcomes-based research on the best application of this knowledge is needed.

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