Hypercoagulable States and Thrombophilias: Risks Relating to Recurrent Venous Thromboembolism

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Abstract

Keywords

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Inherited and acquired thrombophilias and hypercoagulable states, such as active cancer, estrogen-induced, autoimmune disorders, major surgery, hospitalization, and trauma, are well-known risk factors for venous thromboembolism (VTE). The effect of these on recurrent VTE is different for each specific risk factor. The major risk factors affecting VTE recurrence include the presence of active cancer and an unprovoked first VTE. In addition, the use of combined female hormones in a woman with a previous history of estrogen-related VTE is a major risk factor for VTE recurrence. The extent of influence of inherited thrombophilia on the risk of recurrence is controversial. Conversely, the presence of antiphospholipid antibodies, specifically triple positive carriers, appears to increase the risk of VTE recurrence. Understanding the rates of recurrent VTE in a patient and the individual risk of bleeding is important in determining the duration of anticoagulation therapy.

Objectives: Upon completion of this article, the reader will be able to determine the risks of recurrent venous thromboembolism (VTE) among patients with thrombophilias (both inherited or acquired) and hypercoagulable states and to guide management of anticoagulation therapy for these patients.

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Thrombophilias are inherited or acquired blood conditions that increase the propensity for vascular thrombosis. The most common inherited thrombophilias are factor V

Leiden (FVL) and the prothrombin gene FII G20210A (PGM) polymorphisms, both of which are gain-of-function polymorphisms. FVL diminishes the proteolytic inactivation of factor Va, leading to increase generation of thrombin, while PGM is associated with an increased level of plasma prothrombin, promoting the generation of thrombin and impairing inactivation of factor Va by activated protein C. Deficiencies in anticoagulant proteins including antithrombin (AT), protein C, and protein S are less common types of inherited thrombophilias. Carriers of AT, protein C or S deficiencies, tend to have venous thromboembolism (VTE) at a younger age, have several family members affected by VTE, and have thrombosis in unusual sites.¹ Acquired thrombophilias include the antiphospholipid syndrome (APS), the Philadelphia-negative myeloproliferative neoplasms (MPNs), heparin-induced thrombocytopenia (HIT), and paroxysmal nocturnal hemoglobinuria (PNH). The main clinical manifestation of inherited thrombophilias is VTE, whereas acquired thrombophilias can manifest as either venous, arterial, or microvascular thrombosis. Other hypercoagulable states such as those that occur during pregnancy, in patients with active cancer and patients with autoimmune

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disorders, are also associated with an increased propensity toward initial and recurrent VTE. All patients with a history of VTE are prone to recurrence; however, recurrence is more common in males, in the elderly population, in patients who are immobilized, in patients with cancer, and in patients with an unprovoked event.

A frequent dilemma in managing patients with either a thrombophilia (inherited or acquired) or a hypercoagulable state is to discern which patients are at a heightened risk for recurrent VTE. In this article, we will review the risks of recurrent VTE, as these risks relate to the various types of thrombophilias and hypercoagulable states.

Inherited Thrombophilias

Factor V Leiden and PGMs have a relatively high prevalence among the Caucasian population of ~6 and 3%, respectively, in the United States, while only in 1 and 0.2%, respectively, in the non-white population.¹ Homozygous mutations are much less frequent at ~0.02 and 0.014%, respectively. Double heterozygotes are also relatively rare at around 0.1%. All of these individuals are at a significantly increased risk of VTE compared with the noncarriers. For homozygotes, this risk is ~18-fold, and for double heterozygotes it is ~20-fold.¹ The risk of recurrent VTE is an important issue among this population, as it helps in determining who should be screened and the duration of anticoagulation therapy.

In a case-control design within a cohort study of families with thrombophilias, the odds ratios (ORs) of recurrent VTE, adjusted for age and sex, in individuals who were heterozygous carriers of either FVL or PGM, or those who were homozygous for FVL and/or PGM, or double heterozygous carriers of both polymorphisms were 1.2 (95% CI, 0.9–1.6), 0.7 (95% CI, 0.4–1.2), 1.2 (95% CI, 0.5–2.6), and 1.0 (95% CI, 0.6–1.9), respectively, compared with noncarriers of both FVL and PGM.² The authors concluded that persons who are homozygous for FVL and/or PGM or double heterozygous carriers of FVL and PGM did not have a high risk of recurrent VTE.

This was in contrast with a prior systematic review of prospective studies assessing the risk of recurrent VTE in heterozygote carriers of FVL and PGM. This study showed a relative risk (RR) of VTE recurrence conferred by the heterozygous carriage of FVL and PGM was 1.39 (95% CI: 1.15–1.67) and 1.20 (95% CI: 0.89–1.61), respectively.³ Another prospective study showed that among 474 patients, 90 had a recurrent VTE, which translated into a risk of 25.9 per 1,000 patient-years. According to subgroup analysis, patients with FVL or PGM polymorphisms did not have an increased risk of recurrence, whereas patients with deficiencies in natural anticoagulants did have an increased risk of recurrence compared with controls.⁴

Patients with protein C, protein S, or AT deficiencies are also at increased risk of VTE. The prevalence of AT, protein C, or protein S deficiencies is found in ~0.2 to 0.5 in 1,000 persons, but in ~5% of patients who develop a venous thrombosis (—Table 1). Data about recurrence risk of VTE in this population are rather limited, but there was one study in 2006 that showed that there was a 1.5-fold increase for

Table 1 Thrombophilia prevalence in the general population and in patients with VTE¹

Thrombophilia	General prevalence (%)	First VTE (%)	Recurrent VTE (%)
FVL	3–7 (whites) 1% (non-whites)	12–20	40–50
PGM	1–3 (whites) 0.2% (non-whites)	3–8	15–20
AT	0.02–0.04	1–2	2–5
PC	0.2–0.05	2–5	5–10
PS	0.01–1.0	1–3	5–10
APS	3–5	9	12

Abbreviations: APS, antiphospholipid syndrome; AT, antithrombin; FVL, factor V Leiden; PC, protein C; PGM, prothrombin gene FII G20210A; PS, protein S; VTE, venous thromboembolism.

patients with either protein C, protein S, or AT. When this was divided by each individual deficiency, it was the AT deficiency which carried the highest risk of recurrence, with a hazard ratio of 1.9 (95% CI: 1.0–3.9), while the carriers of protein C or S deficiency had a marginal increase in risk (hazard ratio: 1.4, 95% CI: 0.9–2.2).⁵ Furthermore, a meta-analysis of 21 observational studies also showed that there was a 56% risk of recurrent VTE in patients with AT and a 46.4% risk of recurrent VTE in patients with protein C; however for protein S, the data were very heterogeneous and they were unable to identify if there was a clear increased risk of recurrent VTE in this population.⁶ Overall, these data support the potential use of long-term anticoagulation in patients with an AT deficiency after a first thrombotic event but remains uncertain for patients with protein C or S deficiency or heterozygotes, homozygotes, or double heterozygotes carriers of FVL or PGM.² The American College of Chest Physicians (ACCP) recommends that duration of anticoagulation should be determined by the nature of the index VTE event. Namely, patients with unprovoked VTE with a low bleeding risk should continue anticoagulation taking into account patient's preferences.⁷ Therefore, duration of anticoagulation should be individualized.

Acquired Thrombophilias

The most common acquired thrombophilia is the antiphospholipid syndrome (APS), an autoimmune disorder characterized by vascular thrombosis and/or adverse outcomes of pregnancy along with positive antiphospholipid antibodies (aPL) at least in two occasions 12 weeks apart.⁸ The mainstay of treatment for patients with APS is anticoagulation with warfarin to target an INR between 2 and 3. However, despite anticoagulation, the rate of recurrent VTE among patients with aPL was 7.5% shown in an observational practice-based cohort study. In this cohort study, many patients had more than one recurrence, and the second recurrence was more likely to have occurred during oral anticoagulation therapy.⁹ In a cohort of 70

patients with primary APS, there were 24 patients with subsequent persistently negative aPL. After 60 months of follow-up since aPL negativity, 45.8% of patients had thrombosis recurrence. Therefore, this study suggests that in patients with primary APS and persistent negative aPL, discontinuation of anticoagulant therapy may not be safe.¹⁰ The ACCP does not recommend the use of direct oral anticoagulants (DOACs) in patients with APS currently. However, DOACs are frequently administered in clinical practice in patients with APS. The RAPS trial, comparing vitamin K antagonist (VKA) to DOACs in patients with aPL and first thrombotic venous event, demonstrated that APS patients treated with rivaroxaban had a significant twofold increase thrombin potential, suggesting a higher thrombotic risk, in comparison with warfarin users. Nonetheless, the risk of recurrent clinical thrombosis was the same, suggesting that rivaroxaban may be an alternative for certain subset of patients with APS.¹¹ A systematic review identified 122 published APS patients treated with DOACs of whom 19 experienced a recurrent thrombosis while on DOACs. Triple positivity was associated with a 3.5-fold increased risk for recurrent thrombosis. Randomized control trials with clinical primary endpoints assessing clinical efficacy and safety are underway to establish whether DOACs could be a safe alternative to warfarin.¹² A prospective case series of 56 consecutive patients with APS, including 33 (60%) associated with systemic lupus erythematosus (SLE) and 16 (28.6%) with triple APS, started DOACs at least 3 months after the index VTE due to their preferences or unstable anticoagulation with VKA. All patients had a D-dimer below 500 ng/mL. Of the total 56 patients, 49 (87.5%) patients were treated with rivaroxaban, 4 (7.3%) with dabigatran, and 3 (5.4%) with apixaban. During a mean follow-up of 22 months, six patients (10.7%) experienced recurrent thrombosis, four of who were triple positive and two patients (3.6%) experienced severe bleeding. The authors conclude that DOACs are safe in patients with APS.¹³

Based on the available evidence, the use of DOACs in patients with APS should be considered in a case-by-case scenario with evidence-based information provided to the patient.

Besides the APS, other autoimmune disorder associated with a high risk of venous thrombosis is Behcet's disease. Patients with Behcet's disease may experience recurrent thrombosis in spite of adequate anticoagulation; this is due to inflammation of the blood vessel wall. Therefore, these patients usually require systemic therapy with immunomodulators such as infliximab or colchicine to reduce this risk.¹⁴

Myeloproliferative neoplasms are also considered an acquired thrombophilia. Patients with JAK2 V617F mutations are at particular risk of splanchnic vein thrombosis, most commonly hepatic vein thrombosis (Budd-Chiari syndrome) and portal vein thrombosis. JAK2 mutations are present in 95 to 98% of patients with polycythemia vera (PV) and 55% of patients with essential thrombocythemia (ET).¹⁵ The cumulative rate of thrombosis ranges from 2.5 to 5% per patient-year for PV and 1.9 to 3.0% per patient-year for ET. Remarkably, JAK2V617F-positive ET patients seem to have significantly more venous thrombosis than JAK2V617F-negative ET patients, indicating that JAK2V617F-positive ET patients have a clinical phenotype resembling PV.¹⁶ In one multicenter

retrospective analysis of 494 patients with either PV or ET, the rates of recurrent thrombosis was 17.7% at 2 years after first thrombosis, 30.8% after 5 years, and 49.9% at 10 years. According to this study, the primary thrombotic event was either arterial or venous with an initial arterial thrombosis being associated with significantly greater risk of recurrent arterial or VTE, compared with when the index event was a venous thrombosis. Moreover, age greater than 60 was a major risk factor for recurrent VTE, while treatment with anticoagulation reduced the risk of recurrence by 68%.¹⁷ Furthermore, the combination of cytoreduction with anticoagulation was more effective in reducing the risk of recurrence compared with each alone. Therefore, in patients with myeloproliferative disorders who develop thrombosis, prompt treatment with not only an anticoagulant but also cytoreduction is necessary.

A recent study analyzed the efficacy and safety of DOACs in patients with MPNs. The authors collected biological and clinical data from diagnosis to last follow-up for every patient included in the study. There were 760 MPN patients in the registry, and 25 (3.3%) were treated with a DOAC because atrial fibrillation and thrombotic events for 13 and 12 patients, respectively. The median follow-up duration was 2.1 years. There was one thrombotic event (4%) and three major hemorrhagic events (12%). A case-control study did not detect a significant difference in thrombotic or hemorrhagic events in patients treated with low-dose aspirin and DOACs. The authors suggest that DOACs may be highly efficient and safe for use in MPN patients.¹⁸

Thrombophilia Screening

Most patients with VTE do not require thrombophilia testing, since the results will not affect their management. Testing may be considered in younger patients with weak provoking factors, a strong family history, and thrombosis in unusual sites, such as splanchnic or cerebral veins or recurrence at a young age¹⁹ (► Table 2).

In general, screening for AT, protein C, and protein S deficiencies should not be done during acute thrombosis, as levels of these anticoagulants may be decreased during the acute event. However, testing for FVL and PGM can be done at any time bearing in mind that these two common thrombophilias are mainly seen in white patients and rarely in African Americans. These mutations are not identified in patients of south East Asia, African, or Native American ancestries.

Indications for testing for the antiphospholipid antibodies (aPL) which includes the lupus anticoagulant (LA), anticardiolipin, and anti-B2 glycoprotein-1 IgG and IgM is described in ► Table 3.²⁰ If the tests are positive, they should be verified in 12 weeks to confirm the results. Testing for the LA should not be performed while the patient is taking DOACs, as it usually causes a falsely positive result.

Hypercoagulable States

Among hypercoagulable states, the two that are most well studied and worthy of in-depth review are pregnancy and cancer.

Table 2 Rates of initial and recurrent VTE for the various thrombophilias and hypercoagulable states (shown as percent per patient-years)^{3,6,7,20,23}

Thrombophilia/ Hypercoagulable state	Rates of initial VTE (%)	Rates of recurrent VTE (%)
FVL (heterozygous)	0.5	20.5 ³
FVL (homozygous)	1.8	12.5 ³
PGM (heterozygous)	0.4	17.9 ³
AT	1.6	56 ⁶
PC	1.0	46.4 ⁶
PS	0.4	–
APS	8.4 ^a	7.5 ⁹
Pregnancy	0.01	6.2 ²⁴
Cancer	4–20	15.5–38.6 ^{a,27}

Abbreviations: APS, antiphospholipid syndrome; AT, antithrombin; FVL, factor V Leiden; PC, protein C; PGM, prothrombin gene FII G20210A; PS, protein S; VTE, venous thromboembolism.

^aFor patients with overt to occult cancer.

Pregnancy

Venous thromboembolism is a leading nonobstetric cause of maternal death in developed countries. During pregnancy, the risk for VTE increases four- to sixfold, and although the risk is present throughout pregnancy, the mother is at highest risk immediately postpartum. The risk of VTE is increased due to physiologic and anatomic changes that occur in pregnancy. These changes include hypercoagulability, progesterone-induced venous stasis, decreased venous outflow, compression of the inferior vena cava and pelvic veins by the expanding uterus, and decreased mobility. The hypercoagulability of pregnancy is due to increased coagulation factors I (fibrinogen), VII, VIII, X, and von Willebrand factor; decreased free protein S, a natural anticoagulant;

acquired resistance to activated protein C; and decreased fibrinolysis due to increased plasminogen activator inhibitor types 1 and 2. These changes confer increased hemostasis to the mother for delivery but also place her at higher risk for thrombosis. Other risk factors that increase the risk for development of VTE during pregnancy include obesity, older maternal age (>35), multiparity, and birth by cesarean section, smoking, and a personal history of VTE. DVTs occur more commonly in the antenatal period, while PEs predominantly occur in the postpartum.²¹ A review of the literature found that more than 70% of pregnancy-associated DVTs are located in the iliofemoral region most commonly in the left side, as compared with ~9% in nonpregnant patients.²² Women who develop perinatal thrombosis are at risk for recurrent thrombosis. In an observational cohort study involving 270 pregnant women (369 pregnancies) with at least one previous episode of VTE, recurrent VTE occurred in 38 women (7.6%); of those, 12 recurrent VTE happened in 10 (3.3%) women during early pregnancy prior to starting low-molecular-weight heparin (LMWH) and 16 recurrent VTEs (4.3%) developed in 15 women despite LMWH prophylaxis. The risk of antepartum recurrent VTE is considerable in women with a history of two or more previous VTEs, hormonal-related VTE, presence of APS, or long-term anticoagulation. The antepartum prophylaxis with prophylactic dose of LMWH or even with intermediate dose of LMWH might not be sufficient in this high-risk population.²³ Another study demonstrated that among women with prior history of VTE, 6.2% developed a recurrent thrombosis during pregnancy while not on prophylaxis. Moreover, women who had their first VTE in the setting of oral contraceptives had higher rates of recurrent thrombosis during pregnancy compared with those with other risk factors for their initial VTE.²⁴ A multicenter multinational randomized control trial in pregnancy (high-low) is underway to determine the optimal dose of LMWH thromboprophylaxis for the prevention of recurrent VTE in pregnant women with a history of VTE.²⁵

Table 3 Recommendations for thrombophilia screening based on guidelines published by the *British Journal of Hematology*, American College of Pathologists, International Society for Thrombosis and Haemostasis, and the International Consensus Statment²⁰

Inherited thrombophilia	Acquired thrombophilia ⁷
Unprovoked VTE	Unprovoked VTE
VTE in patients <50 y old, including provoked	Unexplained arterial thrombosis in patients <50 y old
VTE in patients with minor provoking risk factor (e.g., estrogen therapy only)	Thrombosis at unusual sites (e.g., splanchnic veins)
Recurrent VTE	Unexplained late spontaneous pregnancy loss
Skin necrosis associated with vitamin K antagonists	Thrombosis or pregnancy morbidity and autoimmune disease
Purpura fulminans in children or neonates	Recurrent early spontaneous pregnancy loss
Strong family history of unprovoked recurrent VTE	Incidentally prolonged aPTT in asymptomatic individuals
Asymptomatic family member with known high-risk thrombophilia	Provoked VTE in young patients

Abbreviations: aPTT, activated partial thromboplastin time; VTE, venous thromboembolism.

Cancer

Patients with cancer have four- to sevenfold increase risk of VTE and VTE is reported to occur in 4 to 20% of cancer patients. Moreover, cancer-associated thrombosis (CT) is the second leading cause of death in cancer patients. From epidemiological studies, it is known that brain cancer; hematological malignancies; and adenocarcinomas of the pancreas, stomach, ovary, uterus, lungs, and kidneys are associated with the highest risk of VTE development.²⁶ Active cancer is the main risk factor for VTE recurrence on treatment. In a study conducted from 1994 to 2012 among 733 patients with incident VTE, the authors compared the risk of VTE recurrence in occult-, overt- and non-cancer-related first VTE. They found that patients with occult cancer had a 1-year cumulative incidence of VTE recurrence of 38.6% compared with patients with overt cancer in whom recurrence was 15.5 and to 3.8% in noncancer patients. The occult cancers associated with VTE recurrence were located at prothrombotic sites (i.e., lung and gastrointestinal) and presented at advanced stages. The majority (69%) of recurrences in subjects with occult cancer occurred before or shortly after cancer diagnosis, and was therefore not treatment related.²⁷

Guidelines from the ACCP (Grade 2C),⁷ a guidance document by the International Society on Thrombosis and Haemostasis (ISTH),²⁸ a guidance document by Anticoagulation FORUM,²⁹ and an informal suggestion from the American Society of Clinical Oncology (ASCO)³⁰ recommend the use of LMWH in cancer patients with VTE. The recommendations or suggestions are based on the superior efficacy of LMWH compared with VKAs in patients with cancer and mainly a first VTE. An ISTH registry of patients with cancer and recurrent VTE who were receiving anticoagulation therapy verified that these patients also experienced fewer recurrences over the next 3 months on LMWH versus VKA (hazard ratio, 0.28; 95% CI, 0.11–0.70).³¹ There were 11% VTE recurrences in patients receiving anticoagulation during the 3-month follow-up in the ISTH registry.

The major advantage of the DOACs, comprising the thrombin inhibitor dabigatran and factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, over VKA is their fixed dosing without the need for laboratory monitoring. Currently available clinical data are insufficient to make evidence-based recommendations on the use of DOACs in CT, even though DOACs are frequently administered in clinical practice in this setting. The combined evidence from six large clinical trials involving 27,000 patients has demonstrated that DOACs are as effective as VKA in preventing recurrent VTE with a lower risk of major bleeding, specifically intracranial bleeding. Therefore, DOACs are also being considered an option in patients with CT.³² Several studies evaluating the efficacy and safety of DOACs in cancer patients are currently underway and will soon provide an answer to this question. One of these ongoing trials comparing a LMWH (dalteparin) versus an oral direct anti-Xa oral anticoagulant (edoxaban) in cancer patients with VTE has completed its accrual and final results which will help determine if a direct oral Xa inhibitor is as efficacious as LMWH in the treatment of VTE in the setting of cancer.³³

Conclusion

The knowledge of the rate of VTE recurrence for specific thrombophilias and hypercoagulable states such as pregnancy and cancer is extremely important. This knowledge determines our approach to the type of initial anticoagulation therapy and the duration of anticoagulation. Given the high burden that recurrent VTE poses in these patients specifically in cancer patients and patients with aPL, one could argue for long-term anticoagulation in these patients providing that the bleeding risk is low. While current guidelines do not specify the time frame for treatment based on specific thrombophilias (with the exception of pregnancy), they do recommend extended period of treatment after an unprovoked VTE.⁷ Recently, the EINSTEIN CHOICE trial found that extended treatment with rivaroxaban (either 10 or 20 mg daily) for 12 months was superior in preventing recurrent thrombosis compared with aspirin 100 mg. This trial included patients with both provoked and unprovoked VTEs.³⁴ It will be interesting to see if further analysis of these data better clarifies the role of extended anticoagulation based on underlying risk factors. Given the data reviewed in this article, it would be reasonable to continue anticoagulation indefinitely in a patient who has significant risk factors as described in detail earlier, whose bleeding risk is low and is willing to continue therapy. Further research is needed to better elucidate recurrence rates for these entities, and to better guide clinical decision making regarding anticoagulation management. Moreover, the management of further anticoagulation after a breakthrough event is based on minimal or no clinical trial evidence.

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