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What is This?
Acquired Thrombophilia

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Abstract

Acquired thrombophilia is associated with an increased risk of venous thromboembolism (VTE). Antiphospholipid syndrome (APS) is the most prevalent acquired thrombophilia and is associated with both venous and arterial thromboses. Human immunodeficiency virus (HIV) is another form of acquired thrombophilia. Risk factors associated with VTE in this population include those related to the disease itself, host factors, and the pharmacotherapy for HIV. A significant proportion of VTE events occur in patients with malignancies. There is an increase in mortality associated with patients having cancer who experience VTE when compared to patients having cancer without VTE. Combination oral contraceptive (COC) use infers risk of thromboembolic events. The risk is dependent upon the presence of an underlying inherited thrombophilia, the estrogen dose, and generation of progestin. Patients at highest risk of VTE include those receiving high-dose estrogen and fourth-generation, progesterone-containing contraceptives. With the exception of APS, thrombophilia status does not alter the acute treatment of an initial VTE in nonpregnant patients.

Keywords

thrombophilia, antiphospholipid antibodies, human immunodeficiency virus, malignancy, oral contraceptives, acquired thrombophilia

Introduction

Venous thromboembolism (VTE) accounts for over 540 000 hospitalizations in the United States annually. More than 28 000 hospitalized adult patients with VTE die each year. The annual cost of VTE in the United States, including both deep vein thrombosis (DVT) and pulmonary embolism (PE), is estimated to exceed $56 000 per patient, leading to an overall cost of $4.9 to $19.8 billion. Thrombophilia is a condition that increases the risk of initial thromboembolic events. They may be inherited or acquired. Acquired disorders include antiphospholipid syndrome (APS), heparin-induced thrombocytopenia (HIT), and conditions resulting in activated protein C deficiency such as oral contraceptive use, pregnancy, and malignancy. Although both inherited and acquired thrombophilia increase the risk of VTE, their effect on arterial thrombosis is not as well defined. An exception is antiphospholipid antibodies (APLAs), which increase the risk of both venous and arterial events. Additionally, APS increases pregnancy-related complications. Human immunodeficiency virus (HIV) has been associated with an increased risk of VTE and thus is considered an acquired thrombophilia. This review will discuss the mechanisms of thrombosis, prevalence, and risk associated with the various acquired thrombophilias as well as considerations for treatment.

Incidence, Mechanisms, and Implications

Antiphospholipid Syndrome

APS is associated with significant thrombosis in the general population and is the most common acquired thrombophilia. APS is characterized by the presence of APLAs in addition to one or more clinical manifestations. APLAs include lupus anticoagulant (LA), anticardiolipin antibodies (aCLs), and anti-β<sub>2</sub> glycoprotein-I antibodies. Detection of aCL (medium
or high titers of immunoglobulin [Ig] G and/or IgM, anti-β₂ glycoprotein-I antibodies (titers > 99th percentile of IgG and/or IgM), or LA on 2 or more occasions, measured at least 12 weeks apart, is considered positive for antibodies. Clinical manifestations include vascular thrombosis or pregnancy-related morbidity. According to the 2006 international consensus statement, pregnancy morbidity classification criteria include 1 or more unexplained fetal deaths after the 10th week of gestation, 1 or more premature births before the 34th week of gestation, or 3 or more consecutive spontaneous abortions prior to the 10th week of gestation.  

Primary APS occurs in those without a coexisting autoimmune condition, while secondary APS occurs in the presence of an autoimmune condition such as systemic lupus erythematosus (SLE). Approximately 36% of patients with APS have SLE. More than 80% of patients with APS are positive for aCL, while LA is less common. LA, however, is more common in patients with SLE (approximately 15%) and is a more specific indicator of APLAs. APS most commonly occurs in young adults and in approximately 4% to 21% of all individuals with thrombosis. Although SLE is more common in African Americans and Hispanics, racial predominance for primary APS is not clearly defined. Thirty-two percent of individuals with APS present with VTE, the most common clinical manifestation. VTE or stroke occurs in approximately 20% of young patients with APS. Presence of APLAs is implicated in roughly half of all strokes in patients 50 years of age or younger. Although catastrophic APS is rare, this presentation of APS is associated with multiple organ thrombosis and high mortality. The mechanism by which APLAs induce thrombosis is not fully understood. Proposed mechanisms include interaction with platelets and endothelial cell membranes, interference with the coagulation cascade, and inhibition of protein C. Titer and isotype are important when determining the strength of association between positive antibodies and thrombosis. Risk of thrombosis is higher with titer elevation and the IgG isotype. LA is more strongly associated with thrombosis when compared to aCL. According to Galli et al, odds ratios for thrombosis ranged from 5.71 to 9.4 for LA, whereas aCLs were not significantly associated with thrombosis. Evidence-based recommendations from the task force on APLAs classify high-risk patients as those with persistent positivity for LA, triple positivity (LA, aCL, and anti-β₂ glycoprotein I), and/or persistently positive aCL at medium to high titers in those with coexisting SLE. Patients with isolated, intermittently positive aCL or low to medium titers of anti-β₂ glycoprotein I are considered low risk.

**Human Immunodeficiency Virus**

The frequency of VTE in patients with HIV ranges from 0.19% to 7.63% per year, similar to rates associated with thrombophilia such as factor V Leiden or protein C deficiency. Although exact mechanisms for thromboembolic risk are unknown, risk factors appear to include those related to the HIV disease itself, HIV pharmacotherapy, and individual patient characteristics. Host factors include age, the presence of additional thrombophilia, and intravenous drug use (IDU). VTE in patients with HIV occurs at an earlier age when compared to the general population. This is thought to be due to a “Premature Aging” process. Studies have demonstrated VTE to occur in the HIV-infected population at a median age of 40 years, approximately 20 years younger than patients without HIV. Others have suggested patients with HIV younger than 50 years of age had significantly higher yearly rates of VTE when compared to age-matched healthy controls (3.31% vs 0.53%, P < .0001). Additional data demonstrated a higher risk in patients with HIV older than 45 years compared to younger patients. It is reasonable that advanced age remains a risk factor for VTE in patients with HIV, although the younger HIV population appears to be at an increased risk compared to the non-HIV population. Concomitant thrombophilia, such as protein C and S deficiency and APS, appear to occur more often in HIV-infected patients as compared to the general population. Protein S deficiency, particularly type III, has been identified in up to 5% of HIV-infected patients compared to less than 0.5% of the general population, correlating to a 6-fold increase in the risk of VTE. Proposed mechanisms of protein S deficiency include decreased liver synthesis, abnormal endothelial function leading to increased binding of free protein S, and abnormal activation of the coagulation cascade. Another proposed mechanism includes increased binding of free protein S to C4b binding protein (C4BP), which is elevated during periods of inflammation. However, at this time, the correlation between elevated C4BP and protein S deficiency is not fully supported. One mechanism supported by most trials is a decrease in protein S seen with declining CD4+ counts.

Protein C deficiency is also more prevalent in patients with HIV as compared to the general population (0%-14% vs <0.2%) and potentially found in as many as 25% of those with opportunistic infections. The frequency of VTE that correlated with protein C deficiency is unclear; however, 1 study found that 7% of patients with HIV who experienced a VTE had protein C deficiency. Like protein S deficiency, a decline in protein C is thought to be associated with a decline in CD4+ levels.

aCL are present in 7.7% to 9.4% of patients with HIV. The IgG isotype in particular is present in 41% to 94% of patients with HIV. The clinical relevance of these elevations and correlation with the incidence of VTE remain controversial, as evidence in the literature is conflicting. The presence of LA in HIV-infected individuals has been found to be more variable, ranging from 0% to 72%. Although one study found LA to be more prevalent in HIV-infected patients than in patients with syphilis, the authors concluded that the LA activity was likely secondary to the reactivity of the immune system of patients with HIV and did not correlate with an increase in thrombosis. Other factors, such as increased tissue factor expression, increased levels of homocysteine, endothelial dysfunction, and P-selectin, may correlate with an increased risk of VTE in HIV-infected patients.
Intravenous drug use (IDU) in this population may also impact rates of VTE. Syed and colleagues found that IDU is an important cause of VTE in young adults. Another study demonstrated the risk of VTE was approximately 15 times higher in IDU HIV-infected patients compared to non-IDU HIV-infected patients. As a result, IDU should be taken into consideration when assessing the risk of VTE in patients with HIV.

Viral risk factors such as a decreasing CD4+ cell count, elevated viral loads, and the presence of opportunistic infections appear to contribute to the risk of patients with HIV. Several studies have found a higher rate of thrombosis in patients with established AIDS and an elevated viral load, which are typically associated with a declining CD4+ cell count. However, there have also been reports of thrombosis at normal CD4+ levels (800 cells/mm$^3$), which suggests the risk of VTE is not limited to severe disease.

Opportunistic infections such as cytomegalovirus (CMV), Pneumocystis jiroveci pneumonia (PJP), and mycobacterium avium complex (MAC) appear to increase the risk of VTE in HIV-infected patients. Cytomegalovirus has been associated with a 9.8% rate of VTE in HIV infection. Patients with active PJP may also be at increased risk of VTE. Interestingly, these patients are often found to have higher rates of APS, particularly LA VTE, especially PE, may be underdiagnosed in these patients due to similarities in symptoms between PE and PJP. Likewise, patients infected with mycobacterium avium-intracellular infection may also induce aCCL, which can increase the risk of VTE.

Antiretroviral therapy, in particular protease inhibitors (PIs), has been associated with thrombosis; however, data are conflicting. PIs are believed to interfere with the hepatic metabolism and regulation of thrombotic proteins, which may lead to a prothrombotic state. They may also downregulate anticoagulant effects within the body or precipitate endothelial or platelet dysfunction. The yearly incidence of VTE in patients with HIV receiving PI-based regimens has been estimated at 0.3% to 0.8%. Implicated PIs include indinavir, saquinavir, ritonavir, and nelfinavir, with VTE occurring anywhere from 72 days to 54 months of therapy.

Megestrol acetate, an appetite stimulant used in patients with AIDS-related anorexia and cachexia, may also contribute to an increased VTE risk. Although the evidence is conflicting, 1 group found an increased rate of VTE in patients receiving megestrol acetate, with an adjusted odds ratio (OR) of 2.0 (95% confidence interval [CI] 1.3–2.9).

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is an antibody-mediated response that increases an individual’s risk of both venous and arterial thromboses. Diagnosis of HIT is based on clinical features, including a decline in the platelet count to $\leq 150,000/\mu$L, or by 50% from baseline, in addition to the presence of HIT antibodies of the IgG subclass. These antibodies are directed toward antigens present on platelet factor 4 (PF4) bound to heparin. After the antibodies bind the FcγII receptors on platelets, platelet activation is triggered, which then leads to thrombin generation. The decline in platelet count is typically seen between 5 and 14 days after initiation of heparin but may occur as early as 24 hours in patients who have received a heparin product within the previous 100 days (ie, early onset HIT). HIT occurs with unfractionated heparin (UFH) more commonly than with low-molecular-weight heparin (LMWH), but cross-reactivity exists between the 2 classes. The risk of HIT is increased in surgical patients (especially in orthopedic and cardiac surgery), females, and those who have had a longer exposure to heparin products.

Malignancy

The association between cancer and VTE has long been established, with the risk of VTE reported to be increased by 6-fold or more in patients with cancer. Approximately 25% of patients with VTE have an underlying cancer, with a reduced survival in patients with cancer having VTE compared to non-cancer patients. Certain cancers, such as malignant brain tumors, hematologic malignancies, and adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, and kidney, carry a higher risk of thromboembolism as compared to other types of cancer. Multiple factors contribute to the occurrence of VTE in cancer; not only do tumor cells express tissue factor and other procoagulants, but tissue factor also acts as a cell-signaling molecule that stimulates tumor proliferation and expansion. Factors commonly seen in patients with cancer such as immobility, infection, surgical procedures, and insertion of central venous catheters are also thought to contribute to the increased risk of thrombosis. In addition, nonsurgical cancer therapies such as tamoxifen, angiogenesis inhibitors, thalidomide, lenalidomide, and bevacizumab have been associated with an increased risk of VTE.

Oral Contraceptive Use

For women taking combination oral contraceptives (COCs), the risk of VTE is dependent upon the presence of an underlying inherited thrombophilia, as well as the estrogen dose and generation of progestin. The presence of an underlying thrombophilia may increase the incidence by as much as 40-fold in those with FVL and 60-fold in those with prothrombin mutation. Women at lowest risk are those without other VTE risk factors taking low–dose, estrogen-containing products (20–40 μg ethinylestradiol) in combination with a first- or second-generation progestin (norethindrone, levonorgestrel, or norgestrel). However, the risk in these individuals is still 4 times that of non-COC users. It appears the risk is highest during the first year of therapy. The risk with third-generation progestins, including desogestrel and gestodene, is 1.4 to 4 times that of second-generation progestins, with the highest risk also seen during the first year of use.

The first and only oral fourth-generation progestin on the US market, drospirenone, has been linked to increased risk of VTE.
VTE. Two studies reported that when combined with low-dose ethinyl estradiol, women taking drospirenone-containing COCs were 1.6 to 3 times more likely to develop VTE compared to women taking levonorgestrel-containing COCs.\(^{53,54}\) Conversely, there have been reports that have failed to find an increased risk.\(^{55,56}\) Based on the conflicting evidence, the Food and Drug Administration (FDA) undertook its own investigation in 2011. Similar to previous findings, analysis of data from this large, retrospective, multicenter investigation suggests that the risk of VTE is increased with use of drospirenone compared to older generation progestins. When compared to COCs containing norethindrone (first-generation progestin) and norgestrel (second generation), patients receiving drospirenone-containing COCs were 1.74 times more likely to experience VTE. New users had a similar risk overall, but the highest risk (2.8 times) was seen during early use between 6 and 12 months of initiation.\(^{57}\) In April 2012, the FDA announced that labeling for drospirenone-containing products be revised to include a warning of increased risk of thrombosis compared to products containing other progestins.\(^{57}\)

### Treatment Considerations

**Anticoagulation With APLAs**

Anticoagulation management in APS is controversial due to conflicting study results and concerns with primary and secondary prophylaxis, leading to inconsistencies in certain treatment recommendations (Table 1). Management of obstetric APS warrants discussion and will be addressed in a separate article in this issue.

The Task Force at the 13th International Congress on Antiphospholipid Antibodies released a report of evidence-based recommendations for the prevention and long-term management of thrombosis in APLA-positive patients. The report addresses primary thromboprophylaxis in patients with and without SLE.\(^{12}\) The task force suggests treatment with hydroxychloroquine and low-dose aspirin as primary prophylaxis in patients with SLE and positive LA or isolated persistent aCL at medium to high titers. Low-dose aspirin is recommended in those without coexisting SLE if they test positive for a high-risk APLA profile, although the risk of thrombosis in this population has not been well established.\(^{12}\)

Treatment recommendations for secondary prophylaxis in patients with APS are mostly consistent among various sources (Table 1). Recommendations from both the American College of Chest Physicians and the Task Force at the 13th International Congress on Antiphospholipid Antibodies suggest warfarin therapy with a target international normalized ratio (INR) range of 2.0-3.0 to 3 in patients with a first episode of VTE.\(^{12,58}\) Controversial issues include the most appropriate intensity of anticoagulation in arterial events as well as the most appropriate approach to treatment of those with recurrent events while on warfarin.

The Antiphospholipid Antibodies and Stroke Study (APASS) found no difference in the risk of cerebral arterial events in those treated with aspirin or warfarin (target INR of 1.4-2.8), suggesting that either warfarin (at a lower target INR) or aspirin are efficacious for the prevention of recurrent events in patients after a cerebral event.\(^{59}\) In this study, however, APS diagnosis was based upon 1 positive test for APLAs, which is not consistent with the current criteria for APS diagnosis.
with the 2006 diagnostic criteria. A review by Ruiz-Irastorza et al concluded that patients with arterial or recurrent events are at high risk of recurrence when treated with warfarin at a target INR of 2.0 to 3.0. Cohort studies also support patients with arterial thrombosis or recurrent events to be treated with warfarin at an INR greater than 3.0. High-intensity warfarin (INR greater than 3.0) is supported by 2 retrospective studies, while additional randomized controlled trials support a moderate intensity INR range (2-3). Recommendations from the American College of Chest Physicians suggest warfarin therapy with a target INR range of 2 to 3 rather than a higher intensity INR (3.0-4.5) in patients with a first arterial event while anticoagulated. Suggestions for recurrent events while on warfarin therapy include treatment of recurrent episodes while anticoagulated or switching to heparin. This recommendation is a 2B graded recommendation (2B = weak recommendation, moderate quality of evidence). It is also important to note that the task force recommendation is a nongraded recommendation, while the American College of Chest Physicians’ recommendation is a 2B graded recommendation.

Due to the high risk of recurrence in patients with APS, indefinite therapy is recommended after an initial thrombotic event. Limited evidence is available, however, for treatment of recurrent episodes while anticoagulated. Suggestions for recurrent events while on warfarin therapy include treatment with warfarin to a higher INR target, the addition of aspirin to warfarin, or switching to heparin. Minimal evidence is available for the addition of aspirin to warfarin in such cases. Okuma et al evaluated a small group of patients with APS with a history of ischemic stroke randomized to receive aspirin or combination of aspirin plus warfarin therapy at a target INR of 2.0 to 3.0. Results demonstrated a higher incidence of stroke in patients treated with aspirin alone (P = .026). Although this study suggests a benefit of combination therapy for secondary prevention in APS in those with a history of stroke, the benefit of combination therapy in recurrent VTE is unclear. Limited evidence is available for the addition of aspirin to warfarin at a standard target INR (2.0 to 3.0) or a higher target INR (>3.0) for recurrent events or difficult cases.

According to the Task Force at the 13th International Congress on Antiphospholipid Antibodies, alternative therapies in those with recurrent events while anticoagulated or in those with major bleeding or with fluctuating INR levels include LMWH, hydroxychloroquine, or statins. This recommendation, however, is a nongraded recommendation. Treatment with LMWH for a median duration of 36 months was shown to be a safe and effective alternative to warfarin therapy in 1 small trial conducted in patients with APS who had not responded or tolerated warfarin previously. There were no recurrent events and good quality of life reported in 9 (39%) patients. There were no recurrent events and “partial clinical improvement” found in 11 (48%) patients. Case reports have also described the use of long-term treatment with LMWH in patients with recurrent events while treated with warfarin. Concerns related to long-term LMWH use include discomfort and inconvenience related to the route of administration, drug acquisition cost, and the risk of HIT and osteoporosis.

Although hydroxychloroquine has been suggested by the task force for use in primary thromboprophylaxis in patients with SLE with high-risk APLAs, limited data are available for treatment of recurrent events in patients with APS without SLE. Proposed mechanisms and advantages of hydroxychloroquine include inhibition of anti-β2 glycoprotein I binding to phospholipids and decreased aPLA-associated platelet activation and clotting. Inhibition of nuclear factor NF-κB, a mediator of platelet activation, and decreased endothelial cell adhesion by anti-β2 glycoprotein I are mechanisms by which statins may be beneficial in patients with APS. In a small trial of patients with APS, fluvastatin was shown to decrease inflammatory and thrombogenic mediators (vascular endothelial growth factor [VEGF], soluble tissue factor [sTF], and tumor necrosis factor α [TNF-α]) after 30 days. Similarly, a trial conducted by Lopez-Pedrera et al demonstrated reduction in monocyte activity after 1 month of treatment with fluvastatin. Due to antithrombotic properties exhibited, statin therapy could have a role in APS management outside lipid lowering.

The new oral anticoagulants such as direct thrombin inhibitors (dabigatran) and antifactor Xa inhibitors (rivaroxaban, apixaban) are potential topics of future research for treatment in APS. Although hydroxychloroquine has been suggested by the task force for use in primary thromboprophylaxis in patients with SLE with high-risk APLAs, limited data are available for treatment of recurrent events in patients with APS without SLE. Proposed mechanisms and advantages of hydroxychloroquine include inhibition of anti-β2 glycoprotein I binding to phospholipids and decreased aPLA-associated platelet activation and clotting. Inhibition of nuclear factor NF-κB, a mediator of platelet activation, and decreased endothelial cell adhesion by anti-β2 glycoprotein I are mechanisms by which statins may be beneficial in patients with APS. In a small trial of patients with APS, fluvastatin was shown to decrease inflammatory and thrombogenic mediators (vascular endothelial growth factor [VEGF], soluble tissue factor [sTF], and tumor necrosis factor α [TNF-α]) after 30 days. Similarly, a trial conducted by Lopez-Pedrera et al demonstrated reduction in monocyte activity after 1 month of treatment with fluvastatin. Due to antithrombotic properties exhibited, statin therapy could have a role in APS management outside lipid lowering.

**Anticoagulation in HIT**

Treatment of HIT requires the immediate discontinuation of all heparin products. Because the patient will still require anticoagulation therapy, an alternative agent such as argatroban, bivalirudin, or fondaparinux should be administered. Although fondaparinux does not have an indication for the treatment of HIT, it has been used extensively off label for this indication. From pooled data of fondaparinux use in 71 patients with HIT, there were no cases of new thrombosis and only 4 patients (5.6%, 95% CI 1.6-13.8) experiencing a major bleed. Warfarin should not be administered in HIT until the platelet count has recovered to 150 000/μL, and once initiated, the direct thrombin inhibitor (or fondaparinux) should be continued until the INR has reached therapeutic levels, with a minimum overlap of 5 days of therapy. In patients receiving argatroban, it should be noted that argatroban can falsely elevate INR values. In order to properly assess the degree of anticoagulation with warfarin during concomitant therapy, the argatroban infusion should be held for 4 to 6 hours prior to INR measurement.

**Anticoagulation in Malignancy**

The use of anticoagulants in individuals with an underlying malignancy depends on patient-specific factors. After an acute VTE, it is recommended that LMWH be used over warfarin.
therapy, as trials have demonstrated a decrease in recurrent VTE with similar rates of bleeding. Current guidelines suggest warfarin over the new oral anticoagulants, dabigatran or rivaroxaban, in patients not treated with LMWH due to limited data with their use in this population. Data are also lacking in regard to the risk of recurrent events in patients with cancer, but the estimated annual rate may be as high as 15%. This is dependent upon whether the cancer is metastatic, rapidly progressing, or being treated with chemotherapy. Other risk factors include location of the VTE and whether the VTE was an initial or recurrent event, with recurrent events being associated with a 50% higher risk of recurrence. Patients with a first episode of VTE should be treated for at least 3 months, with consideration for extended anticoagulation in the absence of high bleeding risk. Factors associated with a lower risk of recurrence, such as an initial event secondary to a reversible risk factor, cancer responding to treatment, nonmetastasized cancer, or an isolated distal DVT, may warrant discontinuation of anticoagulation therapy after 3 months of treatment.

Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. The American College of Chest Physicians recommend prophylactic anticoagulation with either LMWH or UFH be initiated in outpatients with solid tumors who have additional risk factors for VTE, including previous VTE, immobilization, or receiving hormonal therapy, angiogenesis inhibitors, thalidomide, or lenalidomide. This recommendation, however, may overestimate the risk of VTE in patients with breast and prostate cancers and does not consider additional risk factors for risk assessment models. Prophylaxis with LMWH can be considered in highly selected outpatients with solid tumors receiving chemotherapy. Lyman and colleagues recommend patients with multiple myeloma receiving thalidomide or lenalidomide regimens with chemotherapy and/or dexamethasone who are considered lower risk should receive prophylaxis with aspirin or LMWH, while higher risk patients should receive LMWH. In contrast, Streiff et al recommend that patients with low-risk multiple myeloma receive aspirin, whereas patients with 2 or more risk factors or those receiving thalidomide or lenalidomide in combination with high-dose dexamethasone, doxorubicin, or multiagent chemotherapy receive either LMWH or warfarin.

Anticoagulation With Other Acquired Thrombophilia

For the remaining thrombophilia discussed in this review, including both HIV and patients receiving COCs, treatment of VTE is similar to that of patients without underlying thrombophilia. Warfarin therapy targeting an INR range of 2.0 to 3.0 is considered appropriate. Due to the potential for drug interactions with antiretroviral therapy, clinicians should be conscious of the potential for variations in INR values in patients with HIV receiving therapy. In patients who have experienced thrombosis on COCs, if contraceptive therapy is still desired, consideration may be given to hormone-releasing intrauterine devices, as these have not been found to increase the risk of thrombosis.

Conclusions

Patients with acquired thrombophilia are at an increased risk of VTE. Hydroxychloroquine and low-dose aspirin are recommended for primary prophylaxis in patients with SLE and positive LA or isolated persistent aCL at medium to high titers. Low-dose aspirin is also recommended in those without coexisting SLE if they have a high risk APLA profile. Patients taking COCs with an underlying thrombophilia, on high-dose estrogen-containing COCs, or a third- or fourth-generation progesterin are at higher risk of thrombotic events. These individuals warrant close observation and discussion of the risk of VTE as well as patient preferences. Additionally, consideration may be given to utilizing hormone-releasing intrauterine devices rather than COCs. Patients with malignancy-associated thrombosis should be treated with LMWH when possible, while patients with HIT must avoid heparin and LMWH for 100 days. Treatment of thrombosis in the presence of other acquired thrombophilia is similar to that of individuals without thrombophilia, although a higher INR target may be considered in patients with arterial events associated with APS or recurrent events while therapeutic on warfarin. Prophylaxis and treatment of VTE in patients with acquired thrombophilia should be individualized, taking into consideration the type of thrombophilia and additional risk factors.

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