Journal of Thrombosis and Haemostasis, **1**: 1429–1434

REVIEW ARTICLE

Management of thrombophilia

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To cite this article: Bauer KA. Management of thrombophilia. *J Thromb Haemost* 2003; **1**: 1429–34.

Summary. It is now possible to identify acquired and hereditary risk factors in a substantial percentage of patients presenting with a venous thrombotic event. Discovery of the factor V Leiden and prothrombin G20210A mutations has greatly increased the percentage of patients in whom venous thrombosis can be attributed to hereditary thrombophilia. There is, however, considerable uncertainty as to how this information should be used in patient management. Although prolonged anticoagulation at an international normalized ratio of 2–3 is highly effective in preventing thrombotic recurrences, this benefit is partially offset by major bleeding which occurs at an average rate of 2%−3% per year. A decision as to the overall benefit of extended anticoagulation in the individual patient requires assessment of the risk of recurrence in the absence of treatment vs. the bleeding risk associated with prolonged anticoagulation. Low-intensity warfarin therapy or novel anticoagulants such as oral direct thrombin inhibitors may prove effective strategies for preventing recurrent venous thromboembolism in patients with thrombophilia.

Keywords: anticoagulation, factor V Leiden, pregnancy, thrombophilia, venous thromboembolism, warfarin.

Patients with venous thromboembolism can be categorized according to the presence of environmental (acquired) or heritable risk factors. The former include diseases (e.g. malignancy, nephrotic syndrome), conditions (e.g. recent surgery, prolonged immobilization, pregnancy, puerperium, oral contraceptives, postmenopausal hormone replacement) or laboratory abnormalities (i.e. lupus anticoagulant), which predispose to the development of thrombosis. Inherited thrombophilia is a genetic tendency to venous thromboembolism.

Prior to the discovery of activated protein C resistance in 1993, a heritable risk factor (i.e. deficiencies of antithrombin, protein C or protein S) was detectable in a relatively small percentage (5%−15%) of such patients. Characteristic clinical features of these disorders included a first thrombotic event at an early age (<50 years), a positive family history of thrombosis, or recurrent thrombosis [1]. Among Caucasians, the factor V (FV) Leiden and the prothrombin G20210A mutations are the most common heritable risk factors predisposing to venous thromboembolism; many individuals with these mutations however, will sustain their first venous thrombotic event after age 50 and have no family history of venous thrombosis. Overall, the total prevalence of inherited thrombophilia in Caucasian subjects with venous thromboembolism (VTE) ranges from 24% to 37% compared with ∼10% in controls. Management issues related to thromboembolism in patients with thrombophilia are reviewed here. The usefulness of screening for these conditions in various asymptomatic populations and in patients presenting with thrombosis have been reviewed separately [2,3].

The initial management of acute VTE in patients with acquired or inherited risk factors for thrombosis is not different from that in other patients. Less well established is the chronic management of patients with specific risk factors who have had venous thrombosis and that for patients exposed to the increased risk associated with pregnancy and surgery.

Acute VTE

The usual treatment of acute VTE consists of unfractionated heparin or low-molecular-weight heparin followed by anticoagulation with warfarin (or other vitamin K-antagonists). Warfarin can be started within the first 24 h. Heparin or low-molecular-weight heparin (LMWH) is continued for at least 5 days or until the prothrombin time is in the therapeutic range, namely an International Normalized Ratio (INR) of 2.0–3.0 [4]. Special considerations may apply to selected patients with antithrombin deficiency or hereditary protein C deficiency.

Antithrombin deficiency

Some patients with antithrombin deficiency are resistant to heparin and require large doses. This is in part due to the action of heparin to further lower antithrombin levels by approximately 30% over several days. Antithrombin concentrate has been used safely and effectively in patients with antithrombin deficiency and acute venous thrombosis [5,6]. It is recommended in those patients who have unusually severe thrombosis, have difficulty achieving adequate anticoagulation or

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develop recurrent thrombosis despite adequate anticoagulation [7]. It can also be used for antithrombotic prophylaxis in antithrombin-deficient patients in whom anticoagulation is contraindicated. The use of antithrombin concentrate as adjunctive therapy or as an alternative to heparin, however, has not been studied in a controlled trial [8,9].

Antithrombin concentrate is prepared from pooled normal human plasma. The manufacturing process results in a product that is 95% pure and inactivates hepatitis B virus and the human immunodeficiency virus [5,7,10]. A human antithrombin concentrate has also been produced from the milk of transgenic goats using recombinant DNA technology [11], and is undergoing clinical trials in patients with hereditary antithrombin deficiency.

The infusion of 50 units of plasma-derived antithrombin concentrate per kilogram of body weight will usually raise the plasma antithrombin level to approximately 120% in a congenitally deficient individual with a baseline value of 50% [6]. One unit is defined as the amount in 1 mL of pooled normal human plasma. Plasma levels should be monitored to ensure that they remain above 80%; the administration of 60% of the initial dose at 24 h intervals is recommended to maintain antithrombin levels in the normal range [5]. Recovery of plasma-derived antithrombin concentrate *in vivo* in patients with antithrombin deficiency is 1.4%–2.7% unit^{-1} kg^{-1} [5,6]. Recovery is lower in patients with acute thrombotic events and those receiving heparin therapy [6]. The biologic half-life approximates 2.8–4.8 days.

Protein C deficiency

Hereditary protein C deficiency can rarely be associated with warfarin-induced skin necrosis due to a transient hypercoagulable state. The initiation of warfarin at standard doses leads to a decrease in protein C anticoagulant activity to approximately 50% of normal within 1 day; factor (F)VII activity follows a similar pattern but the levels of the other procoagulant vitamin K-dependent factors decline at slower rates, consistent with their longer half-lives [12].

Despite this risk, routine measurement of plasma protein C concentrations in all individuals with thrombosis before the initiation of oral anticoagulants is not recommended. There are three observations underlying this conclusion: the infrequent occurrence of warfarin-induced skin necrosis even among patients with hereditary protein C deficiency; the frequency of asymptomatic hereditary protein C deficiency in the general population (one in 200–500); and the diagnostic difficulty in making a rapid and definitive laboratory diagnosis of the deficiency state.

On the other hand, oral anticoagulation in a patient who is known or likely to be protein C deficient should be started under the cover of full heparinization. The dose of warfarin should be increased gradually, starting from a relatively low level (e.g. 2 mg for the first 3 days and then in increasing amounts of 2–3 mg day^{-1} until therapeutic anticoagulation is achieved).

Patients with heterozygous protein C deficiency and a history of warfarin-induced skin necrosis have been successfully retreated with oral anticoagulants. Protein C administration, either in the form of fresh frozen plasma or protein C concentrate, can provide protection against recurrent skin necrosis until a stable level of anticoagulation is achieved [13–15].

Long-term therapy to prevent recurrence

After initial heparinization, standard therapy for patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) typically includes anticoagulation with warfarin for 3–12 months at a target INR between 2 and 3, this results in more than a 90% reduction in recurrence risk. In patients presenting with a first episode of symptomatic VTE, Prandoni *et al.* [16] found the cumulative incidence of recurrent venous thrombosis after the cessation of anticoagulant therapy to be 24.8% at 5 years and 30.3% at 8 years. Other investigators have confirmed that this risk is about 5%–15% per year for the first several years after a first or even a second episode of unprovoked venous thrombosis [17–19]. One trial found a much higher recurrence risk of 27% in the first year following 3 months of anticoagulation for a first unprovoked venous thrombotic episode [20]. In summary, the lowest recurrence risks after discontinuation of anticoagulant therapy have been found after 6–12 months of initial therapy. Recurrences are less common when the initial event is associated with a transient risk factor (e.g. surgery, trauma, etc.). Despite this recurrence risk, there has not been heretofore an anticoagulant regimen available that has proven to have sufficient benefit (as compared with the bleeding risk of chronic warfarin therapy at an INR of 2–3) to support long-term prophylaxis for all patients at substantial recurrence risk. For example, one controlled trial evaluated the efficacy of long-term warfarin therapy (INR 2–2.85) for 6 months or indefinitely in 227 patients with a second venous thrombotic episode, but not specifically inherited thrombophilia [18]. Long-term warfarin was highly effective in preventing recurrences as compared with 6 months of therapy (2.6% vs. 21% over 4 years); this benefit was partially counterbalanced by a trend toward an increased incidence of major hemorrhage (8.6% vs. 2.3%) and there was no difference in mortality between the two groups.

Risk of recurrence

Due to the relatively high frequency of the FV Leiden mutation (12–21% in unselected patients with a first episode of VTE), there is a substantial amount of data on the risk of recurrence. While two groups initially reported that patients with FV Leiden who had a first venous thrombotic event were more than twice as likely to have a recurrent episode than those without the mutation [21,22], several other centers have not found that heterozygosity for this defect, or the prothrombin G20210 mutation, confers a higher recurrence risk [20,23–27]. Thus, the consensus view at present is that neither of these

defects alone are predictive of recurrence, and several studies have argued against the use of long-term warfarin therapy after a first thromboembolic episode in these patient populations. As an example, the recurrence rate after discontinuation of oral anticoagulant therapy was assessed in 62 patients with FV Leiden [28]. None of the patients had a recurrent event while taking warfarin. The median time to recurrence after stopping warfarin was 9 years; the period was shorter (3.5 years) among patients who suffered an idiopathic rather than a precipitated first event. It was estimated that, even in the latter group, death from hemorrhage would probably exceed the number of fatal pulmonary emboli prevented with chronic warfarin therapy. A decision analysis model concerning the value of extended anticoagulation in patients with FV Leiden who had a first DVT concluded that the number of major induced hemorrhages would exceed the number of clinical pulmonary emboli that would be prevented, and that extension of oral anticoagulation beyond 1 year would not produce clinical benefit [29]. There is no increase in mortality among patients with the FV Leiden mutation [30], further supporting the argument that the mortality risk of chronic warfarin therapy at a target INR of 2–3 in the average thrombophilic patient may exceed the potential benefit.

The recurrence risk appears to be significantly higher in the small subset of patients who are heterozygous for both the FV Leiden and prothrombin G20210 mutations, homozygous for FV Leiden, or who have another thrombophilic defect [27,31–36]. The presence of antiphospholipid antibody syndrome [37,38] or cancer [39,40] are also important risk factors for recurrence.

Due to the relatively low frequency of deficiencies of antithrombin, protein C or protein S in unselected cohorts with an initial episode of VTE, randomized clinical trials have included too few patients with these deficiencies to draw firm conclusions. A literature review and retrospective cohort study suggested that they have a high annual incidence of recurrent VTE during the years immediately following a first episode, which declines thereafter [41]. The application of decision analysis to this problem indicates that optimal anticoagulant treatment duration will vary, depending on the type of initial event (spontaneous or secondary; DVT or PE), patient age and time passed since the initial thromboembolic episode [42]. Interestingly, retrospective studies are unable to demonstrate an increase in mortality in patients with antithrombin [43] or protein C deficiency.

For the individual patient, the decision to continue anticoagulation indefinitely requires estimation of the quantitative risk of recurrent thrombosis (including fatal PE) and major bleeding (including fatal bleeding) over time. Patient compliance has a major impact on the success of therapy, and patient preferences must be factored into the decision. Many clinicians with experience managing these disorders recommend indefinite anticoagulation for patients with heterozygous antithrombin deficiency. Some also recommend such an approach for patients with heterozygous deficiencies of protein C or protein S.

Recommendations

At present, indefinite anticoagulation at a target INR of 2–3 is recommended only in the following high-risk patients [2]:

1. two or more spontaneous thromboses;
2. one spontaneous thrombosis in the case of antithrombin deficiency or the antiphospholipid antibody syndrome;
3. one spontaneous life-threatening thrombosis (e.g. near-fatal PE; cerebral, mesenteric or portal vein thrombosis);
4. one spontaneous thrombosis at an unusual site (e.g. mesenteric or cerebral vein);
5. one spontaneous thrombosis in the presence of more than a single genetic defect predisposing to a thromboembolic event.

Future approaches

Randomized clinical trials involving patients with a prior history of unprovoked VTE have evaluated the efficacy of extended low-intensity warfarin at an INR of 1.5–2 in preventing recurrent events. The PREVENT (Prevention of Recurrent Venous Thromboembolism) trial was closed in December 2002 and demonstrated that low-intensity warfarin reduced the rate of recurrent VTE by more than 60% compared with placebo, without an increase in major bleeding complications [44].

An alternative approach for long-term management is use of a new anticoagulant. Ximelagatran, an oral direct thrombin inhibitor under development, was compared with placebo using a clinical trial design similar to PREVENT and was shown to be highly effective in preventing recurrent venous thrombosis [45].

Pregnancy (see also Ginsberg and Bates [46])

Pregnancy is associated with an increased risk of thrombosis that may be due in part to the progressive increase in resistance to activated protein C that is normally observed in the second and third trimesters. In three large series, thrombosis in pregnancy occurred in 0.13–0.7 per 1000 women; the risk was 3- to 4-fold higher in the puerperium than in pregnancy. A recent study demonstrated that women with a single prior episode of venous thromboembolism have a low antepartum recurrence risk during subsequent pregnancies, particularly if the initial thrombotic event was associated with a transient risk factor [47].

The risk of thrombosis is accentuated in those women with inherited thrombophilia. In one series of 60 women with an inherited deficiency of a naturally occurring anticoagulant (antithrombin, protein C or protein S), the risk of venous thrombosis during pregnancy or the postpartum period was increased 8-fold (4.1% vs. 0.5% in non-deficient women) [48]. The thrombotic risk for a woman with FV Leiden during pregnancy or the puerperium has been estimated at approximately one in 400–500 [49].

Studies of the incidence of pregnancy-related VTE in subjects homozygous for FV Leiden have given conflicting results, perhaps because of the small number of subjects involved and

whether the subjects were preselected from a larger group with a family history of VTE. In one study, none of 18 pregnancies in seven unselected patients was complicated by VTE [50]. In a second study, the incidence of VTE was 4.2% and 4.7% during pregnancy and after delivery, respectively [51]. In a third study of 12 homozygous women with a symptomatic first degree relative, four out of a total of 24 pregnancies were complicated by DVT, for an incidence of 17% per pregnancy (95% confidence limits, 5−37%) [52]. The risk of thromboembolism during pregnancy is higher among women with a past history or family history of thromboembolic events.

In general, pregnant women with anticoagulant factor deficiencies and a personal or familial history of thrombosis should be considered for anticoagulant prophylaxis [48,53]. Pregnant women with antithrombin deficiency appear to have an unusually high risk for thromboembolism, and should receive anticoagulant prophylaxis throughout pregnancy [54]. Antithrombin concentrates are available but should be reserved for use during labor, delivery or obstetric complications where the risks of bleeding from anticoagulation are unacceptable [55].

During pregnancy, adjusted-dose unfractionated heparin or low-molecular-weight heparin administered by the subcutaneous route has been the anticoagulant of choice because its efficacy and safety for the fetus are established [56,57]. Heparin can produce bone loss but is not associated with the embryopathy that can result from the early administration of warfarin. LMWH is an attractive alternative to unfractionated heparin in this setting because of its better bioavailability, longer half-life, and ease of administration. Enoxaparin, for example, is rated by the US Food and Drug Administration (FDA) as pregnancy category B; while not FDA-approved for use in pregnancy, it appears to be safe and effective. The dose and duration of LMWH therapy in pregnancy however are uncertain since appropriately designed clinical trials have not yet been performed. The following approach is suggested.

1 Patients considered to be at high thrombotic risk should receive full-dose heparin or LMWH by subcutaneous injection every 12 h for the duration of pregnancy and approximately 6 weeks postpartum. For unfractionated heparin, the dose should be adjusted to maintain the 6 h postinjection activated partial thromboplastin time (aPTT) at 1.5 times the control value. For LMWH, firm guidelines regarding the need for monitoring have not been established. In view of the increase in total body plasma volume during pregnancy, intermittent monitoring of plasma heparin levels by anti-FXa assay should be performed, starting in the second trimester. The goal is a plasma heparin concentration of 0.5–1.0 U mL^{-1} 2–3 h after injection.

2 Women with a personal or family history of thrombosis and considered to be at intermediate risk can be treated with lower subcutaneous doses of heparin: 5000–10 000 units of unfractionated heparin subcutaneously every 12 h; or prophylactic doses of LMWH every 12 h. Therapy should be started during the second or third trimester and continued for approximately 6 weeks into the postpartum period.

3 Low-risk patients (e.g. asymptomatic carriers without a family history of recurrent thromboses) should be observed closely throughout the pregnancy.

Surgery

Patients with inherited thrombophilia who undergo surgery should generally be treated as a high-risk group and receive prophylactic periperative anticoagulation with LMWH.

Antithrombin deficiency

Surgery is associated with a reduction in antithrombin levels for 3–5 days postoperatively and some patients with antithrombin deficiency and low concentrations of antithrombin may not respond well to heparin. For this reason and to reduce the risk of bleeding from anticoagulation, antithrombin concentrate has been used successfully in several case reports and studies [6].

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