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When to consider thromboprophylaxis in vein treatment?

À quel moment envisager une thromboprophylaxie dans le traitement de la maladie variqueuse ?

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Summary

There are very few management guidelines in regard to the necessity of anticoagulation when treating varicose vein disease.

It is a general rule that pregnant and post-partum patients, patients with limited mobility, cancer, active superficial thrombophlebitis and deep vein thrombosis (DVT) not be treated.

However, there are some grey zones where treatment is most likely safe, especially if the patient is anticoagulated for the treatment.

Such patients include those with thrombophilias, a history of venous thromboembolism, history of extensive superficial thrombophlebitis, and those with chronic venous ulcers.

This presentation will propose my approach to anticoagulation based on available evidence at this time.

Keywords: *prophylaxis, anticoagulation, deep vein thrombosis, varicose vein disease.*

Résumé

Il existe très peu de règles directrices pour la gestion d'une anticoagulation préventive lors du traitement de la maladie variqueuse.
La règle générale proscrit le traitement de la maladie variqueuse chez les patientes enceintes ou en période postnatale ainsi que chez les patients à mobilité réduite et chez ceux atteints de thrombophlébite superficielle évolutive ou de thrombose veineuse profonde (TVP).
Cependant, il existe aussi des zones grises où ce traitement sera néanmoins sûr, surtout si les patients sont anticoagulés préventivement.
Cette catégorie de patients comprend ceux atteints de thrombophilie, ceux ayant des antécédents de thrombo-embolie veineuse ou de thrombophlébite superficielle étendue, ainsi que ceux atteints d'un ulcère veineux chronique.
Cette présentation propose une approche personnelle de la question de l'anticoagulation prophylactique sur la base des preuves disponibles actuelles.

Mots-clés : prophylaxie, anticoagulation, thrombose veineuse profonde, maladie variqueuse.

Introduction

Sclerotherapy and endovenous ablation are both treatments associated with less than 1% rate of venous thromboembolism.

This is comforting considering that recent studies have shown that both acquired and inherited coagulation disorders seem to be over-represented in patients with venous disease as opposed to population controls.

- **The prevalence of thrombophilia in people who have had DVT is about 50%** [1].
- **The prevalence of thrombophilia in people with uncomplicated varicose vein disease, and especially in those with chronic venous ulcers, approaches this rate.**
- **One study found that 75% of chronic venous ulcer cases and 66% of varicose vein case had at least one thrombophilia, and 44% of chronic venous ulcer cases had multiple thrombophilias** [2].

While the low risk of venous thromboembolism associated with sclerotherapy and endovenous ablation does not warrant anticoagulant prophylaxis for all patients undergoing treatment, we should stratify patient risk and tailor treatment to their individual risk to minimize adverse effects, both of anticoagulation and lack of prophylaxis.

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Patients presenting for treatment of venous insufficiency may have the following risk factors for venous thromboembolism:

1. Pregnant or recently post-partum
2. Known or occult malignancy
3. Limited mobility
4. Taking oral contraceptives or hormone replacement
5. Known hereditary thrombophilia and acquired thrombophilia
6. History of venous thromboembolism
7. Chronic venous ulcers
8. Spontaneous superficial venous thrombosis, especially those involving the upper portion of the GSV and those that occur in a vein that is not varicose.

In the first three categories, I do not use any therapeutic modality other than compression.

Clinical indications for prophylactic anticoagulation

However, in patients presenting with the remaining risk factors, I feel treatment can safely be done with the addition of prophylactic anticoagulation when clinically indicated.

The following table gives relative risks for first episode of venous thrombosis according to risk factors:

Risk factor	Relative risk
Factor V Leiden heterozygous	4-8
Factor V Leiden homozygous	24 -80
Prothrombin 20210A gene variant (Factor II mutation)	2-2.8
Antithrombin deficiency	5
Protein C deficiency	3.1-3.4
Protein S deficiency	2
Factor VIII elevation	2.6-4.8
Factor XI elevation	2.2
Hospitalization/immobilization	9-11
Pregnancy	4.2
Recent post-partum state	14
Surgery	6
Oral contraceptives/hormone replacement	2-4
Antiphospholipid antibodies	9
Malignancy	7
One or more first degree relative with history of idiopathic DVT	2

Data from Liem and Deloughery. Seminars in Vasc. Surg. 2008.

As shown above, the relative risk associated with oral contraceptives and hormone replacement is relatively low, at 2-4%.

I do not take patients off their hormones for venous treatment, as long as they understand their slightly increased risk of venous thromboembolism (VTE).

Anticoagulation for inherited and acquired thrombophilia

Inherited and acquired thrombophilias are present in 10-15% of the general population.

- **Heterozygous Factor V Leiden mutation, prothrombin 20210A gene mutation and high Factor level VIII level** are the most prevalent inherited thrombophilias but thankfully are associated with low relative risk of VTE.
- **Antiphospholipid syndrome (APS)** is the most common acquired thrombophilia and is associated with an increased incidence of spontaneous abortions and venous and arterial thrombosis.

To date, there are no prospective studies looking at the rate of VTE after sclerotherapy in patients with diagnosed thrombophilia vs. those without known thrombophilia.

Thus, we really don't have any guidelines to tell us whether or not to use prophylactic anticoagulation on patients with known thrombophilia presenting for treatment.

In my own practice, I do treat people with the low risk thrombophilias but do so using prophylactic anticoagulation.

I feel there is some support behind this in published literature.

Hamel-Desnos et al. published a retrospective study in 2003 where 56 patients with thrombophilia were treated by sclerotherapy [3].

The rate of DVT after sclerotherapy in patients with thrombophilia was found to be 9%, much higher than the rate found after treating the general population.

Secondly, it has been found that in those with thrombophilia, over 50% VTE events occur during high risk periods (ie. peri-operatively).

Patients that do not receive peri-operative prophylaxis are at twice the risk of developing VTE [4].

While sclerotherapy and endovenous ablation procedures are not considered high risk procedures, they are both treatments that involve direct damage to vein walls.

In 2009, *Hamel-Desnos et al.* also published a prospective multicentre study looking at the risk of thrombosis after sclerotherapy performed under thromboprophylaxis with either low molecular weight heparin or warfarin in patients with documented thrombophilia [5].

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They included only patients with the most prevalent forms of thrombophilia, these being factor V Leiden mutation, prothrombin 20210A (factor II) mutation, and high level of factor VIII or combinations of these.

They found that there were no episodes of DVT or pulmonary embolism in 199 sclerotherapy sessions involving 105 patients in the group treated with a single dose of nadroparin (a low molecular weight heparin) on the day of treatment, nor the group treated with warfarin continuously until four weeks after the last sclerotherapy session.

For lower risk thrombophilias, I would feel comfortable, given Hamel-Desnos' study, giving one dose of a low molecular weight heparin on the day of sclerotherapy, and with endovenous ablation, giving one dose of low molecular weight heparin 12 hours before the procedure followed by one dose per day for two days after the procedure.

For higher risk thrombophilias, I consult our hematologist for his direction on each individual case.

Anticoagulation for history of DVT

A history of deep vein clot or pulmonary embolism should always be elicited in the consultation process prior to treatment of venous insufficiency.

Patients with a history of DVT due to a transient risk factor like surgery have no increased risk of recurrent DVT and do not require prophylaxis for sclerotherapy or endovenous procedures [6].

My caveat to this rule is a history of DVT secondary to oral contraceptives where I do consider the use of prophylactic anticoagulation.

Generally healthy, non-obese, and at least moderately active women with no other risk factors for VTE under the age of 50 have only a slightly increased relative risk of VTE.

However, multiple risk factors for VTE can have a synergistic effect on their risk. For example, it has been found that patients who are heterozygous for factor V Leiden mutation and receiving oral contraceptives have a 35-fold increased risk of venous thromboembolism [7].

The thrombophilias with higher relative risk of VTE including antithrombin deficiency, protein C and S deficiency are also associated with a much higher incidence of first VTE with intake of oral contraceptives [8].

There are families in which the use of oral contraceptives is associated with a markedly increased risk of VTE compared with the general population in which thrombophilia testing has been negative. This may reflect an as yet unidentified thrombophilic defect.

A patient with a history of idiopathic DVT that is not associated with identifiable risk factors has a high risk of recurrent DVT even if they were treated with standard anticoagulation therapy for 3-6 months after their initial event.

Studies have shown a 21%-23% recurrence rate at 4-5 years and up to 40% at 10 years [4].

The verdict is out as to whether or not testing for thrombophilia is useful or cost effective after the first idiopathic DVT.

Observational studies show that patients who have had VTE and have thrombophilia are at most at a slightly increased risk for recurrence.

The most important risk factors for recurrent DVTs are idiopathic first event, cancer, proximal extension of DVT, and shorter duration of anticoagulation.

Given the high risk of recurrence of DVT, I generally will use prophylactic anticoagulation for patients before sclerotherapy and definitely before endovenous ablation with a history of idiopathic DVT.

Anticoagulation for history of superficial vein thrombosis

A history of superficial vein thrombosis (SVT) alerts me to a situation where prophylactic anticoagulation prior to vein treatment may be prudent. Between 60-80% of SVT are located in the greater saphenous vein (GSV) [9].

DVT may occur due to propagation of SVT up the GSV or through a perforator.

Alternatively, SVT may be seen concurrently with DVT without being the cause of the DVT. In either case, there is a strong association of SVT with DVT.

Between 6-36% of SVT patients have DVT on echo and 25-33% have concomitant pulmonary embolism.

The patients at highest risk of DVT are those with extensive (more than 5cm) SVT above the knee. The closer the clot is to the saphenofemoral junction, the higher the risk of DVT [10].

There is a strong correlation between SVT and thrombophilic states.

Thrombophilias are more common when SVT's occur in non-varicosed segments of vein and in patients where the SVT have propagated to the deep vein.

Patients with a history of SVT and hypercoagulable state are much more likely to develop new DVT's on prospective follow up [11].

I use prophylactic anticoagulation for anyone who has a history of extensive superficial phlebitis above the knee.

Unfortunately, that information is rarely available during pre-treatment consultation. Superficial phlebitis is generally treated as a benign entity, with little investigation or treatment other than symptomatic treatment.

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However, all cases of superficial phlebitis other than a mildly symptomatic phlebitis involving a small segment of a varicose vein should be investigated by duplex ultrasound to look for extent of involvement of the GSV, proximity to the saphenofemoral junction, and concomitant involvement of the deep venous system.

With any vein practice, you will see cases of spontaneous superficial phlebitis.

After a review of available literature at this time [12]**, my management of patients with SVT are as follows:**

1	Lower leg SVT and those with SVT limited to a varix – symptomatic treatment including graduated compression, ambulation, warm soaks, NSAID. These people have a 4% risk of developing DVT
2	SVT involving the GSV below the upper third of the thigh – conservative treatment as above, however, the clot needs to be monitored by duplex ultrasound for extension
3	SVT involving the GSV greater than 3 cm from the SFJ – prophylactic dose anticoagulation for 4 weeks
4	SVT involving the GSV within 1 cm of the SFJ – therapeutic anticoagulation for 4-6 wks

Anticoagulation in cases with chronic venous ulceration

As mentioned previously, there is a high association of chronic venous ulcers (CVU) and thrombophilia. Studies have shown that 1/3 to 2/3 of patients with CVU have at least 1 inherited thrombophilia [2, 13, 14].

The presence of an inherited thrombophilia should especially be suspected in the 10-12% of CVU patients whose ulcers recur or do not heal.

One study has found that in 88% of these cases, patients have an inherited thrombophilia [1].

Factor V Leiden mutation is the most frequent inherited thrombophilia risk factor in these patients.

While the number and type of inherited defects have no significant impact on the size or location of ulcer, they do carry an increased risk of recurrent DVT and recurrent CVU.

Many patients with CVU will have a history of DVT and post-thrombotic syndrome and about 5% – 8% of patients with DVT will develop CVU's [1].

However, there are also patients without any history or clinical signs of DVT that present with CVU's. These people are assumed to have developed CVU as a result of primary varicose vein disease. The mechanism of ulcer formation is not completely understood, but is generally thought to be due to venous hypertension causing leaky capillaries and activation of white blood cells and inflammatory mediators.

However, it is not possible to predict which patients with varicose vein disease will develop the skin thinning and fibrosis associated with chronic venous insufficiency leading to CVU, while others with similarly dilated varicose veins appear to have healthy skin.

It could be that there is another mechanism involved in the pathogenesis of venous ulceration.

It can be hypothesized that those people without a history of DVT that develop a CVU may have an underlying thrombophilia that predisposes them to distal macrovascular and/or microvascular thrombosis that is under the threshold of clinical detection, even by duplex examination.

This brings up several interesting management options for patients with CVU's – can long term anticoagulation promote the healing and prevent recurrence of venous ulceration?

Should we testing people with simple varicose vein disease for thrombophilia to prevent progression to chronic skin changes and CVU?

Should patients with DVT in association with thrombophilia be offered more prolonged anticoagulation to prevent the development of CVU?

There are some small case series using anticoagulation as treatment for CVU refractory to other treatments.

However, there are no prospective randomized controlled trials to evaluate the use of anticoagulation to prevent progression of venous disease to chronic venous ulceration or as a treatment modality for CVU's.

Conclusion
A note on testing for thrombophilias

It should be evident that a complete history is important prior to treatment for venous insufficiency in order to be able to assess a patient's risk of treatment.

The important risk factors include a history of idiopathic VTE, extensive superficial thrombophlebitis, healed or active venous ulcer, recurrent pregnancy loss, autoimmune rheumatic disease, a positive family history of idiopathic DVT, and a family history of thrombophilia.

The question frequently comes up as to whether or not we should be testing these patients for thrombophilia prior to vein treatment.

Thrombophilia testing panel usually includes antithrombin, protein C and S levels, Factor V Leiden and prothrombin G20120A mutations.

In addition, laboratory features of acquired thrombophilic antiphospholipid antibody syndrome - lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoproten 1 antibodies are usually included.

Elevated levels of several coagulation factors including factors VIII, IX, and XI can also increase the risk of VTE.

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In the case of a history of idiopathic first VTE and extensive superficial thrombophlebitis, routine testing for thrombophilia is not supported at this time. It has not been shown to be helpful in predicting risk of recurrence, deciding the duration of initial treatment, or determining the need for long-term prophylactic anticoagulation [15].

As discussed earlier, I would put these people on prophylactic anticoagulation prior to vein treatment in any case thus testing for thrombophilia will really not change my management.

Whether or not thrombophilia testing should be done for patients with chronic venous ulcers is not known at this time as this association is a fairly new finding.

Further studies may show that long term anticoagulation of difficult to treat or recurrent ulcers as an effective treatment adjunct whether or not the patient tests positive for a thrombophilia.

In the case of a patient with a history or recurrent pregnancy loss (one or more loss of pregnancy after 10 wks gestation or 3 or more consecutive spontaneous abortions under 10 weeks gestation) and/or autoimmune or rheumatic diseases like systemic lupus erythematosis, Sjogren's or rheumatoid arthritis,

I often ask the referring doctor for any history of testing for inherited thrombophilias and antiphospholipid antibodies.

If they have never been looked for and the patient has no history of venous or arterial thrombosis or other associated manifestations of antiphospholipid antibody syndrome, I will generally proceed with venous therapy without anticoagulation.

If I have concerns, I will send them to a hematologist for assessment prior to treatment.

A positive family history for VTE is a poor predictor for the presence of thrombophilia, thus testing an asymptomatic family member prior to vein treatment cannot be justified [8].

There is no conclusive evidence that testing for heterozygous Factor V Leiden or prothrombin G20120A in asymptomatic family members is cost effective.

However, there is evidence that testing for antithrombin, protein C and S deficiency, and homozygous Factor V Leiden with a positive family history is beneficial for the asymptomatic patient in terms of planning for pregnancy, use of oral contraceptives or hormone replacement, and requirement for prophylaxis prior to surgery, with trauma, and by extrapolation, vein treatment. In these cases, I consult a hematologist for his current advice.

It should be pointed out that there are downsides to testing for thrombophilia.

The tests are expensive, a positive result could potentially have a negative psychologic impact to the patient, and a positive result may make it difficult for the patient to get life or disability insurance, even if they are asymptomatic.

It is important as phlebologists to be alerted to conditions that may place the patient at increased risk of complications.

It is an area where a good relationship with a hematologist will help guide us through this ever evolving aspect of venous treatment.

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