Anticoagulation:
How Long to Treat?

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Venous thromboembolism (VTE) is hardly ever "treated" in the sense that the clot is removed and the integrity of the veins restored. The initial anticoagulation is aimed at halting the growth of the thrombus and embolization. After the first few weeks, the role of the anticoagulation gradually becomes that of preventing new VTE. Treatment with thrombolysis or surgical thrombectomy is reserved for a few severe cases with threatened limb circulation.

Meet Walter

Walter, a 46-year-old male, presents with a painful calf, leg swelling but no shortness of breath, 3 weeks after a pelvic fracture he suffered in a motorcycle accident.

Ultrasound of his leg veins demonstrates thrombosis in the trifurcation area of the calf veins but more proximal veins are fully compressible.

Eight years later, Walter presents with contralateral leg swelling, pain in the entire leg and bluish discolouration 4 days after a trans-Pacific flight in economy class. Ultrasound examination confirms thrombosis extending from the trifurcation to the common femoral vein.

There is no family history of venous thromboembolism (VTE). Walter is otherwise healthy, not overweight and a non-smoker.

Risk of recurrence

Over the course of eight years, about 30% of patients with VTE will have a second event.[1] The long-term complications of VTE are venous insufficiency (post-thrombotic syndrome) and pulmonary hypertension. Approximately half of the patients with deep vein thrombosis (DVT) will, after a few years, have mild venous insufficiency with reticular veins, varicose veins and edema. Some of the patients develop skin abnormalities, such as hyperpigmentation, lipodermatosclerosis, atrophie blanche and in a few percent, venous ulcers.[2] Repeated events of DVT in the same leg increase the risk of the post-thrombotic syndrome and with recurrent pulmonary embolism, the risk of pulmonary hypertension is increased. Patients with symptoms of DVT alone will in about 75% of recurrences again have DVT and patients with symptoms of pulmonary embolism alone will mostly recur with pulmonary embolism. The second event of DVT is at least as likely to occur in the contralateral leg as in the leg of the first event.

Risk factors for recurrence

The factors that influence the risk of recurrence can be categorized as related to the thrombus, to demographics, to concomitant diseases and to thrombophilic abnormalities (Table 1). Patients with unprovoked VTE have a 50% higher risk of recurrence than those with an event provoked by a removable risk factor. Those with proximal DVT or pulmonary embolism have the same magnitude of increased risk compared to patients with only calf vein thrombosis. During

Table 1

Risk factors for recurrent VTE

Thrombus characteristics
- Precipitating risk factor unknown or permanent
- Location proximal leg veins or pulmonary embolism
- More than 1 event

Demography
- Older age
- Male sex

Concomitant disorders
- Cancer, including myeloproliferative disorders
- Paresis
- Immobility
- Obesity
- Chronic inflammatory disorders:
  - Systemic lupus erythematosus
  - Inflammatory bowel disease
- Paroxysmal nocturnal hematuria
- Nephrotic syndrome
- Homocysteinuria/-emia
- Medications (estrogens, steroids, chemotherapy, hematopoietics)

Thrombophilic defects
- Deficiency of natural inhibitors (antithrombin, protein C, protein S)
- Procoagulant mutations (Factor V Leiden, prothrombin mutation)
- Antiphospholipid syndrome (lupus anticoagulant, antibodies against cardiolipin and/or β2-glycoprotein I)
- High level of factor VIII

FAQ

How long should the patient be treated for his first event and with what?

For 6 weeks, either with warfarin, requiring frequent monitoring, or with low-molecular-weight heparin (LMWH) (enoxaparin 40-60 mg or dalteparin 5,000-7,500 IU q.d. subcutaneously).

the first year, the patients with pulmonary embolism have an even higher risk of recurrence, but subsequently the cumulative risk becomes similar in patients with proximal DVT.

The lowest risk of recurrence is among patients with distal DVT, triggered by a removable risk factor such as surgery or trauma, corresponding to 8% during six years. Anticoagulation for six weeks is sufficient in this subset and low-molecular-weight heparin (LMWH) for this entire period may be a good alternative to vitamin K antagonists in some patients since laboratory monitoring is unnecessary. At the other end are patients with active cancer with reported rates amounting to 27 per 100 patient years in spite of secondary prophylaxis.[3] Secondary prophylaxis should continue as long as there is active cancer disease, for the first three to six months with LMWH, thereafter with warfarin. However, most patients fall somewhere between these extremes and other factors need to be taken into account.

Risk factors for bleeding

The decision on the duration of secondary prophylaxis must always be balanced between risk factors for recurrent thrombosis without continued anticoagulation and for bleeding complications on treatment. The main risk factors for bleeding, assuming good management of the complicated anticoagulant treatment, are old age, concomitant antiplatelet agents, renal failure, hepatic failure, anemia, cancer and history of bleeding—particularly GI.[4]

In patients > 80-years-of-age, the risk of bleeding is a greater concern than the risk of recurrent VTE. Partly contributing to this is an increasing tendency to fall and poor eating habits. Combination of anticoagulation with any dose of ASA should be avoided.

Table 2

Suggestions for duration of secondary prophylaxis after VTE according to risk factors for recurrence (with reductions in case of bleeding risk)

Setting	Duration of anticoagulation
Thrombophilic defect not known/not found	
First DVT, distal, temporary risk factor	6 weeks
First DVT, distal with unknown/permanent risk factor or proximal DVT	6 months (3 months)
First pulmonary embolism	
First event, life-threatening thromboembolism	12 months (6 months)
First event, active cancer	Until no active cancer
Second event, contralateral DVT	As for first DVT
Second event, ipsilateral DVT or pulmonary embolism	≥ 12 months (6-12 months)
Third (or more) event	Indefinitely
Thrombophilic defect known	
Antithrombin deficiency	Indefinitely
Homozygous for thrombophilic defect*	Indefinitely
Double heterozygous for defects	Indefinitely
Life-threatening event with any defect	Indefinitely
Protein C- or protein S- deficiency	≥ 12 months (6 months)
Lupus anticoagulant/cardiolipin antibodies	Several years
High level of factor VIII (= 2.3 IU/mL)	≥ 6 months (3-6 months)
Heterozygous for Factor V Leiden mutation	As without defect
Heterozygous for prothrombin mutation	As without defect

DVT: Deep venous thrombosis

* Possibly with exception for the prothrombin mutation

Compliance and patient preferences

For patients assessed as requiring long-term anticoagulation, the definitive decision on the duration cannot be made at the initial stage. The treatment has to be evaluated after three to six months. In case of poor compliance with few INRs within the therapeutic range, the treatment has low efficacy and high risk of bleeding and should probably be discontinued unless significant improvements in the management can be achieved. Finally, the preferences of the patient have to be weighed into the decision on duration.

Over the course of eight years, about 30% of patients with VTE will have a second event.

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D-dimer as decision support?

The fibrin split product D-dimer has recently been studied as a tool to predict risk of recurrence. It is positive during anticoagulant therapy in about 15% of patients. That indicates continuing activation of the coagulation system and a high risk of recurrence if treatment is stopped. In the remaining 85%, anticoagulation may be held for four weeks, at which point a new D-dimer test is performed. In 40% of these patients the test will revert to positive and if anticoagulation is not resumed, the risk of recurrence is 15% during 1.4 years.[5] Patients with a negative D-dimer test after one month have a risk of recurrence without resumed anticoagulation of 6% during the same follow-up.[5] The D-dimer test alone is not a sufficient basis for decision and further studies are performed to optimize its use.

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Take-home message

The decision on when to stop anticoagulation after VTE has to take into account risks for recurrence and for bleeding, compliance and patient preferences.

References

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