Venous thromboembolism: risk of recurrence and long-term anticoagulation

Recurrence following initial treatment for venous thromboembolism is a significant cause of morbidity and mortality. Balancing the risks of recurrence against the risks of long-term anticoagulation is essential for optimizing patient outcomes.

Venous thromboembolism is a serious cause of morbidity and mortality and has an incidence of 1–2/1000 per year (Agnelli and Becatti, 2013). Some strategies avoid diagnosing distal deep vein thrombosis; when it is sought and diagnosed it is usually treated for 3 months only. Proximal deep vein thrombosis and pulmonary embolism that is provoked by a transient risk factor should also be treated with a 3-month course of anticoagulation, as there is a low risk of recurrence. However, unprovoked venous thromboembolism carries a higher risk of recurrence; up to 7.4% per year compared with 3.3% per year in provoked events (Iorio et al, 2010).

Case Report 1

A 60-year-old man had an unprovoked proximal deep vein thrombosis 3 months ago and has been treated with warfarin for 3 months. At presentation he was investigated with a chest radiograph, blood tests, urinalysis and computed tomography of the abdomen and pelvis which found no evidence of a malignancy or an anatomical abnormality which may have precipitated the clot. He was a heavy drinker and his international normalized ratio had only been in range 50% of the time (fluctuating above and below). After stopping warfarin for a month, his D-dimer level remained elevated. Should he stop taking warfarin after 3 months? Are there any other tests to consider?

Case Report 2

A 30-year-old woman has been treated with rivaroxaban for 3 months following a proximal deep vein thrombosis. At diagnosis she had a normal chest radiograph, blood tests and urinalysis along with a negative pregnancy test. No anatomical anomaly was found that could account for her deep vein thrombosis and it was presumed to be unprovoked. She has regular heavy bleeding from her nose since starting anticoagulation. She has no other medical problems or family history of venous thromboembolism and is not on any medications. She has an elevated D-dimer level. Is long-term anticoagulation indicated? What would be the best approach to her epistaxis? Should she be tested for hereditary thrombophilias?

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Recurrence is particularly low if venous thromboembolism follows surgery. Which patients with unprovoked thrombosis should be offered long-term anticoagulation beyond the initial 3 months depends on individual risk of recurrence, risk of bleeding and personal preference. The decisions discussed here refer to patients with pulmonary embolism and/or lower limb proximal deep vein thrombosis. This article addresses how doctors can predict the risk of venous thromboembolism recurrence, bleeding risk and decide on long-term anticoagulation. Examples of challenging cases where the risks and benefits of long-term anticoagulation must be balanced are outlined in *Case reports 1* and *2*.

Making decisions about long-term anticoagulation

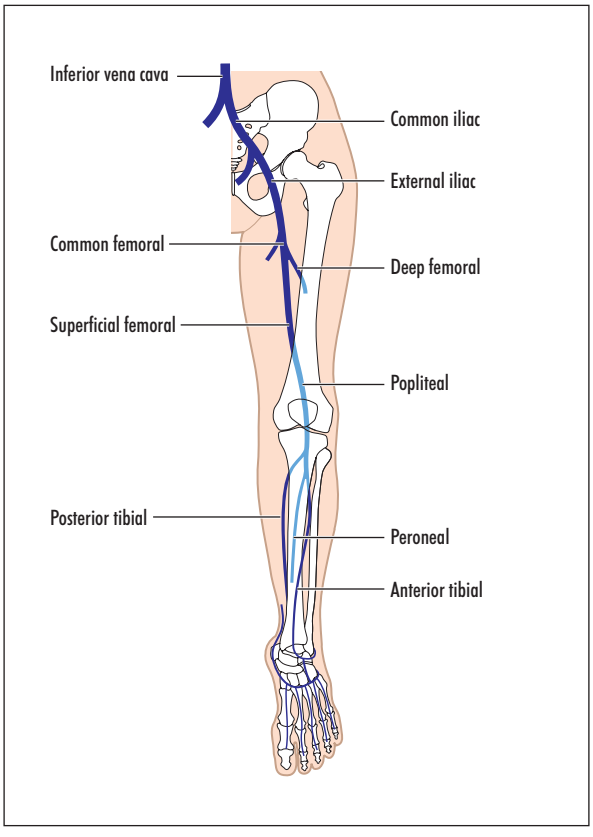
The goal of treatment of deep vein thrombosis is to alleviate symptoms like pain and swelling, prevent pulmonary embolism, reduce the risk of post-thrombotic syndrome and prevent venous thromboembolism recurrences. It is well established that anticoagulation for unprovoked proximal deep vein thrombosis (*Figure 1*) or pulmonary embolism needs to be given for at least 3 months (*Figure 2*). There are differences in the treatment of provoked and unprovoked venous thromboembolism and differentiating between them is important (*Table 1*).

On average patients who have had an unprovoked deep vein thrombosis have a 5% risk per year of recurrence with a 5% case fatality (Palareti et al, 1996; Linkins et al, 2003; Carrier et al, 2010). This equates to a 0.25% (1/400) risk of a fatal venous thromboembolism per year. After a year of anticoagulation, the risk of a fatal bleed is also approximately 0.25% (1/400) (Douketis et al, 2007; Carrier et al, 2010). Consequently any risk factors that suggest the risk of recurrence could be higher than 5% tip the balance in favour of long-term anticoagulation. Risk factors which suggest the risk of recurrence is less than 5% indicate that anticoagulation should be stopped.

Long-term oral anticoagulation has a significant impact on a patient's lifestyle. Patients taking vitamin K antagonists are advised to avoid activities which may cause injury like contact sports and also to avoid medications and herbal remedies that could increase the risk of

bleeding. Patients also need to keep appointments for blood tests to monitor the anticoagulation effect, consume little or no alcohol and have consistent dietary habits. With the exception of an increased bleeding risk, warfarin is associated with few side effects. The novel oral anticoagulants may cause dyspepsia or nausea and the impact of these symptoms on quality of life should also be considered. Overall, the novel oral anticoagulants are likely to be more convenient for patients, as regular blood test monitoring is not required. However, there are fewer long-term data on the effects of the novel oral anticoagulants than warfarin. For patients who choose to continue taking warfarin, consideration can be given to monitoring their anticoagulation with point of care tests such as CoaguChek (which involve a finger prick much like capillary glucose testing for diabetes) rather than venepuncture.

Figure 1. Venous system of the lower limb. Distal deep vein thrombosis = thrombosis in veins below the popliteal vein; proximal deep vein thrombosis = thrombosis in veins down to and including the popliteal vein. From Douketis (2014).



There is emerging evidence from two randomized placebo-controlled trials (WARFASA and ASPIRE) that aspirin may be of benefit in preventing recurrence of venous thromboembolism. Both of these trials assessed patients who had completed 3 months of anticoagulation following a venous thromboembolism and randomized them to aspirin or placebo. The pooled recurrence rate for those taking placebo was 7.5% per year compared to 5.1% per year for those taking aspirin, a relative risk reduction of 32%. This compares unfavourably with anticoagulants which reduce the risk of recurrence by more than 80%. An advantage of aspirin is that the risk of bleeding with aspirin (0.5%) was small and comparable to placebo (0.4%). These trials did not compare aspirin directly with anticoagulation (Simes et al, 2014). Aspirin may be of benefit for a selected group of patients who are not considered to be suitable for anticoagulation.

Studies have shown that:

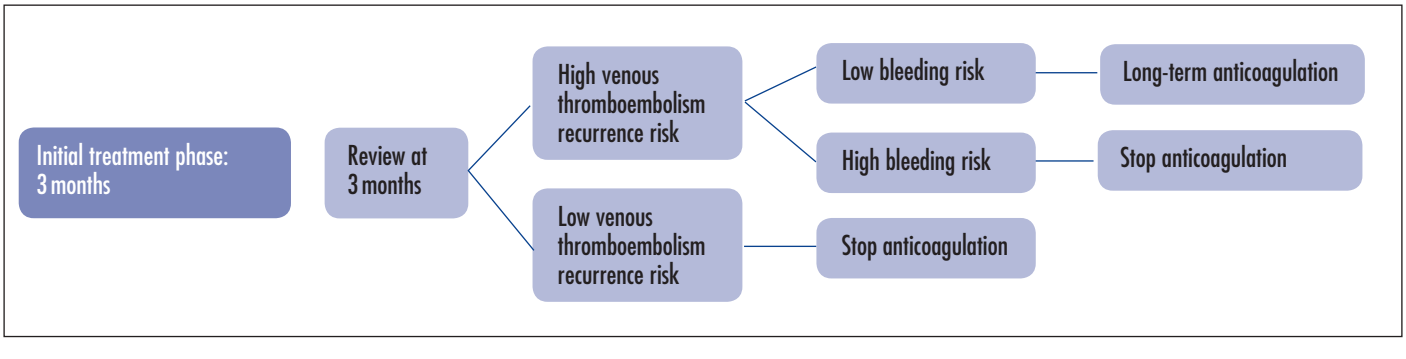
- Patients who initially present with a pulmonary embolism are more likely to have another pulmonary embolism, if they have another venous thromboembolism, compared with patients who initially had a deep vein thrombosis (Murin et al, 2002; Baglin et al, 2010a). The risk of fatal pulmonary embolism is 2–3-fold higher after an episode of pulmonary embolism than after an episode of deep vein thrombosis (Douketis et al, 1998; Carrier et al, 2010).

Table 1. Provoked *vs* unprovoked venous thromboembolism

Provoked: deep vein thrombosis or pulmonary embolism in a patient with an antecedent (within 3 months) and transient major clinical risk factor for venous thromboembolism, e.g. surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium, or in a patient who is having hormonal therapy (oral contraceptive or hormone replacement therapy)*
Unprovoked: no antecedent major clinical risk factor for venous thromboembolism

From National Institute for Health and Care Excellence (2012). *Travel: duration of travel needs to be taken into account but is generally considered a weak provoking factor

Figure 2. Decisions on long-term anticoagulation after first unprovoked venous thromboembolism.



- Men have a higher risk of recurrence (McRae et al, 2006)
- Venous thromboembolism recurrence after stopping anticoagulation seems to be highest in the first 2–3 months. The annual risk of recurrence thereafter was 5–10% in a study that followed patients for up to 24 months (Boutitie et al, 2011).
- Anticoagulation reduces venous thromboembolism recurrence but the risk of bleeding remains significant. The rate of major bleeding on anticoagulation for venous thromboembolism has been shown to be 2.06% during the first 3 months of treatment and 2.74% beyond the initial 3-month period (Linkins et al, 2003).
- Raised D-dimer level 30 days after discontinuation of anticoagulation predicted a higher risk of venous thromboembolism recurrence (Verhovsek et al, 2008; Douketis et al, 2010). Palareti et al (2006) followed up patients with raised D-dimer levels, who had previous venous thromboembolism, 1 month after stopping anticoagulation (follow up period 9–18 months). The venous thromboembolism recurrence rate was 15% for those who stopped anticoagulation, whereas it was significantly lower at 2.9% for those who resumed anticoagulation.
- Patients with venous thromboembolism and cancer have a high rate of venous thromboembolism recurrence. They will be discussed in more detail later.
- Patients with antiphospholipid syndrome have a higher risk of venous thromboembolism recurrence and are usually offered long-term anticoagulation.

Therefore, the decision to extend the duration of treatment should be individualized and the benefits of venous thromboembolism prevention weighed against the risk of bleeding on long-term anticoagulation. Patients should be ideally reviewed after 3 months of anticoagulation to discuss long-term management. It is important to note that the above data on bleeding risk are based on studies conducted in patients taking oral vitamin K antagonists. The bleeding risk with the new oral anticoagulants is known to be lower.

Table 2. DASH score

Variable	D-dimer: raised off anticoagulation	Age <50 years	Sex: male	Hormone therapy: at time of VTE diagnosis
Score	+2	+1	+1	-2

VTE = venous thromboembolism. From Tosetto et al (2012)

Table 3. Stratification of results of DASH score to determine whether benefits of long-term anticoagulation outweigh risks

DASH score	≤ 1	2	≥3
Annual risk of venous thromboembolism recurrence	3.1%	6.4%	12.3%

Clinical decision tools

There are several putative clinical decision tools to try to help predict risk of venous thromboembolism recurrence in the individual patient but none can be recommended as they have not yet been validated prospectively. The tools available are the DASH score (*Tables 2* and *3*), the Vienna prediction model and the rule 'Men Continue and HERDOO2'.

The DASH score

The DASH score is derived from a study of 1818 patients with first unprovoked venous thromboembolism treated with vitamin K antagonists for at least 3 months. The variables associated with increased risk of venous thromboembolism recurrence were male sex, age <50 years and raised D-dimer level after stopping anticoagulation. Hormonal therapy in women was associated with a reduced risk and in any event such thromboses would be regarded as provoked. A scoring system was proposed which predicted risk of venous thromboembolism recurrence (DASH score) (Tosetto et al, 2012).

The Vienna prediction model

A total of 929 patients with first unprovoked venous thromboembolism were assessed. This was the only study to include patients with distal deep vein thrombosis who are not normally given long-term anticoagulation. Male sex, proximal deep vein thrombosis, pulmonary embolism and raised D-dimer levels when off oral vitamin K antagonists were associated with a high risk of venous thromboembolism recurrence (Eichinger et al, 2010).

Men Continue and HERDOO2

Rodger et al (2008) identified patients with low risk (<3% annual risk) of venous thromboembolism recurrence after the first unprovoked event. These patients can be treated for 3 months only with no benefit of extended treatment beyond this period. Risk factors for venous thromboembolism recurrence were male sex, women with two or more of the following risk factors: evidence of post-thrombotic syndrome (hyperpigmentation of the legs, oedema or redness of either leg), a D-dimer level >250 µg/litre (tested when the patient was on warfarin), obesity (body mass index >30 kg/m^2, and older age (>65 years). This resulted in a simple mnemonic summarizing patients' criteria which warrant long-term anticoagulation so Men continue and HERDOO2 (all men continue anticoagulation long term; women with two or more of the following continue anticoagulation: post-thrombotic signs (Hyper-pigmentation, oEdema or Redness in either leg); VIDAS D-dimer >250 µg/litre; Obesity (body mass index >30 kg/m^2); Older age – 65 years or more)).

In all the studies, male sex and a raised D-dimer emerge as consistent, strong predictors of venous thromboembolism recurrence.

The role of the D-dimer test

D-dimer is a surrogate marker of fibrin degradation which takes place whenever a clot is formed. The fibrinolytic system is activated in many conditions leading to a raised D-dimer level, so choosing the D-dimer as a single test to decide about long-term anticoagulation has obvious limitations.

There are different laboratory methods to quantify the D-dimer level and subsequently different reporting units may be used. The reader should be familiar with what constitutes a raised or normal D-dimer level in their lab. Most quantitative tests are reported in μg/litre fibrinogen equivalent units. Many point-of-care tests using a whole blood sample are becoming widely available. As long as the test is validated, it can be used as an equivalent to the traditional D-dimer test performed on a citrated blood sample.

The D-dimer level should be interpreted with caution; it increases with age, infection, inflammation, post-surgery, pregnancy and puerperium, trauma, haematoma, cancer, cirrhosis, thrombolytic therapy and disseminated intravascular coagulation. The population discussed here are outpatients with no other medical conditions complicating the interpretation of the D-dimer test. Rheumatoid factor interferes with the latex agglutination tests and gives falsely high values. Anticoagulation may lower the D-dimer level.

Counselling the patient about long-term risks and benefits of long-term anticoagulation should take into account what risk is acceptable to the patient when he/she makes his/her decision:

- An annual risk of venous thromboembolism recurrence <5% would normally be in favour of stopping anticoagulation
- An annual risk of venous thromboembolism recurrence >5% would normally be in favour of continuing anticoagulation unless the bleeding risk is high.

Bleeding risk

Bleeding risk is less well studied than the risk of venous thromboembolism recurrence in patients with unprovoked venous thromboembolism. However, factors consistently associated with increased bleeding risk include: recent major bleeding, age >75 years, anaemia, creatinine >106 μmol/litre, cancer and pulmonary embolism at baseline (Ruíz-Giménez et al, 2008).

Patients' susceptibility to bleeding is likely to manifest itself in the early phases of treatment, i.e. in the first 3 months (Linkins et al, 2003).

Clinical judgment is paramount in decision making as other factors such as poor anticoagulant control, frequent falls, alcohol abuse, thrombocytopenia and concomitant antiplatelet therapy further increase the risk of bleeding.

Cancer and venous thromboembolism

Patients with cancer have a high risk of venous thrombo-embolism with higher rates of recurrence and inferior survival. Patients with cancer have a 4–7-fold higher incidence of venous thromboembolism than patients without cancer (Heit et al, 2000). Venous thromboembolism is the second most common cause of death in this population (Khorana et al, 2007). Patients with metastatic disease have a much higher rate of venous thromboembolism compared to localized disease (Chew et al, 2006). Chemotherapy and hospitalization further increase the risk of venous thromboembolism.

National Institute for Health and Care Excellence (2012) guidelines recommend investigating all patients with an unprovoked venous thromboembolism with a chest radiograph, blood tests (full blood count, liver function tests and calcium) and urinalysis to check for evidence of cancer. For patients aged over 40 years with a first unprovoked venous thromboembolism, consideration can be given to computed tomography of the abdomen and pelvis to look for evidence of malignancy.

Treatment for cancer-associated venous thromboembolism should be with low molecular weight heparin for 6 months. This recommendation is based on the CLOT trial which demonstrated that dalteparin 200 IU/kg subcutaneously once daily for the first month followed by 75–83% of the full dose (approximately 150 IU/kg) for 5 months reduces the rate of venous thromboembolism recurrence compared with warfarin with a target international normalized ratio 2–3 (Lee et al, 2003). Other low molecular weight heparins can be used as well but prescribers should consult the product specification for dosing regimens (National Institute for Health and Care Excellence, 2012).

If the patient still has active cancer beyond this 6-month period, it would be advisable to discuss the risk of venous thromboembolism recurrence and consider continuing some form of anticoagulation.

Thrombophilia

Testing for thrombophilia in practice does not often change management. Although thrombophilia increases the risk of a first thrombosis in comparison to the general population, finding a thrombophilia in a patient who already had venous thromboembolism does not modify the risk of recurrence sufficiently to alter management (Baglin et al, 2010b). If thrombophilia testing is performed, the recommended time is at the 3-month review after a venous thromboembolism, as the presence or absence of heritable thrombophilia does not alter initial management. Thrombophilia testing should ideally be performed when the patient is off anticoagulation as anticoagulants may interfere with the assays.

When a thrombophilia is detected, there is considerable uncertainty about how to interpret the results. Mild, common thrombophilias such as heterozygosity for factor V Leiden or prothrombin G20210A do not convey a venous thromboembolism recurrence risk of significant

magnitude to alter decisions about long-term anticoagulation. Testing for rare, higher-risk thrombophilias such as deficiencies in antithrombin, protein C or protein S, may be of benefit in some high-risk families. However, the evidence to recommend any change in management is limited (Baglin et al, 2010b).

By contrast to heritable thrombophilia, antiphospholipid syndrome (an acquired thrombophilia) is associated with an increase in venous thromboembolism recurrence, although perhaps not by as much as previously thought (Garcia et al, 2013). Testing for antiphospholipid syndrome should be considered for patients who may be stopping anticoagulation after the initial 3 months of treatment for unprovoked venous thromboembolism (Keeling et al, 2012). This is reflected in National Institute for Health and Care Excellence guidelines (*Table 4*).

It is worth remembering that testing for thrombophilia should ideally be carried out off anticoagulation after completing the initial period of treatment. Testing at diagnosis in the acute phase or while receiving anti-coagulation will not affect management and could give misleading results. Tests for antiphospholipid syndrome can give false positive results in patients with cancer or in the acute phase. Warfarin reduces protein C and protein S levels which makes the results difficult to interpret.

Table 4. National Institute for Health and Care Excellence guidelines on the management of venous thromboembolic diseases and the role of thrombophilia testing

Consider testing for hereditary thrombophilia in patients who have had unprovoked deep vein thrombosis or pulmonary embolism and who have a first-degree relative who has had deep vein thrombosis or pulmonary embolism if it is planned to stop anticoagulation treatment
Consider testing for antiphospholipid antibodies in patients who have had unprovoked deep vein thrombosis or pulmonary embolism if it is planned to stop anticoagulation treatment

From National Institute for Health and Care Excellence (2012)

Case Report 1: suggested management

Using the DASH score, this patient has two risk factors for recurrence of thrombosis: he is male and he has an elevated D-dimer level after a month off treatment. This gives a 12.3% risk of venous thromboembolism recurrence per year, which is approximately a 0.615% annual risk of venous thromboembolism-related mortality. He has two risk factors for bleeding: heavy alcohol intake and a labile international normalized ratio (<60% time in therapeutic range), and his risk of a fatal haemorrhage is likely to be in excess of 0.25% per year.

As the risk of recurrence is high, long-term anticoagulation should be considered despite the increased risk of bleeding. However, it will be important to consider methods for optimizing this patient's international normalized ratio control. This may involve counselling, consideration of low dose vitamin K as a dietary supplement, or consideration of an alternate agent. The novel oral anticoagulants have short half-lives compared to vitamin K antagonists such as warfarin, and for non-compliant patients may result in sub-therapeutic anticoagulation if they are not taken regularly. Decisions should be taken with the patient to optimize concordance with treatment and to find the best solution for the individual.

Discussion of case reports

In both of these cases, a careful balance must be found between the risks and benefits of anticoagulation. This can be used to guide discussion with patients about their treatment taking into account side effects and impact on their quality of life.

Conclusions

Following unprovoked venous thromboembolism, long-term anticoagulation will be favoured in males, those with raised D-dimer levels after completing anticoagulation and those whose initial event was a symptomatic pulmonary embolism. Patient preference is an important determining factor. Annual reviews to determine the risk–benefit ratio of continuing anticoagulation are recommended. BJHM

Figure 1 *is reproduced from Douketis (2014) by kind permission of Merck Manuals.*

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Case Report 2: suggested management

Using the DASH score, this patient has two risk factors for recurrence of thrombosis: she is aged <50 years and has an elevated D-dimer level after a month off treatment. This gives a 12.3% risk of venous thromboembolism recurrence per year, which would justify long-term anticoagulation. Although the scenario states she is not taking any medications, it is important to check whether she is taking the oral contraceptive pill, as this is a significant provoking risk factor and would reduce the risk of recurrence to 3.1% per year according to the DASH score, which would not justify the risks of long-term anticoagulation. This patient does not have any symptoms consistent with a malignancy and is aged under 40 years so a computed tomography scan of her abdomen and pelvis is not recommended. This can be considered for patients aged over 40 years.

This patient is young and if placed on long-term anticoagulation will be committed to this for many decades. Great care must be taken when weighing up whether she should continue to take anticoagulation and the risk will need to be assessed as she ages.

For a patient who needs to continue long-term anticoagulation but who has recurrent bleeding, a multidisciplinary approach is necessary. An opinion from an ear, nose and throat surgeon on the cause of the bleeding and the value of nasal cautery would be advocated in this case. The risks of venous thromboembolism recurrence are high enough to justify ongoing anticoagulation but care must be taken to address the risk of bleeding, as if this remains high then the risks of anticoagulation may start to outweigh the benefits.

This patient does not have a family history of venous thromboembolism, so thrombophilia testing is not indicated.

KEY POINTS

- Recurrence is common after a first unprovoked venous thromboembolism.
- After 3 months of anticoagulation following diagnosis of a venous thromboembolism, the need to stop anticoagulation or to continue it long term should be assessed.
- The risks of a fatal recurrence of venous thromboembolism must be balanced against the risk of fatal bleeding from long-term anticoagulation.
- Thrombophilia testing is a poor predictor of recurrent venous thromboembolism and is not routinely advocated.
- Measuring the D-dimer off anticoagulation is a useful tool for stratifying risk of venous thromboembolism recurrence.
- The use of a risk prediction tool such as the DASH score in conjunction with an assessment of bleeding risk is valuable in balancing the risks and benefits of long-term anticoagulation.