Duration of anticoagulation: the decision-making process

Introduction

Venous thromboembolism, which encompasses deep vein thrombosis and pulmonary embolism, is a common, treatable and preventable condition. Anticoagulant drugs provide extremely effective treatment for venous thromboembolism and the initial management of thrombosis is usually straightforward.

Recommended treatment is usually low molecular weight heparin in combination with a vitamin K antagonist such as warfarin initially, with discontinuation of low molecular weight heparin when the international normalized ratio is greater than 2 for two consecutive days. The oral anticoagulant is continued for a period of time until discontinuation.

Deciding when to stop anticoagulation is often difficult. This decision-making process should ideally weigh up the risk of thrombosis against the risk of bleeding to arrive at a balanced conclusion, which may not be easy. This article gives a pragmatic approach based predominantly on the evidence provided in the ninth American College of Chest Physicians clinical practice guidelines (Kearon et al, 2012; Kearon and Akl, 2014).

The need for anticoagulation

Anticoagulation is the mainstay of venous thromboembolism treatment. However, a common misconception among both clinicians and patients is that anticoagulation is required to break down the recently formed thrombus. The purpose of anticoagulation is to prevent further venous thromboembolism episodes. This should be considered as a two-phase process with a 3-month period of 'active treatment' in the acute phase, followed by an indefinite period of 'secondary prevention' (Kearon and Akl, 2014). The point of active treatment is to inhibit progression and embolisation of the thrombus (Eichinger, 2013). Secondary prevention aims to prevent new episodes of venous thromboembolism that are unrelated to the index event (Kearon and Akl, 2014). This distinction is important since if a patient has a clear (temporary) risk factor, anticoagulation may only be required for the period of active treatment.

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Active treatment

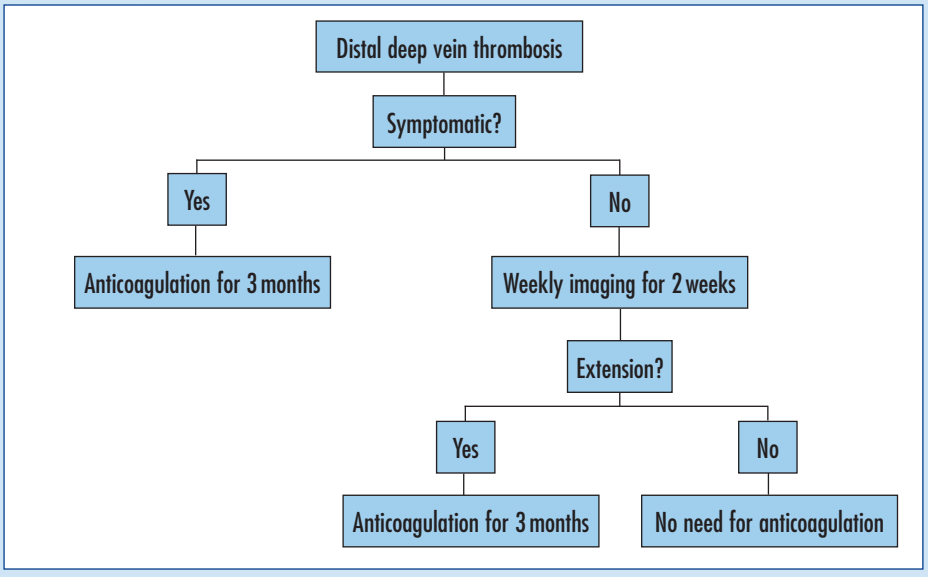
The aim of active treatment is to stop the recently formed thrombus from dissemination. It is common practice among many physicians to anticoagulate all patients with a new episode of venous thromboembolism for 6 months, and then discontinue anticoagulation altogether, especially after the first episode of venous thromboembolism (Thachil, 2014). However, a number of studies have provided evidence that challenges this widespread conventional practice. A number of experts now recommend that anticoagulation is continued either for 3 months to complete active treatment, or indefinitely as secondary prophylaxis (Kearon and Akl, 2014). This decision is dependent on the presence or absence of risk factors for future venous thromboembolism, and influenced by bleeding risk and patient preference (*Figure 1*).

Reducing the duration of anticoagulation to 4–6 weeks doubles the risk of recurrence, with most recurrences taking place in the first 6 months after stopping treatment and in the same leg. This supports the concept that an active treatment phase prevents reactivation of the original thrombus. Once the active treatment phase is completed, extending the duration of anticoagulation to 6, 12 or 24 months does not appear to further reduce the risk of recurrence once anticoagulation is stopped (Boutitie et al, 2011; Kearon and Akl, 2014).

Is 3 months needed for active treatment in all cases?

Patients with an acute isolated distal deep vein thrombosis of the leg, without severe symptoms or risk factors for extension, may undergo serial imaging of the deep veins for 2 weeks instead of anticoagulation. If there is no extension on imaging after 2 weeks, then it is deemed safe to withhold anticoagulation (Kearon et al, 2012). If the patient is symptomatic, anticoagulation is recommended. British Committee for Standards in Haematology guidelines (Keeling et al, 2011) recommend 6 weeks' treatment for a distal calf thrombus, but some authors feel that anticoagulation for 3 months is safer (Kearon and Akl, 2014).

Figure 1. Management of isolated, distal deep vein thrombosis.



Secondary prevention

Once the active treatment phase is completed, a decision needs to be made whether to stop anticoagulation or to continue indefinitely. This decision depends on:

1. Risk from recurrence on stopping treatment
2. Risk from anticoagulation-related bleeding.

Based on risk/benefit analysis carried out in major trials, British Committee for Standards in Haematology recommendations (Keeling et al, 2011) are as follows:

- If the risk of recurrent venous thromboembolism is <3% annually, anticoagulation should be stopped
- If the risk of recurrent venous thromboembolism is >9% annually, anticoagulation should be continued.

This applies to patients with an average risk of anticoagulant-related bleeding. Patients with a venous thromboembolism recurrence risk between 3 and 9% will need further risk/benefit analysis, as will those with a higher risk of bleeding. In any individual patient, it is not easy to predict these opposing risks. In addition, the risks of recurrence and bleeding may alter over time. It is therefore recommended that duration of treatment is reassessed, e.g. annually, and is described as 'indefinite' rather than 'lifelong' (Agnelli and Becattini, 2013).

Risk of recurrent thrombosis

Recurrence is most common in the first 2–3 months after discontinuation of anticoagulation, regardless of anticoagulation duration (Agnelli and Becattini, 2013). There are a number of risk factors for recurrence, some more important than others. In practice, factors influencing clinical decision making are:

- Provocation (e.g. surgery, oestrogen-containing oral contraceptive pill, trauma, pregnancy, immobility)
- Site of initial thrombus (proximal or distal)
- Ongoing provocation, e.g. malignancy.

Risk of bleeding

There is around a 2.6-fold increase in major bleeding with vitamin K antagonist use (Kearon and Akl, 2014). A number of factors are associated with increased bleeding risk (*Table 1*), but there are no validated scoring systems such as the HAS BLED system used in atrial fibrillation (Eichinger, 2013). As an estimate, young healthy patients with good vitamin K antagonist control will have a risk of major bleeding of ≤1% per year, while elderly patients with severe or multiple risk factors will have a risk of ≥4–6% per year (Eichinger, 2013; Kearon and Akl, 2014).

The decision to stop anticoagulation at 3 months

Venous thromboembolism provoked by a reversible or temporary risk factor

A provoking risk factor can be regarded as one that occurs within 3 months of the initial venous thromboembolism (if major provoking factor) or 6 weeks (if minor provoking factor) (Kearon and Akl, 2014). Major provocation, such as recent surgery, carries a very low risk of recurrence, around 1% within the first year of stopping anti-coagulation. Recurrence risk after non-surgical risk factors such as travel (flight longer than 8 hours), pregnancy and oestrogen-containing hormonal therapy use is slightly higher, at 5% within the first year and 15% within 5 years (Kearon and Akl, 2014). This risk is still sufficiently low to recommend stopping anticoagulation.

It is safe to continue the oral contraceptive pill or hormone replacement therapy following oestrogen-provoked venous thromboembolism provided the patient is anticoagulated. The oral contraceptive pill or hormone replacement therapy should be stopped 1 month before discontinuing anticoagulation. If there is a strong indication for continuing oestrogen-containing hormonal therapy, then anticoagulation should also be continued (Baglin et al, 2012).

Table 1. Risk factors for bleeding on anticoagulation

Older age (>65 years, particularly >75 years)
Previous bleeding
Cancer
Renal insufficiency
Liver failure
Diabetes
Previous stroke
Thrombocytopenia
Anaemia
Antiplatelet drugs
Recent surgery
Falls
Alcohol
Reduced functional capacity
Poor control of vitamin K antagonist therapy

Unprovoked isolated distal deep vein thrombosis

Recurrence risk in distal deep vein thrombosis is around half that of proximal deep vein thrombosis or pulmonary embolism. The risk is around 5% in the first year of stopping anticoagulation and ~2% annually thereafter (Kyrle and Eischer, 2013; Kearon and Akl, 2014).

The decision to continue anticoagulation beyond 3 months

Unprovoked proximal deep vein thrombosis or pulmonary embolism

Risk of recurrence after unprovoked venous thromboembolism is >9% per year. However, there is significant heterogeneity among patients with a history of unprovoked venous thromboembolism. The risk of a further venous thromboembolism in men is ~12% after 1 year and ~36% after 5 years, with the risk in women being ~8% after 1 year and ~24% after 5 years (Kearon and Akl, 2014). Recommendations derived from the American College of Chest Physicians guidelines state that 'patients with a first unprovoked proximal deep vein thrombosis/pulmonary embolism who do not have a high risk of bleeding are expected to derive a modest mortality benefit from extended therapy, resulting in a weak recommendation for indefinite anticoagulation' (Kearon and Akl, 2014). Although the above recommendation is weak, other risk factors for recurrence should be taken into account (*Table 2*), and if present, would strengthen the argument for anticoagulation (Baglin et al, 2012).

In particular, British Committee for Standards in Haematology guidelines recommend testing for the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin) if anticoagulation is stopped following an unpro-

Table 2. Risk factors for venous thromboembolism recurrence

Risk factor	Increase (-fold)
Unprovoked venous thromboembolism	2–5
Proximal venous thromboembolism or pulmonary embolism	2.5
Male sex	1.5–2
Cancer	2.2
Overweight	1.6
Prior history of venous thromboembolism	1.7
Post-thrombotic syndrome	2
Residual vein obstruction	1.5
Vena cava filter	1.5
Antiphospholipid antibodies	2
Hereditary thrombophilia	1.5

From Kyrle and Eischer (2013), Prandoni et al (2014)

voked venous thromboembolism. It should be noted that testing in patients with venous thromboembolism provoked by a transient risk factor is not recommended, as there is insufficient evidence to recommend extended anticoagulation even if the patient has antiphospholipid syndrome (Keeling et al, 2012). In antiphospholipid syndrome with unprovoked thrombosis, anticoagulation with warfarin is required; if thrombosis is recurrent despite adequate anticoagulation with warfarin, a target international normalized ratio of 3.0–4.0 is recommended.

Conversely, a number of factors would favour stopping anticoagulation, such as female gender, absent or mild post-thrombotic syndrome, unsatisfactory anticoagulation control, and low D-dimer after stopping anticoagulation (Baglin et al, 2012). A high risk of bleeding would also tip the balance towards stopping anticoagulation (Kearon et al, 2012).

Importantly, patient preference should also be considered. Some patients are reassured by anticoagulation, whereas others would rather not have the burden of regular medication conferring a bleeding risk, especially if monitoring is required. Consequently, patient preference should influence decision making, especially when recommendations are weak (Kearon and Akl, 2014).

Second episode of unprovoked venous thromboembolism

After a further unprovoked venous thromboembolism, the recurrence risk is around 50% higher than after a first event, with estimation of recurrence risk being 15% after 1 year and 45% after 5 years. Again, if there is a high risk of bleeding, anticoagulation should be discontinued (Kearon and Akl, 2014).

Provocation by persistent risk factor

Patients with active cancer have both a high risk of bleeding and a high risk of thrombosis. The risk of recurrent thrombosis is around 20% per year (Kearon and Akl, 2014), which is generally higher than the risk of bleeding. Anticoagulation following venous thromboembolism in malignancy should usually be continued indefinitely, unless the cancer is either cured or in remission with indirect evidence for a lower risk of recurrence (Kearon and Akl, 2014). However, as with all anticoagulation decisions, risk of thrombosis should be balanced against bleeding risk, quality of life, life expectancy and patient preference (Lyman et al, 2013). Low molecular weight heparin is a more effective and safer anticoagulant than a vitamin K antagonist in malignancy, and is recommended as first-line anticoagulation for at least the first 6 months of treatment (Eichinger, 2013).

Old age is a very common risk factor for initial venous thromboembolism and also for recurrent venous thromboembolism. If bleeding risk is low, older age should be considered a 'persistent' risk factor for continuing anticoagulation (Prandoni et al, 2007).

Similarly, obesity may be regarded as a persistent risk factor unless the patient loses weight. In a study of 1107 patients (Eichinger et al, 2008), there was a linear relationship between excess body weight and venous thromboembolism recurrence, with a 1.6-fold increase in recurrence risk among obese individuals.

Another interesting observation is the association between ABO blood group and risk of venous thromboembolism recurrence. In a cohort study of patients with unprovoked venous thromboembolism (Gándara et al, 2013), there was a statistically significant increased risk of recurrent venous thromboembolism in patients with blood groups other than O. This may be related to higher levels of von Willebrand factor in the circulation in non-blood group O individuals. *Figure 2* gives an algorithm for the management of venous thromboembolism.

The role of predictive markers

As already described, a number of factors influence the risk of venous thromboembolism recurrence (*Table 2*). It is often difficult to calculate, in an individual

Figure 2. Suggested venous thromboembolism management algorithm. * Low risk, e.g. female, negative D-dimer, absent post-thrombotic syndrome.

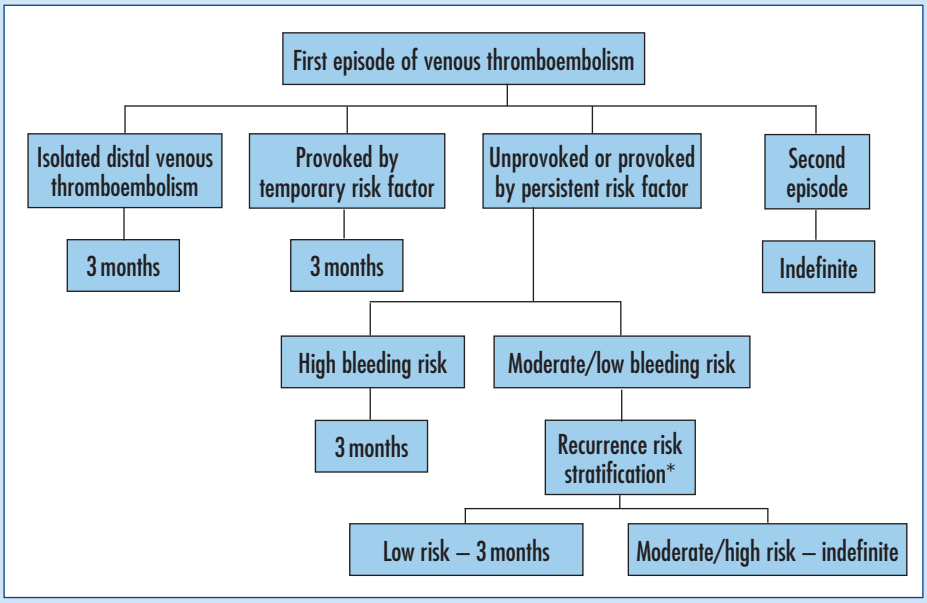


Table 3. Risk stratification models

	Men continue and HER D002	DASH score	Vienna prediction model
Study design	Multicentre prospective cohort study (646 patients)	Pooled data from seven prospective studies (1818 patients)	Prospective cohort study (929 patients)
Predictive variables	Men: none; women: signs of post-thrombotic syndrome (Hyperpigmentation/Edema/Redness of either leg), D-dimer ≥250 μg/litre on warfarin, body mass index ≥30 kg/m², age ≥ 65 years	Elevated D-dimer after anticoagulation, age <50 years, male sex, venous thromboembolism not associated with hormonal therapy	Male sex, proximal deep vein thrombosis/pulmonary embolism, elevated D-dimer after anticoagulation
Recurrence risk (annual)	Women scoring ≤1 = 1.6%, women scoring ≥2 = 14.1%	Score ≤1 = 3.1%, score 2 = 6.4%, score ≥3 = 12.3%	4.4% if score ≤180 points (according to nomogram)

From Kyrle and Eischer (2013), Prandoni et al (2014)

patient, the cumulative effect of these factors and how this balances against the risk of bleeding. The recommendation from Kearon and Akl (2014) states that: 'other risk factors should be taken into account when deciding duration of anticoagulation, but these rarely strongly or consistently influence treatment decisions'.

One risk factor that may influence treatment decisions more consistently in the future is D-dimer positivity. D-dimer is a fibrin degradation product, with high plasma levels indicating activation of the coagulation system. Patients with a negative D-dimer 1 month after stopping anticoagulation have a low risk of venous thromboembolism recurrence. It is therefore possible to identify a low risk cohort of patients who could stop anticoagulation; however, these findings are preliminary so D-dimer testing is currently optional (Kyrle and Eischer, 2013).

It is important to note that some misconceptions exist in relation to risk factors for venous thromboembolism recurrence:

- Although family history of venous thromboembolism is a well-known risk factor for a first venous thromboembolism, it is not a risk factor for recurrence (Prandoni et al, 2014)
- Thrombophilia screening, although widespread, is not a sufficiently strong predictor of risk to influence any treatment decisions (Kyrle and Eischer, 2013).

The role of risk stratification models

To make sense of the various factors that influence venous thromboembolism risk, a number of risk stratification models have been developed to identify patients at low risk of recurrence following unprovoked venous thromboembolism, who could be safely taken off anticoagulation (*Table 3*).

'Men continue and HER D002'

A prospective cohort study of 646 patients with a first, unprovoked venous thromboembolism used a number of characteristics to categorize a cohort of women at very low risk of recurrence. Risk was 1.6% annually if none or one of the following characteristics were present – hyperpigmentation (H), edema (E), or redness of either leg (R), D-dimer ≥250 μg/litre while taking warfarin, body mass index ≥30 kg/m², or age ≥ 65 years. If two or more of the above were present, the annual risk was 14.1% (Rodger et al, 2008).

DASH

Similarly, in another prospective study (Tosetto et al, 2012), patients with unprovoked venous thromboembolism were assigned a score based on presence of the following: abnormal D-dimer after stopping anticoagulation (D), age <50 years (A), male sex (S), venous thromboembolism not associated with hormonal therapy (in women) (H). Annual recurrence risk was 3.1% for a score ≤1, 6.4% for a score = 2 and 12.3% for a score ≥3.

Vienna prediction model

In a cohort of 929 patients with a first unprovoked venous thromboembolism, predictive variables for high recurrence risk were male sex, proximal venous thromboembolism or pulmonary embolism and positive D-dimer after anticoagulation. Based on these variables, the authors developed a nomogram to calculate risk scores and to estimate the cumulative probability of recurrence in an individual patient (Eichinger et al, 2010).

Although potentially extremely useful, these and other risk stratification models require prospective validation before they can be applied in daily routine care (Prandoni et al, 2014).

The role of new oral anticoagulants

Virtually all studies evaluating anticoagulation duration in venous thromboembolism focus on anticoagulation with vitamin K antagonists. However, direct oral anticoagulants such as rivaroxaban, dabigatran, apixaban and edoxaban are licensed or will shortly be licensed for the same indication.

Compared with vitamin K antagonists, the direct oral anticoagulants have similar efficacy and a lower rate of major bleeding (Eichinger, 2013). As direct oral anticoagu-

KEY POINTS

- Anticoagulation following an episode of venous thromboembolism should be continued either for 3 months or indefinitely.
- Venous thromboembolism provoked by a temporary risk factor may be treated for 3 months only.
- Following a second venous thromboembolism, anticoagulation should be continued indefinitely.
- Following an unprovoked venous thromboembolism, risk and benefit of continuing anticoagulation should be considered to reach a balanced decision.
- Isolated distal deep vein thrombosis may not require anticoagulation.

lant use becomes more widespread, their lower bleeding profile will likely alter the balance towards extended anticoagulation in selected patients. However, it should be stressed that there are as yet insufficient data on the use of these agents in patients with recurrent venous thromboembolism; in addition, major trials researching direct oral anticoagulant use had a maximum follow-up of 12 months only. There are also no data on the use of direct oral anticoagulants in patients with thrombosis related to malignancy or antiphospholipid syndrome; consequently treatment with a direct oral anticoagulant in these situations outside the context of a clinical trial cannot yet be recommended.

The role of aspirin

Aspirin has been trialled to identify a benefit in preventing recurrent venous thromboembolism. In the 2012 WARFASA trial (Becattini et al, 2012), patients with unprovoked venous thromboembolism were randomized to aspirin or placebo after 6–18 months of anticoagulation. Aspirin reduced venous thromboembolism recurrence by around 40% compared with placebo, with no apparent increase in the risk of bleeding. A similar randomized control trial, ASPIRE (Brighton et al, 2012), showed a non-significant decrease in the rate of recurrent venous thromboembolism with aspirin compared to placebo, but a significant reduction in the rate of major vascular events. These data show that low dose aspirin may be beneficial in preventing recurrent venous thromboembolism, albeit to a much lesser degree compared with anticoagulant agents.

Aspirin could potentially be used in preference to warfarin in patients with unprovoked venous thromboembolism at low risk of recurrence (such as those with persistently negative D-dimer results and no evidence of post-thrombotic syndrome) or patients with venous thromboembolism associated with minor risk factors (Prandoni et al, 2014).

Conclusions

Following a first episode of venous thromboembolism, patients should be anticoagulated either for 3 months or indefinitely. Patients need to be assessed individually, weighing up thrombosis recurrence and bleeding risks, and their preferences taken into account. A 3-month anticoagulation period is suitable for provoked or distal venous thromboemboli, in the absence of significant risk factors for venous thromboembolism recurrence. Indefinite anticoagulation should be considered following any unprovoked venous thromboembolism, venous thromboembolism provoked by malignancy, or a second venous thromboembolism. However, this decision should be weighed up against the risk of bleeding. Patients who are treated indefinitely should be reviewed regularly to ensure that their bleeding risk has not altered, and to allow discussion on advances in thrombosis risk prediction or treatment. **BJHM**

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Agnelli G, Becattini C (2013) Risk assessment for recurrence and optimal agents for extended treatment of venous thromboembolism. *Hematology* **2013**(1): 471–7 (doi: 10.1182/asheducation-2013.1.471)

Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G (2012) Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH: Unprovoked VTE: duration of anticoagulation. *J Thromb Haemost* **10**(4): 698–702 (doi: 10.1111/j.1538-7836.2012.04662.x)

Becattini C, Agnelli G, Schenone A et al (2012) Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* **366**(21): 1959–67 (doi: 10.1056/NEJMoa1114238)

Boutitie F, Pinede L, Schulman S et al (2011) Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ* **342**(2): d3036 (doi: 10.1136/bmj.d3036)

Brighton TA, Eikelboom JW, Mann K et al (2012) Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* **367**(21): 1979–87 (doi: 10.1056/NEJMoa1210384)

Eichinger S (2013) Anticoagulation after venous thromboembolism. Deciding on the optimal duration. *Hamostaseologie* **33**(3): 211–17 (doi: 10.5482/HAMO-13-03-0015)

Eichinger S, Hron G, Bialonczyk C et al (2008) Overweight, obesity, and the risk of recurrent venous thromboembolism. *Arch Intern Med* **168**(15): 1678–83 (doi: 10.1001/archinte.168.15.1678)

Eichinger S, Heinze G, Jandeck LM, Kyrle PA (2010) Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation* **121**(14): 1630–6 (doi: 10.1161/CIRCULATIONAHA.109.925214)

Gándara E, Kovacs MJ, Kahn SR et al (2013) Non-OO blood type influences the risk of recurrent venous thromboembolism. A cohort study. *Thromb Haemost* **110**(6): 1172–9 (doi: 10.1160/TH13-06-0488)

Kearon C, Akl EA (2014) Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. *Blood* **123**(12): 1794–801 (doi: 10.1182/blood-2013-12-512681)

Kearon C, Akl EA, Comerota AJ et al (2012) Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* **141**(2 Suppl): e419S–94S (doi: 10.1378/chest.11-2301)

Keeling D, Baglin T, Tait C et al (2011) Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol* **154**(3): 311–24 (doi: 10.1111/j.1365-2141.2011.08753.x)

Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in Haematology (2012) Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol* **157**(1): 47–58 (doi: 10.1111/j.1365-2141.2012.09037.x)

Kyrle PA, Eischer L (2013) Predicting the risk of recurrent venous thromboembolism. The Austrian study on recurrent venous thromboembolism (AUREC). *Hamostaseologie* **33**(3): 201–9 (doi: 10.5482/HAMO-13-03-0018)

Lyman GH, Khorana AA, Kuderer NM et al (2013) Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* **31**(17): 2189–204 (doi: 10.1200/JCO.2013.49.1118)

Prandoni P, Noventa F, Ghirarduzzi A et al (2007) The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* **92**(2): 199–205

Prandoni P, Barbar S, Milan M et al (2014) Optimal duration of anticoagulation. Provoked versus unprovoked VTE and role of adjunctive thrombophilia and imaging tests. *Thromb Haemost* **113**(5): 1210–15 (doi: 10.1160/TH14-04-0396)

Rodger MA, Kahn SR, Wells PS et al (2008) Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* **179**(5): 417–26 (doi: 10.1503/cmaj.080493)

Thachil J (2014) How long to anticoagulate? *QJM* **107**(6): 495–7 (doi: 10.1093/qjmed/hcu084)

Tosetto A, Iorio A, Marcucci M et al (2012) Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). *J Thromb Haemost* **10**(6): 1019–25 (doi: 10.1111/j.1538-7836.2012.04735.x)

TOP TIPS

- Antiphospholipid testing should be carried out if anticoagulation is to be stopped following unprovoked venous thromboembolism.
- Further thrombophilia testing is generally not helpful in aiding decision making.
- Provocation is one of the most important risk factors determining recurrence.