Optimal duration of anticoagulation

Provoked versus unprovoked VTE and role of adjunctive thrombophilia and imaging tests

Paolo Prandoni; Sofia Barbar; Marta Milan; Elena Campello; Luca Spiezia; Chiara Piovella; Raffaele Pesavento

Department of Medicine, Vascular Medicine Unit, University of Padua, Italy

Summary

Once anticoagulation is stopped, the risk of recurrent venous thromboembolism (VTE) over years after a first episode is consistently around 30%. This risk is higher in patients with unprovoked than in those with (transient) provoked VTE, and among the latter in patients with medical than in those with surgical risk factors. Baseline parameters that have been found to be related to the risk of recurrent VTE are the proximal location of deep-vein thrombosis, obesity, old age, male sex and non-0 blood group, whereas the role of inherited thrombophilia is controversial. The persistence of residual vein thrombosis at ultrasound assessment has consistently been shown to increase the risk, as do persistently high values of D-dimer and the early development of the post-thrombotic syndrome. Although the latest international guidelines suggest indefinite anticoagulation for most patients with the first episode of unprovoked VTE, strategies that incorporate the assessment of residual vein thrombosis and D-dimer have the potential to identify subjects in whom anticoagulation can be safely discontinued. Moreover, new opportunities are offered by a few emerging anti-Xa and anti-IIa oral compounds, which are likely to induce fewer haemorrhagic complications than vitamin K antagonists while preserving the same effectiveness; and by low-dose aspirin, which has the potential to prevent the occurrence of both venous and arterial thrombotic events.

Keywords

Venous thromboembolism, deep venous thrombosis, pulmonary embolism, anticoagulation, thrombophilia, residual thrombosis, ultrasonography

Correspondence to:
Dr. Paolo Prandoni
Department of Medicine, Vascular Medicine Unit
University of Padua
Via Giustiniani 2, 35128 Padua, Italy
Tel.: +39 049 8212656, Fax: +39 049 8218731
E-mail: paoloprandoni@tin.it

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Once anticoagulation is stopped, recurrent venous thromboembolism (VTE) is expected to develop in at least 30% of patients who receive 3-6 months of anticoagulation after their first episode (1–5). This rate will not change after extending anticoagulation up to 24 months (6–7).

Baseline risk factors for VTE recurrence

1. Provoked versus unprovoked VTE

The risk of VTE recurrence is negligibly low after major surgery or trauma (annual rate, lower than 1.0%), whereas it remains substantial if the thrombotic episode is triggered by "minor" transient factors such as hormonal treatment, minor injury, pregnancy, puerperium or long trips (annual rate, around 4.0%) (5). Patients with permanent risk factors (active cancer, longstanding immobilization, antiphospholipid syndrome) and those without apparent explanations for their thrombotic episode have a remarkable higher risk (annual rate, higher than 7.0%) (1-5).

2. Clinical characteristics

Single studies and meta-analyses have consistently shown that the risk of recurrent VTE is approximately 1.5 times as high in men than in women (8-10). The discrepancy with the gender-specific risk of the first VTE episode is apparent, and most probably explained by sex-specific risk factors at time of first venous thrombosis that are removed later on (11, 12). Indeed, when female reproductive risk factors are taken into account, the risk of a first venous thrombosis is twice as high in men as in women as well (13).

Old age, which is a well-known risk factor of venous thrombosis, has recently been identified – although not consistently (14) - as a predictive factor of recurrent VTE (2). Accordingly, the common practice of giving old patients lower doses or shorter periods of anticoagulation should be reconsidered (15).

Overweight was recently found to be a powerful and independent risk factor of recurrent VTE (16). Obese patients should, therefore, be carefully educated, as weight-loss is likely to play a key role in reducing the risk of relapses.

Finally, in a recent cohort study non-0 blood type has been found to be an independent predictor of recurrent VTE (17). This

information, which can be easily obtained, has the potential to be incorporated in stratification models addressing the risk of recurrent VTE.

3. Modality of VTE presentation

Patients with a first symptomatic unprovoked deep-vein thrombosis (DVT) are at higher risk of recurrent VTE than those with a first unprovoked pulmonary embolism (PE) (18). In addition, patients with symptomatic PE have a risk of recurrent PE that is two- to three-fold higher than those with DVT alone. These findings, which have recently been confirmed by a patient-level meta-analysis (19), should be taken into account when deciding the optimal duration of anticoagulation. Indeed, a PE episode is potentially more dangerous than an event confined to the leg veins.

Inherited thrombophilia and family history

Inherited thrombophilia does not increase the risk of recurrent thromboembolism while on anticoagulation (20), while its role in recurrent VTE once anticoagulation is stopped is controversial. It is generally accepted, although not conclusively demonstrated, that carriers of (even mild) antithrombin, protein C and S defects (21, 22), carriers of hyperhomocysteinaemia (23) and carriers of increased levels of factor VIII or IX (24-26) have a recurrence risk that is higher than that of control subjects. It is, instead, matter of debate if carriers of factor V Leiden or prothrombin G20210A variant have a higher risk of recurrence as well, as there are data in favour and against this association (27, 28). As a consequence, whether detection of these abnormalities, which are highly prevalent in western countries, has the potential to identify subgroups of patients who might benefit from individually adjusted prevention strategies, is uncertain.

Two studies have consistently shown that the family history of VTE – a well known risk factor of VTE (29) - does not increase the risk of recurrent VTE (30, 31).

Post-baseline factors

1. D-dimer

Several studies consistently suggested that positivity of D-dimer at the time of warfarin discontinuation or soon after its interruption helps identify patients at a higher risk of developing recurrent VTE (32-35). These findings have recently been confirmed by a meta-analysis of available investigations (36).

2. Post-thrombotic syndrome

Another post-baseline factor potentially associated with an increased risk of recurrent VTE is the early development of post-thrombotic manifestations (37).

3. Residual vein thrombosis

In a few cohort studies, the ultrasound persistence of residual thrombosis after an episode of proximal DVT was found to be an independent risk factor for recurrent VTE (38, 39). Two recent meta-analyses of available investigations suggest that, whichever the method used for measuring the thrombotic mass, residual vein thrombosis is a powerful and independent predictor of recurrent VTE (40, 41). Of interest, residual vein thrombosis predicts not only the development of recurrent ipsilateral DVT, but also that of contralateral DVT and even of PE apparently not associated with DVT, suggesting that residual vein thrombosis is a marker of hypercoagulability (38-41).

In a recent prospective cohort study, residual vein thrombosis at three months after DVT (defined as the ultrasound incompressibility of at least 4 mm in the transverse section either in the popliteal or in the common femoral vein) was found to double the risk for recurrent VTE and post-thrombotic syndrome (42). The likelihood of residual vein thrombosis was higher in males, in patients with previous VTE and in those with extensive thrombosis. These findings suggest that a single assessment of residual thrombosis at three months can help risk stratify patients with proximal DVT and guide treatment decisions.

Whether the persistence of residual emboli after an episode of PE may predicts the risk of recurrent PE as well is uncertain (43). A recent prospective cohort study showed an unexpectedly high rate (85%) of pulmonary artery recanalisation in patients with PE treated with anticoagulants alone for six months, while in the remaining 15% the thrombotic burden decreased by more than 80% (44). These findings add to the current perception that residual thrombotic obstruction following PE is rare and unlikely to predict recurrent PE.

Risk stratification models

A novel approach for assessing risk of recurrent VTE consists of linking clinical patient characteristics with laboratory testing (▶Table 1). In a Canadian model, women with idiopathic VTE and none or one of several parameters (age older than 65, obesity, D-dimer positivity at time of discontinuing anticoagulation and post-thrombotic manifestations) exhibited a considerably lower risk of recurrent VTE than the remaining patients (45). Another prediction model enables identification of the recurrence risk based on the combination of two baseline factors (sex and type of clinical presentation) and one post-baseline factor (D-dimer) (46). In the third model, based on a patient-level meta-analysis (the DASH score), D-dimer after stopping anticoagulation, age < 50 years, male sex and VTE not associated with hormonal therapy (in women) were found to be the main predictors of recurrence and were used to derive a prognostic recurrence score (47). All these scoring models require prospective validation before they can be applied in daily routine care (48).

Table 1: Models to predict recurrent VTE.

	Men continue and HER D002 (44)	Vienna Prediction Model (45)	DASH-score (46)
Study design	Prospective cohort	Prospective cohort	Patient level meta-analysis
Patients	646	929	1818
Predictive variables	Men: none Women: • age ≥ 60 years • signs of PTS • BMI ≥ 30 kg/m^2 • D-dimer > 250 µg/l during anticoagulation	• Sex • Location of first VTE • D-dimer after anticoagulation	• Abnormal D-dimer after anticoagulation • Age < 50 years • Male sex • Hormonal therapy
Increased risk of recurrent VTE	>1 point	> 180 points (according to a nomogram)	> 1 point
Recurrence rate in patients at low risk	1.6% (95% CI, 0.3–4.6)	4.4% (95% CI, 2.7–6.2)	3.1% (95% CI, 2.3–3.9)

Duration of treatment in patients with unprovoked VTE: old and new scenarios

Patients presenting with a first episode of unprovoked VTE should be offered at least three months of vitamin K antagonists (VKAs), targeting an international normalised ratio (INR) between 2.0 and 3.0 (49), which is the duration that is sommonly recommended for patients whose thrombotic episode is triggered by transient risk factors (50). The decision as to go on or discontinue anticoagulation after the first three months should be individually tailored and balanced against the haemorrhagic risk, taking into account also patients' preferences. An indefinite anticoagulation can be considered in selected patients at low bleeding risk (48), while in all other patients this decision requires caution. Indeed, the annual incidence of major bleeding from long-term anticoagulation is 1.5–2.0%, and the 'case-fatality rate' of major bleeding is considerably higher than that of recurrent VTE (51, 52). Of interest, major bleeding increases the risk of recurrent VTE and decreases life expectancy (53, 54).

Following the demonstration that D-dimer can help stratify the individual risk of recurrent VTE (32-36), a randomised clinical trial showed that in patients in whom anticoagulation was withdrawn because of a negative D-dimer – assessed one month after warfarin discontinuation – the rate of recurrent events is only slightly higher than in patients with positive D-dimer who continue anticoagulation (55). In addition, repeating D-dimer testing after anticoagulation suspension has the potential to identify individuals requiring resuming anticoagulation in order to prevent VTE recurrences (56).

In a few randomised clinical trials it has been shown that adjusting the duration of anticoagulation according to the persistence of residual thrombosis reduces the risk of recurrent VTE by approximately 40% (57, 58).

Of the two multicentre Italian studies, designed to evaluate the value of combining residual vein thrombosis with the serial D-dimer determination in adjusting the duration of anticoagulation the DULCIS study has recently been published (59). In this study, involving almost 1,000 outpatients, D-dimer tests persistently below age and gender specific cut-offs were obtained in more than 50% of patients, and discontinuation of VKAs resulted in a subsequent annual recurrence rate lower than 3.0%. The second – the Morgagni study – is still ongoing.

New opportunities

1. New oral anticoagulants

New categories of oral antithrombotic drugs are emerging. These drugs have the potential to simplify the treatment of patients with VTE by obviating the need for periodic laboratory monitoring, and are associated with a favourable benefit-to-risk ratio. They include compounds that selectively inhibit factor Xa, such as rivaroxaban, apixaban and edoxaban, and compounds that selectively inhibit thrombin, such as dabigatran etexilate. The results of several randomised clinical trials suggest that these drugs have a favorable benefit-to-risk profile in the first 6-12 months after an episode of VTE in comparison with conventional treatment (60-65). The value of long-term administration in preventing recurrent VTE has been evaluated in four studies performed in patients who had completed a 6-18-month period of conventional anticoagulation.

Two clinical trials were designed to assess the efficacy and safety of dabigatran for the extended treatment of VTE. In the RESONATE study 1,343 patients with unprovoked VTE who had completed 6–18 months of anticoagulant therapy were randomised to dabigatran (150 mg bid) or placebo for an additional period of six months (66). A 92% relative reduction in the relative risk for recurrent VTE was shown in favour of dabigatran, with a low risk for major bleeding (0.3% vs 0). In the RE-MEDY study 2,856 patients at a higher risk of recurrent VTE who had been treated for

six months with VKAs for a first VTE were randomised to dabigatran (150 mg bid) or warfarin (INR 2–3) for the long-term prevention of recurrent VTE (66). Dabigatran was shown to be non-inferior to VKAs (1.8% primary outcome events in dabigatran patients vs 1.3% in warfarin patients). Major bleeding complications occurred in 0.9% and 1.8% of patients, respectively (reduction in the relative risk, 48%).

The EINSTEIN Extension trial randomised 1,197 patients with unprovoked VTE who had completed 6-12 months of anticoagulant therapy for an acute index VTE event to an additional 6–12 months of therapy with either rivaroxaban, 20 mg once daily, or placebo (62). Recurrent symptomatic VTE events were recorded in 1.3% of patients in the rivaroxaban group and 7.1% of patients in the placebo group (relative risk reduction, 82%). Major bleeding occurred in 4 (0.7%) rivaroxaban-treated patients as compared to none in the placebo group.

The AMPLIFY-Extension was a 12-month randomised clinical trial where apixaban 2.5 mg and 5 mg bid were compared with placebo for extended treatment to prevent recurrent VTE in approximately 2,500 patients with unprovoked VTE who had completed 6-12 months of treatment for DVT or PE (67). Apixaban demonstrated superiority versus placebo in the reduction of the composite endpoint of symptomatic, recurrent VTE and death from any cause ($p<0.001$). Apixaban was superior to placebo for the predefined secondary efficacy outcome of recurrent VTE and VTE-related death (8.8% in the placebo group, compared with 1.7% in both the apixaban 2.5 mg and 5 mg groups; $p<0.001$). The rates of major bleeding were comparable for 2.5 mg (0.2%), the 5 mg (0.1%), and placebo (0.5%) treatment groups. The rate of the composite of major bleeding and clinically relevant non-major bleeding for the 5 mg treatment group (4.3%) was higher than in the placebo group (2.7%), while 2.5 mg treatment group (3.2%) demonstrated similar rates to placebo.

Because of the potential to induce fewer bleeding complications, the new drugs may open new scenarios for decisions on the optimal duration of anticoagulation in patients with unprovoked VTE. However, these findings should be interpreted with caution for a number of reasons. Only selected patients were included in the clinical trials, thus no information is available for different patients categories, including carriers of major thrombophilias, patients with severe renal or hepatic failure, patients requiring anticoagulation for reasons other than VTE, and so on. In only one study (the REMEDY) was the new anticoagulant (dabigatran) compared with warfarin in patients at a higher recurrence risk (66), whereas in all the remaining the comparator was placebo, and the extent by which recurrent VTE was reduced over placebo did not exceed that achieved by VKAs in studies adopting a similar study design (7). In only one study (the AMPLIFY-Extension) was there a head-to-head comparison between the conventional and a lower dose of the index compound (apixaban), whereas in all the remaining the initial dose was tested unchanged throughout the whole period of anticoagulation. As the duration of these studies did not surpass 6-12 months, the persistence of a favourable benefit-to-risk ratio beyond this period cannot be anticipated. The results of the AMPLIFY-Extension study suggest that halving the initial dose after the first 6 months in patients with unprovoked VTE is likely to preserve protection against recurrent VTE while further reducing the haemorrhagic risk (67).

2. Low-dose aspirin

Recent studies have shown the efficacy of low-dose aspirin in prevention of recurrent VTE. In a multicentre, double-blind study (the WARFASA trial) more than 400 patients with unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment were randomly assigned to aspirin, 100 mg daily, or placebo for at least two years (68). VTE recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs 11.2% per year; hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.36 to 0.93). One patient in each treatment group had a major bleeding episode.

The ASPIRE trial, which involved 822 patients, showed a non-significant decrease in the rate of recurrent VTE with aspirin (100 mg per day) as compared with placebo (rate of recurrence, 4.8% vs 6.5% per year; HR, 0.74; 95% CI, 0.52 to 1.05; $p=0.09$) (69). However, since arterial thrombotic events occurred only about half as often in the aspirin-treated group as in the placebo group (10 events vs 19 events), aspirin was associated with a significant reduction in the rate of major vascular events (HR, 0.66; 95% CI, 0.48 to 0.92; $p=0.01$).

When data from these two trials are pooled, there is a 32% reduction in the rate of recurrence of VTE (HR, 0.68; 95% CI, 0.51 to 0.90; $p=0.007$), and a 34% reduction in the rate of major vascular events (HR, 0.66; 95% CI, 0.51 to 0.86; $p=0.002$). Moreover, these benefits are achieved with a low risk of bleeding (70).

Hence, based on available evidence aspirin in low doses may offer a safe and highly cost-effective option for the long-term prevention of recurrent VTE. However, the degree by which aspirin reduces the rate of recurrent VTE is remarkably lower than that achieved by old and new anticoagulants. In addition, in real practice the bleeding risk related to the use of even low doses of aspirin may not be as low as that observed in the WARFASA and in the ASPIRE studies (71). Finally, aspirin does not seem to confer any appreciable protection against recurrent VTE in patients with symptomatic atherosclerosis (72, 73). An appealing perspective (to be tested in future investigations) may be replacing warfarin with aspirin in patients with unprovoked VTE at low risk of recurrent VTE, such as those with early veins recanalization and/or persistent D-Dimer negativity; and in those with VTE associated with "minor" risk factors.

3. Statins

Finally, recent studies suggest a potential role for statins, whose value has already been shown in the primary prevention of VTE (74), in reducing the risk of recurrent VTE as well (75-77). Although any conclusions are still premature, it cannot be excluded that treatment with statins may become an attractive option, either

alone or in association with antithrombotic compounds, for the long-term anticoagulation of patients with VTE, especially whenever there is the simultaneous need for lowering the lipids level or controlling the development of atherosclerotic lesions.

Conflicts of interest

None declared.

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